(s, C-19H), 4.7-4.07 (m, C-1H, -3H), 1.2 (s, C-26$H_3$, -27$H_3$), 1.0 (br s, C-21$H_3$), 0.6 (s, C-18$H_3$); IR $\nu_{max}$ 3500 (s), 2950 (s), 2900 (sh), 1640 (w), 1480 (m), 1440 (m), 1380 (m), 1360 (m), 1140 (m), 1050 (s) $cm^{-1}$.

**Acknowledgment.** We thank Roussel-Uclaf for a generous gift of 25-hydroxyvitamin $D_3$.

**Registry No.** **1**, 19356-17-3; **3**, 32222-06-3; **5**, 50-14-6; **11**, 104973-27-5; **12**, 2579-08-0; **13**, 104973-28-6; **14**, 104849-48-1; **15**, 51744-66-2; **16**, 104849-49-2; **17**, 20116-64-7; **19**, 87417-00-3; **20**, 87480-21-5; **24**, 104973-29-7; **26**, 104973-30-0; **27**, 104849-50-5; **30**, 104973-31-1; **31**, 67883-18-5; **31** (TES), 87417-17-2; **32**, 1779-49-3; **33**, 104849-54-9; **34**, 87417-16-1; **35**, 104875-13-0; **36**, 104973-32-2; **37**, 104973-33-3; **38**, 36149-00-5; **39**, 87417-20-7; **40**, 87680-65-7; **44**, 87680-61-3; **45**, 87680-62-4; **46**, 87680-63-5; **47**, 87407-52-1; **50**, 87407-65-6; **51**, 104849-51-6; **52**, 87417-12-7; **55**, 87407-67-8; **56**, 87680-64-6; **56** (diol), 104849-52-7; **57**, 87417-31-0; **58**, 2568-33-4; isobutylene epoxide, 558-30-5; phthalhydrazide, 1445-69-8; 3,5-dinitrobenzoyl chloride, 99-33-2; 4-phenyl-1,2,4-triazoline-3,5-dione, 4233-33-4; triethylsilyl chloride, 994-30-9; *p*-toluenesulfonyl chloride, 98-59-9.

# A Short, Stereoselective Synthesis of the Lactone Precursor to 2*R*,4*S*,5*S* Hydroxyethylene Dipeptide Isosteres†

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Lactone **1**, a precursor to the 2*R*,4*S*,5*S* hydroxyethylene dipeptide isostere unit, was synthesized steroselectively in four steps from *N*-Boc-L-leucinal in 13% overall yield. Peptides containing hydroxyethylene dipeptide isosteres with this chirality are potent inhibitors of aspartyl proteases. Addition of the lithium salt of ethyl propiolate to *N*-Boc-L-leucinal (**3**) afforded hydroxy acetylenic esters **4** as a mixture of diastereomers. Reduction of the acetylenic function of **4** and subsequent lactonization gave a readily separable 4.5:1 mixture of the desired 4*S* lactone **2** and the 4*R* lactone **5**. Direct alkylation of **2** with methallyl bromide and lithium hexamethyldisilazide as base yielded the trans lactone **10**, which was catalytically reduced to **1**. The structure of lactone **10** was confirmed by X-ray analysis.

During recent years, there has been a growing interest in the use of enzyme inhibitors as therapeutic agents.[1] One class of proteolytic enzymes that has received particular attention in this regard is the aspartyl proteases (or acid proteases),[2] which includes pepsin and the blood pressure regulating enzyme renin.[3] These enzymes cleave between two internal hydrophobic amino acid residues and have, as the catalytic apparatus, two aspartyl groups in the active site. Recently, a potent series of synthetic peptide inhibitors of aspartyl proteases has been reported that contain a dipeptide mimic known as the "hydroxyethylene dipeptide isostere".[4,5] We describe here an improved, stereoselective synthesis of this isostere unit in its lactone form.

As shown in Figure 1, the hydroxyethylene dipeptide isostere is a 5-aminopentanoic acid derivative which is derived by replacing the amide linkage of the dipeptide residue surrounding the cleavage site of the substrate by the hydroxyethylene moiety of statine, the unusual amino acid found in the naturally occurring pentapeptide inhibitor pepstatin[6] (Iva-Val-Val-Sta-Ala-Sta). The configurations of the three chiral centers of the isostere correspond with the L-amino acids of the peptide substrate and the 3*S* configuration of statine and are thus assigned 2*R*,4*S*,5*S*. The 4*S* configuration is believed to be especially crucial to inhibition since pepstatin analogues with (3*R*)-statine are over 100-fold less potent inhibitors than those with (3*S*)-statine.[7] The possibility that pepstatin may be a transition-state analogue,[8] which is based on the close resemblance between the hydroxyethylene group and the putative tetrahedral intermediate of proteolytic hydrolysis, is discussed by Rich in an excellent review of pepstatin binding.[9]

Syntheses of the hydroxyethylene dipeptide isostere unit were first reported by Szelke[4] and Rich[5] in 1983 and, more recently, by Evans.[10] Of the three routes, which are summarized in Scheme I, the Evans synthesis requires the fewest number of steps, but in terms of stereocontrol, only Rich's synthesis is stereoselective at C-2 and C-4. In Rich's synthesis, the C-2 chiral center is introduced as part of an optically active C-1–C-3 fragment which is added as a Grignard reagent to *N*-Boc-L-leucinal to provide a 4:1 epimeric mixture of the C-4 alcohols enriched in the desired 4*S* diastereomer. Separation of the two diastereomers is postponed until the isostere is incorporated into the peptide. A drawback of this synthesis, however, is the use of excess (2.5 equiv) optically active Grignard reagent, which is prepared in four steps from the chiaral oxazolidinone derived from (1*S*,2*R*)-norephedrine.[11]

† This manuscript is dedicated to Professor Clayton H. Heathcock on the occasion of his 50th birthday.

