Asymmetric Intramolecular Amidation of *N*-(*tert*-Butoxycarbonyl)-3-hydroxy-4-pentenylamine. A New Entry to Chiral Building Blocks for the Synthesis of Biologically Active Nitrogen-Containing Compounds

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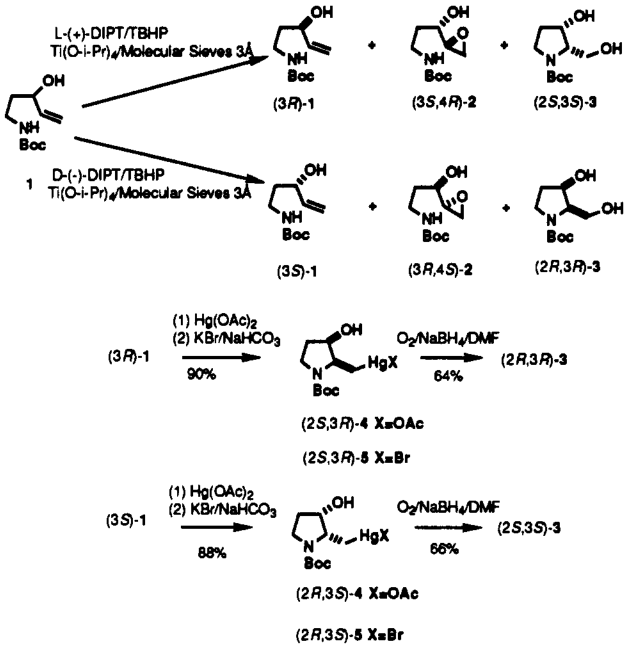
Sharpless reaction of racemic *N*-(*tert*-butoxycarbonyl)-3-hydroxy-4-pentenylamine (**1**) leads to both an asymmetric kinetic resolution to provide optically active **1**, which was subsequently used for intramolecular amidomercuration, and asymmetric epoxidation followed by concomitant cyclization into optically active *cis*-3-hydroxy-2-(hydroxymethyl)pyrrolidine (**3**). Optically active **1** and **3** have been expediently used as chiral building blocks in the asymmetric synthesis of several biologically active natural products.

Diastereoselective electrophilic addition to the double bond of allylic alcohols has received considerable attention, and numerous experimental and theoretical approaches to this subject have been reported recently.[1] The protocol based on the diastereoselective intramolecular addition of heteronucleophiles, directed by an allylic hydroxyl, has proven to be useful for the synthesis of heterocyclic compounds with defined stereochemistry, as exemplified by the synthesis of biologically active compounds.[2] However, asymmetric intramolecular amination of this system has been studied only sparsely.[3] In this paper we describe the finding that the Sharpless asymmetric oxidation[4] of racemic *N*-(*tert*-butoxycarbonyl)-3-hydroxy-4-pentenylamine (**1**) allows not only asymmetric kinetic resolution to provide the optically active compounds (3*R*)-**1** or (3*S*)-**1**, which are used for intramolecular amidomercuration, but also promotes asymmetric epoxidation, accompanied by concomitant intramolecular N-alkylation to give optically active *cis*-3-hydroxy-2-(hydroxymethyl)pyrrolidine (**3**).

Scheme I



We examined the kinetic resolution and asymmetric epoxidation of racemic **1** using the Sharpless reagent [*tert*-butyl hydroperoxide (TBHP) (0.6 equiv), L-(+)-diisopropyl tartrate (L-(+)-DIPT) (1.2 equiv), Ti(O-i-Pr)$_4$ (1 equiv), and molecular sieves (3 Å)/CH$_2$Cl$_2$/–20 °C/15 days], and found that three products [(3*R*)-**1** (36%), the epoxy alcohol (3*S*,4*R*)-**2** (5%), and the pyrrolidine (2*S*,3*S*)-**3** (33%)] were formed (Scheme I). Similar reaction of racemic **1** using D-(–)-DIPT gave (3*S*)-**1** (46%), (3*R*,4*S*)-**2** (11%), and (2*R*,3*R*)-**3** (33%).[5] The pyrrolidine **3** could have resulted from **2** by Ti(O-*i*-Pr)$_4$-mediated intramolecular N-alkylation. In fact, the treatment of (3*S*,4*R*)-**2** with Ti(O-*i*-Pr)$_4$ in dichloromethane at –20 °C provided (2*S*,3*S*)-**3** in 66% yield.

Stereoselective amidomercuration[2j] of (3*R*)- and (3*S*)-**1** with mercuric acetate was carried out to give *cis*-2-[(acetoxymercuri)methyl]-3-hydroxypyrrolidines, (2*S*,3*R*)- and (2*R*,3*S*)-**4**, which, without purification, were converted with

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[5] Enantioselectivities were determined by ^{19}F NMR analysis on the corresponding (+)-α-methoxy-α-trifluorophenylacetic acid (MTPA) ester of **1** or by ^{1}H NMR analysis on the MTPA ester of **7** derived from **3**, and the resulting enantioselectivities were 90% ee for (3*R*)-**1**, 91% ee for (3*S*)-**1**, 91% ee for (2*S*,3*S*)-**3**, and 92% ee for (2*R*,3*R*)-**3**.

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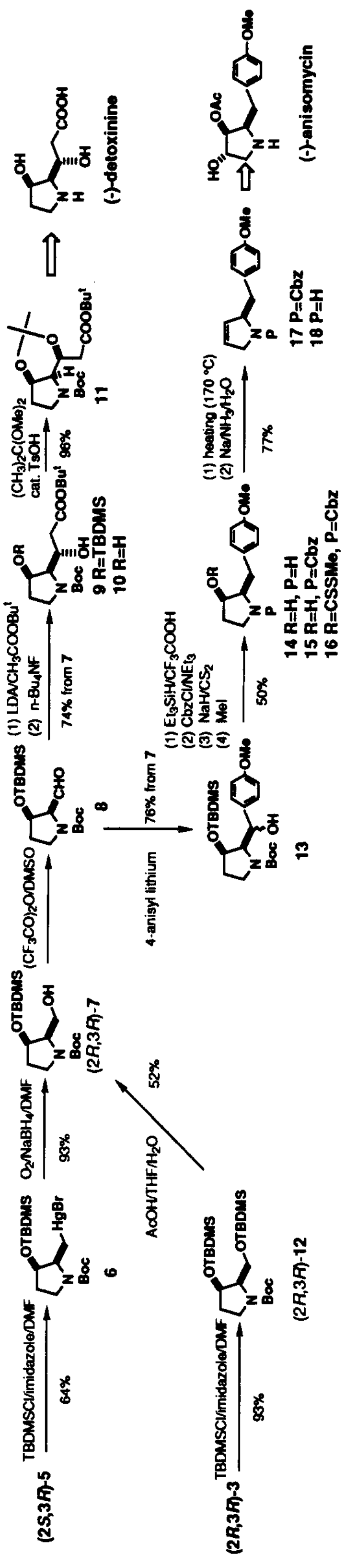
potassium bromide in the presence of sodium bicarbonate to the corresponding mercury bromides (2*R*,3*R*)- and (2*S*,3*S*)-**5** in 90% and 88% yields, respectively. No detectable amounts of the trans isomers were formed. The mercury bromides (2*S*,3*R*)- and (2*R*,3*S*)-**5** underwent oxidative demercuration (O_2/$NaBH_4$/DMF)[6] into (2*R*,3*R*)- and (2*S*,3*S*)-**3** in 56% and 47% yields, respectively, whose spectral data were identical with the above products of the Sharpless reaction.

