(12). A solution of 8 (300 mg, 0.53 mmol) and ethyl propiolate (600 mg, 6 mmol) in toluene (4 mL) was pyrolyzed in a sealed tube for 1 h at 220 °C. Excess ethyl propiolate was removed by fast chromatography on a silicagel suction column, and the residue was separated by using high-performance liquid chromatography (Jobin-Yvon Chromatospac Prep 100, column diameter 8 cm, silicagel from Merck, art. 7736; eluted with 30% ethyl acetate in dichloromethane at 8 bar, 35 mL/min; detection with RI). In this way 0.160 g (48%) of compound 11 and 0.051 g (16%) of the 4-position substituted isothiazole 12 was obtained.

Isothiazole 11 (oil): IR (oil film) 1740 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 8.1–7.85 (m, 6, Ar H), 7.80 (s, 1, H_4), 7.60–7.20 (m, 9, Ar H), 6.1 (t, 4.5 Hz, 1, $H_{2'}$), 5.90 (t, 4.5 Hz, 1, $H_{3'}$), 5.47 (d, 5 Hz, 1, $H_{1'}$), 4.9–4.6 (m, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$), 4.35 (q, 7 Hz, 2, CH_2), 1.26 (t, 7 Hz, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 1.68 (C_3), 166.0–165.2 (COOPh), 159.5 (COOEt), 158.3 (C_5), 133–128 (Ar C), 125.9 (C_4), 80–63 (ribosyl C), 61.8 (CH_2), 13.9 (CH_3); mass spectrum, m/e 601, 573, 556, 479, 357, 105; exact mass calcd for $C_{32}H_{27}NO_9S$ 601.141, found 601.141 ± 0.001.

Isothiazole 12 (oil): ^1H NMR ($CDCl_3$) δ 9.2 (s, 1, H_5), 8.1–7.8 (m, 6, Ar H), 7.5–7.2 (m, 9, Ar H), 6.2 (m, 3, $H_{1'}$, $H_{2'}$, $H_{3'}$), 4.8 (m, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$), 4.3 (q, 6 Hz, 2, CH_2), 1.26 (t, 6 Hz, 3, CH_3); mass spectrum, m/e 601, 584, 572, 556, 479, 357, 105; exact mass calcd for $C_{32}H_{27}NO_9S$, 601.141, found 601.140 ± 0.001.

Ammonolysis of Compounds 10–12: Preparation of the Amides 3–5. A solution of compounds 10–12 (0.2 mmol) in methanol (2 mL) saturated with ammonia was stirred at room temperature for 80 h. After every 24-h period the solvent was evaporated and replaced by freshly prepared methanolic ammonia. After the reaction was completed, the solvent was evaporated and the residue was taken up in water (3 mL) and washed (3 times) with chloroform. The water layer was freeze-dried and the residue was recrystallized from 2-propanol to yield the very hygroscopic amides 3–5.

3-β-D-Ribofuranosyl-1,2,4-thiadiazole-5-carboxamide (3): yield 60%; mp 155–156 °C; IR (oil film) 3310 (OH, NH_2), 1675 cm^{-1} (CO); ^1H NMR (D_2O) δ 5.17 (d, J = 5.6 Hz, 1, $H_{1'}$), 4.48 (dd, 5.6 and 5.3 Hz, 1, $H_{2'}$), 4.29 (t, J = 5.3 Hz, 1, $H_{3'}$), 4.17 (ddd, 5.3, 2.3, and 6.4 Hz, 1, $H_{4'}$), 3.87 (dd, 2.3 and −12.5 Hz, 1, $H_{5'}$), 3.77 (dd, 6.4 and −12.5 Hz, 1, $H_{5''}$); ^{13}C NMR (D_2O) δ 61.6, 71.2, 79.2, 80.8, 84.9 (ribosyl C), 161.2 ($CONH_2$), 174.6 (C_3), 184.5 (C_5); mass spectrum (+4Me_3Si), m/e 549, 534, 459, 446, 356, 316, 256, 244, 230, 217, 159, 158, 129, 103, 73. Anal. Calcd for $C_8H_{11}N_3O_5S$: C, 36.78; H, 4.24; N, 16.08. Found: C, 36.61; H, 3.90; N, 15.66.

3-β-D-Ribofuranosylisothiazole-5-carboxamide (4): yield 55%; mp 135–137 °C; IR (KBr) 3310 (OH, NH_2), 1670 cm^{-1} (CO); ^1H NMR (D_2O) δ 7.8 (s, 1, H_4), 5.0 (d, 6.4 Hz, 1, $H_{1'}$), 4.3 (dd, 6.4 and 5.1 Hz, 1, $H_{2'}$), 4.18 (dd, 5.1 and 4.7 Hz, 1, $H_{3'}$), 4.12 (ddd, 4.7, 3.3, and 5.1 Hz, 1, $H_{4'}$), 3.83 (dd, 3.3 and −12.5 Hz, 1, $H_{5'}$), 3.74 (dd, 5.1 and −12.5 Hz, 1, $H_{5''}$); mass spectrum (+4Me_3Si) m/e 548, 533, 458, 445, 368, 355, 315, 255, 230, 229, 227, 217, 157, 103, 73. Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.53; H, 4.65; N, 10.76. Found: C, 41.91; H, 5.03; N, 10.40.

3-β-D-Ribofuranosylisothiazole-4-carboxamide (5): yield 58%; mp 89–90 °C; the product decomposed on attempted purification preventing proper combustion analysis, but it was stable in aqueous solution or in vacuum; IR (KBr) 3300 (OH, NH_2), 1675, 1620 cm^{-1} (CO); ^1H NMR (D_2O, MeOD) δ 9.41 (s, 1, H_5), 5.45 (d, 5 Hz, 1, $H_{1'}$), 4.48 (dd, 5 and 5.6 Hz, 1, $H_{2'}$), 4.16 (t, 5.6 Hz, 1, $H_{3'}$), 4.16 (ddd, 5.6, 3.3, and 5.1 Hz, 1, $H_{4'}$), 3.89 (dd, 3.3 and −12.4 Hz, 1, $H_{5'}$), 3.77 dd, 5.1 and −12.4 Hz, 1, $H_{5''}$); mass spectrum (+3Me_3Si), m/e 476, 461, 386, 296, 283, 217, 73.

Acetalization of Compounds 3 and 4. Compound 3 (4) (10 mg), 1 mL of dimethoxypropane, and a pinch of *p*-toluenesulfonic acid was stirred at room temperature for 30 min. The mixture was placed directly on a preparative thin layer plate (silicagel) and eluted with 2% methanol in ethyl acetate to yield the desired compound as a clean, slightly yellow oil.

(2′,3′-*O*-Isopropylidene)-β-D-ribofuranosyl-1,2,4-thiadiazole-5-carboxamide (14): yield 8 mg; $_1H$ NMR (D_2O) δ 5.34 (d, 4 Hz, 1, $H_{1'}$), 5.28 (dd, 4 and 6.5 Hz, 1, $H_{2'}$), 4.93 (dd, 6.5 and 3 Hz, 1, $H_{3'}$), 4.38 (td, 3 and 7 Hz, 1, $H_{4'}$), 3.65 (m, 2, H_5 and $H_{5'}$), 1.61 (s, 3, CH_3), 1.41 (s, 3, CH_3).

3-(2′,3′-*O*-Isopropylidene)-β-D-ribofuranosylisothiazole-5-carboxamide (15): yield 5 mg; ^1H NMR ($CDCl_3$) 5.16 (d, 4 Hz, 1, $H_{1'}$), 4.89 (dd, 4 and 6.5 Hz, 1, $H_{2'}$), 4.86 (dd, 6.5 and 2.5 Hz, 1, $H_{3'}$), 4.37 (m, 1, $H_{4'}$), 3.66 (m, 2, $H_{5'}$ and $H_{5''}$), 1.64 (s, 3, CH_3), 1.40 (s, 3, CH_3).

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Registry No. 3, 89873-16-5; 4, 89873-17-6; 5, 89873-18-7; 6, 23316-67-8; 7, 89873-10-9; 8, 89873-12-1; 9, 89873-21-2; 10, 89873-13-2; 11, 89873-14-3; 12, 89873-15-4; 14, 89873-19-8; 15, 89873-20-1; ribavirin, 36791-04-5; 2,5-anhydro-3,4,6-tri-*o*-benzoyl-D-altronamide, 89873-11-0; ethyl cyanoformate, 623-49-4; ethyl propiolate, 623-47-2; ClSCOCl, 2757-23-5.

