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

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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-

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Table I. Regioselective Catalyzed Alkylation and Acylation of *myo*-Inositol (1)

entry	3, equiv	NMI, equiv	RX	products (yield, %, GC) mono	di	tri
1	1.2	1.2	AllBr	**4** (53), **5** (22)	**8** (10)	
2	1.2	1.2	BnBr	**6** (63), **7** (27)		
3	2.4	2.5	BnBr	**6** (12), **7** (8)	**9** (48), **10** (20)	
4	3.5	3.5	BnBr	**6** (9)	**9** (26), **10** (7)	**11** (27), **12** (13)
5	1.2	1.2	BzCl[a]	**13** (25)	(25)	
6	1.2	0.6	BzCl[a]	**13** (43)	(17)	
7	1.2	0.6	pMeOBzCl[a]	**14** (50)		

[a] Only 1.5–2.0 equiv was used.

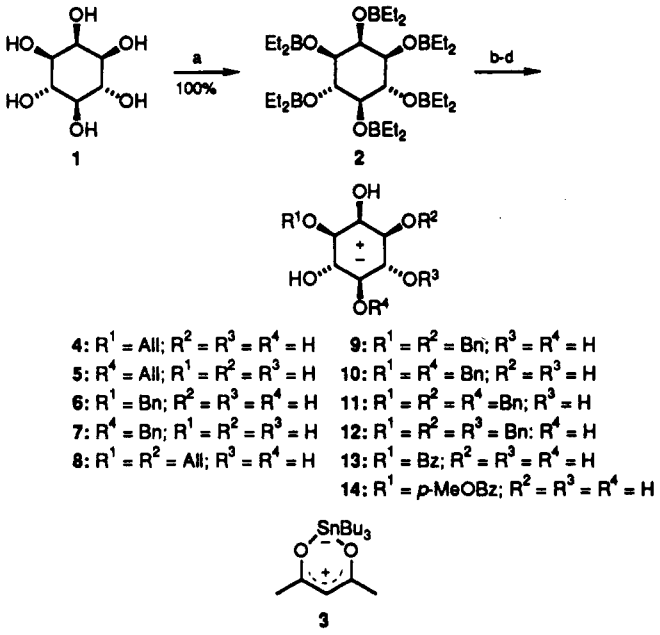
duction of insulin,[9] we have investigated the regioselective mono-O-alkylation of *myo*-inositol in acetonitrile via dibutylstannylidene derivatives[10] with unsatisfactory results.[11] This was probably due to the low solubility of *myo*-inositol in acetonitrile besides the rather scarce difference of reactivity among the hydroxyl groups of *myo*-inositol (**1**). Using an excess of di-*n*-butyltin oxide and allyl bromide in the presence of tetra-*n*-butylammonium bromide, a 60% of the 1,3,4,5-tetra-O-allyl derivative could be obtained.[12]

It has been reported[13] that borylated carbohydrates can be quantitatively O-stannylated by transmetalation with the tri-*n*-butylstannyl enolate of pentane-2,4-dione (**3**). We now report our preliminary results on the application of this reaction to *myo*-inositol and the catalyzed regioselective alkylation and acylation of the intermediate tri-*n*-butylstannyl ethers to give the conveniently protected inositol derivatives.

myo-Inositol (**1**) (Scheme I) was converted into the hexane-soluble hexa-*O*-diethylboryl derivative (**2**) by reaction with excess of activated triethylborane at room temperature.[14] The reaction of **2** with 1 equiv of **3** in toluene at room temperature resulted in the immediate formation of a partially stannylated *myo*-inositol derivative and the yellow diethylboryl acetylacetonate, which was distilled off. This partially borylated–stannylated intermediate was treated in toluene, under different conditions, with benzyl or allyl bromide in the presence of *N*-methylimidazole (NMI) (tetra-*n*-butylammonium bromide and fluoride were also used with similar results). After deborylation by treatment with methanol the reaction mixture was analyzed by GLC of the corresponding trimethylsilyl derivatives (Table I).

