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Procesos secuenciales de escisión radicalaria-oxidación-adición de nucleófilos: aplicación a la modificación selectiva de péptidos y a la síntesis de productos bioactivos

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El trabajo presentado en esta memoria ha sido realizado en los laboratorios del Departamento de Síntesis de Fármacos y Compuesto Bioactivos del Instituto de Productos Naturales y Agrobiología del CSIC, entre Septiembre de 2008 y Enero de 2013, bajo la dirección de la Dra Alicia Boto Castro y del Dr Rosendo Hernández González, a quienes quiero expresar mi agradecimiento por su dedicación, disponibilidad e interés durante todo el proceso.

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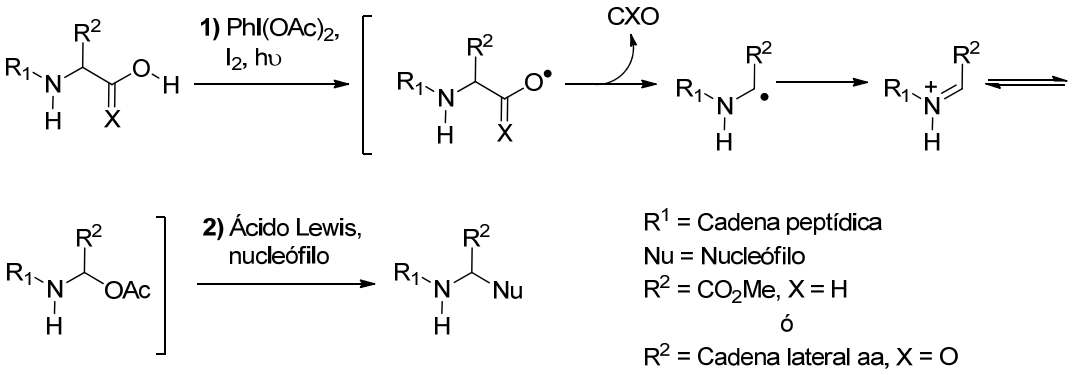
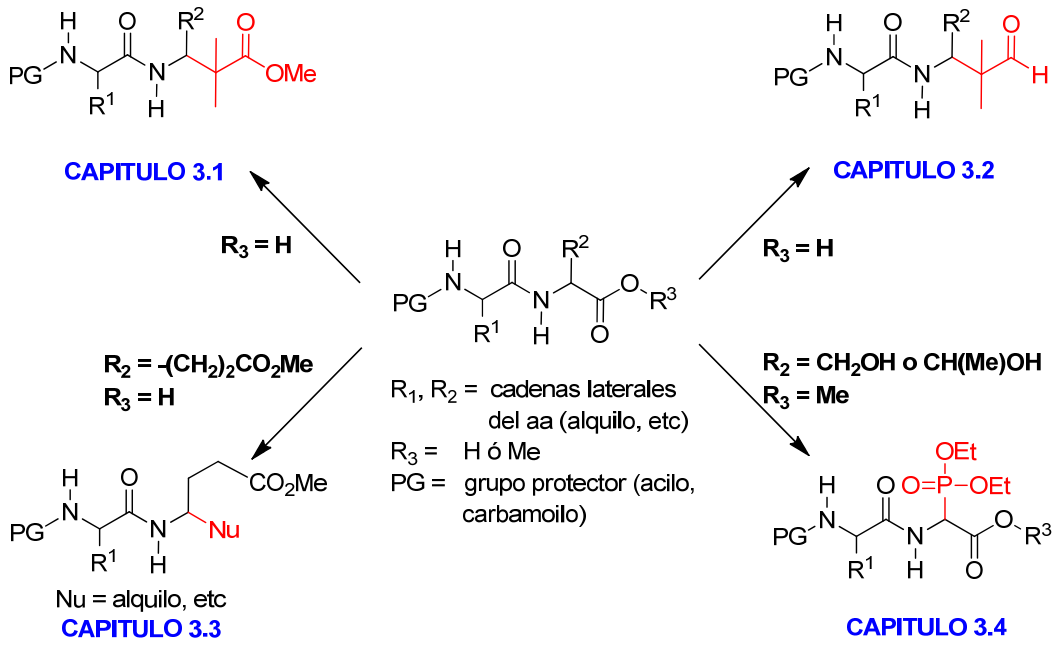
RESUMEN

En esta tesis se describe el desarrollo de procesos secuenciales de escisión radicalaria–oxidación–adición de nucleófilos, dirigidos principalmente a la modificación selectiva de péptidos de pequeño tamaño. Es de destacar que la modificación selectiva de péptidos supone un reto muy importante, dada la similar reactividad de sus unidades.



Este trabajo esta dividido en cuatro capítulos, en los que se consigue la modificación selectiva de un residuo “convertible”.



- **Capítulo 3.1** En este capítulo se describe la ***transformación selectiva del extremo C-terminal*** de péptidos, para dar un β-amino éster, usando procesos secuenciales de descarboxilación radicalaria oxidativa–adición de nucleófilos.

  Además, se detalla la ***formación de α,β,α-tripéptidos y su comportamiento en solución***. Para ello, se realizaron estudios de resonancia magnética nuclear, en dos disolventes ($CDCl_3$ y DMSO-d_6). Se demuestra que los α,β,α-tripéptidos que tienen un β-amino ácido con configuración *S* presentan un enlace de hidrógeno intrarresidual (C_6), en cambio los α,β,α-tripéptidos con un β-amino ácido con configuración *R* presentan un giro δ extendido (C_9). La naturaleza de la cadena lateral del β-amino ácido no influye en los resultados. Estos estudios son claves para diseñar, en un futuro, nuevos foldámeros y modular la actividad de péptidos bioactivos y/o catalíticos.

- **Capítulo 3.2** En este capítulo se ***modifica selectivamente el extremo C-terminal de pequeños péptidos,*** obteniéndose una unidad de β-amino aldehído, usando procesos secuenciales de descarboxilación radicalaria oxidativa–adición de nucleófilos. Estos aldehídos pueden reducirse en condiciones suaves, para generar γ-amino alcoholes análogos de los antibióticos peptaiboles, con buenos rendimientos.

- **Capítulo 3.3** En este capítulo se estudia la ***modificación selectiva de posiciones tanto terminales como internas de péptidos, usando como residuo "convertible" a unidades de ácido glutámico***. Tras usar un proceso secuencial de descarboxilación radicalaria oxidativa–alquilación, la unidad de glutámico se convierte en un γ-amino ácido no natural. De esta forma, péptidos con unidades de glutámico se convierten fácilmente en péptidos α,γ-híbridos. Estos resultados tienen interés para el desarrollo de foldámeros o péptidos de interés farmacológico.

- **Capítulo 3.4** En este capítulo se desarrolla la ***modificación selectiva de péptidos con unidades de serina o treonina***, que se transforman en unidades de deshidroamino ácidos β-sustituidos en dos pasos. En el primero, se realiza un proceso secuencial de escisión radicalaria oxidativa–adición de nucleófilos de *fósforo*, obteniéndose amino fosfonatos en buenos rendimientos. Estos fosfonatos se sometieron a las condiciones de reacción de Horner–Wadsworth–Emmons (HWE) con distintos aldehídos, obteniéndose así péptidos modificados con unidades de *Z*-deshidroamino ácido, con alta estereoselectividad. La HWE también se realizó con cetonas (acetona) dando deshidroamino ácidos β,β-disustituidos (deshidrovalina). Estos péptidos también tienen gran interés para desarrollar foldámeros y compuestos bioactivos.

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Introducción

1 INTRODUCCIÓN.

1.1 Introducción a procesos secuenciales de escisión radicalaria–oxidación–adición de nucleófilos.

1.1.1 Introducción a procesos secuenciales.

El desarrollo de procesos tándem o de procesos secuenciales ha permitido obtener procedimientos más cortos y más eficaces para preparar una gran variedad de productos, incluyendo intermedios sintéticos, fármacos ó catalizadores.[1] Con estos procesos se pueden realizar varias transformaciones consecutivas, no se requiere purificación de los intermedios y además se ahorran reactivos, materiales, energía y tiempo, y también se disminuye la cantidad de residuos.

Los procesos dominó o tándem se caracterizan porque en ellos se forman varios enlaces carbono-carbono o carbono-heteroátomo, en un solo paso de reacción, sin necesidad de aislar y purificar intermedios, y sin modificar las condiciones de reacción. En los procesos secuenciales es necesario modificar las condiciones de reacción, por ejemplo cambiando la temperatura o añadiendo un nuevo reactivo para que la reacción tenga lugar.

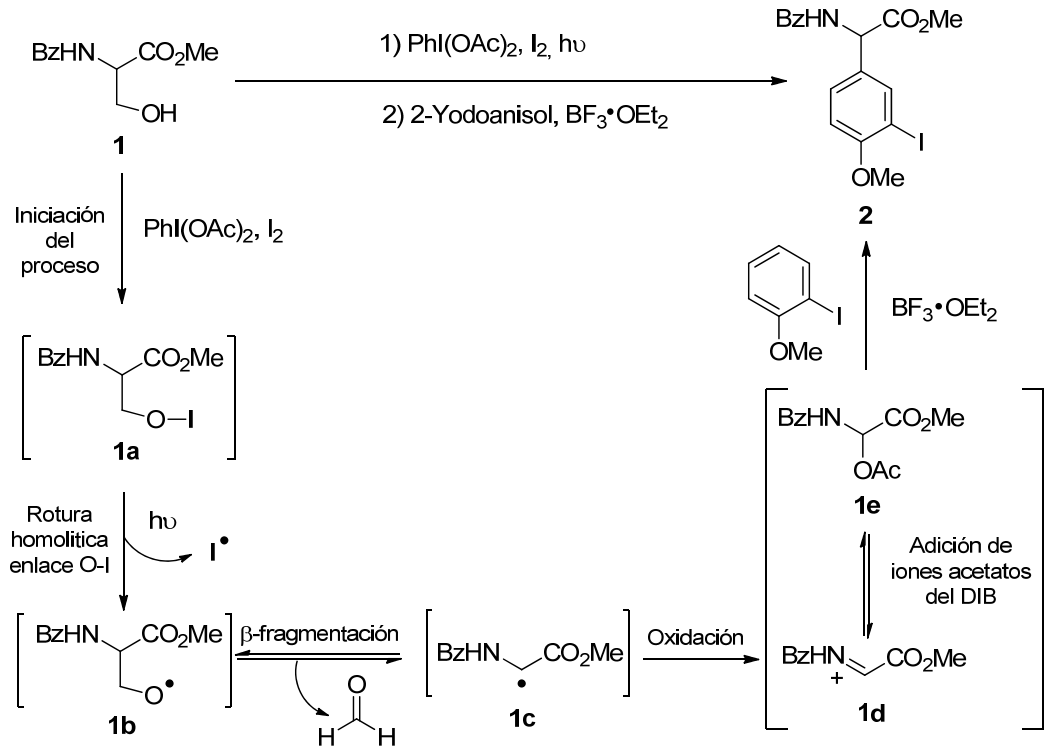
En trabajos anteriores de nuestro grupo,[2] se desarrolló una metodología en la que mediante un proceso secuencial de escisión radicalaria–oxidación–adición de nucleófilos se preparaban productos bioactivos a partir de sustratos de fácil obtención, como amino ácidos o carbohidratos. En el Esquema 1 se muestra como ejemplo la conversión del amino ácido **1** en la

[1] (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581. (c) Nicolaou, K. C.; Edmons, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186. (d) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619–1665 (Part A) and *Tetrahedron* **2006**, *62*, 2143–2173 (Part B). (e) Guo, H.-C.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366. (f) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020 y referencias en él citadas.

[2] (a) Boto, A.; Gallardo, J. A.; Hernández, R.; Ledo, F.; Muñoz, A.; Murguía, J. R.; Menacho-Márquez, M.; Orjales, A.; Saavedra, C. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6073–6077 (artículo en anexo). (b) Boto, A.; Hernández, R.; León, Y.; Murguía, J. R.; Rodríguez-Afonso, A. *Eur. J. Org. Chem.* **2005**, 673–682. (c) Boto, A.; Hernández, D.; Hernández, R.; Álvarez, E. *J. Org. Chem.* **2007**, *72*, 9523–9532. (d) Boto, A.; Hernández, D.; Hernández, R. *Org. Lett.* **2007**, *9*, 1721–1724. (e) Hansen, S. G.; Skrydstrup, T. *Top. Curr. Chem*. **2006**, *264*, 135–162.

arilglicina **2**. El proceso secuencial se inicia con una reacción de escisión radicalaria a temperatura ambiente usando luz visible.[3]

Así, el alcohol de partida **1** (derivado del amino ácido serina) reacciona con el sistema (diacetoxiyodo)benceno (DIB) y yodo, generando un hipoyodito de alquilo **1a**. Este hipoyodito se descompone por irradiación con luz visible, provocando la ruptura homolítica del enlace O–I, generando un radical alcoxilo **1b**. Este *O*-radical sufre un proceso de β-fragmentación, consistente en la ruptura homolítica del enlace C–C α,β al radical. Ello da lugar al *C*-radical **1c**, que en el medio de reacción se oxida al ion acilminio[2a] **1d**. Este intermedio es atrapado por los iones acetato provenientes de DIB, generando el *N*,*O*-acetal **1e**. En presencia de un ácido de Lewis, el *N*,*O*-acetal **1e** regenera el ión **1d** que reacciona con nucleófilos aromáticos (por ejemplo el 2-yodoanisol) dando lugar al amino ácido no proteico **2**.



Esquema 1. Preparación de productos activos a partir de sustratos de fácil obtención.

[3] La escisión radicalaria también puede ser inducida por calentamiento, pero la irradiación con luz visible (como la luz del sol) emplea condiciones más suaves. Para irradiar se usaron lámparas de filamento de wolframio de 80 W.

La primera parte del proceso (la transformación de **1**→**1e**) es un proceso dominó, pero dado que en la conversión **1e**→**2** cambian las condiciones del medio, la transformación global **1**→**2** es un proceso secuencial.

Los procesos dominó suelen caracterizarse por la alta eficacia de cada etapa. La conversión de **1**→**1e** implica al menos cinco etapas consecutivas, que transcurren con altos rendimientos.

A lo largo de esta memoria, desarrollaremos variantes de este proceso de escisión radicalaria–oxidación–adición de nucleófilos, por lo que vamos a comentarlo con más detalle.

El paso más importante de todo el proceso es la etapa radicalaria, por lo que se hará un estudio más exhaustivo de la generación y reactividad de los radicales alcoxilos. Posteriormente se comentará la reactividad de iones aciliminio (o de aciliminas) y su atrapamiento con nucleófilos.

1.1.2 Escisión radicalaria en procesos dominó o secuenciales. Generación y reactividad de los radicales alcoxilo.

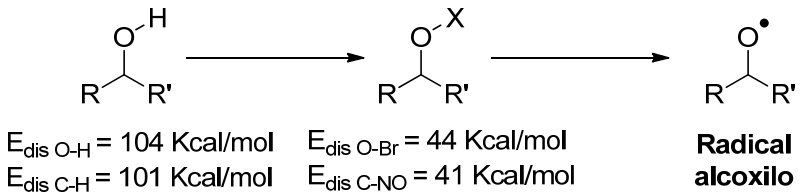
1.1.2.1 Aspectos generales de la generación y reactividad de los radicales alcoxilo.

Las reacciones radicalarias han experimentado un desarrollo creciente desde que se publicara en 1957 el primer libro moderno sobre estos intermedios de reacción.[4] A partir de entonces su uso se ha hecho cada día más importante en síntesis orgánica,[5] especialmente en la síntesis de subestructuras presentes en moléculas biológicamente activas.[6]

Un radical alcoxilo puede definirse como una especie reactiva que presenta un electrón desapareado centrado en el átomo de oxigeno.

[4] Walling, C. *Free Radicals in Solution*, J. Willey & Sons: New York, **1957**.
[5] *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M.P., Eds.; Wiley-VCH: Weinheim, **2001**; vol. 1 y 2.
[6] (a) Giese, B.; Porter, N.; Curran, D. P. *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1995**. (b) Curran, D. P.; Jasperse, C. L.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237–1286. (c) Curran, D. P. *Synthesis* **1988**, 417–439. (d) Curran, D. P. *Synthesis* **1988**, 489–513. (e) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds* en *Organic Chemistry Series*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, **1986**. (f) Sosnovsky, G. *Free Radical Reactions in Preparative Organic Chemistry*, Mc. Millan: London, **1964.**

Formalmente se puede considerar que proviene de la ruptura homolítica del enlace O–H de una molécula R–O–H. Sin embargo, en la práctica los alcoxirradicales no pueden ser preparados directamente a partir del alcohol, acetal o del ácido, debido a la elevada energía del enlace O–H (104 Kcal/mol), superior incluso a la del enlace C–H (95/101 Kcal/mol, C-terciarios/C-primarios)[7] (Esquema 2).



Esquema 2. Generación de radicales alcoxilo a partir de enlaces R–O–H.

Para generar un radical alcoxilo, el enlace O–H se debe transformar en un enlace más débil, tipo oxígeno–heteroatomo O–X (X = halógeno, NO, SAr, $Pb(OAc)_3$, etc). De esta manera, la ruptura homolítica del enlace será más fácil; por ejemplo, la energía de disociación de un enlace O–Br es tan solo de 44 Kcal/mol,[8] casi un tercio de la energía de disociación del enlace O–H.

Los *O*-radicales se pueden generar tanto en medio oxidante como reductor. En medio oxidante destacan la descomposición de alquil hidropéroxidos,[9] de alquil peróxidos,[10] la fotólisis de alquil nitritos (reacción de Barton),[11] y la descomposición térmica o fotoquímica de hipohalogenitos.[12]

[7] (a) Cekovic, Z. *Tetrahedron* **2003**, *59*, 8073–8090. (b) Spicer, C. W.; Villa, A.; Wiebe, H. A. Heicklen, J. *J. Am. Chem. Soc.* **1973**, *95*, 13–20. (c) Mayo, F. R. *Acc. Chem. Res.* **1968**, *7*, 193–201.
[8] Fossey, J.; Lerfort, D.; Sorba, J. *Free Radicals in Organic Chemistry*, Wiley, Chichester, **1995**.
[9] (a) Schreiber, S. L.; Hulin, B.; Liew, W.-F. *Tetrahedron* **1986**, *42*, 2945–2950. (b) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163–6165.
[10] Matsugo, S.; Saito, I. *Dialkyl Peroxides* en *Organic Peroxides*; Ando, W., Ed.; Wiley: Chichester, **1992**, pp. 157–194.
[11] (a) Girard, P.; Guillot, N.; Motherwell, W. B.; Hay-Motherwell, R. S.; Potier, P. *Tetrahedron* **1999**, *55*, 3573–3584. (b) Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1–16. (c) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc*. **1961**, *83*, 4076–4083. (d) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640–2641.
[12] (a) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501–526. (b) Heusler, K.; Kalvoda, J. *Organic Reactions in Stereoid Chemistry*; Freid, J.; Edward, J. A., Eds.; Van Nostran Reinhold: New York,

Dentro del grupo de los hipohalogenitos, los hipoyoditos de alquilo[12a] han sido muy utilizados,[13] ya que se pueden generar *in situ* a partir de un alcohol o un hemiacetal por tratamiento con distintos reactivos. Por ejemplo, tetraacetato de plomo (TAP) o la combinación de yodo (ó NIS) con TAP, HgO, CAN y $AgSO_4$.[14] Más recientemente se han usado reactivos de yodo hipervalente[15] como el (diacetoxiyodo)benceno (DIB)[16] y yodo. Los hipoyoditos así formados (energía de enlace O–I es de 56 Kcal/mol) pueden experimentar descomposición fotoquímica, a temperatura ambiente, o descomposición térmica[12b,17] para dar un radical alcoxilo.

El mecanismo por el que transcurre la reacción (Esquema 3) implica la reacción de DIB con yodo, originando hipoyodito de acetilo. Este reacciona con el sustrato ROH, dando lugar a un hipoyodito de alquilo y ácido acético. El hipoyodito se descompone por calentamiento o por irradiación con luz visible, provocando la ruptura homolítica del enlace O–I, generando el radical alcoxilo. La presencia de estas especies ha sido detectado por experimentos de RMN.[18]

1971; vol. 2, pp 237–287. (c) Heusler, K.; Kalvoda, J. *Angew. Chem. Int. Ed. Engl*. **1964**, *3,* 525–538.

[13] (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis,* Academic Press **1997**. (b) Brun, P.; Waegell, B. *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, **1983**; vol. 3. (c) Doyle, M. P.; Zuidema, L. J.; Bade, T. R*. J. Org. Chem*. **1975**, *40*, 1454–1456.

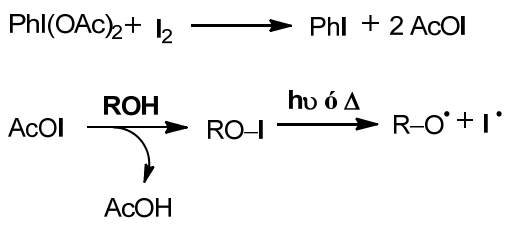
[14] (a) Majestich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095–7129. (b) Suginome, H.; Nakayama, Y., Sanboku, H. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1837–1842. (c) Clerici, A.; Minisci, F.; Ogawa, K.; Suzur, J.-M. *Tetrahedron Lett.* **1978**, *19*, 1149–1152. (d) Trahanovsky, W. S.; Young, M. G.; Nave, P. M*. Tetrahedron Lett*. **1969**, *10*, 2501–2504.

[15] (a) Togo, H.; Katohgi, M. *Synlett* **2001**, 565–581. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (c) Moriarty, R. M. *J. Org. Chem*. **2005**, *70*, 2893–2903. (d) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656–3665.

[16] (a) de Armas, P.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc. Perkin Trans. 1* **1989**, 405–411. (b) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1953–1956.

[17] (a) Montana, A. M.; Ponzano, S. *Tetrahedron Lett.* **2006**, *47*, 8299–8304. (b) Preite, M. D.; Cuellar, M. A. *Chem. Commun.* **2004**, 1970–1971. (c) Krstic, N. M.; Bjelakovic, M. S.; Lorenc, L. B. *J. Serbian Chem. Soc.* **2003**, *68*, 785–794.

[18] (a) Madsen, J.; Viuf, C.; Bols, M. *Chem. Eur. J*. **2000**, *6*, 1140–1146. (b) Courtneidge, J. L.; Lusztyk, J.; Pagé, D. *Tetrahedron Lett.* **1994**, *35*, 1003–1006.



Esquema 3. Mecanismo de formación de un radical alcoxilo utilizando DIB/I_2 como reactivo.

1.1.2.2 Reacciones de los radicales alcoxilo.

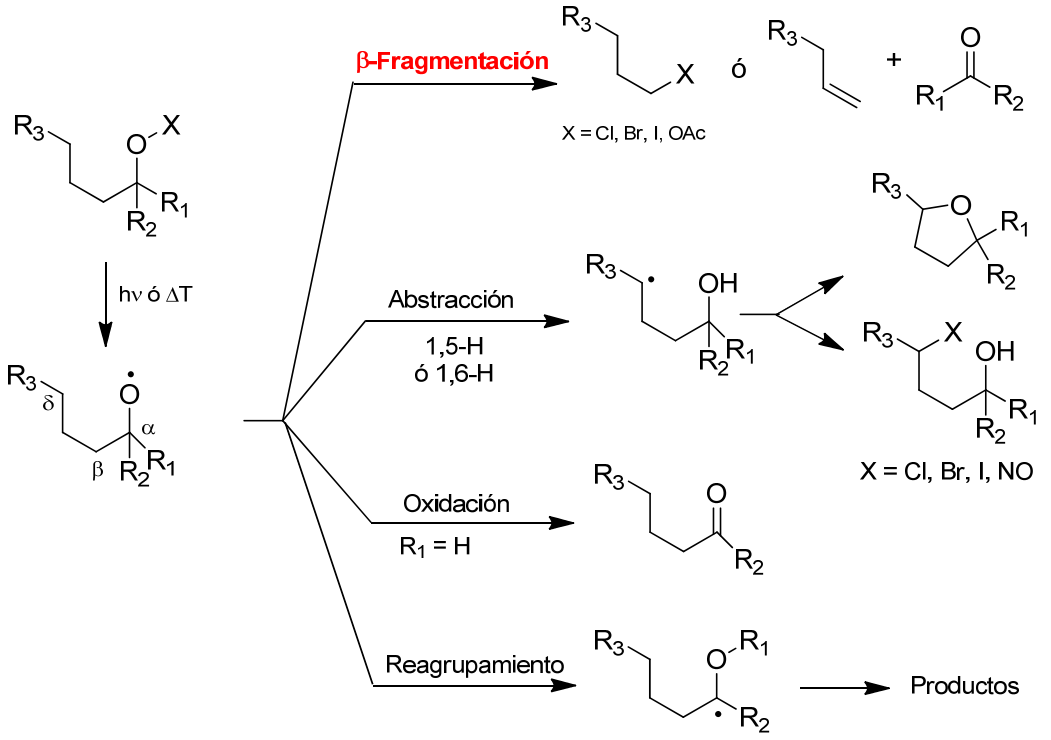
Una vez generados, los radicales alcoxilo pueden sufrir distintas reacciones.[12a,13]

- β-Fragmentación.[15b,19]
- Abstracción de hidrógeno.[4,20]
- Oxidación.
- Reagrupamiento.
- Adición a olefinas.[21]

[19] (a) Hartung, J.; Gottwald, T.; Spehar, K. *Synthesis* **2002**, 1469–1498. (b) McCarrol, A. J.; Walton, J. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 2224–2248. (c) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271–1287. (d) Yet, L. *Tetrahedron* **1999**, *55*, 9349–9403. (e) Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem*. **1999**, *64*, 8801–8811. (f) Suárez, E.; Rodriguez, M. S. *β-Fragmentation of Alkoxyl Radicals: Synthetic Applications* en *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**; vol. 2, pp 440–454.

[20] (a) Feray, L.; Kuznetsov, N.; Renaud, P. *Hydrogen Atom Abstraction* en *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**; vol. 2, pp. 246–278. (b) Robertson, J.; Pillai, R.; Lush, K. *Chem. Soc. Rev.* **2001**, *30*, 94–103.

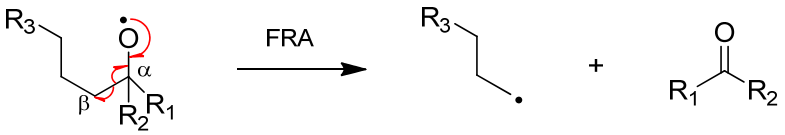
[21] (a) Hartung, J. *Eur. J. Org. Chem*. **2001**, 619–632. (b) Hartung, J. *Cyclization of Alkoxyl Radicals* en *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P. Eds.; Wiley-VCH: Weinheim, **2001**; vol. 2, pp. 427–439.



Esquema 4. Reacciones principales de los radicales alcoxilo.

De ellas las más interesantes, por su utilidad sintética, son las reacciones de β-fragmentación y las de abstracción intramolecular de hidrógeno (Esquema 4) por lo que las comentaremos a continuación.

Se denomina reacción de β-fragmentación a la ruptura homolítica del C–C en posición α,β a un radical alcoxilo, dando lugar a un grupo carbonilo y un *C*-radical (Esquema 5).[22]



Esquema 5. Reacción de β-fragmentación de un radical alcoxilo.

[22] Mihailovic, M. L.; Cekovic, Z. *Synthesis* **1970**, 209–224.

En las reacciones de abstracción intramolecular de hidrógeno, se produce una transferencia 1,5 (y en ocasiones 1,6) de un átomo de hidrógeno desde un carbono δ o ε al radical alcoxilo, originándose un *C*-radical que se estabiliza de distintas formas según las condiciones de reacción. De esta manera se pueden funcionalizar carbonos no activados, un proceso que en general es difícil de realizar por otros métodos.

En general, la reacción de β-fragmentación de radicales alcoxilo (FRA) compite con la reacción de abstracción intramolecular de hidrogeno (AIH), favoreciéndose la reacción de β-fragmentación cuando no hay hidrógenos en el carbono δ o ε, o cuando la distancia entre el carbono δ o ε y el oxígeno del radical alcoxilo no se encuentra entre 2.3–2.8 Å.[23] La estabilidad del *C*-radical formado también determina si predomina la escisión o la abstracción de hidrógeno. Cuanto mayor sea la sustitución en el carbono β más favorecida está la fragmentación, puesto que el *C*-radical resultante es más estable: $R_3C\bullet$ > $R_2HC\bullet$ > $RH_2C\bullet$ > $H_3C\bullet$.

De igual forma, si el radical generado es alílico, bencílico o estabilizado por heteroátomos, la β-fragmentación puede remplazar totalmente a la abstracción de hidrogeno.

Las reacciones de β-fragmentación han tenido gran importancia en nuestro grupo de investigación y como veremos han sido ampliamente utilizadas en el transcurso de esta tesis, por lo que pasaremos a comentarlas con más detalle.

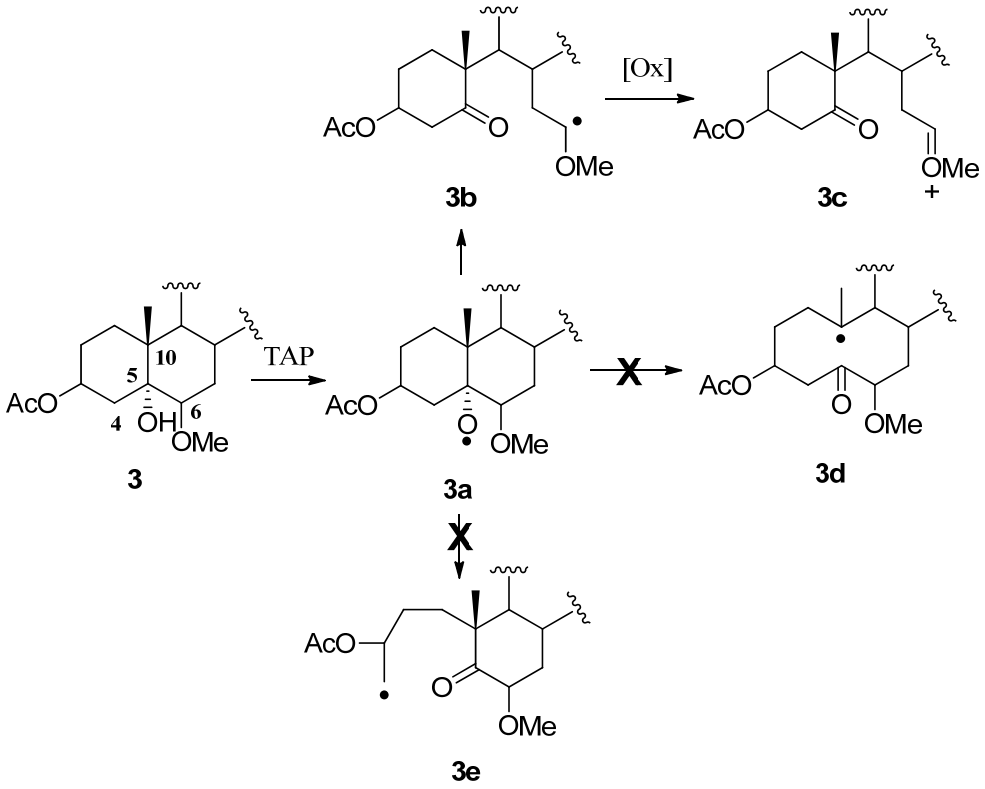
Como se comentaba antes, la β-escisión genera un radical centrado en el carbono, que evoluciona de distintas formas, dependiendo de las condiciones de reacción. Por ejemplo, cuando se utiliza $Pb(OAc)_4$ para generar el radical, se pueden obtener alquenos o acetatos, mientras que en la descomposición de hipohalogenitos[13b] se suele generar derivados halogenados.

[23] (a) Patch, R. E. *J. Org. Chem.* **1963**, *28*, 276–277. (b) Crains, T. L.; Englund, B. L. *J. Org. Chem.* **1956**, *21*, 140–140.

La estabilidad del *C*-radical formado influye en el resultado de la fragmentación,[13,24,25] como ilustra el Esquema 6. Así por ejemplo, al tratar el compuesto **3** con tetraacetato de plomo (TAP) se genera un enlace O–Pb que se rompe homolíticamente, dando lugar al radical **3a**. Este evoluciona por β-escisión, que se podría producir en los enlaces C_4-C_5, C_5-C_6 o C_5-C_{10}. Sin embargo, únicamente se fragmenta el enlace C_5-C_6, ya que el radical resultante **3b** está estabilizado por una función oxigenada en el carbono 6. La oxidación de **3b** generaría el ion oxicarbenio **3c**,[25] lo que hace a la escisión C_5-C_6 irreversible.

La fragmentación del enlace C_5-C_{10} generaría el radical terciario **3d,** menos estable que el radical en α a la función oxigenada.

La fragmentación del enlace C_4-C_5 daría lugar al radical primario **3e**, que es el menos estable de los tres.



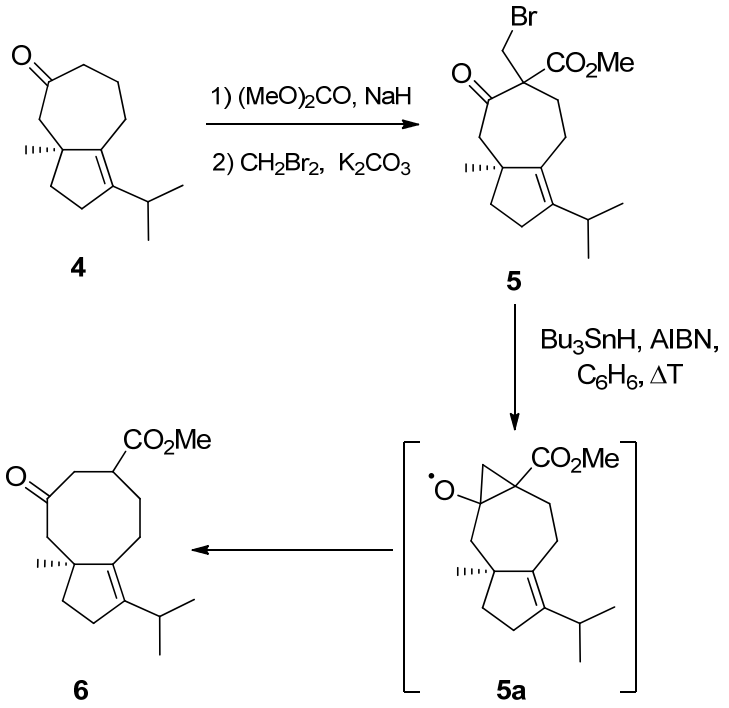
Esquema 6. Fragmentación del radicales alcoxilo derivado del sustrato **3**.

[24] Mihailovic, M.L.; Lorenc, L.; Pavlovic, V. *Tetrahedron* **1977**, *33*, 441–446.
[25] Morand, P.; Kaufman, M. *J. Org. Chem.* **1969**, *7*, 2175–2180.

La β-fragmentación es una reacción rápida pero reversible.[26] Por ello, la rapidez de la etapa siguiente (ej. atrapamiento del *C*-radical con yodo, con acetato, la oxidación de *C*-radical, etc) también es fundamental para que la escisión predomine o no sobre otras reacciones, como se comentó para la conversión de **3b**→**3c** (Esquema 6). Otros factores que influyen en el comportamiento de los radicales alcoxilo son los estéricos[27] o térmicos.[28]

La selectividad en la fragmentación, observada en los ejemplos anteriores, la hace muy útil en procesos sintéticos en los que otras metodologías no dan buenos resultados.[29] El Esquema 7 muestra un ejemplo,[30] en el que la cetona bicíclica **4** se transforma en dos pasos en una α-bromometilcetona sustituida **5**. La homólisis del enlace C–Br en **5** da un radical carbono que se adiciona al grupo carbonilo adyacente. El alcoxirradical **5a** experimenta entonces una β-fragmentación con apertura del ciclopropano, seguida de reducción del *C*-radical resultante, para dar el compuesto bicíclico **6** que es un precursor útil en la síntesis de diterpenos como la fusicoplagina D.

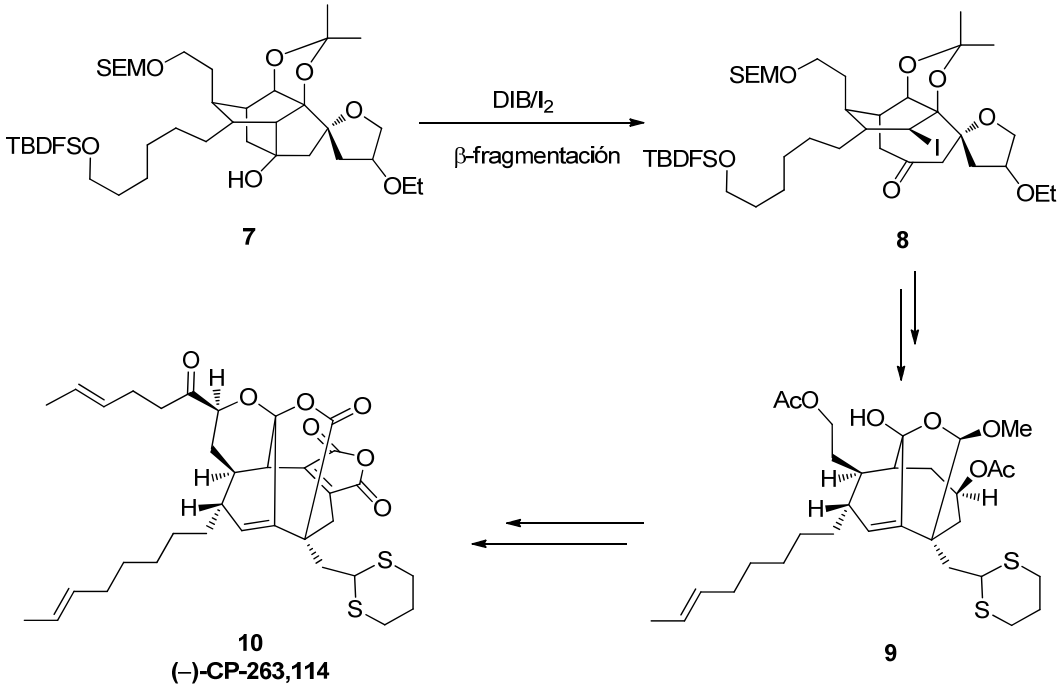
[26] Binkley, R. W.; Koholic, D. J. *J Org. Chem.* **1979**, *44*, 2047–2048.
[27] Bensandoun, N.; Brun, P.; Casanova, J.; Waegell, B. *J. Chem. Res. Synop.* **1981**, 236–237.
[28] Beckwith, A. L. J.; Kazlauskas, R.; Syner-Lyons, M. R. *J. Org. Chem.* **1983**, *48*, 4718–4722.
[29] Zhang, W. *Ring Expansions* en *Radicals in Organic Synthesis*, vol. 2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**, pp. 234–245.
[30] Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc*. **1991**, *113*, 5765–5775.



Esquema 7. Aplicación de la reactividad de radicales alcoxilo a la síntesis del biciclo **6**.

La β-fragmentación de radicales alcoxilos es una metodología muy útil para obtener una gran variedad de compuestos, como olefinas, compuestos halogenados, anillos de mediano y gran tamaño y heterociclos. [15a,b,19a,b,f,29,31] Por ejemplo la β-escisión es la etapa clave en la síntesis del antifúngico natural (−)-CP263,114 (conversión **7**→**10**, Esquema 8).[32]

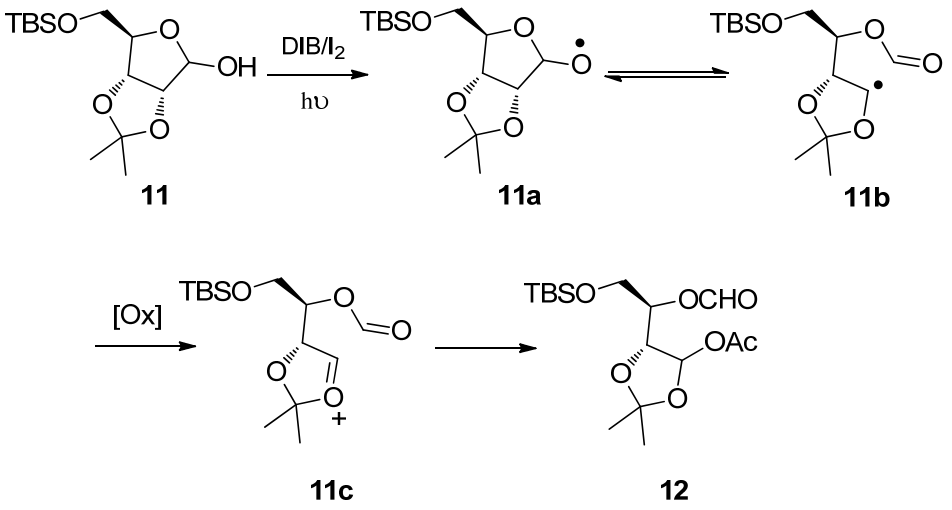
[31] (a) Chiba, S.; Kitamura, M.; Narasaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6931−6937. (b) Ramesh, N. G.; Hassner, A. *Eur. J. Org. Chem.* **2005**, 1892−1902. (c) Takasu, K.; Nagao, S.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 1005−1008. (d) Chai, C. L. L.; Elix, J. A.; Huleatt, P. B. *Tetrahedron* **2005**, *61*, 8722−8739. (e) De Dobbeleer, C.; Ates, A.; Vanherk, J. C.; Marko, I. E. *Tetrahedron Lett.* **2005**, *46*, 3889−3893. (f) Bietti, M.; Gente, G.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 6820−6826.
[32] Yoshimitsu, T.; Sasaki, S.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 9262−9268.



Esquema 8. Síntesis del antifúngico (–)-CP263,114.

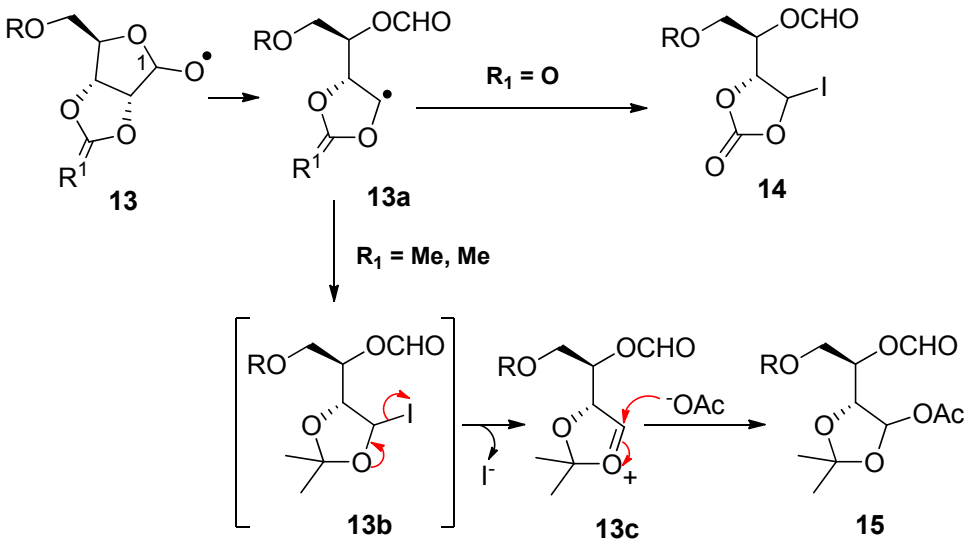
En general, cuando el *C*-radical se genera en alfa a funciones oxigenadas (conversión **11**→**12**, Esquema 9)[33] en medio oxidativo, el *C*-radical es oxidado a un ion oxicarbenio, lo que hace irreversible el proceso. Estos iones pueden ser atrapados por nucleófilos presentes en el medio, por ejemplo, por iones acetatos procedentes del reactivo (DIB, TAP, etc).

[33] (a) de Armas. P.; Francisco, C. G.; Súarez, E. *Angew. Chem. Int. Ed. Engl*. **1992**, *31*, 772–774.
(b) Francisco, C. G.; Martín, C. G.; Suarez, E. *J. Org. Chem.* **1998**, *63,* 8092–8093.



Esquema 9. Oxidación del *C*-radical en α a funciones oxigenadas.

En estudios de la fragmentación de carbohidratos (conversiones **13**→**14** y **13**→**15**, Esquema 10) se comprobó que la naturaleza del grupo protector juega un papel importante en la evolución del *C*-radical generado tras la β-fragmentación.[33b]



Esquema 10. Influencia del grupo protector CR^1 en la evolución del *C*-radical.

Así el *O*-radical **13**, generado de la forma habitual, sufre una β-fragmentación produciendo un radical **13a**. Cuando el grupo protector CR_1 del intermedio **13a** es un grupo atractor de electrones, (por ejemplo C=O), el radical reacciona con yodo generando el α-yodoalquil ester **14**.

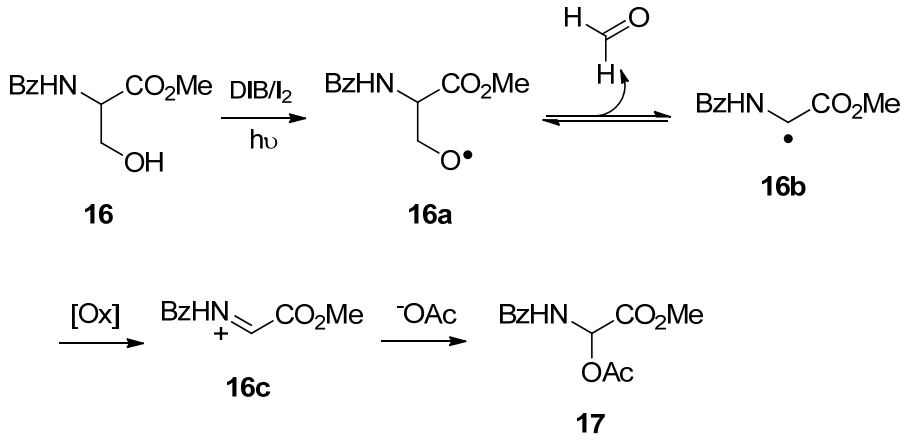
Sin embargo cuando CR_1 es un grupo donor de electrones, (como CMe_2) el *C*-radical es oxidado por el exceso de reactivo dando el ion oxicarbenio **13c**, que puede ser atrapado por iones acetatos del medio, dando el acetil acetal **15**.

Este ejemplo puede sugerir un mecanismo razonable para la etapa de oxidación. Cabe suponer que el ion oxicarbenio **13c** procede de un yodoacetal **13b** que es inestable y evoluciona por extrusión de yoduro. Esta extrusión no se ve favorecida en el caso de **14,** pues el ion oxicarbenio resultante estaría desestabilizado por el sustituyente atractor de electrones.

La oxidación se ve favorecida cuanta mayor capacidad donadora de electrones tenga el sustituyente del intermedio catiónico. Las funciones nitrogenadas estabilizan el catión más que las funciones oxigenadas: NR > NCOOR > NCOR ≥ OR > OCOOR > OCOR.

En efecto, cuando el *C*-radical se genera en alfa a funciones nitrogenadas en medio oxidativo, el radical es oxidado a un ion aciliminio que es atrapado por los iones acetatos de medio (como muestra la conversión de **16**→**17**, Esquema 11).[34]

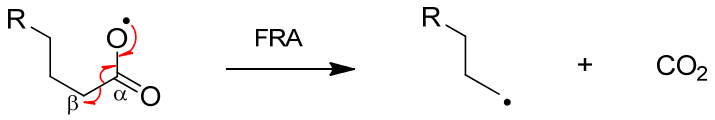
[34] Boto, A.; Gallardo, J. A.; Hernández, D.; Hernández. R. *J. Org. Chem*. **2007**, *72*, 7260−7269.



Esquema 11. Oxidación del *C*-radical en α a funciones nitrogenadas.

1.1.2.3 Fragmentación de radicales carboxilo.

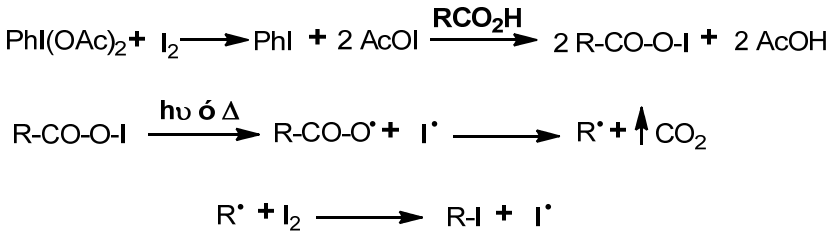
Una variante de los radicales alcoxilo son los radicales carboxilo (R–CO–O•) los cuales evolucionan por fragmentación con desprendimiento de CO_2 (Esquema 12).



Esquema 12. Reacción de β-fragmentación de un radical carboxilo.

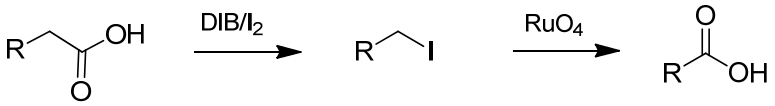
Estos radicales se generan a partir de ácidos carboxílicos, usando los mismos reactivos que para la escisión de alcoholes y acetales. La descarboxilación tiene un mecanismo similar (Esquema 13).

La energía necesaria para la descarboxilación radicalaria es mucho menor que la necesaria para la fragmentación de radicales alcoxilo, siendo $K_{frag.} = 10^6\text{-}10^{10}\ s^{-1}$, ya que el CO_2 generado en la descarboxilación escapa del medio de reacción, desplazando el equilibrio y haciendo el proceso irreversible.



Esquema 13. Mecanismo de formación de un radical carboxilo utilizando DIB/I_2 como reactivo.

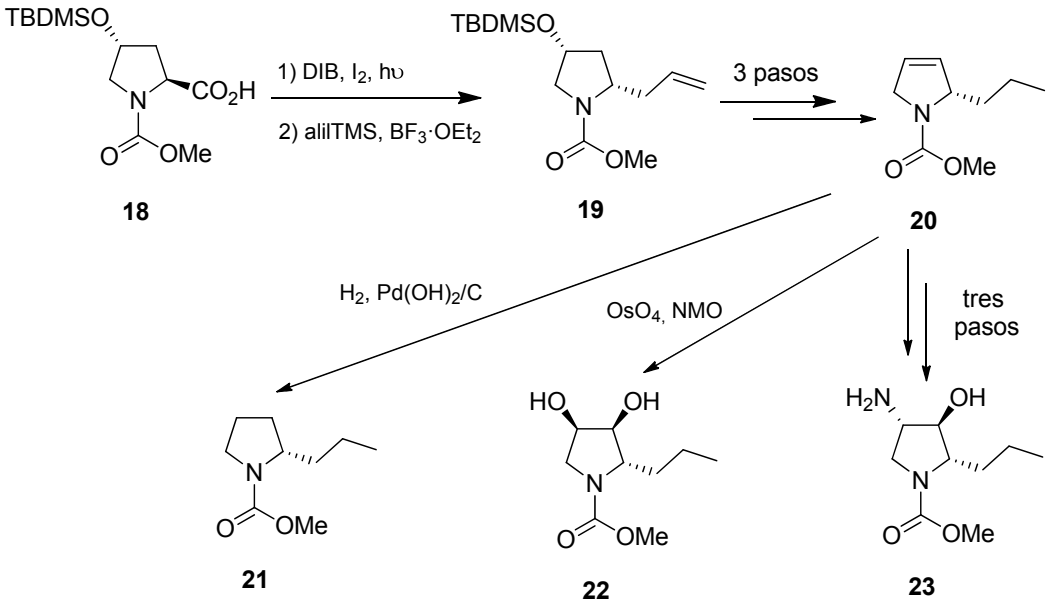
La reacción de descarboxilación radicalaria tiene muchas aplicaciones sintéticas. Por ejemplo, es muy útil para acortar la longitud de la cadena de carbono de ácidos carboxílicos en un átomo de carbono (Esquema 14).[35]



Esquema 14. Reacción de acortamiento de un carbono de ácidos carboxílicos.

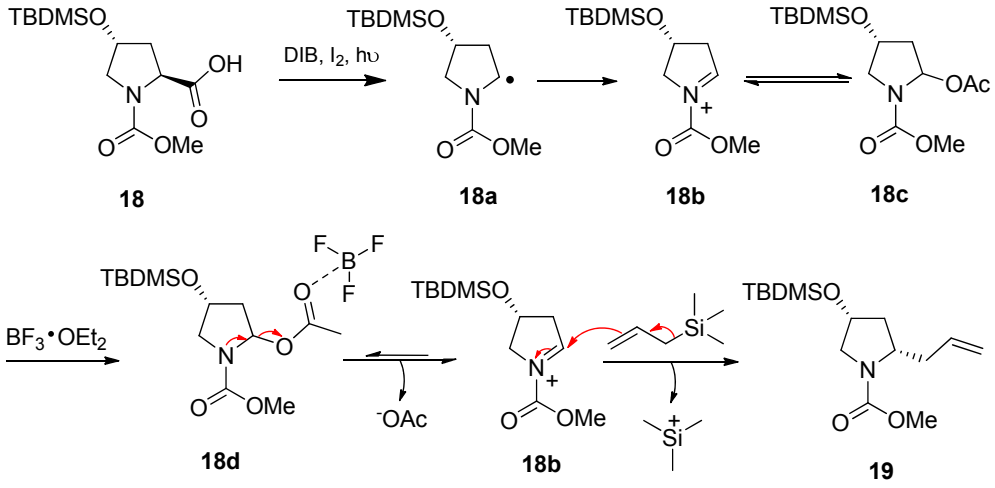
Además, mediante reacciones de descarboxilación radicalaria de amino ácidos se han obtenido análogos de productos bioactivos. Por ejemplo, la conversión de **18**→**21**–**23** (Esquema 15)[36] proporcionó el derivado de norconiina **21** y los derivados de iminoazucar **22** y **23**.

[35] Hernández, R.; Melián, D.; Súarez, E. *Synthesis* **1992**, 653–655.
[36] Boto, A.; Hernández, D.; Hernández, R. *Tetrahedron Lett*. **2009**, *50*, 3974–3977.



Esquema 15. Síntesis del derivado de norconiina **21** y de los iminoazucares **22** y **23**.

El mecanismo de la conversión **18**→**19** se muestra en el Esquema 16. Al tratar con DIB y yodo el derivado de hidroxiprolina **18**, se genera el *C*-radical **18a**. Éste se oxida en el medio de reacción, formando el ion acilminio **18b,** que es atrapado por los iones acetato del reactivo para dar el *N,O*-acetal **18c.**



Esquema 16. Descarboxilación–alilación del sustrato **18**.

Cuando se añade el acido de Lewis ($BF_3 \cdot OEt_2$), el acetal **18c** regenera el ion aciliminio **18b**. A continuación se produce la adición del nucleófilo (aliltrimetilsilano) al ion aciliminio, generando el compuesto **19**.

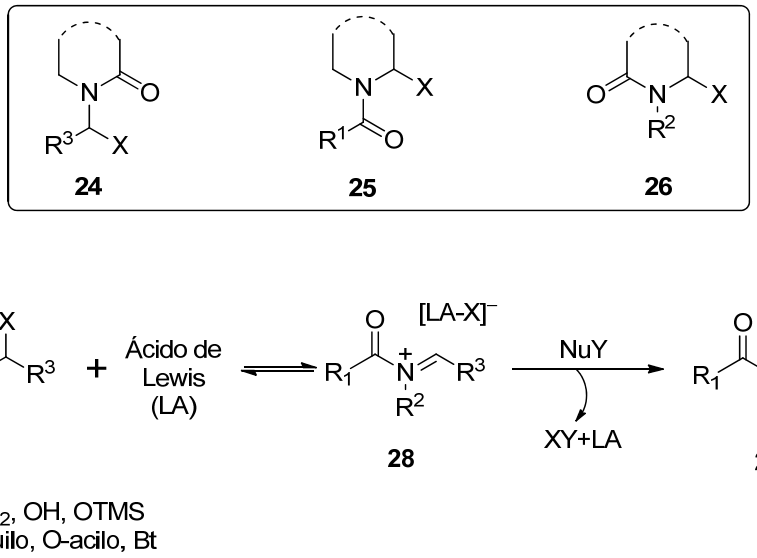
Como hemos visto en el esquema anterior, la adición de nucleófilos a iones aciliminio tiene un papel muy importante en la preparación de productos bioactivos, así como en los procesos secuenciales que se comentarán en la memoria. Por ello se hará un resumen de la adición de nucleófilos a iones aciliminio (o a aciliminas), que no pretende ser exhaustivo.[37]

1.1.3 Reacciones de adición de nucleófilos a iones aciliminio o aciliminas.

1.1.3.1 Aspectos generales.

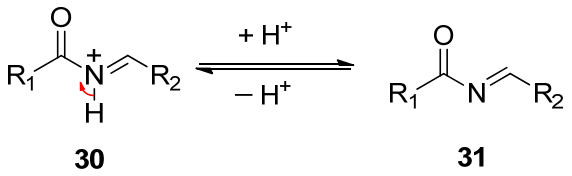
Debido a su alta reactividad, los iones *N*-aciliminio son habitualmente generados *in situ* y reaccionan con reactivos ricos en electrones (nucleófilos). Entre los precursores de los iones aciliminio se encuentran los compuestos **24**–**26** (Esquema 17). Cuando uno de estos compuestos (ej. la *N*-acilamina **27**) es tratado con un acido de Lewis (o ciertos ácidos de Brønsted) se genera un intermedio iminio **28** que puede ser atrapado por nucleófilos para dar aminas α-sustituidas **29**.

[37] (a) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541. (c) Ferraris, D. *Tetrahedron* **2007**, *63*, 9581–9597. (d) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569. (e) Schaus, S. E.; Ting, A. *Eur. J. Org. Chem.* **2007**, 5797–5815. (f) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159–186. (g) Bégué, J. P.; Bonnet-Delpon, D.; Crousse, B.; Legros, J. *Chem. Soc. Rev.* **2005**, *34*, 562–572. (h) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112. (i) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592–600.



Esquema 17. Precursores y reactividad de iones *N*-aciliminio.

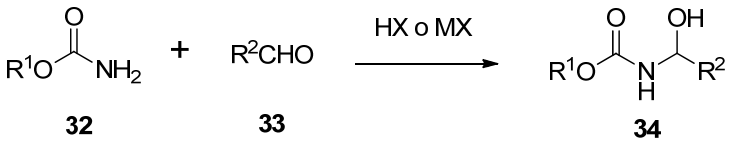
Hay que destacar que cuando R^2 = H (Esquema 18), el ión aciliminio **30** está en equilibrio con su acilimina **31**.



Esquema 18. Equilibrio ión aciliminio-acilimina.

1.1.3.2 Síntesis de iones aciliminio y aciliminas.

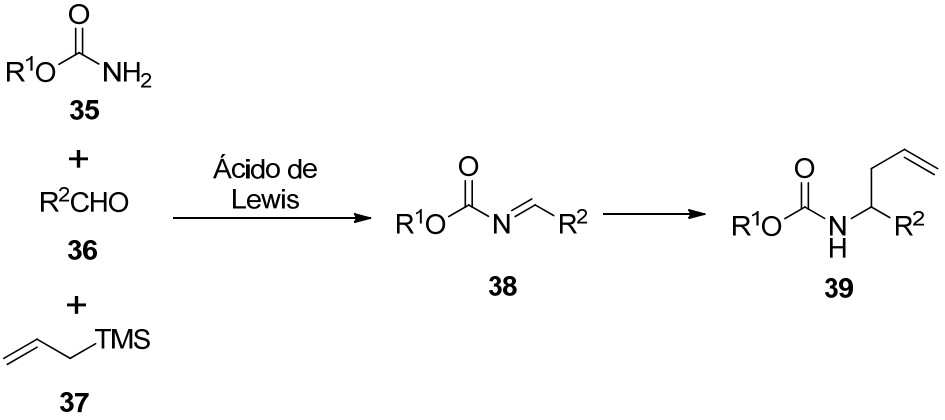
Uno de los métodos más usados para preparar precursores de iones aciliminio o de aciliminas es la adición un carbamato **32** (Esquema 19) a un aldehído (como el compuesto **33**) o un acetal.[37f,38]



Esquema 19. Síntesis de **34** a partir de aldehídos y carbamatos.

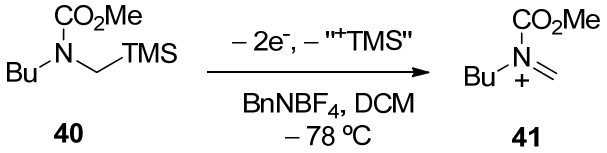
[38] (a) Liu, S.; Ben, R. N. *Org.Lett.* **2005**, *5*, 2385–2388. (b) Yoo, B.; Pagel, M. D. *Tetrahedron Lett.* **2006**, 47, 7327–7330. (c) Petrini, M.; Torregiani, E. *Tetrahedron Lett.* **2005**, *46*, 5999–6003.

Existen también reacciones de tres componentes que generan iones aciliminio o aciliminas,[39] como muestra el Esquema 20, partiendo del carbamato **35**, el aldehído **36** y el nucleófilo **37**. En presencia de un acido de Lewis, se genera una acilimina **38** a la que se le adiciona aliltrimetilsilano **37** para dar lugar al producto final **39**.



Esquema 20. Síntesis de **39** mediante una reacción de tres componentes.

Como se muestra en el Esquema 21, los iones aciliminio **41** también pueden ser generados en disolución por oxidación electroquímica de *N*-(trimetilsililmetil)carbamatos como el compuesto **40**. Estos intermedios han sido caracterizados espectroscópicamente y pueden reaccionar con nucleófilos para dar los compuestos de adición.[40]

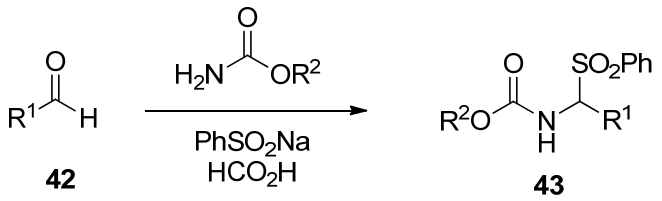


Esquema 21. Generación de iones aciliminio por oxidación electroquímica.

[39] (a) Van Maarseveen, J. H.; Meester, W. J. N.; Veerman, J. J. N.; Kruse, C. G.; Hermkens, P. H. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc. Perkin Trans. 1* **2001**, 994–1001. (b) Meester, W. J. N.; Van Maarseveen, J. H.; Kirchsteiger, K.; Hermkens, P. H. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Arkivoc* **2004**, *(ii)*, 122–151.

[40] (a) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun*. **2003**, 354–355. (b) Suga, S.;Tsutsui, Y. Nagaki, A.; Yoshida, J. *Bull. Chem. Soc. Jpn*. **2005**, *78*, 1206–1217. (c) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666–11675.

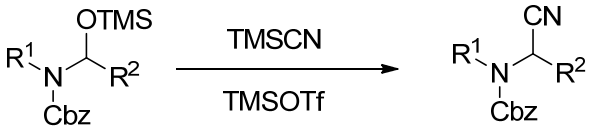
Las α-sulfonil-*N*-alquil amidas y los α-sulfonil-*N*-alquil carbamatos **43** son precursores útiles de iones aciliminio o aciliminas acíclicas, ya que suelen ser sólidos estables. El Esquema 22 muestra como estos compuestos pueden ser preparados por la adición de amidas o carbamatos a aldehídos en presencia de un ácido bencenosulfónico o su sal.[41]



Esquema 22. Síntesis de α-sulfonil-*N*-alquil carbamatos.

1.1.3.3 Reacciones de aciliminas e iones aciliminio con nucleófilos.

Los alilsilanos y los silil enol éteres son un tipo de nucleófilos muy utilizados para la adición a iones aciliminio o aciliminas. Por ejemplo, Suh y colaboradores hicieron reaccionar los α-trimetilsililoxi carbamatos **44** con trimetilsilil cianuro, en presencia de un ácido de Lewis (TMSOTf), para dar los α-amino nitrilos **45** (Esquema 23).[42]

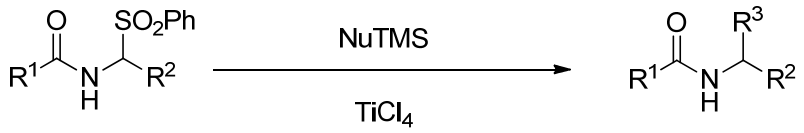


R^1 = Bn, Et, ^{i}Pr
R^2 = Ph, -$(CH_2)_2CH=CH_2$,
-$(CH_2)_2CHOTBDMS$,
-CH_2CHBr, Et

Esquema 23. Conversión de α-trimetilsililoxi carbamatos en α-amino nitrilos.

[41] (a) Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem*. **2006**, *4*, 278–290. (b) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972. (c) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, 115, 2622–2636.
[42] Suh, Y.–G.; Shin, D.–Y.; Jung, J.–K.; Kim, S.–H. *Chem. Commun*. **2002**, 1064–1065.

En el Esquema 24 se muestra como las α-sulfonil-*N*-alquil amidas **46** también reaccionan con nucleófilos de carbono en presencia de un ácido de Lewis ($TiCl_4$) para dar los aductos **47**.[38c]



46 **47** 70-89%

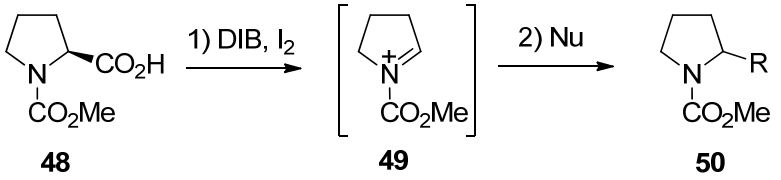
R^1 = OBn, Ph, $Cl(CH_2)_2$, FCH, CH_2=CH
R^2 = $(CH_3)_2CH=CH_2$, $PhCH_2CH_2$, n-C_7H_{15}, (E)-$C_5H_{11}CH=CH(CH_2)_4$, $BnO(CH_2)$

NuTMS	**R^3**
$CH_2=CH_2TMS$	$-CH_2CH=CH_2$
$CH_2=C(OEt)(OTMS)$	$-CH_2CO_2Et$

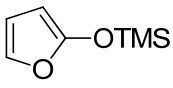
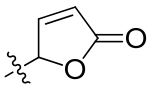
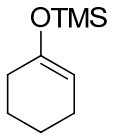
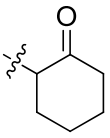
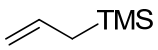
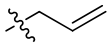
Esquema 24. Reacción de nucleófilos de carbono con α-sulfonil-*N*-alquil amidas.

Los iones aciliminio también pueden generarse por descarboxilación radicalaria oxidativa, tal como se comentaba antes. Así, la descarboxilación del derivado de prolina **48** (Esquema 25) produce el ion aciliminio **49**, que puede ser atrapado por distintos nucleófilos de carbono para dar los compuestos **50**.[43]

[43] Boto, A.; Hernández, R.; Súarez, E. *J. Org. Chem.* **2000**, *65*, 4930–4937.

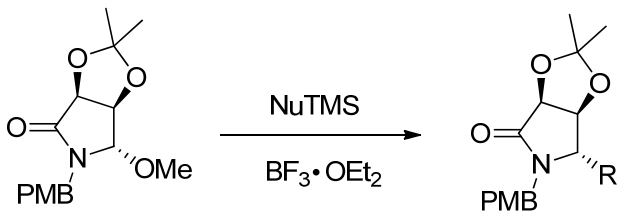


48 **49** **50**

Nu	R	Rdto.
MeOH	-OMe	80 %
		81 %
		68 %
		91 %

Esquema 25. Reacción de nucleófilos con el ión aciliminio obtenido a partir de prolina **48**

Un ejemplo de la utilidad de esta reacción en la síntesis de productos naturales o con actividad biológica se muestra en el Esquema 26, donde el iminoazucar **51** es tratado con un ácido de Lewis y nucleófilos de carbono, originando derivados 5-alil o 5-alquil sustituidos **52**. Es de destacar que estos productos se obtienen como un solo diasterómero.[44]



51 **52**

NuTMS	R	Rdto.
$CH_2CH=CH_2$	$-CH_2CH=CH_2$	96%
$CH_2=C(OTMS)(^tBu)$	$-CH_2CO^tBu$	70%

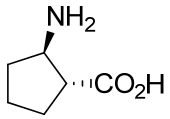
Esquema 26. Reacción del *N,O*-acetal **51** con nucleófilos de carbono.

[44] Muramatsu, T.; Yamashita, S.; Nakamura, Y.; Suzuki, M.; Mase, N.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2007**, *48*, 8956–8959.

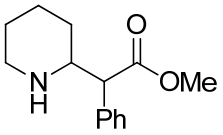
1.2 Aplicación de los procesos secuenciales de escisión radicalaria oxidativa–adición de nucleófilos a la modificación de amino ácidos.

1.2.1 Reacciones de descarboxilación radicalaria oxidativa –adición de sililcetenas. Preparación de β-amino ésteres.

En los últimos años, la formación de derivados de β-amino ácidos ha despertado mucho interés, tanto desde el punto de vista sintético[45,46] como desde el punto de vista farmacéutico.[47] Así, estos compuestos han mostrado interesantes propiedades biológicas (como el antibiótico cispentacina **53**,[48] las β-lactamas[49], ó el fármaco contra la hiperactividad ritalina **54**,[50] Figura 1).



cispentacina
53



ritalina
54

Figura 1. β-amino ácidos bioactivos.

[45] (a) *Enantioselective synthesis of β-amino acids*, Juaristi, E.; Soloshonok, V. A.; Eds.; Wiley-VCH, New York, **2005**. (b) Liljeblad, A.; Kanerva, L. T. *Tetrahedron* **2006**, *62*, 5831–5854. (c) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3196. (d) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639. (e) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891.

[46] (a) Tarrade-Matha, A.; Siqueira-Valle, M.; Tercinier, P.; Dauban, P.; Dodd, R. H. *Eur. J. Org. Chem.* **2009**, 673–686. (b) Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 2246–2249. (c) Paál, T. A.; Forró, E.; Fülöp, F.; Liljeblad, A.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2008**, 19, 2784–2788. (d) Reyes-Rangel, G.; Jiménez-González, E.; Olivares-Romero, J. L.; Juaristi, E. *Tetrahedron: Asymmetry* **2008**, 19, 2839–2849.

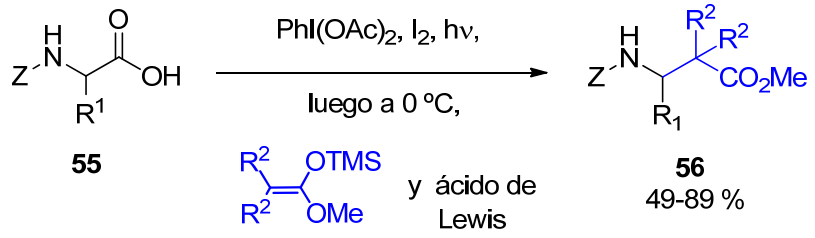
[47] (a) Dixon, M. J.; Nathubhai, A.; Andersen, O. A.; Van Aalten, D. M. F.; Eggleston, I. M. *Org. Biomol. Chem.* **2009**, *7*, 259–268. (b) David, R.; Günther, R.; Baumann, L.; Lühmann, T.; Seebach, D.; Hofmann, H.-J.; Beck-Sickinger, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 15311−15317. (c) Keresztes, A.; Szúcs, M.; Borics, A.; Köver, K. E.; Forró, E.; Fülöp, F.; Tömböly, C.; Péter, A.; Páhi, A.; Fábian, G.; Murányi, M.; Tóth, G. *J. Med. Chem.* **2008**, *51*, 4270–4279. (d) Raghavan, B.; Balasubramanian, R.; Steele, J. C.; Sackett, D. L.; Fecik, R. A. *J. Med. Chem.* **2008**, *51*, 1530–1533.

[48] (a) Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227–1229. (b) Langer, O.; Kahlig, H.; Zierler-Gould, K.; Bats, J. W.; Mulzer, J. *J. Org. Chem.* **2002**, *67*, 6878–6883. (c) Theil, F.; Ballschuh, S. *Tetrahedron: Asymmetry* **1996**, 7, 3565–3572.

[49] Pérez-Faginas, P.; O'Reilly, F.; O'Byrne, A.; García-Aparicio, C.; Martín-Martínez, M.; Pérez de Vega, M. J.; García-López, M. T.; González-Muñiz, R. *Org. Lett.* **2007**, 9, 1593–1596.

[50] Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Tetrahedron* **2000**, 56, 7411–7422.

En nuestro grupo se ha desarrollado una metodología en un paso para la conversión de α-amino ácidos **55** en derivados de β-amino ácidos **56**.[51] La etapa inicial es la generación de un radical carboxilo, que sufre un proceso de β-fragmentación–oxidación, generando un ion aciliminio que es atrapado por sililcetenas. (Esquema 27).



Z = acilo, carbamoilo
R^1 = cadena lateral de amino acido
R^2 = Me ó H

Esquema 27. Transformación directa de α-amino ácidos en β-amino ésteres.

Se probaron varias condiciones de reacción, observándose que la cantidad de yodo es crítica para obtener buenos rendimientos. La fragmentación no ocurre en ausencia de yodo, pero un exceso de este reactivo puede producir la yodación del nucleófilo y la formación de mezclas complejas de productos. Generalmente los mejores rendimientos se obtienen cuando se trata el amino ácido con 0.3 equivalentes de yodo y 1.5 equivalentes de DIB.

De esta manera se prepararon, con buenos rendimientos, una gran variedad de β-amino ésteres, tanto sin sustituyentes en α, como α,α-disustituidos. Algunos ejemplos se muestran en la Figura 2.

[51] (a) Saavedra, C. J.; Hernández, R.; Boto, A.; Álvarez, E. *Tetrahedron Lett.* **2006**, *47*, 8757–8760 (artículo en anexo). (b) Saavedra, C.; Hernández, R.; Boto, A.; Álvarez, E. *J. Org. Chem.* **2009**, *74,* 4655–4665 (artículo en anexo).

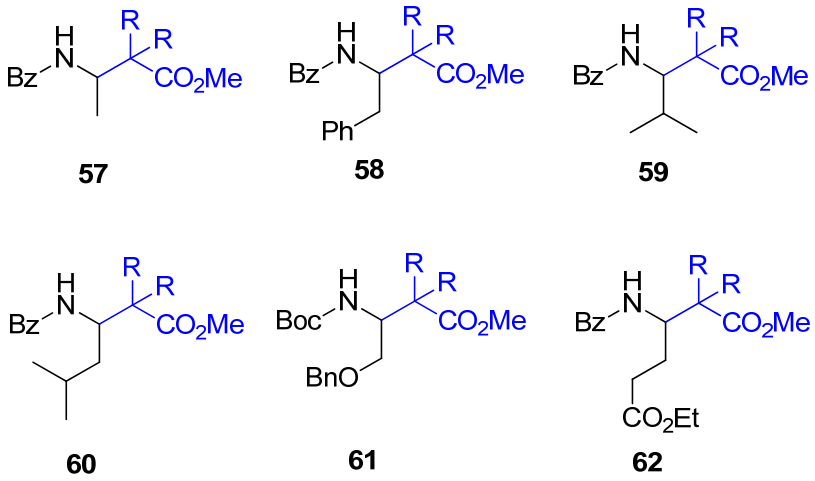


Figura 2. Ejemplos de β-amino ésteres preparados (R=H ó Me) a partir de derivados de α-amino ácidos, usando procesos secuenciales.

1.2.2 Reacciones de descarboxilación radicalaria oxidativa –fosforilación. Preparación de α-amino fosfonatos.

Los α-amino fosfonatos son análogos de amino ácidos, y pueden tener interesantes propiedades biológicas. Por ejemplo, el derivado de leucina **63** (Figura 3) es un potente inhibidor de la leucina peptidasa, el análogo de prolina **64** es un agente antihipertensivo y el α-amino fosfonato **65** tiene actividad herbicida.[52]

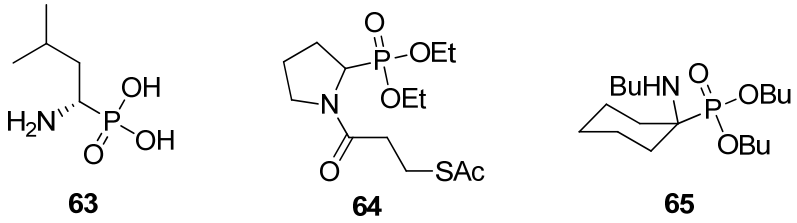
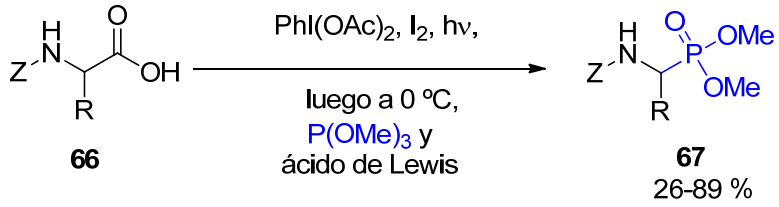


Figura 3. α-Amino fosfonatos bioactivos.

[52] (a) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6251. (b) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley: Chichester, **2000**. (c) Gröger, H.; Hammer, B. *Chem. Eur. J.* **2000**, *6*, 943–948. (d) Field, S. C. *Tetrahedron* **1999**, *55*, 12237–12273. (e) Hildebrand, R. L. *The Role of Phosphonates in Living Systems*; CRC: Boca Ratón, FL, **1982**. (f) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev*. **2005**, *105*, 899–931. (g) Drag, M.; Grembecka, J.; Pawelczak, M.; Kafarski, P. *Eur. J. Med. Chem*. **2005**, *40*, 764–771. (h) Petrillo, E. W. *U.S. Patent* 4,186,268, **1980**; *Chem. Abstr*. **1980**, 93, 8008. (i) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem*. **2002**, *67*, 8123–8129.

En nuestro grupo hemos desarrollado una metodología en un paso para la conversión de α-amino ácidos **66** en α-amino fosfonatos **67**. La etapa principal es la generación de un radical carboxilo, que sufre un proceso de β-fragmentación–oxidación, generando un ion aciliminio que es atrapado por nucleófilos de fósforo (Esquema 28).[53]



Esquema 28. Preparación de α-amino fosfonatos.

De esta manera se prepararon, con buenos rendimientos, una gran variedad de α-amino fosfonatos. Algunos ejemplos se muestran en la Figura 3.

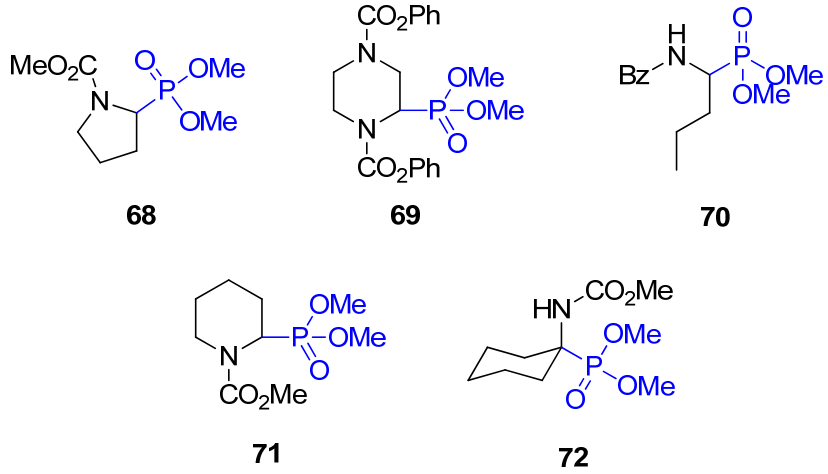
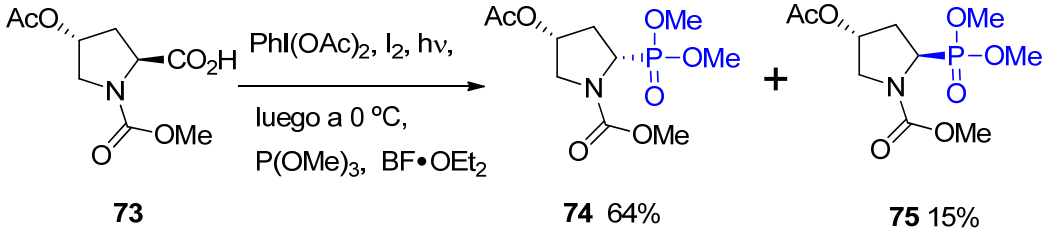


Figura 3. Ejemplos de α-amino fosfonatos preparados a partir de derivados de α-amino ácidos.

[53] Boto, A.; Gallardo, J. A.; Hernández, R.; Saavedra, C. J. *Tetrahedron Lett.* **2005**, *46,* 7807–7811 (artículo en anexo).

El proceso secuencial de descarboxilación–fosforilación también fue estudiado en sustratos con un centro estereogénico próximo al centro reactivo. Por ejemplo, con el derivado de hidroxiprolina **73** (Esquema 29), obteniéndose los fosfonatos **74** y **75** con buen rendimiento global.



73 **74** 64% **75** 15%

Esquema 29. Preparación de α-amino fosfonatos quirales.

1.2.3 Reacciones de escisión radicalaria de serina–oxidación–adición de nucleófilos de carbono. Preparación de amino ácidos no naturales.

Los amino ácidos no proteinogénicos son estructuras muy utilizadas en la síntesis de alcaloides, péptidos y otros productos bioactivos.[54] Por ejemplo se han usado para preparar el alcaloide antiviral castanospermina[55] y para la síntesis del alcaloide citotóxico dragmacidina [56] (Esquema 30).

Los amino ácidos no proteinogénicos también son componentes de glicopéptidos,[57] de antibióticos β-lactámicos[58] y de otros fármacos.[59] Por otro

[54] (a) Bridges, R. J.; Esselinger, C. S. *Pharmacol. Ther.* **2005**, *107*, 271–285. (b) Van Bambeke, F. *Curr. Opin. Pharmacol.* **2004**, *4*, 471–478. (c) Johansen, T. N.; Greenwood, J. R.; Frydenvang, K.; Madsen, U.; Krogsgaard-Larsen, P. *Chirality* **2003**, *15*, 167–179. (d) Beck, G. *Synlett* **2002**, 837-850. (e) Nájera, C. *Synlett* **2002**, 1388–1403. (f) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872.

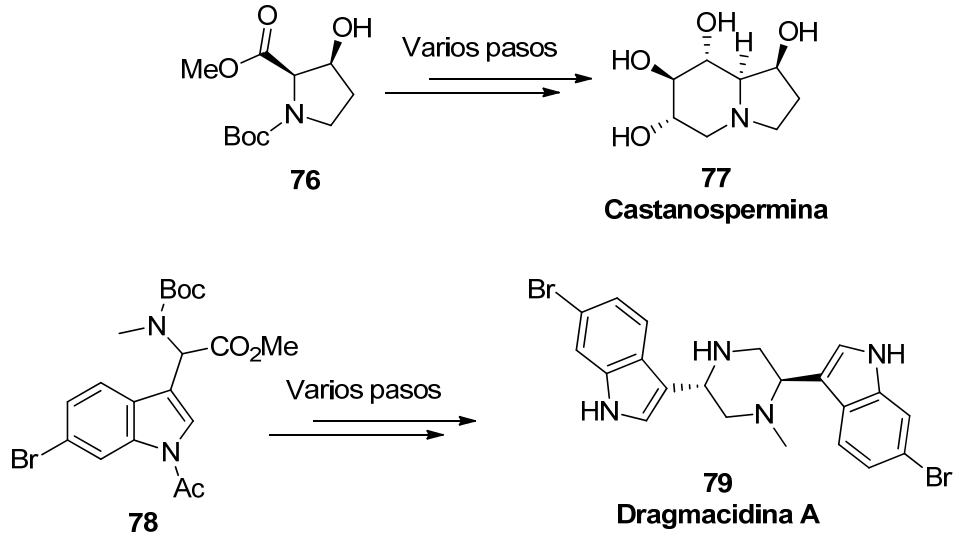
[55] (a) Whitby, K.; Pierson, T. C.; Geiss, B.; Lane, K.; Engle, M.; Zhou, Y.; Doms, R. W.; Diamond, M. S. *J. Virol.* **2005**, *79*, 8698–8706. (b) Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.***1990**, *31*, 4827–4830.

[56] Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027–3029.

[57] (a) Pace, J. L.; Yang, G. *Biochem. Pharmacol.* **2006**, *71*, 968–980. (b) Walker, S.; Chen, L.; Hu, Y.; Rew, Y.; Shin, D.; Boger, D. L. *Chem. Rev.* **2005**, *105*, 449–475. (c) Welzel, P. *Chem. Rev.* **2005**, *105*, 4610–4660. (d) Kahne, D.; Leimkuhler, C.; Lu, W.; Walsh, C. *Chem. Rev.* **2005**, *105*, 425–448.

[58] (a) Morín, R. B.; Gorman, M. *Chemistry and Biology of β-Lactam Antibiotics*, vols. 1–3; **1982**. (b) Townsend, C. A.; Brown, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 913–918.

lado estos amino ácidos han sido incorporados a péptidos para modular su actividad y mejorar su estabilidad ante la hidrólisis.

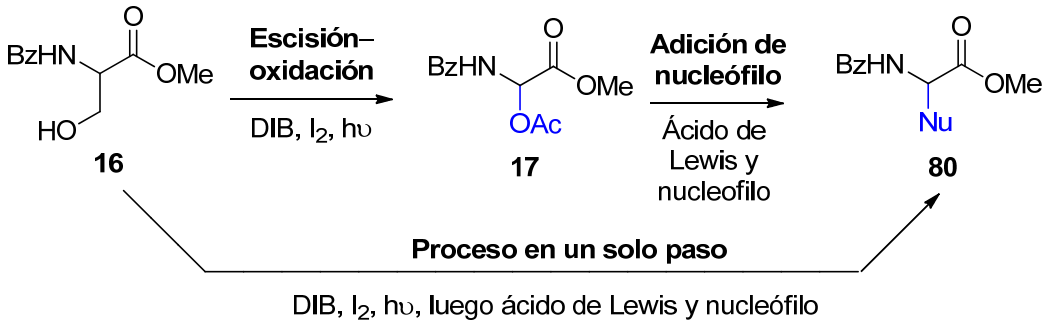


76 **77** **Castanospermina** **78** **79** **Dragmacidina A**

Esquema 30. Preparación de productos bioactivos a partir de amino ácidos no naturales.

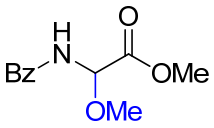
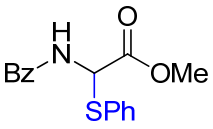
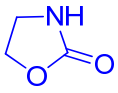
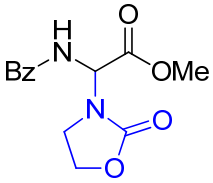
En nuestro grupo se ha desarrollado una metodología en uno y dos pasos para la preparación de α-amino ésteres no naturales partiendo del derivado de serina **16** (Esquema 31).[34] En el proceso en dos pasos el compuesto **16** sufre un proceso de β-fragmentación–oxidación–adición de iones acetatos del reactivo, generando la α-acetoxiglicina **17**. Al ser tratada ésta con un ácido de Lewis, se genera un ión aciliminio (catión glicilo) que es atrapado por distintos nucleófilos (de nitrógeno, oxígeno, azufre y carbono). Posteriormente, se consiguió la conversión directa del sustrato **16** en los derivados **80**.

[59] (a) Moloney, M. G. *Nat. Prod. Rep*. **1999**, *16*, 485–498. (b) Chen, K. X.; Njoroge, F. G.; Arasappan, A.; Venkatraman, S.; Vibulbhan, B.; Yang, W.; Parekh, T. N.; Pichardo, J.; Prongay, A.; Cheng, K. C.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 995–1005. (c) Sollis, S. L. *J. Org. Chem.* **2005**, *70*, 4735–4740. (d) Stilz, H. U.; Guba, W.; Jablonka, B.; Just, M.; Klinger, O.; König, W.; Wehner, V.; Zoller, G. *J. Med. Chem.* **2001**, *44*, 1158–1176.



Esquema 31. Preparación de amino ácidos no naturales a partir de serina en uno o dos pasos.

Este proceso de escisión radicalaria oxidativa–adición de nucleófilos permitió preparar una gran variedad de α-amino no naturales. Algunos ejemplos se muestran en la Tabla 1 y en la Tabla 2.

Nucleófilo	Productos	Rdto. en dos pasos	Rdto. en un paso
MeOH		—	93 %[a]
81	**82**		
PhSH		86 %	37 %
83	**84**		
		70 %	43 %
85	**86**		

[a] Sin usar ácido de Lewis

Tabla 1. Ejemplos de α-amino ácidos no naturales obtenidos por adición de nucleófilos de oxígeno, azufre y nitrógeno al catión glicilo.

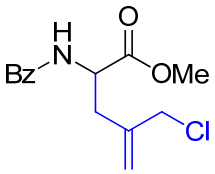
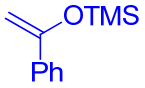
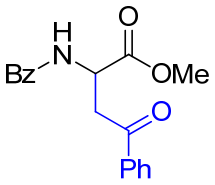
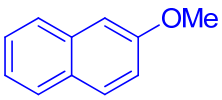
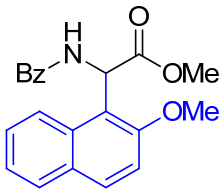
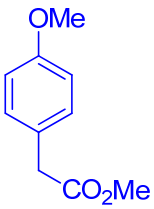
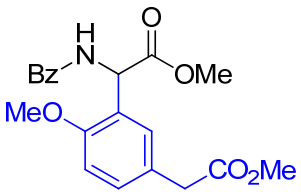
Nucleófilo	Productos	Rdto. en dos pasos	Rdto. en un paso
 **87**	 **88**	58 %	60 %
 **89**	 **90**	67 %	30 %
 **91**	 **92**	90%	95%
 **93**	 **94**	76 %	82%

Tabla 2. Ejemplos de α-amino ácidos no naturales obtenidos por adición de nucleófilos de carbono al catión glicilo.

1.3 Aplicación de los procesos secuenciales a la modificación de péptidos.

1.3.1 Aspectos generales de la modificación de péptidos.

La modificación de péptidos es un área de gran interés tanto en química médica como en química sintética. En efecto, los péptidos naturales juegan un papel fundamental en muchos procesos fisiológicos; sin embargo, rara vez pueden usarse como fármacos debido a que tras su administración son degradados con rapidez por las proteasas endógenas.[60] El potencial terapéutico de estos péptidos aumentaría, en gran medida, mediante la extensión de la vida media *in vivo*.

Para aumentar su estabilidad *in vivo*, se han desarrollado péptidos modificados,[61] que además podrían dar lugar a compuestos de utilidad farmacológica, por ejemplo mejorando la afinidad de la unión con la diana biólogica. La Figura 4 muestra una visión esquemática de la forma en que los péptidos pueden modificarse.

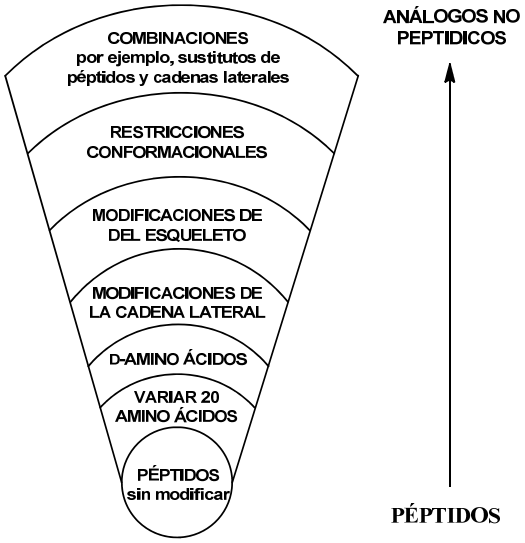


Figura 4. Formas de modificar péptidos.

[60] (a) *Handbook of Biologically Active Peptides*, Kastin, A. J. Ed.; Academic Press, San Diego, **2006**. (b) Sewald, N.; Jakubke, H. D. *Peptides: Chemistry and Biology*, Wiley-VCH, Weinheim, **2002**.

[61] *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins-A survey of Recent Developments*, Weinstein, B., Ed.; Marcel Dekker, Inc., New York, **1983**.

En esta línea se han desarrollado péptidos modificados con α-amino ácidos no proteinogénicos, por ejemplo, amino ácidos con cadenas no naturales, o bien D-amino ácidos, amino ácidos α,α-disustituidos, etc.

También se han preparado péptidos con análogos de amino ácidos como los β-amino ácidos,[62] los α-amino fosfonatos,[63] los α-amino nitrilos,[64] etc. Estos residuos no son reconocidos por las enzimas proteolíticas, y con ello se consiguen compuestos con una mejor biodisponibilidad y estabilidad metabólica y/o con mayor potencia. Esta estrategia ha dado lugar a numerosos fármacos, y la mayoría de las compañías farmacéuticas están investigando activamente en este campo.[65]

Así, el cambio de un α-amino ácido en péptidos bioactivos por un β-amino ácido ha permitido obtener derivados con una mayor estabilidad frente a proteasas, y con una actividad similar o superior. Por ejemplo, el α-dipéptido **95** (Figura 5) es un inhibidor de la hidrólisis de la bradikinina por parte de la enzima aminopeptidasa (APP), y por tanto es un posible agente contra enfermedades cardiovasculares. Sin embargo, el enlace amida en el péptido **95** es fácilmente hidrolizado por las peptidasas del riñón.

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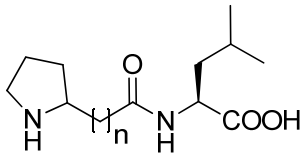
[62] (a) Aguilar, M. I.; Purcell, A. W.; Devi, R.; Lew, R.; Rossjohn, J.; Smith, A. I.; Perlmutter, P. *Org. Biomol. Chem.* **2007**, *5*, 2884−2890. (b) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399−1408. (c) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366−1375. (d) Sharma, G. V. M. ; Manohar, V. ; Dutta, S. K. ; Subash, V. ; Kunwar, A. C. *J. Org. Chem*. **2008**, *73*, 3689−3698. (e) Chakraborty, T. K.; Rao, K. S.; Kiran, M. U.; Jagadeesh, B. *Tetrahedron Lett*. **2008**, *49*, 2228−2231.

[63] (a) Winiarski, L.; Oleksyszyn, J.; Sieńczyk, M. *J. Med. Chem.* **2012**, *55*, 6541−6553. (b) Burchacka, E.; Walczak, M. M.; Sienczyk, M.; Dubin, G.; Zdzalik, M.; Potempa, J.; Oleksyszyn, J. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 5574−5578. (c) Sienczyk, M.; Podgórski, D.; Błazejewska, A.; Kulbacka, J.; Saczko, J.; Oleksyszyn, J. *Bioorg. Med. Chem*. **2011**, *19*, 1277−1284. (d) Sabidó, E.; Tarragó, T., Giralt, E. *Bioorg. Med. Chem*. **2010**, *18*, 8350−8355.

[64] (a) Tsai, T.-Y.; Hsu, T.; Chen, C.-T.; Cheng, J.-H.; Chiou, M.-C.; Huang, C.-H.; Tseng, Y.-J.; Yeh, T.-K.; Huang, C.-Y.; Yeh, K.-C.; Huang, Y.-W.; Wu, S.-H.; Wang, M-H.; Chen, X., Chao, Y.-S.; Jiaang, W.-T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1908−1912. (b) Lu, I. -L.; Lee, S.- J.; Tsu, H.; Wu, S.-Y.; Kao, K. H.; Chien, C.-H.; Chang, Y.-Y.; Chen, Y.-S.; Cheng, J.-H.; Chang, C. N.; Chen, T.-W.; Chang, S.-P.; Chen, X.; Jiaang, W.-T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3271−3275. (c) Pei, Z.; Li, X.; Longenecker, K.; von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2006**, *49,* 3520−3535.

[65] (a) *Acc. Chem. Res.* **2008**, *41*, N°10, Número Especial sobre *Peptidomimetics*. (b) Sieburth, S. M.; Chen, C. A. *Eur. J. Org. Chem.* **2006**, 311−322. (c) *Chem. Rev.* **2006**, *106*, N°7, Número Especial sobre *Process Chemistry*.



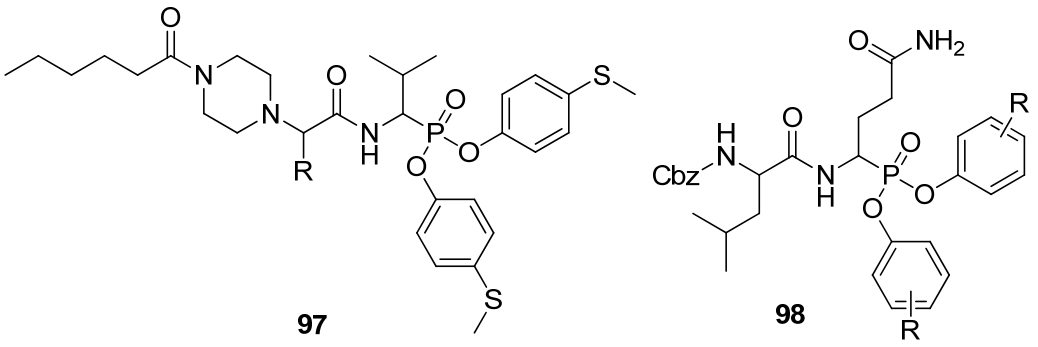
Inhibidor de la hidrólisis de la bradikinina

95 n = 0 K_i = 1.28 mM
96 n = 1 K_i = 7.00 nM

Figura 5. Sustitución de un α-amino ácido por un β-amino ácido en un péptido bioactivo.

Cuando el residuo de prolina en el péptido **95** es sustituido por una β-homoprolina, el péptido modificado **96** muestra un aumento de 500 veces en la actividad inhibidora, con respecto al péptido no modificado **95** (se pasa de una K_i = 1.28 mM a 7.0 nM), y además, es completamente estable a las peptidasas de las membranas de riñón después de 24 h.[52a]

Por otra parte, los ésteres aromáticos de α-amino fosfonatos (como los compuestos **97** y **98**, Figura 6) son unos inhibidores potentes e irreversibles de las proteasas de serina. Estos fosfonatos reaccionan exclusivamente con el grupo hidroxilo de las enzimas.[66] Su gran estabilidad y selectividad (no afectan a otra clase de proteasas como las de cisteína o treonina), ha incrementado las investigaciones sobre esta clase de inhibidores.

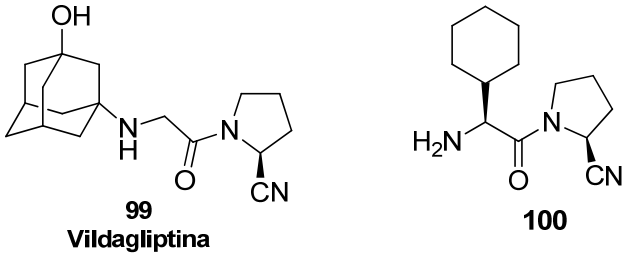


97 **98**

Figura 6. Péptidos bioactivos con unidades de α-amino fosfonato.

[66] (a) Oleksyszyn, J.; Powers, J. C. *BioChemistry* **1991**, *30*, 485–493. (b) Sienczyk, M.; Oleksyszyn, J. *Curr. Med. Chem.* **2009**, *16*, 1673–1687.

Los α-amino nitrilos también han sido introducidos en derivados peptídicos, obteniéndose productos con interesantes propiedades biológicas. Así, la vildagliptina **99** y el compuesto **100** (Figura 7) son inhibidores de la dipeptidil peptidasa IV (DPP-IV o CD26), una enzima natural que degrada a las hormonas incretínicas como la GLP-1. Con ello se pueden incrementar los niveles de GLP-1 en circulación, favoreciendo el control glucémico en pacientes diabéticos tipo 2.



99
Vildagliptina

100

Figura 7. Péptidos bioactivos con unidades de α-amino nitrilos.

Otro planteamiento para la modificación de péptidos es variar los enlaces peptídicos que son susceptibles de hidrólisis. Las modificaciones más usuales de los enlaces peptídicos puede verse en la Tabla 3.[51,67]

Entrada	Tipo de modificación	Isostérico	Resistencia a enzimas	Unión a H	Monómero quiral
I	Péptidos				
II	N-Alquilación	+	+++	+	si
III	α-Ester	+++	+	+++	si
IV	Tioamida	+++	++	+	si
V	N-hidroxilación	+	+++	+	si
VI	β-Ester	+	++	++	si
VII	Sulfonamida	+	++	++	si
VIII	N-Alquilsulfonamida	+	++	++	no
IX	Urea	+	++	++	no
X	Uretano	+	++	++	no
XI	Fosfonato/fosfonamidato	+	++/+++	+++	si

El símbolo "+" hace referencia al grado en que la sustitución está caracterizada por la propiedad dada: + = mínimo, ++ = parcial, +++ = sustancial

Tabla 3. Modificaciones en el enlace peptídico.

[67] (a) Spatola, A. F.; *Peptide Backbone Modifications: A Structure-Activity Analysis of Peptides Containg Amide Bond Surrogates, Conformational Constraints and Related Backbone Replacements*. En *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Weinstein, B. Ed.; Marcel Dekker: New York, **1983**, Vol. III, pp. 287–300. (b) *Peptide-Based Drug Design,* en *Methods in Molecular Biology,* Vol. 494; Otvos, L. Ed. Humana Press, **2008** Vol.494.

Las distintas estructuras de los péptidos modificados mostrados en la Tabla 3, pueden verse en la Figura 8.

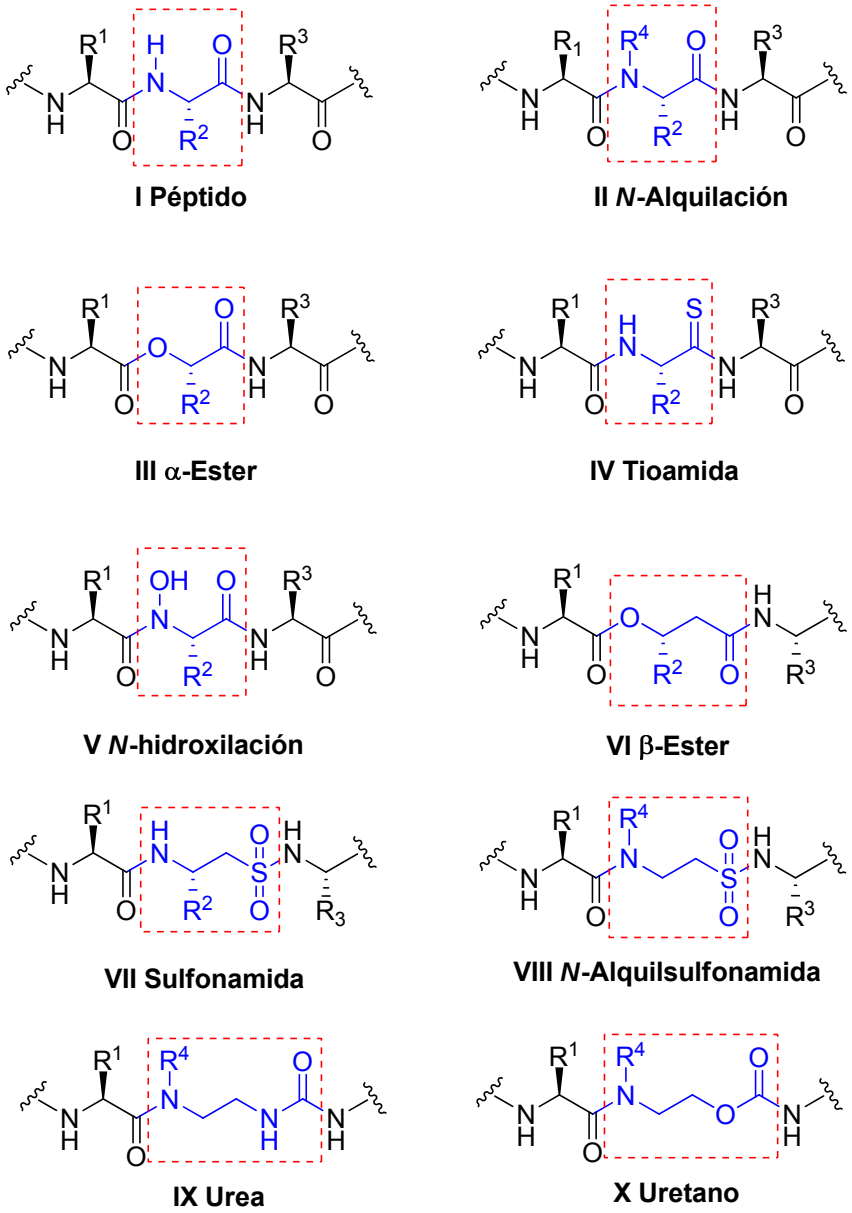
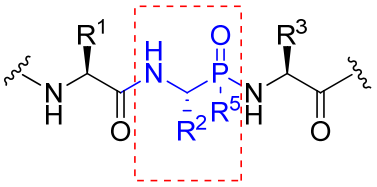


Figura 8. Estructura de las modificaciones de péptidos.



XI Fosfonato/fosfonamidato

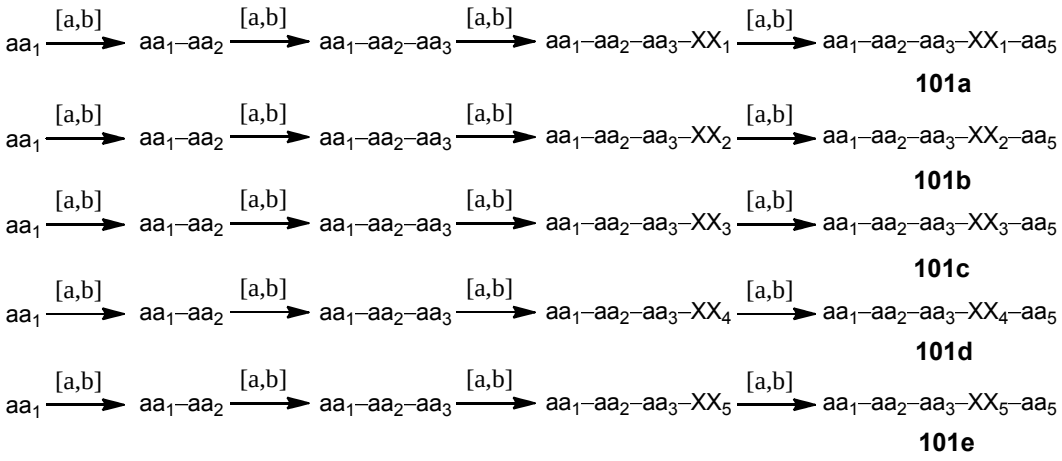
R^1, R^2, R^3 = cadena lateral del amino ácido
R^4 = alquilo
R^5 = O-alquilo, OH, amino ácido o péptido

Figura 8. Estructura de las modificaciones de péptido (continuación).

En esta memoria nos centraremos en las modificaciones de péptidos en los que se introducen análogos de α-amino ácidos, como son los β-amino ésteres, los β-amino aldehídos o los γ-amino ácidos. Para ello usaremos una estrategia de gran potencial: la modificación selectiva de péptidos, que se comentara a continuación

1.3.2 Modificación selectiva de péptidos.

En el proceso tradicional para obtener análogos de péptidos, cada compuesto se sintetiza *de novo,* introduciendo una modificación respecto al péptido de referencia (Esquema 32). Por ejemplo, supongamos que se quieren obtener cinco análogos **101a**–**101e** de un péptido bioactivo aa_1-aa_2-aa_3-aa_4-aa_5 (**101**), modificados en la posición 4, que se considera clave para la actividad. Para preparar los cinco péptidos modificados aa_1-aa_2-aa_3-XX_n-aa_5 por el proceso convencional, se necesitarían al menos cuarenta reacciones, ya que para unir cada unidad aa_n, se necesita al menos un paso de desprotección del residuo terminal del péptido [a] y un paso de acoplamiento [b].

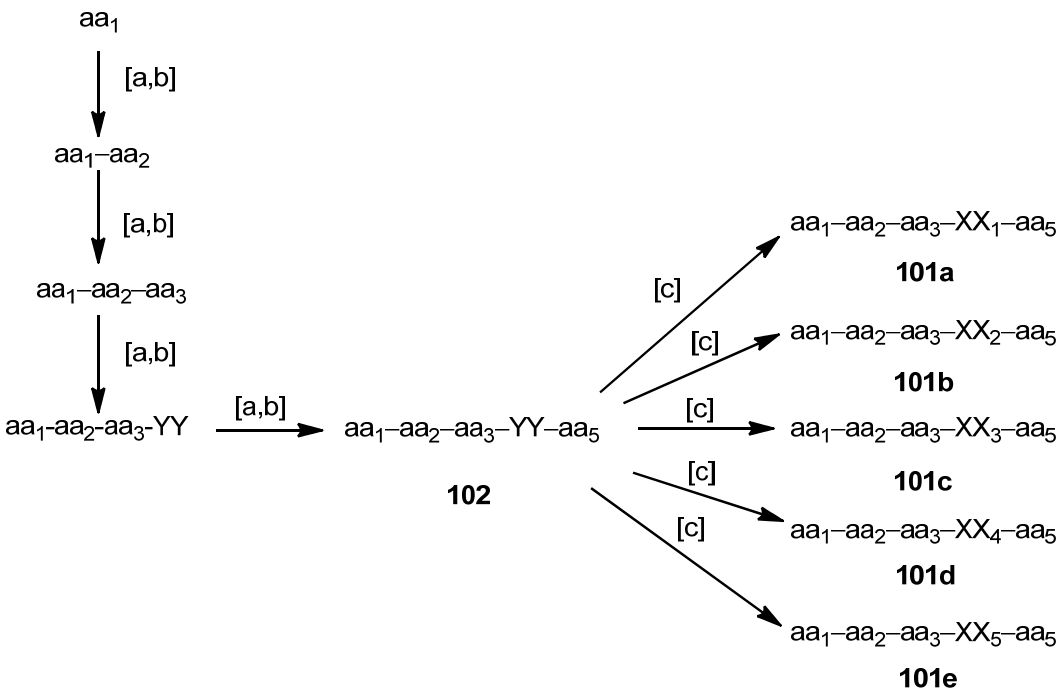


Esquema 32. Síntesis de *novo* de péptidos modificados.

Este procedimiento implica un gasto considerable de tiempo y materiales. Una estrategia alternativa (Esquema 33) consiste en partir de un único péptido (o de unos pocos) que se pudiera manipular selectivamente en determinados amino ácidos, sin afectar al resto de los residuos. Por ejemplo, para preparar los cinco péptidos **101a**–**101e**, se sintetizaría un único péptido de partida **102**, y luego se modificaría selectivamente la posición 4 (etapa [c]). En condiciones ideales, la etapa [c] supondría un solo paso de reacción, y así, el proceso para obtener los cinco productos implicaría solo trece pasos. Lógicamente, cuanto mayor sea el péptido a modificar, mayor es la diferencia entre el número de pasos del proceso convencional y el del proceso de modificación selectiva.

Por otra parte, cuando los péptidos son difíciles de obtener, por ejemplo cuando hay macrociclaciones o si tienen cadenas largas, es muy útil partir de un solo sustrato **102** y aplicar una modificación selectiva para obtener nuevos derivados.

El proceso de modificación selectiva, que permite preparar fácilmente colecciones de compuestos a partir de uno o muy pocos sustratos, ha despertado mucho interés en las compañías químicas y farmacéuticas.



Esquema 33. Síntesis de cinco péptidos por modificación selectiva del sustrato **102**.

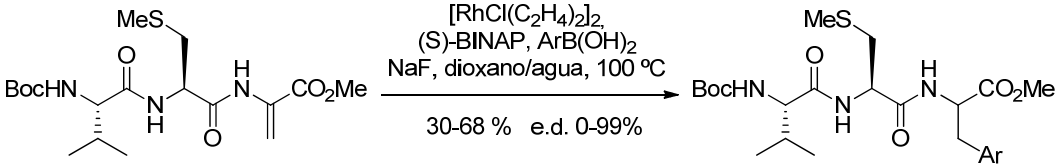
Pese al interés despertado, la modificación selectiva de péptidos presenta aún muchos problemas, dada la reactividad similar de los amino ácidos.[68] De hecho, aunque hay muchos métodos descritos para la modificación de residuos sencillos de amino ácidos, hay pocos que describan la modificación selectiva de residuos que formen parte de un péptido.