(1) *Enzyme Inhibitors as Drugs*; Sandler, M., Ed.; University Park: Baltimore, 1980.
(2) *Acid Proteases: Structure, Function, and Biology*; Tang, J., Ed.; Plenum: New York, 1977.
(3) Peach, M. J. *Physiol. Rev.* **1977**, *57*, 313.
(4) (a) Szelke, M.; Jones, D. M.; Hallett, A. European Patent Application EP 45 665, 1982; *Chem. Abstr.* **1982**, *97*, 39405p. (b) Szelke, M.; Jones, D. M.; Atrash, B.; Hallet, A.; Leckie, B. J. *Proc. Am. Pept. Symp. 8th* **1983**, 579. (c) Leckie, B. J.; Grant, J.; Hallett, A.; Hughes, M.; Jones, D. M.; Szelke, M.; Tree, M. *Scott. Med. J.* **1984**, *29*, 125.
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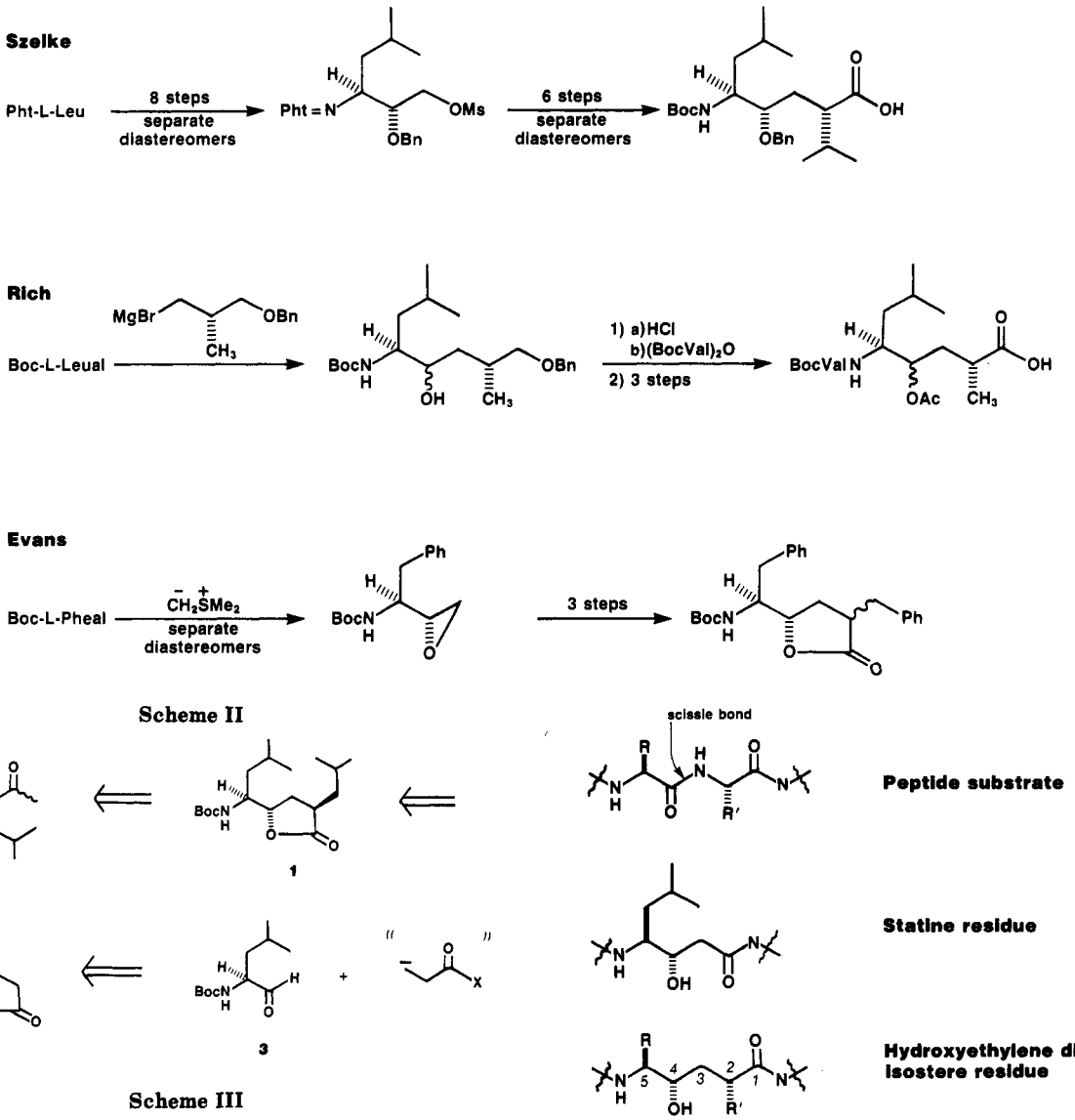
(6) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259.
(7) Rich, D. H.; Sun, E. T. O.; Ulm, E. *J. Med. Chem.* **1980**, *23*, 27.
(8) Wolfenden, R. *Annu. Rev. Biophys. Bioeng.* **1976**, *5*, 271.
(9) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263.
(10) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615.

