9 provided evidence for O–S interactions similar to those that we postulate, no evidence was obtained for symmetrical species such as the anions described here.

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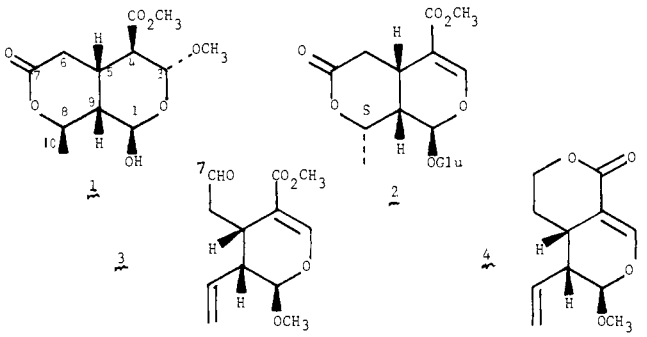
Revision of the Structure of Xylomollin

Sir:

The structure of xylomollin was reported in 1976 to be **1**, a secoiridoid hemiacetal acetal isolated from an East African tree and found to have insect antifeedant and other biological activities.[1] Its structural assignment was based almost solely on NMR and mass spectral data, which, by analogy to all known iridoid structures,[2] appeared to justify that **1** was related to 8(*S*)-secoiridoids like kingiside (**2**)[3] and sarracenin,[4] but having the 8(*R*) configuration. However, it seemed to us that

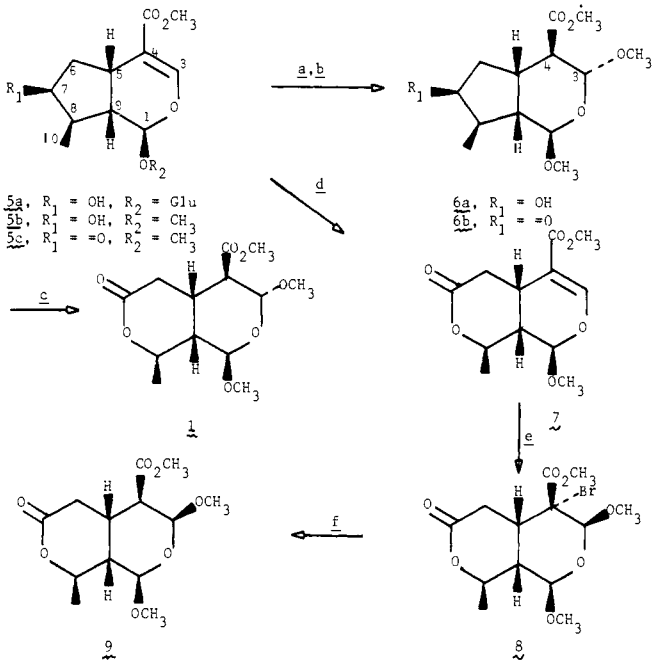


the $^3J_{H_5H_9}$ value of 10 Hz found for **1** was too large for a cis-fused decalin system in view of some NMR data obtained during our recent total synthesis of the secoiridoid aglucone acetals, 1-methoxysecologanin (**3**) and 1-methoxysweroside (**4**).[5] We thus considered that xylomollin could actually be a trans-fused iridoid. This appears to be true since partial synthesis of (−)-1-OMe-**1** and its C-3 epimer (**9**) has provided spectral evidence that xylomollin is not **1**.

The strategy for the partial synthesis of **1** was based on its possible biomimetic relationship to (−)-loganin (**5a**), from which two tactical developments were pursued to provide the target molecules. Addition of methanol to (−)-1-methoxyloganin aglucone (**5b**)[6] or (−)-1-methoxylogan-7-one (**5c**)[6] was effected cleanly under basic conditions (Scheme I) to give **6a** (71%;[7] mp 91–92 °C (Skelly B–Et_2O); $[\alpha]^{24.5}_D$ −56.0° (*c* 3.3 mg/mL, MeOH)) or **6b** (58%;[7] mp 81–82 °C (Skelly B–Et_2O); $[\alpha]^{24.5}_D$ −169.8° (*c* 18 mg/mL, MeOH)) as colorless, crystalline solids.[8] The addition was clearly cis as judged by the appearance of a doublet (δ_H 4.85 ($^3J_{H_3H_4}$ = 8.3 Hz)) for the new acetal proton in **6a** and in **6b** (δ_H 4.93 ($^3J_{H_3H_4}$ = 8.5 Hz)). Presumably the expected trans diaxial addition of methanol is not observed because of the ease of the reversibility of the reaction, although **6a,b** itself appeared to be in equilibrium with **5b,c** since extended reaction times did not increase the amount of the **6a,b** formed relative to unreacted **5b,c**. Conversion of **6a** to **6b** (quantitative) with Cr(VI) and/or subsequent Baeyer-Villiger oxidation gave (−)-1-OMe-**1** (60–70%; mp 99–100.5 °C (Et_2O); $[\alpha]^{24.5}_D$ −102° (*c* 12.2 mg/mL, MeOH)).

