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Optically Active γ-Hydroxy Sulfone Julia Reagents for the Synthesis of Peptidyl Olefin Peptidomimetics

Sima Mirilashvili,[a] Naama Chasid-Rubinstein,[a] and Amnon Albeck*[a]

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Peptidyl olefin peptidomimetics serve as biologically active compounds or as intermediates for other peptidyl isosteres. We developed a chemoenzymatic stereoselective approach to optically active γ-hydroxy sulfones to be assembled into peptidyl olefins by the Julia reaction. Key enzymatic hydrolysis of prochiral diesters to the corresponding hydroxy esters introduces optical activity. The sequence of the subsequent chemical reactions, either protection–hydrolysis–functionalization or functionalization–hydrolysis–protection, determines the absolute stereochemistry of the final sulfone building block.

Introduction

Peptides play a variety of important roles in biological systems as hormones, neurotransmitters, modulators of biological processes, toxins, etc. Peptides are also used as therapeutic agents for various diseases (diabetes, growth disorders). However, the medicinal usage of peptides is limited due to biodegradation, low bioavailability, and several side effects resulting from the conformational flexibility that enables binding to several receptors.[1] Peptide isosteres containing a replacement of a specific amide bond in the peptide have been extensively used as protease and other enzyme inhibitors. Of special interest among these are peptidyl olefin isosteres, in which a specific peptide bond is replaced by a C=C bond. These materials may serve as protease inhibitors[2,3] or as other biologically active compounds,[4,5] as mechanistic probes,[6] or as intermediates for the synthesis of other peptidyl isosteres such as ethylene, diol, epoxide, and hydroxyethylene.[2a,2b,3a,4c,7]

It is relatively straightforward to control the stereochemistry of the chiral center of the P_1 residue of the peptidyl olefin (the chiral center adjacent to the olefin at its N-terminal side), as it may originate directly from an optically active α-amino acid. The situation is much different at the other side of the double bond (the P_1' residue replacement). The vast majority of the synthetic procedures for peptidyl olefins introduce either a glycine mimetic (=CCH_2CO), which is not chiral, at this position[2,3a,5a,5c,8] or a substitution (=CCHRCO) in a nonstereoselective manner to produce a diastereomeric mixture of the product. Many of these procedures employ a Wittig or Emmons–Horner reaction,[2,5c,7a–7c,9] or various alkylations.[5b,5d,10] Some methods provide optically active products after separation of racemic or diastereomeric intermediates.[11] Only a handful of chiral methods have been introduced, based on alkylation,[6] S_N2' organocuprate addition,[4,12] sigmatropic rearrangement,[13] ring-closing metathesis,[14] and Julia reaction between chiral N-terminal sulfone nucleophile and C-terminal aldehyde.[3d,15] These methods require long procedures for the preparation of optically pure starting materials, and they provide the products in low overall yields. Thus, efficient stereoselective synthesis of peptidyl olefins still poses a synthetic challenge and an important target. Here we describe a new synthetic approach for optically active γ-hydroxy sulfones to serve as C-terminal nucleophilic building blocks for the synthesis of peptidyl olefins.

Results and Discussion

Analysis of the above synthetic methods towards peptidyl olefins shows that most chiral methods rely on a key rearrangement of a pre-existing, sterically well-defined C=C bond. In contrast, most polar reactions between a nucleophile and an electrophile to directly form the C=C bond are not stereoselective. We explored the latter approach and used a chemoenzymatic procedure to prepare optically active P_1' (C-terminal) γ-hydroxy sulfone building blocks. These compounds could then be incorporated into peptidyl olefins by a Julia reaction with *N*-protected α-amino aldehydes. These N-terminal (P_1) residues are directly derived from optically active α-amino acids. The dipeptidyl olefin isostere could then be extended by standard coupling pro-

[a] The Julius Spokojny Bioorganic Chemistry Laboratory, Department of Chemistry, Bar Ilan University,
Ramat Gan 52900, Israel
Fax: 972-3-7384053
E-mail: albecka@mail.biu.ac.il