Our attention was focused on the transformation of optically active **1** and **3** as chiral building blocks into biologically active compounds such as (−)-detoxinine,[7] (−)-anisomycin,[8] (+)-galantinic acid,[9] and (+)-3-hydroxyglutamic acid.[10] We first examined the conversion of (2*S*,3*R*)-**5** into (−)-detoxinine, an amino acid component of detoxine and a selective antagonist of the antibiotic blasticidin S. *tert*-Butyldimethylsilylation of (2*S*,3*R*)-**5** gave the silyl ether **6**, and subsequent reductive oxygenation of the latter afforded the primary alcohol (2*R*,3*R*)-**7** as an oil in 60% yield from (2*S*,3*R*)-**5**. Alternatively, (2*R*,3*R*)-**7** could be obtained from (2*R*,3*R*)-**3** by *tert*-butyldimethylsilylation and subsequent selective monodesilylation of the resulting disilylated pyrrolidine (2*R*,3*R*)-**12** in 52% yield. Swern oxidation of (2*R*,3*R*)-**7** gave the aldehyde **8**, and subsequent aldol condensation[12] with lithiated *tert*-butyl acetate afforded only one diastereomer **9** in 74% yield from (2*R*,3*R*)-**7**. Desilylation of **9** with *n*-Bu_4NF provided the diol **10**, which was ketalized to give intermediate **11**, previously converted to (−)-detoxinine.[13]

The efficient transformation of (2*R*,3*R*)-**7** into intermediate **18** for the construction of (−)-anisomycin, an antibiotic and fungistatic agent, was performed via a short route. The reaction of aldehyde **8** with 4-anisyllithium afforded the coupled product **13** in 76% yield from (2*R*,3*R*)-**7**. Exposure of **13** to triethylsilane in trifluoroacetic acid caused simultaneous desilylation, debutoxycarbonylation, and reduction of the benzylic hydroxyl group, providing the pyrrolidine **14**, which was N-protected with benzyloxycarbonyl chloride (CbzCl) to give the 3-hydroxypyrrolidine **15** in 64% overall yield from **13**. Xanthation of **15** provided **16**, which upon thermolysis at 170 °C via a Chugaev reaction produced the 3-pyrroline **17** (78%). Debenzyloxycarbonylation of **17** with sodium/ammonia furnished the known secondary amine **18**,[14,15] which has been converted into (−)-anisomycin by Meyers.[15]

Our synthesis of (+)-galantinic acid, an unusual amino acid component from acidic degradation[16] of the peptide antibiotic galantin I,[17] began with disilylation of (2*S*,3*S*)-**3**, followed by oxidation with catalytic RuO_2 in the presence of excess sodium periodate in ethyl acetate/water[18] affording the lactam (4*S*,5*S*)-**19** in 63% overall yield (Scheme

Scheme II



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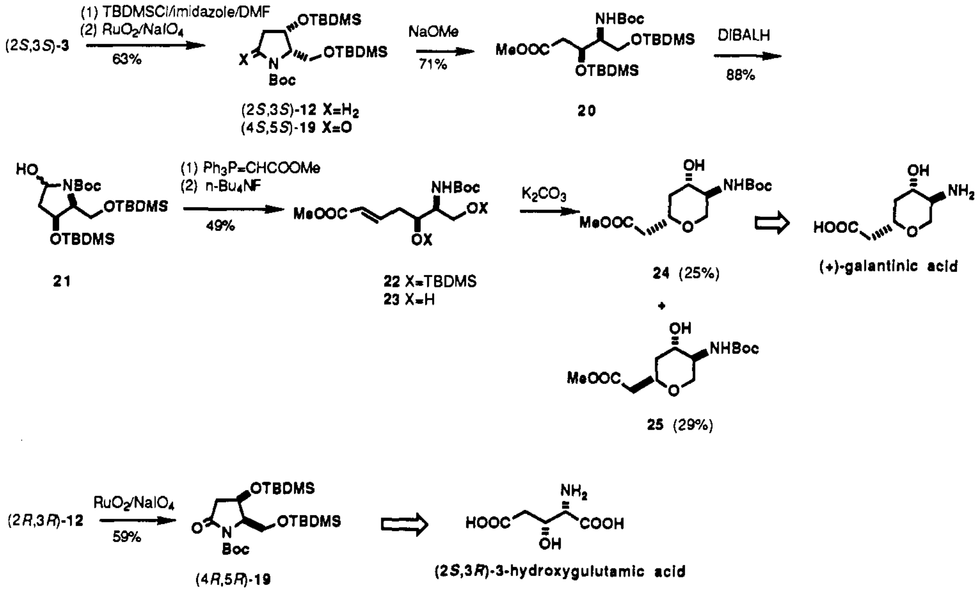
Scheme III



III). Sodium methoxide mediated ring cleavage of **19** and reduction of the resulting methyl ester **20** with diisobutylaluminum hydride afforded a hemiacetal (**21**). Wittig reaction of **21** gave the unsaturated ester **22**, and desilylation with n-Bu$_4$NF, followed by cyclization with potassium carbonate, provided N-Boc-galantinic acid methyl ester (**24**) and its C-3 epimer **25**.[19]

Finally, oxidation of (2R,3R)-**12** with ruthenium(VIII) oxide gave the γ-lactam (4R,5R)-**19**, which has previously been converted via ring opening into (2S,3R)-3-hydroxyglutamic acid,[2k,20] an amino acid component of the peptide antibiotic S-520.

