Formal, Stereoselective Synthesis of Hydroxyethylene Dipeptide Isosteres Utilizing Pseudoephedrine Amides

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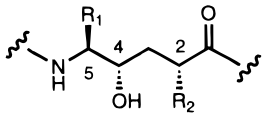
(2*R*,4*S*,5*S*)-Hydroxyethylene dipeptide isosteres (**1**) are frequently utilized in the synthesis of nonpeptidic enzyme inhibitors and many methods for their preparation have been developed.[1] One such method involves conversion



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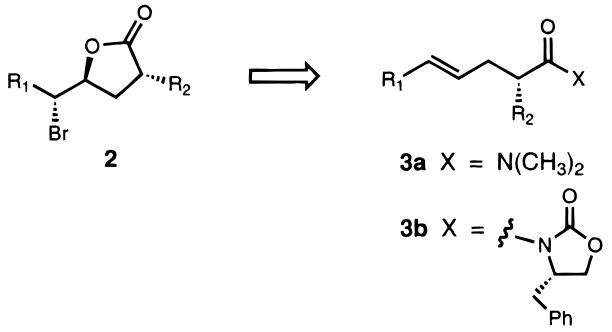
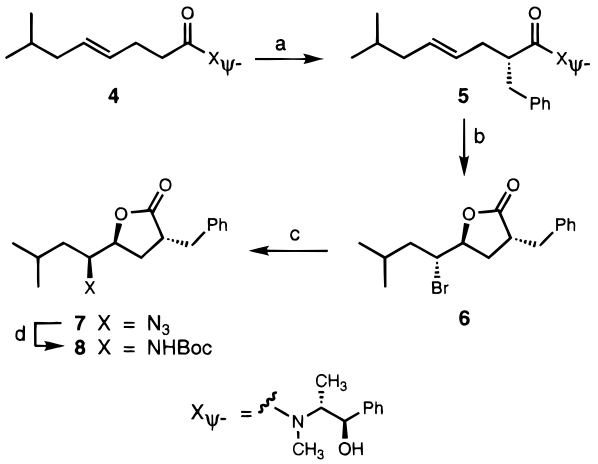
of appropriately substituted bromo γ-lactones (**2**) to the desired isosteres. The lactones, in turn, have previously been synthesized from enantiomerically enriched γ,δ-unsaturated dimethylamides (**3a**) or acyloxazolidinones (**3b**).[2,3] Herein we report that optically active bromo γ-lactone precursors of (2*R*,4*S*,5*S*)-hydroxyethylene dipeptide isosteres can also be conveniently prepared from diastereomerically pure γ,δ-unsaturated pseudoephedrine amides. This method offers several potential advantages over the previously reported syntheses of such compounds.



2 **3a** X = $N(CH_3)_2$ **3b** X =

The following example illustrates the new procedure (Scheme 1). Coupling of (1*R*,2*R*)-(−)-pseudoephedrine

Scheme 1[a]



[a] Reagents and conditions: (a) 2.1 equiv of LDA, 7.0 equiv of LiCl, THF, −78 → 0 °C, 1 h, then 1.5 equiv of BnBr, 0 °C, 30 min, 76%; (b) 1.1 equiv of NBS, 5.0 equiv of AcOH, 4:1 THF:H_2O, 0 °C, 15 min, then reflux 1 h, 65%; (c) 2.0 equiv of NaN_3, DMF, 50 °C, 20 h, 52%; (d) H_2, Pd/C, CH_3OH, 23 °C, 2 h, then 2.0 equiv of (*i*-Pr)$_2$NEt, 1.5 equiv of (Boc)$_2$O, 1,4-dioxane, 23 °C, 2 h, 62%.

with the acid chloride derived from *trans*-7-methyloct-4-enoic acid[4] provided the corresponding *N*-acylated product **4** (93%) in accordance with literature precedent.[5] Alkylation of the dianion of **4** with benzyl bromide in the presence of excess lithium chloride afforded benzylated product **5** in 76% yield and 98% de after purification on silica gel.[5,6] Treatment of **5** in a mixture of THF:H_2O (4:1) containing acetic acid (5 equiv) at 0 °C with a slight excess of *N*-bromosuccinimide followed by reflux for 1 h provided bromo γ-lactone **6** as a single isomer in 65% yield after chromatographic purification.[7,8] A nonpolar intermediate was observed by TLC during the conversion of **5** to **6**, but attempts to isolate and identify this entity were unsuccessful due to its instability on silica gel (see below). Minor amounts of several other compounds were also formed during the bromolactonization reaction, but these side products were neither isolated nor characterized. Compound **6** was subsequently transformed[2a] into aminolactone **8** (via azide **7**) from which compounds of structure **1** can be prepared by a variety of literature methods.[9]

The possibility of employing amides derived from (1*S*,2*S*)-(+)-pseudoephedrine in the construction of

