(Na_2SO_4) and concentrated. Flash column chromatography (SiO_2, eluant D) afforded **5** as a colorless, viscous oil. Peak twinning in the NMR spectrum of **5** was consistent with restricted rotation about the tertiary amide bond in this structure: ^1H NMR ($CDCl_3$) δ 4.03/4.22 (s, 2 H), 3.48/3.59 (t, 2 H, J = 5.7 Hz), 2.72 (m, 4 H), 2.42 (m, 2 H), 2.09/2.10 (s, 3 H), 1.64 (m, 2 H), 1.50 (m, 4 H); IR (film) 3400, 1640 cm^{-1}; CIMS, m/e (relative intensity) 200 (M + 1, 100); TLC R_f (eluant C) 0.15; HPLC retention time (eluant F, 0.5 mL/min) 22.4 min.

To obtain pure **2** directly from the crude acetylation product above, the oily residue was dissolved in absolute ethanol (40 mL), and then malonic acid (2.03 g, 19.5 mmol) and dry pyridine (1.2 mL, 15 mmol) were added. The mixture was heated at reflux for 2 h, cooled, and concentrated in vacuo to remove the bulk of the ethanol. The resultant residue was taken up in water (50 mL), extracted twice with 30-mL portions of CH_2Cl_2, basified to pH 10 with 1 N NaOH, and again extracted twice with CH_2Cl_2. Freeze-drying of the aqueous layer afforded impure **2** contaminated with sodium tosylate, sodium acetate, and sodium hydroxide. The impure solid mixture was loaded onto a 6 in. × 0.5 in. column of Dowex 50 (H^+ form) and eluted with 3:1 H_2O–EtOH (125 mL) to remove neutral and acidic contaminants. The solvent was changed to 5:4:1 H_2O–EtOH–NH_4OH, whereupon the desired acetamide **2** was eluted (0.64 g, 71%). Further purification was achieved by flash column chromatography (SiO_2, 20 g, eluant B) to furnish 0.44 g of **2** as a pale yellow oil [R_f (eluant A) 0.31], which was immediately converted to its dihydrochloride salt by using excess methanolic HCl. The dihydrochloride was dried in vacuo to give **2** as a white solid (0.59 g, 47%); ^1H NMR (D_2O) δ 3.13 (t, 2 H, J = 6.6 Hz), 2.91 (m, 6 H), 1.85 (s, 3 H), 1.74 (m, 2 H), 1.61 (m, 4 H). Analysis by HPLC indicated that **2** was contaminated by ca. 10% of **3**.

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Registry No. 1, 73453-98-2; 2, 14278-49-0; 2·2HCl, 34450-16-3; 3, 13431-24-8; 4, 85681-29-4; 5, 85681-31-8; 6, 85681-32-9; 7, 85681-30-7; 8, 85701-34-4; 18-crown-6, 17455-13-9; *N,N',N'',N'''*-tetraacetylglycoluril, 10543-60-9.

Supplementary Material Available: Reproductions and tabulated data of 300-MHz NMR spectra of all key intermediates and products (8 pages). Ordering information is given on any current masthead page.

Minor and Trace Sterols in Marine Invertebrates. 41.[1] Structure and Stereochemistry of Naturally Occurring 9,11-Seco Sterols

