(m, 3 H), 7.27 (m, 3 H), 7.06 (m, 1 H), 6.92 (m, 1 H), 3.31 (d, J = 16.37 Hz, 1 H), 3.08 (d, J = 16.37 Hz, 1 H), 1.74 (s, 3 H); ^{13}C NMR δ 191.70, 160.02, 142.98, 136.18, 128.63, 126.61, 125.20, 121.05, 118.35, 82.47, 48.08, 29.91; IR (neat) 1696 (s), 1608 (s), 1472 (m), 1461 (s), 1326 (s), 1311 (s), 1235 (s) cm^{-1}; HRMS (exact mass) calcd for $C_{16}H_{14}O_2$ 238.0993, found 238.1006.

Spiro[2*H*-1-benzopyran-2,1'-cyclohexan]-4(3*H*)-one (3d):[2] clear oil; 0.13 g; 90% yield following purification by silica chromatography with 25% ethyl acetate/hexane as the eluent; ^{1}H NMR δ 7.90 (m, 1 H), 7.54 (m, 1 H), 7.01 (m, 2 H), 2.75 (s, 2 H), 2.04 (m, 2 H), 1.78 (m, 8 H); ^{13}C NMR δ 192.73, 159.65, 136.13, 126.50, 120.87, 120.68, 118.41, 80.00, 48.25, 34.79, 25.25, 21.50; IR (neat) 1692 (s), 1609 (s), 1472 (s), 1462 (s), 1321 (s), 1306 (s), 1229 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.40; H, 7.50.

Acknowledgment. We wish to thank Dr. F. J. Urban for helpful discussions. We are grateful to the Analytical Department for their assistance with spectral data.

Registry No. 1, 60068-17-9; **1a**, 122-78-1; **1b**, 104-53-0; **1c**, 98-86-2; **1d**, 108-94-1; **2a**, 130984-32-6; **2b**, 130984-34-8; **2c**, 130984-34-8; **2d**, 130984-35-9; **3a**, 130984-36-0; **3b**, 64838-30-8; **3c**, 62756-35-8; **3d**, 62756-20-1; **4c**, 130984-37-1; hydroxyacetophenone, 41903-50-8.

Substitution in β-Cyclodextrin Directed by Basicity: Preparation of 2-*O*- and 6-*O*-[(*R*)- and (*S*)-2-Hydroxypropyl] Derivatives

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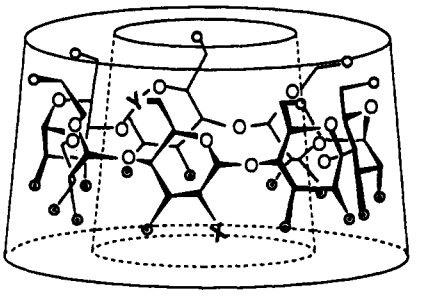
Molecular recognition by substituted cyclodextrins (cycloamyloses) as host compounds has been applied to the studies of enzyme analogues[1] and in chromatographic separations.[2] It has been observed that the substituents at the wider and inherently chiral secondary hydroxyl side of the cyclodextrin toroid (Figure 1) exhibit different host characteristics than those on the narrower achiral primary hydroxyl side.[3] In order to obtain regioselectively substituted derivatives, complex procedures are generally required.[4] We now report a method for directing substitution in β-cyclodextrin [cyclomaltoheptaose (**1**)] which may have wide use.