(1) For recent preparations of (2*R*,4*S*,5*S*)-hydroxyethylene dipeptide isosteres and leading references, see: (a) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771. (b) Wuts, P. G. M.; Ritter, A. R.; Pruitt, L. E. *J. Org. Chem.* **1992**, *57*, 6696. (c) Jones, D. M.; Nilsson, B.; Szelke, M. *J. Org. Chem.* **1993**, *58*, 2286. (d) Ciapetti, P.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1994**, *35*, 3183. (e) Pégorier, L.; Larchevéque, M. *Tetrahedron Lett.* **1995**, *36*, 2753. (f) Peyrat, J.-F.; Chaboche, C.; Figadére, B.; Cavé, A. *Tetrahedron Lett.* **1995**, *36*, 2757. (g) Chakraborty, T. K.; Hussain, K. A.; Thippeswamy, D. *Tetrahedron* **1995**, *51*, 3873. (h) Dondoni, A.; Perrone, D.; Semola, M. T. *J. Org. Chem.* **1995**, *60*, 7927.

(2) (a) Herold, P.; Duthaler, R.; Rihs, G.; Angst, C. *J. Org. Chem.* **1989**, *54*, 1178. (b) Bradbury, R. H.; Revill, J. M.; Rivett, J. E.; Waterson, D. *Tetrahedron Lett.* **1989**, *30*, 3845. (c) Bradbury, R. H.; Major, J. S.; Oldham, A. A.; Rivett, J. E.; Roberts, D. A.; Slater, A. M.; Timms, D.; Waterson, D. *J. Med. Chem.* **1990**, *33*, 2335.

(3) For related studies on the electrophilic cyclization of γ,δ-unsaturated amides, see: (a) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.-i.; Yoshida, Z.-i.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (b) Najdi, S.; Reichlin, D.; Kurth, M. J. *J. Org. Chem.* **1990**, *55*, 6241. (c) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1992**, 728. (d) Moon, H.-s.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504.

(4) *trans*-7-Methyloct-4-enoic acid was prepared in 41% yield from isovaleraldehyde by the following sequence: (i) CH_2=CHMgBr, THF, 0 °C; (ii) diethyl malonate, $Ti(OEt)_4$, 190 °C; (iii) KOH, EtOH, reflux. See ref 2a.

(5) (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. See also: Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

(6) The diastereomeric excess was determined by HPLC analysis and comparison to an independently prepared 1:1 mixture of both diastereomers. See the Supporting Information for additional details.

(7) The assignment of the major product as bromo γ-lactone **6** is based on IR absorbance data and the characteristic coupling pattern in the ^{1}H NMR spectrum. See: Tayyeb Hussain, S. A. M.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480 and ref 2a.

(8) No attempt was made to isolate the pseudoephedrine produced in this step.

(9) For representative examples, see: (a) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (b) Vacca, J. P.; Guare, J. P.; deSolms, S. J.; Sanders, W. M.; Giuliani, E. A.; Young, S. D.; Darke, P. L.; Zugay, J.; Sigal, I. S.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P.

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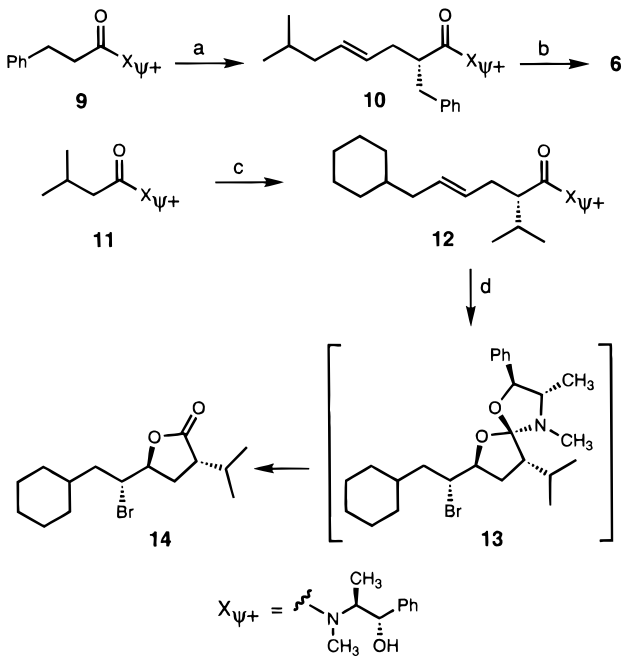
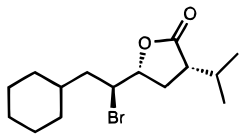
Scheme 2[a]



[a] Reagents and conditions: (a) 2.1 equiv of LDA, 7.0 equiv of LiCl, THF, −78 → 0 °C, 1 h, then 1.5 equiv of *trans*-$(CH_3)_2CHCH_2CH{=}CHCH_2Br$, 0 °C, 2 h, 75%; (b) 1.1 equiv of NBS, 5.0 equiv of AcOH, 4:1 THF:H_2O, 0 °C, 1 h, then reflux 2 h, 68%; (c) 2.1 equiv of LDA, 7.0 equiv of LiCl, THF, −78 → 0 °C, 1 h, then 1.4 equiv of *trans*-$CyCH_2CH{=}CHCH_2Br$, 0 °C, 15 min, 70%; (d) 1.05 equiv of NBS, 5.0 equiv of AcOH, 4:1 THF:H_2O, 0 °C, 15 min, then reflux 14 h, 79%.