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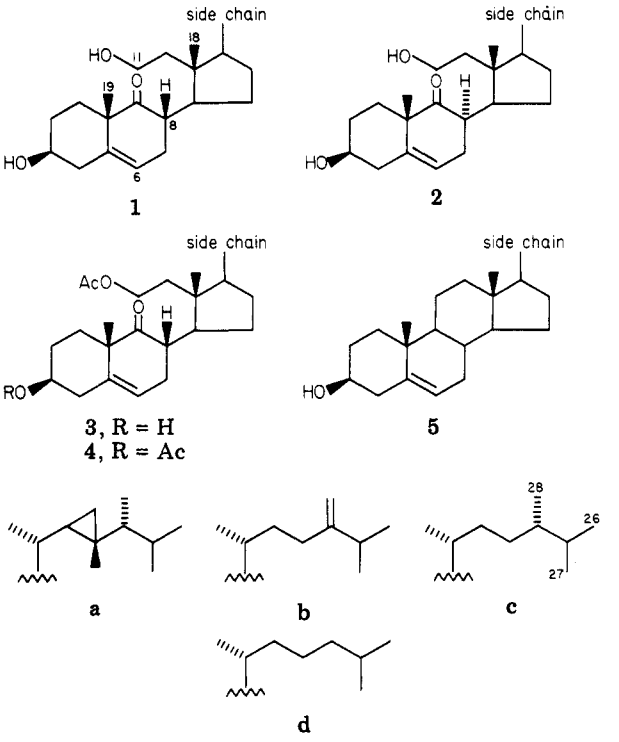
Although a large number of new sterol structures have been discovered from marine organisms during the last decade,[2] relatively few polyhydroxylated and oxygenated analogues have been reported, most of them from soft corals.[3] Until recently the only marine sterol with the unique 9,11-secocholestane system was 3β,11-dihydroxy-9,11-secogorgost-5-en-9-one (**1a**, Chart I)[4] which was isolated from a gorgonian together with the known gorgosterol **5a**.[5] The structure and absolute configuration of the seco sterol **1a** was established[4] by X-ray analysis. Since then two new 9,11-seco sterols (**1b** and **1c**) have been isolated from a soft coral (*Sinularia* sp.),[6] without, however, attributing any stereochemistry to them. We now report a reinvestigation of this *Sinularia* sp. that led to the isolation of new 9,11-seco sterols and also uncovered an interesting stereochemical feature.

Chart I



Chromatography (silica gel) of the dichloromethane extract of the soft coral gave a fraction containing "normal" sterols together with some more polar fractions apparently homogeneous by TLC. Preparative high-performance liquid chromatography (HPLC) of this polar fraction yielded three major peaks together with four other minor components that were collected and analyzed by mass spectrometry and 360-MHz ^1H NMR. The three major components were shown to be the earlier reported 9,11-seco sterols **1a**,[4] **1b**,[6] and **1c**.[6] Comparison of the ^1H NMR data (Table I) of **1a**[7] with those of **1b** and **1c** showed almost

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(1) For preceding paper, see: Li, X.; Djerassi, C. *Tetrahedron Lett.* **1983**, *24*, 665.
(2) (a) Schmitz, F. J. *In* "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. I, pp 241–297. (b) Goad, L. J. In "Marine Natural Products: Chemical and Biological Perspectives"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. II, pp 75–172. (c) Djerassi, C.; Theobald, N.; Kokke, W. C. M. C.; Pak, C. S.; Carlson, R. M. K. *Pure Appl. Chem.* **1979**, *51*, 1815. (d) Djerassi, C. *Ibid.* **1981**, *53*, 873.
(3) (a) Bortolotto, M.; Braekman, J. C.; Daloze, D.; Tursch, B. *Bull. Soc. Chim. Belg.* **1976**, *85*, 27. (b) Sjöstrand, U.; Bohlin, L.; Fisher, L.; Colin, M.; Djerassi, C. *Steroids* **1981**, *38*, 347 and references cited therein.
(4) Enwall, E. L.; Van Der Helm, D.; Nan Hsu, I.; Pattabkiraman, T.; Schmitz, F. J.; Spraggins, R. L.; Weinheimer, A. J. *J. Chem. Soc. Chem. Commun.* **1972**, 215.
(5) (a) Hale, R. L.; Leclercq, J.; Tursch, B.; Djerassi, C.; Gross, R. A.; Weinheimer, A. J.; Gupta, K.; Scheuer, P. J. *J. Am. Chem. Soc.* **1970**, *92*, 2179. (b) Ling, N. C.; Hale, R. L.; Djerassi, C. *Ibid.* **1970**, *92*, 5281.
(6) Kazlauskas, R.; Murphy, P. T.; Ravi, B. N.; Sanders, R. L.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 69.
(7) Weinheimer, A. J., personal communication.

