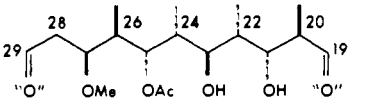
New Strategy for Carbohydrate-Based Syntheses of Multichiral Arrays: Pyranosidic Homologation.[1] 3[2]

Bert Fraser-Reid,*[3] Leon Magdzinski, and Bruce Molino

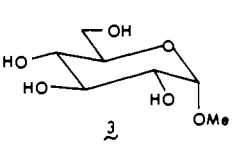
Contribution from the Chemistry Department, University of Maryland, College Park, Maryland 20742. *Received May 5, 1983*

Abstract: A process of *pyranosidic homologation* has been developed whereby "satellite" pyranosides are attached to the front and rear of a "backbone" pyranoside. The resulting manifold has capacity for eight contiguous chiral centers, two of which surive from the starting material, levoglucosan (1,6-anhydro-α-D-glucopyranose). The other six are introduced rationally and with complete stereo- and/or regioselectivity in each case, and configurational assignments are readily made by 200-MHz ^{1}H NMR. The study is outlined with respect to a key intermediate for the ansa chain of rifamycin, but the general applicability to other "pseudo" higher carbon sugars, as well as their "authentic" counterparts, is clearly obvious.

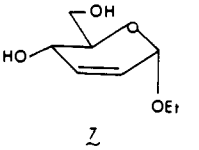
Macrolides and ionophores have, in the past few years, provided a stimulating milieu for the development of synthetic methodologies.[4] Their profound resemblance to sugar derivatives was recognized early,[5,6] and carbohydrate-based maneuvers have frequently proved to be extremely appropriate.[7-10] In this context, many of these polyhydroxylated compounds may be regarded as "pseudo" higher carbon sugars,[11] and these targets present specific challenges—as, indeed, do their "authentic" counterparts.[12] We have been developing a simple, versatile, and reliable strategy for "higher carbon" sugars, "authentic" or "pseudo", particularly relevant to those possessing multiple *contiguous* chiral centers,[13] of which *an essential feature is the capability to establish, ipso facto, all stereocenters as they are created and not having to rely on correlation with the synthetic target for authentication.*[14] In this article we outline the salient features of the new strategy with reference to the ansa chain of rifamycin S, **2**,[15-19] and report the preparation of a key intermediate, **1**.



2



3



7

The Problem

(1) The crucial problem confronting sugar-based approaches to higher carbon "sugars", "pseudo" or "authentic", is exemplified with methyl α-D-glucopyranoside, (**3**), a favorite precursor. This sugar has only five contiguous chiral centers, but since those at C-1 and C-5 give the template its stereochemical integrity,[20-22] synthetic manipulations are permissible only at C-2, C-3, and C-4. C-6 must be regarded as an "off-template" site and hence does not normally display high stereoselection in its reactions.

(2) An equally debilitating defect concerns the assignment of configurations to such diastereomeric products, since they would not be amenable to the simple conclusive NMR analyses normally enjoyed by carbohydrate derivatives.[21]

(3) The selection of protecting groups is of paramount importance with these polyhydroxylated compounds, and any reduction in the number of such groups which must be used is advantageous.

These problems are particularly menacing for arrays such as **2** for which there are no logical sites for disconnection. As a result,

(1) Portions of this work were presented at EUCHEM Conference, "Methods in Organic Synthesis" Lovain-la-Neuve, Belgium, July 1982; XIII IUPAC Symposium on the Chemistry of Natural Products, Pretoria, South Africa, Aug 1982; IV International Conference on Organic Synthesis, Tokyo Japan, Aug 1982; and the 28th National Organic Chemistry Symposium, Bozeman, Montana, June 1983.

(2) Part 1: Molino, B. F.; Magdzinski, L.; Fraser-Reid, B. *Tetrahedron Lett.* **1983**, *24*, 5819. Part 2: Magdzinski, L.; Cweiber, B.; Fraser-Reid, B. *Tetrahedron Lett.* **1983**, *24*, 5823.