(2*R*,4*S*,5*S*)-hydroxyethylene dipeptide isosteres was also investigated (Scheme 2). Specifically, we sought to prepare compound **6** utilizing (1*S*,2*S*)-(+)-pseudoephedrine, although such preparation necessitated nucleophilic and electrophilic species which differed from those described in the example above. Thus, coupling of (1*S*,2*S*)-(+)-pseudoephedrine with hydrocinnamoyl chloride afforded amide **9** in good yield (71%) after purification by recrystallization.[5] Alkylation of the dianion of **9** with *trans*-1-bromo-5-methylhex-2-ene[10] using the conditions described previously for the preparation of **5** provided **10** (the diastereomer of **5**) in 75% yield and 96% de after purification on silica gel.[5,6] This material was subjected to the bromolactonization conditions outlined above and afforded bromo γ-lactone **6** in 68% yield (contaminated with ~5% of an isomeric lactone of undetermined configuration) after flash column chromatography.[8] Thus, it appears that either enantiomer of pseudoephedrine may be utilized for bromo γ-lactone synthesis, although some minor variability in yield and purity of the desired products may be observed.

In order to more rigorously quantitate the amounts of side products formed during the above bromolactonization reaction and to better compare the new procedure with existing literature methods, the synthesis of the known[2] bromo γ-lactone **14** was undertaken (Scheme 2). Alkylation of amide **11**, prepared in 96% yield from (1*S*,2*S*)-(+)-pseudoephedrine and isovaleryl chloride, with (*trans*-4-bromobut-2-enyl)cyclohexane[10] provided **12** in 70% yield and 97% de after purification on silica gel.[5,6] As before, treatment of **12** in a mixture of THF:H_2O (4:1) containing acetic acid (5 equiv) at 0 °C with *N*-bromosuccinimide rapidly afforded a nonpolar intermediate which underwent subsequent conversion to the desired bromo γ-lactone (**14**) at elevated temperature (reflux). However, unlike the examples described above, a much longer reflux period (14 h) was required to effect complete disappearance of this intermediate (see below). Purification of the bromolactonization products by flash column chromatography provided an inseparable mixture of the desired *trans*-lactone **14**, the corresponding *cis*-lactone **15**, and the regioisomeric δ-lactone **16** (configuration undetermined) in a 22:2:1 ratio (79% combined yield).[8,11] Similar isomer ratios and product yields were observed in previous preparations of **14**.[2]



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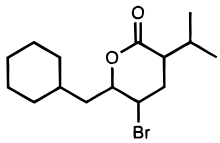

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Due to the greater stability of the intermediate observed in the preparation of **14**, it was possible to isolate this entity by silica gel chromatography. ^1H and ^{13}C NMR data as well as a mass spectral analysis of the purified material were consistent with the spirocyclic structure **13** (Scheme 2).[12] The slow conversion of this species to the desired bromo γ-lactone is presumably due to the steric bulk of the isopropyl substituent adjacent to the hydrolysis center. Similar intermediates are presumably involved in the bromolactonization reactions of γ,δ-unsaturated amides **5** and **10**, but in these less-hindered cases hydrolysis proceeds at a much more rapid rate.

As demonstrated above, γ,δ-unsaturated pseudoephedrine amides can be efficiently transformed into the bromo γ-lactone precursors of (2*R*,4*S*,5*S*)-hydroxyethylene dipeptide isosteres. Some potential advantages of the current method over previous syntheses of such bromo γ-lactones include (1) the ready availability and relatively low cost of either enantiomer of pseudoephedrine, (2) the ability of pseudoephedrine amide enolates to undergo high-yielding, highly diastereoselective alkylations with a wide variety of electrophiles,[5] and (3) the ability to utilize either pseudoephedrine enantiomer as a chiral auxiliary and thus involve either γ,δ-unsaturated amide diastereomer in isostere synthesis. We believe that the above methodology represents a reliable and general means to prepare peptidomimetic compounds and expect that it will find use in organic synthesis.

Experimental Section[13]

All reactions were performed in septum-sealed flasks under a slight positive pressure of argon unless otherwise noted. All

S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1225. (c) Lyle, T. A.; Wiscount, C. M.; Guare, J. P.; Thompson, W. J.; Anderson, P. S.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Dixon, R. A. F.; Sigal, I. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1228. (d) Reference 2.

(10) *trans*-1-Bromo-5-methylhex-2-ene and (*trans*-4-bromobut-2-enyl)cyclohexane were prepared from isovaleraldehyde (52%) and cyclohexylacetaldehyde (63%), respectively, by the following sequence: (i) $CH_2{=}CHMgBr$, THF, 0 °C; (ii) $SOBr_2$, 1,5-hexadiene, $ClCH_2CH_2Cl$, 0 °C. Each product contained ~10% of an isomeric bromide. See ref 2a.

