Notes

A Facile Synthesis of N-Protected Statine and Its Analogue via Stereoselective Iodolactamization

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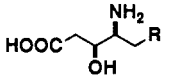
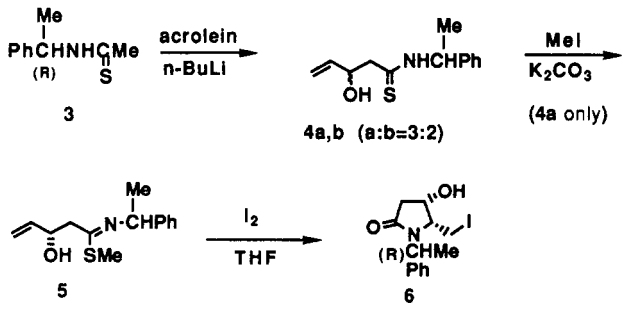
Unusual amino acids possessing β-amino alcohol moieties are widely distributed in biologically important peptides, such as pepstatin,[1] galantin I,[2] didemnins,[3] and dolastatine.[4] Accordingly, the development of methods for their stereocontrolled synthesis continues to receive significant attention. Recently, the use of fascinating functionalized heterocycles such as oxazolidin-2-one[5] and δ-lactones[6] as synthons of β-amino alcohol moieties has been reported. We have recently developed the stereoselective iodine-induced lactamization of γ,δ-unsaturated thioimidates, giving polyfunctionalized γ-lactams.[7] Among them, (4*R*,5*S*)-4-hydroxy-5-(iodomethyl)pyrrolidin-2-one derivative *ent*-**6** was used, in practice, for the transformation into (2*S*,3*R*)-3-hydroxyglutamic acid, a constituent of a peptide antibiotic.[8] In this paper, we describe a facile synthesis of statine (**1**)[9] and its novel side-chain analogue, (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACHPA) (**2**),[10] recognized as the key amino acid con-



1 statine R=isopropyl
2 ACHPA R=cyclohexyl

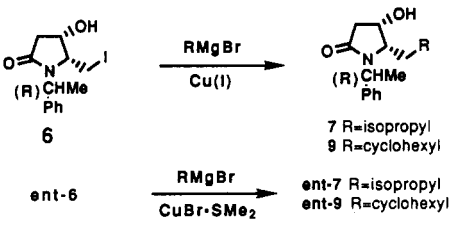
stituents of renin inhibitor,[11] pepstatin and its related peptide, from the enantiomer **6** of the pyrrolidin-2-one *ent*-**6** via Cu(I)-mediated coupling reaction.

Our synthesis of **1** and **2** began with the aldol condensation of a dianion, generated from the thioamide **3** from (*R*)-α-phenylethylamine, with acrolein. Treatment of the dianion, generated from **3** with 2 equiv of *n*-butyllithium (*n*-BuLi), with acrolein in tetrahydrofuran (THF) at −78 °C for 10 s afforded a 3:2 mixture of diastereomers **4a** and **4b** of unsaturated β-hydroxy thioamides with a low selectivity in 64% yield. Methylation of the major diastereomer **4a** readily separated with methyl iodide (K_2CO_3, THF, room temperature, 15 h) gave the thioimidate **5**, which, without purification, underwent highly stereoselective iodolactamization (1.5 equiv of iodine, THF, 5 °C, 2 days) to provide (4*S*,5*R*)-4-hydroxy-5-(iodomethyl)-pyrrolidin-2-one (**6**) [$[\alpha]^{26}_D$ +124.6° (*c* 1.13, $CHCl_3$)] in 66% overall yield from **4a**. Spectral data for **6** were identical with those for *ent*-**6** [$[\alpha]^{25}_D$ −122.3° (*c* 0.965, $CHCl_3$)] except for the direction of rotation.