(3) Address correspondence to this author at Paul M. Gross Chemical Laboratory, Duke University, Durham, NC 27706.

(4) For some leading references see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew Chem., Intl. Ed. Engl.* **1977**, *16*, 585. Wierenga, W. "The Total Synthesis of Ionophores" in "The Total Synthesis of Natural Products"; ApSimon J., Ed.; Wiley: New York and Toronto (1981); Vol. 4 pp 263-351. Kishi, Y. *Aldrichimica Acta* **1980**, *13*, 23. Evans, D. A. *Ibid.* **1982**, *15*, 23.

(5) Miljkovic, M.; Gligorijevic, M.; Satoh, T.; Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 1830. Miljkovic, M., Glissin, D. *Ibid* **1975**, *40*, 3357.

(6) Hanessian, S.; Rancourt, G. *Can J. Chem.* **1977**, *55*, 111. Hanessian, S.; Rancourt, G.; Guidon, Y.; *Ibid.* **1978**, *55*, 1843.

(7) Ireland, R. E.; McGarvey, G. J.; Anderson, R. C.; Badond, R.; Fitzsimmons, B.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1980**, *102*, 6178. Ireland, R. E.; Thrisrivongs, S.; Wilcox, C. W. *Ibid.* **1980**, *102*, 1155. Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Ibid.* **1982**, *104*, 2027. Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *Ibid.* **1981** *103*, 6969. Tatsuta, K.; Amemiya, Y.; Kanemura, Y., Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 2997. Nakahara, Y.; Beppu, Y.; Ogawa, T. *Ibid.* **1981**, *22*, 3197. Hanessian, S.; Tyler, P. C.; Demailly, G.; Chapleur, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6243. Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *Ibid.* **1980**, *102*, 6615. Nakata, M.; Enrai, H.; Kinoshita, *M. Bull, Chem. Soc. Jpn.* **1982**, *55*, 3283.

(8) Nakata, M.; Takao, H.; Ikeyama, Y., Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull, Chem. Soc. Jpn.* **1981**, *54*, 1749.

(9) Hannessian, S.; Pougny, J-R, Boessenkool, I. K. *J. Am. Chem. Soc.* **1982**, *104*, 6164.

(10) Mukaiyama, T.; Noyaic, R. *Kagaku Zokan (Kyoto)* **1981**, *91*, 101.

(11) The name of the seco acid of erthronolide A is 2,4,7,8,10,14,15-heptadeoxy-2,4,6,8,10,12-hexa-*C*-methyl-D-*erythro*-L-*ido*-pentadec-9-ulosonic acid.

(12) For some typical systems see: Secrist, J. A.; Wu, S-R *J. Org. Chem.* **1974**, *44*, 1434. Secrist, J. A.; Barnes, K. D. *Ibid.* **1980**, *45*, 4526.

(13) (a) Fraser-Reid, B.; Magdzinski, L.; Molino, B. In "Current Trends in Organic Synthesis "; Nozaki, H., Ed.; Pergamon Press: Oxford, 183; pp 197-203. (b) Abstracts of the 28th National Organic Symposium, June 20-24, 1983, Bozeman MT.

(14) In many instances,[8,9,15-19] the stereochemistry of linear arrays cannot be independently assigned with complete assurance but must be compared with known fragments or converted into ring systems.

(15) The first synthesis of rifamycin S was achieved by Kishi's group.[16] A carbohydrate-based total synthesis of[8] and an intermediate for[9] the ansa chain have been reported. For other work on the ansa chain see ref 17-19.

(16) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. Iio, H.; Nagaoka, H.; Kishi, Y. *Ibid.* 1980, *102*, 7965.

(17) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105* 2487.

(18) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528.

(19) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, 335.