(11) The product ratios and identities were determined from ^1H NMR signals ($CDCl_3$) as follows: **14**: 4.43 ppm (m); **15**: 4.30 ppm (m), **16**: 4.52 ppm (m). See ref 2a.

(12) The stereochemistry of the spirocyclic center is assumed to result from kinetic addition of the pseudoephedrine hydroxyl moiety opposite the isopropyl substituent.

commercial reagents were used as received from their respective suppliers with the following exceptions. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. Anhydrous lithium chloride was prepared by heating at 110 °C under vacuum overnight. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. Melting points (uncorrected) were determined using a Mel-Temp II apparatus.

***trans*-(1′*R*,2′*R*)-7-Methyloct-4-enoic Acid (2′-Hydroxy-1′-methyl-2′-phenylethyl)methyl Amide (4).** Oxalyl chloride (2.71 mL, 31.1 mmol, 1.05 equiv) was added to a solution of *trans*-7-methyloct-4-enoic acid[4] (4.62 g, 29.6 mmol, 1 equiv) and *N*,*N*-dimethylformamide (0.03 mL, 0.39 mmol, 0.012 equiv) in benzene (100 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h and then was concentrated under reduced pressure. The resulting oil was dissolved in THF (20 mL) and was added via cannula to a solution of (1*R*,2*R*)-(−)-pseudoephedrine (4.45 g, 26.9 mmol, 0.91 equiv) and triethylamine (4.50 mL, 32.3 mmol, 1.1 equiv) in THF (200 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then was partitioned between half-saturated NH_4Cl (150 mL) and EtOAc (2 × 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue purified by flash column chromatography (gradient elution 40 → 50% EtOAc in hexanes) to afford **4** (7.55 g, 93%) as a viscous oil: R_f = 0.27 (50% EtOAc in hexanes); $[\alpha]^{25}_D$ = −70.3 (*c* = 0.97, CH_3OH); IR (cm^{-1}) 3382, 1622; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 0.87 (d, *J* = 6.5 Hz), 0.99 (d, *J* = 6.8 Hz), 1.11 (d, *J* = 7.2 Hz), 1.53−1.66 (m), 1.86 (t, *J* = 6.1 Hz), 2.26−2.54 (m), 2.82 (s), 2.92 (s), 3.99−4.04 (m), 4.29 (s, br), 4.42-4.47 (m), 4.56−4.62 (m), 5.37−5.51 (m), 7.26−7.36 (m); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 14.4, 15.3, 22.2, 26.7, 28.0, 28.3, 28.4, 32.7, 33.7, 34.4, 41.8, 58.3, 75.4, 76.4, 126.4, 126.8, 127.5, 128.2, 128.3, 128.6, 129.6, 129.9, 130.0, 130.1, 141.3, 142.4, 173.6, 174.8. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.31; H, 9.63; N, 4.55.

***trans*-(1′*R*,2*S*,2′*R*)-2-Benzyl-7-methyloct-4-enoic Acid (2′-Hydroxy-1′-methyl-2′-phenylethyl)methyl Amide (5).** *n*-Butyllithium (52.6 mL of a 1.6 M solution in hexanes, 84.2 mmol, 2.1 equiv) was added to a suspension of anhydrous lithium chloride (11.9 g, 282 mmol, 7.0 equiv) and diisopropylamine (12.7 mL, 90.3 mmol, 2.25 equiv) in THF (300 mL) at −78 °C. The reaction mixture was stirred for 20 min at −78 °C maintained at 0 °C for 5 min, and subsequently cooled again to −78 °C. A solution of **4** (12.2 g, 40.1 mmol, 1 equiv) in THF (40 mL) was added via cannula, and the resulting solution was stirred at −78 °C for 1 h, was maintained at 0 °C for 15 min, was stirred at 23 °C for 5 min, and then was cooled again to 0 °C. Benzyl bromide (7.15 mL, 60.1 mmol, 1.5 equiv) was added, and the reaction mixture was stirred at 0 °C for 30 min and then was partitioned between half-saturated NH_4Cl (200 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 200 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (gradient elution 20 → 40% EtOAc in hexanes) provided **5** (12.0 g, 76%) as a viscous oil: R_f = 0.54 (50% EtOAc in hexanes); $[\alpha]^{25}_D$ = −18.6 (*c* = 0.86, CH_3OH); IR (cm^{-1}) 3382, 1617; ^{1}H NMR ($CDCl_3$, mixture of rotamers) δ 0.81−0.90 (m), 1.42−1.61 (m), 1.80−1.95 (m), 2.17−2.25 (m), 2.33−2.54 (m), 2.55 (s), 2.73−2.99 (m), 3.05−3.16 (m), 3.93−4.00 (m), 4.31−4.51 (m), 5.25−5.56 (m), 7.14−7.37 (m); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 14.2, 15.5, 22.2, 22.3, 27.0, 28.3, 32.2, 36.2, 36.5, 39.0, 41.9, 44.6, 45.3, 58.3, 75.1, 76.2, 126.2, 126.4, 126.6, 126.9, 127.6, 127.8, 128.3, 128.3, 128.5, 128.6, 128.9, 129.2, 132.1, 132.2, 139.8, 140.4, 140.9, 142.1, 176.0, 177.3. Anal. Calcd for $C_{26}H_{35}NO_2$: C, 79.35; H, 8.96; N, 3.56. Found: C, 79.35; H, 9.01; N, 3.50.

