by treating 12.0 g (2.95 mmol) of 7 for 2, 2, and 25 min with 1:2 (v/v) TFA/CH_2Cl_2 containing 1:49 (v/v) ethanedithiol, followed by five 2-min washes with CH_2Cl_2. Neutralization was carried out with 1:9 (v/v) triethylamine/CH_2Cl_2 for periods of 2, 2, and 4 min, followed by five 2-min washes with CH_2Cl_2 and one DMF wash. Coupling of the fragment was performed by treating the neutralized resin with a solution of the activated N-terminal fragment prepared as follows: a stirred solution of 6.9 g (5.27 mmol) of **5** and 606 mg (5.27 mmol) of *N*-hydroxysuccinimide (recrystallized) in 15 mL of degassed DMF was cooled in an ice–water bath for 5 min, and 5.27 mL of a 1 M solution of DCC in CH_2Cl_2 was added in one portion. The ice bath was removed, and the thick mixture was stirred for 4 h. After adding this solution to the resin, 159 mg (1.3 mmol) of recrystallized (ethyl acetate) 4-(dimethylamino)pyridine (DMAP) was added, and the mixture was rocked gently for 22 h. Then 1.0 mL of DCC solution was added and mixing continued for 26 h at which time a solution of 159 mg (1.3 mmol) of DMAP in 3.0 mL of degassed DMF was added and mixing continued for an additional 64 h. The resin was washed twice with DMF for 2 min each, followed by six 2-min washes with CH_2Cl_2. After removing the Boc protection using the TFA solution described above for 3- and 25-min periods followed by six 2-min washes with CH_2Cl_2, the peptide–resin was dried to constant weight at reduced pressure to afford 19.5 g (91%) of **2**: aaa avg = 0.138 mmol/g, Arg (Orn) 5.047 (5), Asx 2.285 (2), Glx 1.157 (1), Gly 5.010 (5), Ala 1.120 (1), Ile 1.685 (2), Leu 0.962 (1), Tyr 1.056 (1), Phe 1.678 (2).

Arg-Arg-Ser-Ser-Cys(Acm)-Phe-Gly-Gly-Arg-Ile-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys(Acm)-Asn-Ser-Phe-Arg-Tyr-OH (8). A Kel-F reaction vessel was charged with a slurry of 2.0 g (0.28 mmol) of **2** and 1.0 g (6.7 mmol) of L-methionine in 4.0 mL of *m*-cresol (Aldrich), which was stirred slowly for 1 h. The reaction vessel was attached to a Kel-F manifold and cooled in a dry ice/acetone cold bath for approximately 10 min, and approximately 45 mL of anhydrous HF (Matheson) was condensed into the stirred mixture. The cold bath was replaced with an ice–water bath, the mixture was stirred in the cold for 75 min, and the HF was removed in the cold under reduced pressure (water aspirator for 70 min followed by vacuum pump for 1 h). After triturating the residue with 50 mL of ether for 15 min in the cold, the mixture was filtered and washed with two 30-mL portions of ether and dried briefly under reduced pressure. The peptide was leached from the resin by stirring and filtering with 15 mL of 1:1 (v/v) acetic acid/H_2O. Purification was achieved by applying the combined filtrates onto a Sephadex G-25F column (5 × 100 cm) and eluting with 2.0 M acetic acid. Product purity was checked by assaying the fractions (22 mL) by TLC (system IX) and HPLC (system II, column A). Fractions of appropriate purity were combined and evaporated to dryness at reduced pressure. Material from four identical runs was lyophilized from 150 mL of H_2O to afford 1.765 g (41%) of **8**: aaa avg = 0.259 mmol/g, Arg (Orn) 4.918 (5), Asx 2.038 (2), Ser [3.476] (4), Glx [1.164] (1), Gly [4.369] (5), Ala 1.052 (1), Ile 1.968 (2), Leu 1.032 (1), Tyr 1.017 (1), Phe 1.976 (2); TLC (system X) R_f 0.3; HPLC (system II, column A) 86%, t_R 50 min.

Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Ile-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr-OH, Disulfide Form (1). A solution of 1.39 g (5.5 mmol) of I_2 in 620 mL of 80% HOAc was added rapidly to a briskly stirred solution of 1.21 g (0.3 mmol) of **8** in 37 mL of 50% HOAc. After 2 h the reaction mixture was cooled in an ice–water bath for 5 min and treated with 4.9 g of zinc dust until decolorization of the I_2 was complete. The mixture was filtered, and the filtrate was concentrated at reduced pressure to a volume of about 25 mL, diluted with an equal volume of H_2O, and charged onto a 5 × 100 cm column of Sephadex G-50F in 50% HOAc. The column was eluted with 50% HOAc, and the fractions were pooled on the basis of HPLC analysis (system II, column A), combined, concentrated at reduced pressure, and lyophilized from H_2O to give 0.92 g of crude **1**. A solution of 1.76 g of this material in 50 mL of 0.05 M NH_4OAc (pH adjusted to 5.0 with acetic acid) was applied to a 300-mL (4.0 cm diameter) column of carboxymethylcellulose (CMC) (Whatman) equilibrated with 0.3 M NH_4OAc (prepared by diluting 76.5 mL of concentrated NH_4OH (29% NH_3) and 68.6 mL of glacial acetic acid to 4.0 L with degassed H_2O and acidifying to pH 5.0 with additional acetic acid). The column was eluted with 4 L of 0.3 M NH_4OAc (pH 5.0, prepared as above) and 22-mL fractions were collected over a period of 24 h. Those fractions showing greater than 97% purity by HPLC (system II, column A) were combined, applied directly to a Sephadex G-25F column (5 × 100 cm), and eluted with 2.0 M acetic acid to remove NH_4OAc. The fractions containing product were combined, evaporated to dryness under reduced pressure, and lyophilized from 125 mL of H_2O to give 890 mg (40.6%) of **1** as a colorless solid: aaa avg = 0.286 mmol/g, Arg 5.04 (5), Asx 2.05 (2), Ser 4.06 (4), Glx 1.00 (1), Gly 4.90 (5), Ala 1.00 (1), Ile 1.93 (2), Leu 1.02 (1), Tyr 1.00 (1), Phe 2.00 (2); TLC (system X) R_f 0.33; HPLC (system II, column A) 97.3%, t_R 49 min; GC, acetic acid 6.9%; H_2O, Karl Fischer titration 8.1%; specific rotation $[\alpha]^{26}_D$ +47.3°; cumulative sequence preview ≤3% at Ser^{30} cycle. Combustion analysis (based on tetraacetate minus water). Calcd: C, 49.17; H, 6.66; N, 19.42; S, 2.07. Found: C, 49.11; H, 6.80; N, 19.32; S, 2.42.

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New Approaches to the Synthesis of *trans*-Alkene Isosteres of Dipeptides

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Two new syntheses of protected dipeptide analogues bearing a trans carbon–carbon double bond in place of the amide linkage are reported. One route is a linear synthesis employing the rearrangement of an allylic selenide to a protected allylic amine. The second route is convergent and uses the Julia olefin synthesis in a key step. The latter route is fully stereocontrolled and has been used to prepare protected *trans*-alkene isosteres of the dipeptides TyrAla, PhePhe, LeuPhe, and LeuLeu.

Introduction

Studies of structure–function relationships in the field of biologically active peptides have largely focused on the effects of changes in side chain residues. This is experimentally advantageous, since peptide synthesis is now routine, but does not permit the study of questions regarding the role played by the amide backbone. Changing the amide backbone is in general more synthetically challenging, but, despite this, numerous amide replacements have been pursued.[1] It has been suggested that the

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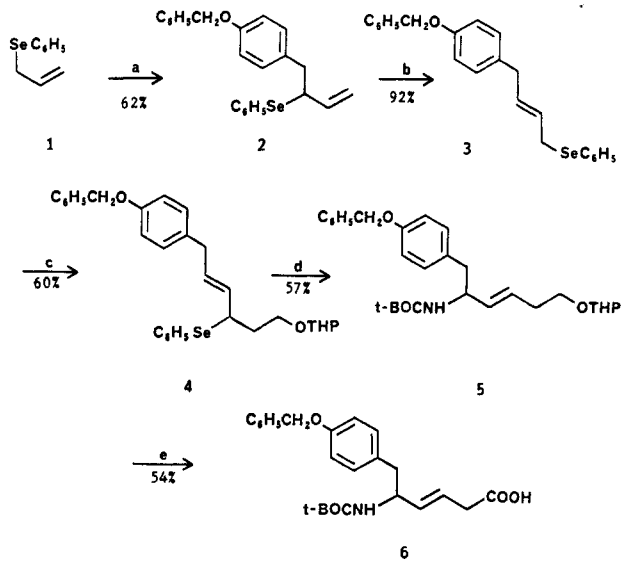
0022-3263/87/1952-3759$01.50/0

Scheme I[a]



1 2 3 4 5 6

[a] (a) (i) LDA, THF, −78 °C, (ii) LDA, $C_6H_5CH_2O$-*p*-$C_6H_4CH_2Br$; (b) PTSA·H_2O, C_6H_6, reflux; (c) (i) LDAz, THF, −78 °C, (ii) THP-OCH_2CH_2Br; (d) *t*-$C_4H_9OCONH_2$, Et_3N, NCS, CH_3OH, 0 °C; (e) (i) 0.2 M HCl (aqueous), THF; (ii) Jones oxidation.

replacement of the amide linkage with a trans carbon–carbon double bond provides a substance which closely mimics the three-dimensional shape of the parent amide but that is inert to enzymatic hydrolysis. It has further been predicted that peptide analogues bearing the so-called *trans*-alkene isostere will retain biological activity if the amide linkage so replaced is not involved in the secondary or tertiary structure of the peptide or in the mechanism whereby it elicits its biological response.[2] One reviewer has called the *trans*-alkene isostere "an ideal replacement".[1]

When this project was initiated, there existed two procedures for the preparation of dipeptide analogues containing the *trans*-alkene isostere.[2,3] It has been shown that these dipeptide mimics could be incorporated into larger peptides. Both routes successfully afforded *trans*-alkene isostere-containing mimics of enkephalin;[2,3] one of the routes also provided a substance P analogue.[3] Subsequently these methods were used to prepare an angiotensin-converting enzyme inhibitor[4] and several renin inhibitors[5,6] containing this replacement. Most of these compounds showed promising biological activity.