En la bibliografía hay descritas algunas modificaciones selectivas de péptidos consistentes en introducir nuevos grupos protectores o nuevas funciones en cadenas preexistentes de un amino ácido. Estas cadenas preexistentes no son eliminadas ni modificadas sustancialmente.[69]

El problema aumenta cuando se quiere modificar la estructura de la cadena preexistente de un amino ácido de forma significativa, pero sin eliminarla

[68] (a) Qi, D.; Tann, C. M.; Distefano, M. D. *Chem. Rev.* **2001**, *101*, 3081–3112. (b) Antos, J. M.; Francis, M. B. *Curr. Opin. Chem. Biol.* **2006**, *10*, 253–262.
[69] (a) Baltzer, L.; Ahlberg, P. *Improved method for site-selective glycosidation*, Patente WO9855501. (b) Baltzer, L.; Ahlberg, P. *Site-selective acylation*, Patente US 7514222.

totalmente. Por ejemplo, en el Esquema 34 se muestra la arilación de deshidroamino ácidos en péptidos mixtos.[70]



103 **104**

Esquema 34. Modificación de unidades de deshidroamino ácidos en péptidos.

Otros ejemplos interesantes son la reducción de residuos de cisteína de péptidos[71] y la adición de radicales a alilglicinas.[72]

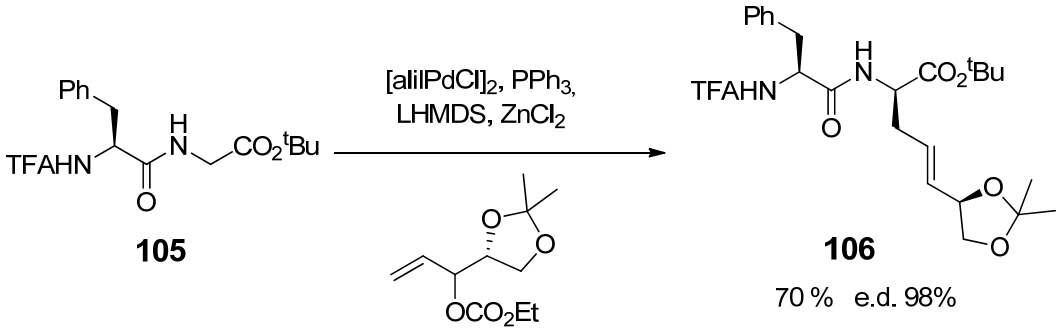
Este tipo de modificaciones tienen el inconveniente de que, cuando hay varios residuos "modificables" del mismo tipo en un péptido, por lo general es muy difícil o imposible distinguir entre ellos al hacer una transformación. Por ejemplo, con la estrategia mostrada en el Esquema 34, al realizar una arilación se modificarían todos los residuos de deshidroamino ácidos del péptido.

Las modificaciones selectivas más complicadas son aquellas en que la antigua cadena de un determinado residuo se elimina totalmente y se reemplaza por una cadena nueva. La mayor parte del trabajo descrito en esta área se refiere a la modificación de residuos de glicina. Así, la cadena lateral de la glicina es reemplazada por otras cadenas de tipo alquilo, alilo, etc. Por ejemplo, Seebach y Skrydstrup han generado enolatos de glicina a bajas temperaturas, que luego se atrapaban con distintos electrófilos.[73]

Recientemente Kazmaier ha logrado una modificación selectiva muy eficaz de derivados de glicina, consistente en la generación de sus enolatos de

[70] Chapman, C. J.; Hargrave, J. D.; Bish, G.; Frost, C. G. *Tetrahedron* **2008**, *64*, 9528–9539.
[71] Wan, Q.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 9248–9252.
[72] Franz, N.; Menin, L.; Klok, H. A. *Org. Biomol. Chem.* **2009**, *7*, 5207–5218.
[73] (a) Seebach, D.; Bech, A. K.; Studer, A. *Modern Synthetic Methods,* vol. 7, Eds. Ernst, B.; Leumann, C.; VCH, Weinheim, **1995**. (b) Ricci, M.; Madariaga, L.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 242–246. (c) Dialer, H.; Steglich, W.; Beck, W. *Tetrahedron* **2001**, *57*, 4855–4861.

zinc, seguida de una alilación o alquilación catalizada por complejos de paladio (Esquema 35).[74]



Esquema 35. Modificación de unidades de glicina en péptidos.

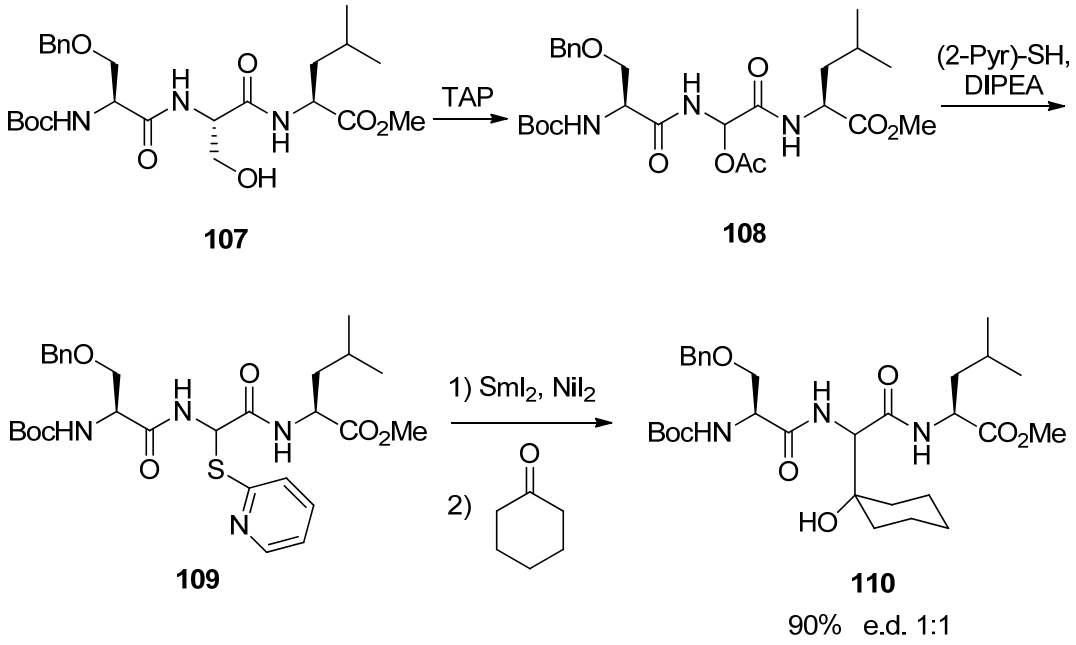
Pese a su eficacia, este método tiene una desventaja importante: si el péptido posee varios residuos de glicina pueden producirse problemas para la funcionalización selectiva de uno solo de ellos.

Una solución a este problema es usar como unidades modificables a amino ácidos cuyas cadenas laterales puedan protegerse con grupos protectores ortogonales. Así se puede hacer una modificación selectiva de un residuo no protegido de ese amino ácido, sin alterar los otros residuos que sí estén protegidos.

Existen muy pocos precedentes de esta estrategia. Un ejemplo, desarrollado por Skrydstrup,[75] consiste en la modificación selectiva de unidades de serina incorporadas a péptidos **107** (Esquema 36).

En una primera etapa se usa una escisión radicalaria oxidativa,[76] transformando la serina en una α-acetoxiglicina **108**. Ésta reacciona con 2-tiopiridina, dando lugar al compuesto **109**. A continuación, en presencia de SmI_2, se genera **un anión que reacciona con electrófilos**, por ejemplo compuestos carbonílicos, obteniéndose el péptido modificado **110**.

[74] (a) Deska, J.; Kazmaier, U. *Chem. Eur. J.* **2007**, *13*, 6204–6211. (b) Datta, S.; Kazmaier, U. *Org. Biomol. Chem.* **2011**, *9*, 872–880.
[75] (a) Blakskjaer, P.; Gavrila, A.; Andersen, L.; Skrydstrup, T. *Tetrahedron Lett.* **2004**, *45*, 9091–9094. (b) Ebran, J. P.; Jensen, C. M.; Johannesen, S. A.; Karaffa, J.; Lindsay, K. B.; Taaning, R.; Skrydstrup, T. *Org. Biomol. Chem.* **2006**,*4*, 3553–3564.
[76] Schuemann, S.; Zeitler, K.; Jäger, M.; Polborn, K.; Steglich, W. *Tetrahedron* **2000**, *56*, 4187–4195.



107 **108** **109** **110**

90% e.d. 1:1

Esquema 36. Modificación selectiva de unidades de serina en péptidos.

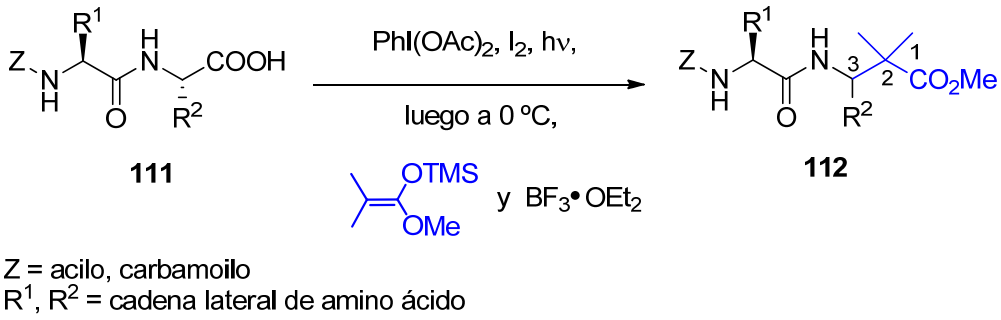
En esta memoria se presentará una estrategia más corta, donde **la escisión genera un catión (ión aciliminio) que reacciona con nucleófilos.**

1.3.3 Precedentes de la memoria en modificación selectiva de péptidos usando procesos secuenciales de escisión radicalaria oxidativa–adición de nucleófilos.

Nuestro grupo posee una línea de investigación dedicada a la preparación de análogos de péptidos bioactivos o catalíticos, reemplazando amino ácidos naturales por otros residuos α no naturales, o bien por β-amino ácidos, etc. El desarrollo de α,β-, α,γ-, o α,β,γ- híbridos es de particular interés. En efecto, muchos β-péptidos o α,β-, α,γ-, o β,γ-péptidos tienen la capacidad de poder formar giros, hélices, β-hojas, o fibrillas, haciendo que estos compuestos tengan interesantes aplicaciones en química médica y en la ciencia de los

materiales.[77] Por ejemplo, los β-amino ácidos son usados para generar giros en péptidos, para así alcanzar conformaciones bioactivas.[78]

En el Esquema 37 se muestra la metodología desarrollada para generar péptidos híbridos α,β, basada en la modificación selectiva del extremo *C*-terminal de pequeños péptidos por descarboxilación radicalaria oxidativa, seguida de la adición de nucleófilos. De esta forma, partiendo de α-dipéptidos **106** se obtienen α,β-dipéptidos **107** en un solo paso, en general con buenos rendimientos globales.[51] Además, a partir de un solo α-péptido, se puede obtener una colección de α,β-péptidos donde el β-amino ácido terminal podría estar o no sustituido en posición α. Los residuos mono- o disustituidos podrían presentar gran variedad de sustituyentes (alquilo, alilo, arilo, halógeno, éter, amina, etc.). Este procedimiento podría resultar muy útil en química médica para obtener diversidad, tomando como compuesto de referencia a un α-péptido bioactivo.



111 **112**

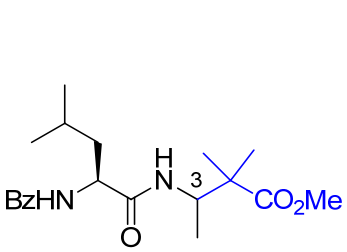
Z = acilo, carbamoilo
R^1, R^2 = cadena lateral de amino ácido

Esquema 37. Preparación de α,β-dipéptidos a partir de α-péptidos usando procesos secuenciales de descarboxilación radicalaria oxidativa–adición de nucleófilos.

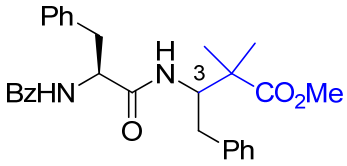
[77] (a) Wright, K.; Sarciaux, M.; de Castries, A.; Wakselman, M.; Mazaleyrat, J.-P.; Toffoletti, A.; Corvaja, C.; Crisma, M.; Peggion, C.; Formaggio, F.; Toniolo, C. *Eur. J. Org. Chem.* **2007**, 3133–3144. (b) Jiang, Z. X.; Yu, Y. B. *J. Org. Chem.* **2007**, *72*, 1464–1467. (c) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323–334. (d) Arvidsson, P. I.; Ryder, N. S.; Weiss, H. M.; Hook, D. F.; Escalante, J.; Seebach, D. *Chem. Biodivers.* **2005**, *2*, 401–420. (e) Cheng, R. P.; Gellman, S. H.; De Grado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.

[78] (a) Rai, R.; Vasudev, P. G.; Anandz, K.; Raghothama, S.; Shamala, N.; Karle, I. L.; Balaram, P. *Chem. Eur. J.* **2007**, *13*, 5917–5926. (b) Abele, S.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1559–1571. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1–15. (d) Para la importancia biológica de los giros ver: Tyndall, J. D. A.; Pfeiffer, B.; Abbenante, G.; Fairlie, D. P. *Chem. Rev.* **2005**, *105*, 793–826. (e) Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Bioorg. Med. Chem.* **2005**, *13*, 11–16.

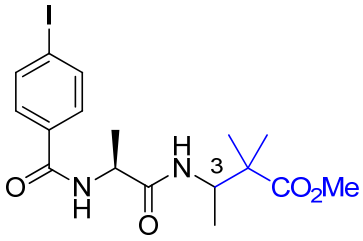
Tras estudiar diferentes condiciones de reacción, se encontró que las mejores dependen de cada péptido, debido a diferencias de solubilidad, impedimento estérico, etc. La mayoría de los productos obtenidos de la reacción fueron fácilmente separados por técnicas cromatográficas. Algunos de los α,β-dipéptidos obtenidos por esta metodología se muestran en la Figura 9 (compuestos **113**–**128**). Mediante Rayos-X de los dipéptidos cristalinos o de productos de acoplamiento con otros amino ácidos (α,β,α-derivados) se determinó que en todos los casos, el isómero mayoritario posee una configuración "natural" (3*S*).



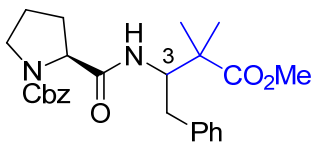
113 (3*S*), **114**(3*R*)
51% 26%



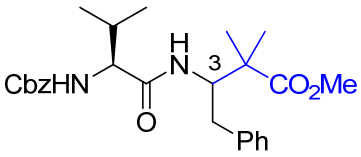
115 (3*S*), **116** (3*R*)
49% 14%



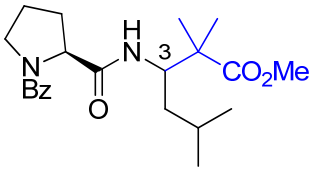
117 (3*S*)**:118** (3*R*)
5:3 74%



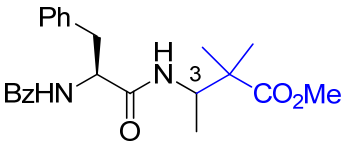
119(3*S*)**:120** (3*R*)
7:5 72%



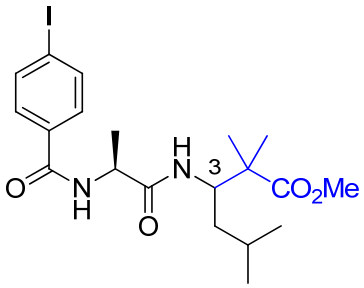
121(3*S*)**:122** (3*R*)
5:4 77%



123 (3*S*), **124** (3*R*)
36% 22%



125 (3*S*), **126**(3*R*)
45% 27%



127 (3*S*)**, 128** (3*R*)
31% 15%

Figura 9. Ejemplos de los α,β-dipéptidos preparados.

Es de destacar que además del procedimiento estándar, donde en la etapa de adición del nucleófilo se usaban cantidades estequiométricas de ácido de Lewis ($BF_3{\cdot}OEt_2$ o TMSOTf) [34,51a,53] para asegurar buenos rendimientos, se desarrolló un proceso de escisión oxidativa–adición de nucleófilo que sólo requería una cantidad catalítica de ácido de Lewis, usando triflato de cobre (0.1 equiv). Se obtuvieron unos rendimientos satisfactorios (41-70%), que en muchos casos son similares o ligeramente inferiores a los obtenidos con cantidades estequiométricas de ácido de Lewis.

Esta versión catalítica podría también permitir el uso de ácidos de Lewis quirales, como por ejemplo los derivados de $Cu(OTf)_2$ y ligandos BOX.[79] Estos catalizadores también serían usados para aumentar la estereoselectividad en la generación de β-amino ácidos y α,β-dipéptidos.

Como veremos en la Memoria, este trabajo metodológico preliminar se ha extendido, sintetizándose nuevos α,β-péptidos (Capítulo 3.1), o desarrollando una variante de estos procesos secuenciales que permite convertir selectivamente el residuo *C*-terminal de péptidos en un β-amino aldehído (Capítulo 3.2). Además, con otra variante de esta metodología se han preparado péptidos híbridos α,γ, (Capítulo 3.3). Finalmente, en el Capítulo 3.4 veremos que la descarboxilación es reemplazada por una escisión radicalaria, y que en la etapa de adición los nucleófilos de carbono son reemplazados por nucleófilos de fósforo, para obtener péptidos con unidades de α-amino fosfonato. Estos residuos se convirtieron luego en deshidroamino ácidos.

Como se indicaba antes, gran parte del interés por desarrollar péptidos híbridos reside en obtener conformaciones que sean inusuales en los α-péptidos y en desarrollar nuevos foldámeros. Dada la importancia de este tema para el Capítulo 3.1 de la memoria, se comentarán brevemente los precedentes.

[79] (a) Nakamura, S.; Nakashima, H.; Sugimoto, H.; Sano, H.; Hattori, M.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 2145–2152. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, **2000**. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Heilderberg, **1999**. (d) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, **1995**.

Durante los estudios para determinar la configuración de los α,β-péptidos híbridos, se prepararon derivados cristalinos por acoplamiento de varios α,β-dipéptidos con α-amino ácidos, dando lugar a los α,β,α-tripéptidos **129–132** (Figuras 10 y 11).

Los análisis de rayos X pusieron de manifiesto que en estado sólido, los α,β,α-tripéptidos forman giros. El tipo de giro dependía de la configuración del β-amino ácido central, como puede observarse comparando las conformaciones de los derivados **129** y **132** en estado sólido.

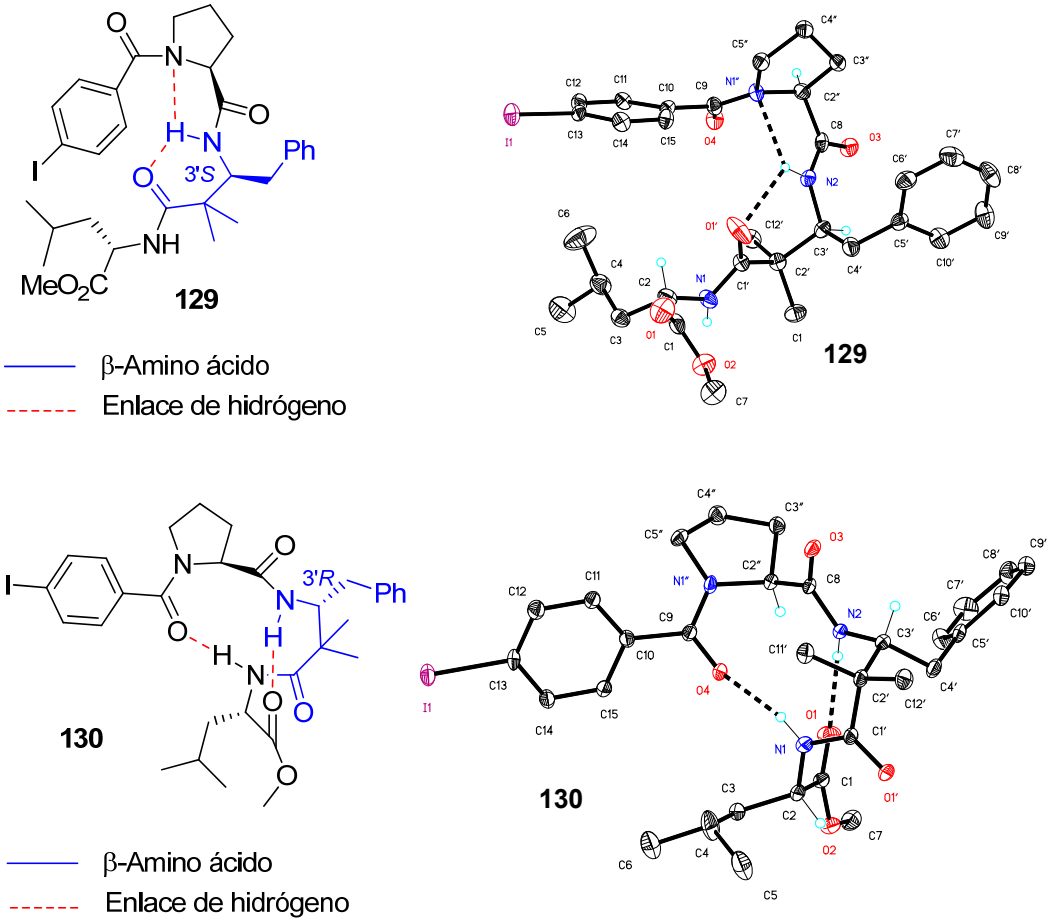
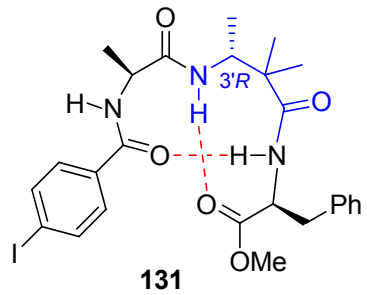


Figura 10 Conformación molecular de **129** y **130** en el cristal.

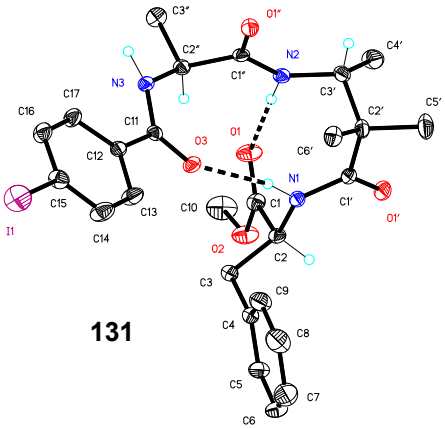
Los giros constituyen uno de los elementos más importantes de la estructura secundaria de los péptidos. Estos elementos limitan su libertad

conformacional, y a menudo se encuentran en péptidos con actividad biológica o catalítica, siendo necesarios para esta actividad.

En los α-péptidos, la formación de giros esta favorecida por la presencia de ciertos amino ácidos, como prolina, glicina, D- o *N*-alquil amino ácidos. En ausencia de este tipo de amino ácidos, los α-péptidos adoptan la conformación extendida.[60b,80] Los tripéptidos **131** y **132** (Figura 11) no presentan ninguno de los α-amino ácidos promotores de giros, así que la formación de éstos es debida a la introducción del β-amino ácido α,α-disustituido.



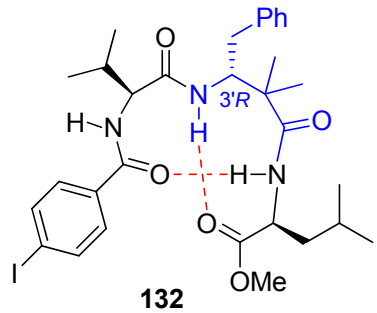
131



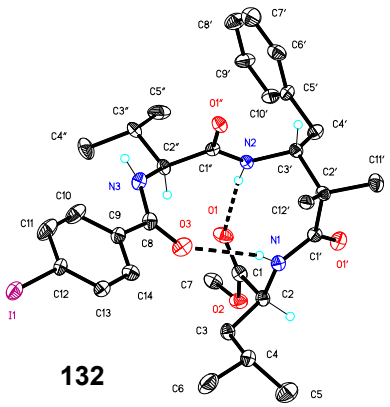
131

β-Amino ácido

Enlace de hidrógeno



132



132

β-Amino ácido

Enlace de hidrógeno

Figura 11 Conformación molecular de **131** y **132** en el cristal.

[80] Para aplicaciones, ver: Blanchette, J. P.; Ferland, P.; Voyer, N. *Tetrahedron Lett.* **2007**, *48*, 4929–4933.

En los α-péptidos, los giros más importantes (Figura 12) son los α (enlace de hidrógeno entre el CO del amino ácido i y el NH del residuo i + 4), los β (enlace de H entre el CO del amino ácido i y el NH del residuo i + 3), y los γ (enlace de H entre el CO del amino ácido i y el NH del residuo i + 2). Mucho menos comunes son los δ (enlace de H entre el NH del amino ácido i y el CO del residuo i + 1).

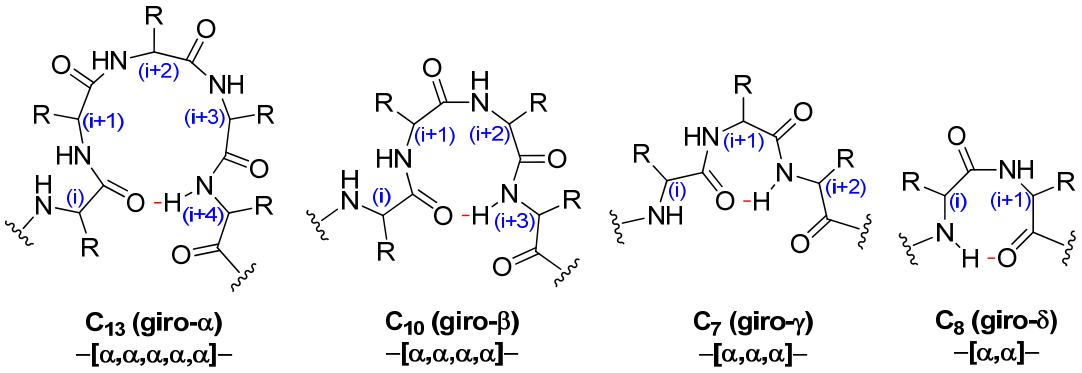


Figura 12. Giros en péptidos formados por α-amino ácidos.

Por otro lado, se sabe que los péptidos compuestos únicamente por β-amino ácidos forman a menudo giros, así como otros elementos de la estructura secundaria (ej. hélices). Estos compuestos con patrones de plegamiento bien definidos reciben el nombre de foldámeros, y han sido muy estudiados por Seebach, Gellman, Fülöp y otros.[81]

Cuando los péptidos están formados por α- y β-amino ácidos (α,β-péptidos híbridos) también suelen generarse estructuras secundarias, aunque estos híbridos están mucho menos estudiados,[82] de ahí el interés por conocer mejor los patrones conformacionales de nuestros tripéptidos.

[81] (a) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem. Int. Ed.* **1999**, *38*, 1595–1597. (b) Cheng, R.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (c) Keresztes, A.; Szucs, M.; Borics, A.; Kövér, K. E.; Forró, E.; Fülöp, F.; Tömböly, C.; Péter, A.; Páhi, A.; Fábián, A.; Murányi, M.; Tóth, G. *J. Med. Chem.* **2008**, *51*, 4270–4279.

[82] (a) Choi, S. H.; Guzei, I. A.; Spencer, L. C.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 2917–2924. (b) Choi, S. H.; Guzei, I. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 13780–13781. (c) Price, J. L.; Horne, W. S.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*,

Los tripéptidos **130**, **131** y **132**, que tienen un β-amino ácido con configuración "no natural" (3′*R*), adoptan un giro-β expandido[78d,e,83] correspondiente a un enlace de hidrógeno entre los grupos CO_i (benzamida) y el NH_{i+3} (del amino ácido terminal). Además se observa un enlace de hidrógeno entre el grupo NH_{i+2} (del β-amino ácido) y el grupo CO_{i+3} (del amino ácido C-terminal), lo que daría lugar a un giro-δ expandido.

En el caso del péptido **129**, cuyo β-amino ácido presenta la configuración "natural", la conformación del péptido es diferente. Se forma un enlace de hidrógeno entre el grupo CO y el NH del β-amino ácido. Además se observa una interacción adicional entre los pares de electrones del nitrógeno de la prolina y el protón del grupo amina del β-amino ácido.

Estas interacciones podrían ser muy útiles para el diseño de nuevos fármacos o catalizadores peptídicos,[84] siempre que al menos parte de ellas se mantuvieran en disolución. El estudio conformacional de los α,β,α-tripéptidos en solución será comentado en el Capítulo 3.1 de la Memoria.

6376–6377. (d) Horne, W. S.; Price, J. L.; Keck, J. L.; Gellman, S. H. *J. Am. Chem. Soc*, **2007**, *129*, 4178–4180.

[83] (a) Rai, R.; Vasudev, P. G.; Anandz, K.; Raghothama, S.; Shamala, N.; Karle, I. L.; Balaram, P. *Chem. Eur. J*. **2007**, 13, 5917–5926. (b) Abele, S.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1559–1571. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1–15.

[84] (a) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev*. **2007**, *107*, 5759–5812. (b) Berkessel, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3677–3679. (c) Sánchez- Roselló, M.; Puchlopek, A. L. A.; Morgan, A. J.; Miller, S. J. *J. Org. Chem.* **2008**, *73*, 1774–1782. (d) Revell, J. D.; Wennemers, H. *Adv. Synth. Catal.* **2008**, *350*, 1046–1052. (e) Tsandi, E.; Kokotos, C. G.; Kousidon, S.; Ragoussis, V.; Kokotos, G. *Tetrahedron* **2009**, *65*, 1444–1449.

Anexo de la Introducción

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Genotoxic activity of halogenated phenylglycine derivatives

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Abstract—The discovery of genotoxic amino acids derived from phenylglycine, and posessing halogen substituents, is described. The utility of hypervalent iodine reagents in the synthesis of this class of compounds is highlighted. The mechanism of action of the (haloaryl)glycines was studied in *Saccharomyces cerevisiae*.

Tumour cells have very active transport systems to capture the amino acids required for protein and nitrogen base biosynthesis. Since these systems are overexpressed with respect to most non-tumour cells, the development of cytotoxic amino acid derivatives[1] is a promising way to achieve more selective anticancer treatments.[2] For instance, melphalan **1**[3] (Fig. 1) is a clinically used alkylating agent whose uptake is performed by active amino acid transport systems.[4] This drug was developed in an effort to reduce the side effects produced by other mustards.

Once into the cell, the amino acid analogues disrupt different physiological processes. For instance, L-alanosine **2** interferes with aspartic acid metabolism.[5] The potent antibiotic and antitumoural acivicin **3**[6] is a specific inhibitor of γ-glutamyl transpeptidase and transmembrane glutathione transport, inducing apoptosis in human lymphoblastoid cells.[7]

In spite of their potential selectivity, the use of amino acids as anticancer agents has yet to be fully explored.[1] In an effort to develop new amino acid-based antitumoural drugs, we turned our attention to aromatic amino acids, such as phenylalanine, phenylglycine and tyrosine analogues. Few examples of cytotoxicity have been reported for this class of compounds. For instance, the azatyrosine derivatives **4** were patented for the treatment of pancreas, colon and thyroid cancer.[8] Recently, phenylglycine and other amino acids were reported to block the ATB^{0+} amino acid transport, which is overexpressed in tumoural cells. Since they were deprived of vital nutrients, a strong growth inhibition was observed for human colon and breast cancer cell lines.[9]

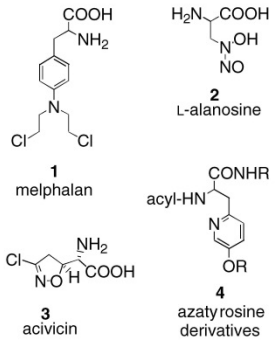

Figure 1. Some cytotoxic amino acid derivatives.

Now we report new cytotoxic agents derived from phenylglycine. The lead compound **5** (Fig. 2) was discovered

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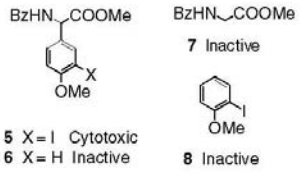


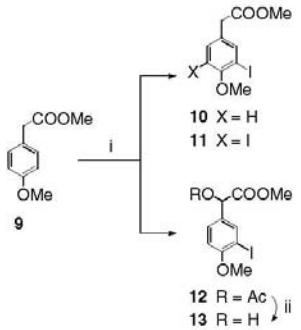
Figure 2. Discovery of the lead compound **5**.

during a screening of the cytotoxic activity of different amino acids in *Saccharomyces cerevisiae*. This yeast is used as a model system to study the mechanism of action of antitumour drugs, and to select, from a given batch, the most promising cytotoxic compounds. It was also observed that the deiodinated analogue **6** did not show activity, nor did methyl *N*-benzoylglycine **7** or 2-iodoanisole **8**.

In order to determine the structure–activity relationships (SAR), different analogues of compound **5** were prepared: (a) by replacement of the benzamide group by oxygen, sulfur and other nitrogen functions; (b) by replacing the ester group by amide, hydroxymethyl, acid, ketone and phosphonate groups; (c) changing the aromatic ring substitution pattern.

The cytotoxic activity of these analogues was then studied with three tumour cell lines: MCF7 (breast), NCI-H460 (lung) and SF-268 (glioma). Their mechanism of action was characterised using mutant strains of *S. cerevisiae*, as will be commented below.

The first analogues were prepared to determine the influence of the nitrogen function on the cytotoxic activity. Thus, the aromatic ring of compound **9** (Scheme 1) was iodinated with hypervalent iodine reagents and iodine, generating products **10**–**12**. The acetate group in product **12** was hydrolysed, yielding the alcohol **13**.

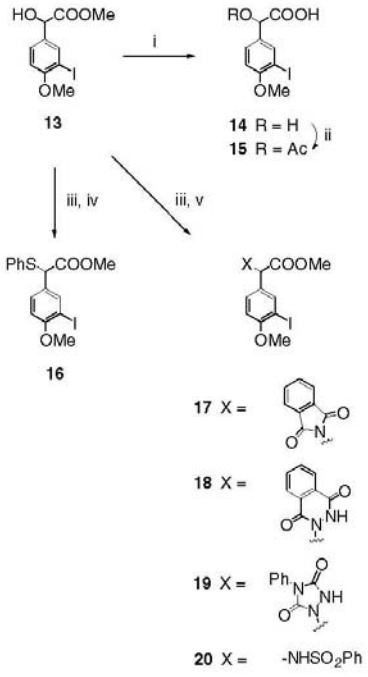


Scheme 1. Replacement of the nitrogen function by hydrogen or oxygen functions. Reagents and conditions: (i) DIB, I_2, CH_2Cl_2, dark, 20 h **10** (55%), **11** (14%), **12** (30%); (ii) MeONa, MeOH, 92%.

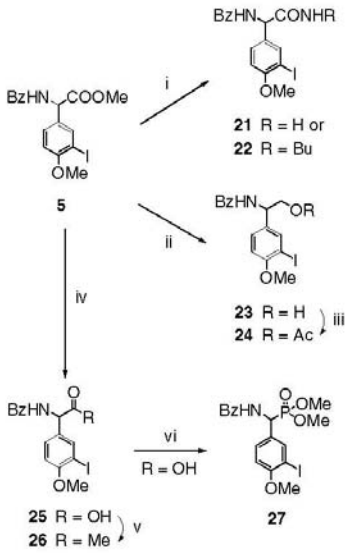
Compound **13** was then transformed into derivatives **14**–**20** (Scheme 2), where the benzamide group was replaced by oxygen functions (compounds **14** and **15**), a thioaryl group (product **16**) and other nitrogen functions (compounds **17**–**20**). Some of these functions have a volume similar to the NHBz group, but lack the ability to form hydrogen bonds and present different polarity (such as the PhS or the phthalimide groups). Others are able to form hydrogen bonds (OH, hydrazide, sulfonamide, etc.) but differ in volume and polarity.

In other group of analogues, the ester function in product **5** was replaced by amide, hydroxymethyl, acid, or ketone groups (Scheme 3), using conventional methodologies. The resulting products **21**–**26** present differences in hydrosolubility, volume and metabolization, with respect to the lead compound.

In order to obtain more structural diversity, the acid **26** was transformed into the phosphonate **27**, using a one-pot fragmentation–phosphorylation reaction developed by our group.[10]



Scheme 2. Replacement of the benzamide group in the lead compound **5** by other functionalities. Reagents and conditions: (i) 2 N NaOH, MeOH, 92%; (ii) Ac_2O, Py, 84%; (iii) MsCl, CH_2Cl_2, Et_3N; (iv) Cs_2CO_3, DMF, reflux, PhSH, 58% for both steps; (v) Cs_2CO_3, DMF, reflux, nucleophile (phthalimide or phthalohydrazide or phenylurazole or phenylsulfonamide). Compounds **17** (74%); **18** (74%); **19** (64%); **20** (46%).



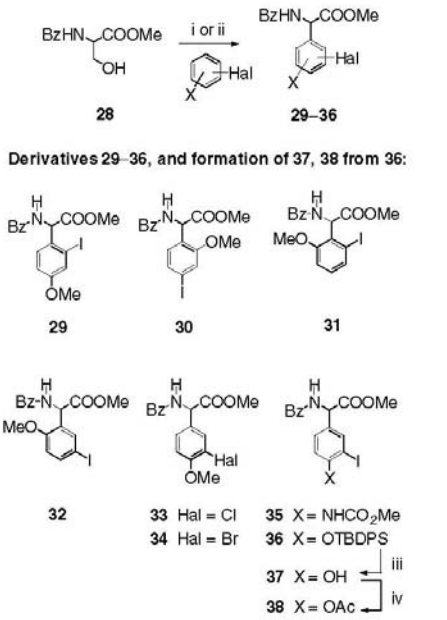
Scheme 3. Replacement of the ester group in the lead compound **5** by other functionalities. Reagents and conditions: (i) RNH_2, THF, reflux; **21** (31%), **22** (81%); (ii) DIBAL-H, CH_2Cl_2, 37%; (iii) Ac_2O, Py, 57%; (iv) NaOH, MeOH, 92%; (v) BuLi, THF, −78 °C; then MeMgI, THF, −78 °C → rt; **26** (20%), **25** (61%); (vi) DIB, I_2, hν, CH_2Cl_2, then $BF_3{\cdot}OEt_2$, $P(OMe)_3$, 84%.

The influence of the aromatic substituents was studied afterwards. Different halogen and X groups were introduced, and their positions changed, as shown in Scheme 4. Thus, starting from serine derivative **28**, a one-pot fragmentation–arylation reaction[11] was carried out, yielding the arylglycines **29**–**36**. The silyl ether **36** was then cleavaged to give the phenol **37**, and this was transformed into the acetate **38**.

The cytotoxic activity of all derivatives was studied (Fig. 3), and those compounds in which the nitrogen function was replaced by hydrogen, oxygen or sulfur functions (products **10**–**16**) proved to be inactive. The phthalimide **17** also was inactive, suggesting that hydrogen bonding was needed for activity. However, the hydrazide **18** and urazole **19** showed little activity, probably due to changes in the position of the NH group or by polarity reasons, since the heteroatom attached to the NH group exerts a strong electron-withdrawing effect. The sulfonamide **20**, which was able to form hydrogen bonds, was cytotoxic. The derivatives **21**–**27**, where the ester group has been replaced by amide, hydroxymethyl, acid, ketone, or phosphonate groups, showed little activity.

The derivatives **29**–**38**, where modifications of the aromatic ring were made, showed that changes in the iodine position were deleterious for activity, and thus products **29**–**31** showed little cytotoxicity.

The changes in the halogen were also important, and the chloro derivative **33** was less active than the lead



Scheme 4. Changes in the aromatic ring substituents. (i) (a) DIB, I_2, hν, CH_2Cl_2, then MeOH; (b) $BF_3{\cdot}OEt_2$, 3-iodoanisole, CH_2Cl_2, **29** (31%), **30** (35%) and **31** (7%); (ii) DIB, I_2, hν, CH_2Cl_2, then $BF_3{\cdot}OEt_2$, Ar. With Ar = 4-iodoanisole: **32** (43%); with Ar = 2-chloroanisole: **33** (71%); with Ar = 2-bromoanisole: **34** (76%); with Ar = 2-iodoaniline methyl carbamate: **35** (30%); with Ar = 2-iodo-*O*-tertbutyldiphenylsilylphenol: **36** (50%); (iii) TBAF, THF, 61%; (iv) Ac_2O, Py, 65%.

compound **5**. However, the bromo analogue **34** presented similar activity.

Some changes in the aromatic X group were also performed. When X = $NHCO_2Me$ or OH (products **35** and **37**) the compounds were not active. On the contrary, compound **38** (X = OAc) retained some cytotoxicity, and the analogue **36** (X = OTBDPS) was more active than the lead compound **5**. Clearly, both substituent volume and polarity are important for activity.

With these results in hand, chiral derivatives[12] of the most active arylglycine, compound **36**, were prepared (Scheme 5). The synthesis was performed from commercial L-(4-hydroxyphenyl)glycine (*S*)-**39**, which was N-benzoylated to compound (*S*)-**40** and then esterified and O-silylated. The resulting product (*S*)-**41** was iodinated, affording product (*S*)-**36** in satisfactory yield. The synthesis of the D-enantiomer (*R*)-**36** was performed in a similar way.

The L-enantiomer (*S*)-**36** showed similar activity to the D-epimer (*R*)-**36**, although this result could be due to in vivo epimerization.

The mechanism of action for the arylglycines and their simplified analogues was then studied in *S. cerevisiae*.

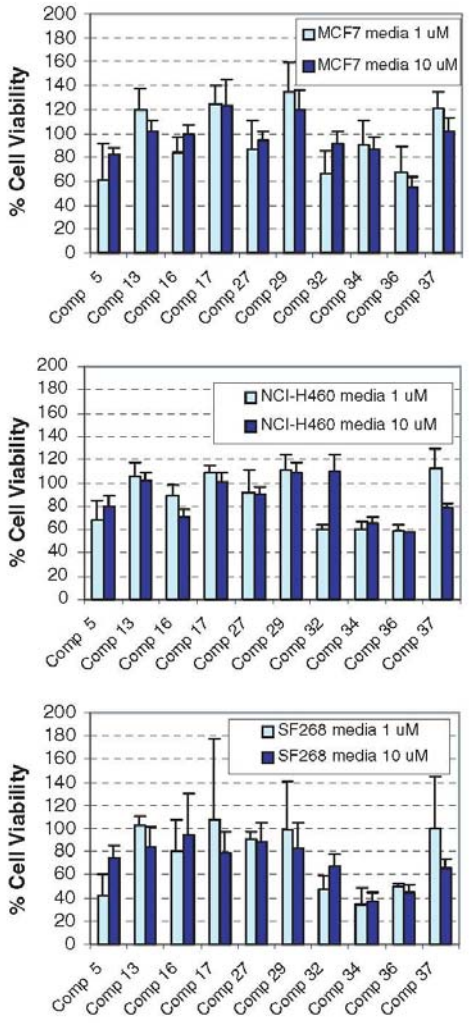
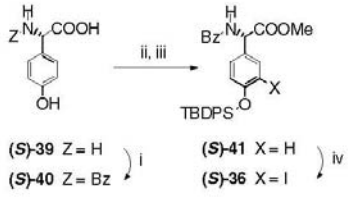


Figure 3. Table of cell viability with respect to control (%) of tumour cell lines SF680, MCF7 and NCI-H460 in the presence of representative compounds **5**, **13**, **16**, **17**, **27**, **29**, **32**, **34**, **36** and **37**.

Cancers accumulate a large number of genetic changes during progression towards malignancy due to an intrinsic genetic instability. These genetic alterations frequently affect DNA repair and cell cycle checkpoint pathways thereby increasing tumour cell sensitivity towards DNA damaging agents. As these pathways are conserved throughout evolution one can explore the therapeutic potential of molecules by using a panel of isogenic yeast strains with defined genetic alterations in DNA repair or checkpoint functions. Indeed, this approach has proven to be extremely useful in the analysis of well-known



Scheme 5. Synthesis of chiral arylglycines. Reagents and conditions: (i) BzCl, $NaHCO_3$ (aq satd), THF; (ii) MeOH, AcCl (80% for the two steps); (iii) TBDPSCl, imidazole, CH_2Cl_2, 96%; (iv) DIB, I_2, CH_2Cl_2, dark, 45% (plus 23% recovered starting material).

cytotoxic compounds which are currently used in cancer therapy.[13]

To further characterise the toxicity mechanism of these compounds, we explored the effect of compounds **5** and **34** on cell growth and viability, using a set of isogenic yeast strains defective in DNA repair (rad52, rad52-ku80 and rad14 strains) and DNA damage checkpoint (mec1-1 and rad53-11) pathways (Fig. 4).

As shown in Figure 4, treatment with both compounds affected yeast cell growth (Fig. 4A) and viability (Fig. 4B) in all strains, indicating that compounds **5** and **34** were cytotoxic in yeast. Interestingly, the growth defect produced by exposure to arylglycines **5** and **34** was exacerbated in the rad52 and rad52,ku80 mutants, respectively. These strains are hypersensitive to alterations in a number or processes involved in genome stability such as DNA replication, DNA damage signaling, double strand break repair, chromatin structure and

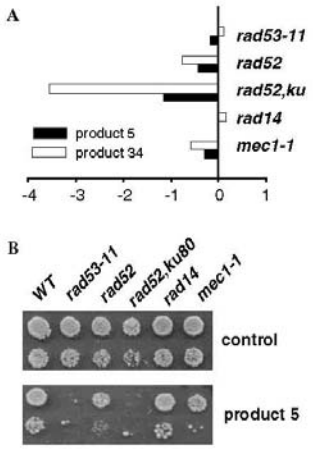


Figure 4. (A) Inhibitory effects of compounds **5** and **34** on the growth of selected DNA damage repair/checkpoint yeast mutants in liquid media (log[% yeast mutant growth/% WT growth]). (B) Growth of selected DNA damage repair/checkpoint yeast mutants in solid media (control vs compound **5**).

assembly, chromosome segregation, telomere maintenance and metabolism of reactive oxygen species.[14] Therefore, these data are consistent with compounds **5** and **34** behaving as genotoxins. Consequently, an attractive hypothesis would be that compounds **5** and **34** induce genomic instability through alteration of one/some of the above-mentioned processes. This hypothesis is currently being addressed.

In summary, new cytotoxic amino acids derived from 3-iodo- or 3-bromo-phenylglycine are described herein. Many of these compounds were synthesized using one-pot fragmentation–arylation or halogenation reactions with hypervalent iodine reagents. The mechanism of action of the (haloaryl)glycines was studied in *S. cerevisiae*, showing that these compounds were genotoxic.

Acknowledgments

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Supplementary data

Spectroscopic data for selected compounds, other cytotoxic activities, materials and general procedures for the determination of the cytotoxic activity and the mechanism of action studies. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.08.111.

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One-pot synthesis of β-amino acid derivatives from α-amino acids

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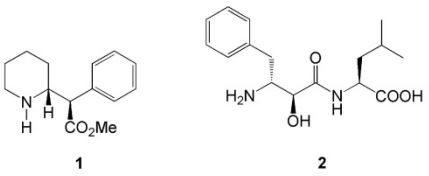
Abstract—The one-pot transformation of α-amino acid into β-amino acid derivatives is described. The application of this method to the synthesis of modified dipeptides was also illustrated.

The synthesis of β-amino acids[1] and peptides containing them[2] has arisen great interest, due to the promising biological activities shown by many of these compounds. For instance, β-amino acid **1** (methylphenidate or Ritalin®, Fig. 1) is clinically used as a treatment for the attention deficit disorder in children,[3] and dipeptide **2** (bestatine or Ubenimex®) is an immunological response modifier.[4]

In previous articles, we have reported the syntheses of alkaloids and α-amino phosphonates from α-amino acids **3** (Scheme 1) using a tandem radical fragmentation–addition of nucleophiles reaction.[5] When substrates **3** were treated with (diacetoxyiodo)benzene (DIB) and iodine, under irradiation with visible light, an O-radical **4** was generated, which underwent β-scission,[6] generating a C-radical **5**. This intermediate was oxidized in the reaction mixture to an acyliminium ion



1 2

Figure 1. Bioactive β-amino acid derivatives.

Keywords: Radicals; β-Amino acids; Dipeptides; Fragmentation; Acyliminium ions; Nucleophilic addition.
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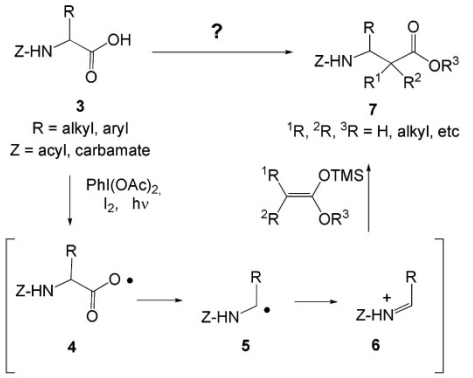
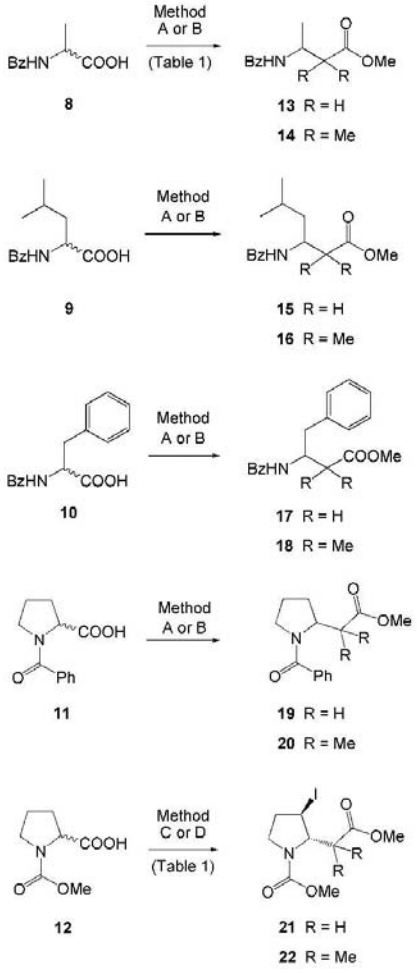


Scheme 1. β-Scission in amino acid derivatives.

6,[7,8] which was trapped by oxygen, nitrogen, phosphorous or carbon nucleophiles. We reasoned that the addition of enolsilylethers to the acyliminium ion could generate β-amino acid derivatives **7** or modified peptides (when $Z = [aa]_n$). The feasibility of this strategy is discussed herein.

In order to study the fragmentation–addition reaction, different amino acid derivatives **8**–**12** (Scheme 2) were prepared, in good yields, by the acylation or carbamoylation of commercial precursors. Substrates **8**–**11** were treated with DIB and iodine at room temperature and under irradiation with visible light (Table 1, entries 1–8). The reaction mixture was then cooled to 0 °C and the enolsilylether and $BF_3{\cdot}OEt_2$ were added,



Scheme 2. One-pot transformation of α-amino acid into β-amino acid derivatives.

affording β-amino acid derivatives **13**–**20**. In spite of their different volume, both nucleophiles gave similar product yields. In this way, α-amino acids were transformed in one step into the corresponding β-analogues.

The biological activities of amino acids **13**–**20** are under study. Thus, the derivatives of β-homophenylalanine (related to compounds **17** and **18**) have been reported as a new treatment for type II diabetes.[9] Moreover, their insertion into more complex structures could also be of interest. For example, related β-amino acids are units of aminopeptidase inhibitors such as bestatine **2** or amastatine,[2d] and several β-amino acids with lipophilic side chains (such as compounds **13**, **15** and **17**) have been used as components of glycine reuptake inhibitors in the CNS.[10]

Table 1. One-pot β-fragmentation alkylation reaction

Entry	Substrate	Conditions[a,b,c,d]	Products[e] (%)
1	**8**	A[a]	**13** (50)
2	**8**	B[b]	**14** (41)
3	**9**	A	**15** (55)
4	**9**	B	**16** (67)
5	**10**	A	**17** (50)
6	**10**	B	**18** (55)
7	**11**	A	**19** (85)
8	**11**	B	**20** (77)
9	**12**	C[c]	**21** (69)
10	**12**	D[d]	**22** (56)

[a] Method A. The substrate (1 mmol) in dry dichloromethane (15 mL) was treated with DIB (2.5 mmol) and iodine (1 mmol) and irradiated with visible light (100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). It was then cooled to 0 °C and $BF_3{\cdot}OEt_2$ (2 equiv) and $CH_2{=}C(OTBS)OMe$ (5 equiv) were added. The reaction mixture was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$ 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[b] Method B. As Method A, but using $Me_2C{=}C(OTMS)OMe$ as the nucleophile.

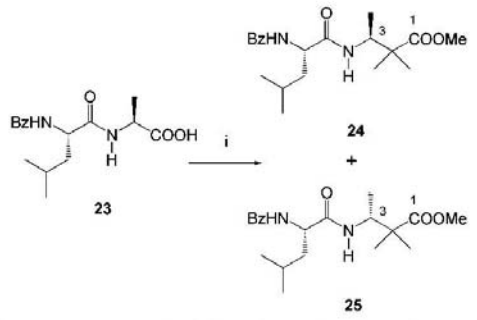
[c] Method C. The substrate (1 mmol) in dry acetonitrile (15 mL) was treated with DIB (2.5 mmol) and iodine (2 mmol) and irradiated with visible light (100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). Dry methanol was then added and the mixture was poured into aqueous 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the crude product was solved in dry acetonitrile, cooled to 0 °C, and treated with $BF_3{\cdot}OEt_2$ (2 equiv) and $CH_2{=}C(OTBS)OMe$ (5 equiv). The reaction mixture was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2.

[d] Method D. As Method C, but using $Me_2C{=}C(OTMS)OMe$ as nucleophile.

[e] Yields are given for products purified by chromatography on silica gel.

The fragmentation–alkylation of methyl carbamate **12** using methods A or B gave a complex mixture of products, so different conditions were tried (methods C or D, entries 9 and 10).[11] In the first step, a tandem fragmentation–β-iodination–addition of methanol reaction took place. The crude product was then treated with the Lewis acid and the nucleophile to give the iodinated β-amino acid derivatives (±)-**21** or (±)-**22** in good yields. The introduction of iodine in a previously non-functionalized position is specially interesting, since these iodinated pyrrolidines could be valuable intermediates in the synthesis of alkaloids and bactericidal iminoglyco acids.[12]

Another interesting application of the scission–alkylation reaction would be the preparation of modified peptides, which is a rapidly growing field in medicinal chemistry.[2] Starting from bioactive peptides, the modification of the C-terminal residue could afford derivatives with different biological activity, potency or selectivity.[13] Since the modified residue would be attached to chiral amino acid units, the reaction was expected to be stereoselective.



Scheme 3. Reagents and conditions: (i) DIB, I_2, hv, CH_2Cl_2, then 0 °C, $BF_3{\cdot}OEt_2$, $Me_2C{=}C(OTMS)OMe$, 58%, **24**:**25** 5:2.

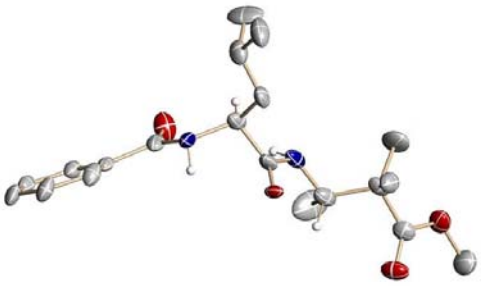


Figure 2. X-ray analysis of dipeptide **24**.

The reaction was studied with the Leu-Ala derivative **23**, using $Me_2C{=}C(OTMS)OMe$ as the nucleophile. The scission–alkylation afforded modified dipeptides **24**[14] and **25** (Scheme 3), which could be separated by chromatography and crystallization. The configuration of **24** was determined by X-ray analysis (Fig. 2).[15] As expected, the reaction was diastereoselective (**24**:**25**, 5:2). However, the isolation of the two possible diastereomers is also interesting, in order to determine the influence of the configuration into the biological activity.

In summary, the one-pot fragmentation–alkylation reaction is a versatile and efficient pathway to obtain many different β-amino acid derivatives from readily available precursors. The synthesis of modified peptides is another interesting application of this reaction.

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15. *Crystal data for* **24**: $C_{20}H_{30}N_2O_4$, $M_r = 362.46$, colourless needle ($0.55 \times 0.11 \times 0.10$ mm^3) from CH_2Cl_2/*n*-hexane, trigonal, space group $P6_5$ (no. 170), $a = b = 11.7280(10)$ Å, $c = 26.998(5)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $V = 3216.0(7)$ Å^3, $Z = 6$. $\rho_{calcd} = 1.123$ g cm^{-3}, λ (Mo Kα) = 0.71073 Å, $F(000) = 1176$, $\mu = 0.078$ mm^{-1}, $T = 100(2)$ K. 26186 reflections measured for the range $3.45° < \theta < 26.37°$. Final refinement with 2240 [$R_{int} = 0.0802$] unique reflections and 317 parameters gave, $R_1 = 0.0774$, $wR_2 = 0.1858$ [for 1336 reflections with $I > 2\sigma(I)$], $R_1 = 0.1434$, $wR_2 = 0.2375$ (all data) ($S = 1.092$). The X-ray crystallographic file, in CIF format, has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 618736 for **24**. Copy of this information may be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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Catalytic, One-Pot Synthesis of β-Amino Acids from α-Amino Acids. Preparation of α,β-Peptide Derivatives

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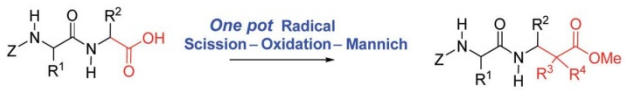

The one-pot conversion of readily available α-amino acid into β-amino acid derivatives was carried out in good yields. The method is a *sequential* process initiated by a *tandem* radical decarboxylation−oxidation reaction; the resulting acyliminium ion was trapped by silyl ketenes. Stoichiometric and catalytic versions of this reaction were developed and then applied to prepare modified di- and tripeptides. Interestingly, some tripeptides formed expanded β-turns in the solid state.

Introduction

The development of tandem and sequential processes has allowed shorter and more efficient procedures to obtain a variety of products, including drugs, catalysts, or synthetic intermediates.[1] Since several transformations are performed consecutively, and no purification of the intermediates is required, these processes save materials, energy, and time and decrease the amount of waste.

In previous work, we developed a one-step methodology to prepare bioactive products from readily available substrates (such as the amino sugar **1**, Scheme 1).[2] The method was a *sequential* process initiated by a *tandem* radical fragmentation−oxidation reaction. Remarkably, the radical scission step, which initiated the reaction cascade, took place at room temperature using visible light, such as sunlight or common lamps.[3] The scission generated a C-radical (such as **2**) which was trapped by iodine, affording an α-iodoacetal (e.g., compound **3**). The replacement of the iodo group by acetate ions from the reagent gave an *N*,*O*-acetal (such as product **4**). When a Lewis acid and a nucleophile were added, the acetal generated an acyliminium ion **5**,[2a] which was trapped by the nucleophile (for instance, the addition of phosphites afforded α-aminophosphonates **6**).[2b] In general, good yields were obtained, and the reaction conditions were mild, compatible with most functional groups.

We reasoned that this process could be applied to the direct transformation of amino acids into nonproteinogenic analogues and, moreover, to the selective transformation of peptides (Scheme 2). In a preliminary work, the conversion of α-amino

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(3) The radical scission can also be promoted by heating, but visible light irradiation allows milder reaction conditions. To set an irradiation standard, 80 W tungsten-filament lamps (from DIY shops) were used herein.

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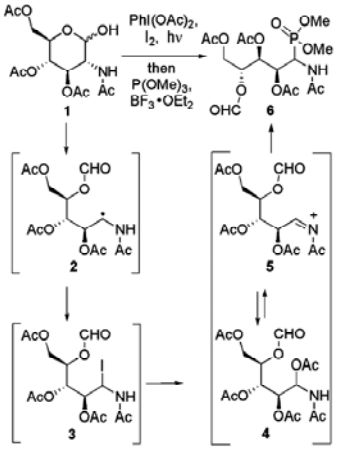
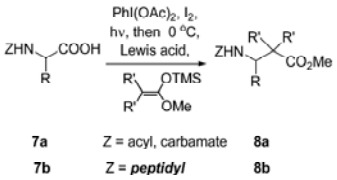
SCHEME 1. One-Pot Radical Fragmentation−Oxidation−Addition of Nucleophile Process



SCHEME 2. One-Pot Scission−Oxidation−Mannich Process for the Direct Conversion of α-Amino Acids into α-Substituted β-Amino Esters and the Selective Modification of Peptides



acids **7a** into substituted β-amino esters **8a** was studied.[4] The decarboxylation−oxidation was carried out, followed by addition of a silylketene[5] in the presence of a Lewis acid. A stoichiometric amount of the Lewis acid (BF_3•OEt_2 or TMSOTf) was required in the nucleophilic addition step. In this article, a catalytic system is reported, which affords similar results.

The sequential process would also allow the *selective transformation* of the C-terminal residue of peptides (conversion **7b**→**8b**, Scheme 2). In compound **7b**, the amino protecting group Z is a peptidyl chain which would act as a chiral auxiliary, and the reaction would be stereoselective. From a single α-peptide substrate, a library of hybrid α,β-peptides could be formed since the terminal β-amino acid could be mono-, di-, or unsubstituted in the α-position (R′ = H, alkyl, allyl, aryl, Hal, OR, NHR, etc.), and up to four different stereoisomers could be generated. Such procedure could be very useful in medicinal chemistry to obtain diversity from a single (or a few) bioactive α-peptide. The feasibility of this site-selective transformation will be commented on later.

In recent years, the formation of β-amino acid derivatives has received much interest, from both the synthetic[6,7] and medicinal[8] standpoints. Among the synthetic methodologies, the Arndt−Eistert homologation, the Curtius rearrangement, the conjugate addition of nitrogen nucleophiles to unsaturated esters, or the addition of carbon nucleophiles to imines have proven very useful.[6,7] For instance, Seebach and others have used the Arndt−Eistert homologation to prepare β-amino acids and β-peptides with high stereoselectivity.[9] This protocol also allows the synthesis of α-substituted α-amino acids but not α,α-disubstituted β-amino acids; it also presents problems for large-scale synthesis.[9f]

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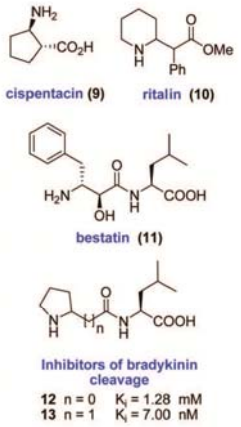


FIGURE 1. Bioactive β-amino acids and hybrid peptides.

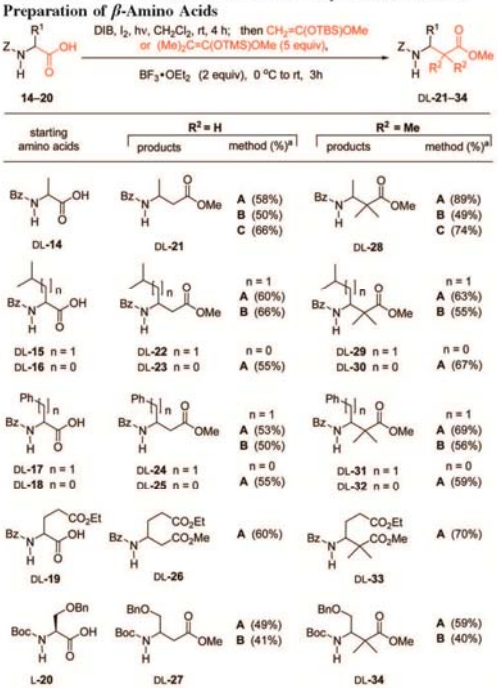
From the medicinal standpoint, the β-amino acid derivatives have displayed interesting biological properties (such as the antibiotic cispentacin **9**[10] and the β-lactams,[11] or the antihyperactivity drug ritalin **10**,[12] Figure 1). In other cases, they are components of bioactive products, such as bestatin (Ubenimex, **11**),[13] a microbial β,α-dipeptide which is under clinical studies to treat lymphomas, myeloid leukemias, and lung carcinoma. Other significant examples are the antitumoral paclitaxel,[14] the antifungal microscleroderdermins,[15] and the antihelmintic jasplakinolide.[16]

Besides, the replacement of α-amino acids by β-amino acids in bioactive peptides has produced derivatives with superior stability to proteases and with similar or increased activity.[17] For instance, the α-dipeptide **12** (Figure 1) is an inhibitor of bradykinin cleavage by aminopeptidase (APP) and thus a potential agent against cardiovascular diseases. However, its Pro−Leu amide bond is easily hydrolyzed by kidney peptidases. When the proline residue in peptide **12** was replaced by a β-homoproline, the modified β,α-peptide **13** displayed a 500-fold increase in inhibitory activity (from K_i = 1.28 mM to 7.0 nM); moreover, it was completely stable to peptidases in kidney membranes after 24 h.[17a]

Finally, the ability of many β-peptides or hybrid α,β- or β,γ-peptides to form turns, helices, β-sheets, or fibrils is rendering interesting applications to medicinal chemistry and materials science.[18] For example, the β-amino acids are used to generate turns in peptides in order to achieve bioactive conformations.[19]

The application of catalytic tandem−sequential processes to the synthesis of these interesting compounds is discussed below, with an emphasis on the preparation of hybrid α,β-peptides.

TABLE 1. One-Pot Scission−Oxidation−Silyl Ketene Addition: Preparation of β-Amino Acids



[a] Method A: The scission step uses DIB (1.5 equiv), I_2 (0.3 equiv). Method B: Scission step: DIB (2 equiv), I_2 (0.5 equiv). Method C: Scission step: DIB (2 equiv), I_2 (1.0 equiv).

Results and Discussion

Development of the Radical Scission−Oxidation−Mannich Reaction. In a first stage, the sequential process was explored with simple substrates, derived from acylation or carbamoylation of commercial amino acids. Thus, compounds **14**−**20** (Table 1) were treated with the system (diacetoxyiodo)benzene and iodine,[2] in the presence of visible light, to induce the scission−oxidation steps, then BF_3•OEt_2 was added to generate an acyliminium intermediate, which was trapped by silylketenes. With unsubstituted ketenes (R^2 = H), the process afforded compounds **21**−**27** in moderate to good yields. Several reaction conditions were tried, showing that the amount of iodine was critical to obtain good yields. The scission did not take place

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(14) (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44. (b) See also: Escalante, J.; Juaristi, E. *Tetrahedron Lett.* **1995**, *36*, 4397–4400. (c) Sánchez-Obregón, R.; Salgado, F.; Ortiz, B.; Díaz, E.; Yuste, F.; Walls, F.; García-Ruano, J. L. *Tetrahedron* **2007**, *63*, 10521–10527, and references cited therein.

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without iodine, but an excess of iodine gave complex product mixtures. With 0.3−0.5 equiv, the reaction proceeded in reasonable yields.

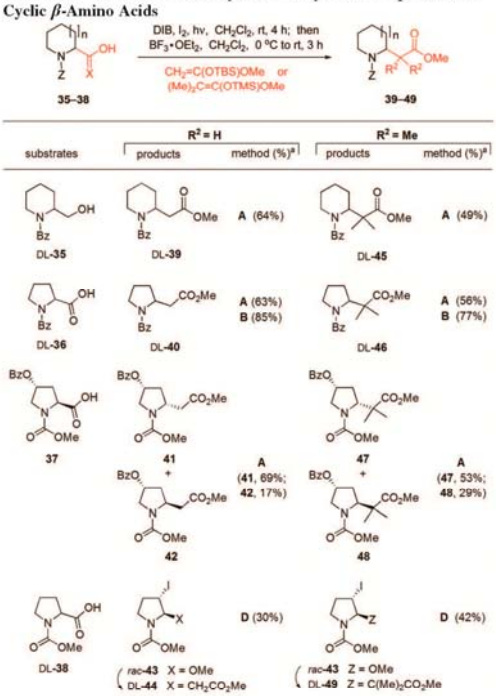
When the disubstituted ketene $Me_2C{=}C(OTMS)OMe$ was used, the yields improved, in particular, with Method A [DIB (1.5 equiv), iodine (0.3 equiv)],[20] which afforded compounds **28**−**34** in good yields. Hence, this methodology is an interesting alternative to the Arndt−Eistert homologation,[6c] not only due to the mild, relatively inexpensive and scalable conditions[9] but also due to the ready formation of α,α-disubstituted β-amino acids.

Similar results were obtained in the scission−alkylation of the cyclic amino alcohol **35** (Table 2) and the cyclic amino acids **36**−**38**. Although the scission of alcohols is less favored than the decarboxylation of amino acids,[21] the fragmentation of the amino alcohol **35** and the alkylation with $CH_2{=}C(OTBS)OMe$ proceeded in a satisfactory yield, affording compound **39**. Remarkably, products derived from possible side reactions, such as hydrogen abstraction, were not detected.

In a similar way, the decarboxylation−alkylation of proline derivative **36** afforded compound **40** in good yield. In the case of hydroxyproline substrate **37**, the stereogenic center on C-4 determined the stereoselectivity of the nucleophilic addition step. Surprisingly, the 2,4-*cis* product **41** predominated upon the 2,4-*trans* isomer **42**. This result could be explained according to the model reported by Woerpel for the addition of nucleophiles to five-membered ring oxocarbenium and iminium ions.[22]

By changing the reaction conditions, different derivatives can be obtained. For instance, when the reaction was carried out in acetonitrile and an excess of iodine was added, the proline carbamate **38** underwent a one-pot decarboxylation−oxidation−β-iodination process.[23a] The polar solvent favored the isomerization of the acyliminium intermediate to an encarbamate, which reacted with iodine affording a β-iodoacyliminium ion. This

TABLE 2. One-Pot Decarboxylation−Alkylation: Preparation of Cyclic β-Amino Acids



[a] Method A: DIB (1.5 equiv), I_2 (0.3 equiv), ketene (5 equiv). Method B: DIB (2.0 equiv), I_2 (0.5 equiv), ketene (5 equiv). Method D: DIB (2 equiv), I_2 (2 equiv), *hv*, CH_3CN, 4 h; MeOH (10 equiv), 0.5 h; solvent removal, then CH_3CN, 0 °C, ketene (5 equiv), $BF_3{\bullet}OEt_2$ (2 equiv), 3 h.

intermediate was trapped by addition of methanol, and a 2,3-*trans*-3-iodo-2-methoxy pyrrolidine **43**[23a] was formed. This compound was not purified, but the solvent was evaporated and the crude product mixture was redissolved, cooled to 0 °C, and treated with the nucleophile and the Lewis acid, yielding the iodinated β-amino ester **44**.[23b] The introduction of iodine in a previously unfunctionalized position is valuable since the iodo group can be replaced by other functionalities. Alternatively, the iodo derivative **43** could undergo elimination, and the resulting 3,4-alkene could be further functionalized.

When the nucleophile was the disubstituted silylketene $Me_2C{=}C(OTMS)OMe$, the α,α-dimethyl-β-amino esters **45**−**49** were isolated. In most cases, yields were similar or superior to

(17) (a) For recent reviews, see: Aguilar, M. I.; Purcell, A. W.; Devi, R.; Lew, R.; Rossjohn, J.; Smith, A. I.; Perlmutter, P. *Org. Biomol. Chem.* **2007**, *5*, 2884–2890. (b) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399–1408. (c) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366–1375. (d) For recent work on the subject, see: Sharma, G. V. M.; Manohar, V.; Dutta, S. K.; Subash, V.; Kunwar, A. C. *J. Org. Chem.* **2008**, *73*, 3689–3698. (e) Chakraborty, T. K.; Rao, K. S.; Kiran, M. U.; Jagadeesh, B. *Tetrahedron Lett.* **2008**, *49*, 2228–2231.

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(19) (a) For the expansion of β-turns with β- and γ-aa, see: Rai, R.; Vasudev, P. G.; Anandz, K.; Raghothama, S.; Shamala, N.; Karle, I. L.; Balaram, P. *Chem.−Eur. J.* **2007**, *13*, 5917–5926. (b) For turns in β-peptides, see: Abele, S.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1559–1571. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1–15. (d) For the biological importance of turns, see: Tyndall, J. D. A.; Pfeiffer, B.; Abbenante, G.; Fairlie, D. P. *Chem. Rev.* **2005**, *105*, 793–826. (e) Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Bioorg. Med. Chem.* **2005**, *13*, 11–16.

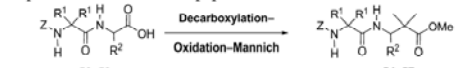
(20) Other methods were also tried, but they are not mentioned in the sake of clarity. For instance, a method using DIB (1.5 equiv) and iodine (0.5 equiv) gave similar results to Method A [DIB (1.5 equiv), iodine (0.3 equiv)].

(21) (a) Zhdankin, V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (b) Togo, H.; Katohgi, M. *Synlett* **2001**, 565–581. (c) Suárez, E.; Rodríguez, M. S. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 440−454. (d) Brun, P.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, pp 367−426 and references cited therein. (e) The decarboxylation of amino acids can also be induced electrochemically: Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401–425. (f) Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689–1691.

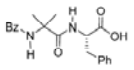
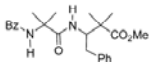
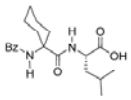
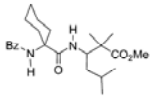
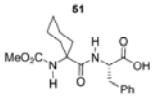
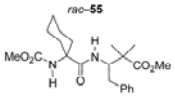
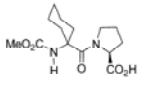
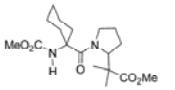
(22) (a) The ring adopts preferentially an envelope conformation, with the acetoxy group in a pseudoaxial position, and the nucleophile adds from the inside face of the envelope, giving the *cis* product. The attack from the outside face is disfavored, due to the eclipsing interactions developed between the substituents at C-2 and C-3 in the transition structure for the *trans* product. (b) For more information, see: Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209. (c) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149–14152. (d) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879–10884.

(23) (a) Boto, A.; Hernández, R.; León, Y.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 7796–7803. (b) The addition of methanol after the scission step was necessary to obtain good yields. If the fragmentation was followed by addition of the nucleophile and the Lewis acid, a complex product mixture was formed. The addition of methanol probably deactivated excess reagents from the first step and generated the stable *N,O*-acetal **43**, which was a good acyliminium precursor.

TABLE 3. One-Pot Decarboxylation−Oxidation−Mannich: Preparation of Modified Dipeptides



50–53 *rac*-**54–57**

starting peptides	products	method (%)[a]
 **50**	 *rac*-**54**	**A** (67%)
 **51**	 *rac*-**55**	**A** (58%)
 **52**	 *rac*-**56**	**A** (54%)
 **53**	 *rac*-**57**	**A** (44%)

[a] Method A: DIB (1.5 equiv), I_2 (0.3 equiv), *hν*, CH_2Cl_2, 4 h, then 0 °C, BF_3•OEt_2 (2 equiv), $Me_2C{=}C$(OTMS)OMe (5 equiv), 3 h.

those obtained with $CH_2{=}C$(OTBS)OMe. The resolution of the enantiomeric mixtures to form hybrid β,α-peptides will be commented on later.

To determine whether the previous reaction conditions were appropriate for more complex substrates, the direct modification of α-dipeptides to give α,β-hybrids was explored. In order to simplify the study, a nonstereoselective scission−Mannich process was first carried out using substrates **50**−**53** (Table 3), whose N-terminal α,α-disubstituted amino acids were not chiral. Using Method A [DIB (1.5 equiv), iodine (0.3 equiv) for the scission step], the process afforded α,β-dipeptides **54**−**57** in moderate to good yields. Since both amino acids were α,α-disubstituted, the resulting peptides were unusually hydrophobic.

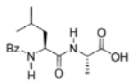
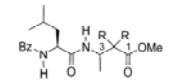
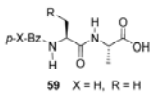
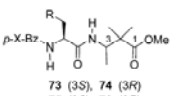
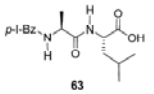
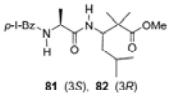
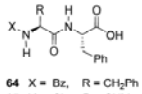
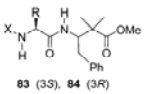
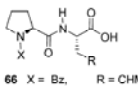
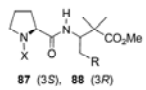
The stereoselective modification of dipeptides was then explored with substrates **58**−**68** (Table 4) which presented chiral N-terminal α-amino acids. Different reaction conditions were studied; only the optimized ones are described in the table. Due to differences in substrate solubility, reactivity, etc., the best conditions varied for each peptide.

Substrate **58** underwent the scission−oxidation reaction and was then treated with the unsubstituted ketene $CH_2{=}$C(OTBS)OMe, affording dipeptides **69** and **70** in moderate yield (36%) and 1:1 diastereomeric ratio. However, when the process was repeated with the disubstituted ketene $Me_2C{=}$C(OTMS)OMe, giving dipeptides **71** and **72**, the yield and the diastereomeric ratio increased (77%; **71**:**72**, 2:1). The X-ray analysis of the crystalline derivative **71** showed that the major product retained the "natural" configuration (3*S*).

Since we were especially interested in peptides with α-disubstituted β-amino acids, we carried out the remaining experiments with the α,α-dimethyl silyl ketene. The scission−Mannich

TABLE 4. Synthesis of Modified Dipeptides

58–68 **69–92**

starting peptides	products	method,[a] yield (%)
 **58**	 R = H: **69** (3*S*), **70** (3*R*) R = Me: **71** (3*S*), **72** (3*R*)	**A** **69** (18), **70** (18) **A** **71** (51), **72** (26)
 **59** X = H, R = H **60** X = I, R = H **61** X = H, R = Ph **62** X = I, R = Ph	 **73** (3*S*), **74** (3*R*) **75** (3*S*), **76** (3*R*) **77** (3*S*), **78** (3*R*) **79** (3*S*), **80** (3*R*)	**C** **73**:**74** 5:3, (73) **C** **75**:**76** 5:3, (74) **C** **77** (45), **78** (27) **C**[b] **79** (30), **80** (11)
 **63**	 **81** (3*S*), **82** (3*R*)	**A** **81** (31), **82** (15)
 **64** X = Bz, R = CH_2Ph **65** X = Cbz, R = $CHMe_2$	 **83** (3*S*), **84** (3*R*) **85** (3*S*), **86** (3*R*)	**B**[c] **83** (49), **84** (14) **A** **85**:**86**, 5:4, (30)
 **66** X = Bz, R = $CHMe_2$ **67** X = Bz-*p*-I, R = $CHMe_2$ **68** X = Cbz, R = Ph	 **87** (3*S*), **88** (3*R*) **89** (3*S*), **90** (3*R*) **91** (3*S*), **92** (3*R*)	**A** **87** (36), **88** (22) **A** **89** (43), **90** (25) **A** **91**:**92**, 7:5, (72)

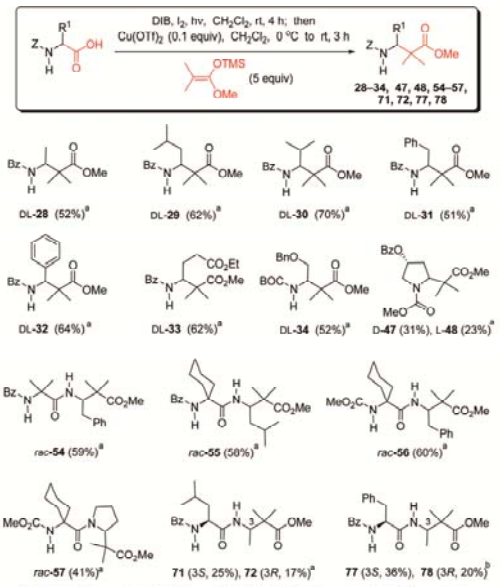
[a] Method A: DIB (1.5 equiv), I_2 (0.3 equiv). Method B: DIB (2.0 equiv), I_2 (0.5 equiv), I_2 (0.5 equiv). Method C: DIB (2 equiv), I_2 (1 equiv). [b] Method C, but using $CHCl_3$, reflux. [c] Method B, but using PhH, 26 °C.

of α-dipeptides **59**−**68** afforded the α,β-hybrids **73**−**92** in good global yields. The X-ray analysis of compounds **78**, **81**, **83**, and **90** showed that, in all of these cases, the major isomer possessed the "natural" configuration. In general, the minor isomers could be readily separated from the major ones. The isolation of the minor isomers is interesting for medicinal SAR studies in order to determine the influence of the stereochemistry in the biological activity.

Development of a Catalytic Mannich Step. In our previous reports,[2] the nucleophilic addition step required stoichiometric amounts of the Lewis acid (e.g., BF_3•OEt_2 or TMSOTf); if catalytic amounts were used, the process afforded very low product yields. For the first time, we report an efficient scission−nucleophilic addition process which only requires a catalytic amount of the Lewis acid. In the modified process (Scheme 3), the boron trifluoride (2 equiv) was replaced by the softer copper(II) triflate (0.1 equiv), affording satisfactory yields (41−70%) of the scission−Mannich products. In most cases, the yields were similar or slighty inferior to those obtained with the stoichiometric Lewis acid.

The catalytic process saves reagents and reduces the amount of acid waste to treat. Besides, this catalytic version will be further refined to allow the use of chiral Lewis acid catalysts,

SCHEME 3. Catalytic One-Pot Decarboxylation−Oxidation−Silyl Ketene Addition



[a] DIB (1.5 equiv), I_2 (0.3 equiv). [b] DIB (2.0 equiv), I_2 (1.0 equiv).

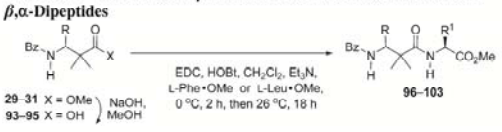
such as those derived from $Cu(OTf)_2$ and BOX ligands.[24] These catalysts, which are currently under study, will be used to increase the stereoselectivity in the generation of β-amino acids and hybrid α,β-dipeptides.

Separation of Isomer Mixtures: Enantiomeric β-Amino Acids or Diastereomeric α,β-Peptides. Once the reaction conditions were optimized, it was clear that the one-pot scission−oxidation−Mannich process was a useful methodology for the direct conversion of α- into β-amino acid derivatives. However, using simple α-amino acids as substrates gave racemic mixtures of β-amino esters since the scission generated an achiral acyliminium intermediate. These enantiomers were separated by formation of hybrid β,α-dipeptides (Table 5). Thus, the β-amino esters **29**−**31** were hydrolyzed to the acids **93**−**95**. Then, the β-homoleucine derivative **93** was coupled to a L-Phe•OMe residue with EDC/HOBt, affording the diastereomeric dipeptides **96** and **97**, which were easily separated (89% global yield). The stereochemistry of these compounds was determined by X-ray analysis.

In a similar way, the β-valine derivative **94** was coupled to L-Phe•OMe, giving dipeptides **98** and **99** (77% global yield), and the β-phenylalanine derivative **95** was coupled to L-Phe•OMe (affording the diastereomeric peptides **100** and **101**) or to L-Leu•OMe (giving dipeptides **102** and **103**). In both cases, good overall yields were obtained. The β,α-dipeptides were analogues of the potent antitumoral bestatin (Ubenimex). Since both possible diastereomers were obtained, it would be possible

(24) (a) Nakamura, S.; Nakashima, H.; Sugimoto, H.; Sano, H.; Hattori, M.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2008**, *14*, 2145–2152. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heilderberg, 1999. (d) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

TABLE 5. Resolution of β-Amino Acids: Formation of Modified β,α-Dipeptides



starting β-amino ester	acid (X = OH), yield (%)	amino ester for separation	dipeptides 96–103 (%)[a]
DL-29	DL-93 (90)	L-Phe•OMe	96 (3'S, 38%) + 97 (3'R, 41%)
DL-30	DL-94 (90)	L-Phe•OMe	98 (3'R, 39%), 99 (3'S, 38%)
DL-31	DL-95 (92)	L-Phe•OMe	100 (3'R, 35%), 101 (3'S, 41%)
		L-Leu•OMe	102 (3'R, 50%), 103 (3'S, 43%)

[a] The diastereomeric dipeptides were readily separated by chromatography on silica gel.

to study the influence of the β-amino acid configuration on the biological activity.

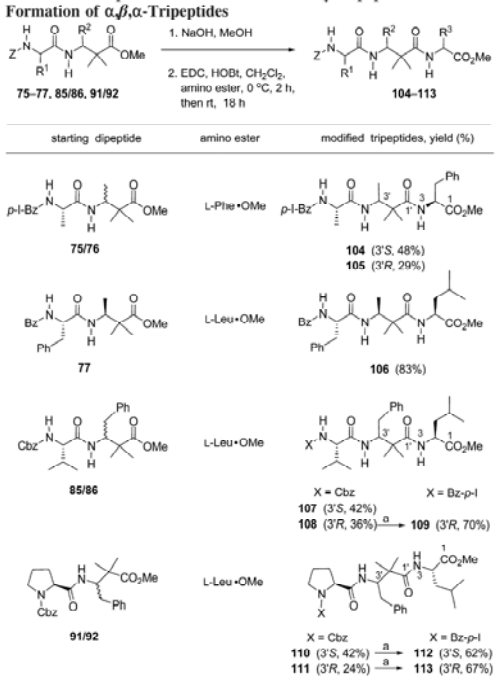
On the other hand, the diastereomeric α,β-peptides resulting from the scission-Mannich reaction were usually separated. In the few cases where unseparable diastereomer mixtures were obtained, we studied the formation of α,β,α-tripeptides (Table 6).

Thus, the mixture **75/76** was saponified and coupled to L-Phe•OMe, affording tripeptides **104** and **105** in 81% yield. These peptides were separated, and the X-ray analysis of compound **105** (Figure 2) showed that it possessed the "unnatural" configuration.

In a similar way, dipeptide **77** was transformed into tripeptide **106** in good yield, and the mixture of dipeptides **85/86** was converted into the α,β,α-tripeptides **107** and **108**. The latter underwent Cbz removal by hydrogenolysis and acylation with *p*-IBzCl, affording derivative **109**, which was suitable for X-ray analysis. Finally, the dipeptide mixture **91/92** was saponified and coupled to L-Leu•OMe, affording tripeptides **110** and **111**. Since their crystals were not appropriate for X-ray analysis, they were transformed into their *p*-iodobenzamides **112** and **113**. The X-ray analysis of compounds **112** and **113** showed that the major isomer presented the "natural" configuration.

These X-ray analysis also highlighted that, in the solid state, the α,β,α-tripeptides **105**, **109**, **112**, and **113** formed turns

TABLE 6. Separation of Diastereomeric α,β-Dipeptides: Formation of α,β,α-Tripeptides



[a] H_2, Pd (10% on carbon), THF/H_2O, then $NaHCO_3$, *p*-I-BzCl.

(Figure 2). In α-peptides, the generation of turns is favored by the presence of certain amino acids, such as proline, glycine, D-, or *N*-alkyl amino acids; in their absence, extended conformations are adopted.[25] None of these amino acids is present in the α,β-hybrids **105** and **109**, so the formation of an expanded β-turn is due to the introduction of the α,α-disubstituted β-amino acid.

The tripeptides whose β-amino acid unit has the "unnatural" configuration (compounds **105**, **109**, and **113**) adopted an expanded β-turn,[19] between the CO_i (benzamide) and the NH_{i+3} groups. Interestingly, these interactions are reinforced by a hydrogen bond between the NH_{i+2} group (from the β-amino acid) and the CO_{i+3} group (from the C-terminal amino acid).

In the case of peptide **112**, whose β-amino acid presents the "natural" configuration, the molecular conformation of the peptide is different. A hydrogen bond was formed between the β-amino acid CO and NH groups. An additional interaction was observed between the proline nitrogen lone pairs and the β-amino acid amine proton.

These interactions could be useful to design new peptide catalysts,[26] and we are currently carrying out additional studies to clarify the conformational effects in solution.

Conclusion

In summary, we have developed a one-pot radical scission−oxidation−Mannich process to transform α-amino acid into β-amino acid derivatives. This method is an interesting alternative to other homologation procedures, such as the Arndt−Eistert reaction, since it allows the easy generation of α,α-disubstituted β-amino esters. Some β-amino acid products were coupled to α-amino esters to form hybrid β,α-dipeptides since these compounds often display interesting biological activities.

Besides, this procedure allows the *selective modification* of the C-terminal residue in small peptides, which could be very useful in medicinal chemistry (a single bioactive α-peptide could be transformed into a library of hybrid α,β-peptides).

The method is a *sequential* process initiated by a *tandem* radical fragmentation−oxidation reaction, which generates an acyliminium ion. This intermediate reacts with silyl ketenes in the presence of a Lewis acid, affording β-amino esters or α,β-dipeptide derivatives. The process is operationally simple and saves materials and time since no purification of the intermediates is needed. The mild reaction conditions are compatible with most functional groups. Moreover, in the scission step, only a catalytic amount of iodine is needed.

When α-dipeptides were used as substrates, the N-terminal residue acted as a chiral auxiliary, and the reaction was stereoselective (predominating the isomer with the "natural" configuration). Some of the resulting α,β-dipeptides were transformed into α,β,α-tripeptides, whose molecular conformation was determined by the configuration of the β-amino acid unit. The "natural" configuration favored hydrogen bonds between the β-amino acid CO and NH groups, and an additional interaction was observed between the proline nitrogen lone pairs and the β-amino acid amine proton.

Interestingly, the unnatural configuration led to the formation of β-turns in the solid state, a structural feature found in some efficient peptide catalysts. Since two hybrid peptides (**105** and **109**) lacked turn-inducing α-amino acids (such as proline, glycine, D-, or *N*-alkyl amino acids), the generation of an expanded β-turn is probably due to the introduction of the α,α-disubstituted β-amino acid.

Finally, a new version of the scission−Mannich process was developed, which only required a catalytic amount of the Lewis acid [thus, boron trifluoride (2 equiv) was replaced by copper triflate (0.1 equiv)]. The modified process, which saves expensive reagents and reduces the acidic waste, took place in moderate to good yields (40−70%). The generation of chiral catalysts from $Cu(OTf)_2$ and chiral ligands is currently under study in order to prepare β-amino acids in high enantiomeric excess and to increase the stereoselectivity in the synthesis of α,β-hybrid peptides.

Experimental Section

General Procedures for the One-Pot Scission−Oxidation−Alkylation Sequence. Method A. To a solution of the starting amino acid or peptide (0.2 mmol) in dry dichloromethane (6 mL) were added iodine (15 mg, 0.06 mmol) and (diacetoxyiodo)benzene (DIB) (97 mg, 0.3 mmol). The reaction mixture was stirred at 26 °C for 4 h, under irradiation with visible light. Then the solution was cooled to 0 °C, and 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (218 μL, 188 mg, 1.0 mmol) or methyl trimethylsilyldim-

(25) (a) Sewald, N.; Jakubke, H. D. *Peptides: Chemistry and Biology*, Wiley-VCH: Weinheim, Germany, 2002; pp 311−337. (b) For applications, see: Blanchette, J. P.; Ferland, P.; Voyer, N. *Tetrahedron Lett.* **2007**, *48*, 4929–4933.

(26) (a) For reviews, see: Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812. (b) Berkessel, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3677–3679. (c) For recent work on the subject, see: Sánchez-Roselló, M.; Puchlopek, A. L. A.; Morgan, A. J.; Miller, S. J. *J. Org. Chem.* **2008**, *73*, 1774–1782. (d) Revell, J. D.; Wennemers, H. *Adv. Synth. Catal.* **2008**, *350*, 1046–1052. (e) Tsandi, E.; Kokotos, C. G.; Kousidon, S.; Ragoussis, V.; Kokotos, G. *Tetrahedron* **2009**, *65*, 1444–1449, and references cited therein.

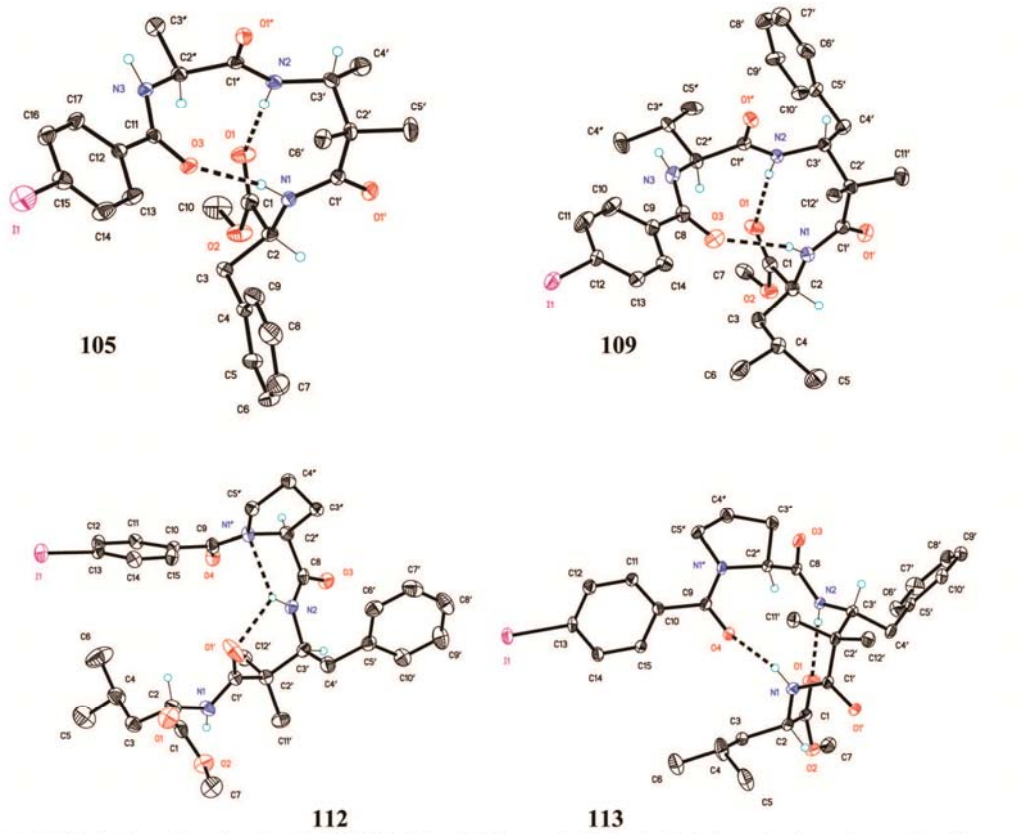


FIGURE 2. Molecular conformation of peptides **105**, **109**, **112**, and **113** in crystals. Intramolecular hydrogen bonds are shown as dotted lines.

ethylketene acetal (203 μL, 174 mg, 1.0 mmol) was injected, followed by dropwise addition of BF_3•OEt_2 (51 μL, 57 mg, 0.4 mmol). The mixture was allowed to reach room temperature and stirred for 3 h; then it was poured into 10% aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1:1, 10 mL) and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate mixtures) to give the products.

Method B. To a solution of the starting amino acid (0.2 mmol) in dry dichloromethane (6 mL), under nitrogen atmosphere, were added iodine (25 mg, 0.1 mmol) and (diacetoxyiodo)benzene (DIB) (129 mg, 0.4 mmol) and treated as in Method A.

Method C. To a solution of the starting amino acid or peptide (0.2 mmol) in dry dichloromethane (6 mL) were added iodine (51 mg, 0.2 mmol) and (diacetoxyiodo)benzene (DIB) (129 mg, 0.4 mmol) and treated as in Method A.

Method D. To a solution of starting material (0.2 mmol) in dry acetonitrile (6 mL) were added iodine (102 mg, 0.4 mmol) and (diacetoxyiodo)benzene (DIB) (129 mg, 0.4 mmol). The reaction mixture was stirred at 24−26 °C for 4 h, under irradiation with visible light. Then dry methanol (1 mL) was added, and the stirring was continued for 1 h. The mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum, and the residue was dissolved in dry acetonitrile (6 mL). The solution was cooled to 0 °C, and 1-*tert*-(dimethylsilyloxy)-1-methoxyethene (218 μL, 188 mg, 1.0 mmol) or methyl trimethylsilyldimethylketene acetal (203 μL, 174 mg, 1.0 mmol) was injected, followed by dropwise addition of BF_3•OEt_2 (51 μL, 57 mg, 0.4 mmol). The mixture was allowed to reach room temperature and stirred for 3 h; then it was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate mixtures) to give the products.

One-Pot Catalytic Scission−Oxidation−Alkylation Sequence. The procedures were similar to previously described Methods A−D, but replacing boron trifluoride by copper(II) triflate (0.1 equiv).

Resolution of *β*-Amino Acids. Formation of Modified Dipeptides. General Procedure for the Generation of Acids 93−95. A solution of esters **29**, **30**, or **31** (0.20 mmol) in methanol (6 mL) at 0 °C was treated with 2 N aqueous NaOH (2 mL). The reaction mixture was allowed to reach rt and stirred overnight. Then it was cooled to 0 °C, poured into 5% aqueous HCl, and extracted with EtOAc. The organic layer was dried and evaporated as usual.

Decarboxylation of Dipeptides Oxidation−Alkylation. The process was carried out according to previously described Method A, B, or C.

Separation of Dipeptides by Formation of Tripeptides: *N*-(*p*-Iodobenzoyl)-L-alanyl-[α,α-dimethyl-L-*β*-homoalanyl]-L-phenylalanine Methyl Ester (104) and *N*-(*p*-Iodobenzoyl)-L-alanyl-[α,α-dimethyl-D-*β*-homoalanyl]-L-phenylalanine Methyl Ester (105). To a solution of the mixture of dipeptides **75/76** (118 mg, 0.26 mmol) in methanol (6 mL) at 0 °C was slowly added 2

N aqueous NaOH (3 mL). The reaction mixture was allowed to reach rt and stirred for 64 h, then it was cooled to 0 °C, diluted with water, poured into 5% HCl, and extracted with EtOAc. The organic layer was dried and evaporated, and the residue was dissolved in dry CH_2Cl_2 (3 mL) and treated with L-phenylalanine methyl ester hydrochloride (57 mg, 0.26 mmol). The solution was cooled to 0 °C, and Et_3N (37 μL, 27 mg, 0.26 mmol), EDC (56 mg, 0.29 mmol), and HOBt (39 mg, 0.29 mmol) were added. The reaction mixture was stirred at 0 °C for 2 h, then it was allowed to reach room temperature and stirred for 18 h and finally was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. After usual drying and solvent removal, the residue was purified by rotatory chromatography (hexanes/EtOAc, 3:2 and 1:1), affording compounds **104** (48%) and **105** (29%).

Compound 104: Syrup; $[\alpha]_D$ +53 (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 3438, 3401, 3089, 3062, 1738, 1652, 1503, 1477 cm^{-1}; ^1H NMR (500 MHz) δ_H 1.08 (3H, d, *J* = 6.6 Hz), 1.14 (3H, s), 1.15 (3H, s), 1.49 (3H, d, *J* = 7.0 Hz), 3.08 (1H, dd, *J* = 6.3, 13.9 Hz), 3.17 (1H, dd, *J* = 6.0, 13.9 Hz), 3.76 (3H, s), 3.89 (1H, dddd, *J* = 6.9, 6.9, 6.9, 9.3 Hz), 4.59 (1H, dddd, *J* = 7.0, 7.0, 7.0, 7.0 Hz), 4.79 (1H, ddd, *J* = 6.0, 6.3, 7.3 Hz), 6.16 (1H, d, *J* = 7.6 Hz), 7.08 (2H, d, *J* = 6.6 Hz), 7.12 (1H, d, *J* = 7.0 Hz), 7.25−7.35 (3H, m), 7.42 (1H, d, *J* = 9.2 Hz), 7.54 (2H, d, *J* = 8.5 Hz), 7.76 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (125.7 MHz) δ_C 16.7 (CH_3), 19.3 (CH_3), 22.7 (CH_3), 24.8 (CH_3), 37.4 (CH_2), 45.0 (C), 49.6 (CH), 52.4 (CH_3), 52.7 (CH), 52.8 (CH), 98.5 (C), 127.3 (CH), 128.7 (4 × CH), 129.1 (2 × CH), 133.6 (C), 135.6 (C), 137.6 (2 × CH), 165.9 (C), 171.3 (C), 171.9 (C), 176.3 (C); MS *m/z* (rel intensity) 593 (M^+, 2), 319 (M^+ − CH(Me)NHBz-*p*-I, 55), 249 (M^+ + H − CH(Me)NHCOCH(Me)NHBz-*p*-I, 59), 231 ([*p*-I-PhCO]$^+$, 100); HRMS calcd for $C_{26}H_{32}IN_3O_5$, 593.1387; found, 593.1407; calcd for C_7H_4IO, 230.9307; found, 230.9301. Anal. Calcd for $C_{26}H_{32}IN_3O_5$: C, 52.62; H, 5.43; N, 7.08. Found: C, 52.79; H, 5.63; N, 7.09. **Compound 105**: Crystalline solid; mp 143−144 °C (from EtOAc/*n*-hexane); $[\alpha]_D$ +33 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3437, 3370, 3090, 3068, 1730, 1655, 1507, 1477 cm^{-1}; ^1H NMR (500 MHz) δ_H = 1.11 (3H, d, *J* = 7.0 Hz), 1.14 (3H, s), 1.19 (3H, s), 1.55 (3H, d, *J* = 7.3 Hz), 3.18 (1H, dd, *J* = 9.9, 13.9 Hz), 3.22 (1H, dd, *J* = 5.4, 13.9 Hz), 3.79 (3H, s), 4.00 (1H, dddd, *J* = 6.6, 6.6, 6.6, 10.1 Hz), 4.43 (1H, dddd, *J* = 7.0, 7.0, 7.0, 7.0 Hz), 4.78 (1H, ddd, *J* = 5.4, 8.2, 9.8 Hz), 7.22 (1H, d, *J* = 7.9 Hz), 7.25 (1H, m), 7.34−7.36 (4H, m), 7.42 (2H, d, *J* = 8.6 Hz), 7.62 (2H, d, *J* = 8.5 Hz), 7.67 (1H, d, *J* = 10.1 Hz), 7.83 (1H, d, *J* = 6.3 Hz); ^{13}C NMR (125.7 MHz) δ_C 16.3 (CH_3), 17.2 (CH_3), 22.5 (CH_3), 23.9 (CH_3), 36.5 (CH_2), 46.7 (C), 51.2 (CH), 52.0 (CH), 52.7 (CH_3), 54.5 (CH), 98.7 (C), 126.9 (CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.2 (2 × CH), 132.5 (C), 137.0 (C), 137.5 (2 × CH), 166.7 (C), 172.7 (C), 174.7 (C), 175.2 (C); MS *m/z* (rel intensity) 593 (M^+, 2), 249 (M^+ + H − CH(Me)NHCOCH(Me)NHBz-*p*-I, 43), 231 ([*p*-I-PhCO]$^+$, 100); HRMS calcd for $C_{26}H_{32}IN_3O_5$, 593.1387; found, 593.1467; calcd for C_7H_4IO, 230.9307; found, 230.9318. Anal. Calcd for $C_{26}H_{32}IN_3O_5$: C, 52.62; H, 5.43; N, 7.08. Found: C, 52.62; H, 5.63; N, 6.99. **X-ray Analysis**: $C_{27}H_{33}Cl_3IN_3O_5$, M_r = 712.81, colorless plate crystal (0.24 × 0.19 × 0.11 mm^3) from EtOAc/*n*-hexane (mp 143−144 °C); orthorhombic, space group $P2_12_12$ (no. 18), *a* = 34.192(2) Å, *b* = 8.269(1) Å, *c* = 11.228(1) Å, *V* = 3174.5(5) $Å^3$, *Z* = 4, ρ_{calcd} = 1.491 g cm^{-3}, *F*(000) = 1491, μ = 1.300 mm^{-1}; 57 660 measured reflections, of which 4044 were unique (R_{int} = 0.0286); 420 refined parameters, final R_1 = 0.0382, for reflections with $I > 2\sigma(I)$, wR_2 = 0.1136 (all data), GOF = 1.030. Flack parameter = 0.015(15). The max/min residual electron density: +0.589/−0.449 e•$Å^{-3}$.

***N*-(Benzoyl)-L-phenylalanyl-[α,α-dimethyl-L-β-homoalanyl]-L-leucine Methyl Ester (106).** It was synthesized from dipeptide **77** following the previous coupling procedure. The residue was purified by rotatory chromatography (hexanes/EtOAc, 3:2), affording compound **106** (83%) as a crystalline solid: mp 97−98 °C (from EtOAc/*n*-hexane); $[\alpha]_D$ +10 (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) 3437, 3382, 3088, 3067, 1740, 1654, 1508, 1483 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.89 (3H, d, *J* = 6.3 Hz), 0.92 (3H, d, *J* = 6.3 Hz), 0.99 (3H, s), 1.07 (3H, d, *J* = 6.6 Hz), 1.20 (3H, s), 1.52−1.66 (3H, m), 3.19 (1H, dd, *J* = 7.3, 13.9 Hz), 3.23 (1H, ddd, *J* = 6.3, 13.9 Hz), 3.71 (3H, s), 3.87 (1H, dddd, *J* = 6.6, 6.6, 6.6, 9.2 Hz), 4.46 (1H, ddd, *J* = 5.0, 8.0, 8.5 Hz), 4.87 (1H, ddd, *J* = 6.9, 7.0, 7.3 Hz), 6.04 (1H, d, *J* = 7.9 Hz), 6.71 (1H, d, *J* = 7.3 Hz), 7.21 (1H, m), 7.26−7.30 (4H, m), 7.40 (2H, dd, *J* = 7.3, 7.9 Hz), 7.48 (1H, dd, *J* = 7.3, 7.6 Hz), 7.51 (1H, d, *J* = 8.9 Hz), 7.71 (2H, d, *J* = 7.8 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 16.7 (CH_3), 21.9 (CH_3), 22.7 (CH_3), 22.9 (CH_3), 24.6 (CH_3), 25.0 (CH), 38.6 (CH_2), 41.1 (CH_2), 44.7 (C), 50.7 (CH), 52.3 (CH_3), 53.0 (CH), 55.0 (CH), 127.0 (3 × CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.4 (2 × CH), 131.6 (CH), 134.1 (C), 136.5 (C), 167.1 (C), 170.1 (C), 173.3 (C), 176.6 (C); MS *m/z* (rel intensity) 509 (M^+, 2), 418 (M^+ − CH_2Ph, 2), 365 (M^+ − NHCH(CH_2CHMe_2)CO_2Me, 4), 105 ([PhCO]$^+$, 100), 77 ([Ph]$^+$, 25); HRMS calcd for $C_{29}H_{39}N_3O_5$, 509.2890; found, 509.2880; calcd for C_7H_5O, 105.0340; found, 105.0339. Anal. Calcd for $C_{29}H_{39}N_3O_5$: C, 68.34; H, 7.71; N, 8.25. Found: C, 68.41; H, 7.89; N, 8.18.

***N*-(Benzyloxycarbonyl)-L-valyl-[α,α-dimethyl-L-β-homophenylalanyl]-L-leucine Methyl Ester (107) and *N*-(Benzyloxycarbonyl)-L-valyl-[α,α-dimethyl-D-β-homophenylalanyl]-L-leucine Methyl Ester (108).** They were synthesized from a mixture of dipeptides **85/86** following the previous coupling procedure. The residue was purified by rotatory chromatography (hexanes/EtOAc, 7:3 and 1:1), affording compounds **107** (42%) and **108** (36%). **Compound 107**: Syrup; $[\alpha]_D$ −49 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3435, 3090, 3067, 1728, 1667, 1499 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.64 (3H, d, *J* = 6.6 Hz), 0.83 (3H, d, *J* = 6.6 Hz), 0.94 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 1.24 (3H, s), 1.34 (3H, s), 1.55−1.75 (3H, m), 2.02 (1H, m), 2.54 (1H, dd, *J* = 11.3, 13.3 Hz), 2.97 (1H, dd, *J* = 4.1, 14.2 Hz), 3.76 (3H, s), 3.87 (1H, dd, *J* = 7.9, 7.9 Hz), 4.20 (1H, ddd, *J* = 3.8, 10.1, 10.4 Hz), 4.58 (1H, ddd, *J* = 5.4, 8.2, 8.5 Hz), 5.01 (1H, d, *J* = 8.2 Hz), 5.10 (2H, s), 6.18 (1H, d, *J* = 7.6 Hz), 7.06−7.15 (6H, m), 7.31−7.38 (5H, m); ^{13}C NMR (125.7 MHz) δ_C 17.1 (CH_3), 19.3 (CH_3), 21.9 (CH_3), 22.7 (CH_3), 23.4 (CH_3), 24.8 (CH_3), 25.0 (CH), 30.4 (CH), 37.2 (CH_2), 41.0 (CH_2), 45.6 (C), 50.8 (CH), 52.4 (CH_3), 57.7 (CH), 60.7 (CH), 66.9 (CH_2), 126.2 (CH), 128.1 (2 × CH), 128.2 (3 × CH), 128.5 (2 × CH), 129.2 (2 × CH), 136.3 (C), 138.4 (C), 156.2 (C), 170.6 (C), 173.4 (C), 176.8 (C); MS *m/z* (rel intensity) 567 (M^+, 1), 476 (M^+ − CH_2Ph, 6), 368 (M^+ − CH_2Ph − $HOCH_2Ph$, 12), 91 ([CH_2Ph]$^+$, 100); HRMS calcd for $C_{32}H_{45}N_3O_6$, 567.3308; found, 567.3286; calcd for C_7H_7, 91.0548; found, 91.0547. Anal. Calcd for $C_{32}H_{45}N_3O_6$: C, 67.70; H, 7.99; N, 7.40. Found: C, 67.74; H, 8.11; N, 7.25. **Compound 108**: Syrup; $[\alpha]_D$ +19 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 3438, 3374, 3336, 1725, 1710, 1680, 1658, 1508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.26 (3H, d, *J* = 6.7 Hz), 0.76 (3H, d, *J* = 6.9 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 1.13 (3H, s), 1.36 (3H, s), 1.60−1.69 (2H, m), 1.76−1.82 (1H, m), 1.92 (1H, ddd, *J* = 4.5, 11.7, 13.6 Hz), 2.39 (1H, dd, *J* = 12.3, 14.5 Hz), 3.12 (1H, dd, *J* = 3.5, 14.5 Hz), 3.33 (1H, dd, *J* = 7.9, 8.8 Hz), 3.82 (3H, s), 4.22 (1H, ddd, *J* = 3.5, 10.4, 12.3 Hz), 4.70 (1H, ddd, *J* = 4.1, 8.5, 11.7 Hz), 5.01 (1H, d, *J* = 12.6 Hz), 5.08 (1H, d, *J* = 12.3 Hz), 5.18 (1H, d, *J* = 7.9 Hz), 7.10−7.16 (4H, m), 7.21 (2H, dd, *J* = 7.3, 7.3 Hz), 7.27−7.35 (5H, m), 7.51 (1H, d, *J* = 10.4 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 18.4 (CH_3), 18.9 (CH_3), 21.1 (CH_3), 23.1 (CH_3), 23.2 (CH_3), 23.3 (CH_3), 25.2 (CH), 29.3 (CH), 35.7 (CH_2), 39.1 (CH_2), 47.4 (C), 51.7 (CH), 52.7 (CH_3), 57.4 (CH), 62.8 (CH), 66.9 (CH_2), 126.1 (CH), 127.7 (2 × CH), 128.2 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 129.2 (2 × CH), 136.1 (C), 138.9 (C), 156.8 (C), 171.7 (C), 175.3 (C), 176.4 (C); MS *m/z* (rel intensity) 567 (M^+, 1), 476 (M^+ − CH_2Ph, 2), 368 (M^+ − CH_2Ph − $HOCH_2Ph$, 9), 91 ([CH_2Ph]$^+$, 100); HRMS calcd for $C_{32}H_{45}N_3O_6$, 567.3308; found, 567.3311; calcd for C_7H_7, 91.0548; found, 91.0549. Anal. Calcd for $C_{32}H_{45}N_3O_6$: C, 67.70; H, 7.99; N, 7.40. Found: C, 67.83; H, 7.95; N, 7.15.

