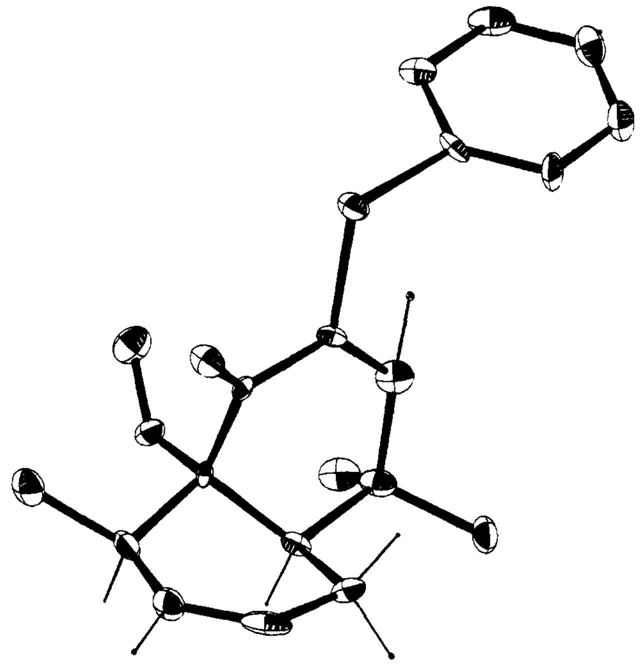
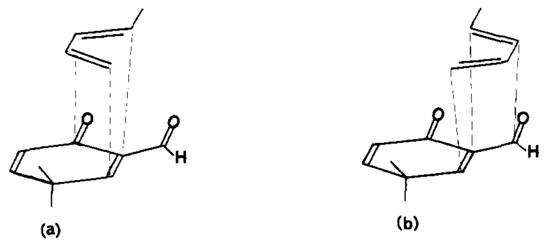
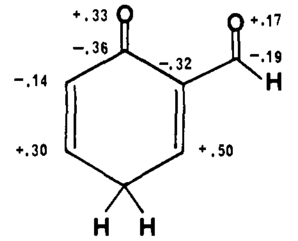


Figure 1. ORTEP representation of **6b**.



(a) (b)

Figure 2. (a) Alder–Stein transtion state for **4a** + **5** involving secondary orbital interactions between the ketone carbonyl carbon and the diene. (b) Alder–Stein transtion state for **4a** + **5** involving secondary orbital interactions between the aldehyde carbonyl carbon and the diene.

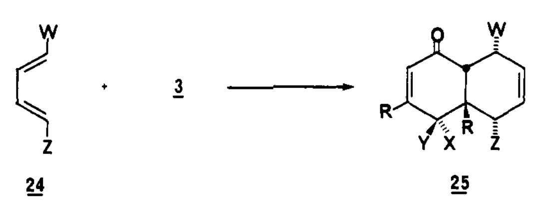


8

Figure 3. LUMO coefficients of **8**, as determined by using MINDO-3 calculations.

upon whether the process is done thermally or under Lewis acid-catalyzed conditions.[13,14] For the catalyzed process the observed diastereoselectivity presumably results from complexation of the hydroxyl group by $SnCl_4$, thereby transforming it into the larger of the two geminal substituents. This does not occur in the catalyzed reaction of **19** with **5** because complexation of the hydroxyl group with the Lewis acid is effectively prohibited by the adjacent methyl substituents.

The implications of these results are quite significant. *Intermolecular Diels–Alder reactions involving cross-conjugaed dienones could in a single reaction produce up to five asymmetric centers with one relative stereochemistry* (illustrated below for the general process **3** + **24** → **25**). Moreover, it may be possible in selected cases to employ dienones as "enone equivalents" for Diels–Alder reactions which fail because of unreactive enones. Further studies involving the synthetic and mechanistic implications of this work will be the subject of future reports.



Acknowledgment. This work was supported by a grant from the National Institutes of Health.

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[14] When compound **23** is allowed to react with PhSeCl, only products derived from simple addition to the unconjugated double bond are observed. For a discussion of these simple addition processes, see: Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, 4977.

A Novel Synthesis of (±)-Cinnamodial

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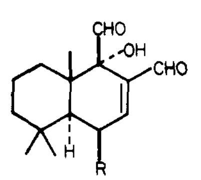
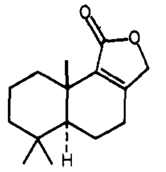
Received January 19, 1981

Cinnamodial (ugandensidial, **1**)[1] and warburganal (**2**), constituents of the genus *Warburgia ugandensis* (Canellaceae),[2] have been shown to possess potent insect antifeedant activity against the African army worm (*spodoptera* species),[3,4] as well as antimicrobial and molluscicidal properties.[3] Current interest in these substances is evidenced by the fact that five syntheses of warburganal have been reported within the past 2 years,[5] and, very recently, one of these[5c] has been extended to a synthesis of cinnamodial.[6] We now wish to describe a total synthesis of (±)-**1** which is different in concept from previous approaches to these sesquiterpene dialdehydes and which affords a convenient entry to related members of the drimane class,[7] including isodrimenin (**3**).