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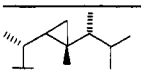
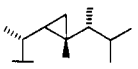
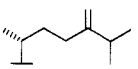
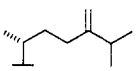
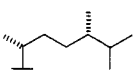
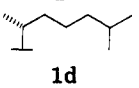
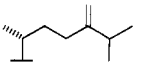
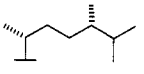
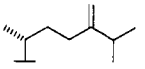
Table I. 360-MHz ^{1}H NMR Chemical Shifts ($CDCl_3$) of Selected Protons of 9,11-Seco Sterols[a]

	C-6	C-8	C-11	C-18	C-19	C-21	C-26	C-27	C-28
 1a	5.48 d	3.05 m	3.80 m, 3.60 m	0.678 s	1.381 s	separate assignments not possible			
 2a	5.58 d	2.71 m	3.78 m	0.803 s	1.221 s	separate assignments not possible			
 1b	5.48 d	3.02 m	3.84 m, 3.70 m	0.679 s	1.379 s	0.982 d (J = 6.7)	1.015 d (J = 6.8)	1.019 d (J = 6.8)	4.67 d (J = 24)
 2b	5.58 d	2.67 m	3.72 t (J = 7.8)	0.803 s	1.225 s	0.992 d (J = 6.8)	1.020 d (J = 6.8)	1.025 d (J = 6.8)	4.68 d (= 24)
 1c	5.48 d	3.05 m	3.85 m, 3.70 m	0.678 s	1.381 s	0.956 d (J = 6.7)	0.770 d (J = 6.8)	0.781 d (J = 6.8)	0.850 d (J = 6.8)
 1d	5.48 d	3.02 m	3.84 m, 3.68 m	0.677s	1.380 s	0.951 d (J = 6.7)	0.858 d (J = 6.6)	0.858 d (J = 6.6)	
 3b	5.48 d	2.99 m	4.17 t (J = 7.4)	0.710 s	1.361 s	1.001 d (J = 6.4)	1.019 d (J = 6.7)	1.019 d (J = 6.7)	4.68 d (J = 24)
 3c	5.48 d	2.99 m	4.16 t (J = 7.4)	0.704 s	1.361 s	0.973 d (J = 6.7)	0.769 d (J = 6.7)	0.779 d (J = 6.8)	0.850 d (J = 6.9)
 4b	5.52 d	2.97 m	4.17 t (J = 7.4)	0.707 s	1.366 s	1.000 d (J = 6.5)	1.019 d (J = 6.7)	1.015 d (J = 6.6)	4.68 d (J = 24)

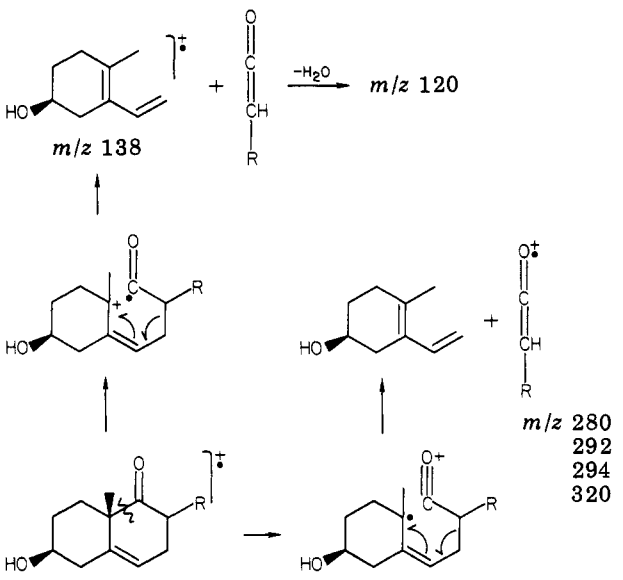
[a] J values are in hertz.