With the requisite chiral γ-lactam **6** in hand, we turned our attention to the coupling reaction of the iodide **6** with

Table I. Coupling Reaction of Iodides 6 and *ent*-6 with Grignard-Derived Cupurates



entry	iodide	Grignard reagent (R)	Cu(I) salt	product	yield, %
1	**6**	isopropyl	CuI	**7**	35[a]
2	**6**	isopropyl	CuBr	**7**	23[b]
3	**6**	isopropyl	2-Th(CuCN)$^-$Li$^+$	**7**	70
4	**6**	isopropyl	CuBr·SMe_2	**7**	91
5	**6**	cyclohexyl	CuBr·SMe_2	**9**	83
6	*ent*-**6**	isopropyl	CuBr·SMe_2	*ent*-**7**	88
7	*ent*-**6**	cyclohexyl	CuBr·SMe_2	*ent*-**9**	91

[a] Compound **8** was obtained in 56% yield. [b] Compound **8** was obtained in 48% yield.

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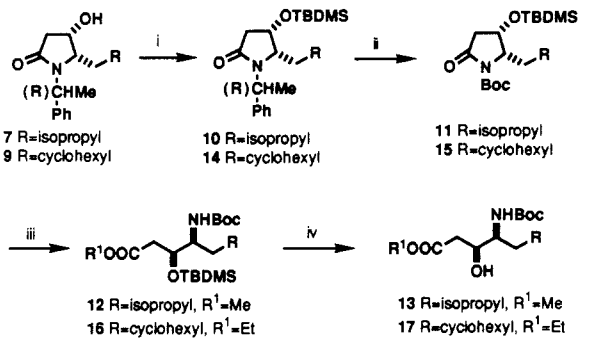
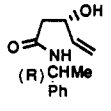
Scheme I[a]



[a] (i) TBDMSCl/imidazole/DMF; (ii) (1) Na/NH_3, (2) $(Boc)_2O$/DMAP; (iii) NaOMe for 11, NaOEt for 15; (iv) n-Bu_4NF.

Grignard-derived cuprates. At the beginning, the reaction of **6** with the cuprates prepared from isopropylmagnesium bromide with several copper(I) salts [CuI, CuBr, 2-thienyl(CuCN)$^-Li^+$,[12] CuBr·SMe_2[13]] was examined. The results are summarized in Table I. The use of CuBr·SMe_2 as a copper(I) salt (THF, −30 °C, 6 h) provided the best result (entry 4). The use of the other copper(I) salts required a long reaction time (15–20 h). In addition, as the reaction time was longer, a side reaction proceeded to provide the ring-opened compound **8** as a byproduct. The reason,



8

however, remains unclear. Accordingly, the reaction of **6** with cyclohexylmagnesium bromide in the presence of copper(I) bromide–dimethyl sulfide gave the coupling product **9** in good yield (entry 5). A similar reaction using *ent*-**6** afforded products *ent*-**7** and *ent*-**9** in satisfactory yields (entries 6 and 7).

Protection of **8** with the *tert*-butyldimethylsilyl (TBDMS) group (TBDMSCl/imidazole/DMF, room temperature, 36 h) provided **10** as a colorless oil in quantitative yield. The exchange of the N-protected group from α-phenylethyl to *tert*-butoxycarbonyl (Boc) (**10** → **11**) was performed in order to facilitate the ring opening [(1) Na/NH_3, THF, −33 °C, 1 h; (2) $(Boc)_2O$/4-(*N*,*N*-dimethylamino)pyridine (DMAP), CH_3CN, room temperature, 4 h; 41% overall yield]. The lactam **11** readily underwent ring cleavage with sodium methoxide (0 °C, 1.5 h) to furnish the methyl ester **12** in 88% yield. Desilylation of **12** with n-Bu_4NF (0 °C, 1 h) gave the known compound **13** [mp 58–60 °C, $[\alpha]^{25}_D$ −36° (*c* 1.02, EtOH)], the methyl ester of *N*-Boc-statine, in 87% yield. A similar sequence from **9** [**9** → **14** (98%) → **15** (76%) → **16** (50%) → **17** [$[\alpha]^{25}_D$ −34.0° (*c* 1.22, MeOH)] (88%)] was performed as shown in Scheme I. The structures of the methyl ester of *N*-Boc-statine **13** and the ethyl ester of *N*-Boc-ACHPA **17** were assigned by comparison to the spectroscopic data in the literature and their absolute configuration was confirmed by comparison of their optical rotation to the literature values.[6,10a]