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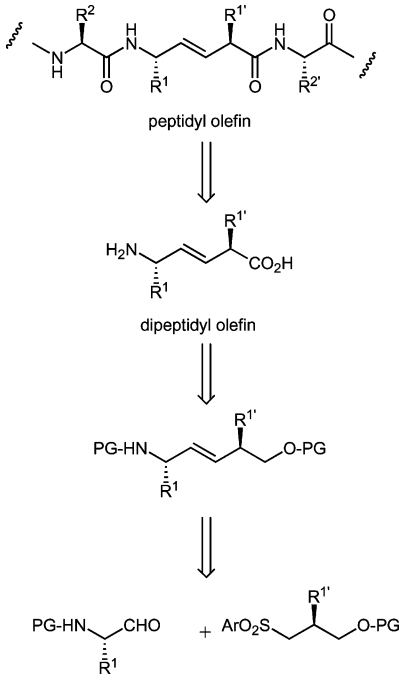
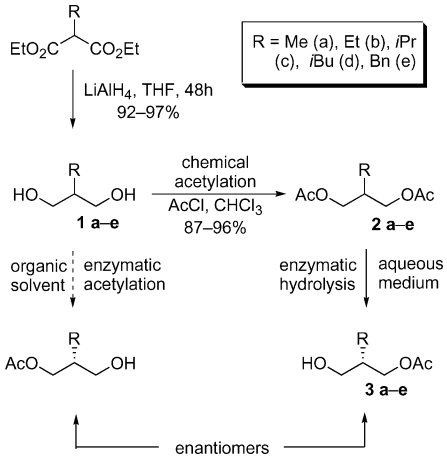
cedures on both its N-terminal and C-terminal sides according to the desired amino acid sequence. The retrosynthetic analysis of this approach is described in Scheme 1.



Scheme 1. Retrosynthetic analysis for peptidyl olefin peptidomimetics.

The key step that determined the stereochemistry of the product was a stereoselective hydrolysis of a prochiral diester, catalyzed by the enzyme lipase from *Pseudomonas Sepacia*. This enzyme can either hydrolyze a prochiral diester to an optically active hydroxy ester in aqueous medium or acylate the corresponding diol to the enantiomeric hydroxy ester in organic solvents (Scheme 2).[16] This approach provides a few advantages: (a) Facile entry to almost any possible substitution by alkylation of diethyl malonate, followed by reduction to the corresponding diol and subsequent diacetylation (Scheme 2). (b) Full conversion to the desired optically active product, which stems from the reaction of the enzyme on a homogeneous prochiral compound rather than enzymatic resolution of a racemic mixture. (c) Control of the stereoselectivity by the mode of the application of the enzyme – either as a hydrolase in aqueous solution or as an acylase in organic solvents (Scheme 2).

This protocol was applied to five different diethyl malonate compounds substituted with methyl, isopropyl, isobutyl, benzyl, and ethyl groups. When incorporated into peptidyl olefins, these building blocks would mimic the natural amino acids alanine, valine, leucine, and phenylalanine, and the unnatural amino acid ethylglycine, respectively. Both the reduction step to the diol and the diacetylation step proceeded in excellent yields (typically >90%) for all the derivatives (Scheme 2 and Table 1). Racemic monoacetates were separately synthesized by partial acetylation of the corresponding diols. These compounds were used as references for chiral HPLC analysis.



Scheme 2. Lipase hydrolysis of prochiral diacetates and lipase acetylation of the corresponding prochiral diols produce enantiomeric hydroxy esters.

Table 1. Reaction yields for the preparation of the diester lipase substrates.