identical chemical shift values for the C-6, C-8, C-11, C-18, and C-19 resonances. Since the absolute configuration of **1a** has been established[4] by X-ray analysis and since alterations of the chiral centers would have dramatically modified some of the chemical shift values in **1b** and **1c**, the stereochemistry at C-8, C-14, C-18, and C-20 must be identical in all three sterols.[8]

The high-resolution mass spectrum of one of the minor components of the polar fraction—eventually shown to be the secocholesterol derivative **1d**—displayed, aside from the molecular ion peak at m/z 418 ($C_{27}H_{46}O_3$), characteristic ions at m/z 280 ($C_{18}H_{32}O_2$), 138 ($C_9H_{14}O$), and 120 (C_9H_{12}) due to allylic cleavage (see Scheme I) of the B ring, with charge retention in both fragments. Analogous peaks occur in the mass spectra of all 9,11-seco sterols and serve as excellent diagnostic markers for this special class of sterols.[9]

Since the chemical shift values of C-6, C-8, C-11, C-18, and C-19 in the 360-MHz ^{1}H NMR spectrum were almost identical with the values of the other 9,11-seco sterols (see Table I), it follows that one of the trace sterols is the hitherto unknown 3β,11-dihydroxy-9,11-secocholest-5-en-9-one (**1d**).

Scheme I



Analysis of the high-resolution mass spectra and of the 360-MHz ^{1}H NMR spectra of the two minor components with longer HPLC relative retention times (rrt) readily led to the conclusion that we were dealing with the monoacetyl derivatives **3b** and **3c** of the 9,11-seco sterols **1b** and **1c**, respectively. The acetate group is attached to the C-11 hydroxyl function (see downfield shift of the C-11 signal for **3b** and **3c** in Table I), and the resemblance of the other chemical shift values suggested that **3b** and **3c** possess the same absolute stereochemistry as **1b** and **1c**. This was

(8) In sterol **1c** the resonances of C-26 (0.770 ppm), C-27 (0.781 ppm), and C-28 (0.850 ppm) closely resembled those of 22-dihydrobrassicasterol (0.774, 0.781, and 0.854 ppm, respectively; see: Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D.; Impellizzeri, G.; Mangiafico, S.; Piatelli, M.; Scinto, S. *Biochem. Syst. Ecol.* **1976**, *4*, 135), which led to the assignment of the 24*S* stereochemistry in **1c**.

(9) All the spectra of the other 9,11-seco sterols showed the same fragmentation pattern with consistent peaks at m/z 120 (usually the base peak), 138, and either 292 (for **1b** and **2b**), 294 (for **1c**) or 320 (for **1a**).

confirmed by acetylation of **3b** and **1b** to the same diacetate **4b**.[10]

The last and most interesting compound (**2b**) (HPLC rrt 0.06) showed a high-resolution mass spectrum almost identical with that of compound **1b** (M^+ = 430, $C_{28}H_{46}O_3$) and peaks at m/z 292, 138, and 120 (base peak), characteristic of 9,11-seco sterols[9] as illustrated above. However, its 360-MHz ^1H NMR spectrum displayed the following substantial differences with respect to **1b** (see Table I): First, the chemical shift values of C-6, C-18, C-19, and C-21 in **2b** changed between 0.01 and 0.15 ppm with respect to the corresponding signals in **1b**. Second, the chemical shift value and the pattern of the C-11 hydroxymethyl group in **2b** (triplet at 3.72 ppm) were completely different from those in **1b** (multiplets at 3.84 and 3.70 ppm). Third, a large upfield shift of the C-8 resonance (from 3.02 ppm in **1b** to 2.67 ppm in **2b**) suggested that a major change has occurred in the stereochemistry of one or more of the chiral centers involved in opening ring C.[11]