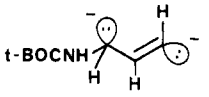
Both of these synthetic routes suffered from lack of stereocontrol with respect to either or both the alkene linkage and the side chain-bearing stereocenters. We envisioned developing a sequence which would surmount these difficulties. Two new synthetic routes to protected *trans*-alkene isosteres of dipeptides have been developed and are reported herein.[7] One of these routes is the first which is fully stereocontrolled.

Results and Discussion

An Organoselenium Route. *trans*-Alkene isosteres contain an embedded allylic amine. The sigmatropic rearrangement of oxidatively activated allylic selenides which yields allylic amines[8] was developed for this application and was used in the preparation of *trans*-alkene isosteres; such a synthesis of the protected TyrGly isostere **6** is illustrated in Scheme I.

The anion of allyl phenyl selenide (**1**)[8] was alkylated[9] with *p*-(benzyloxy)benzyl bromide, and the resulting allylic selenide **2** was treated in refluxing benzene with a trace of *p*-toluenesulfonic acid to afford **3**, the product of allylic rearrangement. Allylic selenide **3** was again alkylated to yield **4**, which was in turn subjected to NCS-promoted rearrangement[8] in the presence of *tert*-butyl carbamate, to yield protected allylic amine **5**. Although the THP ether could be removed and the resulting alcohol oxidized in a single step with Jones reagent,[10] a more reproducible procedure involved hydrolysis of the THP ether[11] followed by Jones oxidation.

It is noteworthy that the acid-catalyzed rearrangement of allylic selenides, as in **2** → **3**, has been previously noted[12] but has not to our knowledege been used as a synthetic reaction. This alkylation–rearrangement–alkylation–rearrangement sequence makes allyl phenyl selenide the synthetic equivalent of the dianion **7**.



7

The organoselenium approach to *trans*-alkene isosteres (Scheme I) is stereocontrolled with respect to the geometry of the alkene[8] but suffers from several drawbacks. Although in principle extendable to the synthesis of peptide mimics with residues other than Gly at the C-terminus, this has proven nontrivial, since the requisite alkylation of **3** with a more substituted halide (for example to directly prepare a TyrAla analogue) could not be achieved. An indirect route involving esterification of a Gly-C-terminal acid (such as **6**), followed by alkylation at the α-carbon[13] and finally saponification, is thus required. A second limitation is that this route does not, in the present form, address the question of stereocontrol of the two chiral centers. A final drawback is the linearity of the sequence, which renders inconvenient the preparation of gram quantities of final isostere by this method. A new route was sought.

An Organosulfur Route. It appeared that the two major flaws with the organoselenium route, linearity and lack of stereocontrol, might be eliminated by a connective scheme such as the Julia olefin synthesis.[14] The simplest

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(7) For a preliminary account of this work, see: Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *Tetrahedron Lett.* **1986**, *27*, 2095.

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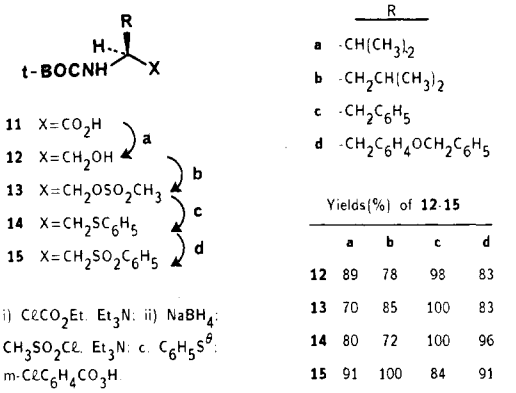
(12) Di Giamberardio, T.; Halazy, S.; Dumont, W.; Krieg, A. *Tetrahedron Lett.* **1983**, *24*, 3413.

(13) Cox[3a] has achieved alkylations on closely related compounds.

Scheme II

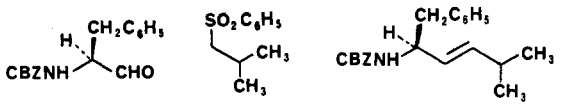


Yields(%) of **12**-**15**

	a	b	c	d
12	89	78	98	83
13	70	85	100	83
14	80	72	100	96
15	91	100	84	91

option was coupling of a protected α-amino aldehyde, available by several methods,[15] with a sulfone anion appropriately functionalized to serve as the eventual C-terminus.

Attempts to couple CBZ-phenylalanal **8** and the anion of isobutyl phenyl sulfone (**9**) followed by sodium amalgam reduction[16] were discouraging, providing, at most, traces of olefinic product **10**, despite extensive variation of reaction conditions. Fortunately, developments along another line allowed us to abandon this approach.

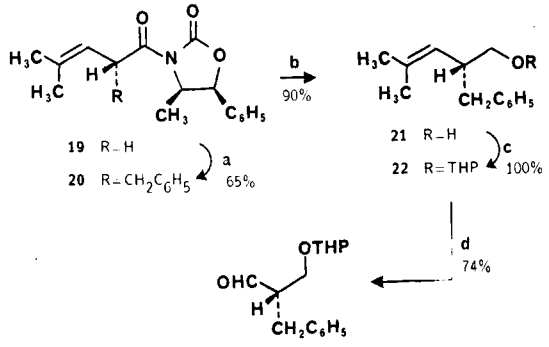


8 **9** **10**

A connective approach in which the N-terminus enters as a sulfone anion and the C-terminus as an aldehyde was more successful. N-protected α-amino acids are readily converted to the requisite N-protected β-amino sulfones by a four-step sequence in which all steps proceed in high yield (Scheme II[17,18]) and chromatography is not required, since the final products can be purified by recrystallization. The *t*-BOC protected β-amino sulfones **15** are stable indefinitely at 25 °C.

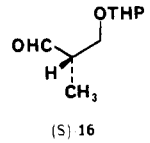
The coupling reaction was studied by using the sulfone **15d** derived from tyrosine and aldehyde (*S*)-**16**, derived from commercially available methyl 3-hydroxy-2(*S*)-methylpropionate by protection as the THP ether (dihydropyran, pyridinium tosylate, CH_2Cl_2), followed by reduction with DIBAL. When the dianion of **15d**, prepared in THF at −78 °C with methyllithium, was treated with 2 equiv of aldehyde (*S*)-**16** and the crude mixture of β-hydroxy sulfones was reduced with sodium phosphate-buffered methanolic sodium amalgam, the yield of alkene **17** was poor (~20%). The problem appeared not to be the reduction step but rather the coupling. Trapping of the β-oxido sulfone was considered as a solution. Mixtures of the dianion of **15d** and (*S*)-**16** were thus treated with

Scheme III[a]

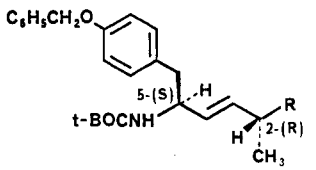


[a] (a) (i) LDA, THF, −78 °C, (ii) $C_6H_5CH_2Br$; (b) $LiAlH_4$, THF, −78 → 0 °C; (c) DHP, $PyrH^+OTS^-$, CH_2Cl_2, 25 °C; (d) (i) O_3, −78 °C, (ii) $(CH_3)_2S$.

oxidophiles such as chlorotrimethylsilane, chloro-*tert*-butyldimethylsilane, and benzoyl chloride but with marginal success.



(S) **16**



17 R=CH_2OTHP
18 R=CO_2H

Better results were obtained in the presence of diisobutylaluminum methoxide. In practice, a solution of 2 equiv of DIBAL in THF at 0 °C was treated with 2 equiv of methanol, cooled to −78 °C, followed by addition of 2 equiv of aldehyde (*S*)-**16**. The resulting mixture was added to 1 equiv of the dianion of **15d**, prepared at −78 °C by the addition of 2 equiv of methyllithium to 1 equiv of **15d**. It was found that the aldehyde/aluminum complex is unstable even at −78 °C and is best used within a few minutes of its preparation. Reduction with sodium amalgam followed by chromatography on silica gel afforded the alkene (2*R*,5*S*)-**17** in 63% overall yield. Direct oxidation[10] of (2*R*,5*S*)-**17** afforded the protected *trans*-alkene isostere of TyrAla, (2*R*,5*S*)-**18**.

A simple technical modification of the above procedure is possible when the C-terminal aldehyde is to be prepared by DIBAL reduction of the corresponding ester. In this case, the DIBAL reduction reaction mixture (in ether) can be directly used in the coupling to the sulfone anion. This method avoids the need to isolate the aldehyde component and, in the case of (2*R*,5*S*)-**17**, provided a superior yield (73%).

To exclude the possibility of racemization at either of the stereocenters of **18**, the *trans*-alkene isostere synthesis was repeated with **15d** and (*R*)-**16**, affording (2*S*,5*S*)-**18**. The methyl doublets in the ^1H NMR spectra of the two diastereomers were clearly resolved at 500 MHz (2*R*,5*S*)-**18** (δ 1.25; (2*S*,5*S*)-**18**, δ 1.22 as a mixture) and conclusively demonstrated that appreciable racemization had not occurred during any step in the synthesis of **18**.

The use of protected β-amino sulfones for the synthesis of protected allylic amines is new. It is interesting and not necessarily expected that only the trans isomer of the product was detected.[14] The presence of a negative charge on the nitrogen is apparently important for the success of this reaction, preventing β-elimination of the nitrogen to yield a vinyl sulfone. Consistent with this was the failure of the *t*-BOC-protected β-aminosulfone derived from proline to undergo coupling under the above conditions,

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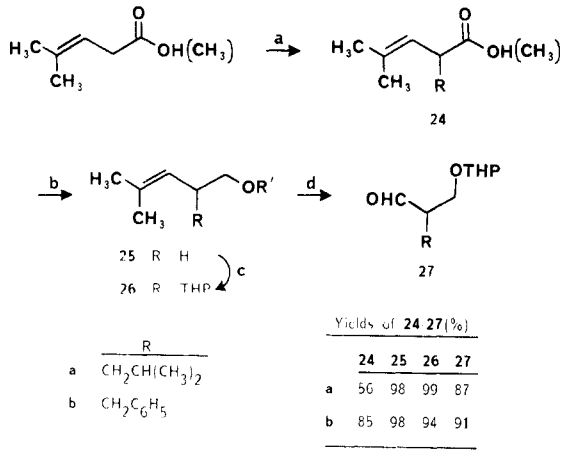
Scheme IV[a]



[a] (a) (i) LDA, THF, 0 °C, (ii) RX, −78 → 25°C; (b) $LiAlH_4$, Et_2O; (c) DHP, $PyrH^+OTs^-$, CH_2Cl_2, 25 °C; (d) (i) O_3, CH_2Cl_2, (ii) $(CH_3)_2S$.

affording instead what was identified as a vinyl sulfone. The β-elimination could be suppressed for the *t*-BOC-protected sulfone derived from proline by carrying out the metalation and coupling at −110 °C, but yields of alkene were quite low (~20%).

