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Regioselective functionalizations and conformational studies of di-*O*-isopropylidene-*myo*-inositol derivatives

Sung-Kee Chung *, Youngha Ryu

Department of Chemistry, Pohang Institute of Science and Technology, Pohang 790-600, South Korea

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Abstract

(±)-1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol (**5**) and (±)-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**6**) could be regioselectively functionalized in reactions including alkylation, acylation, and silylation at HO-3 in preference to HO-6 and HO-4, respectively, under specific conditions. The presence of intramolecular hydrogen bonding was evident in IR and ^{1}H NMR spectra, and the HO-3 group was identified as the hydrogen-bonding donor in **5** and **6**. In their crystalline states, diol **5** prefers a chair conformation and diol **6** a twist boat (skew) conformation. Both compounds appear to have substantial populations of chair conformations in the gas and solution phases, on the basis of the MM-2 energy minimizations and comparisons of vicinal coupling constants observed in the ^{1}H NMR spectra (in $CDCl_3$ and Me_2SO-d_6) and calculated from the crystal and MM-2 conformations. It is suggested as an explanation for the observed selectivities that the kinetic acidity of the HO-3 group may be enhanced through its intramolecular hydrogen bonding with the cis-vicinal oxygen, or the nucleophilicity of the 3-alkoxide may be enhanced due to its interaction with the cis-vicinal oxygen in a manner similar to the through-space α-effect.

1. Introduction

Rapid recent progress in understanding the intracellular signal transduction pathway utilizing inositol phosphate derivatives has stimulated the renewed interest in *myo*-inositol chemistry [1]. Many research groups have developed various reaction conditions under which *myo*-inositol itself or *myo*-inositol derivatives can be regioselectively manipulated [2].

* Corresponding author.

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Cyclic acetals such as cyclohexylidene and isopropylidene have routinely been used as protecting groups in the synthesis of *myo*-inositol derivatives [3]. Due to the conformational rigidity imposed on the inositol ring by cyclic acetals, the remaining free hydroxyl groups could be selectively manipulated under suitable conditions. Early studies showed that benzoylation of both (±)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol and (±)-1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol afforded the 3-benzoate as major products [4,5]. Several additional reaction conditions for regioselective handling of the same substrates and their isopropylidene analogues have also been reported in recent years [6]. However, there have been few systematic investigations on the origins of the differential reactivities of the hydroxyl groups in these compounds.

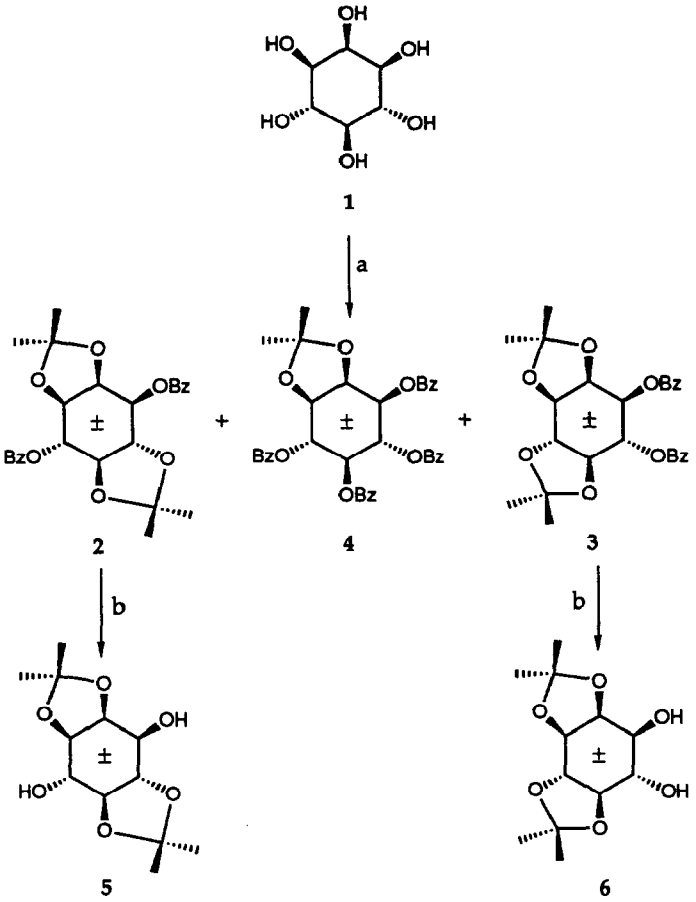
In this paper, we describe the results of regioselective functionalization of (±)-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**5**) and (±)-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**6**) in various reactions such as alkylation, acylation, and silylation, and discuss the possible origins of the regioselectivities observed on the basis of spectroscopic and conformational studies.

2. Results and discussion

Preparation of the di-O-isopropylidene-myo-inositol derivatives.—The starting materials **5** and **6** used in this study were prepared from *myo*-inositol in two steps essentially according to the literature with an improved isolation procedure (Scheme 1) [7]. Isopropylidenation of *myo*-inositol with 2,2-dimethoxypropane followed by benzoylation furnished a mixture of dibenzoates **2** and **3**, and tetrakisbenzoate **4**. Dibenzoate **2** was obtained by simple filtration of the reaction mixture [7a]. We found that dibenzoate **3** and tetrakisbenzoate **4** could also be separated by simple washing with methanol, since the solubility of **3** in methanol is much higher than that of **4**. Dibenzoates **2** and **3** were converted into their corresponding diols **5** and **6** by saponification with NaOH in boiling methanol.

Regioselective functionalizations of 5 and 6.—Various reactions including alkylation, acylation, sulfonylation, silylation, and phosphorylation have been carried out on **5** (Scheme 2), and the product distributions for each reaction are summarized in Table 1. The standard benzylation conditions using benzyl bromide and sodium hydride in DMF effected the preferential functionalization at the 3-position, thus providing the 3-benzyl ether **7a** in essentially pure form after crystallization (entry 1). Benzylation of **5** with NaH and benzyl bromide in refluxing toluene [6d] showed some selectivity, but the products were more complex (entry 2). *p*-Methoxybenzylation of **5** also proceeded with a high degree of regioselectivity, but a substantial amount of the dibenzylated product was obtained (entries 3 and 4).

Selective acylation of **5** was examined. Treatment of **5** with pivaloyl chloride in pyridine provided two mono-acylated products in a ratio of 4.6:1, favoring the HO-3 group (entry 5). Although pyridine was found to be the solvent of choice because of the low solubility of **5** in other solvents such as dichloromethane, some degree of selectivity was evident in other solvents as well.

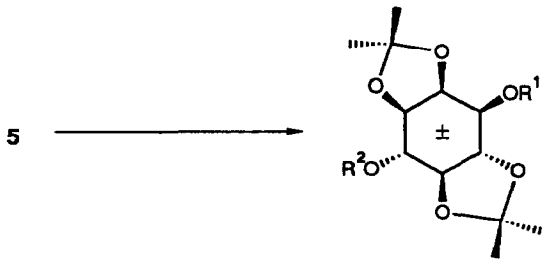


Scheme 1. (a) *i*: $(MeO)_2CMe_2$, *p*-TsOH, DMF; *ii*: BzCl, pyridine. (b) NaOH, MeOH, reflux.

The highly reactive triflic anhydride also exhibited good selectivity for the HO-3 group of **5** at −20°C, giving **10a** in 52% yield after chromatography (entry 6). The actual electrophile in this case may be the *N*-(trifluoromethylsulfonyl)pyridinium salt [8,9]. The position of acylation or triflation could be identified clearly by the ^{1}H NMR spectrum because of the downfield shift of the ring methine proton.

Silylation exhibited regioselectivity toward the HO-3 group. Treatment of **5** with *tert*-butyldimethylsilyl chloride and an excess of imidazole in DMF [10] preferentially afforded the 3-silyl ether **11a** (entry 7). The position of silylation was determined based on the ^{1}H NMR spectrum of the corresponding acetates derived from the silylated products by treatment with acetic anhydride in pyridine.

Regioselective phosphorylation of **5** was also studied. Treatment of **5** with diphenyl phosphorochloridate, triethylamine, and a catalytic amount of 4-dimethylaminopyridine in dichloromethane provided the 3-phosphate **12a** as the major product together with a small amount of 3,6-bisphosphate **12c** (entry 8). The ^{31}P



7a R^1 = Bn, R^2 = H
b R^1 = H, R^2 = Bn
c R^1, R^2 = Bn

8a R^1 = pMeOBn, R^2 = H
b R^1 = H, R^2 = pMeOBn
c R^1, R^2 = pMeOBn

9a R^1 = $(CH_3)_3CC(O)$, R^2 = H
b R^1 = H, R^2 = $(CH_3)_3CC(O)$
c R^1, R^2 = $(CH_3)_3CC(O)$

10a R^1 = CF_3SO_2, R^2 = H
b R^1 = H, R^2 = CF_3SO_2
c R^1, R^2 = CF_3SO_2

11a R^1 = $^tBuMe_2Si$, R^2 = H
b R^1 = H, R^2 = $^tBuMe_2Si$
c R^1, R^2 = $^tBuMe_2Si$

12a R^1 = $(PhO)_2P(O)$, R^2 = H
b R^1 = H, R^2 = $(PhO)_2P(O)$
c R^1, R^2 = $(PhO)_2P(O)$

Scheme 2.

NMR spectrum of **12a** showed a resonance at δ −11.55 ppm corresponding to one phosphate group.

The regioselectivity in the alkylation, acylation, and silylation of **6** was studied under various reaction conditions (Scheme 3), and the results are shown in Table 2. The reaction conditions employing benzyl bromide and sodium hydride in DMF at 0°C or room temperature did not result in selective benzylation of **6** (entries 1 and 2). No discernible selectivity was observed in the reaction utilizing sodium methoxide with 15-crown-5 ether and benzyl bromide in benzene. Use of the less reactive base, sodium methoxide resulted in a low reaction rate and low product yield (entry 3). However, conditions were found for the regioselective benzylation of **6**. With benzyl bromide and NaH in refluxing toluene [6d], benzylation took place preferentially at HO-3, giving the 3-benzyl ether **13a** in 52% yield after chromatography (entry 4). The large regioselectivity difference in benzylation by solvent change might be due to the reactivity difference of the alkoxide in the two solvent systems rather than conformational changes accompaning the solvent change, because ^{1}H NMR spectra of **6** in $CDCl_3$ and Me_2SO-d_6 did not show much difference. A reverse selectivity could be achieved in the benzylation via a tin complex of **6** [6e]. The stannylidene derivative, obtained from **6** by the azeotropic removal of water with toluene, was treated with benzyl bromide and cesium fluoride in DMF. After chromatography, the 4-benzyl ether **13b** was obtained as the major product in ca. 75% yield (entry 5).

