give the diastereomeric epoxide in 54% yield. Subsequent separation by centrifugal thin-layer chromatography (chromatotron) on a rotor coated with silica gel (2 mm thick) with 2.5–10% ethyl acetate in hexane resulted in three major fractions. The higher R_f fraction (0.03 g, 26% theoretical yield) was **13b**: mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.41 (s, 3 H), 2.71 (d, 1 H, J = 4.6 Hz), 2.82 (d, 1 H, J = 4.6 Hz), 3.07 (dd, 1 H, J = 7.6, 15.7 Hz), 3.23 (dd, 1 H, J = 9.9, 15.7 Hz), 4.83 (dd, 1 H, J = 7.6, 9.9 Hz), 6.41 (d, 1 H, J = 8.6 Hz), 7.76 (d, 1 H, J = 8.6 Hz); exact mass for $C_{12}H_{12}O_5$ (M^+), calcd 236.0685, found 236.0688. The middle fraction (0.03 g) was a mixture of the higher and lower R_f isomers. The lower R_f fraction (0.02 g, 17% of theoretical yield) was **13a**: ^{1}H NMR ($CDCl_3$, 470 MHz) δ 1.38 (s, 3 H), 2.7 (d, 1 H, J = 4.7 Hz), 2.94 (d, 1 H, J = 4.7 Hz), 3.11 (dd, 1 H, J = 7.4, 15.7 Hz), 3.30 (dd, 1 H, J = 9.9, 15.7), 4.78 (dd, 1 H, J = 7.4, 9.9 Hz), 6.40 (d, 1 H, J = 8.7 Hz), 7.76 (d, 1 H, J = 8.7 Hz); exact mass for $C_{12}H_{12}O_5$ (M^+), calcd 236.0685, found 236.0684.

3′,4′-Epoxyrotenone (11a,b). To a chloroform solution of **10** (19.72 g, 0.05 mol) was added *m*-chloroperoxybenzoic acid (17.3 g, 0.1 mol) in chloroform dropwise. The reaction was stirred at room temperature for 24 h and then worked up[13] to give a brown solid, 25.49 g. Separation on LPS-1 silica gel (1000 g) in a Michel–Miller column with 40% ethyl acetate in hexane gave **11b** as a yellow solid, 1.96 g (19% crude yield). Purification by trituration (ethanol and hexane) and recrystallization (methylene chloride and methanol) gave white needles: mp 179–181 °C; ^{1}H NMR ($CDCl_3$, 470 MHz), literature values; exact mass for $C_{23}H_{22}O_7$ (M^+), calcd 410.136, found 410.1350. Slow recrystallization from methanol at room temperature yielded the crystal for X-ray analysis.

Crystal Data: $C_{23}H_{22}O_7$, M = 410, orthorhombic, a = 4.536 (2) Å, b = 16.49 (2) Å, c = 25.31 (2) Å, V = 1894 (3) Å^3, Z = 4, ρ_{calcd} = 1.44 g/cm^3, $F(000)$ = 864, μ(Cu Kα) = 7.91, space group $P2_12_12_1$ from systematic absences.

Data Collection: The crystallographic data were collected by Cu Kα X-rays and a monochromator on a Syntex P3 four-circle diffractometer with the θ–2θ scan technique out to a 2θ of 116.0°. A variable scan rate was used with a maximum of 29.30°/min and a minimum of 7.32°/min. The scan range was from 1.2° less than $K\alpha_1$ to 1.2° more than $K\alpha_2$; the length of time the backgrounds at both ends of the scan range were counted was equivalent to the scan time. Three standard reflections were measured every 50 reflections. Of the 1578 reflections collected, 25 were rejected as systematically absent, leaving 1553 unique reflections, of which 915 met the condition $F_o > 5\sigma(F_o)$ and were considered observed. The structure was solved by the MULTAN80 program, and refined by SHELX76, giving a final R = 0.0703 with hydrogens fixed in calculated positions. A final difference map showed no peaks greater than 0.26 e/Å^3. Table VI (supplementary material) shows the final positional parameters.

All melting points are uncorrected and were obtained on a Laboratory Devices Mel-Temp apparatus. IR spectra were obtained in KBr on a Beckman IR-33 spectrophotometer. UV spectra were recorded, in the solvents indicated, on either a Cary 17 or Perkin-Elmer Coleman 124 double-beam spectrophotometer. Electron impact and chemical ionization mass spectra were obtained on a Finnigan Model 4023 mass spectrometer, and high-resolution accurate mass measurements were made on a Kratos MS 50 mass spectrometer. ^{1}H NMR spectra were obtained in the solvent indicated on either a Varian XL-200 or the Nicolet 470 MHz spectrometer at the Purdue University Biological Magnetic Resonance Laboratory. The P388 mouse leukemia assays were carried out at the Illinois Institute of Technology, Life Sciences Division.

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Supplementary Material Available: Tables III–VII listing bond lengths, bond angles, torsion angles, and positional and thermal parameters of epoxyrotenone (5 pages). Ordering information is given on any current masthead page.