The luxury of commercial availability of a direct precursor to the optically active C-terminal aldehyde is unique to alanine. A general route to optically active aldehydes for incorporation at the C-terminus of *trans*-alkene isosteres was found in Evans alkylation[19] of oxazolidone **19** followed by multistep functional group manipulation as shown in Scheme III. The indicated absolute configuration of **21** was verified by chemical correlation with the known (*R*)-2-benzyl-3-(benzyloxy)propanol.[20] C-terminal phenylalanine equivalent **23** was prepared in this manner. Racemic aldehydes such as **27a,b**, C-terminal leucine and phenylalanine equivalents, respectively, were available by an analogous route from the illustrated β,γ-unsaturated carboxylic acid (or ester) (Scheme IV).

Table I illustrates the structures and yields of the *trans*-alkene isosteres prepared by various combinations of the protected β-amino sulfones and protected β-hydroxy aldehydes.

Conclusion

Application of the Julia olefin synthesis of *trans*-alkene isosteres has afforded the first fully stereocontrolled approach to these interesting peptide mimics. The route has provided sufficient quantities of the PhePhe and LeuPhe isosteres to allow testing of some new renin inhibitors.[6] It is possible that the route described herein could be applied to the synthesis of more functionalized *trans*-alkene isosteres bearing side chains such as Ser, Asp, Lys, etc., but this will certainly require judicious choice of protective groups.

Experimental Section[21]

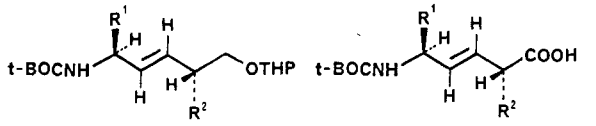
3-(Phenylseleno)-4-[(4-phenylmethoxy)phenyl]butene, Allylic Selenide 2. *n*-Butyllithium (12.7 mL, 33 mmol, 2.6 M in hexanes) was added to a 0 °C solution of diisopropylamine (3.54 g, 35 mmol) in 80 mL of THF, and the mixture was stirred 0.5 h and cooled to −78 °C. Allyl phenyl selenide (1) (6.34 g, 32.2 mmol) was added over 5 min to produce a deep yellow solution, which was stirred 0.5 h at −78 °C and then treated with 7.5 g (27 mmol) of *p*-(benzyloxy)benzyl bromide, added as a solid, and maintained at −78 °C for 2 h. The mixture was quenched with 4 mL of water and diluted with 50 mL of ether. Drying ($MgSO_4$) and concentration in vacuo afforded the product as an orange oil, which was chromatographed on silica gel (4% ethyl acetate/hexanes) to yield 6.6 g (62%) of selenide **2** as a yellow oil: ^1H NMR (500 MHz) δ 2.94 (1 H, dd, J = 6 and 8 Hz, $ArCH_2$), 3.01 (1 H, dd, J = 6 and 7 Hz, $ArCH_2$), 3.92 (1 H, m, SeCH), 4.70 (1 H, d, J = 19 Hz, C=CH), 4.81 (1 H, d, J = 9 Hz, C=CH), 5.05 (2 H, s, OCH_2), 5.83 (1 H, m, CH=C), 6.9 (5 H, m, C_6H_5), 7.1–7.5 (9 H, m, Ar); LRMS, *m/e* 394, 392, 237, 91; IR (NaCl) 3027, 1595, 1490, 1000, 875, 715 cm^{-1}.

1-(Phenylseleno)-4-[(4-phenylmethoxy)phenyl]-*trans*-2-butene, Allylic Selenide 3. A solution of 1.75 g (4.5 mmol) of selenide **2** and 75 mg (0.44 mmol) of *p*-toluenesulfonic acid in 200 mL of benzene was stirred for 3 h at reflux. The mixture was cooled to 25 °C and quenched with 30 mL of saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (5% ethyl acetate/hexanes) to afford selenide **3** as a yellow oil, 1.61 g (92%): ^1H NMR (500 MHz) δ 3.23 (2 H, d, J = 6 Hz, CH_2Ar), 3.51 (2 H, d, J = 6 Hz, CH_2Se), 5.05 (2 H, s, CH_2O), 5.51 (1 H, dt, J = 18 and 8 Hz, HC=C), 5.62 (1 H, dt, J = 18 and 8 Hz, C=CH), 6.9–7.5 (14 H, m, Ar); LRMS, *m/e* 394, 392, 237, 91; IR (NaCl) 3025, 1595, 1490, 1000, 945 cm^{-1}.

4-(Phenylseleno)-1-[4-(phenylmethoxy)phenyl]-6-[(2-tetrahydropyranyl)oxy]-*trans*-2-hexene, Allylic Selenide 4. Allylic selenide **3** (12.4 g, 31.5 mmol) was metalated with LDA (34 mmol) and alkylated with the THP ether of 2-bromoethanol (7.5 g, 36.0 mmol) as described above for the preparation of selenide **2**. Allylic selenide **4** was isolated by chromatography on silica gel (8% ethyl acetate/hexanes), 9.84 g (60%), as a yellow oil: ^1H NMR (500 MHz) δ 1.5–1.7 (6 H, m, THP), 2.0 (2 H, m, OCH_2CH_2), 3.21 (2 H, d, J = 6 Hz, $ArCH_2$), 3.45 (2 H, m, OCH_2), 3.83 (2 H, m, CH_2O), 3.92 (1 H, m, CHSe), 4.55 (1 H, m, OCHO), 5.05 (2 H, s, $ArCH_2O$), 5.33 (1 H, m, C=CH), 5.50 (1 H, m, CH=C), 6.9–7.5 (14 H, m, Ar): LRMS, *m/e* 522, 365, 281, 263, 197, 91, 65; IR ($CHCl_3$) 3020, 2310, 1590, 1480, 880 cm^{-1}.

2-[(*tert*-Butoxycarbonyl)amino]-1-[4-(phenylmethoxy)-phenyl]-6-[(2-tetrahydropyranyl)oxy]-*trans*-3-hexene, Protected Allylic Amine 5. Selenide **4** (1.3 g, 2.5 mmol), *tert*-butyl carbamate (0.87 g, 7.5 mmol), and triethylamine (2.0 g, 19.7 mmol) in 2.5 mL of CH_3OH was cooled to 0 °C and treated with 1.0 g (7.5 mmol) of *N*-chlorosuccinimide over 10 min. The resulting suspension was stirred 0.5 h at 0 °C, diluted with ethyl acetate, and washed sequentially with 10 mL of water and 10 mL

Table I. Synthesis of *trans*-Alkene Isosteres of Dipeptides



28 29

	R^1	R^2
a	$CH_2C_6H_5$	$CH_2C_6H_5$
b	$CH_2CH(CH_3)_2$	$CH_2C_6H_5$
c	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$

protected β-amino sulfone	protected β-hydroxy aldehyde	yield, % THP ether	yield, % acid
15d	(*S*)-**16**	**17**, 63 (73[a])	**18**, 64
15c	(*S*)-**23**	**28a**, 37	**29a**, 68
15b	(*S*)-**23**	**28b**, 65	**29b**, 63
15b	(±)-**27a**	**28c**, 62[b]	**29c**, 65, 60[c]

[a] Method 2, see Experimental Section. [b] Mixture of diastereoisomers at C-2. [c] Diastereoisomers **28c** separated and independently oxidized.

(19) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1727.
(20) Aebi, J. P.; Sutter, M. A.; Wasmuth, D.; Seebach, D. *Liebigs Ann. Chem.* **1983**, 2114.
(21) General procedures are described elsewhere.[8]

of saturated aqueous NaCl. Drying ($MgSO_4$) and concentration in vacuo gave a black oil, which was chromatographed on silica gel (20% ethyl acetate/hexanes) to yield protected allylic amine **5**, 0.69 g (57%), as a colorless solid: ^1H NMR (500 MHz) δ 1.3 (9 H, s, *t*-C_4H_9), 1.5–1.7 (6 H, m, CH_2O), 2.7 (2 H, m, $ArCH_2$), 3.3 (2 H, m, OCH_2), 3.5–3.7 (2 H, m, CH_2O), 4.3 (2 H, m, CHNH), 4.6 (1 H, m, OCHO), 5.05 (2 H, s, $ArCH_2O$), 5.6 (2 H, m, CH=CH), 6.9–7.5 (9 H, m, Ar); LRMS, *m/e* 398, 144, 91, 85, 68, 65, 57; IR ($CHCl_3$) 3300, 1711, 1590, 1480 cm^{-1}.

Protected Racemic TyrGly Isostere 6. THP ether **5** (0.42 g, 0.87 mmol) in 4.0 mL of 0.2 M aqueous HCl and 15 mL of THF was heated for 2.5 h at 55 °C, cooled to 25 °C, diluted with 20 mL of ethyl acetate, and washed sequentially with 10 mL of saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford 0.33 g (95%) of the alcohol as a colorless oil, which solidified on standing: ^1H NMR (80 MHz) δ 1.4 (9 H, s, *t*-C_4H_9), 2.2 (2 H, m, allylic CH_2), 2.7 (2 H, m, $ArCH_2$), 3.5 (2 H, m, OCH_2), 4.3 (2 H, m, CHNH), 5.05 (2 H, s, $ArCH_2$), 5.4 (2 H, m, HC=CH), 6.8–7.4 (9 H, m, Ar); LRMS, *m/e* 281, 280, 237, 200, 197, 144, 100, 91, 83, 65, 57.

The alcohol (50 mg, 0.125 mmol) was oxidized as described below for the preparation of the protected LeuPhe isostere **29b** to afford TyrGly isostere **6**, 29 mg (57%), as a colorless solid: ^1H NMR (500 MHz) δ 1.4 (9 H, s, *t*-C_4H_9), 2.75 (2 H, d, $ArCH_2$), 3.09 (2 H, d, allylic CH_2), 4.40 (2 H, m, NHCH), 5.05 (2 H, s, $ArCH_2$), 5.60 (2 H, m, CH=CH), 6.89 and 7.10 (4 H, m, Ar), 7.35 (5 H, m, Ar).