0022-3263/86/1951-4828$01.50/0 

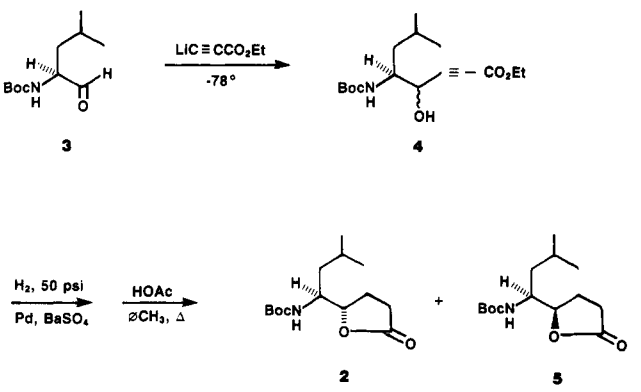
**Scheme I**




**Scheme II**




**Scheme III**




Our approach, outlined in Scheme II, is based on finding an appropriate "homoenolate equivalent"[12] that would add stereoselectively to *N*-Boc-L-leucinal[13] (**3**) to afford, after subsequent lactonization, 4*S* lactone **2**. Alkylation of lactone **2** trans to the 4-substituent would then provide lactone **1**, which has all the necessary chirality for the




**Figure 1.**

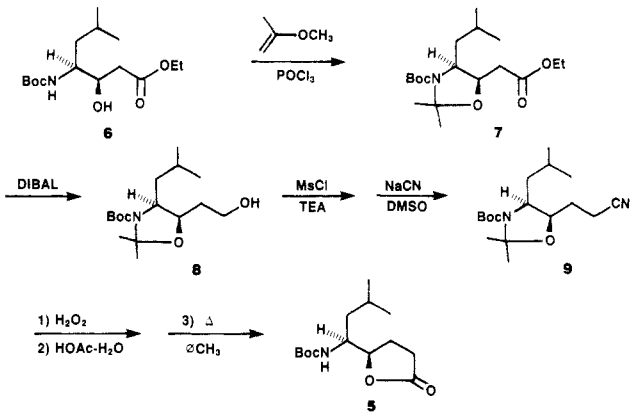
2*R*,4*S*,5*S* hydroxyethylene dipeptide isostere corresponding to L-Leu-L-Leu. A similar lactone was synthesized in the Evans synthesis as a mixture of C-2 epimers and was successfully incorporated into a pentapeptide.

## Results and Discussion

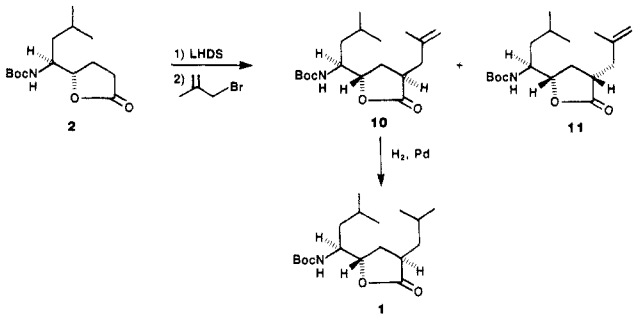
The anion of ethyl propiolate was found to be an extremely useful homoenolate equivalent for the synthesis of lactone **2** (Scheme III). Using a procedure of Tishler,[14] 2 equiv of the lithium salt of ethyl propiolate, generated from lithium diisopropylamide in THF at −78 °C, was allowed to react with *N*-Boc-L-leucinal (**3**) to afford an epimeric mixture of hydroxy acetylenic esters, **4**. The yield of the reaction was modest (36%) but was based on crude aldehyde **3**, which was not chromatographed to avoid possible racemization.[15] Hydrogenation of **4** proceeded smoothly without competing isomerization to the keto ester

(11) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(12) (a) Werstiuk, N. H. *Tetrahedron*, **1983**, *39*, 205. (b) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932.
(13) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624.
(14) Jakubowski, A. A.; Guziec, F. S.; Sugiura, M.; Tam, C. C.; Tishler, M.; Omura, S. *J. Org. Chem.* **1982**, *47*, 1221.
(15) Having previously observed partial racemization of *N*-Boc-α-amino aledhydes during silica gel chromatography, we elected not to chromatograph aldehyde **3**. Apparently, however, racemization can be suppressed if the contact time with the silica gel is short, see: Rittle, K. E.; Homnicke, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016.

**Scheme IV**



**Scheme V**



using catalytic hydrogenation at 50 psi with 5% Pd/$BaSO_4$.[14] The intermediate hydroxy esters were not isolated but lactonized directly in refluxing toluene containing acetic acid. The desired 4*S* lactone **2** and 4*R* lactone **5**, which were readily separable by flash chromatography, were obtained in 78% and 17% yields, respectively.

At this stage, proof of the C-4 stereochemistry of lactones **2** and **5** was accomplished by chemical correlation of the minor lactone (**5**) with the epimer of statine, (3*R*)-*N*-Boc-statine (**6**), which was prepared according to the procedure of Rich[13] by aldol condensation of $\alpha$-lithioethyl acetate with *N*-Boc-L-leucinal (**3**). As shown in Scheme IV, protection of the hydroxyl and Boc-NH functions of **6** as the acetonide, **7**, followed by reduction of the ester with diisobutylaluminum hydride gave alcohol **8** in 81% yield. Cyanide displacement of the mesylate derivative of alcohol **8** afforded nitrile **9** (61% yield) which, after hydrolysis and lactonization, led exclusively to lactone **5** in 57% yield.

Since the optical rotations of the samples of lactone **5** obtained by the parent route (Scheme III) and by conversion of (3*R*)-*N*-Boc-statine (Scheme IV) were identical within experimental error ($[\alpha]_D$ −47.4° and $[\alpha]_D$ −46.9°, respecitvely), it is unlikely that any significant racemization occurred in the acetylide addition step (Scheme III).[16] During a large-scale synthesis, however, we found that minor amounts (<5%) of racemic lactone **2** could conveniently be removed by crystallization from ether/hexane. The origin of the racemic material was most likely *N*-Boc-L-leucinal which, when prepared on large scale, had prolonged contact with the Rochelle salt solution during workup, resulting in slight racemization.

