solution of **3d** (0.084 g, 0.29 mmol) in CH_2Cl_2 (50 mL, 0 °C). The mixture was stirred vigorously for 1 h and then filtered. The filtrate was evaporated in vacuo to give an orange solid (0.111 g) which was chromatographed on acid-washed silica gel. The column was eluted first with benzene/ethyl acetate (5%). Increasing the concentration of ethyl acetate eventually gave orange-colored fractions, which were evaporated to give orange crystals (0.066 g). These recrystallized from petroleum ether/ethyl acetate to give the hydroxyacylnaphthoquinone as orange crystals: mp 147–148 °C; 0.030 g (33%); UV (CH_3OH) λ 375 nm (ε 4200), 282 (9900), 239 (8000); NMR ($CDCl_3$) δ 1.1–1.9 (m, 10 H, CH_2), 3.4–4.0 (s and m overlap, 4 H, $HCC=O$ and CH_3), 7.0–7.8 (m, 3 H, arom H); IR ($CHCl_3$) ν_{max} 3000 (br), 1690, 1665, 1655 cm^{-1}; mass spectrum, m/e (relative intensity) 314.1158 (100), 233.0444 (21), 232.0377 (38), 204.0417 (40) 203.0351 (75); m/e calcd for $C_{18}H_{18}O_5$ 314.1154, $C_{12}H_9O_5$ 233.0438, $C_{12}H_8O_5$ 232.0382, $C_{11}H_8O_4$ 204.0412, $C_{11}H_7O_4$ 203.0358.

Registry No. (*R*)-**1**, 71719-69-2; (*S*)-**1**, 75716-63-1; **2**, 75716-64-2; **3**, 75716-65-3; (*R*)-**6**, 71719-72-7; (*S*)-**6**, 71719-71-6; **7**, 45734-11-0; **8**, 75716-66-4; **9**, 75716-67-5; *O,O*-dimethyl phosphorothioic acid dicyclohexylammonium salt, 13941-61-2; dimethyl phosphonate, 868-85-9; 2-hydroxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane methyltriethylammonium salt, 75716-68-6; 2-methoxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane, 1005-97-6; **4f**, 75716-81-3; **4g**, 607-55-6; **4h**, 64725-89-9; acetyl chloride, 75-36-5; cyclohexanecarbonyl chloride, 2719-27-9; benzoyl chloride, 98-88-4.

Microbial Products. 5. Absolute Configuration of Aminoglycoside X-14847

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Analysis of the ¹H NMR spectrum of X-14847 nonaacetate reduces the number of possible structures for X-14847 to two. A study involving multiple cuprammonium complexation of the *N*-acetyl derivative which contains eight hydroxyl groups, generating five vicinal glycol groupings, permits the identification of X-14847 as 2-amino-2-deoxy-α-D-glucopyranosyl-1-*O*-D-*myo*-inositol. This assignment is confirmed by single-crystal Roentgen analysis of 2-[(5-bromo-2,4-dinitrophenyl)amino]-2-deoxy-α-D-glucopyranosyl-1-*O*-D-*myo*-inositol octaacetate prepared from X-14847 with 1-bromo-3-fluoro-4,6-dinitrobenzene and subsequent peracetylation.

We have recently described the isolation of a novel aminoglycoside, named X-14847, which is produced by *Micromonospora echinospora* sp. X-14847.[1] It exhibited very weak antibacterial activity and was identified as a 2-amino-2-deoxy-α-D-glucopyranosyl-*myo*-inositol.

Of the nine inositols, *myo*-inositol (**1**) belongs to the group of seven which are meso compounds. Since it contains one plane of symmetry bisecting two centers of opposite chirality, substitution of any one of the six hydroxyl groups gives rise to a specific stereoisomer so that six isomers had to be considered for the configuration of X-14847.