Acylation was found to show much higher regioselectivity toward the HO-3 group. Diol **6** was selectively acylated by treatment with 3,4,5-trimethoxybenzoyl chloride and pyridine in dichloromethane at 0°C, to give the 3-trimethoxybenzoate

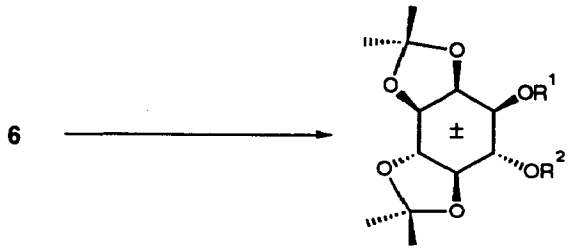
Table 1
Regioselective functionalizatons of diol **5**

Entry	Reaction conditions	Products (isolated yield, %) [a]		Starting material recovered (%)	
1	BnBr (1.2 equiv), NaH (1.2 equiv), DMF, RT [c], 11 h	**7a** (46) [b]	**7b** (0)	**7c** (15)	ND [d]
2	BnBr (1.2 equiv), NaH (1.2 equiv), toluene, reflux, 12 h	**7a** (48.1)	**7b** (11.5)	**7c** (19.0)	8.5
3	*p*-(CH_3O) BnCl (1.0 equiv), NaH (5.0 equiv), DMF, RT, 5h	**8a** (20)	**8b** (0)	**8c** (24)	ND
4	*p*-(CH_3O) BnCl (1.2 equiv), NaH (1.2 equiv), DMF, RT, 3 h	**8a** (30.5)	**8b** (0)	**8c** (29.2)	ND
5	$(CH_3)_3CC(O)Cl$ (1.8 equiv), pyridine, RT, 28 h	**9a** (42.3)	**9b** (9.1)	**9c** (15.0)	7.9
6	$(CF_3SO_2)_2O$ (1.15 equiv), pyridine (2.0 equiv), CH_2Cl_2, −20°C, 3 h	**10a** (52.0)	**10b** (0)	**10c** (24.9)	0
7	*t*-$BuMe_2SiCl$ (1.1 equiv), imidazole (3.3 equiv), DMF, RT, 12 h	**11a** (55.4)	**11b** (0)	**11c** (6.8)	25.3
8	$(PhO)_2P(O)Cl$ (1.2 equiv), TEA (3.0 equiv), cat. DMAP, CH_2Cl_2, RT, 4 h	**12a** (30)	**12b** (trace)	**12c** (8)	ND

[a] Isolated by column chromatography unless indicated otherwise.
[b] Isolated by recrystallization.
[c] RT, Room temperature.
[d] ND, Not determined.

14b in 52% yield (entry 6). Perhaps the relatively low reactivity of trimethoxybenzoyl chloride as an acylating agent is a factor for the high regioselectivity observed. Pivaloylation was found to be most effective for the selective acylation of **6**. After treatment of **6** with pivaloyl chloride and pyridine in dichloromethane at 0°C, the 3-pivalate **15a** was isolated as the sole product in 81% yield by simple recrystallization from hexane (entry 8). However, a similar pivaloylation over an extended period at room temperature resulted in poor selectivity (entry 7), probably due to the base-catalyzed isomerization of the product involving the vicinal *trans*-hydroxyl group. The isomerization was evident in a control experiment employing TLC analysis.

In the silylation experiments using diethylaminotrimethylsilane [11] in dichloromethane at −20°C, or *tert*-butyldimethylsilyl chloride and imidazole in acetonitrile, some discrimination between HO-3 and HO-4 of **6** was observed



13a R^1 = Bn, R^2 = H
b R^1 = H, R^2 = Bn
c R^1, R^2 = Bn

14a R^1 = 3,4,5-$(CH_3O)_3$Bz, R^2 = H
b R^1 = H, R^2 = 3,4,5-$(CH_3O)_3$Bz
c R^1, R^2 = 3,4,5-$(CH_3O)_3$Bz

15a R^1 = $(CH_3)_3CC(O)$, R^2 = H
b R^1 = H, R^2 = $(CH_3)_3CC(O)$
c R^1, R^2 = $(CH_3)_3C(O)$

16a R^1 = $(CH_3)_3Si$, R^2 = H
b R^1 = H, R^2 = $(CH_3)_3Si$
c R^1, R^2 = $(CH_3)_3Si$

17a R^1 = ^{t}BuMe$_2$Si, R^2 = H
b R^1 = H, R^2 = ^{t}BuMe$_2$Si
c R^1, R^2 = ^{t}BuMe$_2$Si

Scheme 3.

(entries 9 and 10). As with **5**, the position of silylation was determined on the basis of ^{1}H NMR data for the corresponding acetates derived from the silylated products.

Spectroscopic studies of 5 and 6.—From the above results, it is evident that the HO-3 groups are more reactive than HO-6 or HO-4 in **5** and **6**, respectively. An explanation for the reactivity differences based solely on steric hindrance [8] appears unlikely since the more reactive HO-3 groups are more sterically hindered than HO-6 and HO-4. We thought that intramolecular hydrogen bonding and the resultant enhanced acidity might play an important role in determining the regioselectivity of the reactions, especially in those cases employing amine bases. Previous workers studying regioselectivity in carbohydrates have suggested that hydrogen bonding of the proton on the reacting hydroxyl group to a cis-vicinal ether oxygen can enhance its reactivity relative to other hydroxyl groups without such possibilities [8,9].

Examination of the IR spectrum for **5** and **6** in a highly diluted (< 0.01 M) dichloromethane solution reveals the presence of intramolecularly hydrogen-bonded and free hydroxyl groups. In the spectrum of **5**, two hydroxyl-stretching bands (3683 and 3585 cm^{-1}) were observed. The high frequency band is due to the free OH and the low frequency band to the intramolecularly hydrogen-bonded OH group [12,13]. The IR spectrum of the diluted dichloromethane solution of **6** also shows similar features at 3686 and 3587 cm^{-1}.

^{1}H NMR spectra of **5** and **6** at 300 MHz in deuteriochloroform reveal two hydroxyl peaks each at δ 2.36 (d, J 8.8 Hz, HO-3), 2.45 (d, J 2.9 Hz, HO-6), and δ 2.62 (d, J 5.1 Hz, HO-3), 2.79 (d, J 2.2 Hz, HO-4), respectively. The larger vicinal

Table 2
Regioselective functionalizations of diol **6**

Entry	Reaction conditions	Products (isolated yield, %) [a]		Starting material recovered (%)	
1	BnBr (1.1 equiv), NaH (1.1 equiv), DMF, 0°C, 72 h	**13a** (16.1)	**13b** (18.6)	**13c** (13.2)	ND [b]
2	BnBr (1.1 equiv), NaH (1.1 equiv), DMF, RT [c], 24 h	**13a** (17.6)	**13b** (19.1)	**13c** (12.1)	ND
3	(a) CH_3ONa (1.1 equiv), 15-Crown-5, C_6H_6 (b) BnBr (2.2 equiv), RT, 36 h	**13a** (12.0)	**13b** (9.9)	**13c** (0)	78.0
4	BnBr (1.1 equiv), NaH (1.1 equiv), toluene, reflux, 12 h	**13a** (52.0)	**13b** (16.6)	**13c** (5.6)	15.0
5	(a) n-Bu_2SnO, toluene, reflux (b) BnBr (2.8 equiv), CsF (2.0 equiv), DMF, RT, 5 h	**13a** (21.2)	**13b** (74.4)	**13c** (0)	0
6	3,4,5-$(CH_3O)_3$BzCl (1.1 equiv), pyridine (1.5 equiv), CH_2Cl_2, 0°C, 36 h	**14a** (51)	**14b** (0)	**14c** (0)	ca. 12
7	$(CH_3)_3CC(O)Cl$ (1.1 equiv), pyridine (1.5 equiv), CH_2Cl_2, RT, 38 h	**15a** (19.4)	**15b** (17.6)	**15c** (ND)	ND
8	$(CH_3)_3CC(O)Cl$ (2.2 equiv), pyridine (2.2 equiv), CH_2Cl_2, 0°C, 7 h	**15a** (81) [d]	**15b** (trace)	**15c** (trace)	trace
9	$(CH_3)_3SiNEt_2$ (2.6 equiv), CH_2Cl_2, −20°C, 27 h	**16a** (35.3)	**16b** (7.1)	**16c** (48.7)	ND
10	t-$BuMe_2SiCl$ (1.1 equiv), imidazole (3.3 equiv), CH_3CN, RT, 12 h	**17a** (46.6)	**17b** (29.5)	**17c** (5.3)	18.0

[a] Isolated by column chromatography unless indicated otherwise.
[b] ND, Not determined.
[c] RT, Room temperature.
[d] Isolated by recrystallization.

coupling constants between the hydroxyl proton and the ring methine proton at C-3 of **5** and **6** could be correlated to dihedral angles of ca. 150° and ca. 125°, respectively, and these angles are attainable only if these hydroxyl protons are hydrogen-bonded to nearby cis-vicinal ether oxygens (see below). The peak assignments were made on the basis of decoupling experiments and 2D-COSY spectra. Thus, the observed regioselectivity may be traced at least in part to the enhanced reactivity of the HO-3 group which is intramolecularly hydrogen-bonded.

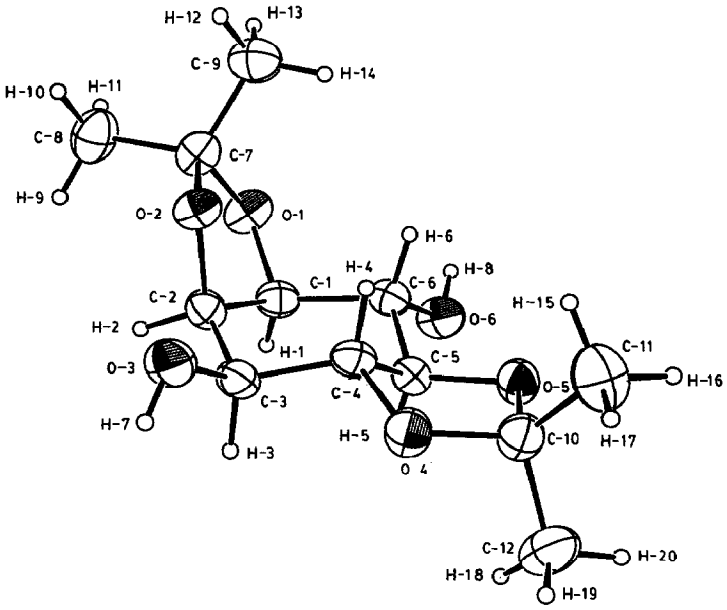


Fig. 1. Crystal structure (ORTEP) of **5**.

For alkylations employing such strong bases as sodium hydride, the explanation based on intramolecular hydrogen bonding may not be applicable because alkylation probably takes place after formation of an alkoxide. For these cases, at least two possibilities might be considered. First, an analogous cation chelation between the alkoxide anion generated and the cis-vicinal ether oxygen may provide a possible explanation for the observed regioselectivity. In fact, such a cation chelation effect has already been invoked to explain a hydroxyl regioselectivity in the alkylation of the mono-orthoformate of *myo*-inositol [14]. A second possibility is that the through-space interaction between the alkoxide anion and the cis-vicinal ether oxygen may enhance the nucleophilicity of the alkoxide *.