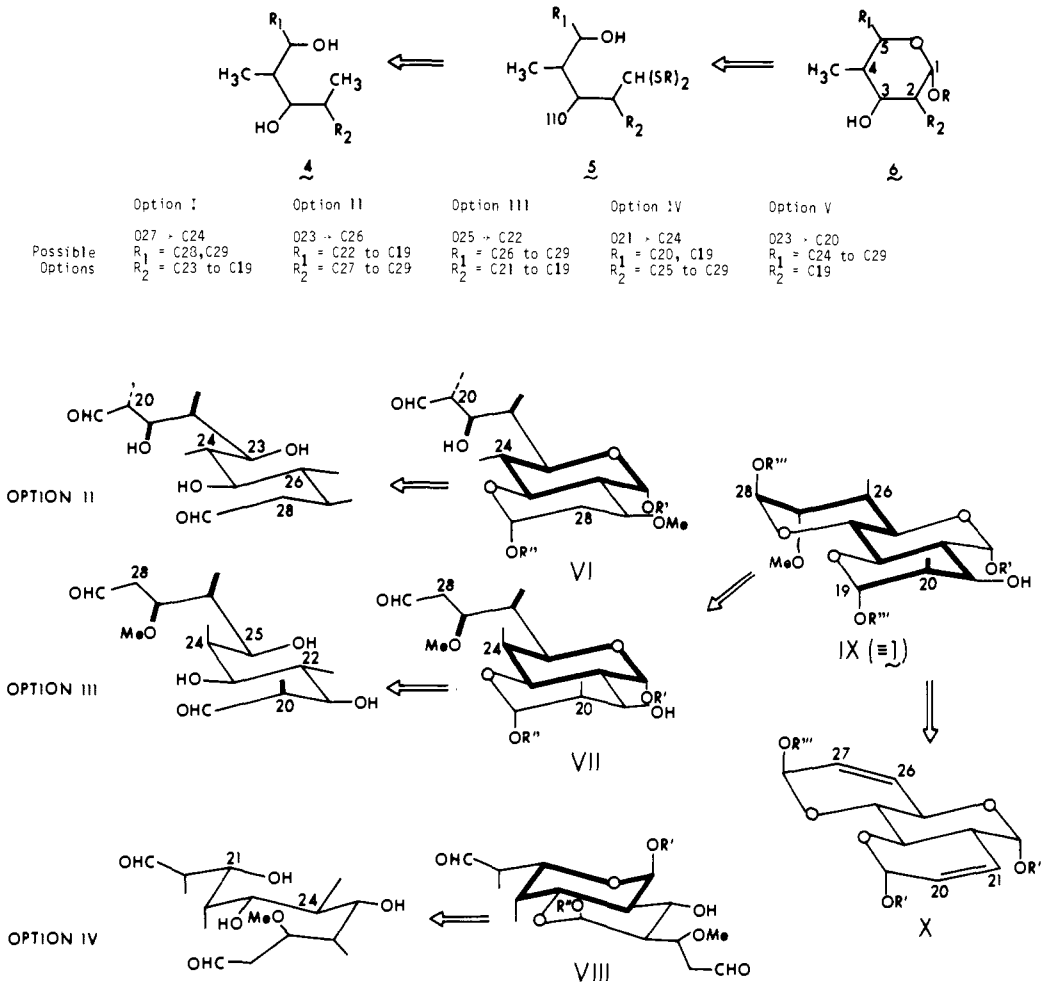
(20) Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159.

(21) Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1.

(22) Fraser-Reid, B. *Acc. Chem. Res.* **1975**, *8*, 192.

0002-7863/84/1506-0731$01.50/0

Scheme I



combination of two (or more) monosaccharide subunits must perforce occur at "off-template" sites where the formation of rich diastereomeric mixtures of unknown configurations threatens to compromise the stereocontrol which had been carefully crafted into the individual subunits.

Retroanalysis

The retroanalysis requires the use of chemical models only, although computer modeling may facilitate some of the conformational evaluations.

The pivotal idea out of which this new strategy grew was the well-known fact that the anomeric carbon of a sugar may be readily converted into a methyl group.[23] Thus as indicated in Scheme I, each 1,4-related CH_3 and OH represent a "hidden" pyranoside as accentuated in the retroanalysis **4**, **5**, **6** shown in Scheme I.[1] Five such potential pyranosides (I–V) exist; we must now narrow our choice(s) in a rational manner.

