(m, 1 H); IR ($CHCl_3$) 3360, 1700, 1650, 1400, 1360, 1180, 1090 cm^{-1}; MS *m/e* 483 ($(M + H)^+$).

***N*-Butyl-2(*S*)-((3-(*tert*-butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*S*)-oxazolidinyl)-(*R*)-(((methylthio)thionyl)oxy)methyl)-3-methylbutanamide (15).** To a solution of **14** (109 mg, 0.23 mmol) in 25 mL of tetrahydrofuran at 0 °C was added carbon disulfide (1 mL, 16.6 mmol) and iodomethane (1 mL, 16.0 mmol). After the mixture was stirred for 5 min at 0 °C, sodium hydride (16 mg, 0.40 mmol, 60% in oil) was added. The resulting mixture was stirred for another 20 min, carefully poured into ice (~10 g), and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an oily residue, which was column chromatographed on silica gel (10% EtOAc–hexane) to provide 108 mg (84%) of **15** as a light yellow solid: mp 135–136 °C; R_f 0.45 (20% EtOAc–hexane); $[\alpha]_D$ +43.5° (*c* 1.27, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.75–1.95 (m, 18 H), 0.94 (t, J = 7.5 Hz, 3 H), 1.02 (br d, J = 6 Hz, 6 H), 1.43 (s, 9 H), 1.50 (s, 3 H), 1.72 (s, 3 H), 2.58 (s, 3 H), 2.69 (dd, J = 6, 7.5 Hz, 1 H), 3.29 (dt, J = 6, 6 Hz, 2 H), 4.06 (m, 1 H), 4.18 (m, 1 H), 5.62 (br t, J = 6 Hz, 1 H), 6.28 (dd, J = 3, 7.5 Hz, 1 H); IR ($CHCl_3$) 1690, 1660, 1400, 1200, 1060 cm^{-1}; MS *m/e* 573 ($(M + H)^+$). Anal. Calcd for $C_{29}H_{52}N_2O_5S_2$: C, 60.82; H, 9.08; N, 4.90; S, 11.18. Found: C, 60.41; H, 9.29; N, 4.96; S, 10.90.

Preparation of 9 by Reduction of 15. To a refluxing solution of tri-*n*-butyltin hydride (800 mg, 2.96 mmol) in toluene (30 mL) under nitrogen was added a solution of **15** (189 mg, 0.33 mmol) in toluene (2 mL). Reflux was continued for another 10 min, at which time TLC analysis indicated the total disappearance of **15**. The reaction mixture was cooled and concentrated under reduced pressure, and the resulting oily residue was chromatographed on silica gel (10% EtOAc–hexane) to provide 135 mg (88%) of **9**: $[\alpha]_D$ −13.6° (*c* 1.36, $CHCl_3$); ^1H NMR and MS match those from the sample prepared by the first route.

Acknowledgment. We would like to express their gratitude to Messrs. William Arnold and Hormoz Mazdiyasni for the preparation of aldehyde **3** and to Professor David A. Evans for sharing a preprint of the lithium hydroperoxide hydrolysis procedure.

Registry No. **2**, 105852-64-0; **3**, 117997-58-7; **4**, 107599-99-5; **5**, 112190-42-8; **6**, 129921-91-1; **7**, 129921-92-2; **8**, 129921-93-3; **9**, 129921-94-4; **10**, 80963-80-0; **11**, 129921-95-5; **13**, 129921-96-6; **14**, 129921-97-7; **15**, 129921-98-8; Me_2CHCH_2COCl, 108-12-3.