The ¹H NMR spectrum of 1,2-*O*-isopropylidene-*myo*-inositol 3,4,5,6-tetraacetate (**4**)[2] shows the protons of the acetoxy group within a close range [δ ($CDCl_3$) 2.00 (s, 6 H), 2.05 (s, 3 H), 2.10 (s, 3 H)] and the acetoxy signals of *myo*-inositol 3,4,5,6-tetraacetate (**3**)[3] fall into the same region [δ ($CDCl_3$) 1.98 (s, 3 H), 1.99 (s, 3 H), 2.07 (s, 3 H), 2.09 (s, 3 H)]. In agreement with the general observation that axial acetoxy groups attached to six-membered rings in the chair conformation absorb at lower field than the equatorial ones, the signal for the axial acetoxy group in the spectrum of *myo*-inositol hexaacetate (**2**),[4] therefore,

could be assigned to the peak at δ 2.18 which is 0.2 ppm further downfield than the remaining five acetoxy signals. The chemical shifts of the acetoxy groups in methyl 2-(acetylamino)-2-deoxy-α-D-glucopyranoside triacetate (**9**)[5] range between δ ($CDCl_3$) 1.93 and 2.08 so that the low-field acetoxy peak at δ 2.28 in nonaacetate **12a** or **12b** could be assigned to the axial acetoxy group. The signals for H5 in **2** [δ ($CDCl_3$) 5.17 (t, $J_{4,5} = J_{5,6} = 10$ Hz)] and **12** [δ ($CDCl_3$) 5.11 (t, $J_{4,5} = J_{5,6} = 10$ Hz)] are very similar, requiring C5 in **12** to carry an acetoxy group as well. The hydroxyl groups located in the inositol symmetry plane in X-14847 are therefore unsubstituted.

The ring protons H2 [δ ($CDCl_3$) 5.60 (t, $J_{1,2} = J_{2,3} = 3$ Hz)], H4 and H6 [δ 5.51 (t, 2 H, $J_{1,6} = J_{3,4} = J_{4,5} = J_{5,6} = 10$ Hz)] in **2** absorb sufficiently far downfield so as not to interfere with the signals of **9**. Thus, the three triplets generated by H2 [δ 5.59 ($J_{1,2} = J_{2,3} = 3$ Hz)], H4 and H6 [δ 5.48 and 5.51 (2 t, $J_{1,6} = J_{3,4} = J_{4,5} = J_{5,6} = 10$ Hz)] are easily recognizable in the spectrum of X-14847 nonaacetate, confirming that the inositol hydroxyl groups at C4 and C6 in X-14847 are likewise free. The possible sugar-attachment sites in X-14847 are therefore limited to C1 and C3 of inositol, leaving structures **10a** and **10b** for consideration.

Similarly substituted *myo*-inositols are already known; (–)-bornesitol (**5a**) corresponds stereochemically to **10a** and
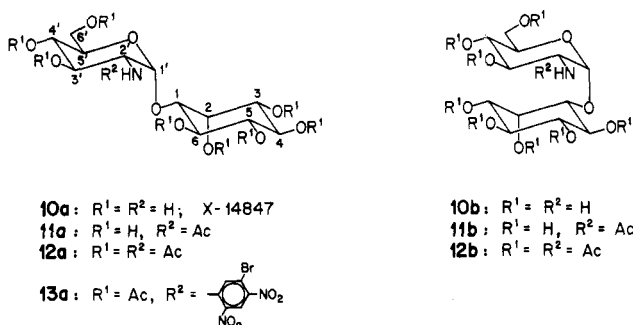
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(5) R. C. G. Moggridge and A. Newberger, *J. Chem. Soc.*, 745 (1938).

1 : R¹ = R² = H;
    myo-inositol
2 : R¹ = R² = Ac
3 : R¹ = H, R² = Ac
4 : R¹ + R¹ = -C(Me)₂-,
    R² = Ac

5a : R¹ = Me, R² = H;
     (-)-bornesitol
5b : R¹ = H, R² = Me;
     (+)-bornesitol
6 : R¹ = H, R² = α-D-galactopyranosyl;
    galactinol