2(*S*)-[(*tert*-Butoxycarbonyl)amino]-3-[4-(phenylmethoxy)phenyl]propanol (12d). A solution of 15.0 g (40.4 mmol) of *t*-BOC-*O*-benzyl-L-tyrosine (**11d**) and 5.56 mL (50 mmol) of triethylamine in 50 mL of THF was cooled to −5 °C. Ethyl chloroformate (3.86 mL, 40.4 mmol) was added dropwise during 0.25 h. The resulting slurry was stirred at −5 °C for 0.5 h and filtered. The residue was washed with 20 mL of THF, and the combined filtrates were added dropwise to a slurry of 3.82 g (100 mmol) of $NaBH_4$ in 50 mL of water at 0 °C. The reaction mixture was stirred for 4 h at 0 °C and extracted with ether and CH_2Cl_2. Drying ($MgSO_4$) and concentration in vacuo (50 °C) afforded a white solid, which could be used without further purification or recrystallized (20% ethyl acetate–hexanes) to yield 13.13 g (91%) of the protected amino alcohol **12d** in two crops as a white solid: mp 108 °C; ^1H NMR (500 MHz) δ 1.42 (9 H, s, *t*-C_4H_9), 2.25 (1 H, s, OH), 2.77 (2 H, d, *J* = 7 Hz, $ArCH_2C$), 3.54 (1 H, dd, *J* = 5 and 11 Hz, CH_2OH), 3.66 (1 H, dd, *J* = 3 and 11 Hz, CH_2OH), 3.82 (1 H, m, C*H*CH_2OH), 4.69 (1 H, s, NH), 5.04 (2 H, s, CH_2OAr), 6.7–7.4 (9 H, m, Ar); IR ($CHCl_3$) 3620, 3440, 3080, 3040, 2980, 2940, 2860, 1702, 1682, 1610, 1510, 1500, 1392, 1369, 1240, 1163, 1205, 865 cm^{-1}; LRMS, *m/e* 357 (M^+), 301, 284, 270, 240, 226, 198, 197, 160, 130, 127, 124, 115, 107, 104, 101, 91 (100), 86, 85, 84, 77, 71, 69, 60, 51; $[\alpha]^{20}_D$ −17.0° (*c* 0.06 g/mL, $CHCl_3$).

2(*S*)-[(*tert*-Butoxycarbonyl)amino]-1-[(methylsulfonyl)oxy]-3-[4-(phenylmethoxy)phenyl]propane, Mesylate 13d. A solution of 2.50 g (7.0 mmol) of the protected amino alcohol **12d** and 2.1 g (21 mmol) of triethylamine in 50 mL of CH_2Cl_2 was cooled to 0 °C and treated dropwise with 1.96 g (17.1 mmol) of methanesulfonyl chloride followed by stirring for an additional 0.33 h at 0 °C. Addition of water and extraction with CH_2Cl_2 followed by drying ($MgSO_4$) and concentration in vacuo afforded crude mesylate **13d** as a yellow solid. Recrystallization (25% ethyl acetate–hexanes) yielded 3.05 g (100%) of mesylate **13d** as a white solid: mp 103–105 °C; ^1H NMR (500 MHz) δ 1.42 (9 H, s, *t*-C_4H_9), 2.79 (2 H, m, $ArCH_2C$), 3.00 (3 H, s, CH_3), 4.11 (2 H, m, CH_2OSO_2), 4.22 (1 H, m, CHN), 4.69 (1 H, s, NH), 5.04 (2 H, s, $ArCH_2O$), 6.9–7.4 (9 H, m, Ar); IR ($CHCl_3$) 3440, 3040, 2980, 2940, 2865, 1760, 1710, 1612, 1585, 1505, 1452, 1370, 1240, 1178, 1028, 978 cm^{-1}; LRMS, *m/e* 318 (M^+ + *t*-$C_4H_9OCONH_2$), 283, 198, 197, 138, 137, 107, 105, 96, 92, 91 (100), 89, 86, 85, 79, 78, 77, 65, 59, 57, 56; $[\alpha]^{20}_D$ −10.4° (*c* 0.02 g/mL, $CHCl_3$).

2(*S*)-[(*tert*-Butoxycarbonyl)amino]-1-(phenylthio)-3-[4-(phenylmethoxy)phenyl]propane, Sulfide 14d. A solution of 1.30 g (25 mmol) of $NaOCH_3$ and 2.64 mL (25.9 mmol) of benzenethiol in 3.75 mL of CH_3OH and 18.75 mL of THF was stirred at 25 °C for 0.25 h. Mesylate **13d** (3.42 g, 7.85 mmol), was added as a solid, and the mixture was heated to 50 °C for 2.5 h. The solution was cooled to 25 °C and diluted with 10% aqueous NaOH. Extraction with CH_2Cl_2 and drying ($MgSO_4$), followed by concentration in vacuo (40 °C), afforded a yellow solid, which was recrystallized (10% ethyl acetate–hexanes) to yield 2.9 g (84%) of sulfide **14d** as a white solid: mp 94 °C; ^1H NMR (500 MHz) δ 1.42 (9 H, s, *t*-C_4H_9), 2.82 (2 H, m, $ArCH_2$), 3.06 (2 H, m, SCH_2), 4.02 (1 H, m, C*H*CH_2S), 4.64 (1 H, s, NH), 6.9–7.5 (14 H, m, Ar); IR ($CHCl_3$) 3440, 3080, 3060, 3020, 2980, 2930, 2860, 1705, 1609, 1552, 1510, 1496, 1452, 1438, 1368, 1297, 1242, 1168, 1043, 1025, 863 cm^{-1}; LRMS, *m/e* 449 (M^+), 376, 359, 283, 270, 252, 227, 226, 223, 197, 196, 153, 152, 135, 99, 97, 92, 91 (100), 86, 85, 84, 81, 77, 69, 65, 59, 57; $[\alpha]^{20}_D$ +9.9° (*c* 0.1 g/mL, $CHCl_3$).

2(*S*)-[(*tert*-Butoxycarbonyl)amino]-3-[4-(phenylmethoxy)phenyl]-1-(phenylsulfonyl)propane, Sulfone 15d. A solution of 2.90 g (6.45 mmol) of sulfide **14d** in 50 mL of CH_2Cl_2 was cooled to 0 °C and treated with 3.56 g (20.6 mmol) in *m*-chloroperoxybenzoic acid. The resulting slurry was stirred 1 h at 25 °C and then partitioned between CH_2Cl_2 and saturated aqueous $NaHSO_3$/10% aqueous NaOH. The aqueous layer was extracted several times with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$). Concentration in vacuo afforded **15d** as a white solid, which was usually used in the next step without further purification. Recrystallization from methanol yielded 2.83 g (91%) of the sulfone **15d** was a white solid: mp 207–209 °C; ^1H NMR (500 MHz) δ 1.35 (9 H, s, *t*-C_4H_9), 2.85–3.05 (2 H, m, $ArCH_2C$), 3.2–3.45 (2 H, m, CH_2SO_2), 4.08 (1 H, m, CH-N), 4.88 (1 H, br s, NH), 5.03 (2 H, s, Ar CH_2O), 6.9–7.9 (14 H, m, Ar); IR ($CHCl_3$) 3440, 3390, 3040, 3010, 2980, 2840, 1710, 1690, 1610, 1510, 1450, 1370, 1320, 1310, 1280, 1245, 1150, 1088, 1050, 1025 cm^{-1}; LRMS, *m/e* 481 (M^+), 446, 425, 408, 364, 309, 308, 273, 248, 235, 229, 228, 198, 197, 184, 173, 172, 128, 110, 107, 91 (100), 82, 78, 77, 72, 57; $[\alpha]^{20}_D$ −29.1 ° (*c* 0.02 g/mL, THF); Anal. C, H, N.

Sulfones 15a-c. Sulfones **15a-c** were prepared from the appropriate *t*-BOC-protected L-amino acid by the four-step sequence described above in detail for **11** → **15d**.

2(*S*)-[(*tert*-Butoxycarbonyl)amino]-3-methyl-1-(phenylsulfonyl)butane, sulfone 15a: mp 103–105 °C (33% ethyl acetate–hexanes); ^1H NMR (80 MHz) δ 0.86 (3 H, d, *J* = 7 Hz, CH_3), 0.89 (3 H, d, *J* = 7 Hz, CH_3), 1.41 (9 H, s, *t*-C_4H_9), 1.75–2.21 (1 H, m, CH), 3.25 (2 H, m, CH_2SO_2), 3.61–3.95 (1 H, m, C*H*NH), 4.66 (1 H, br s, NH), 7.43–7.64 and 7.81–7.96 (5 H, m, Ar); IR (KBr) 3494, 2972, 1688, 1516, 1453, 1372, 1313, 1300, 1249, 1172, 1148, 1088, 880, 758, 698 cm^{-1}; $[\alpha]^{20}_D$ +11.02 (*c* 0.023 g/mL, $CHCl_3$).

2(*S*)-[(*tert*-Butoxycarbonyl)amino]-4-methyl-1-(phenylsulfonyl)pentane, sulfone 15b: mp 95–98 °C (33% ethyl acetate-hexanes); ^1H NMR (80 MHz) δ 0.88 (6 H, d, *J* = 7 Hz, 2 × CH_3), 1.24–1.79 (3 H, m, $CHCH_2$), 1.39 (9 H, s, *t*-C_4H_9), 3.32 (2 H, m, CH_2SO_2), 3.79–4.17 (1 H, m, C*H*NH), 4.71 (1 H, br s, NH), 7.44–7.65 and 7.79–7.96 (5 H, m, Ar); IR (KBr) 3484, 2962, 1692, 1614, 1449, 1365, 1288, 1172, 1149, 1079, 785, 749 cm^{-1}; $[\alpha]^{20}_D$ −9.87° (*c* 0.024 g/mL, $CHCl_3$).