Use of D-Ribonolactone in Organic Synthesis. 2. Scope and Utility

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The scope and utility of D-ribonolactone (1) as a chiral template for the synthesis of optically active γ-lactones which are important precursors for many natural products are discussed. The regio- and stereoselective functionalization of 1 is examined.

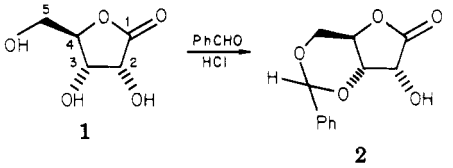
Chiral γ-lactones are important precursors in natural product syntheses. These compounds have been obtained either from the cyclization of acyclic starting materials, such as the stereoselective iodolactonization of unsaturated 3-hydroxy acids,[1] or from sugars such as D-ribofuranose[2] or D-glucosamine.[3] The concept of using "chiral templates" derived from carbohydrates has been ingeniously and widely used in synthesis.[4] Most efforts in this area have traditionally focused on sugars such as D-ribose, D-glucose, etc. Manipulations involving carbohydrates,

(1) Chamberlin, A. R.; Dezube, M.; Dussault, P. *Tetrahedron Lett.* **1981**, *22*, 4611.
(2) Hanessian, S.; Haskell, T. H. *J. Heterocycl. Chem.* **1964**, *1*, 55.
(3) Hecht, S. M.; Rupprecht, K. M.; Jacobs, P. M. *J. Am. Chem. Soc.* **1979**, *101*, 3982.
(4) For a summary, see: Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159.

0022-3263/84/1949-2168$01.50/0

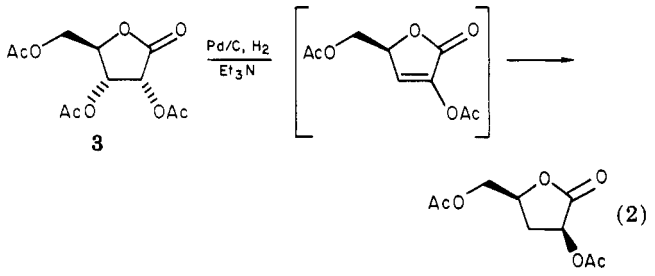
however, require tedious protection/deprotection protocols for the anomeric center and the difficulty in performing regio- and stereoselective transformations among polyhydroxyl groups. To overcome the first shortcoming, we have investigated the use of commercially available D-ribonolactone[5] (1) as an alternative to simple sugars to prepare chiral γ-lactones to be used as precursors in natural product syntheses.

Unlike other common sugars, D-ribonolactone has not been used intensively in organic synthesis to date. In 1968, Zinner[6] prepared a benzylidene derivative of 1 by treating it with benzaldehyde and concentrated hydrochloric acid. The structure of 2 was confirmed by us to be 3,5-*O*-benzylidene-D-ribono-γ-lactone (eq 1).[7,8]



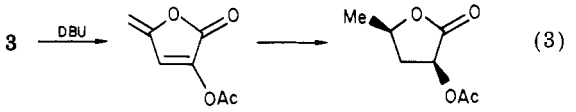
1 2 (1)

In 1981, Bock[9] reported that triacetate 3, when treated with hydrogen in the presence of triethylamine and palladium on carbon, afforded diacetate 4, presumably via elimination of the 3-acetoxy group and subsequent stereoselective hydrogenation of the corresponding unsaturated intermediate (eq 2). During the course of a synthesis



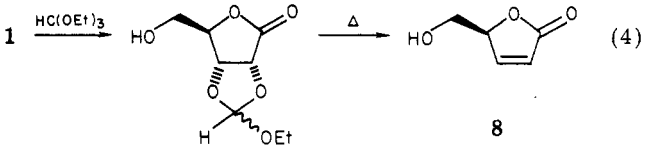
3 4 (2)

of (±)-*tert*-butyl 8-*O*-(*tert*-butyldimethylsilyl)nonactate,[10] Barrett converted 3 into a fully conjugated γ-lactone 5 which was hydrogenated to give racemic γ-lactone 6 (eq 3).



3 5 6 (3)

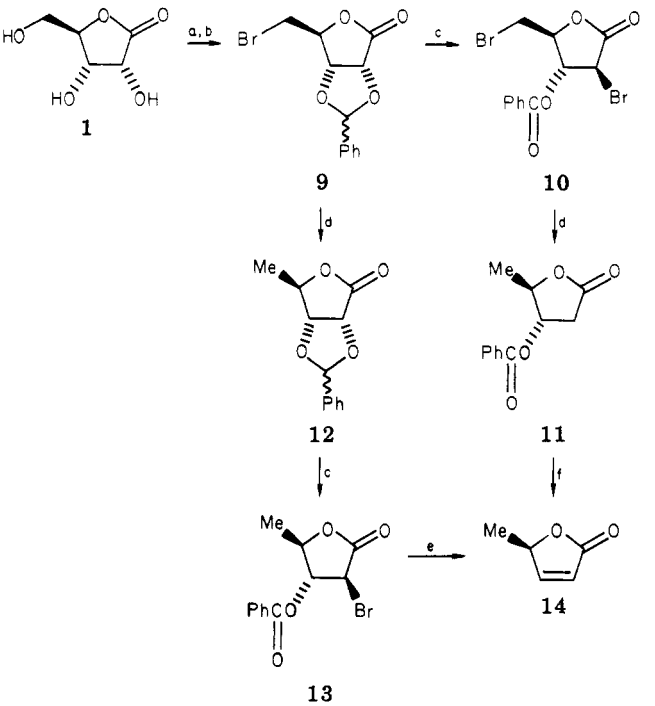
Recently, Font[11] described a facile preparation of orthoformate 7 from D-ribonolactone. Pyrolysis of 7 afforded butenolide 8 in good yield (eq 4).



1 7 8 (4)

(5) Available from Sigma Chemical Co. at $16.25/100 g.
(6) Zinner, H.; Voigt, H.; Voigt, J. *Carbohydr. Res.* **1968**, *7*, 38.
(7) Chen, S. Y.; Joullié, M. M. *Tetrahedron Lett.* **1983**, *24*, 5027.
(8) We also observed that when zinc chloride was used instead of concentrated hydrochloric acid, 2,3-*O*-benzylidene-D-ribonic acid γ-lactone was isolated in 40% yield along with small amounts of 2.
(9) Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scand., Ser. B* **1981**, *B35*, 155.
(10) Barrett, A. G.; Sheth, H. G. *J. Chem. Soc., Chem. Commun.* **1982**, 170.
(11) Camps, P.; Font, J.; Ponsati, O. *Tetrahedron Lett.* **1981**, *22*, 1471.

Scheme I[a]



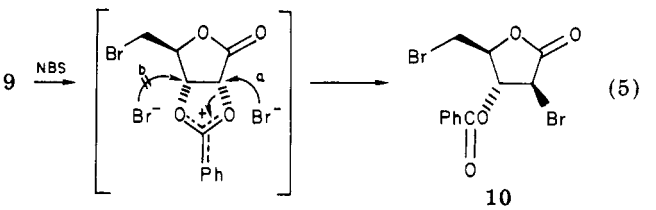
1 9 10 12 11 13 14

[a] a, PPh_3, CBr_4, MeCN; b, PhCHO, $ZnCl_2$; c, NBS, $BaCO_3$, CCl_4, Δ; d, *n*-Bu_3SnH, AIBN, toluene, Δ; e, Zn, EtOH, Δ; f, NH_3, MeOH.

In view of the abundance of natural products containing γ-lactone moieties, we began an intensive investigation of the regio- and stereoselective functionalizations of 1.

Results and Discussion

As shown in Scheme I, the three hydroxyl groups of 1 were converted into different functional groups by regio- and stereocontrolled reactions. Selective bromination of the primary hydroxyl group of 1 with triphenylphosphine and carbon tetrachloride, followed by benzylidene formation with benzaldehyde and anhydrous zinc chloride afforded 2,3-*O*-benzylidene-5-bromo-5-deoxy-D-ribonic acid γ-lactone (9) in 58% yield. When Hanessian's procedure[12] was used (*N*-bromosuccinimide, barium carbonate in refluxing carbon tetrachloride), ring opening of the benzylidene acetal afforded dibromobenzoate 10 in essentially quantitative yield. The exclusive formation of 10 may be explained via a SN2 attack of bromide ion from the more electrophilic and less sterically hindered position (a) of the benzoxonium ion (eq 5). Tri-*n*-butyltin hydride reduction



9 10 (5)

of 10 afforded benzoate 11 in 75% yield. Alternatively, reduction of 9 under the same conditions afforded 12. Stereoselective ring opening of the benzylidene ring of 12 under Hanessian's conditions gave 13 in 88% yield. The structural assignments for 10 and 13 were determined from their ^1H NMR spectra (see Experimental Section).