Treatment of **2** with 1 equiv of **3**, NMI (1.25 equiv), and an excess of allyl bromide gave a 5:2:1 mixture of 1-*O*-allyl- (**4**, 53%), 5-*O*-allyl- (**5**, 22%), and 1,3-di-*O*-allyl-*myo*-inositol (**8**, 10%) (Table I, entry 1) and unreacted starting material. Similar reaction with benzyl bromide led to a mixture of 1-*O*-benzyl- (**6**, 63%) and 5-*O*-benzyl-*myo*-inositol (**7**, 27%) (Table I, entry 2). We have also explored the one-pot regioselective di-O-alkylation of **1**. Thus,

Scheme I[a]



[a] (a) Reference 14; (b) $Bu_3Sn(CH_3COCHCOCH_3)$ **3**, $CH_3C_6H_5$, room temperature, 1 h; (c) NMI, RX, 12 h; (d) MeOH.

treatment of **2** with 2 equiv of **3**, NMI (2.5 equiv), and an excess of benzyl bromide gave 1,3-di-*O*-benzyl- (**9**, 48%), 1,5-di-*O*-benzyl- (**10**, 20%) and mono benzyl derivatives (Table I, entry 3). Transmetalation–alkylation using 3 equiv of **3** gave 1,3-di-*O*-benzyl- (**9**, 26%) and 1,3,5-tri-*O*-benzyl-*myo*-inositol (**11**, 27%) as main products (Table I, entry 4).

We have also examined the regioselectivity of the monoacylation reaction with benzoyl and *p*-methoxybenzoyl chloride. The reaction of **2** with **3** (1 equiv) and 3 equiv of benzoyl chloride, without NMI, led to a complex mixture. When a stoichiometric amount of NMI was added at −5 °C the 1-*O*-benzoyl derivative (**13**, 25%) and an uncharacterized dibenzoyl derivative were obtained as the main products (entry 5). The best yield of monoacyl derivative was obtained when 0.6 equiv of NMI and 1.5 equiv of acyl chloride were added at −5 °C. In these conditions compound **13** (43%) and 1-*O*-(*p*-methoxybenzoyl)-*myo*-inositol (**14**, 50%) respectively, were obtained as the main products. (Table I, entries 6 and 7). The observed influence of the NMI on the regioselectivity of the acylation is noteworthy.[15]

The above results demonstrate that this methodology can be useful for the regioselective preparation of 1-O-substituted *myo*-inositol derivatives in a one-pot manner, although the 1,3-di-O-substituted compound can be also

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(11) The reaction of **1** with di-*n*-butyltin oxide (1.9 equiv), molecular sieve (3 Å) in acetonitrile and tetra-*n*-butylammonium bromide (1 equiv) and excess of benzyl bromide gave 1-*O*-benzyl- (18%), 1,3-di-*O*-benzyl- (20%), and 1,3,4-tri-*O*-benzyl-*myo*-inositol (10%).

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obtained in reasonable yield. The observed regioselectivity may be controlled both by the transmetalation and the electrophilic attack, the presence of the catalyst being crucial in the second step.

The extension of this strategy to the preparation of other 1-O-substituted *myo*-inositol derivatives with different electrophiles as well as the stepwise O-substitution using different alkylating and acylating agents sequentially are presently underway.

Experimental Section

General. All reactions were carried out under an argon atmosphere; solvents were dried by standard procedures and distilled under argon. Gas–liquid chromatographic analysis was carried out on Carlo Erba 5160 and 4130 MEGA chromatographs with FID detector using OV-1 and CP-Sil 19 CB (CHROMPACK) capillary columns of fused silica (25 m × 0.2 mm), and the samples were prepared from an aliquot of the reaction mixture treated with methanol and evaporated. The residue (1 mg) was dissolved in a mixture of pyridine (0.1 mL) and 1-(trimethylsilyl)imidazole (0.1 mL) and heated for 30 min at 65 °C. ^1H and ^{13}C NMR spectra were recorded on Varian XL-300 and Bruker AM-200 spectrometers, respectively. TLC was performed on silica gel GF_{254} (Merck) with detection by charring with sulfuric acid, UV, or aqueous $KMnO_4$ (2%)/Na_2CO_3 (2%). Column chromatography was performed on silica gel (Merck 70–230). Flash column chromatography was carried out on silica gel 40–70 μm (MN). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

