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 $\alpha$-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.

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# Robustadials A and B from *Eucalyptus robusta*

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*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]

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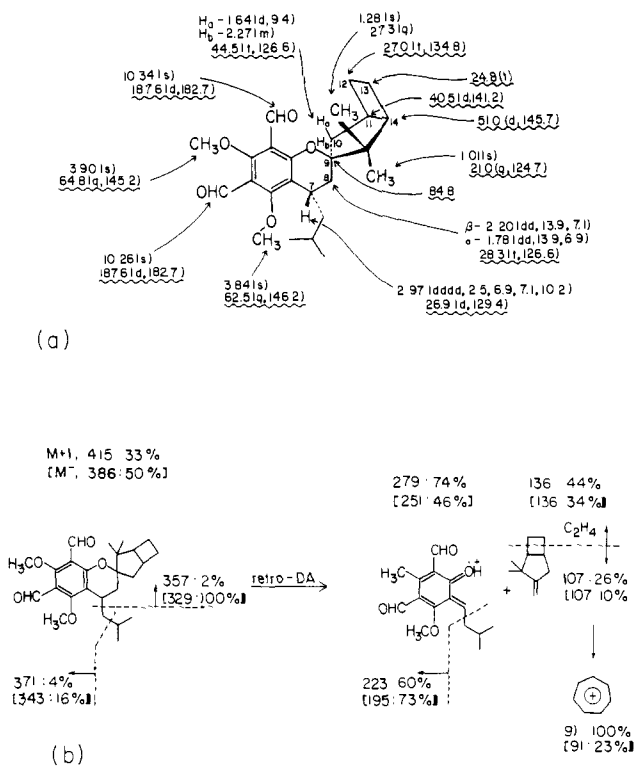
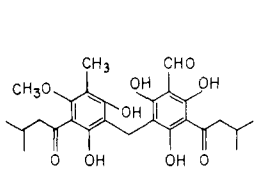
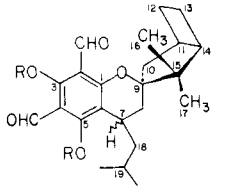



**Figure 1.** (a) $^1H$ NMR (250 MHz $CDCl_3$) and $^{13}C$ NMR (62.9 MHz $CDCl_3$; underlined) of **5**. $J$ values in $^{13}C$ NMR data denote $^1J_{^{13}C-H}$; the $J$ value for C-13 could not be measured due to severe overlap in undecoupled spectrum. See Figure 2 for the $^1H$ NMR data not shown here. (b) Desorption chemical ionization ($NH_3$ carrier gas) MS of **5** and electron-impact MS [in square brackets] of **3**; peak heights are shown in % relative to base peak.

A second fraction contained several compounds that possessed considerably greater activity than **1**.[2] We now report the isolation and structure of two of these compounds, robustadial A (**2**) and robustadial B (**3**). The benzene-soluble fraction was partitioned



**1**



**2** R = H, 7α-H
**3** R = H, 7β-H
**4** R = $CH_3$, 7α-H
**5** R = $CH_3$, 7β-H

with 2% NaOH, and the aqueous layer subsequently was acidified and partitioned with benzene. The active benzene fraction was chromatographed (silica gel, petroleum ether) to give **1** and an oil, which was further chromatographed on silica gel (petroleum ether/EtOAc, 50/1) and then on a Lobar pre-packed reverse-phase column (RP-8, MeOH/$CHCl_3$, 95/5) to yield a mixture of two isomeric compounds, **2** and **3**, which could not be readily separated without derivatization.[3] As preliminary spectral data of the mixture suggested that **2** and **3** were phenolic: $^1H$ NMR ($CDCl_3$)