Conformational studies of 5 and 6.—Obviously, intramolecular hydrogen bonding or cation chelation would be possible only if **5** and **6** have adequate geometry and conformation. Therefore, conformational studies were carried out on the basis of X-ray crystallography, MM-2 calculation, and solution NMR, corresponding respectively to the solid, gas, and solution phase conformations.

As single crystals of both **5** and **6** could be obtained, their crystal structures were determined by X-ray diffraction [16]. Diol **5** has a chair conformation and **6** a twist-boat (skew) conformation in their crystal structures as shown in Figs. 1 and 2, respectively. For **5**, even hydrogen positions could be determined by diffraction (not calculation) because of the exceptionally fine crystal quality ($R = 0.028$).

* It has been suggested [15] that an analogous interaction between lone pair electrons raises the HOMO energy level, thus enhancing the nucleophilicity.

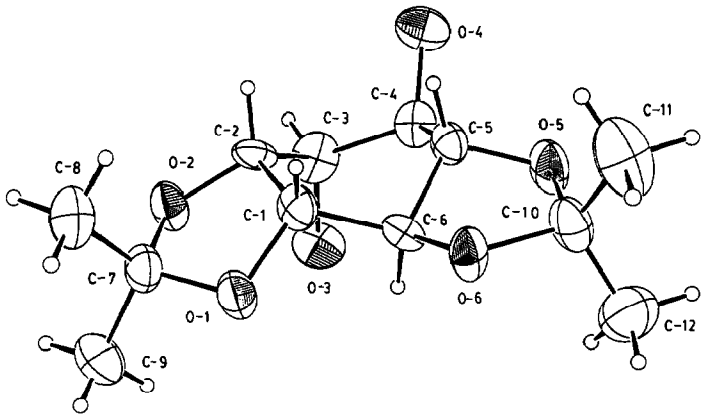


Fig. 2. Crystal structure (ORTEP) of **6**.

Direct evidence for the intramolecular hydrogen bond is not found in the crystal structure of **5**, because intermolecular H-bonding is predominant in its unit cell.

Minimum energy conformations were determined for **5** and **6** by molecular mechanics calculations. Chair conformations were found to be more stable for both **5** and **6**. A larger energy difference of ca. 20 kJ ($K = 3.12 \times 10^4$ at room temperature) between a chair (**C5**, $E = -73.84$ kJ/mol) and twist-boat conformation (**TB5**, $E = -53.74$ kJ/mol) was seen for **5**. Thus, the twist-boat conformation of **5** is not expected to play a significant role. For compound **6**, the chair conformation (**C6**, $E = -77.40$ kJ/mol) is more stable by only 4.5 kJ ($K = 0.16$ at room temperature) than the twist-boat conformation (**TB6**, $E = -72.85$ kJ/mol). Therefore, both the conformations (**C6** and **TB6**) would exist in substantial populations at equilibrium in the gas phase at room temperature.

In order to deduce conformations in the solution phase, vicinal coupling constants were determined from the ^{1}H NMR spectra of **5** and **6** in $CDCl_3$ and

Table 3
^{1}H–^{1}H Vicinal coupling constants between inositol-ring methine protons observed in the ^{1}H NMR ($CDCl_3$ and Me_2SO-d_6) and calculated from the crystal and MM-2 structure by the Altona equation for **5**

Relationship	Coupling constant (J, Hz)			
	Observed		X-ray	MM-2 (**C5**)
	$CDCl_3$	Me_2SO-d_6		
H-1–H-2	4.8	4.6	5.3	5.2
H-2–H-3	4.8	4.6	3.5	3.9
H-3–H-4	9.4	9.5	9.8	9.0
H-4–H-5	9.4	9.5	10.2	10.0
H-5–H-6	10.5	10.6	9.8	9.4
H-6–H-1	6.4	6.4	7.2	7.2

Table 4
^1H–^1H Vicinal coupling constants between inositol-ring methine protons observed in the ^1H NMR ($CDCl_3$ and Me_2SO-d_6) and calculated from the crystal and MM-2 structures by the Altona equation for **6**

Relationship	Coupling constant (J, Hz)				
	Observed		X-ray	MM-2	
	$CDCl_3$	Me_2SO-d_6		**C6**	**TB6**
H-1–H-2	6.2	6.0	7.8	4.8	7.8
H-2–H-3	4.2	3.8	4.2	3.9	3.7
H-3–H-4	5.3	5.6	0.7	8.8	0.7
H-4–H-5	9.1	8.7	6.0	9.7	5.9
H-5–H-6	10.2	10.1	10.2	9.9	10.1
H-6–H-1	8.1	8.1	8.5	8.3	7.1

Me_2SO-d_6. They are listed in Tables 3 and 4. Since observed coupling constants are virtually identical in both solvent systems, it is assumed that conformations (or conformational equilibria) of **5** and **6** are the same. It is difficult to calculate the dihedral angles, the key conformational indicators, from the observed coupling constants, since three-bonded coupling constants through two sp^3-carbons depend on a number of factors including dihedral angle, electronegativities of the substituents, orientation of electronegative substituent, and so on [17–19]. For this reason, comparisions of observed and calculated coupling constants have often been used for conformational analysis [3b,20,21]. Therefore, we compared the observed coupling constants with those derived from the crystal and MM-2 structures by a generalized Karplus equation (Altona equation) [19].

For compound **5**, the coupling constants calculated from X-ray and MM-2 structures match well, and are in good agreement with those from ^1H NMR data (Table 3). It seems likely that **5** has a chair conformation in the solution phase as well. Likewise, the vicinal coupling constants calculated from the crystal structure of **6** agree well with those from **TB6**. But, the coupling constants observed were somewhere in between those from the chair conformation (**C6**) and those from the twist-boat conformation (crystal structure and **TB6**) (Table 4). Based on these results, the solution conformation of **6** appears to be an equilibrium mixture of

Table 5
Selected interoxygen distances from the crystal and MM-2 structures for **5**

Relationship	Interatomic distance (Å)	
	X-ray	MM-2 (**C5**)
O-1–O-3	4.6322	4.547
O-2–O-3	2.7456	2.689
O-4–O-6	4.6357	5.031
O-5–O-6	2.9382	2.929

Table 6
Selected dihedral angles from the crystal and MM-2 structures for **5**

Relationship	Dihedral angle (°)	
	X-ray	MM-2 (**C5**)
O-2–C-2–C-3–O-3	49.3	49.2
O-5–C-5–C-6–O-6	65.1	67.0

Table 7
Selected interoxygen distances from the crystal and MM-2 structures for **6**

Relationship	Interatomic distance (Å)		
	X-ray	MM-2 (**TB6**)	MM-2 (**C6**)
O-1–O-3	3.403	3.310	4.607
O-2–O-3	2.702	2.641	2.801
O-4–O-5	3.191	3.632	2.961
O-4–O-6	4.635	4.595	4.591

chair and twist-boat. This conclusion is also in agreement with a report on the basis of IR evidence that 1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol exists in a chair conformation in equilibrium with others in CCl_4 solution [22].

For each of the X-ray and calculated conformations of **5** and **6**, the interoxygen distances between free hydroxyl groups and adjacent ether oxygens (Tables 5 and 7), and their associated dihedral angles (Tables 6 and 8) were determined as parameters for evaluating the possibility of intramolecular hydrogen bonding or cation chelation. It is apparent that HO-3 and the cis-vicinal ether oxygen (O-2) are more favourably oriented for the hydrogen bonding with shorter distances and smaller dihedral angles in all conformations for both **5** and **6**.

It is somewhat puzzling to note that in many reactions described above the bisfunctionalized products were obtained in much higher yields than the minor products of the monofunctionalization. Based on the comparison of the vicinal coupling constants (in $CDCl_3$) of **5** and **6**, and those of the 3-monofunctionalized products, it is clear that no significant conformational changes have occurred upon reaction at HO-3, although a minor degree of the conformational equilibrium shift

Table 8
Selected dihedral angles from the crystal and MM-2 structures for **6**

Relationship	Dihedral angle (°)		
	X-ray	MM-2 (**TB6**)	MM-2 (**C6**)
O-2–C-2–C-3–O-3	−46.9	−44.6	52.6
O-4–C-4–C-5–O-5	−92.9	−88.7	−66.7

Table 9
Vicinal coupling constants (observed in $CDCl_3$) of **5** and its 3-monofunctionalized products

Compound	Coupling constants (J, Hz)					
	H-1–H-2	H-2–H-3	H-3–H-4	H-4–H-5	H-5–H-6	H-6–H-1
5	4.8	4.8	9.4	9.4	10.5	6.4
7a	4.4	4.4	10.2	9.8	10.2	6.5
8a	4.3	4.3	10.1	9.6	10.0	6.6
9a	4.7	4.7	10.6	9.8	10.7	6.5
10a	4.7	4.5	10.3	9.7	10.6	6.4
11a	4.7	4.3	10.0	9.4	10.5	6.4
12a	4.8	4.3	10.0	9.5	10.6	6.5

may be possible, especially for **6** (Tables 9 and 10). Thus, formation of the bisfunctionalized products does not appear to be related to conformational changes.

3. Experimental

General.—All commercial chemicals were used as obtained without further purification, and all solvents were carefully dried and distilled by standard methods prior to use [23]. DMF was dried by storing over anhyd $MgSO_4$ and vacuum distilled. Toluene was dried over anhyd $MgSO_4$ and distilled over P_2O_5. Pyridine was dried by storing over NaOH and distilled. CH_2Cl_2, MeCN, and benzene were dried and distilled over P_2O_5. Column chromatography was carried out on Silica Gel 60 (Merck, 230–400 mesh) by the flash technique. TLC was performed on Merck 60 F_{254} precoated silica gel plates (0.25-mm layer thickness). Visualization was done with UV light, and/or a spray with 5% phosphomolybdic acid in EtOH followed by charring with a heat gun. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker AM 300 spectrometer. Chemical shifts are reported in ppm relative to $(CH_3)_4Si$ for ^1H and ^{13}C NMR, and 80% H_3PO_4 for ^{31}P NMR. Assignments of ^1H resonances were assisted by the COSY spectral data. IR

Table 10
Vicinal coupling constants (observed in $CDCl_3$) of **6** and its 3-monofunctionalized products

Compound	Coupling constants (J, Hz)					
	H-1–H-2	H-2–H-3	H-3–H-4	H-4–H-5	H-5–H-6	H-6–H-1
6	6.2	4.2	5.3	9.1	10.2	8.1
13a	5.0	4.5	7.2	9.8	10.0	8.6
14a	6.4	3.8	3.4	8.3	10.5	7.1
15a	6.5	4.7	4.7	8.8	10.3	8.0
16a	5.4	4.2	6.4	9.0	10.0	8.4
17a	5.8	4.2	5.7	9.0	10.0	8.2

spectra were recorded with a BOMEM FT-IR M100-C15 spectrometer for liquid films or KBr pellets. Mass spectra were determined on a Kratos MS 25 RFA (EI and FAB) system. Elemental analyses were performed by the Korea Basic Science Center, Seoul, Korea. The standard extractive work-up procedure consisted of partitioning the product mixture into water and the organic solvent indicated, repeatedly separating the organic layer, washing the combined extracts successively with water and brine, drying the extract over anhyd $MgSO_4$ or Na_2SO_4, and evaporating the solvent.

