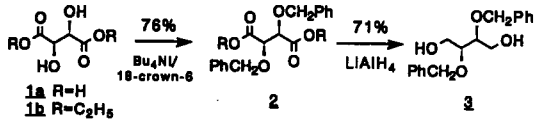
Scheme I



gas ceased. After the deprotonation of the two hydroxy groups was complete, tetrabutylammonium iodide and 18-crown-6 followed by benzyl bromide were added at 0 °C. The benzylation of **1b** was complete within 1 h at room temperature, and the desired product **2** was obtained in 76% yield. Crude **2** was reduced with lithium aluminum hydride according to the reported procedure[4] to give the diol **3** in 54% overall yield from **1b** after recrystallization. The diol **3** was obtained in >99% optical purity.

Conducting the reaction *without either the phase-transfer reagent or 18-crown-6 resulted in lower chemical yield* (30–25%) than with both catalysts. The nucleophilicity of the two alkoxy anions is enhanced by both catalysts, and hence the O-alkylation reaction is complete prior to initiation of side reactions such as elimination or racemization.

Experimental Section

(2*S*,3*S*)-2,3-Bis(phenylmethoxy)-1,4-butanediol (3). A solution of **1b** (209 g, 1.01 mol) in THF (700 mL) was added dropwise over 30 min to a suspension of sodium hydride (77.2 g, 60% in mineral oil, 1.93 mol) in THF (1000 mL) with stirring at 0 °C. After the mixture was stirred for 1 h at 0 °C, tetrabutylammonium iodide (74.9 g, 0.203 mol) and a catalytic amount of 18-crown-6 (600 mg, 2.2 mmol) were added in one portion. Benzyl bromide (331 g, 1.93 mol) was added dropwise over 30 min at 0 °C. The resulting mixture was stirred for 1 h at room temperature, quenched with 1 N aqueous HCl, poured into water, and extracted with three portions of ether. The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude **2** as a colorless oil, which was dissolved in ether (3000 mL) and reduced with lithium aluminum hydride (84.8 g, 94% purity, 2.10 mol) according to the reported procedure[4] to give **3** (164.9 g, 0.545 mol, 54% overall yield from **1b**) after recrystallization: $[\alpha]^{20}_D$ +13.2° (*c* = 4.91, ethanol) (lit.[4] +12.92°).

(4) Cunningham, A. F., Jr.; Kündig, E. P. *J. Org. Chem.* **1988**, *53*, 1823. The optical rotation in the literature is 12.92° in Scheme I, but is 20.88° in the Experimental Section. We prepared the MTPA ester of **3** and found that our sample was optically pure: no diastereomers were detected by 270-MHz ^1H NMR. Therefore, 12.92° is the correct value and 20.88° is incorrect.

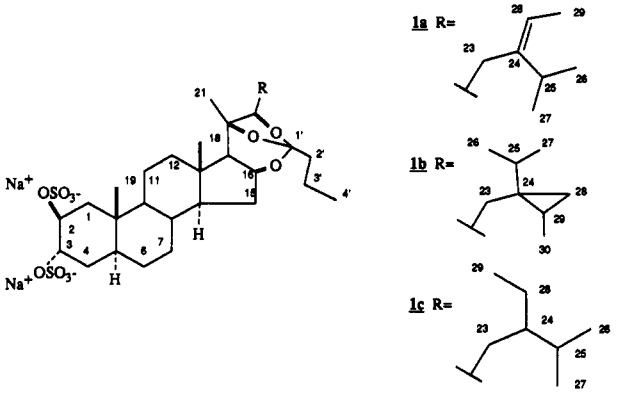
New Antiviral Sterol Disulfate Ortho Esters from the Marine Sponge *Petrosia weinbergi*

Frank E. Koehn,* Malika Gunasekera, and Sue S. Cross

Division of Biomedical Marine Research, Harbor Branch Oceanographic Institution, Inc., 5600 Old Dixie Highway, Ft. Pierce, Florida 34946

Received July 3, 1990

Marine organisms have historically been a rich source of novel sterols,[1] particularly in terms of unique side chain structures and unusual functionalization.[2] During our ongoing program to isolate novel antiviral marine natural products, we have found that extracts of the marine sponge *Petrosia weinbergi* show in vitro activity against feline leukemia virus (FELV), mouse influenza virus (PR8), and mouse coronavirus (A59).[3] We report here the isolation and structure elucidation of orthoesterol disulfates A (**1a**), B (**1b**), and C (**1c**), three new antiviral sterol disulfate ortho esters. We believe these to be the first reported examples in the steroid class of this particular combination of functionalities.