1, R = OAc
2, R = H



3

The plan for introducing the ene-dialdehyde functionality of **1** was based on the assumption that a furan could serve as a latent 1,4-dialdehyde synthon, and the initial phase of the synthesis was therefore directed toward the tricyclic furan **10**. The Diels–Alder adduct **4**[8] of 1-vinyl-2,6,6-trimethylcyclohexene and dimethyl acetylenedicarboxylate was treated with borane–THF, and the

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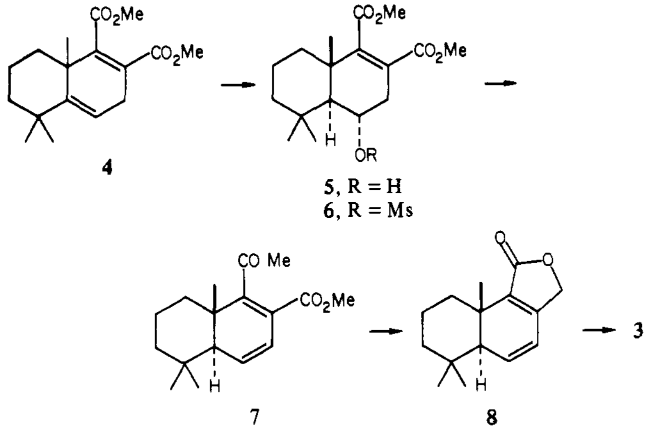


4

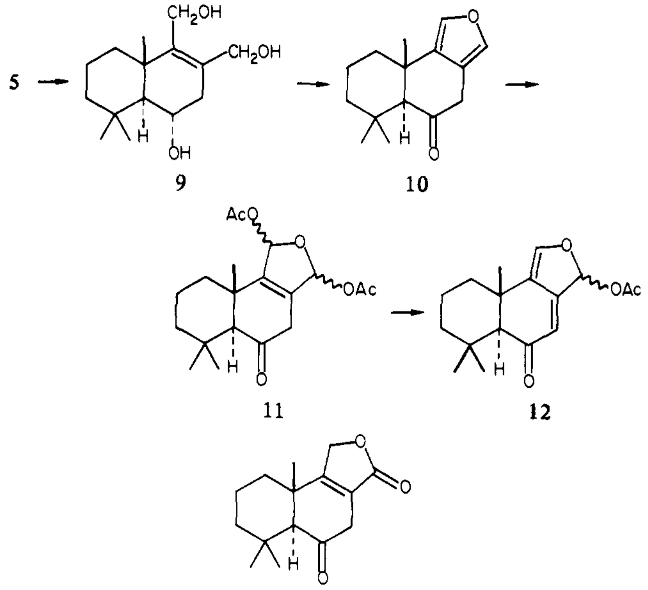
5, R = H
6, R = Ms

7

8

resulting alkylborane was oxidized (H_2O_2–NaOH)[9] to give a hydroxy diester in 75% yield.[10] Contrary to an earlier assignment,[5b] this alcohol (**5**) was shown to possess a trans ring fusion. Thus, conversion of **5** to its mesylate **6** (2 equiv of CH_3SO_2Cl, pyridine, room temperature, 4.5 h), followed by elimination with 1 equiv of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing benzene (22 h), produced in high yield a 4:1 mixture of diene **7**[11] and its nonconjugated isomer, separable by chromatography on silica gel. Reduction of **7** ($LiAlH_4$, Et_2O, 0 °C, 5 h) afforded lactone **8** (80%; mp 102–104 °C), which was hydrogenated (10% Pd–C, EtOAc, 1 h) to give quantitatively (±)-isodrimenin (**3**; mp 91–92 °C), identical by mmp, TLC behavior, and comparison of IR and NMR spectra with a sample of (±)-**3** synthesized independently.[12]