Alternatively, Baeyer–Villiger oxidation of **5c** to **7** (50–60%; mp 84–85 °C (Skelly B–Et_2O); $[\alpha]^{24.5}_D$ −46.0° (*c* 0.87 mg/mL, MeOH)) followed by bromomethoxylation[9] of the enol double bond gave **8** (75%; glass; $[\alpha]^{24.5}_D$ −3.8° (*c* 3.15 mg/mL, MeOH)). The addition of bromine at C-4 was clearly

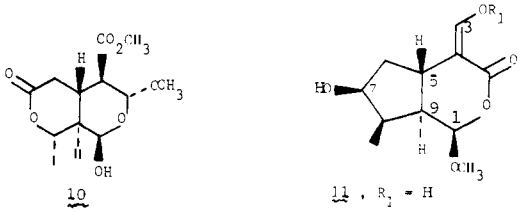
Scheme I



[a] $Mg(OMe)_2$ (10 equiv), MeOH (0.5 M), reflux 6–72 h. [b] Pyridinium chlorochromate (1.7 equiv), CH_2Cl_2 (1.8 M), 25 °C, 1 h. [c] *m*-ClpBzA (3 equiv), $NaHCO_3$ (7 equiv), CH_2Cl_2 (3 M), 25 °C, 4 h. [d] *m*-ClpBzA (1.2 equiv), $NaHCO_3$ (3 equiv), CH_2Cl_2 (0.1 M), 25 °C, 20 h. [e] NBS (1 equiv), MeOH (0.2 M), 0→25 °C, 30 min. [f] (n-Bu)$_3$SnCl (2 equiv), $NaBH_4$ (7 equiv), absolute EtOH (0.015 M), $h\nu$, 15 °C, 45 min.

evident in the ^{1}H NMR spectrum of **8**: downfield shift of the carbomethoxy resonance ($\Delta\delta$ 0.09), and the appearance of new singlets at δ 3.44 (C-3 OCH_3) and 5.16 (H-3). This is shown to occur with the trans diaxial endo stereochemistry by analogy to the known stereoselectivity of bromomethoxylation of pentaacetyl **5a**;[10] the axial C-1 OMe must effectively inhibit formation of the intermediate bromonium ion on the exo face of **7**. Reductive debromination of **8** under free-radical conditions using Corey's catalytic (n-Bu)$_3$SnH method[11] resulted in an ~1:1 mixture of **9** and its C-4 epimer (50%).[12] The formation of two C-4 epimers is consistent with equilibration of the intermediate radical before it can be reductively captured.

Since (−)-1-OMe-**1** and (−)-**9** were prepared from (−)-loganin, whose absolute configuration has been secured by X-ray crystallography,[10b] these two secoiridoid diacetals must have the 5(*S*),8(*R*),9(*S*) absolute stereochemistry originally assigned to **1**. However, synthetic 1-OMe-**1** has an $^3J_{H_5H_9}$ of 4.8 Hz and **9**, 4.0 Hz, consistent with an approximately gauche relationship of the bridgehead hydrogens in a *cis*-decalin system.[13] This and other spectral data[1] lead us to propose that xylomollin's structure be revised to **10**, a 5(*S*),8(*S*),9(*R*)-



secoiridoid, in which the all-trans diaxial orientation of the methine hydrogens is more consistent with the reported ^{1}H NMR coupling constant data than is **1**.[14] Consequently, xylomollin is the first example of a trans-fused iridoid to be found in Nature. Its biogenesis probably parallels that of **2** and morroniside, the 7-hemiacetal analogue of **2**,[3a] which are de-

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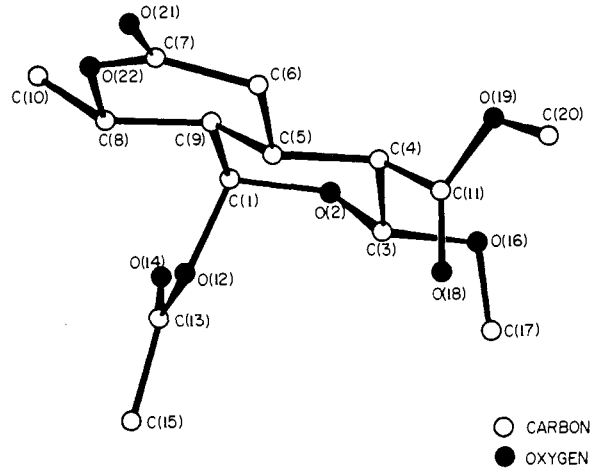