Fractionation of the methanol–chloroform extract of *P. weinbergi* was performed by following the anti-FeLV activity through the purification procedure. The crude extract was partitioned between ethyl acetate and water, and the resulting aqueous layer subsequently partitioned with 1-butanol. Reversed-phase C_{18} vacum liquid chromatography of the antiviral-active butanol fraction followed by reversed-phase C_{18} HPLC in methanol/water mixtures (see the Experimental Section) furnished orthoesterol disulfates A, B, and C in yields of 0.008%, 0.003%, and 0.002%, respectively, from the wet sponge. Early during development of the isolation scheme we noted the presence of sterols in the biologically active semipure fractions, as judged by ^1H and ^{13}C NMR spectroscopy. Solubility and chromatographic characteristics of these compounds suggested a high degree of polar functionality on the steroid skeleton.

Orthoesterol A disulfate (**1a**) was obtained as a white powder from HPLC. The HRFAB mass spectrum shows an $M^+ + Na$ peak at *m/z* 757.2630, indicating a molecular formula of $C_{33}H_{52}O_{11}S_2Na_3$ (Δ 1.6 mmu). The 11 oxygen atoms in the molecular formula taken together with two sulfur and two sodium atoms suggest the presence of two sulfate groups in the molecule. This is confirmed by the presence of IR bands at 1240 and 1060 cm^{-1}. The ^{13}C NMR spectrum is in agreement with the molecular formula, showing 33 carbon lines, including signals for three quaternary carbons at δ 141.9, 43.4, and 36.4, an olefinic CH signal at 120.3, signals for six oxygen bearing carbons, and six methyl groups at δ 21.3, 21.1, 19.0, 15.0, 14.3, and 13.1 (Table I). Comparison of the ^{13}C chemical shifts and results of a DEPT[4] experiment with literature values,[5] in particular those reported for halistanol,[6] strongly suggest the presence of a cholestane ring system with oxygen substitution at C2, C3, and C16, and additional oxygen and

(1) Djerassi, C. *Pure Appl Chem.* **1981**, *53*, 873.
(2) Withers, N. W. *The Biology of the Dinoflagellates*; Taylor, F. J. R., Ed.; Blackwell: London, 1987; pp 316–355.

(3) Against feline leukemia virus in vitro, **1a**, **1b**, and **1c** showed EC_{50} values (50% viral inhibition) at 1.0, 1.3, and 1.0 μg/mL, respectively. Against influenza PR8, all three compounds exhibited complete viral inhibition in vitro at 20 μg/well. Against murine coronavirus A59 all three steroid sulfates showed 50–75% viral inhibition in vitro at 20 μg/well. Details of the biological investigations will be reported elsewhere.
(4) Bendall, M. R.; Pegg, D. T.; Doddrell, D. M.; Williams, D. H. *J. Org. Chem.* **1982**, *47*, 3021.
(5) Kalinowski, H.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Wiley: New York, 1988; p 434.
(6) Fusetani, N.; Matsunaga, S.; Konosu, S. *Tetrahedron Lett.* **1981**, *22*, 1985.

0022-3263/91/1956-1322$02.50/0

Table I. ^{13}C NMR Chemical Shifts for 1a, 1b, and 1c[a,b]

