now a doublet at δ 42.6, and C28, now a triplet at δ 23.6. The proton NMR spectrum of **1c** is very similar to that of **1a** but lacks a signal for an olefinic proton. The H29 methyl group shows triplet multiplicity, as evidenced by a homonuclear 2D *J*-resolved experiment.[12] These data lead us to conclude that **1c** differs from **1a** only by the presence of a saturated C24–C28 bond.

Experimental Section

^1H and ^{13}C NMR 1D and 2D spectra were recorded on a Bruker AM 360 NMR spectrometer in CD_3OD at 305 K with either 5-mm proton–carbon dual or inverse broadband probeheads. The ^1H-detected HMQC experiments were measured with a preceding bilinear (BIRD) pulse.[13] GARP1[10] ^{13}C decoupling during the aquisition period of the HMQC experiment was performed using a Bruker BFX-5 linear amplifier to increase the low power transmitter output during acquisition. HMBC experiments were performed using delay values of 3.5 and 50 ms for *J*-filter and evolution of multiple quantum coherence, respectively.[11] All 2D and NOE difference spectra were recorded nonspinning. FAB mass spectra were recorded in glycerol/thioglycerol matrix. Optical rotations were measured in methanol solution. Melting points are uncorrected.

Isolation of Orthoesterol A, B, and C Disulfates. The sponge *P. weinbergi*, collected by Scuba at 40 m near Acklin Island and Long Island in the Bahamas, was immediately frozen and later thawed for extraction. A voucher sample, HBOI BMR sample number 17-VI-85-1-14, is on deposit at the Indian River Coastal Zone Museum, Fort Pierce, FL. The wet sponge material (150 g) was extracted by homogenization in methanol (250 mL) followed by 1:1 methanol–chloroform (2 × 500 mL). The three extracts were combined and evaporated under reduced pressure at 35 °C. The crude extract was partitioned between ethyl acetate and water. The antiviral-active aqueous fraction was partitioned between 1-butanol and water, with evaporation giving 1.7 g of butanol-soluble material. A 550-mg portion of the antiviral-active butanol fraction was fractionated by vacum liquid chromatography[16] on Amicon C-18 silica gel (50 μm) by step gradient elution with H_2O–MeOH and MeOH–chloroform. Fractions active against feline leukemia virus were subsequently purified by HPLC (Vydac C18 protein and peptide column, 5 μm, 250 × 10 mm) with 1:1 H_2O–MeOH to give **1a** (11 mg), **1b** (5 mg), and **1c** (2 mg). All three compounds showed activity against feline leukemia and influenza PR8 viruses in vitro.

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Registry No. **1a**, 131010-92-9; **1b**, 131010-93-0; **1c**, 131010-94-1.

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An Alternative to the Kabbe Condensation for the Synthesis of Chromanones from Enolizable Aldehydes and Ketones

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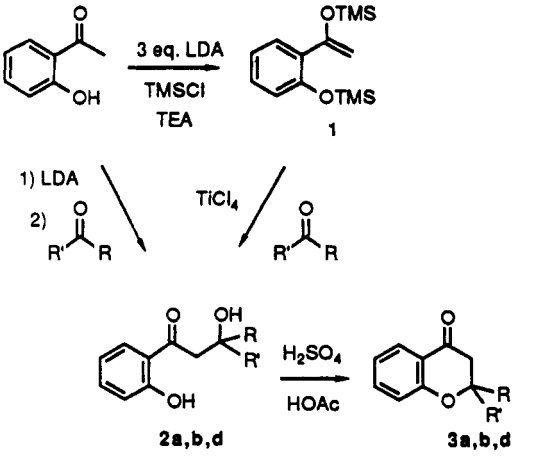
Recently we required a method to prepare chromanones with various substituents at the 2-position.[1] One of the methods commonly utilized is the enamine condensation of 2-hydroxyacetophenone developed by Kabbe.[2] Although we found that the Kabbe condensation worked well for nonenolizable aldehydes, it did not provide satisfactory yields with base-sensitive substrates, as summarized in eq 1.[3] Alternatively, the lithium enolate of 2-hydroxyacetophenone has been reacted with dialkyl ketones to form the β-hydroxy ketone intermediate **2**, depicted in Scheme I.[4] This approach also proved inefficient with base-sensitive carbonyl derivatives. We were able to synthesize the desired β-hydroxy ketones from enolizable aldehydes and ketones by employing a Mukaiyama aldol condensation with bis-silyl enol ether **1**.[5,6] The intermediates **2** were cyclized to the chromanones **3** under acidic conditions.

