Enantioselective Nitration of Chiral (*E*)-Crotylsilanes: A Concise Asymmetric Synthesis of (*E*)-Olefin Dipeptide Isosteres

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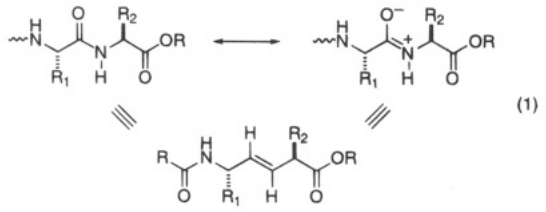
Received August 31, 1995

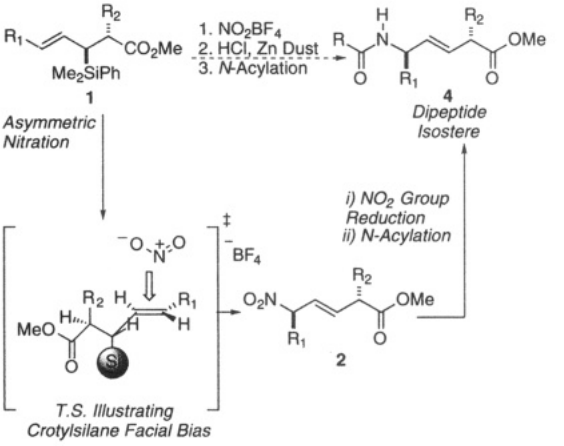
Replacement of the amide bond linkage with an (*E*)-olefin is a proven useful configurationally biased structural mimic for the construction of peptide linkages in a number of different enzyme inhibitors.[1] These analogs of biologically active peptides offer distinct advantages over the naturally occurring compounds, including lower enzymatic degradation, increased oral bioavailability, and a prolonged duration of action.[2] The amide linkage is the primary target for enzymatic degradation; therefore, structural modifications at this site may lead to enhanced metabolic stability. In addition, interest has emerged in peptidomimetics of inverso D-peptides which are resistant to the action of cellular proteases, thereby making them attractive drug candidates.[3] The structural similarities between the contributing resonance structures of the amide linkage and the incorporated (*E*)-olefin isostere produced in this study are illustrated in eq 1.



(1)

(*E*)-Olefin isosteres have been shown to be useful replacements for the amide linkage in drug candidates as the (*E*)-CR=CH group closely approximates the bond lengths, angles, and rigidities of the natural structural type. (*E*)-Olefin peptide mimetics require the generation of a stereocenter at the α-position of a 5-amino-3-hexenoic acid derivative; therefore, any successful chemical synthesis of dipeptide isosteres must address an (*E*)-selective olefination process and also allow for the stereoselective introduction of the α-side chains of the associated amino acids. The lack of general efficient syntheses of (*E*)-olefins bearing bis-allylic stereocenters has impeded their development as peptidomimetics, and reports describing stereoselective approaches to these isosteric units are rare.[4] These methods generally rely on the use of modified amino acids as the source of chirality which typically lead to difficulties in the introduction of the second α-side chain of the associated amino acid.

Scheme 1



We have previously demonstrated the use of stereocontrolled reactions to prepare related dipeptide derivatives possessing a pseudo C_2-symmetric axis[5] and now wish to disclose a new concise stereocontrolled route to these isosteres which may increase their availability for drug discovery programs.

Recent efforts in our laboratories have demonstrated that chiral (*E*)-crotylsilanes act as useful carbon nucleophile equivalents in highly diastereo- and enantioselective condensation reactions with aldehydes, acetals, and certain electrophilic alkenes. These experiments have culminated in efficient methods for the asymmetric synthesis of functionalized homoallylic ethers, tetrahydrofurans, γ-alkoxy-α-amino acid synthons, and tetrasubstituted cyclopentanes.[6] The stereocontrolled synthesis of (*E*)-olefin dipeptide isosteres provides a further application of our crotylsilane methodology. This methodology is capable of solving the problems of stereocontrol in the installation of the (*E*)-double bond and introduction of a variety of alkyl, alkoxy, and allyl groups (amino acid side chains) in either a *syn* or *anti* stereochemical relationship through the stereocontrolled addition of the nitrogen-based cation, NO_2^+. Olah and Rochin have previously demonstrated the feasibility of this type of electrophilic substitution through nitration of unfunctionalized and achiral allylsilanes.[7] In a related study, we have documented a stereocontrolled route for the formation of chiral Δ^2-isoxazolines through nitrosium tetrafluoroborate promoted [3 + 2] annulations of (*E*)-crotylsilanes.[8]

