CO), 140.65 (C4), 113.14 (C3), 78.06 (C1), 41.54, 37.25, 22.11, 17.91 (2 C); IR (film) ν 2060 (*trans*-CO), 1917 (br, *cis*-CO); MS (CI, NH_3) 139 (M - $Cr(CO)_5$ + H^+).

Pentacarbonyl[(benzyl)(3-methyl-3-buten-1-oxy)carbene]chromium(0) (19). Reaction of 1.93 g (5.00 mmol) of pentacarbonyl[(benzyl)[(tetramethylammonio)oxy]carbene]chromium(0) with first 0.45 mL (6.00 mmol) of acetyl bromide in 75 mL of CH_2Cl_2 for 1 h at -35 °C and 0.52 g (6.00 mmol) of 3-methyl-3-buten-1-ol in 6 mL of CH_2Cl_2 as described in the general procedure. After standard isolation by flash chromatography (petroleum ether) an orange oil (1.01 g) was obtained. The oil was rechromatographed (petroleum ether/Et_2O, 95:5) to give 0.38 g (1.00 mmol, 20%) of **19** as orange crystals: mp 43-45 °C; ^1H NMR (300 MHz, $CDCl_3$, broad peaks) δ 7.28 (s, 3 H, Ar), 7.14 (s, 2 H, Ar), 5.09 (s, 2 H, ArCH_2), 4.86 (s, 1 H, H-4), 4.72 (s, 1 H, H-4'), 4.59 (s, 2 H, H-1), 2.61 (s, 2 H, H-2), 1.74 (s, 3 H, Me-C3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 355.93 (Cr=C), 223.00 (*trans*-CO), 216.25 (4 C, *cis*-CO), 140.23, 134.84, 129.61, 128.45, 126.87, 113.32 (C4), 80.11 (C1), 68.27 (ArCH_2), 36.96 (C2), 22.26 (*Me*-C3); IR (film) ν 2062 (*trans*-CO), 1924 (br, *cis*-CO); MS (CI, NH_3) 206 (M - $Cr(CO)_5$ + NH_4^+), 189 (M - $Cr(CO)_5$ + H^+).

1-Cyclopropyl-5-methyl-2-oxabicyclo[3.2.0]heptan-7-one (20). Irradiation of 660 mg (2.00 mmol) of **18** for 22 h, after chromatography (petroleum ether/Et_2O, 1:1), gave 214 mg (1.29 mmol, 65%) of **20** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.01 (ddd, 1 H, $J_{3,3'}$ = 9.4, $J_{3,4'}$ = 8.1, $J_{3,4}$ = 1.2 Hz, H-3), 3.57 (ddd, 1 H, $J_{3',4'}$ = 11.7, $J_{3',3}$ = 9.5, $J_{3',4}$ = 5.5 Hz, H-3'), 2.67 (dd, 1 H, $J_{6,6'}$ = 18.4, J = 0.8 Hz, H-6), 2.54 (d, 1 H, $J_{6',6}$ = 18.5 Hz, H-6'), 1.95 (ddd, 1 H, $J_{4,4'}$ = 11.6, $J_{4,3'}$ = 5.5, $J_{4,3}$ = 0.9 Hz, H-4), 1.77 (dt, 1 H, $J_{4',4}$ = $J_{4',3'}$ = 11.7, $J_{4',3}$ = 8.1 Hz, H-4'), 1.36 (s, 3 H, Me), 0.78 (tt, 1 H, J_1 = 8.2, J_2 = 5.3 Hz, cyclopropyl-CH), 0.43 (m, 3 H, cyclopropyl-CH_2), 0.22 (m, 1 H, cyclopropyl-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.80 (CO), 108.10 (C1), 67.33 (C8), 54.89 (C6), 41.58 (C5), 39.98 (C4), 21.13 (Me), 7.89 (cyclopropyl), 0.55 (cyclopropyl), -0.29 (cyclopropyl); IR (film) ν 1776 cm^{-1}; MS (CI, NH_3) 167 (M + H^+). Anal. ($C_{10}H_{14}O_2$) C, H.

1-Benzyl-5-methyl-2-oxabicyclo[3.2.0]heptan-7-one (21). Irradiation of 380 mg (1.00 mmol) of **19** for 4 h gave, after chromatography (petroleum ether/Et_2O, 3:1), 205 mg (0.95 mmol, 95%) of **21** was white crystals: mp 51-52 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5 H, Ar), 4.14 (ddd, 1 H, $J_{3,3'}$ = 9.3, $J_{3,4'}$ = 8.3, $J_{3,4}$ = 0.9 Hz, H-3), 3.71 (ddd, 1 H, $J_{3',4'}$ = 11.7, $J_{3',3}$ = 9.6, $J_{3',4}$ = 5.6 Hz, H-3'), 3.06 (d, 1 H, J_{gem} = 14.8 Hz, ArCH_2), 2.84 (d, 1 H, J_{gem} = 14.9 Hz, ArCH_2), 2.78 (d, 1 H, $J_{6,6'}$ = 18.7 Hz, H-6), 2.69 (d, 1 H, $J_{6',6}$ = 18.4 Hz, H-6'), 1.99 (dd, 1 H, $J_{4,4'}$ = 12.4, $J_{4,3'}$ = 5.4 Hz, H-4), 1.76 (dt, 1 H, $J_{4',4}$ = $J_{4',3'}$ = 12.1, $J_{4',3}$ = 8.2 Hz, H-4'), 1.34 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.48 (CO), 135.53 (ipso), 130.03, 127.83, 126.27 (para), 100.07 (C1), 67.46 (C3), 54.69 (ArCH_2), 42.06 (C5), 39.72 (C6), 34.29 (C4), 21.09 (Me); IR (film) ν 1776 (CO) cm^{-1}; MS (CI, NH_3) 234 (M + NH_4^+), 217 (M + H^+). Anal. ($C_{13}H_{16}O_2$): C, H.

Acknowledgment. Support for this research under Grant 2 RO1 GM26178-10 from the National Institutes of General Medical Sciences (Public Health Service) is gratefully acknowledged. M.A.S. thanks the Ministerio de Educacion y Cienca Espana for a postdoctoral fellowship. Mass spectrometry determinations were performed by Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation facility (Grant No. CHE-8620177).

A Concise Approach to Enantiomerically Pure Carbocyclic Ribose Analogues. Synthesis of (4*S*,5*R*,6*R*,7*R*)-7-(Hydroxymethyl)spiro[2.4]heptane-4,5,6-triol 7-*O*-(Dihydrogen phosphate)

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Abstract: This paper describes a synthesis of **5**, an analogue of 5-phospho-α-D-ribofuranose and instantiates a unique new approach to optically active carbocyclic analogues of ribofuranosides. The synthesis of **5** follows a general scheme that is outlined in brief retrosynthetic fashion in eq 1. The polyhydroxylated spiro[2.4]heptane (**5**) may be prepared via a suitably protected polyhydroxylated methylene cyclopentane **A**. The novelty of the synthetic approach described here is illustrated in the excision of the exocyclic methylene unit from the cyclopentanoid nucleus to generate a linear pentanose fragment (**B**) and a vinylidene fragment (**C**). In the forward direction, two carbon-carbon bonds are to be formed to the same carbon atom of this excised vinylidene fragment (**C**) and in this way two remote carbons on the pentanose skeleton **B** are "united" to form the methylenecyclopentane ring. The carbocyclic D-ribofuranose analogue **5** is prepared in seven steps and 7% overall yield from a D-ribofuranose starting material. The method is recommended to be generally serviceable for preparing carbocylic furanoside analogues.

The "carba" analogues of carbohydrates include carbocylic analogues, wherein the oxygen atom contained within the usual furanoid or pyranoid rings has been replaced with a carbon atom, and C-glycosides, wherein the anomeric oxygen atom has been replaced with a carbon atom.[1] While carbocylic carbohydrate analogues, for example, aristeromycin (**1**)[2] and neplanocin (**2**),[3] have been isolated from natural sources, the great majority of such analogues have been produced through laboratory syntheses. The synthesis of carbocylic ribonucleoside analogues has been motivated by an urgent need for antiviral agents and continues to be an especially active subdiscipline within this general area.[4]

Carbocylic ribose and deoxyribose analogues have been prepared by several methods in racemic form and, more rarely, in optically pure form. An important early example was the prep-

(1) Slotin, L. A. *Synthesis* **1977**, 737.
(2) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255.
(3) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359-366.
(4) *Antiviral Agents: The Development and Assessment of Antiviral Chemotherapy*; Field, H. J., Ed.; CRC Press: Boca Raton, FL, 1988.