7 : R¹ = R² = H
8 : R¹ = H, R² = Ac
9 : R¹ = R² = Ac

10a : R¹ = R² = H; X-14847
11a : R¹ = H, R² = Ac
12a : R¹ = R² = Ac

10b : R¹ = R² = H
11b : R¹ = H, R² = Ac
12b : R¹ = R² = Ac

13a : R¹ = Ac, R² = (3-bromo-4,6-dinitrophenyl)
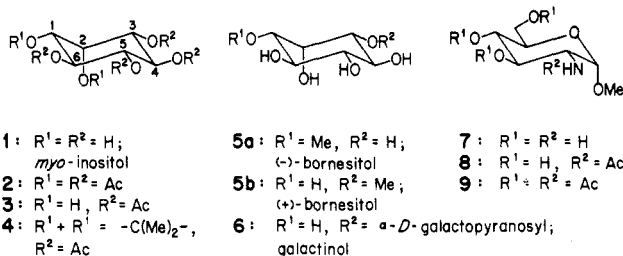
is produced by several members of different plant families, whereas (+)-bornesitol (**5b**) was originally isolated from the Borneo rubber plant in 1871[6] and corresponds to **10b**. Still closer related to **10b** is galactinol (**6**), isolated from the sap of Rocky Mountain sugar beets.[6,7] The assignment of absolute configurations of the bornesitols **5a** and **5b** rests mainly on the chemical conversion of (-)-quebrachitol to **5b**.[8] Structure 6 for galactinol[9] is primarily based on a reaction sequence yielding, inter alia, a pentamethyl-*myo*-inositol upon methylation and hydrolysis. The free hydroxyl group of this degradation product, representing the attachment site of the galactopyranosyl moiety, was oxidized, catalytically hydrogenated, and demethylated to furnish a mixture of *myo*-inositol and (-)-inositol. Since inversion of C3 in 1 yields (-)-inositol, the absolute configuration of galactinol was shown to be 6. Further, (+)-bornesitol was synthesized from 6 by methanolysis of nona-*O*-benzylgalactinol, methylation of the methanolysis mixture, and hydrogenolytic removal of the benzyl groups.[10]

To differentiate between **10a** and **10b** without such elaborate degradation reactions, we argued that the *N*-acetyl derivative of X-14847 (**11a** or **11b**) contains five vicinal diol groupings, three of which could simultaneously be involved in cuprammonium complex formation when treated with Cupra B[11] solution. The observed rotational increment, $\Delta[M]_{436}$(Cupra B),[12] thus produced would be a composite of a maximum of three contributions. One of these contributions is derived from the 2-(acetylamino)-2-deoxy-D-glucopyranosyl portion, identical in both **11a** and **11b** and ascertained by analysis of the known methyl glucoside 8, for which a value of $\Delta[M]_{436}$(Cupra B) = +2064° was experimentally determined. The value of $\Delta[M]_{436}$(Cupra B) for the hypothetical **11a** or **11b** where only the diol of the sugar portion engages in cuprammonium complexing is thus +2064°. The remaining two contributions, associated with the inositol moiety and expected to change this value

Table I. Possible Pairs of Cuprammonium Complexes in the Inositol Moiety of 11a and Calculated $\Delta[M]_{436}$ for 11a

locations of Cu(II) chelate rings	φ	calcd $\Delta[M]_{436}$ for 11a
2-3, 4-5	-, +	+2064°
2-3, 5-6	-, -	-2064°
3-4, 5-6	-, -	-2064°

Table II. Possible Pairs of Cuprammonium Complexes in the Inositol Moiety of 11b and Calculated $\Delta[M]_{436}$ for 11b

locations of Cu(II) chelate rings	φ	calcd $\Delta[M]_{436}$ for 11b
4-5, 6-1	+, +	+6192°
4-5, 1-2	+, +	+6192°
5-6, 1-2	-, +	+2064°