In summary, the Sharpless asymmetric oxidation of racemic **1** simultaneously provides two chiral building blocks (optically active **1** and **3**), whose utilities were demonstrated by asymmetric synthesis of several biologically active compounds. This method provides a promising access to chiral pyrrolidine-related alkaloids and unusual amino acids containing a vicinal amino alcohol functionality. Further investigation is currently ongoing.

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. Proton magnetic resonance (^{1}H NMR) were recorded either at 60 or at 270 MHz. Carbon-13 NMR spectra were determined at 50 MHz. Column chromatography was performed on silica gel (Fuji-Davision 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 was used as eluant unless otherwise specified. All extracts were dried over Na$_2$SO$_4$ unless otherwise specified.

General Procedure for Sharpless Oxidation of Racemic 1. To a mixture of racemic **1**[3j] (10 mmol) and 3-Å molecular sieves (20 mmol %) in CH$_2$Cl$_2$ (88 mL) was added freshly distilled L-(+)- or D-(−)-DIPT (12 mmol). After the mixture was cooled to −20 °C, Ti(O-i-Pr)$_4$ (10 mmol) was added, and then the resulting mixture was stirred for 30 min. TBHP (6 mmol, 3 M in 2,2,4-trimethylpentane, dried with 3-Å molecular sieves) was added to the mixture, and the resulting mixture was kept at −20 °C for 15 days. A solution of FeSO$_4$·7H$_2$O (6 mmol) and citric acid (12 mmol) in H$_2$O (26 mL) was added to the reaction mixture at 0 °C. After the mixture was stirred at room temperature for 30 min, the molecular sieves were removed by filtration. The organic phase of the filtrate was separated, and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried, and evaporated. To a solution of the residue in ether (16 mL) was added a solution of NaOH (7.89 g) and NaCl (1.32 g) in H$_2$O (23.7 mL) at 0 °C, and the resulting mixture was vigorously stirred for 1 h. After addition of H$_2$O (5 mL), the organic phase was separated. The aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was chromatographed to yield optically active **1**, **2**, and **3**.

(3*R*)-*N*-(*tert*-Butoxycarbonyl)-3-hydroxy-4-pentenylamine [(3*R*)-1]: oil; bp 80–90 °C (0.7 mmHg); $[\alpha]^{25}_{D}$ −8.27° (c, 1.34, CHCl$_3$); IR (neat) 3350, 1690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.44 (s, 9 H), 1.56–1.76 (m, 2 H), 3.11–3.22 (m, 1 H), 3.36 (br s, 2 H), 4.19 (br s, 1 H), 5.03 (br s, 1 H), 5.08–5.30 (m, 2 H), 5.82–5.95 (m, 1 H); HRMS calcd for C$_{10}$H$_{19}$NO$_3$ 201.1365, found 201.1373. Anal. Calcd for C$_{10}$H$_{19}$NO$_3$·0.25H$_2$O: C, 58.44; H, 9.55; N, 6.80. Found: C, 58.32; H, 9.24; N, 6.73.

(3*S*,4*R*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-4,5-epoxypentane [(3*S*,4*R*)-2]: oil; $[\alpha]^{25}_{D}$ +10.9° (c 1.625, CHCl$_3$); IR (neat) 3350, 1680 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.40, 1.52–1.65 (m, 1 H), 1.71–1.83 (m, 1 H), 2.71–2.77 (m, 2 H), 2.94–2.98 (m, 1 H), 3.15–3.24 (m, 2 H), 3.32–3.47 (m, 1 H), 3.73 (br s, 1 H), 5.01 (br s, 1 H); HRMS calcd for C$_{10}$H$_{19}$NO$_4$ 217.1313, found 217.1270.

(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3-hydroxypyrrolidine [(2*S*,3*S*)-3]: oil; $[\alpha]^{25}_{D}$ +30.9° (c 3.27, CHCl$_3$); IR (neat) 3400, 1695, 1670 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.46 (s, 9 H), 1.58–1.74 (m, 1 H), 1.78–1.92 (m, 1 H), 2.98–3.13 (br s, 1 H), 3.22–3.33 (m, 1 H), 3.37–3.61 (m, 3 H), 3.72–3.81 (br s, 1 H), 3.82–3.92 (br s, 1 H); HRMS calcd for C$_{10}$H$_{19}$NO$_4$ 217.1313, found 217.1322. Anal. Calcd for C$_{10}$H$_{19}$NO$_4$·0.5H$_2$O: C, 53.08; H, 8.91; N, 6.19. Found: C, 52.83; H, 8.64; N, 6.10.

(3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-hydroxy-4-pentenylamine [(3*S*)-1]: oil; bp 85–90 °C (0.7 mmHg); $[\alpha]^{25}_{D}$ +8.47° (c 1.08, CHCl$_3$); IR (neat) 3360, 1690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.44 (s, 9 H), 1.56–1.76 (m, 2 H), 3.11–3.22 (m, 1 H), 3.36 (br s, 2 H), 4.19 (br s, 1 H), 5.03 (br s, 1 H), 5.08–5.30 (m, 2 H), 5.82–5.95 (m, 1 H); HRMS calcd for C$_{10}$H$_{19}$NO$_3$ 201.1365, found 201.1375. Anal. Calcd for C$_{10}$H$_{19}$NO$_3$·0.25H$_2$O: C, 58.44; H, 9.55; N, 6.80. Found: C, 58.19; H, 9.34; N, 6.62.

(3*R*,4*S*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-4,5-epoxypentane [(3*R*,4*S*)-2]: oil; $[\alpha]^{25}_{D}$ +11.6° (c 1.625, CHCl$_3$); IR (neat) 3360, 1690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.40, 1.52–1.65 (m,

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(20) Recent synthesis of (2S,3R)-3-hydroxyglutamic acid: Kunieda, T.; Ishizuka, T.; Higuchi, T.; Hirobe, M. *J. Org. Chem.* **1988**, *53*, 3381.

1 H), 1.71–1.83 (m, 1 H), 2.71–2.77 (m, 2 H), 2.94–2.98 (m, 1 H), 3.15–3.24 (m, 2 H), 3.32–347 (m, 1 H), 3.73 (br s, 1 H), 5.01 (br s, 1 H); HRMS calcd for $C_{10}H_{19}NO_4$ 217.1313, found 217.1270.

(2*R*,3*R*)-1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3-hydroxypyrrolidine [(2*R*,3*R*)-3]: oil; $[\alpha]^{25}_D$ −31.4° (*c* 1.03, $CHCl_3$); IR (neat) 3380, 1690, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.58–1.74 (m, 1 H), 1.78–1.92 (m, 1 H), 2.98–3.13 (br s, 1 H), 3.22–3.33 (m, 1 H), 3.37–3.61 (m, 3 H), 3.72–3.81 (br s, 1 H), 3.82–3.92 (br s, 1 H). Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.82; N, 6.45. Found: C, 55.10; H, 8.84; N, 6.37.