(1′*R*,3*R*,5*S*)-3-Benzyl-5-(1′-bromo-3′-methylbutyl)dihydrofuran-2-one (6). *N*-Bromosuccinimide (5.97 g, 33.5 mmol, 1.1 equiv) was added in small portions over 5 min to a solution of **5** (12.0 g, 30.5 mmol, 1 equiv) and glacial acetic acid (8.73 mL, 152 mmol, 5.0 equiv) in a 4:1 mixture of THF and H_2O (250 mL) at 0 °C. The resulting yellow solution was stirred for 15 min at 0 °C and then was warmed to 23 °C and subsequently refluxed for 1 h. After being cooled to 23 °C, the reaction mixture was partitioned between half-saturated $NaHCO_3$ (300 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 200 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Careful flash chromatographic purification of the residue (5% EtOAc in hexanes) gave **6** (7.09 g, 65%) as a pale yellow oil: R_f = 0.79 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ = +25.2 (*c* = 0.84, CH_3OH); IR (cm^{-1}) 1777; ^{1}H NMR ($CDCl_3$, coupling constants were obtained from a homonuclear 2DJ spectrum) δ 0.87 (d, 3 H, *J* = 6.5 Hz), 0.94 (d, 3 H, *J* = 6.9 Hz), 1.53−1.72 (m, 2 H), 1.82−1.93 (m, 1 H), 2.15 (ddd, 1 H, *J* = 15.0, 8.3, 6.8 Hz), 2.30 (ddd, 1 H, *J* = 15.0, 9.9, 5.1 Hz), 2.83 (dd, 1 H, *J* = 13.9, 9.0 Hz), 3.10 (dddd, 1 H, *J* = 9.9, 8.8, 6.8, 5.0 Hz), 3.18 (dd, 1 H, *J* = 13.9, 5.0 Hz), 4.08 (ddd, 1 H, *J* = 9.7, 6.1, 3.7 Hz), 4.27 (ddd, 1 H, *J* = 8.1, 6.1, 3.7 Hz), 7.20−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 23.1, 25.8, 30.6, 36.8, 41.0, 43.1, 56.2, 79.9, 126.9, 128.7, 128.9, 137.8, 178.0. Anal. Calcd for $C_{16}H_{21}BrO_2$: C, 59.09; H, 6.51. Found C, 59.01; H, 6.53.

(1′*S*,3*R*,5*S*)-5-(1′-Azido-3′-methylbutyl)-3-benzyldihydrofuran-2-one (7). A suspension of sodium azide (2.83 g, 43.5 mmol, 2.0 equiv) and **6** (7.09 g, 21.8 mmol, 1 equiv) in *N*,*N*-dimethylformamide (50 mL) was heated at 50 °C for 20 h. The reaction mixture was cooled to 23 °C and was partitioned between water (200 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by flash column chromatography (10% EtOAc in hexanes) to give **7** (3.26 g, 52%) as a colorless oil: R_f = 0.47 (20% EtOAc in hexanes); $[\alpha]^{25}_D$ = +10.2 (*c* = 1.2, CH_3OH); IR (cm^{-1}) 2109, 1775; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3 H, *J* = 6.5 Hz), 0.94 (d, 3 H, *J* = 6.5 Hz), 1.32−1.41 (m, 1 H), 1.55−1.65 (m, 1 H), 1.70−1.85 (m, 1 H), 2.03−2.18 (m, 2 H), 2.80 (dd, 1 H, *J* = 13.5, 8.9 Hz), 3.05−3.22 (m, 2 H), 3.27−3.33 (m, 1 H), 4.22−4.27 (m, 1 H), 7.18−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.8, 24.6, 29.8, 36.7, 38.8, 40.6, 62.8, 79.2, 126.8, 128.6, 128.8, 137.8, 178.0. Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.68; H, 7.29; N, 14.47.