The present study illustrates the utility of these chiral silane reagents in the development of an effective method for the asymmetric synthesis of (*E*)-olefin dipeptide isosteres. Six (*E*)-crotylsilanes **1a**−**f** were examined to establish the viability of this approach for the production of a series of related dipeptide isosteres. Previous research conducted in our laboratory has accessed silanes possessing *syn* or *anti* configurations and a variety of alkyl and alkoxy functionalities, as well as developed routes that may easily be applied to the synthesis of novel (*E*)-crotylsilanes.[9] The synthesis of the individual dipeptide isosteres is shown in Scheme 1 and is illustrated with a substrate possessing *anti* stereochemistry. The chiral silane reagents undergo smooth uncatalyzed condensation with nitronium tetrafluoroborate to afford the corresponding allylic nitro compounds **2a**−**f** which are isolated as chromatographically pure materials. The

† Recipient of a Graduate Fellowship from the Organic Chemistry Division of the American Chemical Society, 1994−1995, sponsored by Upjohn Co.

‡ Recipient of a Boston University Presidential Fellowship, 1994−1996.

(1) (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699−1720 (review). (b) Spatola, A. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7, pp 267−357. (c) Also see: Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K.; Essenburg, A. D. *J. Med. Chem.*, **1990**, *33*, 838−845 and references cited therein.

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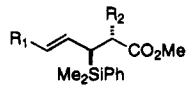
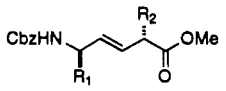
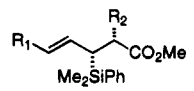
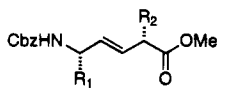
0022-3263/95/1960-7714$09.00/0

Table 1. Asymmetric Synthesis of (*E*)-Olefin Dipeptide Isosteres

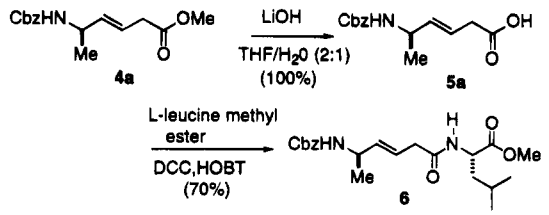
entry	(*E*)-crotylsilane (abs. stereochem) (R_1, R_2)	major product (overall % yield 4[a]; de[b])
1.	 **1a** (3*R*); (Me, H)	 (5*R*)-**4a** (36; > 30:1)
2.	**1b** (2*R*, 3*S*); (Me, Me)	(2*S*, 5*R*)-**4b** (20; > 30:1)
3.	**1c** (2*R*, 3*S*); (Me, allyl)	(2*S*, 5*R*)-**4c** (25; > 30:1)
4.	**1d**[c] (2*R*, 3*S*); (^{i}Pr, Me)	(2*S*, 5*R*)-**4d** (18; > 30:1)
5.	 **1e** (2*R*, 3*R*); (Me, Me)	 (2*S*, 5*S*)-**4e** (45; > 30:1)
6.	**1f** (2*R*, 3*R*); (Me, OMe)	(2*S*, 5*S*)-**4f** (41; > 30:1)

(a) Overall unoptimized yield for the 3 step-sequence based on pure materials isolated by chromatography (SiO_2). (b) Ratios of products were determined by ^{1}H NMR (400 MHz) operating at S/N of >200:1. (c) Silane **1d** was prepared by an analogous Claisen strategy procedure starting from 4-methyl-1-pentyn-3-ol.

