Synthesis of a Triazole Homo-C-nucleoside

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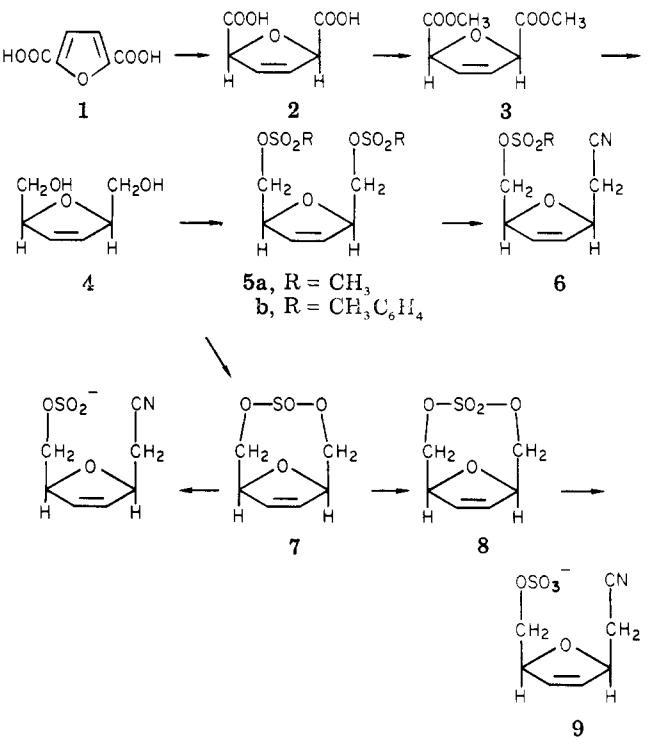
The present paper describes a totally synthetic triazole homo-C-nucleoside. One sequence directed toward this compound started by reducing dimethyl *cis*-2,5-dihydrofuran-2,5-dicarboxylate to *cis*-2,5-bis(hydroxymethyl)-2,5-dihydrofuran with lithium borohydride. The diol could be converted to the dimesyl derivative, the ditosylate, or the cyclic sulfite. None of these compounds reacted with cyanide ion to form the 2-(cyanomethyl) derivative or to form 2,5-bis(cyanomethyl)-2,5-dihydrofuran. This first approach was put aside at this point, so that the planned conversion of the cyclic sulfite by oxidation to the corresponding cyclic sulfate was left untried. The second sequence, which was brought to completion, made use of 2,3,4,4-tetrachloro-8-oxabicyclo[3.2.1]-octa-2,6-diene as the starting material. This with lithium alminum hydride plus lithium hydride yielded 3-chloro-8-oxabicyclo[3.2.1]octa-2,6-diene, which on hydroxylation with hydrogen peroxide and osmium tetraoxide gave 3-chloro-*exo-cis*-6,7-dihydroxy-8-oxabicyclo[3.2.1]oct-2-ene and by combination with acetone 3-chloro-*exo-cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo[3.2.1]oct-2-ene. Ozonolysis in methanol solution followed directly by borohydride reduction produced methyl 2,3-*O*-isopropylidene-β-ribofuranosylacetate. Condensation of the corresponding lactone with aminoguanidine formed 3-[(2,3-*O*-isopropylidene-β-ribofuranosyl)methyl]-5-amino-1,2,4-triazole, and finally acid hydrolysis removed the protective isopropylidene group and yielded the desired homo-C-nucleoside, 3-(β-ribofuranosylmethyl)-5-amino-1,2,4-triazole hydrochloride. Several derivatives of the above-mentioned lactone carrying different functions on the carbon next to the carbonyl group were also prepared.

C-Nucleosides[1] are nucleosides in which the sugar glycosidic position is connected to the pendant heterocyclic base by way of a carbon atom instead of a nitrogen atom. Syntheses in this area often have relied on derivatives of natural pentoses or other sugars as starting materials. We now describe a total synthesis that is independent of such sugars and that opens a convenient way to a variety of C-nucleosides and related compounds.[2]

One of the approaches that we explored sought to reach a key intermediate, lactone **19**, by starting with furan-2,5-dicarboxylic acid (**1**). Partial reduction of **1** with sodium amalgam gave *cis*-2,5-dihydrofuran-2,5-dicarboxylic acid (**2**,[3,4] Scheme I). Further reduction of diester **3** with lithium borohydride led to glycol **4**, which could be smoothly tosylated or mesylated to the disulfonates **5**. But the next step, treatment of **5** with cyanide ion to form either the mononitrile **6** or the corresponding dinitrile, failed. The S_N2 activation that the sulfonate functions would be expected to impart to the methylene groups should also be provided by the cyclic sulfate function as in **8**. Furthermore, we anticipated advantages in using **8**, first because the restraints introduced by the sulfate ring would maintain a geometry favorable to backside S_N2 attack of cyanide and second because of the expectation that reaction of the cyclic sulfate **8** would stop automatically at the monocyano stage, as in **9**, which was a more convenient intermediate on the way to lactone **19** than the dicyano compound. Accordingly, we prepared the cyclic sulfite **7**,[5] planning to obtain the sulfate **8** by oxidation.[5,6] En route, the possibility of the use of the cyclic sulfite **7** to alkylate cyanide was tested.[5-7] The results, however,

Scheme I



were negative, either because attack on sulfur was preferred to attack on carbon[5-7] or because elimination involving a bridgehead hydrogen in **7** occurred faster than substitution. We did not go as far as the cyclic sulfate, since at this point we set aside the first approach in favor of another that was progressing smoothly and showing considerable promise.

The starting point in this synthesis was the tetrachlorobicyclo compound **10**,[8,9] which was readily prepared from furan and tetrachlorocyclopropene. A mixture of lithium aluminum hydride and lithium hydride in refluxing

(1) An incomplete list of reviews and leading references would include the following: Buchanan, J. G.; Edgar, A. R.; Power, M. J.; Williams, G. C. *Carbohydr. Res.* **1977**, *55*, 225. Chang, C.-D.; Hullar, T. L. *Ibid.* **1977**, *54*, 217. Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 111.

(2) A preliminary report describing some of our work has appeared. See: Gensler, W. J.; Chan, S.; Ball, D. B. *J. Am. Chem. Soc.* **1975**, *97*, 436.

(3) Hill, H. B.; Wheeler, A. S. *Am. Chem. J.* **1901**, *25*, 463. Electrolytic reduction at a mercury electrode could offer advantages but was not tried. Cf.: Cypher, G. A., III. Master of Science Dissertation, University of Notre Dame, 1948.

(4) Gagnaire, D.; Monzeglio, P. *Bull. Soc. Chim. Fr.* **1965**, 474.

(5) Breslow, D. S.; Skolnik, H. "Multi-Sulfur and Sulfur and Oxygen Five- and Six-Membered Heterocyclics": Interscience: New York, 1966. Lichtenberger, J.; Hincky, J. *Bull. Soc. Chim. Fr.* **1961**, 1495.

(6) Kaiser, K. T.; Panar, M.; Westheimer, F. H. *J. Am. Chem. Soc.* **1963**, *85*, 602. Baker, W.; Burrows, B. F. *J. Chem. Soc.* **1961**, 2257.

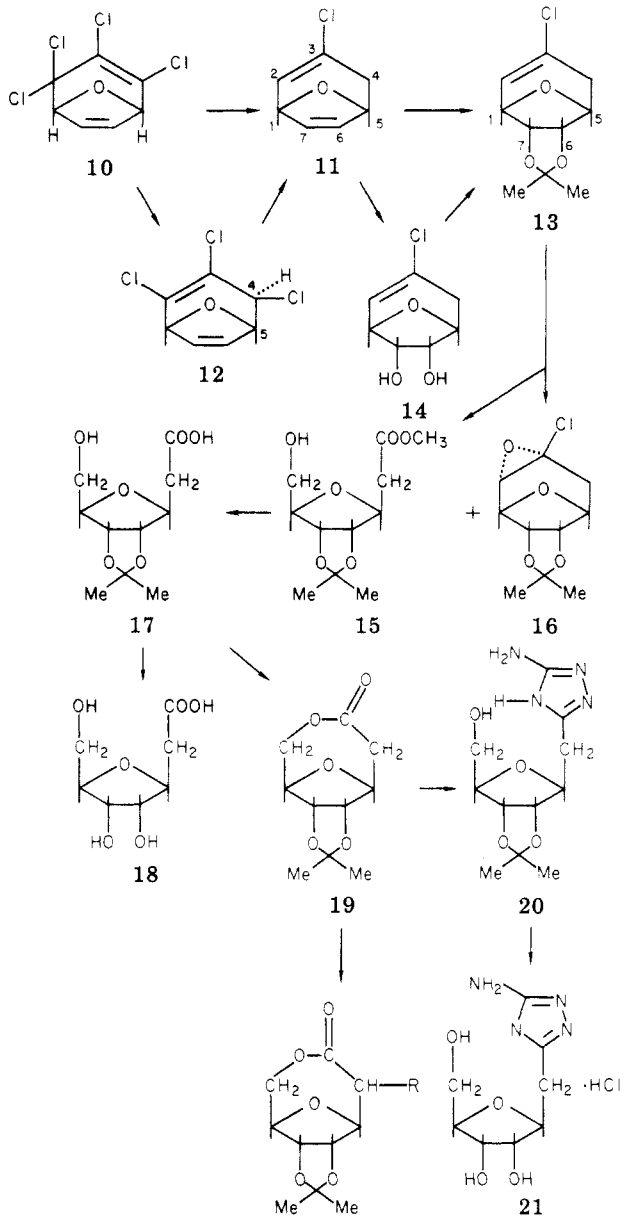
(7) Van Woerden, H. F. *Chem. Rev.* **1963**, *63*, 557. Tillet, J. G. *Ibid.* **1976**, *76*, 747. Voss, W.; Blanke, E. *Justus Liebigs Ann. Chem.* **1931**, *485*, 258. Tillet, T. G. *Int. J. Sulfur Chem., Part C* **1971**, *6C*, 23. Anderson, K. K. In "Comprehensive Organic Chemistry"; Jones, D. N., Ed.; Pergamon Press: New York, 1979; Vol. 3, p 367.