A Catalytic Enantioselective Synthesis of Denopamine, a Useful Drug for Congestive Heart Failure

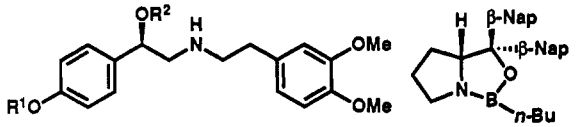
E. J. Corey* and John O. Link

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received April 16, 1990

Recent advances in drug specificity and duration of action have produced β-blockers and agonists that are highly effective in the treatment of cardiovascular disease, cardiac failure, asthma, and glaucoma. Notwithstanding these advances, many β-adrenoreceptor active drugs are sold as racemates[1] despite a clear preference for the use of enantiomerically pure drugs since the biological activity generally resides in a single enantiomer. A catalytic enantioselective method applicable to the synthesis of key arylethanolamine β-adrenoreceptor active drugs is desirable.

A good candidate for enantioselective synthesis is denopamine (**1**), a new selective β_2-agonist important for the treatment of congestive heart failure without promotion of increased myocardial oxygen consumption or heart rate.[2]



1 R^1=R^2=H (*R* form) **2**
8 R^1=TBS R^2=TES

Previous approaches to (*R*)-(−)-denopamine have included optical resolution[3a] or the use of chiral precursors ending with low overall yield[3c] or with significant racemization.[3b] Described here is a practical route to enantiomerically pure (*R*)-(−)-denopamine or its enantiomer in >60% overall yield that does not involve chromatography. This route demonstrates the applicability of the recently described CBS[4b] enantioselective catalytic reduction process to the synthesis of enantiomerically pure members of the therapeutically significant arylethanolamine drug class.

Reaction of 2-chloro-1-(4-hydroxyphenyl)ethanone (**3**)[5] with *tert*-butylchlorodimethylsilane (TBSCl) and imidazole in dimethylformamide (DMF) afforded ketone **4** in 96% yield. Ketone **4** was reduced by borane (0.6 equiv) in the

3 R^1=H
4 R^1=TBS

5 R^2=H R^3=Cl
6 R^2=H R^3=I
7 R^2=TES R^3=I

presence of (*R*)-oxazaborolidine·**2**[4e] as catalyst at 23 °C in tetrahydrofuran (THF) to give, after addition of methanolic hydrogen chloride and filtration, secondary alcohol **5** in 96% yield and 97% enantiomeric excess (ee%) and recovered 2-(di-β-naphthylhydroxymethyl)pyrrolidine as the crystalline hydrochloride salt. Chloro alcohol **5** was converted to iodide **6** (92%) by refluxing in acetone saturated with sodium iodide, which was then protected with ethyltrichlorosilane (TESCl) in DMF with imidazole to produce iodide **7** in 94% yield. Protected amino alcohol **8** was formed in 92% yield by reaction of iodide **7** with 2-(3,4-dimethoxyphenyl)ethylamine and triethylamine in THF at 100 °C in a sealed tube. Deprotection of amine **8** in methanol with potassium fluoride and hydrogen chloride afforded, after extractive isolation and recrystallization, optically pure denopamine (**1**) in 83% yield.

The practicality and effectiveness of this synthetic route can be evaluated from the detailed experimental procedure

(1) Lunts, L. H. C.; Main, B. G.; Tucker, H. In *Medicinal Chemistry, The Role of Organic Chemistry in Drug Research*; Roberts, S. M., Price, B. J., Ed.; Academic Press: New York, 1985; pp 49–92. The biological activity of arylethanolamine β-blockers and agonists is generally dependent on absolute stereochemistry, as exemplified by (*R*)-(−)-denopamine, which is the active form.

(2) (a) Bristow, M. R.; Hershberger, R. E.; Port, J. D.; Minobe, W.; Rasmussen, R. *Mol. Pharmacol.* **1989**, *35*, 295. (b) Yokoyama, H.; Yanagisawa, T.; Taira, N. *J. Cardiovasc. Pharmacol.* **1988**, *12*, 323.