Table III. ¹³C NMR Chemical Shifts (δ) of X-14847 and Various Model Compounds

carbon	1[16]	5a[16]	7	10a
1	72.3	81.5		80.5
2	73.3	69.0		72.2
3	72.3	73.3		73.2
4	73.6	72.1		72.8
5	75.7	75.4		75.2
6	73.6	72.6		73.0
OMe		57.9		-
1'			101.0	102.0
2'			56.0	56.4
3'			75.1	74.6
4'			71.0	71.0
5'			73.0	73.8
6'			61.8	61.8
OMe			56.1	-

drastically, are not a priori constants for each diastereomer **11a** and **11b** but arise from three distinct sets of possibilities which are different for **11a** and **11b**. Each set is governed by the prospect of simultaneous accommodation of two Cu(II) chelate rings, the locations and dihedral angle signs[13,14] of which are summarized in Tables I and II for diastereomers **11a** and **11b**, respectively. As evident from Table I, the *myo*-inositol portion of **11a** can accommodate a pair of cuprammonium complexes in three different ways, two of which involve exclusively negative dihedral angles and are expected to greatly reduce the magnitude of the $\Delta[M]_{436}$(Cupra B) = +2064° inherently present in **11a** and **11b**. Only one pair of chelation sites at the inositol portion comprises a negative and a positive dihedral angle which, when involved simultaneously in complexation, would not be expected to significantly alter the rotational increment due to the sugar portion. The preponderance of vicinal glycols with negative dihedral angles in the inositol portion of **11a** gives rise to an expected overall rotational increment contribution which is negative and large. Assuming identical magnitudes of the three contributing rotational increments comparable to the one exhibited by 8 and further assuming that three cuprammonium complexes are in existence at all times, the calculated $\Delta[M]_{436}$(Cupra B) for **11a** is -688°.

(6) T. Posternak, "The Cyclitols", Holden-Day, San Francisco, 1965.

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(10) C. E. Ballou and L. I. Pizer, *J. Am. Chem. Soc.*, 82, 3333 (1960).

(11) Reeves, *Adv. Carbohydr. Chem.*, 6, 107 (1951).

(12) $\Delta[M]_{436}$(Cupra B) = ([α]₄₃₆(Cupra B) - [α]₄₃₆(water))(mol wt)(10⁻²).

(13) The sign of a dihedral angle φ was defined by Reeves in 1951[11] as positive if a counterclockwise rotation of the frontal bond superimposes frontal and rear bonds. Consequently, diols with positive dihedral angels (0° < φ ≤ 60°) give positive rotational increments in Cupra B and vice versa. We are using the Reeves convention in this paper. Ten years later, unfortunately, Klyne and Prelog defined the dihedral angle in the opposite sense.[14]

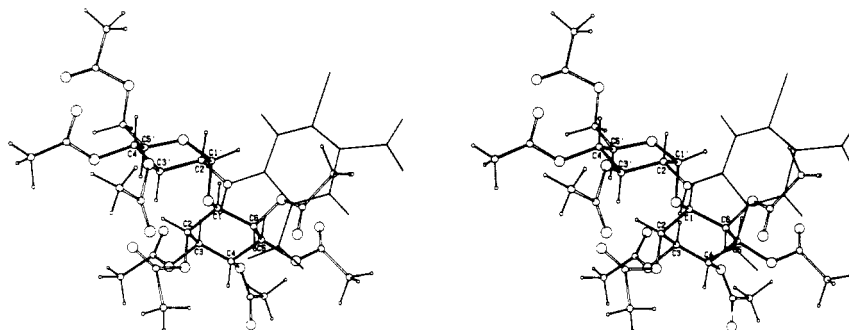(14) W. Klyne and V. Prelog, *Experientia*, 16, 521 (1960).

Figure 1. Stereoscopic drawing of the conformation of **13a** in the crystalline state. Oxygen atoms are shown as large circles. The 3-bromo-4,6-dinitrophenyl moiety is shown as a line drawing.

Isomer **11b** can be analyzed analogously as seen in Table II. Of the three sets of possible Cu(II) chelate rings on the inositol moiety, two of them are due to glycols with only positive dihedral angles. The involvement of either one of these two sets in cuprammonium complexing would be expected to greatly enhance the rotational increment of +2064°, whereas the third pair of chelation sites containing both a negative and a positive dihedral angle would be expected to essentially compensate each other so that $\Delta[M]_{436}$(Cupra B) for **11b** could be calculated to be +4816°.