General Procedure. Preparation of *O*-Allyl- and *O*-benzyl-*myo*-inositols 4–12. A solution of tri-*n*-butylstannylenolate of pentane-2,4-dione[13] (**3**, the corresponding equivalents are shown in Table I) in dry toluene (10 mL) was added to a solution of hexakis-*O*-(diethylboryl)-*myo*-inositol[14] (**2**, 4.4 g, 7.5 mmol) in toluene (10 mL) at room temperature. The resulting yellow solution was stirred for 1 h, and then the volatiles were distilled off (40–60 °C bath temperature, 10^{-3} Torr). The residue was dissolved in toluene (10 mL) and NMI (Table I), and an excess of allyl or benzyl bromide was added. The reaction mixture was stirred at room temperature for 12 h and monitored by GLC. The solvent was evaporated in vacuo, and the residue was treated with methanol (20 mL). After evaporation the residue was washed with hexane and fractionated by column chromatography on silica gel (chloroform/methanol, 6/1 or 3/1) or by crystallization.

General Procedure. Preparation of *O*-Acyl-*myo*-inositols 13 and 14. A solution of **2** (234 mg, 0.4 mmol) in toluene was treated with **3** (0.5 mmol) as described above. Then NMI (see Table I) and benzyl or *p*-methoxybenzoyl chloride (see Table I) was added at −5 °C. The reaction mixture was stirred at 5 °C for 10 h. After usual treatment the mixture was purified by column chromatography on silica gel (chloroform/methanol, 3/1).

1-*O*-Allyl-*myo*-inositol (4): white solid; R_f 0.15 ($CHCl_3$/MeOH, 3/1); mp 122–124 °C (ethanol); ^1H NMR (D_2O) δ 5.75 (m, 1 H, =CH), 5.09 (m, 2 H, CH_2=), 3.98 (m, 1 H, CH_2O), 3.86 (m, 1 H, CH_2O), 3.44 (t, 1 H, H-6), 3.39 (t, 1 H, H-4), 3.26 (dd, 1 H, H-3), 3.13 (dd, 1 H, H-1), 3.04 (t, 1 H, H-5). Characterized also as its per-*O*-acetyl derivative: mp 130–131 °C (ether–hexane); ^1H NMR ($CDCl_3$) δ 5.77–5.63 (m, 1 H, CH=), 5.59 (t, 1 H, J = 2.8 Hz, H-2), 5.39 (t, 1 H, J = 7.9 Hz, CH), 5.31 (t, 1 H, J = 10 Hz, CH), 5.21–5.07 (m, 2 H, $=CH_2$), 5.05 (t, 1 H, J = 9.8 Hz, H-5), 4.90 (dd, 1 H, $J_{2,3}$ = 2.8 Hz, $J_{3,4}$ = 10.5 Hz, H-3), 4.07–3.77 (m, 2 H, CH_2O), 3.54 (dd, 1 H, $J_{1,2}$ = 2.8 Hz, $J_{1,6}$ = 10.1 Hz, H-1), 2.12 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3CO), 1.95 (s, 3 H, CH_3CO), 1.94 (s, 6 H, 2 CH_3CO); ^{13}C NMR ($CDCl_3$) 169.7, 169.6, 169.5, 169.4, 169.3 (6 OCO), 133.5 (CH=), 117.5 (CH_2=), 74.2, 70.9, 70.8, 70.7, 69.3, 68.9, 66.8, 20.51, 20.39, 20.23 (5 $COCH_3$). Anal. Calcd for $C_{19}H_{26}O_{11}$: C, 53.02; H, 6.09. Found: C, 53.22; H, 6.13.