(3) (a) Ikezaki, M.; Umino, N.; Gaino, M.; Aoe, K.; Iwakuma, T.; Ohishi, T. *Yakugaku Zasshi* **1986**, *106*, 80. (b) Noguchi, K.; Irie, K. Jpn. Patent 79 70,233, 1979; *Chem. Abstr.* **1979**, *91*, 630. (c) Noguchi, K.; Irie, K. Jpn. Patent 79 70,231, 1979; *Ibid.* **1979**, *91*, 630.

(4) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *Ibid.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) Corey, E. J. *Proceedings of the 31st National Organic Symposium*; American Chemical Society: Washington, DC, 1989; p 1. (e) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275. (f) Waldrop, M. M. *Science* **1989**, *245*, 354. (g) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

(5) Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Fujisaki, S.; Maeno, K.; Okamoto, T. *Synthesis* **1988**, *7*, 545.

0022-3263/91/1956-0442$02.50/0

that follows. It is noteworthy that in each step the isolation of product is simple and that the chiral amino alcohol 2-(di-β-naphthylhydroxymethyl)pyrrolidine can be recovered efficiently. This synthesis uses the enzyme-like CBS[4] catalyst **2**, which belongs to a new class of nontransition-metal catalysts that behave as structurally programmed molecular robots (chemzymes[4f]) since they recognize two chemical species, bind them in a predictable and precise three-dimensional assembly, and activate them for a reaction leading selectively to one enantiomeric product, which is then released to complete the catalytic work cycle. The synthesis of denopamine illustrates the value of the CBS process in the enantioselective construction of arylethanolamine β-adrenoreceptor active drugs. Other recent applications of the CBS reduction include the enantioselective synthesis of gingkolides A and B,[7a,b] forskolin,[7c] anti-PAF 2,5-diarylfurans,[7d] fluoxetine,[7e] and isoproterenol.[7f,9]

Experimental Section

1-(4-(*tert*-Butyldimethylsiloxy)phenyl)-2-chloroethanone (4). To a vigorously stirred solution of 220 mg (3.3 mmol) of imidazole and 400 mg (2.6 mmol) of TBSCl in 600 μL of DMF at 23 °C was added 2-chloro-1-(4-hydroxyphenyl)ethanone (**3**) (375 mg, 2.2 mmol), and after 3 min the mixture was diluted with 30 mL of diethyl ether (Et_2O). The organic extract was washed sequentially with 3 mL of water, 3 mL of saturated copper sulfate, and brine (3 × 3 mL), then dried ($MgSO_4$), and filtered through Celite. After evaporation of solvent under reduced pressure, residual DMF was removed by twice dissolving the residual colorless oil in 3 mL of dry toluene and concentration in vacuo to give 605 mg of ketone **4** (2.14 mmol, 97% yield) as a colorless waxy solid: mp 26–27 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.88 (d, 2 H, J = 8.8 Hz, Ar), 6.90 (d, 2 H, J = 8.8 Hz, Ar), 4.66 (s, 2 H, CH_2), 0.99 (s, 9 H, *tert*-butyl), 0.24 (s, 6 H, 2-CH_3); IR (neat) 2930, 1696, 1663, 1597 (C=O) cm^{-1}; FAB MS (70 eV) m/e 285 $(M + H)^+$.