In summary, the highly diastereoselective iodolactamization of γ,δ-unsaturated β-hydroxy thioimidate **5** provides functionalized homochiral pyrrolidin-2-one **6** as a synthon of *threo*-β-amino alcohol, which has been expediently converted to statine and ACHPA, constituents of renin inhibitors, by using the coupling reaction with Grignard-derived cuprates as a key reaction. The transformation of **6** and *ent*-**6** as new chiral building blocks should provide an entrance to the wide variety of other statine analogues and unusual amino acids containing the 1,2-amino alcohol units.

Experimental Section

Melting points were determined with a Yanaco micro melting point apparatus and are not corrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a JASCO A 102 spectrophotometer. Proton magnetic resonance (^1H NMR) were recorded either at 60 MHz on a JEOL PMX-60 instrument or at 270 MHz on a JEOL-FX270 instrument with tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined on a Varian XL-200 instrument with tetramethylsilane as an internal standard unless otherwise specified. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 instrument. Optical rotations were measured on a JASCO DIP-140 instrument. Column chromatography was performed on silica gel (Fuji-Davison BW-200, Merck 60 (no. 9385), or Nakarai 60) with a medium pressure apparatus. Separation of diastereomers was performed on a Kusano (Micro Pump KP-6H) apparatus with a silica gel column (Kusano CIG-10 mm and 5 mm). A solution of ethyl acetate/hexane as eluant was used unless otherwise specified. The extracts were dried over Na_2SO_4 unless otherwise specified.

(3*S*)- and (3*R*)-*N*-[(*R*)-1-Phenylethyl]-3-hydroxypent-4-enethioamide (4a,b). According to a procedure similar to that described for ref 7, **4a,b** were prepared from *N*-[(*R*)-1-phenylethyl]thioacetamide (**3**) (1.901 g, 10.6 mmol), **4a** (960.2 mg, 39%) and **4b** (696.1 mg, 28%). **4a**: an oil, $[\alpha]^{25.5}_D$ +167.9° (*c* 3.49, MeOH); IR (neat) 3250, 1640, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (d, J = 6.8 Hz, 3 H), 2.74 (dd, J = 14.9, 8.3 Hz, 1 H), 2.91 (dd, J = 14.9, 2.9 Hz, 1 H), 3.75 (br s, 1 H), 4.53 (br s, 1 H), 5.10–5.14 (m, 1 H), 5.23–5.31 (m, 1H), 5.64–5.88 (m, 2 H), 7.23–7.36 (m, 5 H), 8.47 (br s, 1 H); HRMS calcd for $C_{13}H_{17}NOS$ 235.1030, found 235.1016. **4b**: an oil, $[\alpha]^{25}_D$ +226.3° (*c* 1.005 MeOH); IR (neat) 3250, 1640, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (d, J = 6.8 Hz, 3 H), 2.73 (dd, J = 14.6, 8.5 Hz, 1 H), 2.90 (dd, J = 14.6, 2.9 Hz, 1 H), 3.60 (br s, 1 H), 4.53–4.57 (m, 1 H), 5.10–5.31 (m, 2 H), 5.66–5.89 (m, 2 H), 7.26–7.38 (m, 5 H), 8.57 (br s, 1 H); HRMS calcd for $C_{13}H_{17}NOS$ 235.1030, found 235.1033.