5-*O*-Allyl-*myo*-inositol (5). Characterized as its per-*O*-acetyl derivative: white solid; mp 180–185 °C (ethanol); ^1H NMR ($CDCl_3$) δ 5.87–5.65 (m, 1 H, CH=), 5.54 (t, 1 H, J = 2.8 Hz, H-2), 5.48 (dd, 2 H, J = 9.8 Hz, J = 10.5 Hz, H-4, H-6), 5.40–5.12 (m, 2 H, CH_2=), 5.00 (dd, 2 H, J = 2.8 Hz, J = 10.5 Hz, H-1, H-3), 4.11–4.07 (m, 2 H, CH_2O), 3.54 (t, 1 H, J = 9.7 Hz, H-5), 2.20 (s, 3 H, CH_3CO), 2.06 (s, 6 H, CH_3CO), 1.99 (s, 6 H, CH_3CO).

1-*O*-Benzyl-*myo*-inositol (6): white solid; mp 195–197 °C (ethanol) (lit.[16] mp 190–195 °C (methanol)); ^1H NMR (D_2O) δ 7.2 (m, 5 H, aromatics), 4.52 (d, 1 H, CH_2O), 4.40 (d, 1 H, CH_2O), 4.01 (t, 1 H, H-2), 3.47 (t, 1 H, H-6), 3.39 (t, 1 H, H-4), 3.23 (dd, 1 H, H-3), 3.18 (dd, 1 H, H-1), 3.02 (t, 1 H, H-5); ^{13}C NMR (D_2O) δ 129.4, 129.3, 129.0 (aromatics), 79.3 (C-1), 75.0 (C-5), 72.9 (C-4), 72.4 (C-6), 72.9 (CH_2O), 71.8 (C-3), 69.4 (C-2).

5-*O*-Benzyl-*myo*-inositol (7): white solid; mp 279–282 °C (ethanol–water) (lit.[3a] mp 281–283 °C (ethanol–water)); ^1H NMR of its per-*O*-acetyl derivative ($CDCl_3$) δ 7.33–7.25 (m, 5 H, aromatics), 5.57 (t, 1 H, J = 2.9 Hz, H-2), 5.55 (t, 2 H, J = 10.1 Hz, H-4, H-6), 5.03 (dd, 2 H, J = 2.8 Hz, J = 10.5 Hz, H-1, H-3), 4.64 (s, 2 H, CH_2O), 3.68 (t, 1 H, J = 9.7 Hz, H-5), 2.21 (s, 3 H, CH_3CO), 2.01 (s, 6 H, 2 CH_3CO), 1.97 (s, 6 H, CH_3CO).

1,3-Di-*O*-allyl-*myo*-inositol (8): white solid; R_f 0.6 ($CHCl_3$/methanol, 3/1); mp 119–120 °C (ethyl acetate). Characterized as its per-*O*-acetyl derivative: mp 150–152 °C (ethanol–hexane); ^1H NMR ($CDCl_3$) δ 5.86–5.75 (m, 2 H, CH=), 5.72 (t, 1 H, H-2), 5.37 (t, 2 H, J = 10.0 Hz, H-4, H-6), 5.23–5.20 (m, 4 H, CH_2=), 5.08 (t, 1 H, J = 9.9 Hz, H-5), 4.12 (m, 2 H, CH_2O), 3.93 (m, 2 H, CH_2O), 3.46 (dd, 2 H, J = 2.9 Hz, J = 10.0 Hz, H-1, H-3), 2.18 (s, 3 H, CH_3CO), 2.04 (s, 6 H, 2 CH_3CO), 2.01 (s, 3 H, CH_3CO); ^{13}C NMR δ 170.1, 169.6 (2 OCO), 133.9 (CH=), 117.6 (CH_2=), 74.7, 71.2, 71.1, 70.9 (CH_2O, C-2, C-4, C-5, C-6), 65.8 (C-1, C-3), 20.9, 20.6, 20.5 (4 CH_3CO). Anal. Calcd for $C_{20}H_{28}O_{10}$: C, 56.07; H, 6.59. Found: C, 55.92; H, 6.64.