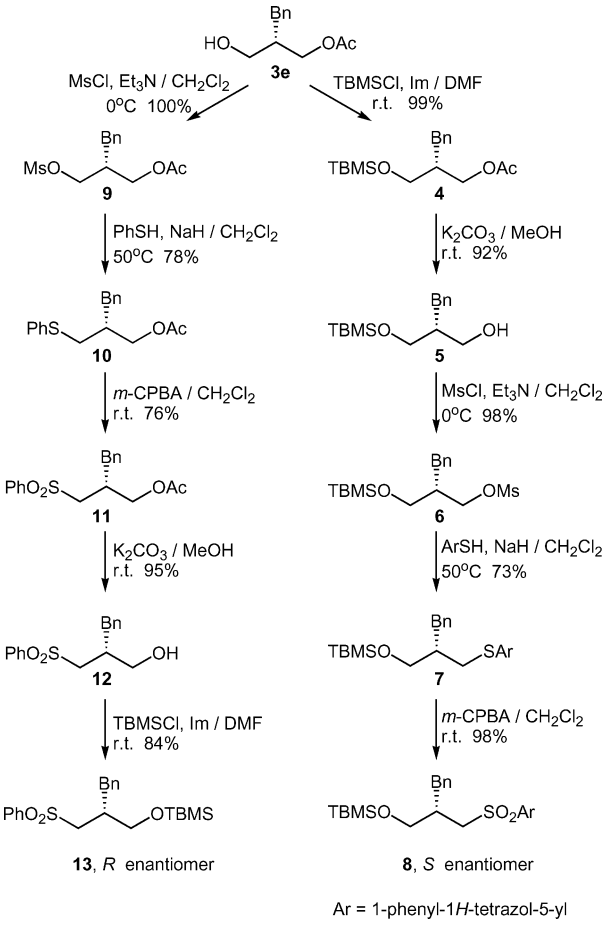
R	Yield of diol **1** [%]	Yield of diester **2** [%]
Me	–[a]	92
Et	95	88
*i*Pr	94	87
*i*Bu	92	90
Bn	97	96

[a] Commercially available.

The enzymatic hydrolysis of the diacetyl substrates yielded the best results in terms of conversion and *ee* when carried out in aqueous solution of 40-mM NaCl, 5-mM $CaCl_2$, and 0.07% BSA, with 12.5–40 mg of the enzyme and 100–1000 mg of the substrate. Chiral HPLC analysis identified a single isomer of the products at conversion rates of 30–50%. The absolute *S* configuration of the products was assigned by comparison to literature data.[16b] When carried out further, the hydrolysis of benzyl derivative **2e** at 65% conversion yielded 94%*ee* of the desired monoester product, and hydrolysis of ethyl derivative **2b** at 90% conversion provided the product in 72%*ee*. Lipase catalyzed acylation of prochiral diols **1** proceeded with poorer enantioselectivity (40–60%*ee* for **1e**), and therefore was not elaborated further.

The enzymatic reaction determined the absolute stereochemistry of hydroxy ester product **3**. The order of further chemical manipulations provided a second opportunity to control the stereochemistry of the final C-terminal nucleophilic sulfone building block. Thus, protection (silylation) of the free hydroxy group, followed by acetyl hydrolysis and transformation of the new free hydroxy group into the final sulfone would provide one enantiomer of the final product. Alternatively, transformation of the original free hydroxy group into the desired sulfone, followed by hydrolysis of the acetate and protection (silylation) of the free hydroxy group would yield the opposite enantiomer. This was demonstrated in the stereoselective preparation of the two opposite isomers of the benzyl building block (phenylalanine an-

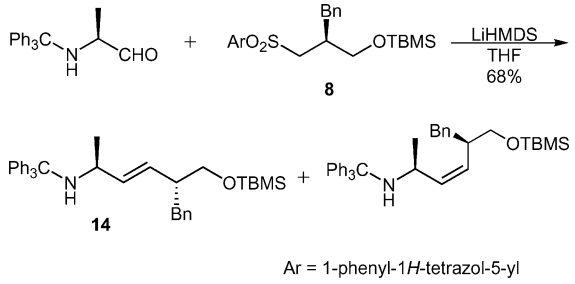
alog) modified by two different aryl sulfone functional groups: **8** (a Julia–Kocienski reagent) and **13** (a "classical" Julia reagent; Scheme 3). The C-terminal building block could be utilized in the synthesis of a peptidyl olefin by the Julia reaction (with phenyl sulfone **13**) or its Julia–Kocienski modification (with phenyl tetrazol analog **8**).[17]



Scheme 3. Stereoselective synthesis of the two isomers of the C-terminal (P_1') sulfone building blocks.