A Method for the Preparation of Stereochemically Defined ψ[CH_2O] Pseudodipeptides[1]

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A short, stereochemically defined synthesis of (2*S*,5*S*)-ψ[CH_2O] pseudodipeptides (**7a, 7b, 10**) using commercially available, chiral amino acids has been developed. The key step of the synthesis is the intramolecular S_N2 displacement of bromine with alkoxide to give 1,4-oxazin-2-ones (**6a, 6b, 9**) that are subsequently hydrolyzed to the desired ψ[CH_2O] pseudodipeptides.

The development of peptides as potential therapeutic agents is an area of intense interest to many organic chemists.[2] A primary drawback to the use of many synthetic peptides is their rapid degradation in vivo by numerous peptidases.[3] One approach to avoiding the rapid hydrolysis of the peptide bond is to substitute nonhydrolyzable bonds for the peptide amide bond.[4] The subject of peptide backbone modifications has recently been reviewed extensively by Spatola.[5] Absent from this discussion, however, are ψ[CH_2O] pseudodipeptides. Only brief mention in the literature (with no experimental de-

(1) The ψ nomenclature has been accepted by IUPAC for peptide amide bond replacements. The unit inside the bracket following ψ is the unit substituting for the peptide amide (–CONH–) bond. IUPAC–IUB Joint Commission on Biochemical Nomenclature *Eur. J. Biochem.* **1984**, *138*, 9.

(2) For general discussions, see, for example: (a) Kaiser, E. T.; Kezdy, F. J. *Science (Washington, D.C.*, 1883–) **1984**, *223*, 246. (b) Farmer, P. S. In *Drug Design*; Ariëns, E. J., Ed.; Academic: New York, 1980; Vol. X, pp 119–143. (c) Freidinger, R. M.; Veber, D. F. *J. Am. Chem. Soc.* **1979**, *101*, 6129. (d) Szelke, M.; Hudson, D.; Sharpe, R.; Mac Intyre, I.; Fink, J.; Pickering, A. M. C. In *Molecular Endocrinology*; Mac Intyre, I., Szelke, M., Eds.; Elsevier/North-Holland Biomedical: Amsterdam, 1977; pp 57–70.

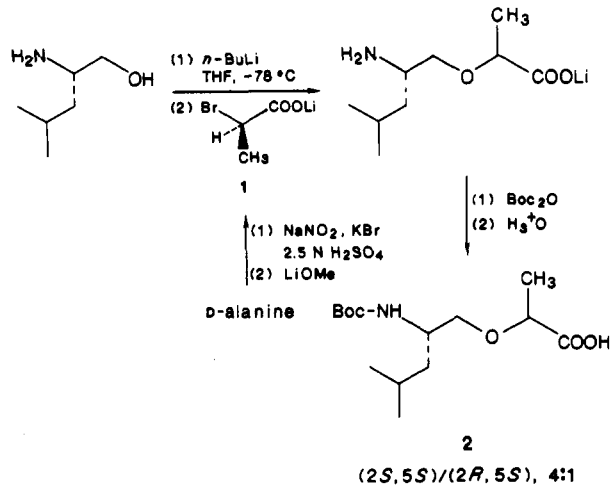
(3) Wiedhup, K. In *Topics in Pharmaceutical Sciences*; Briemer, D. D., Speiser, P., Eds.; Elsevier/North-Holland Biomedical: Amsterdam, 1981; pp 307–324.

(4) (a) Reference 2 (d). (b) Reference 5 and references cited therein. (c) Martinez, J.; Bali, J.-P.; Rodriguez, M.; Castro, B.; Magous, R.; Laur, J.; Lignon, M.-F. *J. Med. Chem.* **1985**, *28*, 1874.

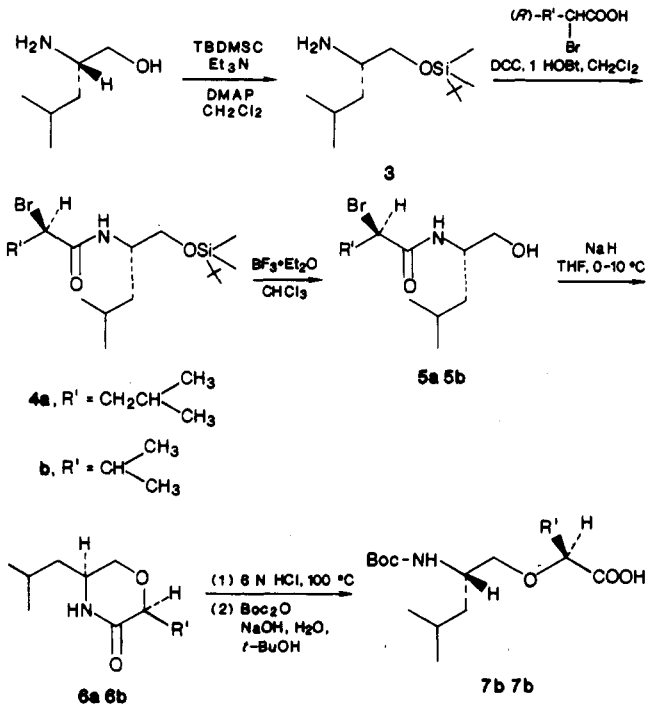
(5) Spatola, A. In Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins; Weinstein, B., Ed.; Dekker: New York, 1983; Vol. 7, pp 267–357.