(4*S*,5*R*)-*N*-[(*R*)-1-Phenylethyl]-4-hydroxy-5-(iodomethyl)pyrrolidin-2-one (6). As described for *ent*-**6** (ref 7), **6** was obtained from **4a** (870.5 mg, 3.7 mmol). **6** (846 mg, 66%) as colorless crystals (CH_2Cl_2/petroleum ether): mp 142–145 °C; $[\alpha]^{26}_D$ +124.6° (*c* 1.13, $CHCl_3$); IR (Nujol) 3300, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (d, J = 7.2 Hz, 3 H), 2.30 (br s, 1 H), 2.80 (m, 3 H), 2.89 (dd, J = 10.0, 3.2 Hz, 1 H), 3.95–4.02 (m, 1 H), 4.54–4.61 (m, 1 H), 5.54 (q, J = 7.2 Hz, 1 H), 7.26–7.35 (m, 5 H). Anal. Calcd for $C_{13}H_{16}INO_2$: C, 45.24; H, 4.67; N, 4.06. Found: C, 45.16; H, 4.83; N, 3.99.

(4*S*,5*S*)-*N*-[(*R*)-1-Phenylethyl]-5-isobutyl-4-hydroxypyrrolidin-2-one (7). To a slurry of CuBr·SMe_2 (1.33 g, 6.49 mmol) in THF (15 mL) was added a 1.23 M isopropylmagnesium bromide–THF solution (8 mL, 6.5 mmol) at −78 °C with stirring. The mixture was gradually warmed to −35 °C and kept for 5 min. After cooling at −78 °C, a solution of **6** (744 mg, 2.16 mmol) in THF (5 mL) was slowly added to the reaction mixture, and the mixture was gradually warmed to −30 °C, stirred for 6 h, and quenched with a mixture of a saturated ammonium chloride solution and an ammonia solution (4:1). The insoluble materials were filtered off through Celite. The filtrate was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Chromatography of the residue yielded **7** (512 mg, 91%) as a white solid (isopropyl ether): mp 88–90 °C; $[\alpha]^{26}_D$ +119.6° (*c* 1.19, $CHCl_3$); IR (Nujol) 3400, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (d, J = 6.0 Hz, 3 H), 0.81 (d, J = 6.0 Hz, 3 H), 0.80–1.60 (m, 3 H), 1.65 (d, J = 6.8 Hz, 3 H), 2.27 (br s, 1 H), 2.40–2.63 (m, 2 H), 3.50–3.92 (m, 1 H), 4.16–4.52 (m, 1 H),

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5.33 (q, J = 6.8 Hz, 1 H), 7.26 (s, 5 H). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.68; H, 8.98; N. 5.43.

(4*S*,5*S*)-*N*-[(*R*)-1-Phenylethyl]-5-(cyclohexylmethyl)-4-hydroxypyrrolidin-2-one (9). According to a procedure similar to that described for **7**, treatment of **6** (582.4 mg, 1.693 mmol) with the cuprate (5.079 mmol) prepared from cyclohexylmagnesium bromide and CuBr·SMe_2 complex yielded **9** (423 mg, 83%) as a white solid (isopropyl ether): mp 123–125 °C; $[\alpha]^{25}_D$ +105.6° (*c* 1.09, $CHCl_3$); IR (Nujol) 3450, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60–1.63 (m, 13 H), 1.57 (d, J = 7.08 Hz, 3 H), 2.38–2.59 (m, 2 H), 3.68 (m, 1 H), 4.28 (m, 1 H), 5.27 (q, J = 7.08 Hz, 1 H), 7.23 (m, 5 H). Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.78; H, 8.98; N, 4.66.

(4*R*,5*R*)-*N*-[(*S*)-1-Phenylethyl]-5-isobutyl-4-hydroxypyrrolidin-2-one (*ent*-7). Treatment of *ent*-**6** (343 mg, 0.997 mmol) with the cuprate provided *ent*-**7** (228 mg, 88%) as colorless crystals (isopropyl ether): mp 88–90 °C; $[\alpha]^{25}_D$ −121.2° (*c* 1.10, $CHCl_3$); IR (Nujol) 3270, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (d, J = 6.59 Hz, 3 H), 0.83 (d, J = 6.59 Hz, 3 H), 0.95–1.65 (m, 3 H), 1.65 (d, J = 7.33 Hz, 3 H), 1.77 (br s, 1 H), 2.45–2.70 (m, 2 H), 3.73 (m, 1 H), 4.36 (m, 1 H), 5.38 (q, J = 7.33 Hz, 1 H), 7.28 (m, 5 H). Anal. calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.81; N, 5.36. Found: C, 73.28; H, 8.70; N, 5.20.