1,3-Di-*O*-benzyl-*myo*-inositol (9). Characterized as its per-*O*-acetyl derivative: white solid; mp 180–183 °C (ethanol) (lit.[16] mp 184 °C (ethanol)); ^1H NMR ($CDCl_3$) δ 7.35–7.22 (m, 10 H, aromatics), 5.82 (t, 1 H, J = 2.8 Hz, H-2), 5.40 (t, 2 H, J = 9.9 Hz, H-4, H-6), 4.99 (t, 1 H, J = 9.8 Hz, H-5), 4.55 (m, 4 H, 2 CH_2O), 3.45 (dd, 2 H, J = 2.8 Hz, J = 9.9 Hz, H-1, H-3), 2.20 (s, 3 H, CH_3CO), 1.98 (s, 9 H, 3 CH_3CO); ^{13}C NMR ($CDCl_3$) δ 170.3, 170.2, 169.6 (4 OCO), 137.1 (aromatics ipso), 128.5–127.8, (aromatics), 74.6, 71.7, 71.3, 71.1 (C-1–C-6, CH_2O), 20.9, 20.7, 20.5 (4 CH_3CO).

1,5-Di-*O*-benzyl-*myo*-inositol (10): white solid; mp 137–140 °C (methanol–hexane). Characterized as its per-*O*-acetyl derivative: ^1H NMR ($CDCl_3$) δ 7.34–7.19 (m, 10 H, aromatics), 5.72 (t, 1 H, J = 2.8 Hz, H-2), 5.53 (t, 1 H, J = 10.7 Hz, CH), 5.48 (t, 1 H, J = 9.4 Hz, CH), 4.88 (dd, 1 H, J = 10.6 Hz, J = 2.8 Hz, H-3), 4.65 (d, 1 H, CH_2O), 4.58 (s, 2 H, CH_2O), 3.48 (d, 1 H, CH_2O), 3.56 (t, 1 H, J = 9.7 Hz, H-5), 3.51 (dd, 1 H, J = 2.8 Hz, J = 10.1 Hz, H-1), 2.18, 1.98, 1.95, 1.93 (4 CH_3CO); ^{13}C NMR δ 170.1, 170.0, 169.4, 169.3 (4 OCO), 137.6, 137.1 (aromatics ipso), 128.37–127.66 (aromatics), 78.9, 74.7, 74.6, 72.2, 71.4, 70.9, 66.7, 64.0 (C-1–C-6, CH_2O), 20.8, 20.6, 20.5 (4 CH_3CO).

1,3,5-Tri-*O*-benzyl-*myo*-inositol (11): white solid; mp 163–164 °C; ^1H NMR ($CDCl_3$) δ 7.34 (m, 15 H, aromatics), 4.87 (s, 2 H, CH_2O), 4.74 (d, 2 H, CH_2O), 4.66 (d, 2 H, CH_2O), 4.24 (t, 1 H, H-2), 4.05 (t, 2 H, H-4, H-6), 3.25 (dd, 2 H, J = 2.9 Hz, J = 9.6 Hz, H-1, H-3), 3.24 (t, 1 H, J = 9.2 Hz, H-5). Per-*O*-acetyl derivative: mp 157–160 °C; ^1H NMR ($CDCl_3$) δ 7.37–7.17 (m, 15 H, aromatics), 5.82 (t, 1 H, J = 2.8 Hz, H-2), 5.47 (t, 2 H, J = 9.9 Hz, H-4, H-6), 4.68 (d, 2 H, CH_2O), 4.40 (d, 2 H, CH_2O), 3.48 (t, 1 H, J = 9.7 Hz, H-5), 3.36 (dd, 2 H, J = 2.8 Hz, J = 10.1 Hz, H-1, H-3), 2.18 (s, 3 H, CH_3CO), 1.94 (s, 6 H, 2 CH_3CO); ^{13}C NMR ($CDCl_3$) δ 170.4, 137.9 (3 OCO), 137.9, 137.3 (aromatics ipso), 128.4, 127.9, 127.7, 127.6 (aromatics), 79.0, 74.9, 74.2, 72.4, 71.4, 65.3 (C-1–C-6, CH_2O), 21.0, 20.9 (CH_3CO). Anal. Calcd for $C_{33}H_{36}O_9$: C, 68.74; H, 6.29. Found: C, 68.44; H, 6.52.