C no.	1a	1b	1c
1	39.1 (t)	39.1 (t)	39.0 (t)
2	76.4 (d)	76.6 (d)	76.5 (d)
3	76.1 (d)	76.2 (d)	76.2 (d)
4	30.4 (t)	30.4 (t)	30.4 (t)
5	40.2 (d)	40.2 (d)	40.2 (d)
6	29.0 (t)	29.0 (t)	29.1 (t)
7	33.0 (t)	33.1 (t)	33.0 (t)
8	35.5 (d)	35.4 (d)	35.6 (d)
9	56.6 (d)	56.5 (d)	56.6 (d)
10	36.4 (s)	36.3 (s)	36.5 (s)
11	21.5 (t)	21.5 (t)	21.6 (t)
12	41.2 (t)	41.1 (t)	41.2 (t)
13	43.4 (s)	43.3 (s)	43.5 (s)
14	55.8 (d)	55.7 (d)	55.8 (d)
15	33.4 (t)	33.3 (t)	33.4 (t)
16	73.1 (d)	73.0 (d)	73.1 (t)
17	58.5 (d)	58.5 (d)	58.5 (d)
18	15.0 (q)	15.0 (q)	15.0 (q)
19	14.3 (q)	14.2 (q)	14.3 (q)
20	83.4 (s)	85.5 (s)	83.5 (s)
21	19.0 (q)	19.0 (q)	18.7 (q)
22	84.5 (d)	83.7 (d)	84.2 (d)
23	34.2 (t)	33.0 (t)	33.3 (t)
24	141.9 (s)	26.0 (s)	42.6 (d)
25	29.8 (d)	33.4 (d)	29.5 (d)
26	21.1 (q)	20.4 (q)	17.7 (d)
27	21.3 (q)	19.9 (q)	20.7 (q)
28	120.2 (d)	20.0 (t)	23.6 (t)
29	13.1 (q)	17.9 (d)	12.8 (q)
30	-	13.7 (q)	-
1′	120.1 (s)	120.1 (s)	120.4 (s)
2′	39.4 (t)	39.5 (t)	39.4 (t)
3′	17.9 (t)	17.9 (t)	18.0 (t)
4′	14.4 (q)	14.5 (q)	14.4 (q)

[a] Solvent CD_3OD. Chemical shifts in ppm downfield from TMS as referenced to $^{13}CD_3OD$ at δ 49.00. [b] Multiplicities determined by DEPT given in parentheses (s = C, d = CH, t = CH_2, q = CH_3).

carbon substituents in the side chain. Notable features of the ^1H NMR spectrum (Table II) included signals for four carbinol methine protons at δ 4.73, 4.69, 4.50, and 4.20, a single olefinic proton at δ 5.25, two angular methyl doublets at δ 1.00 and 1.03, and an additional methyl singlet at δ 1.32.

Proton–proton spin coupling relationships were established by a double quantum filtered phase-sensitive COSY experiment[7] and a series of one-dimensional difference decoupling experiments, the latter used to establish coupling assignments in the congested upfield portion of the proton spectrum. The narrow multiplet signal for H2 at δ 4.73 shows coupling to H3 at δ 4.69, and to both H1 methylene protons at δ 2.07 and 1.42. The narrow multiplet for H3 shows coupling to H2, and to signals for H4 protons at δ 1.83 and 1.67, respectively, thus establishing the proton connectivity of the steroid A ring.

Assignment of the stereochemistry of the sulfoxy groups on the A ring is based on consideration of coupling information from COSY and difference decoupling experiments. The signals for H2 and H3 appear as narrow multiplets, with width at half height of 8 Hz, indicating the lack of a large (>5 Hz) vicinal coupling constant and thus precluding an axial–axial coupling of H2 or H3 with any neighboring protons. This requires a 2β,3α-disulfoxy configuration, which is the same as that reported for halistanol[6] and 5α-cholestane-2β,3α,26-triyl sulfate isolated from the ophiuroid *Ophiarachna incrassata*.[8] In addition,

Table II. ^1H NMR Chemical Shifts for 1a and 1b[a,b]

	δ^1 H (mult) (J_{HH}, Hz)	
C no.	1a	1b
1	2.07 (m), 1.42 (m)	2.05 (m), 1.40 (m)
2	4.73 (sm)[c]	4.73 (m)[c]
3	4.69 (sm)[c]	4.63 (m)[c]
4	1.83 (m), 1.67 (m)	1.81 (m), 1.58 (m)
5	1.58 (m)	1.65 (m)
6	1.26 (m)	1.26 (m)
7	1.67 (m), 0.95 (m)	1.67 (m), 0.95 (m)
8	1.55 (m)	1.50 (m)
9	0.74 (m)	0.72 (m)
10	**	**
11	1.55 (m)	*
12	2.05 (m), 1.20 (m)	2.03 (m), 1.15 (m)
13	**	**
14	1.00 (m)	0.97 (m)
15	2.08 (m), 1.27 (m)	2.07 (m), 1.30 (m)
16	4.50 (m)	4.45 (m)
17	1.14 (d)	1.05 (d)
18	1.03 (s)	1.01 (s)
19	1.00 (s)	1.00 (s)
20	**	**
21	1.32 (s)	1.28 (s)
22	4.20 (dd) (J = 9.7, 3.4)	3.85 (dd) (J = 10.5, 2.4)
23	2.07 (m), 1.86 (m)	1.30 (m), 1.63 (m)
24	**	**
25	2.87 (sep) (J = 6.7)	1.50 (m)
26	1.00 (d) (J = 6.7)	1.00 (d) (J = 6.7)
27	1.00 (d) (J = 6.7)	1.00 (d) (J = 6.7)
28	5.25 (bq) (J = 6.7)	0.66 (dd) (J = 8.6, 4.4), -.20 (dd) (J = 5.5, 4.7)
29	1.63 (d) (J = 6.7)	1.11 (dd) (J = 8.6, 5.5)
30	***	1.13 (d) (J = 6.7)
1′	**	**
2′	1.67 (m)	1.65 (m)
3′	1.45 (m)	1.45 (m)
4′	0.89 (t) (J = 6.7)	0.89 (t) (J = 6.7)