(4*R*,5*R*)-*N*-[(*S*)-1-Phenylethyl]-5-(cyclohexylmethyl)-4-hydroxypyrrolidin-2-one (*ent*-9). The analogous reaction of *ent*-**6** (200 mg, 0.58 mmol) with the cuprate (1.74 mmol) afforded *ent*-**9** (160 mg, 93%) as colorless crystals (isopropyl ether): mp 123–125 °C; $[\alpha]^{25}_D$ −100.1° (*c* 1.05, CHCl); IR (Nujol) 3270, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.50–2.00 (m, 13 H), 1.65 (d, J = 7.0 Hz, 3 H), 2.55 (d, J = 6.9 Hz, 2 H), 3.25 (br s, 1 H), 3.70 (m, 1 H), 4.30 (m, 1 H), 5.33 (q, J = 7.0 Hz, 1 H), 7.35 (m, 5 H). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.90; H, 9.03; N, 4.62.

(3*S*)-*N*-[(*R*)-1-Phenylethyl]-3-hydroxypent-4-enamide (8). In the above procedure for **6**, the use of CuI or CuBr in place of CuBr·SMe_2 produced **8** as a byproduct, a colorless solid (isopropyl ether): mp 106–108 °C; $[\alpha]^{26}_D$ +74.15° (*c* 0.45, $CHCl_3$); IR (Nujol) 3350, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (d, J = 6.8 Hz, 3 H), 2.38 (m, 2 H), 4.08 (br s, 1 H), 4.67 (m, 1 H), 5.00–5.43 (m, 3 H), 5.60–6.27 (m, 1 H), 6.83 (m, 1 H) 7.30 (s, 5 H). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.33; H, 7.82; N, 6.26.

(4*S*,5*S*)-*N*-[(*R*)-1-Phenylethyl]-5-isobutyl-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidin-2-one (10). A mixture of **7** (488 mg, 1.87 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl) (564 mg, 3.74 mmol), imidazole (509 mg, 7.48 mmol), and DMAP (10 mg) in DMF (6 mL) was stirred for 36 h at room temperature. Water (10 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Column chromatography of the residue yielded **10** (700 mg, 100%) as a white solid (petroleum ether): mp 57–59 °C; $[\alpha]^{25}_D$ +101.2° (*c* 1.05, $CHCl_3$); IR (Nujol) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3 H), 0.09 (s, 3 H), 0.75 (d, J = 6.0 Hz, 3 H), 0.80 (d, J = 6.0 Hz, 3 H), 0.92 (s, 9 H), 1.22–1.82 (m, 3 H), 1.67 (d, J = 7.0 Hz, 3 H), 2.52 (d, J = 6.0 Hz, 2 H), 3.43–3.90 (m, 1 H), 4.41 (m, 1 H), 5.45 (q, J = 7.0 Hz, 1 H), 7.33 (m, 5 H). Anal. Calcd for $C_{22}H_{37}NO_2Si$: C, 70.35; H, 9.93; N, 3.73. Found: C, 70.59; H, 9.86; N, 3.93.