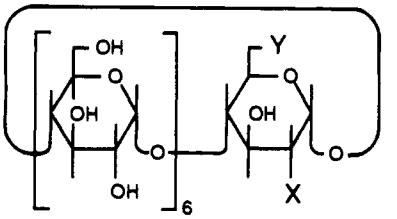
The alkylation of β-cyclodextrin with propylene oxide in aqueous alkali gives mixtures of 2-hydroxypropyl derivatives which have been used to solubilize lipophilic drugs.[5] The distribution of the hydroxyalkyl groups among the 2-O, 3-O, and 6-O positions was investigated[6] in such mixtures and was found to depend on the alkali concentration used in their preparation. While weak alkaline conditions favored alkylations on more acidic secondary hydroxyls, strong alkali favored alkylations at the more accessible primary hydroxyls. Using this observation we have now developed a simple procedure for the preparation of pure 2-*O*-[(*R*)- and -(*S*)-2-hydroxypropyl]- and 6-*O*-[(*R*)- and -(*S*)-2-hydroxypropyl]-β-cyclodextrins (**2a**, **2b**, **3a**, and **3b**, respectively). The procedure is based on the control of the basicity of the reaction medium, on the use of low conversions of cyclodextrin, and on exploiting the distinct differences in complex formation.

†University of Stockholm.



o Primary hydroxyls

● Secondary hydroxyls



1 : X=Y=OH

2a : X=O, (R)-OH; Y=OH

2b : X=O, (S)-OH; Y=OH

3a : X=OH; Y=O, (R)-OH

3b : X=OH; Y=O, (S)-OH

Figure 1. Top: Toroidal shape of the β-cyclodextrin molecule (X = Y = OH). Bottom: Structures of compounds **1**, **2a**, **2b**, **3a**, and **3b**.

Table I. Solubility and Complex Formation by Compounds 1–3b

no.	substituent on β-cyclodextrin	solubility,[a] % in water	solubility,[a] % in water with excess toluene	crystalline complex with toluene	K_{assoc} with phenolphthalein,[b] M^{-1}
1	none	1.80	0.2	yes	2.2×10^4
2a	2-*O*-[(*R*)-2-hydroxypropyl]	0.75	1.55	no	2.3×10^4
2b	2-*O*-[(*S*)-2-hydroxypropyl]	0.32	0.57	no	2.4×10^4
3a	6-*O*-[(*R*)-2-hydroxypropyl]	11.50	0.60	yes	1.6×10^4
3b	6-*O*-[(*S*)-2-hydroxypropyl]	5.50	0.42	yes	1.6×10^4

[a] Solubility of hydrates dried in vacuo at room temperature, 20–22 °C. [b] Association constants with phenolphthalein at pH 10.5 at 20–22 °C and corrected for hydration of **1**–**3b**; cf. ref 7 for methods.

When an excess of β-cyclodextrin was reacted with either (*R*)- or (*S*)-propylene oxide in 0.37 M aqueous NaOH,

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Table II. Characterization of Compounds 1, 2a, 2b, 3a, and 3b

no.	compd	mp,[a] °C	R_f[b]	molecular ion amu[c]	GLC-MS data[d] DS	S_0	S_2	S_6
1	β-cyclodextrin	280	0.18					
2a	2-O-[(R)-2-hydroxypropyl]-β-cyclodextrin	290	0.27	1215.8	1.01	85.6	14.4	
2b	2-O-[(S)-2-hydroxypropyl]-β-cyclodextrin	292	0.27	1215.8	0.95	86.5	13.5	
3a	6-O-[(R)-2-hydroxypropyl]-β-cyclodextrin	284	0.24	1215.7				
3b	6-O-[(S)-2-hydroxypropyl]-β-cyclodextrin	292	0.24	1215.7	0.95	86.5		13.5

[a] Compounds decompose upon melting. [b] Thin-layer chromatography on silica gel; eluted with 1-propanol/water/ethyl acetate/ammonium hydroxide, 6:3:1:1. [c] From ^{252}Cf plasma desorption mass spectra; ion formed from the molecule of carbohydrate and adventitious sodium cation. [d] Mole percentages of permethyl 1,4,5-tri-O-acetylglucitol derivatives: S_0, derivative originating from unsubstituted glucose; S_2, derivative originating from 2-O-(2-hydroxypropyl)glucose; S_6, derivative originating from 6-O-(2-hydroxypropyl)glucose; DS refers to the degree of substitution on cyclodextrin calculated from GLC-MS.