[a] Solvent CD_3OD chemical shifts in ppm downfield from TMS, as referenced to CHD_2OD at δ 3.30. Carbon connectivities assigned by HMQC. [b] Connectivities assigned by HMQC and COSY. [c] sm = narrow multiplet. *Connectivity not assignable due to overlap. **Nonprotonated carbon. ***Carbon not present.

the ^{13}C chemical shift values in 1a for C1, C2, C3, and C4 are in good agreement with those reported for these two known compounds as well.

COSY cross peaks show between the B ring protons of H6 at δ 1.26 and geminally coupled signals for H7 at δ 1.67 and 0.95. Similarly, the C ring proton spin system is established by cross peaks between proton signals at δ 1.55 for H11 and H12 protons at δ 2.05 and 1.20. The C16 proton signal at δ 4.50 shows coupling to the H15 geminal protons at δ 2.08 and 1.27, as well as to H17 at δ 1.14. The carbinol proton H22 at δ 4.20 is coupled to the H23 methylene signals at δ 2.07 and 1.86. Difference decoupling was used to establish couplings between the H26 and H27 methyl doublets and the H25 methine proton at δ 2.87, as well as between H2′ and H3′, and H3′ and H4′ in the ortho ester chain. The single olefinic proton quartet at δ 5.25 is coupled (J = 6.8 Hz) to the H29 vinyl methyl doublet at 1.63 ppm.

The limited amounts of material (<10 mg) isolated necessitated the use of two-dimensional inverse-detected NMR methods for the determination of proton–carbon one bond and long-range couplings. Proton–carbon one bond connectivities were established via a two-dimensional ^1H-detected HMQC[9] experiment with carbon decoupling during acquisition using a GARP[10] sequence. The HMQC

(7) Marion, D.; Wüthrich, K. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 967.
(8) D'Auria, M. V.; Riccio, R.; Minale, L.; La Barre, S.; Pusset, J. *J. Org. Chem.* **1987**, *52*, 3947.
(9) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565.
(10) Shaka, A. J.; Keeler, J. In *Progress in Nuclear Magnetic Resonance* Elmsly, A. W., Feeney, J., Sutcliffe, L. H., Eds.; Pergammon Press: Oxford, 1987; p 47.

Table III. HMBC Multiple Bond Correlations for 1a and 1b

^{1}H	^{13}C correlation	
	1a	1b
1	C2, C10	C2, C3, C10, C5
2	C3, C4	C3, C10
3	C4, C5, C1	C5, C1
4	*	C3, C2, C10
12	*	C11, C10, C13, C14
14	C15	*
15	C16, C13	C16, C13
17	C16, C13	*
18	C12, C13, C14, C15	C13
19	C9, C10, C1, C5	C9, C10
21	C20, C17, C22	C20, C17, C22
22	C17	C17, C30
23	C20, C2	C24, C25, C28
26	C25, C27	C24, C25
27	C25, C26	C24, C25
28	C24, C29	C24, C25, C29, C30
29	C28, C24	*
30	-	C24, C28, C29
2′	C1′, C4′	C3′, C4′
3′	C1′, C2′, C4′	C2′, C4′
4′	C2′, C3′	C2′, C3′

* No correlations observed, or not assignable due to overlap.

data in conjunction with the proton spin coupling data established the connectivities of the protonated carbon atoms of the molecule.