(4*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-isobutyl-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidin-2-one (11). To a solution of **10** (320 mg, 0.853 mmol) in liquid ammonia/THF (10:1) (11 mL) was added metallic sodium (73.6 mg, 3.2 mmol) at −78 °C. The mixture was refluxed for 1 h and quenched with aqueous ammonium chloride. The residual ammonia was evaporated. The mixture was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated to provide the crude product. To a solution of the crude product in acetonitrile (2 mL) were added $(Boc)_2O$ (0.39 mL, 1.7 mmol) and DMAP (104 mg, 0.853 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched with water at 0 °C. The mixture was extracted with ethyl acetate three times. The extracts were washed with brine, dried, and evaporated. Chromatography of the residue yielded **11** (131 mg, 41%) as a white solid (petroleum ether): mp 118–121 °C; $[\alpha]^{25}_D$ +54.2° (*c* 1.00, $CHCl_3$); IR (Nujol) 1790, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.87 (s, 9 H), 0.88 (d, J = 6.84 Hz, 3 H), 0.93 (d, J = 6.84 Hz, 3 H), 1.29 (m, 1 H), 1.51 (s, 9 H), 1.74–1.82 (m, 2 H), 2.54 (d, J = 8.3 Hz, 2 H), 4.14 (m, 1 H), 4.45 (m, 1 H). Anal. Calcd for $C_{19}H_{37}NO_4Si$: C, 61.41; H, 10.04; N, 3.77. Found: C, 61.53; H, 9.94; N, 3.82.

Methyl (3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-6-methylheptanoate (12). To a solution of **11** (112 mg, 0.302 mmol) in methanol (0.5 mL) was added 2 M NaOMe (0.18 mL, 0.36 mmol). The reaction mixture was stirred at room temperature for 1.5 h, quenched with brine (10 mL), and extracted with ether three times. The extracts were dried and evaporated. Column chromatography of the residue yielded **12** (107.5 mg, 88%) as an oil: $[\alpha]^{25}_D$ −37.0° (*c* 1.01, MeOH); IR (neat) 3400, 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 0.93 (dd, J = 6.59, 2.2 Hz, 6 H), 1.29–1.67 (m, 2 H), 1.45 (s, 9 H), 2.48 (m, 2 H), 3.68 (s, 3 H), 3.69 (m, 1 H), 4.18 (m, 1 H), 4.51 (d, J = 9.52 Hz, 1 H); HRMS calcd for $C_{20}H_{41}NO_5Si$ 403.2752, found 403.2755.

Methyl (3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-6-methylheptanoate (13). To a solution of **12** (101 mg, 0.250 mmol) in THF (2 mL) was added a 1 M *n*-Bu_4NF–THF solution (0.5 mL, 0.5 mmol) with ice cooling. The reaction mixture was stirred at the same temperature for 1 h, then quenched with brine, and extracted with ethyl acetate three times. The extracts were dried and evaporated. Column chromatography yielded **13** (63 mg, 87%) as a white solid (petroleum ether): mp 58–60 °C; $[\alpha]^{25}_D$ −36.0° (*c* 1.02, EtOH) [lit.[6] $[\alpha]^{25}_D$ −36.8° (*c*, 1.0, EtOH)]; IR (Nujol) 3400, 2950, 1710, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 6.59 Hz, 6 H), 1.44 (s, 9 H), 1.30–1.75 (m, 3 H), 2.55 (m, 2 H), 3.30 (br d, J = 3.41 Hz, 1 H), 3.62 (m, 1 H), 3.71 (s, 3 H), 4.02 (m, 1 H), 4.74 (d, J = 9.76 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.51, 23.31, 25.03, 28.63, 38.81, 41.94, 52.13, 52.21, 69.91, 79.51, 156.32, 174.11. Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.41; N, 4.84. Found: C, 58.23; H, 9.41; N, 4.80.

(4*S*,5*S*)-*N*-[(*R*)-1-Phenylethyl]-5-(cyclohexylmethyl)-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidin-2-one (14). As described for **10**, treatment of **9** (246 mg, 0.817 mmol) with TBDMSCl (249.1 mg, 1.635 mmol), imidazole, and DMAP (5 mg) in DMF (3 mL) produced **14** (334 mg, 98%) as a white solid (petroleum ether): mp 81–83 °C; $[\alpha]^{25}_D$ +89.5° (*c* 1.14, $CHCl_3$); IR (Nujol) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3 H), 0.09 (s, 3 H), 0.60–1.64 (m, 13 H), 0.88 (s, 9 H), 1.63 (d, J = 7.08 Hz, 3 H), 2.48 (m, 2 H), 3.70 (m, 1 H), 4.34 (m, 1 H), 5.40 (q, J = 7.08 Hz, 1 H), 7.28 (m, 5 H). Anal. Calcd for $C_{25}H_{41}NO_2Si$: C, 72.23; H, 9.94; N, 3.37. Found: C, 72.24; H, 9.93; N, 3.51.