The experimental value of $\Delta[M]_{436}$(Cupra B) of -231° for the *N*-acetyl derivative of X-14847[1] is reasonably close to the calculated value of -688° for **11a** so that the structure of X-14847 is established as **11a**.

In the course of the initial experiments designed to characterize X-14847, we succeeded in crystallizing derivative **13a** containing a heavy atom and prepared by successive reactions with 1-bromo-3-fluoro-4,6-dinitrobenzene[15] and pyridine-acetic anhydride. Single-crystal Roentgen analysis confirmed structure **13a** as shown in Figure 1 so that structure **11a** for X-14847 is confirmed.

The ^{13}C NMR spectrum of **10a**, as interpreted on the basis of model compounds **1**, **5a**, and **7**, is summarized in Table III.

An investigation of the minor aminoglycosides coproduced with neomycin by *Streptomyces fradiae* revealed a compound termed "component G", which was identified as a diaminodideoxyhexosyl-*myo*-inositol,[17] and by analogy to the studies reported here is most likely 2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl-1-*O*-D-*myo*-inositol.

Whereas *myo*-inositol is a precursor in the biosyntheses of the 2-deoxystreptamine-related streptidine and actinamine,[18] which are the carbocyclic components of streptomycin and spectinomycin, respectively, *Streptomyces fradiae* is known not to utilize *myo*-inositol for the synthesis of 2-deoxystreptamine[17,18] in neomycin. The gentamicin-producing micromonospora species are expected to generate 2-deoxystreptamine by the same pathway as used by *S. fradiae*. The biosynthetic routes used by Streptomycetes in the conversion of D-glucose to streptidine and actinamine are indeed very different from the pathway followed by *S. fradiae* in the synthesis of 2-deoxystreptamine[18] so that "component G" and X-14847 appear to be entirely parenthetic to the biosynthesis of

neomycins and gentamicins, respectively.

Experimental Section

Cupra B Solution. The following is a significant simplification of the original procedure.[11] A graduated cylinder (500 mL) filled with a long gas-inlet tube and magnetic stirrer was filled with copper powder (Alfa, 10 μm, 8 g), concentrated ammonium hydroxide solution (500 mL), and glycerol (0.5 g). The cylinder was immersed in an ice bath and covered with a loosely fitting stopper. A stream of oxygen was passed through a large wash bottle containing concentrated ammonium hydroxide solution and then through the cylinder content.

Cooling, stirring, and oxygenation were continued until virtually all copper was dissolved. The resulting cuprammonium solution was carefully decanted into a well-sealable bottle. Cupra B contains 15.0 ± 0.1 g of copper (0.235 mol) and 240 ± 5 g of ammonia (14.1 mol) per liter. The required copper ion concentration was ascertained on the basis of undissolved copper and confirmed complexometrically. The ammonia concentration (Kjeldahl) was invariably too low at this stage and required additional saturation. The final solution was stored in the refrigerator. Optical rotations were measured in 10-cm cells with a Perkin-Elmer spectropolarimeter, using approximately 0.02 M solutions.

2-(Acetylamino)-2-deoxy-α-D-glucopyranosyl-1-*O*-D-*myo*-inositol Octaacetate (12a). A suspension of X-14847 (10 mg) in pyridine (0.3 mL) and acetic anhydride (0.2 mL) was agitated for 18 h. The resulting solution was evaporated to dryness. The residue was redissolved in aqueous ethanol and the solution evaporated. The dried residue was taken up in dichloromethane and the solution filtered and evaporated to yield a white amorphous powder: ^{1}H NMR (CDCl$_3$) δ 1.92 (s, 1 Ac), 1.97 (s, 3 Ac), 1.98 (s, 2 Ac), 2.01, 2.09, 2.28 (3 s, 3 Ac), 4.00 ~4.30 (m, 5 H), 4.95 ~5.07 (m, 4 H), 5.11 (t, H5, $J_{4,5} = J_{5,6}$ = 10 Hz), 5.48, 5.51 (2 t, H4 and H6, $J_{3,4} = J_{4,5} = J_{5,6} = J_{1,6}$ = 10 Hz), 5.53 (d, NH), 5.59 (t, H2, $J_{1,2} = J_{2,3}$ = 3 Hz).