***N*-Benzyl-(*R*)-(+)-proline Methyl Ester.** Benzyl chloride (12.5 mL, 110 mmol) was added to a stirred solution of (*R*)-(+)-proline (10 g, 87 mmol), 65 mL of water, 44 mL of 2 M NaOH, KI (220 mg, 1.3 mmol), and 1 M tetrabutylammonium hydroxide (900 μL) under N_2, and the mixture was heated to 65 °C for 2 h. More 2 N NaOH (11 mL) and benzyl chloride (4.3 mL, 38 mmol) were added, and after further reaction for 1 h the mixture was neutralized with ~12 mL of 1 M HCl to pH 7. Partial concentration in vacuo and addition of ethanol (100 mL) produced a solid, which was washed with 100 mL of ethanol; the washings were concentrated to afford 25 g of crude *N*-benzyl-(*R*)-(+)-proline (containing salts) as previously described,[8] but without chromatography. Acetyl chloride (15 g, 190 mmol) was added dropwise to 50 mL of anhydrous methanol under N_2 at −10 °C followed by crude *N*-benzyl-(*R*)-(+)-proline (25 g) in 35 mL of anhydrous methanol, and the solution was heated at 50 °C for 18 h. After cooling to −10 °C, additional acetyl chloride (4.1 g, 52 mmol) was added dropwise, and the mixture was heated at 50 °C for 3 h. Partial concentration in vacuo, dilution with 200 mL of 0 °C Et_2O, washing with 70 mL of 2 N NaOH (with further addition of 2 N NaOH until pH 12) and brine, drying ($MgSO_4$), and concentration yielded 14.3 g of *N*-benzyl-(*R*)-(+)-proline methyl ester as a yellow oil (65 mmol, 75% from (*R*)-(+)-proline): $[\alpha]^{24}_D$ +73.8° (c = 2.15, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H), 3.88 (d, 1 H, J = 12.7 Hz), 3.64 (s, 3 H), 3.57 (d, 1 H, J = 12.7 Hz), 3.24 (dd, 1 H, J = 8.57, 6.26 Hz), 3.06 (m, 1 H), 2.39 (dd, 1 H, J = 16.5, 8.3 Hz), 2.25–1.7 (m, 4 H); IR (neat) 1748, 1733 cm^{-1}.

***N*-Benzyl-(*R*)-(−)-2-(di-β-naphthylhydroxymethyl)-pyrrolidine.** A flask containing magnesium (1.66 g, 68 mmol) under N_2, THF (55 mL), 2-bromonaphthalene (11.8 g, 57 mmol), and one crystal of iodine was warmed until the iodine color disappeared and the reaction mixture refluxed spontaneously. After 30 min *N*-benzyl-(*R*)-proline methyl ester (5.0 g, 23 mmol, in 20 mL THF) was added dropwise with stirring to the Grignard reagent over 30 min at 0 °C, and the reaction was allowed to proceed for 8 h at 23 °C. The mixture was filtered, diluted with 200 mL of Et_2O, and washed with saturated NH_4Cl (100 mL), and the extracts were dried ($MgSO_4$), concentrated, and chromatographed on a short silica gel column (12:1 hexanes–*tert*-butyl methyl ether). Recrystallization from hexanes–*tert*-butyl methyl ether provided *N*-benzyl-(*R*)-(−)-2-(di-β-naphthylhydroxymethyl)pyrrolidine as colorless crystals (8.3 g, 19 mmol, 83%): mp 78–79 °C; $[\alpha]^{24}_D$ −174° (c = 1.57, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 8.16 (s, 1 H), 7.9–7.4 (m, 12 H), 7.18 (m, 3 H), 7.0 (m, 2 H), 4.27 (dd, 1 H, J = 9.2, 4.6 Hz), 3.32 (d, 1 H, J = 12.5 Hz), 3.10 (d, 1 H, J = 12.5 Hz), 3.0 (m, 1 H), 2.44 (dd, 1 H, J = 16.2, 7.5 Hz), 2.2–1.6 (m, 4 H); FAB MS (70 eV) m/e 444 $(M + H)^+$.