Reaction of (3*S*,4*R*)-2 with Ti(O-*i*-Pr)$_4$. A mixture of (3*S*,4*R*)-2 (25.2 mg, 0.116 mmol) and Ti(O-*i*-Pr)$_4$ (33 μL, 0.116 mmol) in CH_2Cl_2 (1.02 mL) was kept at −20 °C for 10 days. The mixture was washed with saturated $NaHCO_3$ and evaporated. The residue was purified by chromatography to yield (2*S*,3*S*)-3 (16.6 mg, 66%).

General Procedure for Amidomercuration of (3*R*)- or (3*S*)-1. A mixture of (3*R*)-1 or (3*S*)-1 (2 mmol) and $Hg(OAc)_2$ (3 mmol) in THF (22 mL) was stirred at room temperature for 24 h. The mixture was added to saturated $NaHCO_3$ (50 mL), and the resulting mixture was stirred at room temperature for 30 min. To the mixture was added saturated KBr (50 mL), and the resulting mixture was stirred at room temperature for 1.5 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried, and evaporated. The residue was purified by chromatography to yield (2*S*,3*R*)-5 (90%) and (2*R*,3*S*)-5 (88%).

(2*S*,3*R*)-1-(*tert*-Butoxycarbonyl)-2-(bromomercuri)-3-hydroxypyrrolidine [(2*S*,3*R*)-5]: oil; $[\alpha]^{25}_D$ −19.4° (*c* 1.825, $CHCl_3$); IR (neat) 3370, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 1.69–2.32 (m, 4 H), 3.14–3.59 (m, 3 H), 3.86–4.42 (m, 2 H).

(2*R*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-(bromomercuri)-3-hydroxypyrrolidine [(2*R*,3*S*)-5]: oil; $[\alpha]^{25}_D$ +19.1° (*c* 1.40, $CHCl_3$); IR (neat) 3370, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 1.69–2.32 (m, 4 H), 3.14–3.59 (m, 3 H), 3.86–4.42 (m, 2 H).

Oxidative Demercuration of (2*S*,3*R*)- or (2*R*,3*S*)-5. Oxygen was bubbled into a suspension of $NaBH_4$ (150 mg, 3.93 mmol) in DMF (37 mL) for 30 min. While oxygen was bubbled through the mixture, a solution of (2*S*,3*R*)-5 (1.36 g, 2.84 mmol) in DMF (125 mL) was added dropwise over 2 h. Oxygen bubbling was continued for 1 h, and ether was added. The precipitate was removed by filtration through Celite, and the filtrate was evaporated in vacuo. The residue was purified by chromatography to yield (2*R*,3*R*)-3 (397 mg, 64%). Similar treatment of (2*R*,3*S*)-5 (1.67 g, 3.47 mmol) in DMF (149 mL) with $NaBH_4$ (184 mg, 4.86 mmol) in DMF (44 mL) gave (2*S*,3*S*)-3 (500 mg, 66%).

(2*S*,3*R*)-1-(*tert*-Butoxycarbonyl)-2-[(bromomercuri)methyl]-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine (6). A mixture of (2*S*,3*R*)-5 (962 mg, 2 mmol), imidazole (340 mg, 5 mmol), DMAP (49 mg, 0.40 mmol), and TBDMSCl (452 mg, 3 mmol) in DMF (8 mL) was stirred at room temperature for 24 h. To the reaction mixture was added ether (3.0 mL), and the resulting mixture was successively washed with brine (5 mL), 5% HCl (2 × 5 mL), 5% $NaHCO_3$ (5 mL), and brine (5 mL). The organic phase was dried and evaporated. The residue was purified by chromatography to yield 6 (750 mg, 64%): mp 168–169 °C; $[\alpha]^{25}_D$ −14.4° (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 1.86 (s, 9 H), 1.41 (s, 9 H), 1.50–2.10 (m, 4 H), 3.06–3.41 (m, 2 H), 3.76–4.46 (m, 2 H).

(2*R*,3*R*)-1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine (7). According to the reductive oxygenation described above, treatment of 6 (944 mg, 1.59 mmol) with $NaBH_4$ (84 mg, 2.2 mmol) in DMF (20 mL) gave 7 (491 mg, 93%) as an oil: $[\alpha]^{25}_D$ −32.5° (*c* 1.06, $CHCl_3$) [lit.[11] $[\alpha]^{24}_D$ −34.4° (*c* 1.99, $CHCl_3$)]; IR (neat) 3440, 1695, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 3 H), 0.13 (s, 3 H), 0.89 (s, 9 H), 1.47 (s, 9 H), 1.75–2.10 (m, 2 H), 3.38–3.50 (m, 2 H), 3.65–3.95 (m, 3 H), 4.35–4.56 (m, 2 H); HRMS calcd for $C_{16}H_{33}NO_4Si$ 331.2178, found 331.2133.

***tert*-Butyl (3*R*)-3-Hydroxy-3-[(2*R*,3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]propionate (9).** To a solution of DMSO (0.174 mL, 2.38 mmol) in CH_2Cl_2 (1.16 mL) was added a solution of trifluoroacetic anhydride (0.247 mL, 1.78 mmol) at −78 °C. After the mixture was stirred for 20 min, a solution of (2*R*,3*R*)-7 (394 mg, 1.19 mmol) in CH_2Cl_2 (1.16 mL) was added. After the mixture was stirred for 2 h at −78 °C, triethylamine (0.58 mL) was added, and the resulting mixture was gradually warmed to 0 °C. After the mixture was stirred for 1 h, brine (5 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine, dried, and evaporated to yield the crude aldehyde 8 as an oil. To a solution of hexamethyldisilazane (0.376 mL, 1.78 mmol) in THF (2.84 mL) was added *n*-BuLi (1.11 mL, 1.55 M in hexanes) at 0 °C. After being stirred for 20 min, the mixture was cooled to −78 °C, and a solution of *tert*-butyl acetate (0.24 mL, 1.78 mmol) was added dropwise to the mixture. After 30 min, 8 (1.19 mmol) in THF (0.58 mL) was added, and stirring was continued for 90 min. Brine (5 mL) was added to the mixture, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was chromatographed to yield 9 (426 mg, 80%) as an oil: $[\alpha]^{25}_D$ −35.96° (*c* 4.175, $CHCl_3$); IR (neat) 3450, 1731, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.92 (s, 9 H), 1.45 (s, 18 H), 1.94–2.11 (m, 2 H), 2.34–2.71 (m, 2 H), 3.37–3.51 (m, 3 H), 3.82–3.92 (m, 1 H), 4.32–4.57 (m, 2 H); MS *m/z* 388 (M^+ − *t*-Bu).

