ethyl vinyl ether and *N*-bromosuccinimide at 0 °C. Subsequent treatment of **8** with freshly prepared tri-*n*-butyltin hydride containing azobisisobutyronitrile (AIBN) as catalyst in benzene at 65 °C for 4 h gave **9** in 70% yield. By adopting Grieco's procedure,[9] compound **9** was converted in one step into the γ-lactone **10**, which was fully characterized (Scheme II).

Hydrolysis of **9** with 3 N sulfuric acid afforded the hemiacetal **11**, which on Wittig reaction with ethyltriphenylphosphonium bromide by employing Schlosser's conditions[2a,10] gave the *E* olefin **12** in 61% yield. Removal of the benzyl group furnished the known diol **13**.[2g] Alternatively compound **12** was protected as ethoxyethyl derivative (**14**) by reacting with ethyl vinyl ether and pyridinium *p*-toluenesulfonate (PPTS) followed by hydrogenolysis with Li/NH_3 to afford **15**. Compound **15** was transformed[2g] into the key intermediate **3**.

Experimental Section

^1H nuclear magnetic resonance spectra were recorded at 80 or 90 MHz in $CDCl_3$. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co. (India). Thin-layer chromatography was performed on Merck 60 F-254 silica gel plates. Solvents were distilled before use, and petroleum ether refers to bp 60–80 °C. The microwave reaction was performed on Batliboi-Eddy microwave oven with power settings 1–7.

(±)-3-Butene-1,2-diol (5). A mixture of 6.00 g (68.1 mmol) of *cis*-butene-1,4-diol (**4**), 25 mg of mercuric sulfate, 0.035 g of concentrated H_2SO_4, and 2.5 mL of water was kept in a microwave oven with power setting at 1 for 3 min (temperature ca. 50 °C). After usual[3a] workup, 4.0 g (66%) of **5** was isolated by fractional distillation (bp 78–90 °C/15 mm).

(2*RS*,4*R*,5*R*)-5-[(Benzyloxy)methyl]-2-ethoxy-4-methyltetrahydrofuran (9). *N*-Bromosuccinimide (2.93 g, 16.45 mmol) was added to a solution of 2.50 g (14.04 mmol) of *R*-**6** and 1.30 g (18.05 mmol) of ethyl vinyl ether in 25 mL of CH_2Cl_2 at −10 °C. The mixture was stirred at 0 °C and filtered, and the filtrate was successively washed with 5% KOH and water, dried (Na_2SO_4), and concentrated to afford 3.80 g (82%) of **8** as an oil.

To a solution of 2.50 g (7.60 mmol) of **8** and a catalytic amount of azobisisobutyronitrile (AIBN) in dry benzene at 65 °C under nitrogen was added 2.21 g (7.60 mmol) of tri-*n*-butyltin hydride. The reaction was maintained at 65 °C for 4 h and then concentrated. The residue was purified by column chromatography on silica gel with low-boiling petroleum ether as eluent to give 1.33 g (70%) of **9** as an oil: ^1H NMR (80 MHz) δ 0.9–1.8 (m, 1 H), 2.1 (m, 2 H), 2.9–4.0 (m, 3 H), 4.52 (s, 2 H), 5.0 (m, 1 H), 7.25 (s, 5 H).

(4*R*,5*R*)-5-[(Benzyloxy)methyl]-3-methyltetrahydrofuran-2(3*H*)-one. A soluton of 0.217 g (0.868 mmol) of **9**, a catalytic amount of $BF_3{\cdot}OEt_2$, and 0.18 g (1.04 mmol) of *m*-chloroperbenzoic acid in 5 mL of CH_2Cl_2 was stirred at room temperature for 3 h. After workup, the crude product was purified on silica gel with ethyl acetate–petroleum ether (1:9) as eluent to give 0.155 g (81%) of **10** as a oil: $[\alpha]_D$ −16.7° (*c* 2.45, $CHCl_3$); ^1H NMR (80 MHz) δ 1.15 (d, 3 H, *J* = 6.5 Hz), 2.05–3.0 (m, 3 H), 3.85 (m, 2 H), 4.20 (m, 1 H), 4.50 (s, 2 H), 7.25 (s, 5 H); mass spectrum *m/z* 220 (M^+). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.27. Found: C, 70.7; H, 7.12.

(2*R*,3*R*,5*E*)-1-(Benzyloxy)-3-methyl-5-hepten-2-ol (12). A solution of 1.20 g (4.8 mmol) of **9**, 15 mL of methanol, and 4 mL of 3 N H_2SO_4 was stirred at room temperature for 12 h, neutralized with $BaCO_3$, and filtered through Celite. The filtrate was concentrated to give 0.92 g (86%) of **11**.

