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A CONCISE ENANTIOSELECTIVE SYNTHESIS OF *trans*-OLEFIN DIPEPTIDE ISOSTERES

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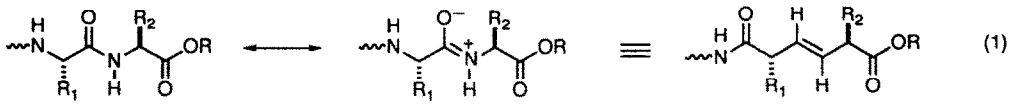
Abstract. A new asymmetric synthesis of *trans*-olefin dipeptide isosteres is described which utilizes chiral allylsilane based-bond construction methodology involving a Lewis acid promoted electrophilic addition of chiral (*E*)-crotylsilanes to the formaldehyde equivalent *s*-trioxane. The reaction results in the simultaneous introduction of a *trans* double bond and both amino acid side chains with high levels of diastereo- and enantioselection. The derived isostere units were incorporated into tetrapeptides and their inhibitory constants determined against the HIV-1 protease.

The replacement of the amide bond linkage with a *trans*-olefin has proven to be a useful configurationally biased structural mimic for the construction of peptide linkages in a number of different enzyme inhibitors.[1] Among the several types of known isosteric units, the *trans*-olefin has been of particular interest because it can simulate the three-dimensional geometry provided by the amide back bone while decreasing the peptide character of these molecules. A combination of factors make these molecules less susceptible to biodegradation, including the fact that the *trans*-olefin does not have the capability for hydrogen bonding interactions, and unlike an amide bond will not undergo proteolytic cleavage at that position. The objective of such a design concept is the eventual production of certain enzyme inhibitors which exhibit improved oral absorption and an enhanced pharmacokinetic profile. A further design consideration which may have implications in the development of HIV protease inhibitors, involves the terminal carboxylate groups of this isostere class that can lead to a pseudo C_2-symmetric isostere which takes advantage of the two fold symmetry of the HIV-protease enzyme.[2] A comparison between the contributing resonance structures of the amide linkage and the incorporated *trans*-olefin isostere produced in this study is illustrated in equation 1.

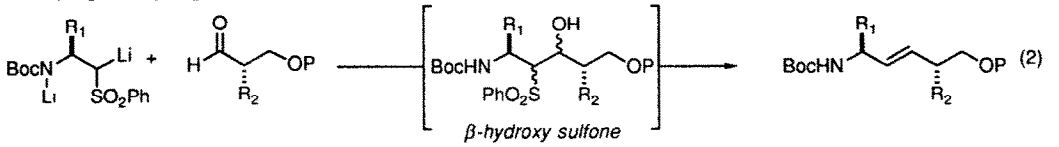


(1)

In considering a chemical synthesis of dipeptide isosteres containing a *trans*-olefin, two problems must be addressed; [i] an *E*-selective olefination process and; [ii] the stereoselective introduction of the α-side chains of associated amino acids. The lack of general efficient syntheses of *trans* olefins bearing allylic stereocenters has impeded their development as peptidomimetics. Reports describing stereoselective approaches to these isosteric units generally rely on the use of modified L-amino acid derivatives as the source of absolute chirality which typically leaves the problem of the introduction of the second α-side chain of the associated amino acid. This issue takes on greater importance since it has been established that a key factor in determining the level of

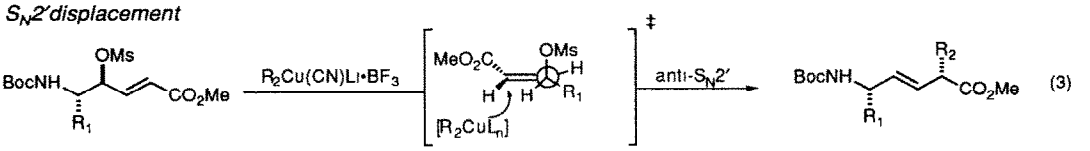
bioactivity is the presence of the second stereogenic center. In this regard, the second amino acid side chain is necessarily introduced in a separate step with varying levels of stereocontrol.[3] Equations 2 and 3 serve to illustrate prototypical reaction sequences for the preparation of *trans* olefin isosteres. A Julia-Lythgo coupling protocol has been utilized for the construction of the *trans*-double bond which involves the condensation of a lithiated β-amino sulfone (derived from an amino acid) with a chiral α-substituted aldehyde (eq. 2).[4] Although the E selectivity is generally high for the oxidation-step, the overall reaction is often compromised by competing β-elimination of the amino group producing a vinylsulfone.