(±)-3,6-Di-O-benzoyl-1,2:4,5-di-O-isopropylidene-myo-*inositol* (**2**).—The preparation was done essentially according to a literature procedure [7a]. A mixture of *myo*-inositol (50 g, 278 mmol), 2,2-dimethoxypropane (150 mL, 1.2 mol), and toluene-*p*-sulfonic acid monohydrate (1 g, 5.2 mmol) in DMF (200 mL) was stirred at 100°C for 3 h. Unreacted *myo*-inositol (6.08 g, 12%) was filtered off. Triethylamine (10 mL) was added to the filtrate, and the low-boiling solvents were evaporated at 40°C. To the mixture at 0°C was added pyridine (150 mL) and then benzoyl chloride (200 mL, 1.74 mol) over 15 min. After stirring for an additional 2 h at room temperature, the precipitate was collected and washed successively with pyridine, water, acetone, and ether to give **2** as a white solid (35.7 g, 27%); mp 322–324°C (lit. [7a] mp 328–330°C); ^{1}H NMR ($CDCl_3$): δ 1.30, 1.43, 1.50, 1.63 (4 s, each 3 H, 2 CMe_2), 3.73 (dd, 1 H, $J_{5,6}$ 11.1, $J_{5,4}$ 9.6 Hz, H-5), 4.36 (dd, 1 H, $J_{4,3}$ 10.6 Hz, H-4), 4.41 (dd, 1 H, $J_{1,6}$ 6.9, $J_{1,2}$ 4.5 Hz, H-1), 4.78 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 5.42 (dd, 1 H, H-3), 5.60 (dd, 1 H, H-6), 7.45 (m, 5 H, Ph), and 8.11 (m, 5 H, Ph).

(±)-3,4-Di-O-benzoyl-1,2:5,6-di-O-isopropylidene-myo-*inositol* (**3**) *and (±)-3,4,5,6-tetra-O-benzoyl-1,2-O-isopropylidene*-myo-*inositol* (**4**).—The combined filtrate and washings from the preparation of **2** were partitioned between water and CH_2Cl_2. The organic layer was separated and concentrated in vacuo. The solid residue was filtered off and washed with MeOH to give **3** (23.1 g, 13%); TLC (1:3 EtOAc–hexane) R_f 0.3; mp 187–189°C (lit. [7b] mp 197–200°C); ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 6 H, CMe_2), 1.47, 1.51 (2 s, each 3 H, CMe_2), 3.87 (dd, 1 H, $J_{5,6}$ 10.5, $J_{5,4}$ 8.4 Hz, H-5), 4.30 (dd, 1 H, $J_{6,1}$ 7.9 Hz, H-6), 4.51 (dd, 1 H, $J_{1,6}$ 7.8, $J_{1,2}$ 6.7 Hz, H-1), 4.72 (dd, 1 H, $J_{2,3}$ 3.8 Hz, H-2), 5.61 (m, 2 H, H-3, 4), 7.43 (m, 4 H, Ph), 7.55 (m, 2 H, Ph), and 8.04 (m, 4 H, Ph); ^{13}C NMR ($CDCl_3$): δ 24.90, 26.71, 26.99, 27.03 (2 CMe_2), 72.81, 73.76, 74.18, 76.52 (2 C), 77.80 (C-1–C-6), 111.37, 113.14 (2 CMe_2), 128.37, 128.47, 129.42, 129.45, 129.85, 129.91, 130.02, 133.32 (Ph), and 164.91, 165.11 (2 C=O).

A crystalline product obtained from the above filtrate by addition of MeOH was washed with boiling MeOH to provide **4** (36.4 g, 28%); TLC (1:3 EtOAc–hexane) R_f 0.25; ^{1}H NMR ($CDCl_3$): δ 1.38, 1.72 (2s, each 3 H, CMe_2), 4.59 (dd, 1 H, $J_{1,6}$ 6.9, $J_{1,2}$ 5.5 Hz, H-1), 4.85 (dd, 1 H, $J_{2,3}$ 3.9 Hz, H-2), 5.72 (m, 2 H, H-3, 4), 5.91 (dd, 1 H, $J_{6,5}$ 9.2 Hz, H-6), 6.19 (dd, 1 H, $J_{5,4}$ 9.3 Hz, H-5), and 7.33–8.00 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.61, 27.41 (CMe_2), 70.06, 70.17, 71.58, 72.98, 73.54, 76.26 (C-1–C-6), 111.37 (CMe_2), 128.24, 128.28, 128.36, 128.45, 128.61, 129.01, 129.19, 129.69, 129.76, 129.84, 130.04, 133.19, 133.26, 133.43 (Ph), and 165.32, 165.41, 165.59, 165.82 (4 C=O).

(±)-1,2:4,5-Di-O-isopropylidene-myo-inositol (**5**).—A mixture of **2** (10 g, 21 mmol), NaOH (4 g, 100 mmol), and MeOH (250 mL) was heated a reflux for 30 min. The resulting solution was cooled, neutralized with solid CO_2, diluted with water (200 mL), and evaporated to dryness. The remaining solid residue was dissolved in CH_2Cl_2, and the undissolved solid was filtered off. The filtrate was evaporated to give **5** (9.02 g, 81.2%); TLC (EtOAc) R_f 0.5; mp 167.0–168.5°C (lit. [7a] mp 171–173°C); ^{1}H NMR ($CDCl_3$) δ 1.38, 1.46, 1.48, 1.54 (4s, each 3 H, 2 CMe_2), 2.36 (d, 1 H, J 8.8 Hz, HO-3), 2.45 (d, 1 H, J 2.9 Hz, HO-6), 3.32 (dd, 1 H, $J_{5,6}$ 10.5, $J_{5,4}$ 9.4 Hz, H-5), 3.83 (dd, 1 H, $J_{4,3}$ 9.4 Hz, H-4), 3.90 (ddd, 1 H, $J_{6,1}$ 6.4, $J_{6,OH}$ 2.9 Hz, H-6), 4.02 (ddd, 1 H, $J_{3,OH}$ 8.8, $J_{2,3}$ 4.8 Hz, H-3), 4.08 (dd, 1 H, $J_{1,2}$ 4.8 Hz, H-1), and 4.48 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ 25.36, 26.91, 26.91, 28.09 (2 C*Me*$_2$), 69.92, 74.96, 77.58, 78.03, 78.03, 81.89 (C-1–C-6), and 110.29, 112.71 (2 *C*Me$_2$). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 54.91; H, 7.74.

(±)-1,2:5,6-Di-O-isopropylidene-myo-inositol (**6**).—A mixture of **3** (3.48 g, 7.4 mmol) and NaOH (1 g, 25 mmol) in MeOH (50 mL) was heated at reflux for 1 h. The resulting solution was cooled, neutralized with a large amount of solid CO_2, and evaporated to dryness. The solid was dissolved in CH_2Cl_2 and the remaining solid was filtered off. The fitrate was evaporated to give a solid product which was recrystallized from EtOAc to give **6** (1.57 g, 81.3%); mp 166–167°C (lit. [7b] mp 172–175°C); ^{1}H NMR ($CDCl_3$): δ 1.38, 1.43, 1.46, 1.53 (4s, 2 CMe_2), 2.62 (d, 1 H, J 5.1 Hz, HO-3), 2.79 (d, 1 H, J 2.2 Hz, HO-4), 3.37 (dd, 1 H, $J_{5,6}$ 10.2, $J_{5,4}$ 9.1 Hz, H-5), 3.82 (ddd, 1 H, $J_{3,4}$ 5.3 $J_{3,OH}$ 5.1, $J_{3,2}$ 4.2 Hz, H-3), 3.90 (dd, 1 H, $J_{6,1}$ 8.1 Hz, H-6), 4.01 (ddd, 1 H, $J_{4,OH}$ 2.2 Hz, H-4), 4.30 (dd, 1 H, $J_{1,2}$ 6.2 Hz, H-1), and 4.47 (dd, 1 H, H-2). The assignment of each proton for **6** was made on the basis of the ^{1}H–^{1}H COSY spectrum; ^{13}C NMR ($CDCl_3$): δ 25.09, 26.91, 26.91, 27.53 (2 C*Me*$_2$), 73.14, 74.26, 76.16, 76.16, 78.25, 78.28 (C-1–C-6), and 110.52, 112.50 (2 *C*Me$_2$). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.47; H, 7.61.

Benzylation of 5.—Run 1: A mixture of **5** (250 mg, 0.96 mmol), NaH (97%, 30 mg, 1.2 mmol), and benzyl bromide (0.14 mL, 1.2 mmol) in DMF (10 mL) was stirred at room temperature for 12h. The mixture was extractively worked up with CH_2Cl_2 to give an oil, which was crystallized from CH_2Cl_2 and hexane to give **7a** as a white solid (160 mg, 46%).

Run 2: A mixture of **5** (100 mg, 0.384 mmol), NaH (80% dispersion in mineral oil, 13.8 mg, 0.461 mmol), and benzyl bromide (0.055 mL, 0.461 mmol) in toluene (2 mL) was heated at reflux for 12 h. Chromatography of the mixture on silica gel with a gradient of hexane–EtOAc provided the solid products, the dibenzyl ether **7c** (32.2 mg, 19.0%), 6-benzyl ether **7b** (15.4 mg, 11.5%), 3-benzyl ether **7a** (64.8 mg, 48.1%), and a small amount of starting material (8.5 mg, 8.5%). Compound **7b** was found moving ahead of **7a** in TLC (R_f 0.26 vs. 0.20).

(±)-3-O-Benzyl-1,2:4,5-di-O-isopropylidene-myo-inositol (**7a**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.2; mp 162–163°C (lit. mp 167–170°C [3b]; 167–169°C [6f]); ^{1}H NMR ($CDCl_3$): δ 1.33, 1.45, 1.48, 1.54 (4s, each 3 H, 2 CMe_2), 2.92 (bs, 1 H, OH), 3.25 (dd, 1 H, $J_{5,6}$ 10.2, $J_{5,4}$ 9.8 Hz, H-5), 3.77 (dd, 1 H, $J_{3,4}$ 10.2, $J_{3,2}$ 4.4 Hz, H-3), 3.86 (dd, 1 H, $J_{6,1}$ 6.5 Hz, H-6), 3.92 (dd, 1 H, $J_{1,2}$ 4.4 Hz, H-1), 4.03 (dd,

1 H, H-4), 4.32 (dd, 1 H, H-2), 4.78 (d, 1 H, *J* 12.5 Hz, PhCH_aH_b), 4.89 (d, 1 H, *J* 12.5 Hz, PhCH_aH_b), and 7.28–7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.79, 26.89, 26.91, 28.13 (2 CMe_2), 71.84, 74.38, 74.55, 76.59, 78.49, 81.69 (C-1–C-6 and CH_2Ph), 110.09, 112.34 (2 CMe_2), and 127.79, 128.23, 128.33, 137.87 (Ph). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.94; H, 7.44.