0022-3263/87/1952-0418$01.50/0

Scheme I



Scheme II



tail) is made of ψ[CH_2O] substitutions, perhaps due to synthetic limitations of the method wherein only Xψ-[CH_2O]Gly and Xψ[CH_2O]Ala (where X is an amino acid) can be prepared.[6] Subsequent to the preparation of this manuscript, a method using essentially the same synthetic strategy has appeared.[11] Presented here is a method for the preparation of certain ψ[CH_2O] pseudodipeptides of defined stereochemistry which is not limited to unhindered (Gly,Ala) amino acids.

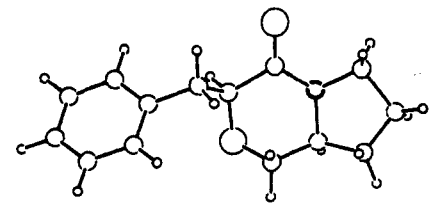
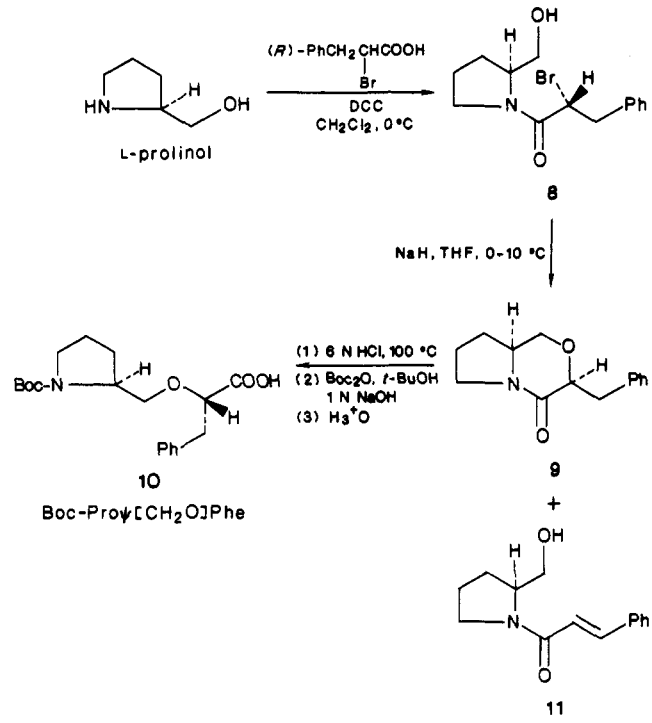


Figure 1. X-ray plot of **9**.

Scheme III



Results and Discussion

Our first attempts to prepare ψ[CH_2O] pseudodipeptides involved the direct displacement of α-bromo acids or esters with alkoxides (Scheme I). However, this method worked only with the simplest, unhindered cases of lithio 2-chloroacetate or lithio 2-bromopropanoate. The preparation of (*R*)-2-bromo acids ($NaNO_2$, KBr, 2.5 N H_2SO_4) from D-amino acids usually occurs with double inversion to give overall retention of configuration. The lithium salt of (*R*)-2-bromopropanoic acid,[7] prepared from D-alanine, is reacted with leucinol alkoxide and protected as the *t*-Boc derivative to give a 4:1 mixture of Boc-Leuψ[CH_2O]Ala-OH and Boc-Leuψ[CH_2O]-D-Ala-OH. The source of the 2*R*,5*S* diastereomer may be the forcing conditions (basic, room temperature to 60 °C) needed to accomplish the displacement.

Attempts to prepare Boc-Leuψ[CH_2O]Val-OH, Boc-Leuψ[CH_2O]Leu-OH, and Boc-Proψ[CH_2O]Phe-OH by this method failed and led us to develop the more general method shown in Scheme II. L-Leucinol, protected as the *tert*-butyldimethylsilyl ether **3**, is coupled with (*R*)-2-bromo-3-methylbutanoic acid and (*R*)-2-bromo-4-methylpentanoic acid (DCC, 1-HOBt, CH_2Cl_2)[8] to give **4b** and **4a**, respectively. The silyl protecting group is removed with BF_3·Et_2O, and the alkoxide is generated with NaH in THF. Best results are obtained if the alkoxide is generated at about −20 °C and the reaction mixture is slowly warmed. Ring formation, with inversion of stereochemistry at C-2, occurs at 0–10 °C to give **6a** and **6b**. Hydrolysis of the lactam with 6 N HCl, followed by protection of the amino group with *tert*-butoxycarbonyl (Boc), gives Boc-

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(10) Acton, N.; Komoriya, A. *Org. Prep. Proced. Int.* **1982**, *14*, 381.
(11) Nicolaides, E. D.; Tinney, F. J.; Kaltenbronn, J. S.; Repine, J. T.; DiJohn, D. A.; Lunney, E. A.; Roark, W. H.; Marriott, J. G.; Davis, R. E.; Voightmann, R. E. *J. Med. Chem.* **1986**, *29*, 959.

Leuψ[CH_2O]Leu-OH (**7a**) and Boc-Leuψ[CH_2O]Val-OH (**7b**).