Our attention was then directed to the conversion of lactone **2** to lactone **1** (Scheme V). Encouraged by previous examples of stereoselective trans alkylations of 4-substituted $\gamma$-lactones,[17] we investigated the alkylation of the dianion of **2**, generated with 2 equiv of lithium hexamethyldisilazide, with various electrophiles. Methallyl chloride was inert at temperatures compatible with the full stability of the dianion. With methallyl iodide some lactone **1** was formed, but there was also a considerable amount of dialkylated material along with unreacted lactone **2**. Best results were achieved with methallyl bromide which, upon reaction with the dianion of **2** at −78 °C followed by slow warming to −40 °C over 2 h, resulted in a 47% yield of trans lactone **10**. The cis lactone **11** was also isolated in 3% yield. The structure of lactone **10** was confirmed by X-ray analysis (Figure 2). Catalytic hydrogenation of lactone **10** then gave our target lactone, **1**, corresponding to the L-Leu-L-Leu dipeptide.

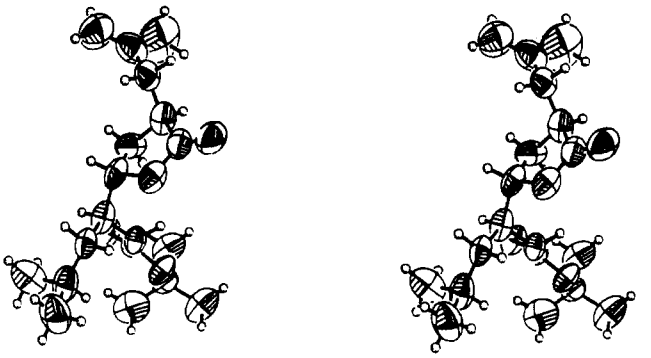


**Figure 2.** Computer-generated ORTEP stereo drawing of lactone **10**.

Synthesis of peptides containing the hydroxyethylene dipeptide isostere derived from lactone **1** and their biological activity will be reported elsewhere.

**Conclusion.** An efficient synthesis of the lactone precursor to the hydroxyethylene dipeptide isostere unit has been developed. The combination of brevity and stereoselective assembly of the isostere corresponding to the natural L-configurations of the amino acids of the peptide substrate at C-2 and C-5 and to the 3*S* configuration of statine at C-4 make this route unique among the three earlier syntheses. This synthesis, which proceeds in four steps from *N*-Boc-L-leucinal (**3**) in 13% overall yield, should also allow easy variation of the C-2 substituent.

## Experimental Section

$^1H$ NMR spectra were determined with a Varian T-60, Varian EM 390, Bruker WM-250, or Varian XL300 spectrometer. Chemical shifts are expressed in ppm relative to internal tetramethylsilane (60 and 90 MHz spectra) or $CDCl_3$ (250 and 300 MHz spectra). $^{13}C$ NMR spectra were determined at 75.429 MHz on a Varian XL-300 by using the 77 ppm resonance of $CDCl_3$ as the internal standard. All NMR spectra were taken in $CDCl_3$. Significant $^1H$ NMR data are tabulated in order (number of protons, multiplicity, coupling constant (hertz)). Infrared (IR) spectra were determined with a Perkin-Elmer Model 283B infrared spectrophotometer. Exact masses were determined on an A.E.I.-MS30 mass spectrometer. Optical rotations were recorded at room temperature on a Perkin-Elmer Model 241 MC polarimeter and are expressed as specific rotations. Elemental analyses were performed by the Pfizer Analytical Chemistry Department. Melting

(16) The formation of (3*R*)-statine and (3*R*-statine from Boc-L-leucinal and $\alpha$-lithioethyl acetate occurs with <0.5% racemization, see: Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016.

(17) (a) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733. (b) Davidson, A. H.; Floyd, C. D.; Jones, A. J.; Myers, P. L. *J. Chem. Soc., Chem. Commun.* **1985**, 1662.

points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus.

Solvents and reagents were commercially available and used directly unless otherwise noted. Prior to use tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone and hexamethyldisilazane was distilled from calcium hydride. Gold label diisopropylamine (Aldrich) was dried over 3-Å sieves (under $N_2$) and used directly. All reactions involving organometallic reagents were performed under a nitrogen atmosphere. Solvents were removed with a rotary evaporator.

Flash chromatography was performed using 32–63-μm silica gel (Woelm) according to the method described by Still et al.[18] Analytical thin-layer chromatography (TLC) was performed on 250-μm, 2.5 × 10 cm silica gel plates (Analtech) using phosphomolybdic acid or potassium permanganate for visualization.

***N*-Boc-L-leucinal (3).** According to the procedure of Rich,[13] *N*-Boc-L-leucine methyl ester (28.0 g, 114 mmol) was reduced in 380 mL of toluene at −78 °C with 285 mL (285 mmol) of a 1 M solution of diisobutylaluminum hydride (DIBAL) in hexane. After workup with Rochelle salt solution, the aldehyde (21.7 g, 88%), contaminated with a small amount of overreduced alcohol, was obtained as an oil and was used without further purification: $^1$H NMR (90 MHz) δ 0.97 (6 H, d, $J$ = 6), 1.43 (9 H, s), 9.54 (1 H, s).