mixtures containing predominantly the starting β-cyclodextrin and its monosubstituted products were obtained. These mixtures were easily separated by the addition of toluene, which decreased the solubility of β-cyclodextrin in water, while the solubility of its 2-O-hydroxypropyl derivatives was increased. When toluene was removed, the former compound was again more soluble than the latter. Thus, crystalline **2a** and **2b** were obtained easily but in rather low yields. Nevertheless, the procedure is economical since no chromatographic separation was required and β-cyclodextrin is inexpensive ($10–15/kg) and can be recovered. When a similar reaction was performed using concentrated aqueous NaOH (10.7 M), the respective 6-O derivatives **3a** and **3b** were obtained. In that case the addition of toluene decreased the water solubility of both β-cyclodextrin and the products, and the mixture had to be separated by chromatography. The above preparation may have a number of other applications, and crystalline 2-O derivatives have already been made by reaction of β-cyclodextrin with (R)- or (S)-glycidol and (R)- or (S)-2-methylglycidol. Nevertheless, when other reagents and solvents are used, factors different from acidity and steric accessibility of hydroxyls may become decisive and the above rule will no longer be applicable.

The position of the substituent in compounds **2a**, **2b**, **3a**, and **3b** was confirmed by chemical methods consisting of complete methylation, hydrolysis, and analysis of hydrolysate as alditol acetates by GLC–MS. The compounds were also characterized by plasma desorption mass spectrometry and ^1H NMR spectroscopy. In the ^1H NMR spectra in D_2O of the 2-O-hydroxypropyl derivatives **2a** and **2b**, the C-1 protons of one of the glucose residues appeared downfield as a separate doublet (δ 5.25) from the remaining six C-1 protons (doublet δ 5.11), while in the 6-O-hydroxypropyl derivatives **3a** and **3b**, all seven C-1 protons appeared as a single doublet (δ 5.08).

The newly prepared compounds showed distinct differences in their ability to form complexes and in water solubility. Results are given in Table I and compared with those on β-cyclodextrin. β-Cyclodextrin and many of its derivatives form inclusion complexes in solution; phenolphthalein at pH 10.5 may be used to assess this ability quantitatively.[7] The 2-O derivatives, **2a** and **2b**, had K_{assoc} values close to that of β-cyclodextrin, while those of the 6-O analogues, **3a** and **3b**, were lower (Table I). The differences between the R diastereomers **2a** and **3a** and their corresponding S counterparts **2b** and **3b** were rather small. When formation of crystalline phases was involved, the effects of 2-O or 6-O substitutions were found to be more substantial. β-Cyclodextrin forms a water-insoluble inclusion complex with toluene,[7] and so do its 6-O derivatives **3a** and **3b** (Table I). On the other hand, 2-O derivatives were not precipitated by toluene and could be recovered from toluene-saturated water as such (Table I). As a matter of fact, 2-O derivatives were solubilized into water by the addition of toluene. Thus, complexes were formed even there, but were more soluble than their carbohydrate components. This finding, that a hydrophilic compound is solubilized into water by the addition of a hydrophobic one, is quite unique. Furthermore, no formation of crystalline complexes occurred with p-nitroaniline and p-iodophenol.[8]

The results on water solubility of **1**–**3b** follow a similar pattern. β-Cyclodextrin (i.e., cyclomaltoheptaose) has rather low water solubility, the stability of its crystal lattice making both the enthalpy and entropy of dissolution less favorable than those of α- or γ-cyclodextrins[9] (cyclomaltohexaose and cyclomaltooctaose, respectively). The solubilities of 2-O derivatives were even lower, while those of the 6-O derivatives were higher than that of β-cyclodextrin.

The substitution on 2-O or 6-O of β-cyclodextrin thus seems to affect the ability of compounds to form crystalline complexes, while their complexation ability in solution is affected less.

Experimental Section

General Methods. ^1H NMR spectra were recorded on a Varian 200-MHz spectrometer. Plasma desorption mass spectra were recorded in the positive ion mode with californium -252 for ionization on a spectrometer designed by Dr. R. D. Mcfarlane for the NHLBI. The method for preparation and analysis of alditols was described previously.[6] Prior to elemental analysis, compounds were dried extensively at an elevated temperature in vacuo.