With compounds 11 and 13 in hand, the possibility of functionalizing the α-position of these γ-lactones was ex-

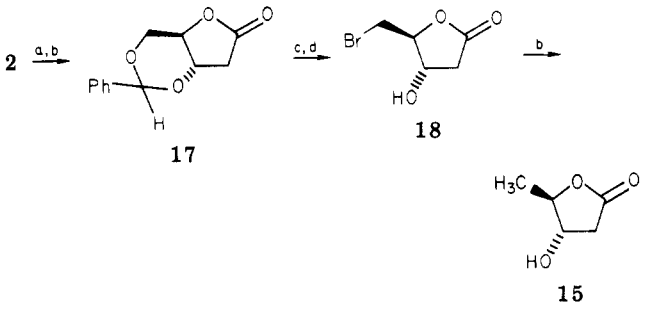
(12) Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86.

Table I. Aldol Condensation of Dianion 15a[a]

compd	R	yield, %	ratio (22/23)	$^3J_{2,3}$, Hz		$^3J_{2,6}$, Hz	
				22	23	22	23
a	C_6H_5	75	3:1	7.5	8.9	3.8	8.7
b	$CH_3(CH_2)_{11}CH_2$	60	1:1.5	8.5	9.3	3.4	3.8
c	$HC{\equiv}C(CH_2)_8CH_2$	72	1:2	8.4	9.2	4.5	5.4

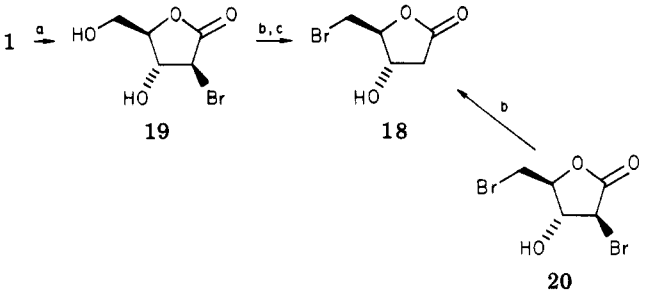
[a] Yields are reported for material isolated by flash chromatography.

Scheme II[a]



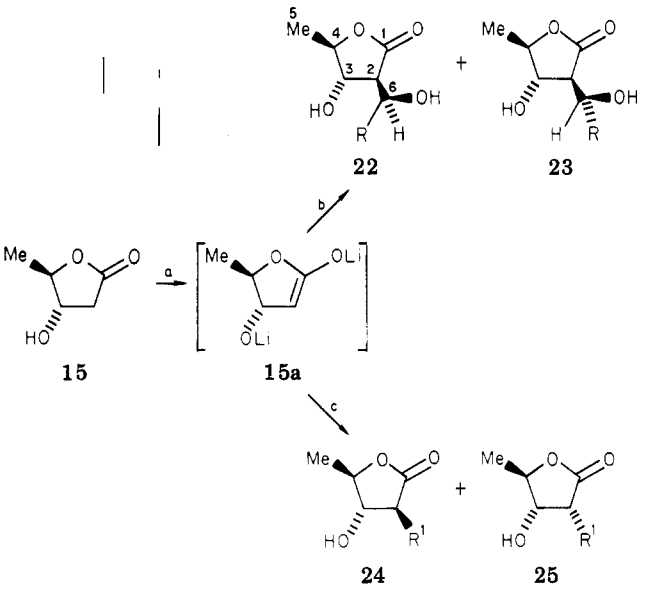
[a] a, NaH/CS_2/MeI, DMF; b, *n*-Bu_3SnH, AIBN, toluene, Δ; c, CF_3CO_2H:H_2O:$CHCl_3$ = 1:1:4, Δ; d, CBr_4, PPh_3, MeCN.

Scheme III[a]



[a] a, (1) 35% HBr, HOAc, (2) MeOH; b, Pd/C, H_2, Et_3N, EtOAc; c, CBr_4, PPh_3, MeCN.

Scheme IV[a]



[a] a, LDA (2.2 equiv), THF, −78 °C; b, $ZnCl_2$, RCHO, THF, −50 °C; c, R^1X, HMPA, −50 °C.

plored. Unfortunately, all attempts to generate an enolate from **11** resulted in decomposition of the starting material, and treatment of **13** with triphenylphosphine or triethyl phosphite did not form the desired precursor of a Wittig-type reagent. In both cases, these failures were due to the presence of the β-benzoxyl group and its facile elimination. Elimination of benzoate from **11** occurred quantitatively and immediately upon treatment of **11** with a methanolic ammonia solution. Treatment of **13** with zinc in refluxing ethanol also afforded butenolide **14** in 93% yield. Therefore, we turned our attention to the preparation of 2,5-dideoxy-D-*erythro*-pentono-γ-lactone (**15**), as shown in Scheme II. Benzylidene derivative **2** was prepared in 93% yield according to Zinner's procedure.[6] The reaction of **2** with carbon disulfide in the presence of sodium hydride in DMF was followed by methylation to form the corresponding xanthate (**16**) which was reduced with tri-*n*-butyltin hydride to **17** in 70% yield. Hydrolysis of **17** with 50% aqueous trifluoroacetic acid in chloroform was followed by selective bromination with triphenylphosphine and carbon tetrabromide to afford **18** in 30% yield. Debromination of **18** with tri-*n*-butyltin hydride gave **15** in 92% yield. The low yield of **18** prompted us to devise an alternate approach to this key intermediate, as seen in Scheme III.

The conversion of **1** to **19** and **20** (65% and 4% yields, respectively) was accomplished by a procedure introduced by Golding[13a] and Bock.[13b] D-Ribonolactone was treated with a 35% solution of hydrogen bromide in acetic acid, followed by deacetylation with methanol. Catalytic hydrogenolysis of **19**, followed by the previously described selective bromination afforded **18** in 72% yield. Selective catalytic hydrogenolysis of **20** also provided **18** in 85% yield. The overall yield for the preparation of **15** from **1** was 46%. The formation of **19** from **1** is believed to proceed through the formation of 5-*O*-acetyl-D-ribono-γ-lactone (**21**) which precipitates if 20% hydrogen bromide in acetic acid is used. When 35% hydrogen bromide in acetic acid is employed, the monoacetate does not precipitate and reacts further to the products.

The dianions of β-hydroxy esters are known to alkylate at the α-position with high stereoselectivity.[14,15] Recently, Shieh and Prestwich[16] reported the stereoselective alkylation and aldol condensation of the dianion of a β-hydroxy γ-lactone. Chamberlin and Dezube[17] also performed the stereoselective methylation of β-hydroxy γ-lactone dianions. Encouraged by these results, we investigated the possibility of carrying out stereoselective aldol condensations and alkylations by using the chiral hydroxyl group of **15** as a control element.

As shown in Scheme IV, dianion **15a** was prepared by the addition of 2.2 equiv of lithium diisopropylamide in THF at −78 °C. Addition of aldehydes in the presence of 1 equiv of zinc chloride,[16] followed by warming to −50 °C for 2 h and quenching with 20% aqueous ammonium

(13) (a) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1214. (b) Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1981**, *90*, 17.

(14) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829.
(15) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197.
(16) Shieh, H. M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319.
(17) Chamberlin, A. R.; Dezube, M. *Tetrahedron Lett.* **1982**, *23*, 3055.

Table II. Alkylation of Dianion 15a[a]

compd	R^1X	yield, %	$^3J_{2,3}$, Hz
24a	CH_3I	57	9.2
24b	$CH_3(CH_2)_{12}CH_2Br$	21	8.6
24c	$BrCH_2(CH_2)_8CH_2Br$	18	8.5

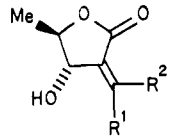
[a] Yields are reported for material isolated by flash chromatography.

chloride at −50 °C, afforded a mixture of diols in good yields (Table I).