In view of the presence of a cyclohexanone system, we investigated the circular dichroism (CD) spectra of the 9,11-seco sterols. As shown in the Experimental Section, while the CD spectra of **1a**, **1b**, **1c**, and **1d** all showed a negative Cotton effect in the 290-nm carbonyl absorption region, the CD spectrum of **2b** displayed a mirror-image curve characterized by a positive Cotton effect. Examination of Dreiding models offers a reasonable explanation for the different Cotton effects. On the basis of the octant rule,[12] the negative Cotton effect for compounds **1a**, **1b**, **1c**, and **1d** (in the half-chair conformation with the bulky C-8 substituent equatorial) is due to the C-18 angular methyl and especially to the C-7 ring carbon.[13] The positive Cotton effect of **2b** (when considering that half-chair in which the C-8 substituent is again equatorial) is due to the axial C-1 → C-10 bond and to the C-7 ring carbon.

These observations strongly suggested that **2b** was the C-8 epimer of 3β,11-dihydroxy-24-methylene-9,11-secocholest-5-en-9-one (**1b**). Confirmation of structure **2b** was provided by base-catalyzed (NaOH/MeOH, 24 h, room temperature) isomerization of **1b** to **2b**.[14] Similar treatment of the secogorgosterol analogue **1a** provided its C-8 epimer **2a**, which showed CD and NMR differences of the type already encountered in the C-8 epimeric pair **1b** and **2b**.

The fact that a group of 9,11-seco sterols with a variety of side chains (**a**, **b**, **c**, **d**) has now been discovered suggests that the *Sinularia* species probably cleaves ring C of exogenously provided sterols, similar to the situation observed in the ring A contraction of sponge sterols.[15] It is relevant to mention that standard sterols (skeleton **5**) with the side chains **a**, **b**, **c**, and **d** have also been isolated from this *Sinularia* sp. Neither the mechanism of ring C cleavage nor the biological function of the seco sterols has so far been established. However, it is very unlikely that the less stable[14] isomer **2b** is an artifact of the isolation procedure.[16] In any future characterization of 9,11-seco sterols with different side chains, CD and ^1H NMR examination can be used confidently to establish the full structure and stereochemistry of such sterols.

Experimental Section

Preparative HPLC was performed with a Waters Associates pump and dual cell refractometer detector, by using a Whatman Partisil M9 10/50 ODS-2 column and two Altex Ultrasphere ODS columns (10 mm i.d. × 25 cm, 5 μm) in series (eluent MeOH/H_2O, 9:1). Low-resolution mass spectra were recorded on a Finnigan MAT 44 spectrometer and high-resolution mass spectra on a Finnigan MAT 711 instrument. The 360-MHz ^1H NMR spectra were recorded on a Brucker HXS-360 NMR spectrometer. Circular dichroism spectra were recorded on a JASCO J-40 instrument in absolute MeOH. Absorption spectra were measured with a Hewlett-Packard HP 8450A UV–vis spectrophotomer in absolute MeOH.

Extraction and Isolation of the 9,11-Seco Sterols. The freeze-dried soft coral (collected at Feather Reef, Australian Great Barrier Reef) was extracted with dichloromethane (10 L) and methanol (10 L). Evaporation of the solvent gave a dichloromethane extract (21.4 g), which was chromatographed on silica gel (200 g, TLC grade) with CH_2Cl_2/AcOEt with different gradients as eluent. Final elution with pure AcOEt gave a mixture of the 9,11-seco sterols (5.2 g).