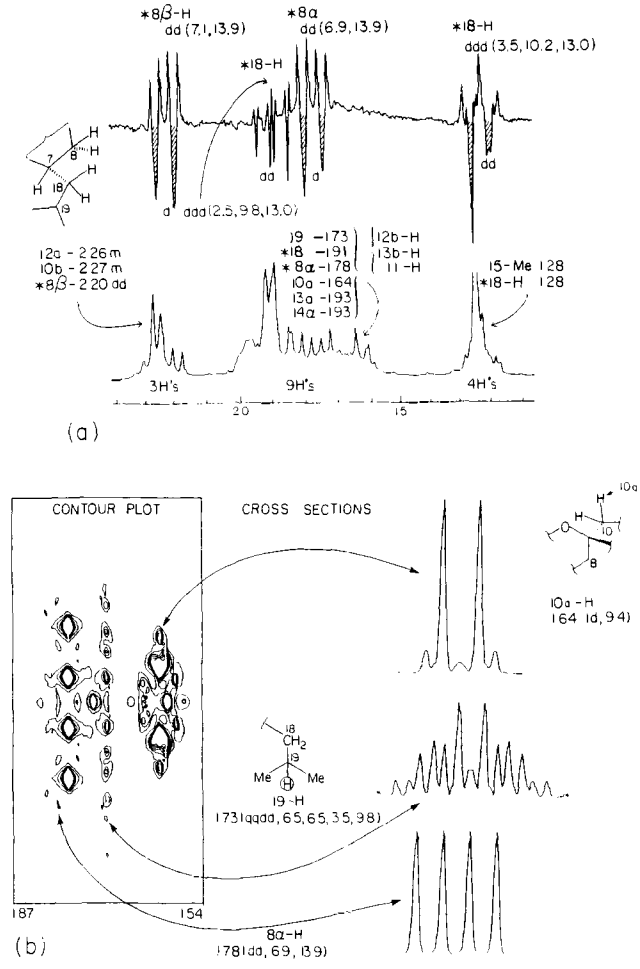



**Figure 2.** (a) Difference decoupling spectrum of **5** ($CDCl_3$) obtained by subtracting the spectrum of **5** with decoupling of 7-H (2.97) from the undecoupled spectrum. The asterisked protons are those which underwent decoupling. The δ's of the 12b-, 13b-, and 11-protons could not be read accurately. (b) $J$-Resolved 2D NMR spectrum of **5** ($CDCl_3$) for determination of coupling partners of 7-H.

δ 13.52, 13.60; IR (NaCl) 3000 $cm^{-1}$ (broad, OH), 1635 $cm^{-1}$ (chelated aldehyde); the mixture was methylated ($CH_3I$/$K_2CO_3$/acetone) to yield the respective dimethyl ethers **4** and **5** which were readily separated on HPLC (Whatman Porasil, $CH_2Cl_2$/0.3% *i*-PrOH). The spectral properties of **4** and **5** were nearly identical. 5: UV(MeOH) 261 nm (ε 11 500), 280 (9200), 320 (2880); CD (MeOH) 227 nm (Δε −2.54), 257 (−2.50), 292 (+1.15), 330 (+0.47), 354 (+0.19); FTIR (NaCl) 1686 $cm^{-1}$ (CHO); HRMS $m/e$ 414.2416 ($M^+$, $C_{25}H_{34}O_5$; calcd, 414.2406). **4**: CD(MeOH) 235 nm (Δε +1.96), 259 (+3.86), 275 (+2.29), 320 (+1.81), 354 (−0.59); MS (DCI) 415 (M + 1, 33%).

The UV and IR spectral data for **5** as well as the $^{13}C$ NMR and $^1H$ NMR spectra ($CDCl_3$) suggested a fully substituted aromatic acetogenin moiety bearing two aldehydes and three ether linkages, two of which are methoxyl groups. The remaining benzylic position is occupied by a tertiary carbon bearing an isobutyl side chain as shown by NMR and MS (Figure 1).[4] The acetogenic chromophore plus the isobutyl side chain account for $C_{15}H_{18}O_5$ and six units of unsaturation leaving a $C_{10}H_{16}$ moiety and three units of unsaturation which must include two terpenoid-Me groups, $^1H$ NMR ($CDCl_3$) δ 1.01 (s) and 1.28 (s). The mass spectra of **4** and **5** show a retro-Diels–Alder cleavage as their major fragmentation pathway, yielding peaks at $m/e$ 279 (74%, $C_{15}H_{19}O_5$) and 136 (44%, $C_{10}H_{16}$), requiring a six-membered ring fused to the aromatic nucleus. Furthermore, the third ether bond links the aromatic ring to a quaternary carbon (δ 84.8 s). With

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(2) Qin, G. W.; Gu, X. M.; Lu, B. F.; Xu, R. S., unpublished results.
(3) Compounds **2** and **3** were finally separated by using reverse-phase HPLC (JASCO, YMC-gel, ODS S-5, 150 × 4.6 mm, $CH_3CN/H_2O$, 85/15) after an exhaustive examination of numerous conditions of columns and solvent systems.

(4) The MS (DCI) of **2** and **3** both show the loss of a $C_4H_9$ moiety as the major fragmentation pathway. This loss is ascribed to cleavage of the isobutyl side chain at the benzylic position.