(1*S*,2′*S*,4′*R*)-[1-(4′-Benzyl-5′-oxo-tetrahydrofuran-2′-yl)-3-methylbutyl]carbamic Acid *tert*-Butyl Ester (8). A suspension of **7** (3.26 g, 11.3 mmol, 1 equiv) and Pd/C (10%, 0.40 g) in CH_3OH (60 mL) was stirred under a hydrogen atmosphere (balloon) for 2 h. The reaction mixture was filtered through Celite and concentrated and the residue dissolved in 1,4-dioxane (80 mL). *N*,*N*-Diisopropylethylamine (3.94 mL, 22.6 mmol, 2.0 equiv) and di-*tert*-butyl dicarbonate (3.70 g, 17.0 mmol, 1.5 equiv) were added sequentially, and the resulting solution was stirred at 23 °C for 2 h. The reaction mixture was then partitioned between water (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (gradient elution, 10 → 15% EtOAc in hexanes) provided **8** (2.53 g, 62%) as a white solid: mp = 84−86 °C; R_f = 0.66 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ = −19.9 (*c* = 1.4, CH_3OH); IR (cm^{-1}) 3338, 1767, 1704; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3 H, *J* = 6.5 Hz), 0.90 (d, 3 H, *J* = 6.5 Hz), 1.18−1.32 (m, 1 H), 1.40 (s, 9 H), 1.43−1.56 (m, 1 H), 1.98−2.07 (m, 1 H), 2.20−2.29 (m, 1 H), 2.78 (dd, 1 H, *J* = 13.7, 9.0 Hz), 2.91−3.01 (m, 1 H), 3.15 (dd, 1 H, *J* = 13.7, 4.4 Hz), 3.71−3.81 (m, 1 H), 4.23−4.28 (m, 1 H), 4.34 (d, 1 H, *J* = 9.7 Hz), 7.16−7.33 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.8, 24.5, 28.1, 29.3, 36.7, 41.4, 51.2, 66.8, 79.4, 80.5, 126.6, 128.5, 128.6, 137.9, 155.8, 178.9. Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.64; N, 3.87. Found: C, 69.78; H, 8.70; N, 3.81.

(1′*S*,2′*S*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-*N*-methyl-3-phenylpropionamide (9). A solution of hydrocinnammoyl chloride (15.7 mL, 106 mmol, 1.15 equiv) in THF (20 mL) was added via cannula over 10 min to a solution of (1*S*,2*S*)-(+)-pseudoephedrine (15.22 g, 92 mmol, 1 equiv) and triethylamine (16.7 mL, 119.6 mmol, 1.3 equiv) in THF (200 mL) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was quenched with H_2O (10 mL) and was partitioned between EtOAc (100 mL) and brine (3 × 100 mL). The organic layer was dried over Na_2SO_4 and was concentrated to afford a yellow solid. Recrystallization from toluene afforded **9** (19.5 g, 71%) as a white solid: mp = 102−104 °C; R_f = 0.48 (50% EtOAc in hexane); IR

(13) General experimental procedures and instrumentation are described in the following: Dragovich, P. S.; Prins, T. J.; Zhou, R. *J. Org. Chem.* **1995**, *60*, 4922.

(KBr pellet, cm^{-1}) 3396, 1814, 1450; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.92 (d, J = 6.9 Hz), 1.08 (d, J = 6.9 Hz), 2.57−2.67 (m), 2.77 (s), 2.94−3.02 (m), 7.21−7.35 (m); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 14.4, 15.2, 26.9, 31.1, 31.5, 32.4, 35.4, 36.1, 58.2, 75.4, 76.4, 126.0, 126.1, 126.4, 126.8, 127.6, 128.3, 128.3, 128.4, 128.4, 128.4, 128.6, 141.1, 141.2, 141.5, 142.2, 173.2, 174.4. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.82; H, 7.83; N, 4.67.

***trans*-(1′*S*,2*S*,2′*S*)-2-Benzyl-7-methyloct-4-enoic Acid (2′-Hydroxy-1′-methyl-2′-phenylethyl)methyl Amide (10).** *n*-Butyllithium (11.42 mL of a 1.6 M solution in hexanes, 18.27 mmol, 2.1 equiv) was added to a solution of anhydrous lithium chloride (2.57 g, 60.6 mmol, 7.0 equiv) and diisopropylamine (2.74 mL, 19.58 mmol, 2.25 equiv) in THF (100 mL) at −78 °C. The reaction mixture was stirred for 20 min at −78 °C, maintained at 0 °C for 5 min, and subsequently cooled again to −78 °C. An ice-cooled solution of **9** (2.59 g, 8.7 mmol, 1 equiv) in THF (20 mL) was added via cannula over 5 min. The reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min and then was cooled to 0 °C. A solution of *trans*-1-bromo-5-methylhex-2-ene[10] (2.31 g, 13.05 mmol, 1.5 equiv) in THF (5 mL) was added via cannula, and the reaction mixture was stirred at 0 °C for 2 h and then was partitioned between half-saturated NH_4Cl (200 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 200 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (25% EtOAc in hexane) to afford **10** (2.44 g, 75%) as a viscous, yellow oil: R_f = 0.72 (50% EtOAc in hexane); $[\alpha]^{23}_D$ = +65.8 (c =1.0, $CHCl_3$); IR (cm^{-1}) 3379, 2955, 1614; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.24 (d, J = 6.6 Hz), 0.84−0.86 (m), 0.94 (d, J = 6.9 Hz), 1.49−1.60 (m), 1.79−1.91 (m), 2.13−2.40 (m), 2.48−2.55 (m), 2.76−2.94 (m), 3.72−3.77 (m), 4.27−4.31 (m), 4.44−4.49 (m), 5.18−5.29 (m), 5.41−5.55 (m), 7.10−7.38 (m); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 14.1, 14.3, 22.1, 22.7, 26.9, 28.2, 28.3, 28.5, 30.8, 33.0, 36.2, 36.5, 38.8, 39.1, 41.8, 41.9, 44.4, 45.0, 45.3, 58.2, 59.2, 75.1, 75.3, 76.0, 126.0, 126.4, 126.5, 126.6, 127.4, 128.1, 128.3, 128.4, 128.9, 131.0, 131.9, 132.1, 139.7, 140.0, 141.2, 142.0, 175.9, 176.9. Anal. Calcd for $C_{26}H_{35}NO_2$: C, 79.35; H, 8.96; N, 3.56. Found: C, 79.25; H, 8.91; N, 3.59.