*(±)-3,6-Di-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol* (**7c**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.6; mp 150–153°C (lit. [7a] mp 153–155°C); ^{1}H NMR ($CDCl_3$): δ 1.33, 1.39, 1.46, 1.49 (4s, each 3 H, 2 CMe_2), 3.34 (dd, 1 H, $J_{5,6}$ 10.5, $J_{5,4}$ 9.4 Hz, H-5), 3.67 (dd, 1 H, $J_{6,5}$ 10.5, $J_{6,1}$ 6.5 Hz, H-6), 3.76 (dd, 1 H, $J_{3,4}$ 10.1, $J_{3,2}$ 4.2 Hz, H-3), 3.99–4.08 (dd, 1 H, $J_{4,3}$ $J_{4,5}$ 9.8 Hz, H-4; dd, 1 H, $J_{1,6}$ 6.9, $J_{1,2}$ 4.5 Hz, H-1), 4.31 (dd, 1 H, $J_{2,1} = J_{2,3} = 4.5$ Hz, H-2), 4.79 (d, 1 H, *J* 12.6 Hz, PhCH_aH_b), 4.81 (bs, 2 H, PhCH_2), 4.89 (d, 1 H, *J* 12.6 Hz, PhCH_aH_b), and 7.27–7.43 (m, 10 H, 2 Ph). The assignments of all protons and coupling constants for compound **7c** were based on COSY and *J*-Resolved spectra. Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found: C, 71.21; H, 7.42.

p-*Methoxybenzylation of* **5**.—*Run 1:* Diol **5** (500 mg, 1.92 mmol) was treated with *p*-methoxybenzyl chloride (0.26 ml, 1.92 mmol) and NaH (97%; 0.231 g, 9.60 mmol) in DMF (20 mL) for 5 h at room temperature. TLC (1:1 EtOAc–chloroform) showed a mixture of di-*p*-methoxybenzyl ether **8c** (R_f 0.8) and mono-*p*-methoxybenzyl ether **8a** (R_f 0.5). The product mixture, after workup, was separated on silica gel with a gradient of hexane–EtOAc, to give **8c** (0.230 g, 24%) and **8a** (0.147 g, 20%).

Run 2: Diol **5** (2.06 g, 7.93 mmol) was treated with *p*-methoxybenzyl chloride (1.29 mL, 9.5 mmol) and NaH (97%, 0.228 g, 9.50 mmol) in DMF (30 mL) for 3 h at room temperature. Workup gave a mixture which was separated on silica gel with a gradient of hexane–EtOAc, to give **8c** (1.46 g, 29.2%) and **8a** (0.92 g, 30.5%) as white solids.

*(±)-1,2:4,5-Di-*O*-isopropyliden-3-*O*-*p*-methoxybenzyl-*myo*-inositol* (**8a**): TLC (1:1 EtOAc–chloroform) R_f 0.5; mp 154–154.5°C (lit. [6f] mp 158–160°C); ^{1}H NMR ($CDCl_3$): δ 1.32, 1.44, 1.46, 1.52 (4s, each 3 H, 2 CMe_2), 2.27 (d, 1 H, *J* 2.5 Hz, OH), 3.24 (dd, 1 H, $J_{5,6}$ 10.0, $J_{5,4}$ 9.6 Hz, H-5), 3.75 (dd, 1 H, $J_{3,4}$ 10.1, $J_{3,2}$ 4.3 Hz, H-3), 3.79 (s, 3 H, OCH_3), 3.83–3.92 (m, 2 H, H-1, 6), 4.01 (dd, 1 H, H-4), 4.27 (dd, 1 H, $J_{2,1}$ 4.3 Hz, H-2), 4.71 (d, 1 H, *J* 12.1 Hz, PhCH_aH_b), 4.82 (d, 1 H, *J* 12.1 Hz, PhCH_aH_b), 6.86 (d, 2 H, *J* 8.6 Hz, Ph), and 7.32 (d, 2 H, *J* 8.6 Hz, Ph).

*(±)-1,2:4,5-Di-*O*-isopropylidene-3,6-di-*O*-*p*-methoxybenzyl-*myo*-inositol (**8c**)*: TLC (1:1 EtOAc–chloroform) R_f 0.8; mp 123–125°C; ^{1}H NMR ($CDCl_3$): δ 1.29, 1.37, 1.43, 1.46 (4s, each 3 H, 2 CMe_2), 3.30 (dd, 1 H, $J_{5,6}$ 10.5, $J_{5,4}$ 9.5 Hz, H-5), 3.63 (dd, 1 H, $J_{6,1}$ 6.4 Hz, H-6), 3.70 (dd, 1 H, $J_{3,4}$ 9.5, $J_{3,2}$ 4.3 Hz, H-3), 3.77, 3.79 (2s, each 3 H, 2 OCH_3), 3.98 (dd, 1 H, H-4), 4.01 (dd, 1 H, $J_{1,2}$ 4.3 Hz, H-1), 4.24 (dd, 1 H, H-2), 4.70 (d, 1 H, *J* 12.2 Hz, PhCH_aH_b), 4.71 (s, 2 H, PhCH_2), 4.80 (d, 1 H, *J* 12.2 Hz, PhCH_aH_b), 6.82–6.89 (m, 4 H, Ph), and 7.27–7.32 (m, 4 H, Ph). Anal. Calcd for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25. Found: C; 67.34; H, 7.29.

Pivaloylation of **5**.—A mixture of **5** (100 mg, 0.384 mmol) and trimethylacetyl chloride (0.071 mL, 0.691 mmol) in pyridine (2 mL) was stirred at room temperature for 28 h. The mixture was diluted with CH_2Cl_2, then washed with 0.1 M HCl

and satd aq $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated to give an oily mixture. The mixture was separated on silica gel with a gradient of hexane–EtOAc, to give dipivalate **9c** (24.7 mg, 15.0%), 6-pivalate **9b** (12.1 mg, 9.1%), 3-pivalate **9a** (56.0 mg, 42.3%), and some starting material (7.9 mg, 7.9%).

*(±)-1,2 : 4,5-Di-*O*-isopropylidene-3-*O*-trimethylacetyl-*myo*-inositol* (**9a**): TLC (7:3) diethyl ether–petroleum ether) R_f 0.3; ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 9 H, CMe_3), 1.29, 1.41, 1.47, 1.51 (4s, each 3 H, 2 CMe_2), 3.05 (bs, 1 H, OH), 3.40 (dd, 1 H, $J_{5,6}$ 10.7, $J_{5,4}$ 9.8 Hz, H-5), 3.89 (dd, 1 H, $J_{6,1}$ 6.5 Hz, H-6), 4.03 (dd, 1 H, $J_{4,3}$ 10.6 Hz, H-4), 4.05 (dd, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 4.58 (dd, 1 H, $J_{2,3}$ 4.7 Hz, H-2), and 5.06 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$): δ 25.57, 26.81, 26.97, 28.03 (2C*Me*$_2$), 26.88 (C*Me*$_3$), 38.90 (C*C*Me$_3$), 70.67, 74.38, 74.77, 74.87, 78.37, 81.74 (C-1–C-6), 109.89, 112.57 (2 *C*Me$_2$), and 178.01 (C=O).

*(±)-1,2 : 4,5-Di-*O*-isopropylidene-6-*O*-trimethylacetyl-*myo*-inositol* (**9b**): ^{1}H NMR ($CDCl_3$): δ 1.27 (s, 9 H, CMe_3), 1.29, 1.41, 1.47, 1.61 (4s, each 3 H, 2 CMe_2), 3.63 (dd, 1 H, $J_{5,6}$ 11.1, $J_{5,4}$ 9.5 Hz, H-5), 4.22 (dd, 1 H, $J_{4,3}$ 10.3 Hz, H-4), 4.30 (dd, 1 H, $J_{1,6}$ 6.7, $J_{1,2}$ 4.7 Hz, H-1), 4.64 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 5.12 (dd, 1 H, H-3), and 5.53 (dd, 1 H, H-6); ^{13}C NMR ($CDCl_3$): δ 25.73, 26.88, 27.05, 27.72 (2 C*Me*$_2$), 27.10 (C*Me*$_3$), 39.10 (C*C*Me$_3$), 70.43, 74.80, 75.04, 75.06, 76.81, 79.51 (C-1–C-6), 110.50, 113.00 (2 *C*Me$_2$), and 178.50 (C=O).

*(±)-1,2 : 4,5-Di-*O*-isopropylidene-3,6-di-*O*-trimethylacetyl-*myo*-inositol* (**9c**): ^{1}H NMR ($CDCl_3$): δ 1.23, 1.25 (2s, each 9 H, 2 CMe_3), 1.27, 1.39, 1.44, 1.55 (4s, each 3 H, 2 CMe_2), 3.46 (dd, 1 H, $J_{5,6}$ 11.0, $J_{5,4}$ 9.5 Hz, H-5), 4.11 (dd, 1 H, $J_{1,6}$ 6.8, $J_{1,2}$ 4.6 Hz, H-1), 4.13 (dd, 1 H, $J_{4,3}$ 10.5 Hz, H-4), 4.56 (dd, 1 H, $J_{2,3}$ 4.6 Hz, H-2), 5.05 (dd, 1 H, H-3), and 5.24 (dd, 1 H, H-6); ^{13}C NMR ($CDCl_3$): δ 25.63, 26.68, 26.93, 27.52 (2 C*Me*$_2$), 26.76, 26.87 (2 C*Me*$_3$), 38.68, 38.83 (2 C*C*Me$_3$), 70.33, 73.88, 74.75, 74.85, 76.51, 79.35 (C-1–C-6), 110.00, 112.44 (2 *C*Me$_2$), and 177.50, 178.20 (2 C=O).

Trifluoromethanesulfonylation of **5**.—A mixture of **5** (100 mg, 0.384 mmol); pyridine (0.621 mL, 7.68 mmol), and triflic anhydride (0.0743 mL, 0.442 mmol) in CH_2Cl_2 (8 mL) was stirred at −20°C for 3 h. The mixture was directly chromatographed on silica gel with a gradient of hexane–EtOAc, to give ditriflate **10c** (50.1 mg, 24.9%) and 3-triflate **10a** (78.3 mg, 52.0%) as white solids.