The carbon connectivity of orthoesterol A disulfate was completed with the aid of results from an HMBC experiment[11] (Table III), which shows the multiple bond proton–carbon couplings necessary to bridge the quaternary centers. The H19 methyl shows long-range correlations to C1, C10, C9, and C5 while the H18 methyl shows correlations to C15, C13, C17, and C14, thus allowing the assemblage of the A and B rings. The H15 protons show correlations to C13, C14, and C16 and likewise, H17 shows long-range couplings to C13, C16, and C18. Placement of the C21 methyl is possible by correlations from H21 to C20, C17, and C22. Two- and three-bond HMBC correlations from H26 to C25, and H27 to C24, along with correlations from H28 to C23, C25, and C29, and H29 to C28 and C24, solidify the side-chain assignment.

The stereochemistry of the C24–C28 double bond is assigned as the *E* configuration based on the chemical shift of the H25 proton and the results of a one-dimensional difference nuclear Overhauser enhancement experiment. The H25 septet in **1a** appears at δ 2.87, indicating an *E* configuration as in isofucosterol[13,14] where it appears at 2.80 ppm, in contrast to fucosterol (*Z* configuration) where it appears at 2.2 ppm. Irradiation of H25 also produced a small (ca. 0.8%), but measurable NOE enhancement of the H29 methyl doublet at δ 1.63. An NOE enhancement of the H18 methyl signal is observed upon irradiation of the H21 methyl group, indicating the usual steroid β configuration at C17 for the side-chain attachment.

The remaining unaccounted elements of the molecule as required by the molecular formula are a four carbon unit of C1′–C2′–C3′–C4′, three oxygen atoms, which must be on C16, C20, and C22 by ^{13}C chemical shift arguments, and two additional degrees of unsaturation. Orthoesterol A disulfate lacks freely accessible hydroxyl groups, as evidenced by a failure to undergo acetylation in acetic anhydride/pyridine. The ^{13}C chemical shift of C1′ at δ 120.1, and the absence of any remaining sp^2 carbons argues for connection of the remaining four carbon unit via an ortho ester linkage.

The HRFAB mass spectrum of orthoesterol B disulfate (**1b**) shows an M$^+$ + Na molecular ion at *m/z* 771.2867, indicating a molecular formula of $C_{34}H_{54}O_{11}S_2Na_3$, ($\Delta$ 8.1 mmu). This is confirmed by the ^{13}C NMR spectrum which contains 34 resonances. Comparison of the proton and carbon chemical shifts and multiplicities of **1b** with those of **1a** strongly suggest the steroid A–D ring portions of both compounds are identical, and that differences between the two compounds are manifested in the side chain. This was confirmed by double quantum filtered phase-sensitive COSY, DEPT, and HMQC experiments, which provide the same proton–proton and proton–carbon connectivities as in **1a** for the entire steroid tetracycle as well as the C21–C20–C22 portion of the side chain. The ortho ester chain also shows nearly identical chemical shifts (Tables I and II) and connectivities.

Examination of the proton and COSY spectra of **1b** shows that the remaining side chain signals consist of two methyl doublets at δ 1.00 (J = 6.8 Hz) which are both coupled to the methine H25 proton multiplet at 1.50 ppm, two geminal H23 protons at δ 1.30 and 1.63 ppm coupled to the carbinol H22 proton at δ 4.20, shielded H28 methylene protons at δ 0.66 and –0.20 ppm, both coupled to the H29 methine proton at 1.11 ppm, and a methyl doublet H30 (J = 6.7 Hz) also coupled to H29.

The chemical shift values and multiplicities for H28, H29, and C28 and C29 (Tables I and II) strongly suggest that they are part of a cyclopropyl system. Since the C22–C23 connection can be made via the observed COSY coupling between H23 and H22, what remains is placement of the cyclopropyl ring, the C26–C25–C27 isopropyl group, and the C30 methyl. The HMBC data for **1b** (Table III) provide two- and three-bond long-range carbon–proton couplings which permit assignment of the remaining carbon connectivities. Correlations are observed from both H28 protons to C29, C24, C30, and C25, from H25 to C29 and C24, from H26 and H27 to C25, and from both H23 protons to C24, C25, and C28.

We employed a series of difference NOE experiments to establish the relative stereochemistry of the side chain and of the ring carbon atoms participating in the ortho ester linkage. Irradiation of the high field H28 double doublet at δ –0.20 ppm results in enhancement of the H23 signal (1.5%) at δ 1.30, and of the H30 methyl signal (0.7%) at δ 1.13, indicating a cis relationship between H28 at δ –0.20, the H30 methyl and the H23 methylene. The H29 methine signal shows a trans (J = 5.5 Hz) cyclopropyl coupling to H28 at δ –0.20 and a cis coupling (J = 8.6 Hz) to H28 at δ 0.66.[15] These data are consistent with the relative stereochemistry shown in **1b**.