***tert*-Butyl (3*R*)-3-Hydroxy-3-[(2*R*,3*S*)-3-hydroxy-2-pyrrolidinyl]propionate (10).** A mixture of 9 (343 mg, 0.769 mmol) and 1 M *n*-Bu_4NF in THF (0.92 mL, 0.92 mmol) in THF (1.4 mL) was stirred at 0 °C for 30 min. After addition of brine (2 mL), the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic solvents were washed with brine, dried, and evaporated. The residue was purified by chromatography to yield 10 (234 mg, 92%): mp 122–123 °C; $[\alpha]^{26}_D$ −53.0° (*c* 3.44, $CHCl_3$); IR (KBr) 3358, 1373, 1721, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H), 1.95–2.05 (m, 1 H), 2.05–2.12 (m, 1 H), 2.59 (br s, 2 H), 2.95 (d, *J* = 7.56 Hz, 1 H), 3.41–3.46 (m, 2 H), 3.91 (dd, *J* = 3.91, 7.08 Hz, 1 H), 4.19 (br s, 1 H), 4.46 (br s, 2 H). Anal. Calcd for $C_{16}H_{29}ON$: C, 57.98; H, 8.80; N, 4.23. Found: C, 57.67; H, 8.70; N, 4.21.

***tert*-Butyl [4*S*-(4α,4aα,7aα)]-5-(*tert*-Butoxycarbonyl)hexahydro-2,2-dimethyl-1,3-dioxino[5,4-*b*]pyrrole-4-acetate (11).** A mixture of 10 (165 mg, 0.498 mmol), 2,2-dimethoxypropane (73.4 μL, 0.598 mmol), *p*-toluenesulfonic acid (0.08 mg), and molecular sieves (3 Å) was refluxed for 1.5 h. After evaporation of the solvent, the residue was purified by chromatography to yield 11 (178 mg, 96%): mp 90–90.5 °C; $[\alpha]^{25}_D$ −103.0° (*c* 2.23, $CHCl_3$) [lit[13] mp 90–91 °C, $[\alpha]^{25}_D$ −100° (*c* 1.8, $CHCl_3$)]; IR (KBr) 1720, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.46 (s, 9 H), 1.78–1.88 (m, 2 H), 2.39 (br s, 1 H), 2.74 (br s, 1 H), 3.38–3.49 (m, 1 H), 3.74–3.81 (m, 2 H), 4.56 (br s, 1 H), 4.57 (br s, 1 H). Anal. Calcd for $C_{19}H_{33}O_6N$: C, 61.43; H, 8.95; N, 3.77. Found: C, 61.27; H, 8.76; N, 3.53.

(2*R*,3*R*)-1-(*tert*-Butoxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine [(2*R*,3*R*)-(12)]. According to the procedure described for 6, treatment of (2*S*,2*R*)-5 (773 mg, 3.56 mmol) with imidazole (1.21 g, 17.8 mmol), TBDMSCl (1.34 g, 8.89 mmol), and DMAP (87 mg, 0.71 mmol) in DMF (9.4 mL) gave (2*R*,3*R*)-12 (1.48 g, 93%) as an oil: $[\alpha]^{25}_D$ −22.1° (*c* 1.235, $CHCl_3$); IR (neat) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00–0.07 (m, 12 H), 0.85 (s, 9 H), 0.88 (s, 9 H), 1.43 (s, 9 H), 1.85–1.95 (m, 1 H), 1.98–2.15 (m, 1 H), 3.18–3.60 (m, 3 H), 3.80 (br s, 2 H), 4.25–4.35 (br s, 1 H); MS *m/z* 334 (M^+ − Boc).

(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine [(2*S*,3*S*)-12]. Similar treatment of (2*R*,3*S*)-5 (653 mg, 3.01 mmol) with imidazole (1.02 g, 15.0 mmol), TBDMSCl (1.13 g, 7.52 mmol), and DMAP (74 mg, 0.060 mmol) in DMF (8 mL) gave (2*S*,3*S*)-12 (1.07 g, 80%) as an oil: $[\alpha]^{25}_D$ +20.6° (*c* 1.05, $CHCl_3$); IR (neat) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00–0.07 (m, 12 H), 0.85 (s, 9 H), 0.88 (s, 9 H), 1.43 (s, 9 H), 1.85–1.95 (m, 1 H), 1.98–2.15 (m, 1 H), 3.18–3.60 (m, 3 H), 3.80 (br s, 2 H), 4.25–4.35 (br s, 1 H); MS *m/z* 388 (M^+ − Boc).

(2*S*,3*R*)-1-(*tert*-Butoxycarbonyl)-2-[1-hydroxy-1-(4-methoxyphenyl)methyl]-3-hydroxypyrrolidine (13). According to the procedure described for 9, treatment of 7 (554 mg, 1.67 mmol) with DMSO (0.24 mL, 3.34 mmol), trifluoroacetic acid (0.35 mL, 2.50 mmol), and triethylamine (0.82 mL) in CH_2Cl_2 (2.5 mL) gave crude 8. To a solution of 4-bromoanisole (0.418 mL, 3.34 mmol) in THF (3.11 mL) was added *n*-BuLi (2.09 mL, 1.5

M in hexane) at −78 °C. After being stirred at −78 °C for 30 min, the mixture was added to a solution of crude aldehyde 8 in THF (5.6 mL). The reaction mixture was stirred at −78 °C for 30 min and then quenched with saturated NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried, and evaporated. The residue was purified by chromtography to yield **13** (556 mg, 76%) as an oil: $[\alpha]^{25}_{\mathrm{D}}$ −28.9° (*c* 3.02, $CHCl_3$); IR (neat) 3425, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (br s, 6 H), 0.92 (s, 9 H), 1.37 (s, 9 H), 1.61–2.14 (m, 2 H), 3.05–3.45 (m, 2 H), 3.77 (s, 3 H), 3.98–4.68 (m, 3 H), 4.81–5.13 (m, 1 H), 6.73 (d, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H); HRMS $C_{23}H_{39}NO_5Si$ 364.1944, found, 364.1954.