**(4*S*,5*S*)- and (4*R*,5*S*)-*N*-Boc-5-amino-4-hydroxy-7-methyloct-2-ynoic Acid Ethyl Ester (4).** To a solution of 8.79 g (12.3 mL, 86.9 mmol) of diisopropylamine in 50 mL of THF at −50 °C was added dropwise 45.3 mL (72.5 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. The mixture was cooled to −78 °C, and 7.3 mL (7.1 g, 72.5 mmol) of freshly distilled ethyl propiolate was added dropwise. The resulting yellow suspension was allowed to stir an additional 30 min at −78 °C. Then, a solution of *N*-Boc-L-leucinal (10.4 g, 48.3 mmol) in 50 mL of THF was added dropwise over a 30-min period. When the addition was complete the mixture became clear with an amber color and was stirred an additional 60 min at −78 °C, as the disappearance of aldehyde was monitored by TLC (1:1 ether–hexane). The reaction was quenched by the addition of a mixture of acetic acid (20 mL) and THF (80 mL) and was allowed to warm to room temperature. The mixture was diluted with ether (500 mL) and washed successively with 10% aqueous citric acid solution (2 × 300 mL) and saturated aqueous $NaHCO_3$ solution (2 × 300 mL), dried ($MgSO_4$), and evaporated to 13.7 g of a red oil. Purification of the oil on 450 g of silica gel with an ethyl acetate–hexane (15:85 to 25:75) eluant afforded 5.45 g (36%) of the acetylenic alcohols **4** as a light yellow oil ($R_f$ 0.40, 3:7 ethyl acetate–hexane): $^1$H NMR (300 MHz) δ 0.97 (6 H, t, $J$ = 7), 1.34 (3 H, t, $J$ = 6), 1.48 (9 H, s), 1.40–1.60 (2 H, m), 1.65–1.80 (1 H, m), 3.30–3.40 (1 H, m), 3.81–3.96 (1 H, m), 4.28 (2 H, q, $J$ = 7), 4.45–4.58 (1 H, m), 4.68–4.78 (1 H, m); IR ($CHCl_3$) 3438, 3340, 2233, 1711 cm$^{-1}$.

Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.38; H, 8.58; N, 4.42.

**(5*S*)-5-[(1*S*)-1-(*N*-Boc-amino)-3-methylbutyl]dihydrofuran-2(3*H*)-one (2).** A 50-mL ethyl acetate solution of acetylenic alcohols **4** (4.60 g, 14.7 mmol) was hydrogenated for 1.5 h at 50 psi in the presence of 2.76 g of 5% Pd/$BaSO_4$ (Aldrich). After filtration of the catalyst and removal of the solvent, the residue of saturated hydroxy esters ($R_f$ 0.49, 7:3 ether–hexane) was refluxed in 200 mL of a mixture of toluene–acetic acid (97.5:2.5) for 3 h. The solvent was removed, and the residue (4.3 g) containing a mixture of lactones **2** and **5** was separated on 470 g of silica gel with an ether–hexane (4:6 to 10:0) eluant. The fractions containing the less polar lactone (**2**) ($R_f$ 0.40, 7:3 ether–hexane) were combined and evaporated to 3.10 g (78%) of a white solid: $^1$H NMR (300 MHz) δ 0.92 (6 H, d, $J$ = 6), 1.28–1.74 (3 H, m), 1.44 (9 H, s), 2.05–2.30 (2 H, m), 2.48–2.58 (2 H, m), 3.79–3.92 (1 H, br s), 4.42–4.58 (2 H, m); $^{13}$C NMR (75 MHz) δ 21.5, 22.9, 23.8, 24.4, 28.0, 28.2, 41.3, 50.8, 78.7, 82.4, 156.0, 177.0; IR ($CHCl_3$) 3439, 1775, 1711 cm$^{-1}$; $[\alpha]_D$ −33.8° (*c* 1.0, $CH_3OH$). The analytical sample was prepared by trituration in hexane, mp 76–77 °C.

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.15; H, 9.26; N, 5.12.

**(3*R*,4*S*)-4-(*N*-Boc-amino)-3-hydroxy-6-methylheptanoic Acid Ethyl Ester [(3*R*)-*N*-Boc-statine Ethyl Ester] (6).** Following the procedure of Rich,[13] Boc-L-leucinal (**3**) was reacted with α-lithioethyl acetate to afford a mixture of diastereomeric aldol products, which were separated by silica gel chromatography. The more polar 3*R*,4*S* diastereomer **6** was obtained as a low-melting solid, $[\alpha]_D$ −20.6° (*c* 0.9, $CH_3OH$) [lit.[13] $[\alpha]_D$ −23.2° (*c* 0.94, $CH_3OH$)].

**(4*S*,5*R*)-*N*-Boc-5-(carbethoxymethyl)-2,2-dimethyl-4-(2-methylpropyl)-1,3-oxazolidine (7).** To a mixture of 1.50 g (4.94 mmol) of *N*-Boc-(3*R*)-statine ethyl ester (**6**) and 1.99 mL (1.50 g, 20.1 mmol) of 2-methoxypropene (Aldrich) was added a trace of phosphorous oxychloride using a capillary dipped into a bottle of phosphorus oxychloride. The mixture was allowed to stir at room temperature as the course of the reaction was monitored by TLC 1:1 ether–hexane. When both the starting material and an intermediate (presumably the uncyclized 2-methoxypropene ether) were consumed (16 h), six drops of triethylamine were added to the mixture, and the solvent was removed. The residue was dissolved in ethyl acetate and washed twice with aqueous 10% citric acid solution and saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated to 1.79 g (100%) of oxazolidine **7** as an oil: $^1$H NMR (60 MHz) δ 0.93 (6 H, d, $J$ = 5), 1.25 (3 H, t, $J$ = 7), 1.46 (9 H, s), 1.53 (6 H, s), 2.58 (2 H, d, $J$ = 7), 4.13 (2 H, q, $J$ = 7), 3.8–4.7 (2 H, m); IR ($CHCl_3$) 1728, 1682 cm$^{-1}$; $[\alpha]_D$ +3.1° (*c* 1.2, $CH_3OH$). The analytical sample was prepared by heating (60 °C) overnight under high vacuum.