(8) Law, D. C. F.; Tobey, S. W. *J. Am. Chem. Soc.* **1968**, *90*, 2376.

(9) Compounds **10-22** are all racemic.

0022-3263/81/1946-3407$01.25/0

Scheme II



22a, R = Li;
reagent = $(CH_3)_3CLi$
b, R = CHO;
reagent = C_6H_5OCHO
c, R = $COOCH_3$;
reagent = $ClCOOCH_3$
d, R = Br; reagent = Br_2
e, R = $CSNHCOOC_2H_5$;
reagent = $SCNCOOC_2H_5$
f, R = SC_6H_5;
reagent = $C_6H_5SSC_6H_5$

tetrahydrofuran removed three of the four chloro groups and furnished monochloro derivative **11** (Scheme II). Double-resonance NMR results obtained for compound **13**, the next in the sequence, served to locate the surviving chlorine on the 3-position as shown. The yield of **11** was lower in the absence of lithium hydride. Stepwise dechlorination was possible by switching to ether as the solvent, with trichloro compound **12** obtained as the product. By replacing the higher boiling tetrahydrofuran solvent, two more chloro groups could be removed from **12** to give the same monochloro compound **11** as before.

The *endo*-chloro stereochemistry assigned in trichloro compound **12** was based on the nuclear magnetic resonance splitting pattern obtained for the newly introduced *exo*-hydrogen at position 4. A Dreiding model of the near-rigid [3.2.1]bicyclo system in **12** shows that the dihedral angle between this *exo*-hydrogen and the vicinal bridgehead hydrogen at position 5 is approximately 30°, so that the anticipated splitting from the Karplus relation would be about 6 Hz. In the model with the hydrogen endo at position 4, the dihedral angle is 90°, and the spin–spin coupling should be close to zero. The observed value, $J_{4,5}$ = 6 Hz, fits the *exo*-hydrogen orientation much better than the *endo*-hydrogen orientation and accordingly supports the 4-*endo*-chloro stereochemistry.

We look upon the lithium aluminum hydride reduction as a series of hydride insertions into vinyl chloride unsaturations, each accompanied by loss of an allylic chloro group and a 1,3-shift of the double bond. The data are not sufficient to show whether all the stages are synfacial or are concerted.[10] Whatever the detailed mechanism, examination of models suggests that the bulky reducing reagent could approach and deposit its hydrogen atom more readily from the more open exo side of the bicyclic system than from the endo side. Finding the added hydrogen atom on the exo side of trichloro compound **12** is consistent with this observation.

Hydroxylation of monochloro compound **11** using hydrogen peroxide in the presence of osmium tetraoxide in acetone as solvent occurred both regiospecifically and stereospecifically. Most of the product already had the vicinal hydroxy groups masked with isopropylidene as in **13**. Whatever material emerged with free hydroxyl groups (**14**) was easily converted to the isopropylidene derivative with 2,2-dimethoxypropane.

We anticipated that the *cis*-hydroxyl groups would be on the exo side of the molecule as shown in **13** and **14** because approach of the large osmium reagent would be expected to be easier from the more exposed exo side than from the endo side. That this orientation was correct was established by the NMR splitting pattern shown by the hydrogens at positions 1, 7, 6, and 5. A model indicates that the dihedral angle between the vicinal hydrogens at positions 1 and 7 and at positions 6 and 5, when the hydroxyl groups are endo, is approximately 30°. When the two hydroxyls are exo, the angle is close to 90°. Accordingly, spin–spin coupling between these two pairs of vicinal hydrogens should be appreciable in the *endo*-hydroxyl arrangement but quite small in the exo arrangement. With this in mind, the clean-cut AB splitting pattern for the vicinal hydrogens at positions 6 and 7 is consistent with the assigned *exo*-hydroxyls but not with the endo orientation.

The lone chloro group in **13** did not survive catalytic hydrogenation, which instead of furnishing the potentially useful *exo-cis*-6,7-(isopropylidenedioxy)-3-chloro-8-oxabicyclo[3.2.1]octane gave only chlorine-free *exo-cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo[3.2.1]octane.

Ozonolysis of vinyl chloride **13** in methanol solvent followed directly by borohydride reduction led to methyl ester **15**. As long as the hydrogen chloride produced was removed as it was formed, the ozonolysis, although slow,[11] proceeded smoothly. The desired product, methyl 2,3-

(10) Other lithium aluminum hydride 1,3-reduction–eliminations in allylic systems have been reported. See, inter alia: Jefford, C. W.; Sweeney, A.; Delay, F. *Helv. Chim. Acta* **1972**, *55*, 2214. Bordwell, F. G.; Mecca, T. G. *J. Am. Chem. Soc.* **1972**, *94*, 5829. Petitpierre, J.-C. Doctoral Dissertation, Boston University, 1969. Jacobs, T. L.; Wilcox, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 2240. Fleet, G. W. J. In "Organic Reaction Mechanisms"; Knipe, A. C., Watts, W. E., Eds.; Wiley: New York, 1978; p 386.

(11) Bailey, P. S. "Ozonation in Organic Chemistry"; Academic Press: New York, 1978; Vol. I. This is Vol. 39 of "Organic Chemistry"; Blomquist, A. T., Wasserman, H. H., Ed.

isopropylidene-β-ribofuranosylacetate (15),[12,13] was obtained in 72% yield accompanied by small amounts of an α-chloro epoxide 16 side product.[14] First-order analysis of a 300-MHz nuclear magnetic resonance spectrum of methyl ester 15 was consistent with the structure as given (see Experimental Section). Among other things, the NMR data showed that no epimerization had occurred at the sugar glycosidic position during the ozonolysis–reduction sequence, that is, that the β-ribofuranoside configuration has been preserved. The observed 0.18-ppm difference in the chemical shifts of the isopropylidene *gem*-dimethyl groups is associated with related isopropylidene β-ribonucleosides but not with the smaller difference (<0.10 ppm) for the α epimers.[15] Although this kind of shift difference is not as marked in epimeric isopropylidene-*C*-ribosyl derivatives, the greater difference, ca. 0.18, is again noted for the β configuration.[13] Further, the observed $J_{2,3}$ = 6.7 Hz (ribose numbering) fits better with a nonzero dihedral angle between the vicinal *cis*-2,3-hydrogens than with a zero angle, i.e., better with an approximately staggered conformation at the ribose 2,3-fusion position than with the eclipsed arrangement. Thus neither the four ribose ring-carbon atoms nor the fused dioxolane 1,3,4,5-positions are planar.[16] Another structural feature concerns the possibility that the hydroxyl and the ester carbonyl groups in 15 through operation of an intramolecular hydrogen bond are constrained to face each other. In fact, the NMR data can be accommodated by this kind of conformation, but the arguments are not unequivocal, and no firm conclusion was reached.

The synthesis continued by saponification of ester 15 to the corresponding acid 17. The ease with which the saponification occurred suggested participation of the neighboring hydroxyl group with formation of lactone 19 as an intermediate. The free acid 17 as well as the sodium salt were isolated and characterized; also, removal of the isopropylidene group furnished the expected β-ribosylacetic acid 18. Dehydration of hydroxy acid 17 with acetic anhydride in hot pyridine closed the ring to form the lactone 19, which has since been obtained in a different way.[17] The last stages involved condensation of this lactone with aminoguanidine[18] to form triazole 20, followed by acid hydrolysis to remove the isopropylidene group. In order to designate the final product, 5-(β-ribofuranosylmethyl)-3-amino-1,2,4-triazole hydrochloride (21), in a way that would serve to differentiate it from the more familiar C-nucleosides in which the glycosyl carbon atom is bonded directly to a ring carbon atom of the N heterocycle, we have proposed the name, homo-C-nucleoside. To the best of our knowledge, triazole 21 is the first homo-C-nucleoside to be described. In the several biological assays tried, this novel nucleoside proved to be devoid of activity. Whether this will prove to be generally true for other homo-C-nucleosides remains to be seen.

Our original program called for synthesizing not only homo-C-nucleoside 21 but also a number of other C-nucleosides. The syntheses were designed so as to proceed through lactone 19, in which the lactone bridge ensured maintenance of the β-glycosidic configuration as late as possible. The lactone proved to be a rich and convenient source of derivatives 22, all of which were intended to serve as precursors for the C-nucleosides. However, our time limitation did not permit us to complete this part of the work.[19] The Experimental Section records procedures for synthesizing the substituted lactones 22, where R is formyl, methoxycarbonyl, bromo, ethoxycarbonyl, thiocarbamyl, and phenylthio.

Experimental Section

General Methods. Analyses for elements and determinations of molecular weight by vapor pressure measurements were performed by Galbraith Laboratories, Inc., and by Chemalitics Inc. Most of the nuclear magnetic resonance spectra were determined with 60-MHz instruments (Varian A-60, JEOL 60 HL, and Hitachi Perkin-Elmer R-24). The thin-layer chromatograms were run on commercial plates precoated with a 0.25-mm layer of silica gel. Column chromatography made use of silica gel 60 (70–230 mesh) from Brinkmann Instruments, Inc. Temperatures are not corrected. All reactions were repeated at least once to check for reproducibility.