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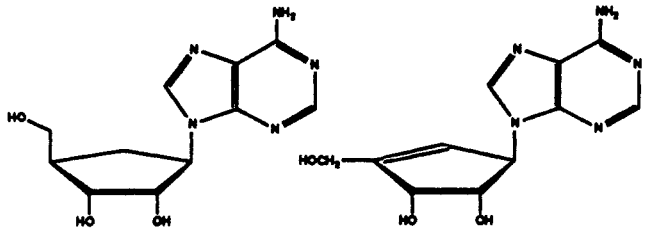
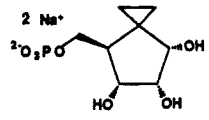


1 2

aration of the carba analogue of thymidine in 1962.[5] Shealy converted norbornadiene to racemic aristeromycin in 12 steps.[6a,b] That process continues to find important applications.[7] Holy has developed an independent approach to racemic carba ribose analogues.[8] In an important body of work, Vince and Daluge have demonstrated that 2-azabicyclo[2.2.1]hept-5-en-3-one can be converted to nucleoside analogues of ribo and lyxo configuration.[9] Saksena has further refined this basic approach and has developed methods for preparing carba C-nucleosides.[10,11] An approach to optically pure ribose analogues that does not require a resolution step was developed by Marquez, who prepared neplanocin from D-ribonolactone.[12] Wilcox and Thomasco reported the first example of the cyclization (via a radical intermediate) of an unsaturated halo-sugar, and the value of the method for the preparation of carbohydrate analogues was illustrated through the synthesis of the carbocyclic analogue of D-fructofuranose.[13] This approach was adopted by Jones and Roberts in a recent synthesis of 5'-homoaristeromycin.[14]

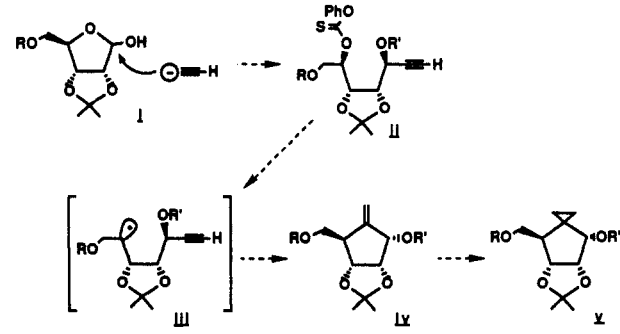
This paper describes a synthesis of **3**, an analogue of 5-phospho-α-D-ribofuranose (**4**) and thereby instantiates a unique new approach to optically active carbocyclic analogues of ribo-

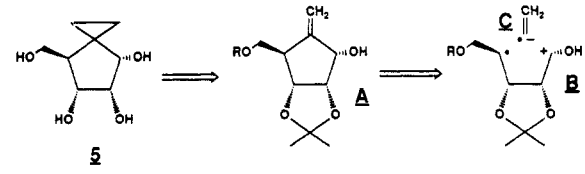


3

furanosides. This approach is more efficient and general than the radical cyclization process we described in 1985.[15] The synthesis of **3** follows a general scheme that is outlined in brief retrosynthetic fashion in eq 1. The penultimate target, a polyhydroxylated spiro[2.4]heptane (**5**), may be prepared via a suitably protected polyhydroxylated methylene cyclopentane **A**.

Scheme I. Schematic Representation of the Synthetic Strategy

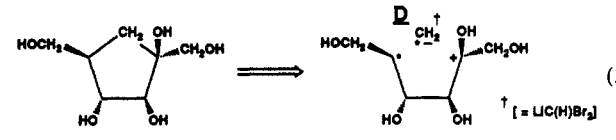




5 (1)

The novelty of the synthetic approach described here is illustrated in the final step of eq 1. The plan is based on the excision of the exocyclic methylene unit from the cyclopentanoid nucleus to generate a linear pentanose fragment (**B**) and a vinylidene fragment (**C**). In the forward direction, two carbon–carbon bonds are to be formed to the same carbon atom of this excised vinylidene fragment (**C**), and in this way two remote carbons on the pentanose skeleton **B** are "united" to form the methylenecyclopentane ring.

In the first synthesis of the carbocyclic analogue of D-fructofuranose it was shown that lithiodibromomethane is a reagent that is synthetically equivalent to a methylene radical anion synthon **D** (eq 2).[13b] These unitive synthons have a useful role to play in the synthesis of carbocyclic molecules.[13c] The application of this idea to the synthesis of (4*S*,5*R*,6*R*,7*R*)-7-(hydroxymethyl)spiro[2.4]heptane-4,5,6-triol 7-*O*-(dihydrogen phosphate) (**3**) is the subject of this paper.



(2)

Biochemical Objective. The de novo construction of purine containing nucleic acids can be said to begin with ribose 5-phosphate. The anomeric hydroxyl group of this compound is pyrophosphorylated by the enzyme 5-phosphoribosylpyrophosphate synthetase (PRPP synthetase) to produce 5-phosphoribosylpyrophosphate (PRPP).[16-18]

The spirocyclopropane analogue **3** and the methylenecyclopentane ribose analogue **6** may be useful as active site directed inactivators of either the PRPP synthetase or any PRPP dependent ribosyltransferase.[19] It is also apparent that **3** will serve as a source

(5) (a) Murdock, K. C.; Angier, R. B. *J. Am. Chem. Soc.* **1962**, *84*, 3758. (b) Murdock, K. C.; Angier, R. B. *J. Org. Chem.* **1962**, *27*, 3317.

(6) (a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885. (b) Shealy, Y. F.; Clayton, J. D. *Ibid.* **1969**, *91*, 3075. (c) Shealy, Y. F.; O'Dell, C. A. *Tetrahedron Lett.* **1969**, 2231.

(7) (a) Shealy, Y. F.; O'Dell, C. A. *J. Heterocycl. Chem.* **1976**, *13*, 1015. (b) Shealy, Y. F.; O'Dell, C. A. *Ibid.* **1976**, 1041. (c) Shealy, Y. F.; O'Dell, C. A. *Ibid.* **1976**, 1353. (d) Shealy, Y. F.; O'Dell, C. A. *Ibid.* **1980**, *17*, 353. (e) Shealy, Y. F.; O'Dell, C. A.; Thorpe, M. C. *Ibid.* **1981**, *18*, 383. (f) Shealy, Y. F. *Ibid.* **1983**, *20*, 655. (g) Montgomery, J. A.; Clayton, S. J.; Thomas, H. J.; Shannon, W. M.; Arnett, B.; Bodner, A. J.; Kion, I.; Cantoni, G. L.; Chiang, P. K. *J. Med. Chem.* **1982**, *25*, 626. (h) Secrist, J. A., III; Clayton, S. J.; Montgomery, J. A. *Ibid.* **1984**, *27*, 534. (i) Houston, D. M.; Borchardt, R. T. *Ibid.* **1985**, *28*, 478.

(8) (a) Holy, A. *Coll. Czechoslov. Chem. Commun.* **1976**, *41*, 647. (b) Holy, A. *Ibid.* **1976**, 2096.

(9) See, for example: (a) Daluge, S.; Vince, R. *Tetrahedron Lett.* **1976**, 3005. (b) Daluge, S.; Vince, R. *J. Org. Chem.* **1978**, *43*, 2311–2320. (c) Cermak, R. C.; Vince, R. *Tetrahedron Lett.* **1981**, *22*, 2331. (d) Vince, R.; Daluge, S. *J. Org. Chem.* **1980**, *45*, 531. (e) Kam, B. L.; Oppenheimer, N. J. *J. Org. Chem.* **1981**, *46*, 3268–3272. (This offers an improvement on the methods originally described by Vince and Daluge.) (f) Vince, R.; Brownell, J.; Daluge, S. *J. Med. Chem.* **1984**, *27*, 1358. (g) Vince, R.; Turakhia, R. H.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1987**, *30*, 2026–2030.