Julia-Lythgo coupling



Ibuka and coworkers[5] have reported that boron trifluoride•organocopper reagents can be used for the introduction of the α-side chains of the *trans* olefin isostere. The reaction is thought to proceed by an *anti*-S_N2' displacement pathway of δ-amino-γ-mesyloxy-α,β-unsaturated esters and represents a highly stereoselective process for the introduction of one of the isostere side chains (eq. 3).

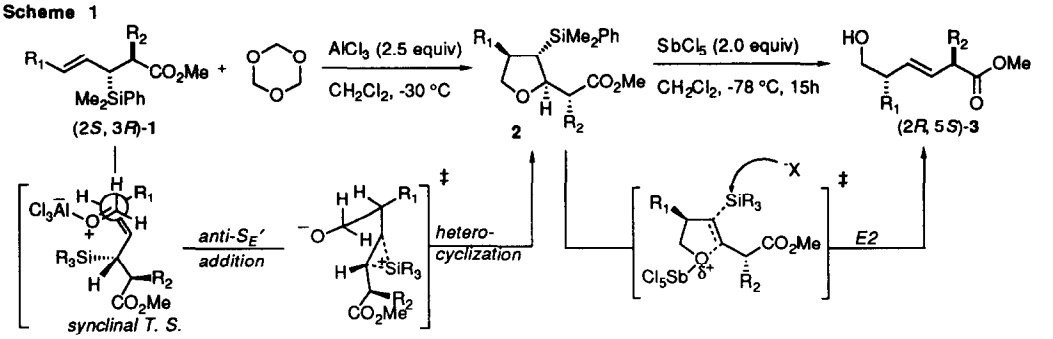
S_N2'displacement



Research conducted in our laboratories has established the ability of chiral (*E*)-crotylsilanes as useful carbon nucleophiles in highly diastereo- and enantioselective condensation reactions with aldehydes, acetals and certain electrophilic alkenes. Those experiments have culminated in an efficient method for the asymmetric synthesis of functionalized homoallylic ethers,[6] tetrahydrofurans,[7] γ-alkoxy-α-amino acid synthons,[8] and tetrasubstituted cyclopentanes.[9] In looking ahead to the application of our chiral allylsilane bond construction methodology in the synthesis of *trans*-olefin dipeptide isosteres, it should be capable of providing a solution to the problem of stereocontrol in the introduction of the α-side chains as well as the configuration of the double bond. This methodology provides for the introduction of a variety of alkyl groups (amino acid side chains) in either a *syn* or *anti* stereochemical relationship and allows the simultaneous introduction of the *trans* double bond in a single operation. The fact that the derived primary alcohol **3** would provide the necessary chemical flexibility for incorporation into a peptide fragment should further enhance the utility of this process. The present study illustrates the utility of these chiral silane reagents in the development of an effective method for the asymmetric synthesis of *trans*-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 trans-olefin dipeptide isosteres. [10] The syntheses of the individual dipeptide isosteres using *syn* and *anti*- (*E*)-crotylsilanes are provided in Scheme 1 and is illustrated with a substrate possessing *anti* stereochemistry. Because the substituted tetrahydrofurans **2** were obtained as

the major product from the initial asymmetric condensation with *s*-trioxane, a stronger Lewis acid was necessarily employed in a second step to ensure complete conversion to the homoallylic alcohol **3**. The choice of *s*-trioxane as the formaldehyde equivalent was based on literature precedent established in chiral allylsilane methodology.[11] As expected the chiral silane reagents underwent smooth *anti*-S_E' addition to *s*-trioxane catalyzed by the action of $AlCl_3$ to afford the tetrahydrofuran **2**.[12] Subsequent Lewis acid catalyzed ring opening with $SbCl_5$ (2.0 equiv) produced the desired isostere **3** in high yield and high levels of stereoselectivity.[13] Attempts to obtain the homoallylic alcohol directly in good yield via Lewis acid catalyzed condensation proved unsuccessful.[14]