Furan-2,5-dicarboxylic Acid (1). This compound, melting at 310–311 °C (sublimes) [lit.[20] mp 310 °C (sublimes)] was prepared according to published directions.[20]

***cis*-2,5-Dihydrofuran-2,5-dicarboxylic Acid (2) and Its Methyl Ester (3).** Reduction of furan-2,5-dicarboxylic acid (1) with sodium amalgam[21] afforded *cis*-2,5-dihydrofuran-2,5-dicarboxylic acid (2):[3,4] mp 147–148 °C dec (lit. mp 149 °C); 24% yield. Better results were obtained by modifying the procedure as follows. A solution of furan-2,5-dicarboxylic acid (120 g, 0.640 mol) in water (1 L) containing 75 g (0.71 mol) of sodium carbonate was held at −8 to 0 °C and, while a rapid stream of carbon dioxide was bubbled through the stirred mixture, 3% sodium amalgam (3.50 kg, containing 4.56 mol of sodium) was added in small portions. After 3 h or when acidification of a test aliquot no longer precipitated starting material, the aqueous phase was filtered. Acidification of the filtrate to pH 2–3 with concentrated hydrochloric acid was followed by 96 h of continuous ether extration. The yellow crude product obtained from the dried extract was crystallized from ether–petroleum ether to give 2,5-dihydrofuran-2,5-dicarboxylic acid (62 g, 51%; mp 127–130 °C) as a mixture of cis and trans isomers.

The acid was esterified by addition of 4.70 g (29.8 mmol) in small portions to a stirred solution of diazomethane (ca. 3.3 g, 79 mmol) in 220 mL of ether at 0 °C. After being allowed to stand overnight at −5 °C, the solution was stripped of solvent, and the residual yellow liquid was distilled through a short-path column. According to estimates based on the intensity of the NMR signals at δ 5.44 (trans) and 5.32 (cis)[4] for the hydrogen atoms at positions 2 and 5, the *cis*-methyl ester obtained in this way (5.53 g, 100%) contained about 5% of the trans isomer.

Esterification of pure *cis*-diacid 2 afforded homogeneous dimethyl *cis*-2,5-dihydrofuran-2,5-dicarboxylate (3): NMR ($CDCl_3$) δ 6.02 (s, 2, ethylenic H's), 5.32 (s, 2 H's at positions 2 and 5), 3.75 (s, 6 H, OCH_3's). From the measured dihedral angle (60–65°) between the ethylenic H's and their vicinal neighbors at positions 2 and 5, the Karplus approximation suggests a coupling of ca. 2 Hz. However, the electronegativity of the ring oxygen as well as of the carbonyl groups decreases the coupling,[22] so that the signals

(12) Ohrui, H.; Emoto, S. *J. Org. Chem.* **1977**, *42*, 1951.
(13) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.
(14) Gensler, W. J.; Chan, S.; Ruchirawat, S. *J. Org. Chem.* **1981**, *46*, 1750.
(15) Imbach, J.-L.; Barascut, J. L.; Kam, B. L.; Tapiero, C. *Tetrahedron Lett.* **1974**, 129. Rayner, B.; Tapiero, C.; Imbach, J.-L. *J. Heterocycl. Chem.* **1973**, *10*, 417.
(16) Abraham, R. J.; Hall, L. D.; Hough, L.; McLauchlan, K. A. *J. Chem. Soc.* **1962**, 3699; **1963**, 748. These authors have suggested that the same is true for the fused five-membered rings in 1,2-isopropylidene derivatives of furanoses.
(17) Noyori, R.; Sato, T.; Hayaka, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2561.
(18) Ried, W.; Valentin, J. *Chem. Ber.* **1968**, *101*, 2117. Also note the paper by: Just, G.; Reader, G. *Tetrahedron Lett.* **1973**, 1525.
(19) The utility of this general approach has since been amply demonstrated (see ref 17). Also compare other relevant work on homo-C-nucleosides which has appeared more recently: Secrist, John A., III. *J. Org. Chem.* **1978**, *43*, 2925. Sato, T.; Marunouchi, K.; Noyori, R. *Tetrahedron Lett.* **1979**, 3469.
(20) Cope, A. C.; Keller, R. T. *J. Org. Chem.* **1956**, *21*, 141.
(21) Audrieth, L. F. *Inorg. Synth.* **1939**, *1*, 5.
(22) (a) Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, 1964. (b) Bothner-by, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195. (c) Booth, H. "Progress in Nuclear Magnetic Resonance Spectroscopy"; Pergamon Press: Oxford, 1969; Vol. 5, p 149.

appear as singlets instead of doublets.

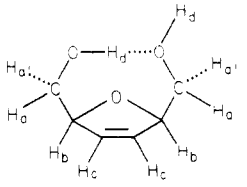
***cis*-2,5-Bis(hydroxymethyl)-2,5-dihydrofuran (4).** Dimethyl 2,5-dihydrofuran-2,5-dicarboxylate (**3**; 15.1 g, 81.0 mmol; 95% cis) in tetrahydrofuran (100 mL) that had been distilled from lithium aluminum hydride was added over a period of 20 min to a stirred, 0 °C suspension of lithium borohydride (2.30 g, 106 mmol) in 15 mL of tetrahydrofuran. The heterogeneous mixture was refluxed for 5.5 h.

After water (5 mL) was added dropwise to the reaction mixture at 0 °C, it was filtered, and the solids were washed with chloroform. The combined organic solutions were dried and then distilled to give 5.2 g (49%) of colorless *cis*-2,5-bis(hydroxymethyl)-2,5-dihydrofuran [**4**, bp 86–87 °C (0.05–0.07 mm)], estimated to contain 5% of the trans isomer.

Reduction of homogeneous *cis*-diacid **2** afforded *cis*-diol **4**, bp 80 °C (0.05 mm).

Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.12; H, 7.74.

The infrared absorption spectrum (neat) showed maxima at 3420 and 1630 cm^{-1}. The NMR ($CDCl_3$) showed the following: δ 5.85 (s, $J_{b,c} \simeq 0$ Hz, 2 H_c's), 4.95 (br s, 2 H_b's), 4.5 (br s, 2 H_d's), 3.97 (dd, $J_{a,a'} = 12$ Hz, $J_{a,b} \simeq J_{a',b} \simeq 1.5$ Hz, 2 H's, a or a'), 3.58 (dd, $J_{a,a'} = 12$, $J_{a,b} \simeq J_{a',b} = 1.5$ Hz, 2 H's, a or a'). Adding 1 drop

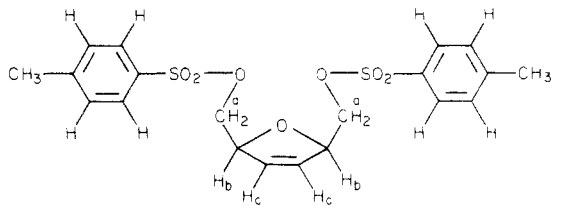


of deuterated water eliminated the 4.5-ppm signal. The hydroxyl groups rapidly exchange their hydrogen bonding roles, so that the two hydroxymethyl groups are equivalent and the whole molecule has a time-averaged plane of symmetry. The nonequivalent H_a and $H_{a'}$ develop two doublets as an AB quartet. Since the measured dihedral angle with the H_b's is 55–60°, a further coupling of ca. 2–3 Hz might be expected. But the electron-withdrawing oxygen atoms would reduce the coupling[22] to the value observed.

***cis*-2,5-Bis[(tosyloxy)methyl]-2,5-dihydrofuran (5b).** Recrystallized *p*-toluenesulfonyl chloride (9.5 g, 50 mmol) was added at 0 °C to a solution of *cis*-diol **4** (3.0 g or 23 mmol) in pyridine (50 mL) that had been dried over potassium hydroxide. The solution was stirred at 0 °C for 1 h and then at room temperature overnight. Solids were separated and rinsed on the funnel with ether. The combined organic solutions were shaken with portions (3 × 80 mL) of 10% hydrochloric acid and then with water. The product, most of which had precipitated, was collected and dried under reduced pressures. Additional product was obtained by processing the filtrate. Crystallization of the yellow solids from absolute ethanol gave 6.2 g (62%) of white *cis*-2,5-bis[(tosyloxy)methyl]-2,5-dihydrofuran (**5b**), mp 105.5–106 °C. Further recrystallizations raised the melting point to 107.5–108 °C.

Anal. Calcd for $C_{20}H_{22}O_7S_2$: C, 54.77; H, 5.05. Found: C, 54.49; H, 5.05.

NMR ($CDCl_3$) δ 7.81 (d, $J = 7.5$ Hz, 4 Ar H's), 7.41 (d, $J = 7.5$ Hz, 4 Ar H's), 5.86 (s, $J_{b,c} \simeq 0$ Hz, 2 H_c's), 5.00 (br t, $J_{a,b} = 3.5$ Hz, 2 H_b's), 4.02 (d, $J_{a,b} = 3.5$ Hz, 4 H_a's), 2.45 (s, 6 H, Ar CH_3's).



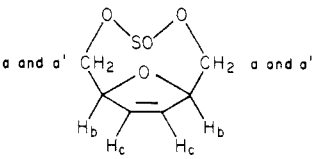
***cis*-2,5-Bis[(mesyloxy)methyl]-2,5-dihydrofuran (5a).** Methanesulfonyl chloride (6.7 mL, 77 mmol) was added by drops to a stirred, 0 °C solution of *cis*-2,5-bis(hydroxymethyl)-2,5-dihydrofuran (**4**; 5.0 g, 39 mmol) in 200 mL of dichloromethane and triethylamine (18 mL). The heterogeneous mixture was stirred at 10 °C for 20 min. It was then shaken with 100-mL portions of ice–water, 10% hydrochloric acid, 10% bicarbonate, and finally water. The solution was dried and evaporated, and the residual brown oil was crystallized from absolute methanol to yield 5.2 g (48%) of *cis*-2,5-bis[(mesyloxy)methyl]-2,5-dihydrofuran (**5a**) as white crystals, mp 59–60 °C.

Anal. Calcd for $C_8H_{14}O_7S_2$: C, 33.56; H, 4.93. Found: C, 33.78; H, 5.01.