Preparation of 2a and 2b. A solution of β-cyclodextrin (1, 188 g, 0.144 mol) in 0.37 M aqueous NaOH (720 mL) was reacted with (R)-propylene oxide (8 mL) at ice-bath temperature for 10 h and then for a further 10 h at room temperature. Upon cooling and neutralization (10 M HCl), 1 and **2a** crystallized out. The crystals were suspended in water (500 mL), toluene (50 mL) was added, and the mixture was stirred for 24 h. The precipitate, which is an inclusion complex of 1 with toluene, was filtered and washed with water (500 mL), and the combined filtrates were evaporated. Recrystallization of the residue from water after evaporation gave pure 2-O-[(R)-hydroxypropyl] derivative **2a** (10 g, 5% yield). Anal. Calcd for $C_{45}H_{76}O_{36}·6H_2O$: C, 41.52; H, 6.77. Found: C, 41.57; H, 6.75. A similar reaction with (S)-propylene oxide gave **2b** (9 g, 4.5% yield). Anal. Calcd for $C_{45}H_{76}O_{36}·7H_2O$: C, 40.96; H, 6.83. Found: C, 40.82; H, 7.10. For further char-

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(8) Hirayama, F., private communication.

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acterization of **2a** and **2b**, see Table II.

Preparation of 3a and 3b. The 6-*O*-[(*R*)-2-hydroxypropyl] derivative **3a** was prepared by reacting a solution of 1 (40 g) in 10.7 M aqueous NaOH (160 mL) with (*R*)-propylene oxide (6 mL) at ice-bath temperature for 3 days. The mixture was neutralized (10 M HCl) and dialyzed for 9 H. The retained solution was concentrated (150 mL) and stirred with toluene (25 mL) whereby a mixture of 1 and **3a** precipitated as inclusion complexes with toluene (33.5 g). The complexes were decomposed by removing the toluene by azeotroping with water to give 27 g of residue. The residue, a mixture of 1 and **3a**, was dissolved in water (1215 mL) and stirred with toluene (5.4 mL) for 10 h. Filtration and evaporation of the filtrate gave a mixture (5.9 g) enriched with **3a**. Pure **3a** was then obtained by paper chromatography (Whatman, 3 mm) of the mixture using 1-propanol/1-butanol/water, 5:3:4, as eluent, followed by precipitation of **3a** as a toluene complex giving eventually pure **3a**, in 5% overall yield. Anal. Calcd for $C_{45}H_{76}O_{36}\cdot 7H_2O$: C, 40.96; H, 6.83. Found: C, 40.87; H, 6.75. The 6-*O*-[(*S*)-2-hydroxypropyl] derivative was prepared in a similar manner. Anal. Calcd for $C_{45}H_{76}O_{36}\cdot 7H_2O$: C, 40.96; H, 6.83. Found: C, 40.92; H, 6.79. For further characterization of **3a** and **3b**, see Table II.

Acknowledgment. We thank Dr. H. Fales for the mass spectra and Dr. K. Harata for the structure confirmation of **2a** by single-crystal X-ray analysis.

Registry No. 1, 7585-39-9; **2a**, 130904-74-4; **2b**, 130981-23-6; **3a**, 130904-75-5; **3b**, 130981-24-7; (*R*)-propylene oxide, 15448-47-2; (*S*)-propylene oxide, 16088-62-3; toluene, 108-88-3; phenolphthalein, 77-09-8.