***N*-(*p*-Iodobenzoyl)-L-valyl-[α,α-dimethyl-D-β-homophenylalanyl]-L-leucine Methyl Ester (109).** To a solution of tripeptide **108**

(38 mg, 0.07 mmol) in a biphasic mixture (2:1 THF/H_2O, 9 mL) was added Pd (10% on carbon, 25 mg), and the reaction was stirred at room temperature and under hydrogen atmosphere (1 atm) for 16 h. Then the mixture was filtered through Celite, and the filtrate was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$ (6 mL) and 4-iodobenzoyl chloride (23 mg, 0.09 mmol). The mixture was allowed to reach rt and stirred for 16 h, then it was poured into 5% aqueous HCl and extracted with EtOAc. After usual drying, the residue were purified by rotatory chromatography (hexanes/EtOAc, 85:15), giving product **109** (31 mg, 70%) as a crystalline solid: mp 131−132 °C (from EtOAc/*n*-pentane); $[\alpha]_D$ +44 (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 3434, 3359, 3089, 1726, 1676, 1654, 1514 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.22 (3H, d, *J* = 6.7 Hz), 0.85 (3H, d, *J* = 6.7 Hz), 0.98 (3H, d, *J* = 6.3 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 1.20 (3H, s), 1.38 (3H, s), 1.66 (1H, ddd, *J* = 4.1, 10.1, 13.6 Hz), 1.84−1.95 (2H, m), 2.05 (1H, m), 2.46 (1H, dd, *J* = 12.7, 14.5 Hz), 3.15 (1H, dd, *J* = 3.5, 14.5 Hz), 3.69 (1H, dd, *J* = 7.6, 10.1 Hz), 3.83 (3H, s), 4.27 (1H, ddd, *J* = 3.5, 10.4, 12.5 Hz), 4.72 (1H, ddd, *J* = 3.8, 8.2, 12.1 Hz), 7.13 (1H, dd, *J* = 6.9, 7.0 Hz), 7.16−7.24 (4H, m), 7.415 (2H, d, *J* = 8.5 Hz), 7.416 (1H, d, *J* = 8.5 Hz), 7.55 (1H, d, *J* = 8.5 Hz), 7.65 (2H, d, *J* = 8.5 Hz), 7.80 (1H, d, *J* = 10.7 Hz); ^{13}C NMR (125.7 MHz) δ_C 18.3 (CH_3), 19.5 (CH_3), 21.1 (CH_3), 23.1 (CH_3), 23.2 (CH_3), 23.5 (CH_3), 25.2 (CH), 28.7 (CH), 35.6 (CH_2), 39.0 (CH_2), 47.4 (C), 51.9 (CH), 52.6 (CH_3), 57.4 (CH), 62.5 (CH), 98.9 (C), 126.1 (CH), 128.3 (2 × CH), 128.7 (2 × CH), 129.1 (2 × CH), 132.7 (C), 137.6 (2 × CH), 138.9 (C), 167.2 (C), 172.1 (C), 175.3 (C), 176.5 (C); MS *m/z* (rel intensity) 664 (M^+ + H, <1), 519 (M^+ − $NHCH(CH_2CHMe_2)CO_2Me$, 4), 449 (M^+ − $C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 3), 330 ($M^+$ − $NHCH(CH_2Ph)$ − $C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 11), 302 ($M^+$ − $CONHCH(CH_2Ph)$ − $C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 17), 243 ($M^+$ − HOMe − $CHMe_2$ − NHCOCH(CHMe$_2$)NH-Bz-*p*-I, 100); HRMS calcd for $C_{31}H_{40}IN_3O_5$, 664.2247; found, 664.2260; calcd for $C_{15}H_{17}NO_2$, 243.1259; found, 243.1249. Anal. Calcd for $C_{31}H_{42}IN_3O_5$: C, 56.11; H, 6.38; N, 6.33. Found: C, 56.42; H, 6.60; N, 6.07. **X-ray Analysis**: $C_{31}H_{42}IN_3O_5$, M_r = 663.58, colorless prism crystal (0.42 × 0.23 × 0.22 mm^3) from EtOAc/*n*-pentane (mp 131−132 °C); trigonal, space group *R*3 (no. 146), *a* = *b* = 44.8052(13) Å, *c* = 8.8254(4) Å, γ = 120°, *V* = 15343.4(9) Å^3, *Z* = 18, ρ_{calcd} = 1.293 g cm^{-3}, *F*(000) = 6156, μ = 0.978 mm^{-1}; 91 627 measured reflections, of which 13 671 were unique (R_{int} = 0.0921); 783 refined parameters, final R_1 = 0.0442, for reflections with $I > 2\sigma(I)$, wR_2 = 0.1238 (all data), GOF = 1.028. Flack parameter = −0.033(13). The max/min residual electron density: +0.645/−0.750 e·Å^{-3}.

***N*-(Benzyloxycarbonyl)-L-prolyl-[α,α-dimethyl-L-β-homophenylalanyl]-L-leucine Methyl Ester (110) and *N*-(Benzyloxycarbonyl)-L-prolyl-[α,α-dimethyl-D-β-homophenylalanyl]-L-leucine Methyl Ester (111).** They were synthesized from a mixture of dipeptides **91**/**92** following the previous coupling procedure. The residue was purified by rotatory chromatography (hexanes/EtOAc, 75:25 and 3:2), affording compounds **110** (42%) and **111** (24%).

Compound 110: Syrup; $[\alpha]_D$ +14 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3448, 3415, 3090, 3067, 1739, 1696, 1684, 1664 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ_H 0.96 (3H, d, *J* = 6.2 Hz), 0.97 (3H, d, *J* = 6.3 Hz), 1.20 (3H, s), 1.30 (3H, s), 1.37 (1H, m), 1.55−1.75 (4H, m), 1.77−1.85 (2H, m), 2.52 (1H, dd, *J* = 11.4, 14.2 Hz), 3.00 (1H, dd, *J* = 4.1, 14.2 Hz), 3.26 (1H, ddd, *J* = 3.5, 9.3, 9.3 Hz), 3.37 (1H, ddd, *J* = 8.2, 8.5, 9.8 Hz), 3.75 (3H, s), 4.23 (1H, dd, *J* = 5.7, 5.7 Hz), 4.34 (1H, ddd, *J* = 4.1, 10.1, 11.0 Hz), 4.59 (1H, ddd, *J* = 5.4, 7.9, 8.5 Hz), 5.10 (1H, d, *J* = 12.3 Hz), 5.20 (1H, d, *J* = 12.6 Hz), 6.15 (1H, br b), 7.08 (1H, br b), 7.12 (1H, m), 7.13 (2H, d, *J* = 7.3 Hz), 7.18 (2H, dd, *J* = 6.3, 8.2 Hz), 7.29 (1H, dd, *J* = 6.9, 7.0 Hz), 7.30−7.40 (4H, m); ^{13}C NMR (125.7 MHz) δ_C 22.1 (CH_3), 22.8 (CH_3), 23.4 (CH_3), 23.5 (CH_3), 23.7 (CH_2), 25.3 (CH), 29.2 (CH_2), 37.2 (CH_2), 41.4 (CH_2), 46.5 (C), 47.1 (CH_2), 51.2 (CH), 52.1 (CH_3), 56.7 (CH), 61.1 (CH), 67.4 (CH_2), 126.2 (CH), 128.1 (2 × CH), 128.15 (CH), 128.2 (2 × CH), 128.5 (2 × CH), 129.2 (2 × CH), 136.7 (C), 138.9 (C), 155.8 (C), 171.4 (C), 173.4 (C), 176.3 (C); MS *m/z* (rel intensity) 566 (M^+ + H, 3), 474 (M^+ − CH_2Ph, 10), 303 (M^+ + H − CH_2Ph − $CONHCH(CH_2CHMe_2)CO_2Me$, 19), 215 ($C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$ + H, 28), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{32}H_{44}N_3O_6$, 566.3230; found, 566.3239; calcd for C_7H_7, 91.0548; found, 91.0544. Anal. Calcd for $C_{32}H_{43}N_3O_6$: C, 67.94; H, 7.66; N, 7.43. Found: C, 68.19; H, 7.76; N, 7.14. **Compound 111**: Syrup; $[\alpha]_D$ +65 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) ν 3364, 3090, 3067, 1726, 1685, 1657, 1552 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.94 (3H, d, *J* = 6.6 Hz), 0.96 (3H, d, *J* = 6.3 Hz), 1.25 (3H, s), 1.35 (3H, s), 1.55 (1H, m), 1.61 (1H, ddd, *J* = 4.1, 9.4, 13.5 Hz), 1.68−1.91 (4H, m), 2.08 (1H, m), 2.44 (1H, dd, *J* = 12.3, 14.2 Hz), 3.10 (1H, dd, *J* = 3.5, 14.5 Hz), 3.40 (1H, ddd, *J* = 6.8, 7.0, 10.4 Hz), 3.54 (1H, ddd, *J* = 5.1, 7.3, 10.4 Hz), 3.80 (3H, s), 3.88 (1H, dd, *J* = 4.8, 7.3 Hz), 4.09 (1H, ddd, *J* = 3.5, 11.5, 12.0 Hz), 4.63 (1H, ddd, *J* = 3.8, 8.2, 11.7 Hz), 5.05 (1H, d, *J* = 12.6 Hz), 5.08 (1H, d, *J* = 12.6 Hz), 7.13−7.17 (3H, m), 7.24 (2H, dd, *J* = 7.6, 7.6 Hz), 7.27−7.34 (5H, m), 7.38 (1H, d, *J* = 8.2 Hz), 7.55 (1H, d, *J* = 10.4 Hz); ^{13}C NMR (100.6 MHz) δ_C 21.1 (CH_3), 22.8 (CH_3), 23.2 (CH_3), 23.8 (CH_3), 24.8 (CH_2), 25.2 (CH), 29.2 (CH_2), 35.6 (CH_2), 39.0 (CH_2), 46.9 (CH_2), 47.3 (C), 51.9 (CH), 52.6 (CH_3), 56.9 (CH), 61.1 (CH), 66.8 (CH_2), 125.8 (CH), 127.5 (2 × CH), 127.9 (CH), 128.0 (2 × CH), 128.4 (2 × CH), 129.0 (2 × CH), 136.5 (C), 139.2 (C), 154.8 (C), 172.0 (C), 175.6 (C), 176.6 (C); MS *m/z* (rel intensity) 566 (M^+ + H, 7), 474 (M^+ − CH_2Ph, 16), 303 (M^+ + H − CH_2Ph − $CONHCH(CH_2CHMe_2)CO_2Me$, 41), 215 ($C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$ + H, 53), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{32}H_{44}N_3O_6$, 566.3230; found, 566.3215; calcd for C_7H_7, 91.0548; found, 91.0547. Anal. Calcd for $C_{32}H_{43}N_3O_6$: C, 67.94; H, 7.66; N, 7.43. Found: C, 67.92; H, 7.72; N, 7.29.

***N*-(*p*-Iodobenzoyl)-L-prolyl-[α,α-dimethyl-L-β-homophenylalanyl]-L-leucine Methyl Ester (112).** To a solution of tripeptide **110** (98 mg, 0.17 mmol) in a biphasic mixture (2:1 THF/H_2O, 15 mL) was added Pd (10% on carbon, 50 mg), and the reaction was stirred at room temperature and under hydrogen atmosphere (1 atm) for 16 h. Then the mixture was filtered through Celite, and the filtrate was cooled to 0 °C and treated with saturated aqueous $NaHCO_3$ (6 mL) and 4-iodobenzoyl chloride (69 mg, 0.26 mmol). The mixture was allowed to reach rt and stirred for 16 h, then it was poured into 5% aqueous HCl and extracted with EtOAc. After usual drying and purification by rotatory chromatography (hexanes/EtOAc, 3:2), product **112** was isolated (71 mg, 62%) as a crystalline solid: mp 169−170 °C (from EtOAc/*n*-pentane); $[\alpha]_D$ +80 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3447, 3362, 1739, 1659, 1504 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ_H 0.86 (3H, d, *J* = 6.2 Hz), 0.91 (3H, d, *J* = 6.3 Hz), 1.26 (3H, s), 1.34 (3H, s), 1.50−1.65 (5H, m), 1.80 (1H, m), 1.94 (1H, m), 2.66 (1H, dd, *J* = 11.5, 13.6 Hz), 3.02 (1H, dd, *J* = 4.5, 13.9 Hz), 3.28−3.36 (2H, m), 3.74 (3H, s), 4.29 (1H, ddd, *J* = 4.1, 9.8, 10.7 Hz), 4.47 (1H, ddd, *J* = 6.9, 7.2, 7.9 Hz), 4.57 (1H, m), 6.18 (1H, d, *J* = 7.9 Hz), 7.13 (1H, m), 7.18−7.21 (4H, m), 7.26 (2H, d, *J* = 8.2 Hz), 7.44 (1H, brb), 7.74 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 21.7 (CH_3), 22.7 (CH_3), 23.1 (CH_3), 24.6 (CH_3), 25.0 (CH + CH_2), 28.6 (CH_2), 36.5 (CH_2), 40.7 (CH_2), 46.2 (C), 50.3 (CH_2), 51.0 (CH), 52.3 (CH_3), 56.9 (CH), 60.8 (CH), 96.5 (C), 126.1 (CH), 128.1 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 135.7 (C), 137.4 (2 × CH), 138.9 (C), 170.0 (C), 170.8 (C), 173.7 (C), 176.9 (C); MS *m/z* (rel intensity) 661 (M^+, 1), 570 (M^+ − CH_2Ph, 6), 328 (M^+ − $NHCH(CH_2Ph)C(Me)_2$ − $CONHCH(CH_2CHMe_2)CO_2Me$, 99), 300 (M^+ − $CONHCH(CH_2Ph)C(Me)_2CO$ − $NHCH(CH_2CHMe_2)CO_2Me$, 57), 231 ($[p\text{-I-PhCO}]^+$, 100); HRMS calcd for $C_{31}H_{40}IN_3O_5$, 661.2013; found, 661.2015; calcd for C_7H_4IO, 230.9307; found, 230.9308. Anal. Calcd for $C_{31}H_{40}IN_3O_5$: C, 56.28; H, 6.09; N, 6.35. Found: C, 56.63; H, 6.43; N, 6.01. **X-ray Analysis**: $C_{31}H_{40}IN_3O_5$, M_r = 661.56, colorless needle crystal (0.15 × 0.11 × 0.10 mm^3) from EtOAc/*n*-pentane (mp 169−170 °C); orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.1613(3) Å, *b* = 15.2508(7) Å, *c* = 32.8063(17) Å, *V* = 3082.6(3) Å^3, *Z* = 4, ρ_{calcd} = 1.425 g cm^{-3}, *F*(000) = 1360, μ = 1.081 mm^{-1}; 35 963 measured reflections, of which 9373 were unique (R_{int} = 0.0737); 372 refined parameters, final R_1 = 0.0472, for reflections with $I > 2\sigma(I)$, wR_2 = 0.0945 (all data), GOF = 0.984. Flack parameter = 0.005(17). The max/min residual electron density: +1.126/−1.692 e·Å^{-3}.

***N*-(*p*-Iodobenzoyl)-L-prolyl-[α,α-dimethyl-D-*β*-homophenylalanyl]-L-leucine Methyl Ester (113).** A solution of tripeptide **111** (40 mg, 0.07 mmol) underwent hydrogenolysis of the Cbz group, followed by acylation with 4-iodobenzoyl chloride, as in the previous case. After purification by rotatory chromatography (hexanes/EtOAc, 85:15), product **113** was isolated (31 mg, 67%) as a crystalline solid: mp 162−163 °C (from EtOAc/*n*-pentane); $[\alpha]_D$ +19 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3354, 3089, 3065, 1725, 1683, 1655, 1620, 1558, 1425 cm^{-1}; ^1H NMR (500 MHz) δ_H 0.90 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.7 Hz), 1.29 (3H, s), 1.36 (3H, s), 1.55−1.65 (2H, m), 1.71 (1H, m), 1.78−1.85 (2H, m), 1.92 (1H, ddd, J = 4.8, 11.4, 13.3 Hz), 2.01 (1H, m), 2.47 (1H, dd, J = 12.3, 14.2 Hz), 3.12 (1H, dd, J = 3.8, 14.2 Hz), 3.43 (1H, ddd, J = 4.4, 6.9, 10.5 Hz), 3.62 (1H, ddd, J = 6.6, 6.9, 10.4 Hz), 3.83 (3H, s), 4.09−4.16 (2H, m), 4.61 (1H, ddd, J = 4.1, 7.9, 11.4 Hz), 7.16 (1H, dd, J = 7.3, 8.5 Hz), 7.18 (2H, d, J = 7.3 Hz), 7.26 (2H, dd, J = 6.6, 7.9 Hz), 7.27 (2H, d, J = 8.5 Hz), 7.59 (1H, d, J = 7.9 Hz), 7.68 (1H, d, J = 10.4 Hz), 7.73 (2H, d, J = 8.2 Hz); ^{13}C NMR (125.7 MHz) δ_C 21.2 (CH_3), 22.8 (CH_3), 23.1 (CH_3), 24.0 (CH_3), 25.1 (CH), 25.7 (CH_2), 28.8 (CH_2), 35.6 (CH_2), 39.1 (CH_2), 47.3 (C), 50.6 (CH_2), 52.1 (CH), 52.6 (CH_3), 57.0 (CH), 61.7 (CH), 96.7 (C), 125.9 (CH), 128.1 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 135.5 (C), 137.3 (2 × CH), 139.3 (C), 168.3 (C), 171.6 (C), 175.8 (C), 176.8 (C); MS *m*/*z* (rel intensity) 661 (M^+, 1), 570 ($M^+ - CH_2Ph$, 2), 328 ($M^+ - NHCH(CH_2Ph)C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 44), 300 ($M^+ - CONHCH(CH_2Ph)C(Me)_2CONHCH(CH_2CHMe_2)CO_2Me$, 35), 231 ([*p*-I-PhCO]$^+$, 100); HRMS calcd for $C_{31}H_{40}IN_3O_5$, 661.2013; found, 661.1989; calcd for C_7H_4IO, 230.9307; found, 230.9314. Anal. Calcd for $C_{31}H_{40}IN_3O_5$: C, 56.28; H, 6.09; N, 6.35. Found: C, 56.60; H, 6.28; N, 5.95. **X-ray Analysis**: $C_{31}H_{40}IN_3O_5$, M_r = 661.56, colorless block crystal (0.41 × 0.35 × 0.24 mm^3) from EtOAc/*n*-pentane (mp 162−163 °C); triclinic, space group *P*1 (no. 1), a = 9.8375(13) Å, b = 10.8487(14) Å, c = 14.9223(18) Å, α = 95.264(4)°, β = 90.527(4)°, γ = 91.967(4)°, V = 1584.8(3) $Å^3$, Z = 2, ρ_{calcd} = 1.386 g cm^{-3}, $F(000)$ = 680, μ = 1.052 mm^{-1}; 42 926 measured reflections, of which 14 751 were unique (R_{int} = 0.0447); 743 refined parameters, final R_1 = 0.0589, for reflections with $I > 2\sigma(I)$, wR_2 = 0.1712 (all data), GOF = 1.060. Flack parameter = 0.02(2). The max/min residual electron density: +3.953/−2.157 e·$Å^{-3}$.

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Supporting Information Available: Experimental procedures to prepare substrates **37**, **50**−**53**, **58**−**64**, **66**, and **67**, and characterization of these compounds. Preparation and spectroscopic data of the scission−Mannich products **21**−**34**, **39**−**49**, **54**−**57**, and **69**−**92**. Synthesis and spectroscopic data of acids **93**−**95** and dipeptides **96**−**103**. X-ray analysis of compounds **71**, **78**, **81**, **83**, **90**, **96**, **98**−**101**, and **103**. ^1H and ^{13}C NMR spectra of the new compounds (**21**−**34**, **37**, **39**−**64**, **66**, **67**, **69**−**113**). This material is available free of charge via the Internet at http://pubs.acs.org.

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One-pot synthesis of α-amino phosphonates from α-amino acids and β-amino alcohols

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Abstract—The one-pot radical fragmentation–phosphorylation reaction of α-amino acids and β-amino alcohols affords α-amino phosphonates in good yields. The reaction was applied to the synthesis of potentially bioactive phosphonates.

The α-amino phosphonates are amino acid analogues, which have elicited considerable attention due to their interesting biological properties.[1] For instance, the leucine surrogate **1** (Fig. 1) is a potent inhibitor of leucine aminopeptidase.[2] The proline analogue **2** is an angiotensin inhibitor, useful as an antihypertensive agent.[3] The amino phosphonate **3** possesses herbicidal activity.[4] Other amino phosphonates are promising antitumoural, fungicidal, antibacterial and antiviral agents.[1–4] As a result, different synthetic methodologies to obtain these compounds have been developed.[1]

We report now on a mild and efficient preparation of these compounds from β-amino alcohols and α-amino acid derivatives, using a sequential fragmentation–phosphorylation reaction (Scheme 1).

It is known that on treatment with $PhI(OAc)_2$–I_2, the β-amino alcohol derivatives **4a** (X = H,H) generate an alkoxyl radical **5a**, while the amino acids **4b** (X = O) generate a carboxyl radical **5b**.[5] These *O*-radicals were expected to undergo a radical β-fragmentation to afford a *C*-radical **6**,[5,6] which would be oxidized in the reaction medium to an *N*-acyliminium ion **7**.[6] This intermediate could be trapped by phosphorous nucleophiles, namely dimethyl phosphonate or trialkylphosphites, to afford α-amino phosphonates **8**.

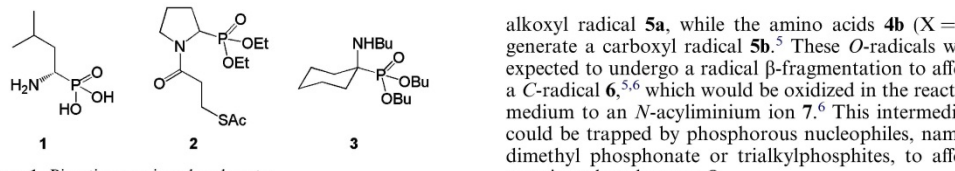
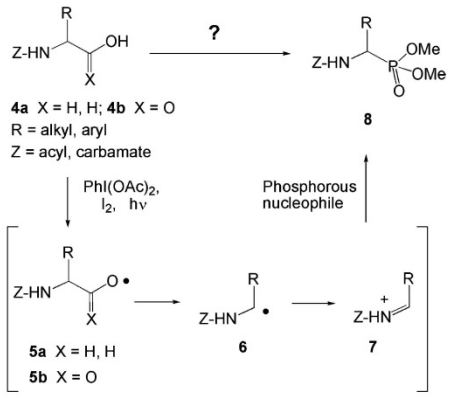


Figure 1. Bioactive α-amino phosphonates.



Scheme 1. Proposed one-pot radical fragmentation–phosphorylation for the synthesis of α-amino phosphonates.

To explore the feasibility and scope of this reaction, several amino alcohol and amino acid derivatives **9**–**15** were prepared in a few steps from commercial products, using standard methodologies.

Keywords: Amino acids; Amino phosphonates; Radicals; Fragmentation; Decarboxylation; Hypervalent iodine reagents.
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Table 1. One-pot β-fragmentation–phosphorylation reaction[a]

Entry	Substrate	Conditions[b]	Products (%)[c]
1	**9**	A	**16** (64)
2	**9**	B	**16** (62)
3	**9**	C	**16** (26), **17** (27)
4	**9**	D	**16** (4), **17** (64)
5	**10**	D	**17** (86)
6	**11**	D	**18** (81)
7	**12**	D	**19** (85)
8	**13**	D	**20** (67)
9	**14**	D	**21b** (89)
10	**15**	D	**22** (26)

[a] General procedure: The substrate (1 mmol) in dry dichloromethane (15 ml) was treated with DIB (2.5 mmol) and iodine (1 mmol) and irradiated with visible light (sunlight, or a 100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). Then it was cooled to 0 °C and the Lewis acid ($BF_3{\cdot}OEt_2$ or TMSOTf, 2 equiv) and the nucleophile [$HP(O)(OMe)_2$ or $P(OMe)_3$, 5 equiv] were added. The reaction was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$–10% $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[b] Condition A: TMSOTf as Lewis acid and $HP(O)(OMe)_2$ as nucleophile. Condition B: $BF_3{\cdot}OEt_2$ as Lewis acid and $HP(O)(OMe)_2$ as nucleophile. Condition C: TMSOTf as Lewis acid and $P(OMe)_3$ as nucleophile. Condition D: $BF_3{\cdot}OEt_2$ as Lewis acid and $P(OMe)_3$ as nucleophile.

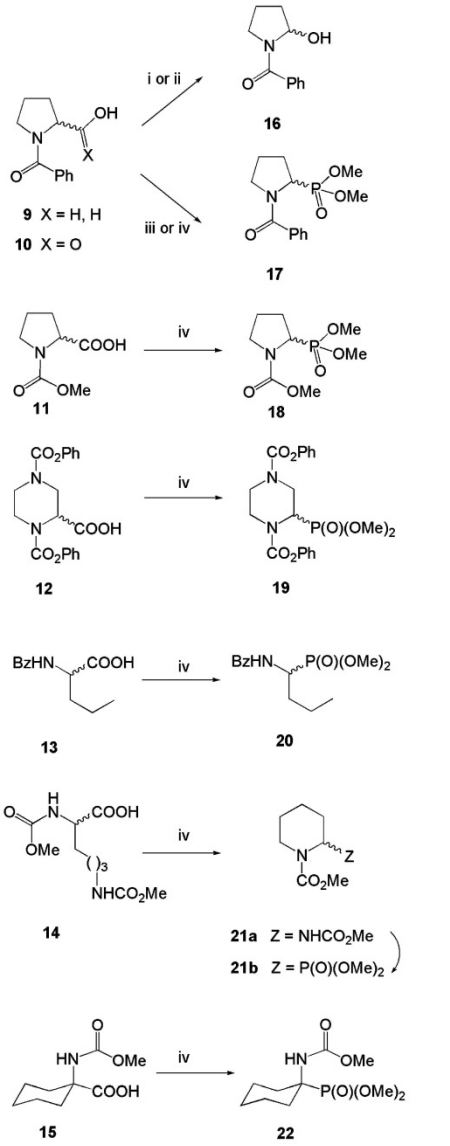
[c] Yields are given for products purified by chromatography on silica gel.

The sequential fragmentation–phosphorylation was studied first with substrate **9** (Table 1, entries 1–4), which was treated with DIB–I_2 and irradiated with visible light to carry out the fragmentation. Once this step was completed, a Lewis acid (TMSOTf or $BF_3{\cdot}OEt_2$)[7] and the nucleophile [$HP(O)(OMe)_2$ or $P(OMe)_3$] were added.[8]

When dimethyl phosphonate was used as nucleophile (entries 1 and 2), no phosphonates were obtained, and the 2-hydroxypyrrolidine **16**[6g,7] was isolated instead. This result implies that this nucleophile was not reactive enough to trap the *N*-acyliminium intermediate, which therefore reacted with water during the work-up. However, by using $P(OMe)_3$ as nucleophile (entries 3 and 4) the desired α-amino phosphonate **17**[9b] was obtained as the major product.

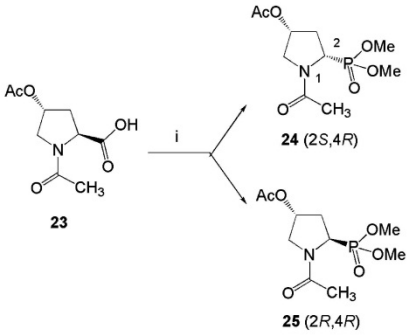
The fragmentation of the amino acid analogue **10** (Scheme 2) was studied next (entry 5) in order to determine whether the reaction results improved by using amino acids as substrates.[10] The one-pot fragmentation–phosphorylation proceeded in good yield, affording the amino phosphonate **17**. The decarboxylation–phosphorylation of proline methyl carbamate **11** (entry 6) also proceeded in good yield, affording product **18**.

When the piperazic acid derivative **12** was used as substrate (entry 7), the reaction gave the desired phosphonate **19** in very good yield.[11] The same occurred with the fragmentation of the unnatural amino acid **13** (entry 8), which afforded the phosphonate analogue **20**.[12]

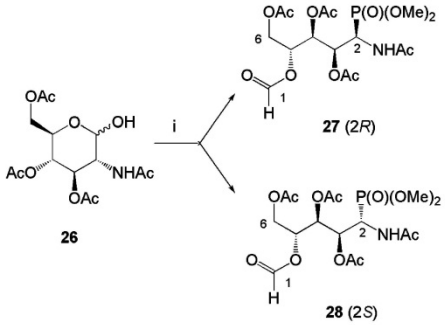


Scheme 2. Reagents and conditions: (i) DIB, I_2, *hv*; then 0 °C, TMSOTf, $HP(O)(OMe)_2$; (ii) DIB, I_2, *hv*; then 0 °C, $BF_3{\cdot}OEt_2$, $HP(O)(OMe)_2$; (iii) DIB, I_2, *hv*; then 0 °C, TMSOTf, $P(OMe)_3$; (iv) DIB, I_2, *hv*; then 0 °C, $BF_3{\cdot}OEt_2$, $P(OMe)_3$. See Table 1 for product yields.

The fragmentation of the lysine derivative **14** (entry 8) surprisingly gave the pipecolinic acid surrogate **21b**[13a] in good yields. This result can be explained via an intermediate **21a**, formed by addition of the ε-carbamate



Scheme 3. Use of precursors from the chiral pool to obtain functionalized amino phosphonates. Reagents and conditions: (i) DIB (2.5 mmol), I_2 (1 mmol), rt, sunlight, 3 h; then 0 °C, $P(OMe)_3$ (5 equiv) and $BF_3{\cdot}OEt_2$ (2 equiv); **24** (64%) and **25** (15%).



Scheme 4. Use of precursors from the chiral pool to obtain functionalized amino phosphonates. Reagents and conditions: (i) DIB (2.5 mmol), I_2 (1 mmol), rt, sunlight, 3 h; then 0 °C, $P(OMe)_3$ (5 equiv) and $BF_3{\cdot}OEt_2$ (2 equiv); **27** (40%) and **28** (26%).

group to the initial *N*-acyliminium ion.[13b] On treatment with the Lewis acid, **21a** generated a cyclic acyliminium ion, which was trapped by the phosphorous nucleophile to afford **21b**.

The fragmentation–phosphorylation of the amino acid **15** (entry 9) posed a challenge since a quaternary centre would be formed. However, the reaction proceeded in low yield, generating the interesting α,α-disubstituted amino phosphonate **22**.[14]

The sequential decarboxylation–phosphorylation reaction was also studied with substrates bearing stereogenic centres next to the reacting centre. For instance, when the (4*R*)-acetoxyproline derivative **23** (Scheme 3) was treated with DIB–iodine and then with $BF_3{\cdot}OEt_2$ and $P(OMe)_3$, the amino phosphonate **24**[15a,16a] and its 2-epimer **25**[15b,16b] were obtained in 64% and 15% yield, respectively (79% overall yield).

The carbohydrate pool can also provide a variety of precursors. For instance, the substrate **26** (Scheme 4) was obtained in two steps from commercial 2-acetamide D-glucopyranose.

The fragmentation of the alkoxyl radical derived from **26**, followed by phosphorylation with $BF_3{\cdot}OEt_2$ and $P(OMe)_3$, afforded a separable 3:2 mixture of the polyhydroxylated products **27**[17a] and **28**[17b] in 66% global yield. Since in this case the reaction proceeded via an acyclic acyliminium ion, a low diastereoselectivity was observed.[18] However, the use of differently protected, more rigid carbohydrate substrates, should increase the stereocontrol.[19] As shown in this example, the fragmentation–phosphorylation of precursors from the chiral pool can allow the synthesis of highly functionalized amino phosphonates.

In summary, the one-pot fragmentation–phosphorylation reaction is a versatile and efficient pathway to obtain many different amino phosphonates from readily available precursors. The biological activity of compounds **17**–**22**, **24**, **25** and **27**, **28**, is currently under study and will be reported in due course.

Acknowledgements

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7. For a discussion of the role of the Lewis acid in similar reactions, see: Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2000**, *64*, 4930–4937, and references cited therein.
8. For examples of addition of phosphorous nucleophiles to imines and iminium ions, see Ref. 1a and also: (a) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989–2991; (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583–2585; (c) De Risi, C.; Perrone, D.; Dondoni, A.; Pollini, G. P.; Bertolasi, V. *Eur. J. Org. Chem.* **2003**, 1904–1914; (d) Stevens, C. V.; Vekemans, W.; Moonen, K.; Rammeloo, T. *Tetrahedron Lett.* **2003**, *44*, 1619–1622, and references cited therein.
9. (a) All new compounds were characterized by ^{1}H and ^{13}C NMR, MS, HRMS, IR and elemental analysis. 2D-COSY, HSQC and NOESY experiments were also carried out. Selected NMR and mass spectra data are given. The NMR spectra were recorded in $CDCl_3$ at 70 °C unless otherwise stated; (b) Compound **17**: ^{1}H NMR (500 MHz) δ 7.51 (2H, d, $J = 8.1$ Hz), 7.4–7.3 (3H, m), 4.82 (1H, m), 3.77 (3H, d, $J_{H,P} = 10.5$ Hz), 3.76 (3H, d, $J_{H,P} = 10.5$ Hz), 3.59 (1H, ddd, $J = 7.6$, 7.7, 10.6 Hz), 3.47 (1H, m), 2.2–2.1 (2H, m), 1.78 (1H, m); ^{13}C NMR (125.7 MHz): δ 170.3 (C), 136.6 (C), 130.2 (CH), 128.2 (2×CH), 127.6 (2×CH), 53.0 (CH_3, d, $J_{C,P} = 7.0$ Hz), 52.7 (CH_3, d, $J_{C,P} = 6.4$ Hz), 52.2 (CH, d, $J_{C,P} = 163$ Hz), 49.9 (CH_2), 26.0 (CH_2), 25.0 (CH_2). MS (EI, 70 eV), *m/z*: 283 (M^+, 8), 178 (4), 174 (69), 105 (100); HRMS: calcd for $C_{13}H_{18}NO_4P$ 283.0973, found 283.0968.
10. The fragmentation of carboxyl radicals proceeds much faster than the fragmentation of alkoxyl radicals. Thus, K_{frag} ($RCOO^{\cdot}$) = 10^{10} s $^{-1}$, K_{frag} ($PhCOO^{\cdot}$) = 10^{6} s $^{-1}$ and K_{frag} ($^{t}BuO^{\cdot}$) = 10^{5} s $^{-1}$. For a discussion on the subject, see: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: Chichester, 1995; pp 96, 148–149, 223–225 and 295.
11. Compound **19**: ^{1}H NMR (500 MHz) δ 7.35 (2H, dd, $J = 7.8$, 8.1 Hz), 7.34 (2H, dd, $J = 8.1$, 8.0 Hz), 7.21–7.13 (6H, m), 4.70 (1H, m), 4.66 (1H, dd, $J = 5.0$, 16.8 Hz), 4.30 (1H, d, $J = 13.5$ Hz), 4.16 (1H, d, $J = 12.1$ Hz), 3.79 (3H, d, $J_{H,P} = 11$ Hz), 3.78 (3H, d, $J_{H,P} = 11$ Hz), 3.70 (1H, m), 3.40 (1H, m), 3.08 (1H, m); ^{13}C NMR (125.7 MHz): δ 153.6 (C), 153.2 (C), 151.6 (C), 151.4 (C), 129.2 (2×CH), 129.1 (2×CH), 125.5 (CH), 125.2 (CH), 121.5 (2×CH), 121.3 (2×CH), 53.0 (CH_3, d, $J_{C,P} = 7.0$ Hz), 52.8 (CH_3, d, $J_{C,P} = 7.0$ Hz), 48.5 (CH, d, $J_{C,P} = 151.0$ Hz), 43.6 (CH_2), 43.0 (CH_2), 41.2 (CH_2); MS (EI, 70 eV), *m/z*: 435 (M^++H, 1), 434 (M^+, 1), 342 (18), 341 (99), 93 (100); HRMS: calcd for $C_{20}H_{23}N_2O_7P$ 434.1243, found 434.1248.
12. For very similar compounds, see: (a) Yuan, C.; Wang, G.; Chen, S. *Synthesis* **1990**, 522–524; (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Tetrahedron Lett.* **1981**, *22*, 3249–3252.
13. (a) Compound **21b**: ^{1}H NMR (500 MHz) δ 4.55 (1H, dd, $J = 6.3$ Hz, $J_{H,P} = 17.4$ Hz), 3.95 (1H, d, $J = 12.8$ Hz), 3.65 (3H, d, $J_{H,P} = 10.5$ Hz), 3.64 (3H, d, $J_{H,P} = 10.6$ Hz), 3.61 (3H, s), 3.14 (1H, ddd, $J = 2.6$, 13.1, 13.3 Hz), 1.96 (1H, m), 1.81 (1H, m), 1.64 (1H, m), 1.55 (2H, m), 1.29 (1H, m); ^{13}C NMR (125.7 MHz): δ 155.9 (C), 52.6 (CH_3), 52.4 (CH_3, d, $J_{C,P} = 6.9$ Hz), 52.1 (CH_3, d, $J_{C,P} = 7.1$ Hz), 48.2 (CH, d, $J_{C,P} = 152.0$ Hz), 41.5 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 20.0 (CH_2); MS (EI, 70 eV), *m/z*: 251 (M^+, 8), 143 (30), 142 (100); HRMS: calcd for $C_9H_{18}NO_5P$ 251.0923, found 251.0935. For a similar result, see: (b) Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1999**, *40*, 5945–5948.
14. Compound **22**: ^{1}H NMR (500 MHz) δ 4.47 (1H, br b, NH), 3.77 (6H, d, $J_{H,P} = 10.5$ Hz), 3.64 (3H, s), 2.33 (2H, m), 1.76 (2H, dddd, $J = 3.9$, 4.0, 13.1, 13.3 Hz), 1.67–1.55 (2H, m), 1.49 (2H, m), 1.27 (2H, m); ^{13}C NMR (125.7 MHz): δ 155.3 (C), 55.9 (C, d, $J_{C,P} = 160$ Hz), 53.1 (2×CH_3, d, $J_{C,P} = 7.2$ Hz), 51.6 (CH_3), 30.0 (2×CH_2), 25.1 (CH_2), 20.4 (CH_2), 20.2 (CH_2); MS (EI, 70 eV), *m/z*: 266 (M^++H, 1), 265 (M^+, 1), 234 (2), 191 (3), 156 (100); HRMS: calcd for $C_{10}H_{20}NO_5P$ 265.1079, found 265.1089.
15. (a) Compound **24**: ^{1}H NMR (500 MHz, 26 °C) δ 5.10 (1H, m), 4.48 (1H, m), 3.89 (1H, dd, $J = 6.5$, 11.5 Hz), 3.71 (3H, d, $J_{H,P} = 10.7$ Hz), 3.70 (3H, d, $J_{H,P} = 10.6$ Hz), 3.45 (1H, dd, $J = 4.7$, 11.5 Hz), 2.5–2.3 (2H, m), 2.00 (3H, s), 1.99 (3H, s); ^{1}H NMR (400 MHz, C_6D_6, 26 °C) δ 4.80 (1H, m), 4.53 (1H, m), 3.74 (3H, d, $J_{H,P} = 10.8$ Hz), 3.57 (3H, d, $J_{H,P} = 10.5$ Hz), 3.33 (2H, m), 2.46 (1H, m), 1.93 (1H, m), 1.82 (3H, s), 1.68 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C): δ 170.5 (C), 168.9 (C), 71.8 (CH), 53.2 (CH_3, d, $J_{C,P} = 6.8$ Hz), 52.6 (CH_3, d, $J_{C,P} = 6.3$ Hz), 52.6 (CH_2), 50.7 (CH, d, $J_{C,P} = 160$ Hz), 31.9 (CH_2), 22.0 (CH_3), 20.8 (CH_3); MS (EI, 70 eV), *m/z*: 280 (M^++H, 2), 219 (M^+, 20), 110 (90), 109 (3), 68 (100); HRMS: calcd for $C_{10}H_{19}NO_6P$ 280.0950, found 280.0947; (b) The spectroscopic data of compound **25** were very similar, the main differences being observed in the ^{1}H NMR spectrum (500 MHz, 26 °C) δ 5.36 (1H, m), 4.73 (1H, m), 3.83 (1H, m), 3.78 (6H, d, $J_{H,P} = 10.3$ Hz), 3.60 (1H, m), 2.61 (1H, m), 2.23 (1H, m), 2.09 (3H, m), 2.01 (3H, s).
16. (a) The stereochemistry of compound **24** was determined with a COSY experiment (400 MHz, C_6D_6). Thus, a strong coupling was observed between 4-H (δ_H 4.80) and 3β-H (δ_H 1.93) and between 3β-H (δ_H 1.93) and 2-H (δ_H 4.53). In contrast, the coupling between 3α-H (δ_H 2.46) and 4-H or 2-H was very weak, as expected for 2-H,3α-H *trans* and 4-H,3α-H *trans* relationships; (b) In the case of compound **25**, the COSY experiment (500 MHz, $CDCl_3$) showed a strong coupling between 4-H (δ_H 5.36) and 3β-H (δ_H 2.61). The coupling between 3α-H (δ_H 2.23) and 2-H (δ_H 4.73) was also observe. The nucleophile was added from the apparently more hindered face. For similar results, see: (c) Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643–1646, and references cited therein.
17. (a) Compound **27**: ^{1}H NMR (500 MHz, −50 °C) δ 7.94 (1H, s, OCHO), 6.44 (1H, d, $J = 9.8$ Hz, NH), 5.59 (1H, dd, $J = 7.1$, 7.4 Hz, 3-H), 5.50 (1H, dd, $J = 4.9$, 6.4 Hz, 4-H), 5.23 (1H, ddd, $J = 5.1$, 5.1, 5.3 Hz, 5-H), 4.89 (1H, ddd, $J = 2.4$, 10.4 Hz, $J_{H,P} = 22.7$ Hz, 2-H), 4.30 (1H, dd, $J = 4.7$, 12.1 Hz, 6-H_a), 4.10 (1H, dd, $J = 6.4$, 11.8 Hz, 6-H_b), 3.77 (3H, d, $J_{H,P} = 9.8$ Hz, OMe), 3.75 (3H, d, $J_{H,P} = 10.3$ Hz, OMe), 2.15 (3H, s, Ac), 2.12 (3H, s, Ac), 2.10 (6H, s, 2×Ac); ^{13}C NMR (125.7 MHz, 26 °C): δ 170.5 (C, CO), 170.1 (C, CO), 169.8 (C, CO), 169.6 (C, CO), 159.4 (CH, CHO), 70.1 (CH, d, $J_{C,P} = 11.5$ Hz, 4-C), 69.0

(CH, 5-C), 68.5 (CH, $J_{C,P} = 4$ Hz, 3-C), 61.3 (CH_2, 6-C), 53.9 (CH_3, d, $J_{C,P} = 6.8$ Hz, OMe), 53.4 (CH_3, d, $J_{C,P} = 6.4$ Hz, OMe), 45.0 (CH, d, $J_{C,P} = 159$ Hz, 2-C), 23.0 (CH_3), 20.6 ($3\times CH_3$); MS (EI, 70 eV), *m/z*: 456 (M^++H, 6), 57 (100); HRMS: calcd for $C_{16}H_{27}NO_{12}P$ 456.1271, found 456.1286; (b) The spectroscopic data of compound **28** were very similar, the main differences being observed in the ^{1}H NMR spectrum (500 MHz, −50 °C): δ 8.07 (1H, s, OCHO), 7.14 (1H, br b, NH), 5.64 (1H, dd, $J = 9.9$, 10.0 Hz, 3-H), 5.44 (1H, dd, $J = 1.0$, 8.9 Hz, 4-H), 5.28 (1H, m, 5-H), 4.77 (1H, ddd, $J = 10.4$, 10.5 Hz, $J_{H,P} = 14.3$ Hz, 2-H), 4.21 (1H, br d, $J = 11.7$ Hz, 6-H_a), 4.00 (1H, dd, $J = 6.6$, 12.7 Hz, 6-H_b), 3.73 (6H, d, $J_{H,P} = 11.9$ Hz, OMe), 2.14 (3H, s, Ac), 2.12 (3H, s, Ac), 2.05 (3H, s, Ac), 1.99 (3H, s, Ac).

18. (a) The stereochemistry of compounds **27** and **28** was tentatively assigned by comparing the theoretical coupling constants calculated over the minimized structures for both diastereomers and the experimental coupling constants at −50 °C. Since at this temperature the interconversion between conformers is very slow, signals for each conformer are recorded in the NMR experiment; the intensity of the signals is related to the conformer population. In our case, the signals of the minor conformations were hardly observed. Presuming that the minimum-energy conformation was the major one, the experimental J would match the theoretical ones; The theoretical J were calculated by using the Karplus–Altona equation implemented in the Macromodel 7.0 program. See: (b) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792; (c) Experimental J for product **27**: $J_{2,3} = 2.4$ Hz, $J_{3,4} = 6.0$ Hz, and for compound **28**: $J_{2,3} = 10.0$ Hz, $J_{3,4} = 10.0$ Hz. Calculated J for the 2*R* diastereomer: $J_{2,3} = 0.3$ Hz, $J_{3,4} = 5.0$ Hz, and for the 2*S* diastereomer: $J_{2,3} = 8.0$ Hz and $J_{3,4} = 4.4$ Hz.
19. Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **2001**, *42*, 9167–9170.

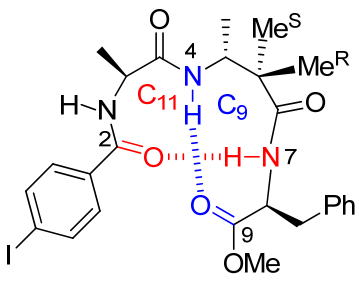
Objetivos

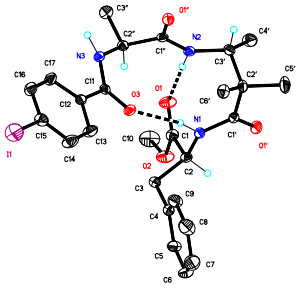
2 OBJETIVOS.

Partiendo de la experiencia adquirida en nuestro laboratorio, nos planteamos desarrollar procesos secuenciales de escisión radicalaria–oxidación–adición de nucleófilos, dirigidos principalmente a la modificación selectiva de péptidos pequeños.

2.1 Conversión de α-péptidos en α,β-híbridos y estudio de la conformación de los α,β,α-tripéptidos en solución.

Se realizará la modificación selectiva del extremo *C*-terminal de pequeños péptidos, transformando dicho α-amino ácido en un β-amino éster. Para ello, se utilizará una reacción de descarboxilación radicalaria oxidativa–adición de *C*-nucleófilos. Los dipéptidos resultantes se convertirán en α,β,α-tripéptidos.



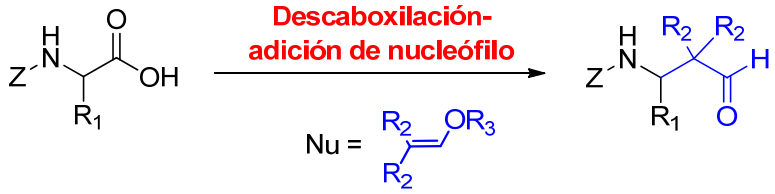


En un trabajo previo, habíamos determinado que los α,β,α-tripéptidos forman interesantes giros en estado sólido. En esta memoria se estudiará la conformación de estos α,β,α-tripéptidos en disolución y se comprobará si presentan los mismos giros que tenían en estado sólido.

2.2 Síntesis de β-amino aldehídos y preparación de péptidos con unidades de β-amino aldehídos.

Se estudiará la modificación selectiva del extremo *C*-terminal de pequeños péptidos, transformándolo en un β-amino aldehído. Para ello, se

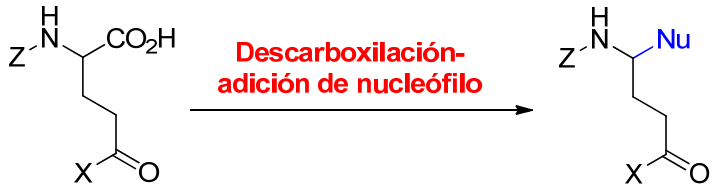
desarrollará un proceso de descarboxilación radicalaria oxidativa–adición de nucleófilos tipo vinil éter o sililenol éter. El proceso se llevará a cabo primero con amino ácidos y posteriormente sobre péptidos.



Z = acilo, carbamoilo, peptidilo
R_1 = H, alquilo, etc
R_2 = H ó Me
R_3 = TMS, Et

2.3 Síntesis de γ-amino ácidos no naturales y preparación de péptidos con unidades de γ-amino ácidos no naturales.

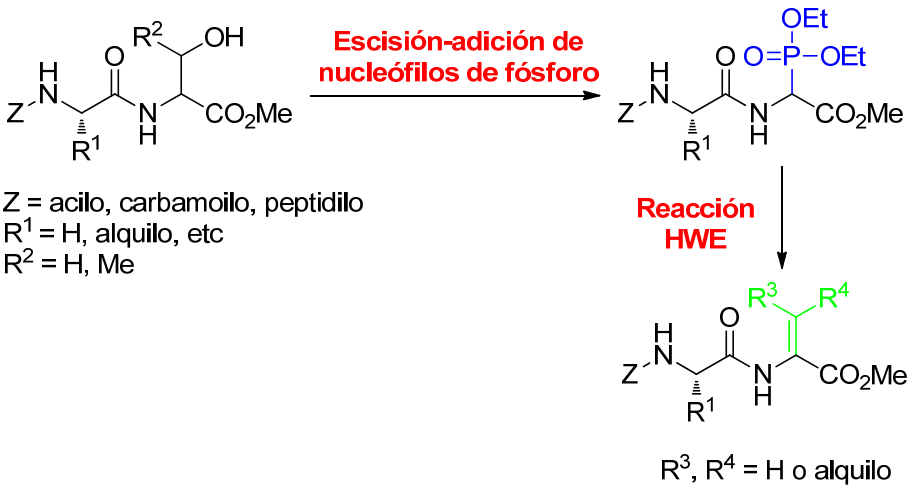
Se desarrollará la modificación selectiva de unidades de glutámico en péptidos, mediante un proceso en un paso de descarboxilación-adición de nucleófilos de carbono. Se estudiará la modificación de residuos de glutámico en distintas posiciones, y su conversión en unidades de γ-amino acido no naturales. La estereoquímica de los péptidos híbridos (α,γ) resultantes se establecerá por correlaciones químicas.



Z = acilo, carbamoilo, peptidilo
X = OMe, peptidilo

2.4 Síntesis de péptidos con unidades de deshidroamino ácido.

Se desarrollará la modificación selectiva de unidades de serina o treonina en péptidos, mediante un proceso en un paso de escisión radicalaria oxidativa de la cadena lateral del amino ácido, acoplada a la adición de nucleófilos de fósforo. Los α-amino fosfonatos resultantes se tratarán con aldehídos o cetonas bajo las condiciones de la reacción de Horner-Wadsworth-Emmons, para generar deshidroamino ácidos β-sustituidos, y se estudiarán las condiciones para obtener una alta estereoselectividad.



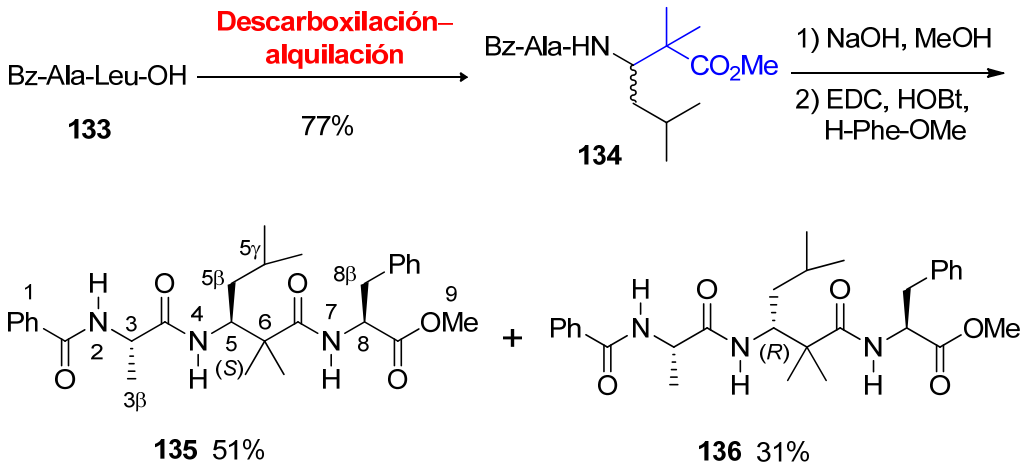
Discusión y Resultados

3 DISCUSIÓN Y RESULTADOS.

3.1 Conformación y efecto quiral en α,β,α-tripéptidos.

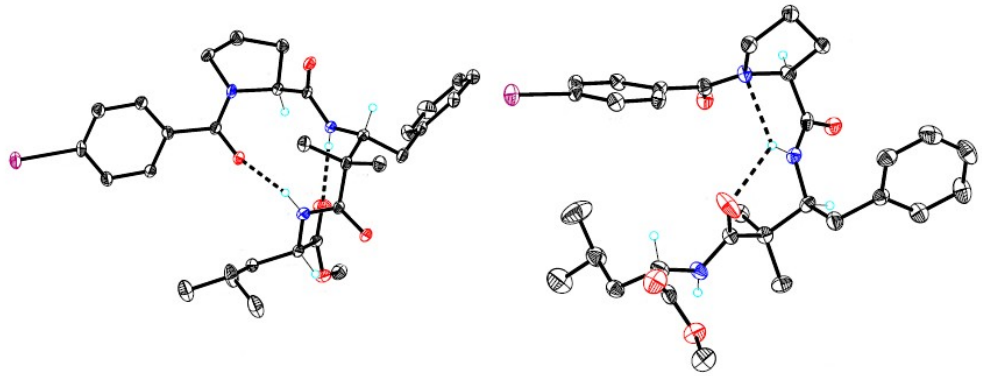
Como se comentaba en la Introducción (apartado **1.3.3**), la selectividad y eficacia de los catalizadores o fármacos peptídicos está a menudo relacionada con la formación de elementos de la estructura secundaria como giros, hélices, hojas, etc. En los últimos años se ha dedicado mucho interés a la estructura secundaria de péptidos no naturales o peptidomiméticos. Gracias a ello se han determinado muchos patrones de plegamiento de β- y γ- péptidos y en menor medida de los α,β-híbridos, permitiendo diseñar antibióticos resistentes a las proteasas y otras aplicaciones biológicas.

Sin embargo, todavía quedan muchas incógnitas, puesto que el plegamiento se ve influido por muchos factores, como la topología de las cadenas laterales, el disolvente, la proporción y disposición de unidades α:β en los híbridos, etc. Por ello, en este capítulo de la Memoria se estudiará la conformación de α,β,α-tripéptidos preparados usando la reacción de descarboxilación–alquilación[51] como etapa clave. A modo de ejemplo en el Esquema 38 se muestra la síntesis completa de los compuestos **135** y **136**



Esquema 38. Preparación de los tripéptidos modelos **135** y **136**.

En estado sólido, estos péptidos forman giros, que son distintos según se traten del isómero *SSS* o *SRS*. En los péptidos *SRS* cristalinos, se observaron giros δ extendidos (C9) y giros β extendidos (C11). En cambio, en los péptidos *SSS* solo se observan enlaces de hidrógenos intrarresiduales (principalmente en el residuo β) (Figura 13).



SRS ***SSS***

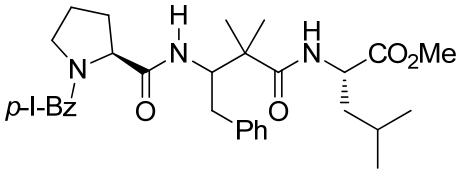


Figura 13. Conformaciones de los α,β,α-péptidos **129** (3'*S*) y **130** (3'*R*) en estado sólido.

Estas interacciones son muy interesantes a la hora de desarrollar nuevos foldámeros, por lo que decidimos estudiar si estos giros se mantenían en solución. Para los estudios se diseñaron varios péptidos modelos con distintas combinaciones de cadenas laterales (Me, i-Pr, i-Bu, Bn) con distintos volúmenes e hidrofilicidades.

Cada péptido se disolvió en cloroformo-*d* y DMSO-d_6 y se asignaron sus protones por medio de experimentos COSY, TOCSY, HSQC y HMBC. Luego se hicieron espectros de protón a distintas temperatura (300-330ºK), para determinar los coeficientes de temperatura para los protones de las amidas, tal como se muestra en la Tabla 1 del artículo (no mostrada aquí). Si un enlace de hidrógeno entre un N-H y un CO es estable (en disolución y al variar la

temperatura), el entorno del protón, y por tanto sus desplazamientos variarán poco.

Se pudo observar que los protones N_4H (los del β-amino ácido), también participan en enlaces de hidrógeno intramoleculares en solución, ya que los coeficientes de temperatura son relativamente pequeños ($\Delta\delta/\Delta T$ de -3.7 a -4.9 ppb/K). En cambio, el N_7H tiene unos valores de coeficientes de temperatura mayores ($\Delta\delta/\Delta T$ de -5.6 a -6.9 ppb/K) lo que indica que este protón está expuesto al disolvente, y no forma enlace de hidrógeno.

Otro dato interesante es la comparación de los desplazamientos químicos de los protones de las amidas al cambiar de cloroformo-*d* a un disolvente más polar, el DMSO-d_6. Al cambiar el disolvente, los cambios en el desplazamiento son muy pequeños para N_4H (0.0-0.4 ppm), en todos los péptidos, en cambio son bastantes mayores para N_2H (que no formaba enlace de hidrógeno) y N_7H (0.3-1.9 ppm). Además, se observó que el N_7H se desplazó a campos más bajos por 1.7-1.8 en los péptidos de configuración *SSS*, mientras que para los péptidos de configuración *SRS* se desplazó sólo 0.3-0.6 ppm. Por tanto, en los péptidos de configuración *SRS* el N_7H está menos expuesto al disolvente coordinante (ej. orientado hacia la parte interna de un giro peptídico).

Éste y otros datos sugieren que la conformación de los péptidos en solución depende de la configuración del β-amino ácido central, y se corresponde con las mostradas en la Figura 14:

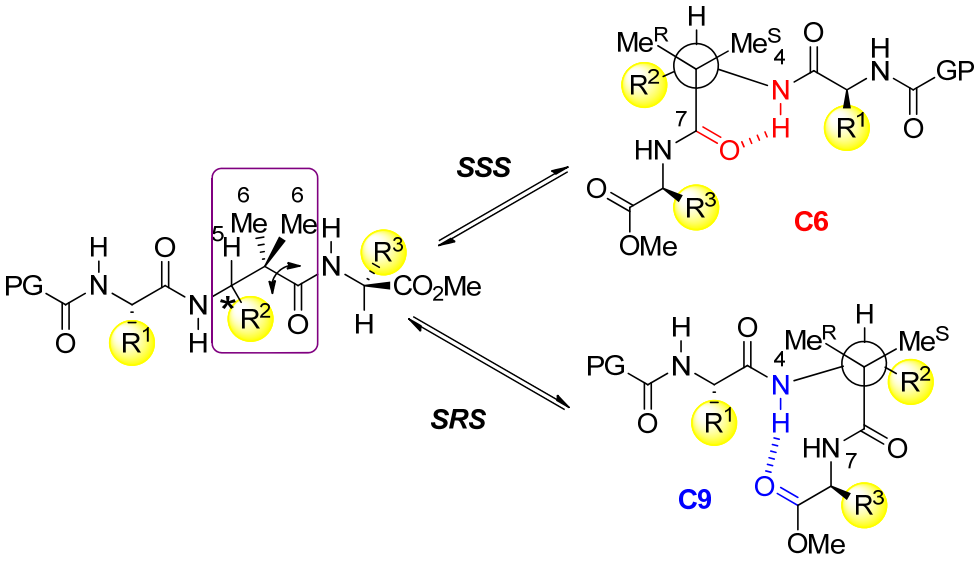


Figura 14. Efecto quiral en los α,β,α-tripéptidos en solución.

1) Todos los valores de ángulos diedros ϕ medidos en solución para los átomos (NH-CαH) de los tres amino ácidos (obtenidos a partir de la constante de acoplamiento y la ecuación de Karplus) fueron altos, en el intervalo 133–180 °C. Los isómeros *SSS* adoptan una conformación angular abierta, estabilizada por un enlace de hidrógeno (C6). Los isómeros *SRS* presentan una conformación en giro cerrada, donde se mantiene el enlace de hidrógeno (C9) que se observaba en estado sólido.
2) Las distancias entre protones no contiguos se determinaron con experimentos NOESY por el método ISPA (Aproximación de pares de espines aislados). Así, en el residuo de β-amino ácido de las parejas de isómeros *SSS*/*SRS*, las distancias $C_5H/Me_6^{pro\text{-}R}$ y $C_5H/Me_6^{pro\text{-}S}$ fueron muy similares en todos los casos, y tenían un valor aproximado de 2.5 Å (Tabla 2 del artículo). Para que esto sea posible, C_5H/CON deben adoptar una disposición antiperiplanar.
3) Por otra parte el protón de amida N_7H podría situarse hacia fuera o hacia dentro del enlace peptídico. Observando las distancias entre el N_7H y los metilos Me_6 (Tabla 2 del artículo) se puede ver que el N_7H está más próximo al $Me_6^{pro\text{-}R}$ que al $Me_6^{pro\text{-}S}$. Para que esto ocurra, el enlace N_7H de los isómeros *SSS* estará hacia afuera del giro peptídico, mientras que en

los *SRS* estará dirigido hacia adentro. Esta disposición coincide con la observada para los isómeros *SRS* en el estado sólido.

4) En los experimentos NOE realizados para el tripéptido modelo *SSS* no se observaron interacciones espaciales N_4H/N_7H, mientras que para el tripéptido *SRS* sí se observaron (integrando para una distancia de 2.5 Å). Además en el experimento NOESY de los isómeros *SSS*, se observaron fuertes correlaciones $N_4H/Me_6^{pro\text{-}S}$ (integrando para una distancia de 2.7 Å). En cambio, para los isómeros *SRS* se observaron fuertes interacciones entre el N_4H y el grupo $Me_6^{pro\text{-}R}$ (integrando para una distancia de 2.7 Å).
5) Otras interacciones NOE (Figura 5 del artículo, no mostradas aquí) apoyan las conformaciones propuestas.

Por tanto, para los isómeros *SSS* se mantiene el enlace de hidrógeno (C6) entre el N_4H y el C_7=O, que también se observa en el cristal; el otro enlace de hidrógeno se ha perdido, y se adopta una forma angular abierta.

En el caso del residuo *SRS* se observa una conformación en giro cerrada, donde se mantiene el enlace de hidrógeno (C9) entre el N_4H y el C_9=O, que también se observa en el cristal. El enlace de hidrógeno que, en estado sólido, se observaba entre N_7H y el C_2=O y que originaba el giro-β expandido no se observa en solución. Estas conclusiones coincidieron con los estudios de mecánica molecular (campo de fuerzas SYBYL) de los α,β,α-tripéptidos.

En resumen: las conformaciones adoptadas por los tripéptidos estudiados son independientes del tamaño y naturaleza de las cadenas laterales de los amino ácidos (R^1, R^2 y R^3). La incorporación de fragmentos de α,β,α-péptidos (con un residuo $\beta^{2,2,3}$*) en péptidos de mayor tamaño, permitiría preparar nuevos peptidomiméticos con conformaciones predecibles en solución, lo que resulta vital para modular la actividad biológica o catalítica.

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Conformation and Chiral Effects in α,β,α-Tripeptides

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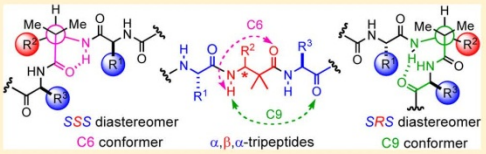
Supporting Information

ABSTRACT: Short α,β,α-tripeptides comprising a central chiral trisubstituted $\beta^{2,2,3}$*-amino acid residue form unusual γ-turns and δ-turns in $CDCl_3$ and DMSO-d_6 solutions but do not form β-turns. Thermal coefficients of backbone amide protons, 2D-NMR spectra, and molecular modeling revealed that these motifs were strongly dependent on the configuration (chiral effect) of the central β-amino acid residue within the triad. Accordingly, *SSS* tripeptides adopted an intraresidual γ-turn like (C6) arrangement in the central β-amino acid, whereas *SRS* diastereomers preferred an extended δ-turn (C9) conformation. A different *SRS*-stabilizing bias was observed in the crystal structures of the same compounds, which shared the extended δ-turn (C9) found in solution, but incorporated an additional extended β-turn (C11) to form an overlapped double turn motif.



INTRODUCTION

β-Amino acids exhibit a stricking ability to attain secondary structures far more efficiently than α-amino acids, and the term "foldamer"[1] has been coined for them and for some α,β-hybrids containing them.[2] As a result of their predictable folding patterns and their improved stability to proteolytic cleavage,[3] β-amino acid containing peptides are the peptidomimetics of choice in many biomedical applications.[4]

In the late 1990s, Gellman[5] and Seebach[6] established the general folding trends for β-peptides containing monosubstituted β^2- and β^3-amino acids or disubstituted $\beta^{2,3}$-amino acid units bearing proteinogenic side chains. Seebach also reported the conformational behavior of β-tripeptides constituted by geminally disubstituted $\beta^{2,2}$-amino acid residues. In the solid state, and depending on the nature of the $\beta^{2,2}$-substituents, such 3-mer peptides adopt either extended γ-turns (C8 hydrogen-bonded) or doubly extended δ-turns (C10), which are reminiscent of the canonical β-turns formed by α-amino acid tetrapeptides.[7] Introduction of a ^{D}Pro-$\beta^{3,3}$-amino acid α,β-dipeptide segment at the $(i-1)-(i+2)$ positions of a longer α-peptide stabilizes β-hairpins through extended β-turns (C11), either in the crystal or in methanol, as demonstrated by Balaram.[8] Far less attention has been drawn to trisubstituted $\beta^{2,2,3}$-amino acid containing hybrid α,β-peptides, despite the valuable protease inhibition properties shown by some of these compounds.[9]

Herein we report the first conformational study conducted in solution for model hybrid α,β,α-tripeptides **1**–**7** (Figure 1) containing a trisubstituted central $\beta^{2,2,3}$-amino acid residue with a single stereocenter at position β^3. The objective of this study was to establish the chiral effect exerted by the configuration of such stereocenter on the stabilization of several turned structures of the types C6–C11 (Figure 1) and to compare them to the C9 + C11 double hydrogen-bond pattern found in the solid state.[10]

According to crystal data (Figure 2), the *N*-(4-iodobenzoyl)-protected tripeptides **2** and **7** with a *SRS* configuration of the central triad feature identical double-turned motifs comprising an extended δ-turn (C9) and an extended β-turn (C11). The two overlapped turns share all the peptide chain atoms of the central $\beta^{2,2,3}$-amino acid residue and are further stabilized by intermolecular NH···O=C bonding. In the case of the C11 turn, a hydrogen bond forms between the 4-iodobenzoyl carbonyl oxygen and the Phe or Leu N_7H amides, whereas for the C9 turn the hydrogen bond is between the N_4H amide and the terminal ester carbonyl oxygen. The structures are further stabilized inside the crystal cell by additional intermolecular hydrogen bonds between the N_2H amide proton and the C=O oxygen of the β-amino acid residue of a contiguous molecule (not shown in Figure 2).

RESULTS AND DISCUSSION

The model tripeptides **1**–**7** were prepared as shown in Scheme 1 for compounds **3** and **4**. Thus, the α-dipeptide **8** underwent a one-pot radical decarboxylation–oxidation–alkylation process[10] to give the α,β-dipeptide **9** in good yield as a 2:1 diastereomer mixture. The saponification of the methyl ester, followed by coupling to H-Phe-OMe, afforded a separable mixture of α,β,α-tripeptides **3** (51%) and **4** (31%), which were used in the conformational studies. The other tripeptides **1**, **2**, and **5**–**7** have been previously reported.[10]

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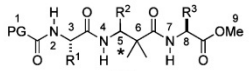


1-7

Peptide	PG	R^1(Aa)	R^2	R^3(Aa)	*	Triad
1	p-I-Bz	Me (Ala)	Me	Bn (Phe)	S	SSS
2	p-I-Bz	Me (Ala)	Me	Bn (Phe)	R	SRS
3	Bz	Me (Ala)	^{t}Bu	Bn (Phe)	S	SSS
4	Bz	Me (Ala)	^{t}Bu	Bn (Phe)	R	SRS
5	Cbz	^{i}Pr (Val)	Bn	^{t}Bu (Leu)	S	SSS
6	Cbz	^{i}Pr (Val)	Bn	^{t}Bu (Leu)	R	SRS
7	p-I-Bz	^{i}Pr (Val)	Bn	^{t}Bu (Leu)	R	SRS

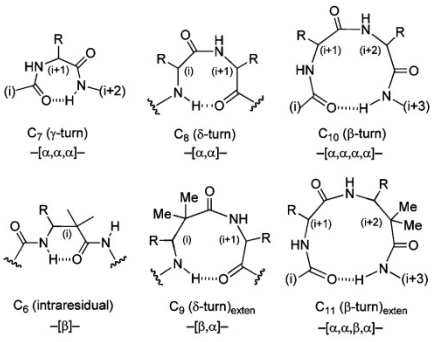


Figure 1. Model α,β,α-tripeptides **1**–**7** selected for conformational analysis and turn motifs in short peptides, comprising α-amino acids (top) and combinations of α- and $\beta^{2,2,3}$-amino acids (bottom). All structures are depicted as N→C sequences.

These model peptides **1**–**7** (Table 1) were designed to have different combinations of side chains (Me, *i*-Pr, *i*-Bu, Bn) with variable steric demand and hydrophobicity in order to study their interference with the intramolecular hydrogen bonding pattern in solution. Peptides **1**–**6** could be grouped into three pairs of

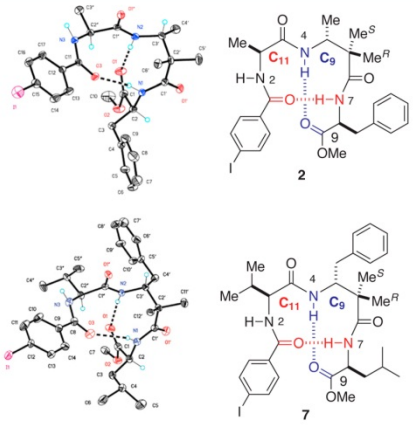
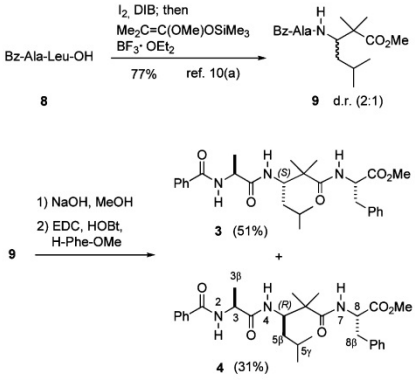


Figure 2. Crystal structures of α,β,α-tripeptides **2** and **7** containing a chiral trisubstituted central $\beta^{2,2,3}$-amino acid residue. A (C9 + C11) hydrogen bonding pattern with two overlapped turns is formed in each case.

Scheme 1. Preparation of Model Tripeptides 3 and 4



diastereomers (**1**/**2**, **3**/**4**, and **5**/**6**) according to the (*S*) or (*R*) configuration of the central β-amino acid residue, but in all instances, the configuration of the flanking α-amino acids was *S* (*L*) to represent natural peptides. Finally, the tripeptides were protected at the N-termini by 4-iodobenzoyl, benzoyl, or Cbz groups and were capped at the C-termini as methyl esters. As mentioned above, the 4-iodobenzoylamido tripeptides of *SRS* configurations provided crystals (**2** and **7**) which were used to compare their C9 + C11 structures with the solution structures of **2** and **6** (the *p*-I-benzoyl analogue of compound **7**), respectively.

Although water was considered first as the most biologically meaningful medium for the study, finally less polar solvents were chosen for solubility reasons. Thus, each peptide was dissolved into DMSO-d_6 and $CDCl_3$ (5×10^{-3} M), and all protons were unambiguously assigned from COSY, TOCSY, HSQC, and HMBC spectra. Compounds **1**–**7** yielded sharp, well-resolved NMR spectra consisting of single sets of signals in both solvents. Experiments were then performed to determine the ^{1}H NMR temperature coefficients[11] for the exchangeable amide protons of the tripeptides in DMSO-d_6 solutions over a temperature range of 300–330 K at 5 K intervals (see Table 1). Vicinal coupling constants ^3J(HN–CαH) were also measured, and the corresponding ϕ dihedral angles were calculated using the Karplus equation.[12] Dihedral angles in the solid state for crystalline compounds **2** and **7** are also included in Table 1.

Relevant noncontiguous interproton distances for peptides **1**–**6** (Table 2; see also Supporting Information Table S1) were calculated following the ISPA (isolated spin-pair approximation) method[13] from the integration of key NOESY crosspeaks recorded in $CDCl_3$ solvent at 300 K (500 MHz) with mixing times of 400 ms. Interproton distances calculated in DMSO-d_6 solutions delivered values essentially identical to those obtained in $CDCl_3$ (see Table 2). Diagnostic interproton distances around the central β-amino acid residue are collected for peptides **1**, **2** and **5**, **6** in Figure 4.

Conformational Analysis. An inspection of the ^{1}H NMR spectra recorded from solutions of the tripeptides **1**–**7** in $CDCl_3$ or DMSO-d_6 soon revealed the absence of some key deshielded amide NH required to support the overlapped double turn conformations of **2** and **7** in the solid state (Figure 2), suggesting that the large extended β-turn (C11) of the crystals could break down when dissolved. Indeed, only the N_4H amide protons of the β-amino acid residues participated in the intramolecular

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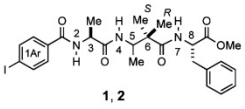
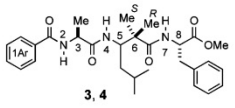
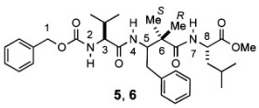
Table 1. Chemical shifts (δ), Amide NH Thermal Coefficients ($\Delta\delta/\Delta T$), and HN−CαH Dihedral Angles (ϕ) Measured for α,β,α-Tripeptides 1−7



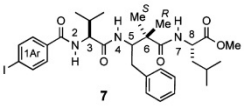
1, 2



3, 4



5, 6

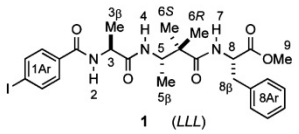


7

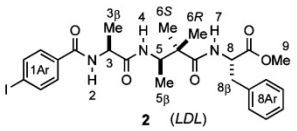
peptide	**1** (*SSS*)	**2** (*SRS*)	**3** (*SSS*)	**4** (*SRS*)	**5** (*SSS*)	**6** (*SRS*)	**7** (*SRS*)
$N_2H(\delta)^a$	7.42 (+1.11)	7.83 (+0.80)	7.08 (+1.34)	7.26 (+1.24)	5.00 (+2.00)	5.24 (+1.99)	6.71 (+1.25)
$N_4H(\delta)^a$	7.12 (+0.46)	7.67 (−0.14)	6.95 (+0.40)	7.19 (+0.17)	7.17 (+0.26)	7.56 (+0.00)	7.72 (+0.11)
$N_7H(\delta)^a$	6.15 (+1.66)	7.22 (+0.55)	6.17 (+1.60)	7.41 (+0.30)	6.17 (+1.84)	7.16 (+0.65)	7.48 (+0.92)
$N_2H(\Delta\delta/\Delta T)^b$	−4.5	−4.9	−4.0	−4.8	−5.9	−6.5	−5.2
$N_4H(\Delta\delta/\Delta T)^b$	−3.7	−3.8	−4.0	−4.6	−3.7	−4.9	−4.7
$N_7H(\Delta\delta/\Delta T)^b$	−5.9	−5.6	−6.4	−5.4	−6.9	−5.4	−6.0
$^3J(\phi\ HN_2{-}C_3H)^c$	6.8 (−140)	6.3 (−136)[−149]^d	5.9 (−133)	7.4 (−142)	8.1 (−152)	7.9 (+147)	7.9 (+147)[−158]^d
$^3J(\phi\ HN_4{-}C_5H)^c$	9.2 (+164)	10.2 (+180)[+137]^d	10.5 (+180)	9.8 (+180)	9.8 (+180)	10.2 (+174)	10.0 (+170)[+166]^d
$^3J(\phi\ HN_7{-}C_8H)^c$	7.5 (−146)	7.9 (−150)[−167]^d	7.8 (−151)	7.7 (−148)	7.5 (+146)	7.8 (+147)	7.9 (+149)[−148]^d

^{a}Chemical shifts (ppm) measured in $CDCl_3$. Values in parentheses represent variations of the chemical shift when the $CDCl_3$ solvent was changed to DMSO-d_6. ^{b}Thermal coefficients in ppb/K measured in DMSO-d_6. ^{c}Coupling constants (J) in Hz. The ϕ dihedral angles, in parentheses, were calculated from the Karplus equation. ^{d}Dihedral angles, in brackets, from X-ray data, ref 10a.

Table 2. Key Interproton Distances (Å) Calculated from NOESY^a Experiments for α,β,α-Tripeptides 1 and 2 in $CDCl_3$ and DMSO-d_6 Solutions



1 (*LLL*)



2 (*LDL*)

NOE	Ha-Hb^b	**1** ($CDCl_3$)	**1** (DMSO-d_6)	**2** ($CDCl_3$)	**2** (DMSO-d_6)	**2** (X-ray)^c
1	$Ar_1^{ortho}{-}N_2H$	2.16^{ref}	2.16^{ref}	2.16^{ref}	2.16^{ref}	[2.2]
2	$N_2H{-}C_3H$	2.9	3.0	3.8	4.0	[2.7]
3	$N_2H{-}C_{3\beta}Me$	2.4	2.4	2.4	2.5	[2.6]
4	$C_{3\beta}Me{-}N_4H$	4.1	4.1		3.8	[3.1]
5	$N_4H{-}C_5H$	3.3	3.1	3.9	4.3	[2.7]
6	$N_4H{-}C_{5\beta}Me$	2.6	3.0		3.1	[2.6]
7	$N_4H{-}C_6Me^R$	4.2		2.7	2.8	[3.0]
8	$N_4H{-}C_6Me^S$	2.7	2.9	4.5	4.1	[4.3]
9	$N_4H{-}N_7H$			2.7	2.9	[2.3]
10	$C_5H{-}C_6Me^R$	2.5	2.7	2.6	2.2	[2.5]
11	$C_5H{-}C_6Me^S$	2.5	3.1	2.6	2.8	[2.5]
12	$N_7H{-}C_6Me^R$	2.5	2.5	2.2	2.8	[2.6]
13	$N_7H{-}C_6Me^S$	3.0	2.7	2.9	2.8	[4.0]
14	$N_7H{-}C_8H$	2.6		4.5	3.4	[2.5]
15	$N_7H{-}C_{8\beta}H$	3.7		2.6	4.1	[2.5]
16	$Ar_8H{-}C_9(OMe)$	3.6			4.3	

^{a}Experiments (500 MHz) carried out at 300 K, mixing time 400 ms. ^{b}Reference distance. ^{c}Crystal interproton distances from X-ray analysis of **2** (C9 + C11 conformer).

hydrogen bond network of the peptides in solution, while the N_7H amide protons were exposed to the solvent. This was evident from the analysis of thermal coefficients in DMSO-d_6[11] (Table 1, rows 4−6) showing absolute values in the range −3.7 to −4.9 ppb/K for N_4H protons, whereas amides N_2H and N_7H gave larger thermal coefficients (up to −6.9 ppb/K). Solvent change from nonacceptor $CDCl_3$ to acceptor DMSO-d_6 resulted in very small chemical shift for β-amino acid N_4H amides in all peptides (0.0−0.4 ppm), but in a significantly larger downfield shift (0.4−1.9 ppm) for α-amino acid amides N_2H and N_7H (Table 1, rows 1−3). Seeking for more insight into the origin of the chiral effect differentiating the *SSS* conformers (**1**, **3** and **5**) and *SRS* conformers (**2**, **4**, **6**, and **7**), we noticed that the chemical shift of amide N_7H protons experienced different downfield displacement upon solvent changing from $CDCl_3$ to DMSO-d_6, depending on the β-amino acid β-carbon configuration. Thus, N_7H amide peak shifted downfield by 1.7−1.8 ppm in peptides **1**, **3** and **5** (*SSS* configuration), whereas peptides **2**, **4**, **6**, and **7** (*SRS* configuration) shifted only 0.3−0.6 ppm. This lower exposition to coordinating solvent suggests a conformation with the N_7H group oriented toward the inner side of the peptide turn backbone in *SRS* diastereomers.

All of the ϕ dihedral angles measured in solution for the vicinal (HN−CαH) atoms in the three amino acids of peptides **1**−**7**

showed large values, in the range 133−180°, and were compatible with quasi-staggered dispositions of the HN−CH bonds (Table 1, rows 7−9). They were also very close to the dihedral angles of the crystalline peptides **2** and **7** (Table 1, values in brackets) suggesting that, after the solution of tripeptides **1**−**7** in $CDCl_3$ or DMSO-d_6, the relative spatial arrangement of the α-amino acid residues around the β-amino acid should resemble an open angular shape in *SSS* diastereomers and a closed turned shape in *SRS* diastereomers (Figure 3). These diastereomeric

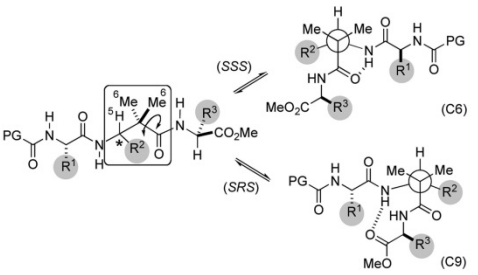


Figure 3. Main folding pattern (chiral effect) for peptides **1**−**6** in solution.

conformers, arising from rotations of the (Me_2C−CO) bond in the central β-amino acid residue, would be spatially directed by the arrangement of the R^2 substituent attached to the β^3 chiral stereocenter *C_5H and further stabilized with the formation of two different intramolecular hydrogen bonds (C6) and (C9).

An examination of the noncontiguous interproton distances collected in Figure 4 (see also Table 2 and Supporting Information Table S1) allowed the identification of some diagnostic NOESY crosspeaks around the central β-amino acid residue to discriminate the prevalent conformations of *SSS* and *SRS* diastereomers in tripeptides **1**, **2** and **5**, **6**. Unfortunately, some key peaks of tripeptides **3** and **4** (e.g., the β-amino acid geminal methyl groups) were overlapped in the ^{1}H NMR spectra, and these compounds were discarded from NOESY-based interproton distance analysis.

In the β-amino acid residue of peptides **1**, **2** and **5**, **6**, distances between the C_5H proton and the geminal diastereotopic methyl groups ($Me_6^{pro\text{-}R}$/$Me_6^{pro\text{-}S}$) were very similar to one another in all instances, either in solution or in the solid state. This confirmed the antiperiplanar disposition of the C_5−H proton and the β-amino acid's carbonyl group as the most stable and largely preferred conformation of the central residue in these tripeptides. Likewise, the distance between the N_7H amide proton and the geminal methyl groups at position C_6 showed a similar pattern in all instances, with the N_7H proton significantly closer to the $Me_6^{pro\text{-}R}$ group than to the $Me_6^{pro\text{-}S}$ group. In the crystal, peptides **2** and **7** had a large N_7H − $Me_6^{pro\text{-}S}$ distance of ∼4.0 Å, which permitted the involvement of the N_7H amide proton in an extended β-turn (C11). Upon solution in $CDCl_3$ such hydrogen bond vanished in *SRS* isomers, the N_7H amide proton approached the $Me_6^{pro\text{-}R}$ group and only the more stable (C9) extended δ-turn remained (Figure 4). Conversely, the conformation of *SSS* tripeptides **1** and **5** was stabilized by an unusual intrarresidual (C6) H-bond.

Assuming (C6) and (C9) preferred conformations for α,β,α-tripeptides **1**−**6** in solution, the N_4H/N_7H and N_4H/$Me_6^{pro\text{-}R}$ pairs of protons were anticipated to be separated from each other

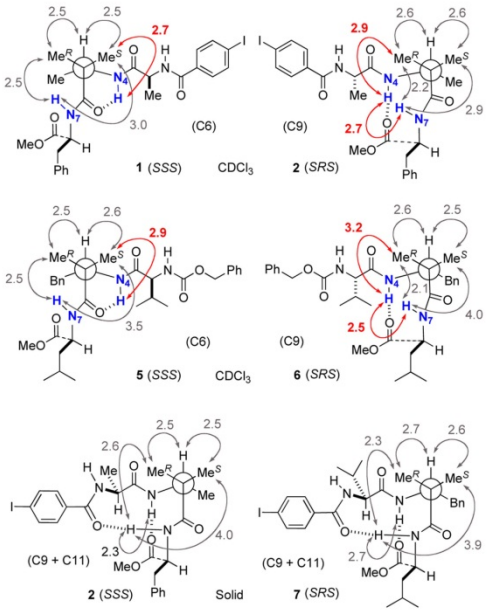


Figure 4. NMR−NOESY interproton distances (in Å) and main conformation structures for peptides **1**, **2** and **5**, **6** in $CDCl_3$ solution and in the solid state (for **2** and **7**). Diagnostic distances are highlighted in red.

in *SSS* tripeptides **1** and **5** but much closer in *SRS* diastereomers **2** and **6**, thus being suitable for diagnostic NOE analysis. As shown in Figure 5 for the NOE signals of peptides **1** and **2**, the crosspeaks between N_4H/N_7H amide protons (NOE **f**) were actually found in the NOESY spectrum of **2**, integrating for a 2.5 Å distance, whereas these crosspeaks were absent in the NOESY spectra of the *SSS* tripeptide **1** (for analogous spectra of **5** and **6**, see the Supporting Information, Figure S13). Consistent with the proposed conformers, strong NOE crosspeaks for N_4H amide protons with $Me_6^{pro\text{-}R}$ group were also found only in the *SRS* tripeptides **2** and **6**, but not in the *SSS* diastereomer counterparts **1** and **5**. In the later tripeptides, the N_4H amide protons gave strong NOE interactions only with the diastereotopic $Me_6^{pro\text{-}S}$ protons (see NOE **d** in Figure 5).

No significant additional long-range inter-residual NOE crosspeaks were found in the NOESY spectra of peptides **1**−**6**. Furthermore, the Molecular Mechanics minimization of **1**−**6** including the NMR interproton distance restrictions and ϕ dihedral angles measured in solution, yielded essentially single-conformer structures in each case. These observations collectively suggested that the chiral conformational bias observed for tripeptides **1**−**6** in solution is roughly independent of the size and nature of the R^1, R^2 and R^3 substituents and, most important, that incorporation of α,β,α-peptide segments with a $\beta^{2,2,3}$*-amino acid in longer peptides could be envisaged to prepare novel peptidomimetics with predictable shapes in solution (Figure 6).[14]

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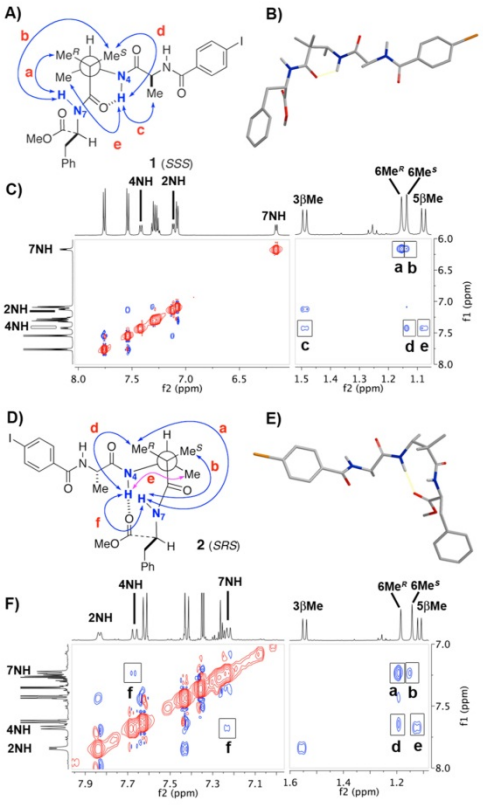

Figure 5. Diagnostic NOE interactions for peptides **1** and **2**: Spatially close protons in **1** (A) and **2** (D). Molecular Mechanics (SYBIL force field) minimum energy conformers of **1** (B) and **2** (E) restrained with NMR interproton distances and ϕ dihedral angles (only amide protons are shown for clarity). Expansions of key NOESY crosspeaks for **1** (C) and **2** (F). For position numbering, see structures in Table 2.

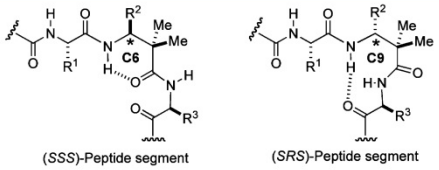

Figure 6. General intramolecular hydrogen-bond patterns populated in solution for α,β-hybrid peptides containing a central $\beta^{2,2,3}$*- chiral residue.

■ CONCLUSIONS

A uniform chiral effect was found to dictate the conformational behavior of α,β,α-tripeptides containing a central $\beta^{2,2,3}$*-amino acid residue with a single stereocenter at β^3 position when such peptides were dissolved in $CDCl_3$ and DMSO-d_6 solvents. Tripeptides with homochiral *SSS* relative configuration populate in solution a conformation characterized by an unusual (C6) turn H-bonded between the N−H and C═O groups of the central β-amino acid residue. Conversely, tripeptides with heterochiral *SRS* relative configuration stabilize an extended δ-turn with a (C9) hydrogen bond between the N−H of the β-amino acid residue and the C═O of the next α-amino acid. These results, based on amide NH thermal coefficient measurements, diagnostic NOESY crosspeak analysis and computational modeling, also evidenced significant differences with the solid state conformations previously reported for similar heterochiral *SRS* tripeptides, which were characterized by the additional stabilization of the extended δ-turn (C9) with an extended β-turn (C11) spanning from the C═O of the protecting group and the N−H of the C-terminal α-amino acid.

■ EXPERIMENTAL SECTION

General Experimental Methods. Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under nitrogen atmosphere. The spray reagents for TLC analysis were 0.25% ninhydrin in ethanol and/or Fleet's reagent [$Ce(SO_4)_2$ (0.5 g) and ammonium phosphomolybdate hydrate (2.5 g) in H_2SO_4 (5 mL) and water (65 mL)]. Once sprayed, the TLC was heated until development of color. Merck silica gel 60 PF_{254} and 60 (0.063−0.2 mm) were used for rotatory chromatography and column chromatography, respectively. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature (26 °C). NMR spectra were determined at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C, and Mass spectra (EI) were determined at 70 eV using an ion trap mass analyzer. ^{1}H NMR references: $CDCl_3$ (δ 7.26), DMSO (δ 2.49). ^{13}C NMR references: $CDCl_3$ (δ 77.0), DMSO (δ 39.5).

Preparation of Compounds 1−7. The preparation and spectroscopic data of compounds **1**, **2**, and **5**−**7** was reported previously.[10a] The syntheses of compounds **3** and **4**, and their precursor **9**, are reported below.

*N-Benzoyl-L-alanyl-α,α-dimethyl-(S)-β-homoleucine Methyl Ester (**9**).* To a solution of Bz-Ala-Leu-OH (**8**) (61 mg, 0.2 mmol) in dry dichloromethane (6 mL) were added iodine (15 mg, 0.06 mmol) and diacetoxyiodobenzene (DIB) (97 mg, 0.3 mmol). The reaction mixture was stirred at 26 °C for 4 h under irradiation with visible light. Then the solution was cooled to 0 °C, and methyl (trimethylsilyl)dimethylketene acetal (203 μL, 174 mg, 1.0 mmol) was injected, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (51 μL, 57 mg, 0.4 mmol). The mixture was allowed to reach room temperature and stirred for 3 h; it was then poured into 10% aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (1:1, 10 mL) and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by rotatory chromatography 85:15 (hexanes/ethyl acetate mixtures) to give the product **8** (56 mg, 77%) as a 2:1 diastereomer mixture: amorphous solid; IR ($CHCl_3$) ν_{max} 3424, 3323, 1721, 1676, 1652, 1511, 1484 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H major diastereomer: 0.75 (3H, d, J = 6.6 Hz, 5γ-Me_a), 0.84 (3H, d, J = 6.3 Hz, 5γ-Me_b), 1.19 (3H, s, 6-Me_a), 1.19−1.35 (2H, m, 5β-H_2), 1.20 (3H, s, 6-Me_b), 1.49 (1H, m, 5γ-H), 1.53 (3H, d, J = 6.9 Hz, 3-Me), 3.66 (3H, s, OMe), 4.15 (1H, m, 5-H), 4.78 (1H, m, 3-H), 6.83 (1H, br d, J = 9.8 Hz, NH_{Leu}), 7.21 (1H, br d, J = 7.3 Hz, NH_{Ala}), 7.40 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.48 (1H, dd, J = 7.6, 7.8 Hz, Ar), 7.78 (2H, d, J = 8.5 Hz, Ar); minor isomer: 0.88 (3H, d, J = 6.6 Hz, 5γ-Me_a), 0.90 (3H, d, J = 6.3 Hz, 5γ-Me_b), 1.11 (3H, s, 6-Me_a), 1.15 (3H, s, 6-Me_b), 1.11−1.20 (2H, m, 5β-H_2), 1.51 (3H, d, J = 6.9 Hz, 3-Me), 1.57 (1H, m, 5γ-H), 3.63 (3H, s, OMe), 4.15 (1H, m, 5-H), 4.78 (1H, m, 3-H), 6.81 (1H, br d, J = 8.5 Hz, NH_{Leu}), 7.23 (1H, br d, J = 9.1 Hz, NH_{Ala}), 7.39 (2H, dd, J = 7.9, 8.0 Hz, Ar), 7.47 (1H, dd, J = 7.6, 7.8 Hz, Ar), 7.79 (2H, d, J = 8.7 Hz, Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C major diastereomer: 19.2 (CH_3), 21.32 (CH_3), 22.1 (CH_3), 23.1 (CH_3), 23.7 (CH_3), 25.0 (CH), 40.1 (CH_2), 46.7 (C), 49.5 (CH), 51.8 (CH_3), 53.3 (CH), 127.0 (2 × CH), 128.5 (2 × CH), 131.7 (CH), 133.9 (C), 167.1 (C), 172.2 (C), 177.0 (C); minor diastereomer: 18.8 (CH_3), 21.27 (CH_3), 21.9 (CH_3), 23.3 (CH_3), 23.8

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(CH_3), 25.2 (CH), 40.3 (CH_2), 46.5 (C), 49.5 (CH), 51.8 (CH_3), 53.3 (CH), 127.0 (2 × CH), 128.5 (2 × CH), 131.7 (CH), 133.8 (C), 167.1 (C), 172.4 (C), 177.1 (C); MS (EI) *m*/*z* (rel intensity) 363 (M^+ + H, 2), 176 ([PhCONHCH(Me)CO]$^+$, 25), 149 ([PhCONHCH(Me) + H]$^+$, 53), 148 ([PhCONHCH(Me)]$^+$, 62), 105 ([PhCO]$^+$, 100), 86 ([$NH_2CHCH_2CHMe_2$], 58); HRMS (EI) calcd for $C_{20}H_{31}N_2O_4$ 363.2284, found 363.2270; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0707; calcd for $C_9H_{11}NO$ 149.0841, found 149.0841; calcd for $C_9H_{10}NO$ 148.0762, found 148.0758; calcd for C_7H_5O 105.0340, found 105.0337; calcd for $C_5H_{12}N$, 86.0970, found 86.0967. Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.26; H, 8.35; N, 7.37.

N-Benzoyl-L-alanyl-[α,α-dimethyl-(S)-β-homoleucyl]-L-phenylalanine Methyl Eester (3) and N-Benzoyl-L-alanyl-[α,α-dimethyl-(R)-β-homoleucyl]-L-phenylalanine Methyl Ester (4). To a solution of the dipeptide mixture **8** (120 mg, 0.33 mmol) in methanol (7 mL) at 0 °C was slowly added 2 N aqueous NaOH (3 mL). The reaction mixture was allowed to reach 26 °C and stirred for 64 h, and then it was cooled to 0 °C, diluted with water, poured into 5% HCl, and extracted with EtOAc. The organic layer was dried and evaporated, and the residue was dissolved in dry CH_2Cl_2 (4 mL) and treated with L-phenylalanine methyl ester hydrochloride (70 mg, 0.33 mmol). The solution was cooled to 0 °C, and Et_3N (45 μL, 33 mg, 0.33 mmol), EDC (69 mg, 0.36 mmol), and HOBt (49 mg, 0.36 mmol) were added. The reaction mixture was stirred at 0 °C for 2 h, and then it was allowed to reach room temperature, stirred for 18 h, and finally poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. After usual drying and solvent removal, the residue was purified by rotatory chromatography (hexanes/EtOAc, 65:35), affording compounds **3** (86 mg, 51%) and **4** (52 mg, 31%).

Compound (3): amorphous solid; $[\alpha]_D$ +26 (0.43, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3439, 3420, 1741, 1652, 1505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.81 (3H, d, *J* = 6.6 Hz, 5γ-Me_a), 0.85 (3H, d, *J* = 6.6 Hz, 5γ-Me_b), 1.13 (3H, s, 6-Me_a), 1.15 (3H, s, 6-Me_b), 1.15−1.27 (2H, m, 5β-H_2), 1.48 (1H, m, 5γ-H), 1.50 (3H, d, *J* = 6.9 Hz, 3-Me), 3.07 (1H, dd, *J* = 6.3, 13.9 Hz, 8β-H_a), 3.15 (1H, dd, *J* = 5.7, 13.9 Hz, 8β-H_b), 3.75 (3H, s, OMe), 3.90 (1H, ddd, *J* = 2.8, 11.1, 11.3 Hz, 5-H), 4.63 (1H, dddd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 3-H), 4.78 (1H, ddd, *J* = 6.0, 6.3, 7.6 Hz, 8-H), 6.11 (1H, br d, *J* = 7.6 Hz, N_7H [NH_{Phe}]), 6.94 (1H, br d, *J* = 9.8 Hz, N_4H [NH_{Leu}]), 7.06 (1H, br d, *J* = 6.6 Hz, N_2H [NH_{Ala}]), 7.08 (2H, d, *J* = 6.8 Hz, Ar), 7.25−7.31 (3H, m, Ar), 7.41 (2H, dd, *J* = 6.6, 7.2 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.80 (2H, d, *J* = 7.1 Hz, Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 19.2 (CH_3), 21.4 (CH_3), 23.2 (CH_3), 23.8 (CH_3), 24.4 (CH_3), 25.0 (CH), 37.5 (CH_2), 40.1 (CH_2), 45.6 (C), 49.5 (CH), 52.4 (CH_3), 52.8 (CH), 54.9 (CH), 127.1 (2 × CH), 127.3 (CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH), 131.5 (CH), 134.2 (C), 135.8 (C), 166.9 (C), 171.9 (2 × C), 176.4 (C); MS (EI) *m*/*z* (rel intensity) 509 (M^+, 1), 361 (M^+ − PhCONHCHMe, 15), 249 ([$Me_2CCONHCH(CH_2Ph)CO_2Me$ + H]$^+$, 39), 148 ([PhCONHCH(Me)]$^+$, 32), 105 ([PhCO]$^+$, 100), 86 ([$NH_2CHCH_2CHMe_2$], 95); HRMS (EI) calcd for $C_{29}H_{39}N_3O_5$ 509.2890, found 509.2888; calcd for $C_{20}H_{29}N_2O_4$ 361.2127, found 361.2120; calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1356; calcd for $C_9H_{10}NO$ 148.0762, found 148.0764; calcd for C_7H_5O 105.0340, found 105.0342; calcd for $C_5H_{12}N$ 86.0970, found 86.0967. Anal. Calcd for $C_{29}H_{39}N_3O_5$: C, 68.34; H, 7.71; N, 8.25. Found: C, 68.65; H, 7.86; N, 8.22.

Compound (4): amorphous solid; $[\alpha]_D$ +38 (0.17, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3442, 3362, 1731, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.88 (3H, d, *J* = 6.6 Hz, 5γ-Me_a), 0.90 (3H, d, *J* = 6.6 Hz, 5γ-Me_b), 1.11 (3H, s, 6-Me_a), 1.12 (3H, s, 6-Me_b), 1.23 (1H, ddd, *J* = 3.8, 12.0, 15.4 Hz, 5β-H_a), 1.34 (1H, ddd, *J* = 2.8, 10.1, 14 Hz, 5β-H_b), 1.52 (3H, d, *J* = 6.9 Hz, 3-Me), 1.56 (1H, m, 5γ-H), 3.23 (2H, d, *J* = 6.8 Hz, 8β-H_2), 3.78 (3H, s, OMe), 3.89 (1H, ddd, *J* = 2.8, 11.0, 11.7 Hz, 5-H), 4.46 (1H, dddd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 3-H), 4.78 (1H, ddd, *J* = 6.3, 6.6, 8.0 Hz, 8-H), 7.15 (1H, d, *J* = 8.2 Hz, N_7H [NH_{Phe}]), 7.24 (1H, br b, N_2H [NH_{Ala}]), 7.24−7.37 (8H, m, Ar + N_4H [NH_{Leu}]), 7.47 (1H, dd, *J* = 7.3, 7.5 Hz, Ar), 7.76 (2H, d, *J* = 6.9 Hz, Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 17.6 (CH_3), 21.3 (CH_3), 22.6 (CH_3), 23.9 (2 × CH_3), 25.3 (CH), 36.6 (CH_2), 38.8 (CH_2), 46.5 (C), 50.8 (CH), 52.7 (CH_3), 54.3 (CH), 54.5 (CH), 126.9 (CH), 127.1 (2 × CH), 128.5 (4 × CH), 129.2 (2 × CH), 131.6 (CH), 133.6 (C), 137.0 (C), 167.6 (C), 172.8 (C), 174.5 (C), 175.6 (C); MS (EI) *m*/*z* (rel intensity) 509 (M^+, 1), 361 (M^+ − PhCONHCHMe, 20), 249 ([$Me_2CCONHCH(CH_2Ph)CO_2Me$ + H]$^+$, 60), 148 ([PhCONHCH(Me)]$^+$, 36), 105 ([PhCO]$^+$, 100), 86 ([$NH_2CHCH_2CHMe_2$], 70); HRMS (EI) calcd for $C_{29}H_{39}N_3O_5$ 509.2890, found 509.2882; calcd for $C_{20}H_{29}N_2O_4$ 361.2127, found 361.2126; calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1358; calcd for $C_9H_{10}NO$ 148.0762, found 148.0767; calcd for C_7H_5O 105.0340, found 105.0336; calcd for $C_5H_{12}N$ 86.0970, found 86.0970. Anal. Calcd for $C_{29}H_{39}N_3O_5$: C, 68.34; H, 7.71; N, 8.25. Found: C, 68.64; H, 7.83; N, 8.20.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR, ^{13}C NMR, and NOESY spectroscopic data of compounds **1**−**6** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Conformation and Chirality Effect in α,β,α-Tripeptides

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SUPPORTING INFORMATION

1D and 2D NMR Spectra of Compounds 1-6. **page**

1. ^{1}H NMR spectra of compounds **1-6** with assigned protons S2

2. NOESY Spectra of compounds **1-6** in $CDCl_3$ S5

3. Inter-proton distances for compounds **3-7** S9

4. ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **4** and **9** S10

^{1}H NMR spectra of compounds 1-6 with assigned protons

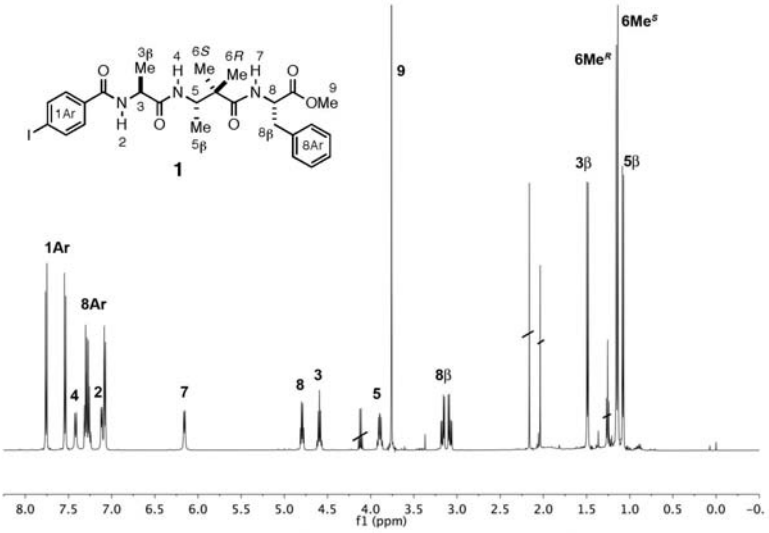


Figure S1. Proton assignation for the ^{1}H NMR spectrum of **1** in $CDCl_3$

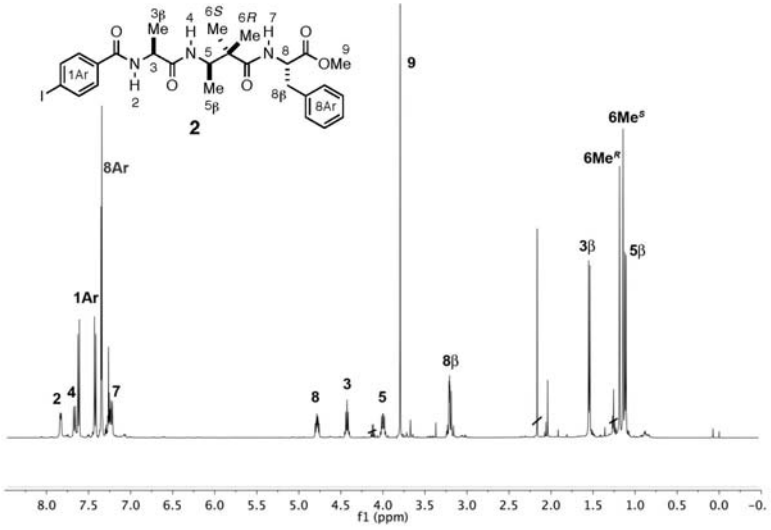


Figure S2. Proton assignation for the ^{1}H NMR spectrum of **2** in $CDCl_3$

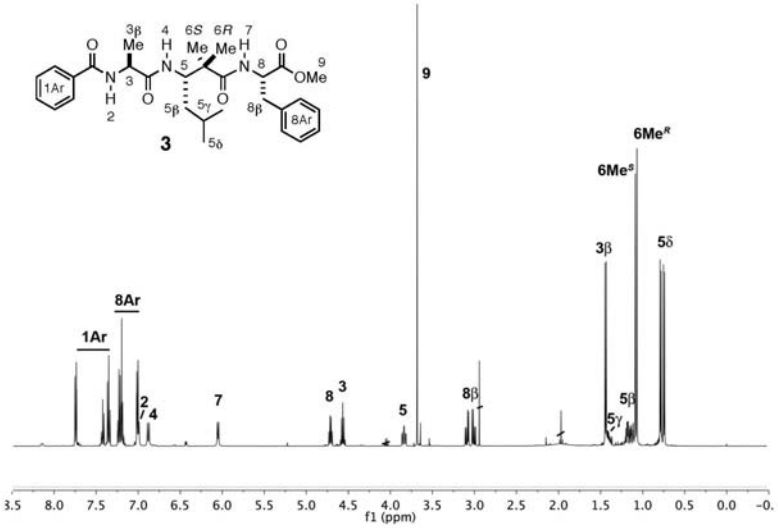


Figure S3. Proton assignation for the ^{1}H NMR spectrum of **3** in $CDCl_3$

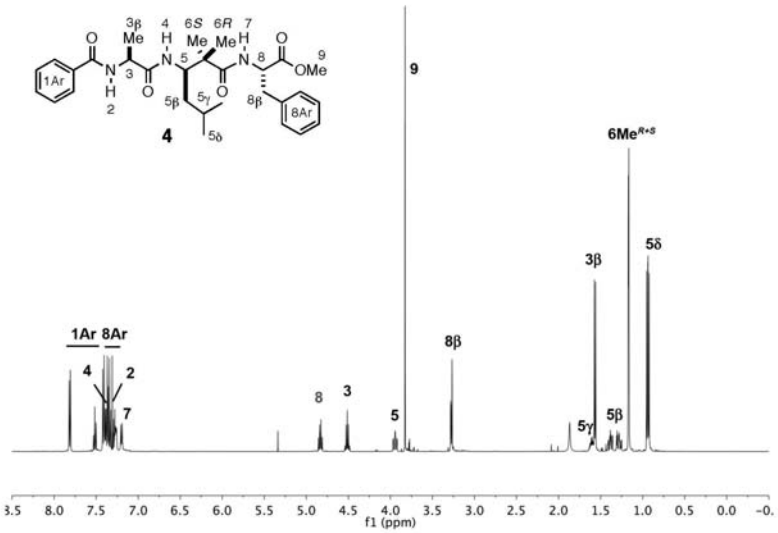


Figure S4. Proton assignation for the ^{1}H NMR spectrum of **4** in $CDCl_3$

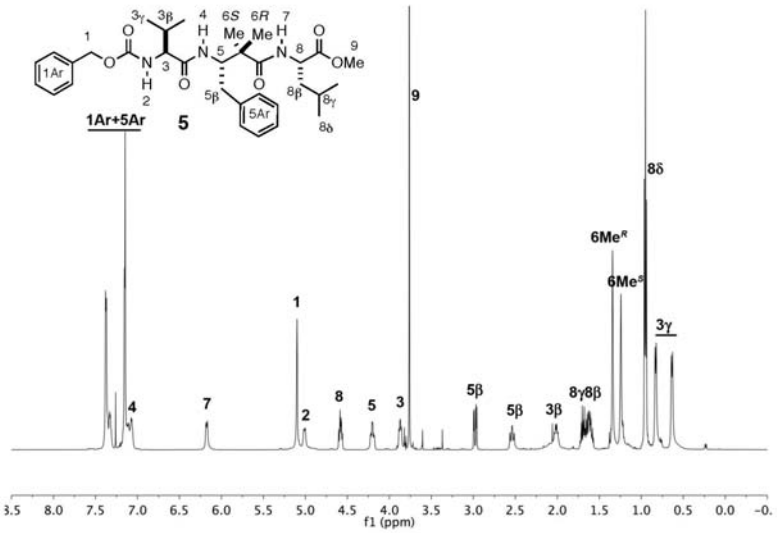


Figure S5. Proton assignation for the ^{1}H NMR spectrum of **5** in $CDCl_3$

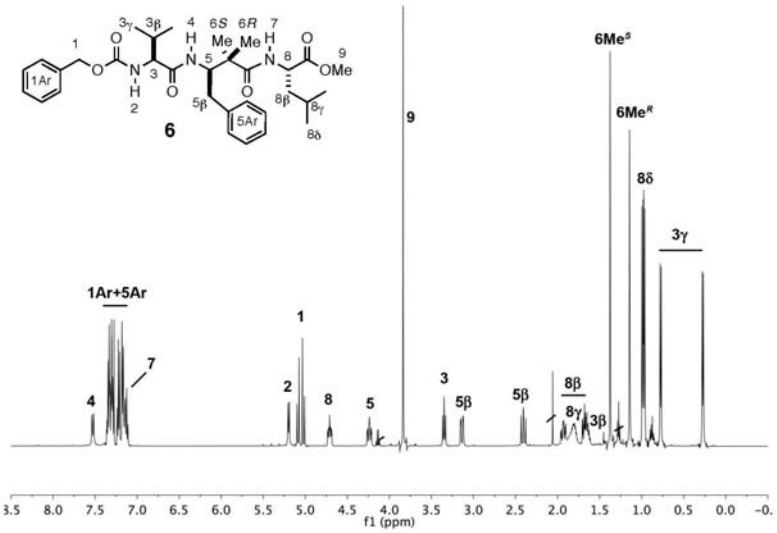


Figure S6. Proton assignation for the ^{1}H NMR spectrum of **6** in $CDCl_3$

2. NOESY Spectra of compounds 1-6 in $CDCl_3$

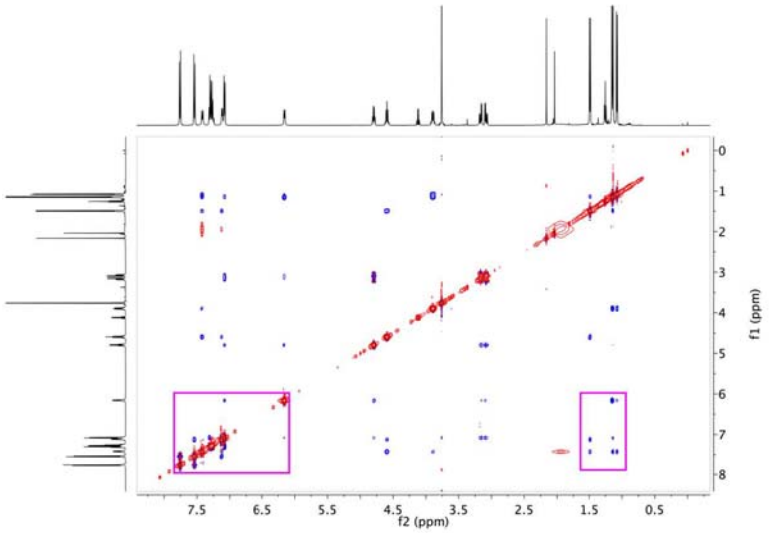


Figure S7. NOESY spectrum of **1** (500 MHz, 300K, mixing time 400 ms) in $CDCl_3$

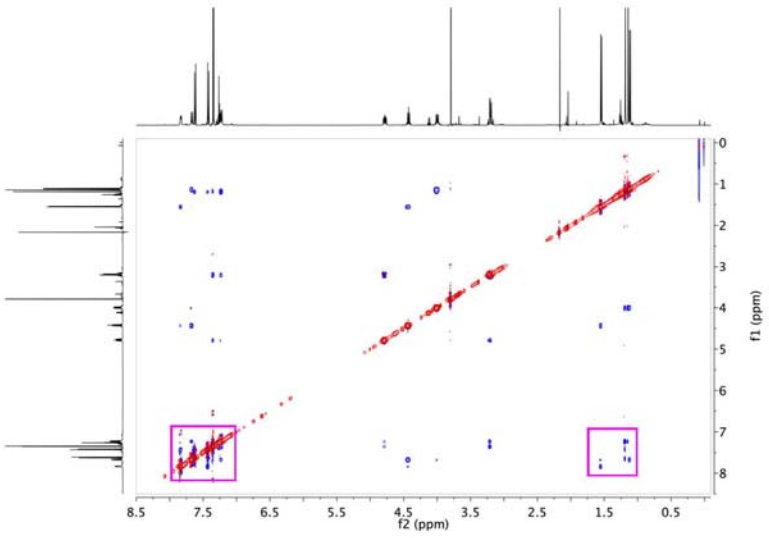


Figure S8. NOESY spectrum of **2** (500 MHz, 300K, mixing time 400 ms) in $CDCl_3$

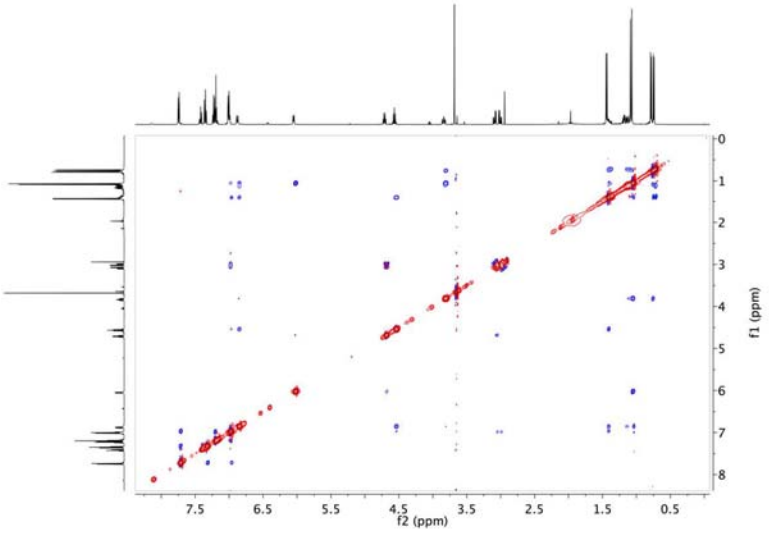


Figure S9. NOESY spectrum of **3** (500 MHz, 300K, mixing time 400 ms) in $CDCl_3$

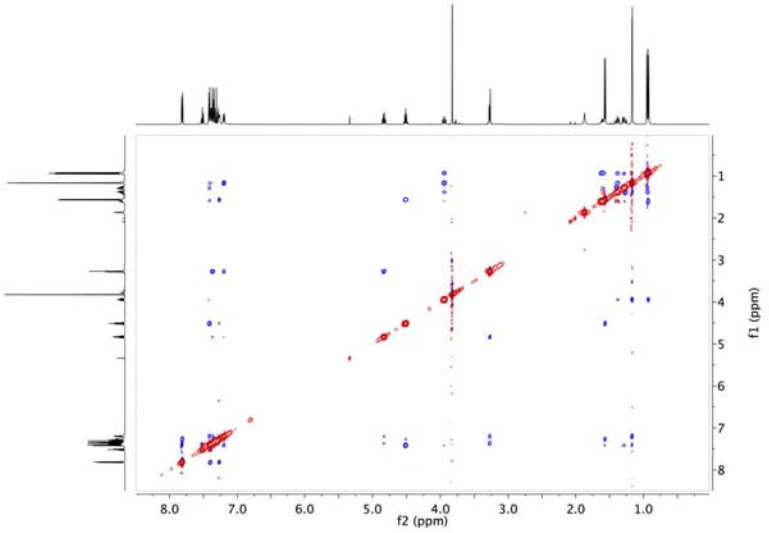


Figure S10. NOESY spectrum of **4** (500 MHz, 300K, mixing time 400 ms) in $CDCl_3$

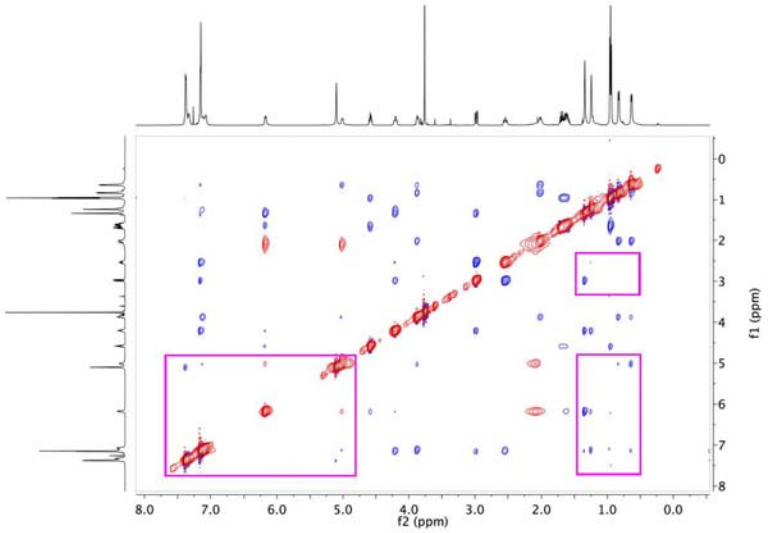


Figure S11. NOESY spectrum of **5** (500 MHz, 300K, mixing time 400 ms) in $CDCl_3$

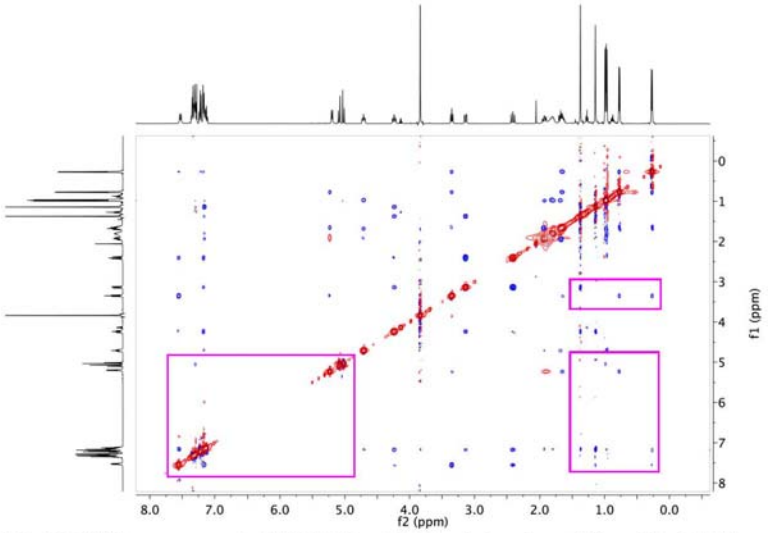


Figure S12. NOESY spectrum of **6** (500 MHz, 300K, mixing time 400 ms) in $CDCl_3$

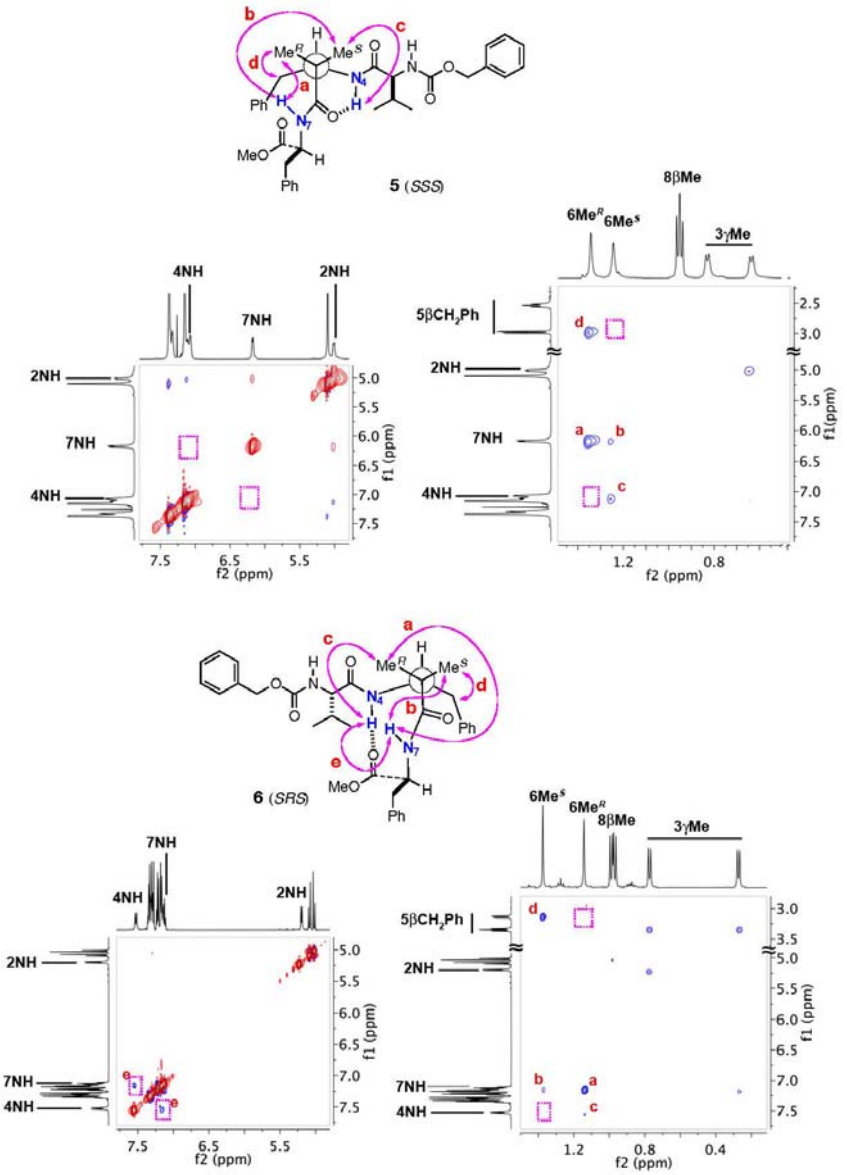
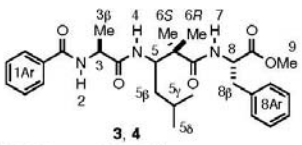
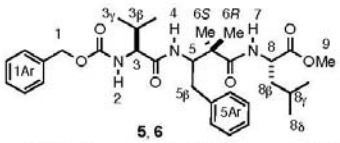
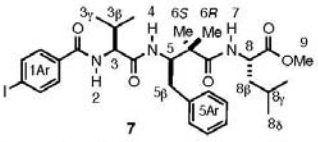


Figure S13. Expansions of the NOESY spectra of **5** and **6**. Rectangles represent diagnostic crosspeak positions for actual and alternative conformers.