Separation of the 9,11-Seco Sterol Mixture. The seco sterol fraction (homogeneous by TLC) was dissolved in MeOH and subjected to preparative reverse-phase HPLC on an ODS-2 column with MeOH/H_2O (9:2 as mobile phase): **2b** (1%, HPLC rrt = 0.06 with cholesterol = 1), **1b** (35%, rrt = 0.08), **1d** (5%, rrt = 0.1), **1c** (38%, rrt = 0.12), **1a** (15%, rrt = 0.16), **3b** (2%, rrt = 0.17), and **3c** (2%, rrt = 0.2). All these compounds were further purified by HPLC on two Altex columns, with MeOH/H_2O (9:1) as mobile phase.

8αH-3β,11-Dihydroxy-24-methylene-9,11-secocholest-5-en-9-one (2b): high-resolution mass spectrum, m/z (relative intensity) 430.436 ($C_{28}H_{46}O_3$, M^+, 6), 412.329 ($C_{28}H_{44}O_2$, $M^+ - H_2O$, 11), 292.238 ($C_{19}H_{32}O_2$, 11), 138.104 ($C_9H_{14}O$, 26), 120.093 (C_9H_{12}, 100); absorption spectrum ϵ_{290} 80; CD $(\theta)_{290}$ 12 000.

8βH-3β,11-Dihydroxy-24-methylene-9,11-secocholest-5-en-9-one (1b): high-resolution mass spectrum identical with that of **2b**; absorption spectrum ϵ_{288} 48; CD $(\theta)_{220}$ −3400, $(\theta)_{285}$ −5600.

(24*S*)-3β,11-Dihydroxy-24-methyl-9,11-secocholest-5-en-9-one (1c): absorption spectrum ϵ_{290} 45; CD $(\theta)_{220}$ −5500, $(\theta)_{290}$ −7600.

3β,11-Dihydroxy-9,11-secocholest-5-en-9-one (1d): mp 112–113 °C (benzene/hexane); high-resolution mass spectrum, m/z (relative intensity) 418.335 ($C_{27}H_{46}O_3$, M^+, 9), 400.343 ($C_{27}H_{44}O_2$, $M^+ - H_2O$, 98), 367.304 ($C_{26}H_{39}O_1$, $M^+ - 2H_2O - CH_3$, 100); 280.241 ($C_{18}H_{32}O_2$, 24), 138.105 ($C_9H_{14}O_1$, 9), 120.094 (C_9H_{12}, 42); absorption spectrum ϵ_{270} 69; CD $(\theta)_{220}$ −4400, $(\theta)_{293}$ −6500.

3β-Hydroxy-11-acetoxy-24-methylene-9,11-secocholest-5-en-9-one (3b): low-resolution mass spectrum, m/z (relative intensity) 472 (M^+, 0.2), 412 (0.9), 232 (1.5), 161 (2), 138 (33), 120 (100); high-resolution mass spectrum, m/z (relative intensity) 412.388 ($C_{28}H_{44}O_2$, M^+ − HOAc, 13), 232.218 ($C_{17}H_{28}$, 9), 138.104 ($C_9H_{14}O$, 41), 120.094 (C_9H_{12}, 100); absorption spectrum ϵ_{285} 56; CD $(\theta)_{220}$ −8500, $(\theta)_{295}$ −13 100.

(24*S*)-3β-Hydroxy-11-acetoxy-24-methyl-9,11-secocholest-5-en-9-one (3c): low-resolution mass spectrum, m/z (relative intensity) 474 (M^+, 0.2), 414 (1), 245 (0.2), 179 (5), 161 (6), 138 (30), 120 (100); high-resolution mass spectrum, m/z (relative intensity) 414.349 ($C_{28}H_{46}O_2$, M^+ − HOAc, 6), 138.105 ($C_9H_{14}O$, 58), 120.093 (C_9H_{12}, 100); absorption spectrum ϵ_{280} 93; CD $(\theta)_{230}$ −8000, $(\theta)_{293}$ −13 000.