(*R*)-(+)-2-(Di-β-naphthylhydroxymethyl)pyrrolidine. A flask containing methanol (17.5 mL), *N*-benzyl-(*R*)-(−)-2-(di-β-naphthylhydroxymethyl)pyrrolidine (250 mg, 0.56 mmol), acetic acid (37 mg, 0.61 mmol), and 20% $Pd(OH)_2$ on carbon (25 mg, 10 wt %) was treated with H_2 at 1 atm. After 36 h the mixture was filtered through Celite with sufficient rinsing (warm methanol, 200 mL) to dissolve the white precipitate that had formed. The filtrate was concentrated and the resulting solid dissolved in Et_2O (100 mL), washed with 10% NaOH (20 mL) and 20 mL brine, dried ($MgSO_4$), and concentrated to afford the solid (*R*)-(+)-2-(di-β-naphthylhydroxymethyl)pyrrolidine (174 mg, 0.49 mmol, 87%). The amino alcohol was further purified by dissolution in a minimum of Et_2O and precipitation with HCl gas at 0 °C. The white salt was filtered and washed (Et_2O), and the free base formed by extraction from 10% NaOH with Et_2O. The resulting solid was crystallized from hexanes–ethyl acetate to give colorless needles of 99.5% ee (determined by HPLC analysis of the MTPA amide[4c]): mp 137–138 °C; $[\alpha]^{24}_D$ +131° (c = 2.50, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 2 H), 7.9–7.4 (m, 12 H), 4.53 (dd, 1 H, J = 6.0, 6.0 Hz), 3.05 (m, 1 H), 2.97 (m, 1 H), 1.76 (m, 2 H), 1.62 (m, 2 H); IR (neat) 3600–3300 cm^{-1}; FAB MS (70 eV) m/e 354 $(M + H)^+$.

Oxazaborolidine 2. A mixture of (*R*)-(+)-2-(di-β-naphthylhydroxymethyl)pyrrolidine (150 mg, 0.42 mmol), *n*-butylboronic acid[4g] (52 mg, 0.51 mmol), and 4 mL of toluene in a 10-mL flask fitted with a Dean–Stark apparatus containing 3-Å molecular sieves in the side arm was heated to reflux under N_2 for 8 h. After concentration of the reaction mixture to 1 mL by distillation, the Dean–Stark apparatus was replaced with a three-way stopcock capped with a rubber septum and also connected to a vacuum line. Complete removal of toluene in vacuo and addition of 2.1 mL of THF under N_2 provided a 0.2 M catalyst solution sufficiently pure for direct use: ^{11}B NMR (96 MHz, THF/BF_3·Et_2O) δ 32.0 (br, monomer), 7.6 (dimer); addition of 1 equiv of BH_3·THF resulted in a BH_3·**2** complex δ 33.7 (ring B-*n*-butyl), −15.2 (NBH_3).

(*R*)-(−)-1-(4-(*tert*-Butyldimethylsiloxy)phenyl)-2-chloroethanol (5). A dry 5-mL flask was flushed with N_2 and charged with 700 μL (0.14 mmol) of oxazaborolidine catalyst **2**[4e] (0.2 M solution in THF) followed by 840 μL (0.84 mmol) of 1.0 M BH_3·THF with stirring. A solution of 412 mg (1.44 mmol) of chloroketone **4** in 1.4 mL of THF was added by cannula over 5 min to the solution of **2** and BH_3·THF at 23 °C. The reaction mixture was stirred for 2 min, cooled to 0 °C, and decomposed by the addition of dry 0.5 M HCl in methanol (340 μL, 0.17 mmol) with stirring for 10 min. After addition of 2 mL of toluene, colorless crystals of (*R*)-(+)-2-(di-β-naphthylhydroxymethyl)-pyrrolidine hydrochloride (49 mg, 89%) were collected by filtration. The filtrate was diluted with 25 mL of Et_2O and washed with brine (3 × 2 mL), dried ($MgSO_4$), and concentrated under

(6) (*R*)-(−)-1-(4-(*tert*-Butyldimethylsiloxy)phenyl-2-chloroethanol obtained in this manner had 97% enantiomeric excess as shown by conversion to the corresponding MTPA ester ((*S*)-(+)-MTPA chloride, DMAP, pyridine, methylene chloride) and analysis by 500-MHz ^1H NMR ($CDCl_3$) δ 3.64 (s, 3 H, OCH_3, major diastereomer), 3.46 (s, 3 H, OCH_3, minor diastereomer); see: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(7) (a) Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111. (b) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201. (c) Corey, E. J.; Da Silva Jardine, P.; Mohri, T. *Ibid.* **1988**, *29*, 6409. (d) Corey, E. J.; Chen, C.-P.; Parry, M. J. *Ibid.* **1988**, *29*, 2899. (e) Corey, E. J.; Reichard, G. A. *Ibid.* **1989**, *30*, 5207. (f) Corey, E. J.; Link, J. O. *Ibid.* **1990**, *31*, 601.