Consider first the "end" options I and II. In I, the C-2 appendage R_2 has four "off-template" stereocenters that, as noted above, would be difficult to control and/or analyze. The same applies to option II. Both are therefore rejected.

For the second phase of the elimination process, options II, III, and IV are coiled into the conformations shown in Scheme I. It is seen that not one, but *two*, pyranose rings can be generated, VI, VII, and VIII, respectively. Option VIII is now eliminated on the ground that the "backbone" pyranoside (heavy lines) would require the use of an L-hexopyranoside as a precursor, and since these are usually expensive, option IV is unacceptable to us.

The remaining viable options are II and III. The obvious benefits accruing to their bipyranose equivalents, VI and VII, could be enhanced even further by elaboration of a third pyranoside—*and it is here that the final selection of option III is mandated. Thus, further "pyranosidic homologation" of either VI and VII would sacrifice the C-24 CH_3 in either case. However, in the case of VI, the anomeric center of the resulting upper "satellite" would require the sacrifice of a second stereocenter (C-20).* Comparable loss would not occur with VII, since the C-28–CH_2 (which is achiral) would coincide with an anomeric center, which, being a masked aldehyde, is potentially achiral anyway! *Thus, all eight contiguous chiral centers of* **2** (≡*III*) *can be accommodated within* the ten-carbon continuum, highlighted in the tricyclic construct IX.

Retrosynthetic analysis of the neighboring CH_3 and OH groups in IX lead to the two olefinic sites in X, each of which would be generated and manipulated at different stages. The unsaturated rings in X are reminiscent of hex-2-enopyranosides such as **7**[24] and would therefore inherit an extensive body of knowledge garnered in this[22] and other laboratories.[25,26]

Results and Discussion

The starting material for our work was the known oxirane **8**,[27] which can be prepared from levoglucosan[28] in four steps in 80%

(23) For a typical example of the transformation **6** to **4** see: Wolform, M. L.; Lemieux, R. U.; Olin, S. M. *J. Am. Chem. Soc.* **1949**, *71*, 2780.

(24) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199; **1965**, *20*, 67.

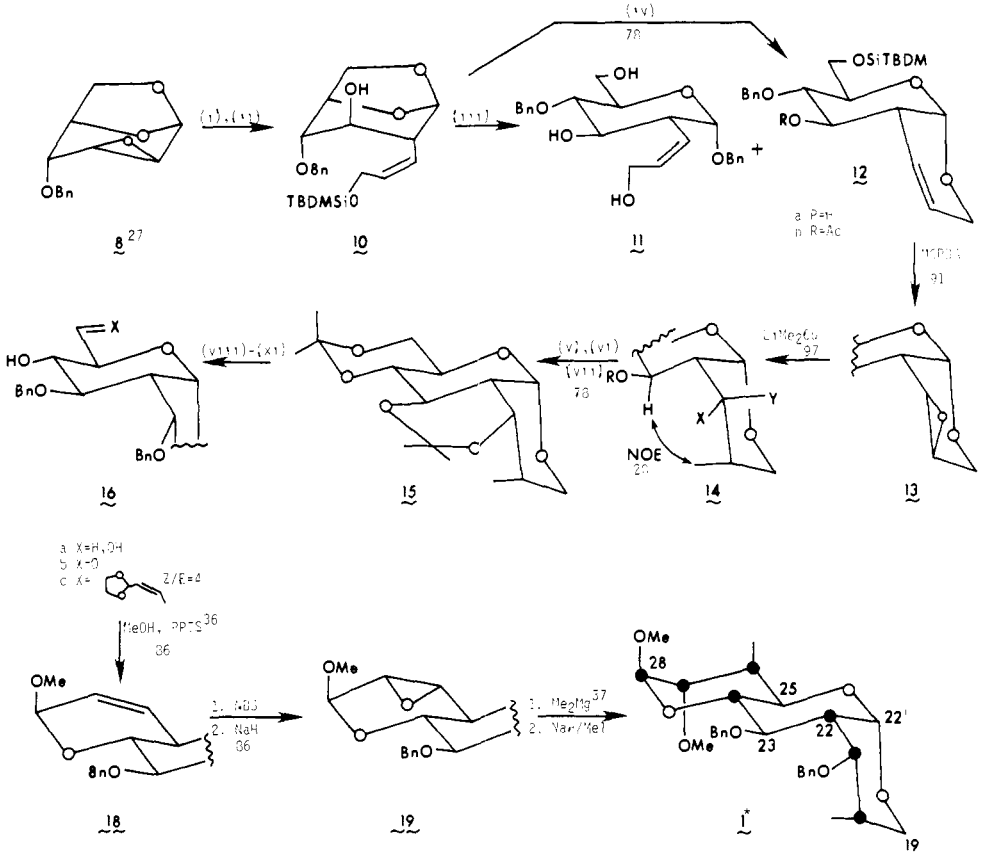
(25) For a recent exhaustive reviews see: Holder, N. *Chem. Rev.* **1982**, *82*, 287.