Cyclic Sulfite of *cis*-2,5-Bis(hydroxymethyl)-2,5-dihydrofuran (7). Thionyl chloride (1.7 g, 14 mmol) was added dropwise to a stirred solution of *cis*-diol **4** (1.00 g, 7.7 mmol, of 95% pure material) in 10 mL of dry pyridine at 15 °C. After 30 min at −15 °C, the heterogeneous mixture was diluted with 60 mL of chloroform and then washed with portions (3 × 20 mL) of 10% hydrochloric acid and once with 10% bicarbonate solution. Removal of all solvent from the dried solution left a yellow solid, which on crystallization from acetone–petroleum ether furnished 0.45 g (40%) of white cyclic sulfite **7**, mp 156–157 °C dec.

Anal. Calcd for $C_6H_8O_4S$: C, 40.91; H, 4.55; S, 18.18. Found: C, 40.99; H, 4.72; S, 18.42.

The cyclic sulfite showed a single spot on thin-layer chromatography (R_f 0.55 with 4:1 methanol–acetone). The spectral data are as follows: IR (KBr pellet) 3195, 1350, 1200, 1100 cm^{-1}; NMR ($CDCl_3$) δ 5.92 (s, $J_{b,c} \simeq 0$ Hz, 2 H_c's), 4.95 (br s, 2 H_b's), 4.62 (dd, $J_{a,a'} = 13.2$ Hz, $J_{a,b} \simeq 1$ Hz, 2 H_a's), 4.23 (dd, $J_{a,a'} = 13.2$ Hz, $J_{a',b} < 0.5$ Hz, 2 $H_{a'}$'s). On the assumption that the sulfite bridge is



flip-flopping between the exo and endo configurations, the chemical shifts for the methylene a and a′ protons as well as the couplings for $H_{a,b}$ and $H_{a',b}$ must be time averaged. Estimates of the couplings based on the measured dihedral angles of the extreme configurations are 0–4 Hz (100° and 50° dihedral angles) for the H's on the side of the double bond, and 8–1 Hz (20° and 70° dihedral angles) for the H's closer to the ring oxygen. If the configurations are equally populated, the average coupling constants would be 2 and ca. 4 Hz, respectively. These approximate vicinal coupling values would be diminished further under the influence of the electronegativity of the ring oxygen as well as that of the sulfite group.

Attempted Substitution of the Sulfonate Groups in 5a and 5b with Cyanide. A solution of the *cis*-bis(mesyloxy) compound **5a** (0.500 g, 1.75 mmol) in 95% alcohol (4 mL) containing potassium cyanide (0.26 g, 4.0 mmol) was stirred at 55 °C for 4.5 h. Processing this reaction mixture gave only unchanged starting material (**5a**; 0.425 g, 85% recovery). A number of variations in the experimental conditions were tried, including changing the solvent to dimethyl sulfoxide, dimethyl formamide, aqueous acetonitrile, aqueous acetone, and aqueous alcohol, using sodium cyanide instead of potassium cyanide, starting with bis(tosyloxy) derivative **5b** instead of with the bis(mesyloxy) compound, and operating at different temperatures and for different periods, but in every case either practically all the starting material was recovered or tars were formed.

Attempted Ring Opening of Cyclic Sulfite 7 with Cyanide. Dry solvent (15 mL; acetonitrile, dimethyl sulfoxide, dimethyl formamide, pyridine, or ethanol) plus cyclic sulfite **7** (0.40 g, 2.22 mmol) and sodium cyanide (0.12 g, 2.45 mmol) were stirred at various temperatures and for various periods. In all cases the reaction produced tars or returned unchanged starting material **7** (80–90%).

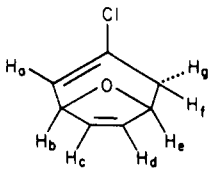
2,3,4,4-Tetrachloro-8-oxabicyclo[3.2.1]octa-2,6-diene (10).[9] Warming a solution of furan (9.8 g, 140 mmol) and tetrachlorocyclopropene (14.0 g, 78.8 mmol) in 20 mL of carbon tetrachloride for 18 h at 79 °C and processing the reaction mixture essentially according to published directions[8] produced the desired starting material **10**, which after crystallizations from hexane was obtained in the form of white crystals: 18.6 g (96%); mp 64–65 °C (lit.[8] mp 59–60 °C). The nuclear magnetic resonance spectrum matched the one described before.

3-Chloro-8-oxabicyclo[3.2.1]octa-2,6-diene (11). A solution of 2,3,4,4-tetrachloro-8-oxabicyclo[3.2.1]octa-2,6-diene (**10**; 40.0

g, 163 mmol) in dry tetrahydrofuran (150 mL) was added dropwise to a stirred slurry of lithium hydride (1.43 g, 179 mmol), lithium aluminum hydride (13.6 g, 358 mmol), and tetrahydrofuran (300 mL with 0.02% water) at 0 °C. After the gray mixture had been refluxed 6 h, it was cooled to 0 °C, diluted with ether (1 L), and treated cautiously with water (18 mL). The solids were collected and rinsed thoroughly on the funnel with ether. The combined ether solutions were dried and stripped of volatile solvents. Distillation of the yellow residual liquid through a short column gave colorless 3-chloro-8-oxabicyclo[3.2.1]octa-2,6-diene: 18.6 g (80%); bp 52–54 °C (1.6 mm).

Anal. Calcd for C_7H_7ClO: C, 58.94; H, 4.91; Cl, 24.91. Found: C, 59.22; H, 5.10; Cl, 25.16.

The product was homogeneous according to thin-layer chromatography (R_f 0.25 with 1:1 chloroform–pentane) and gas–liquid chromatography. The spectral data are as follows: IR (CCl_4) 1630, 1260, 1055, 855 cm^{-1}; NMR ($CDCl_3$) δ 6.53 and 6.03 (2 dd, $J_{b,c} = J_{d,e} = 1.5$ Hz, $J_{c,d} = 5.3$ Hz, 2, H_c and H_d), 6.16 (2 t, $J_{a,f} \simeq J_{a,g} \simeq 1.5$ Hz, $J_{a,b} = 4.5$ Hz, 1, H_a), 4.80 (m, 2, H_e and H_b), 3.05 and 2.75 (two groups of m's, $J_{ag} = 1.5$ Hz, $J_{eg} = 6$ Hz, $J_{f,g} = 16$ Hz, 1, H_g), 1.99 (dd, $J_{a,f} = 1.5$ Hz, $J_{f,g} = 16$ Hz, $J_{e,f} = 0$ Hz, 1, H_f).

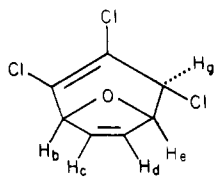


The same reduction could be effected without lithium hydride, but the yields were lower. Sodium hydride alone was ineffective.

2,3,4-*endo*-Trichloro-8-oxabicyclo[3.2.1]octa-2,6-diene (12). The tetrachloro compound **10** (4.9 g, 20 mmol) in ether was added at 0 °C to a stirred suspension of lithium aluminum hydride (0.76 g, 20 mmol) in ether (50 mL). The mixture was refluxed and stirred for 4 h, after which it was quenched at 0 °C with saturated aqueous ammonium chloride. The solids were removed and rinsed, and the combined ether solutions were dried and concentrated. Distillation of the residue gave 3.5 g (83%) of colorless trichloro derivative **12**, bp 61 °C (0.04 mm).

Anal. Calcd for $C_7H_5Cl_3O$: C, 39.75; H, 2.38. Found: C, 39.92; H, 2.60.

The NMR ($CDCl_3$) data are as follows: δ 6.77 (dd, $J_{c,d} = 6.0$ Hz, $J_{b,c} = 1.5$ Hz, 1, H_c), 6.35 (dd, $J_{c,d} = 6.0$ Hz, $J_{d,e} = 1.5$ Hz, 1, H_d), 5.25 (dd, $J_{e,g} = 6.0$, $J_{b,g} = 1.5$ Hz, 1 H_g), 4.83 (m, 2, H_b and H_e). Note that the chemical shift assignments for H_c and H_d may be interchanged.



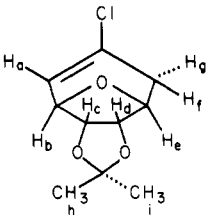
Although the evidence favors the *endo*-chloro assignments, whether the *exo*-chloro isomer can be excluded altogether is not settled. The uncertainty is introduced by noting that different cuts taken during distillation of the trichloro compound **12** show some differences in the pattern of signals at 5.25 ppm which could be interpreted as the result of fractionation, or interconversion and fractionation, of exo and endo forms.

The trichloro compound was recovered unchanged when it was treated with lithium aluminum hydride in refluxing ether, but it was converted to the monochloride **11** when the solvent was refluxing tetrahydrofuran. The trichloro derivative **12** was inert to aqueous silver nitrate as well as to tributyltin hydride[23] in benzene or in mineral oil.

3-Chloro-*exo*-*cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo-[3.2.1]oct-2-ene (13). A 20-mL portion of 30% aqueous hydrogen peroxide (ca. 0.2 mol) was combined with 20 mL of 0.04 M osmium tetraoxide in purified *tert*-butyl alcohol,[24] and the mixture was added to 3-chloro-8-oxabicyclo[3.2.1]octa-2,6-diene (**11**; 20 g, 0.14 mol) dissolved in reagent grade acetone (160 mL) plus ether (40 mL). The brown solution was stoppered and kept at 30–33 °C for 24 h. The filtered mixture was stripped of volatiles, and the yellow residue, after solution in carbon tetrachloride, was washed with portions of 10% aqueous sodium hydroxide until the washings were colorless, then with 1% aqueous hydrochloric acid, and finally with 1% aqueous sodium bicarbonate. The solvent was removed from the dried carbon tetrachloride solution, and the residue was crystallized from ether at −60 °C or from ether–hexane to give 21.2 g (70%) of white 3-chloro-*exo*-*cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo[3.2.1]oct-2-ene (**13**), mp 92–93 °C.