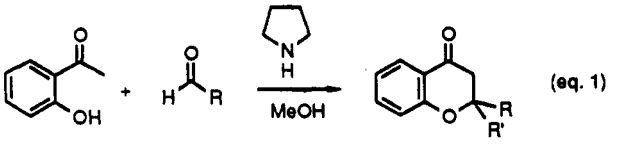
Scheme I



a: R = H, R' = $CH_2C_6H_5$
b: R = H, R' = $CH_2CH_2C_6H_5$
d: R, R' = $-(CH_2)_5-$

Table I. Yields of β-Hydroxy Ketones 2a–d and Chromanones 3a–d

			% yield	
compd	R	R'	2	3
a	H	$CH_2C_6H_5$	92	85
b	H	$CH_2CH_2C_6H_5$	81	91
c	Me	C_6H_5	–	66
d		$-(CH_2)_5-$	85	90



(eq. 1)

R = $CH(CH_3)_2$, 93%
R = $(CH_2)_2C_6H_5$, 30%
R = $CH_2C_6H_5$, <35%

As depicted in Scheme I, bis-silyl enol ether **1** was synthesized from 2-hydroxyacetophenone with lithium diisopropylamide and trimethylsilyl chloride.[6]

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(5) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
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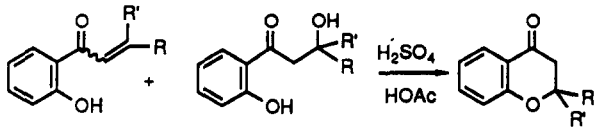
Silyl enol ether 1 was allowed to react with aldehydes or ketones under standard Mukaiyama aldol conditions to form β-hydroxy ketones 2. A variety of Lewis acids, such as $BF_3{\cdot}Et_2O$, $SnCl_4$, and $AlCl_3$, were effective for this transformation, but the highest yields were obtained with $TiCl_4$. For the purposes of characterization, β-hydroxy ketones **2a,b,d** were purified by column chromatography, but in practice these intermediates may be directly cyclized to chromanones **3a,b,d** under acidic conditions. Examples are listed in Table I.

In the case of chromanone **3c**, it was *essential* to use $TiCl_4$ as the Lewis acid since acetophenone was sufficiently unreactive with bis-silyl enol ether 1 that the aldol condensation did not occur in high yield with other Lewis acids. In addition, the best yields of chromanone **3c** were obtained if the reaction was taken directly on to the ring closure without column chromatography purification of the β-hydroxy ketone intermediate **2c**. In this case, the tertiary alcohol produced in the aldol condensation eliminated readily so that both enone **4c** and β-hydroxy ketone **2c** were isolated as an inseparable mixture from the column. As outlined in eq 2, the mixture of both enone **4c** and



4c **2c** **3c**

c: R = Me, R' = C_6H_5

(eq. 2)

β-hydroxy ketone **2c** was cyclized to chromanone **3c** by treatment with H_2SO_4 in acetic acid. Enones **4a–d** were observed as intermediates (by thin-layer chromatography) in all of the cyclization reactions.

Summary

The Mukaiyama aldol reaction followed by acidic ring closure of the β-hydroxy ketone intermediate has proven to be a general and high-yielding method for obtaining sensitive chromanones not readily accessible using base-catalyzed methodology.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Bruker 300-MHz spectrometer in $CDCl_3$ unless otherwise noted. Flash chromatography was performed using Kieselgel 60 (230–400 mesh). Diisopropylamine and trimethylsilyl chloride were distilled from calcium hydride. All other reagents were used as received without further purification.