Supplementary Material Available: ^{1}H NMR spectra of compounds **2a**, **2b**, **3a**, and **3b** (4 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of an Important Prostaglandin Synthetic Intermediate[1]

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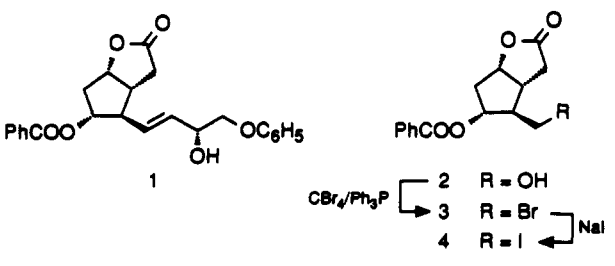
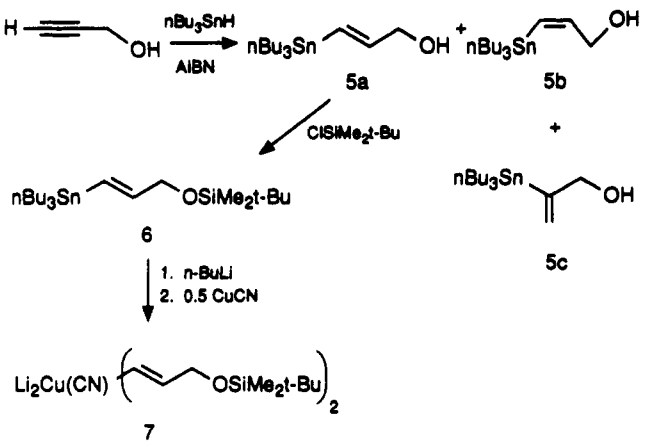
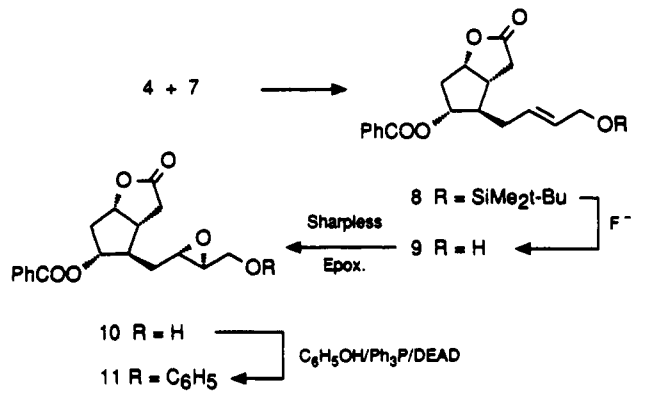
Phenoxy lactone 1[2] and its substituted aromatic congeners are useful in the synthesis of medicinally important prostaglandin analogues.[3] The required *R* configuration of the allylic alcohol in such molecules is usually obtained by hydride reduction of the corresponding α,β-unsaturated ketone.[3,4] In order to obtain high diastereoselectivity in this reduction expensive reagents and very low temperatures (−100 to −120 °C) are required.[5] We required a method which could be conducted on a large scale, would not use expensive reagents, and would avoid the difficult chromatographic separation of even the smallest amount of the allylic alcohol epimer. We report here an approach to such a stereoselective synthesis of 1.



Scheme I



Scheme II



The 1,2-dioxa functionality in the side chain of **1**, which includes the asymmetric alcohol group, suggested the Sharpless asymmetric epoxidation method[6] as a means of introducing the desired stereochemistry. The strategy then was to prepare the α,β-epoxy alcohol **10**, convert it to the phenyl ether **11** and then effect β-elimination of the epoxide to the desired allylic alcohol.

Treatment of lactone benzoate **2**[7] with CBr_4 and Ph_3P in acetonitrile gave the bromide **3**[8] in 90% yield. The bromide was easily converted to the iodide **4** with sodium iodide in acetone in 80% yield. Coupling of iodide **4** with the higher order organocuprate[9] C_3 reagent **7** provided the allylic alcohol needed for the asymmetric epoxidation.

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(1) Contribution number 789 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.
(2) CAS name: [3a*R*-[3aα,4α(1*E*,3*R**),5β,6aα]]-5-(benzoyloxy)hexahydro-4-(3-hydroxy-4-phenoxy-1-butenyl)-2*H*-cyclopenta[*b*]furan-2-one.
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