Scheme 1



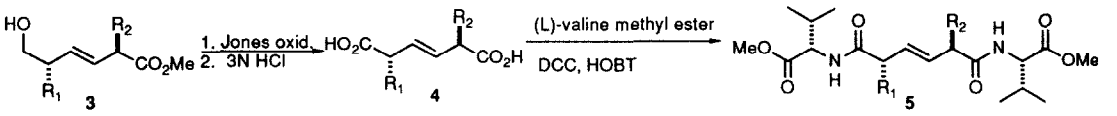
entry	*(E)*-crotylsilane[a] (R_1, R_2)	% yield **2**[b]	diastereomeric ratio **2**[c]	% yield **3**[b]	(abs. stereochem. **3**)
1.	(2S, 3R)-**1a**; Me, Me	91	>50:1	95	(2*R*, 5*S*)-**3a**
2.	(2S, 3S)-**1b**; Me, Me	79	>50:1	92	(2*R*, 5*R*)-**3b**
3.	(2S, 3R)-**1c**; Me, Bn	81	>50:1	87	(2*R*, 5*S*)-**3c**
4.	(2R, 3S)-**1d**; Me, Bn	83	>50:1	76	(2*S*, 5*R*)-**3d**
5.	(2R, 3S)-**1e**; Me, ^{i}Pr	89	>50:1	77	(2*S*, 5*R*)-**3e**
6.	(2R, 3S)-**1f**; ^{i}Pr, Bn	-	>50:1	51[d]	(2*S*, 5*R*)-**3f**

(a) The (*E*)-crotylsilanes were prepared by electrophilic addition to chiral β-(phenyldimethyl)silyl ester enolates **1a**, **1c-f**, or by Ireland-Claisen Rearrangement **1b**. See ref 10. (b) All yields are based on pure materials isolated by chromatography (SiO_2). (c) Ratios of products were determined by ^{1}H NMR (400 MHz) operating at S/N of >200:1. (d) Aluminum trichloride ($AlCl_3$) addition gave a 1:1 mixture of tetrahydrofuran and homoallylic alcohol. The combined yield after ring opening is given.

The effectiveness of this approach for the incorporation of these isosteric units into peptide fragments has been demonstrated employing (L)-valine as the amino acid used to cap the terminal carboxylates of the isostere unit. The assemblage of the six tetrapeptides proceeded according to the general sequence outlined in scheme **2** and is illustrated for the anti diastereomer. The resulting primary alcohols **3** were oxidized with Jones reagent (2.0 equiv, acetone, 0 °C) producing the monoacid-ester (yields of 68-73%) without any appreciable amounts of

racemization as determined by inspection of the ^{1}H-NMR. The derived mono acid-esters were hydrolyzed under acidic conditions (3 N HCl-THF, 3:1, reflux, 5h) to yield the diacids **4**, with complete conversion being observed. Under base catalyzed hydrolysis conditions, the substrates underwent extensive epimerization. The tetrapeptides **5** were produced in yields ranging from 67 to 87% by coupling of the diacids **4** with two molar equivalents of L-valine methyl ester with carboxylate activation by dicyclohexylcarbodiimide in the presence of the racemization inhibitor HOBT.

Scheme 2



entry	*trans*-olefin isostere (R_1 & R_2)	% yield[a] **4** from **3**	tetrapeptide **5** R_1/R_2 [b]	% yield[a] **5**	K_i (μM)
1.	*anti*-**3a**; Me, Me	69	**5a**; Me / Me	71	-[c]
2.	*syn*-**3b**; Me, Me	73	**5b**; Me / Me (R_1 & R_2 syn)	68	-[c]
3.	*anti*-**3c**; Me, Bn	65	**5c**; Me / Bn	67	>67
4.	*anti*-**3d**; Me, Bn[d]	73	**5d**; Me / Bn	79	-[c]
5.	*anti*-**3e**; Me, ^{i}Pr	68	**5e**; Me / ^{i}Pr	87	>67
6.	*anti*-**3f**; ^{i}Pr, Bn	72	**5f**; ^{i}Pr / Bn	74	5

(a) All yields are based on pure materials isolated by chromatography (SiO_2). (b) All reactions were carried out in distilled CH_2Cl_2 (0.2 M) from 0 °C → rt for 24h under N_2 (c) The K_i's were not determined for these compounds (d) Reaction run with the enantiomer of **3c**

The inhibitory constants (K_i's) for compounds **3c**, **3e** and **3f** were determined using an end-point hplc assay with purified HIV-1 protease (HIVP).[15] The K_i values are listed in the table accompanying scheme 2 and represent the dissociation constants for the protease-inhibitor complex. Of the three compounds tested for HIV protease inhibition activity only **3f** exhibited moderate potency. Due to the insolubility of compounds **3c** and **3e** the IC_{50} values could not be reached and therefore only an approximate Ki value is reported.