Trimethyl[2-[1-[(trimethylsilyl)oxy]ethenyl]phenoxy]-silane (1).[6] 2-Hydroxyacetophenone (101 mL, 0.839 mol) was added dropwise to a solution of lithium diisopropylamide [(353 mL, 2.52 mol, of diisopropylamine, and 1007 mL, 2.52 mol, of *n*-butyllithium (2.5 M solution in hexane) in 2.4 L of THF, stirred at 0 °C for 1 h] at 0 °C over 2 h. The reaction mixture was stirred for 1 h, and then a suspension of trimethylsilyl chloride (362 mL, 2.85 mol) and triethylamine (100 mL, 0.72 mol) was added dropwise over 1 h to maintain an internal temperature of 0 °C. After being stirred for 1 h, the reaction was quenched by slow addition of water (50 mL). The reaction mixture was concentrated under vacuum to remove the bulk of the THF, dissolved in pentane (2 L), and washed three times with saturated NaCl. The organic layer was dried (K_2CO_3), the solids were removed by filtration, and the solvent was removed to yield 1 as a clear liquid (224 g, 95%). This material can be distilled for purification: bp 70–75 °C (3 mmHg); ^1H NMR δ 7.53 (m, 1 H), 7.18 (m, 1 H), 6.97 (m, 1 H), 6.80 (m, 1 H), 5.13 (s, 1 H), 4.67 (s, 1 H), 0.21 (s, 9 H), 0.15 (s, 9 H); ^{13}C NMR δ 152.81, 128.89, 128.73, 121.05, 120.03, 96.28, 0.45, 0.12.

General Procedure for the Mukaiyama Aldol Additions of 1 to Carbonyl Compounds: 3-Hydroxy-1-(2-hydroxyphenyl)-4-phenyl-1-butanone (2a). A solution of silyl enol ether 1 (0.93 g, 0.0033 mol) and phenylacetaldehyde (0.39 mL, 0.0033 mol) in CH_2Cl_2 (10 mL) was stirred and cooled to −78 °C. $TiCl_4$ (0.35 mL, 0.0033 mol) was added dropwise. The reaction mixture immediately turned deep orange in color. After 30 min, the cooling bath was removed and the reaction mixture was allowed to come slowly to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine and dried ($MgSO_4$). The crude material was purified by silica column chromatography using 25% ethyl acetate/hexane as the eluent to yield **2a** (0.78 g, 0.0030 mol, 92% yield) as a yellow oil: ^1H NMR δ 12.11 (s, 1 H), 7.65 (m, 1 H), 7.46 (m, 1 H), 7.34 (m, 2 H), 7.27 (m, 3 H), 6.98 (m, 1 H), 6.88 (m, 1 H), 4.49 (m, 1 H), 3.15 (m, 2 H), 2.95 (m, 1 H), 2.86 (m, 1 H); ^{13}C NMR δ 205.96, 162.54, 137.81, 136.80, 130.10, 129.48, 128.66, 126.74, 119.08, 118.64, 68.78, 44.07, 43.10; IR (neat) 3426 (br m), 1635 (s), 1613 (s), 1580 (m), 1488 (s), 1446 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.75; H, 6.15.

3-Hydroxy-1-(2-hydroxyphenyl)-5-phenyl-1-pentanone (2b): yellow oil, 0.42 g, 81% yield following purification by silica column chromatography with 25% ethyl acetate/hexane; ^1H NMR δ 12.13 (s, 1 H), 7.69 (m, 1 H), 7.47 (m, 1 H), 7.27 (m, 5 H), 6.99 (m, 1 H), 6.89 (m, 1 H), 4.26 (m, 1 H), 3.22 (s, 1 H), 3.13 (m, 2 H), 2.89 (m, 1 H), 2.77 (m, 1 H), 1.95 (m, 1 H), 1.85 (m, 1 H); ^{13}C NMR δ 206.24, 162.52, 141.78, 136.86, 130.11, 128.95, 128.73, 128.52, 125.99, 119.51, 119.15, 118.66, 66.91, 45.01, 38.22, 31.87; IR (neat) 3420 (br, m), 1637 (s), 1613 (s), 1580 (m), 1487 (s), 1446 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.30; H, 6.57.

2-(1-Hydroxycyclohexyl)-1-(2-hydroxyphenyl)ethanone (2d): white solid; 0.24 g; mp 67–68 °C; 85% yield following purification by silica column chromatography with 25% ethyl acetate/hexane; ^1H NMR δ 12.16 (s, 1 H), 7.72 (m, 1 H), 7.41 (m, 1 H), 6.91 (m, 1 H), 6.84 (m, 1 H), 3.52 (s, 1 H), 3.06 (s, 2 H), 1.67 (m, 4 H), 1.43 (m, 5 H), 1.23 (m, 1 H); ^{13}C NMR δ 207.40, 162.73, 136.85, 130.55, 120.16, 119.00, 118.64, 71.20, 47.72, 37.82, 25.66, 21.93; IR (KBr): 3506 (m), 1628 (s), 1611 (s), 1483 (m), 1447 (m), 1402 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.43; H, 7.73.