2-[(5-Bromo-2,4-dinitrophenyl)amino]-2-deoxy-α-D-glucopyranosyl-1-*O*-D-*myo*-inositol Octaacetate (13a). To a solution of X-14847 (350 mg) and sodium hydrogen carbonate (350 mg) in water (3.5 mL) were added 1-bromo-3-fluoro-4,6-dinitrobenzene[15] (240 mg) and acetone (3.5 mL). The mixture was shaken at room temperature overnight, the resulting yellow paste was repeatedly dissolved in pyridine, and the solution was evaporated to remove water. The residue was dissolved in pyridine (2 mL), and the solution cooled in an ice bath, mixed with acetic anhydride (8 mL), and kept overnight at room temperature. The mixture was concentrated to dryness, crystallized from 2-propanol, and recrystallized repeatedly from the same solvent to give yellow needles: mp 144 °C; [α]$_D$ 27.6° (*c* 0.2, 2-propanol); IR (KBr) 3330 (NH), 1758 (C=O), 1612 (Ar), 1577, 1370 (NO$_2$), 1225 (COC), 1045 (COC) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.60, 1.82, 1.93, 1.98, 2.01, 2.05, 2.13, 2.35 (8 s, 3 H each, 8 Ac), 3.80~4.50 (m, 5 H), 4.90~5.30 (m, 5 H), 5.51 (t, H4 and H6, $J_{4,5} = J_{5,6}$ = 10 Hz), 5.64 (t, H2, $J_{1,2} = J_{2,3}$ = 3 Hz), 7.21 (s, H6 of aryl), 8.46 (d, NH, $J_{2',NH}$ = 10 Hz), 8.95 (s, H3 of aryl).

Anal. Calcd for C$_{34}$H$_{40}$BrN$_3$O$_{22}$ (mol wt 922.61): C, 44.26; H, 4.37; N, 4.55. Found: C, 44.01; H, 4.39; N, 4.66.

Crystallographic Analysis. **13a** exhibited space group $P2_12_12_1$ with unit-cell dimensions a = 13.930 (3), b = 15.332 (5),

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(16) (a) D. E. Dorman, S. J. Angyal, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 1351 (1970); (b) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, p 458.

(17) P. L. Claes, F. Compernolle, and H. Vanderhaeghe, *J. Antibiot.*, **27**, 931 (1974).

(18) K. L. Rinehart, Jr., and R. M. Stroshane, *J. Antibiot.*, **29**, 319 (1976).

c = 22.127 (4) Å and d_{calcd} = 1.296 g cm^{-3} for Z = 4. The data were corrected for absorption (μ(Cu Kα) = 20.0 cm^{-1}). Diffraction data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination) using a crystal with the dimensions 0.10 × 0.20 × 1.0 mm.

Of the 3575 independent reflections for θ <57°, 2531 had intensities significantly greater than background [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[19] and was

refined by block-diagonal least squares in which the matrix was partitioned into two blocks. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.114 and wR = 0.127 for the 2531 observed reflections. The final difference map had no peaks greater than ±0.6 e A^{-3}.

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Totally Synthetic Steroid Heterocycles. 9.[1] Straightforward and Stereocontrolled Synthesis of Stereoisomeric 16-Thia-*D*-homoestrane Derivatives

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A simple preparative route for the total synthesis of stereoisomeric 16-thia-*D*-homoestrogens is described. The key step involves a novel annelation method utilizing a cationic cyclization reaction induced by sulfur participation. By this route, 16-thia-*D*-homoestradiol and 16-thia-*D*-homoestrone 3-methyl ethers are conveniently prepared in only four or five steps by starting from 2-methyl-5-thiacyclohexane-1,3-dione.