The structural assignments of these diols were based on an analysis of the ^1H NMR spectra of these compounds. The large $^3J_{2,3}$ value (7.5–9.3 Hz) confirmed the anti relation of H-2 and H-3[17] while the smaller $^3J_{2,6}$ in **22** is consistent with the results of House,[18] Prestwich,[16] and Widdowson.[19]

The methylation of dianion **15a** at −50 °C gave 59% of **24a** and **25a** in a 20:1 ratio. The alkylation of dianion **15a** with myristyl bromide and 1,10-dibromodecane afforded low yields of a single product (Table II).

Compounds **22b** and **23b** were converted into the naturally occurring Lauraceae lactones, (−)-litsenolides C_1 (**26**) and C_2 (**27**),[7] while compounds **22c** and **23c** were transformed into (−)-litsenolides B_1 (**28**) and B_2 (**29**).[20]



26, R^1 = H; R^2 = $(CH_2)_{12}CH_3$
27, R^1 = $(CH_2)_{12}CH_3$; R^2 = H
28, R^1 = H; R^2 = $(CH_2)_9C{\equiv}CH$
29, R^1 = $(CH_2)_9C{\equiv}CH$; R^2 = H

In conclusion, D-ribonolactone has proved to be an excellent precursor for the synthesis of optically active γ-lactones which, in turn, are important intermediates in the synthesis of many natural products. Further synthetic applications of **1** are still under investigation.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WM 250 (250 MHz) or an IBM WP 200 SY (200 MHz) Fourier transform spectrometer. Chemical shifts are in parts per million (δ) relative to tetramethylsilane. Coupling constants (*J* values) are in Hertz (Hz). Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). The peaks are integrated in units of protons. Infrared spectra (IR) were run on Perkin-Elmer Model 281 A and 281 B spectrometers. Mass spectra data were provided by the Mass Spectrometry Center at the Chemistry Department at the University of Pennsylvania. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line and ambient temperatures. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plates (250 μm). Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in 95% ethanol containing 2% acetic acid, and phosphomolybdic acid (PMA) reagent (7% w/v) in 95% ethanol.

3,5-*O*-Benzylidene-D-ribonic Acid γ-Lactone (2). A mixture of D-ribonolactone (4.43 g, 0.03 mol), freshly distilled benzaldehyde (40 mL), and concentrated hydrochloric acid (4 mL) was stirred at ambient temperature for 7 h. Ether (50 mL) was added to precipitate the product which was collected by filtration. The crude product was washed successively with 5% sodium bicarbonate, water, and petroleum ether. After drying (P_2O_5) the white product was recrystallized from acetone–petroleum ether to afford needles, mp 230–231.5 °C (lit.[6] mp 233–235.5 °C); $[\alpha]_D$ −177.0° (c 2.37, DMF) (lit.[6] $[\alpha]_D$ −174.1° (c 2.26, DMF); ^1H NMR (250 MHz, Me_2SO-d_6) δ 4.33 (d, 1 H, $J_{5,5'}$ = 13.4), 4.42 (dd, 1 H, $J_{4,5}$ = 1.2), 4.62 (dd, 1 H, $J_{2,3}$ = 3.1, $J_{2,2OH}$ = 6.7), 4.63 (dd, 1 H, $J_{3,4}$ = 7.9), 4.69 (dd, 1 H), 5.74 (s, 1 H), 5.86 (d, 1 H, D_2O exchangeable), 7.40–7.43 (s, br, 5 H); ^{13}C NMR (62.9 MHz, Me_2SO-d_6) δ 66.8, 67.7, 73.3, 76.7, 102.6, 127.1, 128.1, 129.7, 136.0, 171.6; IR (KBr) 3335, 2876, 1750, 1445, 1403, 1180, 1140, 1078, 1055, 1042, 1010, 950, 767, 717 cm^{-1}; HRMS calcd for $C_{12}H_{12}O_5$, 236.0685; found, 236.0686.

2,3-*O*-Benzylidene-5-bromo-5-deoxy-D-ribonic Acid γ-Lactone (9). A stirred suspension of 2.962 g (20 mmol) of D-ribonolactone and 8.300 g (25 mmol, 1.25 equiv) of carbon tetrabromide in 40 mL of acetonitrile was treated with 7.840 g (30 mmol, 1.5 equiv) of triphenylphosphine in portions under ice bath cooling. The mixture was stirred at room temperature for 2 h. The clear yellow solution was concentrated and the residue washed with petroleum ether. The crude product was not isolated but treated directly with 30 mL of freshly distilled benzaldehyde and 3.0 g of anhydrous zinc chloride. The mixture was stirred for 7 h at ambient temperatures and then diluted with 100 mL of ether. The ether extracts were washed successively with 5% aqueous sodium bicarbonate and water. The brown syrup obtained after solvent removal was dissolved in toluene and chromatographed with toluene to afford a separable mixture of two diastereomeric forms of **9** in a 2:1 ratio (3.495 g, 58.4% yield). The major fraction (**9a**) was recrystallized from ether–petroleum ether to afford colorless plates: mp 84–85 °C; $[\alpha]_D$ −11.5° (c 2.0, $CHCl_3$); HRMS calcd for $C_{12}H_{11}O_4Br$, 297.9841; found, 297.9833; ^1H NMR (250 MHz, $CDCl_3$) δ 3.68 (dd, $J_{5,5'}$ = 11.4, $J_{4,5}$ = 2.6), 3.72 (dd, $J_{4,5'}$ = 3.7), 4.77 (d, 1 H, $J_{2,3}$ = 6.3), 5.02 (dd, 1 H), 5.13 (d, 1 H), 5.95 (s, 1 H), 7.3–7.6 (m, 5 H); IR ($CHCl_3$) 2950, 1795, 1335, 1240, 1175, 1090, 1075, 1030, 980, 685 cm^{-1}.

The minor fraction (**9b**) was recrystallized from acetone to afford needles: mp 157.5–159 °C; $[\alpha]_D$ −26.5° (c 2.0, acetone); HRMS calcd for $C_{12}H_{11}O_4Br$, 297.9841; found, 297.9835; ^1H NMR (250 MHz, acetone-d_6) δ 3.88 (dd, 1 H, $J_{5,5'}$ = 11.4, $J_{4,5}$ = 3.4), 3.98 (dd, 1 H, $J_{4,5'}$ = 4.4), 5.02 (d, 1 H, $J_{2,3}$ = 6.3), 5.08 (dd, 1 H), 5.13 (d, 1 H), 6.03 (s, 1 H), 7.35–7.55 (m, 5 H); IR ($CHCl_3$) 2950, 1800, 1395, 1345, 1250, 1170, 1095, 1078, 1035, 940, 695 cm^{-1}.

3-*O*-Benzoyl-2,5-dibromo-2,5-dideoxy-D-arabonic Acid γ-Lactone (10). *N*-Bromosuccinimide (0.828 g, 4.653 mmol, 1.2 equiv) and barium carbonate (0.918 g, 4.653 mmol, 1.2 equiv) were added to a diastereomeric mixture (1.160 g, 3.878 mmol) of **9a** and **9b** in carbon tetrachloride (35 mL). The mixture was refluxed for 2 h and allowed to cool to room temperature. Solids were removed by filtration and the filtrate washed successively with saturated aqueous sodium thiosulfate, aqueous sodium bicarbonate, and water. After drying ($MgSO_4$), the solvent was removed in vacuo to afford **10** as a syrup which showed a single spot on TLC: $[\alpha]_D$ −49.5° (c 3.11, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.81 (dd, 1 H, $J_{5,5'}$ = 11.2, $J_{4,5}$ = 6.3), 3.85 (dd, 1 H, $J_{4,5'}$ = 5.5), 4.62 (d, 1 H, $J_{2,3}$ = 3.3), 4.85 (ddd, 1 H, $J_{3,4}$ = 2.8), 5.73 (dd, 1 H), 7.4–7.7 (m, 3 H), 8.0–8.1 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 30.2 (t), 38.9 (d), 78.6 (d), 82.3 (d), 128.3 (s), 128.8 (d), 130.1 (d), 134.2 (d), 165.2 (s), 169.1 (s); IR (CCl_4) 2900, 1760, 1730, 1310, 1260, 1180, 1150, 1103, 1090, 1070, 1030, 710 cm^{-1}.