Table S1. Inter-proton distances (Å) calculated from NOESY[a] experiments for α,β,α-tripeptides **3–6** in $CDCl_3$ solution and for **7** from X-ray diffraction data.







NOE	Ha-Hb	**3** (*SSS*)	**4** (*SRS*)	**5** (*SSS*)	**6** (*SRS*)	[**7**][b] (*SSS*)
1	$Ar_1^{ortho} - N_2H$	2.16[ref c]	---	---	---	[---]
2	$N_2H - C_3H$	---	3.8	3.5	---	[2.7]
3	$N_2H - C_{3\beta}H$	3.0	2.7	---	2.7	[2.4]
4	$N_2H - C_{3\gamma}Me$	---	---	3.0	2.8	[2.6]
5	$C_{3\beta}Me - N_4H$	2.8	4.1	4.4	---	[3.9]
6	$N_4H - C_5H$	---	---	2.7	---	[2.8]
7	$N_4H - C_{5\beta}H$	2.8	3.0	3.0	3.3	[2.6]
8	$N_4H - C_6Me^R$	---[c]	---[c]	4.1	---	[3.5]
9	$N_4H - C_6Me^S$	---[c]	---[c]	2.9	---	[4.2]
10	$N_4H - N_7H$	---	2.6	---	2.5	[2.7]
11	$C_{5\beta}H^R - C_{5\beta}H^S$	---	---	1.80[ref c]	1.80[ref c]	[1.7]
12	$C_5H - C_6Me^R$	---[d]	---[d]	2.8	2.6	[2.7]
13	$C_5H - C_6Me^S$	---[d]	---[d]	2.9	2.5	[2.6]
14	$C_5H - N_7H$	---	---	4.6	3.1	[3.9]
15	$C_{5\beta}H - N_7H$	---	---	---	2.7	[4.1]
16	$N_7H - C_6Me^R$	---[d]	---[d]	2.5	2.1	[2.3]
17	$N_7H - C_6Me^S$	---[d]	---[d]	3.5	4.0	[3.9]
18	$N_7H - C_8H$	3.4	---	3.1	---	[2.7]
19	$N_7H - C_{8\beta}H$	---	2.5	2.6	4.0	[2.4]
20	$N_7H - C_{8\gamma}H$	---	---	3.9	---	[2.4]

[a]Experiments (500MHz) carried out at 300K, mixing time 400 ms. [b]Crystal inter-proton distances from X-ray analysis of **7** (C9 + C11 conformer). [c]Reference distance. [d]Overlapped C_6Me^R/ C_6Me^S signals and indistinguishable inter-proton distances.

4. ^{1}H NMR and ^{13}C NMR spectra of compound 9 and ^{13}C NMR spectra of compounds 3, 4

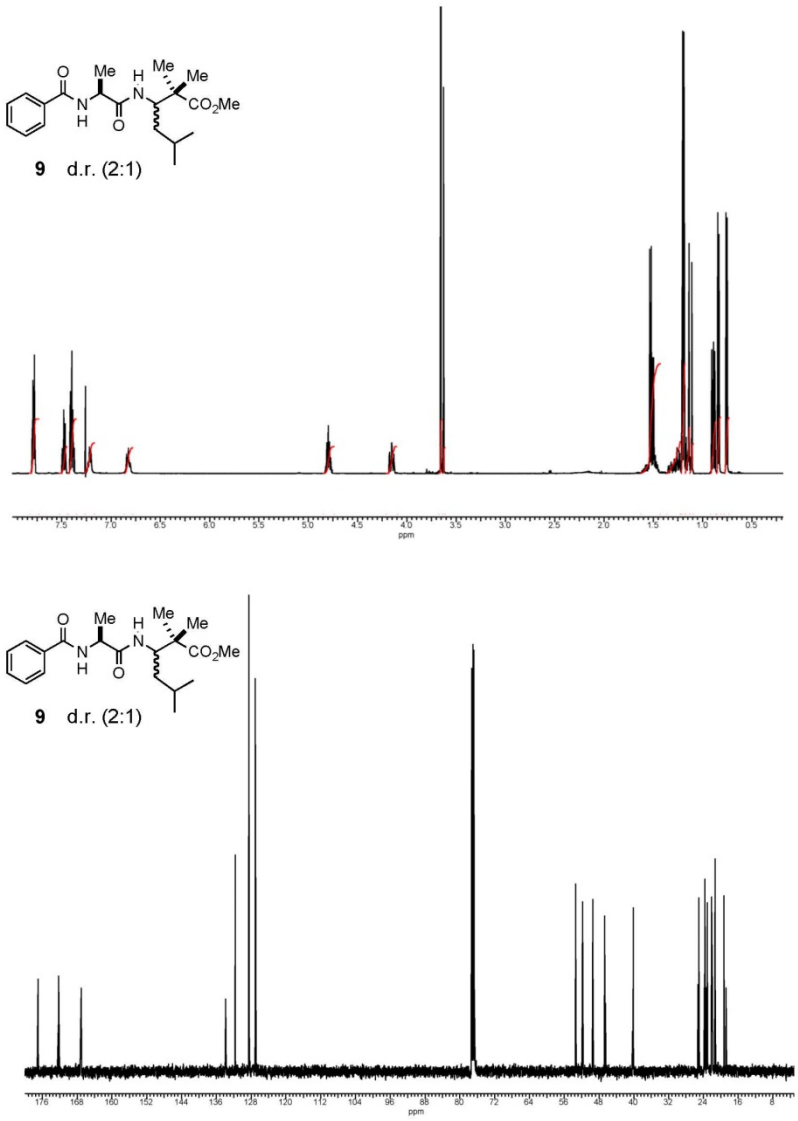


Figure S14. ^{1}H NMR and ^{13}C NMR spectra of **9** in $CDCl_3$ (mixture of isomers).

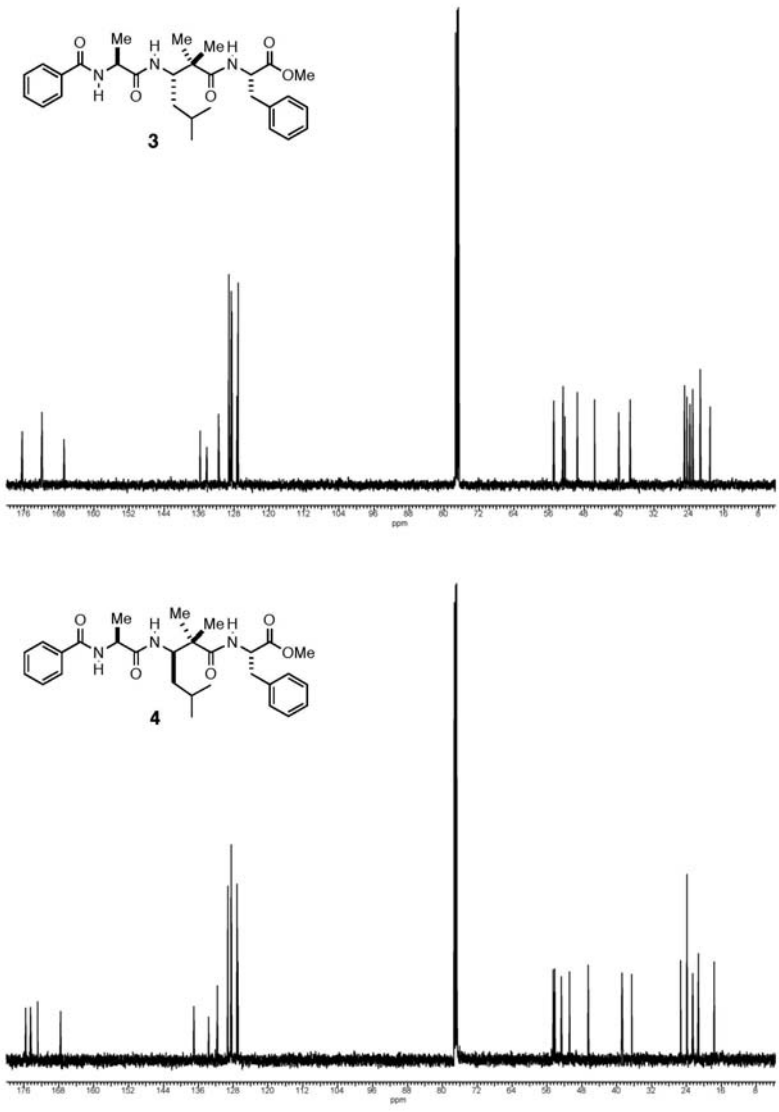
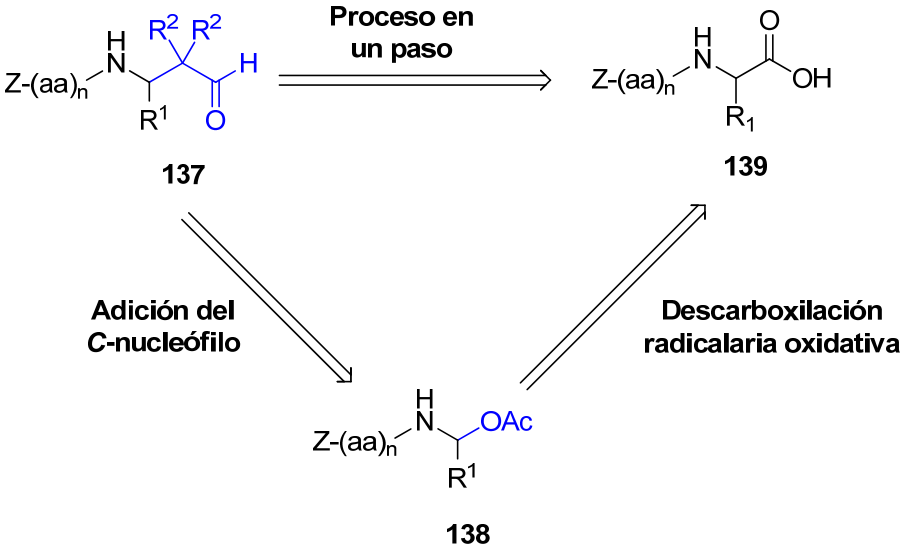


Figure S15. ^{13}C NMR spectra of compounds **3** and **4** in $CDCl_3$.

3.2 Preparación de péptidos modificados: conversión directa de α-amino ácidos en β-amino aldehídos.

Existen bastantes péptidos con unidades de α- o β-amino aldehído que presentan una potente actividad biológica, con posibles aplicaciones como agentes antivirales, antitumorales, antiinflamatorios, antitrombóticos, etc. Sin embargo, apenas se han estudiado derivados peptídicos con residuos de β-amino aldehído α-sustituidos, por lo que su preparación podría ser muy útil para el descubrimiento de nuevos fármacos.

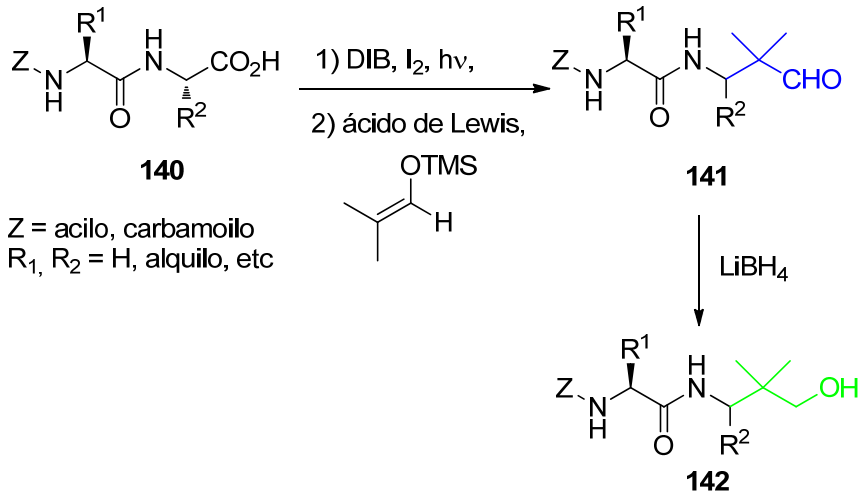
La formación de péptidos con residuos de β-amino aldehído **137**, podría realizarse por reacción de un nucleófilo (un vinil éter o un sililenol éter) con el *N*,*O*-acetal **138**. Este acetal a su vez puede ser generado por una descarboxilación radicalaria oxidativa del sustrato **139** (Esquema 39).



Esquema 39. Formación de aldehídos peptídicos a partir de α-péptidos.

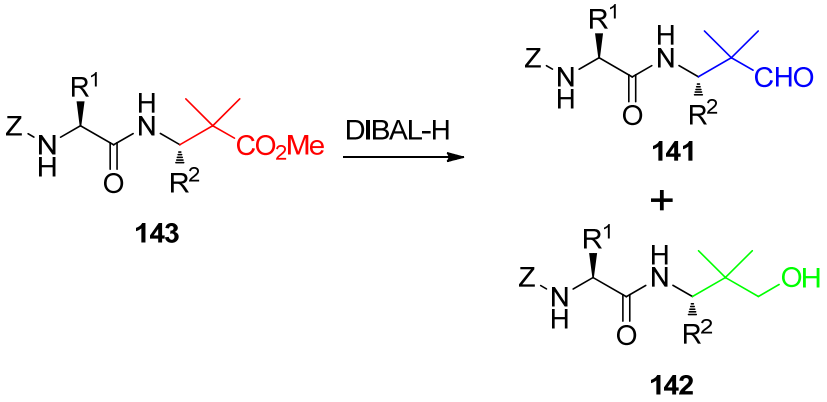
Este proceso podría hacerse en un solo paso, usando un proceso secuencial de descarboxilación radicalaria oxidativa–adición de *C*-nucleófilos. De esta manera se podría obtener una colección de péptidos con distintas unidades de β-amino aldehído a partir de un solo péptido de partida.

Los primeros estudios de descarboxilación radicalaria–oxidación–adición de nucleófilos se llevaron a cabo sobre amino ácidos para optimizar las condiciones de reacción. A continuación este proceso se extendió a péptidos **140** (Esquema 40), transformando selectivamente la unidad *C*-terminal de α-amino ácido en un β-amino aldehído (como en el compuesto **141**). Los aldehídos fueron reducidos en condiciones suaves, dando lugar a péptidos con residuos de γ-amino alcohol **142**. Estos péptidos son análogos estructurales de los peptaiboles, una familia de antibióticos con potente actividad antibacteriana y antifúngica.



Esquema 40. Preparación de péptidos con unidades de β-amino aldehído y reducción de los mismos dando derivados de γ-amino alcoholes.

Para conocer la configuración absoluta de los péptidos **141** o **142**, se prepararon estos mismos productos partiendo de sustratos de estructura conocida, por ejemplo por reducción del β-amino ester[51] **143** (Esquema 41). En todos los casos, el isómero mayoritario del proceso secuencial de escisión–alquilación presentó la configuración "natural" (3*S*).



143 **141** + **142**

Esquema 41. Correlación química para conocer la configuración absoluta de los péptidos **141** y **142**.

One-Pot Conversion of α-Amino Acids into β-Amino Aldehydes or 2-Acetoxyazetidines: Application to the Synthesis of Modified Peptides

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Dedicated to Prof. Gerry Pattenden on the occasion of his 70th birthday.

Abstract: A direct method for the transformation of α-amino acids into β-amino aldehydes or 2-acetoxyazetidines is described. This work was applied to the modification of peptides.

Key words: amino aldehydes, heterocycles, peptides, radical reactions, domino reactions

The replacement of α-amino acids in peptides by α-amino aldehydes has been used to create peptide analogues with remarkable biological activities.[1] Thus, different peptide aldehydes are potent inhibitors of aspartyl, serine, and cysteine proteases, such as papain, thrombin, trypsin, and viral proteases.[2] For instance, the dipeptide SJA6017 (**1**) inhibits calpain and is a promising anticataract agent.[3a,b] The tetrapeptide Ac-DEVD-H (**2**) is a potent inhibitor of caspase-3, an apoptosis effector.[3c,d]

In contrast, the introduction of β-amino aldehyde units has been scarcely explored.[4] In most cases, α-unsubstituted β-amino aldehyde[5] or α-amino glyoxal units[6] are used. Two representative examples are compounds **3** and **4** (Figure 1); while product **3** is a caspase-1 inhibitor,[4b] the glyoxal **4** inhibits cathepsin L, a protease which degrades bone collagen.[4c]

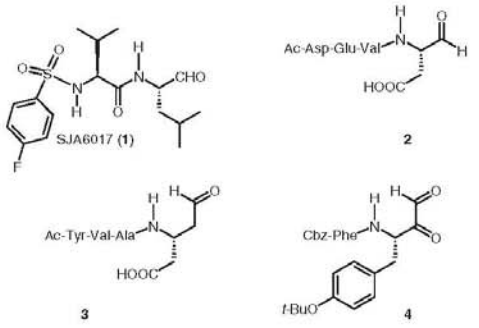
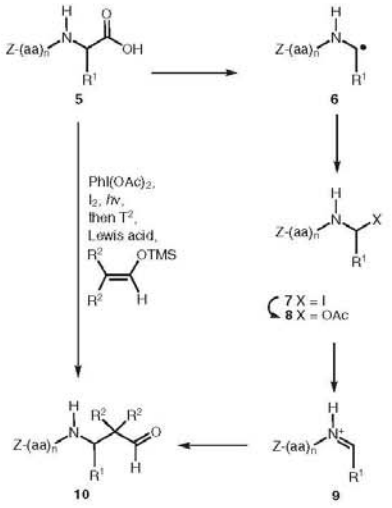


Figure 1 Bioactive peptidyl α- or β-aldehydes

In order to increase the diversity of peptidyl β-aldehyde libraries, α-substituted β-amino aldehydes could be incorporated into the peptide. Such units could bear substituents of different size and polarity, in order to allow the study of their influence on biological activity.

In this communication we report a one-pot methodology to transform the *C*-terminal amino acid in peptides into a β-amino aldehyde, whose α-position may be either substituted or unsubstituted. This direct transformation would allow the preparation of a library of modified peptide aldehydes from a single peptide precursor **5** (Scheme 1).[7]

The process is initiated by a radical decarboxylation, on treatment of the precursor **5** with (diacetoxyiodo) benzene (DIB) and iodine. The decarboxylation affords a *C*-radical **6** which reacts with iodine to give the unstable α-iodoamine **7**.[7j] The iodide is replaced by acetate derived from the DIB, to give the *N*,*O*-acetal **8**. This acetal is in equilibrium with the acyliminium ion **9**, which can be trapped by silyl enol ethers, to afford the peptide β-aldehydes **10**.



Scheme 1 One-pot conversion of peptides into peptidyl β-aldehydes

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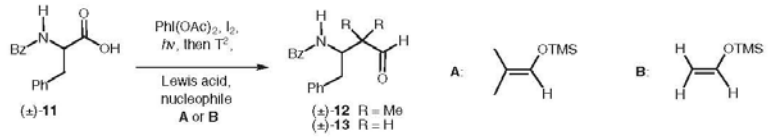
DOI: 10.1055/s-0029-1219156; Art ID: D30909ST

Table 1 Tandem Scission–Alkylation to Yield Compounds **12** and **13**



Ratio of DIB/I_2 (equiv)	Nu (equiv)	Lewis acid (equiv)	Addition temp T^2 (°C)	Product (yield, %)[a]
1.5:0.3	**A** (3)	$TiCl_4$ (2)	–78	**12** (25)
1.5:0.3	**A** (3)	$SnCl_4$ (2)	–78	**12** (51)
1.5:0.3	**A** (3)	TMSOTf (2)	0	**12** (58)
1.5:0.3	**A** (3)	$BF_3{\cdot}OEt_2$ (2)	0	**12** (61)
1.5:0.5	**A** (3)	$BF_3{\cdot}OEt_2$ (2)	0	**12** (53)
2.0:1.0	**A** (5)	$BF_3{\cdot}OEt_2$ (2)	0	**12** (38)
1.5:0.3	**B** (3)	$BF_3{\cdot}OEt_2$ (2)	0	**13** (41)
1.5:0.3	**B** (3)	TMSOTf (2)	0	**13** (40)

[a] Yields for purified products.

Initially, the tandem scission–alkylation was optimized using single amino acid derivatives as substrates. Thus, Bz-DL-Phe-OH (**11**) was treated under the conditions listed in Table 1, varying quantities of reagents and using different Lewis acids and temperatures, to afford the β-amino aldehydes **12** (R = Me) or **13** (R = H).

The best conditions used a catalytic amount of iodine (0.3 equiv) in the scission step, and $BF_3{\cdot}OEt_2$ or TMSOTf at 0 °C in the addition step. These conditions were then used with the other amino acid and peptide substrates **14**–**19** (Scheme 2), to afford the β-amino aldehyde derivatives **20**–**28** in good global yields. Interestingly, in the case of peptides, TMSOTf gave better results than $BF_3{\cdot}OEt_2$.

In the case of substrates **18** and **19**, the reacting residue is attached to an L-amino acid which serves as a chiral auxiliary. Therefore, the scission–addition reaction is stereoselective, affording the L-β-amino aldehyde as the major isomer (L/D ≈ 2:1 in both cases). The diastereomers were readily separated by chromatography, in order to determine structure–biological activity relationships.

The stereochemistry of these compounds was determined by comparison with similar peptides,[7a] and it was confirmed by oxidation of aldehyde **27** to an acid followed by esterification,[8] to the known dipeptide Bz-L-Leu-L-β-hAla-OMe (58%).[7a]

Interestingly, when the silyl enol ether used as the nucleophile was replaced by vinyl acetate[7e] (Scheme 3), the expected β-amino aldehyde derivatives were not formed, and 2-acetoxyazetidines were obtained instead. Thus, substrates **29**, **30**, and **14** were treated under the modified scission–alkylation conditions, affording the 2-acetoxyazetidines **31**–**33** in satisfactory yields.

The different results observed in the use of silyl enol ethers and vinyl acetate can be explained using substrate **14** as an example (Scheme 3). The scission–oxidation steps, followed by addition of the nucleophile to the acyliminium intermediate, generated an oxycarbenium ion **34**. When R = TMS, a silyl cation was readily lost to give the aldehyde **20**. However, when R = Ac, the loss of an acyl cation was not favored, so the addition of the amide took place instead, affording the 2-acetoxyazetidine **33**.

The cyclization was stereoselective, and only the 2,4-*cis*-azetidine was isolated. The 2,4-*trans*-isomer was not detected.[9] A minimum-energy conformation for the oxycarbenium intermediate **34** prior to ring closure is shown in Figure 2.[10] In this conformation, where unfavorable steric interactions are greatly reduced, the nitrogen is correctly positioned for ring closure to occur, affording the 2,4-*cis*-azetidine **33**. The same applied to the other substrates **29** and **30**, affording the 2,4-*cis*-azetidines **31** and **32**, respectively.

The resulting 2-acetoxyazetidines are remarkably useful, not only as aldehyde prodrugs, but also as precursors of azetidines. The introduction of azetidines in peptides by conversion of common amino acids into 2-acetoxyazetidines and addition of other nucleophiles to the *N*,*O*-acetal is particularly interesting.[11] The azetidine ring could be used to generate turns and other secondary structure elements.[12] This possibility is currently under study in our group and will be published in due course.

In conclusion, we have developed an efficient methodology for the direct conversion of α-amino acid derivatives into β-amino aldehydes, using a sequential procedure which couples a radical decarboxylation to an oxidation and to a nucleophilic addition. The procedure allows the

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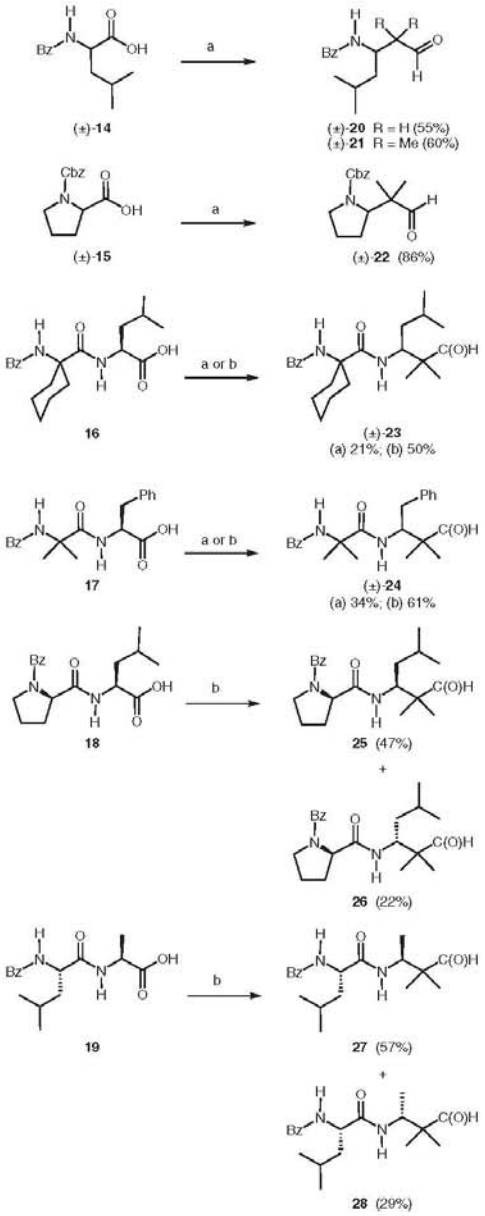
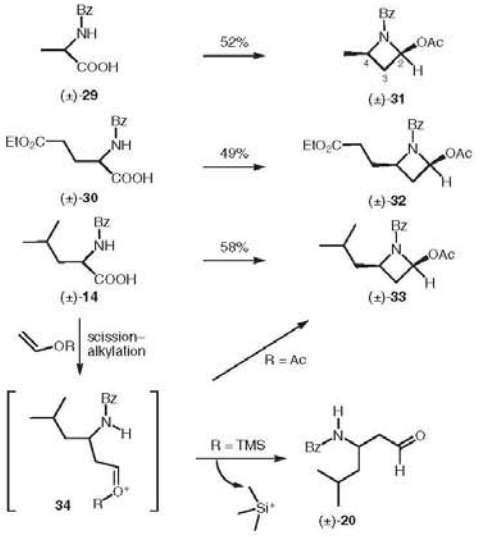


Scheme 2 *Reagents and conditions*: Method A: DIB (1.5 equiv), I_2 (0.3 equiv), CH_2Cl_2, *hv*, r.t., 4 h, then 0 °C, BF_3·OEt_2 (2 equiv), R_2C=C(OTMS)H (3 equiv), 3 h. Method B: similar to A but using TMSOTf as Lewis acid.



Scheme 3 Formation of 2-acetoxyazetidines. *Reagents and conditions*: DIB (1.5 equiv), I_2 (0.3 equiv), CH_2Cl_2, *hv*, r.t., 4 h, then 0 °C, BF_3·OEt_2 (2 equiv), CH_2=C(OAc)H (10 equiv), 3 h.

selective modification of the *C*-terminal residue in small peptides, and therefore, a single α-peptide could be transformed into a library of α,β-peptidyl aldehydes.

Moreover, by changing the reaction conditions, the α-amino acids can be transformed into 2-acetoxyazetidines, which could be useful aldehyde prodrugs. Furthermore, the 2-acetoxyazetidines could be converted into azetidines following reported procedures, in order to generate turns or other secondary structure elements in peptides.

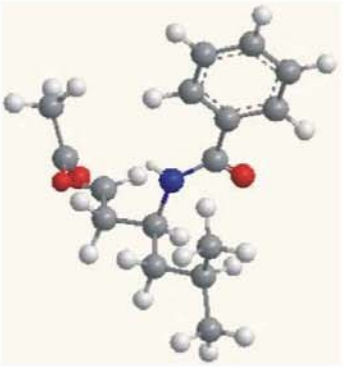


Figure 2 Minimized conformation for oxycarbenium intermediate **34** prior to ring closure

General Procedures for the Scission–Oxidation–Alkylation Sequence

Method A

To a solution of the starting amino acid or peptide (0.2 mmol) in dry CH_2Cl_2 (6 mL) were added I_2 (15 mg, 0.06 mmol, 0.3 equiv) and DIB (97 mg, 0.3 mmol, 1.5 equiv). The reaction mixture was stirred at 25–26 °C for 4 h, under irradiation with visible light. Then the solution was cooled to 0 °C, and vinyloxytrimethylsilane (89 μL, 70 mg, 0.6 mmol, 3 equiv) or 2-methyl-1-(trimethylsilyloxy)-1-propene (110 μL, 86 mg, 0.6 mmol, 3 equiv) or vinylacetate (184 μL, 172 mg, 2 mmol, 10 equiv) was injected, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (51 μL, 57 mg, 0.4 mmol, 2 equiv). The mixture was allowed to reach r.t. and stirred for 3 h; then it was poured into 10% aq $Na_2S_2O_3$–sat. aq $NaHCO_3$ (1:1, 10 mL) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes–EtOAc) to give the products.

Method B

As in method A but using TMSOTf (72 μL, 89 mg, 0.4 mmol, 2 equiv) as the Lewis acid.

***N*-Benzoyl-α,α-dimethyl-DL-β-homophenylalaninal (12)**

Phenylalanine derivative (±)-**11** was treated as in method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by column chromatography on silica gel (hexanes–EtOAc, 9:1), giving the aldehyde (±)-**12** (61%) as a crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (s, 3 H), 1.31 (s, 3 H), 2.75 (dd, *J* = 11.2, 14.6 Hz, 1 H), 3.10 (dd, *J* = 4.1, 14.2 Hz, 1 H), 4.69 (ddd, *J* = 4.1, 10.2, 10.8 Hz, 1 H), 6.38 (d, *J* = 9.8 Hz, 1 H), 7.18 (dd, *J* = 6.8, 6.8 Hz, 1 H), 7.23–7.28 (m, 4 H), 7.36 (dd, *J* = 7.5, 7.8 Hz, 2 H), 7.45 (dd, *J* = 7.1, 7.8 Hz, 1 H), 7.52 (d, *J* = 7.1 Hz, 2 H), 9.59 (s, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.5 (CH_3), 20.1 (CH_3), 36.7 (CH_2), 50.5 (C), 54.7 (CH), 126.7 (3 × CH), 128.5 (4 × CH), 128.9 (2 × CH), 131.3 (CH), 134.6 (C), 137.8 (C), 167.4 (C), 205.3 (CH) ppm. MS: *m/z* (%) = 295 (<1) [M$^+$], 105 (100) [PhCO]$^+$, 91 (14) [$PhCH_2$]$^+$, 77 (28) [Ph]$^+$. HRMS: *m/z* calcd for $C_{19}H_{21}NO_2$: 295.1572; found: 295.1580; calcd for C_7H_5O: 105.0340; found: 105.0343

***N*-Benzoyl-DL-β-homophenylalaninal (13)**

Amino acid (±)-**11** was treated as indicated in method A, using vinyloxytrimethylsilane as nucleophile. The reaction mixture was purified by column chromatography on silica gel (hexanes–EtOAc, 7:3), yielding product (±)-**13** (41%) as an amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.73 (ddd, *J* = 1.6, 6.0, 17.3 Hz, 1 H), 2.77 (ddd, *J* = 1.3, 5.4, 17.7 Hz, 1 H), 2.97 (dd, *J* = 7.6, 13.6 Hz, 1 H), 3.09 (dd, *J* = 6.9, 13.6 Hz, 1 H), 4.76 (m, 1 H), 6.58 (d, *J* = 8.2 Hz, 1 H), 7.21–7.25 (m, 3 H), 7.32 (dd, *J* = 7.3, 7.6 Hz, 2 H), 7.40 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.48 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.68 (d, *J* = 7.6 Hz, 2 H), 9.77 (dd, *J* = 0.6, 0.9 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 40.1 (CH_2), 46.7 (CH_2), 46.9 (CH), 126.9 (3 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.2 (2 × CH), 131.6 (CH), 134.3 (C), 137.3 (C), 167.0 (C), 201.2 (CH) ppm. MS: *m/z* (%) = 268 (12) [M$^+$ + H], 176 (69) [M$^+$ – $PhCH_2$], 105 (100) [PhCO]$^+$, 91 (37) [$PhCH_2$]$^+$, 77 (81) [Ph]$^+$. HRMS: *m/z* calcd for $C_{17}H_{18}NO_2$: 268.1338; found: 268.1327; calcd for C_7H_5O: 105.0340; found: 105.0341.

(Benzoyl-L-leucyl)-α,α-dimethyl-L-β- (27) and (Benzoyl-L-leucyl)-α,α-dimethyl-D-β-homoalaninal (28)

The products were generated from dipeptide **19** according to method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography on silica gel (hexanes–EtOAc, 4:1), affording compounds **27** (57%) and **28** (29%).

Compound **27**: ^{1}H NMR (500 MHz): δ = 0.95 (d, *J* = 6.3 Hz, 6 H), 1.05 (d, *J* = 8.2 Hz, 3 H), 1.06 (s, 3 H), 1.07 (s, 3 H), 1.67–1.72 (m, 3 H), 4.23 (dddd, *J* = 6.8, 6.8, 6.8, 9.4 Hz, 1 H), 4.67 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1 H), 6.87 (br d, *J* = 9.0 Hz, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 7.40 (dd, *J* = 7.7, 7.7 Hz, 2 H), 7.49 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.78 (d, *J* = 7.5 Hz, 2 H), 9.45 (s, 1 H) ppm. ^{13}C NMR (100.7 MHz): δ = 15.8 (CH_3), 17.9 (CH_3), 19.2 (CH_3), 22.2 (CH_3), 22.8 (CH_3), 25.0 (CH), 41.4 (CH_2), 48.6 (CH), 50.0 (C), 52.5 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.8 (C), 167.6 (C), 171.9 (C), 204.7 (CH) ppm. MS: *m/z* (%) = 333 (1) [M$^+$ + H], 190 (100) [M$^+$ – $CONHCH(Me)CMe_2CHO$], 105 (91) [PhCO]$^+$. HRMS: *m/z* calcd $C_{19}H_{29}N_2O_3$: 333.2178; found: 333.2181; calcd for $C_{12}H_{16}NO$: 190.1232; found: 190.1239.

Compound **28**: ^{1}H NMR (500 MHz): δ = 0.96 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 6.3 Hz, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.63–1.82 (m, 3 H), 4.24 (1 H, dddd, *J* = 6.9, 6.9, 6.9, 9.5 Hz), 4.61 (ddd, *J* = 6.0, 6.3, 8.2 Hz, 1 H), 6.67 (d, *J* = 8.2 Hz, 1 H), 6.75 (d, *J* = 9.8 Hz, 1 H), 7.43 (dd, *J* = 7.4, 7.4 Hz, 2 H), 7.50 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.78 (d, *J* = 6.9 Hz, 2 H), 9.43 (s, 1 H) ppm. ^{13}C NMR (100.7 MHz): δ = 16.0 (CH_3), 17.9 (CH_3), 19.0 (CH_3), 22.3 (CH_3), 22.9 (CH_3), 25.0 (CH), 40.4 (CH_2), 48.4 (CH), 50.1 (C), 52.2 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.9 (C), 167.9 (C), 171.3 (C), 204.8 (CH) ppm. MS: *m/z* (%) = 333 (2) [M$^+$ + H], 190 (86) [M$^+$ – $CONHCH(Me)CMe_2CHO$], 105 (100) [PhCO]$^+$. HRMS: *m/z* calcd $C_{19}H_{29}N_2O_3$: 333.2178; found: 333.2177; calcd for C_7H_5O: 105.0340; found: 105.0340.

1-Benzoyl-4-isobutylazetidin-2-yl Acetate (33)

Formed from leucine derivative (±)-**14** according to method A, using vinyl acetate as the nucleophile. After purification by column chromatography on silica gel (hexanes–EtOAc, 97:3) the product was isolated as a syrup (58%).

^{1}H NMR (500 MHz): δ = 0.98 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 1.40 (m, 1 H), 1.58–1.69 (m, 2 H), 2.00 (ddd, *J* = 6.6, 6.9, 13.6 Hz, 1 H), 2.17 (s, 3 H), 2.20 (ddd, *J* = 3.8, 4.4, 13.2 Hz, 1 H), 3.67 (m, 1 H), 6.47 (dd, *J* = 3.8, 8.8 Hz, 1 H), 7.35 (dd, *J* = 7.3, 7.6 Hz, 2 H), 7.41 (dd, *J* = 6.9, 7.6 Hz, 1 H), 7.92 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125.7 MHz): δ = 21.1 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 24.6 (CH), 32.0 (CH_2), 46.2 (CH_2), 49.7 (CH), 91.0 (CH), 127.4 (2 × CH), 128.0 (2 × CH), 130.6 (CH), 132.8 (C), 152.8 (C), 169.4 (C) ppm. MS: *m/z* (%) = 275 (7) [M$^+$], 105 (100) [PhCO]$^+$. HRMS: *m/z* calcd for $C_{16}H_{21}NO_3$: 275.1521; found: 275.1532; calcd for C_7H_5O: 105.0340; found: 105.0340.

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(10) (a) Representation using ChemDraw 3D 8.0 (CambridgeSoft), which agrees with calculations performed with Macromodel 7.0. The aldehyde **20** adopts a similar conformation. (b) For the formation of related 2,4-cis-azetidines, see: Ghorai, M. K.; Kumar, A.; Halder, S. *Tetrahedron* **2007**, *63*, 4779.

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PAPER

Preparation of modified peptides: direct conversion of α-amino acids into β-amino aldehydes†‡

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A direct method for the transformation of α-amino acids into β-amino aldehydes was developed, and applied to the modification of the C-terminal residue of peptides. The method takes place in good yields and under mild conditions. The application of this methodology to the preparation of small peptides with γ-amino alcohol units, which are precursors of analogues of peptaibol antibiotics, is also described.

Introduction

The replacement of amino acid residues in peptides by amino aldehyde units has provided several peptide analogues with remarkable biological activities.[1] Some derivatives presenting an α-amino aldehyde unit are potent inhibitors of proteases, such as papain, thrombin, trypsin, calpain, caspases and viral proteases. Their applications range from antiviral drugs to antithrombotic, anticataract or antitumoral agents.[2]

On the other hand, there are few examples of peptide derivatives with β-amino aldehyde units.[3] In most cases, an amino glyoxal residue[4] is introduced, as occurs with the caspase-3 inhibitor **1**[5a] (Fig. 1) and the collagen-degradation inhibitor **2**.[5b]

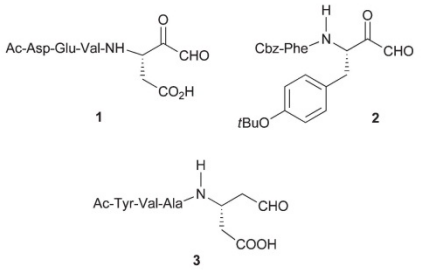

Fig. 1 Bioactive peptides with β-amino aldehyde units.

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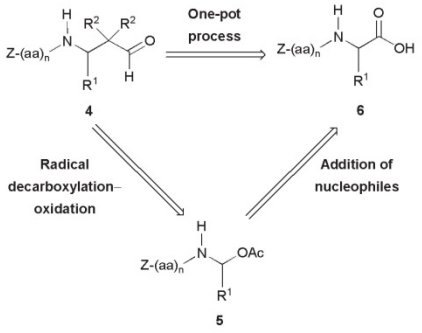
† Dedicated to Prof. Gerry Pattenden.

‡ Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of the amino acids **8**, **14**, **16**, **18**, **19**, **21**, **24**, and **26–29**, the peptide aldehydes **38–48** and the amino alcohol derivatives **52–57**. See DOI: 10.1039/c2ob25433f.

Some bioactive peptides also present α-unsubstituted β-amino aldehyde units,[6] such as product **3**, a potent inhibitor of interleukin 1-β converting enzyme, used as a drug lead for the treatment of inflammatory diseases.[6a]

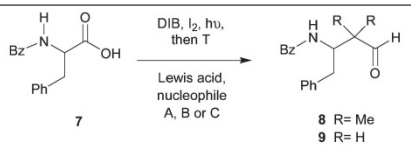
The development of new derivatives, especially those with α-substituted β-amino aldehyde residues, could be useful to discover new drug leads. We reasoned that a peptide aldehyde **4** (Scheme 1) could be formed by addition of carbon nucleophiles (such as vinyl ethers or silylenol ethers) to the *N*,*O*-acetals **5**.[7] These acetals, in turn, could be generated by radical decarboxylation–oxidation of α-peptides such as substrate **6**.[8] The direct formation of peptide aldehydes **4** from α-peptides **6** would be particularly interesting. With the one-pot process, a single α-peptide **6** could be transformed into a variety of peptide aldehydes with different substituents, allowing the generation of libraries of derivatives **4** to study structure–activity relationships.

In previous work from our group,[8] the oxidative decarboxylation of α-amino acids followed by addition of different carbon nucleophiles had proven useful to obtain unnatural amino acids,



Scheme 1 Formation of peptide aldehydes from α-peptides.

Table 1 One-pot oxidative radical decarboxylation–alkylation



Entry	DIB/I_2 (equiv)	Nucleophile/Lewis acid (equiv)[a]	T (°C)	Products (%)[b]
1	2.0/1.0	A (5)/$BF_3{\cdot}OEt_2$ (2)	0	**8** (38)
2	1.5/0.5	A (3)/$BF_3{\cdot}OEt_2$ (2)	0	**8** (53)
3	1.5/0.3	A (3)/$BF_3{\cdot}OEt_2$ (2)	0	**8** (61)
4	1.5/0.3	A (3)/TMSOTf (2)	0	**8** (58)
5	1.5/0.3	A (3)/$SnCl_4$ (2)	−78	**8** (51)
6	1.5/0.3	A (3)/$TiCl_4$ (2)	−78	**8** (25)
7	1.5/0.3	B (3)/$BF_3{\cdot}OEt_2$ (2)	0	**9** (41)
8	1.5/0.3	B (3)/TMSOTf (2)	0	**9** (40)
9	1.5/0.3	C (3)/$BF_3{\cdot}OEt_2$ (2)	0	**9** (60)

[a] A = (TMSO)–CH=C(Me)$_2$; B = (TMSO)CH=CH$_2$; C = (EtO)-CH=CH$_2$. [b] Yield for products purified by chromatography.

alkaloid precursors and α,β-peptide hybrids. In the current article, a variation of this methodology is described, to allow the direct conversion of α-amino acids or α-peptides into β-amino aldehydes or peptide β-aldehydes, under mild conditions and good overall yields.

Results and discussion

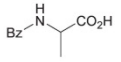
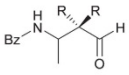
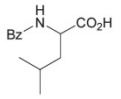
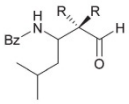
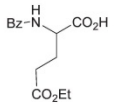
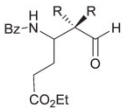
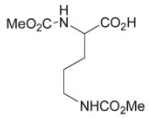
The initial studies on the one-pot decarboxylation–alkylation process were carried out with the DL-phenyl alanine derivative **7** (Table 1),[8e] which was treated with (diacetoxyiodo)benzene (DIB) and iodine under irradiation with visible light, to induce the oxidative decarboxylation.[8] The scission generated an *N*,*O*-acetal intermediate, which was not isolated, but treated with a Lewis acid and a nucleophile (entries 1–9). When 1-(trimethylsilyloxy)-2-methyl-1-propene was used as the nucleophile, the β-aminoaldehyde **8** was formed, while the use of 1-(trimethylsilyloxy)-1-ethene or ethyl vinyl ether as nucleophiles provided the β-amino aldehyde **9**.[9]

The amount of the scission reagents was important to obtain satisfactory yields (entries 1–3). The best result was obtained with a substrate/DIB/I_2 ratio of 1/1.5/0.3 (entry 3). Different Lewis acids were also tried (entries 3–6 and 7–8); boron trifluoride and TMSOTf provided the best yields. The nucleophiles B [1-(*tert*-butyldimethylsilyloxy)-1-ethene] and C [1-ethoxy-1-ethene] were then compared (entries 7 and 9), and the vinyl ether C proved superior to the silyl enol ether B, probably due to increased reagent stability.

The best conditions for each nucleophile were then used with other amino acids, such as DL-substrates **10–13**[8e,10] (Table 2), to afford the β-amino aldehyde derivatives **14–21**.[11]

Interestingly, the oxidative decarboxylation–alkylation of the ornithine derivative **13** (Table 2, entry 10) afforded the proline analogue **21**, probably due to intramolecular cyclization of the intermediate *N*,*O*-acetal to give the *N*,*N*-acetal **20**,[12] which then reacted with the Lewis acid to give a five-membered acyliminium ion, followed by the addition of the nucleophile.

Table 2 One-pot oxidative radical decarboxylation–alkylation[a]

Entry	Substrate	Nu (equiv)[b]	Products[c] (%)
			
1	Bz-Ala-OH **10**	A (3)	**14** R = Me (69)
2		B (3)	**15** R = H (45)
3		C (3)	**15** R = H (79)
			
4	Bz-Leu-OH **11**	A (3)	**16** R = Me (60)
5		B (3)	**17** R = H (55)
6		C (3)	**17** R = H (56)
			
7	Bz-Glu(OEt)-OH **12**	A (3)	**18** R = Me (66)
8		B (3)	**19** R = H (51)
9		C (3)	**19** R = H (45)
			
10	**13**	A (3)	**20** → **21** (83) **20** X = $NHCO_2Me$ **21** X = $C(Me)_2$-CHO

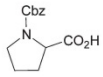
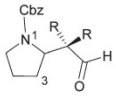
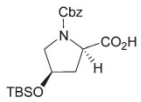
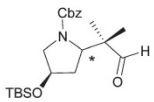
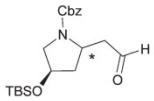
[a] DIB, I_2, *hv*, then 0 °C, nucleophile, Lewis acid. [b] A = (TMSO)–CH=C(Me)$_2$; B = (TMSO)CH=CH$_2$; C = (EtO)CH=CH$_2$; $BF_3{\cdot}OEt_2$ was used as the Lewis acid. [c] Yield for products purified by chromatography.

Similar products were obtained when the DL-proline and hydroxy L-proline derivatives **22**[13] (Table 3, entries 1–3) and **23**[14] (entries 4–6) underwent the decarboxylation–alkylation reaction. In the case of the proline derivative **22**, the process took place in 82–86% yields, affording products **24** (R = Me) or **25** (R = H).[15a–d] When hydroxyproline substrate **23** was used, the process afforded compounds **26–27** (R = Me) and **28–29** (R = H).[15e] Remarkably, the 2,4-*cis* products predominated over the 2,4-*trans* isomers, due to an stereoelectronic effect described by Woerpel and coworkers.[16]

The one-pot process was then tried with peptides, using compounds **30–36**[17] (Scheme 2) as substrates. Interestingly, with peptides TMSOTf proved superior to boron trifluoride as the Lewis acid (conversions **30** → **37** and **31** → **38**).

In the case of substrates **30** and **31**, whose N-terminal residue was an α,α-disubstituted amino acid, the process afforded a racemic mixture of the peptide aldehydes **37** and **38**, respectively. In the case of substrates **32–36**, the reacting residue was attached to a chiral amino acid, so the process was stereoselective (dr from 3 : 2 to 3 : 1), affording compounds **39–46** in good overall yields.

Table 3 One-pot oxidative radical decarboxylation–alkylation[a]

Entry	Substrate	Nu (equiv)[b]	Products[c] (%)
			
1	**22**	A (3)	**24** R = Me (86)
2		B (3)	**25** R = H (82)
3		C (3)	**25** R = H (85)
			
4	**23**	A (3)	**26** (2*R*) (63) **27** (2*S*) (19)
			
5	**23**	B (3)	**28** (2*R*) (34) **29** (2*S*) (20)
6	**23**	C (3)	**28** (2*R*) (27) **29** (2*S*) (13)

[a] DIB, I_2, *hν*, then 0 °C, nucleophile, Lewis acid. [b] A = (TMSO)–CH═C(Me)$_2$; B = (TMSO)CH═CH$_2$; C = (EtO)CH═CH$_2$. [c] Yield for products purified by chromatography.

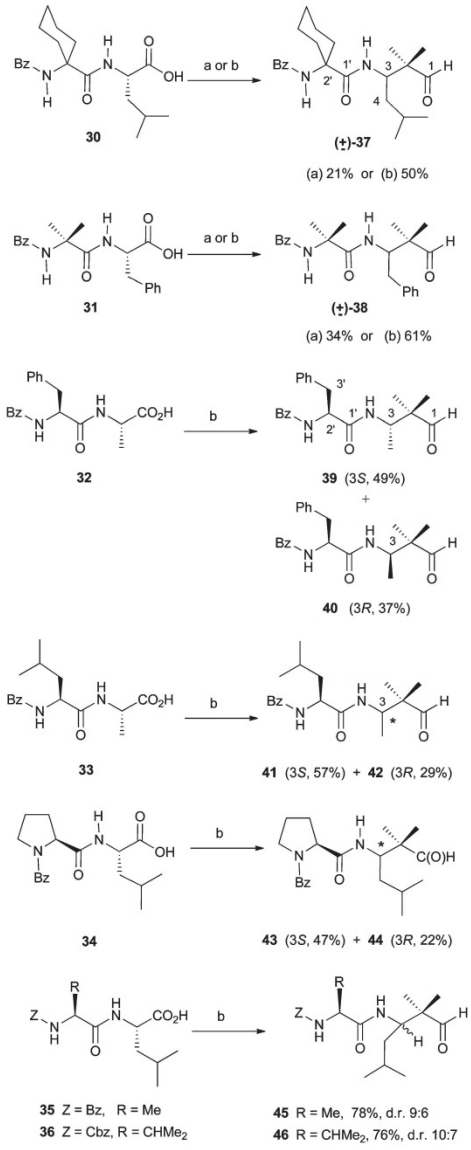
Their stereochemistry was unambiguously determined by correlation to known compounds, as will be commented later.

The aldehydes are not only potential drug candidates, but also useful precursors of other compounds, such as diamines, amino alcohols, *etc.* Especially interesting are the amino alcohol derivatives (Scheme 3) which are precursors of analogues of the peptaibol antibiotics.[18] The peptaibols present a short peptidic chain with a C-terminal β-amino alcohol unit. The presence of non-proteinogenic amino acids (in particular Aib, α-amino isobutyric acid) is key for their potent activity against bacteria and fungi. These antibiotics present interesting folding patterns which can allow the creation of holes in the bacterial membrane.

Our scission–alkylation methodology, followed by mild reduction of the aldehydes, would allow the preparation of precursors of peptaibol analogues, such as compounds **47–56** (Scheme 3). These precursors present unusual C-terminal β,β-dimethyl γ-amino alcohol units (instead of the peptaibol β-amino alcohol units), and with their β,β-substitution they also resemble an Aib-derived amino alcohol. This new terminal residue could modify the conformational and biological properties of the derivatives, and thus be useful to understand SAR relationships.

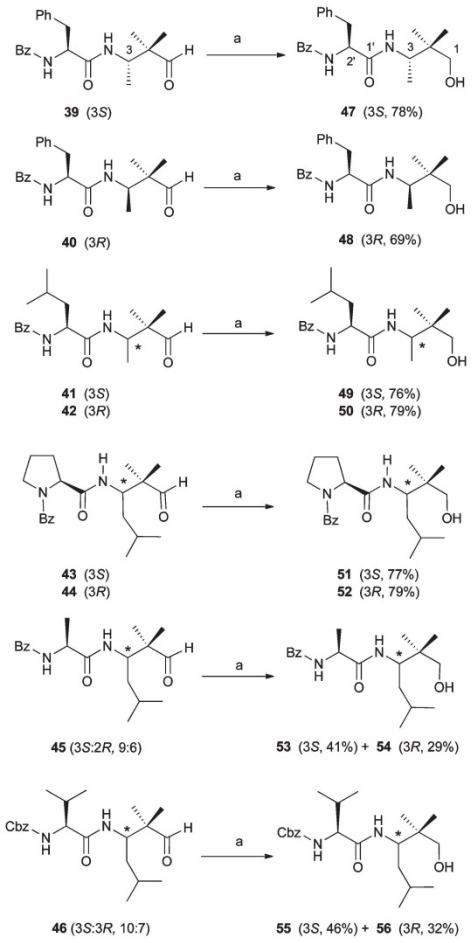
The reduction of peptide aldehydes **39–46** was tried under different conditions (DIBAL-H, $NaBH_4$, or $LiBH_4$ in different solvents), and the best results were obtained with $LiBH_4$ in ^{i}PrOH, affording the amino alcohols in good yields (69–79%).

To our satisfaction, in the case of aldehyde mixtures, such as compounds **45** and **46**, the reduction allowed the separation of the diastereomeric products.

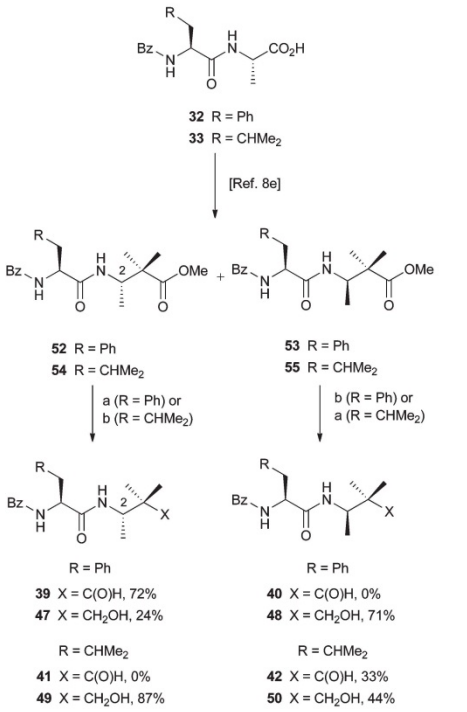


Scheme 2 Conversion of α-dipeptides into derivatives with a C-terminal β-amino aldehyde. Reaction conditions: [a] DIB, I_2, *hν*, then 0 °C, BF_3·OEt_2, (TMSO)CH═C(Me)$_2$; [b] DIB, I_2, *hν*, then 0 °C, TMSOTf, (TMSO)CH═C(Me)$_2$.

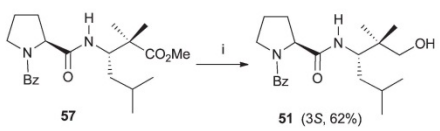
The stereochemistry of the amino aldehydes and the amino alcohols was determined by correlation to known compounds



Scheme 3 Conversion of dipeptides with a β-amino aldehyde unit into alcohol derivatives. Reaction conditions: [a] $LiBH_4$, ^iPrOH.



Scheme 4 Determination of the stereochemistry of the aldehydes by correlation to known compounds. Reaction conditions: [a] DIBAL-H, CH_2Cl_2, −78 °C; [b] DIBAL-H, CH_2Cl_2, 0 °C.



Scheme 5 Determination of the stereochemistry of the aldehydes by correlation to known compounds. Reaction conditions: [i] DIBAL-H, CH_2Cl_2, 0 °C.

(Scheme 4).[8e] Thus, the acids **32** and **33** were transformed into the known β-amino esters **52–53** and **54–55**, respectively, using a sequential scission–alkylation process.[8e]

The known esters **52–55** were then reduced with DIBAL-H to give the corresponding aldehydes **39–42** or the amino alcohols **47–50**,[19] confirming the assigned stereochemistries. In a similar way, the amino ester **57**[8e] (Scheme 5) was reduced to give the γ-amino alcohol derivative **51**. In all the cases, the major isomer presented the "natural" (3*S*) configuration.

The formation of peptaibol analogues from these simpler precursors is under way, and together with their conformational properties, will be reported in due course.

Conclusions

An efficient and mild one-pot process for the conversion of α-amino acid derivatives into β-amino aldehydes has been developed, and applied to the *selective modification* of the C-terminal residue in small peptides, giving peptide aldehydes in good overall yields. With this procedure, a single α-peptide could be transformed into a library of α,β-peptidyl aldehydes with different α-substituents. The aldehydes are useful precursors of other compounds, as illustrated by transformation of several peptide aldehydes into precursors of peptaibol analogues, which present γ-hydroxyamino units.

Experimental section

General remarks

Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use.[20] All reactions involving air- or moisture-sensitive materials were carried out under nitrogen atmosphere. Three alternative spray reagents for TLC analysis were used: (a) 0.5% vanillin in H_2SO_4–EtOH (4 : 1); (b) 0.25% ninhydrin in ethanol; and (c) Fleet's reagent [$Ce(SO_4)_2$ (0.5 g) and ammonium phosphomolybdate hydrate (2.5 g) in H_2SO_4 (5 mL) and water (65 mL)]. Once sprayed, the TLC was heated until development of color. Merck silica gel 60 PF_{254} and 60 (0.063–0.2 mm) were used for rotatory chromatography and column chromatography, respectively. Melting points were determined with a hot-stage apparatus and are uncorrected; the term "net" is used for crystals resulting from evaporation of the chromatography eluents. Optical rotations were measured at the sodium line at ambient temperature (26 °C). NMR spectra were determined at 500 or 400 MHz for ^1H and 125.7 or 100.6 MHz for ^{13}C in $CDCl_3$ as solvent and at 25 °C (δ_H 7.26; δ_C 77.0), unless otherwise stated.

Amino aldehyde derivatives **9**, **15**, **17**, and **25** are known but some are partially described; for comparison purposes their spectroscopic and physical data are also included.

General procedures for the scission–oxidation–alkylation sequence

Method A. To a solution of the starting amino acid or peptide (0.2 mmol) in dry dichloromethane (8 mL) were added iodine (15 mg, 0.06 mmol, 0.3 equiv) and (diacetoxyiodo)benzene (DIB) (97 mg, 0.3 mmol, 1.5 equiv). The reaction mixture was stirred at 25–26 °C for 4 h, under irradiation with visible light. Then the solution was cooled to 0 °C, and 2-methyl-1-(trimethylsilyloxy)-1-propene (110 μL, 86 mg, 0.6 mmol, 3 equiv) or vinyloxytrimethylsilane (89 μL, 70 mg, 0.6 mmol, 3 equiv) or ethyl vinyl ether (86 μL, 65 mg, 0.6 mmol, 3.0 equiv) was injected, followed by dropwise addition of $BF_3{\cdot}OEt_2$ (51 μL, 57 mg, 0.4 mmol, 2 equiv). The mixture was allowed to reach room temperature and stirred for 3 h; then it was poured into 10% aqueous $Na_2S_2O_3$-saturated aqueous $NaHCO_3$ (1 : 1, 10 mL) and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes–EtOAc) to give the products.

Method B. As in Method A but using trimethylsilyl triflate (TMSOTf) (72 μL, 89 mg, 0.4 mmol, 2 equiv) as the Lewis acid.

***N*-Benzoyl-α,α-dimethyl-DL-β-homophenylalaninal (8).** Obtained from *N*-benzoyl-DL-phenylalanine (**7**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 90 : 10), giving the aldehyde (±)-**8** (61%) as a crystalline solid; Mp 133–134 °C (EtOAc–*n*-hexane); ν_{max}/cm^{-1} 3439, 3083, 3067, 1724, 1660; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, s, 2-Me_a), 1.31 (3H, s, 2-Me_b), 2.75 (1H, dd, J = 11.2, 14.6 Hz, 4-H_a), 3.10 (1H, dd, J = 4.1, 14.2 Hz, 4-H_b), 4.69 (1H, ddd, J = 4.1, 10.2, 10.8 Hz, 3-H), 6.38 (1H, d, J = 9.8 Hz, NH), 7.18 (1H, dd, J = 6.8, 6.8 Hz, Ar), 7.23–7.28 (4H, m, Ar), 7.36 (2H, dd, J = 7.5, 7.8 Hz, Ar), 7.45 (1H, dd, J = 7.1, 7.8 Hz, Ar), 7.52 (2H, d, J = 7.1 Hz, Ar), 9.59 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 19.5 (CH_3), 20.1 (CH_3), 36.7 (CH_2), 50.5 (C), 54.7 (CH), 126.7 (3 × CH), 128.5 (4 × CH), 128.9 (2 × CH), 131.3 (CH), 134.6 (C), 137.8 (C), 167.4 (C), 205.3 (CH); *m/z* 295 (M^+, <1%), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1580; calcd for C_7H_5O 105.0340, found 105.0343. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74%. Found: C, 77.18; H, 7.43; N, 4.74.

***N*-Benzoyl-DL-β-homophenylalaninal (9).**[9] *N*-Benzoyl-DL-phenylalanine (**7**) was treated as in Method A, using ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 60 : 40), giving the aldehyde (±)-**9** (60%) as a syrup; ν_{max}/cm^{-1} 3437, 3065, 1723, 1657; δ_H (500 MHz, $CDCl_3$) 2.73 (1H, ddd, J = 1.6, 6.0, 17.3 Hz, 2-H_a), 2.77 (1H, ddd, J = 1.3, 5.4, 17.7 Hz, 2-H_b), 2.97 (1H, dd, J = 7.6, 13.6 Hz, 4-H_a), 3.09 (1H, dd, J = 6.9, 13.6 Hz, 4-H_b), 4.76 (1H, m, 3-H), 6.58 (1H, d, J = 8.2 Hz, NH), 7.21–7.25 (3H, m, Ar), 7.32 (2H, dd, J = 7.3, 7.6 Hz, Ar), 7.40 (2H, dd, J = 7.6, 7.6 Hz, Ar), 7.48 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.68 (2H, d, J = 7.6 Hz, Ar), 9.77 (1H, dd, J = 0.6, 0.9 Hz, CHO); δ_C (125.7 MHz, $CDCl_3$) 40.1 (CH_2), 46.7 (CH_2), 46.9 (CH), 126.9 (3 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.2 (2 × CH), 131.6 (CH), 134.3 (C), 137.3 (C), 167.0 (C), 201.2 (CH); *m/z* 268 (M^+ + H, 12%), 176 (69, M^+ − $PhCH_2$), 105 (100, $[PhCO]^+$), 91 (37, $[PhCH_2]^+$), 77 (81, $[Ph]^+$); HRMS calcd for $C_{17}H_{18}NO_2$ 268.1338, found 268.1327; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0708; calcd for C_7H_5O 105.0340, found 105.0341; calcd for C_7H_7 91.0548, found 91.0549; calcd for C_6H_5 77.0391, found 77.0388. $C_{17}H_{17}NO_2$ requires C, 76.38; H, 6.41; N, 5.24%. Found: C, 76.38; H, 6.41; N, 5.03.

***N*-Benzoyl-α,α-dimethyl-DL-β-homoalaninal (14).** Obtained from *N*-benzoyl-DL-alanine (**10**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 70 : 30), giving the aldehyde (±)-**14** (69%) as a syrup; ν_{max}/cm^{-1} 3439, 3081, 1725, 1650, 1519, 1487; δ_H (500 MHz, $CDCl_3$) 1.14 (3H, s, 2-Me_a), 1.18 (3H, s, 2-Me_b), 1.23 (3H, d, J = 6.9 Hz, 3-Me), 4.43 (1H, m, 3-H), 6.58 (1H, d, J = 8.8 Hz, NH), 7.41 (2H, dd, J = 7.3, 7.6 Hz, Ar), 7.48 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.73 (2H, d, J = 6.9 Hz, Ar), 9.54 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 16.3 (CH_3), 18.9 (CH_3), 20.0 (CH_3), 49.4 (CH), 49.9 (C), 126.8 (2 × CH), 128.6 (2 × CH), 131.5 (CH), 134.5 (C), 166.8 (C), 205.9 (CH); *m/z* 220 (M^+ + H, 6%), 219 (M^+, <1%), 148 (32, M^+ − H − Me_2CCHO), 105 (100, $[PhCO]^+$), 77 (36, $[Ph]^+$). HRMS calcd for $C_{13}H_{18}NO_2$ 220.1338, found 220.1333; calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1270; calcd for $C_9H_{10}NO$ 148.0762, found 148.0764; calcd for C_7H_5O 105.0340, found 105.0339; calcd for C_6H_5 77.0391, found 77.0394. $C_{13}H_{17}NO_2$ requires C, 71.21; H, 7.81; N, 6.39%. Found: C, 71.10; H, 8.04; N, 6.51.

***N*-Benzoyl-DL-β-homoalaninal (15).**[11a,b] *N*-Benzoyl DL-alanine (**10**) was treated as in Method A, using ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 50 : 50), giving the aldehyde (±)-**15**

(79%) as an oil; ν_{max}/cm^{-1} 3440, 3063, 1724, 1656, 1517; δ_H (500 MHz, $CDCl_3$) 1.36 (3H, d, J = 6.8 Hz, 3-Me), 2.74 (1H, dd, J = 5.7, 17.3 Hz, 2-H_a), 2.80 (1H, ddd, J = 1.9, 5.7, 17.3 Hz, 2-H_b), 4.61 (1H, m, 3-H), 6.56 (1H, br b, NH), 7.40 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.48 (1H, dd, J = 7.6 Hz, Ar), 7.73 (2H, d, J = 8.2 Hz, Ar), 9.81 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 20.5 (CH_3), 41.6 (CH), 49.6 (CH_2), 126.9 (2 × CH), 128.5 (2 × CH), 131.5 (CH), 134.3 (C), 166.8 (C), 201.1 (CH); m/z 191 (M^+, <1%), 163 (2, M^+ – CO), 121 (4, $[PhCONH_2]^+$), 105 (100, $[PhCO]^+$), 77 (75, $[Ph]^+$); HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0941; calcd for $C_{10}H_{13}NO$ 163.0997, found 163.1004; calcd for C_7H_7NO 121.0528, found 121.0524; calcd for C_7H_5O 105.0340, found 105.0344; calcd for C_6H_5 77.0391, found 77.0389. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32%. Found: C, 69.23; H, 7.02; N, 7.43.

***N*-Benzoyl-α,α-dimethyl-DL-β-homoleucinal (16).** Obtained from *N*-benzoyl DL-leucine (**11**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 9 : 1), giving the aldehyde (±)-**16** (60%) as an oil; ν_{max}/cm^{-1} 3440, 3081, 3065, 1725, 1706, 1657, 1519; δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, J = 6.7 Hz, 5-Me_a), 0.95 (3H, d, J = 6.7 Hz, 5-Me_b), 1.13 (3H, s, 2-Me_a), 1.17 (3H, s, 2-Me_b), 1.30 (1H, ddd, J = 2.6, 9.8, 14.4 Hz, 4-H_a), 1.46 (1H, ddd, J = 3.6, 11.4, 14.0 Hz, 4-H_b), 1.64 (1H, m, 5-H), 4.44 (1H, ddd, J = 2.6, 9.8, 11.0 Hz, 3-H), 6.29 (1H, br d, J = 9.3 Hz, NH), 7.42 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.49 (1H, dd, J = 7.2, 7.8 Hz, Ar), 7.74 (2H, d, J = 7.2 Hz, Ar), 9.54 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 19.2 (CH_3), 19.6 (CH_3), 21.4 (CH_3), 23.8 (CH_3), 25.2 (CH), 39.8 (CH_2), 50.5 (C), 51.9 (CH), 126.8 (2 × CH), 128.6 (2 × CH), 131.5 (CH), 134.5 (C), 167.3 (C), 205.8 (CH); m/z 262 (M^+ + H, 3%), 190 (31, M^+ – H – Me_2CCHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{16}H_{24}NO_2$ 262.1807, found 262.1801; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1223; calcd for C_7H_5O 105.0340, found 105.0344. $C_{16}H_{23}NO_2$ requires C, 73.53; H, 8.87; N, 5.36%. Found: C, 73.43; H, 9.09; N, 5.27.

***N*-Benzoyl-DL-β-homoleucinal (17).**[11c] *N*-Benzoyl DL-leucine (**11**) was treated as in Method A, using ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 70 : 30), giving the aldehyde (±)-**17** (56%) as a oil; ν_{max}/cm^{-1} 3437, 3065, 1704, 1655, 1518, 1486; δ_H (500 MHz, $CDCl_3$) 0.94 (3H, d, J = 6.6 Hz, 5-Me_a), 0.95 (3H, d, J = 6.9 Hz, 5-Me_b), 1.42 (1H, ddd, J = 5.0, 10.1, 15.1 Hz, 4-H_a), 1.67 (1H, m, 4-H_b), 1.68 (1H, m, 5-H), 2.72 (1H, ddd, J = 2.2, 5.9, 17.3 Hz, 2-H_a), 2.78 (1H, br dd, J = 5.5, 17.3 Hz, 2-H_b), 4.61 (1H, m, 3-H), 6.50 (1H, br d, J = 8.8 Hz, NH), 7.40 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.48 (1H, dd, J = 7.6, 7.8 Hz, Ar), 7.73 (2H, d, J = 7.0 Hz, Ar), 9.80 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 22.0 (CH_3), 22.9 (CH_3), 25.2 (CH), 43.7 (CH_2), 44.0 (CH), 48.8 (CH_2), 126.9 (2 × CH), 128.6 (2 × CH), 131.5 (CH), 134.4 (C), 167.0 (C), 201.4 (CH); m/z 234 (M^+ + H, 3%), 233 (M^+, <1%), 190 (3, M^+ – CH_2CHO), 105 (100, $[PhCO]^+$), 77 (53, $[Ph]^+$). HRMS calcd for $C_{14}H_{20}NO_2$ 234.1494, found 234.1502; calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1419; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1228; calcd for C_7H_5O 105.0340, found 105.0345; calcd for C_6H_5 77.0391, found 77.0394. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%. Found: C, 72.23; H, 8.24; N, 6.01.

Ethyl 4-benzamido-5,5-dimethyl-6-oxo hexanoate (18). Obtained from Bz-Glu(OEt)-OH (**12**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotary chromatography (hexanes–EtOAc, 85 : 15), giving the aldehyde (±)-**18** (66%) as an oil; ν_{max}/cm^{-1} 3428, 1725, 1658, 1519; δ_H (500 MHz, $CDCl_3$) note: the usual numbering (CHO as C-1) is used, not the one given by IUPAC nomenclature: 1.13 (3H, dd, J = 6.7, 7.0 Hz, Et), 1.15 (3H, s, 2-Me_a), 1.20 (3H, s, 2-Me_b), 1.81 (1H, m, 4-H_a), 1.96 (1H, dddd, J = 3.2, 6.9, 6.9, 13.9 Hz, 4-H_b), 2.30–2.45 (2H, m, 5-H_2), 3.94–4.08 (2H, m, Et), 4.35 (1H, ddd, J = 3.2, 9.8, 12.9 Hz, 3-H), 6.55 (1H, d, J = 9.8 Hz, NH), 7.41 (2H, dd, J = 7.3, 7.6 Hz, Ar), 7.48 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.74 (2H, d, J = 7.5 Hz, Ar), 9.53 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 14.1 (CH_3), 19.1 (CH_3), 19.8 (CH_3), 25.0 (CH_2), 31.3 (CH_2), 50.3 (C), 53.6 (CH), 60.6 (CH_2), 126.9 (2 × CH), 128.6 (2 × CH), 131.7 (CH), 133.9 (C), 167.3 (C), 173.6 (C), 205.4 (CH); m/z 306 (M^+ + H, 1%), 234 (43, M^+ – Me_2CCHO), 105 (100, $[PhCO]^+$), 77 (48, $[Ph]^+$). HRMS calcd for $C_{17}H_{24}NO_4$ 306.1705, found 306.1714; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1131; calcd for C_7H_5O 105.0340, found 105.0343; calcd for C_6H_5 77.0391, found 77.0388. $C_{17}H_{23}NO_4$ requires C, 66.86; H, 7.59; N, 4.59%. Found: C, 66.63; H, 7.77; N, 4.58.

Ethyl 4-benzamido-6-oxohexanoate (19). Obtained from Bz-Glu(OEt)-OH (**12**) according to Method A, using vinyloxytrimethylsilane as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 50 : 50), giving the aldehyde (±)-**19** (51%) as a oil; ν_{max}/cm^{-1} 3434, 1724, 1658, 1518; δ_H (500 MHz, $CDCl_3$) 1.18 (3H, dd, J = 6.9, 7.3 Hz, Et), 1.97 (1H, m, 4-H_a), 2.06 (1H, m, 4-H_b), 2.38–2.51 (2H, m, 5-H_2), 2.75 (1H, dd, J = 5.7, 17.1 Hz, 2-H_a), 2.83 (1H, ddd, J = 1.9, 5.7, 17.3 Hz, 2-H_b), 4.01–4.11 (2H, m, Et), 4.51 (1H, m, 3-H), 6.94 (1H, d, J = 8.2 Hz, NH), 7.40 (2H, dd, J = 7.8, 7.9 Hz, Ar), 7.47 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.75 (2H, d, J = 7.3 Hz, Ar), 9.79 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 14.0 (CH_3), 28.9 (CH_2), 31.2 (CH_2), 45.7 (CH), 48.5 (CH_2), 60.7 (CH_2), 126.9 (2 × CH), 128.5 (2 × CH), 131.6 (CH), 133.9 (C), 167.0 (C), 173.7 (C), 200.8 (CH); m/z 278 (M^+ + H, 6%), 234 (12, M^+ – CH_2CHO), 172 (99, M^+ – PhCO), 144 (60, M^+ – PhCO – CHO), 105 (100, $[PhCO]^+$), 77 (99, $[Ph]^+$); HRMS calcd for $C_{15}H_{20}NO_4$ 278.1392, found 278.1395; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1123; calcd for $C_8H_{14}NO_3$ 172.0974, found 172.0976; calcd for $C_7H_{14}NO_2$ 144.1025, found 144.1020; calcd for C_7H_5O 105.0340, found 105.0344; calcd for C_6H_5 77.0391, found 77.0393. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%. Found: C, 64.98; H, 6.96; N, 5.19.

***N*-Methoxycarbonyl-α,α-dimethyl-DL-β-homoprolinal (21).** Obtained from the ornithine derivative **13** according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 60 : 40), giving the aldehyde (±)-**21** (83%) as a syrup; ν_{max}/cm^{-1} 1719, 1690, 1454, 1386; δ_H (500 MHz, $CDCl_3$, 70 °C) 1.00 (3H, s, 2-Me_a), 1.01 (3H, s, 2-Me_b), 1.74–1.90 (3H, m, 4-H_a + 5-H_2), 2.00 (1H, m, 4-H_b), 3.19

(1H, m, 6-H_a), 3.65 (3H, s, OMe), 3.71 (1H, m, 6-H_b), 4.14 (1H, m, 3-H), 9.53 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) 16.3 (CH_3), 20.0 (CH_3), 24.4 (CH_2), 27.1 (CH_2), 47.9 (CH_2), 50.5 (C), 52.2 (CH_3), 62.0 (CH), 156.4 (C), 203.4 (CH); *m/z* 200 (M^+ + H, <1%), 199 (M^+, <1%), 128 (100, M^+ – Me_2CCHO). HRMS calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1284; calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1199; calcd for $C_6H_{10}NO_2$ 128.0712, found 128.0717. $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.60; N, 7.03%. Found: C, 59.99; H, 8.61; N, 7.36.

***N*-Benzyloxycarbonyl-α,α-dimethyl-DL-β-homoprolinal (24).** Obtained from DL-proline benzyl carbamate (**22**) according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 70 : 30), giving the aldehyde (±)-**24** (86%) as a syrup; ν_{max}/cm^{-1} 1689, 1451, 1416; δ_H (500 MHz, $CDCl_3$, 70 °C) 1.01 (3H, s, 2-Me), 1.02 (3H, s, 2-Me), 1.74–1.90 (3H, m, 3-H_a + 4-H_2), 1.98 (1H, m, 3-H_b), 3.24 (1H, m, 5-H_a), 3.75 (1H, m, 5-H_b), 4.18 (1H, m, 2-H), 5.06 (1H, d, *J* = 12.4 Hz, OCH_aPh), 5.12 (1H, d, *J* = 12.3 Hz, OCH_bPh), 7.25–7.36 (5H, m, Ar), 9.54 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) 16.5 (CH_3), 20.1 (CH_3), 22.4 (CH_2), 27.1 (CH_2), 47.9 (CH_2), 50.5 (C), 62.1 (CH), 67.2 (CH_2), 128.0 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.9 (C), 155.9 (C), 203.5 (CH); *m/z* 275 (M^+, <1%), 204 (80, M^+ – Me_2CCHO), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1512; calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1026; calcd for C_7H_7 91.0548, found 91.0548. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%. Found: C, 69.62; H, 7.75; N, 5.13.

***N*-Benzyloxycarbonyl-DL-β-homoprolinal (25).**[15a–d] Obtained from the proline derivative **22** according to Method A, using 2-ethyl vinyl ether as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 50 : 50), giving the aldehyde (±)-**25** (85%) as a syrup; ν_{max}/cm^{-1} 1717, 1692, 1420; δ_H (500 MHz, $CDCl_3$, 70 °C) 1.69 (1H, m, 3-H_a), 1.81–1.92 (2H, m, 4-H_2), 2.14 (1H, m, 3-H_b), 2.50 (1H, ddd, *J* = 1.9, 7.9, 16.4 Hz, 1′-H_a), 2.90 (1H, br b, 1′-H_b), 3.43 (1H, ddd, *J* = 5.4, 6.9, 10.7 Hz, 5-H_a), 3.49 (1H, m, 5-H_b), 4.30 (1H, m, 2-H), 5.13 (2H, s, OCH_2Ph), 7.28–7.35 (5H, m, Ar), 9.75 (1H, br s, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) 23.5 (CH_2), 31.5 (CH_2), 46.6 (CH_2), 48.9 (CH_2), 53.0 (CH), 66.9 (CH_2), 128.0 (2 × CH), 128.5 (3 × CH), 137.0 (C), 154.8 (C), 200.0 (CH); *m/z* 247 (M^+, 2%), 204 (27, M^+ – CH_2CHO), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1205; calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1027; calcd for C_7H_7 91.0548, found 91.0546. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%. Found: C, 68.35; H, 7.14; N, 5.30.

(2*R*,4*R*)-Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-methyl-1-oxopropan-2-yl)pyrrolidine-1-carboxylate (26) and (2*S*,4*R*)-benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-methyl-1-oxo propan-2-yl)pyrrolidine-1-carboxylate (27). Obtained from hydroxyproline derivative **23** according to Method A, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 90 : 10), giving the 2,4-*cis* product **26** (63%) and the 2,4-*trans* isomer **27** (19%).

Product ***26***. Syrup; $[\alpha]_D$ +8 (*c* 1.05 in $CHCl_3$); ν_{max}/cm^{-1} 1724, 1691, 1471; δ_H (500 MHz, $CDCl_3$, 70 °C) note: the usual numbering (CHO as C-1) is used, not the one given by IUPAC nomenclature: 0.07 (3H, s, $SiMe_a$), 0.08 (3H, s, $SiMe_b$), 0.91 (9H, s, *t*Bu), 1.00 (3H, s, 2-Me_a), 1.07 (3H, s, 2-Me_b), 1.72 (1H, ddd, *J* = 7.6, 7.6, 13.2 Hz, 4-H_a), 2.27 (1H, ddd, *J* = 7.5, 7.5, 13.2 Hz, 4-H_b), 2.96 (1H, dd, *J* = 7.9, 11.3 Hz, 6-H_a), 3.99 (1H, dd, *J* = 7.3, 11.1 Hz, 6-H_b), 4.19 (1H, dd, *J* = 8.0, 8.1 Hz, 3-H), 4.24 (1H, dddd, *J* = 7.4, 7.5, 7.5, 7.6 Hz, 5-H), 5.04 (1H, br d, *J* = 12.6 Hz, OCH_aPh), 5.13 (1H, d, *J* = 12.3 Hz, OCH_bPh), 7.30–7.35 (5H, m, Ar), 9.56 (1H, br b, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) −4.8 (2 × CH_3), 16.0 (CH_3), 18.0 (C), 20.2 (CH_3), 25.8 (3 × CH_3), 36.3 (CH_2), 50.2 (C), 54.6 (CH_2), 60.7 (CH), 67.3 (CH_2), 69.7 (CH), 128.1 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 136.7 (C), 155.7 (C), 203.2 (CH); *m/z* 334 (14, M^+ – Me_2CCHO), 290 (41, M^+ – $Me_3CSi(Me)_2$), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{18}H_{28}NO_3Si$ 334.1838, found 334.1823; calcd for $C_{16}H_{20}NO_4$ 290.1392, found 290.1378; calcd for C_7H_7 91.0548, found 91.0545. $C_{22}H_{35}NO_4Si$ requires C, 65.15; H, 8.70; N, 3.45%. Found: C, 65.02; H, 8.82; N, 3.56.

Product ***27***. Syrup; $[\alpha]_D$ −37 (*c* 0.18 in $CHCl_3$); ν_{max}/cm^{-1} 1722, 1694, 1469, 1415; δ_H (500 MHz, $CDCl_3$, 70 °C) 0.04 (3H, s, $SiMe_a$), 0.06 (3H, s, $SiMe_b$), 0.86 (9H, s, *t*Bu), 1.00 (6H, s, 2-Me_2), 1.86 (1H, ddd, *J* = 3.5, 7.9, 13 Hz, 4-H_a), 1.97 (1H, m, 4-H_b), 3.20 (1H, dd, *J* = 3.6, 11.9 Hz, 6-H_a), 3.77 (1H, m, 6-H_b), 4.33 (1H, m, 5-H), 4.38 (1H, br dd, *J* = 7.6, 7.9 Hz, 3-H), 5.06 (1H, m, OCH_aPh), 5.14 (1H, m, OCH_bPh), 7.28–7.34 (5H, m, Ar), 9.56 (1H, br b, CHO); δ_C (125.7 MHz, $CDCl_3$, 70 °C) −4.8 (2 × CH_3), 15.9 (CH_3), 18.0 (C), 20.0 (CH_3), 25.7 (3 × CH_3), 37.0 (CH_2), 50.0 (C), 56.8 (CH_2), 61.0 (CH), 67.3 (CH_2), 70.8 (CH), 128.0 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.9 (C), 156.8 (C), 203.5 (CH); *m/z* 334 (5, M^+ – Me_2CCHO), 290 (20, M^+ – $Me_3CSi(Me)_2$), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{18}H_{28}NO_3Si$ 334.1838, found 334.1850; calcd for $C_{16}H_{26}NO_4$ 290.1392, found 290.1400; calcd for C_7H_7 91.0548, found 91.0548. $C_{22}H_{35}NO_4Si$ requires C, 65.15; H, 8.70; N, 3.45%. Found: C, 65.45; H, 8.88; N, 3.67.

(2*R*,4*R*)-Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxoethyl) pyrrolidine-1-carboxylate (28) and (2*S*,4*R*)-benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (29). Obtained from hydroxyproline derivative **23** according to Method A, using vinyloxytrimethylsilane as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 90 : 10), giving the 2,4-*cis* product **28** (34%) and the 2,4-*trans* isomer **29** (20%).

Product ***28***. Colorless oil; $[\alpha]_D$ +5 (*c* 0.63 in $CHCl_3$); ν_{max}/cm^{-1} 1694, 1417; δ_H (500 MHz, $CDCl_3$, 70 °C) note: the usual numbering (CHO as C-1) is used, not the one given by IUPAC nomenclature: 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, *t*Bu), 1.78 (1H, br d, *J* = 13.2 Hz, 4-H_a), 2.24 (1H, ddd, *J* = 5.2, 8.4, 13.5 Hz, 4-H_b), 2.85 (1H, m, 2-H_a), 3.09 (1H, m, 2-H_b), 3.37 (1H, br d, *J* = 12.6 Hz, 6-H_a), 3.64 (1H, m, 6-H_b), 4.37 (1H, m, 3-H), 4.39 (1H, m, 5-H), 5.13 (1H, d, *J* = 12 Hz, OCH_aPh), 5.16 (1H, d, *J* = 11.5 Hz, OCH_bPh), 7.30–7.36 (5H, m, Ar), 9.77 (1H, br b, CHO); δ_C (100.6 MHz, $CDCl_3$, 25 °C) A mixture of rotamers was observed: −5.0 (CH_3), −4.9 (CH_3), 17.9 (C), 25.7 (3 × CH_3), 39.7/40.4 (CH_2), 49.2/49.9 (CH_2), 51.9/52.5 (CH), 55.2/55.7 (CH_2), 66.9/67.1 (CH_2), 70.6/71.3 (CH), 127.9 (2 × CH),

128.1 (CH), 128.5 (2 × CH), 136.5/136.7 (C), 154.5/154.8 (C), 201.1/201.2 (CH); *m/z* 320 ($M^+ - Me_3C$, 9%), 292 (11, $M^+ - Me_3C - CO$), 276 (15, $M^+ - Me_3C - CH_2CHO$), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{16}H_{22}NO_4Si$ 320.1318, found 320.1320; calcd for $C_{15}H_{22}NO_3Si$ 292.1369, found 292.1363; calcd for C_7H_7 91.0548, found 91.0544. $C_{20}H_{31}NO_4Si$ requires C, 63.63; H, 8.28; N, 3.71%. Found: C, 63.59; H, 8.15; N, 3.78.

Product **29**. Colorless oil; $[\alpha]_D$ −35 (*c* 0.26 in $CHCl_3$); ν_{max}/cm^{-1} 1694, 1416, 1357; δ_H (500 MHz, $CDCl_3$, 70 °C) 0.06 (3H, s, $SiMe_a$), 0.07 (3H, s, $SiMe_b$), 0.88 (9H, s, *t*Bu), 1.77 (1H, ddd, *J* = 4.7, 7.3, 12.0 Hz, 4-H_a), 2.17 (1H, m, 4-H_b), 2.58 (1H, br dd, *J* = 6.9, 16.0 Hz, 2-H_a), 2.96 (1H, m, 2-H_b), 3.46 (1H, dd, *J* = 4.4, 11.4 Hz, 6-H_a), 3.50 (1H, m, 6-H_b), 4.37 (1H, m, 5-H), 4.41 (1H, m, 3-H), 5.12–5.18 (2H, m, OCH_2Ph), 7.29–7.35 (5H, m, Ar), 9.75 (1H, br b, CHO); δ_C (100.6 MHz, $CDCl_3$, 25 °C) A mixture of rotamers was observed: −4.9 (CH_3), −4.8 (CH_3), 17.9 (C), 25.7 (3 × CH_3), 40.9/41.8 (CH_2), 48.5/49.4 (CH_2), 51.3/51.9 (CH_2), 55.0/55.3 (CH), 66.8/67.0 (CH_2), 69.5/70.0 (CH), 127.8 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 136.8 (C), 155.4 (C), 200.3/200.5 (CH); *m/z* 292 ($M^+ - Me_3C - CO$, 33%), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{15}H_{22}NO_3Si$ 292.1369, found 292.1364; calcd for C_7H_7 91.0548, found 91.0544. $C_{20}H_{31}NO_4Si$ requires C, 63.63; H, 8.28; N, 3.71%. Found: C, 63.61; H, 8.28; N, 3.70.

***N*-(*N*-Benzoyl-1-aminocyclohexanecarbonyl)-α,α-dimethyl-DL-β-homoleucinal (37).** Obtained from the dipeptide **30** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 70 : 30), giving product **37** (50%) as a syrup; ν_{max}/cm^{-1} 3433, 1724, 1662, 1515; δ_H (500 MHz, $CDCl_3$) 0.86 (3H, d, *J* = 6.6 Hz, 5-Me), 0.88 (3H, d, *J* = 6.3 Hz, 5-Me), 1.02 (3H, s, 2-Me), 1.05 (3H, s, 2-Me), 1.15 (1H, ddd, *J* = 2.5, 11.8, 13.3 Hz, 4-H_a), 1.33 (1H, ddd, *J* = 3.2, 11.7, 14.1 Hz, 4-H_b), 1.38 (1H, m, 5′-H_a), 1.46 (2H, m, 4′-H_a + 6′-H_a), 1.56 (1H, m, 5-H), 1.66 (1H, m, 5′-H_b), 1.70 (2H, m, 4′-H_b + 6′-H_b), 1.96 (2H, m, 3′-H_a + 7′-H_a), 2.25 (2H, dd, *J* = 13.2, 13.2 Hz, 3′-H_b + 7′-H_b), 4.23 (1H, ddd, *J* = 2.2, 9.8, 11.8 Hz, 3-H), 6.05 (1H, s, NH), 7.45 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.50 (1H, d, *J* = 7.6 Hz, NH), 7.53 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.73 (2H, d, *J* = 7.0 Hz, Ar), 9.46 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 18.0 (CH_3), 18.6 (CH_3), 21.4 (CH_3), 21.6 (CH_2), 21.7 (CH_2), 23.8 (CH_3), 25.0 (CH), 25.2 (CH_2), 32.2 (CH_2), 32.5 (CH_2), 39.4 (CH_2), 50.6 (CH), 50.8 (C), 61.1 (C), 126.8 (2 × CH), 128.8 (2 × CH), 131.9 (CH), 134.8 (C), 168.5 (C), 173.8 (C), 205.1 (CH); *m/z* 387 (M^+ + H, <1%), 230 (21, M^+ − NH-CH(CH_2CHMe_2)-C($Me)_2$-CHO), 202 (73, M^+ − CONH-CH(CH_2CHMe_2)-C($Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{23}H_{35}N_2O_3$ 387.2648, found 387.2641; calcd for $C_{14}H_{16}NO_2$ 230.1181, found 230.1183; calcd for $C_{13}H_{16}NO$ 202.1232, found 202.1235; calcd for C_7H_5O 105.0340, found 105.0341. $C_{23}H_{34}N_2O_3$ requires C, 71.47; H, 8.87; N, 7.25%. Found: C, 71.36; H, 8.97; N, 6.93.

***N*-(*N*-Benzoyl-2-methylalanyl)-α,α-dimethyl-β-α,α-dimethyl-β-homophenylalaninal (38).** Obtained from the dipeptide **31** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by chromatography (hexanes–EtOAc, 60 : 40), giving product **38** (61%) as a crystalline solid; Mp 138–139 °C (EtOAc–*n*-hexane); ν_{max}/cm^{-1} 3439, 3088, 1722, 1671, 1512, 1484; δ_H (500 MHz, $CDCl_3$) 1.19 (3H, s, 2-Me or 2′-Me), 1.21 (3H, s, 2-Me or 2′-Me), 1.37 (3H, s, 2-Me or 2′-Me), 1.41 (3H, s, 2-Me or 2′-Me), 2.59 (1H, dd, *J* = 11.7, 14.2 Hz, 4-H_a), 2.98 (1H, dd, *J* = 4.1, 14.2 Hz, 4-H_b), 4.48 (1H, ddd, *J* = 4.1, 9.8, 11.7 Hz, 3-H), 6.62 (1H, br s, NH), 7.07 (1H, br d, *J* = 9.8 Hz, NH), 7.13–7.20 (5H, m, Ar), 7.42 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.50 (1H, dd, *J* = 7.6, 7.8 Hz, Ar), 7.70 (2H, d, *J* = 6.9 Hz, Ar), 9.50 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 19.1 (CH_3), 19.5 (CH_3), 24.6 (CH_3), 25.3 (CH_3), 36.4 (CH_2), 50.5 (C), 54.2 (CH), 57.8 (C), 126.5 (CH), 126.9 (2 × CH), 128.3 (2 × CH), 128.6 (2 × CH), 129.0 (2 × CH), 131.6 (CH), 134.7 (C), 137.9 (C), 167.5 (C), 173.9 (C), 204.8 (C); *m/z* 381 (M^+ + H, 5%), 309 (6, $M^+ - Me_2CCHO$), 190 (64, M^+ − NHCH(CH_2Ph)-C($Me)_2$-CHO), 162 (70, M^+ − CONHCH(CH_2Ph)-C($Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{23}H_{29}N_2O_3$ 381.2178, found 381.2170; calcd for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1616; calcd for $C_{11}H_{12}NO_2$ 190.0868, found 190.0861; calcd for $C_{10}H_{12}NO$ 162.0919, found 162.0925; calcd for C_7H_5O 105.0340, found 105.0343. $C_{23}H_{28}N_2O_3$ requires C, 72.61; H, 7.42; N, 7.36%. Found: C, 72.77; H, 7.68; N, 7.07.

***N*-(*N*-Benzoyl-L-phenylalanyl)-α,α-dimethyl-L-β-homoalaninal (39) and *N*-(*N*-benzoyl-L-phenylalanyl)-α,α-dimethyl-D-β-homoalaninal (40).** Obtained from the dipeptide **32** according to Method B, but using DIB (0.4 mmol) and iodine (0.1 mmol) in the scission step, and 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile in the addition step. The reaction mixture was purified by chromatography (hexanes–EtOAc, 75 : 25), giving the diastereomeric products **39** (49%) and **40** (37%), in 86% overall yield.

Product **39**. Crystalline solid; Mp 133–134 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −8 (*c* 0.24 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 3310, 1723, 1653, 1512; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, s, 2-Me_a), 0.94 (3H, s, 2-Me_b), 1.02 (3H, d, *J* = 6.9 Hz, 3-Me), 3.12 (1H, dd, *J* = 7.9, 13.9 Hz, 3′-H_a), 3.21 (1H, dd, *J* = 6.6, 13.9 Hz, 3′-H_b), 4.17 (1H, m, 3-H), 4.86 (1H, ddd, *J* = 6.6, 7.6, 7.9 Hz, 2-H), 6.43 (1H, d, *J* = 9.5 Hz, NH), 6.91 (1H, d, *J* = 7.6 Hz, NH), 7.21–7.30 (5H, m, Ar), 7.40 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.71 (2H, d, *J* = 7.3 Hz, Ar), 9.35 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 16.1 (CH_3), 18.4 (CH_3), 19.0 (CH_3), 38.3 (CH_2), 49.0 (CH), 49.6 (C), 55.2 (CH), 127.0 (2 × CH), 127.1 (CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.3 (2 × CH), 131.8 (CH), 133.7 (C), 136.5 (C), 167.4 (C), 170.5 (C), 204.8 (CH); *m/z* 366 (M^+, 1%), 224 (17, M^+ − CONHCH(Me)-C($Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{22}H_{26}N_2O_3$ 366.1943, found 366.1944; calcd for $C_{15}H_{14}NO$ 224.1075, found 224.1074; calcd for C_7H_5O 105.0340, found 105.0338. $C_{22}H_{26}N_2O_3$ requires C, 72.11; H, 7.15; N, 7.64%. Found: C, 72.24; H, 7.35; N, 7.76.

Product **40**. Syrup; $[\alpha]_D$ −13 (*c* 0.21 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 3310, 1723, 1648, 1510; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, d, *J* = 6.9 Hz, 3-Me), 0.93 (3H, s, 2-Me_a), 0.95 (3H, s, 2-Me_b), 3.12 (1H, dd, *J* = 8.2, 13.6 Hz, 3′-H_a), 3.24 (1H, dd, *J* = 6.3, 13.6, 3′-H_b), 4.15 (1H, m, 3-H), 4.88 (1H, ddd, *J* = 6.9, 7.9, 7.9 Hz, 2′-H), 6.59 (1H, br b, NH), 7.16 (1H, m, Ar), 7.20–7.30 (5H, m, Ar + NH), 7.39 (2H, dd, *J* = 6.8, 7.3 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.72 (2H, d, *J* = 8.1 Hz, Ar), 9.32 (1H,

br b, CHO); δ_C (125.7 MHz, $CDCl_3$) 15.6 (CH_3), 18.0 (CH_3), 18.7 (CH_3), 38.3 (CH_2), 48.5 (CH), 49.6 (C), 55.2 (CH), 127.0 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.3 (2 × CH), 131.8 (CH), 133.7 (C), 136.7 (C), 167.6 (C), 170.6 (C), 204.3 (CH); *m/z* 366 (M^+, 5%), 224 (18, M^+ – CONHCH(Me)-$C(Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{22}H_{26}N_2O_3$ 366.1943, found 366.1948; calcd for C_7H_5O 105.0340, found 105.0343. $C_{22}H_{26}N_2O_3$ requires C, 72.11; H, 7.15; N, 7.64%. Found: C, 72.23; H, 6.89; N, 7.77.

N-(N-Benzoyl-L-leucyl)-α,α-dimethyl-L-β-(41) and N-(N-benzoyl-L-leucyl)-α,α-dimethyl-D-β-homoalaninal (42). The products were generated from dipeptide **33** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 80 : 20), affording compounds **41** (57%) and **42** (29%).

Compound 41. Crystalline solid; Mp 184–185 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −22 (*c* 0.43 in $CHCl_3$); ν_{max}/cm^{-1} 3428, 1723, 1656, 1517; δ_H (500 MHz, $CDCl_3$) 0.95 (6H, d, *J* = 6.3 Hz, 4′-Me_2), 1.05 (3H, d, *J* = 8.2 Hz, 3-Me), 1.06 (3H, s, 2-Me_a), 1.07 (3H, s, 2-Me_b), 1.67–1.72 (3H, m, 3′-H_2 + 4′-H), 4.23 (1H, dddd, *J* = 6.8, 6.8, 6.8, 9.4 Hz, 3-H), 4.67 (1H, ddd, *J* = 7.5, 7.5, 7.5 Hz, 2′-H), 6.87 (1H, br b, NH), 6.94 (1H, d, *J* = 7.9 Hz, NH), 7.40 (2H, dd, *J* = 7.7, 7.7 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.78 (2H, d, *J* = 7.5 Hz, Ar), 9.45 (1H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 15.8 (CH_3), 17.9 (CH_3), 19.2 (CH_3), 22.2 (CH_3), 22.8 (CH_3), 25.0 (CH), 41.4 (CH_2), 48.6 (CH), 50.0 (C), 52.5 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.8 (C), 167.6 (C), 171.9 (C), 204.7 (CH); *m/z* 333 (M^+ + H, 1%), 190 (100, M^+ – CONHCH(Me)CMe_2CHO), 105 (91, $[PhCO]^+$); HRMS calcd for $C_{19}H_{29}N_2O_3$ 333.2178, found 333.2181; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1239. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.49; N, 8.43%. Found: C, 68.90; H, 8.35; N, 8.14.

Compound 42. Crystalline solid; Mp 152–153 °C (net); $[\alpha]_D$ −28 (*c* 0.60 in $CHCl_3$); ν_{max}/cm^{-1} 3428, 1721, 1656, 1517; δ_H (500 MHz, $CDCl_3$) 0.96 (3H, d, *J* = 6.5 Hz, 4′-Me_a), 0.97 (3H, d, *J* = 6.3 Hz, 4′-Me_b), 1.00 (3H, s, 2-Me_a), 1.03 (3H, s, 2-Me_b), 1.13 (3H, d, *J* = 6.9 Hz, 3-Me), 1.63–1.82 (3H, m, 3′-H_2 + 4′-H), 4.24 (1H, dddd, *J* = 6.9, 6.9, 6.9, 9.5 Hz, 3-H), 4.61 (1H, ddd, *J* = 6.0, 6.3, 8.2 Hz, 2′-H), 6.67 (1H, d, *J* = 8.2 Hz, NH), 6.75 (1H, d, *J* = 9.8 Hz, NH), 7.43 (2H, dd, *J* = 7.4, 7.4 Hz, Ar), 7.50 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.78 (2H, d, *J* = 6.9 Hz, Ar), 9.43 (1H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 16.0 (CH_3), 17.9 (CH_3), 19.0 (CH_3), 22.3 (CH_3), 22.9 (CH_3), 25.0 (CH), 40.4 (CH_2), 48.4 (CH), 50.1 (C), 52.2 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.9 (C), 167.9 (C), 171.3 (C), 204.8 (CH); *m/z* 333 (M^+ + H, 2%), 190 (86, M^+ – CONHCH(Me)CMe_2CHO), 105 (100, $[PhCO]^+$); HRMS calcd $C_{19}H_{29}N_2O_3$ 333.2178, found 333.2177; calcd for C_7H_5O 105.0340, found 105.0340. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.49; N, 8.43%. Found: C, 68.80; H, 8.32; N, 8.10.

N-(N-Benzoyl-L-prolyl)-α,α-dimethyl-L-β-homoleucinal (43) and N-(N-benzoyl-L-prolyl)-α,α-dimethyl-D-β-homoleucinal (44). The products were generated from dipeptide **34** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 80 : 20), affording compounds **43** (47%) and **44** (22%).