With the configuration of **5** thus established, this diester was



9

10

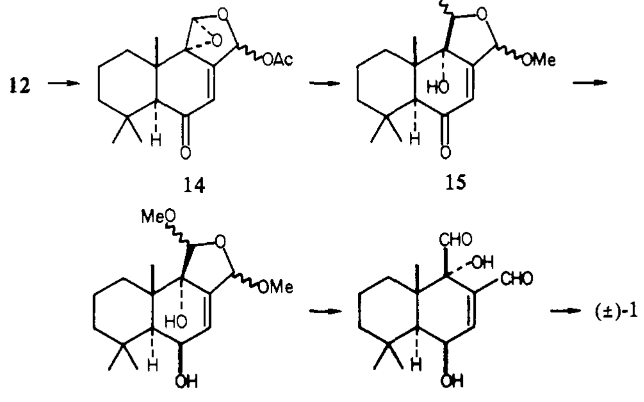
11

12

13

reduced to triol **9** [$(i\text{-}Bu)_2AlH$, toluene, −78 °C and then 0 °C for 2 h], which was oxidized directly (pyridinium chlorochromate, CH_2Cl_2, room temperature, 1 h) to the ketofuran **10** (68% yield from **5**). The furan moiety of **10** underwent facile oxidation with lead tetraacetate (generated from Pb_3O_4, HOAc, and Ac_2O) in benzene (room temperature, 2 h) to yield 90% of a mixture of epimeric diacetates **11**.[13] Brief treatment of **11** with DBU (1 equiv, THF, room temperature, 20 min) afforded the dienone **12** (70%), whereas more prolonged exposure of the diacetate to excess DBU furnished a substance (72%) identified as (±)-fragrolide (**13**).[14]

Installation of the 9α-hydroxyl group of **1** was envisaged through epoxidation of **12**, since it was expected that attack would occur preferentially at the more nucleophilic γ,δ unsaturation[15] from the less hindered α direction. In fact, the reaction of **12** with *m*-chloroperbenzoic acid (CH_2Cl_2, anhydrous Na_2CO_3, room temperature, 1 h) yielded a product (76%), which was sufficiently stable to permit chromatographic purification and which, according to NMR evidence [δ 6.92 (1 H, d, J = 1.5 Hz), 5.46 (1 H, s)], was the desired epoxide **14**. Exposure of **14** to methanol



14

15

16

17

containing a catalytic amount of *p*-toluenesulfonic acid (reflux, 10 h) gave the bis acetal **15** in 70% yield as a mixture of methoxy epimers, and, with the dialdehyde functionality now suitably protected, **15** was reduced [$(i\text{-}Bu)_2AlH$, THF, −5 °C, 0.5 h)[16] to diol **16** (90%). The 6β configuration of the newly formed alcohol is assigned on the presumption of a sterically controlled approach[16] of the reductant to the α face of the keto group of **15**, and is supported by the NMR spectrum of **17**, in which the C*H*OH proton (δ 4.79) is clearly cis ($J \simeq 6$ Hz) to the vicinal angular proton.

Brief treatment of **16** with 10% HCl in acetone gave a single dialdehyde **17** in 92% yield. Although relatively hindered, the secondary alcohol of **17** could be acetylated with Ac_2O in pyridine containing 4-(dimethylamino)pyridine[17] (room temperature, 4 h) to give (±)-**1** (81%), identical with a sample of racemic cinnamodial[6] by comparison of TLC behavior and IR, NMR, and mass spectra. The synthesis of **1** by this route suggests that the furanoid strategy employed may be applicable to other antifeedants possessing similar functional group aggregations.[2] Experiments designed to test the generality of this approach will be reported in due course.

Acknowledgment. We are indebted to Dr. Takeshi Oishi, Rikagaku Kenkyusho, Saitama, Japan, for samples and IR and

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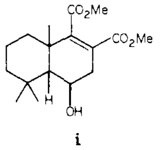
(9) H. C. Brown and R. M. Gallivan, *J. Am. Chem. Soc.*, **90**, 2906 (1968).

(10) A second alcohol, with spectral properties consistent with a cis fused structure (i), was isolated in ca. 5% yield.



i

(11) Assigned structures are fully supported by IR, NMR, and mass spectral measurements.

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(13) N. Elming in "Advances in Organic Chemistry: Methods and Results", Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Eds., Interscience, New York, 1960, p 67.

(14) L. Canonica, A. Corbella, P. Garibaldi, G. Jommi, J. Krepinsky, G. Ferrari, and C. Casagrande, *Tetrahedron*, **25**, 3903 (1969). It was found that **12** can also be converted to fragrolide (**13**) under these conditions. The acetoxyfuran, derived by isomerization of the double bond in **12**, is a putative intermediate.

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NMR spectra of (±)-isodrimenin and (±)-cinnamodial. Financial support was provided by the M. J. Murdock Charitable Trust.

Supplementary Material Available: IR, NMR, and mass spectral data for **1**, **3**, **5–8** and **10–15** (4 pages). Ordering information is given on any current masthead page.