(2*R*,3*R*)-1-(Benzyloxycarbonyl)-2-[(4-methoxyphenyl)methyl]-3-hydroxypyrrolidine (15). A mixture of **13** (251 mg, 0.573 mmol), trifluoroacetic acid (663 μL, 8.6 mmol), and triethylsilane (1.01 mL, 0.631 mmol) was stirred at room temperature for 18 h. After evaporation, 10% HCl (2.5 mL) was added to the residue. The mixture was washed with CH_2Cl_2 (3 × 2 mL) and evaporated to yield crude pyrrolidine **14**. To a mixture of crude **14** in CH_2Cl_2 (4.3 mL) was added triethylamine (0.2 mL, 1.43 mmol) and then benzyloxycarbonyl chloride (0.12 mL, 0.86 mmol) with ice cooling. The mixture was stirred at room temperature for 4 h. After evaporation of the solvent, the residue was chromatographed to yield **15** (121 mg, 62%) as an oil: $[\alpha]^{25}_{\mathrm{D}}$ −4.99° (*c* 1.145, $CHCl_3$); IR (neat) 3440, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–1.77 (m, 1 H), 1.80–2.06 (br s, 1 H), 2.23–2.51 (m, 1 H), 2.84–2.96 (m, 2 H), 3.37–3.54 (m, 2 H), 3.73 (s, 3 H), 3.98–4.05 (m, 1 H), 4.24 (br s, 1 H), 5.11 (br s, 2 H), 6.75 (br s, 2 H), 7.08–7.29 (m, 2 H), 7.33 (s, 5 H); HRMS calcd for $C_{20}H_{24}NO_4$ 341.1627, found 341.1582.

(2*R*,3*R*)-1-(Benzyloxycarbonyl)-2-[(4-methoxyphenyl)methyl]pyrrolidin-3-yl *S*-Methyl Xanthate (16). To a suspension of NaH (15.8 mg, 0.395 mmol) and imidazole (0.8 mg) in THF (0.79 mL) was added a solution of pyrrolidine **15** (81 mg, 0.237 mmol) in THF (0.59 mL). After the mixture was refluxed for 3 h, carbon disulfide (79 μL, 1.3 mmol) was added. The mixture was refluxed for 30 min, methyl iodide (79 μL, 1.3 mmol) was added, and the mixture was refluxed for one additional hour. After addition of water (2 mL), the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography to yield **16** (83 mg, 81%) as an oil: $[\alpha]^{25}_{\mathrm{D}}$ −10.1° (*c* 2.175, $CHCl_3$); IR (neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81–1.94 (m, 1 H), 1.94–2.18 (br s, 1 H), 2.57 (s, 3 H), 2.82–2.97 (m, 2 H), 3.31–3.43 (m, 1 H), 3.51–3.62 (m, 2 H), 3.74 (s, 3 H), 4.33–4.45 (m, 1 H), 5.14 (br s, 2 H), 5.70–5.79 (m, 1 H), 6.74 (br d, 1 H), 6.93–7.21 (m, 1 H), 7.36 (br s, 9 H); HRMS $C_{22}H_{25}NO_4S_2$ calcd for 431.1223, found 431.1205.

(2*R*)-1-(Benzyloxycarbonyl)-2-[(4-methoxyphenyl)methyl]-3-pyrroline (17). Compound **16** (57.2 mg, 0.132 mmol) was heated at 170 °C under reduced pressure (12 mmHg) in a Kughelrohr apparatus. After 2 h the mixture was purified by chromatography to yield **17** (33 mg, 77%) as an oil: $[\alpha]^{25}_{\mathrm{D}}$ −199° (*c* 1.17, $CHCl_3$); IR (neat) 1690, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73–3.15 (m, 2 H), 3.67–3.85 (m, 1 H), 4.16 (dd, J = 15.4, 16.9 Hz, 1 H), 3.76, 3.77 (each s, 3 H), 4.67–4.82 (m, 1 H), 5.17–5.30 (m, 2 H), 5.63–5.72 (m, 2 H), 6.73–6.78 (m, 2 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.03 (d, J = 8.6 Hz, 1 H), 7.27–7.48 (m, 5 H); HRMS calcd for $C_{20}H_{22}NO_3$ 323.1522, found 323.1539.

(2*R*)-2-[(4-Methoxyphenyl)methyl]-3-pyrroline (18). To a solution of **17** (35.1 mg, 0.108 mmol) in aqueous ammonia (1.94 mL) and THF (0.2 mL) was added sodium metal (8.8 mg, 0.38 mmol). The mixture was stirred for 5 min and then quenched with aqueous ammonium chloride (1 mL). After evaporation of ammonia, the mixture was extracted with CH_2Cl_2 (5 × 2 mL). The extract was washed with brine, dried, and evaporated. The residue was purified by chromatography using a mixture of $CHCl_3$ and NH_3–MeOH (1:30) as an eluant to yield 18 (20.4 mg, 100%) as an oil: $[\alpha]^{25}_{\mathrm{D}}$ −93.8° (*c* 0.485, THF) [lit.[14] $[\alpha]^{24}_{\mathrm{D}}$ −101° (*c* 1.44, THF)]; IR (neat) 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (br s, 1 H), 2.71 (d, J = 6.83 Hz, 2 H), 3.54 (br s, 2 H), 3.78 (s, 3 H), 4.19 (br s, 1 H), 5.76 (*m, 1 H*), 5.85 (m, 1 H), 6.83 (d, J = 8.55 Hz, 2 H), 7.12 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 41.73, 53.13, 55.24, 66.77, 13.85, 128.35, 130.15, 130.66, 131.55, 158.15; HRMS calcd for $C_{12}H_{15}NO$ 189.1152, found 189.1136.

(4*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidin-2-one [(4*S*,5*S*)-19]. A mixture of RuO_2 (50 mg) in 10% aqueous $NaIO_4$ (7.5 mL, 3.5 mmol) was vigorously stirred, and a solution of (4*S*,5*S*)-**12** (868 mg, 1.95 mmol) in ethyl acetate (5.75 mL) was added. After stirring the mixture for 20 h, the precipitate was removed by filtration through Celite. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography to yield (4*S*,5*S*)-**19** (708 mg, 79%): mp 82–84 °C; $[\alpha]^{25}_{\mathrm{D}}$ +51.53° (*c* 0.75, $CHCl_3$); IR (Nujol) 1790, 1770, 1750, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H), 0.86 (s, 9 H), 0.91 (s, 9 H), 1.52 (s, 9 H), 2.50 (dd, J = 16.5, 10.0 Hz, 1 H), 3.91–4.06 (m, 3 H), 4.42–4.52 (m, 1 H). Anal. Calcd for $C_{22}H_{45}NO_5Si_2$: C, 57.47; H, 9.87; N, 3.05. Found: C, 57.43; H, 9.96; N, 3.23.