Isomerization of 1b to 2b. To a 50-mg sample of **1b**, dissolved in MeOH, was added 5 mL of 2 N NaOH. The solution was stirred at room temperature for 24 h and then concentrated in vacuo;

(10) Another important chemical shift value for **4b**, not shown in Table I, is the downfield shift of the C-3 proton (4.55 ppm in **4b** vs. 3.51 ppm in **1b** and 3.48 ppm in **3b**) due to acetylation of the C-3 secondary hydroxyl group.

(11) The fact that the signals of the side-chain methyl groups (C-26, C-27, and C-28) have almost the same values in **1b** and **2b** indicates that no stereochemical change has occurred in that portion of the molecule.

(12) Moffit, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.

(13) Djerassi, C.; Klyne, W., *Proc. Natl. Acad. Sci. U.S.A.* **1962**, *48*, 1093.

(14) The reverse isomerization process, starting with **2b**, led to the same equilibrium mixture of ca. 95:5 (**1b**/**2b**).

(15) Bohlin, L.; Sjöstrand, U.; Sodano, G.; Djerassi, C. *J. Org. Chem.* **1982**, *47*, 5309.

(16) During the workup of the organism and in every step of the separation process, very mild conditions were used (temperature used always below 45 °C) with absence of either acidic or basic reagents. Silica gel chromatography of the "normal" isomer **1** did not produce epimerization to **2**.

the solid residue, dissolved in MeOH, was filtered and dried in vacuo, followed by HPLC separation (Altex columns with MeOH/H_2O (9:1) as mobile phase), to yield 1.5 mg of **2b** and 32 mg of starting compound **1b**. The high-resolution mass and ^1H NMR spectra of **2b** were identical in all respects with those of natural **2b**.

3β,11-Dihydroxy-9,11-secogorgost-5-en-9-one (1a):[4] absorption spectrum ϵ_{285} 51; CD $(\theta)_{220}$ −3350, $(\theta)_{295}$ −4800.

Isomerization of 3β,11-Dihydroxy-9,11-secogorgost-5-en-9-one (1a) to 8α-H Isomer 2a. A 50-mg sample of **1a** was treated in the same way as described above for **1b**. The final HPlC separation yielded 2 mg of **2a** (HPLC rrt 0.14 with cholesterol = 1) and 35 mg of **1a**. Absorption spectrum of **2a**: ϵ_{285} 147; CD $(\theta)_{300}$ 32 500.

Acetylation of 1b and 3b to 3β,11-Diacetoxy-24-methylene-9,11-secocholest-5-en-9-one (4b). Both **1b** and **3b** were acetylated under standard conditions (Ac_2O/py, room temperature, 2 h) to yield the same diacetate **4b**, which was purified by HPLC on Altex columns with MeOH/H_2O (95:5) as mobile phase (rrt 0.3 with cholesterol = 1): low-resolution mass spectrum, m/z (relative intensity) 454 (M^+ − HOAc, 0.5), 394 (M^+ − 2HOAc, 0.5), 359 (0.5), 232 (3), 161 (10), 120 (100); absorption spectrum ϵ_{285} 56; CD $(\theta)_{225}$ −7000, $(\theta)_{290}$ −12 000.

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Registry No. **1b**, 81419-47-8; **1c**, 85700-72-7; **1d**, 85650-23-3; **2a**, 34290-98-7; **2b**, 85700-73-8; **3b**, 85650-24-4; **3c**, 85650-25-5; **4b**, 85650-26-6.