(10) Saksena, A. K.; Ganguly, A. K. *Tetrahedron Lett.* **1981**, *22*, 5227.

(11) (a) Saksena, A. K. *Ibid.* **1981**, 2067. (b) See, also: Paulsen, H.; Maab, U. *Chem. Ber.* **1981**, *114*, 346.

(12) (a) Lim, M.; Marquez, V. E. *Tetrahedron Lett.* **1983**, *24*, 5559–5562. (b) Tseng, C. K. H.; Marquez, V. E. *Tetrahedron Lett.* **1985**, *26*, 3669–3672. (c) Marquez, V. E.; Lim, M.; Tseng, C. K. H.; Markovac, A.; Priest, M. A.; Khan, M. S.; Kashar, B. *J. Org. Chem.* **1988**, *53*, 5709–5714.

(13) (a) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546–547. (b) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102–3104. (c) Gaudino, J. J.; Wilcox, C. S. *Carbohydrate Res.* **1990**. In press.

(14) Jones, M. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2927–2932.

(15) The molecules described by Wilcox and Thomasco are derived from a D-ribo starting material but are best suited for preparing L-ribo analogues. The use of that process for preparing D-ribo analogues entails, therefore, the prior preparation of an L-ribo precursor. This was deemed to be an unacceptable complication and therefore more direct routes to the target were sought.

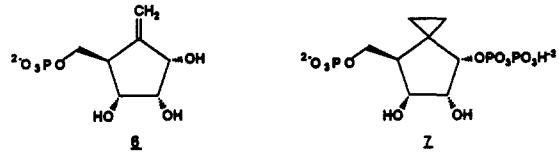
(16) Khorana, H. G.; Fernandes, J. F.; Kornberg, A. *J. Biol. Chem.* **1958**, *230*, 941–948.

(17) Miller, G. A.; Rosenzweig, S.; Switzer, R. L. *Arch. Biochem. Biophys.* **1975**, *171*, 732–736.

(18) Schendel, F. J.; Cheng, Y. S.; Otvos, J. D.; Wehrli, S.; Stubbe, J. *Biochemistry* **1988**, *27*, 2614–2623.

(19) (a) *The Chemistry of the Cyclopropyl Group*; Rappaport, Z., Ed.; Interscience: New York, 1987; Part I, Chapter 11. (b) *The Chemistry of the Cyclopropyl Group*; Rappaport, Z., Ed.; Interscience: New York, 1987; Part II, Chapter 16.

of a new PRPP analogue (7) and this analogue may be tested as

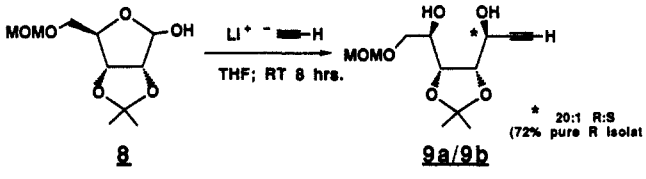


an inactivator of PRPP dependent transferases. In this case the analogue is expected to enter into an active site that is specifically designed to catalyze a substitution reaction at the cyclopropylcarbinyl position. If cationic intermediates are formed, alkylation of the active site may follow.[20] These ideas stimulated the development of this new approach to carbocyclic D-ribose derivatives.

Results and Discussion

The synthesis of the target molecule follows the plan presented in Scheme I. This plan amplifies the general idea illustrated in eq 1. The essential aspects of the scheme include nucleophilic addition of an ethyne anion to lactol **i** followed by selective protection and activation to afford the radical precursor **ii**. This precursor provides the secondary radical **iii** which was expected to lead to the methylene cyclopentanoid product **iv**. Finally, this olefin was envisioned as a precursor to the spirocyclopentane target **v**. The scheme illustrates that in this context lithioacetylene is synthetically equivalent to the vinylidene radical anion presented in eq 1. The first required carbon–carbon bond is made in an ionic process. The second carbon–carbon bond is made to the same carbon through a radical process.

The synthesis was carried out starting with the ribose derivative 2,3-*O*-isopropylidene-5-(methoxymethyl)-D-ribofuranose (**8**).[21] Treatment of **8** with excess lithioacetylene in THF at room temperature according to the method of Bukownik and Wilcox[22] produced a 20:1 mixture of diastereomeric propargylic diols **9a** and **9b** in excellent yield. The crude product is an amorphous



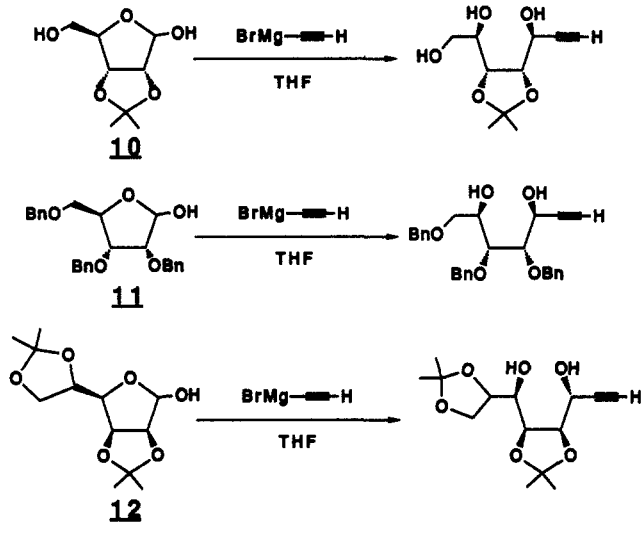
8 **9a/9b**

solid which can be triturated with ethyl acetate/hexane to provide a 72% yield of the major diastereomer **9a** in pure form.

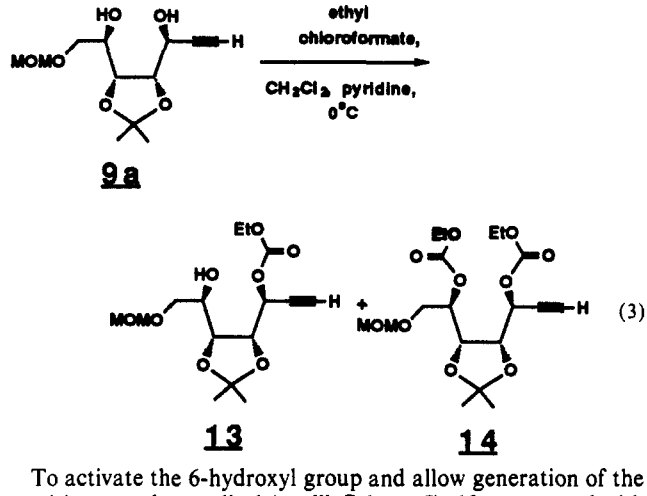
Buchanan demonstrated that ethynyl magnesium bromide could be added to a variety of carbohydrate based lactols including 2,3-*O*-isopropylidene-D-ribofuranose (**10**), 2,3,5-tri-*O*-benzyl-D-ribofuranose (**11**), and 2,3:5,6-bis-*O*-isopropylidene-D-mannofuranose (**12**) with similarly high levels of stereocontrol (see Scheme II).[23,24] Bukownik and Wilcox showed that lithioacetylene addition to carbohydrate lactols produces the same major diastereomer as does Buchanan's ethynyl magnesium bromide additions.[22] To the extent that the 5-*O*-methoxymethyl group of **8** behaves similarly to a 5-hydroxyl group or a 5-*O*-*tert*-butyldimethylsilyl group in an acetylenic nucleophile addition, it is reasonable that product **9a** is in fact the major diastereomer in this reaction.