Compound 43. Syrup; $[\alpha]_D$ −85 (*c* 0.65 in $CHCl_3$); ν_{max}/cm^{-1} 3300, 1723, 1674, 1610, 1536; δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.92 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.96 (3H, s, 2-Me_a), 1.05 (3H, s, 2-Me_b), 1.18 (1H, ddd, *J* = 2.2, 9.8, 12.6 Hz, 4-H_a), 1.32 (1H, ddd, *J* = 3.5, 11.3, 13.0 Hz, 4-H_b), 1.65 (1H, m, 5-H), 1.81 (1H, m, 4′-H_a), 1.91–2.04 (2H, m, 4′-H_b + 3′-H_a), 2.50 (1H, m, 3′-H_b), 3.37 (1H, m, 5′-H_a), 3.50 (1H, m, 5′-H_b), 4.26 (1H, dd, *J* = 10, 11.7 Hz, 3-H), 4.82 (1H, m, 2′-H), 7.26 (1H, d, *J* = 9.8 Hz, NH), 7.41 (3H, m, Ar), 7.54 (2H, m, Ar), 9.47 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 17.0 (CH_3), 18.9 (CH_3), 21.4 (CH_3), 23.8 (CH_3), 25.0 (CH), 25.2 (CH_2), 26.3 (CH_2), 38.6 (CH_2), 50.0 (CH_2), 50.5 (CH), 51.0 (C), 59.5 (CH), 126.8 (2 × CH), 128.5 (2 × CH), 130.1 (CH), 136.3 (C), 170.7 (C), 171.5 (C), 204. 7 (CH); *m/z* 358 (M^+, 3%), 202 (50, M^+ – NHCH(CH_2CHMe_2)-$C(Me)_2$-CHO), 174 (95, M^+ – CONHCH(CH_2CHMe_2)-$C(Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{21}H_{30}N_2O_3$ 358.2256, found 358.2262; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0858; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0921; calcd for C_7H_5O 105.0340, found 105.0341. $C_{21}H_{30}N_2O_3$ requires C, 70.36; H, 8.44; N, 7.81%. Found: C, 70.48; H, 8.42; N, 8.10.

Compound 44. Syrup; $[\alpha]_D$ −97 (*c* 0.34 in $CHCl_3$); ν_{max}/cm^{-1} 3424, 3303, 1725, 1674, 1660, 1602, 1420; δ_H (500 MHz, $CDCl_3$) 0.83 (3H, d, *J* = 6.9 Hz, 5-Me_a), 0.90 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.07 (3H, s, 2-Me_a), 1.08 (3H, s, 2-Me_b), 1.16 (1H, m, 4-H_a), 1.31 (1H, m, 4-H_b), 1.56 (1H, m, 5-H), 1.83 (1H, m, 4′-H_a), 1.99–2.08 (2H, m, 4′-H_b + 3′-H_a), 2.43 (1H, m, 3′-H_b), 3.45 (1H, m, 5′-H_a), 3.53 (1H, m, 5′-H_b), 4.24 (1H, dd, *J* = 9.5, 9.8 Hz, 3-H), 4.76 (1H, dd, *J* = 4.8, 7.3 Hz, 2′-H), 7.11 (1H, br d, *J* = 9.8 Hz, NH), 7.40–7.50 (5H, m, Ar), 9.49 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) 18.4 (CH_3), 18.7 (CH_3), 21.5 (CH_3), 23.8 (CH_3), 25.2 (CH), 25.4 (CH_2), 27.1 (CH_2), 39.6 (CH_2), 50.4 (CH_2), 50.5 (C), 51.0 (CH), 59.9 (CH), 126.9 (2 × CH), 128.5 (2 × CH), 130.3 (CH), 136.2 (C), 170.9 (C), 171.5 (C), 205.2 (CH); *m/z* 358 (M^+, 2%), 202 (27, M^+ – NHCH(CH_2CHMe_2)-$C(Me)_2$-CHO), 174 (74, M^+ – CONHCH(CH_2CHMe_2)-$C(Me)_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{21}H_{30}N_2O_3$ 358.2256, found 358.2251; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0863; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0925; calcd for C_7H_5O 105.0340, found 105.0336. $C_{21}H_{30}N_2O_3$ requires C, 70.36; H, 8.44; N, 7.81%. Found: C, 70.19; H, 8.43; N, 7.76.

N-(N-Benzoyl-L-alanyl)-α,α-dimethyl-DL-β-homoleucinal (45). The products were generated from dipeptide **35** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 75 : 25), affording compound **45** (78%) as a 9 : 6 mixture of diastereomers; ν_{max}/cm^{-1} 3422, 3307, 1724, 1676, 1645, 1514; δ_H (500 MHz, $CDCl_3$) major isomer: 0.90 (3H, d, *J* = 6.8 Hz, 5-Me_a), 0.91 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.98 (3H, s, 2-Me_a), 1.01 (3H, s, 2-Me_b), 1.14 (1H, m, 4-H_a), 1.39 (1H, m, 4-H_b), 1.49 (3H, d, *J* = 6.9 Hz, 2′-Me), 1.61 (1H, m, 5-H), 4.24 (1H, m, 3-H), 4.81 (1H, m, 2′-H), 7.07 (1H, br d, *J* = 10.4 Hz, NH), 7.22 (1H, br d, *J* = 7.6 Hz, NH), 7.40 (2H, dd, *J* = 7.8, 7.8 Hz, Ar), 7.49 (1H, dd, *J* = 7.3, 7.5 Hz, Ar), 7.79 (2H, d, *J* = 8.1 Hz, Ar), 9.46 (1H, s, CHO); minor

isomer: 0.75 (3H, d, J = 6.7 Hz, 5-Me$_a$), 0.84 (3H, d, J = 6.5 Hz, 5-Me$_b$), 1.08 (3H, s, 2-Me$_a$), 1.09 (3H, s, 2-Me$_b$), 1.12 (1H, m, 4-H$_a$), 1.34 (1H, m, 4-H$_b$), 1.50 (3H, d, J = 6.9 Hz, 2′-Me), 1.51 (1H, m, 5-H), 4.24 (1H, m, 3-H), 4.81 (1H, m, 2′-H), 7.04 (1H, br d, J = 10.4 Hz, NH), 7.24 (1H, br d, J = 8.2 Hz, NH), 7.40 (2H, dd, J = 7.8, 7.8 Hz, Ar), 7.49 (1H, dd, J = 7.3, 7.5 Hz, Ar), 7.76 (2H, d, J = 7.5 Hz, Ar), 9.51 (1H, s, CHO); δ_C (125.7 MHz, $CDCl_3$) major isomer: 18.2 (CH_3), 18.4 (CH_3), 18.6 (CH_3), 21.2 (CH_3), 23.8 (CH_3), 25.1 (CH), 39.1 (CH_2), 49.4 (CH), 50.7 (C), 50.9 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 131.8 (CH), 133.7 (C), 167.6 (C), 172.5 (C), 204.9 (CH); minor isomer: 18.0 (CH_3), 18.4 (CH_3), 19.1 (CH_3), 21.2 (CH_3), 23.6 (CH_3), 24.9 (CH), 38.8 (CH_2), 49.4 (CH), 50.7 (C), 50.9 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 131.8 (CH), 133.8 (C), 167.4 (C), 172.5 (C), 204.8 (CH); m/z 333 (M^+ + H, 1%), 176 (31, M^+ – NHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 148 (55, M^+ – CONHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 105 (100, $[PhCO]^+$). HRMS calcd for $C_{19}H_{29}N_2O_3$ 333.2178, found 333.2166; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0706; calcd for $C_9H_{10}NO$ 148.0762, found 148.0763; calcd for C_7H_5O 105.0340, found 105.0345. $C_{19}H_{28}N_2O_3$ requires C, 68.65; H, 8.49; N, 8.43%. Found: C, 68.50; H, 8.61; N, 8.69.

***N*-(*N*-Benzyloxycarbonyl-L-valyl)-α,α-dimethyl-DL-β-homoleucinal (46).** The products were generated from dipeptide **36** according to Method B, using 2-methyl-1-(trimethylsilyloxy)-1-propene as the nucleophile. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 85 : 15), affording compound **46** (76%) as a 10 : 7 mixture of diastereomers: syrup; ν_{max}/cm^{-1} 3426, 1714, 1672, 1506, 1469; δ_H (500 MHz, $CDCl_3$) major isomer: 0.86–0.90 (9H, m, 5-Me$_2$ + 3′-Me$_a$), 0.95 (3H, d, J = 6.6 Hz, 3′-Me$_b$), 1.01 (3H, s, 2-Me$_a$), 1.06 (3H, s, 2-Me$_b$), 1.16 (1H, m, 4-H$_a$), 1.32 (1H, m, 4-H$_b$), 1.52 (1H, m, 5-H), 2.14 (1H, m, 3′-H), 3.92 (1H, ddd, J = 8.8, 8.8, 8.9 Hz, 2′-H), 4.21 (1H, br dd, J = 12.0, 12.0 Hz, 3-H), 5.08 (1H, d, J = 12.0 Hz, OCH$_a$Ph), 5.11 (1H, d, J = 12.5 Hz, OCH$_b$Ph), 5.37 (1H, br b, NH), 6.11 (1H, br d, J = 9.8 Hz, NH), 7.30–7.35 (5H, m, Ar), 9.44 (1H, s, CHO); minor isomer: 0.85 (3H, d, J = 6.6 Hz, 5-Me$_a$), 0.86–0.90 (6H, m, 5-Me$_b$ + 3′-Me$_a$), 0.95 (3H, d, J = 6.5 Hz, 3′-Me$_b$), 1.01 (3H, s, 2-Me$_a$), 1.03 (3H, s, 2-Me$_b$), 1.15 (1H, m, 4-H$_a$), 1.32 (1H, m, 4-H$_b$), 1.52 (1H, m, 5-H), 2.14 (1H, m, 3′-H), 3.92 (1H, ddd, J = 8.8, 8.8, 8.9 Hz, 2′-H), 4.21 (1H, br dd, J = 12.0, 12.0 Hz, 3-H), 5.09–5.15 (2H, m, OCH$_2$Ph), 5.38 (1H, br b, NH), 6.14 (1H, br d, J = 12.0 Hz, NH), 7.30–7.35 (5H, m, Ar), 9.45 (1H, s, CHO); major isomer: δ_C (125.7 MHz, $CDCl_3$) 17.7 (CH_3), 18.7 (CH_3), 19.0 (CH_3), 19.4 (CH_3), 21.1 (CH_3), 23.8 (CH_3), 24.9 (CH), 30.3 (CH), 39.3 (CH_2), 50.3 (C), 51.0 (CH), 61.0 (CH), 67.1 (CH_2), 128.0 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 136.2 (C), 156.5 (C), 171.2 (C), 205.0 (CH); minor isomer: δ_C (125.7 MHz, $CDCl_3$) 17.7 (CH_3), 18.5 (CH_3), 18.7 (CH_3), 19.4 (CH_3), 21.2 (CH_3), 23.7 (CH_3), 25.0 (CH), 30.1 (CH), 39.4 (CH_2), 50.4 (C), 51.2 (CH), 61.0 (CH), 67.1 (CH_2), 128.0 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 136.2 (C), 156.6 (C), 171.2 (C), 204.9 (CH); m/z 391 (M^+ + H, <1%), 390 (M^+, <1%), 319 (8, M^+ – C(Me)$_2$-CHO), 234 (12, M^+ – NHCH(CH_2CHMe_2)-C(Me)$_2$-CHO), 91 (100, $[PhCH_2]^+$). HRMS calcd for $C_{22}H_{34}N_2O_4$ 390.2518, found 390.2519; calcd for $C_{18}H_{27}N_2O_3$ 319.2022, found 319.2027; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1122; calcd for C_7H_7 91.0548, found 91.0552. $C_{22}H_{34}N_2O_4$ requires C, 67.66; H, 8.78; N, 7.17%. Found: C, 67.57; H, 8.93; N, 7.11.

General procedure for the reduction of the amino aldehydes to the amino alcohols

To a solution of the starting β-peptide aldehydes (0.4 mmol) in dry ^{i}PrOH (12 mL) cooled at 0 °C, was added $LiBH_4$ (17 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 40 min. Then it was poured into saturated brine and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes–EtOAc) giving the γ-amino alcohol derivatives.

***N*-(*N*-Benzoyl-L-phenylalanyl)-α,α-dimethyl-L-β-homoalaninol (47).** Obtained by reduction of the peptide aldehyde **39** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 70 : 30), affording compound **47** (78%) as a crystalline solid: Mp 187–188 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −17 (c 0.27 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 1650, 1509, 1484; δ_H (500 MHz, $CDCl_3$) 0.47 (3H, s, 2-Me$_a$), 0.90 (3H, s, 2-Me$_b$), 1.01 (3H, d, J = 6.9 Hz, 3-Me), 2.91 (1H, d, J = 11.7 Hz, 1-H$_a$), 3.10 (1H, d, J = 11.7 Hz, 1-H$_b$), 3.15 (1H, dd, J = 8.5, 13.9 Hz, 3′-H$_a$), 3.25 (1H, dd, J = 6.3, 13.9 Hz, 3′-H$_b$), 3.93 (1H, dddd, J = 6.8, 6.8, 6.9, 8.7 Hz, 3-H), 4.92 (1H, ddd, J = 6.3, 7.9, 8.2 Hz, 2′-H), 6.34 (1H, br d, J = 9.0 Hz, NH), 6.85 (1H, brd, J = 7.3 Hz, NH), 7.24 (1H, m, Ar), 7.29–7.34 (4H, m, Ar), 7.42 (2H, dd, J = 7.3, 7.9 Hz, Ar), 7.51 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.72 (2H, d, J = 8.2 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 15.3 (CH_3), 18.3 (CH_3), 23.0 (CH_3), 38.5 (CH_2 + C), 49.6 (CH), 55.2 (CH), 69.6 (CH_2), 127.0 (2 × CH), 127.2 (CH), 128.6 (2 × CH), 128.9 (2 × CH), 129.3 (2 × CH), 131.9 (CH), 133.6 (C), 136.4 (C), 167.4 (C), 171.3 (C); m/z 368 (M^+, 1%), 350 (3, M^+ – H_2O), 252 (26, M^+ – NHCH(Me)C(Me)$_2$CH$_2$OH), 224 (21, M^+ – CONHCH(Me)C(Me)$_2$CH$_2$OH), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{22}H_{28}N_2O_3$ 368.2100, found 368.2107; calcd for $C_{22}H_{26}N_2O_2$ 350.1994, found 350.1985; calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1019; calcd for $C_{15}H_{14}NO$ 224.1075, found 224.1070; calcd for C_7H_5O 105.0340, found 105.0343. $C_{22}H_{28}N_2O_3$ requires C, 71.71; H, 7.66; N, 7.60%. Found: C, 71.79; H, 7.68; N, 7.68.

***N*-(*N*-Benzoyl-L-phenylalanyl)-α,α-dimethyl-D-β-homoalaninol (48).** Obtained by reduction of the peptide aldehyde **40** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 75 : 25), affording compound **48** (69%) as a crystalline solid: Mp 134–135 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −11 (c 0.19 in $CHCl_3$); ν_{max}/cm^{-1} 3423, 1731, 1650, 1510; δ_H (500 MHz, $CDCl_3$) 0.54 (3H, s, 2-Me$_a$), 0.86 (3H, d, J = 6.9 Hz, 3-Me), 0.91 (3H, s, 2-Me$_b$), 2.92 (1H, d, J = 11.7 Hz, 1-H$_a$), 3.14 (1H, dd, J = 7.9, 13.2 Hz, 3′-H$_a$), 3.21 (1H, dd, J = 6.6, 13.3 Hz, 3′-H$_b$), 3.25 (1H, d, J = 12 Hz, 1-H$_b$), 3.87 (1H, dddd, J = 6.6, 6.6, 6.7, 9.1 Hz, 3-H), 4.02 (1H, OH), 4.99 (1H, ddd, J = 6.6, 8.2, 8.2 Hz, 2′-H), 6.95 (1H, br d, J = 9.5 Hz, NH), 7.19 (1H, m, Ar), 7.21–7.25 (4H, m, Ar), 7.35 (1H, brb, NH), 7.37 (2H, dd, J = 7.6, 7.8 Hz, Ar), 7.49 (1H, dd, J = 7.3, 7.6 Hz, Ar), 7.70 (2H, d, J = 8.2 Hz, Ar);

δ_C (100.6 MHz, $CDCl_3$) 14.8 (CH_3), 18.1 (CH_3), 22.9 (CH_3), 38.6 (C), 38.8 (CH_2), 49.0 (CH), 55.2 (CH), 69.7 (CH_2), 126.9 (CH), 127.1 (2 × CH), 128.5 (4 × CH), 129.4 (2 × CH), 131.8 (CH), 133.6 (C), 136.6 (C), 167.6 (C), 171.8 (C); *m/z* 368 (M^+, 1%), 350 (1, $M^+ - H_2O$), 252 (58, M^+ – NHCH(Me)C-$(Me)_2CH_2OH$), 224 (44, M^+ – CONHCH(Me)C$(Me)_2CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{22}H_{28}N_2O_3$ 368.2100, found 368.2104; calcd for $C_{22}H_{26}N_2O_2$ 350.1994, found 350.1984; calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1014; calcd for $C_{15}H_{14}NO$ 224.1075, found 224.1072; calcd for C_7H_5O 105.0340, found 105.0341. $C_{22}H_{28}N_2O_3$ requires C, 71.71; H, 7.66; N, 7.60%. Found: C, 71.64; H, 7.48; N, 7.62.

***N*-(*N*-Benzoyl-L-leucyl)-α,α-dimethyl-L-β-homoalaninol (49).** Obtained by reduction of the peptide aldehyde **41** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 60 : 40), affording compounds **49** (76%) as a crystalline solid; Mp 186–187 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −35 (*c* 0.62 in $CHCl_3$); ν_{max}/cm^{-1} 3427, 1651, 1516; δ_H (500 MHz, $CDCl_3$) 0.69 (3H, s, 2-Me_a), 0.95 (6H, d, *J* = 6.6 Hz, 2 × Me), 0.96 (3H, s, 2-Me_b), 0.97 (3H, d, *J* = 6.3 Hz, Me), 1.71 (1H, m, 3′-H_a), 1.77 (1H, m, 4′-H), 1.82 (1H, m, 3′-H_b), 3.03 (1H, brdd, *J* = 9.1, 11.0 Hz, 1-H_a), 3.33 (1H, brd, *J* = 11.4 Hz, 1-H_b), 3.92 (1H, dddd, *J* = 6.6, 6.9, 6.9, 8.8 Hz, 3-H), 4.09 (1H, brb, OH), 4.89 (1H, ddd, *J* = 5.1, 5.4, 8.8 Hz, 2′-H), 7.34 (1H, dd, *J* = 7.3, 8.2 Hz, Ar), 7.46 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.44–7.50 (2H, brb, 2 × NH), 7.81 (1H, d, *J* = 8.0 Hz, Ar); δ_C (100.6 MHz, $CDCl_3$) 14.9 (CH_3), 18.4 (CH_3), 22.1 (CH_3), 22.9 (CH_3), 23.0 (CH_3), 25.0 (CH), 38.9 (C), 41.8 (CH_2), 49.0 (CH), 52.5 (CH), 69.8 (CH_2), 127.2 (2 × CH), 128.4 (2 × CH), 131.7 (CH), 133.8 (C), 167.6 (C), 173.4 (C); *m/z* 335 (M^+ + H, <1%), 261 (5, M^+ – $C(Me)_2CH_2OH$), 218 (66, M^+ – NHCH(Me)C$(Me)_2CH_2OH$), 190 (57, M^+ – CONHCH(Me)C$(Me)_2CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2339; calcd for $C_{15}H_{21}N_2O_2$ 261.1603, found 261.1592; calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1180; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1227; calcd for C_7H_5O 105.0340, found 105.0340. $C_{19}H_{31}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.59; H, 8.95; N, 8.48.

***N*-(*N*-Benzoyl-L-leucyl)-α,α-dimethyl-D-β-homoalaninol (50).** Obtained by reduction of the peptide aldehyde **42** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 60 : 40), affording compounds **50** (79%) as a crystalline solid; Mp 163–164 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −39 (*c* 0.66 in $CHCl_3$); ν_{max}/cm^{-1} 3425, 1654, 1510; δ_H (500 MHz, $CDCl_3$) 0.62 (3H, s, 2-Me_a), 0.95 (3H, d, *J* = 6.9 Hz, Me), 0.96 (3H, s, 2-Me_b), 0.97 (3H, d, *J* = 6.9 Hz, Me), 1.12 (3H, d, *J* = 6.9 Hz, Me), 1.67–1.75 (2H, m, 3′-H_a + 4′-H), 1.77 (1H, m, 3′-H_b), 2.94 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.25 (1H, d, *J* = 11.9 Hz, 1-H_b), 3.98 (1H, dddd, *J* = 6.6, 6.8, 6.9, 9.4 Hz, 3-H), 4.69 (1H, ddd, *J* = 6.0, 6.3, 7.9 Hz, 2′-H), 6.95 (1H, brd, *J* = 8.2 Hz, NH), 7.03 (1H, br d, *J* = 9.5 Hz, NH), 7.41 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.50 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.76 (2H, d, *J* = 8.0 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 15.3 (CH_3), 18.3 (CH_3), 22.4 (CH_3), 22.8 (CH_3), 23.1 (CH_3), 25.0 (CH), 38.9 (C), 40.7 (CH_2), 49.1 (CH), 52.5 (CH), 69.8 (CH_2), 127.1 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.8 (C), 167.9 (C), 172.7 (C); *m/z* 335 (M^+ + H, 1%), 261 (9, M^+ – $C(Me)_2CH_2OH$), 218 (97, M^+ – NHCH(Me)C$(Me)_2CH_2OH$), 190 (92, M^+ – CONHCH(Me)C$(Me)_2CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2343; calcd for $C_{15}H_{20}N_2O_2$ 260.1525, found 260.1515; calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1177; calcd for $C_{12}H_{16}NO$ 190.1232, found 190.1229; calcd for C_7H_5O 105.0340, found 105.0342. $C_{19}H_{31}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.06; H, 8.88; N, 8.41.

***N*-(*N*-Benzoyl-L-prolyl)-α,α-dimethyl-L-β-homoleucinol (51).** Obtained by reduction of the peptide aldehyde **43** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 1 : 1), affording compound **51** (77%) as a syrup; $[\alpha]_D$ −92 (*c* 0.41 in $CHCl_3$); ν_{max}/cm^{-1} 3426, 1656, 1613; δ_H (500 MHz, $CDCl_3$) 0.64 (3H, s, 2-Me_a), 0.89 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.94 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.00 (3H, s, 2-Me_b), 1.28–1.33 (2H, m, 4-H_2), 1.64 (1H, m, 5-H), 1.84 (1H, m, 4′-H_a), 2.03 (1H, m, 3′-H_a), 2.08 (1H, m, 4′-H_b), 2.48 (1H, m, 3′-H_b), 2.93 (1H, brb, OH), 3.01 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.30 (1H, d, *J* = 11.9 Hz, 1-H_b), 3.46 (1H, m, 5′-H_a), 3.55 (1H, m, 5′-H_b), 3.92 (1H, ddd, *J* = 3.5, 10.2, 10.7 Hz, 3-H), 4.80 (1H, m, 2′-H), 7.02 (1H, brd, *J* = 9.5 Hz, NH), 7.40–7.48 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.3 (CH_3), 21.3 (CH_3), 23.1 (CH_3), 23.9 (CH_3), 25.4 (CH), 25.5 (CH_2), 27.0 (CH_2), 38.1 (CH_2), 39.0 (C), 50.3 (CH_2), 51.2 (CH), 59.7 (CH), 70.3 (CH_2), 126.8 (2 × CH), 128.5 (2 × CH), 130.3 (CH), 136.0 (C), 171.2 (C), 172.4 (C); *m/z* 360 (M^+, 1%), 287 (73, M^+ – $C(Me)_2CH_2OH$), 202 (51, M^+ – $NHCH(CH_2CHMe_2)C(Me)_2CH_2OH$), 174 (54, M^+ – $CONHCH(CH_2CHMe_2)C(Me)_2CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for $C_{21}H_{32}N_2O_3$ 360.2413, found 360.2404; calcd for $C_{17}H_{23}N_2O_2$ 287.1760, found 287.1752; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0864; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0918; calcd for C_7H_5O 105.0340, found 105.0345. $C_{21}H_{32}N_2O_3$ requires C, 69.97; H, 8.95; N, 7.77%. Found: C, 70.13; H, 9.01; N, 7.83.

***N*-(*N*-Benzoyl-L-prolyl)-α,α-dimethyl-D-β-homoleucinol (52).** Obtained by reduction of the peptide aldehyde **44** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 1 : 1), affording compound **51** (79%) as a syrup; $[\alpha]_D$ −130 (*c* 0.13 in $CHCl_3$); ν_{max}/cm^{-1} 3449, 1656, 1615; δ_H (500 MHz, $CDCl_3$) 0.68 (3H, s, 2-Me_a), 0.82 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.87 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.02 (3H, s, 2-Me_b), 1.26–1.32 (2H, m, 4-H_2), 1.52 (1H, m, 5-H), 1.85 (1H, m, 4′-H_a), 1.99–2.09 (2H, m, 3′-H_a + 4′-H_b), 2.50 (1H, m, 3′-H_b), 3.02 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.38 (1H, d, *J* = 11.6 Hz, 1-H_b), 3.47 (1H, m, 5′-H_a), 3.53 (1H, m, 5′-H_b), 3.89 (1H, ddd, *J* = 4.4, 9.4, 9.5 Hz, 3-H), 4.88 (1H, dd, *J* = 4.4, 7.3 Hz, 2′-H), 7.12 (1H, brd, *J* = 9.5 Hz, NH), 7.41–7.48 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.4 (CH_3), 21.3 (CH_3), 23.0 (CH_3), 23.8 (CH_3), 25.4 (CH_2), 25.5 (CH), 26.9 (CH_2), 38.3 (CH_2), 38.9 (C), 50.4 (CH_2), 51.5 (CH), 59.7 (CH), 70.3 (CH_2), 126.9 (2 × CH), 128.5 (2 × CH), 130.4 (CH), 136.0 (C), 171.7 (C), 172.3 (C); *m/z* 360 (M^+, 1%), 287 (7, M^+ – $C(Me)_2CH_2OH$), 202 (36, M^+ – $NHCH(CH_2CHMe_2)C(Me)_2CH_2OH$), 174 (55, M^+ – $CONHCH(CH_2CHMe_2)C(Me)_2CH_2OH$), 105 (100, $[PhCO]^+$); HRMS calcd for

$C_{21}H_{32}N_2O_3$ 360.2413, found 360.2415; calcd for $C_{12}H_{12}NO_2$ 202.0868, found 202.0875; calcd for $C_{11}H_{12}NO$ 174.0919, found 174.0924; calcd for C_7H_5O 105.0340, found 105.0344. $C_{21}H_{32}N_2O_3$ requires C, 69.97; H, 8.95; N, 7.77%. Found: C, 69.76; H, 8.87; N, 7.68.

***N*-(*N*-Benzoyl-L-alanyl)-α,α-dimethyl-L-β-homoleucinol (53) and *N*-(*N*-benzoyl-L-alanyl)-α,α-dimethyl-D-β-homoleucinol (54).** Obtained by reduction of the peptide aldehyde **45** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 60 : 40), affording compounds **53** (41%) and **54** (29%).

Product 53. Syrup; $[\alpha]_D$ +1 (*c* 0.29 in $CHCl_3$); ν_{max}/cm^{-1} 3421, 1653, 1647, 1512; δ_H (500 MHz, $CDCl_3$) 0.59 (3H, s, 2-Me_a), 0.87 (3H, d, *J* = 6.3 Hz, 5-Me_a), 0.90 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.98 (3H, s, 2-Me_b), 1.26 (1H, ddd, *J* = 2.5, 10.5, 13.3 Hz, 4-H_a), 1.41 (1H, ddd, *J* = 3.5, 11.3, 13.9 Hz, 4-H_b), 1.51 (3H, d, *J* = 6.9 Hz, 2′-Me), 1.62 (1H, m, 5-H), 2.92 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.26 (1H, d, *J* = 11.7 Hz, 1-H_b), 3.90 (1H, ddd, *J* = 2.5, 9.5, 12.0 Hz, 3-H), 4.88 (1H, dddd, *J* = 6.9, 6.9, 7.3, 7.3 Hz, 2′-H), 7.28 (1H, d, *J* = 9.5 Hz, NH), 7.38 (1H, d, *J* = 7.6 Hz, NH), 7.41 (2H, dd, *J* = 7.3, 7.9 Hz, Ar), 7.51 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.79 (2H, d, *J* = 7.8 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.3 (CH_3), 18.6 (CH_3), 21.0 (CH_3), 23.0 (CH_3), 23.9 (CH_3), 25.4 (CH), 37.8 (CH_2), 38.9 (C), 49.4 (CH), 51.4 (CH), 70.1 (CH_2), 127.1 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.5 (C), 167.6 (C), 174.0 (C); *m/z* 335 (M^+ + H, <1%), 316 (2, M^+ − H_2O), 176 (34, [BzNH-CH(Me)CO), 148 (45, [BzNH=CH(Me)]$^+$), 105 (96, [PhCO]$^+$), 86 (100, [NH_2=$CHCH_2CH(Me)_2$]$^+$), 77 (32, [Ph]$^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2351; calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2141; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0707; calcd for $C_9H_{10}NO$ 148.0762, found 148.0760; calcd for C_7H_5O 105.0340, found 105.0338; calcd for $C_5H_{12}N$ 86.0970, found 86.0973; calcd for C_6H_5 77.0391, found 77.0392. $C_{19}H_{30}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.44; H, 8.96; N, 8.30.

Product 54. Crystalline solid; Mp 158–159 °C (EtOAc–*n*-hexane); $[\alpha]_D$ −40 (*c* 0.36 in $CHCl_3$); ν_{max}/cm^{-1} 3421, 1655, 1649, 1512, 1484; δ_H (500 MHz, $CDCl_3$) 0.71 (3H, s, 2-Me_a), 0.76 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.79 (3H, d, *J* = 6.6 Hz, 5-Me_b), 1.02 (3H, s, 2-Me_b), 1.25 (1H, m, 4-H_a), 1.31 (1H, ddd, *J* = 3.5, 11.0, 14.5 Hz, 4-H_b), 1.48 (1H, m, 5-H), 1.55 (3H, d, *J* = 6.9 Hz, 2′-Me), 3.05 (1H, d, *J* = 11.7 Hz, 1-H_a), 3.35 (1H, d, *J* = 11.9 Hz, 1-H_b), 3.90 (1H, ddd, *J* = 2.5, 9.5, 11.7 Hz, 3-H), 4.88 (1H, dddd, *J* = 6.9, 6.9, 7.3, 7.3 Hz, 2′-H), 7.01 (1H, br d, *J* = 9.1 Hz, NH), 7.13 (1H, br d, *J* = 7.3 Hz, NH), 7.43 (2H, dd, *J* = 7.6, 7.8 Hz, Ar), 7.52 (1H, dd, *J* = 7.3, 7.6 Hz, Ar), 7.78 (2H, d, *J* = 8.2 Hz, Ar); δ_C (125.7 MHz, $CDCl_3$) 18.6 (CH_3), 19.1 (CH_3), 21.1 (CH_3), 23.0 (CH_3), 23.7 (CH_3), 25.2 (CH), 37.9 (CH_2), 39.0 (C), 49.3 (CH), 51.5 (CH), 70.2 (CH_2), 127.0 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.6 (C), 167.4 (C), 173.7 (C); *m/z* 335 (M^+ + H, <1%), 316 (1, M^+ − H_2O), 176 (23, [PhCONH-CH(Me)CO]), 148 (37, [PhCONH=CH(Me)]$^+$), 105 (100, [PhCO]$^+$), 86 (100, [NH_2=$CHCH_2CH(Me)_2$]$^+$), 77 (31, [Ph]$^+$); HRMS calcd for $C_{19}H_{31}N_2O_3$ 335.2335, found 335.2344; calcd for $C_{19}H_{28}N_2O_2$ 316.2151, found 316.2156; calcd for $C_{10}H_{10}NO_2$ 176.0712, found 176.0711; calcd for $C_9H_{10}NO$ 148.0762, found 148.0760; calcd for C_7H_5O 105.0340, found 105.0336; calcd for $C_5H_{12}N$ 86.0970, found 86.0968; calcd for C_6H_5 77.0391, found 77.0391. $C_{19}H_{30}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%. Found: C, 68.58; H, 9.10; N, 8.22.

***N*-(*N*-Benzoyloxycarbonyl-L-valyl)-α,α-dimethyl-L-β-homoleucinol (55) and *N*-(*N*-benzoyloxycarbonyl-L-valyl)-α,α-dimethyl-D-β-homoleucinol (56).** Obtained by reduction of the peptide aldehyde **46** according to the General Procedure. The reaction mixture was purified by rotatory chromatography (hexanes–EtOAc, 85 : 15), affording compounds **55** (46%) and **56** (32%).

Product 55. Amorphous solid; $[\alpha]_D$ +2 (*c* 0.21 in $CHCl_3$); ν_{max}/cm^{-1} 3425, 1718, 1653, 1506; δ_H (500 MHz, $CDCl_3$) 0.61 (3H, s, 2-Me_a), 0.86 (3H, d, *J* = 6.3 Hz, 5-Me_a), 0.91 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.94 (3H, d, *J* = 6.9 Hz, 3′-Me_a), 0.97 (3H, d, *J* = 6.9 Hz, 3′-H_b), 0.98 (3H, s, 2-Me_b), 1.24–1.30 (2H, m, 4-H_2), 1.55 (1H, m, 5-H), 2.11 (1H, m, 3′-H), 2.95 (1H, d, *J* = 11.9 Hz, 1-H_a), 3.23 (1H, d, *J* = 11.7 Hz, 1-H_b), 3.87–3.95 (2H, m, 3-H + 2′-H), 5.07 (1H, d, *J* = 12.0 Hz, OCH_aPh), 5.12 (1H, d, *J* = 12.3 Hz, OCH_bPh), 5.40 (1H, d, *J* = 8.8 Hz, NH), 6.10 (1H, d, *J* = 9.5 Hz, NH), 7.31–7.37 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 17.9 (CH_3), 18.5 (CH_3), 19.4 (CH_3), 21.0 (CH_3), 23.1 (CH_3), 24.0 (CH_3), 25.3 (CH), 30.2 (CH), 38.2 (CH_2), 38.9 (C), 51.5 (CH), 61.1 (CH), 67.1 (CH_2), 70.0 (CH_2), 128.0 (2 × CH), 128.2 (CH), 128.6 (2 × CH), 136.1 (C), 156.6 (C), 172.8 (C); *m/z* 393 (M^+ + H, 1%), 319 (9, M^+ − $C(Me)_2$-CHO), 234 (14, M^+ − NHCH(CH_2CHMe_2)-$C(Me)_2$-CH_2OH), 108 (18, [$PhCH_2OH$]$^+$), 91 (100, [$PhCH_2$]$^+$), 86 (29, [NH_2=$CHCH_2CH(Me)_2$]$^+$). HRMS calcd for $C_{22}H_{37}N_2O_4$ 393.2753, found 393.2749; calcd for $C_{18}H_{27}N_2O_3$ 319.2022, found 319.2015; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1130; calcd for C_7H_8O 108.0575, found 108.0574; calcd for C_7H_7 91.0548, found 91.0549; calcd for $C_5H_{12}N$ 86.0970, found 86.0967. $C_{22}H_{36}N_2O_4$ requires C, 67.32; H, 9.24; N, 7.14%. Found: C, 67.34; H, 8.98; N, 7.29.

Product 56. Amorphous solid; $[\alpha]_D$ −30 (*c* 0.26 in $CHCl_3$); ν_{max}/cm^{-1} 3422, 1715, 1653, 1520, 1506; δ_H (500 MHz, $CDCl_3$) 0.63 (3H, s, 2-Me_a), 0.83 (3H, d, *J* = 6.6 Hz, 5-Me_a), 0.89 (3H, d, *J* = 6.6 Hz, 5-Me_b), 0.92 (3H, d, *J* = 6.6 Hz, 3′-Me_a), 0.99 (3H, d, *J* = 6.9 Hz, 3′-H_b), 1.00 (3H, s, 2-Me_b), 1.23–1.30 (2H, m, 4-H_2), 1.50 (1H, m, 5-H), 2.21 (1H, m, 3′-H), 3.01 (1H, br d, *J* = 11.5 Hz, 1-H_a), 3.34 (1H, br d, *J* = 12.0 Hz, 1-H_b), 3.89 (1H, m, 3-H), 3.96 (1H, m, 2′-H), 5.08 (1H, d, *J* = 12.3 Hz, OCH_aPh), 5.13 (1H, d, *J* = 12.3 Hz, OCH_bPh), 5.27 (1H, br b, NH), 6.03 (1H, br d, *J* = 8.8 Hz, NH), 7.32–7.38 (5H, m, Ar); δ_C (125.7 MHz, $CDCl_3$) 17.7 (CH_3), 18.7 (CH_3), 19.5 (CH_3), 21.1 (CH_3), 23.1 (CH_3), 23.9 (CH_3), 25.2 (CH), 30.0 (CH), 38.3 (CH_2), 38.8 (C), 51.6 (CH), 61.0 (CH), 67.2 (CH_2), 70.0 (CH_2), 128.1 (2 × CH), 128.3 (CH), 128.6 (2 × CH), 136.0 (C), 156.5 (C), 172.4 (C); *m/z* 393 (M^+ + H, 1%), 319 (12, M^+ − $C(Me)_2$-CHO), 234 (20, M^+ − NHCH(CH_2CHMe_2)-$C(Me)_2$-CH_2OH), 91 (100, [$PhCH_2$]$^+$), 86 (21, [NH_2=$CHCH_2CH(Me)_2$]$^+$). HRMS calcd for $C_{22}H_{37}N_2O_4$ 393.2753, found 393.2743; calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1138; calcd for C_7H_7 91.0548, found 91.0544; calcd for $C_5H_{12}N$ 86.0970, found 86.0967. $C_{22}H_{36}N_2O_4$ requires C, 67.32; H, 9.24; N, 7.14%. Found: C, 67.37; H, 9.13; N, 7.18.

General procedure for the reduction of the β-amino esters to the β-amino aldehydes

A solution of the β-amino ester (0.2 mmol) in methanol (8 mL), was cooled to −78 °C and DIBAL-H was added (1 M solution in dichloromethane, 2 mL, 2 mmol). The reaction mixture was stirred for 6 h; then the solution was poured into a saturated solution of Rochelle's salt and extracted with CH_2Cl_2. The organic layer was dried on anhydrous sodium sulfate, filtered and evaporated under vacuum. The residue was purified by column chromatography (hexanes–EtOAc) to give the β-amino aldehydes.

General procedure for the reduction of the β-amino esters to the γ-amino alcohols

A solution of the β-amino ester (0.2 mmol) in methanol (8 mL), was cooled to 0 °C; then DIBAL-H was added (1 M solution in dichloromethane, 2 mL, 2 mmol; except in the case of substrate **57**, where 0.6 mmol of the reducing agent were used). The reaction mixture was stirred for 3 h at 0 °C, and then was extracted, evaporated and purified as before to give the γ-amino alcohols.

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PAPER

Supplementary Information

Preparation of modified peptides: direct conversion of α-amino acids into β-amino aldehydes

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Dedicated to Prof. Gerry Pattenden

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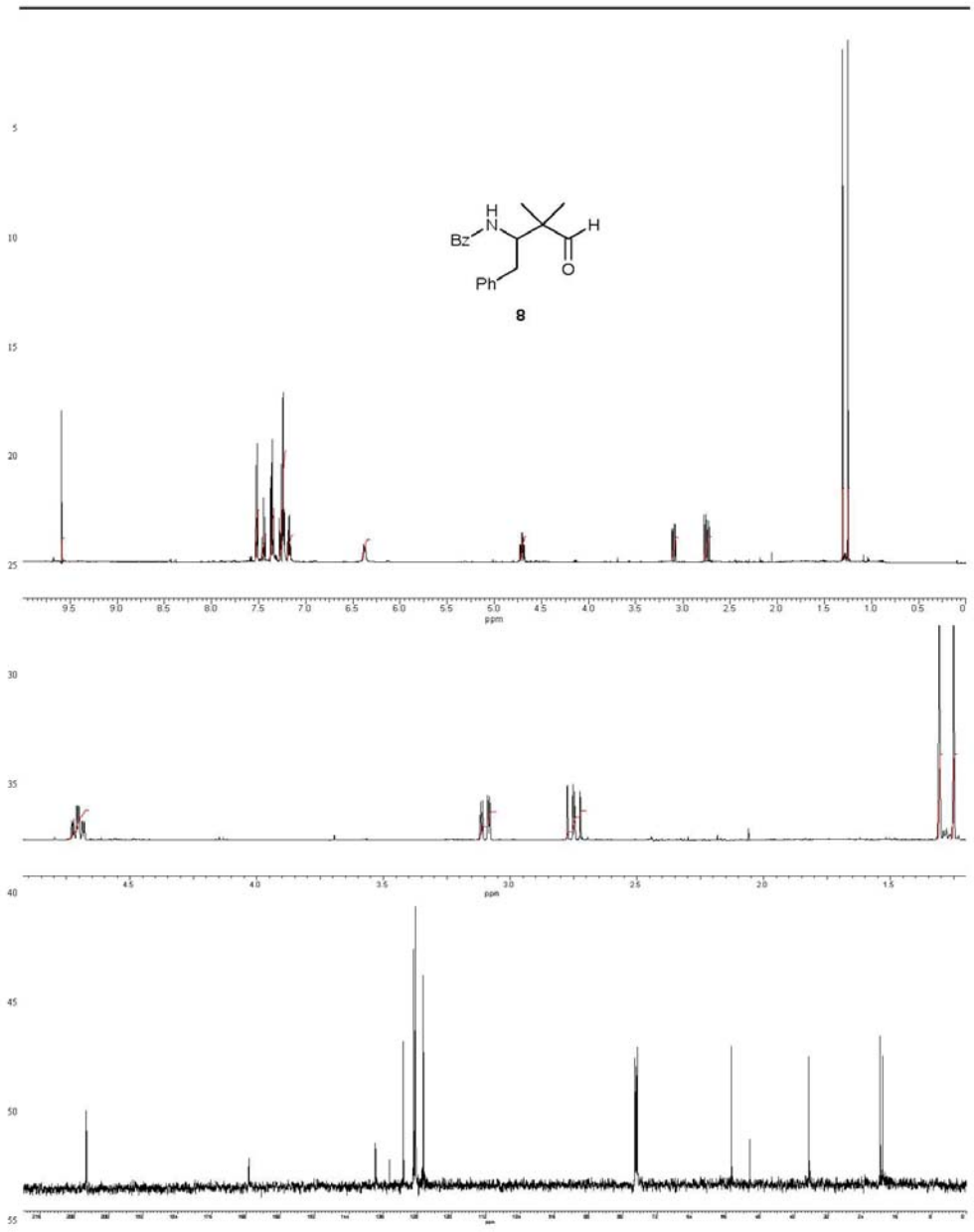

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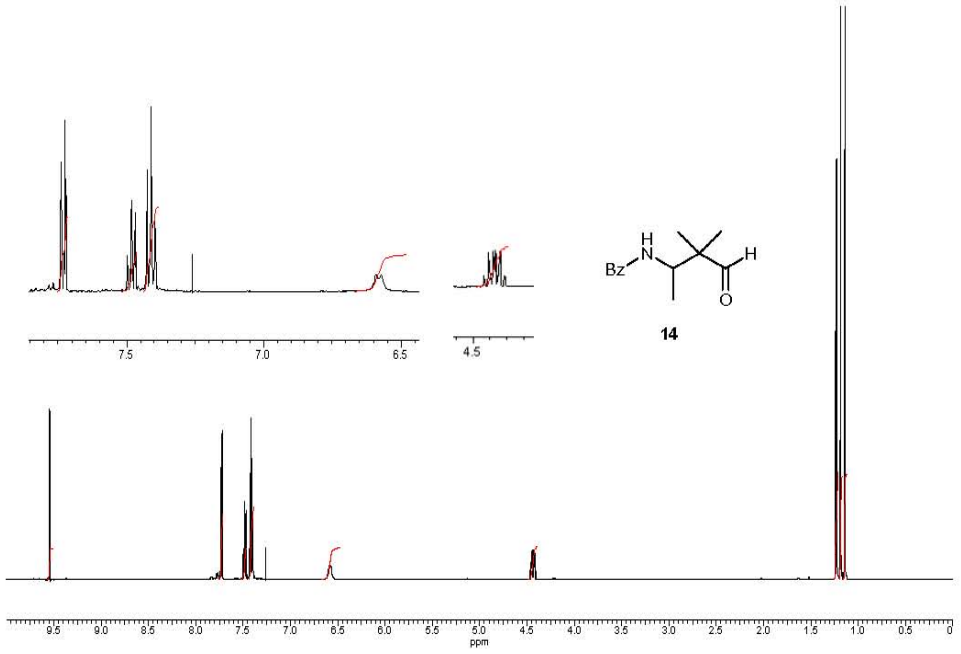

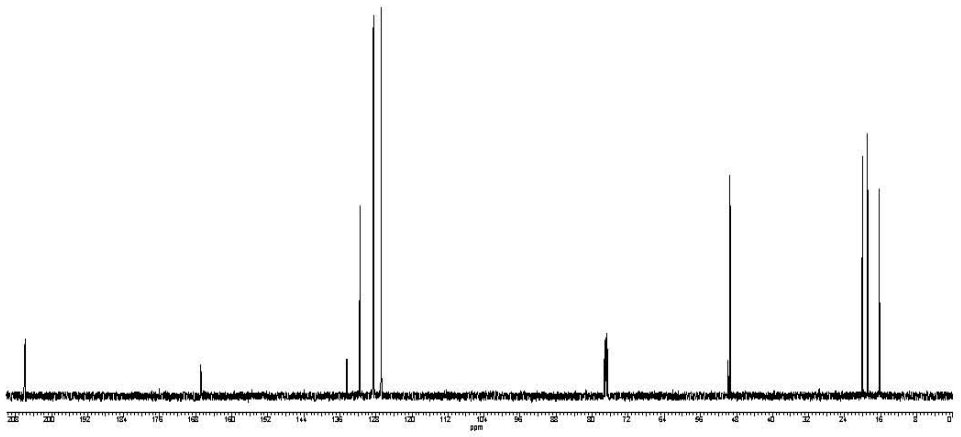

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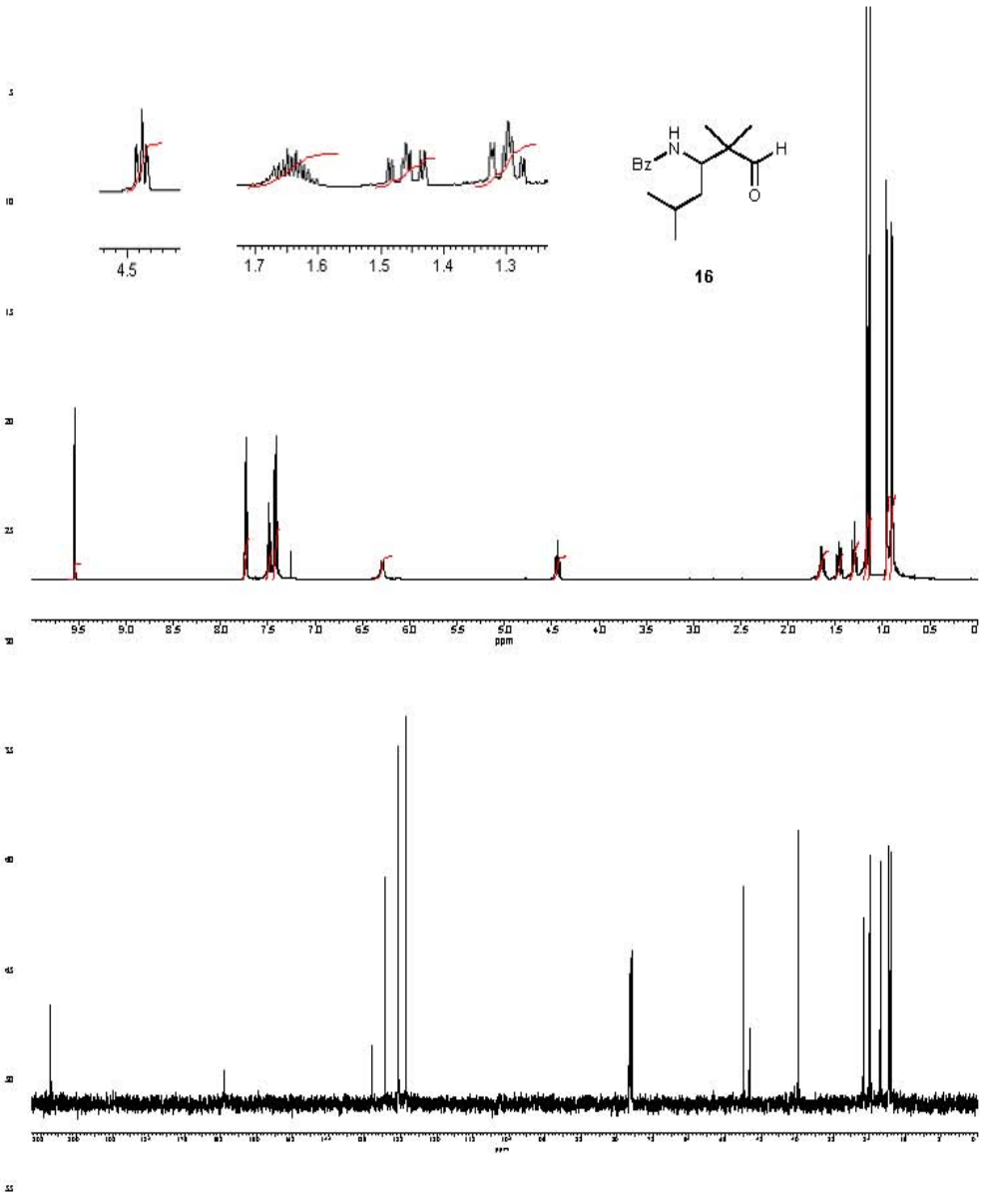

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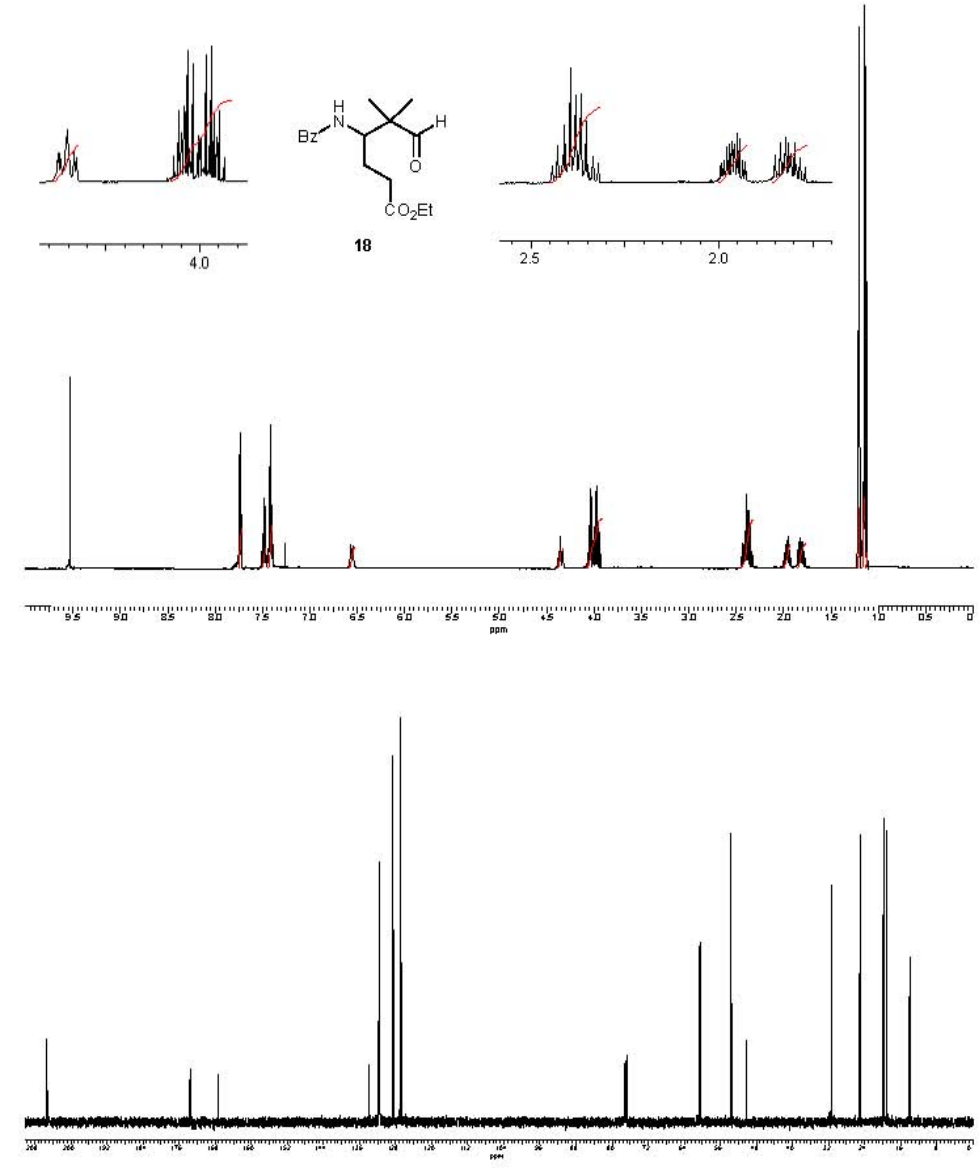

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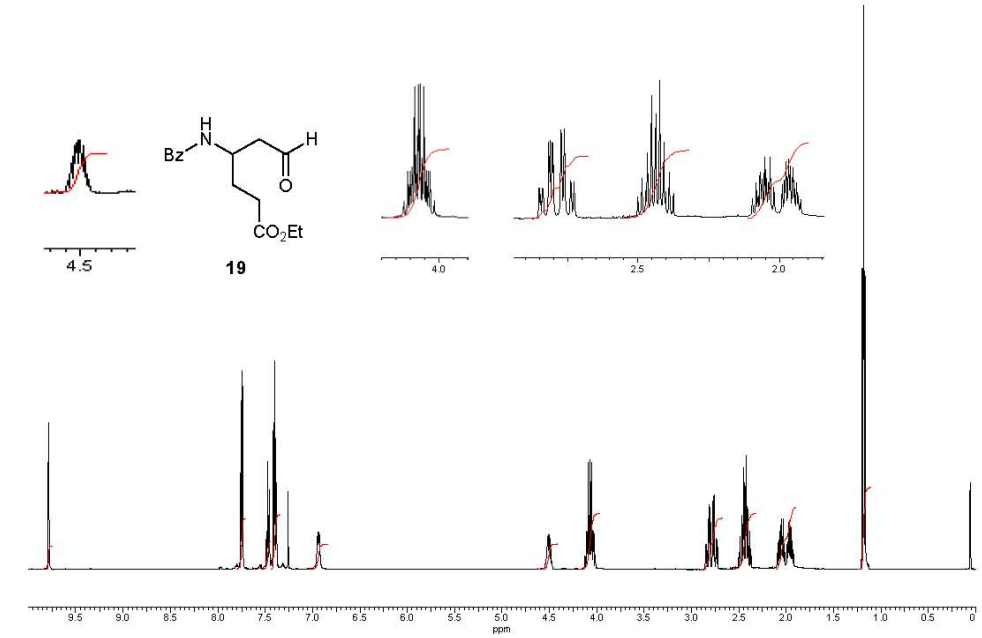

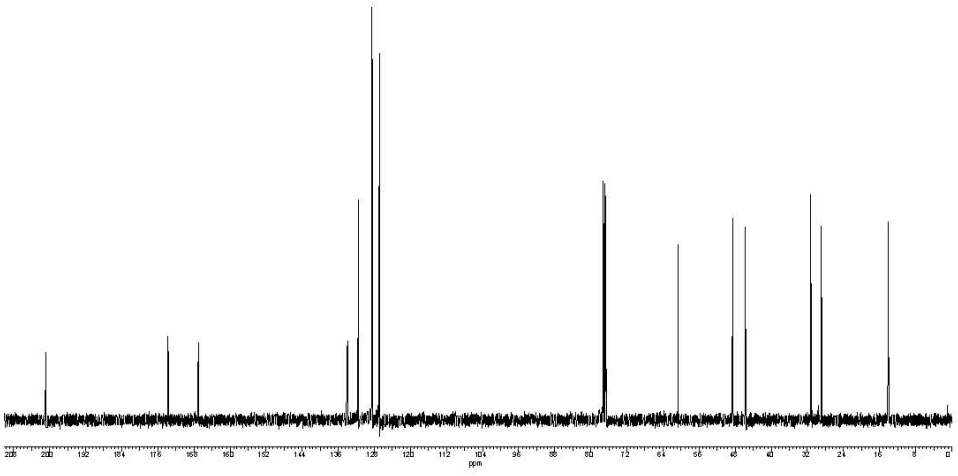

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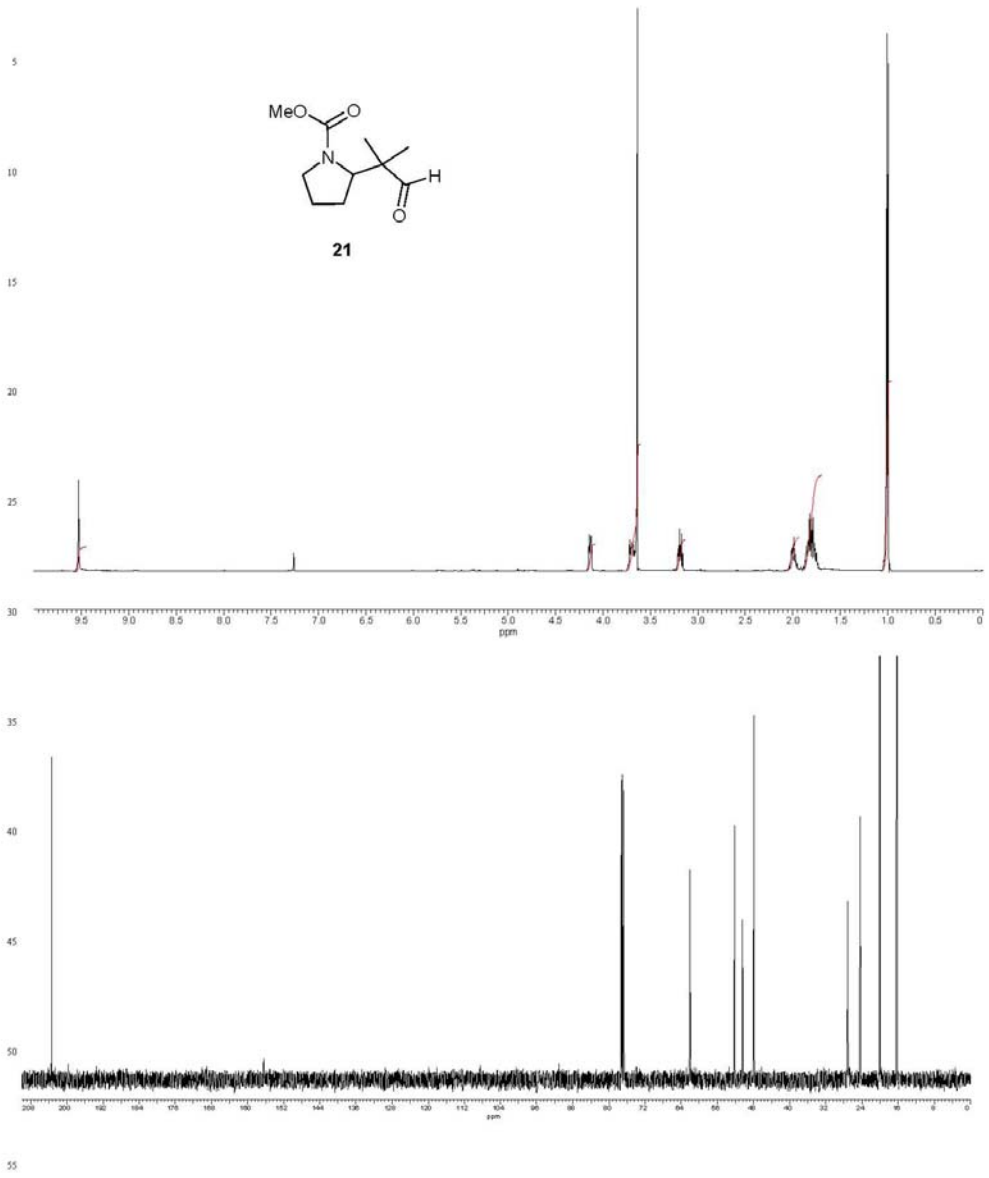

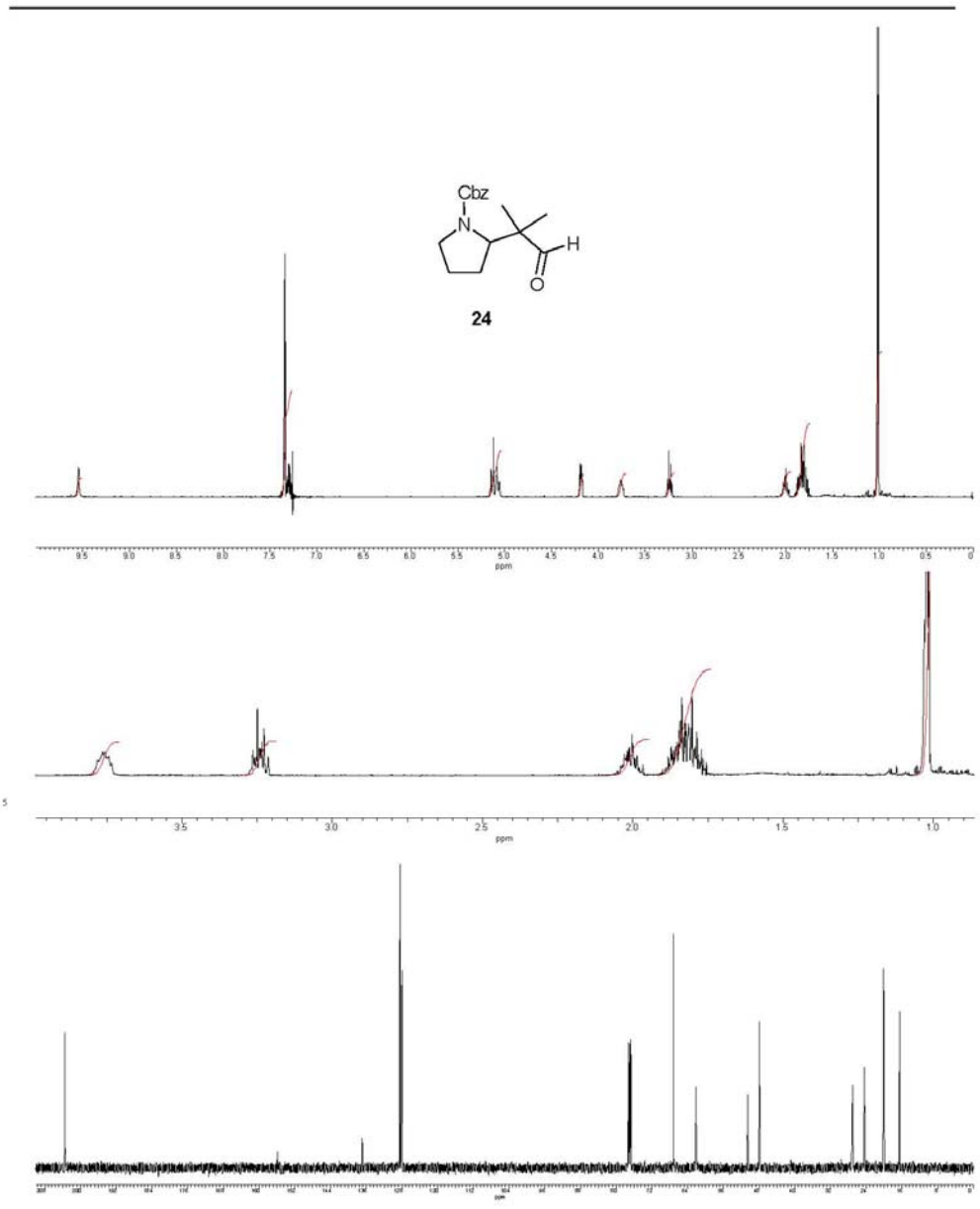

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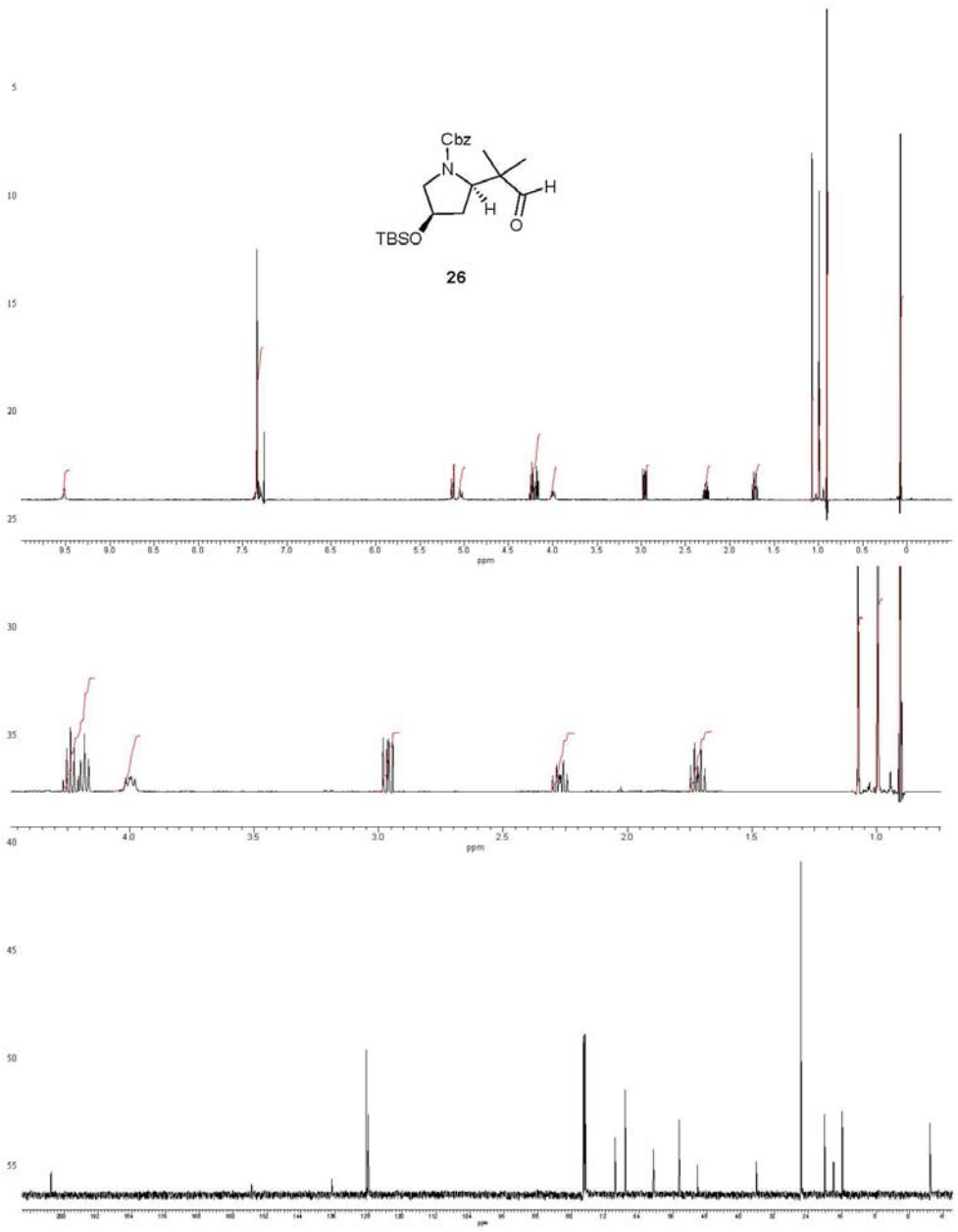

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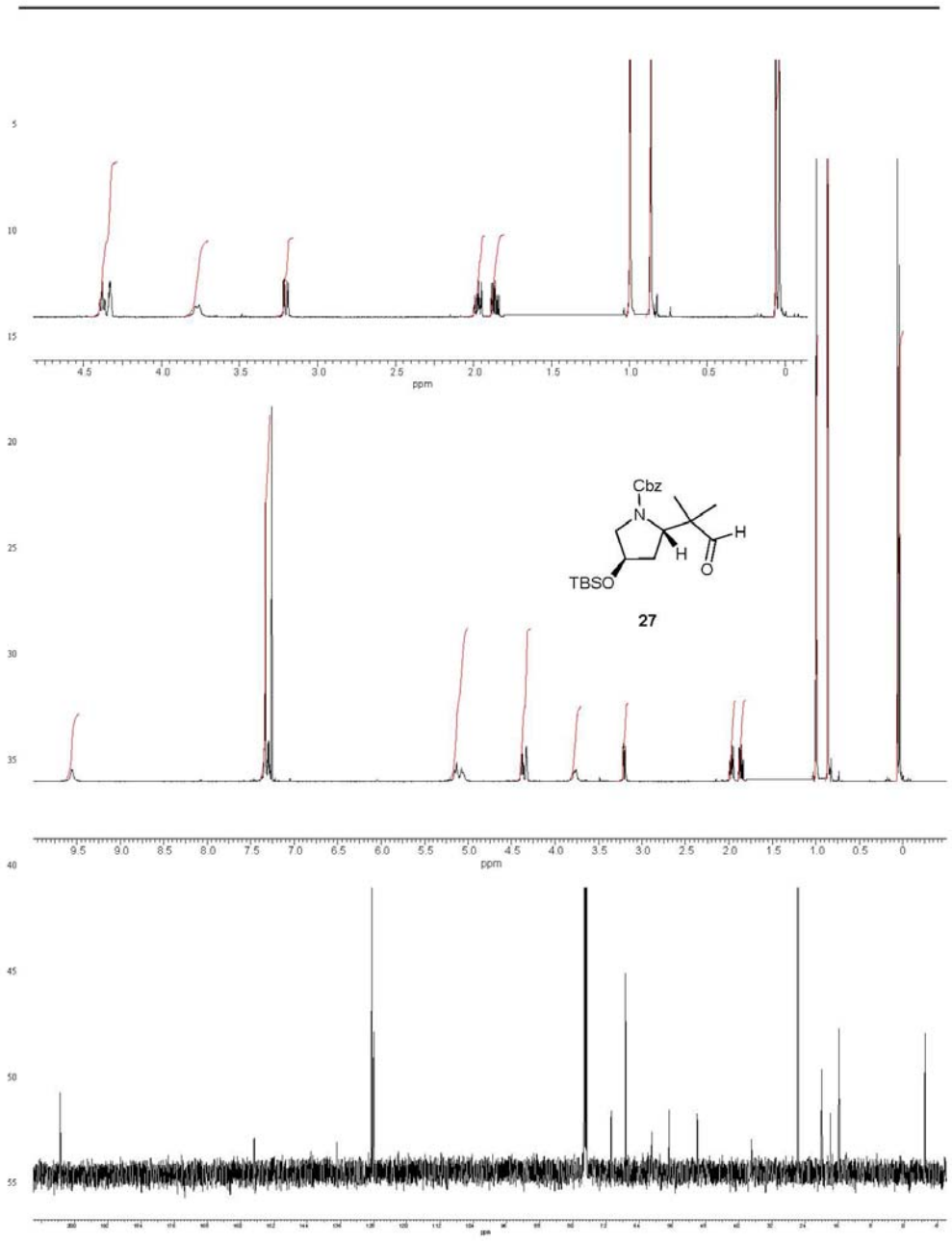

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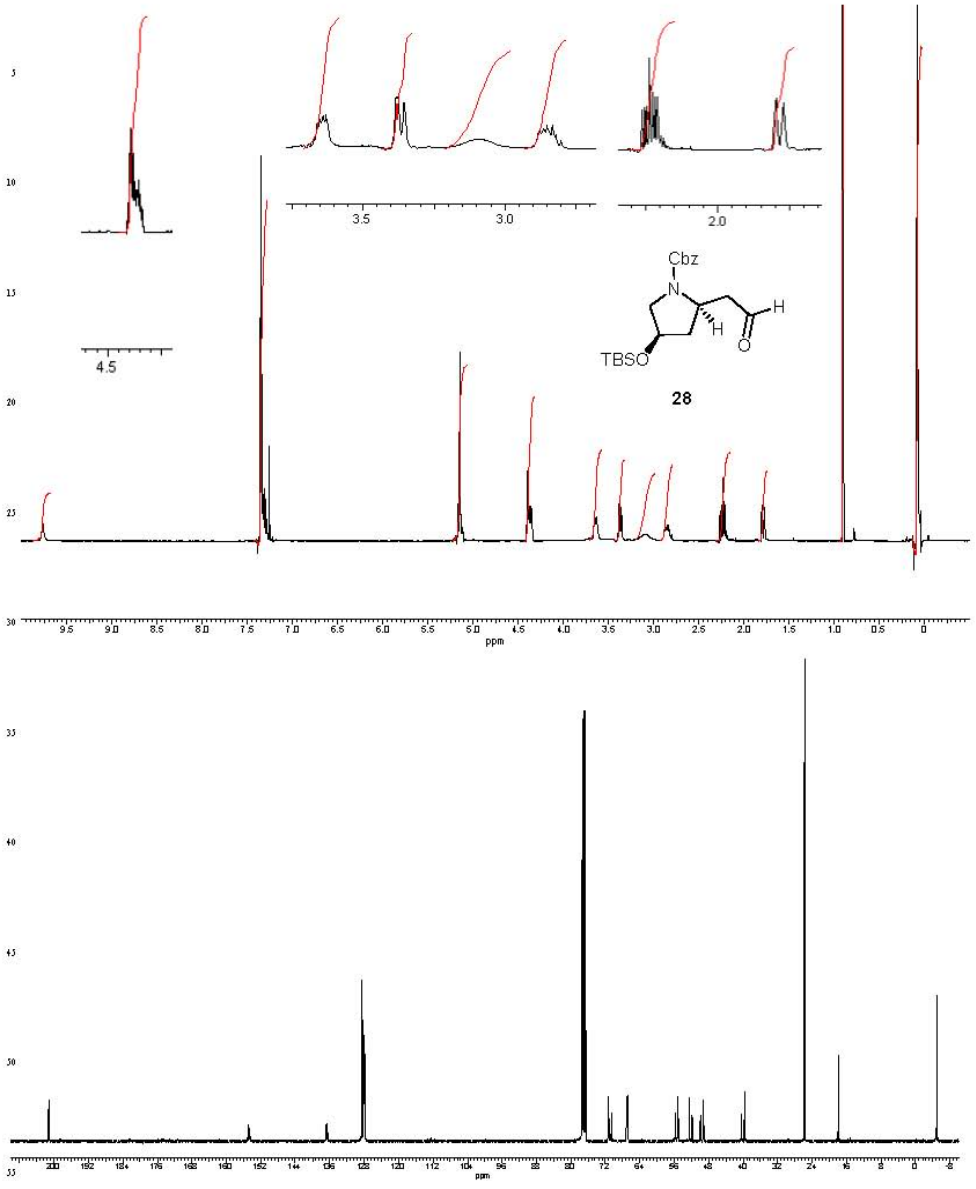

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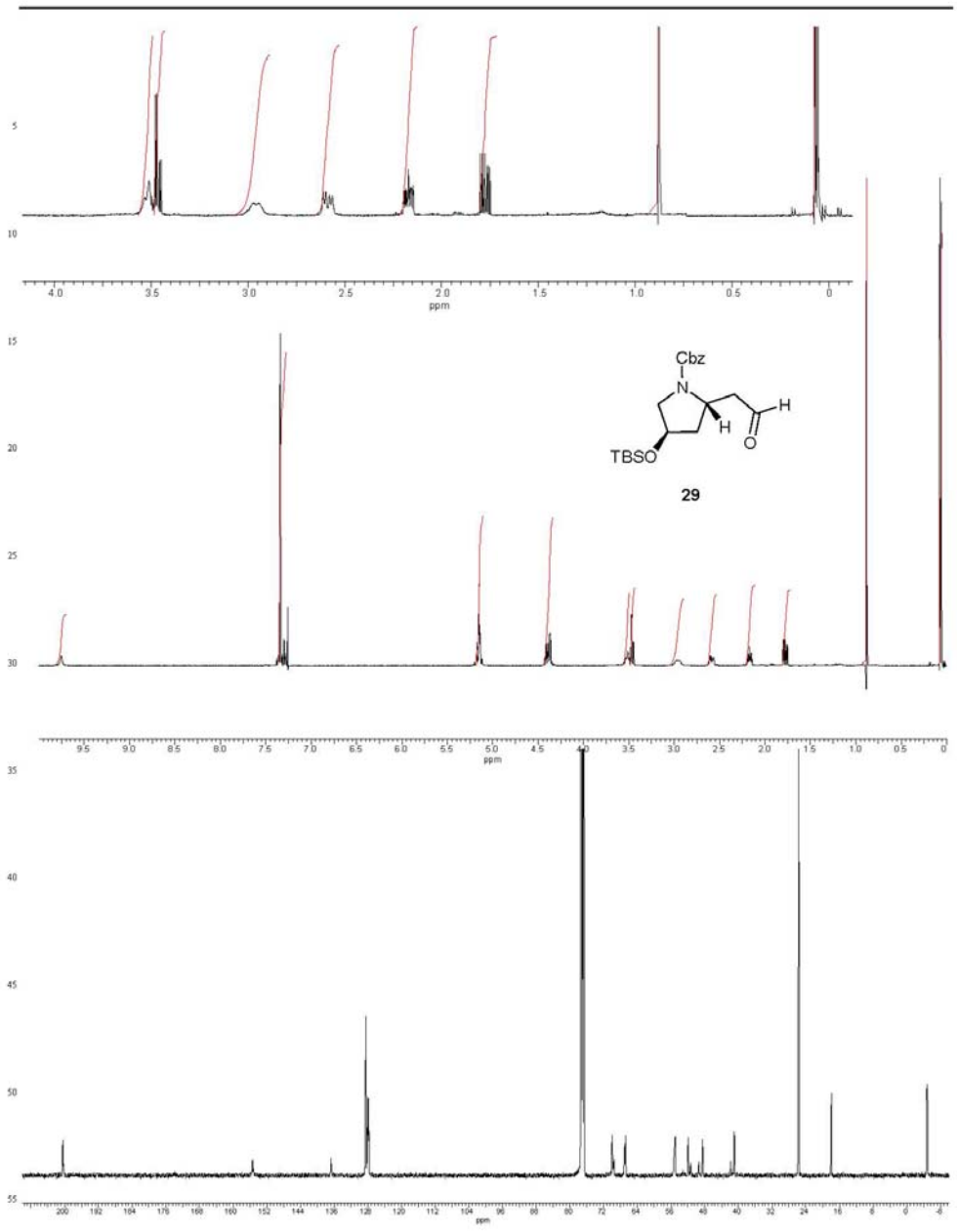

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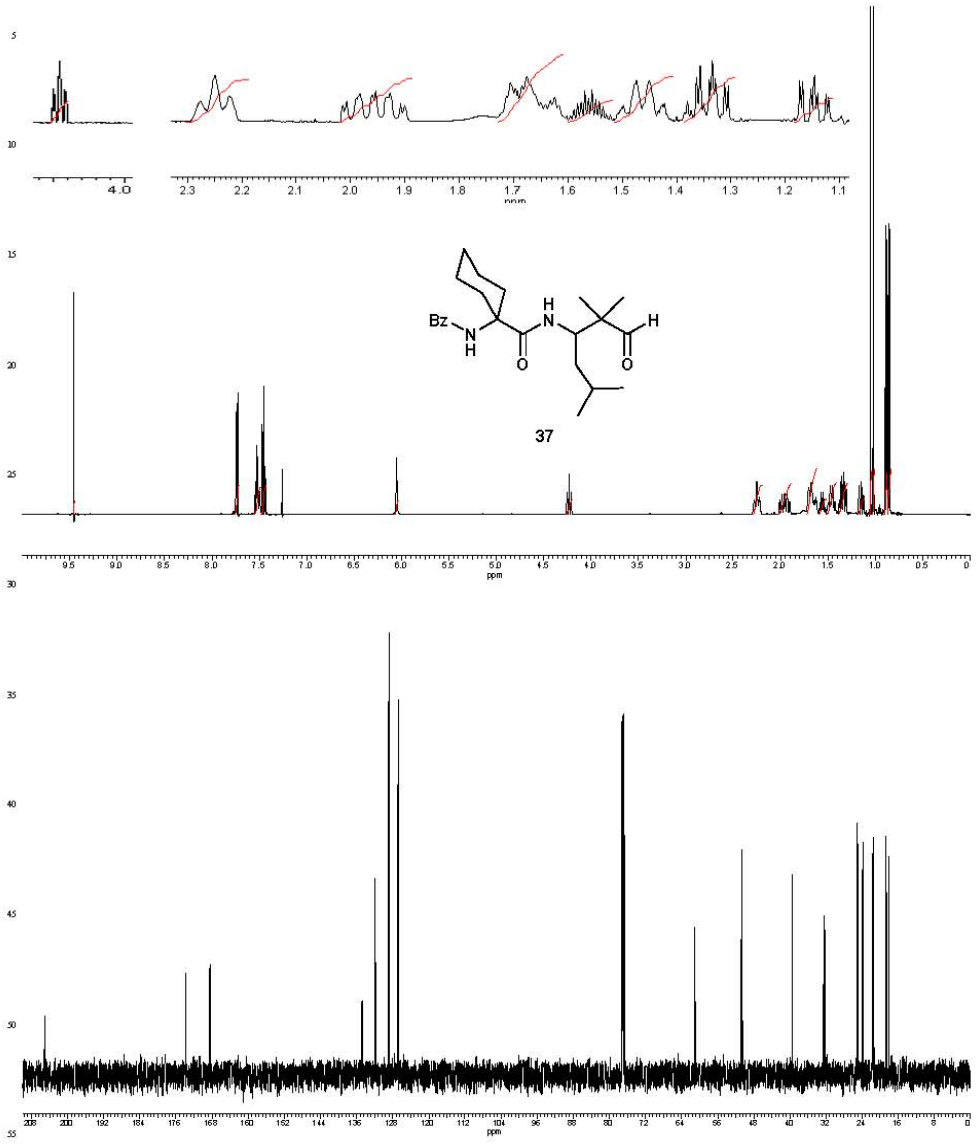

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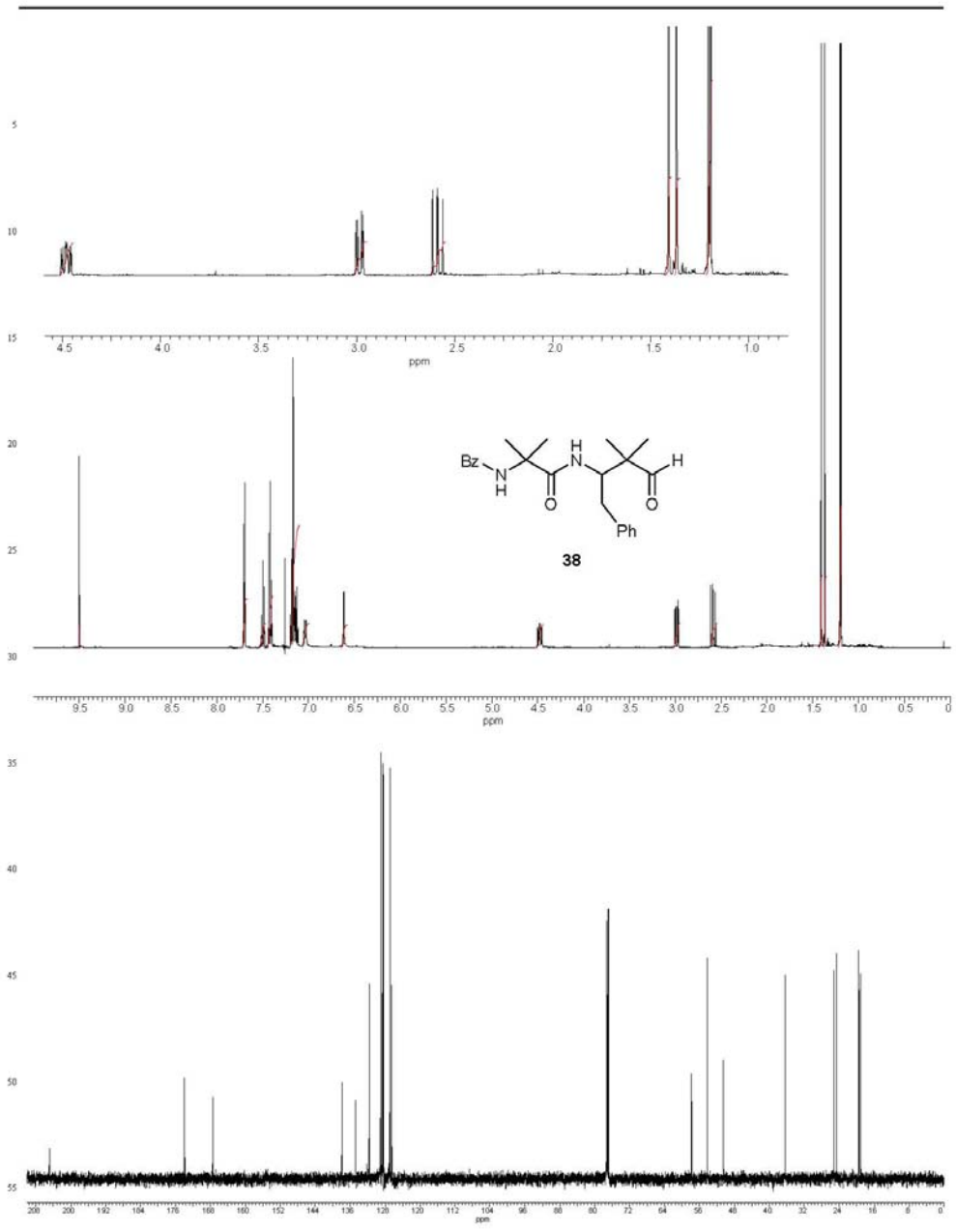

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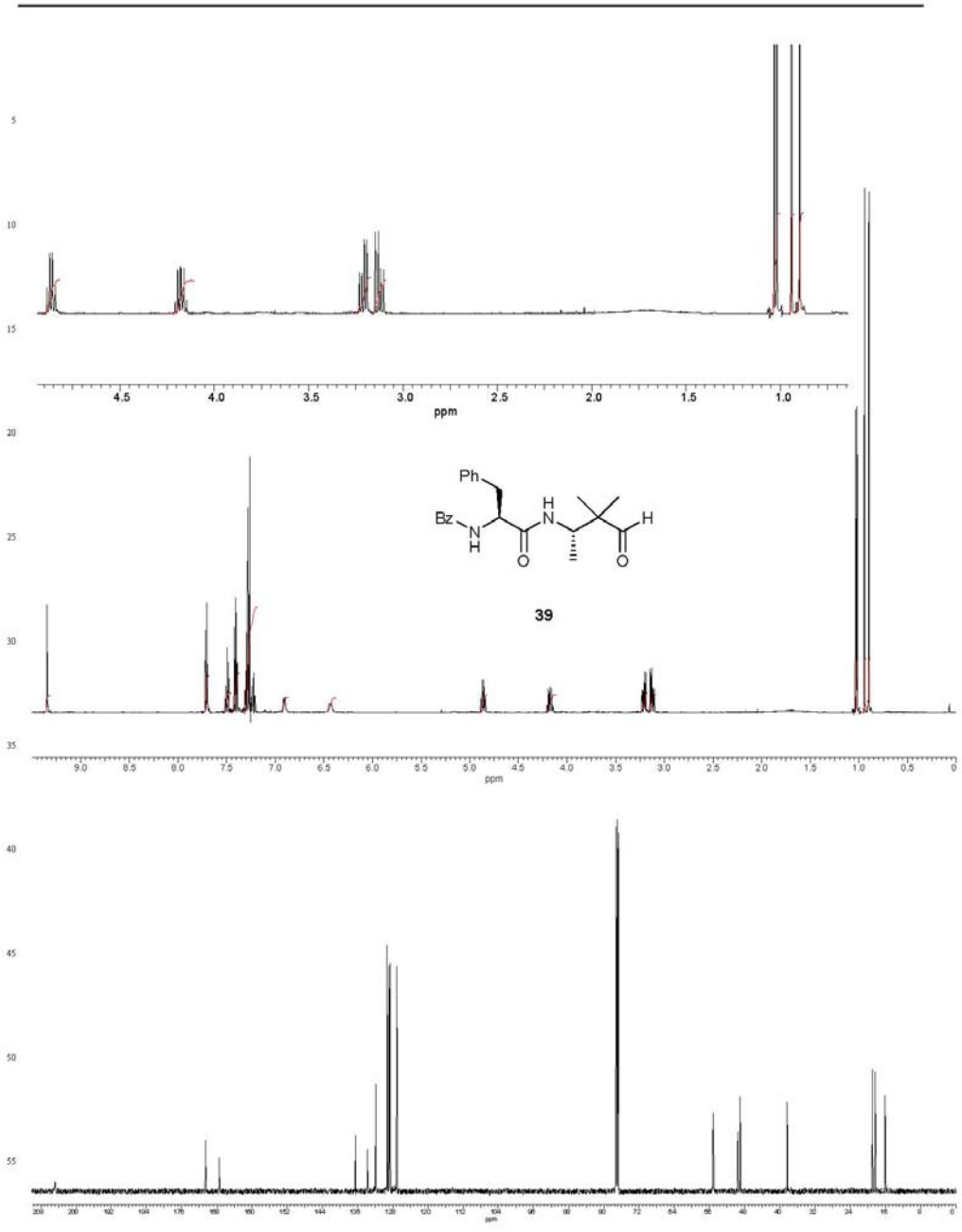

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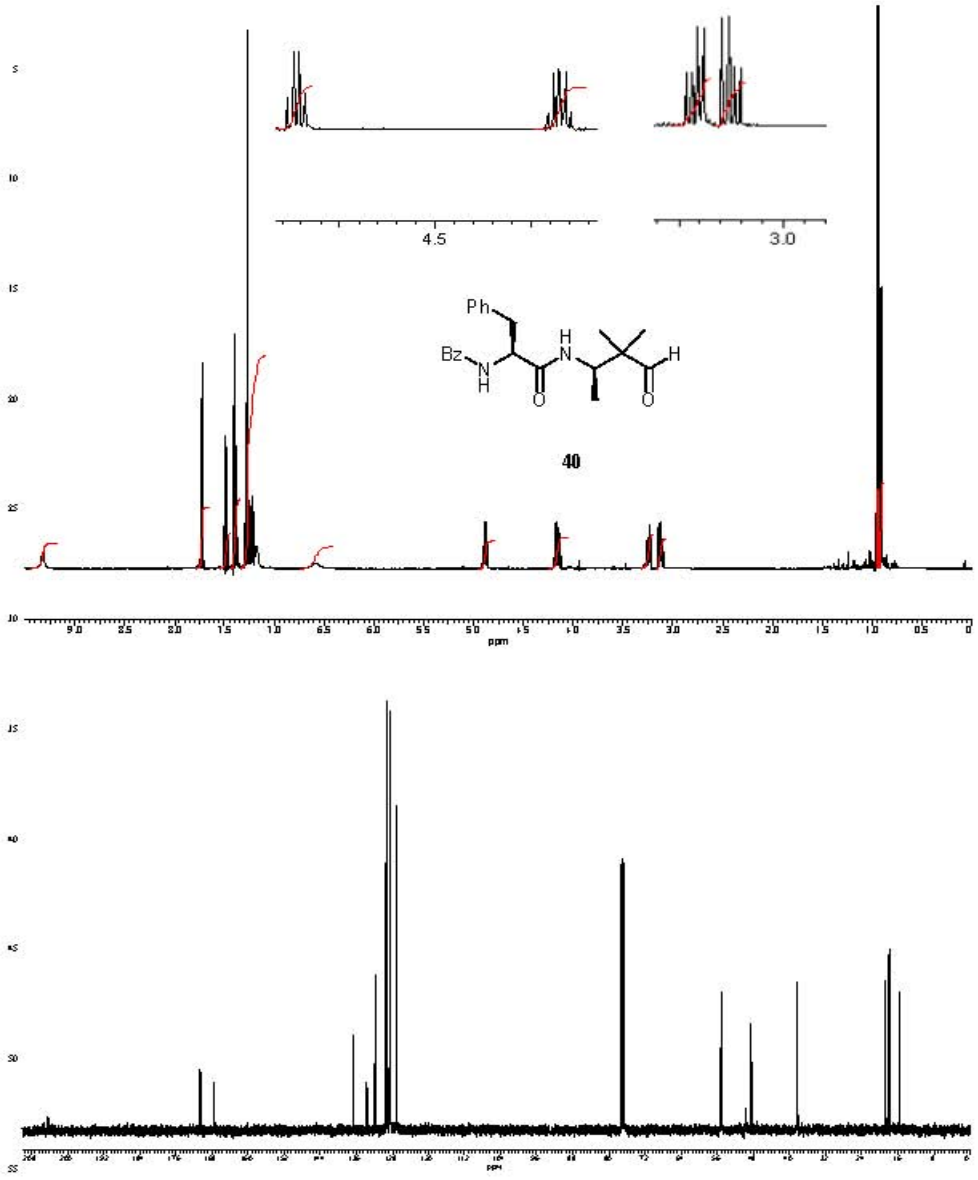

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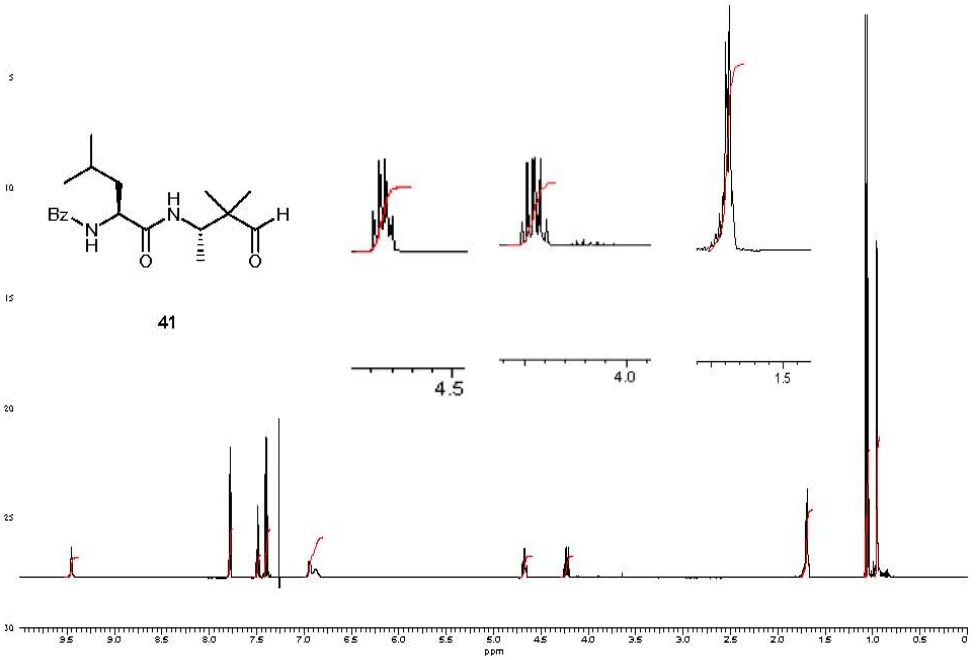

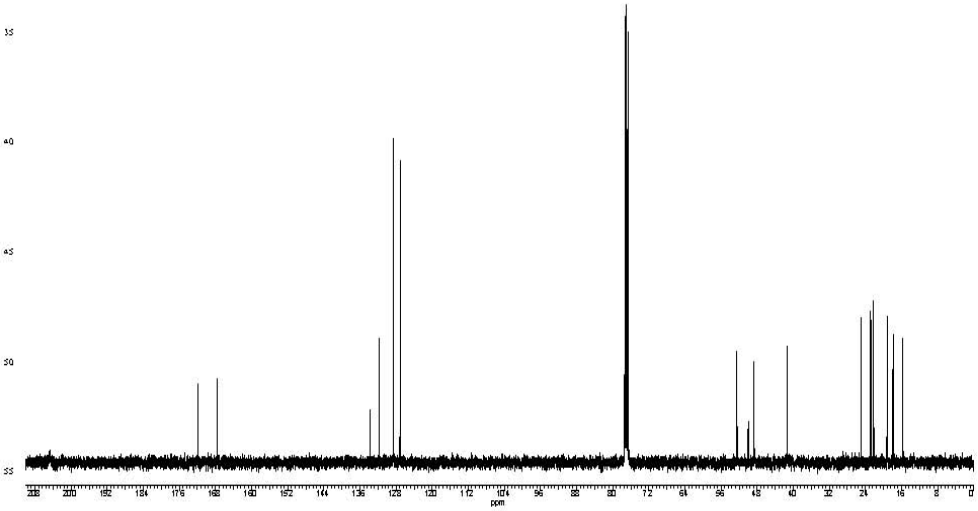

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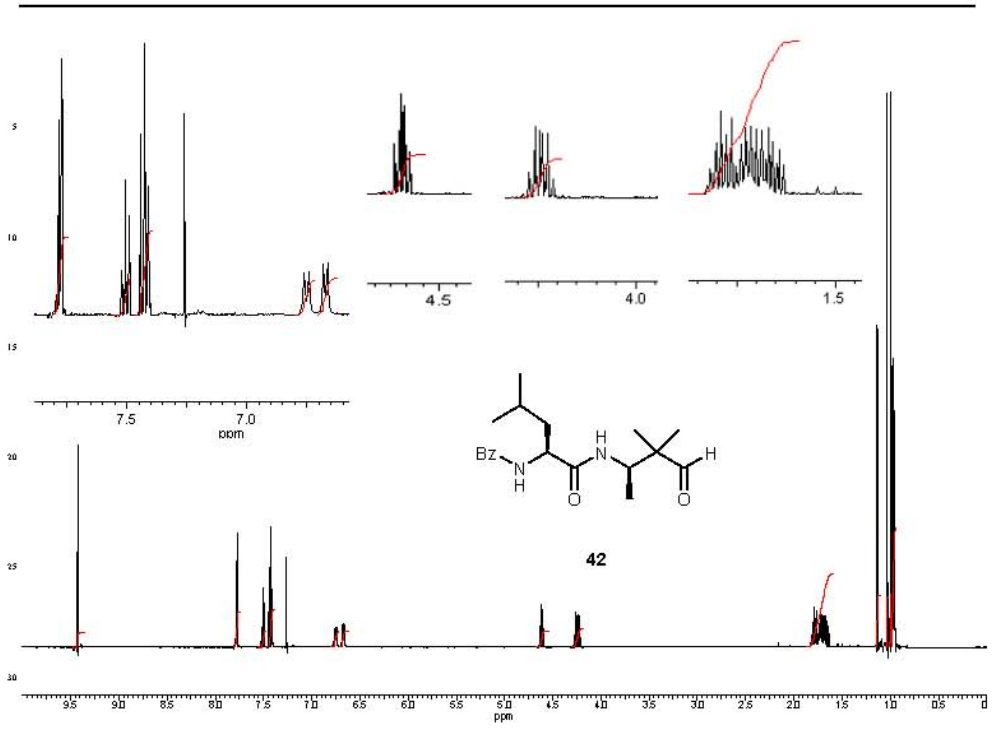

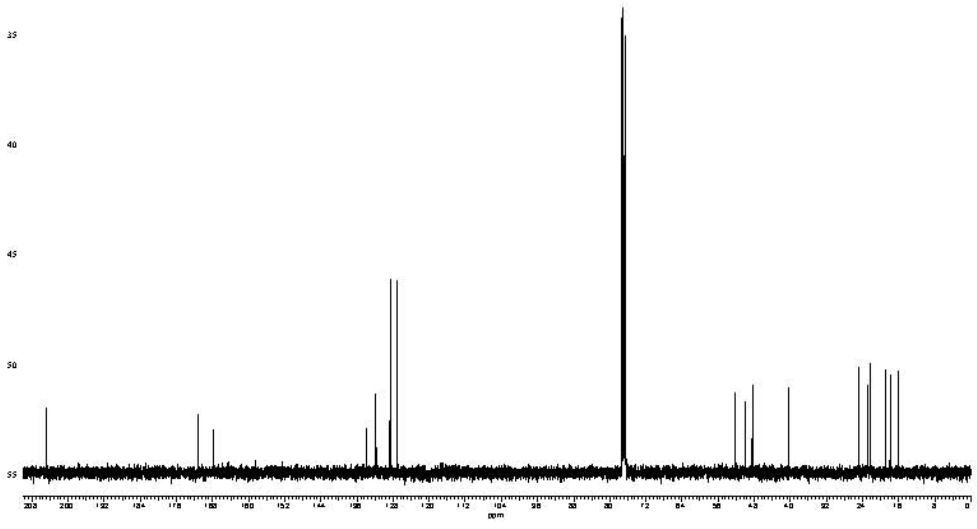

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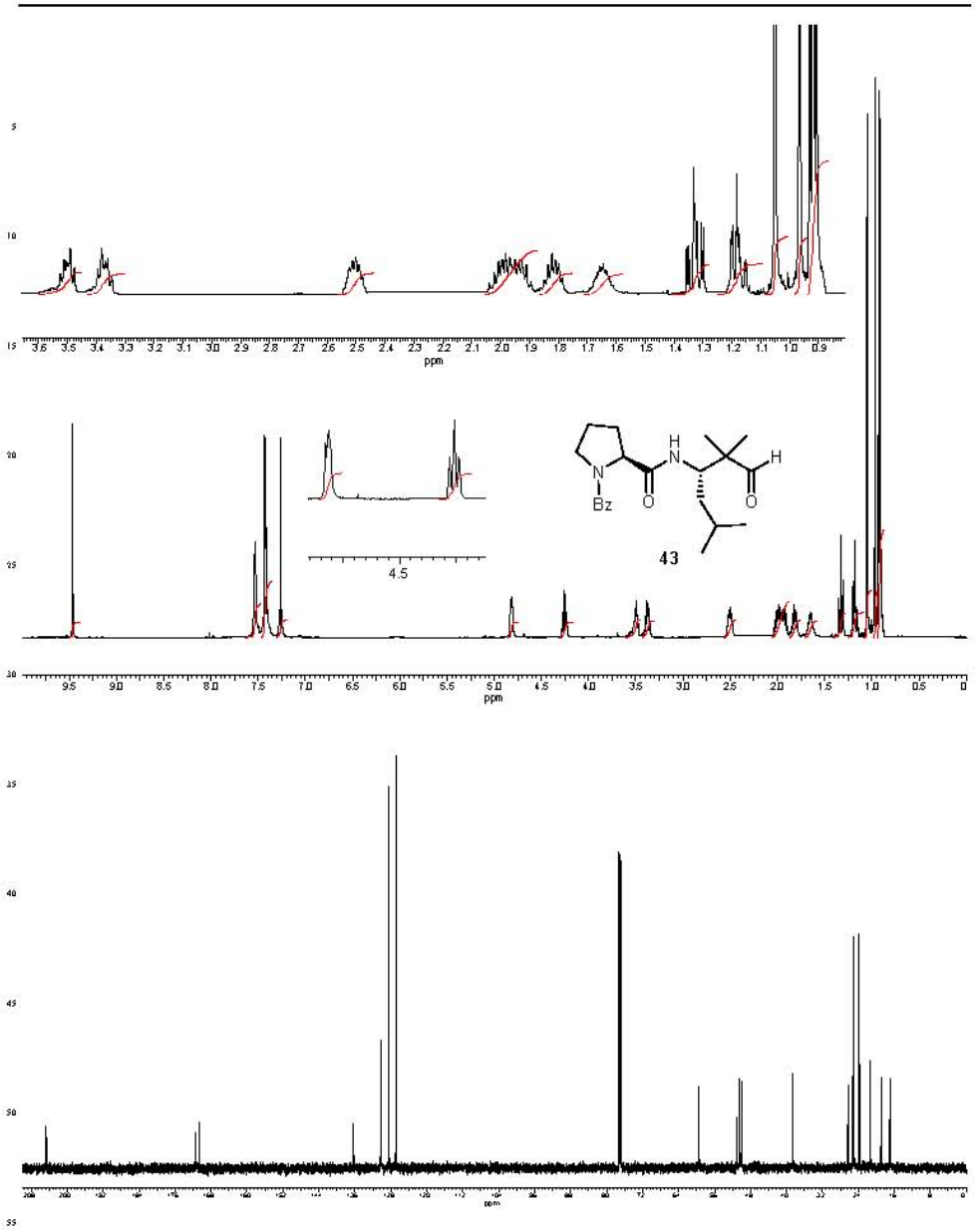

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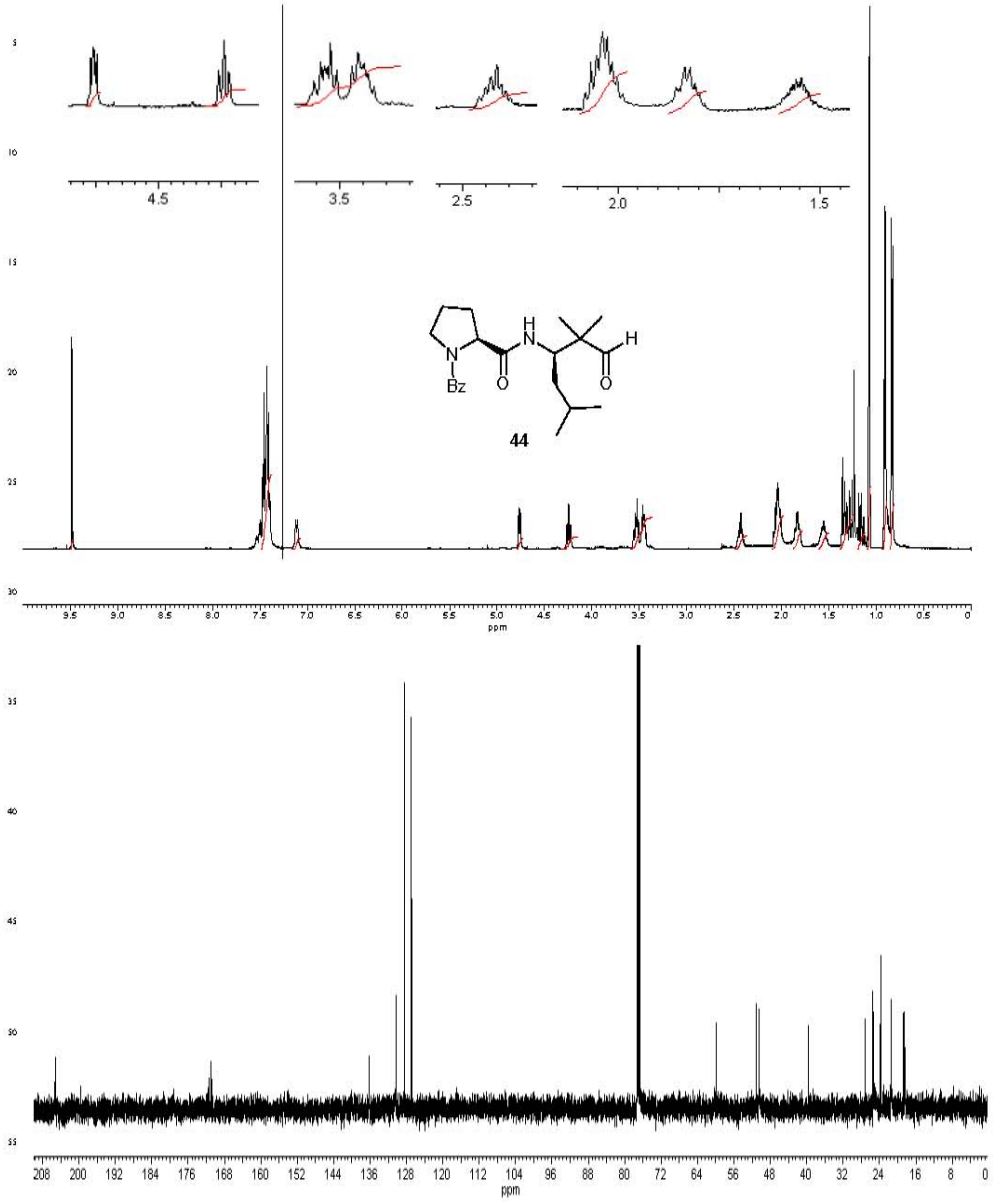

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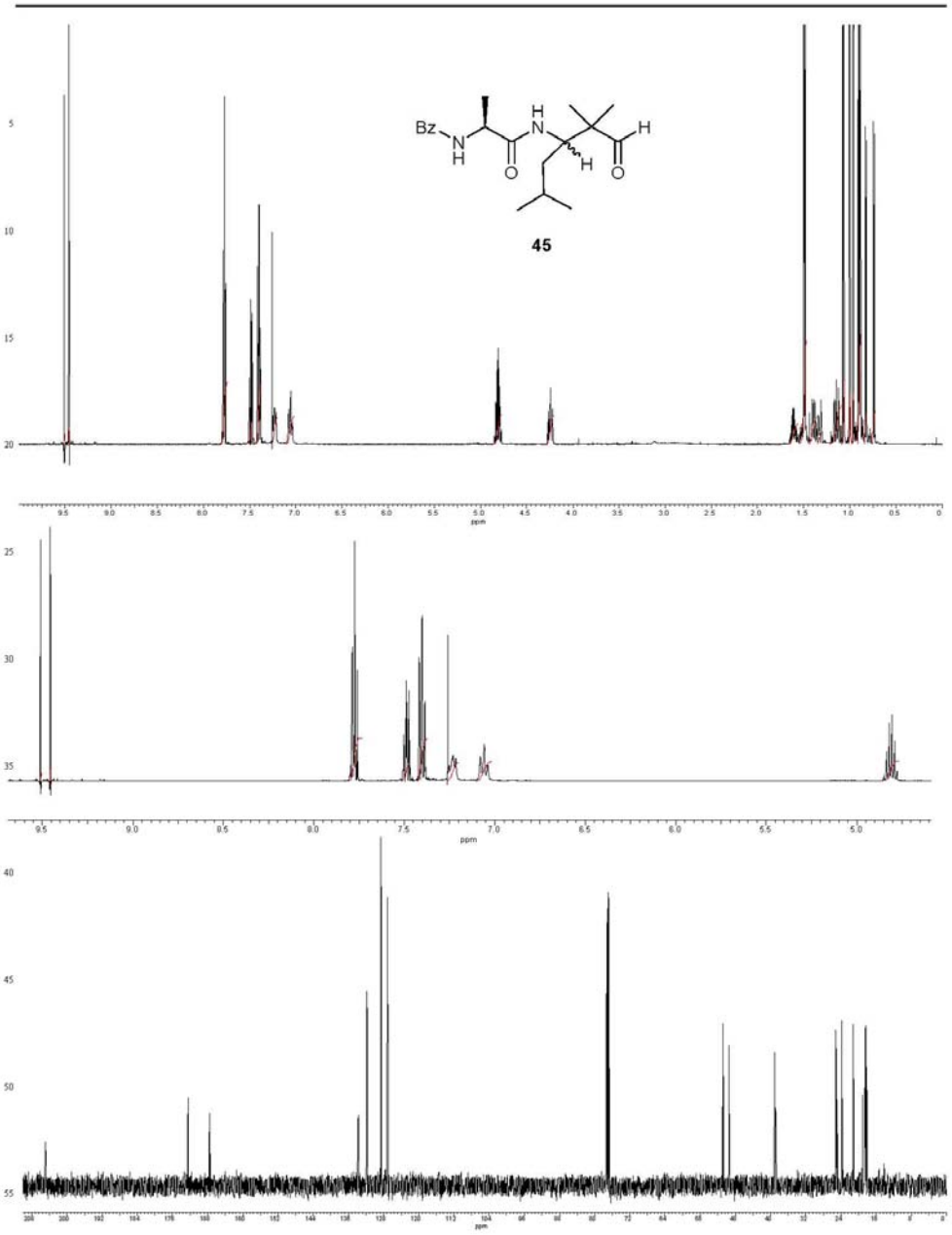