(1′*R*,3*R*,5*S*)-3-Benzyl-5-(1′-bromo-3′-methylbutyl)dihydrofuran-2-one (6, Alternate Synthesis). *N*-Bromosuccinimide (1.54 g, 8.64 mmol, 1.1 equiv) was added in small portions over 5 min to a solution of **10** (3.09 g, 7.85 mmol, 1 equiv) and glacial acetic acid (2.25 mL, 39.25 mmol, 5.0 equiv) in a 4:1 mixture of THF and H_2O (50 mL) at 0 °C. The resulting yellow solution was stirred for 1 h at 0 °C and then was warmed to 23 °C and subsequently refluxed for 2 h. After being cooled to 23 °C, the reaction mixture was partitioned between half-saturated $NaHCO_3$ (200 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 200 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (5% EtOAc in hexane) provided **6** as yellow oil (1.73 g, 68% yield, contaminated with ∼5% of an isomeric lactone of undetermined configuration as observed by ^1H NMR).

(1′*S*,2′*S*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-*N*,3-dimethylbutyramide (11). A solution of (1*S*,2*S*)-(+)-pseudoephedrine (2.00 g, 12.1 mmol, 1 equiv) and triethylamine (2.19 mL, 15.7 mmol, 1.3 equiv) in THF (30 mL) was cooled to 0 °C. A solution of isovaleryl chloride (1.70 mL, 13.9 mmol, 1.15 equiv) in THF (6 mL) was added dropwise over a 5 min period, producing a white precipitate. After 10 min of stirring at 0 °C, H_2O (2 mL) and EtOAc (70 mL) were added. The mixture was transferred to a separatory funnel and washed with brine (3 × 60 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was dried under vacuum for 3 h to give **11** (2.90 g, 96%) as a white solid: mp = 66−68 °C; R_f = 0.31 (50% EtOAc in hexanes); IR (cm^{-1}) 3378, 1614; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.92−1.00 (m), 1.13 (d, J = 7.2 Hz), 2.07−2.33 (m), 2.81 (s), 2.92 (s), 3.98−4.08 (m), 4.37−4.64 (m), 7.23−7.40 (m); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 14.4, 15.3, 22.5, 22.6, 22.7, 22.8, 25.4, 25.5, 26.7, 33.0, 42.4, 42.9, 58.2, 75.3, 76.3, 126.2, 126.8, 127.4, 128.0, 128.2, 128.5, 141.5, 142.4, 173.5, 174.8. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.31; H, 9.34; N, 5.67.

***trans*-(1′*S*,2*S*,2′*S*)-6-Cyclohexyl-2-isopropylhex-4-enoic Acid (2′-Hydroxy-1′-methyl-2′-phenylethyl)methylamide (12).** *n*-Butyllithium (6.67 mL of a 1.6 M solution in hexanes, 10.7 mmol, 2.1 equiv) was added to a suspension of anhydrous lithium chloride (1.52 g, 35.9 mmol, 7.0 equiv) and diisopropylamine (1.60 mL, 11.4 mmol, 2.25 equiv) in THF (10 mL) at −78 °C. The reaction mixture was stirred for 20 min at −78 °C, maintained at 0 °C for 5 min, and subsequently cooled again to −78 °C. A solution of **11** (1.27 g, 5.09 mmol, 1 equiv) in THF (15 mL) was added dropwise via cannula over 10 min. After the mixture was stirred for 1 h, the reaction vessel was warmed to 0 °C for 15 min, then to 23 °C for 5 min, and then cooled again to 0 °C. (*trans*-4-Bromobut-2-enyl)cyclohexane[10] (1.43 g, 7.12 mmol, 1.4 equiv) was added dropwise, and the reaction mixture was stirred for 15 min at 0 °C and then was subsequently partitioned between saturated NH_4Cl (45 mL) and EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (25% EtOAc in hexanes) afforded **12** (1.38 g, 70%) as a thick oil: R_f = 0.76 (50% EtOAc in hexanes); $[\alpha]^{25}_D$ = +47.5 (c = 1.1, $CHCl_3$); IR (cm^{-1}) 3378, 1614; ^1H NMR ($CDCl_3$, mixture of rotamers) δ 0.75−0.99 (m), 0.92 (d, J = 6.8 Hz), 0.95 (d, J = 6.8 Hz), 1.07−1.26 (m), 1.09 (d, J = 6.8 Hz), 1.57−1.71 (m), 1.75−1.94 (m), 2.16−2.41 (m), 2.86 (s), 2.88 (s), 4.34−4.64 (m), 5.11−5.23 (m), 5.36−5.48 (m), 7.24−7.40 (m); ^{13}C NMR ($CDCl_3$, mixture of rotamers) δ 14.5, 15.2, 19.8, 19.9, 21.1, 21.2, 26.2, 26.2, 26.4, 26.7, 28.1, 30.7, 30.8, 30.8, 30.9, 32.9, 33.0, 33.1, 33.5, 33.7, 34.8, 37.9, 37.9, 38.1, 40.4, 48.3, 49.1, 49.7, 58.4, 75.0, 76.2, 126.3, 127.0, 127.2, 127.4, 128.2, 128.2, 128.5, 128.8, 129.9, 130.8, 131.6, 140.9, 142.5, 176.3, 177.8. Anal. Calcd for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.76; H, 10.22; N, 3.55.