To a solution of 2.52 g (6.8 mmol) of ethyltriphenylphosphonium bromide in 20 mL of THF-OEt_2 (3:5) was added 2 mL of *n*-BuLi in hexane (2.8 M) at −70 °C. After 0.5 h, 0.85 g (3.82 mmol) of **11** dissolved in 5 mL of ether was introduced followed by the addition of 0.8 mL of *n*-BuLi. The reaction mixture was warmed to −30 °C at which 0.28 mL of *tert*-butyl alcohol and 0.43 g of potassium *tert*-butoxide were added. After being stirred at room temperature for 1.5 h, the solution was poured over water. The aqueous layer was repeatedly extracted with ether, and then combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with ethyl acetate–petroleum ether (1:9) as eluent to give 0.54 g (61%) of **12**, homogeneous on silver nitrate impregnated silica gel: TLC, $[\alpha]_D$ −4.5° (*c* 1.85, $CHCl_3$); ^1H NMR (90 MHz) δ 1.0 (d, 3 H, *J* = 7 Hz), 1.65 (d, 3 H, *J* = 5.3 Hz), 1.7–2.5 (m, 3 H), 2.35 (d, 1 H, D_2O exchangeable), 3.8 (m, 1 H), 3.95 (m, 2 H), 4.5 (s, 2 H), 5.75 (m, 2 H), 7.25 (s, 5 H). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40. Found: C, 76.76; H, 9.02.

(2*R*,3*R*,5*E*)-2-(1-Ethoxyethoxy)-3-methyl-5-hepten-1-ol (15). A solution of 0.45 g (1.92 mmol) of **12**, 140 mg of ethyl vinyl ether, and a catalytic amount of PPTS in 15 mL of CH_2Cl_2 was stirred at 0 °C for 2 h. The reaction mixture was concentrated to give 0.56 g (95%) of the crude **14**.

A solution of 0.306 g (1 mmol) of crude **14** in 10 mL of ether was added to 50 mL of condensed ammonia; 14 mg of lithium metal was added, and after 1 h solid NH_4Cl was introduced. The ammonia was allowed to evaporate, and the residue was partitioned between ether and water. The ethereal layer was dried (Na_2SO_4) and concentrated. The residue was purified on silica gel with ethyl acetate–petroleum ether (1:9) as eluent to give 0.18 g (83%) of the known **15**. The spectral properties of **15** are consistent with the reported values.[2g]

(2*R*,3*R*,5*E*)-3-Methyl-5-heptene-1,2-diol (13). The debenzylation of 0.20 g (0.85 mmol) of **12** was carried out with Li/NH_3 as described above to afford 0.10 g (81%) of **13**, as an oil: $[\alpha]_D$ −5.13° (*c* 0.9, $CHCl_3$) (lit.[2g] $[\alpha]_D$ −5.7° ($CHCl_3$)).

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An Improved and Practical Method for the Synthesis of Optically Active Diethyl Tartrate Dibenzyl Ether

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Tartaric acid (**1a**) is one of the most useful chiral building blocks of asymmetric synthesis.[1] Although methods for the preparation of tartrate derivatives having the two hydroxy groups protected by cyclic acetals have been developed,[2] protection by *O*-benzyl groups, which are more stable than acetals under acidic conditions, is not easily effected. It was believed that protection of the secondary alcohol groups of **1** with alkyl halides via alkoxy anions under strongly basic conditions would be accompanied by racemization of the two chiral centers or by elimination of the resulting alkoxy groups. To overcome this difficulty, Seeback and co-workers developed[3] a thallium alkoxide reagent for the protection of the hydroxy groups. However, a major drawback of this reagent is its severe toxicity and high price.

We now report a practical method for the large-scale preparation of the dibenzyl ether **2** using sodium hydride, tetrabutylamminoum iodide, and a catalytic amount of 18-crown-6 (Scheme I). The tartrate **1b** was deprotonated with slightly less than 2 equiv of sodium hydride at 0 °C in anhydrous tetrahydrofuran (THF). The resulting suspension was stirred for 30 min until evolution of hydrogen

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(2) Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y. Y. *Tetrahedron Lett.* **1987**, *28*, 1431. Mukaiyama, T.; Goto, Y.; Shode, S. *Chem. Lett.* **1983**, 671.
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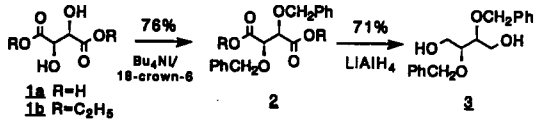
Scheme I



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*

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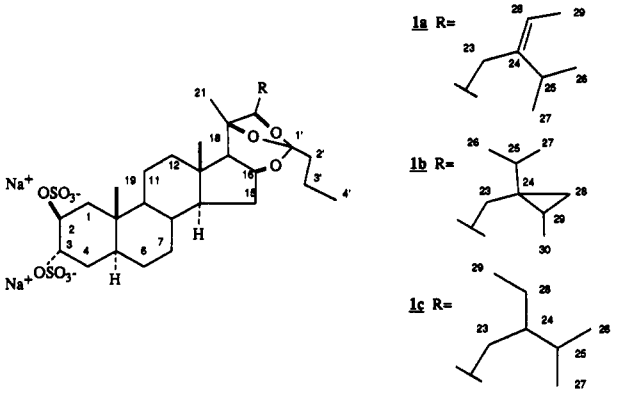
Marine organisms have historically been a rich source of novel sterols,[1] particularly in terms of unique side chain structures and unusual functionalization.[2] During our ongoing program to isolate novel antiviral marine natural products, we have found that extracts of the marine sponge *Petrosia 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

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(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.
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