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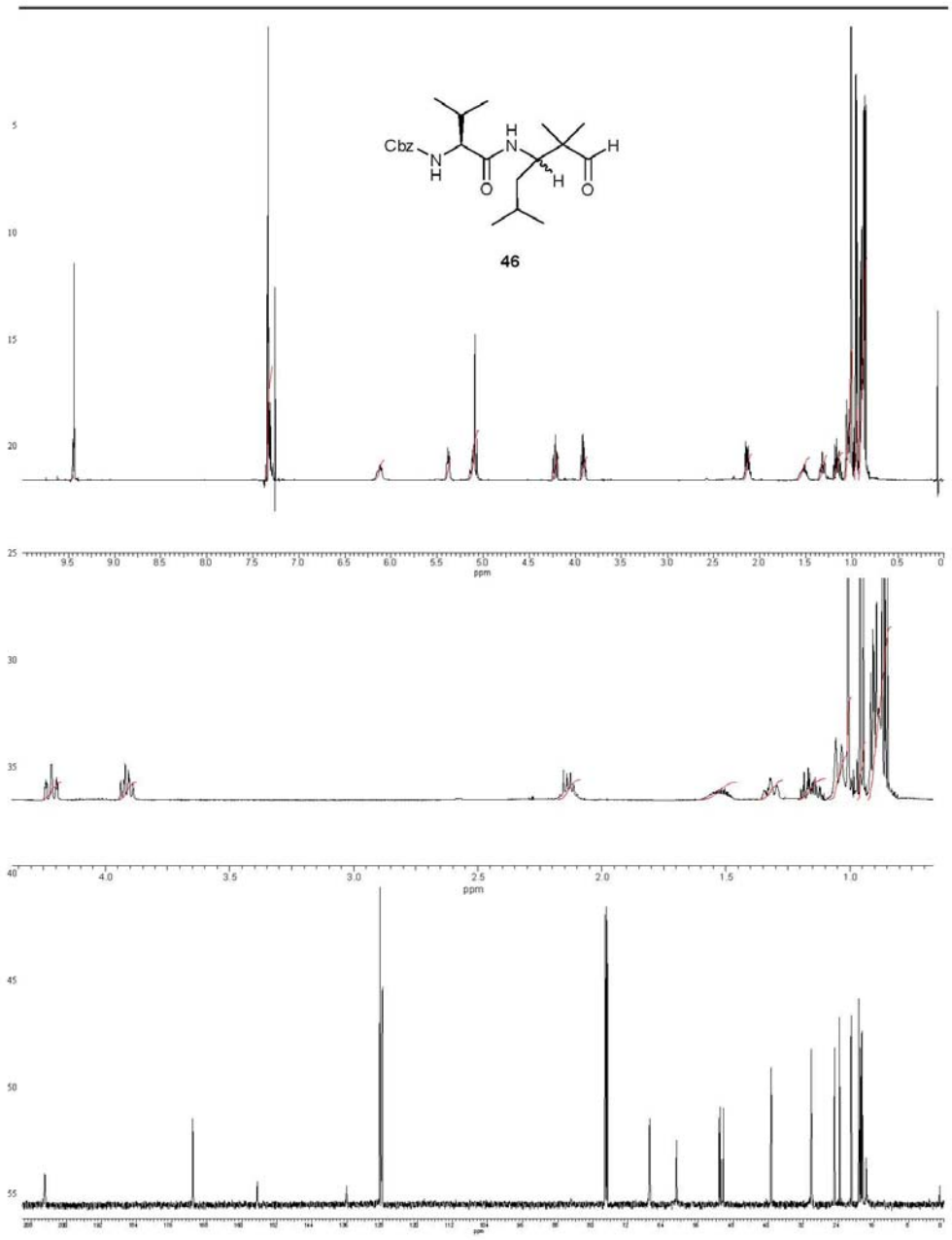

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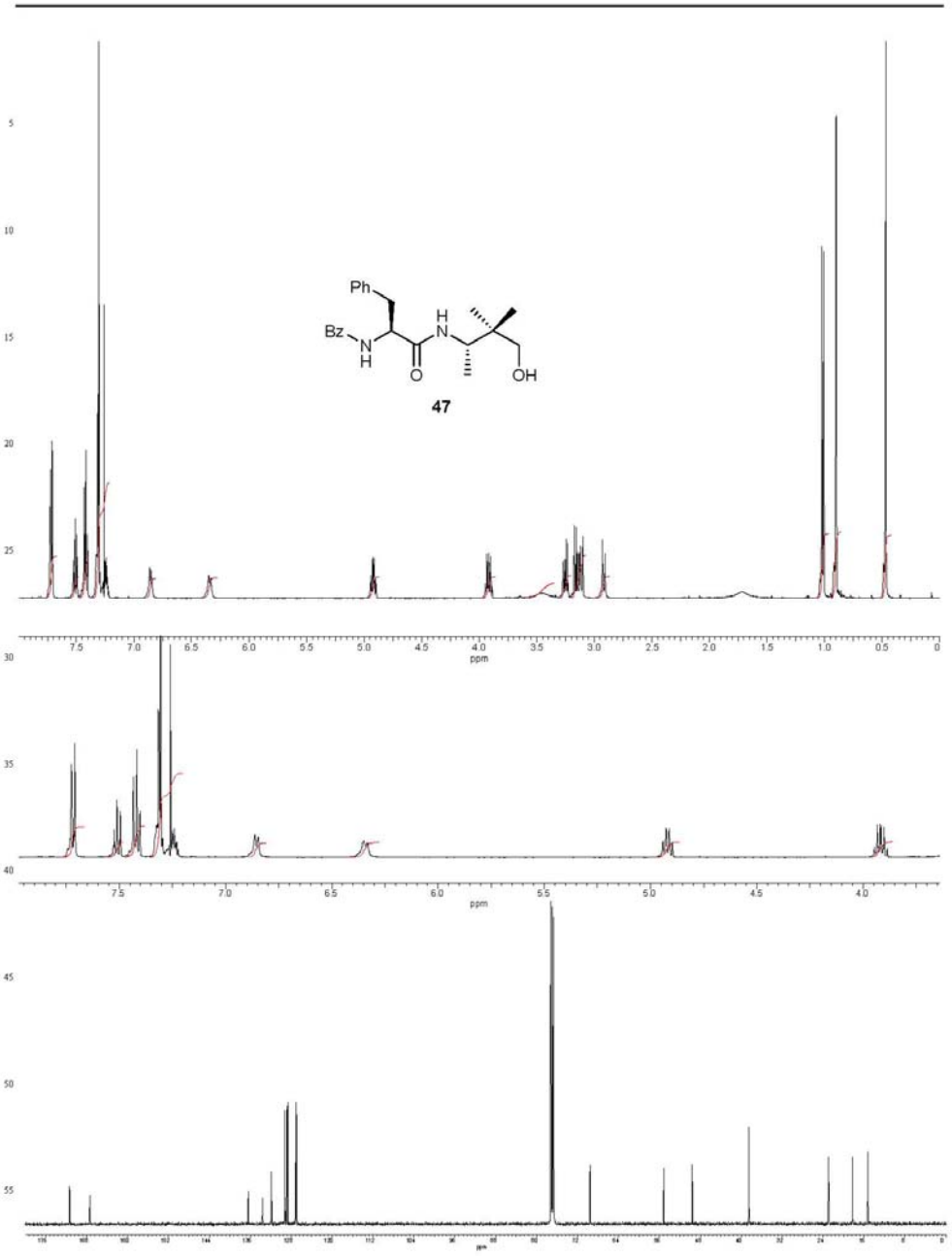

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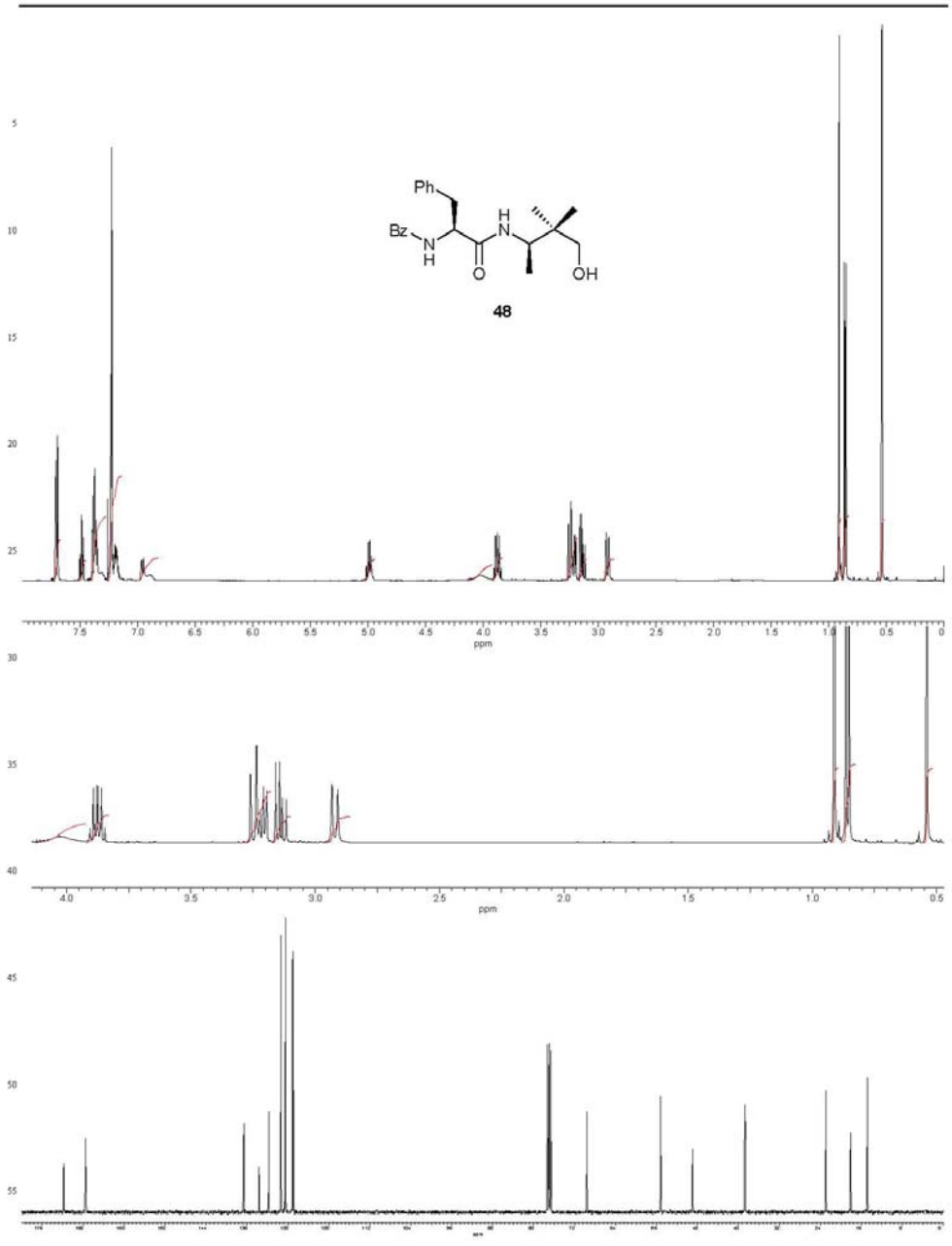

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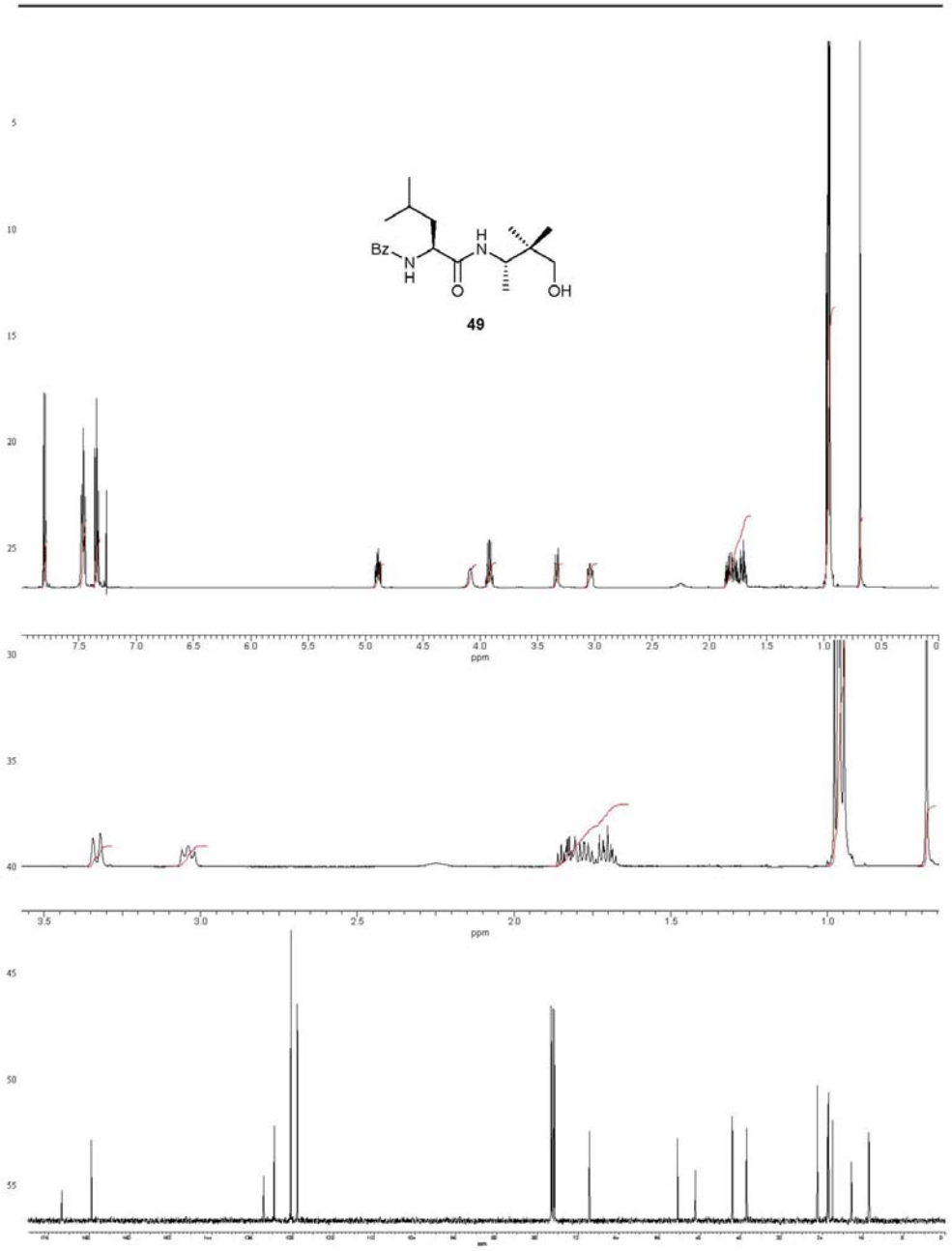

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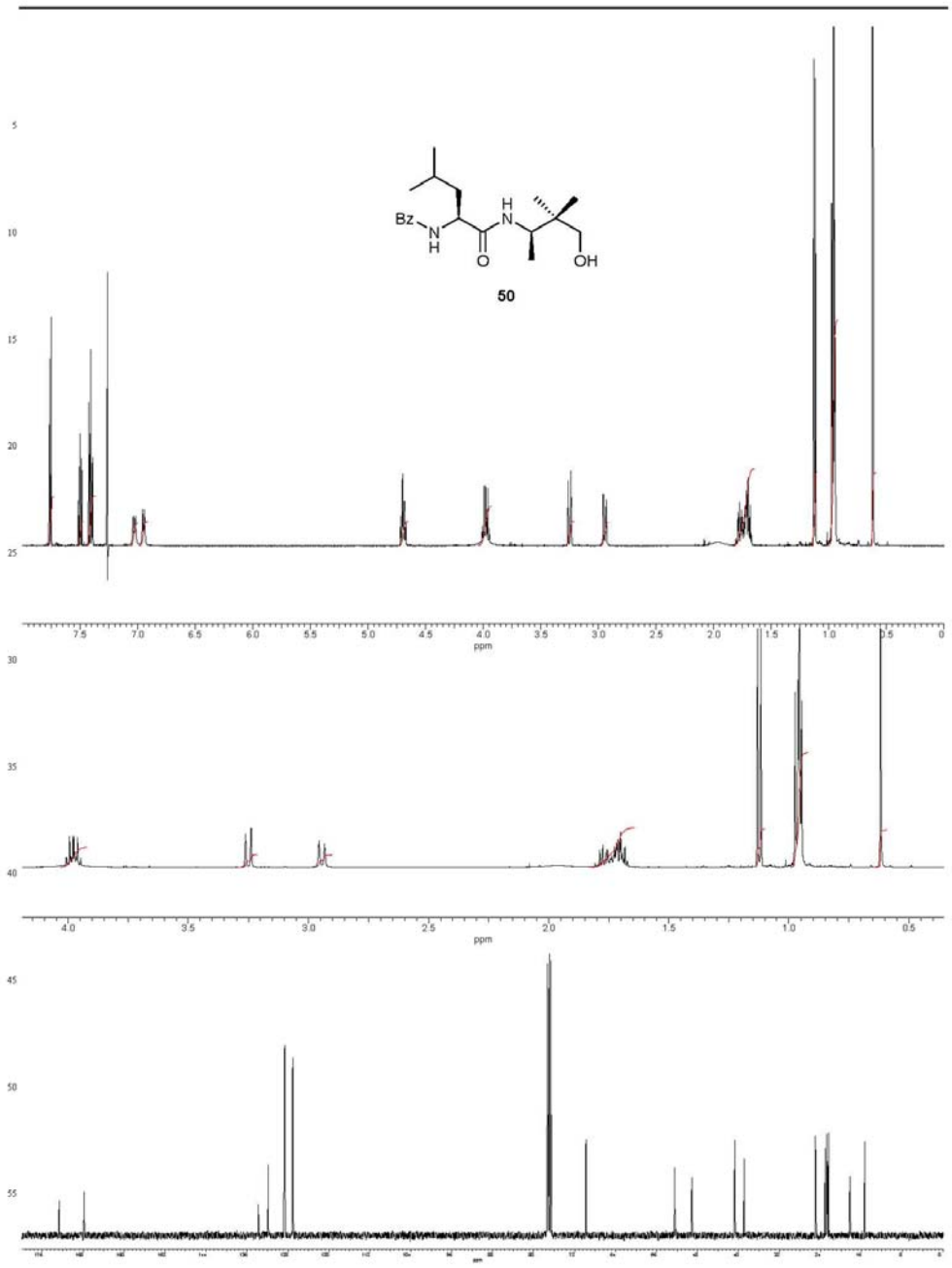

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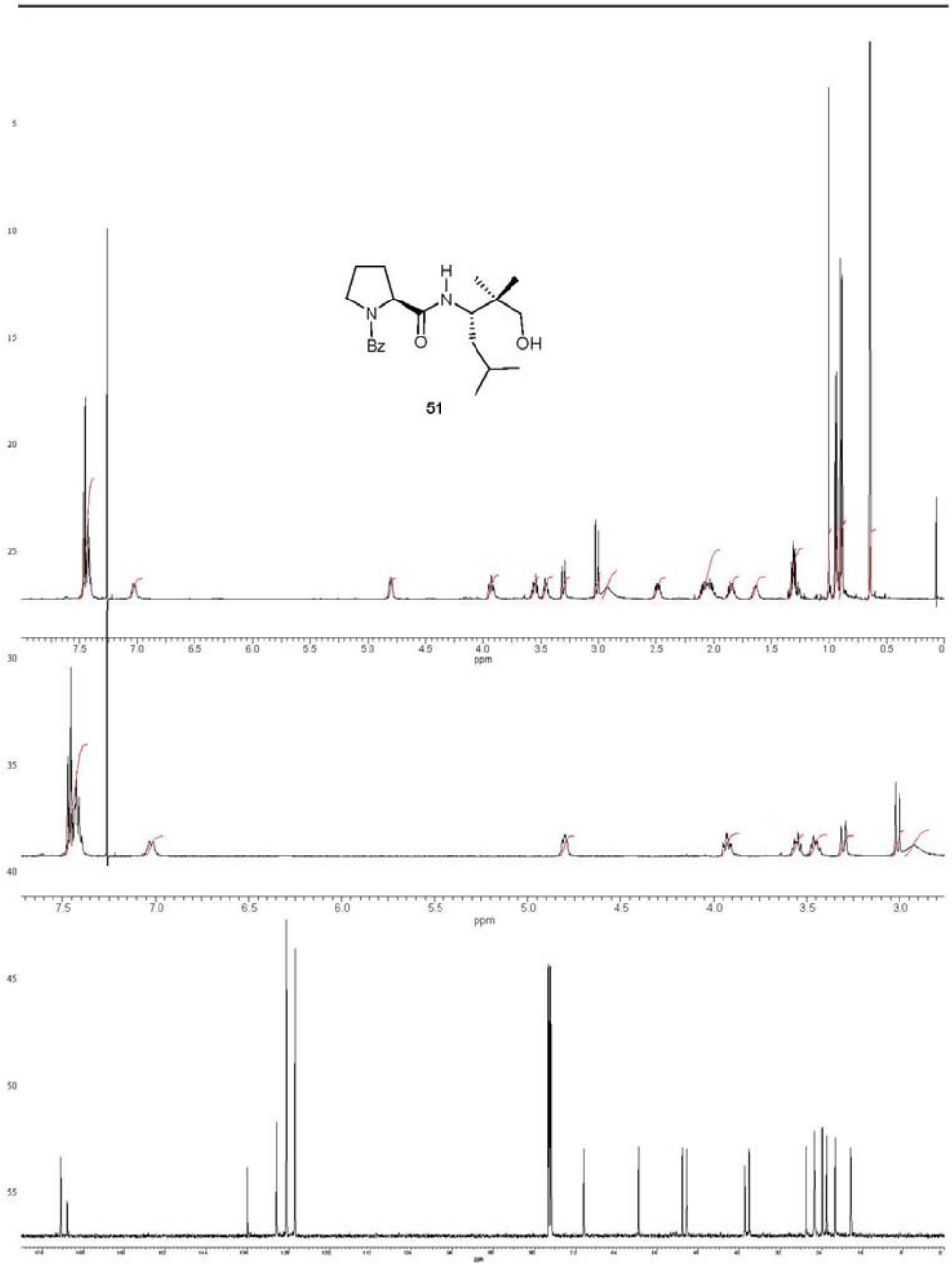

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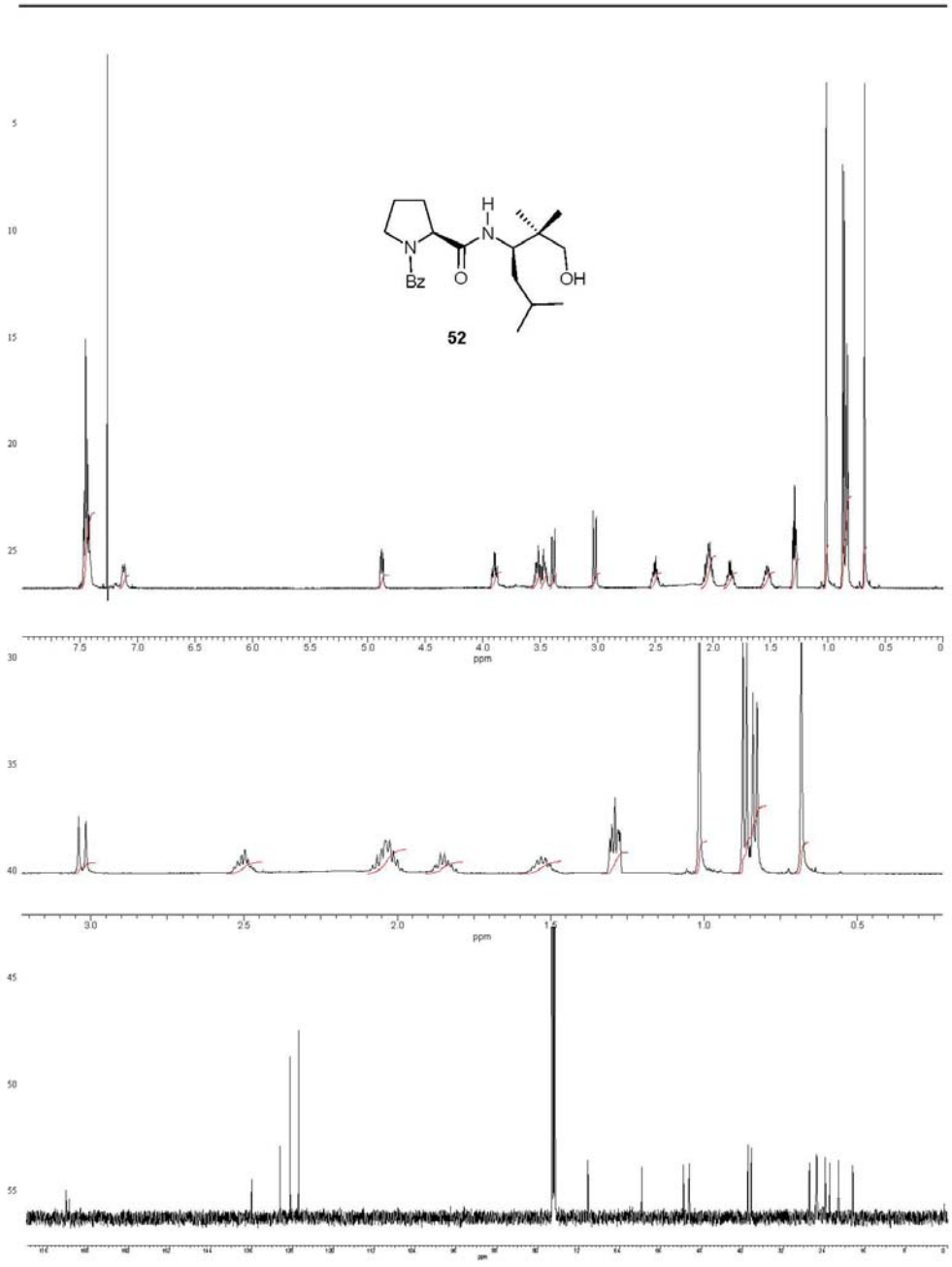

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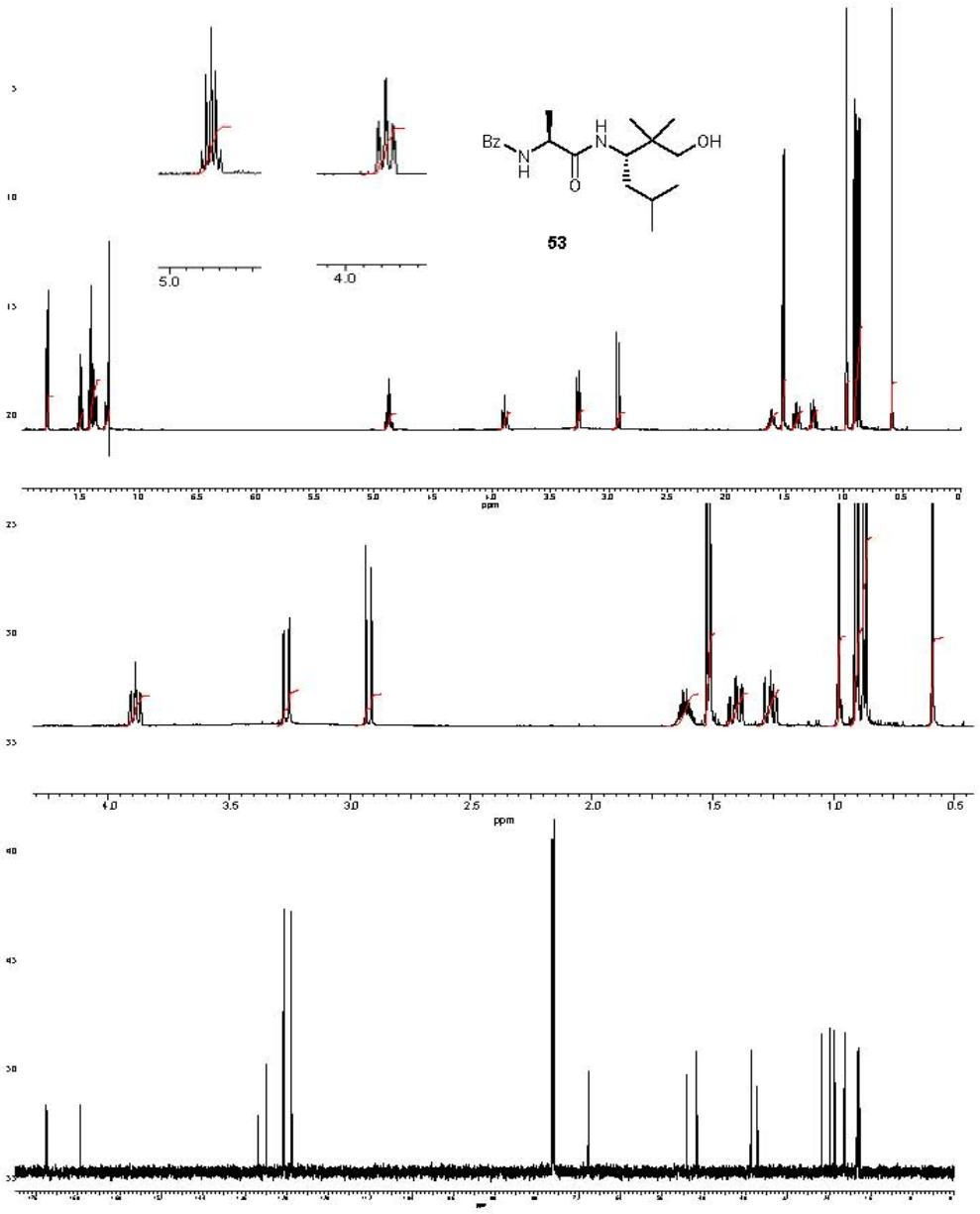

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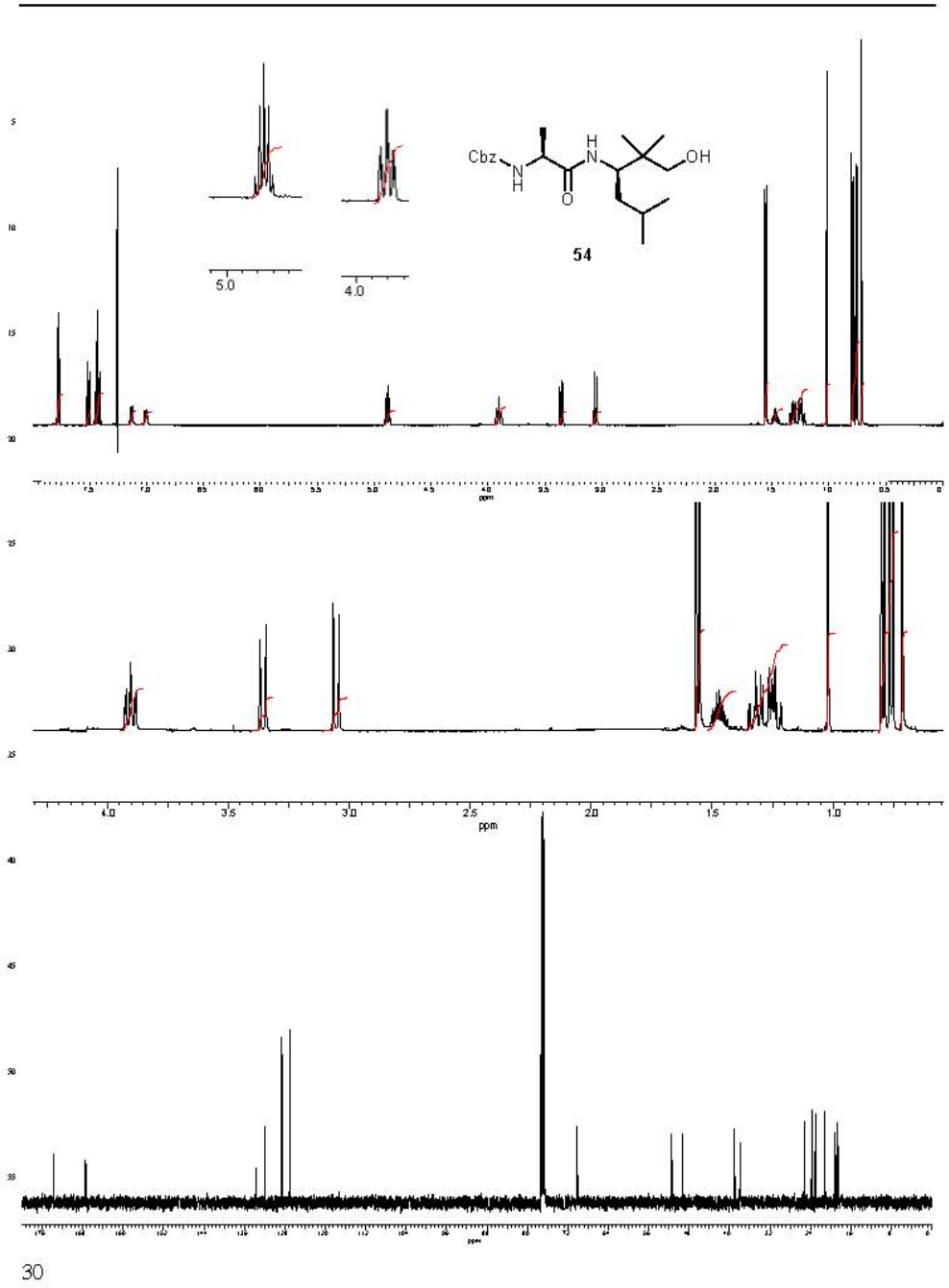

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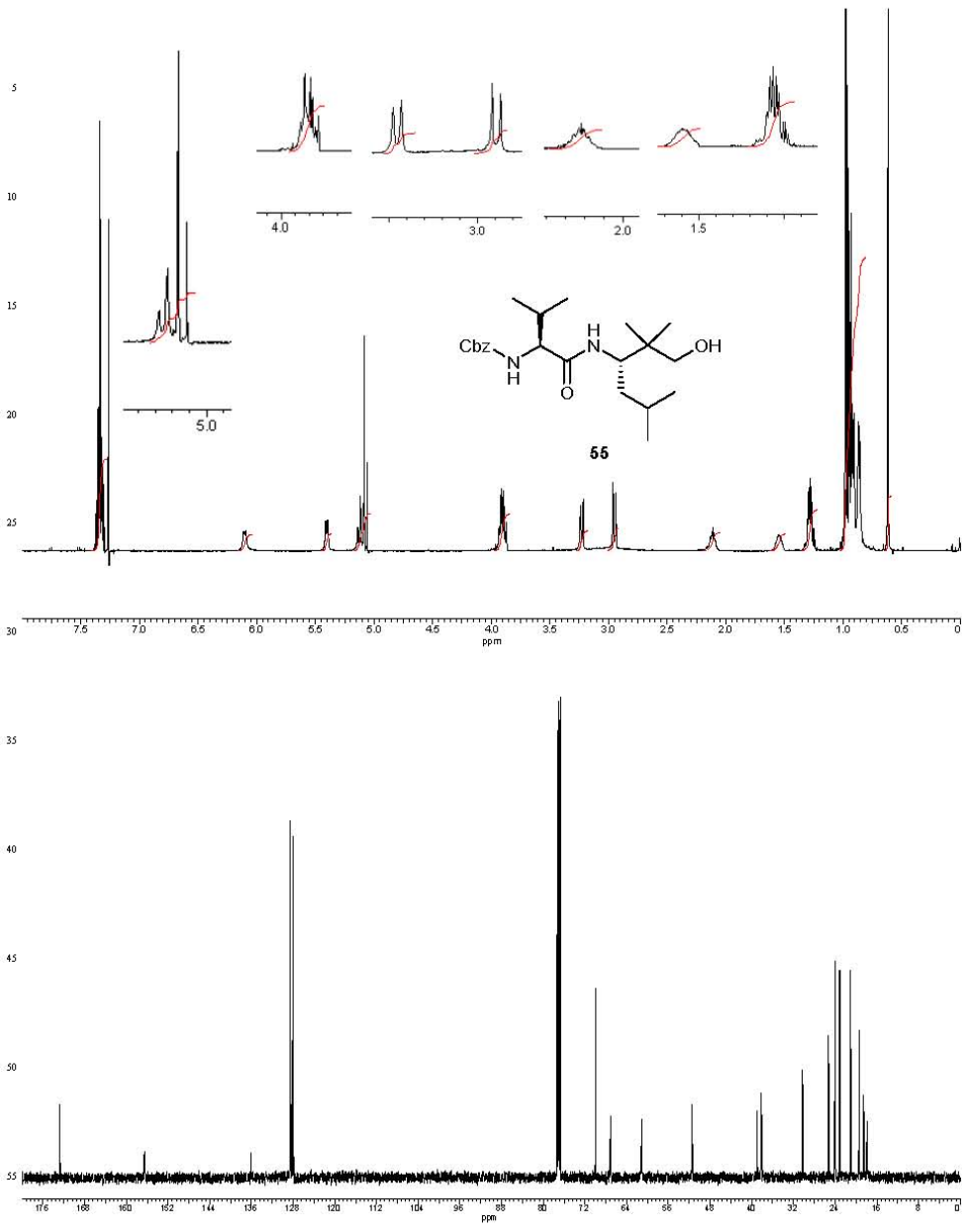

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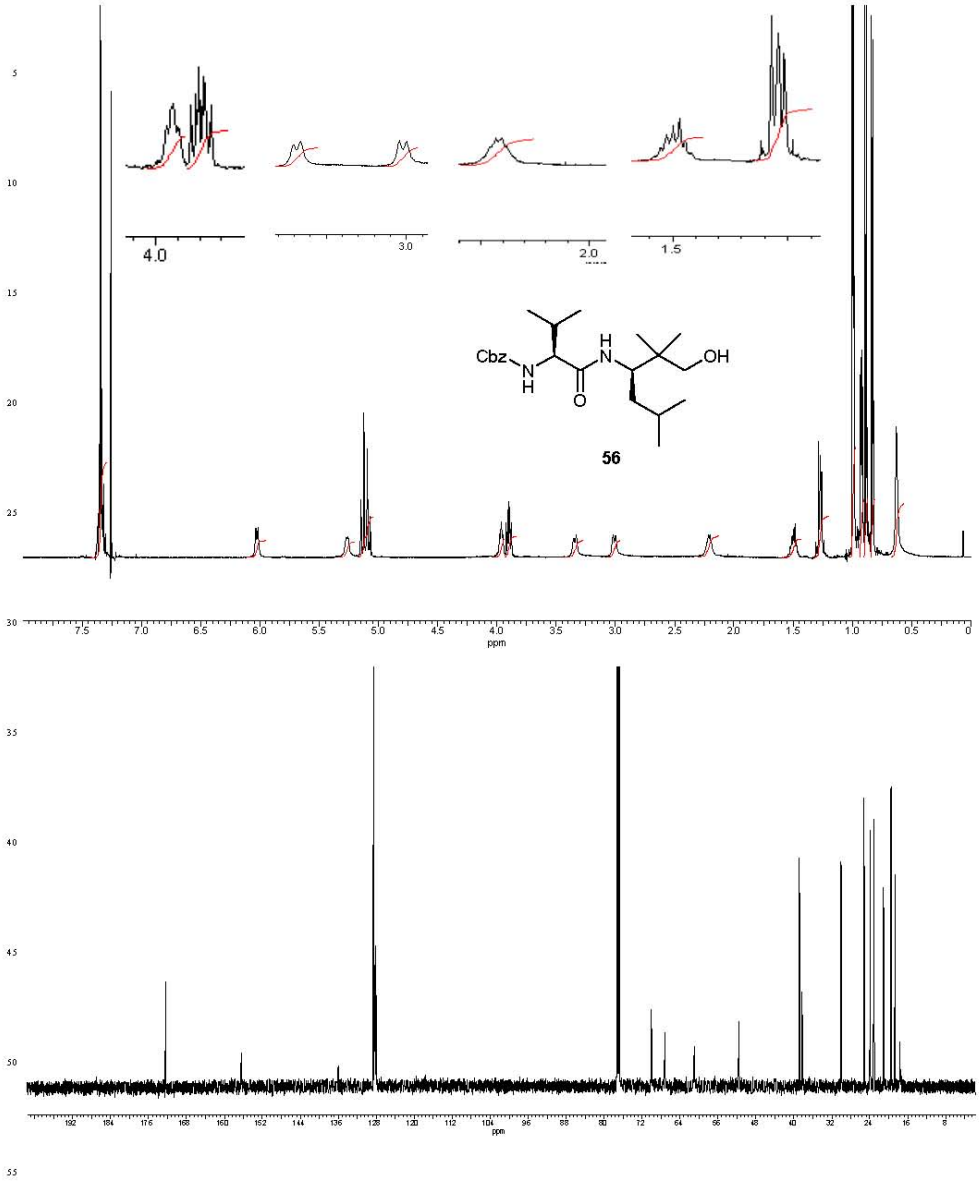

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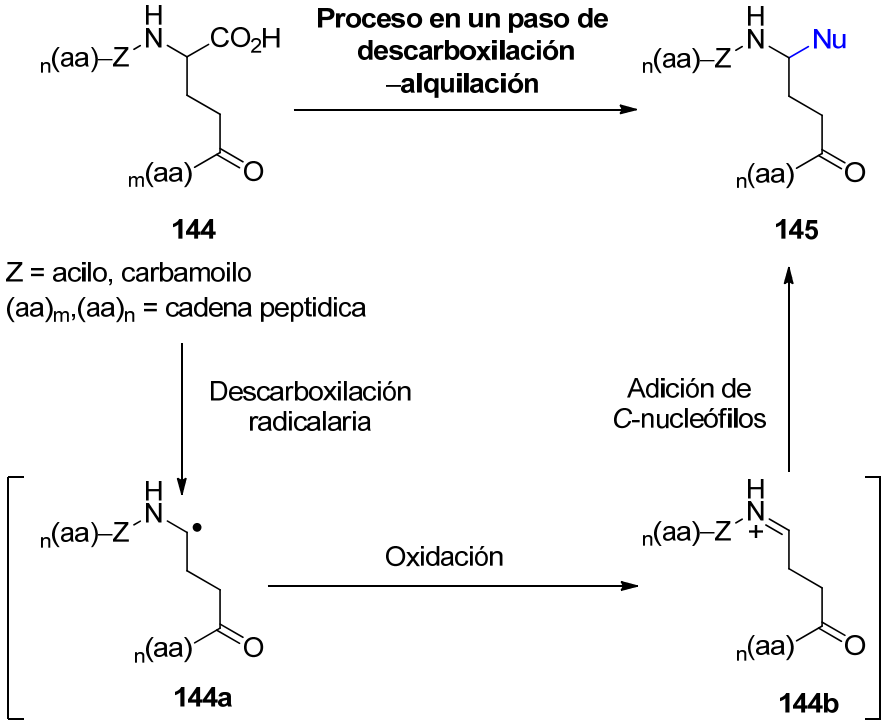
3.3 Síntesis de α,γ-péptidos híbridos por modificación selectiva de unidades de ácido glutámico.

La preparación de α,γ-péptidos ha generado recientemente mucho interés tanto desde el punto de vista sintético como farmacéutico. Estos péptidos muestran prometedoras actividades biológicas (ej. antibiótica, antiviral, antihipertensiva o anti-Alzheimer). Además, a diferencia de los péptidos naturales, los α,γ-péptidos son resistentes a la degradación in vivo.

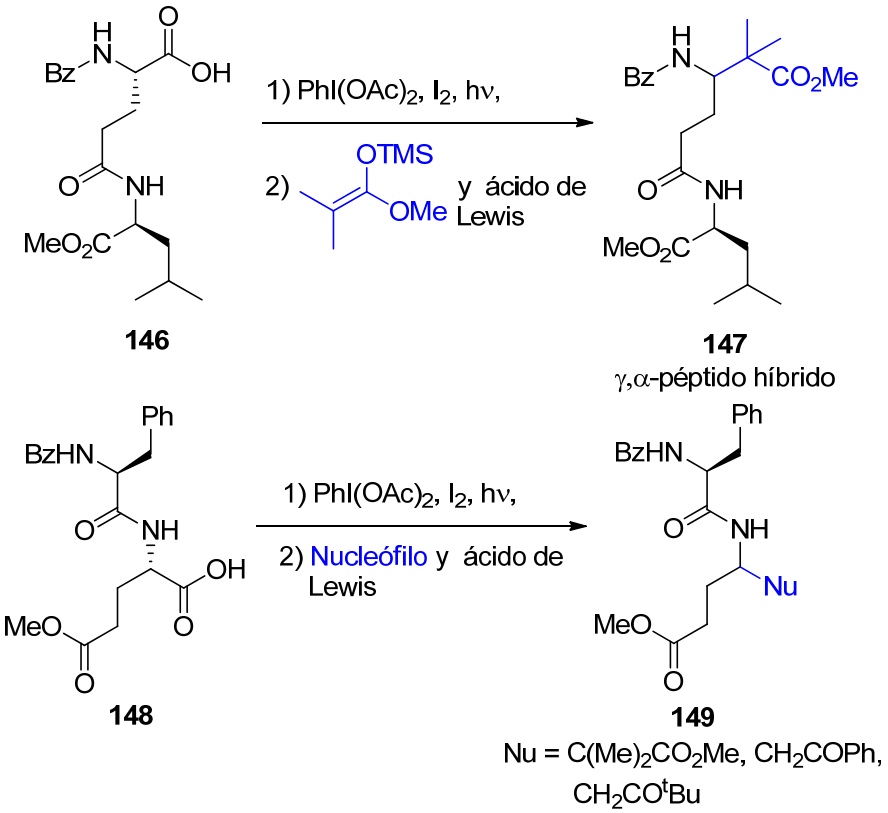
En este capítulo se describe un proceso para la **modificación selectiva de unidades de ácido glutámico en péptidos 144** (Esquema 42), usando procesos secuenciales de descarboxilación radicalaria oxidativa-alquilación. Con ello, las unidades de glutámico se convierten selectivamente en γ-amino ácidos no naturales. A diferencia de los métodos anteriores, se pueden modificar selectivamente distintas posiciones del péptido.



Esquema 42 Modificación selectiva de unidades de ácido glutámico.

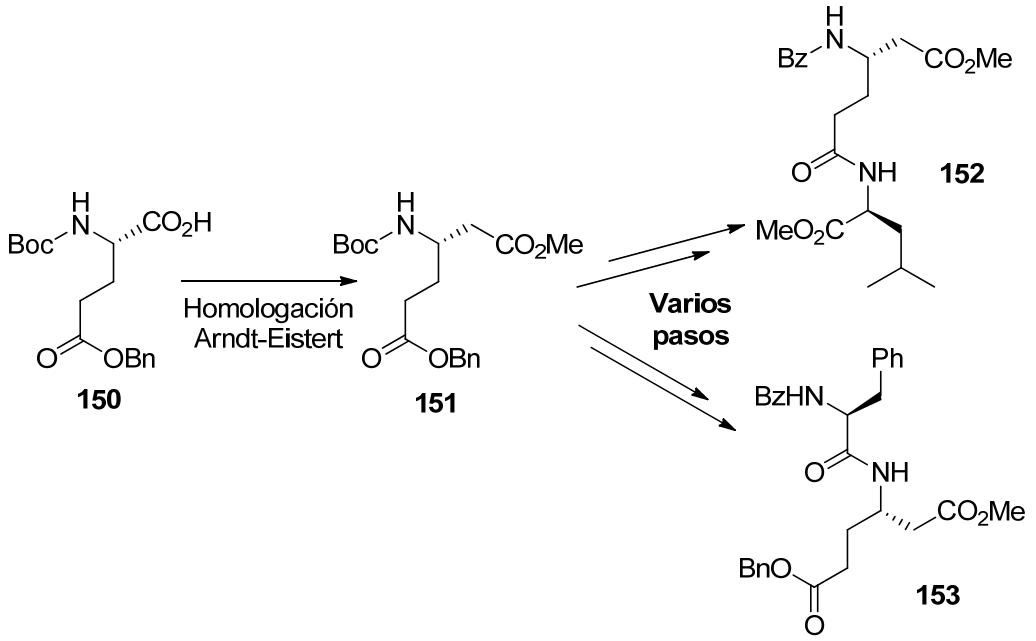
Como en los casos anteriores, la descarboxilación radicalaria genera un *C*-radical **144a**. Este radical es oxidado en el medio de reacción al intermedio **144b** que puede ser atrapado por nucleófilos de carbono. Así, desde un único péptido inicial **144** se puede preparar numerosos derivados de α,γ-péptidos **145** de alto valor añadido.

El proceso de escisión–alquilación fue estudiado primero en derivados de ácido glutámico para optimizar las condiciones de reacción. A continuación este proceso se aplicó a péptidos con residuos de glutámico como **146** (Esquema 43). Como en los casos anteriores la descarboxilación radicalaria oxidativa es inducida por tratamiento con DIB y yodo, en presencia de luz visible. En el paso de adición, se usan como nucleófilo sililcetenas o sililenol éteres. De esta manera se obtuvieron α,γ-péptidos híbridos como **147.** De forma similar, se pueden funcionalizar otras posiciones del péptido, como muestra la conversión **148**→**149**.



Esquema 43. Modificación selectiva de unidades de ácido glutámico en péptidos.

Para conocer la configuración de los péptidos híbridos sintetizados, se recurrió a las correlaciones químicas. Se prepararon análogos de estos productos y se compararon los valores de actividad óptica (conversiones **150**→**152** y **150**→**153**, Esquema 44).



Esquema 44. Preparación de análogos de los productos preparados.

Este es el primer trabajo de modificación selectiva de péptidos que permite preparar α,γ-híbridos. El uso de unidades de glutámico para generar diversidad es particularmente interesante, ya que sus grupos carboxilo pueden ser protegidos con diferentes grupos ortogonales. El péptido inicial puede contener varias unidades de glutámico, pero solo la que está desprotegida será modificada.

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Synthesis of α,γ-Peptide Hybrids by Selective Conversion of Glutamic Acid Units

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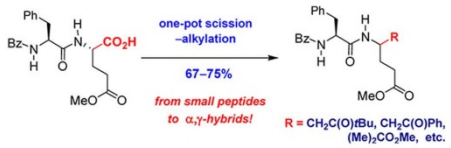
ABSTRACT



The site-selective modification of small peptides at a glutamate residue allows the ready preparation of α,γ-hybrids. In this way, a single peptide can be transformed into a variety of hybrid derivatives. The process takes place under very mild conditions, and good global yields are obtained.

The synthesis of α,γ-peptide hybrids has recently elicited much interest both from the synthetic and the pharmaceutical fields. These peptides display promising antibiotic, antiviral, antihypertensive, antimalaric, and anti-Alzheimer properties.[1] In addition, unlike natural peptides, they are resistant to in vivo degradation.

Thus, pepstatin **1** (Figure 1) is a potent inhibitor of aspartic acid protease and displays antibiotic activity,[1b] while the cyclic peptide **2** acts as an antagonist of the chemokine receptor at nanomolar concentrations and is a promising drug lead for the prevention of tumor metastasis.[1c] Other useful hybrid peptides or peptidomimetics are the antitumorals dolastatin, tamandarin A, and hapalosin, the anti-HIV drug indinavir, etc.[1a]

Traditionally, to obtain collections of these hybrids, each peptide is prepared de novo from the starting α- or γ-amino acids.[1,2] This method is time-consuming and also requires a supply of different and often expensive γ-amino acids.

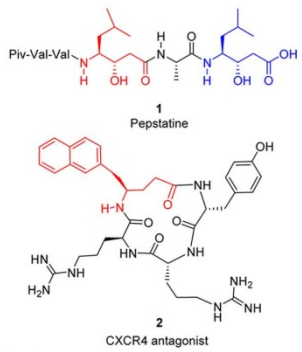


Figure 1. Bioactive α,γ-peptide hybrids.

An attractive alternative would start from a single α, γ-hybrid that could be selectively modified at one residue, converting it into a variety of unnatural γ-amino acids. However, the site-selective modification of peptides is usually very difficult[3] because of the similar reactivity of the amino acid units.[4]

In this work, we report an efficient method for the one-pot conversion of peptides **3** (Scheme 1) containing glutamic

(1) (a) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3–99. (b) Pesenti, C.; Arnone, A.; Bellosta, S.; Bravo, P.; Canavesi, M.; Corradi, E.; Frigerio, M.; Meille, S. V.; Monetti, M.; Panzeri, W.; Viani, F.; Venturini, R.; Zanda, M. *Tetrahedron* **2001**, *57*, 6511–6522. (c) Tamamura, H.; Araki, T.; Ueda, S.; Wang, Z.; Oishi, S.; Esaka, A.; Trent, J. O.; Nakashima, H.; Yamamoto, N.; Peiper, S. C.; Otaka, A.; Fujii, N. *J. Med. Chem.* **2005**, *48*, 3280–3289.

(2) (a) For two representative examples, see: Dai, C. F.; Cheng, F.; Xu, H. C.; Ruan, Y. P.; Huang, P. Q. *J. Comb. Chem.* **2007**, *9*, 386–394. (b) Wipf, P.; Wang, Z. *Org. Lett.* **2007**, *9*, 1605–1607.

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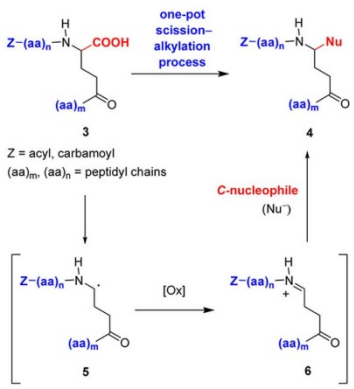
acid residues into α,γ-peptides **4** with unnatural γ-aminoacids. In this transformation, the α-carboxyl group from the glutamic residue is replaced by different alkyl chains. Since the starting peptides **3** are readily available and cheaper than the α,γ-hybrid derivatives **4**, this method allows the preparation of high-value products that can be used as drug leads.

The transformation is achieved using a sequential radical decarboxylation–oxidation–alkylation process.[5] The radical decarboxylation is induced by treatment of the acid **3** (Scheme 1) with (diacetoxyiodo)benzene (DIB) and iodine, in the presence of visible light (sunlight or 80 W tungsten-filament lamps). The initial carboxyl radical undergoes scission to give a *C*-radical **5**. Under the reaction conditions, this radical is oxidized to an acyliminium ion **6**,[6,7] which can be trapped by carbon nucleophiles,[8] forming the α,γ-hybrids **4**.

The scission–alkylation process was studied first using simple glutamic acid derivatives **7**[9a] and **8**[9b,c] (Table 1). Different reaction conditions were tried, and the best results were obtained when the scission step proceeded at room temperature, using a ratio substrate/DIB/I_2 of 1/1.5/0.3, while the addition of the nucleophile was carried out at

Scheme 1



0 °C, using $BF_3 \cdot OEt_2$ as the Lewis acid. The process took place in good yields, affording products **9**–**14**, which present a variety of alkyl chains. Noteworthy, the mild reaction conditions were compatible with acid-labile groups, such as Boc.

The process was then tried with the known dipeptide **15**[10] (Scheme 2), which presents an *N*-terminal glutamate residue. Although side-reactions (such as chain scission) could take place in peptides, the process proceeded in good yield, generating the α,γ-hybrid peptides **16** and **17**. The modified residue is an aspartate analogue and can be used to extend the peptide chain in other direction.

The configuration of dipeptides **16** (*S*) and **17** (*R*) was assigned by chemical correlation to related compounds, as commented later.

Since the reacting position is away from stereogenic centers, a 1:1 mixture of the two possible diastereomers **16** and **17** was formed. The stereoselectivity should improve when the glutamic residue is placed at other positions in the peptide. For instance, in the dipeptide **18** (Scheme 3), the glutamate amino group is attached to a phenylalanine unit, which could act as a chiral auxiliary during the addition step.

In effect, when the decarboxylation–alkylation was carried out, the diastereomeric α,γ-dipeptides **19** and **20** were obtained (dr 2:1, 71% yield).[11] Their configuration was determined as commented later.

The introduction of other alkyl chains also took place satisfactorily (Scheme 4). Using 1-phenyl-1-(trimethylsiloxy)-ethene as the nucleophile, the diastereomeric peptide hybrids **21** and **22** were obtained in 2:1 ratio (75% global yield).

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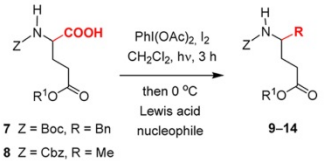
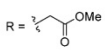
Table 1. One-Pot Scission–Alkylation[a]



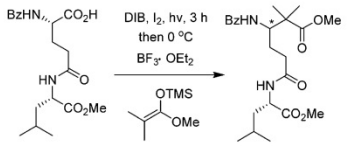
7 Z = Boc, R = Bn
8 Z = Cbz, R = Me

9–14

entry	substrate	nucleophile	product (%)[b]
1	**7**		 **9** (66)
2	**7**		 **10** (68)
3	**8**		 **11** (67)
4	**8**		 **12** (70)
5	**8**		 **13** (73)
6	**8**		R = CH_2-CH=CH_2 **14** (84)

[a] DIB (1.5 equiv), I_2 (0.3 equiv), hν, 25 °C, 3 h; then 0 °C, $BF_3 \cdot OEt_2$ (2 equiv), nucleophile (3 equiv), 0 → 25 °C, 3 h. [b] Yields for products purified by chromatography.

Scheme 2

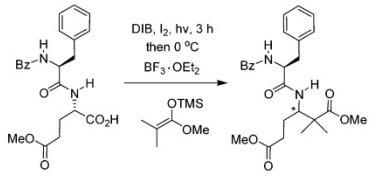


15 **16** (*S*, 37%), **17** (*R*, 35%)

When the reaction was carried out with 1-*tert*-butyl-1-(trimethylsiloxy)ethene as the nucleophile, a separable mixture of dipeptides **23** and **24** was formed (67% overall yield, dr 6:5).

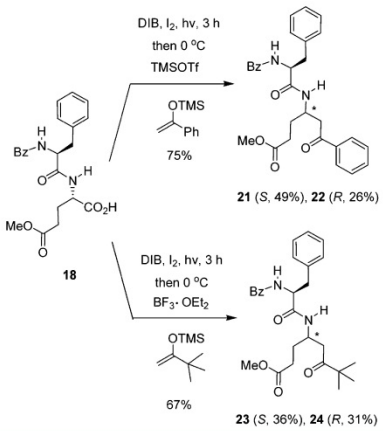
The formation of both diastereomers could be useful in medicinal chemistry studies to determine structure–activity relationships. Therefore, it was necessary to confirm the stereochemistry of both isomers.

Scheme 3



18 **19** (*S*, 48%), **20** (*R*, 23%)

Scheme 4



In order to determine the configuration of the scission–addition products, the solid compounds **21** and **22** were crystallized, but the crystals proved unsuitable for X-ray analysis. Therefore, a chemical correlation with related α,γ-hybrids was explored. Thus, compound **7** underwent the Arndt–Eistert homologation[12] to give compound **25**, which was transformed in four steps into the α,γ-dipeptide **26** (Scheme 5). The $[\alpha]_D$ of this compound ($[\alpha]_D = -48$) was very similar to the optical rotation of compound **16** ($[\alpha]_D = -40$) but quite different than that of compound **17** ($[\alpha]_D = +37$). The other spectroscopic data were also very similar for **26** and **16**. Therefore, we propose the (*S*) configuration for compound **16**.

In a similar way, compound **25** was transformed into compound **27**, precursor of the α,γ-dipeptide **28**, whose optical rotation ($[\alpha]_D = -11$) matches that of compound

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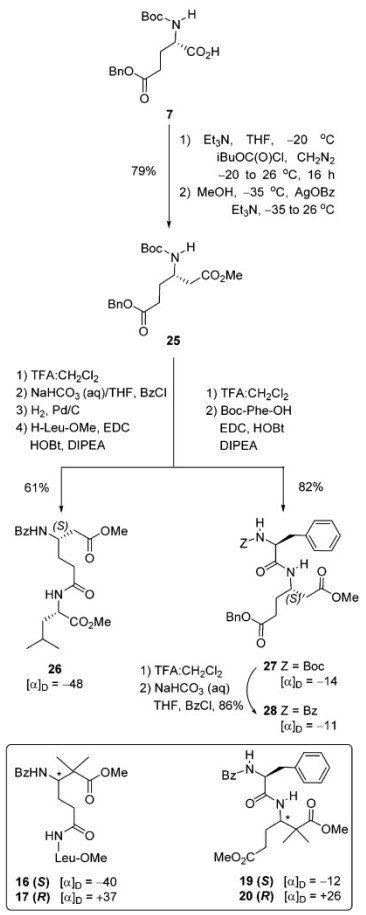
Scheme 5



19 ($[\alpha]_D = -12$) but differs from the one of isomer **20** ($[\alpha]_D = +26$). Compounds **19** and **20** were then assigned the *S* and *R* configurations, respectively.

Finally, compounds **21** and **23** were also assigned the *S* configuration because of the optical and spectroscopical similarities with respect to isomers **19** and **28**.

It should be pointed out that the Arndt–Eistert homologation allows the generation of α-unsubstituted or α-monosubstituted amino esters but not α,α-disubstituted derivatives. In those cases, the present methodology is a useful alternative to the Arndt–Eistert homologation. Moreover, as shown by compounds **21**–**24**, a variety of other alkyl chains can be introduced in a straightforward way.

In summary, the one-pot decarboxylation–alkylation process allows the efficient conversion of peptides with glutamic acid residues into α,γ-peptide hybrids with unnatural γ-amino acids. The process takes place under mild conditions in good yields. From a single peptide a collection of α,γ-peptide hybrids can be obtained in good global yield. Although epimer mixtures are generated, the isomers can be readily separated, which is quite useful to study structure–activity relationships. The dr could also be improved by using chiral catalysts, as will be reported in due course.

Nevertheless, this is the first reported site-selective peptide modification that allows the preparation of α,γ-hybrids. The use of the glutamate unit to generate diversity is particularly interesting. Since the carboxyl group of the glutamic units can be protected with different orthogonal groups, the starting peptide could contain several glutamic residues, but only the unprotected one(s) would be modified. For further modifications, the orthogonal protecting groups could be sequentially removed. The application of this methodology to the synthesis of bioactive or catalytic α,γ-hybrids is very promising.

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Supporting Information Available. Procedures for the synthesis of compounds **9**–**14**, **16**–**28**, the precursors of the scission substrates **30** and **31**, and their ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

Supporting Information

Synthesis of α,γ-Peptide Hybrids by Selective Conversion of Glutamic Acid Units

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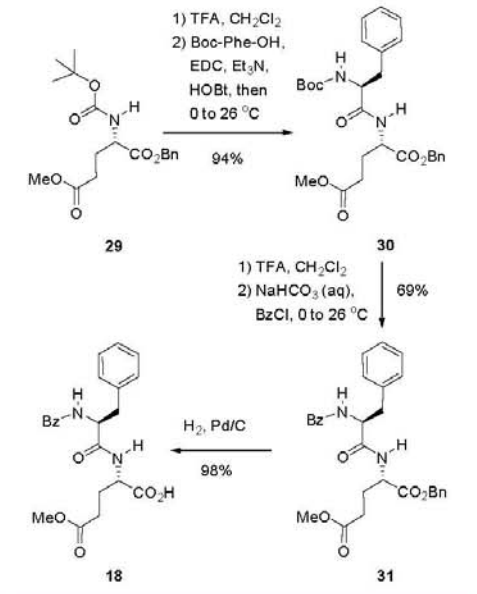
Supporting Information. Procedures for the synthesis of compounds **9–14**, **16–28**, the precursors of the scission substrates **30** and **31**, and their ^{1}H and ^{13}C NMR spectra.

General Methods. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature (26 °C) in $CHCl_3$ solutions. NMR spectra were determined at 500 or 400 MHz for ^{1}H and 125.7 or 100 MHz for ^{13}C in the presence of TMS as internal standard, unless otherwise stated. Mass spectra were determined at 70 eV. Merck silica gel 60 PF_{254} and 60 (0.063–0.2 mm) were used for preparative thin layer chromatography and column chromatography, respectively. All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. Three alternative spray reagents for TLC analysis were used: (a) 0.5% vanillin in H_2SO_4–EtOH (4:1); (b) 0.25% ninhydrin in ethanol; and (c) Fleet's reagent [$Ce(SO_4)_2$ (0.5 g) and ammonium phosphomolybdate hydrate (2.5 g) in H_2SO_4 (5 mL) and water (65 mL)]. Once sprayed, the TLC was heated until development of color. NMR references: $CDCl_3$ (δ_H 7.26; δ_C 77.0).

Synthesis of Substrate 18 for the Scission–alkylation Reaction. Compound **18** was obtained from commercial L-glutamic acid derivative **29**[1] according to Scheme 1.

Scheme 1: Preparation of Substrate **18**



[1] (a) Stolze, S. C.; Meltzer, M.; Ehrmann, M.; Kaiser, M. *Eur. J. Org. Chem.* **2012**, 1616–1625. (b) Koseki, Y.; Yamada, H.; Usuki, T. *Tetrahedron:Asymmetry* **2011**, *22*, 580–586. (c) Kondo, T.; Nekado, T.; Sugimoto, I.; Ochi, K.; Takai, S.; Kinoshita, A.; Hatayama, A.; Yamamoto, S.; Kawabata, K.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2008**, *16*, 190–208. (d) Boudreault, P. L.; Voyer, N. *Org. Biomol. Chem.* **2007**, *5*, 1459–1465 and references cited therein.

1-Benzyl 5-Methyl *N*-(*tert*-Butoxycarbonyl)-L-phenylalanyl-L-glutamate (30): A solution of the glutamate **29**[1] (3.40 g, 9.69 mmol) was dissolved in 1:1 TFA:CH_2Cl_2 (20 mL) at 0 °C and stirred for 2 h while allowed to slowly reach 26 °C. Then the solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (25 mL). The solution was treated with *N*-(*tert*-butoxycarbonyl)-L-phenylalanine (2.57 g, 9.69 mmol), and cooled to 0 °C. Afterwards, Et_3N (3.4 mL, 24.4 mmol), EDC (2.04 g, 10.65 mmol) and HOBt hydrate (1.44 g, 10.65 mmol) were added. The mixture was stirred for 2 h at 0 °C, allowed to reach 26 °C and stirred for other 16 h. Then it was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried on anhydrous Na_2SO_4, filtered and evaporated under vacuum, and the residue was purified by column chromatography (hexanes/EtOAc, 70:30) affording the dipeptide **30** (4.55 g, 94%) as a crystalline solid; mp 103–104 °C (EtOAc/ hexane); $[\alpha]_D$ −5 (0.58, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3425, 3030, 1736, 1680, 1495 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.40 (9H, s), 1.95 (1H, m), 2.16–2.34 (3H, m), 3.05 (2H, br d, *J* = 6.6 Hz), 3.64 (3H, s), 4.33 (1H, m), 4.60 (1H, ddd, *J* = 5.0, 7.8, 7.9 Hz), 4.97 (1H, br b), 5.11 (1H, d, *J* = 12.0 Hz), 5.16 (1H, d, *J* = 12.3 Hz), 6.57 (1H, br d, *J* = 7.6 Hz), 7.18 (2H, d, *J* = 7.3 Hz), 7.21 (1H, dd, *J* = 7.3, 7.5 Hz), 7.26 (2H, dd, *J* = 7.3, 7.6 Hz), 7.30–7.39 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 27.3 (CH_2), 28,2 (3 × CH_3), 29.7 (CH_2), 38.1 (CH_2), 51.7 (CH + CH_3), 55.8 (CH), 67.3 (CH_2), 80.3 (C), 127.0 (CH), 128.3 (2 × CH), 128.5 (CH), 128.6 (2 × CH), 128.7 (2 × CH), 129.3 (2 × CH), 135.1 (C), 136.4 (C), 171.1 (C), 171.2 (C), 173.1 (C). The signal corresponding to the carbamate carbonyl was not clearly observed; MS (EI) *m/z* (rel intensity) 499 (M^+ + H, < 1), 307 (M^+ + H − [CO_2CH_2Ph − CMe_3], 40), 91 ($[PhCH_2]^+$, 100), 57 ($[CMe_3]^+$, 59); HRMS calcd for $C_{27}H_{35}N_2O_7$, 499.2444; found, 499.2426; calcd for $C_{15}H_{19}N_2O_5$, 307.1294; found, 307.1293; calcd for C_7H_7, 91.0548; found, 91.0544; calcd for C_4H_9, 57.0704; found, 57.0706. Anal. Calcd for $C_{27}H_{34}N_2O_7$: C, 65.04; H, 6.87; N, 5.62. Found: C, 65.23; H, 6.72; N, 5.56.

1-Benzyl 5-Methyl *N*-Benzoyl-L-phenylalanyl-L-glutamate (31): A solution of the dipeptide **30** (1.23 g, 2.47 mmol) was dissolved in 1:1 TFA:CH_2Cl_2 (20 mL) at 0 °C and stirred for 2 h while allowed to slowly reach 26 °C. Afterwards, the solvent was removed under vacuum and the residue was dissolved in THF (15 mL) and then a saturated aqueous $NaHCO_3$ solution (15 mL) was added. The mixture was cooled to 0 °C, and benzoyl chloride (430 µL, 3.70 mmol) was added dropwise. The mixture was allowed to reach 26 °C and stirred for 16 h. Then it was cooled to 0 °C, poured into 5% aqueous HCl, and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, dried and evaporated as usual. The residue was purified by chromatography (hexanes/EtOAc, 70:03) giving the dipeptide **31** (856 mg, 69%) as a a crystalline solid; mp 138–139 °C (EtOAc); $[\alpha]_D$ −3 (0.19, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3416, 3020, 1737, 1679, 1656, 1511 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.97 (1H, m), 2.17 (1H, m), 2.22–2.35 (2H, m), 3.15 (1H, dd, *J* = 7.3, 13.9 Hz), 3.22 (1H, dd, *J* = 6.0, 13.9 Hz), 3.58 (3H, s), 4.59 (1H, ddd, *J* = 5.0, 7.6, 7.9 Hz), 4.92 (1H, ddd, *J* = 6.9, 6.9, 6.9 Hz), 5.13 (1H, d, *J* = 12.0 Hz), 5.17 (1H, d, *J* = 12.3 Hz), 6.77 (1H, d, *J* = 6.9 Hz), 6.85 (1H, d, *J* = 7.3 Hz), 7.19–7.27 (5H, m), 7.32–7.38 (5H, m), 7.40 (2H, dd, *J* = 7.8, 7.9 Hz), 7.51 (1H, dd, *J* = 7.6, 7.8 Hz), 7.73 (2H, d, *J* = 7.3 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 27.0 (CH_2), 29.7 (CH_2), 38.3 (CH_2), 51.7 (CH_3), 52.0 (CH), 54.7 (CH), 67.3 (CH_2), 127.1 (3 × CH), 128.3 (2 × CH), 128.5 (CH), 128.6 (2 × CH), 128.7 (4 × CH), 129.4 (2 × CH), 131.8 (CH), 133.8 (C), 135.1 (C), 136.3 (C), 167.2 (C), 170.9 (2 × C), 173.1 (C); MS (EI) *m/z* (rel intensity) 502 (M^+, 1), 252 ($[Bz\text{-}NH\text{-}CH(CH_2Ph)\text{-}CO]^+$, 11), 224 ($[Bz\text{-}NH\text{-}CH(CH_2Ph)]^+$, 32), 105 ($[PhCO]^+$, 100), 91 ($[PhCH_2]^+$, 69); HRMS calcd for $C_{29}H_{30}N_2O_6$, 502.2104; found, 502.2092; calcd for $C_{16}H_{14}NO_2$, 252.1025; found, 252.1013; calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1069; calcd for $C_{16}H_{14}NO_2$, 252.1025; found, 252.1013; calcd for C_7H_5O, 105.0340; found, 105.0337; calcd for C_7H_7, 91.0548; found, 91.0544. Anal. Calcd for $C_{29}H_{30}N_2O_6$: C, 69.31; H, 6.02; N, 5.57. Found: C, 69.47; H, 5.88; N, 5.52.

5-Methyl *N*-Benzoyl-L-phenylalanyl-L-glutamate (18): The dipeptide **31** (830 mg, 1.65 mmol) was dissolved in a 3:2 MeOH:THF mixture (25 mL), and then palladium (10% on carbon, 60 mg) was added. The mixture was stirred under hydrogen atmosphere (1 atm) for 6 h, and then was filtered through celite (MeOH). The solvent was removed under vacuum giving the acid **18** (667 mg, 98%) as a syrup: $[\alpha]_D$ −19 (0.21, MeOH); IR ($CHCl_3$) ν_{max} 3411, 3346, 3026, 1733, 1672, 1649, 1518 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.02 (1H, m), 2.22 (1H, m), 2.29–2.42 (2H, m), 3.19 (2H, br d, *J* = 6.4 Hz), 3.57 (3H, s), 4.56 (1H, ddd, *J* = 5.6, 7.1, 7.1 Hz), 5.07 (1H, ddd, *J* = 6.9, 7.1, 7.3 Hz), 7.16 (1H, m), 7.22–7.23 (4H, m), 7.35 (1H, br b), 7.36 (1H, br b), 7.38 (2H, dd, *J* = 7.5, 7.7 Hz), 7.48 (1H, dd, *J* = 7.3, 7.5 Hz), 7.73 (2H, d, *J* = 7.3 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.7 (CH_2), 29.9 (CH_2), 38.2 (CH_2), 51.8 (CH_3), 52.0 (CH), 54.7 (CH), 127.0 (CH), 127.2 (2 × CH), 128.6 (4 × CH), 129.3 (2 × CH), 132.0 (CH), 133.3 (C), 136.1 (C), 167.7 (C), 171.7 (C), 173.4 (C), 173.8 (C); MS (EI) *m/z* (rel intensity) 412 (M^+, < 1), 394 ($M^+ - H_2O$, 3), 224 ($[Bz\text{-}NH\text{-}CH(CH_2Ph)]^+$, 12), 105 ($[PhCO]^+$, 100), 91 ($[PhCH_2]^+$, 27); HRMS calcd for $C_{22}H_{24}N_2O_6$, 412.1634; found, 412.1634; calcd for $C_{22}H_{22}N_2O_5$, 394.1529; found, 394.1536; calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1074; calcd for C_7H_5O, 105.0340; found, 105.0345; calcd for C_7H_7, 91.0548; found, 91.0544. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.05; H, 5.96; N, 7.10.

Studies of the Scission–alkylation reaction: Synthesis of γ-amino acid derivatives 9–14 and α,γ-peptide hybrids 16,17, and 19–24.

Benzyl 4-(*tert*-Butoxycarbonylamino)-6-oxo-6-phenylhexanoate (9). To a solution of the glutamic acid derivative **7**[2] (51 mg, 0.15 mmol) in dry CH_2Cl_2 (6 mL), was added iodine (11 mg, 0.04 mmol) and DIB (72 mg, 0.22 mmol). The reaction mixture was stirred for 3 h at room temperature, under irradiation with visible light (80 W tungsten-filament lamp). Then it was cooled to 0 °C and 1-phenyl-1-(trimethylsilyloxy)ethylene (92 μL, 0.45 mmol) and BF_3•OEt_2 (38 μL, 0.30 mmol) were added dropwise. The mixture was allowed to reach 26 °C and stirred for 3 h. Afterwards, it was poured into a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by rotatory chromatography (hexanes/EtOAc, 80:20), giving the phenyl ketone **9** (41 mg, 66 %) as a syrup; IR ($CHCl_3$) ν_{max} 3439, 3091, 3067, 1729, 1706, 1498, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.40 (9H, s), 1.92– 2.04 (2H, m), 2.48 (2H, ddd, J = 3.3, 7.3, 7.6 Hz), 3.14 (1H, dd, J = 6.0, 17.0 Hz), 3.32 (1H, d, J = 15.8, Hz), 4.08 (1H, ddddd, J = 4.9, 4.9, 4.9, 10.4, 10.4 Hz), 5.10 (2H, s), 5.17 (1H, br b), 7.30–7.37 (5H, m), 7.46 (2H, dd, J = 7.6, 7.9 Hz), 7.57 (1H, dd, J = 7.3, 7.6 Hz), 7.93 (2H, d, J = 7.3 Hz); NMR ^{13}C (125.7 MHz, $CDCl_3$) δ_C 28.3 (3 × CH_3), 29.7 (CH_2), 31.3 (CH_2), 42.8 (CH_2), 47.5 (CH), 66.3 (CH_2), 79.3 (C), 128.0 (2 × CH), 128.2 (2 × CH), 128.5 (2 × CH), 128.6 (3 × CH), 133.3 (CH), 135.9 (C), 136.9 (C), 155.4 (C), 173.1 (C), 198.7 (C); MS (EI) ***m/z*** (rel intensity) 411 (M^+, <1), 310 ($M^+ - CO_2CMe_3$, 18), 220 ($M^+ + H - [OCH_2Ph + CO_2CMe_3]$, 9), 192 ($M^+ + H - [CO_2CMe_3 + CH_2COPh]$, 8), 105 ($[COPh]^+$, 72), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{24}H_{29}NO_5$, 411.2046; found, 411.2033; calcd for $C_{19}H_{29}NO_3$, 310.1443; found, 310.1436; calcd for $C_{12}H_{14}NO_3$, 220.0974; found, 220.0972; calcd for $C_{11}H_{14}NO_2$, 192.1025; found, 192.1024; calcd for C_7H_5O, 105.0340; found, 105.0339; calcd for C_7H_7, 91.0548; found, 91.0550. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.23; H, 7.13; N, 3.18.

Cyclohexanone derivative 10. Obtained from compound **7** (51 mg, 0.15 mmol) according to the scission–alkylation procedure, using 1-(trimethylsilyloxy)-1-cyclohexene (88 μL, 0.45 mmol) as the nucleophile. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 70:30), affording the cyclohexanone derivative **10** (40 mg, 68%) as a syrup; IR ($CHCl_3$) ν_{max} 3440, 3091, 3069, 1728, 1705, 1498, 1452, 1235, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.21 – 1.33 (2H, m), 1.41 (9H, s), 1.61–1.74 (2H, m), 1.83–1.92 (2H, m), 1.95–2.08 (2H, m), 2.22–2.51 (5H, m), 3.64–3.70 (1H, m), 5.11 (2H, s), 5.12/5.17 (1H, d, J = 7.8/9.8 Hz), 7.30–7.88 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 24.7/24.9 (CH_2), 25.9/30.8 (CH_2), 27.2/28.0 (CH_2), 28.3/28.3 (3 × CH_3), 29.3/29.6 (CH_2), 31.3/32.2 (CH_2), 42.4/42.9 (CH_2), 50.8/51.4 (CH), 54.6/54.9 (CH), 66.2/66.2 (CH_2), 79.0/79.1 (C), 128.1/128.1 (CH), 128.2/1282 (2 × CH), 128.5128.5 (2 × CH), 136.0/136.0 (C), 155.7/156.1 (C), 173.1/173.2 (C), 212.3/213.1 (C); MS (EI) ***m/z*** (rel intensity) 333 ($M^+ + H - CMe_3$, 1), 316 ($M^+ - OCMe_3$, 2), 288 ($M^+ - CO_2CMe_3$, 19), 192 ($M^+ + H - [CO_2CMe_3$ + cyclohexanone], 29), 91 ($[CH_2\text{-}Ph]^+$, 100), 57 ($[CMe_3]^+$, 65); HRMS calcd for $C_{18}H_{23}NO_5$, 333.1576; found, 333.1575; calcd for $C_{18}H_{22}NO_4$, 316.1549; found, 316.1534; calcd for $C_{17}H_{22}NO_3$, 288.1600; found, 288.1610; calcd for $C_{11}H_{14}NO_2$, 192.1025; found, 192.1020; calcd for C_7H_7, 91.0548; found, 91.0551; calcd for C_4H_9, 57.0704; found, 57.0715. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.96; H, 7.78; N, 3.67.

Methyl 3-(Benzyloxycarbonylamino)-6-oxo-6-*tert*-butylhexanoate (11). Obtained from compound **8**[3] (45 mg, 0.15 mmol) according to the scission–alkylation procedure, using 1-butyl-1-(trimethylsilyloxy)ethene (97 μL, 0.45 mmol) as the nucleophile. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 85:15, affording the *t*-butyl ketone **11** (35 mg, 67%) as a syrup; IR ($CHCl_3$) ν_{max} 3432, 3066, 1718, 1506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.10 (9H, s), 1.80 (1H, m), 1.91 (1H, m), 2.37 (2H, dd, J = 7.3, 7.6 Hz), 2.66 (1H, dd, J = 6.0, 17.7 Hz), 2.89 (1H, dd, J = 4.1, 17.6 Hz), 3.63 (3H, s), 3.94 (1H, m), 5.06 (2H, s), 5.43 (1H, d, J = 8.5 Hz), 7.28–7.38 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.1 (3 × CH_3), 29.0 (CH_2), 31.1 (CH_2), 40.6 (CH_2), 44.3 (C), 47.8 (CH), 51.6 (CH_3), 66.5 (CH_2), 128.0 (3 × CH), 128.4 (2 × CH), 136.5 (C), 155.9 (C), 173.7 (C), 214.8 (C); MS (EI) ***m/z*** (rel intensity) 349 (M^+, <1), 292 ($M^+ - CMe_3$, 15), 214 ($M^+ - C(O)OCH_2Ph$, 40), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{19}H_{27}NO_5$, 349.1889; found, 349.1887; calcd for $C_{15}H_{18}NO_5$, 292.1185; found, 292.1189; calcd for $C_{11}H_{20}NO_3$, 214.1443; found, 214.1438; calcd for C_7H_7, 91.0548; found, 91.0545. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.65; H, 7.64; N, 4.13.

Methyl 4-(Benzyloxycarbonylamino)-5,5-dimethyl-6-oxohexanoate (12). Obtained from compound **8** (45 mg, 0.15 mmol) according to the scission–alkylation procedure, using 2-methyl-1-(trimethylsilyloxy)-1-propene (83 μL, 0.45 mmol) as the nucleophile. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 85:15, affording the aldehyde **12** (34 mg, 70%) as a syrup; IR ($CHCl_3$) ν_{max} 3433, 3089, 3021, 1725, 1508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.08 (3H, s), 1.10 (3H, s),

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1.62 (1H, m), 1.86 (1H, dddd, J = 2.9, 7.3, 7.6, 14.5 Hz), 2.38 (2H, dd, J = 7.3, 7.6 Hz), 3.62 (3H, s), 3.85 (1H, ddd, J = 2.5, 9.6, 11.9 Hz), 4.92 (1H, d, J = 10.4 Hz), 5.05 (1H, d, J = 12.0 Hz), 5.09 (1H, d, J = 12.3 Hz), 7.29–7.36 (5H, m), 9.48 (1H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 18.7 (CH_3), 19.0 (CH_3), 25.6 (CH_2), 30.9 (CH_2), 50.3 (C), 51.7 (CH_3), 55.2 (CH), 66.9 (CH_2), 128.0 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.3 (C), 156.5 (C), 173.7 (C), 204.7 (CH); MS (EI) *m/z* (rel intensity) 321 (M^+, <1), 250 ($M^+ - CMe_2CHO$, 24), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{17}H_{23}NO_5$, 321.1576; found, 321.1577; calcd for $C_{13}H_{16}NO_4$, 250.1079; found, 250.1086; calcd for C_7H_7, 91.0548; found, 91.0551. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.81; H, 7.26; N, 4.20.

Dimethyl 3-(Benzyloxycarbonylamino) hexadionoate (13).[4] Obtained from compound **8** (45 mg, 0.15 mmol) according to the scission–alkylation procedure, using 1-(*tert*butyldimethylsilyloxy)-1-(methoxy)ethene (98 µL, 0.45 mmol) as the nucleophile. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 60:40), affording the ester derivative **13** (35 mg, 73%) as a syrup; IR ($CHCl_3$) ν_{max} 3430, 3090, 3066, 1730, 1509 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.88 (2H, ddd, J = 6.6, 7.3, 7.6 Hz), 2.39 (2H, dd, J = 7.3, 7.6 Hz), 2.54–2.60 (2H, m), 3.64 (3H, s), 3.66 (3H, s), 4.00 (1H, m), 5.08 (2H, s), 5.32 (1H, br d, J = 8.8 Hz), 7.29–7.37 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 29.3 (CH_2), 30.8 (CH_2), 38.9 (CH_2), 47.7 (CH), 51.6 (CH_3), 51.7 (CH_3), 66.6 (CH_2), 127.9 (CH), 128.0 (2 × CH), 128.4 (2 × CH), 136.4 (C), 155.8 (C), 171.6 (C), 173.5 (C); MS (EI) *m/z* (rel intensity) 323 (M^+, <1), 188 ($M^+ - OCOCH_2Ph$, 13), 91 ($[CH_2Ph]^+$, 100); HRMS calcd for $C_{16}H_{21}NO_6$, 323.1369; found, 323.1358; calcd for $C_8H_{14}NO_4$, 188.0923; found, 188.0926; calcd for C_7H_7, 91.0548; found, 91.0548. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.12; H, 6.44; N, 4.56.

Methyl 4-(Benzyloxycarbonylamino)hept-6-enoate (14). Obtained from compound **8** (45 mg, 0.15 mmol) according to the scission–alkylation procedure, using allyltrimethylsilane (72 µL, 0.45 mmol) as the nucleophile. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 80:20), affording the allyl derivative **14** (37 mg, 84%) as a syrup. IR ($CHCl_3$) ν_{max} 3434, 3020, 1722, 1513 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.70 (1H, m), 1.89 (1H, m), 2.20–2.29 (2H, m), 2.39 (2H, dd, J = 7.3, 7.6 Hz), 3.64 (3H, s), 3.73 (1H, m), 4.63 (1H, br d, J = 7.9 Hz), 5.06–5.10 (4H, m), 5.76 (1H, m), 7.28–7.40 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 29.6 (CH_2), 30.8 (CH_2), 39.7 (CH_2), 50.5 (CH), 51.6 (CH_3), 66.6 (CH_2), 118.3 (CH_2), 128.0 (CH), 128.1 (2 × CH), 128.5 (2 × CH), 133.7 (CH), 136.5 (C), 156.0 (C), 173.9 (C); MS (EI) *m/z* (rel intensity) 292 (M^+ + H, <1), 250 ($M^+ - CH_2CH{=}CH_2$, 20), 91 ($[CH_2Ph]^+$, 100), 77 ($[Ph]^+$, 11); HRMS calcd for $C_{16}H_{22}NO_4$, 292.1549; found, 292.1550; calcd for $C_{13}H_{16}NO_4$, 250.1079; found, 250.1089; calcd for C_7H_7, 91.0548; found 91.0549; calcd for C_6H_5, 77.0391; found, 77.0392. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.69; H, 7.18; N, 4.71.

α,γ-Dipeptides 16 and 17. A solution of substrate **15**[5] (76 mg, 0.2 mmol) in dry CH_2Cl_2 (8 mL) was treated with iodine (15 mg, 0.06 mmol) and DIB (97 mg, 0.3 mmol). The mixture was stirred for 3 h at room temperature, under irradiation with visible light (80 W tungsten-filament lamp). Then it was cooled to 0 °C and 2,2-dimethyl-1-methoxy-1-(trimethylsilyloxy)ethene (202 µL, 174 mg, 1 mmol) and $BF_3{\bullet}OEt_2$ (51 µL, 0.4 mmol) was added dropwise. The mixture was allowed to reach 26 °C and stirred for 3 h. Afterwards, it was poured into a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by rotatory chromatography (hexanes/EtOAc, 60:40) and afterwards by HPLC (3 mL/min, hexanes/EtOAc, 55:45) giving peptide-α,γ **16** (32 mg, 37%) and **17** (30 mg, 35%).

Peptide **16**: Syrup; $[\alpha]_D$ −40 (0.19, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3423, 3020, 1740, 1711, 1664, 1519 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.95 (6H, d, J = 6.6 Hz), 1.28 (3H, s), 1.29 (3H, s), 1.59–1.69 (3H, m), 1.73 (1H, m), 2.10 (1H, m), 2.30 (2H, dd, J = 6.6, 6.9 Hz), 3.67 (3H, s), 3.73 (3H, s), 4.14 (1H, dd, J = 10.0, 11.7 Hz), 4.57 (1H, ddd, J = 6.0, 8.2, 8.2 Hz), 6.65 (1H, br d, J = 5.7 Hz), 7.23 (1H, br d, J = 10.1 Hz), 7.46 (2H, dd, J = 7.3, 7.9 Hz), 7.52 (1H, dd, J = 7.3, 7.6 Hz), 7.82 (2H, d, J = 8.8 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 21.8 (CH_3), 22.9 (CH_3), 23.0 (CH_3), 24.7 (CH), 25.0 (CH_3), 27.1 (CH_2), 33.3 (CH_2), 41.4 (CH_2), 45.9 (C), 50.9 (CH), 52.1 (CH_3), 52.2 (CH_3), 56.2 (CH), 127.0 (2 × CH), 128.7 (2 × CH), 131.7 (CH), 134.0 (C), 167.7 (C), 172.4 (C), 173.3 (C), 177.6 (C); MS (EI) *m/z* (rel intensity) 435 (M^+ + H, 2), 434 (M^+, 1), 333 ($M^+ - C(Me)_2CO_2Me$, 13), 290 (M^+ + H − H-Leu-OMe, 14), 212 ($M^+ - [C(Me)_2CO_2Me + NH_2COPh]$, 50), 105 ($[COPh]^+$, 100); HRMS calcd for $C_{23}H_{35}N_2O_6$, 435.2495; found, 435.2515; calcd for $C_{23}H_{34}N_2O_6$, 434.2417; found, 434.2425; calcd for $C_{18}H_{25}N_2O_4$, 333.1814; found, 333.1801; calcd for $C_{16}H_{20}NO_4$, 290.1392; found, 290.1401; calcd for $C_{11}H_{18}NO_3$, 212.1287; found, 212.1289; calcd for C_7H_5O, 105.0340; found, 105.0345. Anal. Calcd for $C_{23}H_{34}N_2O_6$: C, 63.57; H, 7.89; N, 6.45. Found: C, 63.67; H, 7.83; N, 6.17.

Peptide **17**: Syrup; $[\alpha]_D$ + 37 (0.28, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3423, 3006, 1740, 1711, 1662, 1519 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.89 (3H, d, J = 6.0 Hz),

[4] Compound **13** is known, but its spectroscopic data were not described: Burgess, L. F. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859.

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0.93 (3H, d, J = 6.2 Hz), 1.32 (3H, s), 1.33 (3H, s), 1.58–1.75 (4H, m), 2.09 (1H, m), 2.26–2.31 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 4.36 (1H, br dd, J = 9.9, 11.0 Hz), 4.49 (1H, m), 7.36 (1H, br b), 7.46 (1H, br b), 7.47 (2H, dd, J = 7.0, 7.6 Hz), 7.53 (1H, dd, 7.2, 7.3 Hz), 7.84 (2H, d, J = 7.3 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 21.8 (CH_3), 22.8 (CH_3), 23.0 (CH_3), 25.0 (CH + CH_3), 27.5 (CH_2), 33.3 (CH_2), 40.9 (CH_2), 45.9 (C), 51.2 (CH), 52.1 (CH_3), 52.2 (CH_3), 56.2 (CH), 127.0 (2 × CH), 128.7 (2 × CH), 131.8 (CH), 134.0 (C), 167.9 (C), 173.0 (C), 173.6 (C), 178.0 (C); MS (EI) *m/z* (rel intensity) 434 (M^+, 2), 333 (M^+ – $C(Me)_2CO_2Me$, 12), 290 (M^+ – H-Leu-OMe, 13), 212 (M^+ – [$C(Me)_2CO_2Me$ + NH_2COPh], 43), 105 ([COPh]$^+$, 100); HRMS calcd for $C_{23}H_{34}N_2O_6$, 434.2417; found, 434.2398; calcd for $C_{18}H_{25}N_2O_4$, 333.1814; found, 333.1818; calcd for $C_{16}H_{20}NO_4$, 290.1392; found, 290.1382; calcd for $C_{11}H_{18}NO_3$, 212.1287; found, 212.1280; calcd for C_7H_5O, 105.0340; found, 105.0342. Anal. Calcd for $C_{23}H_{34}N_2O_6$: C, 63.57; H, 7.89; N, 6.45. Found: C, 63.33; H, 7.79; N, 6.14.

α,γ-Dipeptides 19 and 20. Obtained from compound **18** (82 mg, 0.2 mmol) according to the scission –alkylation procedure, using 2,2-dimethyl-1-methoxy-1-(trimethylsilyloxy)ethene (202 μL, 1 mmol) as the nucleophile and BF_3•OEt_2 (51 μL, 0.4 mmol) as the Lewis acid. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 65:35), affording the α,γ-peptides 19 (45 mg, 48%) and **20** (22 mg, 23%).

Compound 19. Syrup; $[\alpha]_D$ −12 (0.36, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3422, 3025, 1731, 1661, 1511, 1483 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.98 (3H, s), 1.16 (3H, s), 1.47 (1H, m), 1.89 (1H, dddd, J = 2.8, 7.9, 8.0, 12.9 Hz), 2.20–2.35 (2H, m), 3.18 (1H, dd, J = 7.6, 13.9 Hz), 3.24 (1H, dd, J = 6.6, 13.9 Hz), 3.58 (6H, s), 3.95 (1H, m), 4.89 (1H, ddd, J = 6.6, 7.6, 7.6 Hz), 6.63 (1H, br d, J = 10.1 Hz), 6.70 (1H, br d, J = 7.3 Hz), 7.20–7.35 (5H, m), 7.42 (2H, dd, J = 7.3, 7.9 Hz), 7.50 (1H, dd, J = 6.5, 7.0 Hz), 7.72 (2H, d, J = 6.9 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 23.2 (2 × CH_3), 26.0 (CH_2), 30.8 (CH_2), 37.9 (CH_2), 45.9 (C), 51.5 (CH_3), 51.9 (CH_3), 55.2 (CH), 55.3 (CH), 127.0 (2 × CH), 127.1 (CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.3 (2 × CH), 131.8 (CH), 133.8 (C), 136.4 (C), 167.4 (C), 171.1 (C), 173.7 (C), 176.8 (C); MS (EI) *m/z* (rel intensity) 468 (M^+, 1), 377 (M^+ – CH_2Ph, 2), 252 ([BzNH-CH(CO)CH_2Ph]$^+$, 5) 224 ([BzNH=$CHCH_2Ph$]$^+$, 16), 105 ([COPh]$^+$, 100), 91 ([CH_2Ph]$^+$, 88); HRMS calcd for $C_{26}H_{32}N_2O_6$, 468.2260; found, 468.2270; calcd for $C_{19}H_{25}N_2O_6$, 377.1713; found, 377.1727; calcd for $C_{16}H_{14}NO_2$, 252.1025; found, 252.1025; calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1081; calcd for C_7H_5O, 105.0340; found, 105.0344; calcd for C_7H_7, 91.0548; found, 91.0545. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.84; H, 6.86; N, 5.85.

Compound 20. Syrup; $[\alpha]_D$ +26 (0.13, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3421, 1734, 1673, 1656, 1509 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.10 (3H, s), 1.16 (3H, s), 1.30 (1H, m), 1.86 (1H, m), 2.08 (1H, ddd, J = 5.3, 9.1, 15.0 Hz), 2.15 (1H, ddd, J = 7.2, 8.9, 16.4 Hz), 3.15 (1H, dd, J = 8.3, 13.7 Hz), 3.27 (1H, dd, J = 6.3, 13.8 Hz), 3.59 (3H, s), 3.68 (3H, s), 3.92 (1H, ddd, J = 2.4, 10.5, 10.8 Hz), 4.87 (1H, ddd, J = 6.2, 6.3, 8.1 Hz), 6.43 (1H, br d, J = 10.2 Hz), 6.80 (1H, br d, J = 7.7 Hz), 7.23–7.30 (5H, m), 7.43 (2H, dd, J = 7.8, 8.0 Hz), 7.51 (1H, dd, J = 7.4, 7.5 Hz), 7.73 (2H, d, J = 7.1 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 23.1 (CH_3), 23.3 (CH_3), 26.1 (CH_2), 30.9 (CH_2), 38.2 (CH_2), 46.0 (C), 51.7 (CH_3), 52.0 (CH_3), 55.2 (2 × CH), 127.0 (2 × CH), 127.1 (CH), 128.5 (2 × CH), 128.9 (2 × CH), 129.4 (2 × CH), 131.9 (CH), 133.8 (C), 136.7 (C), 167.3 (C), 171.0 (C), 173.7 (C), 176.7 (C); MS (EI) *m/z* (rel intensity) 468 (M^+, 3), 377 (M^+ – CH_2Ph, 4), 252 ([BzNH-CH(CO)CH_2Ph]$^+$, 12) 224 ([BzNH=$CHCH_2Ph$]$^+$, 31), 105 ([COPh]$^+$, 100), 91 ([CH_2Ph]$^+$, 9); HRMS calcd for $C_{26}H_{32}N_2O_6$, 468.2260; found, 468.2252; calcd for $C_{19}H_{25}N_2O_6$, 377.1713; found, 377.1694; calcd for C_7H_5O, 105.0340; found, 105.0338; calcd for C_7H_7, 91.0548; found, 91.0546. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.32; H, 6.80; N, 5.68.

α,γ-Dipeptides 21 and 22. Obtained from compound **18** (82 mg, 0.2 mmol) according to the scission –alkylation procedure, using 1-phenyl-1-(trimethylsilyloxy)-1-ethene (205 μL, 1 mmol) as the nucleophile and TMSOTf (72 μL, 0.4 mmol) as the Lewis acid. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 65:35), affording the α,γ-peptides **21** (48 mg, 49%) and **22** (25 mg, 26%).

Compound 21. Crystalline solid; mp 136–137 °C (EtOAc/hexane); $[\alpha]_D$ −5 (0.62, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3416, 1731, 1677, 1655, 1510, 1483 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.82–1.91 (2H, m), 2.26–2.35 (2H, m), 2.78 (1H, dd, J = 6.3, 17.3 Hz), 3.03 (1H, dd, J = 8.5, 13.6 Hz), 3.19 (1H, dd, J = 3.9, 17.0 Hz), 3.26 (1H, dd, J = 5.7, 13.6 Hz), 3.57 (3H, s), 4.31 (1H, m), 4.83 (1H, ddd, J = 6.0, 8.2, 8.2 Hz), 6.70 (1H, br d, J = 7.9 Hz), 6.96 (1H, br d, J = 7.6 Hz), 7.02 (1H, dd, J = 7.3, 7.3 Hz), 7.16 (2H, dd, J = 7.3,7.9 Hz), 7.22 (2H, d, J = 7.3 Hz), 7.42 (2H, dd, J = 7.3, 7.9 Hz), 7.47 (2H, dd, J = 7.9, 7.9 Hz), 7.50 (1H, dd, J = 7.6, 8.3 Hz), 7.58 (1H, dd, J = 7.3, 7.6 Hz), 7.77 (2H, d, J = 7.0 Hz), 7.87 (2H, d, J = 7.2 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 28.6 (CH_2), 30.8 (CH_2), 38.8 (CH_2), 42.0 (CH_2), 46.1 (CH), 51.7 (CH_3), 55.2 (CH), 127.0 (CH), 127.1 (2 × CH), 128.1 (2 × CH), 128.5 (2 × CH), 128.6 (4 × CH), 129.3 (2 × CH), 131.7 (CH), 133.5 (CH), 133.8 (C), 136.5 (C), 136.6 (C), 167.0 (C), 170.4 (C), 173.8 (C), 198.1 (C); MS (EI) *m/z* (rel intensity) 486 (M^+, 1), 224 ([BzNH=$CHCH_2Ph$]$^+$, 33), 105 ([COPh]$^+$, 100), 77 ([Ph]$^+$, 69); HRMS calcd for $C_{29}H_{30}N_2O_5$, 486.2155; found, 486.2137; calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1066; calcd for C_7H_5O, 105.0340; found, 105.0338; calcd for C_6H_5, 77.0391; found, 77.0395. Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.65; H, 6.43; N, 5.70.

Compound 22. Crystalline solid; mp 177–178 °C (EtOAc/hexane); $[\alpha]_D$ +17 (0.27, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3420, 3025, 1731, 1675, 1653, 1509 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.75–1.90 (2H, m), 2.14 (1H, ddd, J = 7.6, 7.6, 16.7 Hz), 2.25 (1H, ddd, J = 7.6, 7.9, 16.7 Hz), 3.04 (1H, dd, J = 6.3, 17.0 Hz), 3.13 (1H, dd, J = 7.9, 13.5 Hz), 3.22 (1H, dd, J = 6.0, 13.6 Hz), 3.30 (1H, dd, J = 4.4, 17.0 Hz), 3.63 (3H, s), 4.31 (1H, m), 4.83 (1H, ddd, J = 7.9, 7.9, 7.9 Hz), 6.71 (1H, br d, J = 7.9 Hz), 6.84 (1H, br d, J = 7.6 Hz), 7.21 (1H, dd, J = 7.3, 7.5 Hz), 7.24–7.30 (4H, m), 7.40 (2H, dd, J = 7.3, 8.5 Hz), 7.41 (2H, dd, J = 7.3, 8.4 Hz), 7.49 (1H, dd, J = 7.6, 7.6 Hz), 7.53 (1H, dd, J = 7.3, 7.5 Hz), 7.71 (2H, d, J = 7.9 Hz), 7.86 (2H, d, J = 8.2 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 28.7 (CH_2), 30.7 (CH_2), 38.6 (CH_2), 42.3 (CH_2), 46.5 (CH), 51.7 (CH_3), 55.1 (CH), 127.0 (3 × CH), 128.1 (2 × CH), 128.5 (2 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 129.3 (2 × CH), 131.7 (CH), 133.4 (CH), 133.8 (C), 136.5 (C), 136.6 (C), 167.1 (C), 170.6 (C), 173.7 (C), 198.2 (C); MS (EI) *m/z* (rel intensity) 486 (M^+, <1), 224 ($[BzNH{=}CHCH_2Ph]^+$, 23), 105 ($[COPh]^+$, 100), 77 ($[Ph]^+$, 62); HRMS calcd for $C_{29}H_{30}N_2O_5$, 486.2155; found, 486.2153; calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1068; calcd for C_7H_5O, 105.0340; found, 105.0336; calcd for C_6H_5, 77.0391; found, 77.0389. Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.60; H, 6.44; N, 5.70.

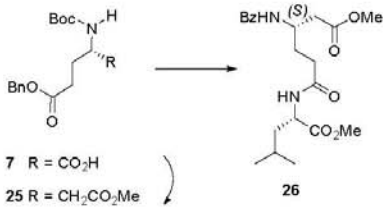
α,γ-Dipeptides 23 and 24. Obtained from compound **15** (82 mg, 0.2 mmol) according to the scission –alkylation procedure, using 1-*tert*-butyl-1-(trimethylsilyloxy)-1-ethene (216 μL, 1 mmol) and BF_3•OEt_2 (51 μL, 0.4 mmol) as the nucleophile and the Lewis acid, respectively. After the extraction and solvent evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 70:30), affording the α,γ-peptides **23** (34 mg, 36%) and **24** (29 mg, 31%).

Compound 23. Syrup; $[\alpha]_D$ +2 (0.27, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3416, 1728, 1705, 1657, 1512, 1483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.06 (9H, s), 1.71 (2H, ddd, J = 7.3, 7.3, 7.6 Hz), 2.20–2.32 (3H, m), 2.73 (1H, dd, J = 4.1, 18.0 Hz), 3.04 (1H, dd, J = 8.5, 13.6 Hz), 3.26 (1H, dd, J = 5.7, 13.6 Hz), 3.59 (3H, s), 4.13 (1H, m), 4.79 (1H, ddd, J = 7.9, 7.9, 8.2 Hz), 6.64 (1H, br d, J = 8.8 Hz), 6.83 (1H, br d, J = 7.6 Hz), 7.20–7.35 (5H, m), 7.43 (2H, dd, J = 7.3, 7.9 Hz), 7.51 (1H, dd, J = 7.6 Hz), 7.76 (2H, d, J = 7.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.1 (3 × CH_3), 28.4 (CH_2), 30.9 (CH_2), 38.7 (CH_2), 40.0 (CH_2), 44.3 (C), 46.0 (CH), 51.7 (CH_3), 55.2 (CH), 127.0 (CH), 127.1 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 129.4 (2 × CH), 131.8 (CH), 133.9 (C), 136.6 (C), 167.0 (C), 170.2 (C), 173.9 (C), 214.8 (CH); MS (EI) *m/z* (rel intensity) 466 (M^+, 1), 409 ($M^+ - CMe_3$, 3), 224 ($[BzNH{=}CHCH_2Ph]^+$, 24), 105 ($[COPh]^+$, 100); HRMS calcd for $C_{27}H_{34}N_2O_5$, 466.2468; found, 466.2484; calcd for $C_{23}H_{25}N_2O_5$, 409.1763; found, 409.1782; calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1080; calcd for C_7H_5O, 105.0340; found, 105.0336; Anal. Calcd for $C_{27}H_{34}N_2O_5$: C, 69.51; H, 7.34; N, 6.00. Found: C, 69.49; H, 7.28; N, 5.79.

Compound 24. Syrup; $[\alpha]_D$ +32 (0.17, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3418, 1731, 1704, 1656, 1511, 1483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.06 (9H, s), 1.65–1.75 (2H, m), 2.08 (1H, ddd, J = 7.0, 7.9, 16.7 Hz), 2.18 (1H, ddd, J = 7.6, 7.9, 16.7 Hz), 2.59 (1H, dd, J = 6.3, 17.7 Hz), 2.79 (1H, dd, J = 4.1, 17.7 Hz), 3.12 (1H, dd, J = 8.2, 13.6 Hz), 3.22 (1H, dd, J = 6.0, 13.6 Hz), 3.65 (3H, s), 4.14 (1H, m), 4.80 (1H, ddd, J = 6.5, 7.6, 7.9 Hz), 6.60 (1H, br b), 6.83 (1H, br b), 7.20–7.35 (5H, m), 7.41 (2H, dd, J = 7.3, 7.9 Hz), 7.50 (1H, dd, J = 7.3, 7.5 Hz), 7.73 (2H, d, J = 8.2 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 26.1 (3 × CH_3), 28.6 (CH_2), 30.8 (CH_2), 38.7 (CH_2), 40.2 (CH_2), 44.3 (C), 46.1 (CH), 51.7 (CH_3), 55.1 (CH), 127.1 (3 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 129.3 (2 × CH), 131.8 (CH), 133.8 (C), 136.5 (C), 167.0 (C), 170.4 (C), 173.7 (C), 214.6 (C); MS (EI) *m/z* (rel intensity) 466 (M^+, 4), 409 ($M^+ - CMe_3$, 10), 252 ($[BzNH{=}CH(CO)CH_2Ph]^+$, 15), 224 ($[BzNH{=}CHCH_2Ph]^+$, 58), 105 ($[COPh]^+$, 100); HRMS calcd for $C_{27}H_{34}N_2O_5$, 466.2468; found, 466.2468; calcd for $C_{23}H_{25}N_2O_5$, 409.1763; found, 409.1744; calcd for $C_{16}H_{14}NO_2$, 252.1025; found, 252.1013; calcd for $C_{15}H_{14}NO$, 224.1075; found, 224.1081; calcd for C_7H_5O, 105.0340; found, 105.0341. Anal. Calcd for $C_{27}H_{34}N_2O_5$: C, 69.51; H, 7.34; N, 6.00. Found: C, 69.69; H, 7.24; N, 5.95.

Chemical correlation studies: preparation of α,γ-hybrids 26–28.

Scheme 2: Preparation of Dipeptides **25** and **26**



Preparation of compound 25 by Arndt-Eistert homologation: To a solution of δ-benzyl *N*-Boc glutamic acid **7** (1.69 g, 5.0 mmol) and triethylamine (730 μL, 5.24 mmol) in dry THF (19 mL), at −20 °C, was added dropwise isobutyl chloroformate (807 μL, 6.22 mmol) and stirred for 30 min. Then, a 0.3 M diazomethane solution in Et_2O (70 mL, 21 mmol) was slowly added and the mixture is stirred for 16 h, while allowed to reach 26 °C. Then AcOH was added until gas evolution finished, and the mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, and the organic layer was

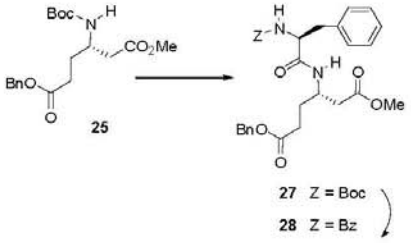
dried on sodium sulfate, filtered and evaporated under vacuum.

The residue was dissolved in dry MeOH (23 mL) and cooled to −35 °C. The reaction flask was covered with aluminium film to avoid exposure to light, and then a solution of AgOBz (121 mg, 0.53 mmol) in recently-distilled Et_3N (1.5 mL) was added. The mixture was stirred for 16 h, allowing it to reach 26 °C, then the solvent was removed under vacuum and the residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated as usual. After purification by column chromatography (Hexanes/EtOAc, 80:20) the amino ester **25** was obtained (1.44 g, 79%) as a crystalline solid; mp 64–65 °C (EtOAc/hexane); $[\alpha]_D$ −13 (0.28, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3436, 1731, 1710, 1502 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.41 (9H, s), 1.81–1.91 (2H, m), 2.44 (2H, dd, J = 7.3, 7.6 Hz), 2.51–2.56 (2H, m), 3.66 (3H, s), 3.94 (1H, m), 5.01 (1H, br d, J = 9.1 Hz), 5.09 (1H, d, J = 12.6 Hz), 5.12 (1H, d, J = 12.3 Hz), 7.30–7.36 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 28.3 (3 × CH_3), 29.4 (CH_2), 31.0 (CH_2), 39.2 (CH_2), 47.1 (CH), 51.6 (CH_3), 66.3 (CH_2), 79.3 (C), 128.2 (3 × CH), 128.5 (2 × CH), 135.8 (C), 155.3 (C), 171.8 (C), 172.9 (C); MS (EI) *m/z* (rel intensity) 309 (M^+ + H − *t*Bu, 4), 264 (M^+ − CO_2*t*Bu, 13), 102 ([CO_2*t*Bu + H]$^+$, 47), 91 ([CH_2Ph]$^+$, 100), 57 ([*t*Bu]$^+$, 79); HRMS calcd for $C_{15}H_{19}NO_6$, 309.1212; found, 309.1197. Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.27; H, 7.27; N, 4.08.

Conversion of the amino ester 25 into the α,γ-dipeptide 26. The amino ester **25** (110 mg, 0.3 mmol) was dissolved in 1:1 TFA:CH_2Cl_2 (4 mL) and stirred for 1.5 h. Then the solvent was removed under vacuum, and replaced by THF (5 mL). The solution was cooled to 0 °C and a saturated aqueous $NaHCO_3$ solution was added (5 mL), followed by BzCl (45 µL, 0.39 mmol). The solution was stirred for 16 h, while allowed to reach 26 °C, then was poured into 5% aqueous HCl, and extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, then brine, and dried and evaporated as usual.

The residue was dissolved in methanol (6 mL), and treated with Pd (10% on carbon, 50 mg) under hydrogen atmosphere (1 atm). The mixture was stirred for 16 h and then filtered through celite. The solvent was evaporated and replaced by CH_2Cl_2 (4 mL)., and then EDC (63 mg, 0.33 mmol) and HOBt (45 mg, 0.33 mmol) were added. After stirring for 10 min, a solution of H-Leu-OMe (54 mg, 0.3 mmol) and DIPEA (103 µL, 0.6 mmol) in CH_2Cl_2 (4 mL) was added. The mixture was stirred for 1.5 h, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. After usual solvent drying and evaporation, the residue was purified by column chromatography (hexanes/EtOAc 40:60) affording the dipeptide **26** (74 mg, 0.18 mmol, 61%) as a crystalline solid; mp 147–148 °C (EtOAc/hexane); $[\alpha]_D$ −48 (0.27, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3431, 1737, 1661, 1520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.90 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 6.3 Hz), 1.50–1.61 (2H, m), 1.65 (1H, m), 1.89–2.03 (2H, m), 2.29–2.42 (2H, m), 2.60 (1H, dd, J = 6.0, 15.8 Hz), 2.69 (1H, dd, J = 5.1, 16.0 Hz), 3.57 (3H, s), 3.66 (3H, s), 4.42 (1H, m), 4.54 (1H, ddd, J = 5.7, 8.5, 9.1 Hz), 6.71 (1H, brd, J = 7.9 Hz), 7.38 (2H, dd, J = 7.9, 8.0 Hz), 7.44 (1H, brd, J = 7.3 Hz), 7.45 (1H, dd, J = 7.5, 7.6 Hz), 7.78 (2H, d, J = 6.9 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 21.8 (CH_3), 22.7 (CH_3), 24.8 (CH), 29.5 (CH_2), 32.9 (CH_2), 38.8 (CH_2), 41.2 (CH_2), 46.6 (CH), 50.8 (CH), 51.7 (CH_3), 52.0 (CH_3), 127.0 (2 × CH), 128.4 (2 × CH), 131.5 (CH), 133.9 (C), 167.1 (C), 172.1 (C), 172.7 (C), 173.3 (C); MS (EI) *m/z* (rel intensity) 406 (M^+, <1), 301 (M^+ − Bz, 9), 220 ([BzNH-CH(CH_2CO_2Me)-CH_2]$^+$, 11), 206 ([BzNHCH-CH_2CO_2Me]$^+$, 3), 105 ([COPh]$^+$, 100), 77 ([Ph]$^+$, 22); HRMS calcd for $C_{21}H_{30}N_2O_6$, 406.2104; found, 406.2120 Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44; N, 6.89. Found: C, 62.17; H, 7.40; N, 7.13.