The next task to be undertaken was the selective protection of the 3-hydroxyl group prior to activation of the 6-hydroxyl group of heptyne **9a**. The heptyne diol **9a** was first treated with ethyl chloroformate and pyridine in methylene chloride at 0 °C. The treatment of a similar diol with tosyl chloride had been reported previously, and the result of that experiment suggested that the

Scheme II

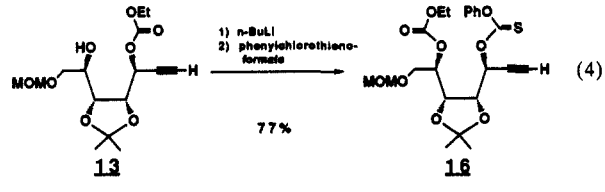


propargylic alcohol was the more reactive of the two hydroxyl groups. As expected, ethyl chloroformate/pyridine treatment of propargylic diol **9a** in methylene chloride at 0 °C (eq 3) produced a 9:1 mixture of monocarbonate **13** and dicarbonate **14** in 94% total yield.



(3)

To activate the 6-hydroxyl group and allow generation of the requisite secondary radical (see **iii**, Scheme I), **13** was treated with an excess of phenyl chlorothionoformate and pyridine in methylene chloride at 0 °C; the reaction was very slow, and only low conversion was observed. When the carbonate **13** was deprotonated in THF with 1 equiv of *n*-butyllithium and the resulting alkoxide was treated with phenyl chlorothionoformate, the major product was not the desired molecule **15** but was **16**, the product arising from carbonate migration followed by acylation of the isomeric carbonate (eq 4). This result may be explained in two ways.

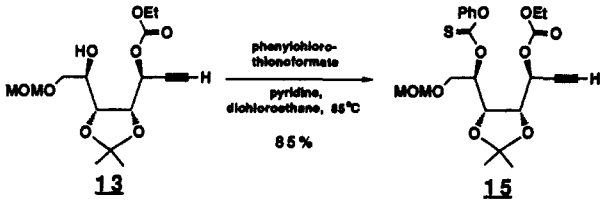


(4)

Either the carbonate migrates rapidly relative to acylation of the alkoxide and the chlorothionoformate reagent is kinetically selective for the demonstrably more reactive propargylic alcohol or a preponderance of the 6-carbonate is quickly formed and the ratio of products is a direct reflection of the thermodynamic stability of the two isomeric carbonates. The available data do not allow either possibility to be rigorously excluded, but in one experiment protonation of the alkoxide solution at 0 °C provided a 2:1 mixture of isomeric carbonates and the major isomer was the 6-carbonate, the product of migration.

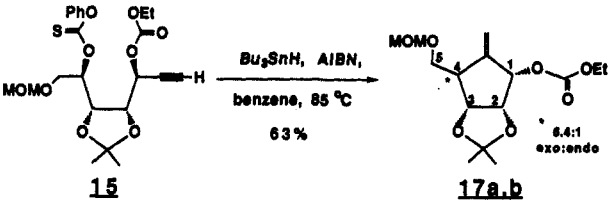
(20) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537–552.
(21) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48–61.
(22) Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 463–471.
(23) Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *Carbohydr. Res.* **1974**, *36*, C5–C7.
(24) Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *J. Chem. Soc., Perkin Trans. I* **1975**, 1191–1200.

Alternative acylation conditions were more successful. Treatment of the carbonate **13** in refluxing dichloroethane with pyridine and phenyl chlorothionoformate provided the desired thionocarbonate **15** in 85% yield.



13 **15**

With this molecule in hand, the stage was set for formation of the methylenecyclopentane nucleus. Thionocarbonates were shown to react with tri-*n*-butyltin hydride to produce carbon-based radicals by Barton.[25] Clive demonstrated that alkynes bearing a γ-thionocarbonate would undergo radical cyclization to exomethylene cycloalkanes.[26] When **15** was treated with tri-*n*-butyltin hydride and AIBN catalyst in benzene at 85 °C for 4 h, a mixture of radical cyclization products **17a** and **17b** were produced in a 6.4:1 ratio and isolated in 63% yield.



15 **17a,b**

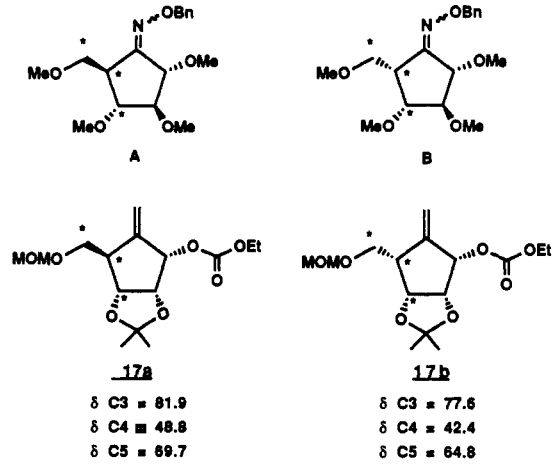
The stereochemical assignments given for **17a** and **17b** were made by comparison of observed ^1H NMR coupling constants with those predicted for each diastereomer by Altona's method and by comparison of ^{13}C NMR chemical shift values for each diastereomer with those of similar compounds prepared by Bartlett and Rajanbabu.[27-29]

Analysis of the possible ground-state conformers of **17a** and **17b** using the methods of Altona predicted obvious differences in the $J_{3,4}$ (carbohydrate numbering) values of each compound. Compound **17a** was predicted to have a $J_{3,4}$ of 0.8 Hz, while **17b** was predicted to have a $J_{3,4}$ value of 5.2 Hz. Experimentally the $J_{3,4}$ values in compounds **17a** and **17b** were found to be 1 and 5.1 Hz, respectively, in good agreement with the predicted values.

In his studies of highly functionalized cyclopentane derivatives, Rajanbabu points out that side chains of a cyclopentane that are cis to adjacent functionality on the ring exhibit marked upfield shifts in the ^{13}C NMR signals of the carbon atoms of the side chain and of neighboring carbon atoms of the ring itself.[29] An interesting example of this phenomena is presented by Bartlett in a synthesis of carbocylic furanose analogues.[28] Bartlett prepared the oximes **A** and **B** shown in Chart I and noted that there is a significant upfield shift in the ^{13}C NMR signals of the marked (*) carbons in compound **B** when compared to compound **A**. In the structurally related compounds **17a** and **17b**, an anlogous trend in ^{13}C NMR shift values is observable. The marked carbon atoms (Chart I) of compound **17b** each have NMR signals greater than 4 ppm upfield from the corresponding signals in compound **17a**.

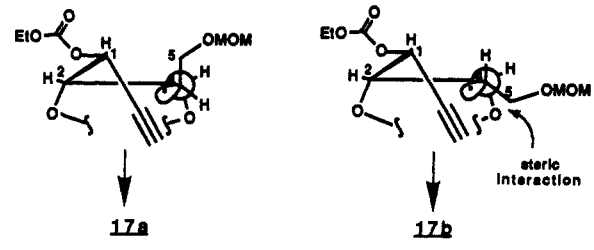
The stereochemical preference for formation of diastereomer **17a** during this radical cyclization reaction may be considered to be the result of differences in transition-state energies leading to the two different diastereomers. The transition state leading to **17a** would allow the C5 side chain and 3-oxygen (carbohydrate numbering) to be free of steric interaction and result in a relatively

Chart I. Two Cyclopentanoid Molecules (**A** and **B**) Prepared by Bartlett[28] and Selected Chemical Shifts for Three Carbon Atoms of **17a** and **17b**



17a **17b**

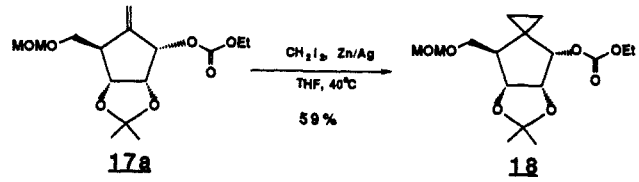
Scheme III. Illustration of Potential Steric Interactions That May Destabilize the Transition State Leading to **17b**



17a **17b**

low-energy transition state. On the other hand, the transition state leading to **17b** would force the C5 side chain and the 3-oxygen syn to one another resulting in steric interaction and therefore relatively high energy in the transition state (see Scheme III).