2(*S*)-[(*tert*-Butoxycarbonyl)amino]-3-phenyl-1-(phenylsulfonyl)propane, sulfone 15c: mp 215–216 °C (50% $CHCl_3$–ethyl acetate); ^1H NMR (80 MHz) δ 1.37 (9 H, s, *t*-C_4H_9), 2.99 (2 H, d, CH_2), 3.25 (2 H, m, CH_2SO_2), 3.88–4.30 (1 H, m, C*H*NH), 4.80 (1 H, br s, NH), 7.04–7.29 (5 H, m, Ar), 7.45–7.64 and 7.77–7.91 (10 H, m, Ar); IR (KBr) 3388, 2980, 1692, 1520, 1448, 1368, 1287, 1173, 1149, 1138, 1088, 752, 707 cm^{-1}; $[\alpha]^{20}_D$ −32.7° (*c* 0.0052 g/mL, Me_2SO).

Methyl 3-[(2-Tetrahydropyranyl)oxy]-2(*S*)-methylpropionate. A solution of 5.33 g (45.1 mmol) of (*S*)-methyl 3-hydroxy-2-methylpropionate, 4.93 g (58.7 mmol) of 3,4-dihydropyran, and 0.22 g of pyridinium *p*-toluenesulfonate in 75 mL of CH_2Cl_2 was stirred at 25 °C for 3 h. The mixture was extracted sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$). Concentration in vacuo (50 °C) afforded the THP ether as a colorless liquid (9.12 g, 100%): ^1H NMR (500 MHz) δ 1.18 and 1.19 (3 H, 2 × d, *J* = 7 Hz, ratio 1:1, CH_3), 1.47–1.90 (6 H, m, $CH_2CH_2CH_2$), 2.79 (1 H, m, CHCOO), 3.4–3.95 (4 H, m, 2 × OCH_2), 3.695 and 3.69 (3 H, 2 x s, ratio 1:1, OCH_3), 4.59 (1 H, m, OCHO); IR (NaCl) 201 (M^+ −1), 184, 171, 147, 129, 119, 115, 102, 101, 88, 86, 85 (100), 84, 73, 69, 67, 56, 55 cm^{-1}; $[\alpha]^{20}_D$ +17.1° (*c* 0.11 g/mL, $CHCl_3$).

2(*S*)-Methyl-3-[(2-tetrahydropyranyl)oxy]propionaldehyde, (*S*)-16. A solution of 9.0 g (44 mmol) of the ester from

the preceding reaction in 150 mL of CH_2Cl_2 was cooled to −78 °C, treated dropwise with 50.0 mL (47.5 mmol) of DIBAL (0.95 M in hexane), stirred at −78 °C for 10 min, and quenched with saturated aqueous NH_4Cl. Filtration, drying ($MgSO_4$), and concentration of the organic layer in vacuo (50 °C) afforded 9.16 g of crude aldehyde (*S*)-**16** as a liquid. This material was normally used in the next step without further purification. For full characterization of the compound, 4.95 g of the above sample were chromatographed on silica gel (30% ethyl acetate–hexanes) to yield 3.57 g (87%) of the aldehyde (*S*)-**16** as a colorless liquid: ^1H NMR (500 MHz) δ 1.15 and 1.16 (3 H, 2 × d, J = 7 Hz, ratio 1:1, CH_3), 1.45–1.85 (6 H, m, $CH_2CH_2CH_2$), 2.63 (1 H, m, *CH*CHO), 3.48–3.62 and 3.78–4.00 (2 H, m, CH_2O), 4.58 (1 H, m, OCHO), 9.83 (1 H, m, CHO); IR (NaCl) 2940, 2870, 2720, 1720, 1452, 1441, 1386, 1352, 1323, 1261, 1202, 1120, 1078, 1062, 1040, 972, 903, 872, 818, 754 cm^{-1}; LRMS, m/e 172 (M^+), 171, 115, 102, 101, 88, 86, 85 (100), 84, 71, 67, 59, 57, 56, 55; $[\alpha]^{20}_D$ +28.0° (*c* 0.053 g/mL, $CHCl_3$).

5(*S*)-[(*tert*-Butoxycarbonyl)amino]-2(*R*)-methyl-6-[4-(phenylmethoxy)phenyl]-1-[(2-tetrahydropyranyl)oxy]-*trans*-3-hexene, THP Ether 17. Method 1. A solution of sulfone **15d** (100 mg, 0.208 mmol) in 3 mL of THF at −78 °C was treated over 5 min with 0.25 mL (0.458 mmol) of CH_3Li (1.8 M in ether) and stirred 0.33 h. In a separate flask, 72 mg (0.416 mmol) of aldehyde (*S*)-**16** in 0.5 mL of THF at −78 °C was treated with 0.42 mL of diisobutylaluminum methoxide (1 M in THF; prepared by the addition of 1 equiv of methanol to a 1.0 M solution of DIBAL in THF). The solution of the aluminum complex was transferred via cannula into the solution of the sulfone anion, and the whole was stirred 0.5 h at −78 °C. The reaction was quenched at −78 °C with saturated aqueous NH_4Cl and was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. The crude mixture of β-hydroxy sulfone diastereoisomers was dissolved in 3 mL of methanol, cooled to 0 °C, and treated sequentially with Na_2HPO_4 (0.17 g, 3 mmol) and 1.7 g (10 mmol) of 5% Na (Hg). The mixture was stirred 4 h at 0 °C, diluted with water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration in vacuo followed by chromatography on silica gel (10% ethyl acetate–hexanes) afforded 64 mg (63%) of **1** as a colorless oil. Spectroscopic data were the same as described in the following procedure.

5(*S*)-(tert-Butoxycarbonylamino)-2(*R*)-methyl-6-[4-(phenylmethoxy)phenyl]-1-[(2-tetrahydropyranyl)oxy]-*trans*-3-hexene, THP Ether 17. Method 2. Methyl 3-[(2-tetrahydropyranyl)oxy]-2(*S*)-methylpropionate, (4.025 g, 20 mmol) in 60 mL of ether was cooled to −78 °C, treated dropwise with 21.9 mL (21.9 mmol) of DIBAL (1 M in ether), and stirred for 0.5 h to yield solution A. In a separate flask, a solution of sulfone **15d** (4.0 g, 8.3 mmol) in 100 mL of THF at −78 °C was treated over 5 min with 11.0 mL (17.6 mmol) of CH_3Li (1.6 M in ether) and stirred 0.5 h. The latter sulfone anion solution was treated with solution A added via cannula over 0.25 h, and the whole was stirred 0.25 h at −78 °C. The reaction was quenched at −78 °C with saturated aqueous NH_4Cl, and the product was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. The crude mixture of β-hydroxy sulfone diastereoisomers was dissolved in 150 mL of CH_3OH and cooled to 0 °C. Disodium hydrogen phosphate (13 g, 78 mmol) and 50 g (100 mmol) of 5% Na (Hg) were added sequentially. The mixture was stirred 4 h at 0 °C, diluted with water, and extracted with CH_2Cl_2 and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica gel (40% ethyl acetate–hexanes) afforded 2.98 g (73%) of the THF-protected alcohol **17** as a colorless oil, which solidified upon standing at 25 °C: ^1H NMR (500 MHz) δ 0.99 (3 H, m, CH_3), 1.2–1.9 (6 H, m, THP ether), 1.42 (9 H, s, t-C_4H_9), 2.41 (1 H, m, CHC=), 2.77 (2 H, m, $ArCH_2C$), 3.10, 3.37, 3.45, 3.82 (1 H, m, CH_2O), 4.30 (1 H, br m, CHN), 4.40 (1 H, br s, NH), 4.53 (1 H, m, OCHO), 5.04 (2 H, s, $ArCH_2O$), 5.45 (2 H, m, CH=CH), 6.90 (2 H, d, J = 9 Hz, para Ar), 7.11 (2 H, d, J = 9 Hz, para Ar), 7.3–7.5 (5 H, m, Ar); IR ($CHCl_3$) 3440, 3040, 3010, 2940, 2865, 1700, 1608, 1578, 1505, 1492, 1451, 1367, 1165, 1118, 1076, 1061, 1038, 972, 907, 868 cm^{-1}; LRMS, m/e 446, 395, 379, 338, 326, 324, 322, 320, 310, 308, 292, 282, 280, 279, 270, 268, 256, 254, 242, 214, 197, 196, 176, 158, 142, 140, 127, 117, 115, 107, 101, 98, 97, 96, 92, 91 (100), 86, 85, 67, 65, 57, 56; $[\alpha]^{20}_D$ +6.6° (*c* 0.35 g/mL, $CHCl_3$).

5(*S*)-[(*tert*-Butoxycarbonyl)amino]-2(*R*)-methyl-6-[4-(phenylmethoxy)phenyl]-*trans*-3-hexenoic acid, Protected TyrAla Isostere 18. Method 1, Direct Oxidation. A solution of 0.400 g (0.807 mmol) of THP ether **17** in 50 mL of acetone was cooled to 0 °C and treated dropwise with 1.40 mL (2.7 mmol) of Jones reagent (1.92 M). After 3 h, the mixture was diluted with water and extracted with several portions of ether. The etheral fractions were extracted with five portions of 5% aqueous NaOH and the resulting aqueous extracts were combined and acidified to pH 2 with 10% aqueous HCl. Extraction of the acidified aqueous extracts with ether, drying ($MgSO_4$), concentration in vacuo (50 °C), and recrystallization (1:2 ethyl acetate–hexanes) afforded the acid **18**, 219 mg (66%), as a white solid; ^1H NMR (500 MHz) δ 1.25 (3 H, d, J = 8 Hz, CH_3) [other diastereoisomer; δ 1.22 (3 H, d, J = 8 Hz, CH_3)], 1.41 (9 H, s, t-C_4H_9), 2.80 (2 H, m, $ArCH_2C$), 3.12 (1 H, m, CHCOO), 4.30 (1 H, m, CHN), 4.50 (1 H, br s, NH), 5.03 (2 H, s, $ArCH_2O$), 5.54 (1 H, dd, J = 5 and 16 Hz, CH=), 5.62 (1 H, dd, J = 8 and 16 Hz, CH=) [other isomer, δ 5.53 and 5.58 (same J values)], 6.90 (2 H, d, J = 9 Hz, para Ar), 7.08 (2 H, d, J = 9 Hz, para Ar), 7.3–7.45 (5 H, m, Ar); ^{13}C NMR (50 MHz) δ 16.9 (CH_3CH), 28.1 (CH_3CO), 40.7 (*C*HN), 42.1 (CH_3 Ar), 52.8 (*C*HCOOH), 69.7 ($ArCH_2O$), 79.6 (CCH_3), 114.5 (Ar CCH_2CN), 127.3, 127.7, 128.3, 129.1, 129.7, 130.4, 131.6 (Ar and C=C), 137.0 (CHNC=), 156.2 (O=*C*N), 157.3 (Ar *C*O), 179.4 (*C*OOH); IR ($CHCl_3$) 3500–2400, 3435, 3040, 2975, 2930, 2870, 1703, 1609, 1582, 1492, 1452, 1391, 1268, 1240, 1167, 1075, 1061, 1020, 971, 863 cm^{-1}; LRMS, m/e 425 (M^+), 352, 309, 308, 272, 248, 228, 197, 173, 172, 145, 129, 128, 117, 115, 107, 104, 91 (100), 85, 83 (96), 77, 65, 57; $[\alpha]^{20}_D$ +1.0° (*c* 0.023 g/mL, $CHCl_3$); Anal. C, H, N.