In summary, the experiments described have demonstrated that chiral allylsilane bond construction methodology is useful for the asymmetric synthesis of *trans*-olefin dipeptide isosteres. High levels of stereocontrol are reached in the introduction of amino acid side chains (R^1 and R^2). Depending on the stereochemistry of the R-groups on the silane reagent either *syn* or *anti*- orientations can be introduced into the isosteric unit. Further studies concerning the synthesis of peptides containing *trans* olefin dipeptide isosteres as well as their effectiveness as inhibitors of HIV-1 protease will be reported in due course.

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12 (a) The relative stereochemistry of the derived tetrahydrofurans **2** was assigned by ^{1}H-NMR experiments and by analogy with closely related structures obtained from asymmetric (*E*)-crotylsilane additions to achiral, heterosubstituted aldehydes, for details see reference 7. The absolute stereochemical assignment of the derived tetrahydrofuran products and the acyclic homoallylic alcohols is based on literature precedent documenting that electrophilic substitution reactions of optically active allylsilanes proceed only through an *anti* -S_E' mechanism (*anti* attack). The ee was determined to be 96% and refers to product ratios obtained from an *anti* S_E' addition for the *syn* or *anti*-2, 5 susbtitution on the derived homallylic alcohols. These assignments are based on the fact that the C2-stereocenter of the (*E*)-crotylsilanes **1** does not show any appreciable signs of epimerization under the described reaction conditions (see ref. 6a). As a result it utilized as a stereochemical indicator which allows the detection of any stereochemical defect associated with the formation of the other diastereomer which would be derived from a *syn*-S_E' addition. For relevant discussions concerning the mechanism and stereochemistry of S_E'-type reactions see: (b) Matassa, V. G.; Jenkins, P. R.; Kumin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Israel J. Chem.* **1989**, *29*, 321-343 andreferences cited therein. (c) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**,*104*, 4962-4963. (d) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron*, **1989**,*45*, 1053-1065.

13 A proposed mechanism for the $SbCl_5$ promoted ring opening may involve coordination of the Lewis acid to the furan oyxgen facilitating an E2-like process. All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

14 Attempts to achieve the homoallylic alcohol directly were unsuccessful as several different Lewis acids that were surveyed (TMSOTf, BF_3·OEt_2, $SnCl_4$, $TiCl_4$) proved to sufficiently unreactive. However, $SbCl_5$ did promote the reaction producing the desired homoallylic alcohol in low yield.

15 Determination of the inhibition constants for the HIV protease was conducted as follows; a diluted solution of HIVP (100-150 fold dilution of 183 mg/mL, Bachem Biosciences, Philadelphia) was prepared immediately before the assay. The working enzyme stock solution contained 50 mM citrate, pH 5.0, with 2.0 mM EDTA, 5 mM DDT and 10% glycerol. The final assay mixture 216 μL) was comprised of 10 μL of 1M citrate solution, pH 4.5; 10mL of 24 mM DTT; 60 mL of 4 mM EDTA and 124 mL of H_2O. To each assay tube 4μL of a DMSO solution containing the inhibitor (or neat DMSO for the control reaction) and the tubes left at room temperature for 15 minutes prior to initiating the enzyme reaction. The reactions were initiated by adding 20mL of HIV substrate (0.5 mM, Bachem) and the tubes incubated at 37 °C. After 30 minutes, the reactions were quenched with 60 mL of 20% trifluoroacetic acid, before being transfered to the autosampler microvials for the HPLC analysis. The reverse-phase HPLC conditions used for the separation of the product peak were conducted as follows. A 10 minute gradient was run from 15 to 40% acetonitrile-0.1% trifluoroacetic (TFA) acid, where the balance was 0.1% TFA-H_2O. The enzyme rate data at varying concentrations of inhibitor were used to calculate the Ki by fitting to a non-linear equation for competative inhibition using the program KineTic (BioKin Ltd., Madison, WI).