1,3,4-Tri-*O*-benzyl-*myo*-inositol (12): white solid; mp 100–103 °C (ether–hexane) (lit.[3d] mp 102–104 °C (ether–hexane)); ^1H NMR δ 7.31 (m, 15 H, aromatics), 4.96 (d, 1 H, CH_2O), 4.76 (d, 1 H, CH_2O), 4.70 (s, 2 H, CH_2O), 4.68 (d, 2 H, CH_2O), 4.25 (t, 1 H, H-2), 3.97 (t, 1 H, CH), 3.83 (t, 1 H, CH), 3.41 (t, 1 H, H-4), 3.40 (dd, 1 H, CH), 3.28 (dd, 1 H, CH). Per-*O*-acetyl derivative: mp 148–150 °C; ^1H NMR ($CDCl_3$) δ 7.34–7.23 (m, 15 H, aromatics), 5.83 (t, 1 H, J = 2.8 Hz, H-2), 5.33 (t, 1 H, J = 10.0 Hz, H-6), 5.02 (t, 1 H, J = 9.8 Hz, H-5), 4.87–4.38 (6 H, CH_2O), 3.88 (t, 1 H, J = 9.7 Hz, H-4), 3.52 (dd, 1 H, J = 2.8 Hz, J = 9.8 Hz, CH), 3.45 (dd, 1 H, J = 2.7 Hz, J = 9.9 Hz, CH), 2.19 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3CO), 1.91 (s, 3 H, CH_3CO); ^{13}C NMR

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($CDCl_3$) δ 170.2, 170.0 (OCO), 138.3, 137.3, 137.2 (aromatics ipso), 128.4-127.7 (aromatics), 78.7-66.2 (C-1-C-6, CH_2O), 21.0, 20.7, 20.7 (3 CH_3CO).

1-*O*-Benzoyl-*myo*-inositol (13): white solid; mp 84-87 °C (hexane-methanol); ^1H NMR (DMSO-d_6 + D_2O) δ 8.03-7.51 (m, 5 H, aromatics), 4.65 (dd, 1 H, J = 2.6 Hz, J = 10.3 Hz, H-1), 3.93 (br s, H-2), 3.73 (t, 1 H), 3.43 (t, 1 H, J = 9.3 Hz), 3.26 (dd, 1 H, J = 2.4 Hz, J = 9.5 Hz, H-3), 3.06 (t, 1 H, J = 9.0 Hz); ^{13}C NMR (DMSO-d_6) δ 165.6 (OCO), 133.0, 130.3, 129.4, 128.4 (aromatics), 75.5, 75.1, 72.3, 72.2, 71.3, 71.2, 70.1 (C-1-C-6).

1-*O*-(*p*-Methoxybenzoyl)-*myo*-inositol (14): white solid; mp 185-187 °C (methanol); ^1H NMR (DMSO-d_6 + D_2O) δ 7.95 (d, 2 H, J_{ortho} = 8.9 Hz, aromatics), 7.01 (d, 2 H, J_{ortho} = 8.9 Hz, aromatics), 4.59 (dd, 1 H, J = 2.7 Hz, J = 10.1 Hz, H-1), 3.90 (t, 1 H, J = 2.6 Hz, H-2), 3.80 (s, 3 H, CH_3O), 3.71 (t, 1 H), 3.41 (t, 1 H, J = 9.5 Hz), 3.24 (dd, 1 H, J = 2.6 Hz, J = 9.8 Hz, H-3) 3.04 (t, 1 H, J = 9.1 Hz); ^{13}C NMR (DMSO-d_6 + D_2O) δ 165.3 (OCO), 162.9 (para aromatics), 131.5 (ortho aromatics), 122.6 (meta aromatics), 113.7 (ipso aromatics), 75.1, 72.3, 71.4, 70.1, 70.0 (C-1-C-6), 55.5 (CH_3O). Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.73; H, 5.51.