The preparation of Boc-Proψ[CH_2O]Phe-OH (Scheme III) follows that of Boc-Leuψ[CH_2O]Leu-OH and Boc-Leuψ[CH_2O]Val-OH. L-Prolinol is coupled with (*R*)-2-bromo-3-phenylpropanoic acid (DCC, CH_2Cl_2) to give **8**. Generation of the alkoxide with NaH in THF gives the bicyclic oxa lactam **9** in 74% yield with 15–20% of the dehydrohalogenated byproduct **11**. The X-ray structure of **9** (Figure 1) confirms the *S,S* stereochemistry of the bicyclic intermediate. Hydrolysis of **9** and amine protection gives Boc-Proψ[CH_2O]Phe-OH (**10**). In no case (**7a**, **7b**, **10**) was any racemized product seen by NMR or HPLC.

An attempt to prepare Boc-Pheψ[CH_2O]Phe-OH by this method led almost exclusively to the dehydrohalogenated product. That this is the major product in this case is due to a combination of the lack of conformational organization in the phenylalanine moiety (which is present in the proline moiety of Scheme III), coupled with the ease of formation of the conjugated dehydrohalogenated product.

Models show that the 2*S*,5*S* cyclic product (**9**) would be expected to form readily via S_N2 displacement of bromine from the 2*R*,5*S* acyclic precursor whereas the 2*R*,5*S* cyclic product would not be formed readily from the 2*S*,5*S* acyclic precursor. Indeed, an attempt to prepare Boc-Pheψ[CH_2O]-D-Phe via the cyclization route of Scheme III using L-prolinol and (*S*)-2-bromo-3-phenylpropionic acid gave only unreacted starting material and dehydrohalogenated byproduct after prolonged stirring at room temperature. Thus any contamination of the acyclic precursor **8** with the *S*-bromo diastereomer leads only to nonproductive byproducts in the cyclization step.

A comparison was made via reverse-phase HPLC (acetonitrile–water, phosphate pH 3 buffer) of the relative mobilities of Boc-Proψ[CH_2O]Phe-OH and Boc-Pro-Phe-OH. Boc-Proψ[CH_2O]Phe-OH had a k' of 11.5 and Boc-Pro-Phe-OH had a k' of 4.7, thus demonstrating that as judged by relative reverse-phase mobilities, the ψ[CH_2O] derivative is considerably more lipophilic than the parent dipeptide.

In summary, we have demonstrated the synthesis of several hindered and unhindered ψ[CH_2O] pseudodipeptides using commercially available amino acids and their derivatives. The compounds obtained are single diastereomers of known configuration which should be of general use in the preparation of semisynthetic peptides.

Experimental Section

General Remarks. L-Prolinol, L-leucinol, D-leucine, and D-valine were obtained from Sigma Chemical Co.[9] D-Phenylalanine was obtained from U.S. Biochemical Corp. and L-phenylalanine was obtained from ICN Nutritional Biochemicals. 1,3-Dicyclohexylcarbodiimide (DCC), *tert*-butyldimethylsilyl chloride (TBDMSC), and 4-(dimethylamino)pyridine (DMAP) were obtained from Aldrich. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) (stored over 4-Å molecular sieves) were Burdick and Jackson distilled in glass and were used without further purification. 1-Hydroxybenzotriazole (1-HOBt) was obtained from Sigma. DCU is dicyclohexylurea. Boc_2O is di-*tert*-butyl dicarbonate (Fluka). Yields are unoptimized.

Mass spectra, elemental analyses, and optical rotations were performed by the Physical and Analytical Chemistry Department of The Upjohn Co. ^1H NMR spectra were obtained on a Varian Model CFT-20 FT spectrometer operated at 80 MHz with tetramethylsilane as an internal standard. Chromatographies were done on E. Merck silica gel 60 with Burdick and Jackson solvents. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

(*R*)-2-Bromopropionic Acid, Lithium Salt (1). To 5.00 g (0.0327 mol) of (*R*)-2-bromopropionic acid[7] in 150 mL of THF at −78 °C was added 0.0327 mol of 1.6 M *n*-BuLi. Solvent was then removed and ether was added to the residue. The resulting solid was collected, washed with ether, dried, and used in the next step without further purification.

Boc-Leuψ[CH_2O]Ala-OH (2). To 2.00 g (0.01706 mol) of L-leucinol in 100 mL of THF at −78 °C was added (slowly) 10.7 mL (0.0171 mol) of 1.6 M *n*-BuLi in hexane. After stirring for 10 min, 3.25 g (0.0205 mol) of (*R*)-lithium 2-bromopropionate (1) was added, and the reaction was allowed to warm to room temperature. After 18 h, the reaction mixture was heated at 60 °C for 3 h and then cooled. The solvent was removed in vacuo, and ether was added to solidify the residue. Ether was decanted, and the solid was dissolved in water and extracted with ethyl acetate. The aqueous solution was then stirred with 3.7 g (0.017 mol) of Boc_2O and 50 mL of *t*-BuOH overnight. *t*-BuOH was then removed in vacuo, and the aqueous layer was washed with pentane. The aqueous layer was then acidified with 3 N HCl and extracted with CH_2Cl_2. The organic layer was filtered through Na_2SO_4 and taken to dryness. The crude product was chromatographed on silica gel using 3% MeOH/CH_2Cl_2 (0.1% HOAc) to give 2.02 g (41% overall) of **2**. HPLC [LiChrosorb C_{18}, 37% CH_3CN (0.2% TFA)/63% H_2O (0.2% TFA), 229 nM] indicates a 4:1 ratio of diastereomers: MS, *m/z* 289; ^1H NMR ($CDCl_3$) δ 0.92 (d, 6 H), 1.12–1.70 (m, 6 H), 1.45 (s, 9 H), 3.5 (m, 2 H), 3.8 (br m, 1 H), 4.00 (q, 1 H), 4.7 (br m, 1 H), 8.40 (br s, 1 H). Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.10; H, 9.41; N, 4.84. Found: C, 58.19; H, 9.39; N, 4.69.