Scheme 3: Preparation of Dipeptides **27** and **28**

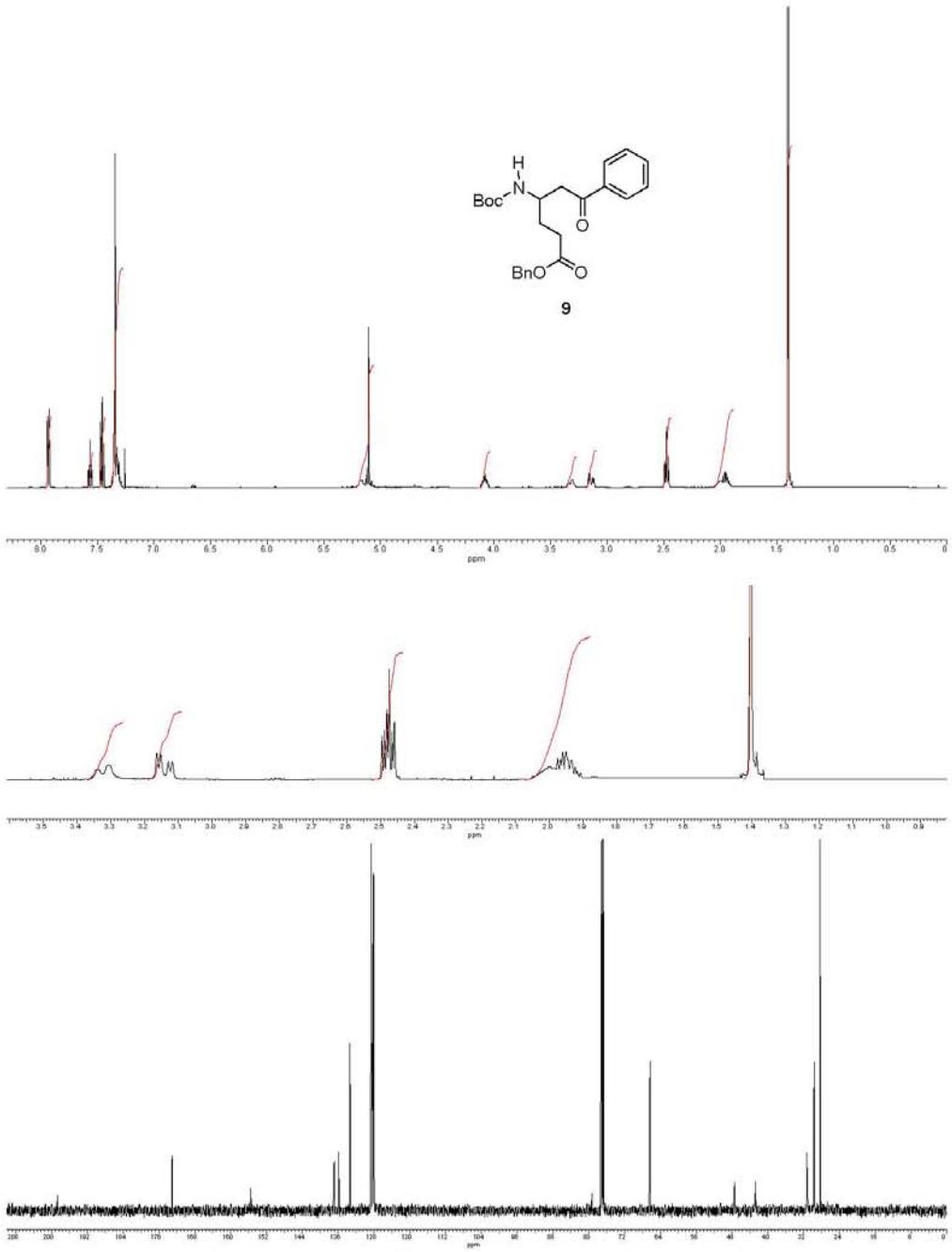


Conversion of the amino ester 25 into dipeptide 27. The amino ester **25** (110 mg, 0.3 mmol) was dissolved in 1:1 TFA:CH_2Cl_2 (4 mL) and stirred for 1.5 h. Then the solvent was removed under vacuum, and replaced by CH_2Cl_2 (4 mL) and DIPEA (103 µL, 0.6 mmol). Then solution was slowly added to a mixture of Boc-Phe-OH (80 mg, 0.3 mmol), EDC (63 mg, 0.33 mmol) and HOBt (45 mg, 0.33 mmol) in CH_2Cl_2 (4 mL). After stirring for 1.5 h, the solution was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine, and the organic layer was dried and evaporated as usual. The residue underwent column chromatography (hexanes/EtOAc 65:35) to give dipeptide **27** (126 mg, 82%) as a crystalline solid; mp 102–103 °C (EtOAc/hexane); $[\alpha]_D$ −14 (0.27, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3424, 1731, 1674, 1495 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.39 (9H, s), 1.75–1.83 (2H, m), 2.23 (1H, br dd, J = 5.4, 16.7 Hz), 2.29–2.37 (2H, m), 2.40 (1H, br dd, J = 5.1, 17.9 Hz), 2.96 (1H, dd, J = 7.6, 13.6 Hz), 3.08 (1H, dd, J = 6.0, 13.6 Hz), 3.61 (3H, s), 4.18 (1H, m), 4.26 (1H, m), 5.04 (1H, br b), 5.07 (1H, d, J = 12.3 Hz), 5.09 (1H, d, J = 12.8 Hz), 6.50 (1H, br d, J = 8.7 Hz), 7.15–7.20 (3H, m), 7.21–7.30 (2H, m), 7.30–7.40 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 28.2 (3 × CH_3), 28.7 (CH_2), 30.8 (CH_2), 38.1 (CH_2), 38.4 (CH_2), 45.2 (CH), 51.6 (CH_3), 56.1 (CH), 66.3 (CH_2), 80.1 (C), 126.8 (CH), 128.2 (3 × CH), 128.5 (2 × CH), 128.6 (2 × CH),

129.3 (2 × CH), 135.8 (C), 136.6 (C), 155.2 (C), 170.7 (C), 171.5 (C), 172.9 (C); MS (EI) *m/z* (rel intensity) 512 (M^+, <1), 264 (M^+ − BocNH-CH(CH_2Ph)-CO, 4), 164 ([$CH_2CH_2CO_2$Bn + H]$^+$, 7), 91 ([CH_2Ph]$^+$, 100); HRMS calcd for $C_{28}H_{36}N_2O_7$, 512.2523; found, 512.2523. Anal. Calcd for $C_{28}H_{36}N_2O_7$: C, 65.61; H, 7.08; N, 5.47. Found: C, 65.81; H, 6.99; N, 5.67.

Conversion of dipeptide 27 into dipeptide 28. Compound **27** (90 mg, 0.18 mmol) was dissolved in 1:1 TFA:CH_2Cl_2 (4 mL) and stirred for 1.5 h. Then the solvent was removed under vacuum, and replaced by THF (5 mL). The solution was cooled to 0 °C and a saturated aqueous $NaHCO_3$ solution was added (5 mL), followed by BzCl (27 μL, 0.23 mmol). The solution was stirred for 16 h, while allowed to reach 26 °C, then was poured into 5% aqueous HCl, and extracted with EtOAc. After usual solvent drying and evaporation, the residue was purified by rotatory chromatography (hexanes/EtOAc, 1:1) to give the α,γ-peptide **28** (78 mg, 0.15 mmol, 86%; 71% global yield from **25**) as a crystalline solid; mp 97–98 °C (EtOAc/hexane); $[\alpha]_D$ −11 (0.22, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3419, 1732, 1655, 1509 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.76–1.85 (2H, m), 2.26 (1H, dd, *J* = 5.7, 16.4 Hz), 2.30–2.36 (2H, m), 2.42 (1H, dd, *J* = 4.7, 16.4 Hz), 3.06 (1H, dd, *J* = 8.2, 13.2 Hz), 3.26 (1H, dd, *J* = 6.0, 13.6 Hz), 3.61 (3H, s), 4.19 (1H, m), 4.79 (1H, ddd, *J* = 5.7, 7.9, 8.2 Hz), 5.02 (1H, d, *J* = 12.3 Hz), 5.06 (1H, d, *J* = 12.3 Hz), 6.50 (1H, br d, *J* = 8.8 Hz), 6.86 (1H, br d, *J* = 7.6 Hz), 7.20–7.32 (10H, m), 7.40 (2H, dd, *J* = 7.9, 8.2 Hz), 7.50 (1H, dd, *J* = 7.3, 7.8 Hz), 7.73 (2H, d, *J* = 7.8 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 28.6 (CH_2), 30.8 (CH_2), 38.1 (CH_2), 38.7 (CH_2), 45.6 (CH), 51.7 (CH_3), 55.2 (CH), 66.4 (CH_2), 127.0 (3 × CH), 128.2 (2 × CH), 128.5 (3 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 129.3 (2 × CH), 131.8 (CH), 133.8 (C), 135.7 (C), 136.6 (C), 167.0 (C), 170.3 (C), 171.5 (C), 172.9 (C); MS (EI) *m/z* (rel intensity) 516 (M^+, 1), 425 (M^+ − Bn, 1), 224 ([BzNH=CHCH_2Ph]$^+$, 13), 105 ([COPh]$^+$, 100), 91 ([CH_2Ph]$^+$, 68); HRMS calcd for $C_{30}H_{32}N_2O_6$, 516.2260; found, 516.2273. Anal. Calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42. Found: C, 69.54; H, 6.09; N, 5.63.

^{1}H and ^{13}C NMR spectra for compounds 9–14, 16–28, 30 and 31



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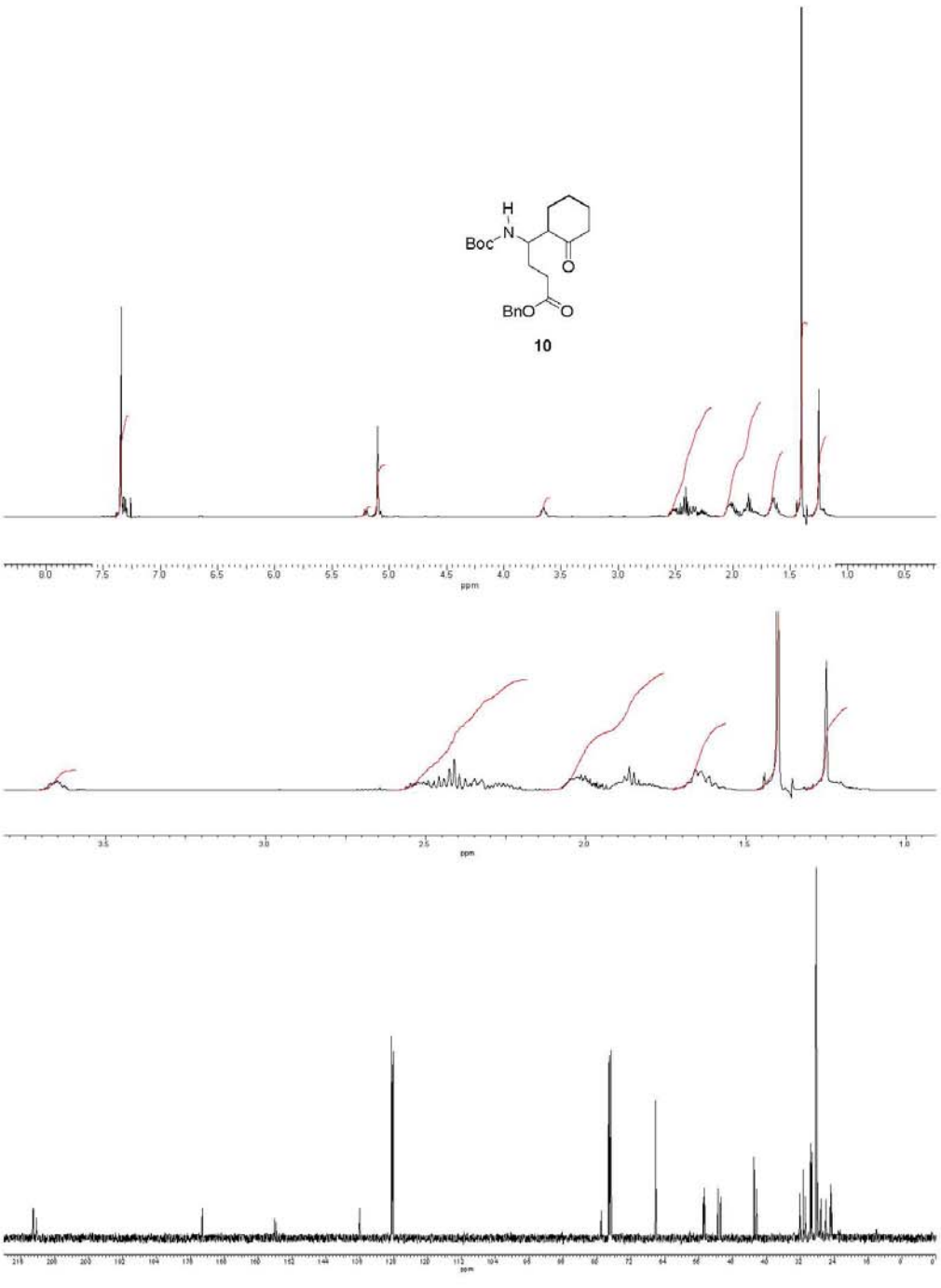
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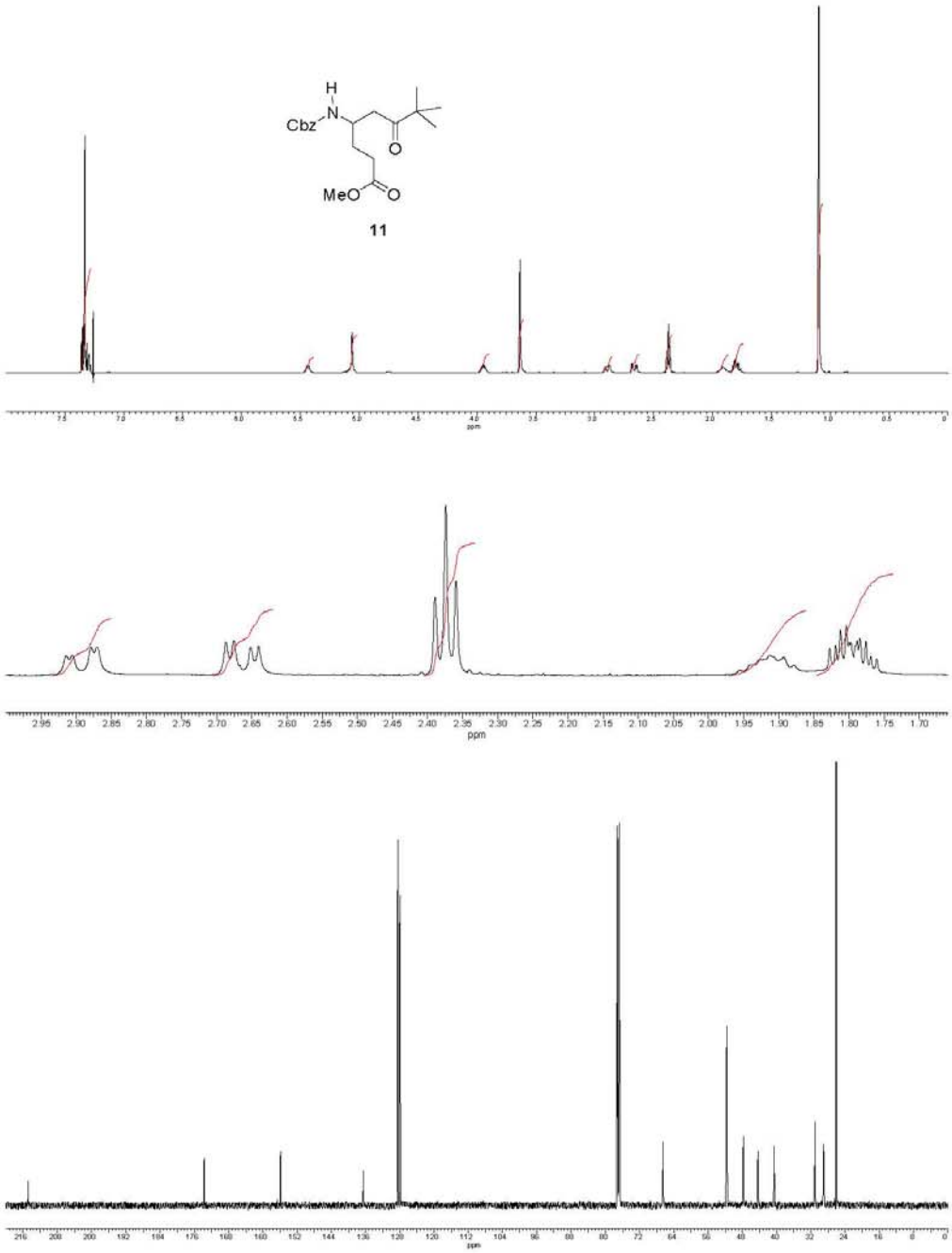

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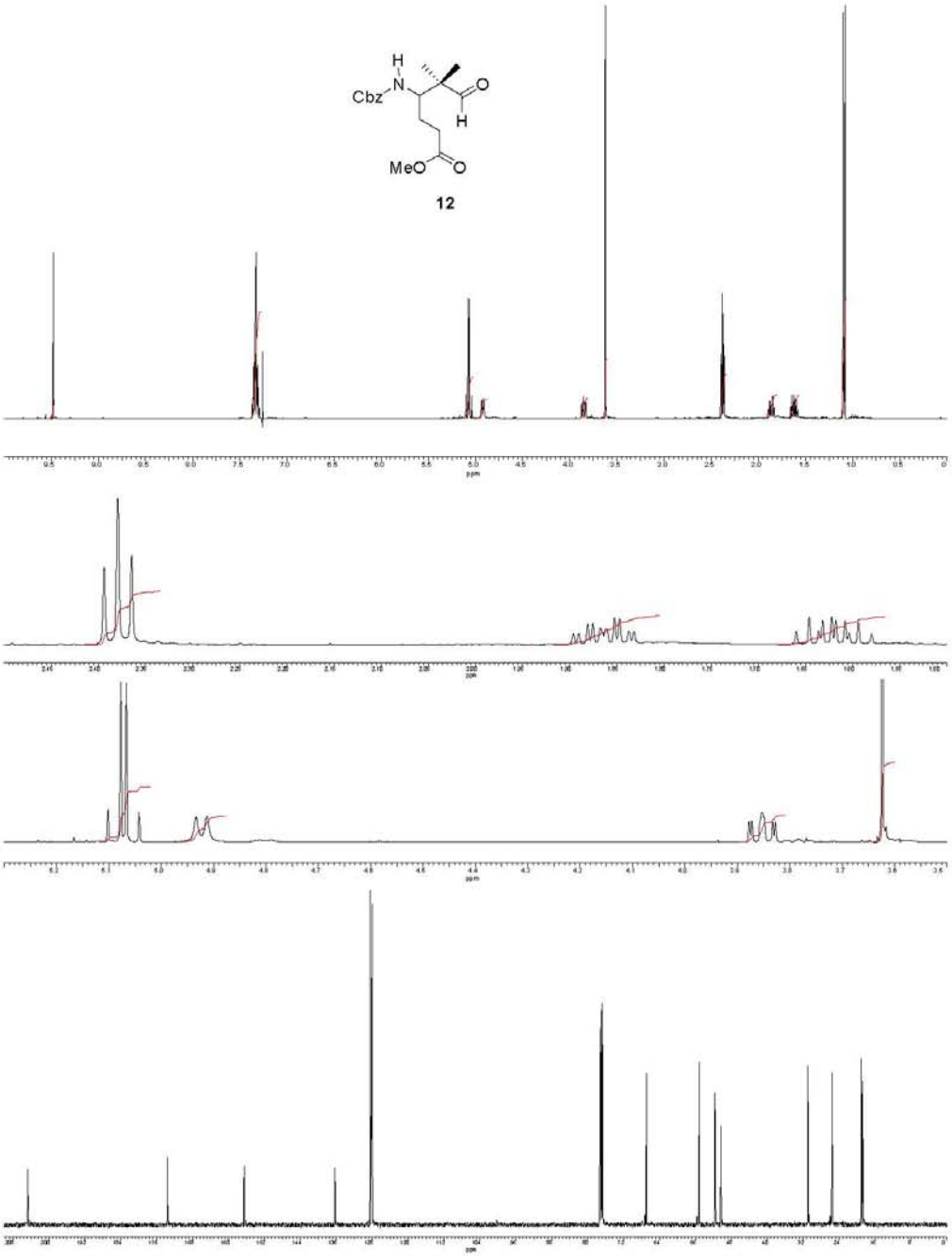

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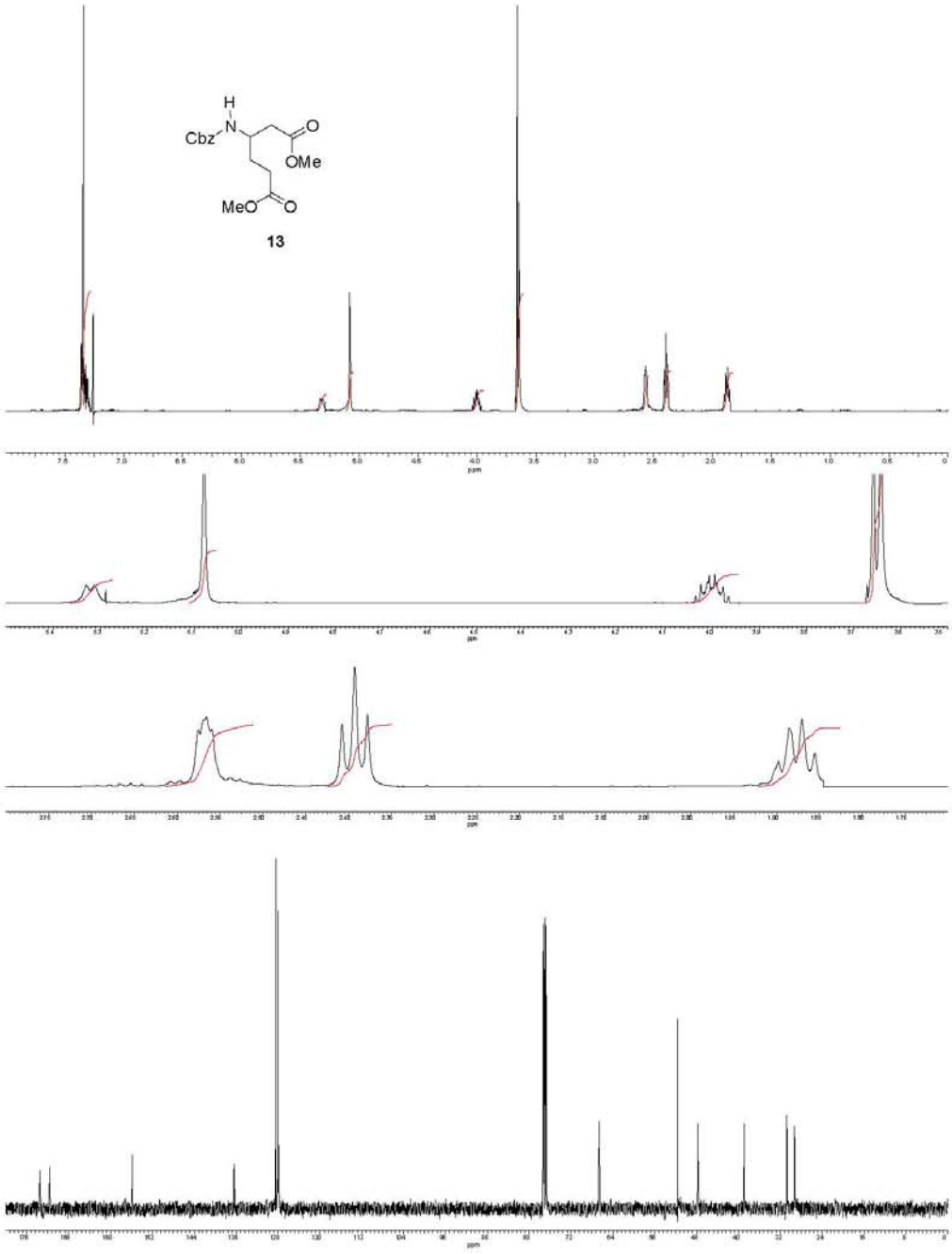

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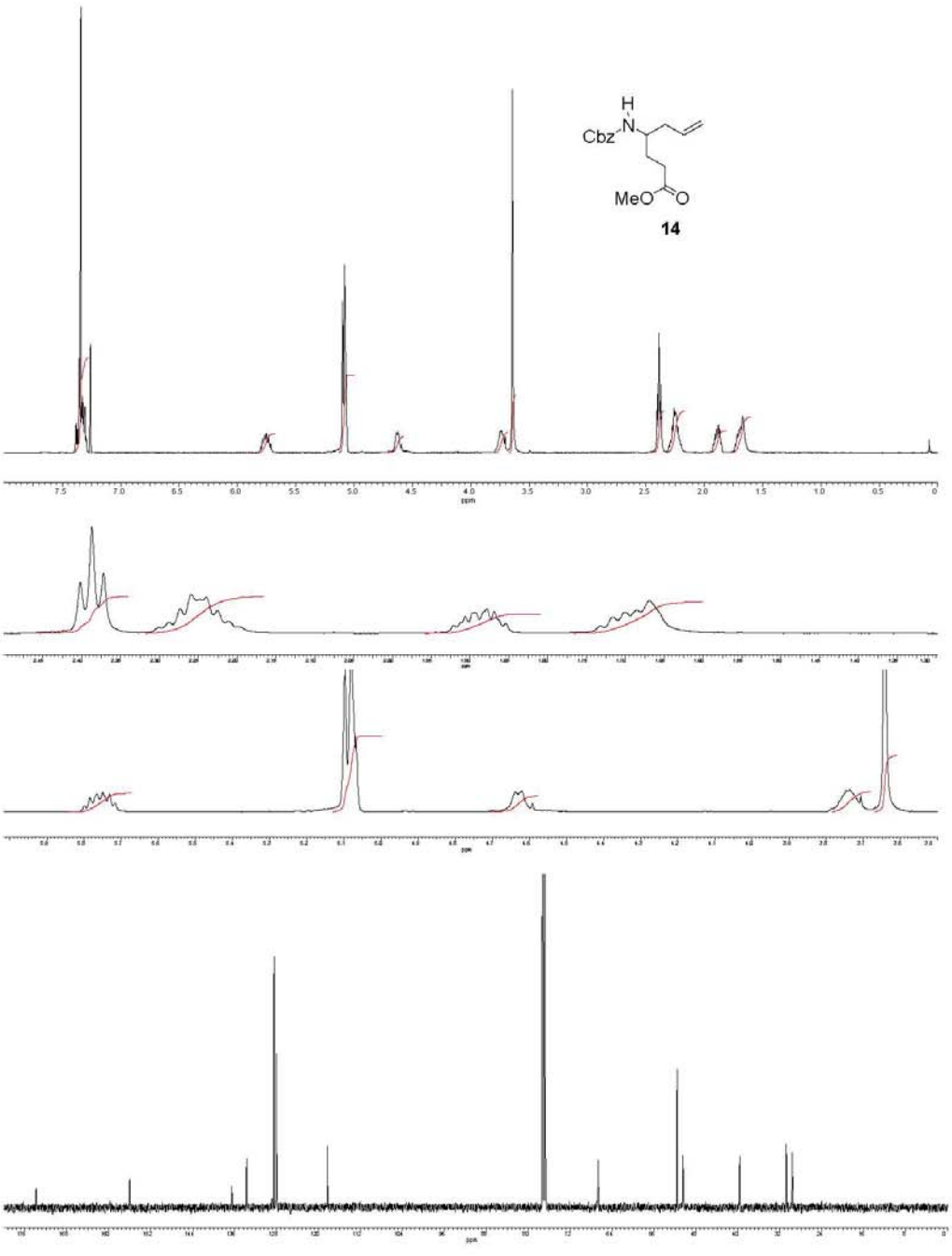

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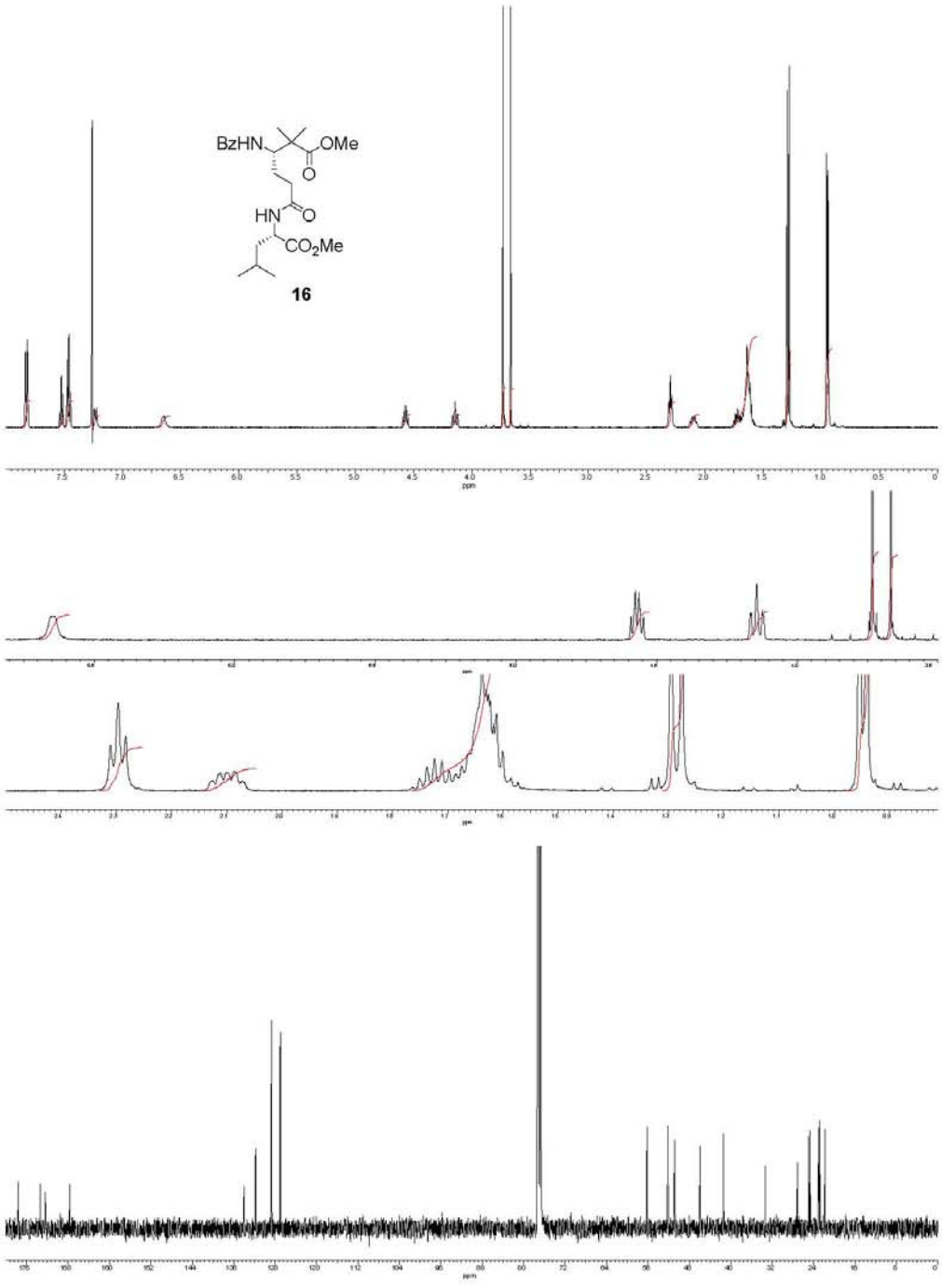

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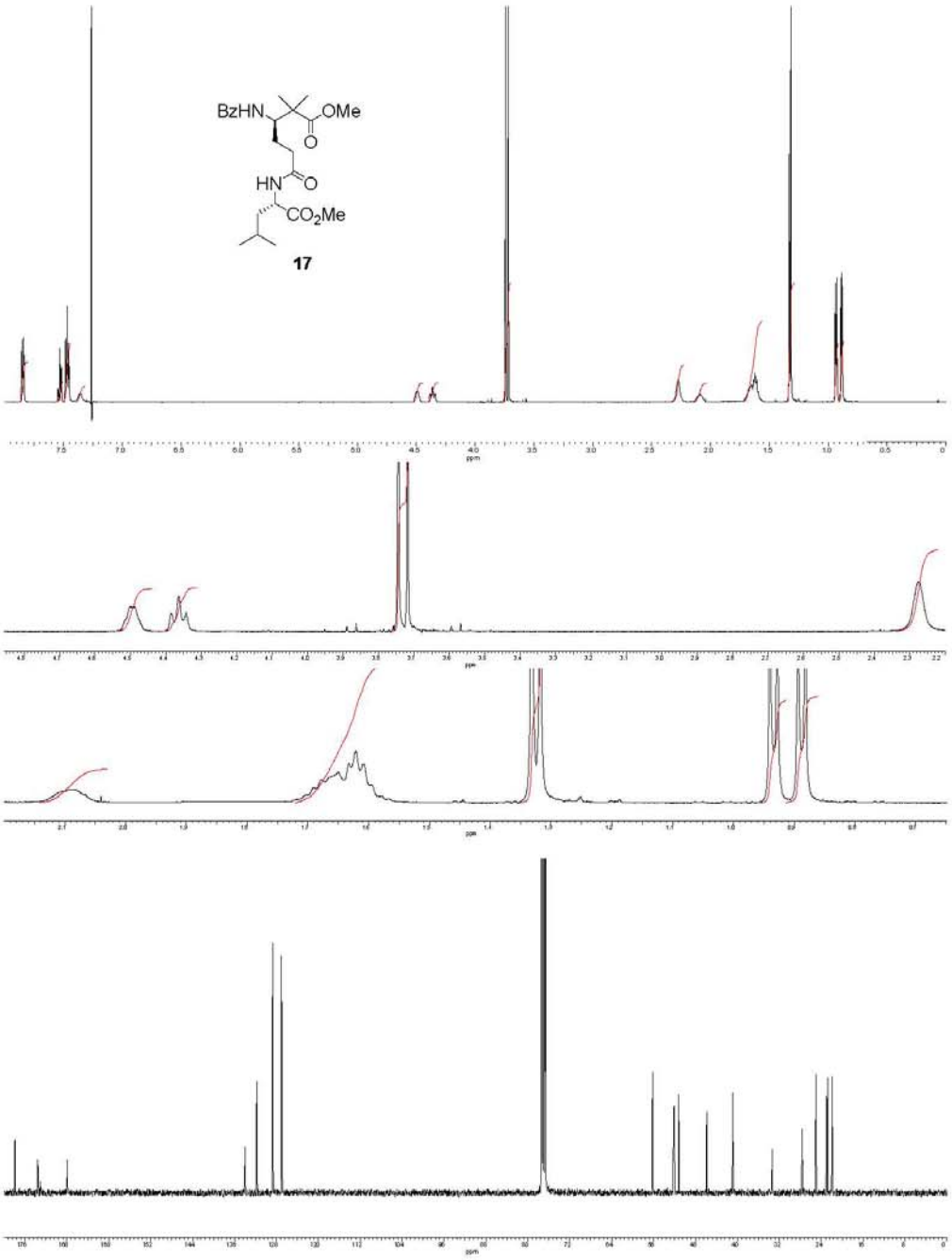

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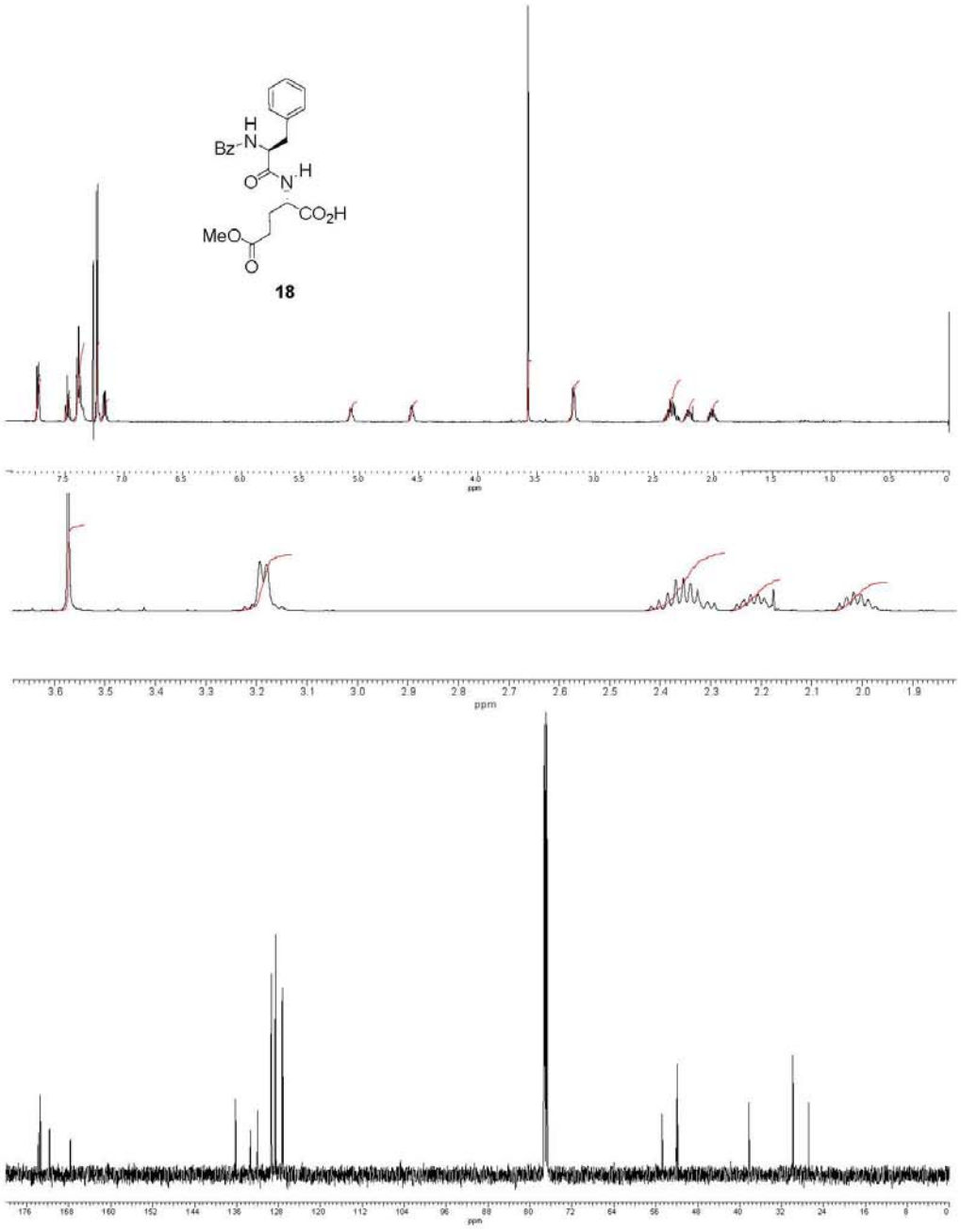

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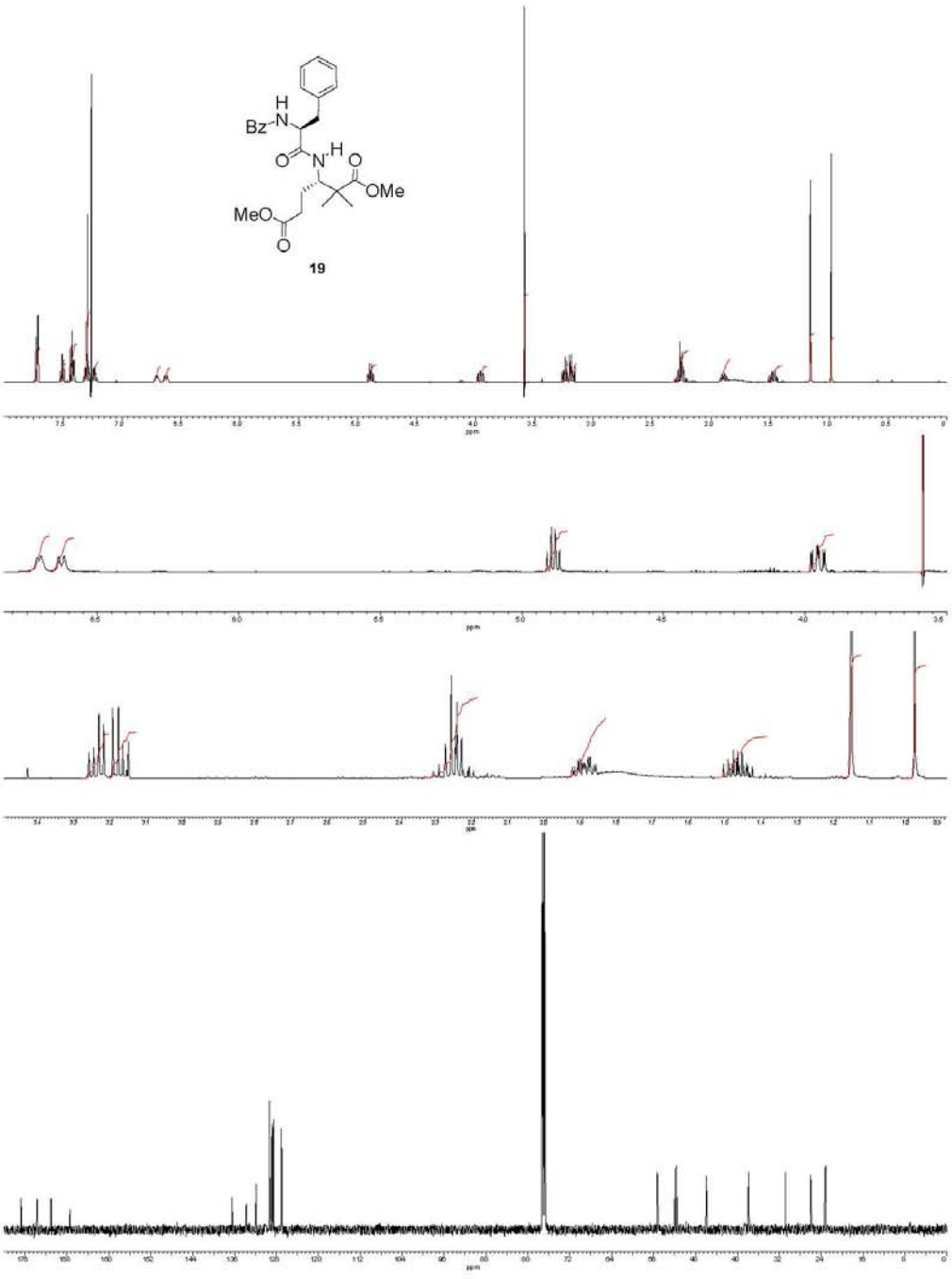

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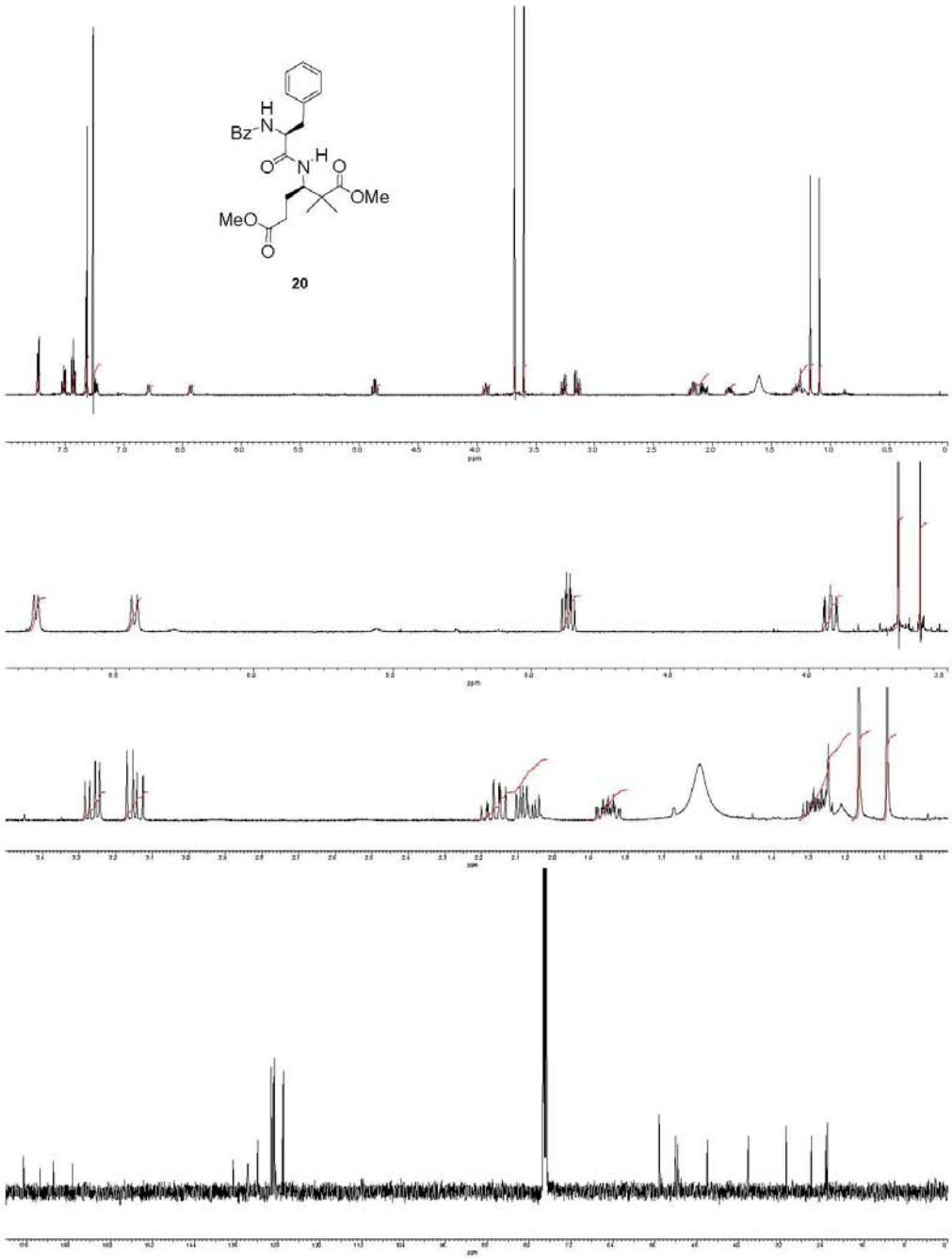

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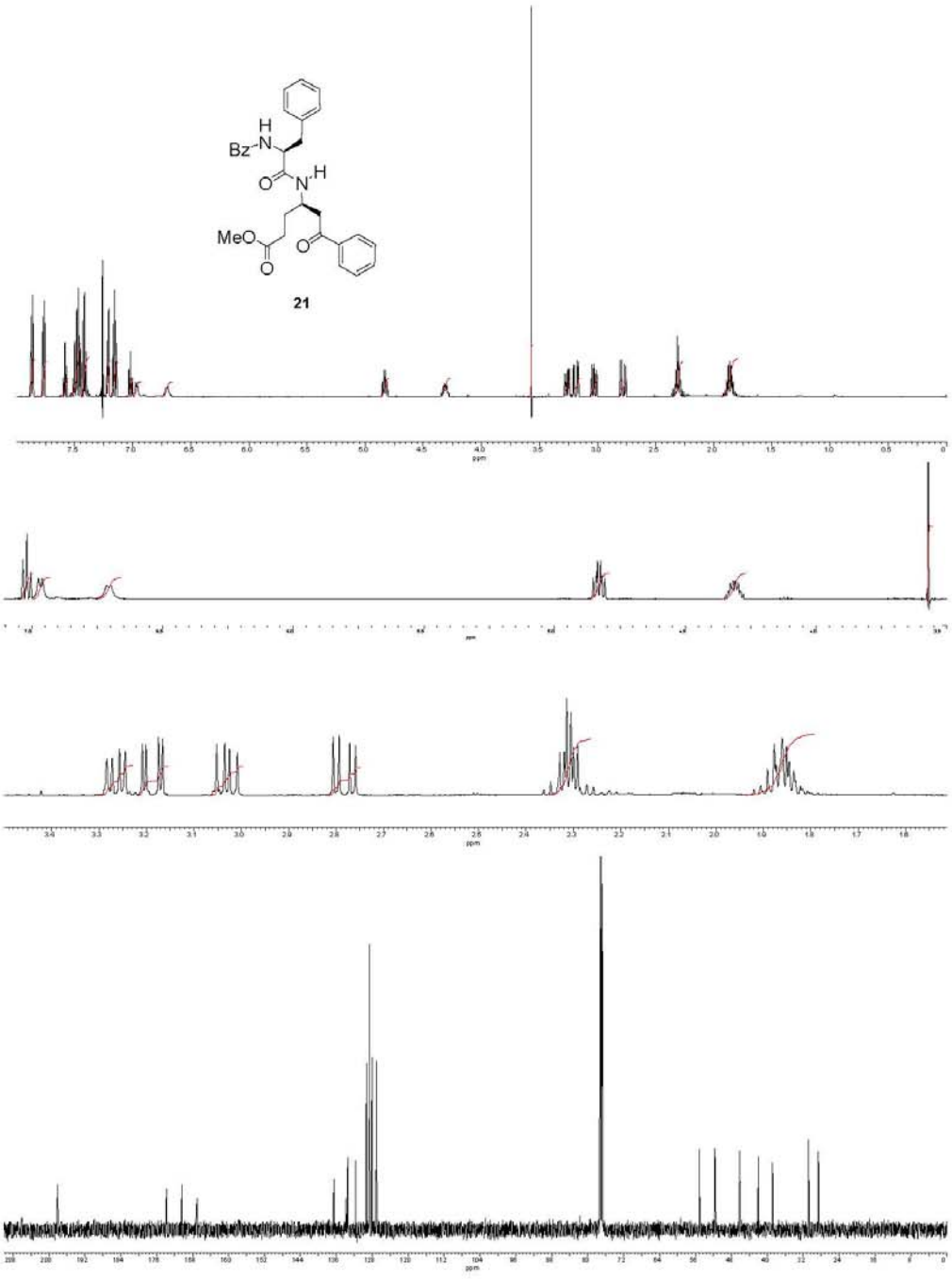

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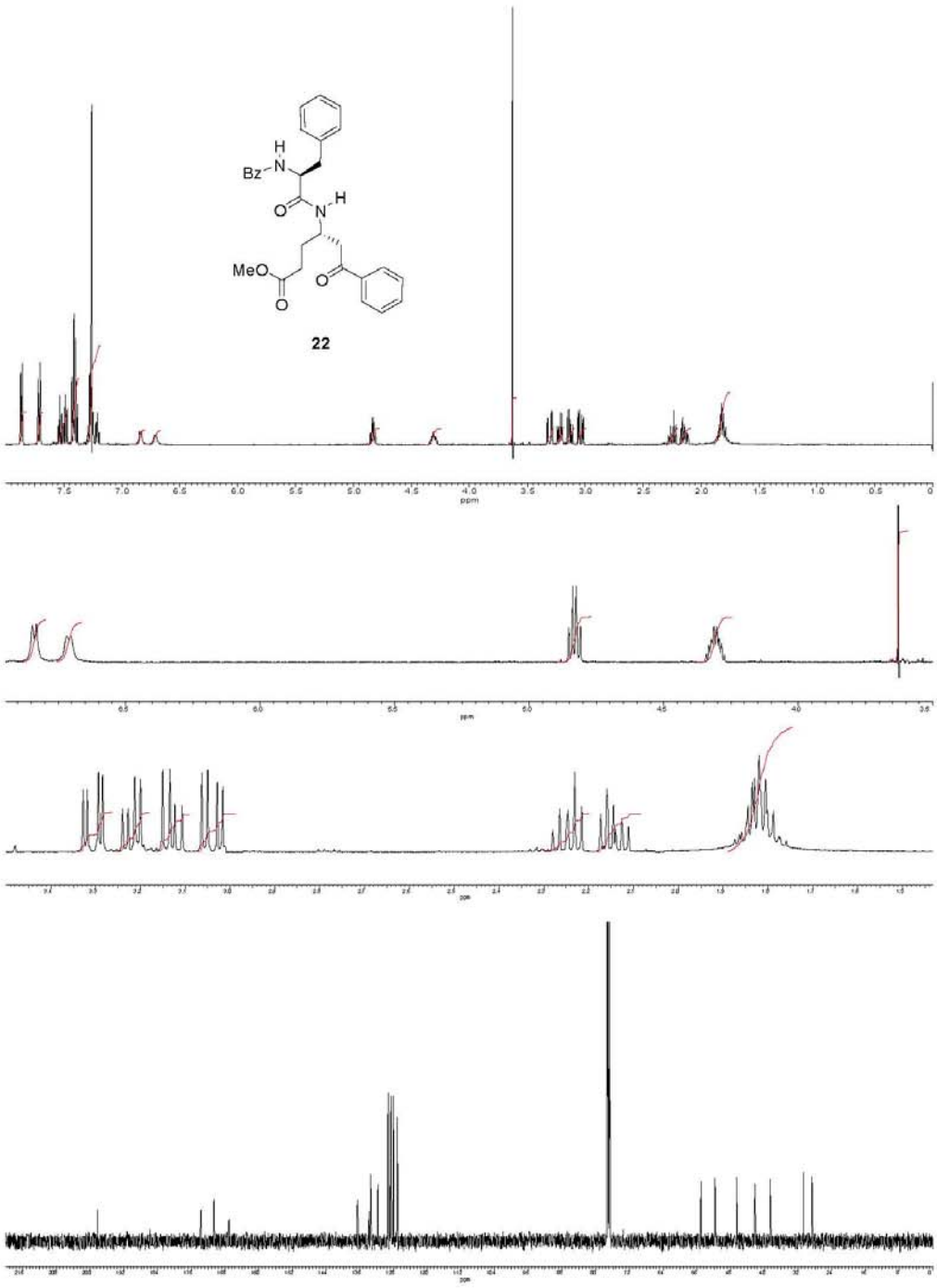

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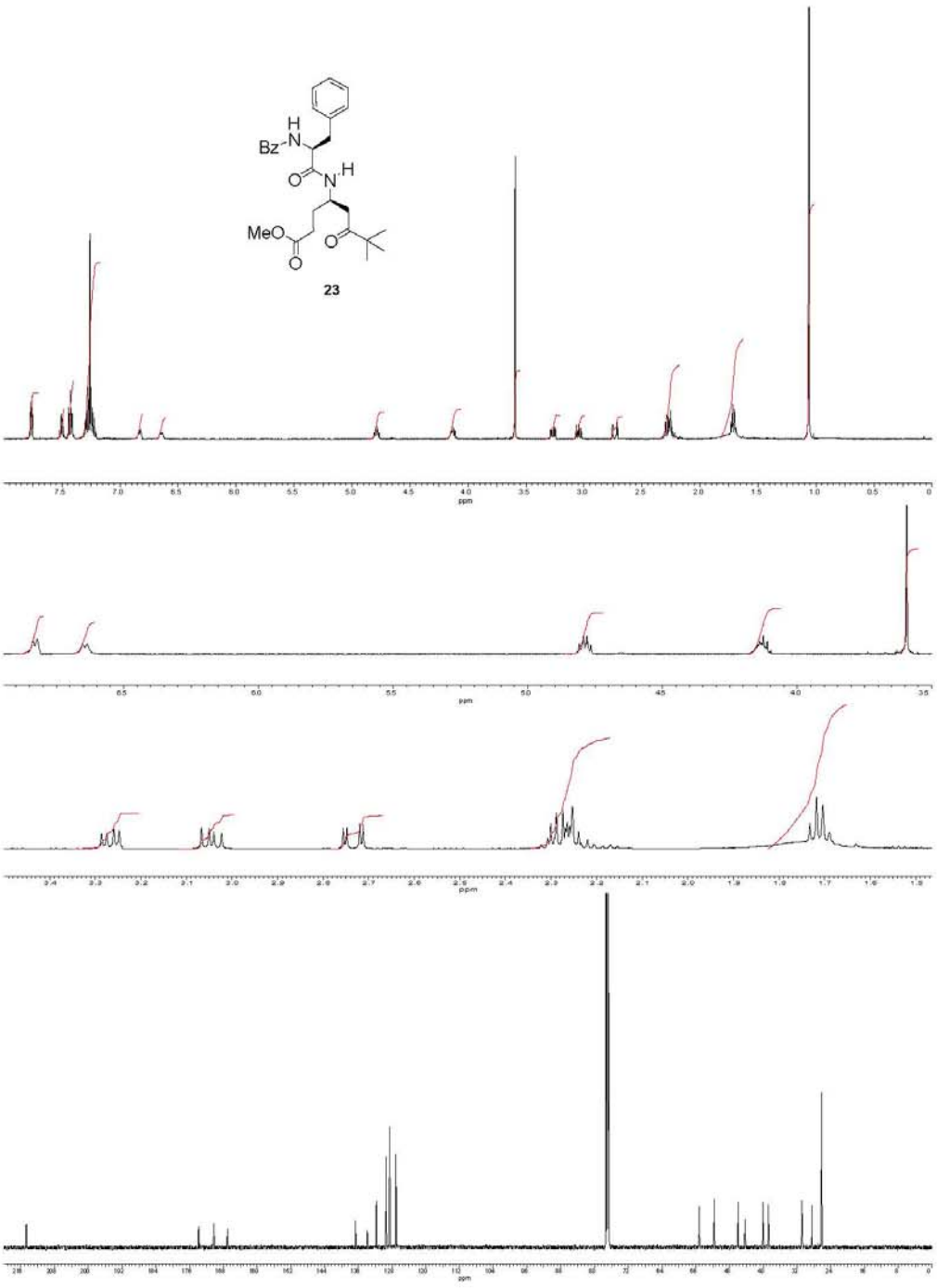

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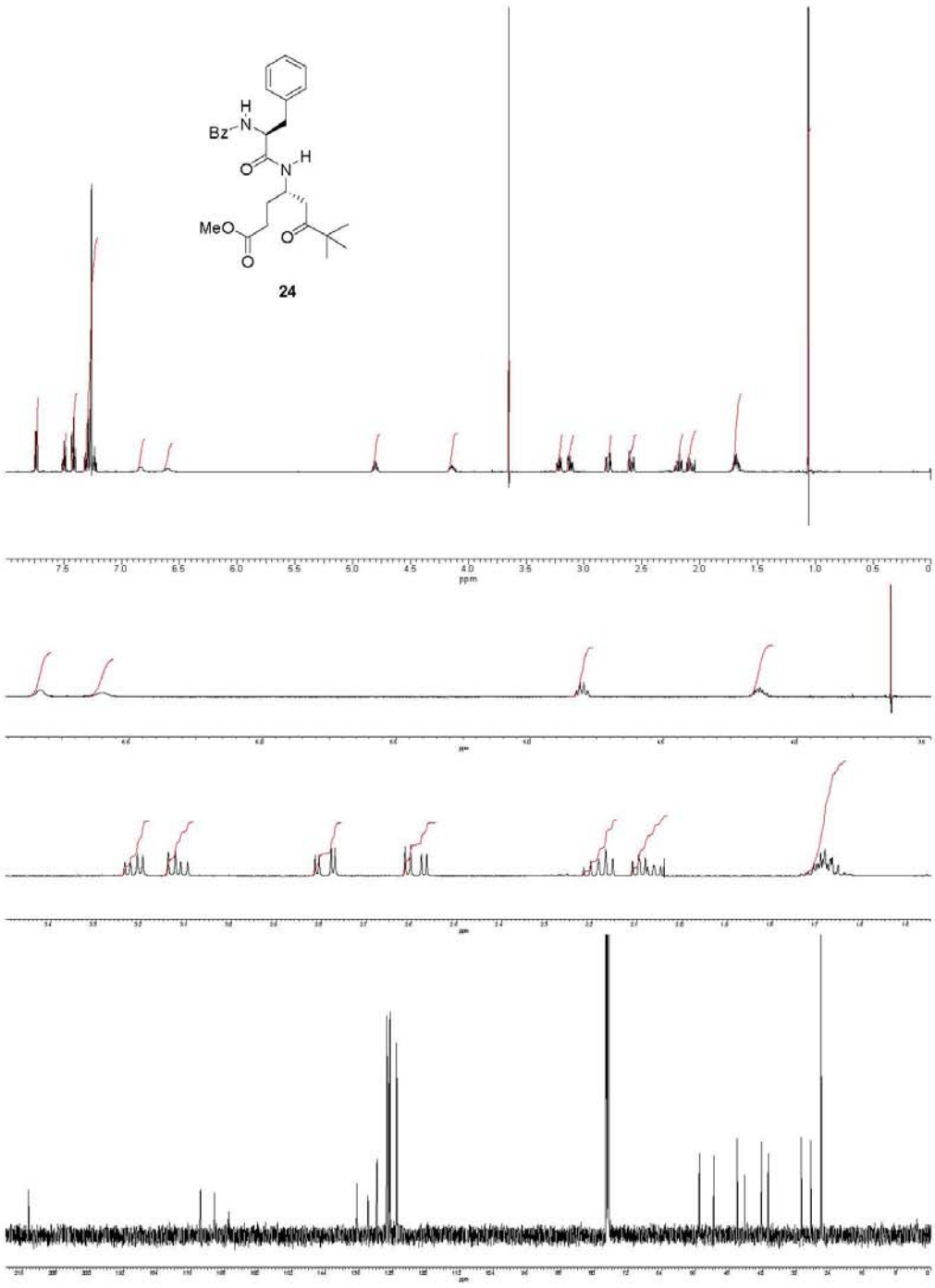

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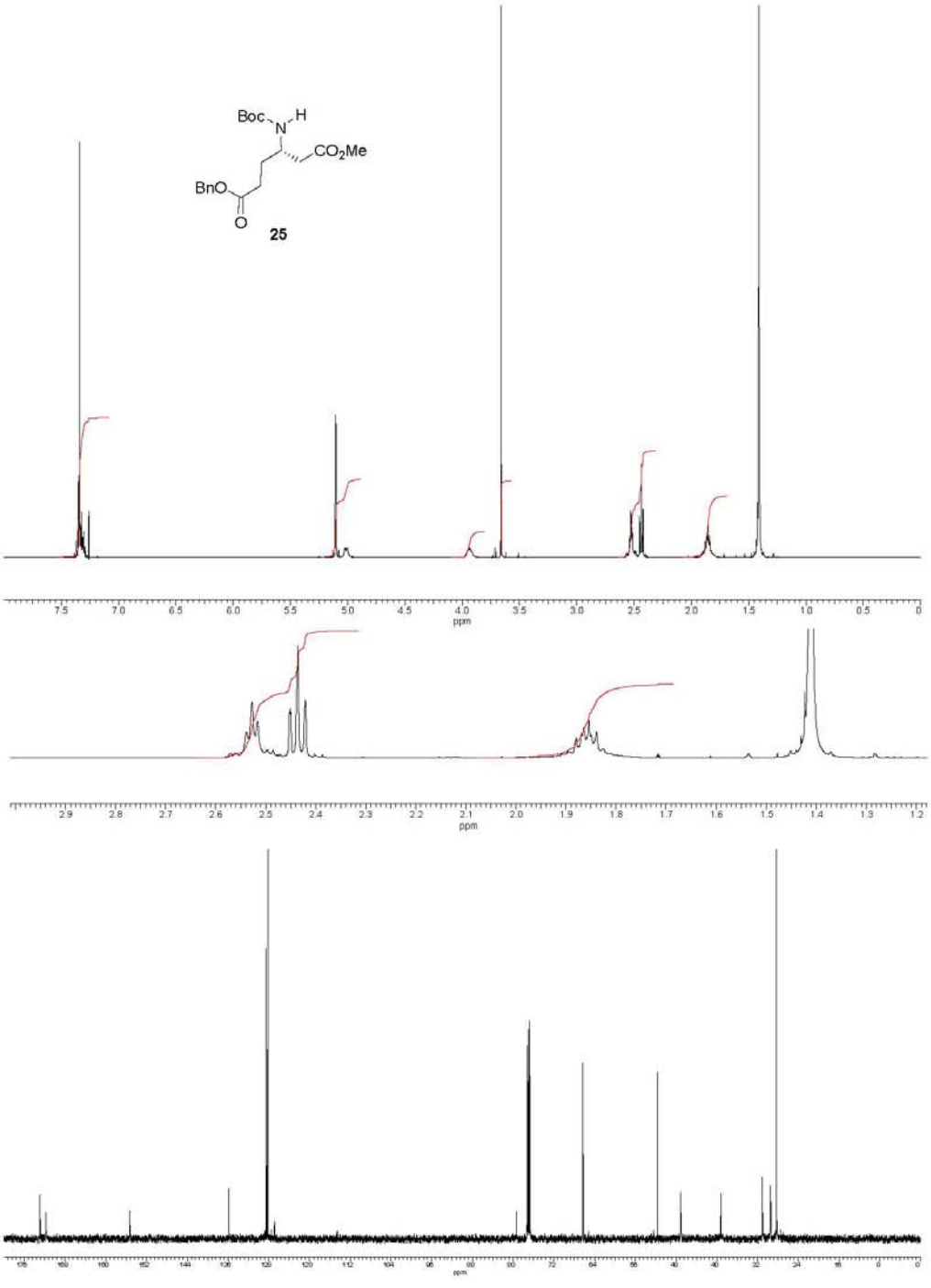
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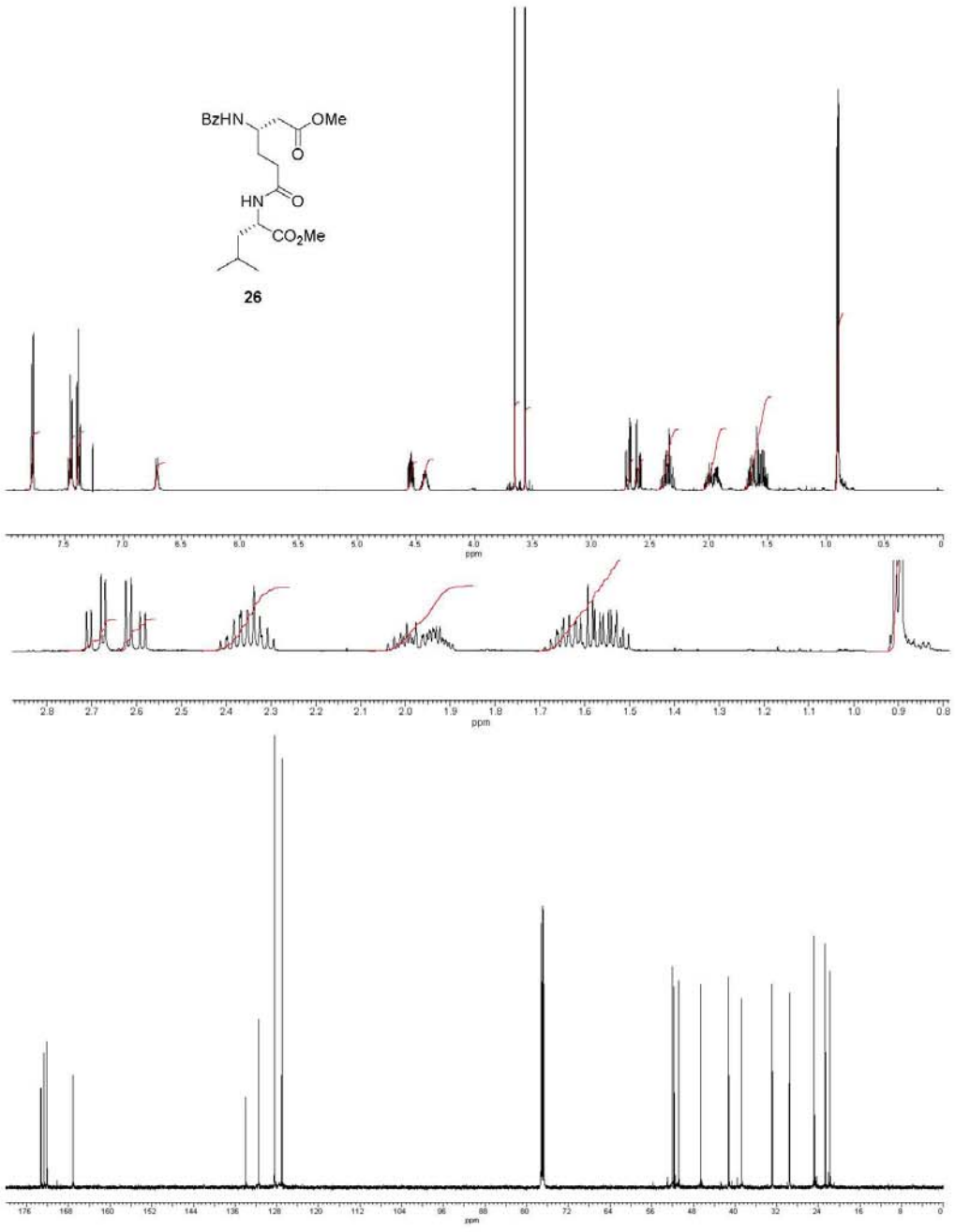

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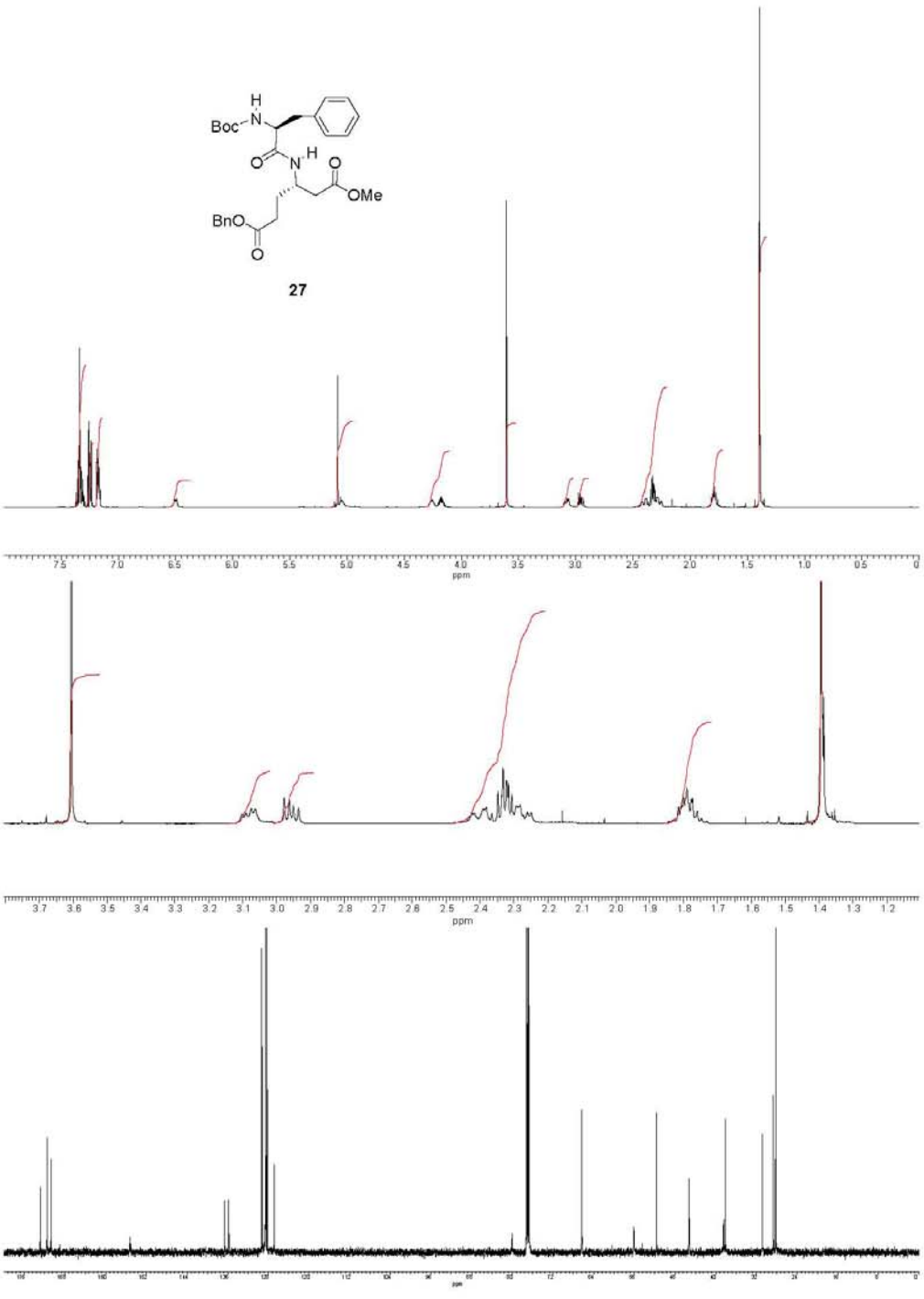

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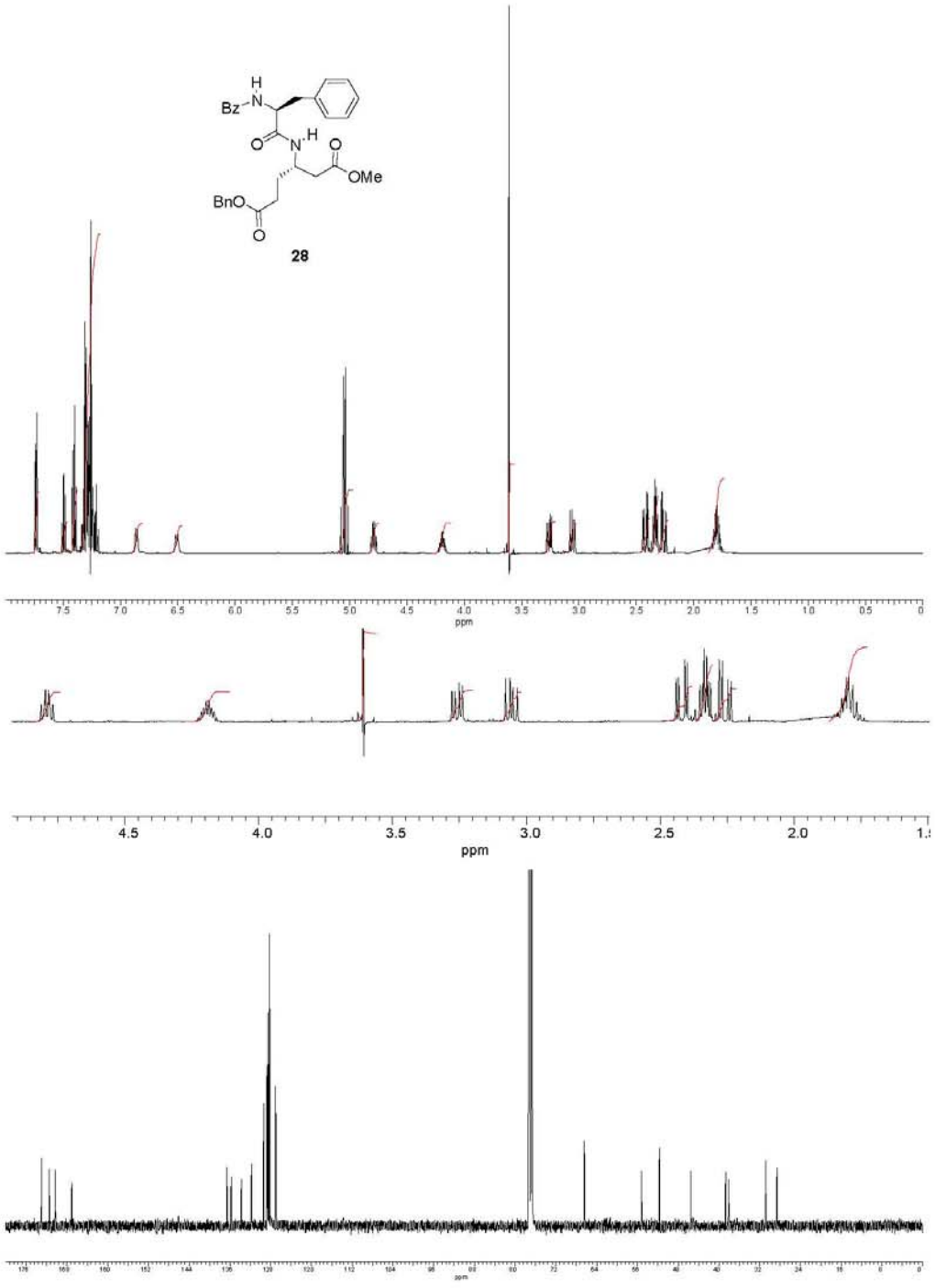

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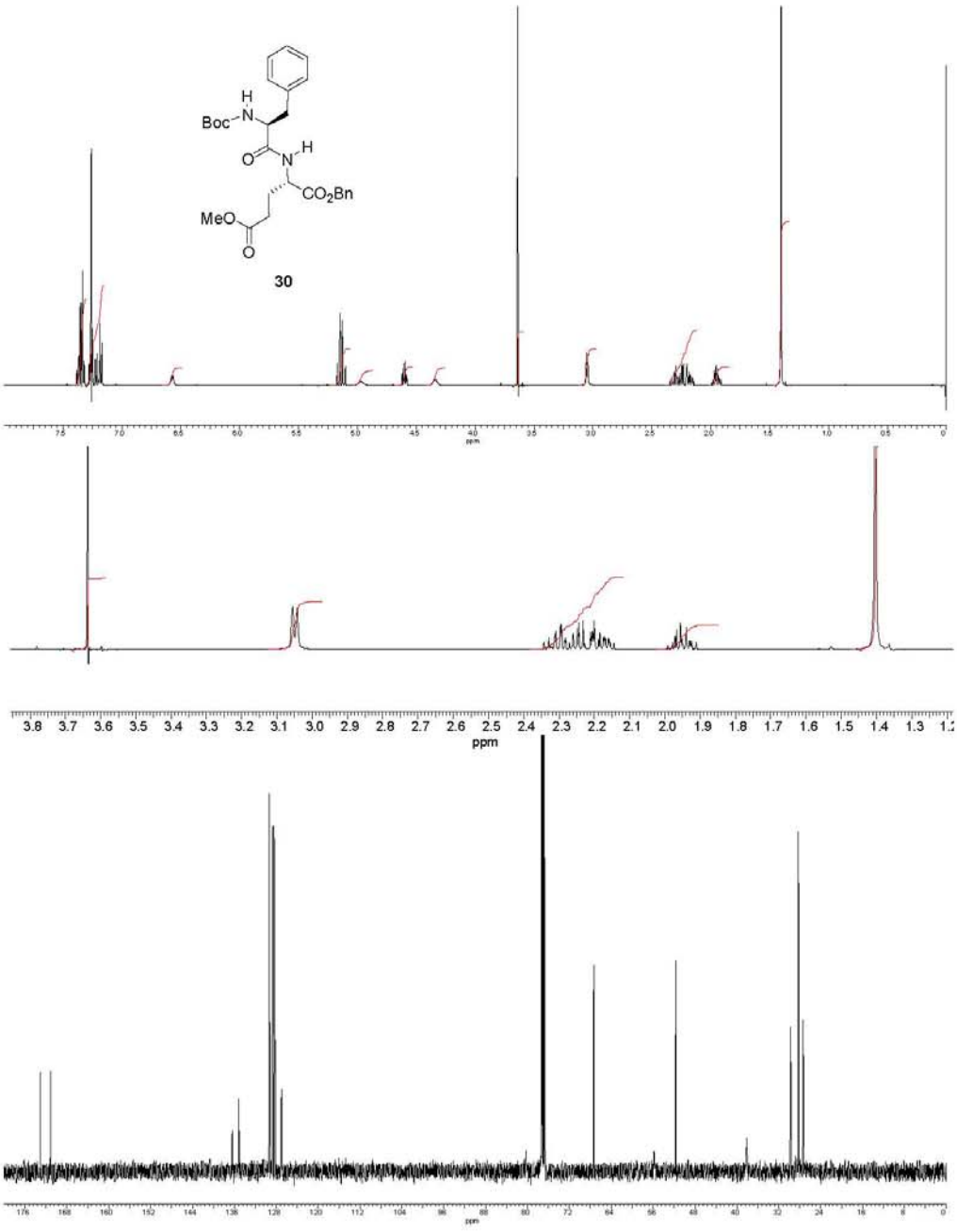
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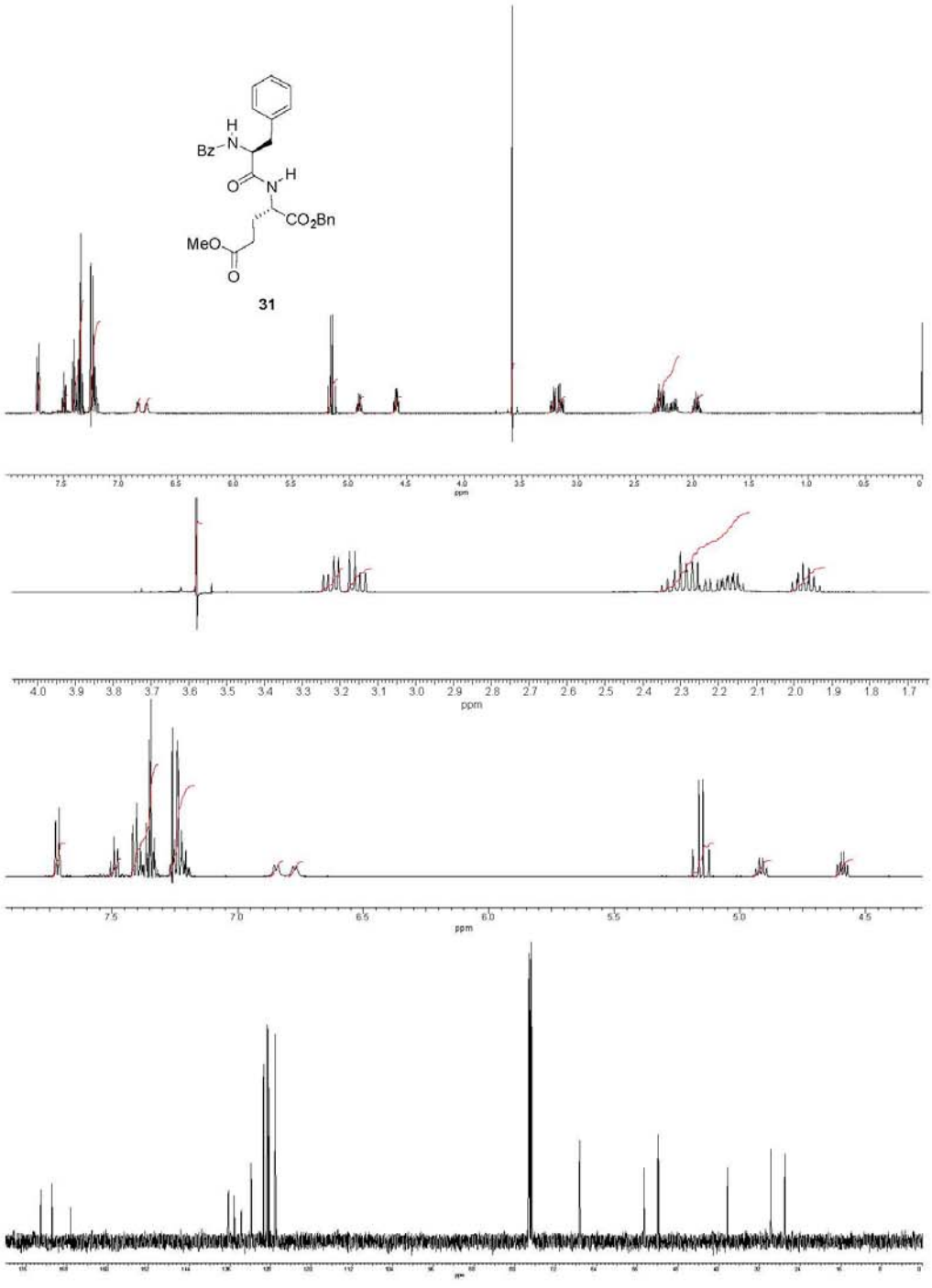
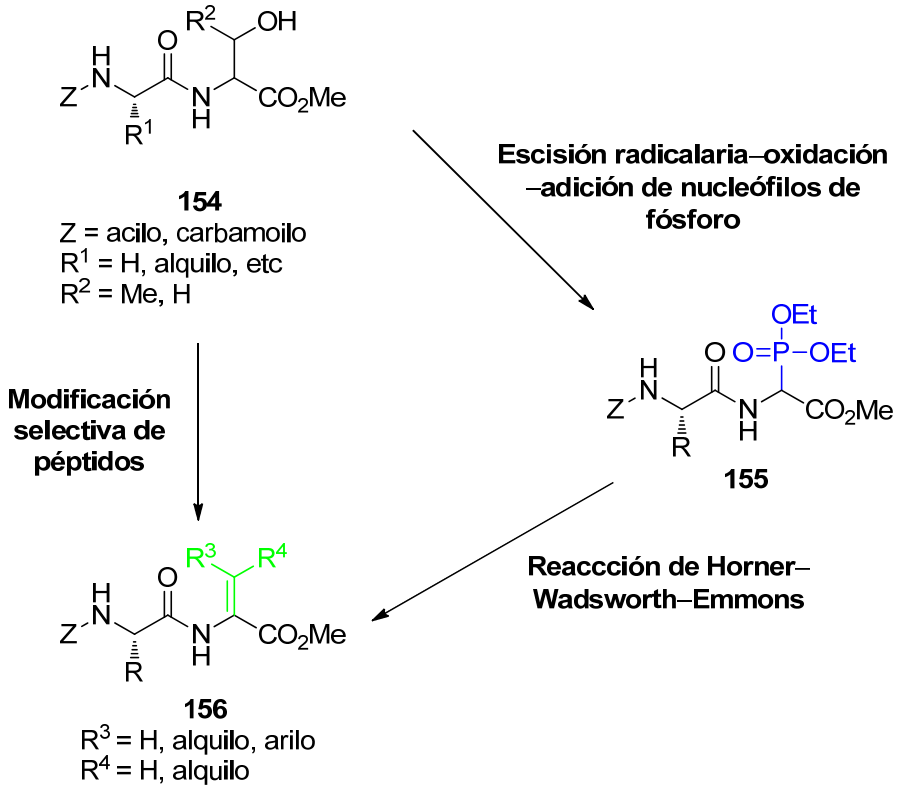


29

3.4 Unidades "convertibles" en di- y tripéptidos: conversión selectiva en deshidroamino ácidos sustituidos.

Los deshidroamino ácidos pueden encontrarse en muchos péptidos con potente actividad biológica, desde antibióticos a antitumorales y toxinas. Además, la introducción de deshidroamino ácidos en análogos sintéticos de péptidos bioactivos puede incrementar su resistencia a la degradación enzimática y permite modular sus propiedades biológicas.

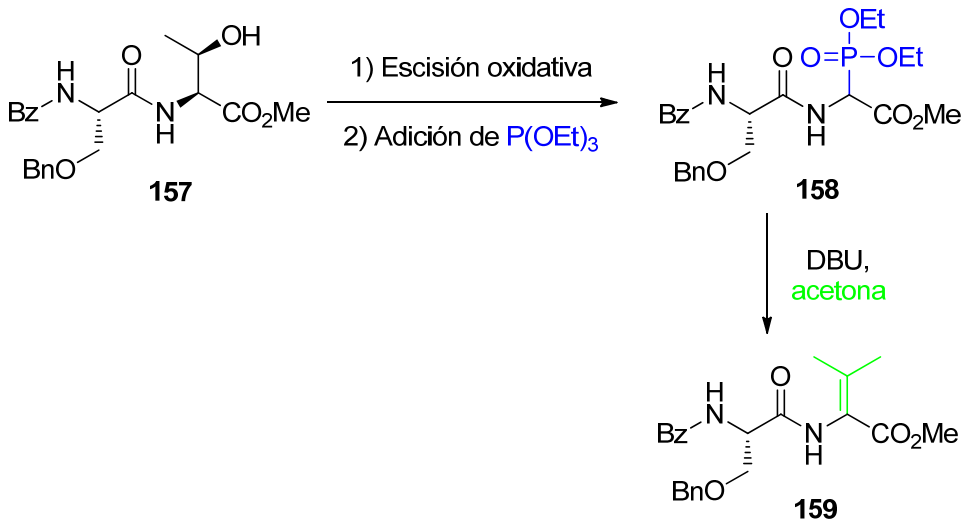
En este capítulo se describe la modificación selectiva de péptidos **154** (Esquema 45) donde los residuos "convertibles" son unidades de serina o treonina. A diferencia de los capítulos anteriores, no se produce una descarboxilación, sino la escisión radicalaria oxidativa del grupo hidroximetileno.



Esquema 45. Modificación selectiva de residuos de serina o treonina en péptidos. Síntesis de unidades de deshidroamino ácido.

Esta escisión también genera un ión aciliminio, que es atrapado por nucleófilos. En esta ocasión se utilizan nucleófilos de fósforo, dando lugar a residuos de α-amino fosfonato (péptidos **155**). Posteriormente, una reacción de Horner-Wadsworth-Emmons con diferentes aldehídos o cetonas permite obtener péptidos **156** que contienen deshidroamino ácidos β-sustituidos.

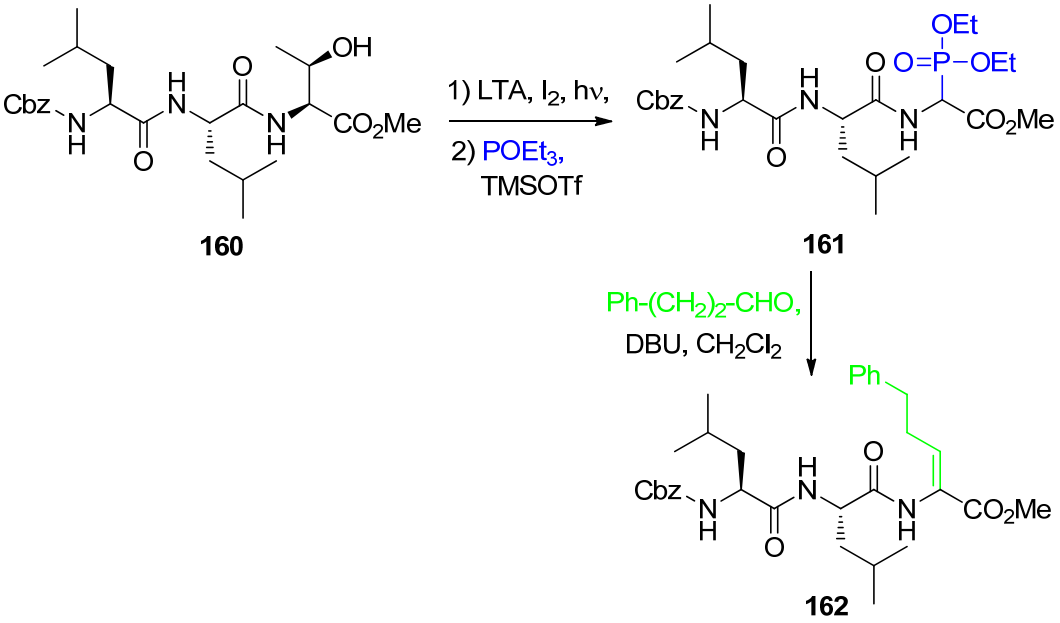
El uso de residuos de serina o treonina como unidades modificables permite transformar selectivamente incluso péptidos con varias unidades "convertibles". En efecto, las cadenas laterales de diferentes unidades de serina o treonina pueden ser protegidas con grupos ortogonales. De esta manera solo el residuo de serina/treonina libre sería transformado, mientras que los demás no se alterarían, como demostró la conversión del dipéptido Bz-Ser(Bn)-Thr-OMe **157** (Esquema 46) en el dipéptido **158** y posteriormente en el dipéptido con residuo de deshidrovalina **159**.



Esquema 46. Estudio de la escisión oxidativa–fosforilación.

Se estudiaron distintas condiciones para la etapa de escisión radicalaria oxidativa y para la adición de nucleófilos. En el primer caso, el sistema DIB/I_2 dio peores resultados que el sistema LTA/I_2. En la etapa de adición nucleofílica, los mejores resultados fueron obtenidos con fosfitos como nucleófilos y TMSOTf como ácido de Lewis (ej. conversión **160**→**161**, Esquema 47). Como muestra el

ejemplo, es de destacar que en la reacción de Horner-Wadsworth-Emmons con aldehídos se obtienen deshidroamino ácidos β-sustituidos con elevada estereoselectividad, para dar los isómeros *Z* (compuestos **162**).



160 **161** **162**

Esquema 47. Síntesis de unidades de *Z*-deshidroamino ácidos en tripéptidos.

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"Customizable" Units in Di- and Tripeptides: Selective Conversion into Substituted Dehydroamino Acids

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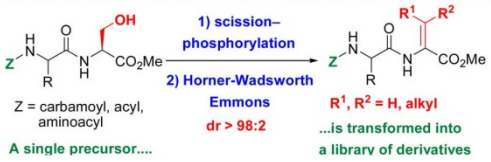
ABSTRACT



The selective conversion of serine or threonine units of di- and tripeptides into substituted dehydroamino acids is reported. Thus, these common α-amino acids undergo a scission–phosphorylation process to give α-amino phosphonate residues. A Horner–Wadsworth–Emmons reaction with aldehydes or ketones follows to afford the final products with excellent *Z*-stereoselectivity (*Z*:*E* > 98:2). In this way, a single peptide precursor can selectively be transformed into a variety of derivatives.

Dehydroamino acids can be found in a variety of bioactive peptides, such as the cyclic peptide tentoxin,[1] the lantibiotics[2] and thiopeptide antibiotics,[3] the protease inhibitor somamide,[4a] the cytotoxic kahalalide F,[4] yaku'amides,[5] and dolastatin,[6] the fungicide pseudomycin,[7] and many others.

In addition, the introduction of dehydroamino acids into synthetic analogues of bioactive peptides can increase their resistance to enzymatic degradation and allow the modulation of their biological properties.[8,9] Several drug analogues with improved properties have been developed,[9] such as gramicidin analogues with potent antibiotic but much lower hemolytic activity[9a] and endorphine analogues for pain control[9b] with high μ opioid receptor selectivity.

The rigidity provided by dehydroamino acids could also be useful to generate folded conformations for new materials or peptide catalysts.[10]

In order to generate libraries of peptides with dehydroamino acid units, each peptide is usually prepared de novo from the starting amino acids. Herein, we report an alternative strategy where a single parent peptide is

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transformed into a variety of derivatives by selective conversion of certain α-amino acid units (serine or threonine) into β-substituted dehydroamino acids.

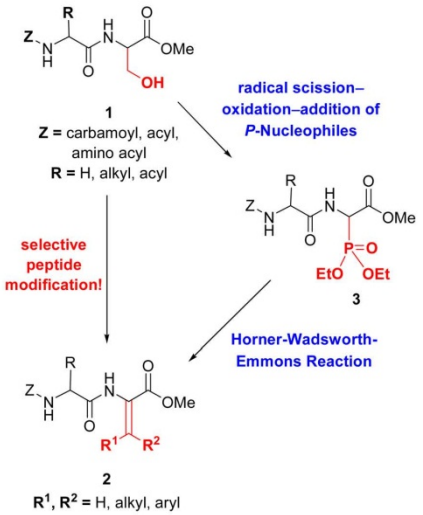
Recently, the use of "customizable" (or "tunable") amino acids in the site-selective modification of peptides has elicited much interest.[11,12] This selective approach requires less time and materials than the conventional de novo synthesis. For instance, Seebach has reported the selective alkylation of enolates from *N*-alkylglycines,[12a] while Kazmaier has achieved the stereoselective allylation and alkylation of glycine residues in dipeptides.[12b,c] Klok has described the addition of *S*-radicals to allylglycines in peptides with 4–16 residues,[12d] and Skrydstrup has generated enolates in "tunable" residues of di- to tetrapeptides, which were trapped by electrophiles.[11a,12e]

Despite these advances, the site-selective modification of peptides remains difficult,[11] even for small peptides, because of the similar reactivity of the amino acid units. The task is particularly difficult when several units of the "tunable" amino acid (glycine, dehydroamino acids, etc) are present in the peptide. The use of serine (or threonine) residues as customizable units solves this problem, since the lateral chains of different serine units can be protected with orthogonal groups. Thus, free serine residues would be selectively transformed, while the protected ones would remain unchanged.

To determine the feasibility of this approach to obtain a variety of peptides with dehydroamino acid units, we used the strategy shown in Scheme 1 (conversion **1**→**2**). Thus, peptide **1** would undergo the radical scission of serine (or threonine) to give a glycyl radical, which would be oxidized in situ to a cation, and the latter would be trapped by phosphorus nucleophiles to give the aminophosphonate **3**. Then, a Horner–Wadsworth–Emmons reaction with different aldehydes or ketones would afford peptides with dehydroamino acids **2**.

For the first step, we used a variation of our reported amino acid decarboxylation–phosphorylation process.[13]

Scheme 1. Site-Selective Scission of Serine Residues and Addition of *P*-Nucleophiles



Since the decarboxylation is much more favored than the radical scission of alcohols (in particular, primary alcohols such as serine), there were concerns that the scission–phosphorylation process would not work as desired or that side reactions (*H*-abstraction, oxidation of the alcohol, cleavage of the peptide chain) would take place.[14,15]

The selective radical scission–oxidation was studied with peptides **4** and **5** (Scheme 2), which present two serine residues or a serine/threonine pair. Using the reported procedure [(diacetoxyiodo)benzene (DIB)/I_2, *hν*, 26 °C, 2–4 h, then 0 °C, Lewis acid, nucleophile],[13,15] a complex mixture of compounds was formed, due either to side reactions or to the formation of unstable scission products, such as a peptide with an α-acetoxyglycine unit.

In order to determine whether the low yields were due to the generation of unstable N,O-intermediates or to other causes, the scission–oxidation was followed by addition of methanol, since this nucleophile usually adds in good to excellent yields, providing stable methoxy acetals.[16] Therefore, peptide **4** was treated with $PhI(OAc)_2$ (DIB) and iodine under irradiation with visible light, affording the methoxy derivative **6** in improved but still moderate yield (<40%).

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(14) In other complex substrates, such as carbohydrates, the *H*-abstraction often predominates over the scission: Boto, A.; Hernández, D.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2006**, *71*, 1938–1948.

(15) (a) For other work on scission–addition processes, see: Saavedra, C.; Boto, A.; Hernandez, R. *Org. Biomol. Chem.* **2012**, *10*, 4448–4461. (b) Boto, A.; Romero-Estudillo, I. *Org. Lett.* **2011**, *13*, 3426–3429. (c) Saavedra, C.; Hernandez, R.; Boto, A.; Alvarez, E. *J. Org. Chem.* **2009**, *74*, 4655–4665. (d) Boto, A.; Gallardo, J. A.; Hernández, D.; Hernández, R. *J. Org. Chem.* **2007**, *72*, 7260–7269.

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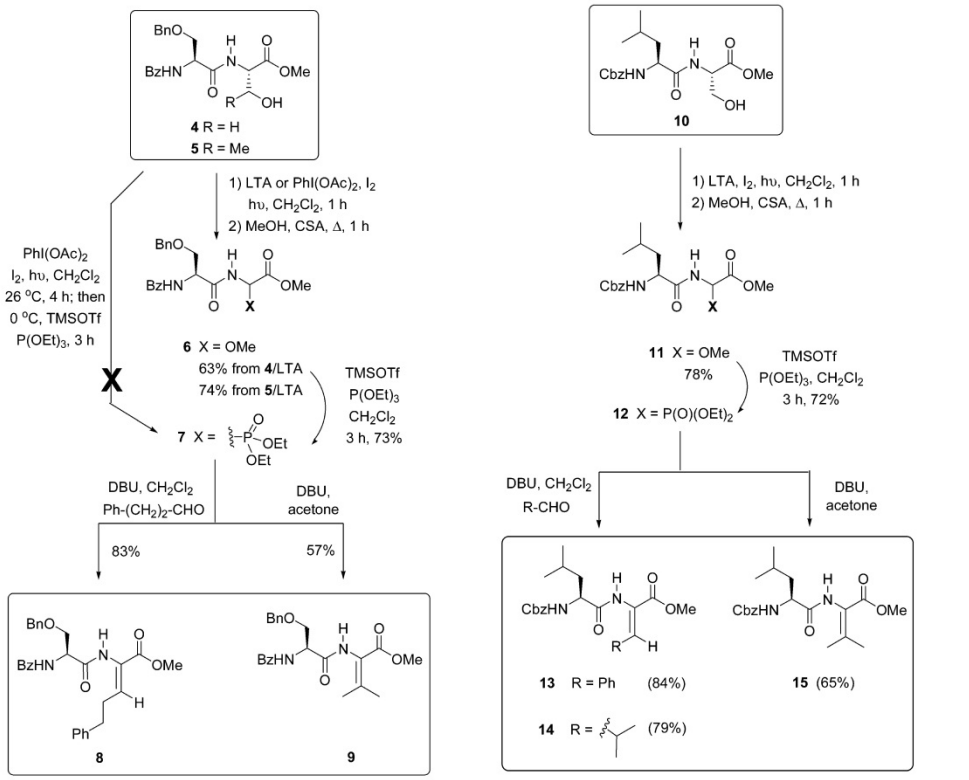
Scheme 2. Formation of a Set of Compounds from a Peptide Precursor by Selective Conversion of Ser and Thr Units into Dehydroamino Acids



Fortunately, when the system DIB–iodine was replaced by lead tetraacetate (LTA) and iodine, a single product was formed. After purification by chromatography, the dipeptide **6** was isolated in 63% yield. Interestingly, the scission of the threonine analogue **5** resulted in increased yield (74%). To account for this result, both the scission and the addition of methanol must have proceeded in good to excellent yields.

The conversion of dipeptide **6** into the aminophosphonate **7** was studied under several conditions, using different phosphorus nucleophiles and Lewis acids. The best results were obtained with $P(OEt)_3$ and TMSOTf, affording compound **7** in 73% yield.

The aminophosphonate **7** underwent the Horner–Wadsworth–Emmons reaction with dihydrocinnamaldehyde to give the dehydro(phenyl)norvaline **8** in good yield and excellent *Z*-stereoselectivity. The reaction also proceeded with ketones (acetone) to give the dehydrovaline derivative **9**. It should be noticed that in both cases the protected *N*-terminal serine unit remained unaffected.

In a similar way, the Cbz-protected peptide **10** (Scheme 2) underwent the scission–addition of methanol process, affording the methoxyglycine derivative **11** in 78% yield. Then compound **11** was converted into the aminophosphonate **12** in good yield.

Product **12** was treated with different aryl and akyl aldehydes[17] to provide compounds **13** and **14**, which present units of dehydrophenyl alanine and dehydroleucine, respectively. The reaction also proceeded with acetone to give the dehydrovaline derivative **15** in good yield.

In the case of compounds **13** and **14**, the process took place with complete stereoselectivity to give the *Z*-isomers. An important concern was that the basic reaction conditions would produce the epimerization of the adjacent amino acid(s). We compared the optical activity of compound **13** and a sample formed by coupling the leucine and

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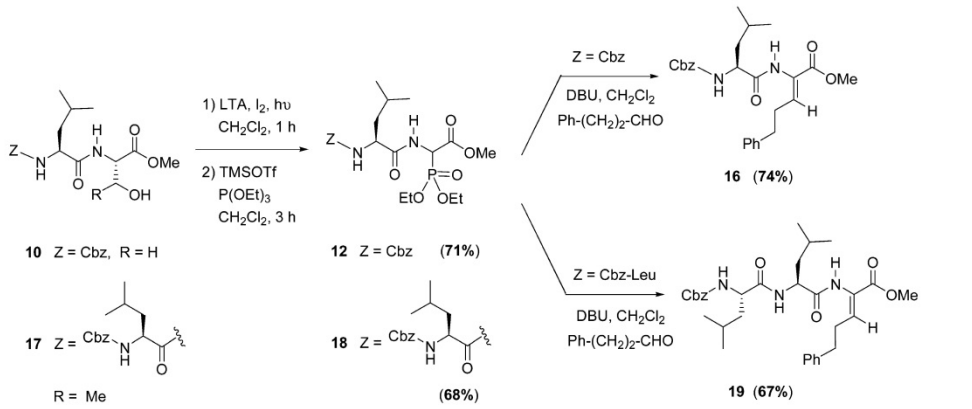
Scheme 3. Simplified Scission–Phosphorylation Procedure and Application to the Synthesis of Modified Peptides



the *Z*-dehydrophenylalanine units;[18a] to our satisfaction, both activities matched completely.

We reasoned that a simplification of the previous procedure could allow the direct transformation of peptide **10**[18] into the phosphonate **12**. Thus, the dipeptide **10** (Scheme 3) underwent scission with LTA/I_2 followed by aqueous workup. The intermediate was not purified but treated with the phosphorylation reagents to give compound **12** in 54% yield (the global yield for the two-step procedure was 56%). The aminophosphonate **12** was treated with dihydrocinnamaldehyde to give the dehydro(phenyl)norvaline derivative **16** in 74% yield.

Finally, we studied the process with tripeptide **17** where the customizable unit is threonine. We are interested in polyleucine-substituted peptides where one of the residues is replaced by a dehydroamino acid since these derivatives present interesting conformational and biological properties.[19]

The tripeptide **17** underwent the simplified scission–phosphorylation process to give the aminophosphonate **18** in good yield. Then, compound **18** was treated with dihydrocinnamaldehyde to give the dehydro(phenyl)norvaline derivative **19**.

In summary, a scission of serine/threonine units–phosphorylation process was developed, which is suitable for the selective modification of peptides; other alternative procedures reported in the literature do not work with these substrates. The resulting aminophosphonates underwent a Horner–Wadsworth–Emmons reaction with aldehydes or ketones to give the corresponding dehydroamino acids with excellent (*Z*) stereoselectivity, and no epimerization of other positions was observed.

This methodology allows for the preparation of a variety of peptide derivatives from a single precursor. The process takes place under mild conditions in good yields.

The use of the serine (or threonine) units to generate diversity is particularly interesting. Since its hydroxymethylene group can be protected with different orthogonal groups, the starting peptide could contain several serine residues, but only the unprotected one(s) would be modified. For further modifications, the orthogonal protecting groups could be sequentially removed. The application of this methodology to the synthesis of other peptides of different sizes will be reported in due course.

Acknowledgment. This work was supported by the Research Program CTQ2009-07109 of the Plan Nacional de I+D, Ministerio de Ciencia e Innovación (currently Economía y Competitividad), Spain, and European Regional Development Funds (FEDER). C.J.S. thanks Gobierno de Canarias for a predoctoral grant.

Supporting Information Available. Procedures for the synthesis of substrates **4**, **5**, and **17**. Formation of the α-methoxyglycine derivatives **4**, **5**, and **11**, the amino phosphonates **7**, **12**, and **18**, and the dehydroamino acid-containing peptides **8**, **9**, **13**–**16**, and **19**. ^{1}H and ^{13}C NMR spectra of products **4**–**9** and **11**–**19**. NOE experiments for compounds **8**, **13**, **14**, **16**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org

(18) (a) Falorni, M.; Giacomelli, G.; Satta, M.; Cossu, S. *Synthesis* **1994**, 391–395. (b) Falorni, M.; Satta, M.; Conti, S.; Giacomelli, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2389–2398.

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The authors declare no competing financial interest.

Supporting Information

"Customizable" Units in Di- and tripeptides: Selective Conversion into Substituted Dehydroamino Acids

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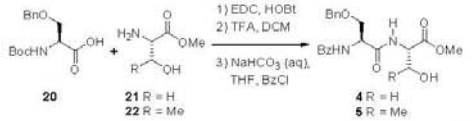
Supporting Information. Procedures for the synthesis of the substrates for the scission-phosphorylation process **4**, **5** and **17** (pp 1–2), study of the scission–oxidation reaction and formation of the α-methoxyglycine derivatives **4**, **5** and **11** (pp 2–3), procedure for the phosphorylation reaction and synthesis of phosphorylated compounds **7**, **12** and **18** (pp 2–4), procedures for the Horner-Wadsworth-Emmons Reaction and preparation of dehydroamino acid-containing peptides **8**, **9**, **13**–**16** and **19** (pp 4–7). ^{1}H and ^{13}C NMR spectra of compounds **4**–**9** and **11**–**19** and NOE experiments for compounds **8**, **13**, **14**, **16** and **19**. (pp 8–27). This material is available free of charge via the Internet at http://pubs.acs.org.

General Methods. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature (26 °C) in $CHCl_3$ solutions. NMR spectra were determined at 500 MHz for ^{1}H and 125.7 or 100 MHz for ^{13}C in the presence of TMS as internal standard, unless otherwise stated. Mass spectra were determined at 70 eV. Merck silica gel 60 PF_{254} and 60 (0.063–0.2 mm) were used for preparative thin layer chromatography and column chromatography, respectively. All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The reagent for TLC analysis was $KMnO_4$ in $NaOH/K_2CO_3$ aqueous solution and the TLC was heated until development of color.

Preparation of Substrates 4, 5 and 17.

Scheme 1. Preparation of substrates 4 and 5



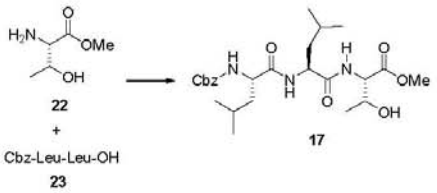
20 **21** R = H, **22** R = Me → **4** R = H, **5** R = Me

***N*-(*O*-Benzyl-*N*-benzoyl-L-seryl)-L-serine Methyl Ester (4).** To a solution of Boc-Ser(OBn)-OH (**20**) (2.96 g, 10 mmol) and and H-Ser-OMe•HCl (**21**) (1.56 g, 10 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C, was added diisopropylethylamine (3.4 mL, 2.59 g, 20 mmol), 1-hydroxybenzotriazol hydrate (HOBt) (1.49 g, 11 mmol), and N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC, 2.1 g, 11 mmol). The reaction mixture was stirred for 2 h at 0 °C, then was allowed to reach room temperature (26 °C) and stirred for 18 h. Then it was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried on sodium sulfate, filtered and evaporated under vaccum. The residue was dissolved in 1:1 TFA:CH_2Cl_2 (25 mL) and the solution was stirred at 26 °C for 1.5 h. Then the solvent was removed under vaccum and the residue was dissolved in THF (15 mL). Then saturated aqueous $NaHCO_3$ (15 mL) was added, the mixture was cooled to 0 °C, and benzoyl chloride was added dropwise (1.51 mL, 1.83 g, 13 mmol). After stirring for 16 h, the mixture was poured into 5% aqueous HCl at 0°C and extracted with EtOAc. The residue was purified by column chromatography (hexanes/EtOAc, 30:70), to give compound **4** (2.68 g, 67%) as a syrup; $[\alpha]_D$ +51 (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3418, 1747, 1679, 1660, 1512 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.05 (1H, brb),

3.70 (1H, dd, J = 6.9, 9.5 Hz), 3.75 (3H, s), 3.90–3.98 (2H, m), 3.99 (1H, dd, J = 4.4, 9.2 Hz), 4.60 (2H, s), 4.66 (1H, ddd, J = 3.8, 3.8, 7.3 Hz), 4.84 (1H, ddd, J = 4.7, 6.6, 6.9 Hz), 7.17 (1H, brd, J = 6.6 Hz), 7.28 (1H, m), 7.31–7.35 (4H, m), 7.42 (2H, dd, J = 7.3, 7.9 Hz), 7.51 (1H, dd, J = 7.8, 7.9 Hz), 7.53 (1H, d, J = 7.6 Hz), 7.77 (2H, d, J = 7.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 52.7 (CH_3), 53.2 (CH), 55.1 (CH), 62.8 (CH_2), 69.5 (CH_2), 73.6 (CH_2), 127.2 (2 × CH), 127.9 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.5 (C), 137.3 (C), 167.6 (C), 170.3 (C), 170.5 (C); HRMS calcd for $C_{20}H_{22}N_2O_5$ (M^+ + H −OMe), 370.1529; found, 370.1513. Anal. calcd for $C_{21}H_{24}N_2O_6$ C 62.99, H 6.04, N 7.00; found C 62.73, H 6.13, N 7.10.