The selectively protected ribofuranose analogue **17a** is therefore readily available from ribose lactol **8** in the remarkably good overall yield of 30%. To complete the synthesis, a simple cyclopropanation was planned and was expected to provide a spirocyclopropyl carbocylic α-D-ribose derivative.[30] Cyclopropanation was not as simple as anticipated however, and, after trying a variety of methods,[31-34] the following protocol was finally settled upon. Ten equivalents of flame dried zinc–silver couple (prepared according to the method of Conia[34]) was stirred in THF and treated first with **17a** and then carefully with 20 equivs of diiodomethane. After stirring 24 to 48 h at 40 °C, these conditions provided 59% of the desired spirocyclopropyl carbocycle **18**.



17a **18**

Carbonate **18** was deprotected with methanolic sodium methoxide at 0 °C to produce an intermediate cyclopropyl carbinol **19** (not shown, but see Experimental Section) in 85% yield. Treatment of **19** with a 4:1 solution of THF:10% aqueous hydrochloric acid at 50 °C for 4 h[35] then provided, after anion

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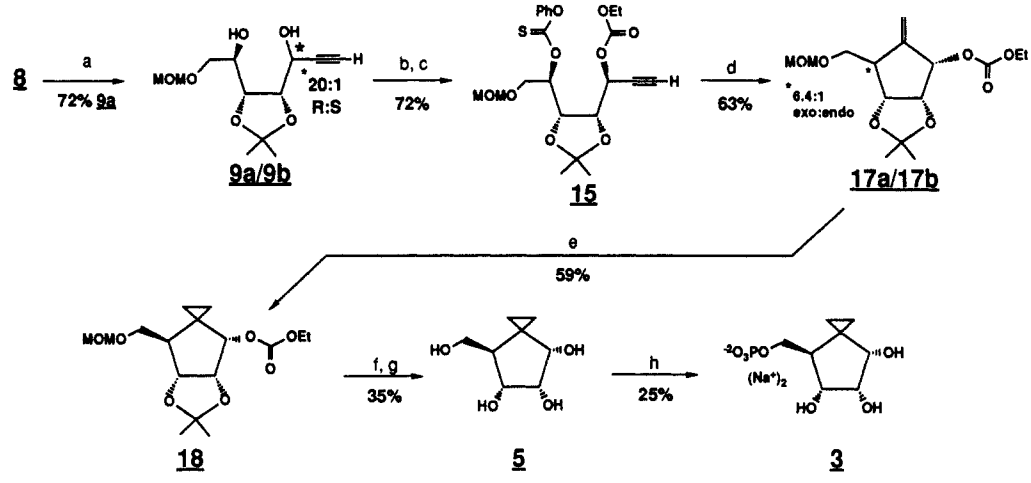
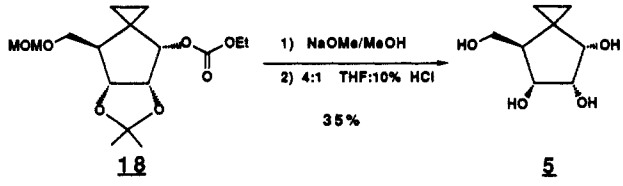
Scheme IV.[a]



[a](a) Lithioacetylene, THF, −78 °C to room temperatre, 8 h; (b) ethyl chloroformate, pyridine, CH_2Cl_2, 0 °C, 1.25 h; (c) phenylchlorothionocarbonate, pyridine, dichloroethane, 85 °C, 45 min; (d) nBu_3SnH, AIBN, benzene, 85 °C, 4 h; (e) CH_2I_2, Zn–Ag, THF, 40 °C, 24–48 h; (f) NaOMe, MeOH, 0 °C; (g) 4:1 THF:10% HCl(aq), 50 °C, 4 h; (h) $POCl_3$, $PO(OMe)_3$, 0 °C, 1 h, then 1 M triethylammonium bicarbonate.

exchange and cellulose chromatography,[36,37] a 41% yield of the completely deprotected, water soluble, spirocyclopropyl carbocyclic α-D-ribose analogue **5**.



The preparation of spirocyclopropyl carbocyclic α-D-ribose 5-phosphate from **3** was carried out according to the method of Pal, Schmidt, and Farrelly.[38] A solution of **5** in trimethyl phosphate was treated at 0 °C with phosphorous oxychloride. After 1 h, the reaction was quenched with 1 M triethylammonium bicarbonate (pH 7.5), passed through anion exchange resin (acetate form), and lyophilized. By ^1H NMR the crude product appeared to be a mixture of four materials in a 3:2:1:1 ratio of desired product, starting material, and two unknown byproducts. Anion exchange chromatography on DEAE Sepharose with a 5 mM to 0.25 M gradient of triethylammonium bicarbonate (pH 7.5) provided a pure sample of the major product (triethylammonium salt) which was submitted to cation exchange chromatography to produce the disodium salt **3**.

For the purpose of clarity the entire synthesis of spirocyclopropyl α-D-carbocylic ribose **5** and its 5-phosphate **3** is shown in Scheme IV.

Conclusions

This synthesis affirms the effectiveness of using radical cyclization methodology in conjunction with a unitive synthon approach for the construction of carbocylic sugar analogues. Chemistry inspired by the work of Buchanan provided access to an acyclic, stereochemically rich, and enantiomerically pure radical cyclization substrate. The particular radical cyclization utilized for the construction of the spirocyclopropyl carbocyclic ribose carbon skeleton proceeded with good though not excellent stereochemical control and provides an interesting new demonstration that a pro-stereogenic radical can be trapped with predictable diastereoface selectivity. It was proposed that the result depends predominantly upon the steric properties of two competing transition states.

It is important to note that the plan utilized here illustrates a general scheme for the conversion of any carbohydrate furanose ring to its corresponding carbocylic analogue. As summarized in Scheme I, a D-ribose precursor is converted in a few steps to a D-ribose analogue. By a similar process, D-arabinofuranose precursors would lead to D-arabinofuranose analogues and 2-deoxyribose precursors could lead to 2-deoxyribose analogues. This unique feature of the synthetic route may be contrasted with the route to carbocyclic fructose which utilized arabinose as a starting material in order to create a fructose analogue. The methods described here may be effectively applied to the synthesis of new carbocyclic nucleoside analogues and other carbohydrate isosteres. The results of such work will be the subject of future publications.

Experimental Section[39]

1,2-Dideoxy-4,5-*O*-(1-methylethylidene)-7-*O*-(methoxymethyl)-D-*allo*-hept-1-ynitol (9a). To a rapidly stirred solution of 280 mL of THF at −78 °C under nitrogen was added 3.7 L of acetylene gas at a flow rate of 120 cc³/min. A solution of 5.86 g (91.5 mmol) of *n*-butyllithium in 50 mL of hexane was then added by syringe. The resulting clear solution was stirred for 15 min. 2,3-*O*-(1-Methylethylidene)-5-(methoxymethyl)-D-ribofuranose (**8**)[21] (7.14 g, 30.5 mmol) in 25 mL of THF was then added by cannulation. The cooling bath was then removed, and the reaction was allowed to warm to room temperature. After 8 h, the reaction was quenched with 30 mL of saturated ammonium chloride solution and neutralized to pH 7 with 10% hydrochloric acid solution. The solution was then concentrated under reduced pressure to about 50 mL and diluted to 100 mL with water. The biphasic mixture was then extracted 3 × 200 mL with dichloromethane. The combined organic extracts were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an orange oil which solidified upon standing. This crude product appeared to be a 20:1 mixture of diastereomers **9a**:**9b** by proton NMR. The solid was then powdered in a minimum volume of 1:1 ethyl acetate:hexane and rinsed until white. Filtration yielded 5.10 g (64%) of the powder as the pure major diastereomer **9a**. Concentration of the mother liquor under reduced pressure back to the orange solid and repetition of the powdering and rinsing procedure yielded another 651 mg (8%) of pure **9a** bringing the overall yield up to 72%. Concentration of the mother liquor again failed to provide any more solid material. Major diastereomer **9a**: mp 88–90 °C; R_f 0.35 (SiO_2, 60% EtOAc–hexane); $[\alpha]^{22}_D$ −9.3° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3399, 3307, 2993, 2937, 1752, 1442, 1375, 1229, 1040 cm⁻¹; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (d, 1 H, *J* = 6.8 Hz), 4.68 (d, 1 H, *J* = 6.8 Hz), (ddd, 1 H, *J* = 8.6 Hz, *J* = 4.5 Hz, *J* = 2.2 Hz), 4.31 (dd, 1 H, *J* = 8.6 Hz, *J* = 5.3 Hz), 4.14 (dd, 1 H, *J* = 9.4 Hz, *J* = 5.3 Hz), 4.13 (d, 1 H, *J* = 4.5 Hz), (ddd, 1 H, *J* = 9.4 Hz, *J* = 2.3 Hz, *J* = 5.9 Hz), 3.94 (s, 1 H), (dd, 1 H, *J* = 12.7 Hz, *J* = 2.3 Hz), 3.71 (dd, 1 H, *J* = 11.1 Hz, *J* = 5.9 Hz), 3.42