A sample of **2** ($[\alpha]_D$ −53° (*c* 1.01, EtOH)) prepared by the method of Scheme II gave a single peak on reverse-phase HPLC (acetonitrile–water, phosphate pH 3 buffer). This peak corresponded to the major isomer of **2** prepared by the route of Scheme I.

***O*-(*tert*-Butyldimethylsilyl)-L-leucinol (3).** To an ice-cooled solution of L-leucinol (3.67 g, 0.0313 mol), Et_3N (3.80 g, 0.0375 mol), and 4-dimethylaminopyridine (0.15 g, 0.0012 mol) in 30 mL of CH_2Cl_2 was added *tert*-butyldimethylsilyl chloride (5.19 g, 0.0344 mol). After stirring overnight, the precipitated Et_3N·HCl was filtered off, and the filtrate was extracted with water and aqueous NH_4Cl. The organic layers were filtered through Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed on a short column of silica gel using 4% MeOH/CH_2Cl_2 as eluant to give 6.76 g (93%) of **3** (clear liquid): $[\alpha]_D$ +1.9° (*c* 0.914, CH_2Cl_2); MS, CI (NH_3), *m/z* 249; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 0.88–0.95 (m, 6 H), 1.15 (t, 2 H), 1.45 (s, 2 H), 1.70 (m, 1 H), 2.85 (m, 1 H), 3.15–3.65 (m, 2 H).

***N*-[2(*R*)-Bromo-4-methylpentanoyl]-*O*-(*tert*-butyldimethylsilyl)-L-leucinol (4a).** A mixture of 2.86 g (0.01466 mol) of (*R*)-2-bromo-4-methylpentanoic acid[7] and 2.24 g (0.01466 mol) of 1-HOBt was stirred in CH_2Cl_2 at 0 °C. To this was added 3.02 g (0.01466 mol) of DCC. Stirring was continued at 0 °C for 1 1/2 h, at which time the mixture was added to 3.23 g (0.014 mol) of **3** in CH_2Cl_2 cooled to 0 °C. After 2 h, the mixture was concentrated, and DCU was filtered off and discarded. The filtrate was extracted with aqueous $NaHCO_3$ (2×), 0.5 M citric acid (1×), and brine. The organic layers were filtered through Na_2SO_4 and taken to dryness. Ethyl acetate was added to the residue, and DCU was again filtered off. The crude product was chromatographed on silica gel with 5% ethyl acetate/hexane to give 3.26 g (57%) of crystalline **4a**, mp 74.5–75.5 °C; $[\alpha]_D$ −12.2° (*c* 0.9445, CH_2Cl_2); MS, *m/z* 408; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.92 (s, 9 H), 0.85–1.00 (m, 12 H), 2.35 (m, 4 H), 1.80 (m, 2 H), 3.59 (d, 2 H), 4.0 (br m, 1 H), 4.30 (m, 1 H), 6.45 (br d, 1 H). Anal. Calcd for $C_{18}H_{38}BrNO_2Si$: C, 52.92; H, 9.38; N, 3.43. Found: C, 53.18; H, 9.37; N, 3.81.

***N*-[2(*R*)-Bromo-4-methylpentanoyl]-L-leucinol (5a).** A solution of 1.03 g (0.00252 mol) of silyl ether **4a** in 20 mL of chloroform was cooled to 0 °C. To this was added 0.34 mL (0.00277 mol) of BF_3·Et_2O. After 5 min the ice bath was removed, and the solution was allowed to warm to room temperature. After 1 1/2 h an additional 0.34 mL of BF_3·Et_2O was added. The reaction was stirred for 1 h, after which it was extracted with H_2O and saturated aqueous $NaHCO_3$ (2×). The organic layers were filtered through Na_2SO_4, and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using 4% MeOH/CH_2Cl_2 as eluant to give 0.66 g (89%) of crystalline **5a**, mp 57–58 °C: $[\alpha]_D$ +8.7° (*c* 0.859, CH_2Cl_2); MS, *m/z* at 262

(–CH_2OH); ^1H NMR ($CDCl_3$) δ 0.89–1.00 (m, 12 H) 1.31–2.05 (m, 6 H), 2.40 (br t, 1 H), 3.61 (m, 2 H), 4.00 (m, 1 H), 4.31 (m, 1 H), 6.37 (br d, 1 H). Anal. Calcd for $C_{12}H_{24}BrNO_2$: C, 48.98; H, 8.22; N, 4.76. Found: C, 49.13; H, 8.36; N, 4.63.