Anal. Calcd for $C_{18}H_{33}NO_5$: C, 62.95; H, 9.69; N, 4.08. Found: C, 63.07; H, 9.66; N, 4.04.

**(4*S*,5*R*)-*N*-Boc-2,2-dimethyl-5-(2-hydroxyethyl)-4-(2-methylpropyl)-1,3-oxazolidine (8).** To a solution of 1.20 g (3.94 mmol) of ester **7** in 3 mL of THF at 0 °C was added dropwise 8.75 mL (8.75 mmol) of a 1 M solution of DIBAL in toluene. After being stirred several minutes at 0 °C, the mixture was poured onto ice and diluted with ether. After transferring to a separatory funnel, a half-saturated aqueous solution of Rochelle salt was added, and the mixture was shaken. The organic layer was separated, dried ($MgSO_4$), and evaporated to 1.32 g of an oil. Purification of the oil by silica gel chromatography (15-cm height, 4.5-cm diameter) with an ether–hexane (55:45) eluant afforded 0.853 g (81%) of alcohol **8** as a clear oil: $^1$H NMR (60 MHz) δ 0.93 (6 H, d, $J$ = 5), 1.46 (s, 9 H), 1.51 (s, 6 H), 2.61 (1 H, br s), 3.73 (2 H, br t), 3.7–4.3 (2 H, m); IR ($CHCl_3$) 3519, 1683 cm$^{-1}$; $[\alpha]_D$ + 14.7° (*c* 1.1, $CH_3OH$); high-resolution mass spectrum, calcd for $C_{16}H_{31}NO_4$ *m/e* 301.2253, found *m/e* 301.2298.

**(4*S*,5*R*)-*N*-Boc-5-(2-cyanoethyl)-2,2-dimethyl-4-(2-methylpropyl)-1,3-oxazolidine (9).** To a solution of

(18) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

0.720 g (2.39 mmol) of alcohol **8** in 6 mL of dry methylene chloride at 0 °C was added 0.499 mL (0.362 g, 3.49 mmol) of triethylamine followed by 0.278 mL (0.414 g, 3.59 mmol) of methanesulfonyl chloride. After 2.25 h of stirring at 0 °C, the mixture was washed twice with aqueous 10% citric acid solution and saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated. The residue of crude mesylate was dissolved in 8 mL of dry $Me_2SO$ and heated to 50 °C with 135 mg (2.75 mmol) of sodium cyanide for 16 h, at which time an additional 135 mg of sodium cyanide was added as TLC analysis (2:1 ether–hexane) indicated remaining starting mesylate. After 6 h of additional stirring, the mixture was cooled to room temperature, diluted with water, and extracted with ether. The combined ether extracts were backwashed four times with water, dried ($MgSO_4$), and evaporated to 0.553 g of an oil. Silica gel purification (12-cm height, 4.5-cm diameter) of the oil with an ether–hexane (1:3) eluant gave 0.454 g (61%) of nitrile **9** as a clear oil: $^1H$ NMR (60 MHz) $\delta$ 0.93 (6 H, d, $J$ = 5), 1.46 (9 H, s), 1.50 (6 H, s), 2.36–2.60 (2 H, m), 3.7–4.2 (2 H, m); IR ($CHCl_3$) 2242, 1682 $cm^{-1}$; high-resolution mass spectrum, calcd for $C_{17}H_{30}N_2O_3$ $m/e$ 310.2256, found $m/e$ 310.2299.

**(5*R*)-5-[(1*S*)-1-(*N*-Boc-amino)-3-methylbutyl]dihydrofuran-2(3*H*)-one (5). From Reduction and Lactonization of Acetylenic Alcohols (4).** The fractions containing the more polar lactone **5** ($R_f$ 0.31 (7:3 ether–hexane) were pooled and evaporated to 0.68 g (17%) of a white solid: $^1H$ NMR (300 MHz) $\delta$ 0.90 (3 H, d, $J$ = 6), 0.92 (3 H, d, $J$ = 6), 1.22–1.5 (2 H, m), 1.43 (9 H, s), 1.62–1.82 (1 H, m), 1.98–2.14 (1 H, m), 2.20–2.37 (1 H, m), 2.50–2.60 (2 H, m), 3.68–3.84 (1 H, m), 4.37–4.64 (2 H, m); $^{13}C$ NMR (75 MHz) $\delta$ 21.4, 23.6, 24.2, 24.5, 28.2, 28.3, 38.8, 51.7, 79.7, 82.9, 155.6, 176.9; IR ($CHCl_3$) 3441, 1778, 1711 $cm^{-1}$; $[\alpha]_D$ −47.4° ($c$ 1.1, $CH_3OH$). The analytical sample was prepared by trituration in hexane, mp 114–116 °C.

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.75; H, 9.19; N, 5.11.