In a recent paper, we reported that seco compounds **4** and **5** under solvolytic conditions are capable of undergoing entirely stereospecific cyclization leading in a single step to cyclized products **7** and **9**, respectively, in good yield (Scheme I). The structures have been established by X-ray crystallographic analyses[2] with further chemical and spectroscopic evidence. This result undoubtedly suggests that the novel annelation process is based on cationic olefin cyclization reaction via sulfur participation. The stereochemical courses of both solvolytic cyclizations are thus illustrated as shown in Scheme I. This procedure provides a convenient preparative route to possible biologically interesting 16-thia-*D*-homoestrogens. In the present paper, we report a short stereocontrolled synthesis of 16-thia-*D*-homoestradiol and 16-thia-*D*-homoestrone 3-methyl ethers and their stereoisomers by this methodology.

The key intermediate seco diols **4a** and **5a** were, in practice, prepared together by complete hydride reduction of the already known seco dione **1**,[3] readily available from 2-methyl-5-thiacyclohexane-1,3-dione and [(6-methoxy-1,2,3,4-tetrahydronaphthylidene)ethyl]isothiuronium acetate (Scheme II). Various aluminum hydrides were used for this reduction. However, the best method for producing both diols in high yields was reduction of **1** with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) in benzene and then allowing the mixture to stand at room temperature for 7 h. The crude product was purified by preparative high-performance liquid chromatography (LC) on silica gel columns, giving about 40% each of **4a** and **5a** along with small amounts of **6a**. The stereochemistry assigned to these epimers was confirmed by
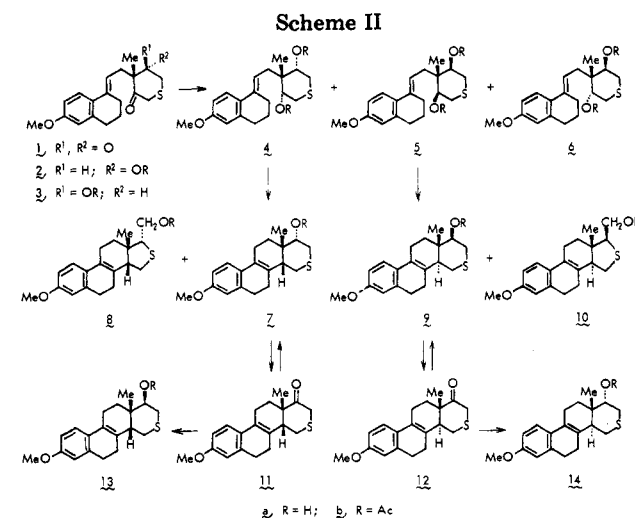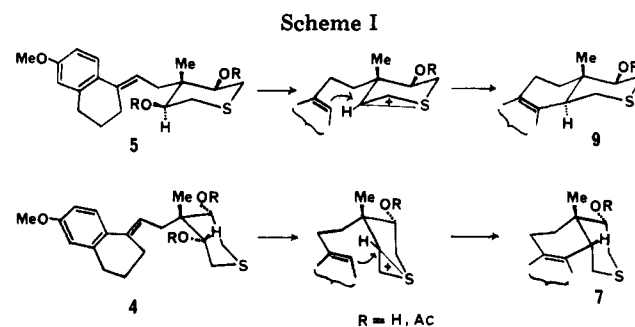
identification with those derived from the previously established seco ketol derivatives **2** and **3** (see Experimental Section).

Treatment of **4a** with glacial acetic acid in the presence of 1 equiv of methanesulfonic acid (MsOH) at 55–60 °C for 2.5 h effected facile ring closure to afford C/D-cis

Scheme I

R = H, AC

Scheme II

1, R^1, R^2 = O
2, R^1 = H; R^2 = OR
3, R^1 = OR; R^2 = H

a, R = H; b, R = Ac

(1) Part 8: Terasawa, T.; Okada, T. *Tetrahedron Lett.* 1980, 21, 2549.
(2) Ultimately, X-ray analyses were undertaken on **14b** and its rearranged derivative, thereby confirming the assigned structures for the compounds of this series. The X-ray data will shortly be submitted for publication in *Cryst. Struct. Commun.*
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