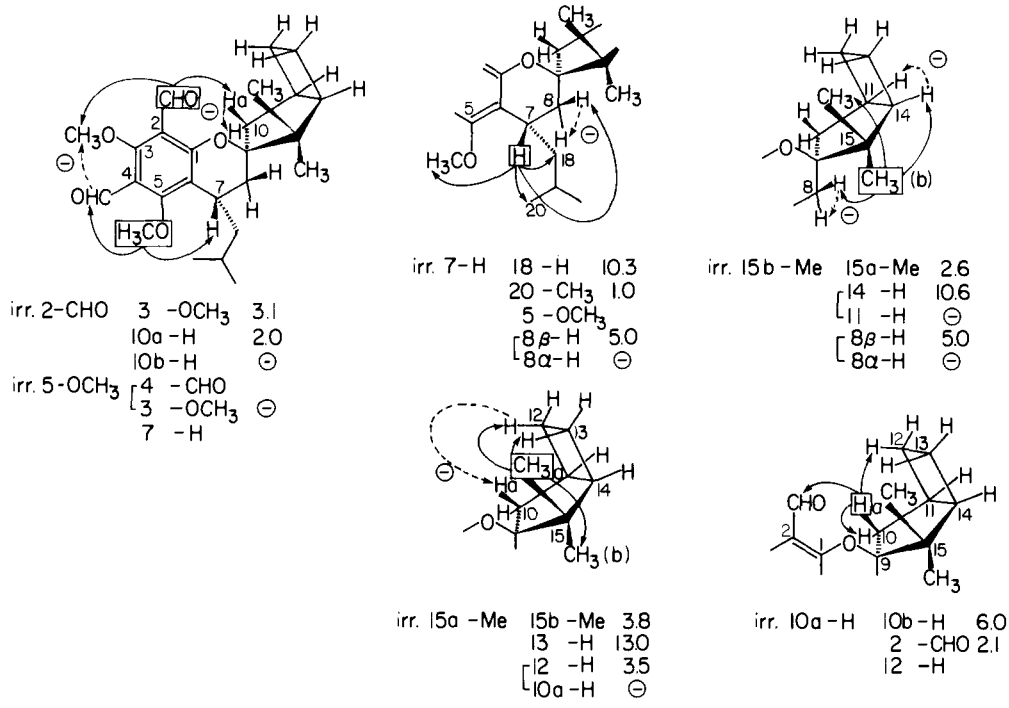


**Figure 3.** Difference NOE (%) of **5**, 250 MHz $CDCl_3$. The dashed arrows denote negative NOE's. The % increment of some positive NOE's could not be measured accurately due to overlap of methyl singlet.

the requirement of a six-membered B ring, the remaining six non-methyl carbons must form a bicyclic structure to account for the final two units of unsaturation. The absence of high-field signals in the $^{13}C$ and $^{1}H$ NMR spectra rules out a cyclopropyl unit.

The nine overlapping proton signals in the 1.5–2.0 ppm region were clarified by the techniques of difference decoupling (Figure 2a) and *J*-resolved 2D NMR (Figure 2b). Irradiation of 7-H (Figure 2a) decoupled four protons, two each attached to C-8 and C-18. Therefore C-7 (benzylic) is vicinal to two methylenes, one of which belongs to the isobutyl side chain; the qqdd signal of the isobutyl 19-H is resolved in Figure 2b. The methylene group at C-8 requires that the remaining six non-methyl carbons form a bicyclo[3.2.0]heptane unit linked to the B ring via a quaternary spirocenter at C-9. The appearance of a peak in the high-resolution mass spectrum at *m/e* 28 ($C_2H_4$) as well as the large $^{1}J_{C-H}$ coupling constants,[5] 51.0 (d, 145.7), 40.5 (d, 141.2), 27.0 (t, 134.8), and 24.8 (t) (Figure 1a) confirms the presence of a bimethylene bridge in a cyclobutyl moiety.[6] Thus the *gem*-dimethyl and the spiro center are both located on the cyclopentyl ring. This spiro center is not vicinal to a bridgehead carbon of the bicyclo[3.2.0]heptyl moiety, as shown by the multiplicities of the 10-H's (Figure 1a) as well as the nuclear Overhauser enhancements (NOE) (Figure 3).

The relative stereochemistry of the cyclobutyl fusion, the location of the *gem*-dimethyl at C-15 rather than C-10, and the relative stereochemistry at the C-7 position (as the $\beta$-epimer) were all confirmed by appropriate NOE's (Figure 3). That dimethylrobustadial A (**4**) is the C-7 $\alpha$-epimer of **5** was suggested by the close similarity of the $^{1}H$ NMR and $^{13}C$ NMR spectra except for the downfield shift of its C-8 peak at 31.0 ppm. The C-7 stereochemistry was confirmed by a 5% NOE enhancement observed in **4** for the 10-Hb proton upon irradiation of 7$\alpha$-H. All other NOE's observed in the spectra of **4** were in accord with the assigned structure.

Robustadial A and B are structurally related to the euglobals, potent granulation inhibitors isolated from *Eucalyptus globulus*.[7] Further studies on the absolute stereochemistry of **2** and **3** as well as their biological activities are in progress.

**Acknowledgment.** We thank Hideo Naoki of the Suntory Institute for Bioorganic Research for the high-resolution mass spectra and Dr. Allan Croteau for the FT-IR spectra. This work was supported by NIH Grant AI 10187.

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