A similar approach involving the sulfone introduction–hydrolysis–silylation sequence, provided the *S* enantiomer of the ethylglycine C-terminal building block (the ethyl derivative modified by the phenyl tetrazol sulfone, analogous to **8**) in five steps and 68% overall yield from the corresponding hydroxy ester starting material **3b**. All of the benzyl derivative intermediates were analyzed by chiral HPLC for their steric integrity. This analysis demonstrated retention of optical purity to at least 90% in each of the chemical transformations leading to final sulfone products **8** and **13**.

In order to demonstrate their utility as C-terminal building blocks for the synthesis of peptidyl olefins by the Julia–Kocienski reaction, we treated the lithium salt of sulfone **8** with *N*-tritylalaninal[18] in THF (Scheme 4). The desired product (2*S*,5*S*)-*N*-trityl-5-amino-2-benzyl-1-(*tert*-butyldimethylsilyloxy)hex-3-ene (**14**), the olefin isostere of *N*-tritylalanylphenylalaninol, was obtained as a 1:1 mixture of *E*/*Z* isomers (which were separated by chromatography) in 68% yield. No racemization at the chiral centers was detected. The product could then be transformed into the dipeptidyl olefin by alcohol deprotection and oxidation, as previously demonstrated.[3c,7b,10]



Scheme 4. The Julia–Kocienski reaction of C-terminal (P_1') sulfone building block **8** towards a dipeptidyl olefin.

Optically active β-alkyl-γ-hydroxy sulfones could also find other applications. For example, such compounds were previously used as Julia reagents for the synthesis of various natural products or their analogs.[19]

Conclusions

In this study we developed a new approach for the preparation of optically active γ-hydroxy sulfone C-terminal (P_1') building blocks for the synthesis of peptidyl olefin peptidomimetics. This approach is based on a key enzymatic step: stereoselective hydrolysis of prochiral diesters to optically active hydroxy esters. The role of the enzymatic reaction is only to provide high optical activity, rather than to define the stereochemistry of the final sulfone product. The absolute configuration is determined by the sequence of the subsequent chemical reactions towards the final sulfone building block: either protection–hydrolysis–functionalization or functionalization–hydrolysis–protection. The optically active sulfone could be used in the Julia reaction with an α-amino aldehyde to form a precursor of a dipeptidyl olefin isostere in pure enantiomeric form.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for all new compounds.

Acknowledgments

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[1] C. J. Barrow, P. E. Thompson in *Advances in Amino Acid Mimetics and Peptidomimetics* (Ed.: A. Abell), Jai Press Inc., Greenwich CN, **1997** p. 251.

[2] a) C. S. Lee, N. Choy, C. Park, H. Choi, Y. C. Son, S. Kim, J. H. Ok, H. Yoon, S. C. Kim, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 589; b) J. S. Kaltenbronn, J. P. Hudspeth, E. A. Lunney, B. M. Michniewicz, E. D. Nicolaides, J. T. Repine, W. H. Roark, M. A. Stier, F. J. Tinny, P. K. W. Woo, A. D. Essenburg, *J. Med. Chem.* **1990**, *33*, 838; c) R. L. Johnson, *J. Med. Chem.* **1984**, *27*, 1351.

[3] a) A. Grubb, M. Abrahamson, I. Ólafsson, J. Trojnar, R. Kasprzykowska, F. Kasprzykowski, Z. Grzonka, *Biol. Chem.*

Hoppe-Seyler **1990**, *371 Suppl*., 137; b) P. A. Bartlett, A. Otake, *J. Org. Chem.* **1995**, *60*, 3107; c) R. Beresis, J. S. Panek, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1609; d) K. Fearon, A. Spaltenstein, P. B. Hopkins, M. H. Gelb, *J. Med. Chem.* **1987**, *30*, 1617.