*(±)-1,2 : 4,5-Di-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-*myo*-inositol* (**10a**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.35; mp 107–110°C (dec); ^{1}H NMR ($CDCl_3$): δ 1.38, 1.46, 1.48, 1.56 (4s, each 3 H, 2 CMe_2), 2.58 (bs, 1 H, OH), 3.40 (dd, 1 H, $J_{5,6}$ 10.6, $J_{5.4}$ 9.7 Hz, H-5), 3.93 (dd, 1 H, $J_{6,1}$ 6.4 Hz, H-6), 4.11 (dd, 1 H, $J_{4,3}$ 10.3 Hz, H-4), 4.12 (dd, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 4.57 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), and 5.06 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$): δ 25.69, 26.66, 26.81, 27.93 (2 C*Me*$_2$), 73.96, 73.99, 75.52, 77.84, 82.13, 83.00 (C-1–C-6), and 111.29, 113.67 (2 *C*Me$_2$); IR (thin film): ν_{max} 3501 (OH stretch), 3015, 1363 [asymmetric S(=O)$_2$ stretch], 1221 [symmetric S(=O)$_2$ stretch], 1059, 849, and 636 cm^{-1}; MS(EI): *m/z* 392 (M^+), 148 (CF_3SO_3); Anal. Calcd for $C_{13}H_{19}F_3O_8S$: C, 39.80; H, 4.88; S, 8.17. Found: C, 39.94; H, 4.90; S, 8.34.

*(±)-1,2 : 4,5-Di-*O*-isopropylidene-3,6-di-*O*-trifluoromethanesulfonyl-*myo*-inositol* (**10c**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.80; mp 125–127°C (dec); ^{1}H

NMR ($CDCl_3$): δ 1.40, 1.47, 1.50, 1.59 (4s, each 3 H, 2 CMe_2), 3.59 (dd, 1 H, $J_{5,6}$ 11.0, $J_{5,4}$ 9.5 Hz, H-5), 4.18 (dd, 1 H, $J_{4,3}$ 10.4 Hz, H-4), 4.35 (dd, 1 H, $J_{1,6}$ 6.5, $J_{1,2}$ 4.7 Hz, H-1), 4.62 (dd, 1 H, $J_{2,3}$ 4.4 Hz, H-2), 4.87 (dd, 1 H, H-6), and 5.07 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$): δ 25.53, 26.54, 25.56, 27.41 (2 CMe_2), 74.06, 74.82, 75.84, 78.66, 81.39, 87.08 (C-1–C-6), and 112,30, 114.75 (2 CMe_2); IR (thin film): ν_{max} 3021, 2920, 1404[asymmetric $S(=O)_2$ stretch], 1228 [symmetric $S(=O)_2$ stretch], 1143, 955, 880, and 791 cm^{-1}.

tert-*Butyldimethylsilylation of* **5**.—To a solution of **5** (100 mg, 0.384 mmol) and imidazole (86.3 mg, 1.268 mmol) in DMF (1 mL) at 0°C was added *tert*-butyldimethylsilyl chloride (63.7 mg, 0.423 mmol). After stirring for 12 h at room temperature, the mixture was directly chromatographed on silica gel with a gradient of hexane–EtOAc, to give disilyl ether **11c** (12.8 mg, 6.8%), 3-silyl ether **11a** (79.7 mg, 55.4%), and starting material (25.3 mg, 25.3%).

*(±)-3-*O-tert-*Butyldimethylsilyl-1,2 : 4,5-di-*O-*isopropylidene*-myo-*inositol* (**11a**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.43; mp 149–151°C; ^1H NMR ($CDCl_3$): δ 0.14 (s, 6 H, $SiMe_2$), 0.93 (s, 9 H, CMe_3), 1.35, 1.42, 1.44, 1.53 (4s, each 3 H, 2 CMe_2), 2.87 (bs, 1 H, OH), 3.26 (dd, 1 H, $J_{5,4}$ 10.4, $J_{5,6}$ 9.4 Hz, H-5), 3.87 (dd, 1 H, $J_{4,3}$ 6.4 Hz, H-4), 3.90 (dd, 1 H, $J_{6,1}$ 10.0 Hz, H-6), 3.97 (dd, 1 H, $J_{3,2}$ 4.4 Hz, H-3), 4.03 (dd, 1 H, $J_{1,2}$ 4.4 Hz, H-1), and 4.29 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ −4.91, −4.37 ($SiMe_2$), 18.40 ($SiCMe_3$), 25.65, 26.81, 26.95, 28.28 (2 CMe_2), 25.81 (CMe_3), 70.76, 74.57, 77.39, 78.37, 78.84, 81.71 (C-1–C-6), and 109.82, 111.96 (2 CMe_2); MS(FAB): *m/z* 375 ($M^+ + 1$), 359 ($M - CH_3$), 317 ($M - CMe_3$), 259 ($M - SiMe_2{}^tBu$). Anal. Calcd for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15. Found: C, 57.94; H, 9.13.

*(±)-3,6-Di-*O-tert-*butyldimethylsilyl-1,2 : 4,5-di-*O-*isopropylidene*-myo-*inositol* (**11c**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.81; ^1H NMR ($CDCl_3$): δ 0.09, 0.10, 0.13, 0.13 (4s, 2 $SiMe_2$), 0.90, 0.92 (2s, each 9 H, 2 CMe_3), 1.26, 1.33, 1.36, 1.38 (4s, each 3 H, 2 CMe_2), 3.18 (dd, 1 H, $J_{5,4}$ 10.0, $J_{5,6}$ 9.4 Hz, H-5), 3.78 (dd, 1 H, $J_{4,3}$ 6.2 Hz, H-4), 3.83 (dd, 1 H, $J_{6,1}$ 10.0 Hz, H-6), 3.91 (dd, 1 H, $J_{3,2}$ 4.4 Hz, H-3), 3.97 (dd, 1 H, $J_{1,2}$ 4.4 Hz, H-1), and 4.24 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ −4.90, −4.68, −4.53, −4.33 (2 $SiMe_2$), 18.25, 18.45 (2 $SiCMe_3$), 25.78, 25.86 (2 CMe_3), 25.86, 26.88, 26.94, 29.29 (2 CMe_2), 70.95, 75.66, 77.40, 78.94, 79.17, 82.76 (C-1–C-6), and 109.27, 11.07 (2 CMe_2).

Diphenyloxyphosphorylation of **5**.—To a mixture of **5** (200 mg, 0.77 mmol), triethylamine (TEA; 0.3 mL, 2.2 mmol), and 4-dimethylaminopyridine (DMAP; 5 mg, 0.04 mmol) in CH_2Cl_2 (30 mL) was added diphenyl phosphorochloridate (0.2 mL, 0.96 mmol) at room temperature, and the resulting solution was stirred for 4 h. A standard workup with CH_2Cl_2 gave an oil. Chromatography of the crude product on silica gel with 2:1 hexane–EtOAc provided bisphosphate **12c** (42 mg, 8%) and 3-phosphate **12a** (112 mg, 30%).

*(±)-3-*O-*Diphenoxyphosphoryl-1,2 : 4,5-di-*O-*isopropylidene*-myo-*inositol* (**12a**): TLC (1:1 hexane–EtOAc) R_f 0.3; ^1H NMR ($CDCl_3$): δ 1.23, 1.42, 1.45, 1.51 (4s, each 3 H, 2 CMe_2), 2.74 (d, 1 H, *J* 3.1 Hz, HO-6), 3.34 (dd, 1 H, $J_{5,6}$ 10.6, $J_{5,4}$ 9.5 Hz, H-5), 3.89 (ddd, 1 H, $J_{6,1}$ 6.5, $J_{6,OH}$ 3.1 Hz, H-6), 4.01 (dd, 1 H, $J_{1,2}$ 4.8 Hz, H-1), 4.06 (dd, 1 H, $J_{4,3}$ 10.0 Hz, H-4), 4.52 (dd, 1 H, $J_{2,3}$ 4.3 Hz, H-2), 4.90 (ddd, 1

H, $J_{H,P}$ 8.2 Hz, H-3), and 7.30 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.73, 26.86, 26.86, 28.09 (2 CMe_2), 74.35, 75.28, 75.79, 76.41, 77.99, 81.79 (C-1–C-6), 110.49, 112.93 (2 CMe_2), and 120.34, 120.40, 120.51, 120.57, 125.40, 120.51, 120.57, 125.40, 125.43, 129.55, 129.62, 150.50, 150.54 (Ph); ^{31}P NMR ($CDCl_3$): δ −11.55; MS(FAB): m/z 493 ($M^+ + 1$).

*(±)-3,6-Di-O-diphenoxyphosphoryl-1,2 : 4,5-di-O-isopropylidene-*myo*-inositol* (**12c**): TLC (1:1 EtOAc–hexane) R_f 0.65; mp 140–143°C; ^1H NMR ($CDCl_3$): δ 1.20, 1.30, 1.41, 1.53 (4s, each 3 H, 2 CMe_2), 3.47 (dd, 1 H, $J_{5,6}$ 10.9, $J_{5,4}$ 9.6 Hz, H-5), 4.11 (dd, 1 H, $J_{4,3}$ 10.1 Hz, H-4), 4.16 (dd, 1 H, $J_{1,6}$ 6.5, $J_{1,2}$ 4.5 Hz, H-1), 4.50 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 4.79 (ddd, 1 H, $J_{H,P}$ 8.5 Hz, H-6), 4.88 (ddd, 1 H, $J_{H,P}$ 8.2 Hz, H-3), and 7.32 (m, 20 H, 4 Ph); ^{13}C NMR ($CDCl_3$): δ 25.74, 26.70, 26.73, 27.72 (2 CMe_2), 75.09, 75.17, 76.16, 76.40 (C-1,2,4,5), 79.63 (d, $J_{C,P}$ 3.7 Hz, C-6), 80.74 (d, $J_{C,P}$ 5.7 Hz, C-3), 110.86, 113.09 (2 Me_2C), and 120.24, 120.30, 120.40, 120.47, 125.13, 125.40, 125.44, 129.06, 129.41, 129.46, 129.51, 129.59, 150.22, 150.33, 150.44, 150.58, 150.66 (4 Ph); ^{31}P NMR ($CDCl_3$): δ −12.01 (d, $J_{P,H}$ 8.5 Hz, P-6), −11.58 (d, $J_{P,H}$ 8.2 Hz, P-3); MS(FAB): m/z 725 ($M^+ + 1$).

Benzylation of **6**.—*Run 1:* A mixture of **6** (168.4 mg, 0.647 mmol), NaH (97%, 17.6 mg, 0.712 mmol), and benzyl bromide (0.085 mL, 0.712 mmol) in DMF (4 mL) was stirred at 0°C. After 72 h, the mixture was worked up with CH_2Cl_2 to give an oily product which was separated on silica gel with a gradient of hexane–EtOAc, to give the dibenzyl ether **13c** (35.5 mg, 13.2%) as an oil, 4-benzyl ether **13b** (40.2 mg, 18.6%) as a heavy oil, and 3-benzyl ether **13a** (34.7 mg, 16.1%) as a white solid.