Anal. Calcd for $C_{10}H_{13}ClO_3$: C, 55.42; H, 6.00; Cl, 16.40. Found: C, 55.17; H, 6.06; Cl, 16.64.

Thin-layer chromatography produced only a single spot (R_f 0.59 with 3:2 chloroform–acetone); GLC showed one peak emerging at 1.3 min with the column temperature at 205 °C. The spectral data are as follows: IR (KBr) 1645, 1160, 1070, 975, 850 cm^{-1}; NMR ($CDCl_3$) δ 6.00 (2 t, $J_{a,g} \simeq J_{a,f} \simeq 1.5$ Hz, $J_{a,b} = 5.25$ Hz, 1, H_a), 4.71 and 4.63 (2 d, $J_{c,d} = 6$ Hz, $J_{d,e} = J_{b,c} \simeq 0$, 2 Hz, H_c and H_d), 4.45 (m, 2, H_b and H_e), 2.90 (ddd, $J_{g,a} = 1.5$, $J_{g,e} = 6$ Hz, $J_{g,f} = 18$ Hz, 1, H_g), 2.05 (dd, $J_{f,a} = 1.5$ Hz, $J_{f,g} = 18$ Hz, $J_{f,e} = 0$ Hz, 1, H_f), 1.50 (s, 3, H_h), 1.33 (s, 3, H_i). Decoupling irradiation at



the olefinic chemical shift (6.00 ppm) changed the multiplet at 4.45 ppm to an uneven doublet and largely obliterated the 1.5-Hz splitting in the H_g and H_f signals. This kind of change would be expected for the compound with chlorine at the 3-position as in **13** but would be hard to interpret if chlorine were on the 2-position.

There was some indication that use of a Teflon-coated stirring bar inhibited the hydroxylation.

3-Chloro-*exo*-*cis*-6,7-dihydroxy-8-oxabicyclo[3.2.1]oct-2-ene (14). In some preparations of isopropylidene compound **13**, a small amount of solid precipitated from the alkali-washed carbon tetrachloride solution. After this solid was rinsed with small volumes of 10% sodium hydroxide solution and water, it was crystallized from acetone to give white crystals of 3-chloro-*exo*-*cis*-6,7-dihydroxy-8-oxabicyclo[3.2.1]oct-2-ene (**14**): mp 212–213 °C dec; IR (KBr) 3400, 1650, 815 cm^{-1}.

Anal. Calcd for $C_7H_9ClO_3$: C, 47.59; H, 5.10; Cl, 20.11. Found: C, 47.56; H, 5.17; Cl, 20.20.

It was suspected that the appearance of the dihydroxy compound was related to excessively long storage of the osmium tetraoxide solution at room temperature.

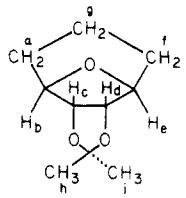
The isopropylidene group could be attached to the *cis*-hydroxy groups in **14** by stirring the compound (0.5 g) in acetone (10 mL) containing 2,2-dimethoxypropane (5 mL) and *p*-toluenesulfonic acid (10 mg) for 19 h at room temperature. Homogeneous isopropylidene product **13** was obtained as white crystals: mp 92–93 °C; 77% yield.

***exo*-*cis*-6,7-(Isopropylidenedioxy)-8-oxabicyclo[3.2.1]octane.** A mixture of monochloro compound **13** (217 mg, 1.00 mmol) and platinum oxide (10 mg) in 25 mL of ethyl acetate was stirred under an atmosphere of hydrogen until no more hydrogen was absorbed (10 min). The mixture was filtered, and the filtrate was stripped of all volatiles. Sublimation of the residue at 90 °C (0.01 mm) gave pure *exo*-*cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo[3.2.1]octane (121 mg, 66%), showing only a single spot on thin-layer chromatography (R_f 0.45 with 4:1 chloroform–acetone) and melting sharply at 61–62 °C.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.21; H, 8.70. Found: C, 65.02; H, 8.62.

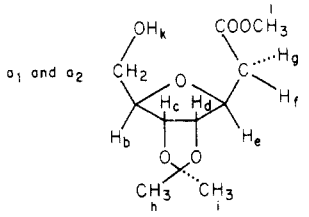
The infrared absorption spectrum (CCl_4) showed the following maxima: 2940, 2860, 1375, 1270 cm^{-1}. The NMR ($CDCl_3$) data are as follows: δ 4.60 (s, $J_{b,c} = J_{d,e} = 0$ Hz, 2, H_c and H_d), 4.23 (br s, 2, H_b and H_e), 1.55 (m, 9, $H_{a,g,f,h}$), 1.35 (s, 3, H_i).

(23) Breslow, R.; Ryan, G. *J. Am. Chem. Soc.* **1967**, *89*, 3073.
(24) Daniels, R.; Fischer, J. L. *J. Org. Chem.* **1963**, *28*, 320. Cf.: Schröder, M. *Chem. Rev.* **1980**, *80*, 187.



The results were essentially the same (70% yield) when the starting material **13** was hydrogenated in the presence of an equal weight of 5% palladium on charcoal.

Methyl 2,3-*O*-Isopropylidene-β-ribofuranosylacetate (15). Ozonolysis followed directly by borohydride reduction converted 3-chloro-*exo*-*cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo[3.2.1]-oct-2-ene (**13**) to pure methyl ester **15** in 72% yield.[2,12-14] Since column chromatography employed as part of purification decreased the yield by about 20%, the chromatography step was generally omitted, once-distilled methyl ester of ca. 92% purity being found satisfactory for the succeeding steps. A first-order analysis of the nuclear magnetic resonance spectrum of the pure ester **15** at 300 MHz confirmed its structure as shown: NMR ($CDCl_3$) δ 4.75 (dd, $J_{b,c}$ = 4.1 Hz, $J_{c,d}$ = 6.7 Hz, 1, H_c), 4.55 (dd, $J_{d,c}$ = 6.7 Hz, $J_{d,e}$ = 5.1, Hz, 1, H_d), 4.29 (m, 1, H_e), 4.09 (q in AX_3 pattern, $J_{b,c} \simeq J_{b,a_1} \simeq J_{b,a_2} \approx 4$ Hz, 1, H_b), 3.73 (m with singlet for CH_3O at 3.7, 5, H_{a_1} and H_{a_2} plus H_l), 3.15 (t, J = 6 Hz, H_k), 2.75 (dd, $J_{f,e}$ = 6.0 Hz, $J_{f,g}$ = 18 Hz, H_f) 2.65 (dd, $J_{g,e}$ = 7.5, $J_{g,f}$ = 18 Hz, H_g), 1.53 (s, 3, H_h), 1.35 (s, 3, H_i). The integration value

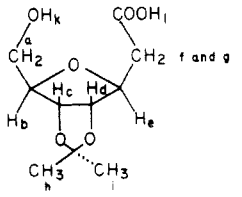


over the δ 3.15–2.65 signals corresponded to three protons. Decoupling irradiation at the δ 2.75 and 2.65 signals (H_g and H_f) changed the H_e multiplet at 4.29 ppm to a broad doublet ($J_{e,d}$ = 5.1 Hz). NMR data published elsewhere[12,13] for methyl ester **15** with benzene as the solvent show chemical shifts that are all upfield[22a,25] from the values given here. Otherwise there is good agreement.

Sodium 2,3-*O*-Isopropylidene-β-ribofuranosylacetate. A solution of pure methyl ester **15** (2.46 g, 0.010 mol) in 100 mL of 0.10 N sodium hydroxide was refluxed for 1 min. The colorless neutral solution was evaporated at room temperature, and the remaining white solid was dried at 30–40 °C (0.01 mm). Crystallization from methanol–acetone afforded 2.46 g (97%) of the desired sodium salt, mp 183–184 °C dec. Infrared maxima (KBr pellet) were noted at 3160 and 1600 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}NaO_6$: C, 47.24; H, 5.95; Na, 9.05. Found: C, 47.49; H, 5.94; Na, 9.16.

2,3-*O*-Isopropylidene-β-ribofuranosylacetic Acid (17). The slow addition of 0.515 mg of 95.0% sulfuric acid (5.00 mmol) to a stirred solution of the sodium salt (2.54 g, 10.0 mmol) in methanol (30 mL) plus acetone (30 mL) precipitated sodium sulfate. The filtered solution (Celite) was stripped of all solvent to leave 2,3-*O*-isopropylidene-β-ribofuranosylacetic acid (**17**; 2.32 g, 100%) as a viscous residue: NMR (CD_3COCD_3) δ 6.32 (s, 2, $H_{k,l}$), 4.81–3.92 (m, 4, H_{b-e}), 3.68 (d with sign of further splitting, $J_{a,b}$ = 3 Hz, 2, H_a), 2.64 (d with sign of further splitting, J_e = 4 Hz, 2, H_f and H_g), 1.50 (s, 3, H_h), 1.35 (s, 3, H_i). The 6.32-ppm signal disappeared on adding a drop of deuterated water.

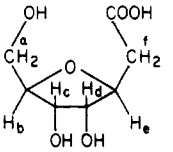


Since acid **17** decomposed slowly on standing at room temperature, it was generally lactonized to **19** without delay. Other ways of converting the sodium salt to the acid **17**, e.g., using ion exchange, or substituting hydrochloric acid or *p*-toluenesulfonic acid plus magnesium sulfate for the sulfuric acid, gave mixtures.

β-Ribofuranosylacetic Acid (18). The isopropylidene group in 2,3-*O*-isopropylidene-β-ribofuranosylacetic acid (**17**) was easily removed by allowing 0.550 g (2.37 mmol) of the compound as a solution in reagent grade acetone (40 mL, 0.5% water) to stand at 25 °C for 24 h. Evaporation of all volatiles left a white solid, which was rinsed with 0.5 mL of acetone and dried to give 0.440 g (97%) of analytically pure β-ribofuranosylacetic acid (**18**), mp 145–146 °C dec.