3-*O*-Benzoyl-2,5-dideoxy-D-ribonic Acid γ-Lactone (11). Compound **10** (1.466 g, 3.878 mmol) was dissolved in anhydrous toluene (10 mL) and treated with tri-*n*-butyltin hydride (3.950 g, 13.57 mmol, 3.5 equiv) and α,α′-azobis(isobutyronitrile) (10 mg) under a nitrogen atmosphere. The reaction was heated overnight at 80–90 °C. The solvent was evaporated in vacuo and the residue washed with petroleum ether to remove the organotin compounds. Removal of solvent and subsequent recrystallization from ether–petroleum ether afforded **11** (0.606 g, 71% yield) as colorless plates: mp 100.5–101.5 °C; $[\alpha]_D$ −42.5° (c 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.50 (d, 3 H, $J_{4,5}$ = 6.6), 2.74 (dd, 1 H, $J_{2,2'}$ = 18.8, $J_{2,3}$ = 2.2), 3.08 (dd, 1 H, $J_{2',3}$ = 7.0), 4.78 (dq, 1 H, $J_{3,4}$ = 1.8), 5.30 (ddd, 1 H), 7.4–8.1 (m, 5 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.8 (q), 34.2 (d), 75.0 (d), 81.6 (d), 128.6 (d), 129.3 (s), 129.8 (d), 133.6 (d), 165.8 (s), 173.7 (s); IR ($CHCl_3$) 2930, 1785, 1725, 1275, 1180, 1110, 1100 cm^{-1}.

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(19) Widdowson, D. A.; Wiebecke, G. H.; Williams, D. J. *Tetrahedron Lett.* **1982**, *23*, 4285.
(20) Details will be published somewhere else.

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.61; H, 5.47.

2,3-*O*-Benzylidene-5-deoxy-D-ribonic Acid γ-Lactone (12). Compound **9** (0.260 g, 0.869 mmol) in toluene (2 mL) was reduced with tri-*n*-butyltin hydride (0.379 g, 1.304 mmol, 1.5 equiv) and α,α′-azobis(isobutyronitrile) (5 mg) as described for **11**. Two diasteromeric forms of **12** (0.149 g, 77.9% yield) were separated by column chromatography (ether–petroleum ether, 1:1). **12a**: mp 66–66.5 °C; $[\alpha]_D$ −47.4° (*c* 1.36, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.44 (d, 3 H $J_{4,5}$ = 7.0), 4.55 (dd, 1 H, $J_{3,4}$ = 0.74, $J_{2,3}$ = 5.9), 4.83 (q, 1 H), 5.03 (d, 1 H), 5.98 (s, 1 H), 7.3–7.6 (m, 5 H); IR (KBr) 2900, 2800, 1775, 1460, 1350, 1340, 1280, 1235, 1225, 1185, 1175, 1105, 1090, 1075, 1045, 1030, 1000, 980, 920, 895, 875, 793, 765 cm^{-1}. **12b**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.44 (d, 3 H, $J_{4,5}$ = 6.6), 4.67 (d, 1 H, $J_{2,3}$ = 5.9), 4.82 (q, 1 H), 4.93 (d, 1 H), 6.01 (s, 1 H), 7.3–7.6 (m, 5 H); HRMS calcd for $C_{12}H_{11}O_4$ (M^+ − 1), 219.0657; found, 219.0658. The other diasteromer, **12b**, was recrystallized from ether–petroleum ether to afford needles: mp 141–141.5 °C; $[\alpha]_D$ −95.6° (*c* 0.87, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.44 (d, 3 H, $J_{4,5}$ = 6.6); 4.67 (d, 1 H, $J_{2,3}$ = 5.9), 4.82 (q, 1 H), 4.93 (d, 1 H), 6.01 (s, 1 H), 7.3–7.6 (m, 5 H); IR ($CHCl_3$) 2880, 1780, 1455, 1395, 1380, 1345, 1180, 1100, 1075, 978, 925, 915 cm^{-1}; HRMS calcd for $C_{12}H_{11}O_4$ (M^+ − 1), 219.0657; found, 219.0658.

3-*O*-Benzoyl-2-bromo-2,5-dideoxy-D-arabonic Acid γ-Lactone (13). *N*-Bromosuccinimide (0.145 g, 0.812 mmol, 1.2 equiv) and barium carbonate (0.160 g, 0.812 mmol, 1.2 equiv) were added to a stirred solution of **12** (0.149 g, 0.677 mmol) in 5 mL of carbon tetrachloride. The mixture was heated at reflux for 2 h and purified as described for **10** to afford a syrup which was recrystallized from methanol to give 0.178 g of **13** (88.0% yield) as needles: mp 91.5–92.5 °C; $[\alpha]_D$ −98.6° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.70 (d, 3 H, $J_{4,5}$ = 6.6), 4.58 (d, 1 H, $J_{2,3}$ = 2.9), 4.76 (dq, 1 H, $J_{3,4}$ = 2.9), 5.48 (t, 1 H), 7.4–8.1 (m, 5 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.3, 39.0, 80.6, 81.1, 128.4, 128.7, 129.9, 134.0, 165.2, 170.2; IR ($CHCl_3$) 2950, 1785, 1730, 1380, 1345, 1310, 1260, 1180, 1105, 1095, 1070, 1035, 1030, 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}O_4Br$: C, 48.18; H, 3.71; Br, 26.72. Found: C, 48.44; H, 3.65; Br, 26.42.

(−)-5(*R*)-Methyl-2(5*H*)-furanone (14). Preparation from 13. A mixture of **13** (0.600 g, 2.00 mmol) and zinc (0.500 g, 7.65 mmol) in absolute ethanol (7 mL) was refluxed for 1 h. The solution was cooled to room temperature and the insoluble byproduct removed by filtration. The filtrate was concentrated to dryness and dissolved in ether (15 mL). The ether layer was washed with water, dried ($MgSO_4$), concentrated in vacuo, and distilled at 60 °C (0.025 mmHg) to give 0.341 g (93.2% yield) of **14**: $[\alpha]_D$ −107.0° (*c* 1.61, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.47 (d, 3 H, $J_{4,5}$ = 6.9), 5.15 (tq, 1 H), 6.10 (dd, 1 H, $J_{3,4}$ = 1.9, $J_{2,3}$ = 5.6), 7.48 (dd, 1 H, $J_{2,4}$ = 1.4); IR (neat) 3050, 2900, 1765, 1320, 1165, 1110, 1075, 1030, 960, 893, 853, 820 cm^{-1}; HRMS (CI) calcd for $C_5H_6O_2$ (M^+), 98.0368; found, 98.0369.

Preparation from 11. A solution of **11** (0.220 g, 1.00 mmol) in methanol (5 mL) was treated with gaseous ammonia for 3 min. The solution was evaporated to dryness and purified as described in the preparation from **13**. The desired product was obtained as a colorless oil, 0.099 g, 100% yield.

2,5-Dideoxy-D-*erythro*-pentono-γ-lactone (15). Preparation from 18. To a solution of **18** (3.610 g, 18.51 mmol) in dry toluene (50 mL) was added tri-*n*-butyltin hydride (12.914 g, 40.72 mmol, 2.2 equiv) and α,α′-azobis(isobutyronitrile) (20 mg) under a nitrogen atmosphere. The reaction mixture was heated for 18 h at 90 °C. The residue obtained by evaporation of volatile materials under reduced pressure was dissolved in aceonitrile and washed with hexane. Evaporation of the solvent afforded a yellow syrup which was purified by flash column chromatography with ether to afford **15** (1.971 g, 91.7% yield) as a colorless liquid: bp 108–110 °C (0.025 mmHg), $[\alpha]_D$ +10.87° (*c* 2.42, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (d, 3 H, $J_{4,5}$ = 6.6), 2.53 (dd, 1 H, $J_{2,2'}$ = 18.0, $J_{2,3}$ = 3.6), 2.85 (dd, 1 H, $J_{2',3}$ = 6.5), 3.37 (d, 1 H, $J_{3OH,3}$ = 4.4, D_2O exchangeable), 4.24 (m, 1 H), 4.52 (dq, 1 H, $J_{3,4}$ = 2.8); ^{13}C NMR (50 MHz, acetone-d_6) δ 18.6, 37.6, 73.1, 84.6, 175.6; IR (neat) 3300, 2900, 1760, 1350, 1185, 1100, 1050, 1030, 940 cm^{-1}; HRMS calcd for $C_5H_9O_3$ (M^+ + 1), 117.0551; found, 117.0560.

Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.46; H, 7.08.

Hydrogenolysis of 18. A solution of **18** (1.405 g, 7.204 mmol) in ethyl acetate (30 mL) and triethylamine (1.0 mL) was treated with hydrogen in a Parr apparatus using 10% palladium on carbon (200 mg) as the catalyst. The only products isolated were triethylamine hydrobromide and a mixture of **15** and 3-hydroxypentanoic acid in a 1:2 ratio.

3,5-*O*-Benzylidene-2-*O*-[(methylthio)thiocarbonyl]-D-ribonic Acid γ-Lactone (16). To a stirred solution of **2** (0.824 g, 3.48 mmol) and carbon disulfide (2.1 mL, 34.80 mmol) in dry dimethylformamide (13 mL) was added in portions sodium hydride (0.153 g, 3.83 mmol, 60% dispersion in oil), and the stirring was continued at room temperature for 30 min. Methyl iodide (2.2 mL, 10 equiv) was then added and the stirring continued for a further 30 min at room temperature. The reaction mixture was concentrated and then diluted with 15 mL of water. The aqueous layer was extracted with ethyl acetate, washed with a saturated sodium chloride solution, and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was crystallized twice from chloroform–ether to give a crystalline xanthate (0.716 g): mp 145–146 °C; $[\alpha]_D$ −314.3° (*c* 2.01, $CHCl_3$). The mother liquor was concentrated and purified by column chromatography with methylene chloride to afford additional product (0.143 g): total yield, 0.859 g, 75.5%; ^1H NMR (250 MHz, $CDCl_3$) δ 2.64 (s, 3 H), 4.42 (dd, 1 H, $J_{5,5'}$ = 13.6, $J_{5,4}$ = 1.5), 4.62 (d, 1 H), 4.73 (dd, 1 H, $J_{3,4}$ = 8.1), 4.97 (dd, 1 H, $J_{2,3}$ = 2.9); 5.81 (s, 1 H), 6.45 (d, 1 H), 7.35–7.55 (m, 5 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.4, 67.6, 73.6, 74.4, 75.4, 104.8, 127.3, 128.6, 130.3, 134.9, 164.6, 201.6; IR ($CHCl_3$) 2950, 2850, 1785, 1460, 1403, 1390, 1190, 1160, 1120, 1085, 1055, 1030, 1018, 1005 cm^{-1}.

3,5-*O*-Benzylidene-2-deoxy-D-ribonic Acid γ-Lactone (17). To a solution of xanthate **16** (2.583 g, 7.914 mmol) in dry toluene (100 mL) was added tri-*n*-butyltin hydride (3.312 mL, 11.87 mmol, 1.5 equiv) and α,α′-azobis(isobutyronitrile) (20 mg) under a nitrogen atmosphere. The mixture was refluxed under nitrogen for 2 h. The solvent was removed in vacuo and the residue was washed with petroleum ether. Recrystallization from methanol afforded 1.612 g (92.5% yield) of **17** as needles: mp 139–139.5 °C; $[\alpha]_D$ −172.3° (*c* 1.71, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.63 (dd, 1 H, $J_{2,2'}$ = 15.8, $J_{2,3}$ = 3.7), 3.05 (dd, 1 H, $J_{2',3}$ = 2.6), 4.23 (dd, 1 H, $J_{4,5}$ = 1.8, $J_{5,5'}$ = 12.9), 4.58 (d, 1 H), 4.59 (dd, 1 H, $J_{3,4}$ = 1.1), 4.79 (ddd, 1 H), 5.76 (s, 1 H), 7.3–7.6 (m, 5 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.4, 68.2, 72.4, 72.5, 103.8, 127.2, 128.5, 130.1, 135.5, 169.0; IR (KBr) 2880, 1745, 1410, 1390, 1345, 1265, 1160, 1102, 1065, 1045, 1030, 975, 782, 760 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.67; H, 5.67.

5-Bromo-2,5-dideoxy-D-*erythro*-pentono-γ-lactone (18). Preparation from 17. A stirred solution of **17** (0.670 g, 3.042 mmol) in 18 mL of trifluoroacetic acid, water, and chloroform (1:1:4) was heated to reflux for 10 h. After solvent removal, the presumed deprotected diol was not isolated but dissolved in acetonitrile (10 mL) and treated directly with carbon tetrabromide (1.261 g, 3.803 mmol) and triphenylphosphine (1.200 g, 4.564 mmol). After concentration of the solution, the residue was purified by column chromatography with ethyl acetate–ether (1:1) to give 0.177 g of **18** (29.8% yield) as a colorless syrup: $[\alpha]_D$ +13.8° (*c* 1.70, acetone); ^1H NMR (250 MHz, acetone-d_6) δ 2.46 (dd, 1 H, $J_{2,2'}$ = 18.0, $J_{2,3}$ = 7.0), 2.99 (dd, 1 H, $J_{2',3}$ = 3.4), 3.70 (dd, 1 H, $J_{5,5'}$ = 11.3, $J_{4,5}$ = 5.4), 3.77 (dd, 1 H, $J_{4,5'}$ = 4.8), 4.47 (m, 1 H, $J_{3,4}$ = 3.1), 4.58 (m, 1 H), 4.93 (d, 1 H, $J_{3,3OH}$ = 3.9, D_2O exchangeable); IR (neat) 3400, 2900, 1750, 1160, 1040, 985 cm^{-1}; HRMS calcd for $C_4H_7O_2Br$ (M^+ − CO), 169.9629; found, 169.9630.

Preparation from 19. A solution of **19** (5.00 g, 23.69 mmol) in ethyl acetate (80 mL) and triethylamine (3.4 mL) was treated with hydrogen in a Parr apparatus using 10% palladium on carbon (300 mg) as catalyst. The catalyst was removed by filtration and the filtrate concentrated to afford a syrup (3.465 g, 26.23 mmol) contaminated with triethylamine hydrobromide. The crude product was dissolved in 70 mL of dry acetonitrile and treated with carbon tetrabromide (10.22 g, 30.80 mmol, 1.3 equiv) and triphenylphosphine (8.08 g, 30.80 mmol, 1.3 equiv) at room temperature for 0.5 h. The solution was concentrated in vacuo and redissolved in a 2:1 acetone–ether mixture (30 mL). After cooling overnight, the insoluble byproducts were removed by filtration and the remaining syrup was purified by column chromatography with ethyl acetate–ether (1:1) to afford a colorless oil (3.319 g,

17.02 mmol, 71.8% yield) which was identical with previously prepared 18.

Preparation from 20. When the procedure described for the preparation of 18 from 19 was used, dibromide 20 was selectively reduced to 18 in 85.0% yield.

2-Bromo-2-deoxy-D-arabinono-γ-lactone (19) and 2,5-Dibromo-2,5-dideoxy-D-arabinono-γ-lactone (20). A solution of hydrogen bromide in acetic acid (~35%) was prepared by saturating glacial acetic acid with anhydrous hydrogen bromide first at room temperature and than at 0 °C. A solution of 1 (30.0 g, 0.202 mol) in ~35% hydrogen bromide in glacial acetic acid was kept at room temperature for 4 h. Methanol (210 mL) was added and the resulting solution allowed to stir overnight. After concentration and removal of acetic acid from the residue, the crude product was diluted with water and extracted with chloroform, and the solution was dried ($MgSO_4$) and concentrated to afford crude **20**[13b] (2.43 g, 8.87 mmol, 4.3% yield). The aqueous layer was extracted continuously with ether (250 mL) for 24 h. The extract was dried ($MgSO_4$) and concentrated to afford a brown syrup (39.4 g) which was recrystallized from ether to afford **19** (25.68 g, 0.166 mol, 65.1% yield): mp 74–78 °C. Further recrystallization gave a higher melting product: mp 79–81 °C; $[\alpha]_D$ +70.3° (*c* 3.85, ethyl acetate), (lit.[13b] mp 79–81 °C; $[\alpha]_D$ +72° (*c* 4.1, ethyl acetate). The absolute configuration of **19** was confirmed by X-ray crystallography:[20] ^1H NMR (250 MHz, Me_2SO-d_6) δ 3.56 (ddd, 1 H, $J_{5,5'}$ = 12.8, $J_{5,4}$ = 4.3, $J_{5,5OH}$ = 6.0), 3.73 (ddd, 1 H, $J_{5',4}$ = 2.4, $J_{5',5OH}$ = 5.1), 4.22 (ddd, 1 H, $J_{4,3}$ = 7.4), 4.23 (m, 1 H), 4.96 (d, 1 H, $J_{2,3}$ = 8.4), 5.19 (t, 1 H, D_2O exchangeable), 6.38 (d, 1 H, $J_{3,3OH}$ = 5.8, D_2O exchangeable); IR (KBr) 3350, 2900, 1780, 1340, 1320, 1180, 1170, 1108, 1065, 1025 cm^{-1}. **20**: ^1H NMR (250 MHz, $CDCl_3$) δ 2.7–3.2 (s, br, 1 H), 3.67 (dd, 1 H, $J_{5,5'}$ = 11.5, $J_{5,4}$ = 4.8), 3.75 (dd, 1 H, $J_{5',4}$ = 6.0), 4.51 (d, 1 H, $J_{2,3}$ = 6.7), 4.55 (m, 1 H), 4.62 (m, 1 H).