(1′*R*,3*S*,5*S*)-5-(1′-Bromo-2′-cyclohexylethyl)-3-isopropyldihydrofuran-2-one (14). *N*-Bromosuccinimide (0.294 g, 1.65 mmol, 1.05 equiv) was added in small portions over 5 min to a solution of **12** (0.606 g, 1.57 mmol, 1 equiv) and glacial acetic acid (0.450 mL, 7.86 mmol, 5.0 equiv) in a 4:1 mixture of THF and H_2O (18 mL) at 0 °C. The resulting yellow solution was stirred for 15 min at 0 °C, warmed to 23 °C, and subsequently refluxed for 14 h. After being cooled to 23 °C, the reaction mixture was partitioned between half-saturated $NaHCO_3$ (20 mL) and a 1:1 mixture of EtOAc and hexanes (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Flash chromatographic purification of the residue (50% CH_2Cl_2 in hexanes) gave **14** (0.392 g, 79%) as a white solid (containing minor amounts of other isomers by ^1H NMR): mp = 86−90 °C; R_f = 0.32 (7% acetone in hexanes); IR (cm^{-1}) 1772; ^1H NMR ($CDCl_3$, major isomer) δ 0.73−0.90 (m, 1H), 0.92−1.09 (m, 1H), 0.95 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.8 Hz), 1.11−1.36 (m, 3H), 1.54−1.81 (m, 8H), 2.12−2.32 (m, 3H), 2.64−2.73 (m, 1H), 4.12−4.20 (m, 1H), 4.39−4.47 (m, 1H); ^{13}C NMR ($CDCl_3$, major isomer) δ 18.2, 20.1, 25.6, 25.9, 26.2, 27.0, 29.0, 31.3, 33.6, 34.9, 41.5, 45.4, 56.1, 79.9, 177.7.

(1′*R*,2*S*,3*S*,5*S*,7*S*,9*S*)-7-(1′-Bromo-2′-cyclohexylethyl)-9-isopropyl-3,4-dimethyl-2-phenyl-1,6-dioxa-4-azaspiro[4.4]-nonane (13). *N*-Bromosuccinimide (0.047 g, 0.26 mmol, 1.05 equiv) was added in small portions to a solution of **12** (0.097 g, 0.25 mmol, 1 equiv) and glacial acetic acid (0.072 mL, 1.26 mmol, 5.0 equiv) in a 4:1 mixture of THF and H_2O (2.5 mL) at 0 °C. The resulting yellow solution was stirred for 15 min at 0 °C and then partitioned between half-saturated NaCl (4 mL) and a 1:1 mixture of EtOAc and hexanes (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. The residue was passed through a plug of silica gel (eluting with 4% EtOAc in hexanes) and then purified by preparative thin layer chromatography (10% EtOAc in hexanes) to give **13** (0.067 g, 57%) as a clear, colorless glass (containing minor impurities by ^1H NMR): R_f = 0.91 (25% EtOAc in hexanes); ^1H NMR ($CDCl_3$) δ 0.74−1.38 (m, 6H), 0.92 (d, 3H, J = 6.5 Hz), 1.04 (d, 3H, J = 6.5 Hz), 1.10 (d, 3H, J = 5.9 Hz), 1.61−2.25 (m, 11H), 2.35 (s, 3H), 2.83−2.93 (m, 1H), 4.06−4.21 (m, 2H), 4.46 (d, 1H, J = 8.9 Hz), 7.24−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.5, 21.3, 22.3, 26.0, 26.2, 26.5, 28.9, 31.4, 31.8, 32.3, 34.0, 35.2, 42.4, 45.6, 58.7, 65.6, 76.3, 86.4, 122.0, 127.1, 127.8, 128.3, 140.6; HRMS calcd for $C_{25}H_{38}BrNO_2$ [MCs^+] 596.1140, found 596.1161.

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Supporting Information Available: Procedures for the preparation of both relevant diastereomers corresponding to compounds **5**, **10**, and **12** and conditions for HPLC analyses of these mixtures (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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