Anal. Calcd for $C_7H_{12}O_6$: C, 49.97; H, 6.29. Found: C, 50.12; H, 6.42.

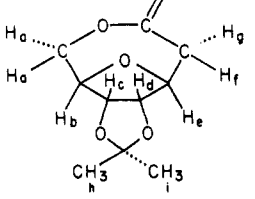
The spectral data are as follows: IR (KBr) 3490, 1720 cm^{-1}; NMR (saturated solution in dry 1:1 CD_3COCD_3–CD_3CN) δ 6.64 (s, 4, all OH's), 4.80–3.90 (m, 4, H_{b-e}), 3.68 (d, $J_{a,b}$ = 4 Hz, 2, H_a), 2.65 (d, $J_{e,f}$ = 6, 2, H_f). Addition of 1 drop of D_2O eliminated the 6.64-ppm signal.



Lactone 19 of 2,3-*O*-Isopropylidene-β-ribofuranosylacetic Acid. A solution of 2,3-*O*-isopropyliden-β-ribofuranosylacetic acid (**17**; 696 mg, 3.00 mmol) in 10 mL of pyridine was added over a 10-min period to a vigorously boiling, stirred solution of acetic anhydride (0.34 mL, 3.3 mmol) in 10 mL of pyridine (0.1% H_2O). After an additional 3 min of reflux, all volatile materials were removed at room temperature. Chromatography of the colorless lactone product (0.53 g) through a 12-in. column of silica gel (30 g) with 9:1 chloroform–acetone as solvent afforded 495 mg (77%) of lactone **19**, mp 140–141 °C (lit.[17] mp 146–147 °C). This material developed one spot on thin-layer chromatography (R_f 0.45 with 4:1 chloroform–acetone). Sublimination at 120–130 °C (0.01 mm) did not change the melting point.

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59; mol wt 214.2. Found: C, 55.94; H, 6.61; mol wt (vapor pressure measurement in $CHCl_3$) 204.

The spectral data are as follows: IR ($CHCl_3$) 2980, 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.95 and 4.65 (2 d in AB pattern, $J_{c,d}$ = 5.5 Hz, $J_{b,c} = J_{d,e}$ = 0 Hz, 2, $H_{c,d}$), 4.3 (m, 4, $H_{a,b,e}$), 2.96 (d, $J_{g,e} \simeq J_{f,e} \simeq$ 4 Hz, 2, $H_{g,f}$), 1.49 (s, 3, H_h), 1.32 (s, 3, H_i). The signals for H_f



and H_g at δ 3.02 call for comment. Dreiding models of lactone **19** show that there are four extreme conformations for the lactone bridge (two "boats" and two "zig-zag"), each positioning H_f and H_g differently and each having different sets of dihedral angles for H_e–H_g and H_e–H_f. We have postulated that the absence of geminate coupling between H_g and H_f as well as the appearance of the H_g plus H_f signal as a simple two-proton doublet is the consequence of the time-averaged geometry, which by coincidence places the two H's in similar magnetic environments and which presents the same dihedral angle between H_e and H_g as between H_e and H_f so that the vicinal coupling constants $J_{e,g}$ and $J_{e,f}$ are equal.

In connection with this interpretation, however, and in contrast to our observations, the NMR curve for lactone **19** as determined elsewhere[17] does show geminate coupling (14 Hz) for H_g and H_f. Possibly the different results stem from the fact that the solvent was benzene instead of chloroform. To check this, we redetermined the ^1H NMR curve in benzene: δ (C_6D_6) 4.67 and 4.49 (2 d in AB pattern, $J_{c,d}$ = 5.6 Hz, $J_{b,c} = J_{d,e}$ = 0 Hz, H_c and H_d), 4.06 (m, width at half-height 7 Hz, H_b and H_e), 3.45 (m, width at

(25) Bovey, F. A. "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1969.

half-height 7 Hz, H_a's), 2.35 (m, width at half-height 7 Hz, H_f and H_g), 1.52 (s, H_h), 1.12 (s, H_i).

Again we could not find the geminate coupling. The differences in the chemical shifts when benzene is substituted for chloroform as solvent are quite marked, an effect attributable to the anisotropic association of benzene with the lactone molecule.

Lactonization with *N,N'*-dicyclohexylcarbodiimide failed, as did lactonization of methyl ester **15** by methoxide-catalyzed internal ester interchange.[13]

For preparative purposes the following procedure, starting with methyl ester **15**, was followed. After a solution of methyl 2,3-*O*-isopropylidene-β-ribofuranosylacetate (**15**; 2.46 g, 10.0 mmol) in 100 mL of 0.10 N sodium hydroxide was boiled for 1 min, the solvent was evaporated, and the residue of sodium salt was dried in vacuo. Concentrated sulfuric acid (515 mg of 95.0% acid, 5.0 mmol) was added dropwise to the solid dissolved in 1:1 methanol–acetone. The resulting mixture was filtered, and after 1.0 mL of pyridine had been added to the filtrate, it was stripped of all volatiles. The residual pale yellow oil was kept in a 0.01-mm vacuum for 0.5 h. A solution of the oil in 20 mL of pyridine was added by drops to a vigorously refluxing, stirred solution of acetic anhydride (1.1 mL, 12 mmol) in pyridine (30 mL). Reflux was continued for another 3 min. Evaporating the solution under reduced pressures left the crude solid lactone **19**, which was dissolved in 60 mL of 1:1 ether–acetone and treated with decolorizing carbon. All solvent was removed, and the white solid was purified by column chromatography through 40 g of silica gel to furnish 1.63 g (73% from ester **15**) of homogeneous (TLC) lactone **19**, mp 140–141 °C.

Isopropylidene Derivative 20 of the Triazole Homo-C-nucleoside. A mixture of lactone **19** (0.50 g, 2.3 mmol) and aminoguanidine bicarbonate (0.326 g, 2.40 mmol) suspended in 10 mL of pyridine[18] was stirred and refluxed under an atmosphere of argon for 3 h. The pyridine was removed, and the liquid residue was chromatographed through a 25-cm column of silica gel (20 g) with 7:3 chloroform–methanol as the developing solvent. Triazole homo-C-nucleoside derivative **20** (305 mg, 80%) was obtained; mp 69–70 °C. This product produced a single spot on a TLC plate (R_f 0.48 with 3:2 chloroform–methanol): IR ($CHCl_3$) 3600–3020, 1645 cm^{-1}; UV (H_2O) no maxima between 210–330 nm at pH 1, 7, or 12;[26] NMR (CD_3OD) δ 5.55 (br s, 4, NH's and OH or CD_3OH) 4.75–3.90 (m, 4, CH's), 3.65 (distorted d, J = 3.7 Hz, 2, CCH_2O), 2.88 (uneven d, J = 6 Hz, 2, CCH_2C), 1.58 and 1.30 (2 s, 3 H each, $(CH_3)_2C$).

The mass molecular peak observed at m/e 270 corresponded to that calculated for $C_{11}H_{18}N_4O_4$. An $M^+ - CH_3$ peak at m/e 255 was also noted.

5-(β-Ribofuranosylmethyl)-3-amino-1,2,4-triazole Hydrochloride (21). A solution of isopropylidene derivative **20** (505 mg, 1.87 mmol) in 95% ethanol (10 mL) in which the pH had been adjusted to 0.5 with 37% hydrochloric acid was refluxed for 1 h. The reaction mixture was then stirred at −12 °C for 20 min, during which time a white solid gradually precipitated. The solids were collected, washed on the funnel with two 10-mL portions of acetone, and crystallized from ethanol. Two crops of the desired hydrochloride **21** were taken, the combined yield of product (mp 183–184 °C) amounting to 410 mg (82%).

Anal. Calcd for $C_8H_{15}ClN_4O_4$: C, 36.03; H, 5.67; N, 21.01; Cl, 13.30. Found: C, 36.00; H, 5.54; N, 20.93; Cl, 13.16.

The material was homogeneous according to thin-layer chromatography (R_f 0.58 with methanol solvent); IR (KBr) 3500, 3350–2600, 1685 cm^{-1}; UV (H_2O) no maxima observed.[26]

A peak at m/e 230 appeared on the mass spectrum of the hydrochloride, a value that corresponded to that calculated for $C_8H_{15}ClN_4O_4$ − HCl. The NMR (D_2O) data are as follows: δ 4.50 (s, 7, HOD), 3.80 (m, 4, tetrahydrofuran CH's), 3.47 (m, 2, CCH_2O), 2.80 (m, 2, CCH_2C). The complex methylene signals at 3.47 and 2.80 ppm suggest that the two H's on the methylene groups are not equivalent or, in other words, that rotation around the bonds to the tetrahydrofuran ring may not be unrestricted.

Biological Activity of Homo-C-nucleoside 21. No significant activity was detected. The assays included trials against the RNA viruses rhino and influenza and the DNA virus herpes simplex (types I and II), with the work performed at Southern Research Institute in Birmingham and at Roswell Park Memorial Institute in Buffalo, against cultured mammary tumor cells (TA-3), with the tests performed at Roswell Park Memorial Institute, against mouse leukemia (P 815) in tissue culture, carried out at Sloan-Kettering Institute for Cancer Research, and against in vitro human lymphoblastic leukemia (CEM), performed at Sidney Farber Cancer Institute. The compound was also inactive in an in vivo assay using TLX/5 ascites cells in mice, with the work done at Chester Beatty Research Institute in London.