(4*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(cyclohexylmethyl)-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidin-2-one (15). Similar reaction of **14** (265 mg, 0.639 mmol) with sodium (55 mg, 2.4 mmol) in liquid ammonia (8 mL) followed by the treatment with $(Boc)_2O$ (279 mg, 1.28 mmol) and DMAP (78 mg, 0.639 mmol) in CH_3CN (2 mL) as described for **11** afforded **15** (198 mg, 76%) as a white solid (petroleum ether): mp 132–133 °C; $[\alpha]^{25}_D$ +46.6° (*c* 0.62, $CHCl_3$); IR (Nujol) 1795, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.87–1.83 (m, 13 H), 0.90 (s, 9 H), 1.53 (s, 9 H), 2.55 (d, J = 8.30 Hz, 2 H), 4.22 (m, 1 H), 4.48 (m, 1 H). Anal. Calcd for $C_{22}H_{41}NO_4Si$: C, 64.19; H, 10.04; N, 3.40. Found: C, 64.21; H, 10.06; N, 3.37.

Ethyl (3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-5-cyclohexylpentanoate (16). To a solution of **15** (179 mg, 0.436 mmol) in ethanol (1 mL) was add 2 M NaOEt in EtOH (0.24 mL, 0.479 mmol). A similar workup to that described for **15** yielded **19** (99.5 mg, 50%) as an oil: $[\alpha]^{25}_D$ −33.5° (*c* 1.07, MeOH); IR (neat) 3400, 1740, 1710 cm^{-1}; ^1H NMR $CDCl_3$) δ 0.05 (s, 3 H), 0.10 (s, 3 H), 0.85–1.85 (m, 13 H), 0.88 (s, 9 H), 1.26 (t, J = 7.08 Hz, 3 H), 1.45 (s, 9 H), 2.37–2.56 (m, 2 H), 3.75 (m, 1 H), 4.13 (q, J = 7.08 Hz, 2 H), 4.18 (m, 1 H), 4.49 (d, J = 9.52 Hz, 1 H); HRMS calcd for $C_{24}H_{47}NO_5Si$ 457.3221, found 457.3217.

Ethyl (3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5-cyclohexyl-3-hydroxypentanoate (17). Treatment of **16** (97.8 mg, 0.214 mmol) with 1 M *n*-Bu_4NF (0.47 mL, 0.47 mmol) in THF (1 mL) yielded **20** (64.5 mg, 88%) as an oil: $[\alpha]^{25}_D$ −34.0° (*c* 1.22, MeOH) [lit.[10a] $[\alpha]^{30}_D$ −31.2° (*c* 1.1, MeOH)]; IR (neat) 3450, 1740, 1710 cm^{-1}; ^1H NMR (CD_3OD) δ 0.82–1.95 (m, 13 H), 1.25 (t, J = 7.08 Hz, 3 H), 1.44 (s, 9 H), 2.42 (ABX, J_{AB} = 16, J_{AX} = 8.5, J_{BX} = 4.9 Hz, 2 H), 3.66 (m, 1 H), 3.98 (m, 1 H), 4.13 (d, J = 7.08 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.92, 26.00, 26.11, 26.30, 28.14, 32.72, 33.47, 34.01, 38.49, 40.06, 51.05, 60.61, 69.40, 78.78, 155.77,

173.34; HRMS calcd for $C_{18}H_{33}NO_5$ 343.2358, found 343.2398.