(8) (a) Belokoń, Y. N.; Zel'tzer, I. E.; Bakhmutov, V. I.; Saporovskaya, M. B.; Rhyzhov, M. G.; Yanovsky, A. I.; Struchkov, Y. T.; Belikov, V. M. *J. Am. Chem.* Soc. **1983**, *105*, 2010.

(9) This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

reduced pressure to give 398 mg (1.38 mmol, 96% yield) of chloro alcohol **5**: $[\alpha]^{24}_D$ -28.7° (c = 0.90, $CHCl_3$), enantiomeric excess 97%;[6] ^1H NMR (270 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.8 Hz, Ar), 6.84 (d, 2 H, J = 8.8, Ar), 4.84 (dd, 1 H, J = 3.6, 8.8 Hz, carbinyl), 3.71 (dd, 1 H, J = 11.0, 3.6 Hz, CH_2), 3.62 (dd, 1 H, J = 11.0, 8.8 Hz, CH_2), 0.98 (s, 9 H, *tert*-butyl), 0.19 (s, 6 H, 2-CH_3); IR (neat) 2930, 1511, 1260 cm^{-1}; FAB MS (70 eV) m/e 286 $(M)^+$; HRMS calcd for $C_{14}H_{23}SiO_2Cl$ 286.1155, found 286.1147.

(*R*)-(-)-1-(4-(*tert*-Butyldimethylsiloxy)phenyl)-2-iodoethanol (6). A dry 25-mL flask containing 380 mg (1.3 mmol) of chloro alcohol **5** was shielded from light with aluminum foil. After flushing with N_2, 15 mL of saturated sodium iodide in acetone was added with magnetic stirring. The mixture was heated at reflux for 72 h, cooled, and poured into 50 mL of 3:1 hexanes-ethyl acetate. The inorganic salts were removed by filtration and the filtrate was concentrated to give a viscous red oil, which was dissolved in 30 mL of 3:1 hexanes-ethyl acetate and washed sequentially with 5% aqueous sodium bisulfite (2 × 3 mL), water (2 × 3 mL), and 3 mL of brine. Drying ($MgSO_4$) and removal of solvent in vacuo afforded iodo alcohol **6** as a colorless viscous oil (460 mg, 1.2 mmol, 92%): $[\alpha]^{24}_D$ -24.3° (c = 1.75, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.23 (d, 2 H, J = 8.5 Hz, Ar), 6.83 (d, 2 H, J = 8.5 Hz, Ar), 4.79 (dd, 1 H, J = 8.8, 4.0 Hz, carbinyl), 3.45 (dd, 1 H, J = 10.1, 4.0 Hz, CH_2) 3.38 (dd, 1 H, J = 10.1, 8.8 Hz, CH_2), 0.97 (s, 9 H, *tert*-butyl) 0.19 (s, 6 H, 2-CH_3); IR (neat) 3400, 2940, 1610, 1260 cm^{-1}; FAB MS (70 eV) m/e 361 $(M + H - H_2O)^+$.