(2*S*,5*S*)-2,5-Diisobutyl-1,4-oxazin-3-one (6a). NaH (0.34 g, 0.00709 mol, 50% in oil) was washed 3 times with hexane to remove oil. To the NaH was added 5 mL of THF. The suspension was cooled at –25 °C (MeOH–ice). To the NaH suspension was added 1.98 g (0.006755 mol) of **5a** in 25 mL of THF which had been precooled to –25 °C. To this was added (slowly) 30 mL of THF. After 10 min, the MeOH–ice bath was replaced with an ice–H_2O bath. After stirring for 1 h (allowed to warm slowly), the reaction was extracted with water and brine. The organic layers were filtered through Na_2SO_4 and taken to dryness. The crude product was filtered through a short silica gel column (4% MeOH/CH_2Cl_2) to give 1.39 g of **6a**. The product was recrystallized from ether–hexane to give 1.28 g (89%) of **6a**: mp 108.5–110.0 °C $[\alpha]_D$ –78.0° (*c* 0.924, CH_2Cl_2); MS, *m/z* 213; ^1H NMR ($CDCl_3$) δ 0.94 (m, 12 H), 1.30–2.80 (m, 6 H), 3.48 (m, 1 H), 3.71 (m, 2 H), 4.10 (m, 1 H), 5.98 (br, 1 H). Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57. Found: C, 67.32; H, 11.23; N, 6.59.

Boc-Leuψ[CH_2O]Leu-OH (7a). One gram (0.00469 mol) of **6a** and 25 mL of 6 N HCl were heated at 100 °C for 19 h and then cooled and concentrated on the roto vap. Ether was added to the wet solid. The solid was collected (0.82 g) and washed with ether.

The solid was dissolved in 2 mL of water and the pH was adjusted to 8–10 with 1 N NaOH. To this was added 10 mL of *t*-BuOH and 0.63 g of Boc_2O. The pH was kept at 8–9 with the addition of 1 N NaOH as needed. In the same manner, the Et_2O–H_2O filtrate was treated with aqueous NaOH, *t*-BuOH, and Boc_2O (0.50 g). After the mixture had been stirred overnight, *t*-BuOH was removed from the reactions in vacuo, and the aqueous residue was washed once with pentane. The aqueous layers were acidified with 3 N HCl and extracted with CH_2Cl_2. The organic layers were filtered through Na_2SO_4 and taken to dryness. The crude product was chromatographed on silica gel eluting with a gradient of 100% CH_2Cl_2 to 4% MeOH/CH_2Cl_2 to give, in total, 0.93 g (60% overall) of **7a**: $[\alpha]_D$ –62.6° (*c* 0.7695, EtOH); MS [m + H]$^+$, *m/z* 332; ^1H NMR ($CDCl_3$) δ 0.92 (d, 12 H), 1.44 (s, 9 H), 1.20–1.70 (m, 6 H), 3.48 (m, 2 H), 3.90 (m, 2 H), 4.78 (br, 1 H), 5.25 (br, 1 H). Anal. Calcd for $C_{17}H_{33}NO_5$: C, 61.60; H, 10.03; N, 4.23. Found: C, 61.62; H, 10.13; N, 4.34.

***N*-[2(*R*)-Bromo-3-methylbutanoyl]-*O*-(*tert*-butyldimethylsilyl)-L-leucinol (4b).** A mixture of 1.84 g (0.0102 mol) of (*R*)-2-bromo-3-methylbutanoic acid[7] and 1.55 g (0.0102 mol) of 1-HOBt was stirred at 0 °C in CH_2Cl_2. DCC (2.10 g, 0.0102 mol) was added, and the mixture was stirred for 30 min. After 30 min, an ice-cooled CH_2Cl_2 solution of **3** (2.35 g, 0.0102 mol) was added. The reaction was stirred for an additional hour, after which the precipitated DCU was filtered off. The filtrate was extracted with saturated aqueous $NaHCO_3$. The organic layers were filtered through Na_2SO_4, and the solvent was removed in vacuo. The crude product was chromatographed on silica gel with 5% ethyl acetate/hexane as eluant to give 3.69 g (92%) of crystalline **4b**: mp 97–98 °C; $[\alpha]_D$ –22.4° (*c* 0.915, CH_2Cl_2); MS, *m/z*, 393, 395 (EI), 411, 413 (CI, NH_3); ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 0.90–1.10 (m, 12 H), 1.25–1.67 (m, 3 H), 2.35 (br m, 1 H), 3.59 (d, 2 H), 3.95 (br m, 1 H), 4.32 (d, 1 H), 6.12 (br d, 1 H). Anal. Calcd for $C_{17}H_{36}BrNO_2Si$: C, 51.76; H, 9.20; N, 3.55. Found: C, 51.68; H, 9.15; N, 3.57.

***N*-[2(*R*)-Bromo-3-methylbutanoyl]-L-leucinol (5b).** To an ice-cooled solution of 3.62 g (0.00918 mol) of silyl ether (**4b**) in 100 mL of chloroform was added 2.31 mL (0.0188 mol) of BF_3·Et_2O. After 20 min, the ice bath was removed. The reaction was stirred an additional 100 min and was then extracted with water, saturated aqueous $NaHCO_3$, and brine. The organic layers were filtered through Na_2SO_4, and the solvent was removed in vacuo. The solid product was recrystallized from ether–hexane to give (in two crops) 2.41 g (94%) of **5b**: mp 98–99 °C; $[\alpha]_D$ –4.4° (*c* 0.786, CH_2Cl_2); MS, *m/z* 279, 281; ^1H NMR ($CDCl_3$) δ 0.96 (m, 12 H), 1.30–1.85 (m, 3 H), 2.35 (m, 2 H), 3.64 (m, 2 H), 4.03 (br m, 1 H), 4.32 (d, 1 H), 6.52 (br d, 1 H). Anal. Calcd for $C_{11}H_{22}BrNO_2$: C, 47.14; H, 7.92; N, 5.00. Found: C, 47.21; H, 8.02; N, 4.93.