Oxazolidone 19. A solution of 6.0 g (53 mmol) of 4-methyl-3-pentenoic acid in 20 mL of thionyl chloride and 30 mL of benzene was refluxed for 2 h. The volatiles were removed in vacuo (40 °C) to give the crude acid chloride as a yellow oil: ^1H NMR (500 MHz) δ 1.11 (3 H, s, CH_3), 1.12 (3 H, s, CH_3), 3.55 (2 H, d, J = 7 Hz, CH_2), 5.27 (1 H, m, CH=). In a separate flask, 6.0 g (33.9 mmol) of 5(*S*)-phenyl-4(*R*)-methyl-1,3-oxazolid-2-one in 80 mL of THF was cooled to −78 °C, treated with 14.1 mL (31 mmol) of n-BuLi (2.2 M in hexanes), and stirred at −78 °C for 0.5 h. The acid chloride was added, and the mixture was stirred at −78 °C for 0.5 h. The yellow solution was allowed to warm to 25 °C and was quenched with saturated aqueous NaCl. Extraction with ether, drying ($MgSO_4$), and concentration in vacuo, followed by chromatography on silica gel (25% ethyl acetate–hexanes) afforded oxazolidone **19** as a white solid (6.49 g, 77%). The material obtained was (like the starting carboxylic acid) a mixture of α,β- and β,γ-unsaturated carbonyl compounds (27:73, determined by NMR). Oxazolidone **19**: ^1H NMR (500 MHz) δ 0.90 (3 H, d, J = 7 Hz, CH_3CHN), 1.69 (3 H, s, CH_3C=), 1.77 (3 H, s, CH_3C=), 3.68 (2 H, d, J = 7 Hz, CH_2), 4.76 (1 H, m, *CH*CH_3), 5.38 (1 H, m, CH=), 5.66 (1 H, d, J = 7 Hz, ArCH), 7.2–7.5 (5 H, m, Ar); IR (NaCl) 3040, 2970, 2938, 2920, 2880, 1781, 1700, 1632, 1455, 1371, 1352, 1235, 1192, 1178, 1122, 1068, 1042, 991 cm^{-1}; LRMS: m/e 173 (M^+), 230, 178, 177, 160, 134, 119, 118, 117, 115, 105, 97, 96 (100), 95, 91, 86, 84, 81, 77, 70, 69, 67, 53.

Oxazolidone 20. A solution of 0.66 mL (4.7 mmol) of diisopropylamine in 3.5 mL of THF was cooled to 0 °C and treated with 2.09 mL (4.6 mmol) of n-BuLi (2.2 M in hexane). After being stirred for 0.5 h at 0 °C, the solution was cooled to −78 °C, and 1.0 g (3.65 mmol) of the oxazolidone **19** in 1 mL of THF was added dropwise. The mixture was kept at −78 °C for 0.5 h followed by dropwise addition of 0.86 mL (7.2 mmol) of benzyl bromide. After 1 h at −78 °C, the solution was warmed to −20 °C over 1.5 h and then to 0 °C over 1 h. Addition of saturated aqueous NH_4Cl, acidification with 5% aqueous HCl, extraction with ether, drying ($MgSO_4$) of the organic extract, and concentration in vacuo followed by chromatography on silica gel (5% ethyl acetate–hexanes) afforded the oxazolidone **20** as a colorless liquid (625 mg, 65% based on purity of oxazolidone **19**, 88% diastereoisomeric excess by ^1H NMR analysis), which solidified upon standing at 25 °C. A more polar fraction was eluted and identified as the unreacted α,β-unsaturated isomer of **19** (99 mg). **20**: ^1H NMR (500 MHz) δ 0.68 (3 H, d, J = 7 Hz, CH_3CHN), 1.48 (3 H, s, CH_3C=), 1.70 (3 H, s, CH_3C=), 2.75 (1 H, dd, J = 8 and 13 Hz, $ArCH_2$), 3.09 (1 H, dd, J = 8 and 13 Hz, $ArCH_2$), 4.69 (1 H, m, CH_3CHN), 5.09 (1 H, m, *CH*COH), 5.25 (1 H, d, J = 10 Hz, CH=), 5.58 (1 H, d, J = 7 Hz, ArCHO), 7.2–7.5 (10 H, m, Ar); IR ($CHCl_3$) 3070, 3040, 2970, 2930, 2860, 1776, 1688, 1600, 1491, 1457, 1346,

1182, 1120, 1031, 942, 887, 872 cm^{-1}; LRMS, *m/e* 273, 233, 232, 222, 220, 204, 178, 174, 148, 147, 145, 132, 131, 130, 129, 128, 117, 115, 104, 101, 92, 91, 85 (100), 79, 77, 67, 65, 57, 55; $[\alpha]^{20}_D$ -2.7° (as a 94:6 mixture of diastereoisomers); Anal. C, H, N.

4-Methyl-2(*R*)-(phenylmethyl)-3-penten-1-ol, Homoallylic Alcohol 21. A solution of 0.500 g (1.37 mmol) of oxazolidone **20** in 7 mL of THF was cooled to -78 °C and treated dropwise with 1.37 mL (1.37 mmol) of $LiAlH_4$ (1 M in THF). The mixture was stirred at -78 °C for 0.5 h and allowed to warm to 0 °C over 1 h. After 0.5 h at 0 °C, the clear solution was cooled to -78 °C, and 1 mL of ethyl acetate was added. The reaction mixture was quenched with saturated aqueous NH_4Cl at -78 °C and, after warming to 25 °C, diluted with water. Extraction with ether, drying ($MgSO_4$), and concentration in vacuo (40 °C), followed by chromatography on silica gel (25% ethyl acetate–hexanes), yielded the alcohol **21** as a colorless oil (0.235 g, 90%). 4(*S*)-Phenyl-5-(*R*)-methyloxazolidone was recovered (eluent, ethyl acetate) in 70% yield. **21**: ^1H NMR (500 MHz) δ 1.42 (3 H, s, CH_3), 1.5 (1 H, br s, OH), 1.70 (3 H, s, CH_3), 2.51 (1 H, dd, *J* = 7 and 14 Hz, $ArCH_2$), 2.69 (1 H, dd, *J* = 7 and 14 Hz, $ArCH_2$), 2.77 (1 H, m, C*H*), 3.40 (1 H, dd, *J* = 8 and 10 Hz, CH_2O), 3.57 (1 H, dd, *J* = 5 and 10 Hz, CH_2O), 4.94 (1 H, d, *J* = 10 Hz, =C*H*), 7.1–7.3 (5 H, m, Ar); IR (NaCl) 3380, 3090, 3060, 3030, 2970, 2930, 2860, 1860, 1500, 1450, 1070, 1030 cm^{-1}; LRMS, *m/e* 190 (M^+), 130, 117, 99, 98, 92, 91, 86, 85, 84, 83, 82, 81, 79, 77, 71, 69, 57 (100), 55; $[\alpha]^{20}_D$ - 20.9° (*c* 0.12 g/mL, $CHCl_3$).

2-Methyl-4(*R*)-(phenylmethyl)-5-[(2-tetrahydropyranyl)oxy]-2-pentene, THP Ether 22. Alcohol **21** (0.200 g) was converted to the THP ether **22** as a colorless liquid (after chromatography with 25% ethyl acetate–hexanes) (0.299 g, 100%) as described above for the synthesis of methyl 3-[(2-tetrahydropyranyl)oxy]-2(*S*)-methylpropionate. **22**: ^1H NMR (500 MHz) δ 1.41 (3 H, d, *J* = 5 Hz, CH_3), 1.5–1.9 (6 H, m, THP ether), 1.64 (3 H, s, CH_3), 2.50 (1 H, m, $ArCH_2$), 1.75–2.97 (2 H, $ArCH_2$ and CHC=), 3.25 (1 H, m, CH_2O), 3.64 (1 H, m, CH_2O), 3.49 (1 H, m, CH_2O), 3.87 (1 H, m, CH_2O), 4.56 (1 H, m, OCHO), 4.99 (1 H, m, CH=), 7.1–7.3 (5 H, m, Ar); IR (NaCl) 3065, 2930, 2860, 1738 (w), 1492, 1451, 1350, 1201, 1138, 1119, 1078, 1031, 975, 908, 870, 815, 742, 699 cm^{-1}; LRMS, *m/e* 274 (M^+), 244, 214, 175, 174, 158, 157, 143, 131, 129, 128, 118, 117, 115, 101, 91, 85 (100), 84, 77, 67, 57, 55; $[\alpha]^{20}_D$ -27.40° (*c* 0.16 g/mL in $CHCl_3$); Anal. C, H.

2(*S*)-(Phenylmethyl)-3-[(2-tetrahydropyranyl)oxy]-propionaldehyde, Aldehyde 23. A solution of 1.20 g (4.37 mmol) of **22** in 15 mL of CH_2Cl_2/CH_3OH (5:1) was cooled to -78 °C. A stream of ozone was passed through the solution until a faint blue color was observed (5 min). The mixture was quenched with excess dimethyl sulfide at -78 °C, followed by warming to 25 °C and concentration in vacuo (25 °C). The resulting colorless oil was normally used in the next step without further purification (the only major impurity being dimethyl sulfoxide). Chromatography on silica gel (25% ethyl acetate–hexanes) afforded pure aldehyde **23** as a clear liquid (0.78 g, 74%): ^1H NMR (500 MHz) δ 1.4–1.8 (6 H, m, THP ether), 2.83 (2 H, m, C*H*CHO and $ArCH_2$), 3.07 (1 H, m, $ArCH_2$), 3.45–3.6 (2 H, m, OCH_2), 3.8 (1 H, m, OCH_2), 3.95–4.05 (1 H, m, OCH_2), 4.55 (1 H, dt, OCHO), 7.2–7.4 (5 H, m, Ar), 9.93 (1 H, 2 × d, *J* = 1 Hz, CHO); IR (NaCl) 3090, 3060, 3040, 2940, 2880, 2830, 2780, 1725, 1500, 1470, 1455, 1360, 1350, 1328, 1135, 1080, 1040, 1000, 973, 908, 872, 812 cm^{-1}; LRMS, *m/e* 248 (M^+), 157, 145, 139, 133, 131, 129, 128, 91, 86, 85 (100), 84, 79, 78, 77, 76, 67, 65, 57, 55; $[\alpha]^{20}_D$ +42.8° (*c* 0.111 g/mL, $CHCl_3$).