Irradiation of H22 gives an NOE enhancement of H16 (1.5%), indicating these protons are on the same face of the molecule. Assuming a normal β configuration at C17, as in **1a**, examination of Dreiding molecular models shows that these NOE constraints are best satisfied with H16 and H17 in the α-position. We are unable to construct a stable model structure with H16 in the β-position and where H22 is sufficiently close for NOE interaction.

Orthoesterol C disulfate (**1c**) was isolated by HPLC (C_{18}, 40% MeOH/H_2O) along with **1a** and **1b**. The FAB mass spectrum shows a molecular ion of nominal mass 759 while the ^{13}C NMR spectrum (Table I) differs from **1a** at C24,

(11) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
(12) Aue, W. P.; Karhan, J.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 4226.
(13) Frost, D. J.; Ward, J. P. *Tetrahedron Lett.* **1968**, 3779.
(14) Bates, R. B.; Brewer, A. D.; Knights, B. A.; Rowe, J. W. *Tetrahedron Lett.* **1968**, 6163.
(15) Pretsch, E.; Seibel, J.; Simon, W.; Clerc, T. *Spectral Data for Structure Determination of Organic Compounds*; Springer: New York, 1983; p H185.

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.

Acknowledgment. We are grateful to Dr. S. Pomponi for identification of the sponge sample and to Dr. S. Gunasekera for helpful discussions. We thank Dan Pentek of Yale University Chemical Instrumentation Center for mass spectral measurements. This publication is Harbor Branch Oceanographic Institution Contribution No. 811.

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

(16) Blunt, J. W.; Calder, V.; Fenwick, G. D.; Lake, R. J.; McCombs, J. D.; Munro, M. H. G.; Perry, N. *J. Nat. Prod.* **1987**, *50*, 290.

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

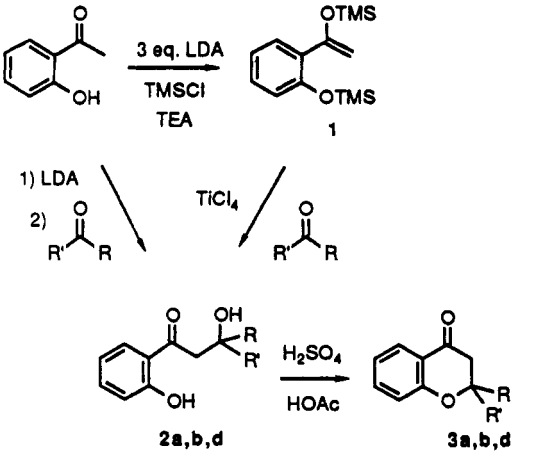
Sarah E. Kelly* and Brian C. Vanderplas

Process Research and Development, Central Research Division, Pfizer Inc., Groton, Connecticut 06340

Received August 2, 1990

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.

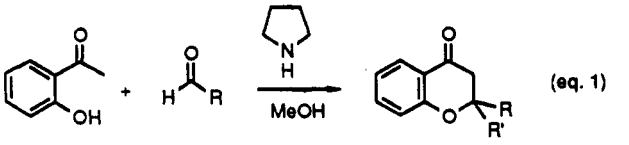
Scheme I



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]

(1) For reviews of chromanones, see (a) *The Chemistry of Heterocyclic Compounds* Ellis, G. P., Ed.; Wiley: New York, 1977; Vol. 31. (b) Wallace, T. W. *Nat. Prod. Rep.* **1986**, 465.
(2) Kabbe, H. J. *Synthesis* **1978**, 886. (b) Kabbe, H. J.; Widdig, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 247.
(3) Unpublished results of Mr. D. Pirie and Dr. P. W. Weeks of this department. The Kabbe condensation with 2-hydroxyacetophenone and phenyl acetaldehyde resulted in a less than 35% yield of chromanone **3a**.
(4) Banerji, A.; Goomer, N. C. *Tetrahedron Lett.* **1979**, 3685.
(5) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
(6) Kita, Y.; Yasuda, H.; Tamura, O.; Tamura, Y. *Tetrahedron Lett.* **1984**, 1813.

0022-3263/91/1956-1325$02.50/0