General Procedure for the Ring Closure of 2 to Chromanones: 2,3-Dihydro-2-(2-phenylmethyl)-4*H*-1-benzopyran-4-one (3a). **2a** (61.2 g, 0.239 mol) was dissolved in acetic acid (250 mL) and 50% H_2SO_4 (250 mL). The reaction was heated to 60 °C for 30 min. The reaction mixture was cooled and quenched by pouring into ice water. The aqueous phase was neutralized by addition of a 50% solution of NaOH and extracted with isopropyl ether. The organic phase was washed with saturated brine and dried ($MgSO_4$). Following removal of solvent, the chromanone (**3a**) was purified by silica gel chromatography using 25% ethyl acetate/hexane to give a yellow oil (48.4 g, 0.203 mol, 85% yield): ^1H NMR δ 7.87 (m, 1 H), 7.46 (m, 1 H), 7.34 (m, 2 H), 7.26 (m, 3 H), 6.99 (m, 2 H), 4.66 (m, 1 H), 3.20 (dd, J = 6.61, 13.61 Hz, 1 H), 3.02 (dd, J = 6.43, 13.61 Hz, 1 H), 2.65 (m, 2 H); ^{13}C NMR δ 192.18, 161.45, 136.22, 136.01, 129.64, 128.62, 126.95, 121.34, 121.07, 118.03, 78.29, 42.23, 41.18; IR (neat) 1693 (s), 1605 (s), 1578 (s), 1472 (s), 1464 (s), 1322 (s), 1305 (s), 1227 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.33; H, 5.80.

2,3-Dihydro-2-(2-phenylethyl)-4*H*-1-benzopyran-4-one (3b):[2] yellow oil; 0.19 g; 91% yield following purification by silica column chromatography with 25% ethyl acetate/hexane; ^1H NMR δ 7.88 (m, 1 H), 7.48 (m, 1 H), 7.29 (m, 5 H), 6.99 (m, 2 H), 4.43 (m, 1 H), 2.87 (m, 2 H), 2.70 (m, 2 H), 2.22 (m, 1 H), 1.99 (m, 1 H); ^{13}C NMR δ 192.29, 161.54, 140.93, 136.01, 128.57, 128.48, 127.00, 126.18, 121.30, 121.08, 117.92, 76.81, 43.02, 36.54, 31.13; IR (neat) 1692 (s), 1605 (s), 1577 (m), 1496 (m), 1472 (s), 1463 (s), 1320 (s), 1307 (s), 1228 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.70; H, 6.32.

2,3-Dihydro-2-methyl-2-phenyl-4*H*-1-benzopyran-4-one (3c): white solid; 0.27 g; mp 78–79.3 °C; 66% yield from ketone following purification by silica column chromatography with 25% ethyl acetate/hexane as the eluent. The general procedure for the Mukaiyama aldol addition of 1 to acetophenone was followed. A mixture of **2c** and **4c** was produced which was cyclized by the general procedure for ring closure: ^1H NMR δ 7.75 (m, 1 H), 7.42

(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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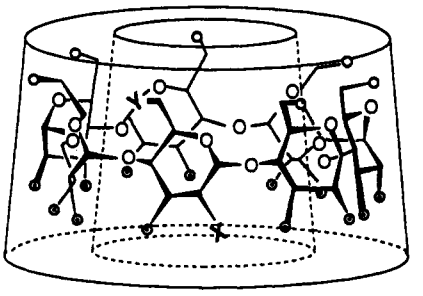
Molecular recognition by substituted cyclodextrins (cycloamyloses) as host compounds has been applied to the studies of enzyme analogues[1] and in chromatographic separations.[2] It has been observed that the substituents at the wider and inherently chiral secondary hydroxyl side of the cyclodextrin 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.

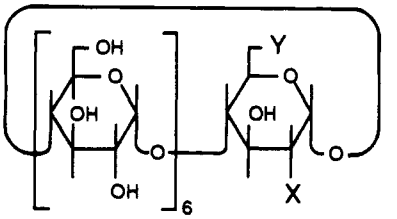
The alkylation of β-cyclodextrin with propylene oxide in aqueous alkali gives mixtures of 2-hydroxypropyl derivatives which have been used to solubilize lipophilic drugs.[5] The distribution of the hydroxyalkyl groups among the 2-O, 3-O, and 6-O positions was investigated[6] in such mixtures and was 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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