***N*-(*O*-Benzyl-*N*-benzoyl-L-seryl)-L-threonine Methyl Ester (5).** Obtained from commercial Boc-Ser(OBn)-OH (**20**) (2.95 g, 10 mmol) and H-Thr-OMe•HCl (**27**) (1.70 g, 10 mmol) as described before for the synthesis of dipeptide **4**. After purification by column chromatography (hexanes/EtOAc, 30:70), dipeptide **5** was isolated (3.31 g, 80%) as a syrup; $[\alpha]_D$ +34 (c 0.23, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3419, 1747, 1680, 1660, 1653, 1511 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.19 (3H, d, J = 6.3 Hz), 3.70 (1H, m), 3.72 (3H, s), 3.99 (1H, dd, J = 4.4, 9.1 Hz), 4.34 (1H, m), 4.59-4.62 (3H, m), 4.91 (1H, m), 7.22 (1H, brb), 7.28 (1H, m), 7.29-7.38 (4H, m), 7.41 (2H, dd, J = 7.6, 7.9 Hz), 7.48 (1H, brb), 7.50 (1H, dd, J = 7.3, 7.6 Hz), 7.79 (2H, d, J = 6.9 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 19.9 (CH_3), 52.5 (CH_3), 53.0 (CH), 57.7 (CH), 67.9 (CH), 69.6 (CH_2), 73.5 (CH_2), 127.1 (2 × CH), 127.9 (3 × CH), 128.4 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.5 (C), 137.3 (C), 167.5 (C), 170.7 (C), 171.0 (C); HRMS calcd for $C_{21}H_{22}N_2O_5$ (M^+ −HOMe), 382.1529; found, 382.1512. Anal. calcd for $C_{22}H_{26}N_2O_6$ C 63.76, H 6.32, N 6.76; found C 63.67, H 6.27, N 6.73.

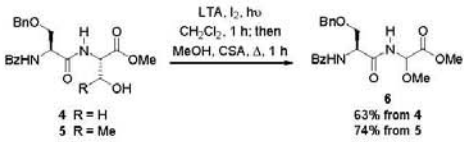
Scheme 2. Preparation of substrate **17**



***N*-(*N*-Benzyloxycarbonyl-L-leucyl-L-leucyl)-L-threonine Methyl Ester (17).** Obtained from commercial H-Thr-OMe•HCl (**22**) (1.70 g, 10 mmol) and Cbz-Leu-Leu-OH (**23**) (3.78 g, 10 mmol) as described before for the synthesis of dipeptide **4**. After purification by column chromatography (hexanes/EtOAc, 40:60), tripeptide **17** was isolated (3.95 g, 80%) as a syrup; $[\alpha]_D$ −48 (c 0.23, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3425, 1731, 1673, 1508 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.89–0.93 (12H, m), 1.17 (3H, d, J = 6.3 Hz), 1.49–1.75 (6H, m), 3.75 (3H, s), 4.19 (1H, m), 4.29 (1H, m), 4.52 (1H, ddd, J = 6.3, 7.9, 8.2 Hz), 4.58 (1H, br d, J = 7.5 Hz), 5.06 (1H, d, J = 13.0 Hz), 5.11 (1H, d, J = 12.0 Hz), 5.46 (1H, d, J = 6.6 Hz), 6.59 (1H, br b), 7.13 (1H, br b), 7.30–7.40 (5H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 19.7 (CH_3), 22.0 (CH_3), 22.3 (CH_3), 22.5 (CH_3), 22.8 (CH_3), 24.5 (CH), 24.6 (CH), 40.7 (CH_2), 41.1 (CH_2), 52.2 (CH), 52.5 (CH_3), 53.5 (CH), 57.6 (CH), 67.0 (CH_2), 68.3 (CH); 128.0 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.1 (C), 156.4 (C), 171.2 (C), 172.4 (C), 173.0 (C); HRMS calcd for $C_{22}H_{31}N_3O_7$ (M^+ − H − $CHMe_2$), 449.2162; found, 449.2173. Anal. calcd for $C_{25}H_{39}N_3O_7$ C 60.83, H 7.96, N 8.51; found C 60.74, H 7.75, N 8.61.

Study of the scission−oxidation reaction.

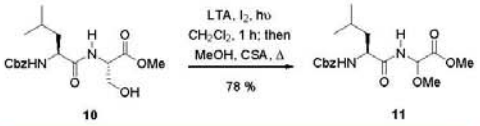
Scheme 3. Preparation of the α-methoxyglycine derivative **6**



Procedure for the Radical Scission−Oxidation −Addition of *O*-Nucleophiles Process: Synthesis of *N*-(*O*-Benzyl-*N*-benzoyl-L-seryl)-2-(methoxy)glycine Methyl Ester (6). To a solution of Bz-Ser(Bn)-Ser-OMe (**4**) (80 mg, 0.2 mmol) or Bz-Ser(Bn)-Thr-OMe (**5**) (83 mg, 0.2 mmol) in dry dichloromethane (8 mL) was added iodine (51 mg, 0.2 mmol) and lead tetraacetate (LTA, 178 mg, 0.4 mmol). The reaction mixture was stirred for 1 h at room temperature (26 °C) under irradiation with visible light (80-W tungsten-filament lamp). Then the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered, and the solvent was removed under vacuum. The residue was dissolved in dry methanol (8 mL), and camphorsulfonic acid (CSA) was added (139 mg, 0.6 mmol). The mixture was stirred for 1 h at reflux temperature; then was cooled to 26 °C, poured into water and extracted with dichloromethane. The organic layer was dried and filtered as before. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (hexanes/EtOAc 60:40), to afford product **6** (50 mg, 63% from substrate **4**; 59 mg, 74% from substrate **5**) as a 1:1 diastereomer mixture. Syrup; IR ($CHCl_3$) ν_{max} 3420, 1753, 1691, 1660, 1508, 1482 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.41/3.42 (3H, s/s), 3.65/3.71 (1H, m), 3.75 (3H, s), 4.02/4.04 (1H, [dd, J = 4.1, 6.3 Hz/ dd, J = 4.1, 6.3 Hz]), 4.57/4.59 (1H, [d, J = 12 Hz/ d, J = 11.3 Hz]), 4.62/4.64 (1H, [d, J = 12 Hz/ d, J = 11.9 Hz]), 4.89 (1H, m), 5.57/5.59 (1H, [d, J = 5.7 Hz/ d, J = 5.9 Hz]), 7.15 (1H, d, J = 6.6 Hz), 7.28

(1H, m), 7.30–7.35 (4H, m), 7.42 (2H, dd, J = 7.3, 7.9 Hz), 7.51 (1H, dd, J = 7.3, 7.6 Hz), 7.58/7.70 (1H, [d, J = 9.1 Hz/ d, J = 8.8 Hz]), 7.79 (2H, d, J = 8.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 52.8 (CH_3), 52.96/53.03 (CH), 56.4/56.5 (CH_3), 69.16/69.21 (CH_2), 73.6 (CH_2), 78.3/78.4 (CH), 127.1 (2 × CH), 127.8 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.4 (C), 137.08/137.12 (C), 167.3 (C), 167.8 (C), 170.9/171.0 (C); HRMS (EI) calcd for $C_{21}H_{24}N_2O_6$ (M^+) 400.1634; found, 400.1622. Anal. calcd for $C_{21}H_{24}N_2O_6$ C 62.99, H 6.04, N 7.00; found C 62.64, H 6.06, N 6.92.

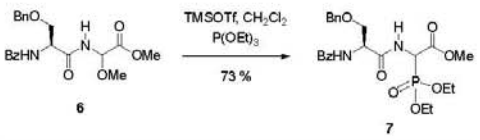
Scheme 4. Preparation of α-methoxyglycine Derivative **11**



***N*-(*N*-Benzyloxycarbonyl-L-leucyl)-2-(methoxy) glycine Methyl Ester (11).** Obtained from commercial Cbz-Leu-Ser-OMe (**10**) (73 mg, 0.2 mmol) as described for the α-methoxyglycine derivative **6**. Usual work-up and purification by column chromatography (hexanes-EtoAc 60:40) gave the methoxy derivative **11** (57 mg, 78%) as a 10:7 diastereomer mixture. White solid; m.p. 109-110 °C (EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3423, 1751, 1719, 1697, 1504 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 0.92 (3H, d, J = 6.3 Hz), 0.93 (3H, d, J = 6.4 Hz), 1.53 (1H, m), 1.60–1.74 (2H, m), 3.38/3.40 (3H, s/s), 3.76/3.77 (3H, s/s), 4.31 (1H, m), 5.08 (1H, d, J = 14 Hz), 5.12 (1H, d, J = 14.5 Hz), 5.44/5.47 (1H, [d, J = 7.9 Hz /d, J = 8.2 Hz]), 5.52/5.53 (1H, [d, J = 8.8 Hz/ d, J = 9.1 Hz]), 7.26–7.32 (6H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 21.7/21.8 (CH_3), 22.8/22.9 (CH_3), 24.6/24.7 (CH), 41.3/41.4 (CH_2), 52.8 (CH_3), 53.7 (CH), 56.4/56.5 (CH_3), 67.1 (CH_2), 78.3 (CH), 128.0 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.1 (C), 156.2 (C), 168.2 (C), 173.2 (C). HRMS (EI) calcd for $C_{16}H_{23}N_2O_4$ (M^+ – CO_2Me) 307.1664; found, 307.1658. Anal. calcd for $C_{18}H_{26}N_2O_6$ C 59.00, H 7.15, N 7.65; found C 58.71, H 7.07, N 7.86.

Study of the Phosphorylation Reaction.

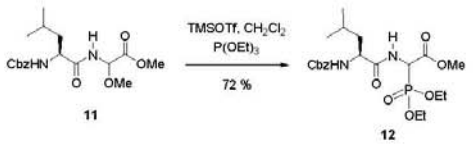
Scheme 5. Synthesis of the phosphorylation product **7**



General Procedure for the Phosphorylation Reaction. To a solution of the methoxyderivative (0.2 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added triethylphosphite (174 μL, 166 mg, 1 mmol) and TMSOTf (109 μL, 133 mg, 0.6 mmol). The reaction mixture was stirred for 3 h, then it was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and evaporated as usual, and the residue was purified by chromatography on silica gel (hexanes/EtOAc), to afford the α-aminophosphonate derivatives.

***N*-(*N*-Benzoyl-*O*-benzyl-L-seryl)-2-(diethoxyphosphoryl)glycine Methyl Ester (7).** Obtained from compound **6** (80 mg, 0.2 mmol) according to the General Procedure for the phosphorylation reaction. After purification by rotatory chromatography (hexanes/EtOAc 50:50), compound **7** was isolated as a 1:1 diastereomer mixture (74 mg, 73%): Syrup; IR ($CHCl_3$) ν_{max} 3419, 1748, 1684, 1660, 1508 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 1.20–1.35 (6H, m), 3.64/3.68 (1H, dd, J = 7.9, 9.5 Hz/dd, J = 7.3, 9.8 Hz), 3.79/3.80 (3H, s/s), 4.04/4.05 (1H, dd, J = 4.0, 9.3 Hz/dd, J = 4.0, 9.5 Hz), 4.08-4.20 (4H, m), 4.60 (1H, d, J = 11.9 Hz), 4.65 (1H, d, J = 11.9 Hz), 4.88 (1H, m), 5.16/5.20 (1H, dd, J = 8.0, 21.8 Hz/ dd, J = 7.3, 20.5 Hz), 7.14/7.15 (1H, d, J = 7.0, 7.3 Hz), 7.30–7.40 (5H, m), 7.42 (2H, dd, J = 7.6, 7.9 Hz), 7.51 (1H, dd, J = 7.6, 7.9 Hz), 7.63/7.64 (1H, d, J = 8.8 Hz/d, J = 8.9 Hz), 7.80/7.81 (2H, brd, J = 8.0 Hz/brd, J = 8.5 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C 16.2 (2 × CH_3, d, $J_{C,P}$ = 5.7 Hz), 50.95/51.00 (CH, d, $J_{C,P}$ = 147.2 Hz), 52.5/52.8 (CH), 53.2 (CH_3), 63.8 (CH_2, d, $J_{C,P}$ = 7.4 Hz), 63.9 (CH_2, d, $J_{C,P}$ = 7.4 Hz), 69.2 (CH_2), 73.5/73.6 (CH_2), 127.1 (2 × CH), 127.8 (CH), 127.9 (2 × CH), 128.5 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.5 (C), 137.1/137.2 (C), 166.8 (C), 167.2/167.3 (C), 169.8/170.2 (C, d, $J_{C,P}$ = 6.4 Hz); HRMS calcd for $C_{24}H_{31}N_2O_8P$ [M^+], 506.1818; found, 506.1831.

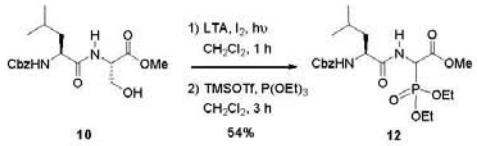
Scheme 6. Synthesis of the phosphorylation product **12**



***N*-(*N*-Benzyloxycarbonyl-L-leucyl)-2-(diethoxyphosphoryl)glycine Methyl Ester (20).** Obtained from compound **11** (73 mg, 0.2 mmol) according to the General Procedure for the phosphorylation reaction. After purification by rotatory chromatography (hexanes/EtOAc 50:50), compound **12** (68 mg, 72%) was isolated as a 1:1 diastereomer mixture: Syrup; IR ($CHCl_3$) ν_{max} 3429, 1746, 1719, 1688, 1507 cm^{-1},^{1}H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 0.92 (6H, d, J = 6.3 Hz), 1.25–1.32 (6H, m), 1.51 (1H, m), 1.60–1.73 (2H, m), 3.77 (3H, s), 4.05–4.20 (4H, m), 4.34 (1H, m),

5.09 (2H, s), 5.15/5.17 (1H, [dd, J = 8.8 Hz, $J_{H,P}$ = 22.4 Hz/ dd, J = 8.9 Hz, $J_{H,P}$ = 22.3 Hz]), 5.47 (1H, br b), 7.20 (1H, br d, J = 7.9 Hz), 7.28–7.35 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C): δ_C 16.2 (2 × CH_3, d, $J_{C,P}$ = 5.7 Hz), 21.8 (CH_3), 22.8 (CH_3), 24.6 (CH), 41.5 (CH_2), 50.6 (CH, d, $J_{C,P}$ = 147.9 Hz), 52.97/53.03 (CH_3), 53.44/53.51 (CH), 63.7 (CH_2, d, $J_{C,P}$ = 7.0 Hz), 63.9 (CH_2, d, $J_{C,P}$ = 5.2 Hz), 67.0 (CH_2), 127.9 (CH), 128.1 (2 × CH), 128.5 (2 × CH), 136.2 (C), 156.0 (C), 166.9 (C), 172.1 (C); HRMS calcd for $C_{21}H_{33}N_2O_8P$ [M^+], 472.1975; found, 472.1978.

Scheme 7. Simplified procedure for the preparation of the scission-phosphorylation product **12**

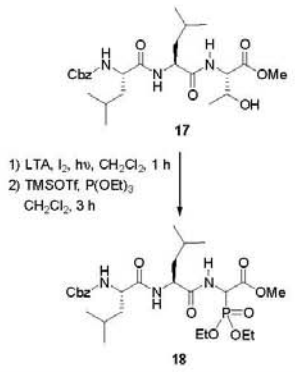


10 12

General Procedure for the Simplified Scission –Phosphorylation Process. To a solution of the starting material (0.2 mmol) in dry dichloromethane (8 mL) was added iodine (51 mg, 0.2 mmol) and lead tetraacetate (LTA, 178 mg, 0.4 mmol). The reaction mixture was stirred for 1 h at room temperature (26 °C) under irradiation with visible light (80-W tungsten-filament lamp). Then the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2, and the solvent was dried and evaporated as usual. The unpurified residue was dissolved in dry CH_2Cl_2 (8 mL), the solution was cooled to 0 °C and triethylphosphite (174 µL, 166 mg, 1 mmol) and TMSOTf (109 µL, 133 mg, 0.6 mmol) were added. The reaction mixture was stirred for 3 h, then it was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. After usual solvent drying and evaporation, the residue was purified by chromatography on silica gel (hexanes/EtOAc), to afford the α-aminophosphonate derivatives.

***N*-(*N*-Benzyloxycarbonyl-L-leucyl)-2-(diethoxy phosphoryl)glycine Methyl Ester (12).** Obtained from Cbz-Leu-Ser-OMe (**10**) (73 mg, 0.2 mmol) according to the General Procedure for the scission-phosphorylation reaction. After purification by rotatory chromatography (hexanes/EtOAc 50:50), compound **12** (67 mg, 71%) was isolated as a 1:1 diastereomer mixture.

Scheme 8. Synthesis of the scission–phosphorylation **18**

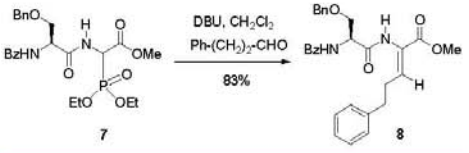


17 18

***N*-(*N*-Benzyloxycarbonyl-L-leucyl-L-leucyl)-2-(diethoxy phosphoryl)glycine Methyl Ester (18).** Obtained from compound **17** (80 mg, 0.2 mmol) according to the Simplified Scission–Phosphorylation Procedure. After purification by rotatory chromatography (hexanes/EtOAc 40:60), compound **18** was isolated as a 1:1 diastereomer mixture (71 mg, 61%): Syrup; IR ($CHCl_3$) ν_{max} 3426, 3318, 1747, 1712, 1678, 1506 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 0.85–0.92 (12H, m), 1.24–1.35 (6H, m), 1.50–1.70 (6H, m), 3.75/3.77 (3H, s/s), 4.11–4.25 (5H, m), 4.61/4.69 (1H, m/m), 5.09 (2H, s), 5.13/5.16 (1H, m/m), 5.49/5.68 (1H, [d, J = 7.9 Hz/ d, J = 7.9 Hz]), 6.66/6.76 (1H, [d, J = 8.2 Hz/ d, J = 7.6 Hz], 7.26-7.35 (5H, m), 7.34/7.56 (1H, [m/ d, J = 8.5 Hz]); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C 16.2 (2 × CH_3, d, $J_{C,P}$ = 5.8 Hz), 21.8 (CH_3), 22.0/22.1 (CH_3), 22.7/22.8 (CH_3), 22.9 (CH_3), 24.5 (CH), 24.6 (CH), 41.1 (CH_2), 41.2 (CH_2), 50.5/50.6 (CH, [d, $J_{C,P}$ = 146 Hz/ d, $J_{C,P}$ = 147.2 Hz), 51.4/51.5 (CH), 53.0/53.1 (CH_3), 53.4/53.5 (CH), 63.6 (CH_2, d, $J_{C,P}$ = 7.4 Hz), 63.9 (CH_2, d, $J_{C,P}$ = 6.4 Hz), 67.0 (CH_2), 128.0 (2 × CH), 128.1 (CH), 128.4 (2 × CH), 136.2 (C), 156.3 (C), 166.8/166.9 (C), 171.8 (C), 172.3/172.5 (C); HRMS calcd for $C_{27}H_{44}N_3O_9P$ [M^+], 585.2815; found, 585.2804.

Preparation of Dehydroamino Acids.

Scheme 9. Preparation of the HWE product **8**



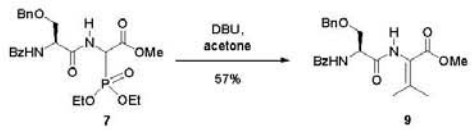
7 8

General Procedures for the Horner-Wadsworth-Emmons Reaction. Method A. To a solution of the α-phosphonate (0.2 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of DBU (151 μL, 76 mg, 0.5 mmol) in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred for 10 min, and then was added the aldehyde (0.4 mmol) in dry CH_2Cl_2 (1 mL). After stirring for 16 h, the solution was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc) affording the dehydroamino acid derivatives.

Method B. To a solution of the amino phosphonate (0.2 mmol) in dry acetone (4 mL) was added DBU (302 μL, 152 mg, 1.0 mmol). The reaction mixture was stirred for 24 h, followed by work-up and purification as described for Method A, giving the dehydroamino acid derivatives.

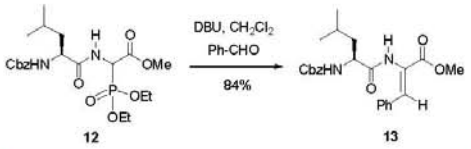
(*Z*)-(*N*-Benzoyl-*O*-benzyl-L-seryl)-α,β-dehydro-5-(phenyl)norvaline Methyl Ester (8). Obtained from the amino phosphonate **7** (101 mg, 0.2 mmol) and hydrocinnamaldehyde (53 μL, 54 mg, 0.4 mmol), according to the General HWE Procedure, Method A. After purification by column chromatography (hexanes/EtOAc 65:35), compound **8** (81 mg, 83%) was isolated as a syrup; $[\alpha]_D$ = +12 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3409, 1722, 1695, 1659, 1506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 2.39 (2H, ddd, *J* = 6.6, 7.6, 7.6 Hz), 2.69 (2H, dd, *J* = 7.6, 7.6 Hz), 3.63 (1H, dd, *J* = 7.6, 9.1 Hz), 3.66 (3H, s), 4.00 (1H, dd, *J* = 4.1, 9.2 Hz), 4.54 (1H, d, *J* = 11.7 Hz), 4.58 (1H, d, *J* = 11.8 Hz), 4.83 (1H, m), 6.67 (1H, dd, *J* = 7.3, 7.6 Hz), 7.09 (1H, br b), 7.10 (2H, dd, *J* = 7.8, 7.9 Hz), 7.11 (1H, dd, *J* = 7.4, 7.8 Hz), 7.19 (2H, dd, *J* = 7.6, 7.8 Hz), 7.24 (1H, m), 7.25–7.28 (4H, m), 7.37 (2H, dd, *J* = 7.8, 7.9 Hz), 7.46 (1H, dd, *J* = 7.6, 7.8 Hz), 7.74 (2H, d, *J* = 7.5 Hz), 7.88 (1H, br b); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C 30.3 (CH_2), 34.1 (CH_2), 52.3 (CH_3), 52.9 (CH), 69.3 (CH_2), 73.6 (CH_2), 125.2 (C), 126.1 (CH), 127.1 (2 × CH), 127.9 (2 × CH), 128.0 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.5 (C), 137.2 (C), 137.8 (CH), 140.8 (C), 164.5 (C), 167.3 (C), 168.7 (C); HRMS calcd for $C_{29}H_{30}N_2O_5$ [M^+], 486.2155; found, 486.2147.

Scheme 10. Preparation of the HWE product **9**



(Z)-(*N*-Benzoyl-*O*-benzyl-L-seryl)-α,β-dehydro valine Methyl Ester (9). Obtained from the amino phosphonate **7** (101 mg, 0.2 mmol), according to the General HWE Procedure, Method B. After purification by column chromatography (hexanes/EtOAc 60:40), compound **9** (47 mg, 57%) was isolated as a syrup; $[\alpha]_D$ = +16 (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3414, 1723, 1687, 1658, 1507 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 1.78 (3H, s), 2.15 (3H, s), 3.68 (1H, m), 3.69 (3H, s), 4.08 (1H, dd, *J* = 4.4, 9.5 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.68 (1H, d, *J* = 11.8 Hz), 4.87 (1H, m), 7.19 (1H, d, *J* = 6.0 Hz), 7.32 (1H, m), 7.33–7.36 (4H, m), 7.44 (2H, dd, *J* = 7.6, 7.8 Hz), 7.52 (1H, dd, *J* = 7.0, 7.8 Hz), 7.81 (2H, d, *J* = 7.9 Hz), 7.86 (1H, brb); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C 21.2 (CH_3), 22.3 (CH_3), 51.7 (CH_3), 52.6 (CH), 69.3 (CH_2), 73.7 (CH_2), 120.7 (C), 127.1 (2 × CH), 127.9 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.6 (C), 137.2 (C), 145.9 (C), 164.9 (C), 167.3 (C), 168.9 (C); HRMS calcd for $C_{23}H_{26}N_2O_5$ [M^+] 410.1842, found 410.1829.

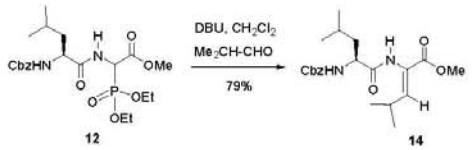
Scheme 11. Preparation of the HWE product **13**



(Z)-(*N*-Benzyloxycarbonyl-L-leucyl)-α,β-dehydrophenylalanine Methyl Ester (13).[1] Obtained from the amino phosphonate **12** (94 mg, 0.2 mmol) and benzaldehyde (41 μL, 42 mg, 0.4mmol) according to the General HWE Procedure, Method A. After purification by rotatory chromatography (hexanes/EtOAc 80:20), compound **13** (71 mg, 84%) was isolated as a syrup; $[\alpha]_D$ = −11 (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3430, 1716, 1705, 1504 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 0.94 (3H, d, *J* = 7.3 Hz), 0.95 (3H, d, *J* = 6.3 Hz), 1.54 (1H, m), 1.70–1.78 (2H, m), 3.80 (3H, s), 4.35 (1H, m), 5.09 (1H, d, *J* = 12.6 Hz), 5.13 (1H, d, *J* = 12.0 Hz), 5.26 (1H, d, *J* = 8.2 Hz), 7.29–7.34 (8H, m), 7.41 (1H, s), 7.45 (2H, m), 7.74 (1H, br b); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C 22.0 (CH_3), 22.8 (CH_3), 24.6 (CH), 40.6 (CH_2), 52.6 (CH_3), 53.7 (CH), 67.2 (CH_2), 123.8 (C), 128.0 (2 × CH), 128.2 (2 × CH), 128.5 (4 × CH), 129.5 (CH), 129.7 (CH), 132.9 (CH), 133.5 (C), 136.0 (C), 156.4 (C), 165.4 (C), 170.8 (C); HRMS calcd for $C_{24}H_{28}N_2O_5$ [M^+], 424.1998; found, 424.1982.

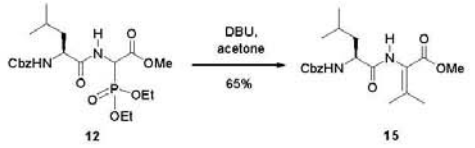
[1] Buck, R. T.; Clarke, P. A.; Coe, D. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Swann, E. *Chem. Eur. J.* **2000**, *6*, 2160–2167.

Scheme 12. Preparation of the HWE product **14**



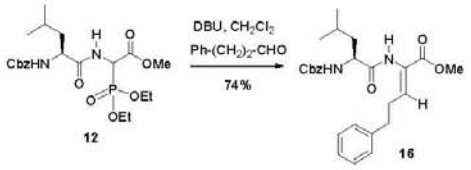
(Z)-(*N*-Benzyloxycarbonyl-L-leucyl)-α,β-dehydro leucine Methyl Ester (14). Obtained from the amino phosphonate **12** (94 mg, 0.2 mmol) and isobutyraldehyde (37 μL, 29 mg, 0.4 mmol), according to the General HWE Procedure, Method A. After purification by column chromatography (hexanes/EtOAc 85:15), compound **15** (62 mg, 79%) was isolated as a syrup; $[\alpha]_D = -25$ (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3430, 1717, 1701, 1508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 0.95 (6H, d, *J* = 6.3 Hz), 1.00 (3H, d, *J* = 6.6 Hz), 1.02 (3H, d, *J* = 6.3 Hz), 1.56 (1H, m), 1.69–1.78 (2H, m), 2.54 (1H, m), 3.72 (3H, s), 4.34 (1H, m), 5.11 (2H, s), 5.38 (1H, d, *J* = 7.3 Hz), 6.51 (1H, d, *J* = 10.4 Hz), 7.28–7.37 (5H, m), 7.51 (1H, br b). ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C): δ_C 21.5 (CH_3), 21.6 (CH_3), 21.9 (CH_3), 22.9 (CH_3), 24.7 (CH), 27.9 (CH), 41.1 (CH_2), 52.2 (CH_3), 53.6 (CH), 67.1 (CH_2), 122.9 (C), 127.9 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 136.1 (C), 146.0 (CH), 156.3 (C), 165.0 (C), 171.2 (C); HRMS calcd for $C_{21}H_{30}N_2O_5$ [M^+], 390.2155; found, 390.2163.

Scheme 13. Preparation of the HWE product **15**



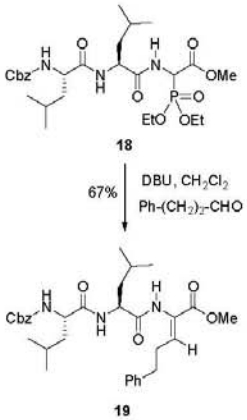
(Z)-(*N*-Benzyloxycarbonyl-L-leucyl)-α,β-dehydrovaline Methyl Ester (15). Obtained from the amino phosphonate **12** (94 mg, 0.2 mmol), according to the General HWE Procedure, Method B. After purification by column chromatography (hexanes/EtOAc 75:25), compound **15** (49 mg, 65%) was isolated as a syrup; $[\alpha]_D = -39$ (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3428, 1718, 1507 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 0.93 (3H, d, *J* = 6.0 Hz), 0.94 (3H, d, *J* = 6.3 Hz), 1.54 (1H, m), 1.67–1.73 (2H, m), 1.76 (3H, s), 2.12 (3H, s), 3.67 (3H, s), 4.30 (1H, m), 5.09 (2H, brs), 5.39 (1H, brb), 7.26–7.38 (5H, m), 7.50 (1H, brb); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C 21.2 (CH_3), 22.1 (CH_3), 22.4 (CH_3), 22.8 (CH_3), 24.7 (CH), 40.9 (CH_2), 51.6 (CH_3), 53.5 (CH), 67.1 (CH_2), 120.7 (C), 128.0 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 136.1 (C), 146.3 (C), 156.3 (C), 164.9 (C), 170.9 (C); HRMS calcd for $C_{20}H_{28}N_2O_5$ [M^+], 376.1998; found, 376.2004.

Scheme 14. Preparation of the HWE product **16**



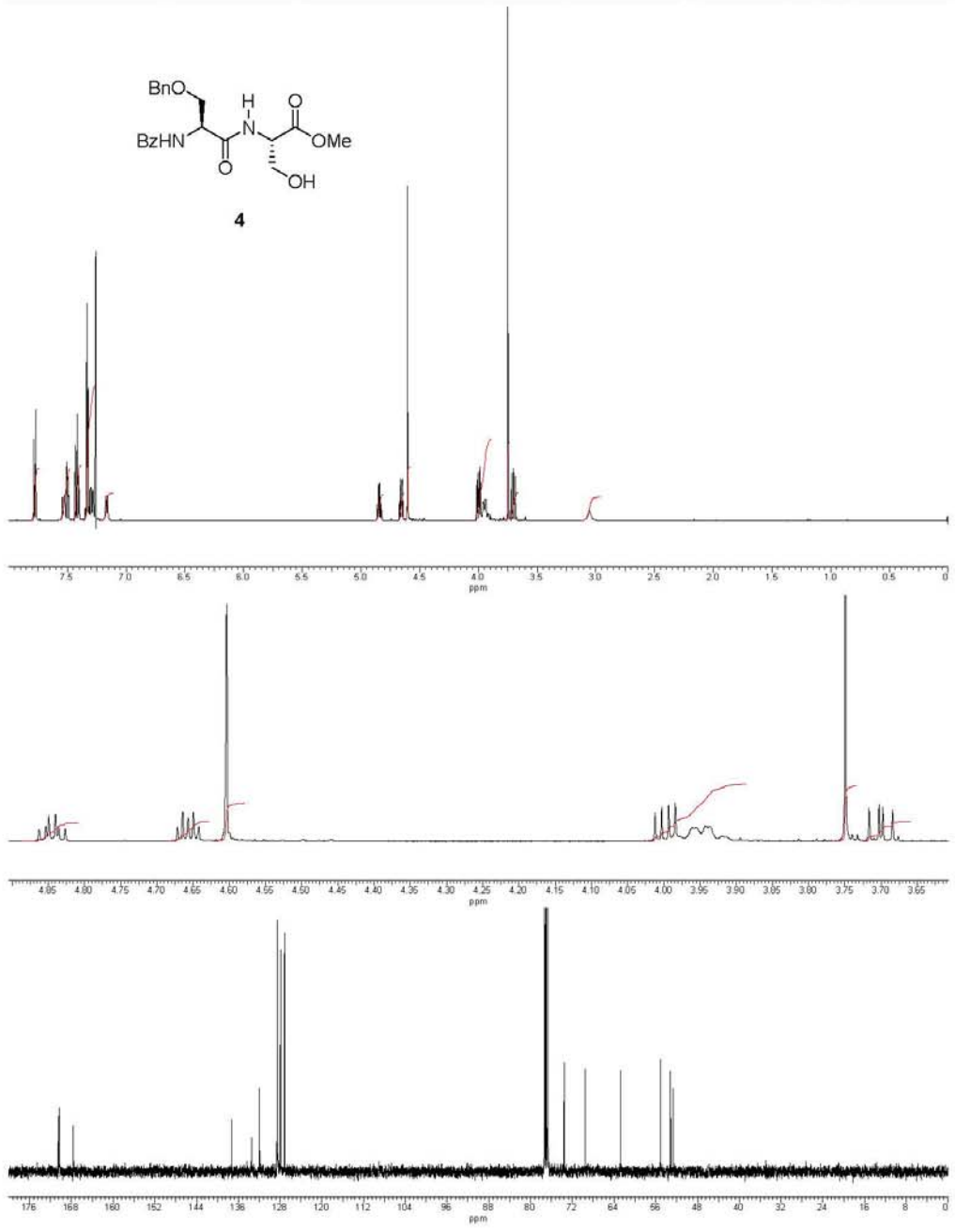
(Z)-(*N*-Benzyloxycarbonyl-L-leucyl)-α,β-dehydro-5-(phenyl)norvaline Methyl Ester (16). Obtained from the amino phosphonate **12** (94 mg, 0.2 mmol) and hydrocinnamaldehyde (53 μL, 54 mg, 0.4mmol), according to the General HWE Procedure, Method A. After purification by column chromatography (hexanes/EtOAc 75:25), compound **16** (67 mg, 74%) was isolated as a syrup; $[\alpha]_D = -27$ (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3420, 1716, 1703, 1504 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 0.95 (6H, d, *J* = 6.6 Hz), 1.53 (1H, m), 1.65–1.75 (2H, m), 2.45 (2H, m), 2.77 (2H, dd, *J* = 7.2, 7.6 Hz), 3.73 (3H, s), 4.25 (1H, m), 5.08 (1H, d, *J* = 12.6 Hz), 5.12 (1H, d, *J* = 12.0 Hz), 5.17 (1H, br b), 6.72 (1H, dd, *J* = 7.6, 7.6 Hz), 7.17–7.21 (4H, m), 7.28 (2H, dd, *J* = 7.3, 7.3 Hz), 7.33–7.40 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C): δ_C. 21.9 (CH_3), 22.9 (CH_3), 24.7 (CH), 30.3 (CH_2), 34.1 (CH_2), 41.2 (CH_2), 52.3 (CH_3), 53.7 (CH), 67.1 (CH_2), 125.2 (C), 126.1 (CH), 128.0 (2 × CH), 128.2 (CH), 128.4 (2 × CH), 128.44 (2 × CH), 128.49 (2 × CH), 136.1 (C), 137.8 (CH), 140.9 (C), 156.2 (C), 164.6 (C), 170.8 (C); HRMS calcd for $C_{26}H_{32}N_2O_5$ [M^+], 452.2311; found, 452.2297.

Scheme 15. Preparation of the HWE product **19**



(*Z*)-(*N*-Benzyloxycarbonyl-L-leucyl-L-leucyl)-α,β-dehydro-5-(phenyl)norvaline Methyl Ester (19). Obtained from the amino phosphonate **18** (117 mg, 0.2 mmol) and hydrocinnamaldehyde (53 μL, 54 mg, 0.4 mmol), according to the General HWE Procedure, Method A. After purification by column chromatography (hexanes/EtOAc 40:60), compound **19** (76 mg, 67%) was isolated as a syrup; $[\alpha]_D$ = –50 (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3422, 1716, 1504 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 26 °C): δ_H 0.81–0.87 (12H, m), 1.38–1.71 (6H, m), 2.35–2.40 (2H, m), 2.65–2.72 (2H, m), 3.64 (3H, s), 4.13 (1H, m), 4.45 (1H, ddd, *J* = 6.0, 8.2, 8.2 Hz), 4.98 (1H, d, *J* = 11 Hz), 5.03 (1H, d, *J* = 12.0 Hz), 5.24 (1H, br d, *J* = 7.6 Hz), 6.58 (1H, br d, *J* = 8.2 Hz), 6.62 (1H, dd, *J* = 7.3, 7.3 Hz), 7.10–7.14 (3H, m), 7.19–7.30 (7H, m), 7.50 (1H, br b); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): δ_C 21.8 (CH_3), 22.0 (CH_3), 22.8 (CH_3), 22.9 (CH_3), 24.7 (2 × CH), 30.2 (CH_2), 34.1 (CH_2), 40.6 (CH_2), 41.1 (CH_2),. 51.8 (CH), 52.3 (CH_3), 53.6 (CH), 67.2 (CH_2), 125.3 (C), 126.1 (CH), 128.1 (2 × CH), 128.2 (CH), 128.4 (2 × CH), 128.5 (4 × CH), 136.0 (C), 137.8 (CH), 140.9 (C), 156.4 (C), 164.6 (C), 170.4 (C), 172.5 (C); HRMS calcd for $C_{32}H_{43}N_3O_6$ [M^+], 565.3152; found, 565.3165.

^{1}H and ^{13}C NMR spectra for compounds 4–9 and 11–19; NOE experiments for products 8, 13, 14, 16 and 19



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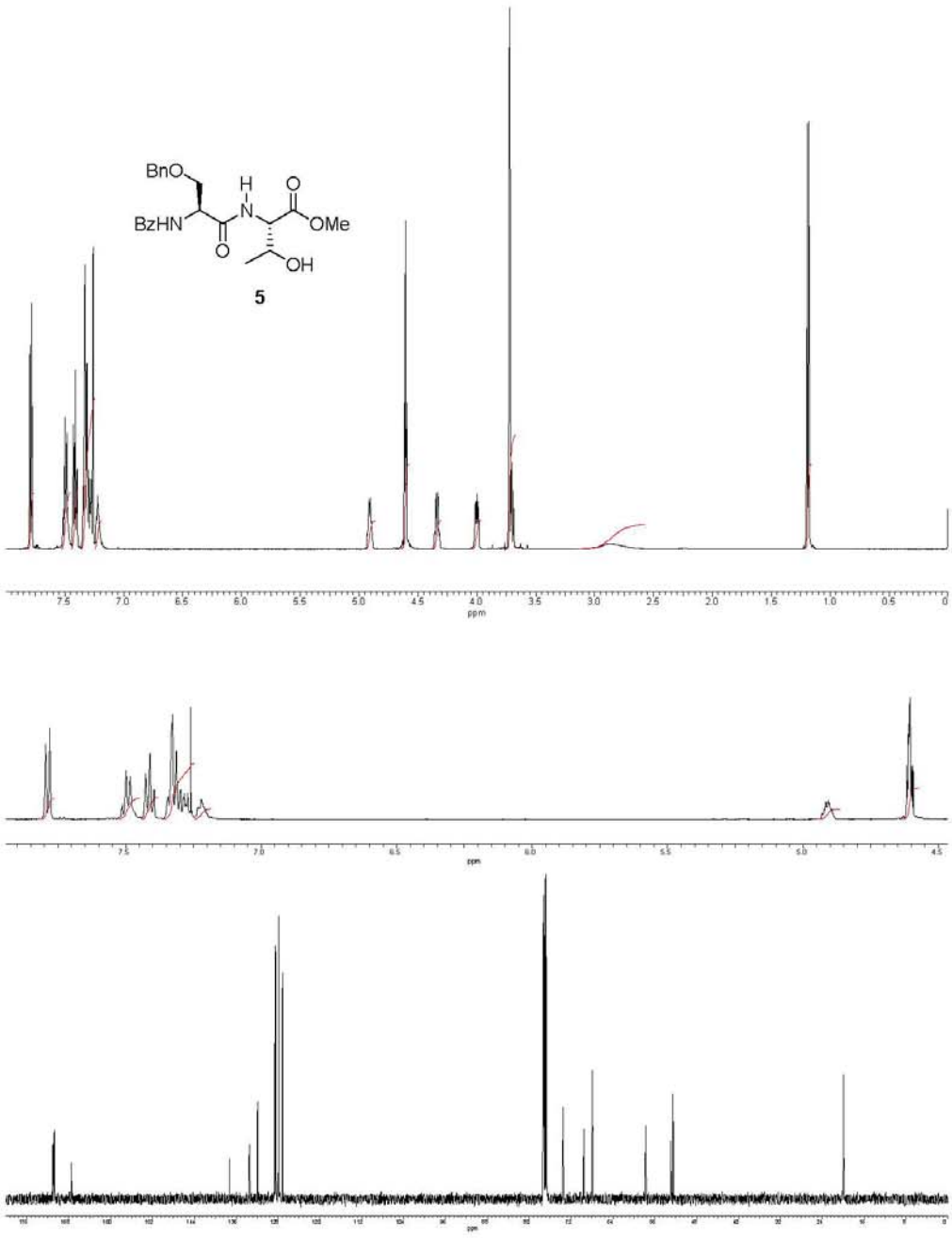
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N
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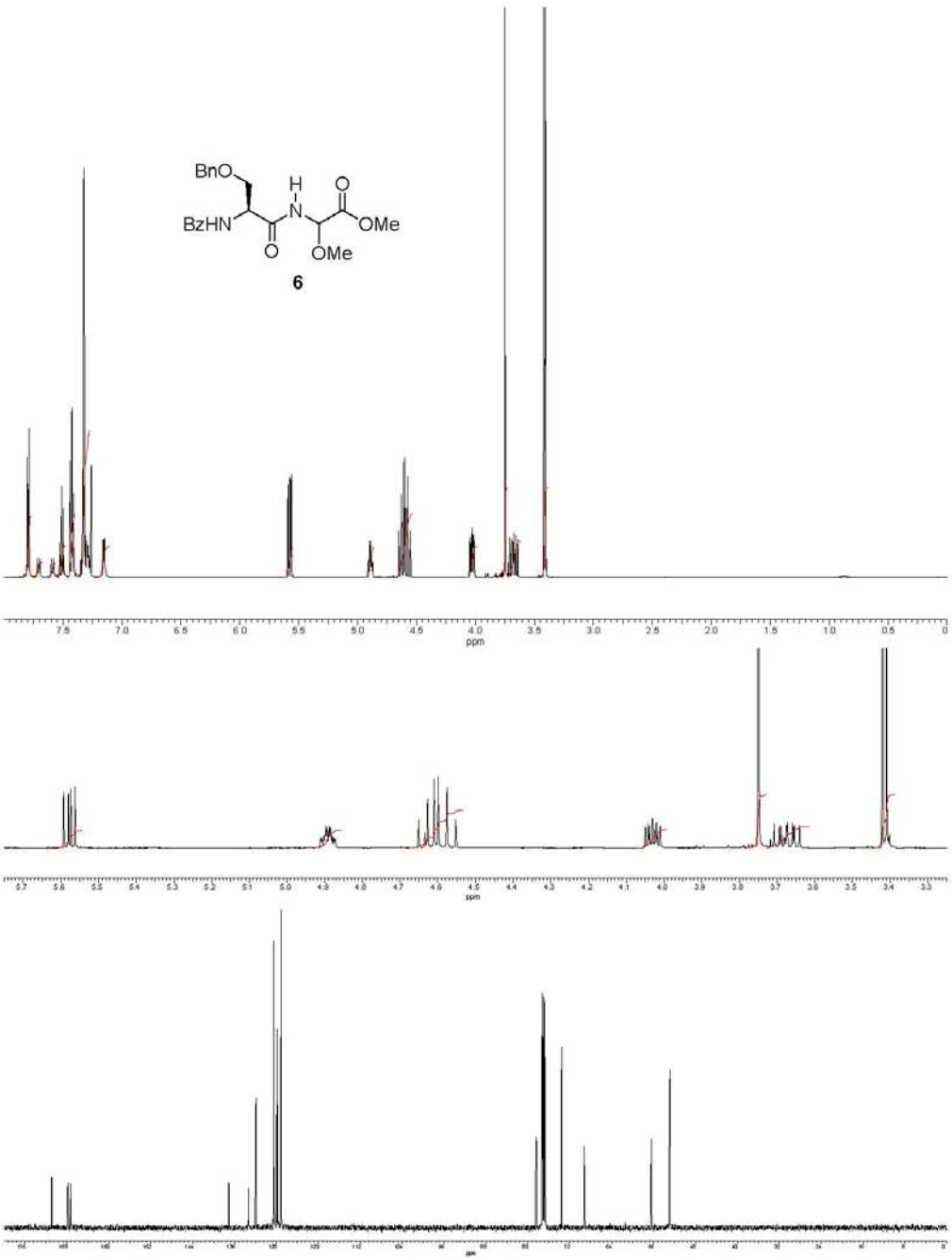
BzHN
OMe
O
OH
5



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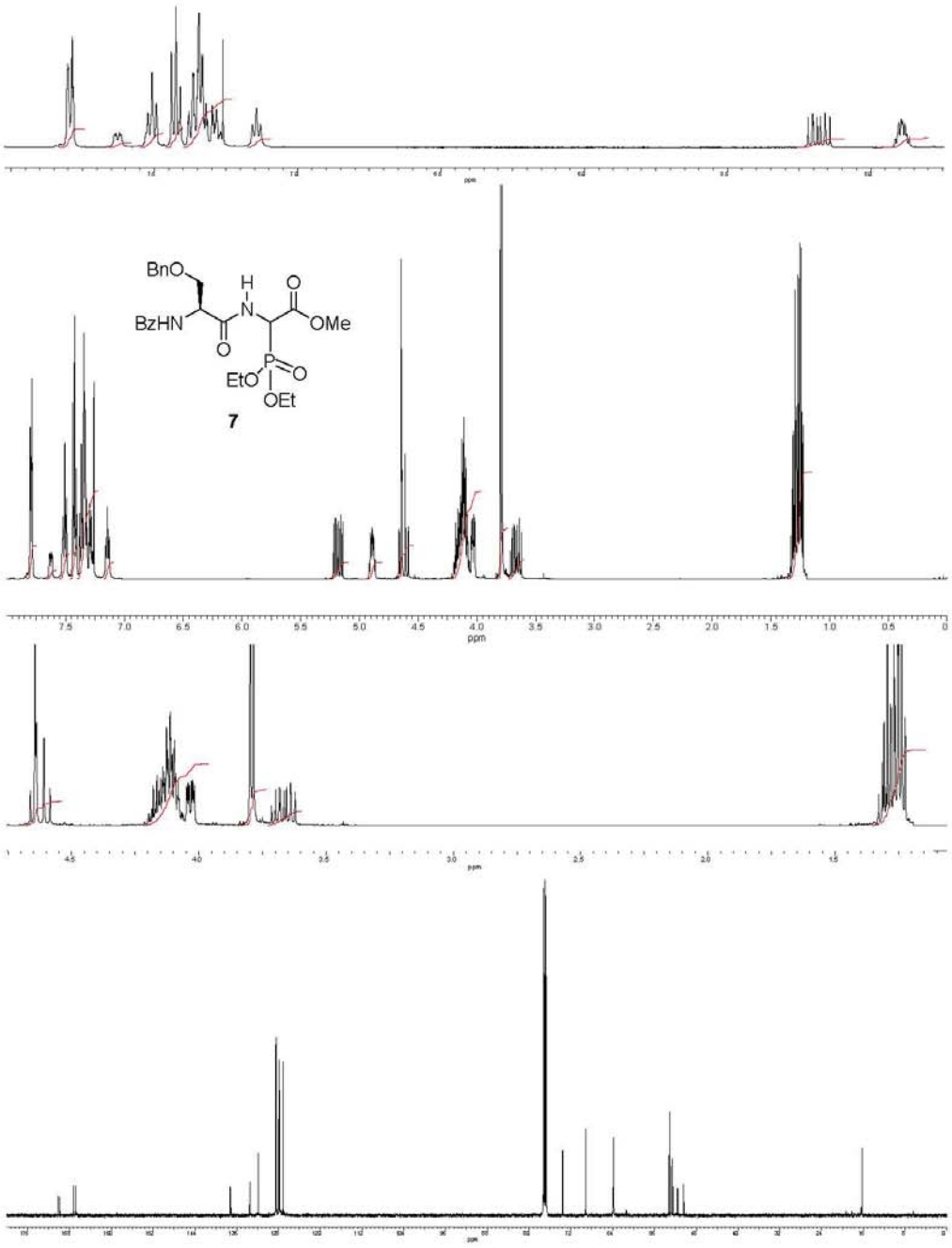

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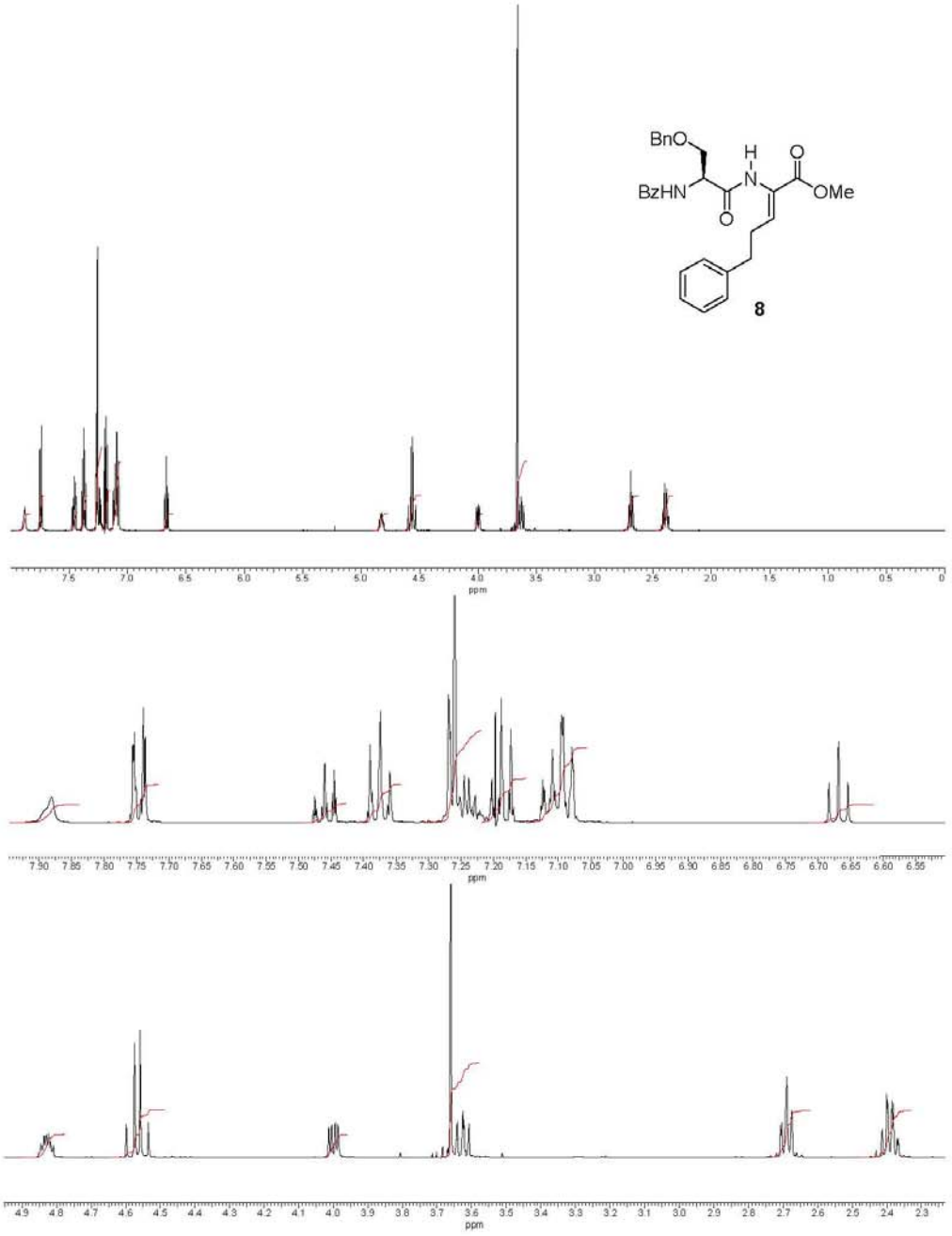

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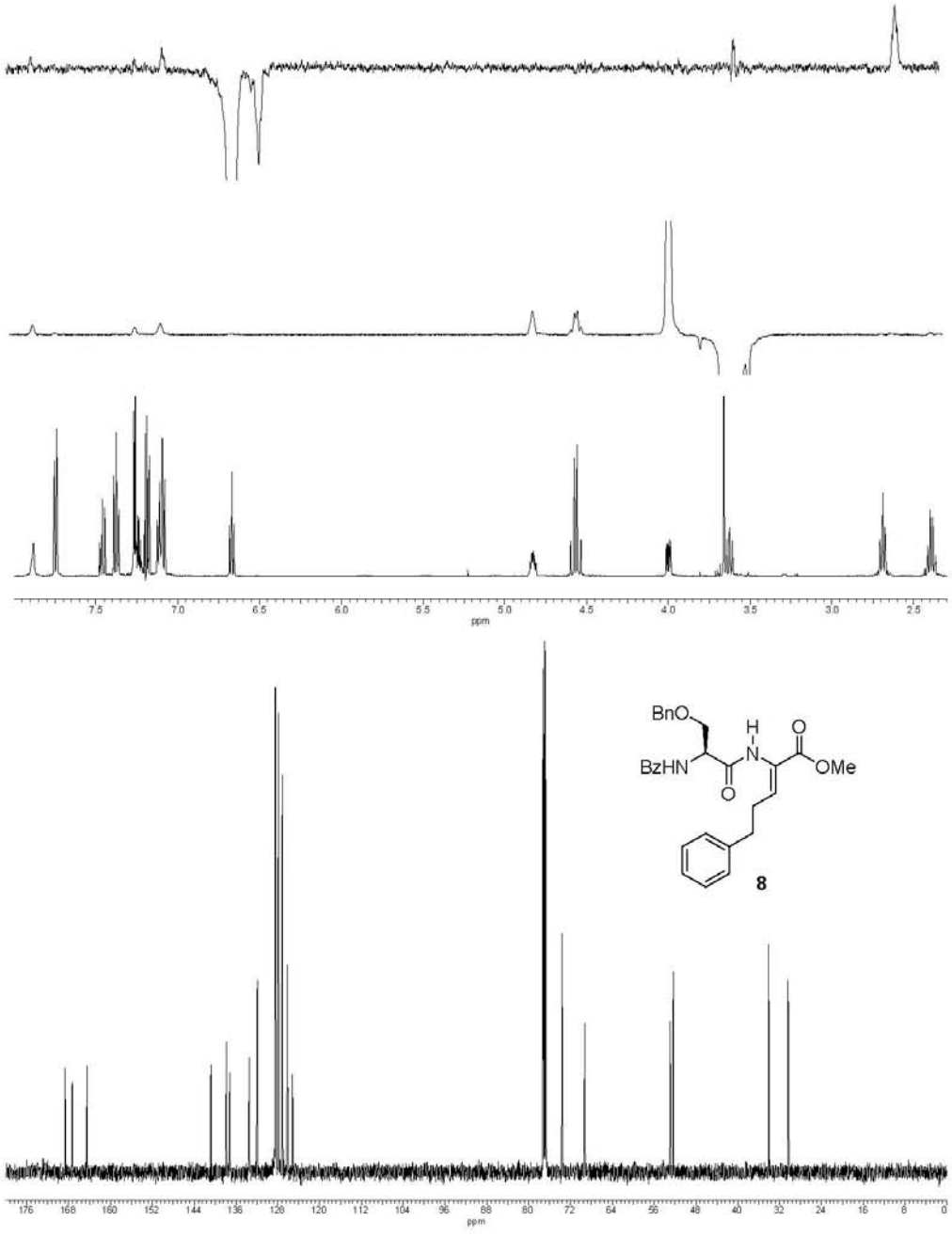

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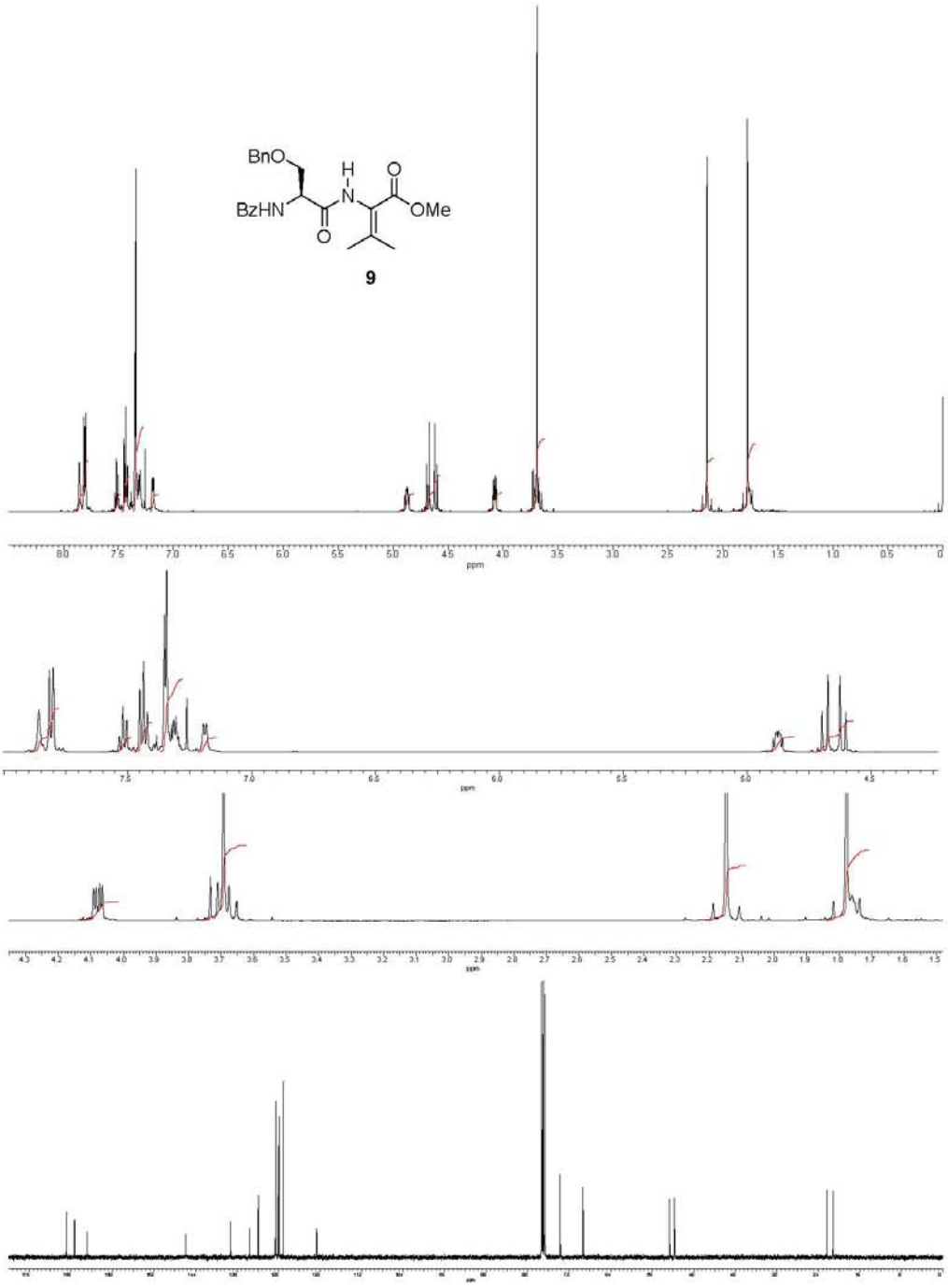

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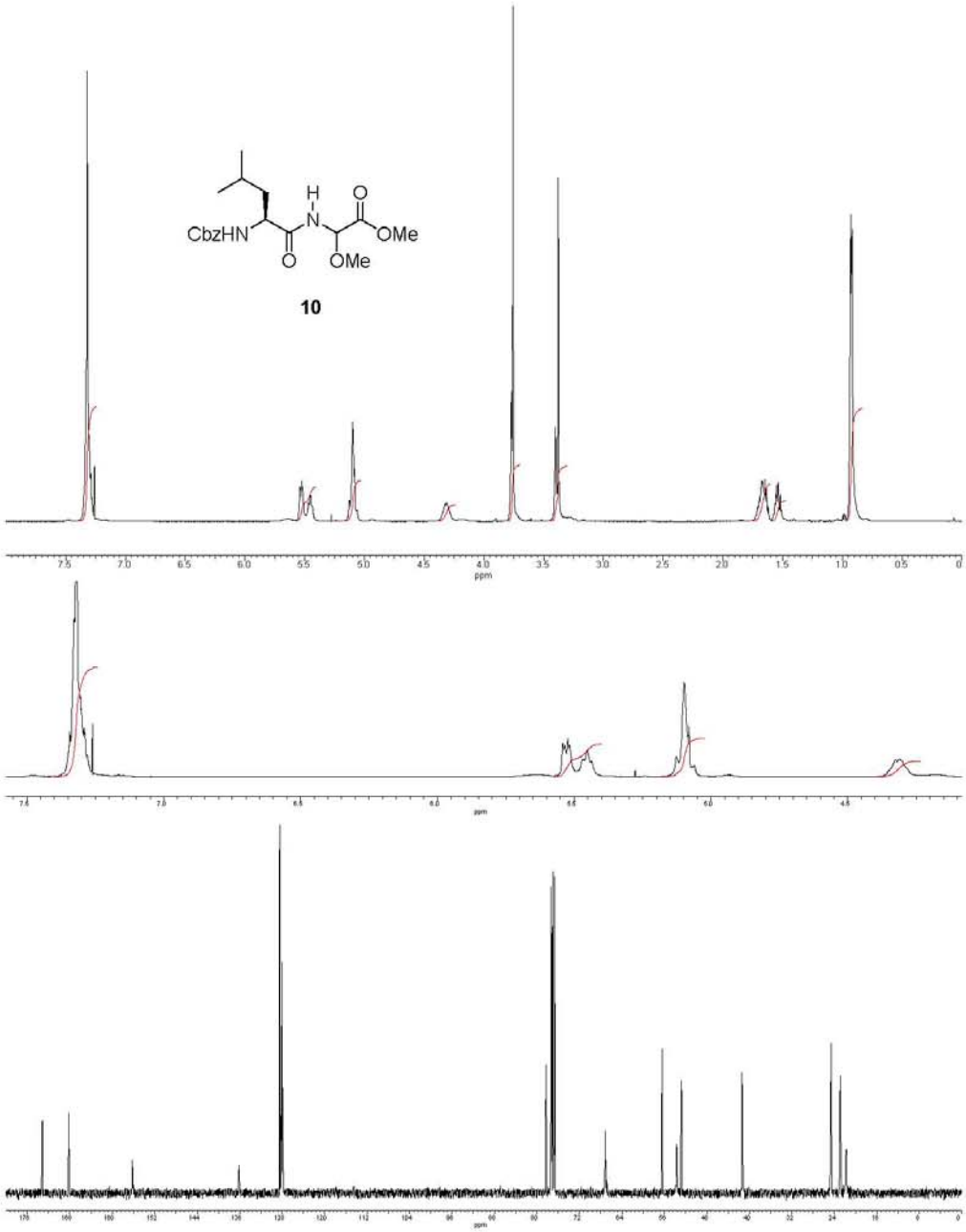
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N
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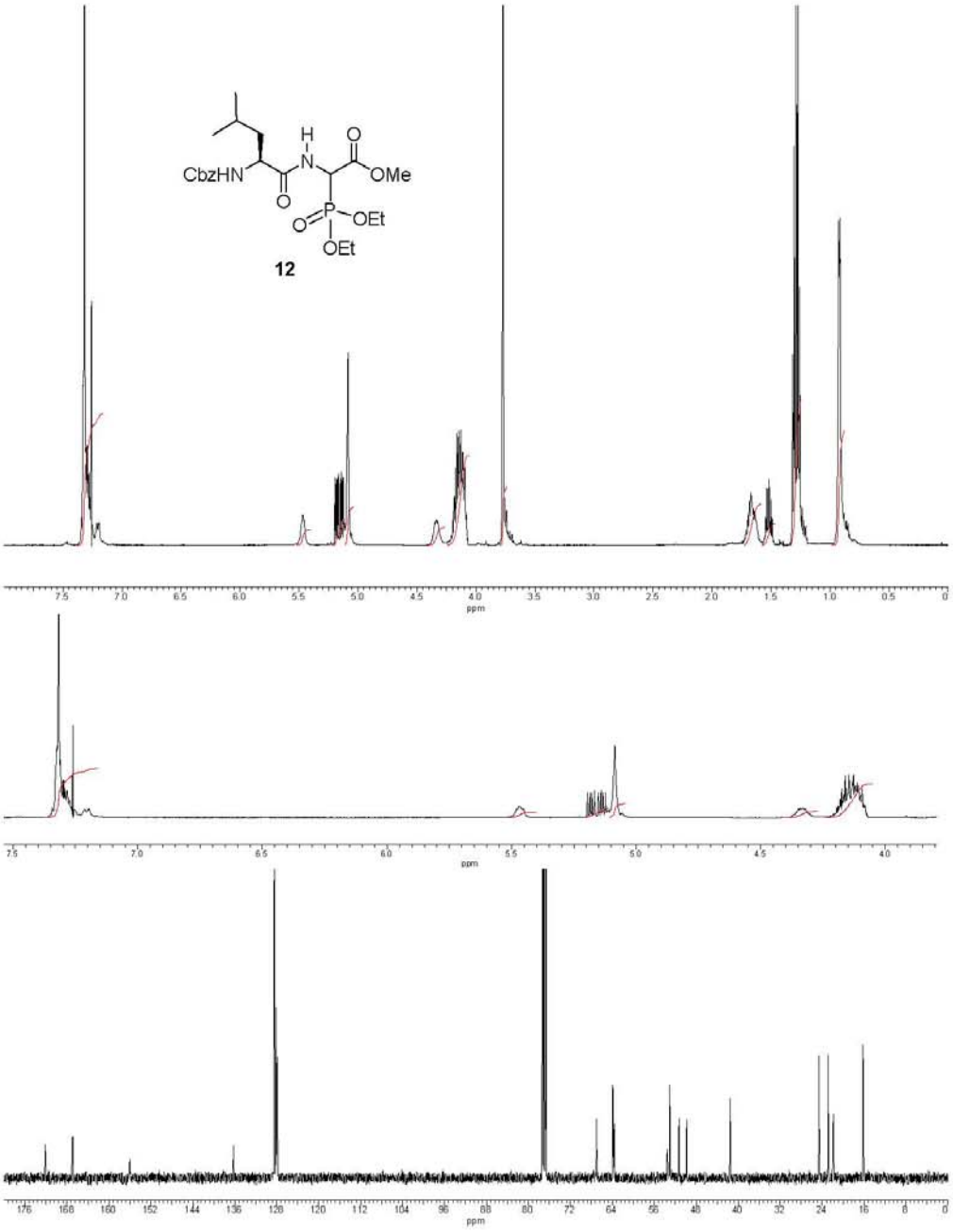
O
OMe
O
OMe
10
ppm



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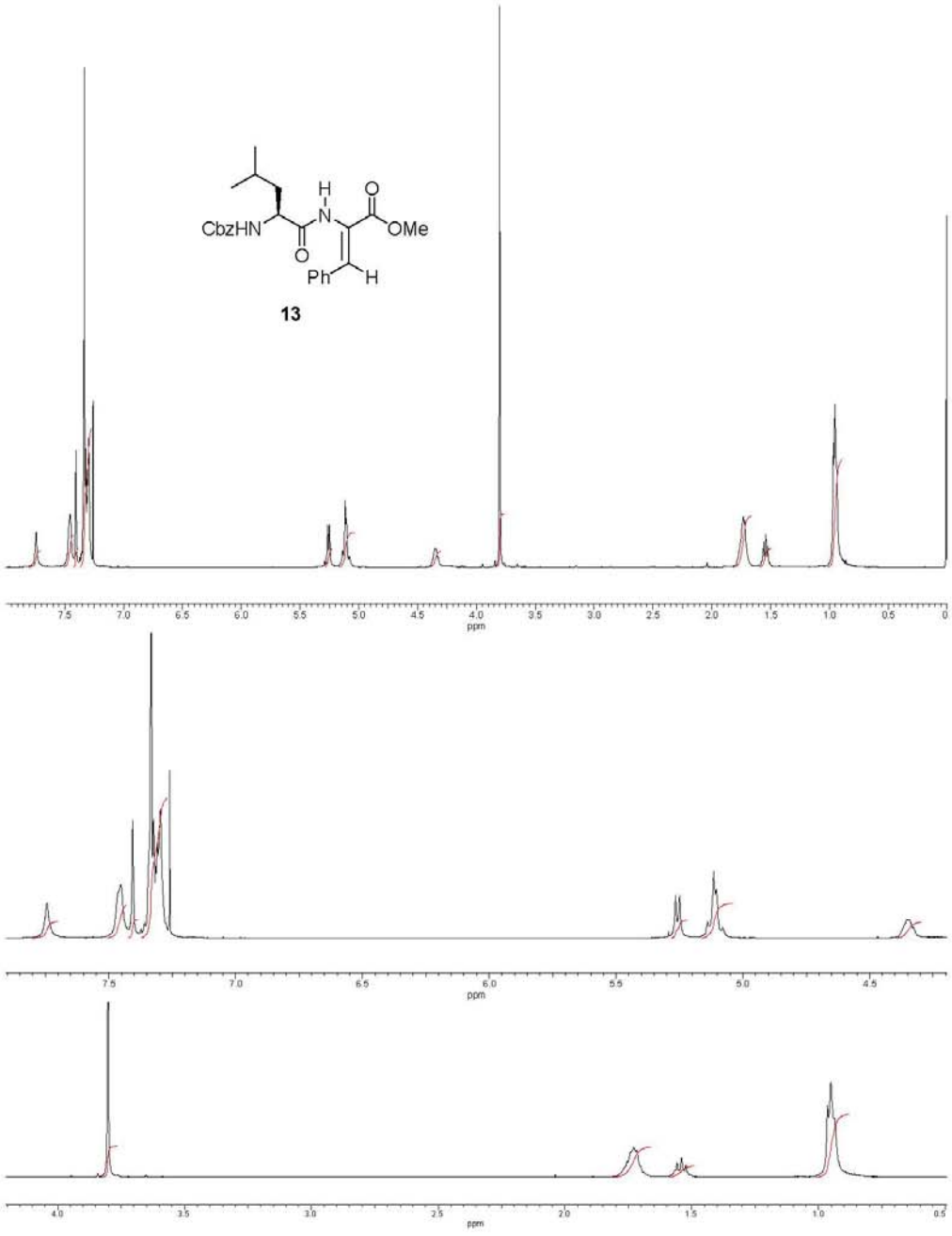

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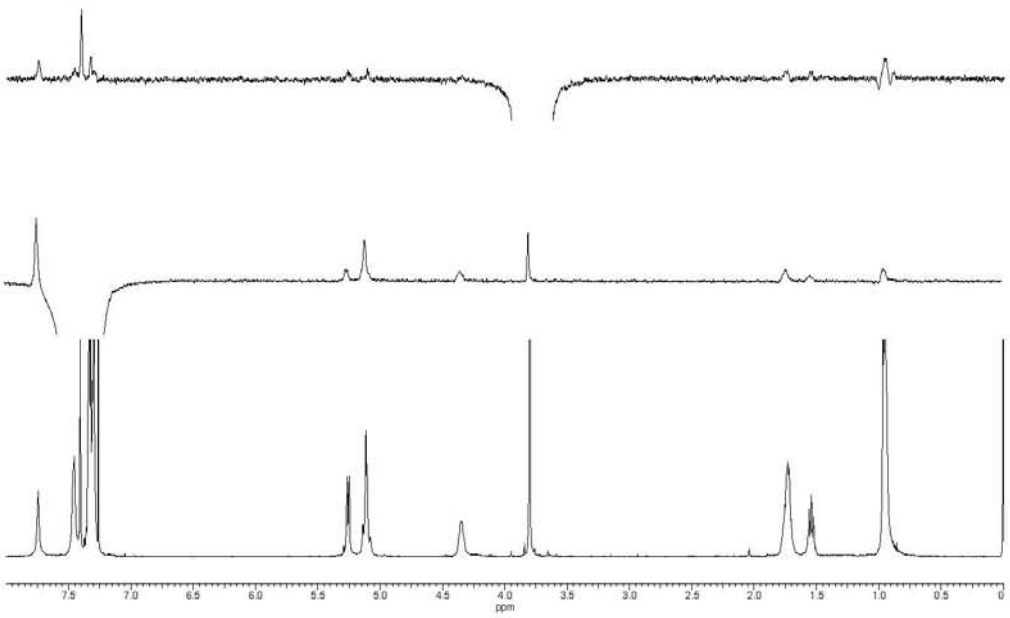
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5.5
5.0
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4.0
3.5
3.0
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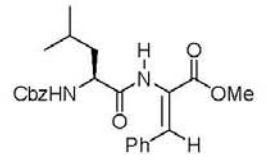
2.0
1.5
1.0
0.5
0
ppm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H
N
O
O
OMe
O
Ph
H

13

176
168
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24
16
8
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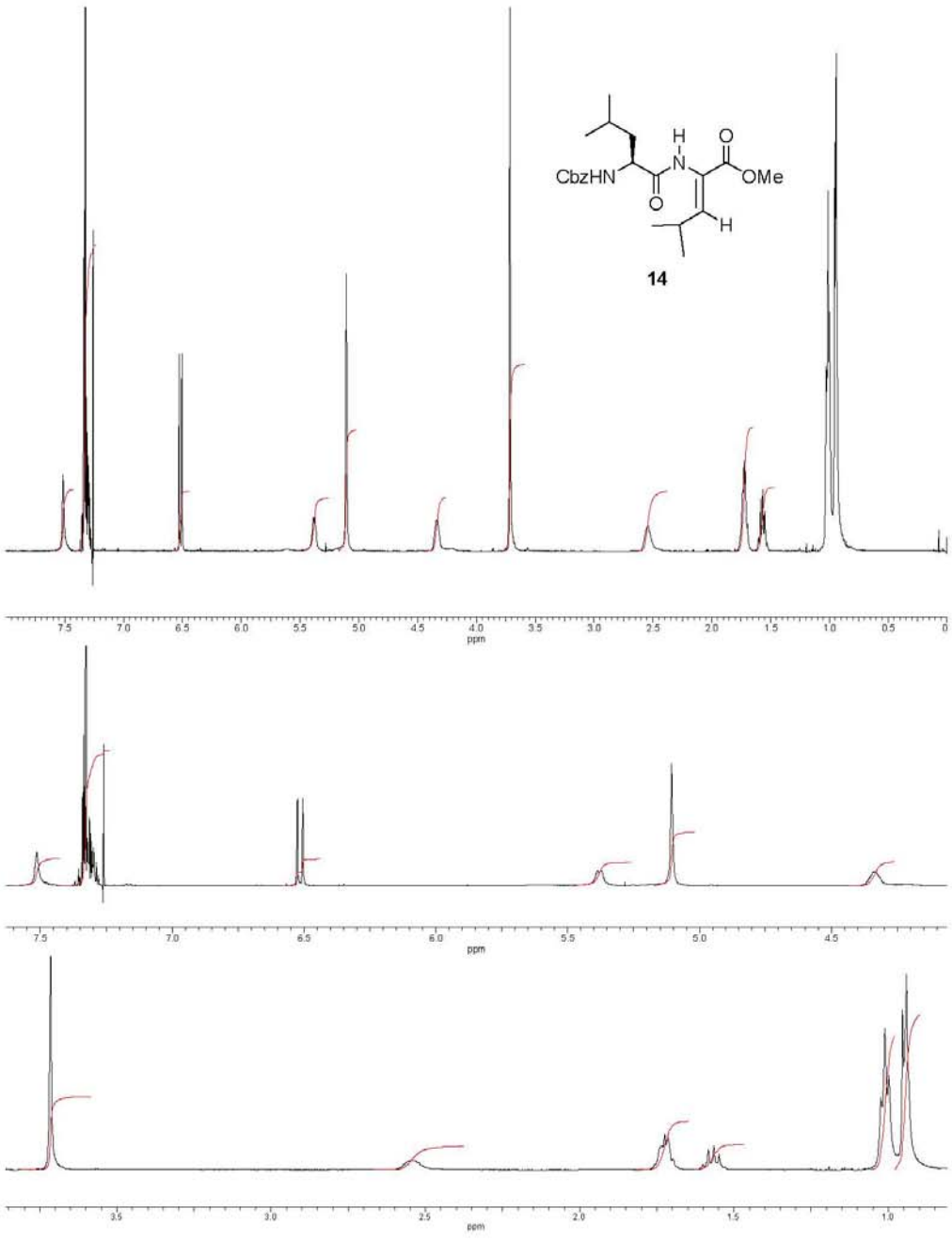
ppm



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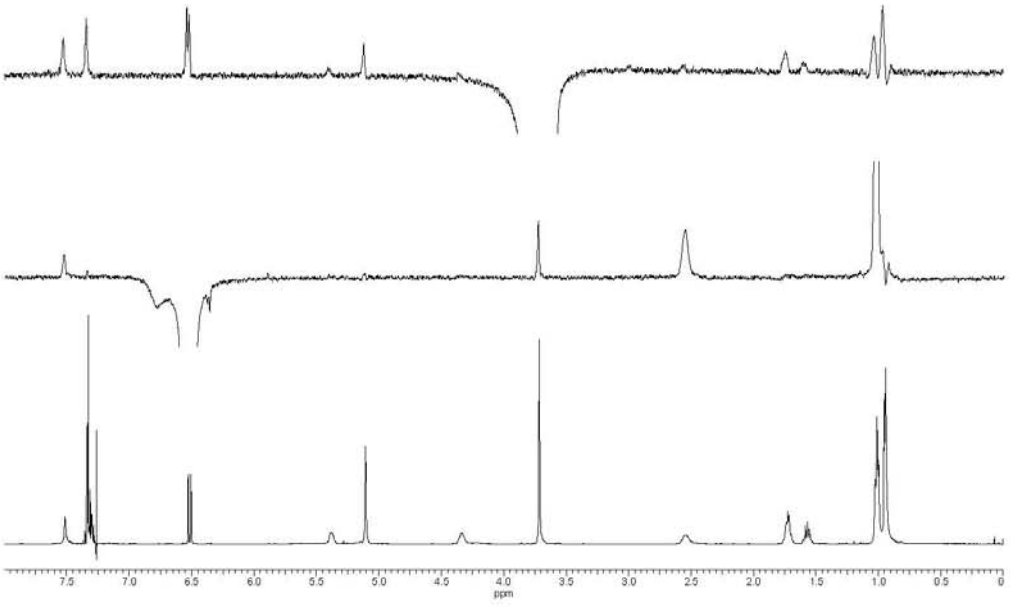
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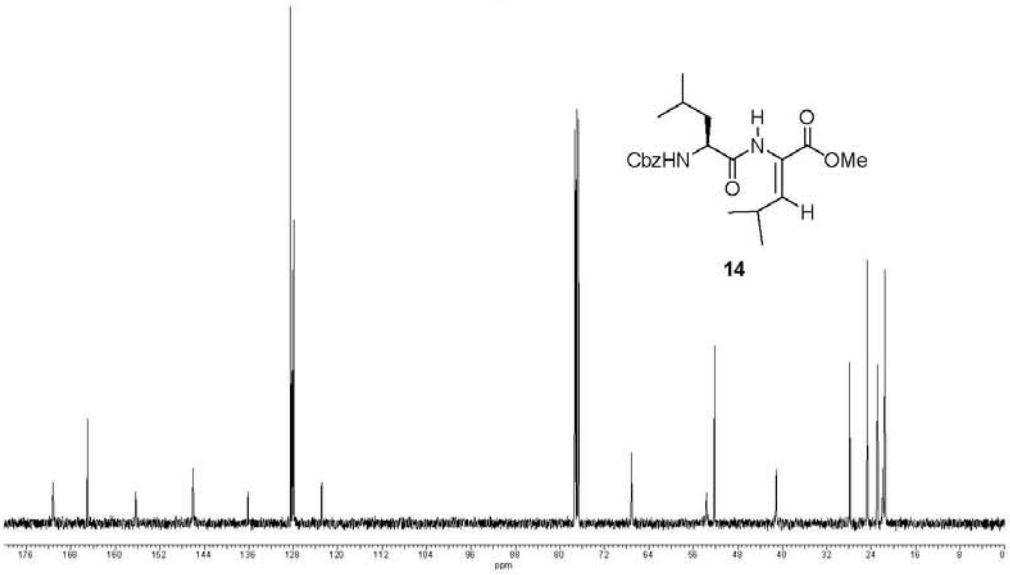
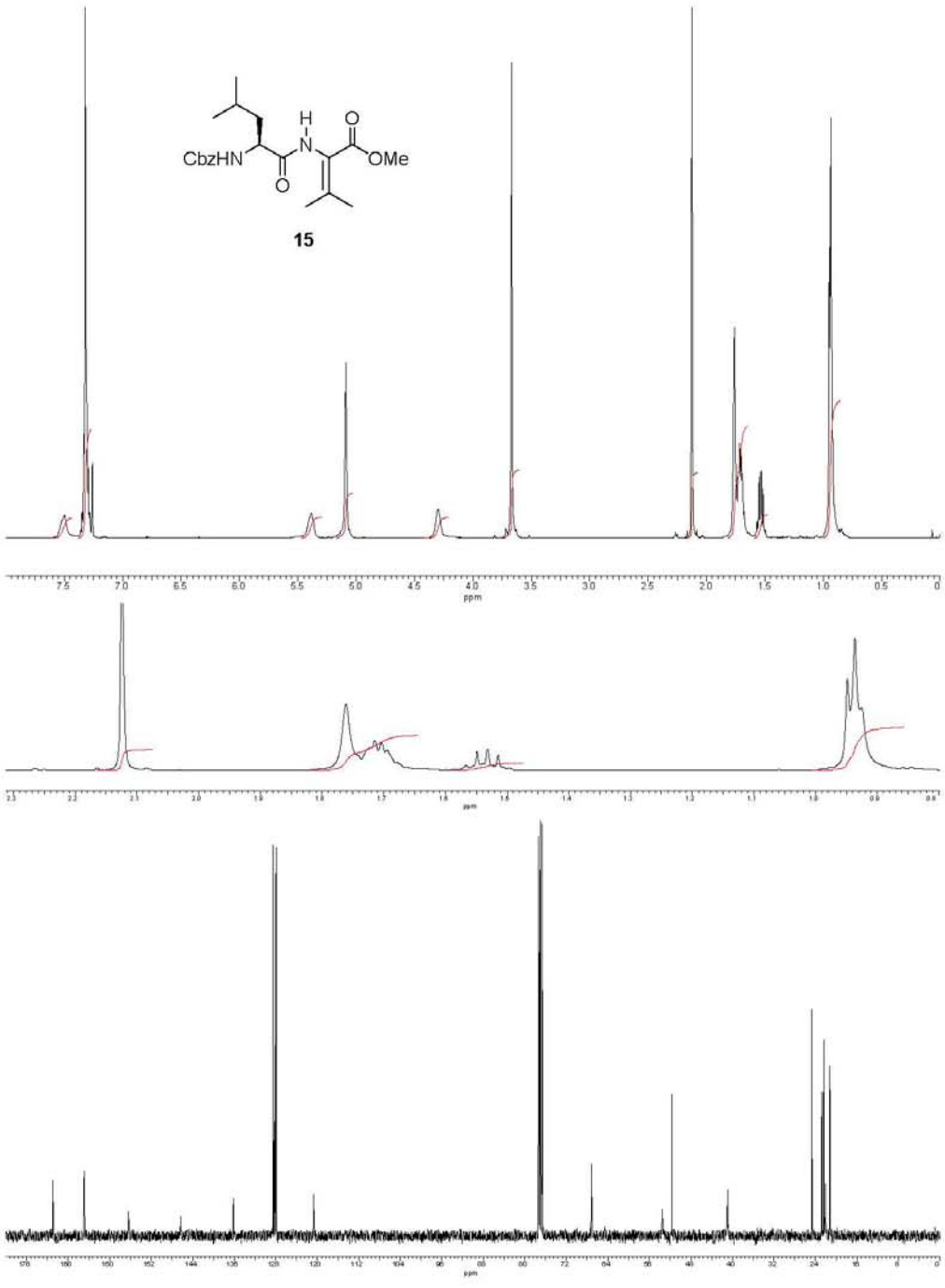
0
ppm


176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
ppm

H
O
N
CbzHN
OMe
O
H

14



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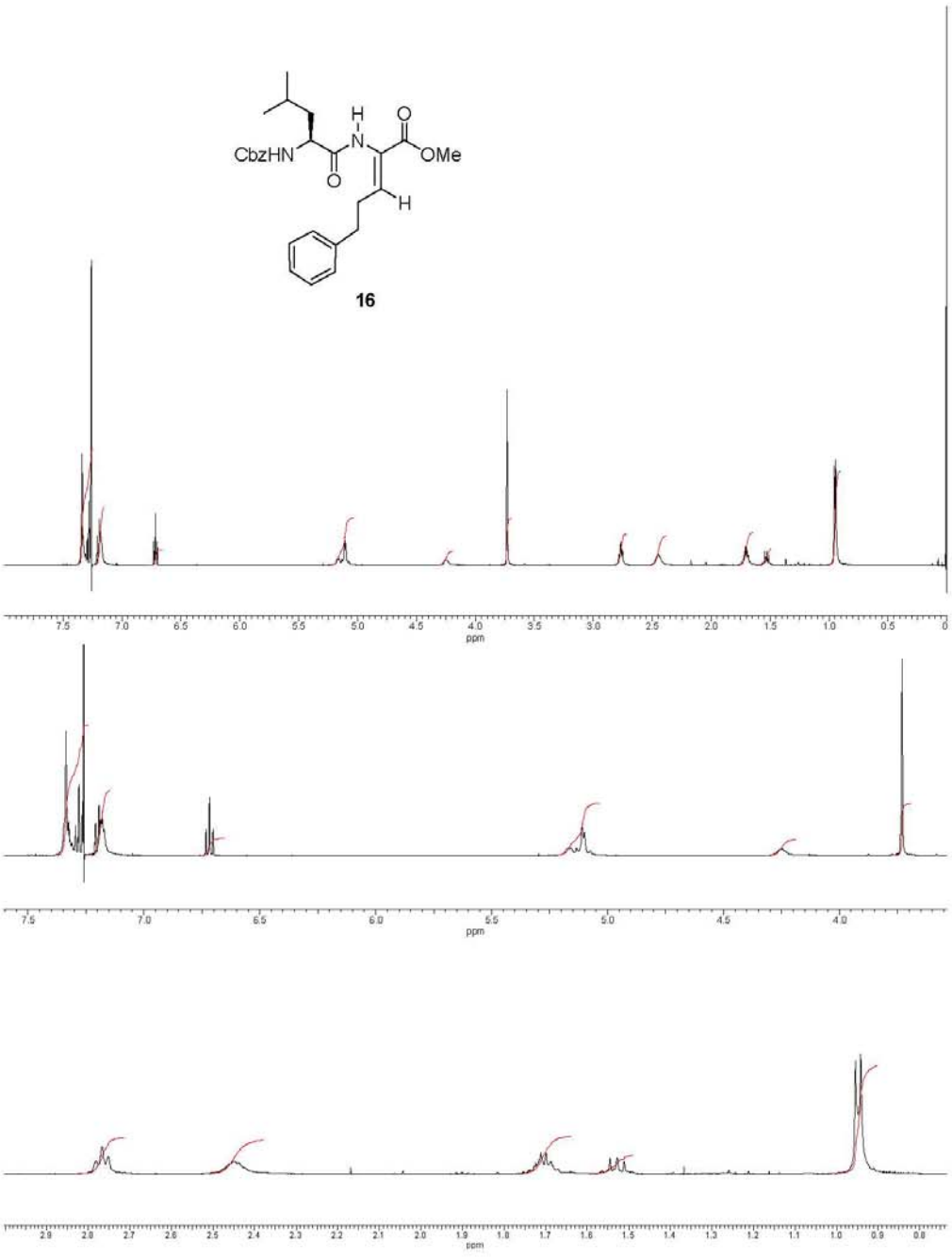
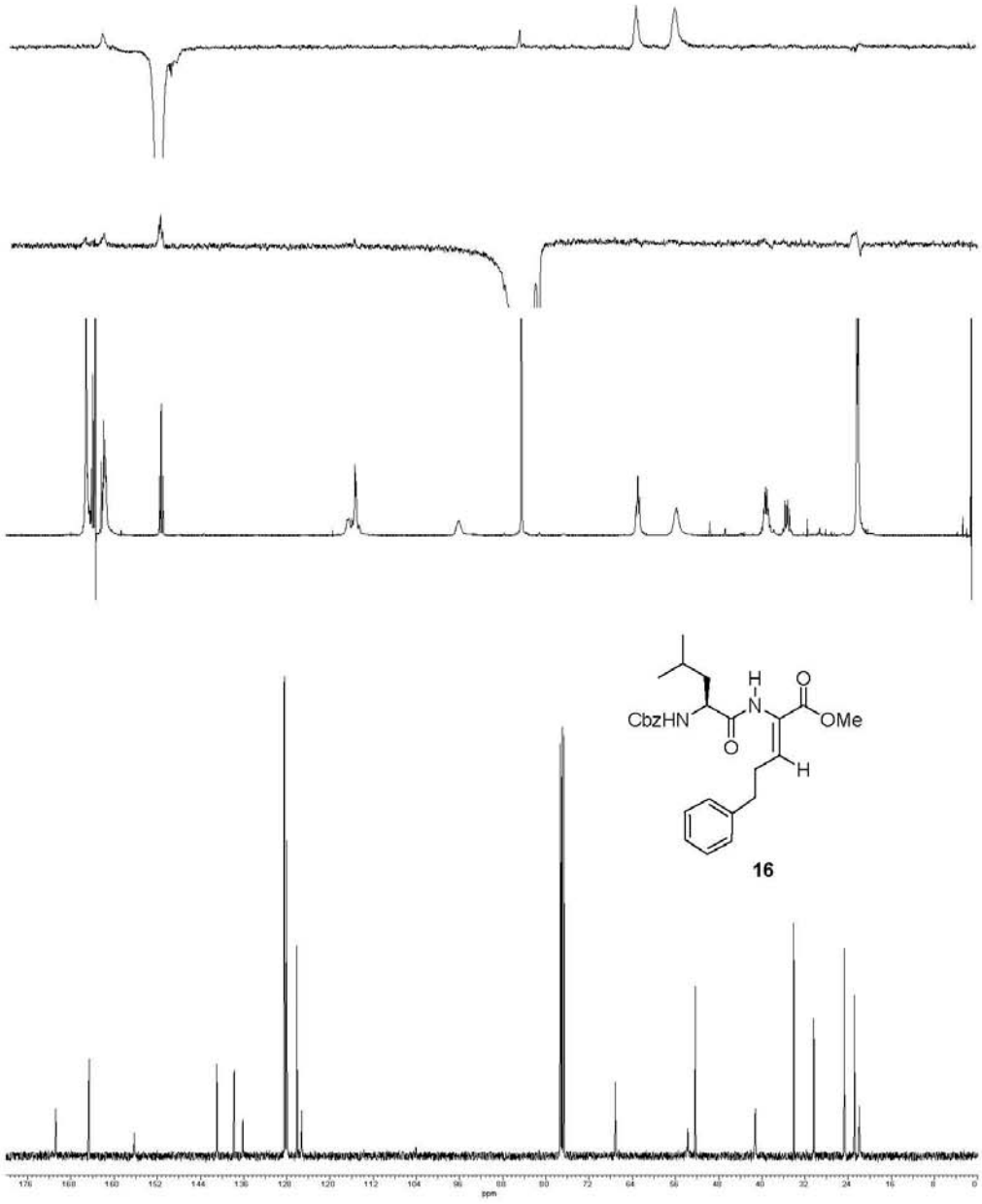
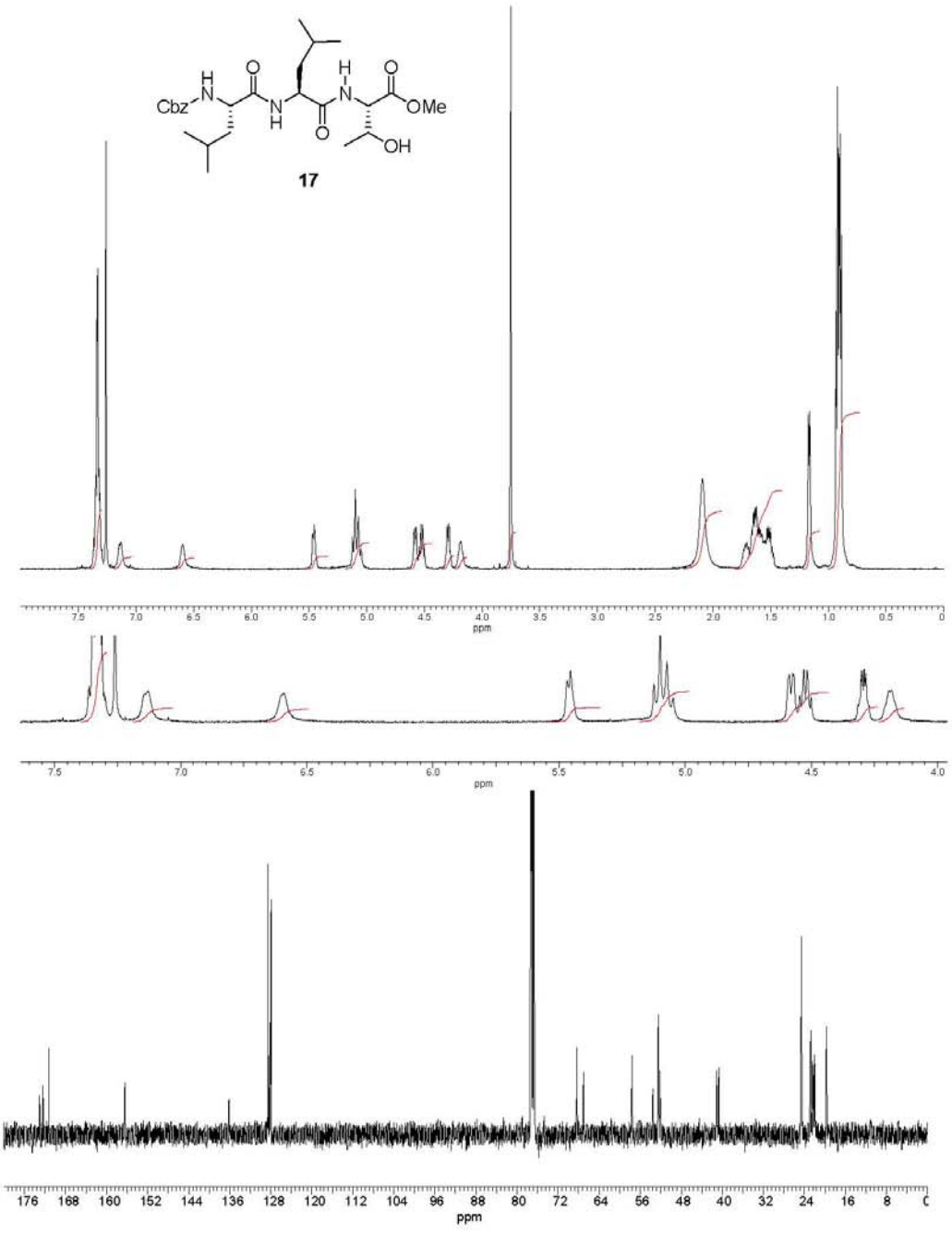

CbzHN
H
N
O
O
OMe
H
16
ppm
ppm
ppm



16

23


Cbz
H
N
O
N
H
O
H
N
O
OMe
OH
17
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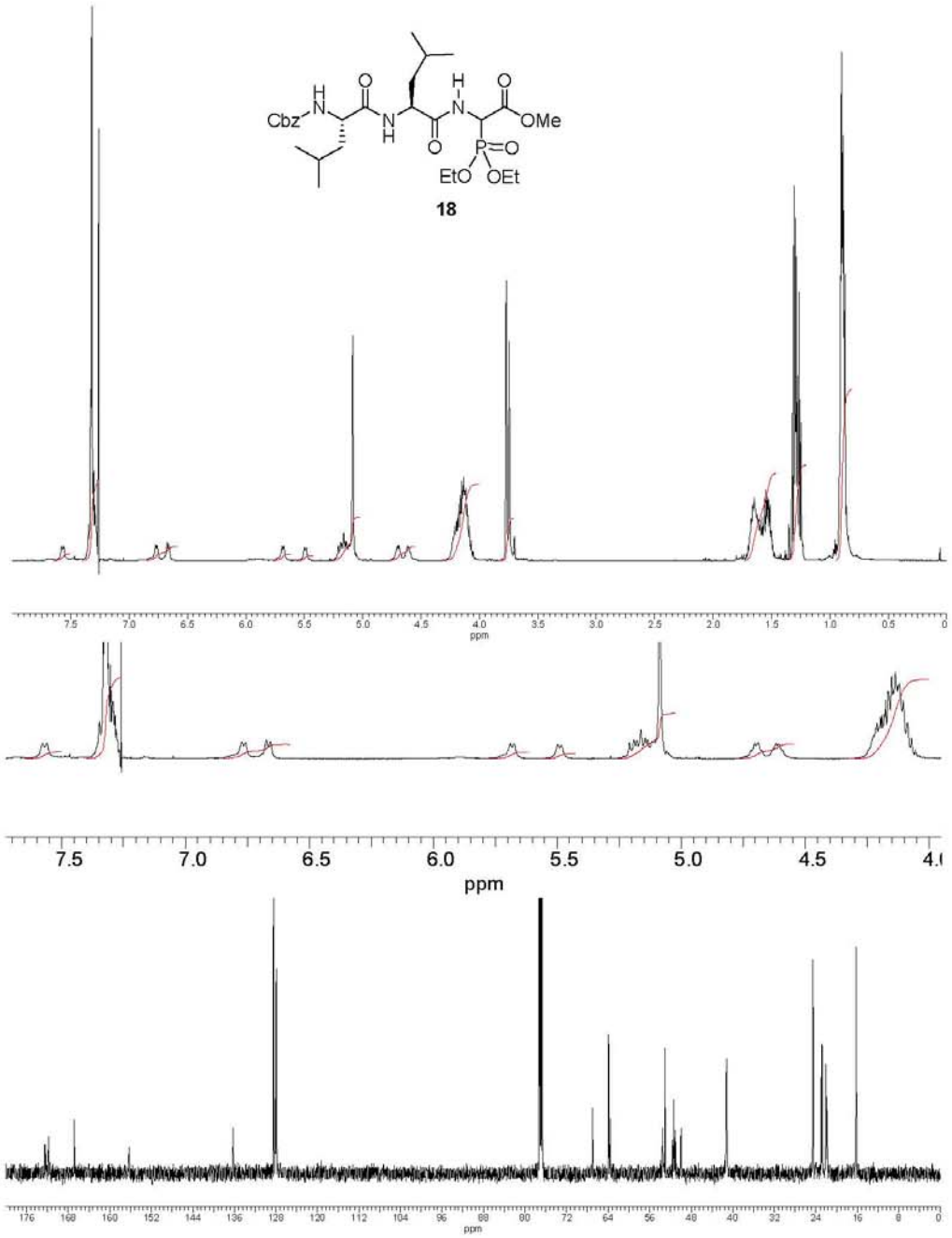
ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0
ppm
176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
ppm


Cbz
OMe
EtO
OEt
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ppm
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6.5
6.0
5.5
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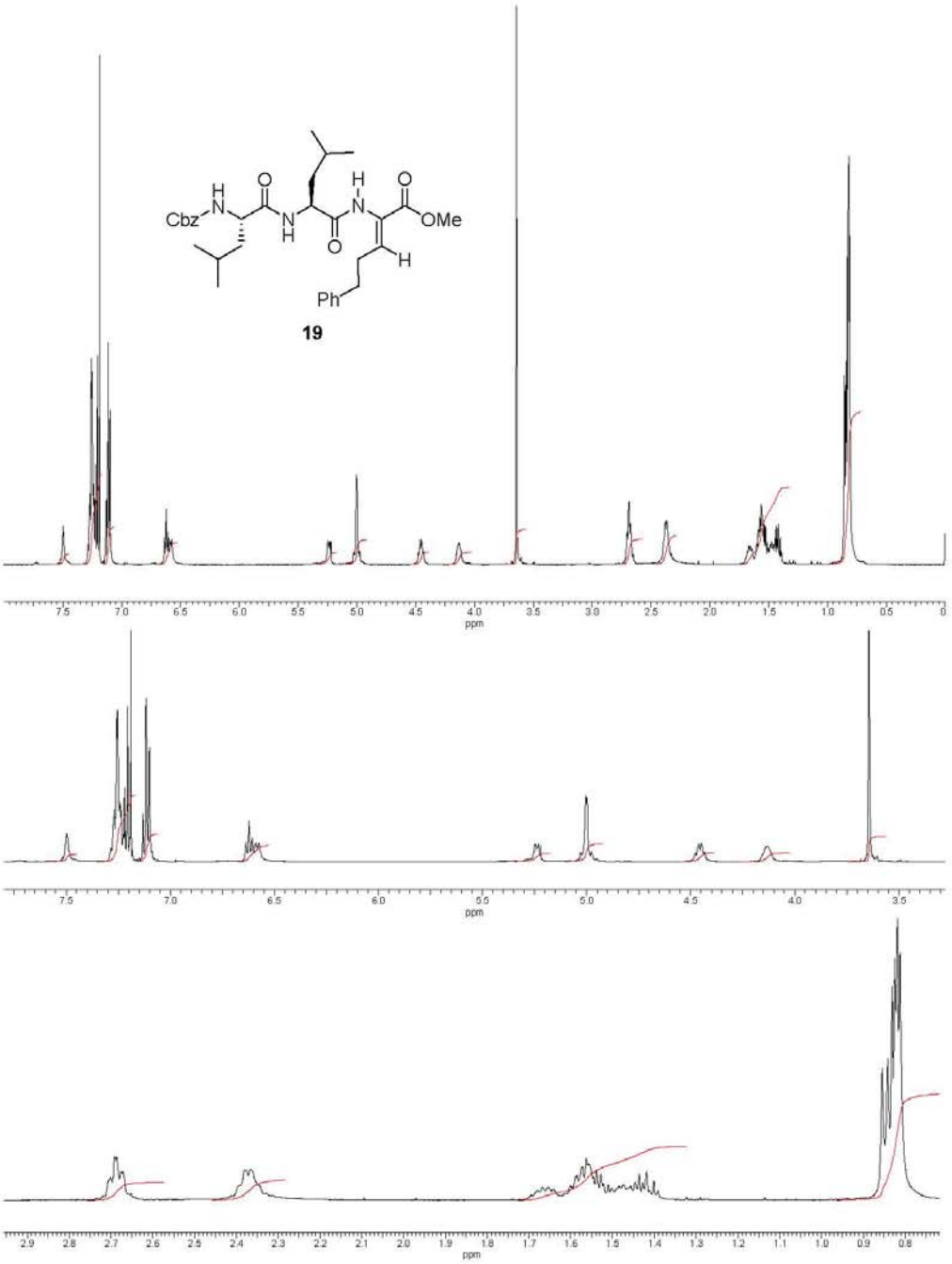
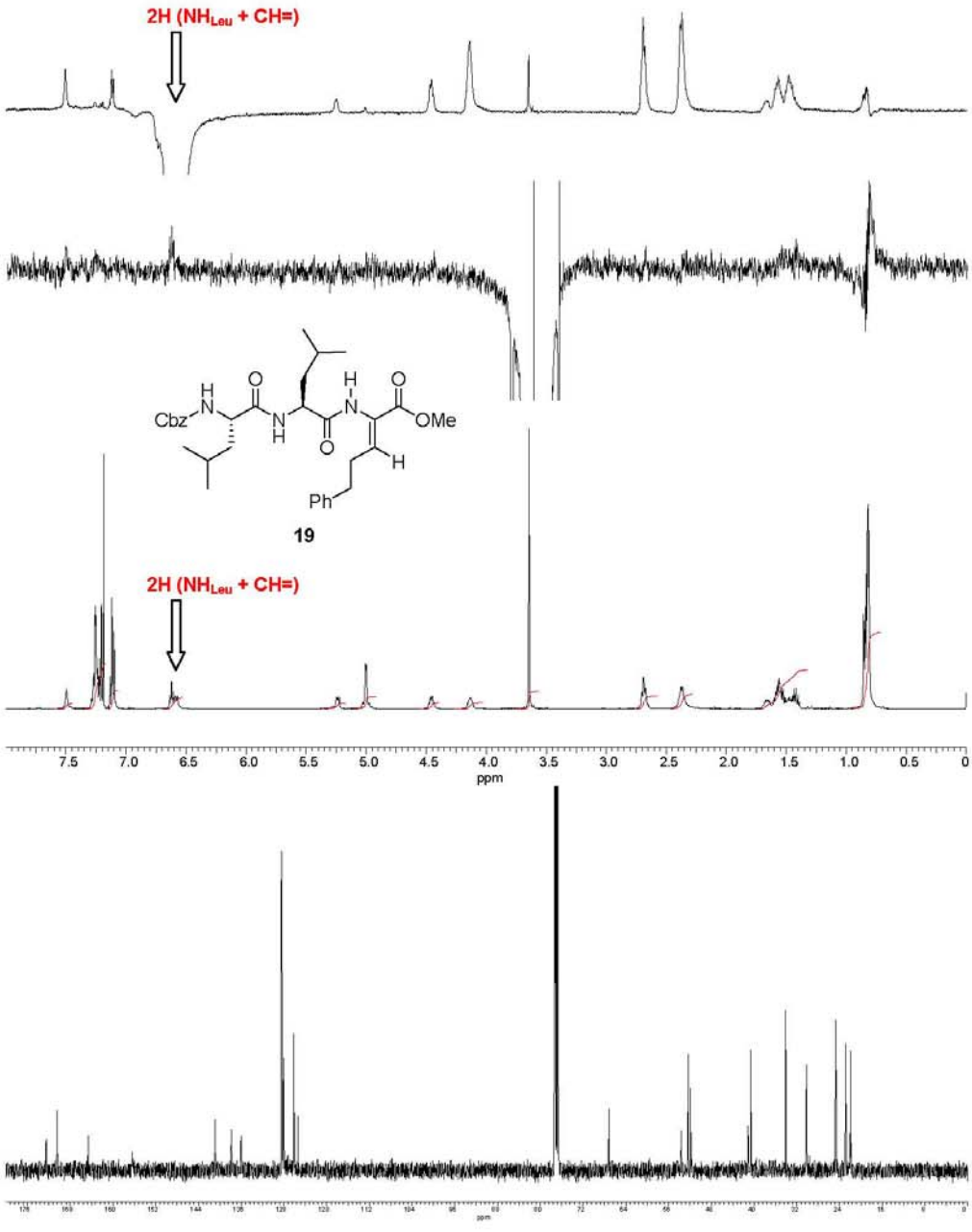
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


Cbz
OMe
Ph
19
ppm
ppm
ppm


2H (NHLeu + CH=)
Cbz
OMe
Ph
19
2H (NHLeu + CH=)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
ppm

27

Conclusiones

4 CONCLUSIONES.

4.1 Conclusiones generales.

El proceso secuencial de escisión radicalaria–oxidación–adición de nucleófilos permite la modificación selectiva de péptidos, bien del extremo *C*-terminal o de otras posiciones. En la memoria se comenta el uso de unidades "convertibles" para lograr estos objetivos.

4.2 Conclusiones específicas

4.2.1 Conclusiones del capítulo 3.1.

Se ha conseguido la modificación selectiva del residuo *C*-terminal de un α-péptido, convirtiéndolo en una unidad de β-amino éster α,α-disustituido. Para ello se ha empleado un proceso secuencial de descarboxilación radicalaria oxidativa–adición de sililcetenas.

Los péptidos resultantes se han acoplado con α-amino ácidos para dar α,β,α-tripeptidos que tienen un residuo central $\beta^{2,2,3*}$-amino ácido con un solo centro estereogénico en posición β^3. Se ha encontrado un efecto quiral que predice el comportamiento conformacional de dichos tripéptidos cuando son disueltos en $CDCl_3$ y DMSO-d_6.

Los tripéptidos con configuración *SSS* presentan en disolución un enlace de hidrógeno entre el N–H y el C=O del β-amino ácido, lo que da lugar a un giro (C6).

Los tripéptidos con configuración *SRS,* en cambio, presentan un enlace de hidrógeno entre el N–H del β-amino ácido y el C=O de siguiente amino ácido, generando un inusual giro-δ (C9).

Las conformaciones adoptadas por los tripéptidos estudiados son independientes del tamaño y naturaleza de las cadenas laterales de los amino ácidos (R^1, R^2 y R^3). Los resultados sugieren que la incorporación de fragmentos de α,β,α-péptidos (con un residuo $\beta^{2,2,3}$*) en péptidos de mayor tamaño, permitiría preparar nuevos peptidomiméticos con conformaciones predecibles en solución, lo que resulta vital para modular su actividad biológica o catalítica.

4.2.2 Conclusiones del capítulo 3.2.

Se ha desarrollado un proceso en un paso para la transformación de α-amino ácidos en β-amino aldehídos. Este proceso es aplicado también a la modificación selectiva del extremo C-terminal de pequeños péptidos dando lugar a péptido aldehídos con buenos rendimientos.

Con este procedimiento un simple α-péptido puede ser transformado en una colección de α,β-péptido aldehídos con diferentes sustituyentes en α.

Los aldehídos son útiles precursores de otros compuestos, como se muestra en la transformación de varios péptido aldehídos en análogos de precursores de los peptaiboles, una familia de potentes antibióticos y fungicidas. Los análogos poseen una unidad de γ-amino alcohol en el extremo C-terminal.

4.2.3 Conclusiones del capítulo 3.3.

El proceso en un paso de descarboxilación–alquilación permite la modificación selectiva de péptidos con unidades de ácido glutámico, convirtiéndolos en α,γ-péptidos híbridos con γ-amino ácidos no naturales. El proceso se lleva a cabo bajo condiciones suaves con buenos rendimientos. A partir de un simple péptido se puede generar con buenos rendimientos una colección de α,γ-péptidos híbridos. Es de destacar que se puede modificar selectivamente tanto la posición C-terminal como otras del péptido de partida.

Este es el primer trabajo de modificación selectiva de péptidos que permite preparar α,γ-híbridos. El uso de unidades de glutámico para generar diversidad es particularmente interesante. Los grupos carboxilos de las unidades de glutámico pueden ser protegidos con diferentes grupos ortogonales. El péptido inicial puede contener varias unidades de glutámico, pero solo la que esté libre sería modificada. A continuación se podrían hacer modificaciones sucesivas eliminando los grupos protectores ortogonales.

4.2.4 Conclusiones del capítulo 3.4.

Se ha desarrollado un proceso de modificación selectiva de péptidos que usa unidades de serina o treonina como residuos “convertibles”. Para ello, se emplea un proceso secuencial donde tiene lugar una escisión radicalaria oxidativa de la cadena de hidroximetileno de la serina (o treonina), seguida de la adición de nucleófilos de fósforo. Los α-amino fosfonatos obtenidos son sometidos a una reacción de Horner-Wadsworth-Emmons con aldehídos o cetonas, obteniéndose en el primer caso los correspondientes *Z*-deshidroamino ácidos con excelente estereoselectividad *Z*; además no se observa epimerización de las demás posiciones.

Esta metodología permite la preparación de una gran variedad de derivados peptídicos partiendo de un único precursor. Además este proceso tiene lugar bajo condiciones de reacción suaves y en buenos rendimientos.

El uso de unidades de serina/treonina es muy interesante para generar diversidad. El péptido inicial puede poseer varias unidades de serina/treonina con diferentes grupos protectores ortogonales, pero sólo aquella unidad que no esté protegida será modificada. Luego se pueden eliminar consecutivamente los grupos protectores ortogonales y realizar nuevas modificaciones.