Run 2: A mixture of **6** (100 mg, 0.384 mmol), NaH (97%; 10.5 mg, 0.423 mmol), and benzyl bromide (0.05 mL, 0.423 mmol) in DMF (2 mL) was stirred at room temperature for 24 h. The mixture was worked up with CH_2Cl_2 to give an oily product which was separated on silica gel with a gradient of hexane–EtOAc, to provide **13c** (18.2 mg, 12.1%), **13b** (22.9 mg, 19.1%), and **13a** (21.1 mg, 17.6%).

Run 3: To the well-stirred mixture of **6** (100 mg, 0.384 mmol), NaOMe (22.8 mg, 0.422 mmol), and 15-Crown-5 (0.1 mL, 0.84 mmol) in benzene (5 mL) was added benzyl bromide (0.1 mL, 0.84 mmol) at room temperature. After 36-h, the mixture was directly chromatographed on silica gel with a gradient of hexane–EtOAc, to give **13b** (13.3 mg, 9.9%), **13a** (16.2 mg, 12.0%), and the starting material (80.4 mg, 80.4%).

Run 4: A mixture of **6** (100 mg, 0.384 mmol), NaH (80% dispersion in mineral oil; 12.7 mg, 0.422 mmol), and benzyl bromide (0.5 mL, 0.422 mmol) in toluene (2 mL) was heated at reflux for 12 h. The mixture was worked up to give an oil. Chromatography of the crude oil on silica gel furnished **13c** (9.5 mg, 5.6%), **13b** (22.3 mg, 16.6%), **13a** (70.0 mg, 52.0%), and the starting material (15.0 mg, 15.0%).

Run 5: A mixture of **6** (130 mg, 0.5 mmol) and dibutyltin oxide (126 mg, 0.506 mmol) in toluene (3 mL) was heated at reflux for 3.5 h, with removal of water as azeotrope. The solution was evaporated to dryness in vacuo. Cesium fluoride (150 mg, 0.99 mmol) was added to the resulting solid and the mixture was further dried in vacuo for 2 h, and then dissolved in DMF (3 mL) containing benzyl bromide (0.17 mL, 1.4 mmol) and stirred under an Ar atmosphere at room temperature for 4.5 h. The mixture was worked up to give an oil. The oily mixture was separated on

silica gel with a gradient of hexane–EtOAc, to give **13b** (130.4 mg, 74.4%) and **13a** (37.2 mg, 21.2%).

*(±)-3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol* (**13a**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.27; mp 158–159°C (lit. [3b] mp 156–159°C); ^{1}H NMR ($CDCl_3$): δ 1.34, 1.42, 1.44, 1.54 (4s, each 3 H, 2 CMe_2), 2.68 (bs, 1 H, OH), 3.31 (dd, 1 H, $J_{5,6}$ 10.0, $J_{5,4}$ 9.8 Hz, H-5), 3.58 (dd, 1 H, $J_{3,4}$ 7.2, $J_{3,2}$ 4.5 Hz, H-3), 3.79 (dd, 1 H, $J_{6,1}$ 8.6 Hz, H-6), 4.10 (dd, 1 H, H-4), 4.19 (dd, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.38 (dd, 1 H, H-2), 4.71 (d, 1 H, *J* 12.0 Hz, PhCH_aH$_b$), 4.79 (d, 1 H, *J* 12.0 Hz, PhCH$_a$$H_b$), and 7.26–7.43 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.74, 26.84, 26.84, 28.12 (2 CMe_2), 72.17, 73.02, 74.73, 76.22, 77.53, 78.77, 80.70 (C-1–C-6 and PhCH_2), 110.40, 112.26 (2 CMe_2), and 128.06, 128.37, 128.53, 137.66 (Ph); MS(EI): *m/z* 350(M^+), 335 (M − CH_3), 91 ($PhCH_2$). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.75; H, 7.44.

*(±)-4-*O*-Benzyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol* (**13b**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.52; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.40 (s, 6 H), 1.49 (s, 3 H, 2 CMe_2), 2.53 (bs, 1 H, OH), 3.51 (dd, 1 H, $J_{5,4}$ 10.6, $J_{5,6}$ 7.5 Hz, H-5), 3.86 (dd, 1 H, $J_{3,4}$ 7.8, $J_{3,2}$ 2.4 Hz, H-3), 3.98 (dd, 1 H, $J_{2,1}$ 3.8 Hz, H-2), 4.13 (dd, 1 H, H-4), 4.29 (dd, 1 H, $J_{6,1}$ 7.3 Hz, H-6), 4.39 (dd, 1 H, H-1), 4.60 (d, 1 H, *J* 11.7 Hz, PhCH_aH$_b$), 4.73 (d, 1 H, *J* 11.7 Hz, PhCH$_a$$H_b$), and 7.20–7.33 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$): δ 24.19, 26.58, 27.02, 27.13 (2 CMe_2), 71.86, 72.24, 75.67, 76.84, 76.84, 79.25, 80.04 (C-1–C-6 and PhCH_2), 110.54, 112.31 (2 CMe_2), and 127.69, 127.76, 128.37, 137.92 (Ph); MS(EI): *m/z* 350 (M^+), 335 (M − CH_3), 91 ($PhCH_2$).

*(±)-3,4-Di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol* (**13c**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.67; ^{1}H NMR ($CDCl_3$): δ 1.35, 1.44, 1.44, 1.52 (4s, each 3 H, 2 CMe_2), 3.51 (dd, 1 H, $J_{5,4}$ 10.6, $J_{5,6}$ 7.8 Hz, H-5), 3.76 (dd, 1 H, $J_{2,1} = J_{2,3} = 3.5$ Hz, H-2), 3.89 (dd, 1 H, $J_{3,4}$ 7.9 Hz, H-3), 4.13 (dd, 1 H, H-4), 4.29 (dd, 1 H, $J_{6,1}$ 6.7 Hz, H-6), 4.37 (dd, 1 H, H-1), 4.52 (d, 1 H, *J* 12.0 Hz, PhCH_aH$_b$), 4.64 (d, 1 H, *J* 9.0 Hz, PhCH_cH$_d$), 4.68 (d, 1 H, *J* 9.0 Hz, PhCH$_c$$H_d$), 4.72 (d, 1 H, *J* 12.0 Hz, PhCH$_a$$H_b$), and 7.25–7.36 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.32, 26.88, 27.06, 27.11 (2CMe_2), 71.97, 73.38, 75.51, 76.68, 77.24, 79.04, 79.30, 79.77 (C-1–C-6 and 2 PhCH_2), 110.87, 112.20 (2 CMe_2), and 127.61, 127.65, 127.83, 128.33, 138.08 (Ph); MS(EI): *m/z* 440(M^+), 425(M − CH_3), 349 (M − $PhCH_2$), 91 ($PhCH_2$).

Trimethoxybenzoylation of **6**.—A mixture of **6** (100 mg, 0.384 mmol), pyridine (0.05 mL, 0.618 mmol), and 3,4,5-trimethoxybenzoyl chloride (100 mg, 0.434 mmol) in CH_2Cl_2 (2 mL) was stirred at 0°C for 36 h. A single product was observed in TLC (7:3 diethyl ether–petroleum ether) at R_f 0.3. The mixture was worked up with CH_2Cl_2 to give an oil, which was purified by chromatography on silica gel with 3:1 hexane–EtOAc, to give 3-trimethoxybenzoate **14a** (89 mg, 51%) as a white solid.

*(±)-1,2 : 5,6-Di-*O*-isopropylidene-3-*O*-(3,4,5-trimethoxybenzoyl)-*myo*-inositol* (**14a**): mp 173–175°C; ^{1}H NMR ($CDCl_3$): δ 1.35, 1.41, 1.44, 1.45 (4s, each 3 H, 2 CMe_2), 2.95 (bs, 1 H, OH), 3.59 (dd, 1 H, $J_{5,6}$ 10.5, $J_{5,4}$ 8.3 Hz, H-5), 3.89, 3.90, 3.91 (3s, each 3 H, 3 OCH_3), 4.07 (dd, 1 H, $J_{6,1}$ 7.1 Hz, H-6), 4.19 (dd, 1 H, $J_{4,3}$ 3.4

Hz, H-4), 4.45 (dd, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 4.65 (dd, 1 H, $J_{2,3}$ 3.8 Hz, H-2), 5.23 (dd, 1 H, H-3), and 7.32 (2H, Ph); ^{13}C NMR ($CDCl_3$): δ 25.05, 26.94, 26.94, 27.05 (2, CMe_2), 56.30, 56.30, 60.90 (3 OCH_3), 72.40, 73.75, 75.79, 77.00, 77.66, 78.56 (C-1–C-6), 111.03, 112.72 (2, CMe_2), and 107.36, 107.36, 124.32, 142.86, 152.95, 153.04 (Ph), and 165.41 (C=O); IR (film): ν_{max} 3466 (OH stretch), 2940, 1717 (C=O stretch), 1591, 1503, 1349, 1239, 988, 860, and 730 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_{10}$: C, 58.14; H, 6.65. Found: C, 57.94; H, 6.66.

Pivaloylation of **6**.—*Run 1:* To a solution of **6** (100 mg, 0.384 mmol) and pyridine (0.05 mL, 0.618 mmol) in CH_2Cl_2 (1.5 mL) was added trimethylacetyl chloride (0.052 mL, 0.422 mmol) at 0°C. After stirring at room temperature for 38 h, the mixture was worked up with CH_2Cl_2 to give an oil, which was separated on silica gel with 5:1 hexane–EtOAc to give the 4-pivalate **15b** (23.3 mg, 17.6%) and 3-pivalate **15a** (25.7 mg, 19.4%) as white solids.

Run 2: A mixture of the diol **6** (1.0 g, 3.84 mmol), pyridine (0.66 mL, 8.19 mmol), and trimethylacetyl chloride (1.02 mL, 8.28 mmol) in CH_2Cl_2 (20 mL) was stirred at 0°C for 7 h. The mixture was worked up with CH_2Cl_2 to give a colorless oil. Crystallization of the product from hot hexane gave the 3-pivalate **15a** (1.07 g, 81%) as a white solid.

*(±)-1,2 : 5,6-Di-*O*-isopropylidene-3-*O*-trimethylacetyl*-myo-*inositol* (**15a**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.4; mp 100–102°C; ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9 H, CMe_3), 1.30, 1.41, 1.43, 1.49 (4s, each 3 H, 2 CMe_2), 2.75 (bs, 1 H, OH, exchangeable), 3.44 (dd, 1 H, $J_{5,6}$ 10.3, $J_{5,4}$ 8.8 Hz, H-5), 3.86 (dd, 1 H, $J_{6,1}$ 8.0 Hz, H-6), 4.01 (dd, 1 H, $J_{4,3}$ 4.7 Hz, H-4), 4.31 (dd, 1 H, $J_{1,2}$ 6.5 Hz, H-1), 4.54 (dd, 1 H, $J_{2,3}$ 4.7 Hz, H-2), and 4.90 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$): δ 24.97, 26.92, 26.92, 27.18 (2 CMe_2), 27.08 (CMe_3), 38.88 (CMe_3), 72.13, 73.58, 75.24, 76.34, 77.81, 78.33 (C-1–C-6), 110.63, 112.60 (2 CMe_2), and 178.14 (C=O); IR (film): ν_{max} 3586 (OH stretch), 29.62, 1730 (C=O stretch), 1466, 1376, 1251, 1150, 1054, 859, and 729 cm^{-1}; MS(FAB): *m/z* 345 ($M^+ + 1$), 329 ($M - CH_3$), 314 ($M - 2CH_3$), 57 (CMe_3).