**From Hydrolysis and Lactonization of Cyano Acetonide 9.** Nitrile **9** (0.374 g, 1.20 mmol) was dissolved in 8.8 mL of ethanol, cooled to 0 °C in an ice bath, and successively treated with 2.1 mL of an aqueous 1 N sodium hydroxide solution and 6.9 mL of an aqueous 30% hydrogen peroxide solution. After 5 h of stirring in an ice bath, the mixture was placed in the refrigerator overnight. TLC analysis (2:1 ether–hexane) of a worked up aliquot showed consumption of the starting nitrile. The mixture was chilled to −30 °C and 15 mL of aqueous 20% sodium thiosulfate was added dropwise keeping the temperature less than 10 °C. Most of the ethanol was removed by rotary evaporation, and the residue was extracted four times with ethyl acetate. Washing the combined extracts with brine, drying ($MgSO_4$), and evaporation gave a white gum, which was stirred for 3 days in a mixture of acetic acid–water (65:35) at room temperature. The solvent was removed, and the residue was coevaporated with toluene and methylene chloride to remove traces of water. The resulting gum (383 mg) was then refluxed in toluene for 1 h. Evaporation of the toluene and purification of the residue by silica gel chromatography (11-cm height, 4.5-cm diameter) with an ether–hexane (2:1) eluant afforded 0.186 g (57%) of lactone **5** after hexane trituration: $[\alpha]_D$ −46.9° ($c$ 1.0, $CH_3OH$); mp 116–118 °C. This material was identical by TLC and NMR with lactone **5** prepared from acetylenic alcohols **4**.

**(3*R*,5*S*)-5-((1*S*)-1-(*N*-Boc-amino)-3-methylbutyl)-3-(2-methylprop-2-enyl)dihydrofuran-2(3*H*)-one (10) and (3*S*,5*S*)-5-((1*S*)-1-(*N*-Boc-amino)-3-methylbutyl)-3-(2-methylprop-2-enyl)dihydrofuran-2(3*H*)-one (11).** To a −78 °C suspension of lithium hexamethyldisilazide, prepared by the dropwise addition of 5.1 mL (8.11 mmol) of a 1.6 M solution of $n$-butyllithium in hexane to 1.79 mL (1.39 g, 8.49 mmol) of hexamethyldisilazane in 3.5 mL of THF at 0 °C, was added dropwise a solution of 1.00 g (3.69 mmol) of lactone **2** in 3 mL of THF. At the end of the addition the mixture became clear, and it was allowed to stir an additional 15 min at −78 °C. A solution of 0.548 g (4.06 mmol) of freshly distilled methallyl bromide[19] in 2 mL of THF was then added dropwise over 5 min, and the mixture was allowed to slowly warm to −40 °C over 2 h before being quenched with 2 mL of saturated aqueous $NH_4Cl$ solution. After warming to room temperature the reaction mixture was partitioned between 30 mL of ether and 30 mL of aqueous 10% citric acid solution. The organic layer was separated and washed with aqueous 10% citric acid solution (3 × 30 mL) and saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to 1.11 g of a crude mixture of lactones **10** and **11**, which were separated on 88 g of silica gel with an ether–hexane (1:9 to 3:7) eluant. The fractions containing the less polar trans lactone **10** ($R_f$ 0.55 1:1 ether–hexane) were combined and evaporated to 0.613 g (51%) of a white solid, mp 132–135 °C. Minor impurities (as indicated by TLC) were removed by trituration in hexane to afford 0.562 g (47%) of analytically pure lactone **10**, mp 133–135 °C. Crystals suitable for X-ray analysis were prepared by slow evaporation from hexane–methylene chloride: $^1H$ NMR (250 MHz) $\delta$ 0.90 (3 H, d, $J$ = 6), 0.92 (3 H, d, $J$ = 6), 1.42 (9 H, s), 1.70 (3 H, s), 1.92–2.15 (2 H, m), 2.26–2.39 (1 H, m), 2.57 (1 H, dd, $J$ = 15 and 3), 2.72–2.88 (1 H, m), 3.77–3.90 (1 H, m), 4.34 (1 H, d, $J$ = 9), 4.33–4.51 (1 H, m), 4.70 (1 H, s), 4.81 (1 H, s); $^{13}C$ NMR (75 MHz) $\delta$ 21.8, 23.0, 24.7, 28.3, 30.0, 37.9, 39.5, 41.8, 51.7, 79.8, 80.7, 112.8, 141.9, 156.0, 179.3; IR($CHCl_3$) 3439, 1768, 1712, 1654 $cm^{-1}$; $[\alpha]_D$ −25.0 ($c$ 0.5, $CH_3OH$).

Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.47; H, 9.59; N, 4.27.

**Single-Crystal X-ray Analysis.** A representative crystal was surveyed and a 1-Å data set (maximum (sin $\theta$)/$\lambda$ = 0.5 was collected on a Nicolet R3m/$\mu$ diffractometer. The diffractometer was equipped with a graphite monochromator and copper radiation ($\lambda$ = 1.54178 Å). Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*.[20] All crystallographic calculations were facilitated by the SHELXTL[21] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table I.

A trial structure was obtained by direct methods. This trial structure refined routinely. Because the synthesis incorporated a portion of the molecule with known absolute configuration, the correct enantiomorph was assigned directly. Hydrogen positions were calculated wherever possible. The methyl and amide hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least-squares refinement were all less than 0.04 of their corresponding standard deviations. The final $R$ index was 0.080. A final difference Fourier revealed no missing or misplaced electron density.