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(s, 3 H), 2.54 (d, 1 H, J = 2.18 Hz), 1.46 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.3, 97.0, 82.6, 79.4, 76.6, 74.0, 70.3, 68.5, 61.2, 55.4, 27.8, 25.4; MS, m/e calcd for $C_{11}H_{17}O_6$ ($M^+ - CH_3$) 245.1025, measured 245.1025. Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.14; H, 7.81.

1,2-Dideoxy-3-*O*-[(ethyloxy)carbonyl]-4,5-*O*-(1-methylethylidene)-7-*O*-(methoxymethyl)-D-*allo*-hept-1-ynitol (13) and 1,2-Dideoxy-3,6-bis-*O*-[(ethyloxy)carbonyl]-4,5-*O*-(1-methylethylidene)-7-*O*-(methoxymethyl)-D-*allo*-hept-1-ynitol (14). To a stirred solution of 3.46 g (13.3 mmol) of the propargylic diol **9a** in 40 mL of dichloromethane at 0 °C under nitrogen was added 2.10 g (26.6 mmol) of pyridine followed by 2.89 g (26.6 mmol) of ethyl chloroformate. After stirring the bright yellow solution for 1.25 h, the solution was quenched with 4 mL of water and stirred for 15 min. The reaction mixture was then diluted to 100 mL with dichloromethane, washed 3 × 100 mL with 10% hydrochloric acid solution and 3 × 100 mL with saturated sodium bicarbonate solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a yellow oil. Flash chromatography[40] (6 in. × 60 mm column, SiO_2, 40% EtOAc–hexane) in 1-g batches yielded 3.84 g (87%) of pure monocarbonate **13** and 516 mg (9.6%) of pure dicarbonate byproduct **14**. Monocarbonate **13**: R_f 0.20 (SiO_2, 40% EtOAc–hexane); $[\alpha]^{22}_D$ −12.6° (c 1.07, $CHCl_3$); IR ($CHCl_3$) 3585, 3308, 2990, 2939, 1750, 1373, 1265, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (dd, 1 H, J = 2.2 Hz, J = 4 Hz), 4.70 (d, 1 H, J = 6.6 Hz), 4.67 (d, 1 H, J = 6.6 Hz), 4.45 (dd, 1 H, J = 4.3 Hz, J = 6.2 Hz), 4.24 (q, 2 H, J = 7.2 Hz), 4.15 (dd, 1 H, J = 7.2 Hz, J = 17.8 Hz), 4.13 (dddd, 1 H, J = 17.8 Hz, J = 5.5 Hz, J = 2.4 Hz, J = 5.0 Hz), 3.84 (dd, 1 H, J = 10.9 Hz, J = 2.4 Hz), 3.69 (dd, 1 H, J = 10.7 Hz, J = 5.5 Hz), 3.40 (s, 3 H), 3.00 (d, 1 H, J = 5 Hz), 2.59 (d, 1 H, J = 2.1 Hz), 1.54 (s, 3 H), 1.37 (s, 3 H), 1.31 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 109.7, 97.1, 78.7, 77.6, 76.3, 75.9, 70.8, 68.2, 67.0, 64.4, 55.3, 26.8, 25.0, 14.1; MS, m/e calcd for $C_{14}H_{21}O_8$ ($M^+ - CH_3$) 317.1236, measured 317.1236.

Dicarbonate **14**: R_f 0.36 (SiO_2, 40% EtOAc–hexane); $[\alpha]^{22}_D$ −6.9° (c 1.06, $CHCl_3$); IR ($CHCl_3$) 3308, 3030, 3013, 2991, 2940, 1752, 1466, 1456, 1374, 1270, 1231, 1151, 1112, 1089, 1038, 1025, 1011 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (dd, 1 H, J = 2.2 Hz, J = 5.5 Hz), 4.96 (ddd, 1 H, J = 2.4 Hz, J = 3.4 Hz, J = 9.3 Hz), 4.65 (d, 1 H, J = 6.7 Hz), 4.62 (d, 1 H, J = 7.0 Hz), 4.53 (dd, 1 H, J = 5.7 Hz, J = 9.3 Hz), 4.41 (dd, 1 H, J = 5.7 Hz, J = 5.7 Hz), 4.21 (m, 4 H), 3.93 (dd, 1 H, J = 2.4 Hz, J = 11.5 Hz), 3.35 (s, 3 H), 2.56 (d, 1 H, J = 2.2 Hz), 1.51 (s, 3 H), 1.39 (s, 3 H), 1.32 (t, 6 H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 153.4, 109.3, 96.1, 76.4, 75.7, 73.5, 72.9, 65.6, 65.2, 64.3, 63.9, 54.9, 27.0, 25.0, 13.8; MS, m/e calcd for $C_{17}H_{25}O_{10}$ ($M^+ - CH_3$) 389.1457, measured 389.1448.

1,2-Dideoxy-3-*O*-[(ethyloxy)carbonyl]-4,5-*O*-(1-methylethylidene)-6-*O*-[phenoxy(thiocarbonyl)]-7-*O*-(methoxymethyl)-D-*allo*-hept-1-ynitol (15). To a stirred solution of 3.80 g (11.4 mmol) of the monocarbonate **13** in 34.2 mL of dichloroethane at 85 °C under nitrogen was added 2.80 g (35.3 mmol) of pyridine neat by syringe followed by 5.90 g (34.2 mmol) of phenyl chlorothionocarbonate neat by syringe. After stirring for 45 min, the heating bath was removed. The resulting dark green solution was cooled to ice bath temperature and quenched with 3.4 mL of water and stirred for 15 min. The solution was then diluted to 250 mL with dichloromethane, washed 3 × 200 mL with 10% hydrochloric acid solution and 3 × 200 mL with saturated sodium bicarbonate solution, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting dark green oil was preflash chromatographed (6 in. × 40 mm column, SiO_2, 30% EtOAc–hexane) and then concentrated under reduced pressure to an orange oil which was flash chromatographed (6 in. × 60 mm column, SiO_2, 30% EtOAc–hexane) in 1-g batches to yield 4.84 g (90%) of pure product thionocarbonate **15** as a yellow glass: R_f 0.25 (20% EtOAc–hexane); $[\alpha]^{22}_D$ +3.5° (c 1.01, $CHCl_3$); IR ($CHCl_3$) 3307, 2997, 2941, 2891, 1750, 1490, 1374, 1262, 1200, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, 2 H, J = 7.5 Hz, J = 7.5 Hz), 7.31 (d, 1 H, J = 7.2 Hz), 7.17 (d, 2 H, J = 7.4 Hz), 5.50 (ddd, 1 H, J = 9.2 Hz, J = 2.4 Hz, J = 2.4 Hz), 5.39 (dd, 1 H, J = 6.0 Hz, J = 2.2 Hz), 4.77 (dd, 1 H, J = 5.8 Hz, J = 9.2 Hz), 4.70 (d, 1 H, J = 6.6 Hz), 4.67 (d, 1 H, J = 6.6 Hz), 4.48 (dd, 1 H, J = 5.8 Hz, J = 5.9 Hz), (m, 2 H), (dd, 1 H), 3.94 (dd, 1 H, J = 2.7 Hz, J = 11.8 Hz), 3.41 (s, 3 H), 2.59 (d, 1 H, J = 2.2 Hz), 1.55 (s, 3 H), 1.43 (s, 3 H), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 153.8, 129.5, 126.6, 122.0, 109.8. 96.5, 79.2, 78.1, 76.8, 76.3, 73.6, 66.0, 64.7, 64.3, 60.3, 55.2, 27.3, 25.3, 14.1; MS, m/e calcd for $C_{21}H_{25}O_9S$ ($M^+ - CH_3$) 453.1219, measured 453.1219.