Formyl Derivative 22b of the Lactone. A solution of vacuum-dried triphenylmethane (1.07 g, 4.40 mmol) and distilled hexamethylphosphorictriamide (0.6 mL) in tetrahydrofuran (20 mL) that had just been distilled from lithium aluminum hydride was cooled to −78 °C. An atmosphere of argon dried by passage through Drierite was maintained over the reaction mixture. Commercial butyllithium in hexane (20.9% by weight) was added dropwise with a syringe until the solution was permanently red (ca. 0.06 mL). Another 1.34 mL (4.4 mmol) of butyllithium solution was introduced followed after 5 min of stirring at −78 °C by a solution of lactone **19** (428 mg, 2.00 mmol) in tetrahydrofuran (4 mL). Formation of the lithio derivative **22a** was allowed to proceed for 15 min at −78 °C and then for 5 min at −12 °C.

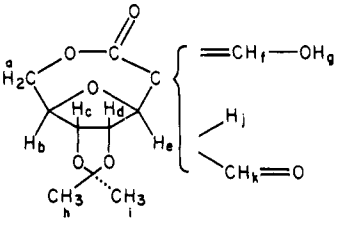
Dry phenyl formate[27] (0.700 mL, 5.75 mmol) was injected, and the yellow solution was stirred at −12 °C for 15 min.

Acetic acid (0.30 mL, 4.7 mmol) was added to quench the reaction, and after the resulting heterogeneous mixture had been stirred at −12 °C for 5 min, it was diluted with ether (150 mL) and filtered. All volatiles were stripped away, and the remaining crude product was chromatographed through 40 g of silica gel with 9:1 chloroform–acetone as solvent. Unchanged starting lactone **19** (120 mg, 28% recovery) emerged first followed by the formyl derivative **22b** as a colorless liquid (220 mg, 64% corrected yield) that slowly solidified to a solid, mp 111–112 °C. Crystallization from carbon tetrachloride or from ether–hexane yielded 207 mg (60%) of product with the same melting point. Sublimination at 115 °C (0.01 mm) was also feasible.

Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.82; mol wt 242. Found: C, 54.69; H, 5.92; mol wt (vapor pressure method using $CHCl_3$ solvent) 492, a value corresponding to the hydrogen-bonded dimer.

The formylation product **22b** showed one spot on TLC, (R_f 0.30 with 4:1 chloroform–acetone). A wine-red color developed when the compound was treated with 5% aqueous ferric chloride. An orange precipitate formed with ethanolic 2,4-dinitrophenylhydrazine in the presence of sulfuric acid.

The spectral data are as follows: IR ($CHCl_3$) 3500, 1725, 1670 cm^{-1}; NMR ($CDCl_3$) δ 12.03 and 11.80 (2 br s, H_k's, exo and endo), 7.58 and 7.36 (2 s, H_f, cis and trans), 4.99 and 4.63 (2 d, J = 6 Hz, 2, H_c and H_d), 4.45–4.25 (m, 4.5, $H_{a,b,e,j}$), 1.50 (s, 3, H_h), 1.35 (s, 3.5, H_i and *cis*- and *trans*-H_g). The integration value of the



signals at 11.91–7.36 ppm corresponded to a single H. The fact that the four peaks were approximately equal in intensity suggested that the solution contained a 1:1 mixture of aldehyde and hydroxymethylene forms. Addition of 1 drop of acetic acid removed the peaks at 11.91 and 7.58 ppm and left only the signal at 7.36 ppm, which now integrated to 1 H. Furthermore, the multiplets at 4.45–4.25 ppm decreased from 4.5 to 4 H's while the singlet at 1.35 ppm in creased from 3.5 to 4 H's. This behavior is consistent with the existence of only one form, an enol, in the presence of acetic acid. Adding 1 drop of deuterated water to the chloroform solution produced a small but distinct decrease

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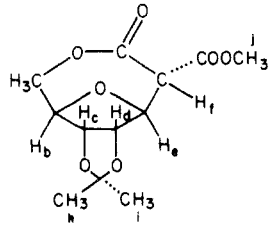
in the intensity of the singlet at 1.35 ppm (OH exchange) as well as in the multiplet at 4.45–4.25 ppm (exchange at H_j).

In modifications of this procedure, lithio derivative **22a** was generated with lithium *N*-isopropyl-*N*-cyclohexylamide in tetrahydrofuran containing a little hexamethyl phosphorictriamide and a catalytic amount of (triphenylmethyl)lithium. But attempted formylations with methyl formate, *p*-nitrophenyl formate,[28] or dichloromethyl methyl ether failed. Formylation with formyl fluoride[29] in the absence of a secondary amine likewise failed. Clearly the conditions for a successful formylation are very narrowly defined.[17] In all the trials, formation of the lithio derivative **22a** was assured by quenching the solution with acetic acid-d_4. Unchanged lactone **19** (mp 138–140 °C) was recovered in high yield. Estimates based on the decreased intensity of the lactone ^1H NMR signal at 3.02 ppm as a consequence of monodeuteration showed that conversion to the lithio derivative was 90–100% complete.

***exo*-Methoxycarbonyl Derivative 22c of Lactone 19.** *tert*-Butyllithium in pentane (0.97 M as standardized) was injected dropwise into a stirred, cold (−78 °C) solution of triphenylmethane (1 mg) and hexamethylphosphoric triamide (0.3 mL) in 10 mL of dry tetrahydrofuran until the solution was permanently red (0.01–0.02 mL). Argon blanketed the reaction mixture at all times. Another 1.2 mL of *tert*-butyllithium solution (1.1 mmol) was added, and the mixture was stirred at −78 °C for 5 min. Lactone **19** (214 mg, 1.00 mmol) dissolved in 2 mL of tetrahydrofuran was injected dropwise and, after the red solution had been stirred further for 15 min, was followed by 0.10 mL (1.0 mmol) of methyl chloroformate. After 10 min, the sequence was repeated at −78 °C by introducing another portion of *tert*-butyllithium (1.0 mL, 0.97 mmol), stirring for 15 min, adding methyl chloroformate (0.05 mL, 0.5 mmol), and stirring for 10 min. A third cycle made use of 0.50 mL (0.49 mmol) of *tert*-butyllithium and 0.05 mL (0.5 mmol) of methyl chloroformate.

Acetic acid (0.18 mL, 2.8 mmol) was injected into the mixture at −12 °C which, after a short period of stirring, was then stripped of volatiles. Adding 60 mL of chloroform produced a suspension. This was shaken with two 20-mL portions of 10% aqueous bicarbonate and dried, the solution evaporated, and the remaining liquid product chromatographed through a 30-cm column of silica gel with 1:19 acetone–chloroform as solvent. The triphenylmethane and excess methyl chloroformate emerged in the early fractions, followed by the desired exo ester **22c** and then by unchanged pure lactone **19** (22 mg, 10% recovery). The exo ester product **22c** was obtained as a colorless viscous liquid (190 mg, 70% conversion, 78% cor) showing a single spot on a TLC plate (R_f 0.42 with 1:9 acetone–chloroform): IR (CCl_4) 2990, 2977, 1775, 1690 cm^{-1}; NMR ($CDCl_3$) δ 5.22 (d, $J_{f,e}$ = 8 Hz, 1, H_e), 4.90 and 4.70 (2 d, $J_{c,d}$ = 6 Hz, 2, H_c and H_d), 4.60–4.22 (m, 4, $H_{a,b,f}$), 3.90 (s, 3, H_j), 1.55 (s, 3, H_h), 1.38 (s, 3, H_i).

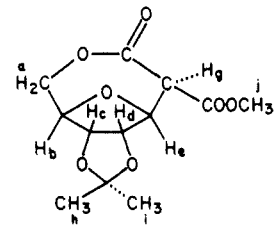


***endo*-Methoxycarbonyl Derivative 22c of Lactone 19.** The directions for preparing the lithio derivative **22a** were the same as those used for the exo isomer except that *tert*-butyl alcohol (0.15 mL, 2.0 mmol) was present. After methyl chloroformate (0.2 mL, 2 mmol) had been added, the pale yellow reaction mixture was stirred at −12 °C for 15 min. Then acetic acid (0.2 mL, 3 mmol) was injected, and the cold heterogeneous mixture was stirred further for 3 min before being flooded with ether. Filtration and solvent evaporation of the filtrate left a yellow oil, which was chromatographed as described above. Exo ester **22c** (16 mg, 6%), homogeneous and identical with the material obtained before, came out just before the endo isomer **22c**. The slower moving fractions contained unchanged, homogeneous starting lactone **19**: 64 mg (30% recovery); mp 139–140 °C.

The endo ester **22c** was obtained as a viscous oil (120 mg, 69% cor) showing one spot on thin-layer chromatography (R_f 0.40 with 1:9 acetone–chloroform). A sample distilled at bp 160–165 °C (0.01 mm) showed the same single spot at R_f 0.40.

Anal. Calcd for $C_{11}H_{16}O_7$: C, 52.94; H, 5.92; mol wt 272.2. Found: C, 53.04; H, 5.95; mol wt 280 (vapor pressure in chloroform solution).

The spectral data are as follows: IR (CCl_4) 2990, 2975, 1750 cm^{-1}; NMR ($CDCl_3$) δ 5.02 (uneven d, $J_{c,d}$ = 6 Hz, 2, H_e plus H_c or H_d), 4.75–4.00 (m, 5, $H_{a,b,g}$ plus H_c or H_d), 3.88 (s, 3, H_j), 1.52 (s, 3, H_h), 1.35 (s, 3, H_i).



Epimerization of Endo to Exo Ester 22c. A chloroform solution of endo ester **22c** (0.100 g in 50 mL) was shaken with 40 mL of 10% aqueous bicarbonate for 3 min. The recovered ester was chromatographed as described above. Fractions of endo ester (38 mg, 38%) and exo ester (40 mg, 40%), both homogeneous according to TLC, were cleanly separated. A control experiment showed that passing the endo ester in chloroform through a column of silica gel was not enought to cause this extent of epimerization; here approximately 75% of the endo ester was recovered unchanged plus 6.5% of the exo form. Exposing pure exo ester **22c** to the bicarbonate treatment or to the chromatography control procedure returned only the exo form.