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**Table I. Single-Crystal X-ray Crystallographic Analysis**

| | |
|---|---|
| A. Crystal Parameters | |
| formula | $C_{18}H_{30}NO_4$ (324.4) |
| crystallization medium | hexane/dichloromethane |
| crystal size, mm | 0.06 × 0.09 × 0.09 |
| cell dimensions | |
| a, Å | 11.2775 (8) |
| b, Å | 11.2775 (8) |
| c, Å | 27.646 (3) |
| α, deg | 90.0 |
| β, deg | 90.0 |
| γ, deg | 120.0 |
| ν, Å$^3$ | 3045 (1) |
| space group | $P6_1$ |
| molecules/unit cell | 6 |
| density | |
| obsd, g/cm$^3$ | 1.03 |
| calcd, g/cm$^3$ | 1.06 |
| linear absorption coefficient, cm$^{-1}$ | 5.66 |
| B. Refinement Parameters | |
| number of reflections | 2033 |
| nonzero reflections ($1 > 3.0\sigma$) | 1435 |
| $R$ index = $\sum\|\|F_o\| - \|F_c\|\|/\sum\|F_o\|$ | .080 |
| GOF = $[\sum w(F_o^2 - F_c^2)^2/(m-s)]^{1/2}$ | 1.40 |
| scale factor | 1.266 (5) |
| secondary extinction coefficient | 12 (5) × 10$^{-4}$ |

The refined structure was plotted using the SHELXTL plotting package (Figure 2). Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material (Tables S1-S5).

The fractions containing the more polar cis lactone **11** ($R_f$ 0.44 1:1 ether-hexane) were combined and evaporated to 39 mg (3%) of a white solid: mp 96-98 °C; $^1$H NMR (250 MHz) δ 0.92 (6 H, d, $J$ = 6), 1.43 (9 H, s), 1.72 (3 H, s), 2.02-2.14 (1 H, m) 2.23-2.36 (1 H, m), 2.60-2.87 (2 H, m), 3.74-3.89 (1 H, m), 4.35-4.47 (2 H, m), 4.69 (1 H, s), 4.78 (1 H, s); $^{13}$C NMR (75 MHz) δ 21.9, 22.0, 23.0, 24.8, 28.3, 30.7, 38.8, 38.9, 42.3, 50.1, 79.6, 80.4, 112.6, 142.0, 155.9, 178.7; IR ($CHCl_3$) 3443, 1774, 1714, 1656 cm$^{-1}$; $[\alpha]_D$ -0.6° ($c$ 0.5, $CH_3OH$).

Anal. Calcd for $C_{18}H_{31}NO_4$; C, 66.43; H, 9.60; N, 4.30. Found: C, 66.94; H, 9.45; N, 4.27.

**(3*R*,5*S*)-5-((1*S*)-1-(*N*-Boc-amino)-3-methylbutyl)-3-(2-methylpropyl)dihydrofuran-2(3*H*)-one (1).** An ethyl acetate (10 mL) solution of 438 mg (1.35 mmol) of lactone **10** containing 44 mg of 10% Pd/C was hydrogenated on a Parr Shaker apparatus at 50 psi for 2 h. After filtration of the catalyst and evaporation of the solvent, 437 mg (99%) of lactone **1** was obtained as a white solid: mp 130-131 °C; $^1$H NMR (300 MHz) δ 0.84-0.97 (12 H, m), 1.41 (9 H, s) 1.86-1.96 (1 H, m), 2.30-2.42 (1 H, m), 2.56-2.68 (1 H, m), 3.76-3.89 (1 H, m), 4.35 (1 H, d, $J$ = 8), 4.45 (1 H, br t); $^{13}$C NMR (75 Hz) δ 21.3, 21.8, 22.9, 23.0, 24.8, 26.1, 28.3, 31.0, 37.7, 40.5, 41.9, 51.7, 79.8, 80.5, 156.0, 180.3; IR ($CHCl_3$) 3439, 1769, 1713 cm$^{-1}$, [α] -32.1° ($c$ 1.0, $CH_3OH$).

Anal. Calcd for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16; N, 4.28. Found: C, 66.07; H, 10.03; N, 4.05.

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**Registry No.** **1**, 105018-80-2; **2**, 105018-81-3; **3**, 58521-45-2; (4*S*,5*S*)-**4**, 105018-82-4; (4*R*,5*S*)-**4**, 105018-89-1; **5**, 105018-83-5; **6**, 67010-44-0; **7**, 105018-84-6; **8**, 105018-85-7; **9**, 105018-86-8; **10**, 105018-87-9; **11**, 105018-88-0; *N*-Boc-L-leucine methyl ester, 63096-02-6; ethyl propiolate, 623-47-2; α-lithio ethyl acetate, 26954-26-7; 2-methoxypropene, 116-11-0; methallyl bromide, 1458-98-6.

**Supplementary Material Available:** Crystallographic data including tables of the atomic positional and thermal parameters and bond angles for **10** (4 pages). Ordering information is given on any current masthead page.

# Iodination of Aryltrimethylsilanes: A Mild Approach to Iodophenylalanine

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Phenylalanine has been labeled with the radioactive isotopes of iodine by using harsh conditions or toxic mercury compounds. A mild method of incorporating iodine onto an aryl ring was developed that combines two methods that have been used separately for the production of aryl iodides: (1) the use of a Lewis acid to activate the electrophile, $I_2$, and (2) the use of a trimethylsilyl group to direct the introduction of iodine. Simple aryltrimethylsilanes and a phenylalanine-containing peptide were successfully iodinated by this method.

The use of iodine-125-containing compounds for metabolic and radiolabeling studies is widespread.[1] The various iodophenylalanine isomers have been used for pancreatic imaging studies,[2] and other radioiodinated drugs have been studied to ascertain their accumulation in the various parts of the body.[3] The thyroid hormones, amphetamines, and the numerous corticosteroids have been investigated by using radioiodine derivatives.[1]

The methods for introducing iodine onto a phenyl ring are numerous and vary greatly.[1,2,4-8,13] Most of them re-

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