(3a*R*,4*S*,6*R*,6a*R*)-Ethyl Tetrahydro-6-[(methoxymethoxy)methyl]-2,2-dimethyl-5-methylene-4*H*-cyclopenta-1,3-dioxol-4-yl Carbonate (17a) and (3a*R*,4*S*,6*S*,6a*R*)-Ethyl Tetrahydro-6-[(methoxymethoxy)methyl]-2,2-dimethyl-5-methylene-4*H*-cyclopenta-1,3-dioxol-4-yl Carbonate (17b). To a stirred solution of 4.84 g (10.3 mmol) of the thionocarbonate **15** in 206 mL of benzene at 85 °C under nitrogen was added 3.31 g (11.3 mmol) of tri-*n*-butyltin hydride neat by syringe followed by 171 mg (1.03 mmol) of AIBN as a solid. After stirring for 4 h, the reaction was concentrated under reduced pressure to a yellow oil and chromatographed quickly on a small column (6 in. × 40 mm column, SiO_2, 30% EtOAc–hexane) to remove residual organotin impurities. Gas chromatography of this crude product (200 °C isothermal, BP-5 silated capillary column) indicated a 6.4:1 mixture of diastereomers was present. Flash chromatography (6 in. × 60 mm column, SiO_2, 30% EtOAc–hexane) yielded 1.00 g (34%) of pure major diastereomer **17a**, 204 mg (6%) of pure minor diastereomer **17b**, and 762 mg (23%) of a mixture of diastereomers (63% overall). Major diastereomer **17a**: bp 45 °C (0.1 mmHg); R_f 0.29 (30% EtOAc–hexane); $[\alpha]^{22}_D$ −107° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3027, 2990, 2940, 1743, 1375, 1266, 1150, 1111, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (m, 1 H), 5.28 (m, 1 H), 5.23 (m, 1 H), 4.77 (dd, 1 H, J = 5.5 Hz, J = 5.5 Hz), 4.60 (d, 1 H, J = 6.6 Hz), 4.57 (d, 1 H, J = 6.6 Hz), (dd, 1 H, J = 5.4 Hz, J = 1 Hz), 4.25 (q, 2 H, J = 7.2 Hz), 3.65 (dd, 1 H, J = 4.0 Hz, J = 9.3 Hz), 3.53 (dd, 1 H, J = 5.1 Hz, J = 9.2 Hz), 3.33 (s, 3 H), 2.83 (m, 1 H), 1.43 (s, 3 H), 1.33 (s, 3 H), 1.33 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 147.4, 111.7, 111.6, 96.4, 81.9, 78.5, 77.5, 69.7, 64.2, 55.3, 48.8, 26.5, 25.3, 14.3; MS, m/e calcd for $C_{14}H_{21}O_7$ ($M^+ - CH_3$) 301.1285, measured 301.1287. Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.88; H, 7.70.

Minor diastereomer **17b**: R_f 0.21 (SiO_2, 30% EtOAc–hexane); $[\alpha]^{22}_D$ −54.0° (c 1.03, $CHCl_3$); IR ($CHCl_3$) 3026, 3014, 2992, 2938, 1744, 1383, 1375, 1268, 1231, 1218, 1211, 1208, 1204, 1164, 1152, 1109, 1046, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (dd, 1 H, J = 2.3 Hz, J = 2.4 Hz), 5.08 (m, 1 H), 5.03 (dd, 1 H, J = 2.5 Hz, J = 2.5 Hz), 4.76 (dd, 1 H, J = 5.5 Hz, J = 5.5 Hz), 4.71 (dd, 1 H, J = 5.1 Hz, J = 5.5 Hz), 4.68 (s, 2 H), 4.25 (q, 2 H, J = 7.1 Hz), 3.86 (dd, 1 H, J = 14.9 Hz, J = 8.5 Hz), 3.83 (dd, 1 H, J = 18.5 Hz, J = 10.0 Hz), 3.39 (s, 3 H), 2.64 (m, 1 H), 1.37 (s, 3 H), 1.34 (t, 3 H, J = 7.1 Hz), 1.31 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 145.0, 111.9, 108.0, 96.8, 78.6, 76.9, 76.5, 66.7, 65.3, 64.8, 64.5, 55.4, 42.4, 26.1, 25.2, 14.4; MS, m/e calcd for $C_{14}H_{21}O_7$ ($M^+ - CH_3$) 301.1285 measured 301.1287.

(4*S*,5*R*,6*R*,7*R*)-4-*O*-[(Ethyloxy)carbonyl]-5,6-*O*-(1-methylethylidene)-7-[(methoxymethoxy)methyl]spiro[2.4]heptane-4,5,6-triol (18). To a reaction flask containing 471 mg (7.13 mmol) of zinc–silver couple[34] which was flame dried was added 188 mg (0.587 mmol) of the olefin **17a** by cannulation from 1.8 mL of THF under nitrogen. To the rapidly stirred slurry at 60 °C was added 3.98 g (14.8 mmol) of neat diiodomethane by syringe at a rate such that gentle reflux was barely maintained. After addition was complete, the reaction was stirred until starting material was completely consumed as determined by proton NMR (usually from 24–48 h). The yellow slurry was then cooled to room temperature, diluted to 60 mL with dichloromethane, and washed 2 × 60 mL with 10% hydrochloric acid solution, 1 × 60 mL with 1 M sodium bisulfite solution, and 3 × 60 mL with saturated sodium bicarbonate solution. The organic layer was then dried ($MgSO_4$), filtered, concentrated under reduced pressure, and flash chromatographed (6 in. × 25 mm column, SiO_2, 30% EtOAc–hexane) to yield after concentration under reduced pressure 112 mg (59%) of cyclopropanated product **18**: bp 80 °C (0.1 mmHg); R_f 0.29 (30% EtOAc–hexane); $[\alpha]^{22}_D$ −82° ($CHCl_3$); IR ($CHCl_3$) 2991, 2940, 1742, 1458, 1375, 1267, 1151, 1113, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (dd, 1 H, J = 5.2 Hz, J = 5.2 Hz), 4.75 (dd, 1 H, J = 5.2 Hz, J = 5.2 Hz), 4.59 (m, 1 H), 4.59 (s, 2 H), 4.18 (q, 2 H, J = 7.2 Hz), 3.45 (m, 2 H), 3.35 (s, 3 H), 2.04 (m, 1 H), 1.50 (s, 3 H), 1.33 (s, 3 H), 1.30 (t, 3 H, J = 7.2 Hz), 1.06 (m, 1 H), 0.60 (m, 1 H), 0.49 (m, 1 H), 0.39 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 112.2, 96.6, 82.5, 79.3, 78.8, 67.6, 64.0, 55.4, 48.2, 26.6, 26.3, 25.4, 14.3, 8.9, 3.8; MS, m/e calcd for $C_{13}H_{28}O_7$ ($M^+ - CH_3$) 315.1445, measured 315.1444. Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 57.99; H, 7.98.