chirality of the emerging nitro-bearing center solely originates from and is controlled by the nature of the silyl stereocenter in an *anti*-S_E' addition process.[10] Subsequent reduction of the allylic nitro compounds using Zn/HCl furnishes the allylic amines **3**. The crude amines were *N*-acylated with carbobenzoxy chloride to yield the allylic carbamates as the desired isosteres **4a**–**f** in good overall yields with high levels of stereoselectivity[11] and excellent levels of 1,4-remote asymmetric induction. The results of the dipeptide isostere synthesis are summarized in Table 1.

In these examples, solid NO_2BF_4[12] (1.1 equiv) in anhydrous CH_2Cl_2 was determined to be the most effective nitrating agent–solvent combination for efficient electrophilic substitution and formation of the allylic nitro compounds in yields ranging between 40 and 66%. The modest yields in the nitration step were primarily due to partial desilation of the starting crotylsilane induced by the presence of free fluoride ion in solution. The amount of desilation was partially reduced by allowing the mixture to slowly warm to room temperature over 10 h and diluting with an aqueous saturated $NaHCO_3$ solution. The allylic nitro compounds proved to be especially labile and were subject to partial decomposition during column chromatography and under strongly basic conditions. Attempts to carry out the asymmetric nitration reaction on substrates containing benzyl substituents (R_2 = Bn) failed, due to competing nitration of the aromatic ring.[13] Reduction of the labile allylic nitro compounds proved to be an unexpectedly difficult transformation. Numerous conditions were surveyed to cleanly effect this reduction including transfer hydrogenation,[14] $CoCl_2 \cdot 6H_2O/NaBH_4$,[15] Fe/acetic acid,[16] and $NaBH_4$/S,[17] all of which resulted in complex mixtures. The transformation was finally accomplished using Zn/HCl in methanol at 0 °C which cleanly afforded the allylic amines in crude yields on the order of 95%. The crude amines were immediately *N*-acylated with carbobenzoxy chloride (Cbz-Cl) followed by purification by chromatography on silica gel to give the allylic carbamate isosteres.

Scheme 2



The potential utility of this technology is illustrated with a short synthesis of a structural mimetic of the tripeptide sequence Cbz-Ala[Ψ(*E*)-CH=CH]Gly-Leu-OMe. Our interest in this structural class arises from a recent report demonstrating potent inhibition of the zinc endopeptidase thermolysin by similar peptidomimetics.[4j] The synthesis of the tripeptide analog **6** was accomplished by methyl ester hydrolysis of **4a** using LiOH followed by coupling of the derived acid **5a** with the methyl ester of L-leucine as illustrated in Scheme 2.

In summary, the asymmetric nitration of chiral (*E*)-crotylsilanes with NO_2BF_4 provides a highly diastereo- and enantioselective method for the asymmetric synthesis of (*E*)-olefin dipeptide isosteres and continues to expand the scope and utility of this developing chiral allylsilane methodology.

Acknowledgment. This work has been financially supported by the National Institutes of Health (RO1CA56304).

Supporting Information Available: General experimental procedures for the asymmetric nitration, transformation to the isosteres, and peptide coupling as well as spectral data for all reaction products (4 pages).

JO9515889

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(10) (a) The relative stereochemistry of the derived allylic nitro compounds is dictated by the chirality of the C–Si bond (see the supporting information for details).

(11) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

(12) (a) NO_2BF_4 is commercially available from Aldrich Chemical Co. (b) The use of other nitronium ion sources possessing less nucleophilic counterions (e.g., NO_2OTf) which are less likely to promote protodesilation were less practical as these reagents are not commercially available and less stable than NO_2BF_4. Since NO_2OTf must be independently synthesized (*cf.* Effenberger, F.; Geke, J. *Synthesis* **1975**, 40–41), it reduces the overall simplicity of the methodology.

(13) The crude ^{1}H NMR of these substrates indicated substantial desilation and showed a *para*-substituted splitting pattern of the aromatic protons.

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