(2*S*,5*S*)-2-Isopropyl-5-isobutyl-1,4-oxazin-2-one (6b). The cyclic lactam **6b** was prepared in the same manner as **6a** by using 0.50 g (0.00178 mol) of the alcohol **5b** and 0.094 g (0.00196 mol) of 50% NaH in oil. Obtained was 0.16 g (45%) of **6b**: mp 79–81 °C; $[\alpha]_D$ –96.0° (*c* 0.971, CH_2Cl_2); MS, *m/z* 199; ^1H NMR ($CDCl_3$) δ 1.02 (dd, 12 H), 1.25–2.85 (m, 3 H), 2.42 (m, 1 H), 3.35 (br m, 1 H), 3.76 (d, 2 H), 3.93 (d, 1 H), 6.86 (br d, 1 H). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 65.87; H, 10.59; N, 6.93.

Boc-Leuψ[CH_2O]Val-OH (7b). A mixture of 0.44 g (0.0022 mol) of **6b** and 2.5 mL of 6 N HCl was heated at 100 °C for 16 h and then allowed to cool slowly. The aqueous solution was washed once with hexane, and the aqueous layer was taken to dryness in vacuo. TLC (50% ethyl acetate/hexane) indicated that a significant amount of starting material remained. The hexane wash was returned to the flask, and hexane was removed in vacuo. The residue was heated for an additional 10 h with 6 N HCl, cooled, and taken to dryness with a toluene azeotrope to give the amino acid hydrochloride salt as a gum.

The amino acid hydrochloride salt (crude, from above) was treated with 0.48 g of Boc_2O, 4 mL of 1 N NaOH, and 5 mL of *t*-BuOH. After 5 1/2 h the *t*-BuOH was removed in vacuo, and the residue was extracted with ethyl acetate and 3 N HCl, followed by a brine wash. The organic layers were filtered through Na_2SO_4 and taken to dryness in vacuo. The crude material was chromatographed on silica gel first with a gradient of 100% CH_2Cl_2 to 4% MeOH/CH_2Cl_2 and a second time with 3% MeOH/CH_2Cl_2 (0.2% HOAc) as eluant to give 0.42 g (60% for both steps) of **7b** as a gum; $[\alpha]_D$ –57.4° (*c* 0.716, EtOH); MS, *m/z* 317; ^1H NMR ($CDCl_3$) δ 0.95 (m, 12 H), 1.28 (m, 2 H), 1.44 (s, 9 H), 1.66 (br m, 1 H), 2.05 (br m, 1 H), 3.45 (m, 2 H), 3.66 (d, 1 H), 3.77 (br m, 1 H), 4.60 (br m, 1 H), 6.5 (br, 1 H). Anal. Calcd for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41. Found: C, 60.18; H, 9.78; N, 4.41.

***N*-[2(*R*)-Bromo-3-phenylpropionyl]-L-proline (8).** To a CH_2Cl_2 solution of 12.5 g (0.055 mol) of (*R*)-2-bromo-3-phenylpropionic acid[10] cooled at 0 °C was added 11.3 g (0.055 mol) DCC. After stirring for 15 min, the mixture was added to a solution of 5.50 g (0.055 mol) of L-proline in CH_2Cl_2 at 0 °C. The reaction was stored overnight in the refrigerator, after which DCU was filtered off and discarded. The filtrate was extracted with 0.5 M citric acid (1×) and saturated aqueous $NaHCO_3$ (2×). The organic layers were filtered through Na_2SO_4 and concentrated. DCU was again filtered off, and the residue was chromatographed on silica gel, eluting with 4% MeOH/CH_2Cl_2. DCU coelutes with many of the product fractions. Mixed fractions were rechromatographed to give 5.87 g (69%) of **8**. $[\alpha]_D$ –83.8 (*c* 0.956, EtOH); MS, *m/z* at 312, 314; ^1H NMR ($CDCl_3$) δ 1.78 (m, 5 H), 3.05–3.72 (m, 6 H), 4.07 (br m, 1 H), 4.18 (m, 1 H), 4.51 (dd, 1 H), 4.92 (t), 7.26 (s, 5 H). Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.85; H, 5.81; N, 4.49. Found: C, 53.98; H, 5.98; N, 4.54.

(3*S*,6*S*)-2-Oxo-3-(phenylmethyl)-1-aza-4-oxabicyclo[4.3.0]nonane (9). A suspension of 0.048 g (0.001 mol) of 50% NaH (in oil) in THF was cooled at 0 °C. To this was added 0.31 g (0.001 mol) of **8** dissolved in THF (precooled at 0 °C). After 1 h, the ice bath was removed, and the reaction was allowed to warm slowly for an additional 2 h. Water was then added to the reaction, and the solvent was removed in vacuo. The residue was extracted with CH_2Cl_2 and 1 M citric acid, H_2O, and brine. The organic layers were filtered through Na_2SO_4 and then taken to dryness. The crude product was chromatographed on silica gel using 4% MeOH/CH_2Cl_2 to give 0.17 g (74%) of **13**. The product was crystallized from ether/hexane to give 0.13 g of a colorless solid: mp 92–93 °C; $[\alpha]_D$ –166° (*c* 0.734, EtOH); MS, *m/z* 231, most intense ions 231 (9999), 201 (3669), 70 (2241), 232 (1583), 91 (1519), 112 (806), 131 (705), 132 (705), 202 (600); ^1H NMR ($CDCl_3$) δ 1.9 (m, 4 H), 3.0–4.1 (m, 7 H), 4.42 (dd, 1 H), 7.30 (s, 5 H). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.40; H, 7.55; N, 6.07.