(26) Achmatowicz, O. "An Approch to the Synthesis of Higher-carbon Sugars," In "Organic Synthesis - Today and Tomorrow,"; Trost, B. M., Hutchison, C. R., Eds.; Pergamon Press: Oxford, 1981; p 307.

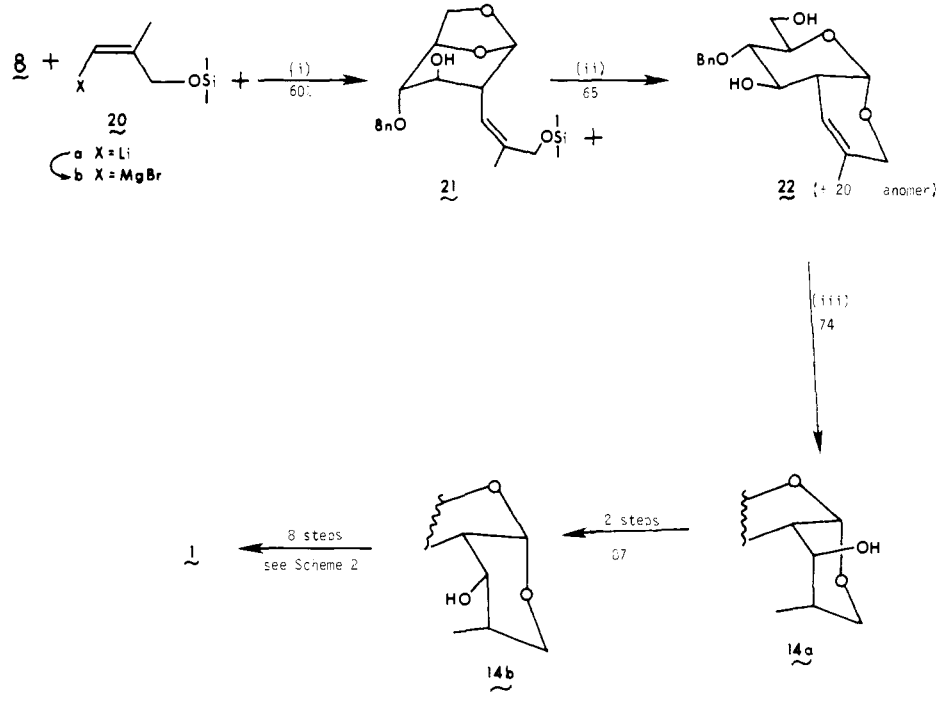
(27) Trana, T.; Cerny, M. *Collect. Czech. Chem. Commun.* **1971**, *36*, 2216.

(28) Levoglucosan is obtained in 30–40% by the vacuum pyrolysis of starch: Ward, R. B. *Methods Carbohydr. Chem.* **1963**, *2*, 394.

Scheme II[24]



Scheme III



overall yield. Reaction with the ethnylalane **9**,[30] followed by Lindlar hydrogenation, gave compound **10**, which upon solvolysis with benzyl alcohol gave a mixture of the external and internal glucosides, **11** and **12a**, respectively. It is the former that is required for the bipyranoside IX, but compound **12** proved to be a better prospect[31] since it could be obtained as the exclusive product by treatment of **10** with trifluoroacetic acid. Accordingly, the preferred target is **1**, rather than the stereochemically equivalent IX.