Direct Preparation of Bromoacetaldehyde

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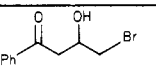
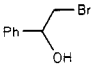
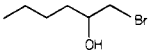
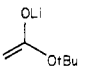
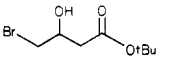
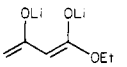
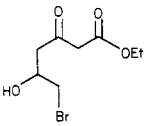
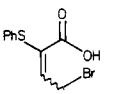
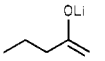
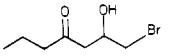
Halo aldehydes or their equivalents have been widely employed in heterocyclic synthesis. Such aldehydes are useful for ring-forming reactions in that they represent units with two adjacent electrophilic sites. However, the simplest representatives, bromo- or chloroacetaldehyde, have been little used because the anhydrous aldehyde is difficult to prepare. House and co-workers prepared chloroacetaldehyde by hydrolysis of the chloro acetal, trimerization, and thermal cracking of the trimer.[1] In this paper we report a preparation of bromoacetaldehyde by an ozonolysis reaction. Except for an isolated example,[2] the reaction of bromo- or chloroacetaldehyde with enolate anions has not previously been studied. We report herein the reaction of bromoacetaldehyde with various carbanions.

While Roberts[3] has observed that the ozonolysis of several allylic derivatives is complicated by undesirable side reactions, he found that allylic bromides and chlorides could be ozonized without any side reactions. We therefore examined the ozonolysis of 1,4-dichloro-2-butene and 1,4-dibromo-2-butene. In practice the cleavage of the latter compound in methylene chloride at −78 °C followed by the slow addition of triphenylphosphine afforded the highest yield. After distillation, 1 M solutions of bromoacetaldehyde in hexane can be stored for weeks without noticeable decomposition.

Table I. Reaction of Anions with Bromoacetaldehyde

anion	% yield	product
	100	
PhLi	100	
n-BuLi	60	
	82	
	85	
		
	60	

The aldehyde solution in hexane reacts with a variety of anions generated under anhydrous conditions. The results are depicted in Table I. It is interesting to note that the reaction of bromoacetaldehyde with the dianion of ethyl acetoacetate does not produce any cyclopentanone-containing products. The intramolecular alkylation of the β-keto ester anion would be a 5-endo trig-type process and should be disfavored according to Baldwin's rules.[4]

Experimental Section

Bromoacetaldehyde. A solution of 40 mmol of 1,4-dibromo-*trans*-2-butene in 60–70 mL of dry CH_2Cl_2 (over sieves or distilled from P_2O_5) was cooled to −78 °C and treated with ozone until a blue color persisted (~30 min). A nitrogen stream was passed through the solution until the blue color disappeared, giving a colorless solution. After a dried magnetic stirring bar was added to the flask, 40 mmol of triphenylphosphine was added portionwise over 1 h while the temperature was kept at −78 °C. After the addition of triphenylphosphine the solution was slowly warmed to 0 °C. An aliquot of slightly yellow solution was checked by NMR ($CDCl_3$ solvent) for the absence of ozonide. If the ozonide was still present (m, δ 3.5–4.0) stirring was continued at 0 °C until the reaction was complete. Methylene chloride was distilled at 0–5 °C (90-100 mmHg). The residue was then distilled at 1 mmHg into a receiving flask at −78 °C. As the residue became viscous, it was heated with an oil bath at ~50 °C. Distillation yielded 11.26 g (56%) of bromoacetaldehyde and methylene chloride (1:1.5). This mixture was used in the reactions described in the text. **Caution**: the aldehyde is a lachrymator, NMR ($CDCl_3$) δ 3.88 (d, J = 2.5 Hz, 2 H), 5.32 (s, CH_2Cl_2), 9.55 (t, J = 2.5 Hz, 1 H); IR (film) 1728 cm^{-1}.

General Procedure for the Reaction of Bromoacetaldehyde with Anions. To a solution of the anion at −78 °C

(1) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.
(2) Semmelhack, M. F.; Tomesch, J. C.; Czarny, M.; Boettger, S. *J. Org. Chem.* **1978**, *43*, 1259.
(3) Young, W. G.; McKinnis, A. C.; Webb, I. D.; Roberts, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 293.
(4) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233.

0022-3263/83/1948-2111$01.50/0