Iodide 7. A solution of imidazole (110 mg, 1.6 mmol), iodo alcohol **6** (205 mg, 0.54 mmol), DMF (600 μL), and 4-(dimethylamino)pyridine (DMAP) (3 mg, 0.025 mmol) was stirred under N_2 as TESCl (110 μL, 0.65 mmol) was added. After 15 min at 23 °C the solution was diluted with 20 mL of 3:1 hexanes-ethyl acetate and washed successively with 3 mL of water, saturated aqueous $CuSO_4$ (2 × 3 mL), water (2 × 3 mL) and 3 mL of brine, and then dried ($MgSO_4$) and filtered through Celite. After removal of solvent under reduced pressure, DMF was removed by addition of dry toluene (3 mL) to the residual colorless oil and concentration in vacuo (twice) to give iodide **7** (255 mg, 0.52 mmol, 96%): $[\alpha]^{24}_D$ -24.3° (c = 1.05 $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.18 (d, 2 H, J = 8.4 Hz, Ar), 6.78 (d, 2 H, J = 8.4 Hz, Ar), 4.72 (dd, 1 H, J = 6.9, 4.9 Hz, carbinyl), 3.30 (m, 2 H, CH_2), 0.97 (s, 9 H, *tert*-butyl), 0.88 (t, 9 H, J = 7.7 Hz, 3-CH_3), 0.55 (q, 6 H, J = 7.7 Hz, 3-CH_2), 0.18 (s, 6 H, 2-CH_3); IR (neat) 2980, 1605, 1510, 1260 cm^{-1}; FAB MS (70 eV) m/e 365 $(M + H - HI)^+$.

Silylated Denopamine 8. A 12-cm Pyrex tube with one sealed end containing 137 mg (0.28 mmol) of iodide **7** was fitted with a rubber septum, flushed with N_2, and charged with 66 μL (70 mg, 0.39 mmol) of 2-(3,4-dimethoxyphenyl)ethylamine, 108 μL (79 mg, 0.78 mmol) of triethylamine, and 400 μL of THF. The tube was cooled with powdered dry ice and sealed under reduced pressure, shaken to mix the contents, and heated for 24 h at 100 °C. During reaction the mixture slowly separated into two liquid phases, and upon cooling the lower phase solidified (excess 2-(3,4-dimethoxyphenyl)ethylamine hydroiodide salt). The mixture was filtered through a silica gel plug with 10 mL of ethyl acetate and concentrated in vacuo to afford 141 mg (0.26 mmol, 92%) of amine **8** as a colorless oil: $[\alpha]^{24}_D$ -36.9° (c = 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.14 (d, 2 H, J = 8.6 Hz, Ar), 6.6-6.9 (m, 5 H, Ar), 4.73 (dd, 1 H, J = 8.4, 3.8 Hz, carbinyl), 3.87 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 2.65-2.90 (m, 6 H, $CH_2NHCH_2CH_2$), 0.96 (s, 9 H, *tert*-butyl), 0.79 (t, 9 H, J = 7.8 Hz, 3-CH_3), 0.43 (q, 6 H, J = 7.8 Hz, 3-CH_2), 0.17 (s, 6 H, 2-CH_3); IR (neat) 2950, 1510, 1260 cm^{-1}; FAB MS (70 eV) m/e 546 $(M + H)^+$.

(*R*)-(-)-Denopamine (1). A solution of 130 mg (0.24 mmol) of amine **8** was stirred vigorously under N_2 as 1.9 mL (3.8 mmol) of 2 M anhydrous potassium fluoride in methanol and 250 μL (2.5 mmol) of 1 M dry hydrogen chloride in methanol were added. After stirring for 8 h at 23 °C, the mixture was diluted with 8 mL of ethyl acetate and cooled to 0 °C for 15 min. The mixture was filtered to remove potassium fluoride, the filtrate was concentrated in vacuo, and the residue was dissolved in 30 mL of ethyl acetate and washed with 2 mL of 10% aqueous sodium chloride. Drying ($MgSO_4$) and evaporation of solvent afforded 74 mg of denopamine (**1**) as a colorless amorphous solid. Recrystallization from hexanes-ethyl acetate afforded a first crop of 56 mg and a second crop of 7 mg (0.20 mmol, 83%) of colorless crystals of optically pure denopamine (**1**) unchanged by further recrystallization: mp 163-164 °C; $[\alpha]^{24}_D$ -27.5° (c = 0.95, methanol) (lit.[3a] mp 167 °C dec, $[\alpha]^{20}_D$ -27.7° (c = 1.0, methanol)); ^1H NMR (270 MHz, $CDCl_3$) δ 7.14 (d, 2 H, J = 8.2 Hz, Ar), 6.6-6.9 (m, 5 H, Ar), 4.64 (dd, 1 H, J = 3.5, 1.0 Hz, carbinyl), 3.84 (s, 6 H, 2-OCH_3), 2.7-3.0 (m, 6 H, $CH_2NHCH_2CH_2$); IR (neat) 2950, 1615, 1595, 1520 cm^{-1}; EIMS (70 eV) m/e 318 $(M + H)^+$; HRMS calcd for $(C_{18}H_{23}NO_4 + H)^+$ 318.1704, found 318.1765.