5-*O*-Acetyl-D-ribono-γ-lactone (21). A solution of hydrogen bromide in acetic acid (~20%) was prepared by saturating glacial acetic acid with anhydrous hydrogen bromide at room temperature. A solution of 1 (5.0 g, 33.76 mmmol) in 20% hydrogen bromide in acetic acid was stirred for 1 h at room temperature. The white precipitate formed was removed by filtration, washed with methanol, and dried in vacuo to afford **21** (3.552 g, 18.67 mmol, 55.3%): mp 148–150 °C; ^1H NMR (250 MHz, Me_2SO-d_6) δ 2.04 (s, 3 H), 4.13 (m, 1 H), 4.16 (dd, 1 H, $J_{5,5'}$ = 12.1, $J_{5,4}$ = 5.9), 4.26 (dd, 1 H, $J_{5',4}$ = 3.6), 4.41 (dd, 1 H, $J_{3,2}$ = 5.3, $J_{2,2OH}$ = 7.5), 4.44 (m, 1 H), 5.58 (d, 1 H, $J_{3,3OH}$ = 4.0, D_2O exchangeable), 5.88 (d, 1 H, $J_{2,2OH}$ = 7.5, D_2O exchangeable).

Reaction of Dianion 15a with Myristyl Aldehyde. A solution of **15** (0.365 g, 3.143 mmol) in 3 mL of THF was added to a solution of 6.916 mmol of lithium diisopropylamide (prepared from 0.453 mL of diisopropylamine and 4.60 mL of 1.55 M of *n*-BuLi) in 3 mL of THF at −78 °C under nitrogen. The mixture was stirred for 1 h. Dry zinc chloride (0.428 g, 3.143 mmol, 1.0 equiv) in 9 mL of THF was added and stirred for 5 min. Myristyl aldehyde (0.734 g, 3.450 mmol, 1.1 equiv) in 2 mL of THF was then added, and the solution was warmed to −50 °C and stirred for 2 h. The reaction was quenched (2 mL of 20% aqueous ammonium chloride), brought to ambient temperature, and diluted with ether (15 mL). The ether layer was washed with a saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to a syrup. Flash column chromatography with ether–petroleum ether (2:1) afforded a mixture (1:1.5) of diastereomers (0.617 g, 1.878 mmol, 59.8%) as white solids: $[\alpha]_D$ +12.66° (*c*, 1.23, $CHCl_3$). **22b**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3 H, $J_{18,19}$ = 6.9)8 1.30 (bs, 22 H), 1.43 (d, 3 H, $J_{4,5}$ = 6.0), 1.68 (m, 2 H), 2.69 (dd, 1 H, $J_{2,6}$ = 3.4, $J_{2,3}$ = 8.5), 3.4, 3.5 (bs, 2 H), 4.14 (m, 1 H), 4.18 (m, 1 H), 4.26 (dq, 1 H, $J_{3,4}$ = 7.3); IR ($CHCl_3$) 3350, 2880, 2810, 1755, 1170, 1055 cm^{-1}. **23b**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3 H, $J_{18,19}$ = 6.5), 1.31 (bs, 22 H), 1.43 (d, 3 H, $J_{4,5}$ = 6.2), 1.85 (m, 2 H), 2.65 (dd, 1 H, $J_{2,6}$ = 3.8, $J_{2,3}$ = 9.3), 3.86 (m, 2 H), 3.97 (dd, 1 H), 4.25 (dq, 1 H, $J_{3,4}$ = 7.7), 4.40 (bs, 1 H); IR ($CHCl_3$) 3330, 2870, 2800, 1755, 1170, 1055 cm^{-1}. The major isomer was **23b** and the minor isomer was **22b**.

Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.36; H, 10.99.

Reaction of Dianion 15a with 11-Dodecynal. A solution of **15** (0.404 g, 3.480 mmol) in 4 mL of THF was added to a solution of 7.655 mmol of lithium diisopropylamide (prepared from 1.07 mL of diisopropylamine and 5.47 mL of 1.4 M *n*-butyllithium) in 4 mL of THF, at −78 °C under nitrogen. Dry zinc chloride (0.474 g, 3.480 mmol) in 10 mL of THF was added, followed by addition of 11-dodecynal (0.690 g, 3.827 mmol, 1.1 equiv) in 4 mL of THF as described for the preparation of **22b** and **23b**. When the same purification procedure was used, a 1:2 mixture of diastereomers (0.741 g, 2.457 mmol, 71.8% yield) was obtained as a colorless syrup: $[\alpha]_D$ +4.06° (*c* 1.13, $CHCl_3$). **22c**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (s, br), 1.25–1.80 (m, 14 H), 1.46 (d, 3 H, $J_{4,5}$ = 5.9), 1.95 (t, 1 H, $J_{15,17}$ = 2.6), 2.18 (m, 4 H), 2.40 (d, br, 1 H), 2.70 (dd, 1 H, $J_{2,3}$ = 8.4, $J_{2,6}$ = 4.5), 2.82 (s, br, 1 H), 4.12 (m, 1 H), 4.22 (m, 2 H); IR ($CHCl_3$) 3620, 3460, 3305, 2940, 2860, 1770, 1170, 1060 cm^{-1}. **23c**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (s, br), 1.20–1.84 (m, 14 H), 1.46 (d, 3 H, $J_{4,5}$ = 6.2), 1.95 (t, 1 H, $J_{15,17}$ = 2.6), 2.18 (m, 4 H), 2.69 (dd, 1 H, $J_{2,6}$ = 5.4, $J_{2,3}$ = 9.2), 3.08 (s, br, 1 H), 3.41 (m, 1 H), 3.93 (s, br, 1 H), 4.00 (t, 1 H), 4.25 (dq, 1 H, $J_{3,4}$ = 7.7); IR ($CHCl_3$) 3620, 3450, 3310, 3005, 2990, 2940, 2860, 1765, 1455, 1390, 1320, 1200, 1180, 1105, 1060, 700 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{29}O_4$ (M^+ + 1), 297.2065; found 297.2071.

Reaction of Dianion 15a with Benzaldehyde. When a procedure similar to that described for **22c** and **23c** was used, the dianion prepared from **15** (0.165 g, 1.507 mmol) and 3.126 mmol (2.2 equiv) of lithium diisopropylamide in 5 mL of THF, at −78 °C under nitrogen, was added to a solution of zinc chloride (0.205 g, 1.507 mmol) in 4 mL of THF and followed by the addition of benzaldehyde (0.150 g, 1.507 mmol) in 2 mL of THF. When the same purification procedure was used, a 3:1 mixture of diastereomers (0.233 g, 75.3% yield) was obtained. **22a**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (d, 3 H, $J_{4,5}$ = 5.9), 2.59 (d, 1 H, $J_{6OH,6}$ = 4.0), 2.90 (dd, 1 H, $J_{2,3}$ = 7.5, $J_{2,6}$ = 3.8), 3.63 (d, 1 H, $J_{3OH,3}$ = 4.6), 4.08–4.22 (m, 2 H), 5.21 (t, 1 H), 7.25–7.40 (m, 5 H); IR ($CHCl_3$) 3500, 3400, 1745, 1160, 1100, 1075, 1025 cm^{-1}. **23a**: mp 91–93 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.39 (d, 3 H, $J_{4,5}$ = 6.2), 1.64 (bs, 1 H), 2.94 (dd, 1 H, $J_{2,3}$ = 8.9), 3.80 (dd, 1 H), 4.06 (bs, 1 H), 4.22 (dq, 1 H, $J_{3OH,3}$ = 7.6), 4.93 (d, 1 H, $J_{2,6}$ = 8.7), 7.3–7.5 (m, 5 H); IR ($CHCl_3$) 3500, 3400, 1750, 1310, 1170, 1050, 1035, 1010 cm^{-1}; HRMS (CI) calcd for $C_{12}H_{14}O_4$ (M^+), 222.0892; found, 222.0889.