Epoxidation proceeded with greatest exoselectivity with the acetate **12b**, and the product, **13**, reacted smoothly with lithium

(29) All compounds in Scheme II gave satisfactory elemental analyses and/or HRMS data as well as consistent ^{1}H NMR spectra.

(30) For a comprehensive review of ethynyl alanes see: Brono, G. "The Use of Aluminum Alkyls in Organic Syntheses,"; 1969–1972 supplement; Ethyl Corporation: Baton Rouge, LA, 1973.

(31) For a fuller discussion of this aspect see ref 13b.

dimethylcuprate to give the alcohol **14a**. Oxidation followed by immediate reduction after workup afforded the epimer **14b** (87% yield) whose stereochemistry was confirmed by the NOE shown in Scheme II. In order to prepare for the upper "satellite" some straightforward functional group manipulations were required to give **15** and thence **16**. Of special note is the selective hydrolysis of the more-hindered isopropylidene ring engaging the two secondary hydroxyls of **15**.

Elaboration of the upper "satellite" was problematic.[31] Painstaking investigations educed (a) that a modified[32] Corey–Kim procedure[33] was the reagent of choice for selective oxidation of the primary alcohol to the aldehyde **16b** (96%), (b) that the ethylenic acetal **17**, of Sargent and co-workers[34] was the preferred version of the Trippett–Bestmann reagent[35] for obtaining the 4:1 *Z/E* mixture **16c**, and (c) That *both of these geometric isomers upon treatment with methanol and, specifically, Grieco's acid*[36] *led directly to* ***18*** *as the only anomer in 86%* Yield.

Epoxidation of the olefinic sugar **17** with MCPBA was extremely slow; however, aqueous NBS generated a mixture of bromohydrins, which gave a single epoxide **19**, upon reaction with sodium hydride. The opening of epoxide **19** was effected best by Me_2Mg in THF,[37] generated by mixing equimolar amounts of methyllithium and methylmagnesium chloride. The resulting product was methylated to afford the targeted intermediate **1**.

The reactions in Scheme II proceed with very high yields, but the length of the sequence diminishes its attractiveness and hence efforts have been made to provide shorter pathways. We have had encouraging results with respect to the bipyanose **14b** (Scheme III).

By application of Normant's chemistry[38] we obtained the vinyllithium derivative **20a** which was converted into the Grignard **20b**. The latter reacted with **8** to give **21** in 60% yield. This moderate yield is not serious since the only other product is a bromohydrin that is recycled to **8**. Solvolysis of **21** gave the α-anomer **22** predominantly.

Hydroboration of **22** occurred from the exo face, giving **14a**, making it possible to obtain **14b** from **8** in five steps instead of the eight shown in Scheme II. Eight more steps are presently required to go from **14b** to **1**, but efforts are under way to reduce these.

Conclusion

There are several features about the new strategy outlined above that are noteworthy:

(a) Each of the seven centers highlighted in the tripyranose **1**, obtained by either route (Schemes II or III), has been created with *complete stereo- and/or regioselectivity, and therefore no troublesome separations of isomers are required.* This is due to the fact that each ring is a reliable pyranose and hence there are no "off-template" stereocenters! Problem 1 (vide supra) is therefore obviated.

(b) Although each center was introduced rationally and was easily monitored, *all protons in the entire assembly* ***1*** *can be assigned, readily and simply, by [only!] 200-MHz ^1H NMR*, as is apparent from the data shown in Scheme II. The easy proof of configuration common to carbohydrate derivatives (see problem 2 above) is therefore observed in **1**.

(c) The folding pattern adopted cuts down upon the number of "external" protecting groups that would be required by a linear array, since **1** (or IX) protects itself. Note also that **1** requires one less protecting group than IX.

(d) Since the oxirane moeity is a synthon for "pyranosidic homologation" (e.g., **8** → **12**), an iterative procedure should be applicable to either **13** or **19**.