Supplementary Material Available: ^1H NMR spectra for compounds **1** and **4-8** (6 pages). Ordering information is given on any current masthead page.

Novel Highly Regioselective O-Alkylation and O-Acylation of *myo*-Inositol

Amparo Zapata, Roberto Fernández de la Pradilla, Manuel Martín-Lomas,* and Soledad Penadés*

Grupo de Carbohidratos, Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

Received February 21, 1990 (Revised Manuscript Received May 8, 1990)

Recent research in the biochemistry of inositol phosphates[1] has brought about a renewed interest in the chemistry of *myo*-inositol (**1**).[2] An impresive number of papers have appeared on the preparation of synthetic intermediates, generally using quite a number of conventional hydroxyl protection and deprotection steps.[2,3] However very few useful regioselective reactions have been reported, most of them dealing with selective protection of diol and triol *myo*-inositol derivatives[4] and only a regioselective phosphitylation of a tetrahydroxy-*myo*-inositol derivative has been published.[5] To our knowledge only three synthetically useful regioselective reactions starting from unprotected *myo*-inositol (**1**) have appeared: the formation of the 1,2-*O*-isopropylidene-*myo*-inositol with 2,2-dimethoxypropane in dimethyl sulfoxide[6] in 20% yield, the reaction with triethyl orthoformate to give 1,3,5-*myo*-inositol orthoformate in 76% yield[7] and that with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane to afford a symmetrical bis(disiloxane) *myo*-inositol derivative in 66% yield.[8]

As part of a project on the synthesis of some glycosylphosphatidylinositol residues, which may be implicated in a second messenger mechanism for the signal trans-

(1) (a) Berridge, M. J. *Ann. Rev. Biochem.* **1987**, *56*, 159. (b) Ferguson, M. A. J.; Williams, A. F. *Ibid.* **1988**, *57*, 285.
(2) Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83.
(3) (a) Garegg, P. J.; Iversen, T.; Johansson, R.; Lindberg, B. *Carbohydr. Res.* **1984**, *130*, 322. (b) Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2411. (c) Ozaki, S.; Kohno, M.; Nakahira, H.; Bunya, M.; Watanabe, Y. *Chem. Lett.* **1988**, 77. (d) Vacca, J. P.; de Solms, S. J.; Huff, J. R.; Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M. *Tetrahedron* **1989**, *45*, 5679. (e) Elie, C. J. J.; Dreef, C. E.; Verduyn, R.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1989**, *45*, 3477.
(4) (a) Dreef, C. E.; Elie, C. J. J.; Hoogerhout, P.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1988**, *29*, 6513. (b) Billington, D. C.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1987**, 1011.
(5) Meek, J. L.; Davidson, F.; Hobbs, F. W., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 2317.
(6) Gigg, J.; Warren, D. C. *J. Chem. Soc. C* 1969, 2367.
(7) Lee, H. V.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402.
(8) Watanabe, Y.; Mitani, M.; Morita, T.; Ozaki, S. *J. Chem. Soc., Chem. Commun.* **1989**, 482.

0022-3263/91/1956-0444$02.50/0