2-(2-Methylpropyl)-4-methyl-3-pentenoic Acid, 24a. At 0 °C 45.5 mL (100 mmol) of *n*-BuLi (2.2 M in hexane) was added to a solution of 14.5 mL (105 mmol) of diisopropylamine in 75 mL of THF. After being stirred at 0 °C for 0.5 h, the pale yellow solution was cooled to -78 °C, treated with 5.0 g (43 mmol) of 4-methyl-3-pentenoic acid, stirred at -78 °C for 0.5 h, warmed to 25 °C for 0.5 h, and finally cooled to -78 °C, where 11.5 mL (100 mmol) of isobutyl iodide was added. The mixture was stirred at -78 °C for 0.5 h, warmed to 25 °C over 2 h, and stirred 1 h. Quenching with 5% HCl and extracted with ether, followed by drying ($MgSO_4$) and concentration in vacuo, afforded the crude product, which was chromatographed on silica gel (25% ethyl acetate–hexanes) to yield 4.0 g (56%) of the acid **24a** as a colorless oil, which solidified upon standing at 25 °C: ^1H NMR (500 MHz) δ 0.89 (3 H, d, *J* = 6 Hz, CH_3 (*i*-Bu)), 0.93 (3 H, d, *J* = 6 Hz, CH_3 (*i*-Bu)), 1.37 (1 H, m, CH (*i*-Bu)), 1.61 (2 H, m, CH_2), 1.69 (3 H, s, CH_3C=), 1.74 (3 H, s, CH_3C=), 3.32 (1 H, m, CHC=), 5.08 (1 H, d, *J* = 7 Hz, C*H*=C); IR (NaCl) 3500–2500, 2980, 2860, 1704, 1650, 1469, 1440, 1412, 1388, 1378, 1370, 1290, 1212, 1190, 1111, 939, 842, 829, 805, 680 cm^{-1}; LRMS, *m/e* 170 (M^+), 153, 137, 127, 125, 115, 114, 99, 98, 97, 96, 95, 86, 85, 84, 83, 82, 81, 70, 69 (100), 67, 59, 56, 55, 53, 51.

2-(2-Methylpropyl)-4-methyl-3-penten-1-ol, Alcohol 25a. A solution of 3.0 g (17.6 mmol) of acid **24a** in 10 mL of THF was added dropwise at 0 °C to a slurry of 1.0 g (26.4 mmol) of $LiAlH_4$ in 30 mL of THF. The mixture was stirred at 25 °C for 1 h and warmed to 50 °C for 2 h. Excess 5% aqueous HCl was carefully added at 0 °C and the resulting solution was extracted several times with ether. Drying ($MgSO_4$) and concentration in vacuo (50 °C) afforded 2.70 g (98% of the alcohol **25a** as a colorless liquid: ^1H NMR (500 MHz) δ 0.85 (3 H, d, *J* = 7 Hz, CH_3CH), 0.89 (3 H, d, *J* = 7 Hz, CH_3CH), 1.11 (2 H, m, CH_2-*i*-Pr), 1.5 (1 H, br s, OH), 1.55 (1 H, m, C*H*CH_3), 1.68 (3 H, d, *J* = 1 Hz, CH_3C=), 1.75 (3 H, d, *J* = 1 Hz, CH_3C=), 2.58 (1 H, m, CHC=), 3.26 (1 H, dd, *J* = 8 and 11 Hz, C*H*$_2$OH), 3.50 (1 H, dd, *J* = 5 and 11 Hz, C*H*$_2$OH), 4.81 (1 H, d, *J* = 9 Hz, CH=C); IR (NaCl) 3350, 2980, 2870, 1670, 1470, 1450, 1385, 1370, 1170, 1055, 1020, 840 cm^{-1}; LRMS, *m/e* 156 (M^+), 125, 109, 81, 69 (100), 67, 57, 55.

2,6-Dimethyl-4-[[(2-tetrahydropyranyl)oxy]methyl]-2-heptene, THP Ether 26a. Alcohol **25a** (3.2 g) was converted to the THP ether **26a** (4.88 g, 99%) as a colorless liquid (after chromatography with 25% ethyl acetate–hexanes) as described above for the synthesis of methyl 3-[2-(tetrahydropyranyl)-oxy]-2(*S*)-methylpropionate. **25a**: ^1H NMR (500 MHz) δ 0.86 (3 H, d, *J* = 7 Hz, CH_3CH), 0.91 (3 H, d, *J* = 7 Hz, CH_3CH), 1.28 (2 H, m, CH_2-*i*-Pr), 1.45–1.85 (7 H, m, THP ether and C*H*$(CH_3)_2$), 1.68 (3 H, s, CH_3C=), 1.73 (3 H, s, CH_3C=), 2.61 (1 H, m, CHC=), 3.20 (1 H, m, CH_2O), 3.50 (2 H, m, CH_2O), 3.83 (1 H, m, CH_2O), 4.54 (1 H, m, OCHO), 4.76 (1 H, m, CH=); IR (NaCl) 2980, 2870, 1468, 1452, 1441, 1385, 1377, 1368, 1352, 1342, 1322, 1282, 1261, 1200, 1183, 1139, 1120, 1078, 1030, 980, 909, 871, 819 cm^{-1}; LRMS, *m/e* 240 (M^+), 169, 157, 140, 139, 126, 124, 123, 115, 109, 102, 101, 95, 86, 85 (100), 83, 82, 81, 69, 67, 57, 55; HRMS, *m/e* 240.2104 (calcd 240.2119).

4-Methyl-2-[[(2-tetrahydropyranyl)oxy]methyl]pentanal, Aldehyde 27a. THP ether **26a** (2.0 g, 8.3 mmol) was ozonized as described above for the preparation of aldehyde **23**, to yield 1.55 g (87%) of aldehyde **27a** after chromatography (25% ethyl acetate–hexanes) on silica gel: ^1H NMR (500 MHz) δ 0.92 (6 H, m, CH_3), 1.30 (2 H, m, CH_2), 1.42–1.82 (7 H, m, THP ether and C*H*$(CH_3)_2$), 2.63 (1 H, m, C*H*CHO), 3.45–4.02 (4 H, m, 2 × CH_2O), 4.58 (1 H, m, OCHO), 9.690 and 9.692 (1 H, 2 × d, ratio 1:1, *J* = 5 Hz, CHO); IR (NaCl) 2970, 2870, 2720, 1726, 1468, 1454, 1442, 1388, 1371, 1354, 1204, 1125, 1080, 1038, 908, 872, 819 cm^{-1}; LRMS, *m/e* 214 (M^+), 157, 139, 129, 114, 113, 102, 101, 95, 86, 85 (100), 83, 71, 69, 67, 57, 56, 55, 53.

5(*S*)-[(*tert*-Butoxycarbonyl)amino]-6-phenyl-2(*R*)-(phenylmethyl)-1-[(2-tetrahydropyranyl)oxy]-*trans*-3-hexene, THP ether 28a: ^1H NMR (500 MHz) δ 1.40 (9 H, s, *t*-C_4H_9), 1.35–1.90 (6 H, m, THP ether), 2.4–2.95 (5 H, m, $ArCH_2$ and C*H*CH_2Ar), 3.25, 3.50, 3.68, and 3.82 (each 1 H, m, CH_2O), 4.33 (2 H, br m, NH and CHN), 4.54 (1 H, m, OCHO), 5.26 (1 H, m, CH=), 5.45 (1 H, m, CH=), 7.05–7.35 (10 H, m, Ar); LRMS, *m/e* 374, 318, 305, 304, 273, 272, 256, 249, 248, 234, 230, 227, 218, 216, 204, 200, 186, 178, 177, 174, 173, 172, 162, 161, 160, 144, 143, 142, 136, 134, 130, 129, 122, 118, 117, 115, 107, 105, 101, 97, 96, 92, 91, 89, 86, 85 (100), 84, 77, 67, 57, 51; $[\alpha]^{20}_D$ -24.5° (*c* 0.05 g/mL, $CHCl_3$); Anal. C, H, N.; HRMS (CI), *m/e* 465.2930 (calcd 465.2879).

5(*S*)-[(*tert*-Butoxycarbonyl)amino]-7-methyl-2(*R*)-(phenylmethyl)-1-[(2-tetrahydropyranyl)oxy]-*trans*-3-octene, THP ether 28b: ^1H NMR (500 MHz) δ 0.88 (6 H, m, CH_3CH), 1.15–1.9 (9 H, m, THP ether and $CH_2CH(CH_3)_2$), 1.44 (9 H, s, *t*-C_4H_9), 2.55 (2 H, m, $ArCH_2$) and C*H*CH_2Ar), 2.85 (1 H, m, $ArCH_2$), 5.30, 5.51, 5.67, and 5.82 (each 1 H, m, CH_2O), 4.05 (1 H, m, CHN), 4.26 (1 H, br s, NH), 4.55 (1 H, m, OCHO), 5.20 (1 H, m, CH=), 5.49 (1 H, m, CH=), 7.2–7.3 (5 H, m, Ar); IR ($CHCl_3$) 3340, 3085, 3058, 3025, 2960, 2870, 1705, 1601, 1510, 1496, 1455, 1390, 1368, 1248, 1201, 1170, 1122, 1078, 1032, 975, 908, 871, 825, 755, 701 cm^{-1}; LRMS, *m/e* 291, 290, 274, 261, 246, 234, 230, 218, 201, 174, 173, 172, 164, 159, 157, 155, 144, 138, 130, 129, 117, 115,

112, 101, 100, 96, 92, 91, 85, 67, 57 (100); $[\alpha]^{20}_D$ -33.7° (c 0.1 g/mL, $CHCl_3$).