(e) Retroanalysis of many other propionate-derived entities, e.g., the ansa chains of streptovaricin and maytansine, according to the five principles outlined above indicate other opportunities for the *pyranosidic homologation* appraoch.

The two tasks remaining for conversion of **1** into **2** are deconvoluting the tricycle and adding the C-24 CH_3. Procedures for carrying these out are being developed.

Registry No. **1**, 88392-88-5; **8**, 33208-47-8; **9**, 88412-16-2; **10**, 88392-78-3; **11**, 88392-79-4; **12a**, 88392-80-7; **12b**, 88412-17-3; **13**, 88412-18-4; **14a**, 88392-81-8; **14b**, 88424-60-6; **15**, 88392-82-9; **16a**, 88392-83-0; **16b**, 88392-84-1; **16c**, 88392-85-2; **17**, 78950-65-9; **18**, 88392-86-3; **19**, 88392-87-4; **20a**, 88392-89-6; **21**, 88412-19-5; **22**, 88392-90-9; rifmaycin S, 13553-79-2; levoglucosan, 498-07-7.

Supplementary Material Available: ^1H NMR data for compounds **1**, **10**, **12**, **13**, **14a**, **14b**, **16b**, **16c**, **18**, **19**, **21**, and **22** (6 pages). Ordering information in given on any current masthead page.

(32) *N*-Chlorosuccinimide (800 mg, 6.0 mmol) was added to a solution of thioanisole (0.78 mL, 818 mg, 6.6 mmol) in 20 mL of dry CH_2Cl_2 under argon at −20 °C. After 30 min, a solution of the diol **16a** (1.1220 g, 3.0 mmol) in 10 mL of CH_2Cl_2 was added dropwise. After an additional 30 min, diisopropylethylamine (1.05 mL, 6.0 mmol) was added dropwise at −20 °C. After stirring at −20 °C for 20 min, the reaction was warmed to 0 °C. TLC indicated the starting diol **16a** (R_f 0.24, 5% MeOH–CH_2Cl_2) to have formed a clean product (R_f 0.40). The reaction was diluted with CH_2Cl_2 (50 mL), successively washed with sat $NaHCO_3$ (30 mL), 2% HCl (30 mL), and sat $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, and evaporated.

(33) Corey, E. J.; Kim, C. U. *J. Org. Chem.* **1973**, *38*, 1233.

(34) Cresp, T. M.; Sargent, M. V.; Vogel, P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 37.

(35) Bestmann, H. J.; Roth, K.; Ettlinger, M. *Chem. Ber.* **1982**, *115*, 161; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 687. Trippett, S.; Walder, D. M. *J. Chem. Soc.* **1961**, 1266.

(36) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(37) Parker, K. A.; Babine, R. E. *Tetrahedron Lett.* **1982** *23*, 1763.

(38) Cahiez, G.; Bernard D.; Normant, J. F. *Synthesis* **1976**, 245.

Robustadials A and B from *Eucalyptus robusta*

Ren-sheng Xu,† John K. Snyder, and Koji Nakanishi*

Contribution from the Department of Chemistry, Columbia University, New York, New York 10027. *Received June 13, 1983*

Abstract: The structures of two new compounds, robustadial A and B, isolated from the active fraction of the antimalarial extract of *Eucalyptus robusta* leaves, a plant used in Chinese herbal medicine to treat malaria, have been determined as **2** and **3**. The structures were resolved by using spectroscopic methods, especially two-dimensional NMR and difference nuclear Overhauser enhancement techniques. The monoterpenoid moiety containing the spiro linkage has not been encountered previously.

The leaves of *Eucalyptus robusta* Sm. (Myrtaceae) are used in Chinese herbal medicine for the treatment of dysentery, malaria, and other bacterial diseases. The benzene-soluble fraction of the crude 95% ethanol extract of the leaves showed significant inhibition against *Plasmodium berghei*, a malaria-inducing protozoan. From this fraction, an active compound, robustaol A (**1**) was isolated.[1]

† On leave from Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

0002-7863/84/1506-0734$01.50/0