Boc-Proψ[CH_2O]Phe-OH (10). A mixture of 3.14 g (0.0316 mol) of **9** and 30 mL of 6 N HCl was heated at 100 °C for 10 h, allowed to cool (overnight), and heated again at 100 °C for 1 h. After cooling, the aqueous solution was washed twice with ethyl acetate. The aqueous layer was made basic with 50% NaOH and was stirred with 2.96 g (0.0136 mol) of di-*tert*-butyl dicarbonate (Boc_2O) and *t*-BuOH. After 2 1/4 h, *t*-BuOH was removed in vacuo, and the residue was diluted further with water and ex-

tracted with hexane. (An oily layer, which is probably product, develops.) The hexane layer was backwashed with 1 N NaOH, and the aqueous layers were combined. After acidification (3 N HCl), the aqueous mixture was extracted with ethyl acetate (3×), and the organic layers were filtered through Na_2SO_4. The solvent was removed in vacuo, and the residue was chromatographed on silica gel using a gradient of 100% CH_2Cl_2 to 4% MeOH/CH_2Cl_2 to give 4.13 g (87%) of **10** as a gum: $[\alpha]_D$ −65.9° (*c* 0.9075, EtOH); MS, *m/z* at 349, most intense ions 114, (9999), 70 (7771), 57 (4699), 170 (3531); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.73 (m, 4 H), 2.95–3.47 (m, 6 H), 3.85 (br m, 1 H), 4.11 (dd, 1 H), 6.20 (br, 1 H), 7.25 (s, 5 H). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.20; H, 7.70; N, 3.98.

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Synthesis of Functionalized Styrenes via Palladium-Catalyzed Coupling of Aryl Bromides with Vinyl Tin Reagents

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Highly functionalized styrene derivatives have been synthesized in a single step by the palladium-catalyzed coupling of aryl bromides with tributylethenylstannane. Aryl bromides substituted with electron-withdrawing groups couple rapidly under the reaction conditions while bromides containing electron-donating substituents require further addition of catalyst for complete conversion. 1,4-Dibromobenzene can be coupled in a highly selective fashion with either 1 or 2 equiv of tin reagent to give 4-bromostyrene or diethenylbenzene, respectively.

The recent interest in specialty polymers, particularly in the areas of polymer-bound reagents and catalysts, has created a need for the preparation of styrene monomers or intermediates that contain sensitive functionality on the aromatic ring.[1] Most of the traditional methods for the preparation of styrene derivatives use strong acidic or basic conditions. With many reactive functional groups, these methods would require protection and deprotection steps in order to avoid destruction of the sensitive group.

Transition-metal-catalyzed vinylation reactions have been exploited for the preparation of many styrene derivatives.[2-6] Although most of these methods proceed under neutral reaction conditions, undesirable side reactions are observed in many cases.

The cross coupling of organotin reagents with various electrophiles in the presence of catalytic quantities of palladium has been demonstrated to be a highly efficient method[7] for the preparation of a wide variety of organic compounds. The reaction proceeds under neutral conditions, is generally not particularly sensitive to water or oxygen, and possesses a high degree of selectivity with respect to organic group transfer from unsymmetrical tin reagents. This paper discusses the application of this coupling method to the synthesis of styrene derivatives from the corresponding aryl bromides.[8,9]

$$\underset{}{\mathrm{ArBr}} + \underset{\mathbf{1}}{\mathrm{CH_2{=}CHSnBu_3}} \xrightarrow{\mathrm{Pd}} \mathrm{ArCH{=}CH_2}$$

Table I. Conditions and Percent Conversion for the Coupling of 4-Bromoacetophenone and 1[a]

solvent	catalyst (2 mol %)	temp, °C	% conversion
DMF	$PdCl_2(PPh_3)_2$	24	10
THF	$PdCl_2(PPh_3)_2$	60	50
toluene	$Pd(PPh_3)_4$	110	100

[a] Reactions were carried out until no further conversion was observed by GLC.

Results and Discussion

A number of reaction conditions were tried in order to optimize the conversion to coupled product (Table I). The best conversion was obtained by using $Pd(PPh_3)_4$ catalyst in toluene at reflux. The organotin bromide byproduct was removed by reaction with a pyridinium fluoride solution,[10,11] followed by flash chromatography, which removed residual tin.

The method has been extended to a number of aromatic bromide substrates (Table II). From a synthetic standpoint, the yields obtained are quite good, and in most cases the reaction proceeds rapidly to completion. No significant

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(11) Nearly complete tributyltin bromide removal can be accomplished by pyridinium fluoride treatment followed by washing with a 1:1 NH_4OH/H_2O solution during workup.

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