[4] a) K. Fujimoto, R. Doi, R. Hosotani, M. Wada, J.-U. Lee, T. Koshiba, T. Ibuka, H. Habashita, K. Nakai, N. Fujii, M. Imamura, *Life Sci.* **1996**, *60*, 29; b) M. Wada, R. Doi, R. Hosotani, S. Higashide, T. Ibuka, H. Habashita, K. Nakai, N. Fujii, M. Imamura, *Pancreas* **1995**, *10*, 301; c) J. S. Wai, D. L. Bamberger, T. E. Fisher, S. L. Graham, R. L. Smith, J. B. Gibbs, S. D. Mosser, A. I. Oliff, D. L. Pompliano, E. Rands, N. E. Kohl, *Bioorg. Med. Chem.* **1994**, *2*, 939.

[5] a) K. Tomita, T. Narumi, A. Niida, S. Oishi, H. Ohno, N. Fujii, *Biopolymers* **2007**, *88*, 272; b) P. Wipf, J. Xiao, J. Jiang, N. Belikova, V. A. Tyurin, M. P. Fink, V. E. Kagan, *J. Am. Chem. Soc.* **2005**, *127*, 12460; c) M. M. Hann, P. G. Sammes, P. D. Kennewell, J. B. Taylor, *J. Chem. Soc. Perkin Trans. 1* **1982**, 307; d) M. T. Cox, J. J. Gormley, C. F. Hayward, N. N. Petter, *J. Chem. Soc., Chem. Commun.* **1980**, 800.

[6] Y. Fu, J. Bieschke, J. W. Kelly, *J. Am. Chem. Soc.* **2005**, *127*, 15366.

[7] a) A. Nadin, A. P. Owens, J. L. Castro, T. Harrison, M. S. Shearman, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 37; b) N. Perlman, M. Livneh, A. Albeck, *Tetrahedron* **2000**, *56*, 1505; c) A. Jenmalm, W. Berts, Y.-L. Li, K. Luthman, I. Csöregh, U. Hacksell, *J. Org. Chem.* **1994**, *59*, 1139; d) J. Marchand-Brynaert, D. Ferroud, B. Serckx-Poncin, L. Ghosez, *Bull. Soc. Chim. Belg.* **1990**, *99*, 1075; e) D. H. Rich, *Comprehensive Medicinal Chemistry* **1990**, Pergamon Press, Oxford, vol. 2, pp. 391, 402; f) R. D. Allan, H. W. Dickenson, G. A. R. Johnston, R. Kazlauskas, H. W. Tran, *Aust. J. Chem.* **1985**, *38*, 1651.

[8] a) N. Perlman, A. Albeck, *Synth. Commun.* **2000**, *30*, 4443; b) F. Garro-Hélion, F. Guibé, *Chem. Commun.* **1996**, 641.

[9] N. J. Miles, P. G. Sammes, P. D. Kennewell, R. Westood, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2299.

[10] M. T. Cox, D. W. Heaton, J. Horbury, *J. Chem. Soc., Chem. Commun.* **1980**, 799.

[11] a) X. Wang, S. A. Hart, B. Xu, M. D. Mason, J. R. Goodell, F. A. Etzkorn, *J. Org. Chem.* **2003**, *68*, 2343; b) C. E. Masse, B. S. Knight, P. Stavropoulos, J. S. Panek, *J. Am. Chem. Soc.* **1997**, *119*, 6040; c) H. Tamamura, M. Yamashita, H. Muramatsu, H. Ohno, T. Ibuka, A. Otaka, N. Fujii, *Chem. Commun.* **1997**, 2327; d) T. Ibuka, N. Mimura, H. Aoyama, M. Akaji, H. Ohno, Y. Miwa, T. Taga, K. Nakai, H. Tamamura, N. Fujii, *J. Org. Chem.* **1997**, *62*, 999; e) P. Wipf, T. C. Henninger, *J. Org. Chem.* **1997**, *62*, 1586; f) R. T. Beresis, C. E. Masse, J. S. Panek, *J. Org. Chem.* **1995**, *60*, 7714; g) M. J. Daly, R. A. Ward, D. F. Thompson, G. Procter, *Tetrahedron Lett.* **1995**, *36*, 7545; h) A. C. Bohnstedt, J. V. N. V. Prasad, D. H. Rich, *Tetrahedron Lett.* **1993**, *34*, 5217.