4(*S*)-[(*tert*-Butoxycarbonyl)amino]-2,9-dimethyl-7-[[(2-tetrahydropyranyl)oxy]methyl]-*trans*-5-decene, THP Ether 28c. Diastereoisomer I: ^1H NMR (500 MHz) δ 0.83-0.91 (6 H, m, CH_3), 1.15-1.85 (9 H, m, THP ether and $CH_2CH(CH_3)_2$), 1.42 (9 H, s, t-C_4H_9), 2.36 (1 H, m, CHC=), 3.22, 3.48, 3.58, and 3.83 (each 1 H, m, CH_2O), 4.08 (1 H, m, CHN), 5.30 (1 H, br s, NH), 4.57 (1 H, m, OCHO), 5.25-5.45 (2 H, m, CH=CH). Diastereoisomer II: ^1H NMR (500 MHz) δ 0.82-0.91 (6 H, m, CH_3), 1.1-1.9 (9 H, m, THP ether and $CH_2CH(CH_3)_2$), 1.42 (9 H, s, t-C_4H_9), 2.38 (1 H, m, CHC=), 3.26, 3.45, 3.57, and 3.85 (each 1 H, m, CH_2O), 4.09 (1 H, m, CHN), 4.32 (1 H, br s, NH), 4.55 (1 H, m, OCHO), 5.35-5.43 (2 H, m, CH=CH). Diastereoisomers I and II were virtually indistinguishable by IR and LRMS: IR (NaCl) 3340, 2960, 2875, 1700, 1510, 1468, 1452, 1386, 1368 cm^{-1}; LRMS, m/e 340, 312, 284, 283, 257, 256, 240, 227, 200, 196, 182, 166, 140, 138, 130, 123, 110, 95, 86, 85 (100); diastereoisomer I, $[\alpha]^{20}_D$ -27.6° (c 0.1 g/mL, $CHCl_3$); diastereoisomer II, $[\alpha]^{20}_D$ +0.7° (c 0.1 g/mL, $CHCl_3$).

5(*S*)-[(*tert*-Butoxycarbonyl)amino]-6-phenyl-2(*R*)-(phenylmethyl)-*trans*-3-hexenoic Acid, protected PhePhe isostere 29a: ^1H NMR (500 MHz) δ 1.40 (9 H, s, t-C_4H_9), 2.76 (3 H, m, $ArCH_2CHN$ and $ArCH_2CHCO$), 3.08 (1 H, m, $ArCH_2CHCO$), 3.29 (1 H, m, CHCOO), 4.35-4.55 (2 H, br m, CHNH), 5.44 (1 H, dd, J = 7 and 16 Hz, CH=C), 5.58 (1 H, dd, J = 10 and 16 Hz, CH=C), 7.05-7.35 (10 H, m, Ar); ^{13}C NMR (50 MHz) δ 28.3 (CH_3CO), 38.3, (CHN), 41.6 ($ArCH_2CN$), 50.5 ($ArCH_2CHCOO$), 52.7 (CHCOOH), 79.6 ($OCCH_3$), 126.4, 127.1, 127.4, 128.3, 129.1, 129.5, 130.1 (Ar and C=C), 133.5 (Ar CCH_2CN), 137.2 (CHC=C), 138.4 (Ar CCH_2CCOOH), 155.1 (O=CN), 178.4 (COOH); IR ($CHCl_3$) 3500-2500, 3440, 3040, 2980, 2940, 2860, 1705, 1685, 1600, 1492, 1453, 1369, 1286, 1165, 1075, 1031, 972, 922 cm^{-1}; LRMS, m/e 318, 317, 305, 304, 249, 248, 234, 230, 214, 204, 200, 187, 186, 170, 161, 143, 130, 129, 128, 117, 115, 105, 97, 95, 92, 91 (100), 85, 81, 77, 65, 57, 55; $[\alpha]^{20}_D$ -17.0° (c 0.1 g/mL, $CHCl_3$); HRMS (CI), m/e 395.2107 (calcd 395.2104).

5(*S*)-[(*tert*-Butoxycarbonyl)amino]-7-methyl-2(*R*)-(phenylmethyl)-*trans*-3-octenoic Acid, Protected LeuPhe Isostere 29b. Method 2, Hydrolysis/Oxidation. A solution of 0.1313 g (0.3 mmol) of the THP ether **29a** and 0.5 mg of pyridinium p-toluenesulfonate in 5 mL of CH_3OH was stirred at 25 °C for 10 h. The volatiles were removed in vacuo, and the residue was dissolved in 5 mL of acetone and cooled to 0 °C. Jones reagent (2.5 mL, 4.8 mmol, 1.92 M) was added, and the mixture was stirred 1 h at 0 °C. Ether and water were added, and the layers were separated. The aqueous layer was extracted with several portions of fresh ether, and the product was recovered by extraction of the combined etheral layers with 5% aqueous NaOH. The aqueous extracts were acidified with 10% aqueous HCl and extracted with ether. Drying ($MgSO_4$) followed by concentration in vacuo (50 °C) afforded 68.5 mg (63%) of **29b** as a pale yellow oil: ^1H NMR (500 MHz) δ 0.86 (3 H, d, J = 6 Hz, CH_3), 0.87 (3 H, d, J = 6 Hz, CH_3), 1.23 (2 H, m, CH_2-i-Pr), 1.44 (9 H, s, t-C_4H_9), 1.54 (1 H, m, $CH(CH_3)_2$), 2.81 (1 H, dd, J = 7 and 13 Hz, $ArCH_2$), 3.11 (1 H, dd, J = 7 and 13 Hz, $ArCH_2$), 3.28 (1 H, m, CHCOO), 4.05 (1 H, m, CHN), 4.28 (1 H, s, NH), 5.35 (1 H, dd, J = 6 and 15 Hz, CH=), 5.63 (1 H, dd, J = 8 and 15 Hz, CH=), 7.14-7.28 (5 H, m, Ar); ^{13}C NMR (50 MHz) δ 2.5 (CH_3CH), 24.5 ($CHCH_3$), 28.3 (CH_3CO), 38.4 (CHN), 44.4 (CH_2CHN), 50.4 ($ArCH_2$), 65.8 (CHCOOH), 79.8 ($OCCH_3$), 126.4, 126.5 (Ar para C and CHC=C), 128.3 (Ar ortho C), 129.1 (Ar meta C), 134.9 (CHC=C), 138.4 (Ar CCH_2), 155.3 (O=CN), 178.2 (COOH); IR ($CHCl_3$) 3500-2500, 3440, 3080, 3040, 2960, 2935, 2875, 1703, 1650, 1502, 1492, 1452, 1392, 1370, 1282, 1165, 1067, 972, 912, 870 cm^{-1}; LRMS, m/e 304, 260, 259, 249, 248, 244, 205, 204, 200, 161, 156, 144, 143, 130, 117, 115, 112, 105, 96, 92, 91 (100), 86, 84, 77, 65, 59, 57; $[\alpha]^{20}_D$ -32.1° (c 0.025 g/mL, $CHCl_3$); HRMS (CI), m/e 361.2222 (calcd 361.2261).

5(*S*)-[(*tert*-Butoxycarbonyl)amino]-7-methyl-2-(methylpropyl)-*trans*-3-octenoic Acid, Protected LeuLeu Isostere 29c. Diastereoisomer I: ^1H NMR (500 MHz) δ 0.87 (1.5 H, d, J = 6 Hz, CH_3), 0.90 (4.5 H, m, CH_3), 1.34 (1 H, m, $CH(CH_3)_2$), 1.43 (9 H, s, t-C_4H_9), 1.63 (2 H, m, CH_2-i-Pr), 3.09 (1 H, m, CHCOO), 4.12 (1 H, br m, CHN), 4.40 (1 H, br s, NH), 5.54 (2 H, m, CH=CH). Diastereoisomer II: ^1H NMR (500 MHz) δ 0.87 (1.5 H, d, J = 6 Hz, CH_3), 0.90 (4.5 H, m, CH_3), 1.34 (1 H, m, $CH(CH_3)_2$), 1.44 (9 H, s, t-C_4H_9), 1.62 (2 H, m, CH_2-i-Pr), 3.07 (1 H, m, CHCOO), 4.10 (1 H, br m, CHN), 4.40 (1 H, br s, NH), 5.46 (1 H, dd, J = 6 and 16 Hz, CH=), 5.56 (1 H, dd, J = 8 and 16 Hz, CH=). The ^{13}C NMR, MS, and IR spectra for both diastereoisomers were virtually indistinguishable: ^{13}C NMR (50 MHz) δ 22.4, 22.6 (2 × CH_3CH), 24.7, 25.5 (2 × $CHCH_3$), 28.4 (CH_3CO), 41.3 (CHN), 44.6 (CH_2CN), 47.0 (CH_2CCOOH), 50.2 (CHCOOH), 79.6 ($OCCH_3$), 127.7 (C=C), 134.3 (C=C), 155.3 (O=CN), 179.7 (COOH); IR ($CHCl_3$) 3500-2500, 3440, 2960, 2875, 1702, 1492, 1468, 1453, 1389, 1320, 1280, 1240; 1168, 1076, 1062, 1051, 970, 870 cm^{-1}; LRMS, m/e 272, 271, 270, 226, 225, 215, 184, 182, 170, 157, 156, 154, 152, 130, 117, 112, 109, 105, 96, 95, 91, 86, 85, 84, 82, 77, 69, 67, 57 (100); HRMS (CI), m/e 327.2409 (calcd 327.2418); diastereoisomer I, $[\alpha]^{20}_D$ +18.1° (c 0.05 g/mL, $CHCl_3$); diastereoisomer II, $[\alpha]^{20}_D$ -29.3° (c 0.02 g/mL, $CHCl_3$).

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New Spongiane Diterpenes from an Australian Nudibranch

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Nine new spongiane-type diterpenes have been isolated from a nudibranch collected in South Australia and tentatively identified as *Ceratosoma brevicaudatum* (Abraham). Variation in extent and site of oxidation distinguishes these diterpenes from others of this skeletal class. Structures were determined by detailed spectroscopic analyses with emphasis on ^1H and ^{13}C NMR data. Relayed coherence transfer and long-range COSY ^1H NMR experiments were used to identify spin systems of partial structures involving unresolved, overlapping signals.

A family of diterpenes sharing a common skeleton represented by **1**[1] and designated spongianes[2] have been reported from various sponge sources.[3,4] Metabolites with rearranged versions of this skeleton have been isolated

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