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3-*exo*-Methylenecephalosporins: Structure and Thermodynamics by Experiment and Theory

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Although X-ray crystal structures of cephalosporins[1] **1** and their Δ2 isomers[2] **2** have been reported, little is known of the details of the structure of the 3-*exo*-methylene isomer **3**, with the exception of its stereochemistry.[3] From a thermodynamic standpoint, it is known that **1** and **2** are nearly isoenergetic. For example, when R_1 is hydrogen, the isomer ratio of **1**:**2** is about 3:7 at equilibrium, but when R_1 is larger, the ratio is about 7:3.[4] This dearth of structural and thermodynamic information is surprising

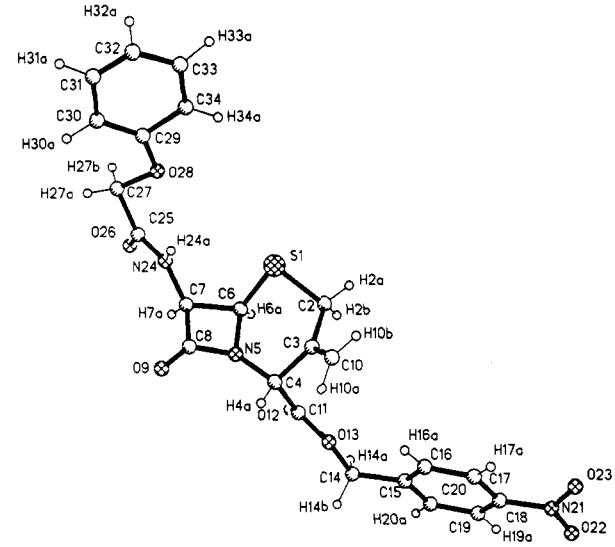


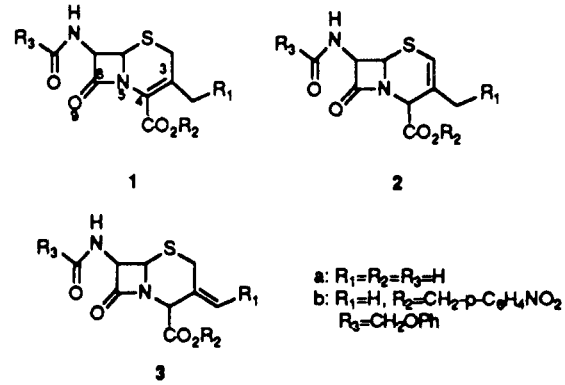
Figure 1.

Table I. Key Structural Features of Cephalosporin Isomers from X-ray Crystallography[a]

	1[b]	2[c]	3b[d]
C8-O9	1.223 (0.065)	1.216 (0.017)	1.225
N5-C8	1.396 (0.070)	1.343 (0.009)	1.347
C4-N5	1.429 (0.040)	1.430 (0.021)	1.464
C3-C4	1.340 (0.035)	1.539 (0.017)	1.551
N height[e]	0.18 (0.062)	0.04 (0.026)	0.02

[a] Distances in angstroms. Values in parentheses are one standard deviation. [b] Average of data from structures ACMPXC, BODKOU, BZCMXC, CEFMEN, CEPHGLY, CEPHAP, CEPHHM, CEPHNA, CEPHNB, CETHNA, and TZACOL from Cambridge Crystallographic Database. See ref 1b. [c] Average of data from structures DMCXCM, PAMXCP, and PODACE. [d] This work. [e] Defined in text.

given the large amount of synthetic effort directed toward **3**[5] and its importance as a precursor to cephalosporins such as cefaclor which contain a heteroatom at C3 rather than a carbon atom.[6] This paper reports the first X-ray crystal structure of a 3-*exo*-methylenecepham, **3b**, calorimetric data for its isomerization to **1b**, and a comparative study of semiempirical molecular orbital methods for the study of cephalosporins and their isomers.



Results and Discussion

Compound **3b** was prepared by known procedures and was crystallized from a mixture of toluene, ethyl acetate,

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