Figure 1. A computer-generated perspective drawing of 1-*O*-acetyl xylomollin. Hydrogens are omitted for clarity.

rived from secologanin.[3c] Both the addition of methanol at C-3,4 and the C-9 epimerization may be artifactual results of isolation. For example, treatment of **5a** (R_2 = H) with methanolic methoxide (25 °C, 16 h) results in the formation of **11** ($^3J_{H_5H_9}$ = 11.50 Hz), which underscores the ease of C-9 epimerization in an iridoid aglucone.

The revised structure proposed for **1** is confirmed by the following crystallographic analysis. Crystals of (−)-xylomollin acetate[15] formed in orthorhombic crystal class with a = 7.344 (1), b = 8.890 (1), and c = 23.565 (4) Å. Systematic extinctions uniquely indicated space group $P2_12_12_1$ and a density measurement suggested one molecule of composition $C_{14}H_{20}O_8$ in the asymmetric unit. Intensity data were collected on a fully automated four-circle diffractometer using graphite monochromated Mo Kα (0.71069 Å) radiation and a variable speed ω scan. Of the 1892 reflections surveyed, 1381 (73%) were judged observed ($F_o \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects.[16] A phasing model was achieved using a multiple solution weighted tangent formula approach and full-matrix least-squares refinement with anisotropic nonhydrogen atoms and isotopic hydrogens have converged to a standard crystallographic residual of 0.044.[22]

Figure 1 is a computer-generated perspective drawing of the final X-ray model less hydrogens. This X-ray experiment defines only the relative configuration of xylomollin acetate as C-1(S^*), -3(R^*), -4(R^*), -5(S^*), -8(S^*) and -9(R^*). The ether ring has a chair conformation and the lactone ring a slightly flattened chair. The bridgehead hydrogens are trans to each other with an ~180° dihedral angle. All substituents are equatorial save the acetoxy group at C-1. Bond distances and angles generally agree with accepted values; there were no abnormally short intermolecular contacts or unusually high electron density on a final difference synthesis. Additional crystallographic details may be found in the supplementary material described at the end of this paper.

Acknowledgment. We are indebted to Drs. J. J. Partridge and Milan Uskokovic for experimental details of the preparation of **7**, a generous supply of the rich natural source of **5a**, and helpful discussions; to Professors W. A. Gibbons and H. Schnoes, Department of Biochemistry, University of Wisconsin, for high resolution spectral determinations; to Jim Blackbourn and Gary Girdaukas, School of Pharmacy, University of Wisconsin, for low resolution spectral determinations; and to the National Institutes of Health for partial support of this research by an NIH grant (CA 17127-04). The diffractometer used in this study was purchased from funds provided by the National Science Foundation. We are especially grateful to Professor K. Nakanishi and Dr. I. Kubo for a sample of natural xylomollin.

Supplementary Material Available: Fractional coordinates, bond distances, and bond angles with errors for xylomollin acetate (2 pages). Ordering information is given on any current masthead page.

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(12) This mixture was exceedingly difficult to separate by preparative chromatography on silica gel in ether–hexane (6:4). Thus the $[\alpha]^{24.5}_D$ −45.2° (*c* 1.86 mg/mL, MeOH) of **9** was taken on a sample containing ~10% C-4 epimer.
(13) E. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, pp 279–281.
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(15) Prepared from (−)-xylomollin, $[\alpha]^{24}_D$ −44.3° (MeOH), by acetylation using acetic anhydride/pyridine: mp 162–164 °C; $J_{H_1,_9}$ = 3.4, $J_{H_5H_9}$ = 10.8 Hz. Acetylation in the presence of AcOD did not result in incorporation of deuterium into this acetate.
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(17) Career Development Awardee of the National Institutes of Health, 1976–1981 (CA 00257).

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Evidence for a Preassociation Mechanism for Acid Catalyzed Addition of Semicarbazide to 4-Methoxyphenyl Formate[1]

Sir:

We report kinetic α-deuterium isotope effects for attack of semicarbazide on 4-methoxyphenyl formate which strongly suggest that catalysis of this reaction by the conjugate acid of the nucleophile, and probably by the hydrated proton, occurs by a preassociation mechanism rather than by trapping of the zwitterionic addition compound by proton transfer from these species.

Satterthwait and Jencks have established that general acid catalysis of addition of basic amines to phenyl acetates occurs with rate-determining transfer of a proton from the catalyst

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