The R_f values, the infrared spectra, and the NMR spectra of the separated fractions were identical, respectively, with those obtained with the authentic materials.

The epimeric assignments in the esters **22c** have been made on the assumption that the exo epimer is less crowded and therefore is thermodynamically more stable than the endo form.

Bromo Derivative 22d of Lactone 19. Lithio derivative **22a** was prepared as described above for the exo ester **22c**. The molar ratio of *tert*-butyllithium (3.2 mL of a 0.97 M solution, 3.0 mmol) to lactone **19** (214 mg, 1.00 mmol) was 3:1. Bromine (0.640 g, 4.00 mmol) in 2 mL of dry tetrahydrofuran was added dropwise from a syringe to the lithio derivative solution held at −78 °C. After an additional 3 min of stirring, the brown solution was warmed to −12 °C and quenched with 4 drops of acetic acid. Concentration of the reaction mixture left a brown liquid which, as a solution in chloroform, was shaken with two 25-mL portions of 5% aqueous sodium thiosulfate followed by 1% aqueous sodium bicarbonate. The chloroform solution was dried and stripped of volatiles, and the residual yellow oil was chromatographed through a 30-cm column of silica gel (30 g) with 9:1 chloroform–acetone as the developing solvent. Two homogeneous fractions were obtained, one of the bromination product **22d** and the second (slower moving) of unchanged starting lactone **19** (12 mg, 6% recovery) showing R_f 0.45 (chloroform–acetone, 4:1).

The bromo compound **22d** [205 mg (70% conversion, 75% yield); mp 138–139 °C; R_f 0.53 (chloroform–acetone, 4:1)] was sublimed at 120–125 °C (0.01 mm).

Anal. Calcd for $C_{10}H_{13}BrO_5$: C, 40.96, H, 4.47; Br, 27.26; mol wt 293.1. Found: C, 41.00; H, 4.54; Br, 27.69; mol wt 279 (vapor pressure measurement).

The sublimed material melted at 139–140 °C: R_f 0.53; IR ($CHCl_3$) 1735 cm^{-1}; NMR ($CDCl_3$) δ 5–4 (m, 7, all protons except CH_3's), 1.50 and 1.32 ppm (2 s, 3 H each, CH_3's). The exo configuration for the bromo derivative **22d** is favored on the assumption of a kinetic as well as a thermodynamic preference for the exo side and also because no marked downfield shift is noted for the bridgehead H next to the bromine. If bromine were endo oriented, it would be close to the adjacent bridgehead H and in all the accessible conformations would be expected to deshield this hydrogen. The observation that the carbonyl stretch frequency for the bromo lactone is not greater—and, in fact, is 5 cm^{-1} less—than that for the parent lactone **19** suggests that the dihedral

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angle between Br and the carbonyl oxygenation is large.[30] However, this is not useful in making the epimeric assignment since both endo and exo arrangements provide for a large dihedral angle.

Ethoxycarbonyl Isothiocyanate. The following procedure was more convenient than that described in the literature.[31] Ethyl chloroformate (10.9 g, 0.100 mmol) was slowly added to a vigorously stirred suspension of potassium thiocyanate (9.70 g, 0.100 mmol) in reagent grade acetonitrile (45 mL) held at 70–75 °C, after which the thick yellow mixture was stirred at 70–75 °C for 15–20 min and then at 25 °C for 10 min. With the temperature at 0 °C, 20 mL of acetonitrile was added just before filtration. The solids were rinsed on the funnel, the combined filtrates were evaporated, and the crude yellow product was distilled through a short Vigreaux column. Colorless ethoxycarbonyl isothiocyanate (9.5 g, 73%) was obtained: bp 50–52 °C (10–12 mm); IR (CCl_4) 1980, 1760 cm^{-1}.[27] The liquid was sealed in amber ampules under argon and was kept no longer than 4 days at −5 °C before use.

***N*-(Ethoxycarbonyl)thiocarbamyl Derivative 22e.** Lithio derivative **22a** was prepared essentially as described before for the synthesis of exo ester **22c** by using 214 mg of lactone **19** (1.00 mmol) in 3 mL of tetrahydrofuran with 2.0 mL of 0.97 M *tert*-butyllithium solution. Drops of ethoxycarbonyl isothiocyanate (0.26 mL, ca. 2.0 mmol) were injected, and the yellow solution was stirred for 10 min at −45 °C and then for 1 min at 0 °C. Acetic acid (0.13 mL, 2.0 mmol) was introduced followed by 90 mL of ether. The precipitate of lithium acetate was removed, the filtrate was concentrated, and the crude residual product was chromatographed through a 30-cm column of silica gel (30 g) with chloroform–acetone (9.5:0.5) as the developing solvent. A small amount of unchanged starting lactone **19** (11 mg, 5% recovery) emerged after the expected product. Solvent-free *N*-(ethoxycarbonyl)thiocarbamyl compound **22e** (mp 167–168 °C) was obtained as a homogeneous (TLC) solid (245 mg, 71%). A sample for analysis, prepared by crystallization from ether at −50 °C, melted at 168.5–169.5 °C.

Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 48.69; H, 5.56; N, 4.06; S, 9.28. Found: C, 48.95; H, 5.66; N, 4.29; S, 9.28.

The infrared absorption spectrum (CCl_4) showed peaks at 3445, 3280, 1775, 1740 cm^{-1}. The NMR ($CDCl_3$) spectrum showed the following: δ 9.38 (br s, 1, NH), 5.40 (d, J = 0.5 Hz, 1, bridgehead H vicinal to new group), 5.02–4.05 (m, 8), 1.55–1.20 (m, 9, CH_3's).

The exo configuration was assigned provisionally on the basis of both kinetic and thermodynamic preference for this epimer.

Phenylthio Derivative 22f. Lithio enolate **22a** was obtained from 214 mg (1.00 mmol) of lactone **19** plus 2.1 mL of 0.97 M *tert*-butyllithium solution essentially according to the procedure used in the synthesis of exo ester **22c**. After diphenyl disulfide (240 mg, 1.10 mmol) in dry tetrahydrofuran (3 mL) had been injected, the resulting yellow solution was stirred at −12 °C for 15 min. Adding acetic acid (0.061 mL, 1.0 mmol) by syringe quenched the reaction. The resulting heterogeneous mixture was stirred at 0 °C for 3 min before diluting with ether and filtering. The yellow liquid left after removal of all volatiles from the filtrate was chromatographed through 30 g of silica gel 60 with 9:1 chloroform–acetone as solvent. The solvent-free phenylthio product **22f** was isolated as a white solid (280 mg, 87%), which was taken as a mixture of exo and endo forms. Sublimation at 150 °C (0.01 mm) provided a sample for analysis.

Anal. Calcd for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63. Found: C, 59.63; H, 5.71.

The product developed two spots on a TLC plate, R_f 0.50 and 0.59 (9:1 chloroform–acetone). The spectral data are as follows: IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.65–7.15 (m, 5, aromatic H's), 5.07–4.10 (m, 7), 1.52 and 1.45 (2 s, 3, *endo*-*gem*-CH_3), 1.32 (s, 3, *exo*-*gem*-CH_3 in both epimers).

The two singlets at 1.52 and 1.45 ppm were consistent with the presence of *exo*- and *endo*-phenylthio epimers of derivative **22f**. Very little change was noted in the nuclear magnetic resonance curve after the product had been shaken vigorously for 5 min with 10% carbonate or after refluxing the product in pyridine for 24 h. However, the phenylthio derivative **22f** did form a lithio derivative with *tert*-butyllithium.

Formation of the corresponding methylthio compound by treating lithio derivative **22a** with dimethyl disulfide failed.

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Registry No. **1**, 3238-40-2; **2**, 2043-98-3; **3**, 22555-42-6; **4**, 59482-77-8; **5a**, 77984-40-8; **5b**, 77984-41-9; **7**, 77984-42-0; **10**, 20137-88-6; **11**, 51145-10-9; **12**, 77984-43-1; **13**, 78038-57-0; **14**, 77984-44-2; **15**, 67773-47-1; **17**, 78038-58-1; **18**, 77984-45-3; **19**, 78038-59-2; **20**, 78038-60-5; **21**, 78038-61-6; **22a**, 77984-46-4; **22b** aldehyde (isomer 1), 77984-47-5; **22b** aldehyde isomer 2, 78038-62-7; **22b** (*E*)-hydroxymethylene, 77984-48-6; **22b** (*Z*)-hydroxymethylene, 78038-63-8; *endo*-**22c**, 77984-49-7; *exo*-**22c**, 78038-64-9; *exo*-**22d**, 77984-50-0; *exo*-**22e**, 78003-78-8; *endo*-**22f**, 77984-51-1; *exo*-**22f**, 78038-65-0; *p*-toluenesulfonyl chloride, 98-59-9; methanesulfonyl chloride, 124-63-0; thionyl chloride, 7719-09-7; *exo-cis*-6,7-(isopropylidenedioxy)-8-oxabicyclo[3.2.1]octane, 77984-52-2; sodium 2,3-*O*-isopropylidene-β-ribofuranosylacetate, 78038-66-1; aminoguanidine bicarbonate, 2582-30-1; ethyl chloroformate, 541-41-3; potassium thiocyanate, 333-20-0; ethoxycarbonyl isothiocyanate, 16182-04-0; diphenyl disulfide, 882-33-7.

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Syntheses of Seleno Estrogens

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The syntheses of phenylseleno and methylseleno analogues of estradiol are described.

For studies of the noninvasive differentiation of hormone-dependent from hormone-independent mammary tumors, we required seleno analogues of estradiol. The synthesis of several such analogues is the subject of this

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