(4*S*,5*R*,6*R*,7*R*)-5,6-*O*-(1-Methylethylidene)-7-[(methoxymethoxy)-methyl]spiro[2.4]heptane-4,5,6-triol (19). To a stirred solution of 112 mg (0.331 mmol) of cyclopropyl carbonate **18** in 0.5 mL of methanol at 0 °C under nitrogen was added 27 mg (0.50 mmol) of sodium methoxide as a solution in 0.5 mL of methanol by syringe. After stirring for 4 h, the reaction was quenched with 120 mg of Biorex 70 cation exchange resin (H^+ form) for 5 min, filtered through glass wool, concentrated under reduced pressure, dissolved in 1 mL of ether, filtered through glass wool again, and reconcentrated to yield 75 mg (85%) of cyclopropyl carbinol **19**: R_f 0.25 (SiO_2, 30% EtOAc–hexane); $[\alpha]^{22}_D$ −87.6° (c 1.22 $CHCl_3$); IR ($CHCl_3$) 3553, 2995, 2937, 1458, 1375, 1250, 1151, 1112, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (dd, 1 H, J = 6.0 Hz, J = 9.9 Hz), 4.59 (d, 1 H, J = 6.9 Hz), 4.57 (d, 1 H, J = 6.9 Hz), 4.06 (dd, 1 H, J = 5.3 Hz, J = 10.1 Hz), 3.53 (dd, 1 H, J = 4.2 Hz, J = 9.7 Hz), 3.44 (dd, 1 H, J = 5.8 Hz, J = 9.7 Hz), 3.35 (s, 3 H), 2.33 (d, 1 H, J = 10.1 Hz), 1.80 (m, 1 H), 1.50 (s, 3 H), 1.36 (s, 3 H), 0.90 (m, 1 H), 0.50 (m, 1 H), 0.34 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

110.9, 96.5, 81.9, 79.5, 72.8, 68.1, 55.3, 49.2, 26.5, 26.3, 24.4, 8.4, 1.58.

(4S,5R,6R,7R)-7-(Hydroxymethyl)spiro[2.4]heptane-4,5,6-triol (5). To a stirred solution of 72 mg (0.27 mmol) of the cyclopropylcarbinol **19** in 2.2 mL of THF at 50 °C under nitrogen was added 0.54 mL of 10% hydrochloric acid solution by pipette. After stirring for 4 h, the green reaction mixture was cooled to room temperature and eluted through an anion exchange column (6 in. × 10 mm column, Dowex AG-1 ×8 resin (hydroxide form, 20–50 mesh), 1 M NH_4OH) with 100 mL of eluant. After lyophillization, the crude product was eluted through a gravity cellulose column (6 in. × 10 mm column, microgranular cellulose, 9% *n*-butanol–water). Fractions of 0.5 mL were collected and each was assayed for product content by TLC employing 4:1 dichloromethane: methanol with $KMnO_4$ visualization. The product-containing fractions were pooled and concentrated under reduced pressure to yield 20 mg (41%) of pure tetrol **5**: R_f 0.31 (SiO_2, 20% MeOH–CH_2Cl_2); $[\alpha]^{22}_D$ −61.7° (*c* 1.15 H_2O); ^1H NMR (300 MHz, D_2O) δ 4.03 (dd, 1 H, *J* = 3.7 Hz, *J* = 4.7 Hz), 4.03 (dd, 1 H, *J* = 4.7 Hz, *J* = 9.9 Hz), 3.74 (d, 1 H, *J* = 3.7 Hz), 3.55 (dd, 1 H, *J* = 5.1 Hz, *J* = 11.5 Hz), 3.43 (dd, 1 H, *J* = 4.7 Hz, *J* = 11.6 Hz), 2.13 (dd, 1 H, *J* = 5.1 Hz, *J* = 11.1 Hz), 0.89 (m, 1 H), 0.73 (m, 1 H), 0.34 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.9, 75.9, 75.2, 63.0, 51.7, 26.6, 10.0, 9.5.

(4S,5R,6R,7R)-7-(Hydroxymethyl)spiro[2.4]heptane-4,5,6-triol 7-(Dihydrogen phosphate) (Disodium Salt) (3). To a stirred solution of 20.0 mg (0.097 mmol) of tetrol **5** in 250 μL of triethyl phosphate at 0 °C under nitrogen was added 29.7 mg (0.194 mmol) of phosphorous oxychloride. After stirring for 1.5 h, the solution was treated at 0 °C with 600 μL of 1 M triethylammonium bicarbonate solution (pH 7.5) and stirred for 5 min. The reaction mixture was then passed through a 6″ × 10 mm column of DEAE sepharose (bicarbonate form) with a gradient of triethylammonium bicarbonate (0 mM to 0.25 M), and the eluant was collected in 0.5 mL fractions. The fractions were analyzed for phosphate by TLC (SiO_2, 50% 1 M NH_4OAc–EtOH) by using an ammonium molybdate/anthranalic acid containing visualization spray. At this stage all carbohydrate-containing fractions were pooled and lyophilized. Proton NMR indicated that the reaction had produced a 3:2:1:1 mixture of 5′-phosphate:**3**:unknown:unknown. Resubmission of this mixture to a second DEAE sepharose column and chromatography using conditions identical with those used in the first instance provided a pure sample of 5′-phosphate which was passed through a 1″ × 10 mm column of Biorex 70 cation exchange resin (Na^+ form) and lyophilized to yield 7.1 mg (25%) of pure **3**: $[\alpha]^{22}_D$ −47.7° (*c* 0.66 H_2O); ^1H NMR (300 MHz, D_2O) δ 4.13 (m, 2 H), 3.77 (d, 1 H, *J* = 3 Hz), 3.66 (ddd, 1 H, *J* = 5.5 Hz, *J* = 10.4 Hz, *J* = 4.9 Hz), 3.61 (ddd, 1 H, *J* = 5.1 Hz, *J* = 10.3 Hz, *J* = 6.4 Hz), 2.33 (m, 1 H), 0.89 (m, 2 H), 0.48 (m, 1 H), 0.37 (m, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 79.3, 75.8, 75.4, 66.1, 50.3, 26.8, 9.4.

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Supplementary Material Available: Details of general experimental procedures and actual copies of ^1H and ^{13}C nuclear magnetic resonance spectra for each molecule described in the Experimental Section (42 pages). Ordering information is given on any current masthead page.

Structures and Configurations of Ciguatoxin from the Moray Eel *Gymnothorax javanicus* and Its Likely Precursor from the Dinoflagellate *Gambierdiscus toxicus*[1]

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Abstract: Ciguatoxin (CTX) is the toxic principle of ciguatera, which is responsible for the most widespread food poisoning of nonbacterial origin. The toxin, isolated from the moray eel *Gymnothorax javanicus*, and its congener, from the causative dinoflagellate *Gambierdiscus toxicus*, were used for this study. The structure elucidation was carried out by combined use of ^1H NMR 2D correlation and NOE experiments done with no more than 0.35 mg of CTX and 0.74 mg of the congener. Broadening of ^1H NMR signals due to a slow conformational change around a nine-membered ring was sharpened by measurements at −20 °C, in which all ^3J proton connectivities and NOE's around angular protons were clearly indicated. The structure of CTX, which had a molecular formula of $C_{60}H_{86}O_{19}$, was disclosed to be a brevetoxin-type polyether comprising 13 continuous ether rings (7/6/6/7/7/9/7/6/8/6/7/6-spiro-5). The congener was shown to be a less oxygenated analogue of CTX. Their relative stereochemistries, except for C2 of CTX, were clarified by detailed analyses of ^1H NMR NOE experiments, MM2 energy calculations, and spectral simulations.

Ciguatera is a term applied to food poisoning caused by ingestion of coral reef fish. The worldwide occurrence of ciguatera not only endangers public health but also hampers local fisheries in subtropical and tropical regions. It is estimated that roughly 20 000 people suffer annually from the poisoning, making it one of the largest-scale food poisonings of non-bacterial origins.

The toxification mechanism of fish had not been known until one of the authors (T.Y.) identified an epiphytic dinoflagellate, *Gambierdiscus toxicus*, as a causative organism in 1977.[3] The dinoflagellate toxins are transferred through the food chain among coral biota and accumulated most in carnivorous fish.

Ciguatoxin (CTX), the principal toxin causing ciguatera, is extremely potent; its lethal potency against mice is ca. 100 times greater than that of tetrodotoxin on a molar basis. Although many investigators have been attracted by the unique nature of the toxin, lack of knowledge about its structure hampered biological and biochemical research on ciguatera. After a Hawaiian group reported the isolation and partial chemical characterization of the toxin, including its polyether nature,[4] additional progress was blocked due chiefly to extreme difficulties in obtaining enough

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