*(±)-1,2 : 5,6-Di-*O*-isopropylidene-4-*O*-trimethylacetyl*-myo-*inositol* (**15b**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.5; mp 127–129°C; ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9 H, CMe_3), 1.27, 1.41, 1.45, 1.49 (4s, each 3 H, $2CMe_2$), 2.64 (bs, 1 H, OH), 3.37 (dd, 1 H, $J_{5,4}$ 10.5, $J_{5,6}$ 10.5 Hz, H-5), 3.87 (dd, 1 H, $J_{6,1}$ 6.5 Hz, H-6), 4.01 (dd, 1 H, $J_{3,2}$ 4.7, $J_{3,4}$ 4.4 Hz, H-3), 4.01 (dd, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 4.56 (dd, 1 H, H-2), and 5.04 (dd, 1 H, H-4); IR (film): ν_{max} 3545 (OH stretch), 2958, 1731 (C=O stretch), 1467, 1377, 1289, 1237, 1156, 1055, 862, and 790 cm^{-1}; MS(FAB): *m/z* 345 ($M^+ + 1$), 57(CMe_3).

Trimethylsilylation of **6**.—A mixture of **6** (100 mg, 0.384 mmol) and *N,N*-dimethyltrimethylsilylamine (0.19 mL, 1.00 mmol) in CH_2Cl_2 (4 mL) was stirred at −20°C for 27 h. The mixture was chromatographed directly on silica gel with a gradient of hexane–EtOAc, to give disilyl ether **16c** (75.6 mg, 48.7%) as an oil, 4-silyl ether **16b** (9.1 mg, 7.1%) as a heavy oil, and 3-silyl ether **16a** (45.1 mg, 35.3%) as a white solid.

*(±)-1,2:5,6-Di-*O*-isopropylidene-3-*O*-trimethylsilyl*-myo-*inositol* (**16a**): mp 160–161°C; ^{1}H NMR ($CDCl_3$): δ 0.15 (s, 9 H, $SiMe_3$), 1.31, 1.39, 1.40, 1.49 (4s, each 3

H, $2CMe_2$), 2.60 (bs, 1 H, OH), 3.30 (dd, 1 H, $J_{5,6}$ 10.0, $J_{5,4}$ 9.0 Hz, H-5), 3.75 (dd, 1 H, $J_{3,4}$ 6.4, $J_{3,2}$ 4.2 Hz, H-3), 3.83 (dd, 1 H, $J_{6,1}$ 8.4 Hz, H-6), 3.90 (dd, 1 H, H-4), 4.20 (dd, 1 H, $J_{1,2}$ 5.4 Hz, H-1), and 4.28 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ 0.18 ($SiMe_3$), 25.59, 26.85, 26.85, 27.99 (2 CMe_2), 73.28, 75.10, 76.33, 76.95, 77.88, 78.54 (C-1–C-6), and 110.40, 112.20 (2 CMe_2); MS(EI): m/z 317 ($M - CH_3$), 259 ($M - SiMe_3$), 73 ($SiMe_3$).

(±)-1,2:5,6-Di-O-*isopropylidene-4*-O-*trimethylsilyl*-myo-*inositol* (**16b**): ^{1}H NMR ($CDCl_3$): δ 0.16 (s, 9 H, $SiMe_3$), 1.36, 1.39, 1.39, 1.52 (4s, each 3 H, 2 CMe_2), 2.47 (bs, 1 H, OH), 3.36 (dd, 1 H, $J_{5,6}$ 10.5, $J_{5,4}$ 8.0 Hz, H-5), 3.79 (dd, 1 H, $J_{3,2}$ 3.8, $J_{3,4}$ 3.1 Hz, H-3), 3.97 (dd, 1 H, H-4), 4.04 (dd, 1 H, $J_{6,1}$ 7.7 Hz, H-6), 4.30 (dd, 1 H, $J_{1,2}$ 7.1 Hz, H-1), and 4.45 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ 0.09 ($SiMe_3$), 24.41, 26.86, 26.97, 27.05 (2, CMe_2), 73.98, 75.17, 75.71, 77.20, 77.42, 79.85 (C-1–C-6), and 110.43, 111.94 (2 CMe_2).

(±)-1,2:5,6-Di-O-*isopropylidene-3,4-di*-O-*trimethylsilyl*-myo-*inositol* (**16c**): ^{1}H NMR ($CDCl_3$): δ 0.13, 0.14 (2s, each 9 H, 2 $SiMe_3$), 1.31, 1.37, 1.38, 1.49 (4s, each 3 H, 2 CMe_2), 3.26 (dd, 1 H, $J_{5,6}$ 10.3, $J_{5,4}$ 7.9 Hz, H-5), 3.75 (dd, 1 H, $J_{3,4}$ 4.4, $J_{3,2}$ 3.9 Hz, H-3), 3.84 (dd, 1 H, H-4), 4.00 (dd, 1 H, $J_{6,1}$ 7.9 Hz, H-6), 4.20 (dd, 1 H, $J_{1,2}$ 6.4 Hz, H-1), and 4.28 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ 0.20, 0.26 (2 $SiMe_3$), 25.34, 26.91, 27.03, 27.41 (2 CMe_2), 74.92, 75.80, 76.63, 76.86, 77.32, 79.91 (C-1–C-6), and 110.33, 111.52 (2 CMe_2); MS(FAB): m/z 405 ($M^+ + 1$), 389 ($M\text{-}CH_3$), 331 ($M\text{-}SiMe_3$), 73 ($SiMe_3$).

tert-*Butyldimethylsilylation of* **6**.—A mixture of **6** (100 mg, 0.384 mmol), imidazole (86.3 mg, 1.268 mmol), and *tert*-butyldimethylsilyl chloride (63.7 mg, 0.423 mmol) in MeCN (1 mL) was stirred at room temperature for 12 h. The mixture was separated directly on silica gel with a gradient of hexane–EtOAc, to give the disilyl ether **17c** (10 mg, 5.3%) as an oil, 4-silyl ether **17b** (42.5 mg, 29.5%) as a heavy oil, and 3-silyl ether **17a** (67 mg, 46.6%) as a solid. Some starting material was recovered (18.0 mg, 18.0%).

(±)-3-O-tert-*Butyldimethylsilyl-1,2:5,6-di*-O-*isopropylidene*-myo-*inositol* (**17a**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.56; ^{1}H NMR ($CDCl_3$): δ 0.09, 0.10 (2s, each 3 H, $SiMe_2$), 0.89 (s, 9 H, CMe_3), 1.30, 1.39, 1.39, 1.49 (4s, each 3 H, $2CMe_2$), 2.64 (bs, 1 H, OH), 3.31 (dd, 1 H, $J_{5,6}$ 10.0, $J_{5,4}$ 9.0 Hz, H-5), 3.78 (dd, 1 H, $J_{3,4}$ 5.7, $J_{3,2}$ 4.2 Hz, H-3), 3.91 (dd, 1 H, $J_{6,1}$ 8.2 Hz, H-6), 3.92 (dd, 1 H, H-4), 4.20 (dd, 1 H, $J_{1,2}$ 5.8 Hz, H-1), and 4.29 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ −4.78, −4.66 ($SiMe_2$), 18.07 ($SiCMe_3$), 25.28, 26.83, 26.89, 27.68 (2 CMe_2), 25.79 (CMe_3), 73.70, 75.25, 76.32, 76.69, 78.20, 78.44 (C-1–C-6), and 110.24, 112.15 (2 CMe_2); MS(EI): m/z 374 (M^+), 359 ($M - CH_3$), 317 ($M - CMe_3$), 259 ($M - SiMe_2{}^tBu$).

(±)-4-O-tert-*Butyldimethylsilyl-1,2:5,6-di*-O-*isopropylidene*-myo-*inositol* (**17b**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.71; ^{1}H NMR ($CDCl_3$): δ 0.10, 0.11 (2s, each 3 H, $SiMe_2$), 0.87 (s, 9 H, CMe_3), 1.35, 1.37, 1.38, 1.51 (4s, each 3 H, 2 CMe_2), 2.46 (bs, 1 H, OH), 3.35 (dd, 1 H, $J_{5,6}$ 10.5, $J_{5,4}$ 7.8 Hz, H-5), 3.79 (dd, 1 H, $J_{3,2}$ 3.8, $J_{3,4}$ 2.8 Hz, H-3), 3.99 (dd, 1 H, H-4), 4.06 (dd, 1 H, $J_{6,1}$ 7.7 Hz, H-6), 4.29 (dd, 1 H, $J_{1,2}$ 7.1 Hz, H-1), and 4.43 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ −5.04, −4.66 ($SiMe_2$), 18.06 ($SiCMe_3$), 24.32, 26.74, 26.94, 27.05 (2 CMe_2), 25.74 (CMe_3),

74.04, 75.36, 75.69, 76.58, 77.00, 80.24 (C-1–C-6), and 110.38, 111.83 (2 CMe_2); MS(EI): m/z 374 (M^+), 359 (M − CH_3), 317 (M − CMe_3), 259 (M − $SiMe_2{}^tBu$).

(±)-3,4-Di-O-tert-*butyldimethylsilyl-1,2 : 5,6-di*-O-*isopropylidene*-myo-*inositol* (**17c**): TLC (7:3 diethyl ether–petroleum ether) R_f 0.82; ^1H NMR ($CDCl_3$): δ 0.07, 0.08 (2s, each 6 H, 2 $SiMe_2$), 0.86, 0.90 (2s, each 9 H, 2 CMe_3), 1.32, 1.37, 1.37, 1.48 (4s, each 3 H, 2 CMe_2), 3.28 (1 H), 3.82 (1 H), 3.87 (1 H), and 4.27–4.30 (3 H); MS(EI): m/z 488 (M^+), 473 (M − CH_3), 431 (M − CMe_3), 373 (M − $SiMe_2{}^tBu$).

Molecular mechanics calculations.—The molecular modeling system at POSTECH consists of an Evans and Sutherland PS 390 graphics station or a Machintosh terminal linked to a VAX8800 running the MacroModel Molecular Modeling Software (version 2.5 primer) [24]. The energy minimizations were carried out to the preset convergence criterion (RMS energy gradient 0.05 kJ/A) initially by the Steepest Descent (SD) method followed by block diagonal Newton–Raphson (BDNR) method [25]. For the given structure, molecular hydrogens were added in the Organic Input mode before the MM-2 calculation. For compounds **5** and **6**, each local minimum was obtained and refined by multiplication of energy minimizations on the MM-2 force field by starting with several chair and boat conformations as input structures.

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