(4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidin-2-one [(4*R*,5*R*)-19]. Similar treatment of (4*R*,5*R*)-**12** (308 mg, 0.670 mmol) with RuO_2 (21 mg) and 10% $NaIO_4$ (5.57 mL, 2.6 mmol) in ethyl acetate (2.04 mL) for 20 h gave (4*R*,5*R*)-**19** (186 mg, 59%): mp 77–79 °C; $[\alpha]^{27}_{\mathrm{D}}$ −43.5° (*c* 1.44, $CHCl_3$) [lit.[11] $[\alpha]^{26}_{\mathrm{D}}$ −43° (*c* 1.6, $CHCl_3$), mp 78–79 °C]; IR (Nujol) 1789, 1764, 1750, 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H), 0.08 (s, 6 H), 0.86 (s, 9 H), 0.91 (s, 9 H), 1.52 (s, 9 H), 2.23–3.06 (m, 2 H), 3.78–4.12 (br s, 3 H), 4.23–4.60 (m, 1 H). Anal. Calcd for $C_{22}H_{45}NO_5Si_2$: C, 57.47; H, 9.87; N, 3.05. Found: C, 57.34; H, 9.60; N, 3.07.

(3*S*,4*S*)-Methyl 4-[(*tert*-Butoxycarbonyl)amino]-3,5-bis[(*tert*-butyldimethylsilyl)oxy]pentanoate (20). To a solution of (4*S*,5*S*)-**19** (54 mg, 0.11 mmol) in dry MeOH (0.194 mL) was added 2 M NaOMe (67.4 μL, 0.135 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. After addition of brine (2 mL), the resulting mixture was extracted with ether (3 × 3 mL). The combined organic extracts were washed with brine (2 mL), dried, and evaporated. The residue was purified by chromatography to yield **20** (39 mg, 71%): mp 40–42 °C; $[\alpha]^{25}_{\mathrm{D}}$ −2.98° (*c* 1.42, $CHCl_3$); IR (Nujol) 3640, 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06–0.10 (m, 12 H), 0.87 (s, 9 H), 0.90 (s, 9 H), 1.44 (s, 9 H), 2.51 (br d, J = 6.6 Hz, 2 H), 3.66 (s, 3 H), 3.37–3.80 (m, 3 H), 4.32–4.88 (m, 2 H). Anal. Calcd for $C_{23}H_{49}NO_4Si_2$: C, 56.17; H, 10.04; N, 2.85. Found: C, 56.01; H, 10.14; N, 2.80.

(2*S*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-hydroxypyrrolidine (21). To a solution of **20** (252 mg, 0.513 mmol) in toluene (1.18 mL) was added 1.5 M DIBAL in toluene (0.7 mL, 1.05 mmol) by syringe over 15 min at −78 °C. After the mixture was stirred for 1.5 h, 5 M CH_3COOH in benzene (0.67 mL) was added to the mixture, and the resulting mixture was warmed to room temperature. After addition of 10% aqueous tartaric acid (1.97 mL), the organic phase was separated. The aqueous phase was extracted with toluene (3 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried, and evaporated. The residue was purified by chromatography to yield **21** (207 mg, 88%) as an oil: $[\alpha]^{25}_{\mathrm{D}}$ +35.3° (*c* 0.975, $CHCl_3$); IR (neat) 3640, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.07 to 0.03 (m, 12 H), 0.79 (s, 9 H), 0.82 (s, 9 H), 1.41 (s, 9 H), 1.88–1.91 (m, 1 H), 2.09–2.31 (m, 1 H), 3.57–3.94 (m, 4 H), 4.47–4.60 (m, 1 H), 5.23–5.38 (m, 1 H); HRMS calcd for $C_{22}H_{47}NO_3Si_2$ 446.2833, found 446.2858.

(5*S*,6*S*)-Methyl 6-[(*tert*-Butoxycarbonyl)amino]-5,7-bis[(*tert*-butyldimethylsilyl)oxy]-2-heptenoate (22). A mixture of **21** (100 mg, 0.216 mmol) and (carbomethoxymethylene)triphenylphosphorane (109 mg, 0.320 mmol) in CH_3CN (93 mL) was refluxed for 18 h. After evaporation of the solvent, the residue was purified by chromatography to yield **22** (84 mg, 75%) as an oil: $[\alpha]^{25}_{\mathrm{D}}$ +31.3° (*c* 1.57, $CHCl_3$); IR (neat) 3460, 1730, 1720, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) −0.05 to 0.02 (m, 12 H), 0.83 (s, 9 H), 0.85 (s, 9 H), 1.39 (s, 9 H), 2.22–2.50 (m, 2 H), 3.32–3.44 (m, 2 H), 3.44–3.59 (m, 1 H), 3.66 (s, 3 H), 4.01–4.11 (m, 1 H), 4.63–4.74 (m, 1 H), 5.80 (d, J = 15 Hz, 1 H), 6.81–6.96 (m, 1 H); HRMS calcd for $C_{25}H_{49}NO_5Si_2$ 517.3253, found 517.3220.

(5*S*,6*S*)-Methyl 6-[(*tert*-Butoxycarbonyl)amino]-5,7-dihydroxy-2-heptenoate (23). A mixture of **22** (157 mg, 0.304 mmol) and 1 M *n*-Bu_4NF in THF (1.33 mL, 1.33 mmol) in THF

(1.42 mL) was stirred at 0 °C for 1.5 h. After addition of brine (2 mL), the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by chromatography to yield **23** (57 mg, 65%) as an oil: $[\alpha]^{25}_D$ −2.29° (*c* 1.245, $CHCl_3$); IR (neat) 3460, 1720, 1710, 1660 cm^{-1}; ^1H NMR ($CdCl_3$) δ 1.46 (s, 9 H), 2.38–2.42 (m, 2 H), 2.99 (br s, 1 H), 3.72 (s, 3 H), 3.58–3.76 (m, 2 H), 3.82–4.07 (m, 2 H), 5.41 (d, $J = 9.0$ Hz, 1 H), 5.92 (d, $J = 16$ Hz, 1 H), 6.96–7.05 (m, 1 H); HRMS calcd for $C_{13}H_{23}NO_6$ 289.1526, found 289.1559.