Reaction of Dianion 15a with Methyl Iodide. A solution of **15** (0.158 g, 1.361 mmol) in 2.5 mL of THF was added to 2.993 mmol of lithium diisopropylamide (prepared from 0.42 mL of diisopropylamine and 1.88 mL of 1.59 M *n*-butyllithium in 4 mL of THF) at −78 °C under nitrogen. Addition of methyl iodide (0.579 g, 4.082 mmol) in 0.5 mL of HMPA and 2 mL of THF was followed by stirring at −50 °C for 4 h. The reaction mixture was purified as previously described (flash chromatography, ether) and afforded a mixture of diastereomers. The major isomer **24a** was purified further (100.2 mg, 56.5%): mp 66.5–67.5 °C; $[\alpha]_D$ +29.9° (*c* 1.67, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (d, 3 H, $J_{2,6}$ = 7.2), 1.45 (d, 3 H, $J_{4,5}$ = 6.3), 2.61 (dq, 1 H, $J_{2,3}$ = 9.2), 2.71 (ddd, 1 H), 3.95 (d, 1 H, $J_{3,3OH}$ = 5.6), 4.24 (dq, 1 H, $J_{3,4}$ = 7.4); IR ($CHCl_3$) 3450, 3300, 2950, 1760, 1170, 1055, 960 cm^{-1}.

Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.12, H, 7.94. The minor isomer **25a** (4.8 mg, 2.7%) was presumed to be the cis product ($J_{2,3}$ = 5.8) but was not characterized further.

Reaction of Dianion 15a with Tetradecyl Bromide. When the previously described procedure was used, a mixture of the dianion prepared from **15** (0.225 g, 1.938 mmol) and 4.263 mmol (2.2 equiv) of lithium diisopropylamide in 4 mL of THF, at −78 °C under nitrogen, was treated with tetradecyl bromide (0.591 g, 2.132 mmol) in 3 mL of THF and 0.5 mL of HMPA. The product was purified as usual to afford 0.129 g (21.3% yield) of **24b**: mp 91–92 °C (lit.[21] 90–92°); $[\alpha]_D$ +11.5° (*c* 0.58, $CHCl_3$) (lit. $[\alpha]_D$ +10.4°, ±1.0° (*c* 0.52, dioxane)); ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, 3 H, $J_{18,19}$ = 6.8), 1.26 (bs, 24 H), 1.48 (d, 3 H, $J_{4,5}$ = 6.3), 1.62 (bs, 1 H), 1.85 (m, 1 H) 2.23 (d, 1 H, $J_{3OH,3}$ = 5.4), 2.56 (m, 1 H), 3.84 (ddd, 1 H, $J_{2,3}$ = 8.6, $J_{3,4}$ = 7.0), 4.20 (dq, 1 H); IR (KBr) 3350, 2860, 1745, 1465, 1340, 1320, 1290, 1280, 1190, 1185, 1085, 1048 cm^{-1}.

Reaction of Dianion 15a with 1,10-Dibromodecane. When the previously described procedure was used, a mixture of the dianion from **15** (0.146 g, 1.257 mmol) and 2.766 mmol (2.2 equiv)

(21) Takeda, K.; Sakurawi, K.; Ishii, H. *Tetrahedron* **1972**, *28*, 3757.

of lithium diisopropylamide in 2 mL of THF, at -78 °C under nitrogen, was treated with 1,10-dibromodecane (0.396 g, 1.320 mmol) in 0.5 mL of THF and 0.4 mL of HMPA. The product was purified as usual to afford 77 mg (18.2% yield) of **24c**: mp 73-74.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.2-1.7, 1.30 (m, bs, 16 H), 1.45 (d, 3 H, $J_{4,5}$ = 6.5), 1.85 (m, 2 H), 2.41 (d, 1 H, $J_{3OH,3}$ = 5.1), 2.57 (m, 1 H, $J_{2,3}$ = 8.5), 3.41 (t, 2 H $J_{14,15}$ = 6.8), 3.84 (ddd, 1 H), 4.21 (dq, 1 H, $J_{3,4}$ = 6.8); IR (KBr) 3320, 2860, 2800, 1730, 1460, 1355, 1340, 1320, 1300, 1280, 1270, 1205, 1190, 1180, 1085, 1050 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{26}O_3Br$ (M^+ - 1), 333.1065; found, 333.1056.

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Competitive Bridgehead Substitution in Electrophilic Oxidation Reactions of Ethanoadamantane

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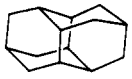
In contrast to an earlier report, it is shown that oxidation of ethanoadamantane with lead tetraacetate, chromic acid, or a mixture of *tert*-butyl bromide and aluminum bromide occurs by competitive attack at the C-1, C-6, *and* C-8 bridgehead positions. The structure assignments of 6- and 8-ethanoadamantanol have been firmly established by ^{13}C NMR spectroscopy.

Although no quantitative study has been carried out, Schleyer has noted that the qualitative ease of ionic bromination of some polycyclic hydrocarbons seems to parallel the solvolysis rates of the resulting bromides.[1-3] These observations have led him to suggest that the relative proclivity for bromination at alternative intramolecular sites in these substrates can be related to the calculated change in strain energy (Δ strain) for carbocation formation at these positions. Since ionic bromination of hydrocarbons shows a strong preference for attack at tertiary C-H bonds, attention is directed to the bridgehead positions. For example, the ionic brominations of protoadamantane[1] (1) and diamantane[2] (2) take place exclu-

1



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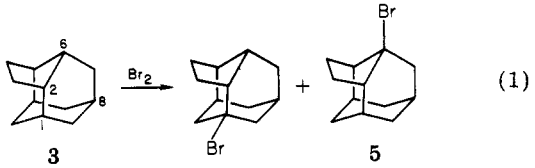
sively at the bridgehead position in each compound which has the lowest calculated Δ strain value. In view of these results, it is striking that ionic bromination of ethanoadamantane (3) is reported to occur only at C-1 and C-6



3 4 5 (1)

since the bridgehead position in 3 which is calculated by the Bingham-Schleyer force field to have the lowest Δ strain value is C-8.[3] When the more sophisticated Engler-Schleyer force field is employed and a correction term is included for the hyperconjugative stabilizing effect of β-alkyl branching, then the cation at C-6 in 3 is found to be the most stable and cations at C-1 and C-8 in 3 are calculated to be of equal stability.[3] The same relative stabilities of the ethanoadamantyl bridgehead cations are also obtained with MINDO/3.[3]

The relative amounts of 4 and 5 obtained in the ionic bromination of 1 are reported to vary with the reaction conditions.[3] However, even when the bromination is carried out in the presence of aluminum bromide to achieve thermodynamic control,[4] the only products isolated were 4 and 5.[3] This is particularly surprising since calculations with Allinger's halide force field show that 8-bromoethanoadamantane should be the most stable isomer.[3] In view of these circumstances, we were prompted to investigate the relative reactivities of the bridgehead positions of ethanoadamantane in other electrophilic reactions.

Results and Discussion

Jones and Mellor have reported that bridgehead functionalization of bicyclic and polycyclic hydrocarbons can be achieved by oxidation of these substrates with lead tetraacetate and chloride ion in a solution of trifluoroacetic acid and methylene chloride.[5] Subsequent hydrolysis of the resulting trifluoroacetates gives the corresponding alcohols. The identity of the oxidizing agent in this reaction has not been established. However, it is clear that oxidation does not occur via a radical cation intermediate.[6] At present, a mechanism proceeding by electrophilic attack at a carbon-hydrogen bond is favored.[6] Oxidation of ethanoadamantane with lead tetraacetate under these conditions proceeds by competitive substitution at C-1, C-6, *and* C-8 in 3 to give alcohols 6, 7, and 8 in a ratio of 62:27:11, respectively (Scheme I).

We were not successful in separating these alcohols by chromatography. Our structure assignments for these compounds are based on the following observations. (1) Treatment of a mixture of 6-8 with concentrated hydro-

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