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Convenient Route to Functionalized Styrenes via Pyrolysis of Functionalized Polystyrene

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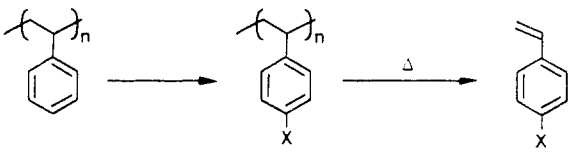
Functionalized styrenes have been shown to be useful starting materials for a number of organic syntheses[1] as well as polymer syntheses.[2] It is important, therefore, to develop a convenient preparative method for styrene monomers or intermediates that contain functionality on the aromatic ring. So far, the conventional procedure for the preparation of functionalized styrene monomers consists of several steps involving dehydration or dehydrobromination at the last stage of the synthesis to generate the styrenic double bond.[3] The overall yields are usually low to moderate. Recently, Stille demonstrated an elegant procedure to prepare functionalized styrenes by palladium-catalyzed coupling of aryl bromide with vinyltin reagents. An expensive vinyltributyltin is required for this method.[4]

Although polystyrene is known to be thermally depolymerized to give monomer,[5] pyrolysis has not been used actively for the preparation of functionalized styrene monomers. Various kinds of functionalized polystyrenes have been prepared quantitatively by chemical modification of polystyrene.[2,6] We have found that these functionalized polystyrenes were pyrolyzed readily under reduced pressure to give the corresponding monomers, as will be discussed in this paper (Scheme I).

Scheme I



Functionalized polystyrenes are considered to be double-bond-protected, functional styrenes that can be deprotected by pyrolysis. Protected styrene can stand exposure to vigorous reaction conditions for functionalization. The functionalized polystyrenes shown in Table I were prepared by chemical modifications of polystyrene according to the procedures given in the literature. Almost quantitative conversions were obtained in all cases. These polymeric reactions show high para selectivity in electrophilic ring substitution reactions due to steric hindrance in the ortho positions caused by the polymeric structure. This saves separation of the other ring isomers, which are sometimes unavoidable in conventional preparations. Brominated polystyrene was obtained directly from polystyrene and bromine in the presence of a catalytic amount of $FeCl_3$ in 93% yield. The degree of bromination is easily controlled by the quantity of bromine added to the polystyrene. A gel-type copolymer of styrene–divinylbenzene was also brominated by the same procedure. Pyrolysis experiments were carried out by using a typical distillation apparatus under reduced pressure. At a temperature below 300 °C, the polystyrene derivatives degrade with no volatile products. Use of an open flame (500–650 °C) was effective for pyrolysis of the functionalized polystyrenes, to give volatile monomers. Indeed, brominated polystyrene was readily pyrolyzed to give a deep orange colored liquid, which was redistilled to give a colorless liquid of 4-bromostyrene in 78% isolated yield. Meta and ortho isomers were not detected after the redistillation.

This method has been extended to a number of functionalized polystyrenes, as summarized in Table I. Insoluble polymer beads of styrene–divinylbenzene copolymer can be utilized also for the pyrolysis (entries 2, 5, 10). Starting from partially functionalized polystyrenes, the desired monomers obtained were contaminated with styrene and other volatiles (entries 2, 11). Reduced isolated yields of the desired monomers come from their purification process. In comparison with the conventional method, the pyrolysis method appears to be a much easier and more efficient method by which to obtain functionalized styrene monomers. For example, in a conventional method, 4-cyanostyrene was prepared from dibromobenzene in an overall yield of only 6%.[14] Polymeric reactions such as bromination and cyanation of polystyrene have been demonstrated to proceed almost quantitatively. In the pyrolysis method, 4-cyanostyrene was obtained in 64% yield from polystyrene (run 3). In addition, the pyrolysis method needs no workup process, as is usually required in organic synthesis. In another example, many preparative routes to 4-vinylbenzyl chloride have been reported with the overall yield only up to 22%.[17] These routes involve the separation of the intermediates of ortho and para isomers. A greater than 50% isolated yield of 4-vinylbenzyl chloride was attained by the pyrolysis method.

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