Methyl *N*-(*tert*-Butoxycarbonyl)galantinate (24) and the C-3 Epimer 25. A mixture of **23** (21.4 mg, 0.074 mmol) and K_2CO_3 (0.51 mg, 0.0037 mmol) in MeOH (0.2 mL) was stirred at room temperature for 20 h. After evaporation of the solvent, the residue was chromatographed to yield **24** (5.4 mg, 25%) and **25** (6.1 mg, 29%).

24: mp 106–106.5 °C; $[\alpha]^{25}_D$ −5.7° (*c* 0.19, $CHCl_3$) [lit[19b] $[\alpha]^{24}_D$ −5.4° (*c* 0.8, $CHCl_3$), mp 104.5–106 °C]; IR (KBr) 3457, 3404, 1734, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41–1.47 (m, 1 H), 1.44 (s, 9 H), 2.10 (ddd, $J = 1.95, 4.64, 12.09$ Hz, 1 H), 2.45 (dd, $J = 5.19, 15.6$ Hz, 1 H), 2.60 (dd, $J = 7.93, 15.6$ Hz, 1 H), 3.09 (dd, $J_1 = J_2 = 11.0$ Hz, 1 H), 3.40–3.51 (m, 1 H), 3.51–3.62 (m, 1 H), 3.70 (s, 3 H), 3.76–3.86 (m, 1 H), 4.01 (dd, $J = 4.88, 11.3$ Hz, 1 H), 4.48 (br s, 1 H). Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 54.38; H, 8.03; N, 4.37.

25: oil; $[\alpha]^{25}_D$ +19.2° (*c* 0.31, MeOH), [lit.[19a] $[\alpha]^{26}_D$ +20.8° (*c* 1.5, MeOH)]; IR (neat) 3448, 1736, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H), 1.68–1.73 (m, 2 H), 2.39 (dd, $J = 4.9, 15.1$ Hz, 1 H), 2.50 (dd, $J = 8.3, 15.1$ Hz, 1 H), 3.30–3.60 (m, 1 H), 3.67 (d, $J = 12.0$ Hz, 1 H), 3.70 (s, 3 H), 4.04–4.21 (m, 3 H), 5.18 (d, $J = 7.8$ Hz, 1 H); HRMS calcd for $C_{13}H_{23}NO_6$ 289.1526, found 289.1529.

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Registry No. (±)-**1**, 108998-71-6; (3*R*)-**1**, 130192-96-0; (3*S*)-**1**, 130192-97-1; (3*S*,4*R*)-**2**, 130096-82-1; (3*R*,4*S*)-**2**, 130193-00-9; (2*S*,3*S*)-**3**, 130193-01-0; (2*R*,3*R*)-**3**, 130193-02-1; (2*S*,3*R*)-**5**, 130194-08-0; (2*R*,3*S*)-**5**, 130194-09-1; **6**, 130193-03-2; **7**, 123287-88-7; **9**, 130096-76-3; **10**, 89985-84-2; **11**, 90011-42-0; (2*S*,3*S*)-**12**, 130192-98-2; (2*R*,3*R*)-**12**, 123287-87-6; **13**, 130096-77-4; **15**, 130120-89-7; **16**, 130096-78-5; **17**, 127852-65-7; **18**, 120409-91-8; (4*S*,5*S*)-**19**, 130192-99-3; (4*R*,5*R*)-**19**, 123163-94-0; **20**, 130096-79-6; **21**, 130096-80-9; **22**, 130096-81-0; **23**, 129397-16-6; **24**, 89985-68-2; **25**, 92143-26-5; AcOBu-*t*, 540-88-5; 4-BrC_6H_4OMe, 104-92-7; $Ph_3P{=}CHCOOMe$, 2605-67-6; (−)-detoxinine, 54963-44-9; (−)-anisomycin, 22862-76-6; (+)-galantinic acid, 78330-63-9; (3*S*,3*R*)-3-hydroxyglutamic acid, 6208-98-6.

Investigations into a Mild Diels–Alder Approach to 6-Substituted Quinazoline-2,4-dione Derivatives

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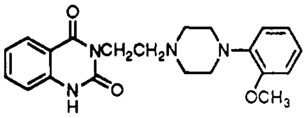
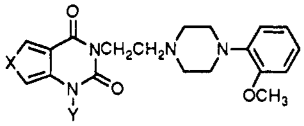
Furo[3,4-*d*]pyrimidine-2,4-dione (**2**) has been reacted with a number of dienophiles to give the Diels–Alder adducts such as **3** and **4** under very mild reaction conditions. Methyl acrylate gives only two regioisomeric endo products which have been isolated and characterized. Other dienophiles give mixtures of endo and exo products as well as of regioisomers. The product ratios were determined by high field ^1H NMR analysis. These adducts are dehydrated by treatment with acid to form some novel quinazoline-2,4-dione derivatives.

During the course of our work investigating the potent antihypertensive quinazoline-2,4-dione **1** (SGB 1534),[1] we prepared the furan isostere **2a**[2] as well as the thiophene isostere **2b**.[3] Investigation of the structure–activity relationships in these series of compounds led us to study N-substitution of furo[3,4-*d*]pyrimidinedione **2a** and we discovered an interesting Diels-Alder reaction which occurred in good yield under unusually mild conditions.



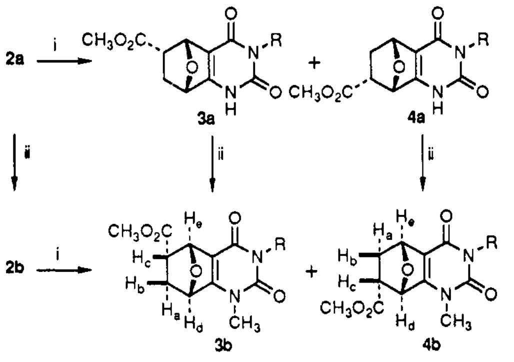
1



2a, X=O, Y=H
2b, X=S, Y=H
2c, X=O, Y=CH_3

In general, *N*1-alkyl derivatives may be prepared in the expected way by treatment of furo[3,4-*d*]pyrimidine-2,4-dione **2a** with sodium hydride and the appropriate alkyl halide in DMF at 0 °C to room temperature. However, when methyl 3-bromopropionate is used as the alkylating agent, no *N*-alkyl derivative was isolated, which is in sharp contrast to the analogous reaction for thiophene **2b**.[3] Instead, a mixture of two products is formed which was

Scheme I[a]



R=$CH_2CH_2N(CH_2CH_2)_2NC_6H_5$-*o*-$OCH_3$

[a] (i) Methyl 3-bromopropionate/NaH/DMF or methyl acrylate, DMF, room temperature. (ii) NaH, CH_3I, DMF, room temperature.

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