[12] a) A. Niida, K. Tomita, M. Mizumoto, H. Tanigaki, T. Terada, S. Oishi, A. Otaka, K. Inui, N. Fujii, *Org. Lett.* **2006**, *8*, 613; b) S. Oishi, T. Kamano, A. Niida, Y. Odagaki, N. Hamanaka, M. Yamamoto, K. Ajito, H. Tamamura, A. Otaka, N. Fujii, *J. Org. Chem.* **2002**, *67*, 6162; c) S. Oishi, A. Niida, T. Kamano, Y. Miwa, T. Taga, Y. Odagaki, N. Hamanaka, M. Yamamoto, K. Ajito, H. Tamamura, A. Otaka, N. Fujii, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1786; d) P. Wipf, P. C. Fritch, *J. Org. Chem.* **1994**, *59*, 4875.

[13] H. Imogai, Y. Petit, M. Larcheveque, *Synlett* **1997**, 615.

[14] a) V. Boucard, H. Sauriat-Dorizon, F. Guibe, *Tetrahedron* **2002**, *58*, 7275; b) H. Sauriat-Dorizon, F. Guibé, *Tetrahedron Lett.* **1998**, *39*, 6711.

[15] A. Spaltenstein, P. A. Carpino, F. Miyake, P. B. Hopkins, *J. Org. Chem.* **1987**, *52*, 3759.

[16] a) J. D. Moseley, J. Staunton, *Tetrahedron: Asymmetry* **2000**, *11*, 3197; b) C. Bertucci, A. Petri, G. Felix, B. Perini, P. Salvadori, *Tetrahedron: Asymmetry* **1999**, *10*, 4455; c) I. Izquierdo, M. T. Plaza, M. Rodriguez, J. Tamayo, *Tetrahedron: Asymmetry* **1999**, *10*, 449.

[17] a) A. Furstner, M. Albert, J. Mlynarski, M. Matheu, E. DeClercq, *J. Am. Chem. Soc.* **2003**, *125*, 13132; b) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, *1*, 26; c) For a recent review, see: P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563.

[18] A. Albeck, R. Perski, *J. Org. Chem.* **1994**, *59*, 653.

[19] a) Y. Arima, M. Kinoshita, H. Akita, *Tetrahedron: Asymmetry* **2007**, *18*, 1701; b) J. Pospisil, I. E. Marko, *J. Am. Chem. Soc.* **2007**, *129*, 3516; c) L.-S. Deng, X.-P. Huang, G. Zhao, *J. Org. Chem.* **2006**, *71*, 4625; d) Y. Ishii, S. Nagumo, T. Arai, M. Akuzawa, N. Kawaharaa, H. Akita, *Tetrahedron* **2006**, *62*, 716; e) M. T. Crimmins, A. C. DeBaillie, *J. Am. Chem. Soc.* **2006**, *128*, 4936; f) P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge, D. J. Wardrop, J. D. White, *J. Org. Chem.* **2005**, *70*, 5449; g) T. Brandl, R. W. Hoffmann, *Eur. J. Org. Chem.* **2004**, 4373; h) J.-F. Duckert, L. Balas, J.-C. Rossi, *Tetrahedron Lett.* **2001**, *42*, 3709; i) T. Suzuki, K. Ohmori, K. Suzuki, *Org. Lett.* **2001**, *3*, 1741; j) M. G. B. Drew, L. M. Harwood, A. Jahans, J. Robertson, S. Swallow, *Synlett* **1999**, *2*, 185; k) N. W. Hird, T. V. Lee, A. J. Leigh, J. R. Maxwell, T. M. Peakman, *Tetrahedron Lett.* **1989**, *30*, 4867; l) I. Paterson, I. Boddy, I. Mason, *Tetrahedron Lett.* **1987**, *28*, 5205.

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