A Monohydroxo Bridged, Strongly Antiferromagnetically Coupled Dicopper(II) Center in a Binucleating Macrocycle. Comparisons with Binuclear Copper Sites in Biology

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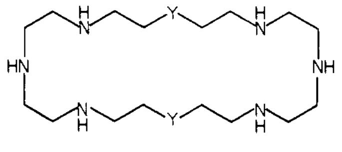
Received February 20, 1981

Strongly antiferromagnetically coupled ($J \leq -500$ cm^{-1}) dicopper(II) centers exist in met- and oxyhemocyanin, laccase, and related copper proteins.[1-3] The nature of the bridging ligand or ligands is unknown, although tyrosine or oxo oxygen atoms have been proposed.[3] Here we report that the binucleating macrocycle A, previously used to coordinate the imidazolate (im) bridged dicopper(II) ion (Cu–Cu distance, 5.86 Å),[4,5] readily incorporates



Macrocycles A (Y = O), A' (Y = CH_2)

a monohydroxo bridged dicopper(II) center (Cu–Cu distance, 3.64 Å) that exhibits very strong antiferromagnetic coupling, $J \sim -500$ cm^{-1}. The large magnitude of the magnetic exchange interaction through a single bridging oxygen atom and the ability of the binucleating macrocycle to expand and contract to accommodate bridged binuclear copper(II) ions with variable metal–metal distances are features of likely relevance to binuclear copper centers in biology.

The compound was synthesized by dropwise addition of 2 mL of a 120 mM methanolic solution of $Cu(ClO_4)_2 \cdot 6H_2O$ to 4 mL of a stirred solution of the macrocycle[4] dissolved to 30 mM concentration in methanol, followed by dropwise addition of 0.116 mL of 1 N NaOH to the resulting dark blue solution. After 2 min a dark blue microcrystalline precipitate formed, leaving an almost colorless supernatant. When 1 mL of water was added to this mixture, the solid completely redissolved. Vapor diffusion of chloroform into this solution gave the product in 57% yield as dark blue monoclinic prisms. Analytical,[6] spectroscopic,[6] and X-ray crystallographic[7,8] data showed the composition to be $[Cu_2(OH)(ClO_4)\subset A](ClO_4)_2 \cdot CHCl_3$.

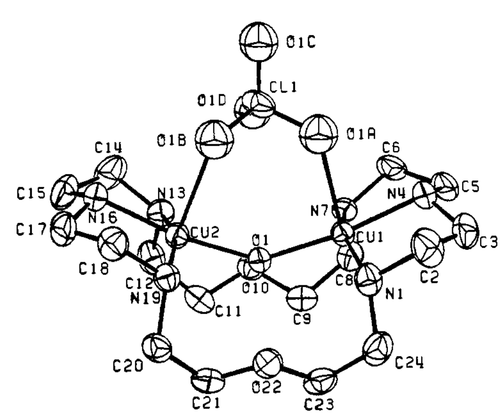


Figure 1. Structure of the $[Cu_2(OH)(ClO_4)\subset A]^{2+}$ cation showing the 40% probability thermal ellipsoids. For clarity, only one of two positions is depicted for the disordered, bridging perchlorate group, the oxygen atoms of which are assigned arbitrarily as spheres of 0.3 Å radius. Hydrogen atoms are omitted.

Table I. Selected Geometric Features of the $[Cu_2(OH)(ClO_4)\subset A]^{2+}$ Cation[a]

distance, Å		distance, Å		angle, deg	
Cu1–O1	1.920	Cu2–O1	1.912	Cu1–O1–Cu2	143.7
Cu1–N1	2.055	Cu2–N13	2.056	O1–Cu1–N4	171.7
Cu1–N4	1.995	Cu2–N16	1.988	O1–Cu2–N16	170.6
Cu1–N7	2.040	Cu2–N19	2.053	N1–Cu1–N7	158.2
Cu1–O1A	2.606	Cu2–O1B	2.594	N13–Cu2–N19	160.5
Cu1–Cu2	3.642				

Possible Hydrogen Bonding

distance, Å		angle, deg		angle, deg	
O1–O10	3.025	O1–O10–C9	82.6	O1–O22–C21	85.21
O1–O22	2.962	O1–O10–C11	84.3	O1–O22–C23	84.8

Best Planes Calculations

through O1, N1, N4, N7 dev from plane, Å		through O1, N13, N16, N19 dev from plane, Å	
O1	−0.22	O1	−0.21
N1	+0.24	N13	+0.22
N4	−0.26	N16	−0.24
N7	+0.24	N19	+0.22
Cu1	−0.09	Cu2	−0.06

[a] Atoms are labeled as in Figure 1. Standard deviations in bond lengths are less than 0.02 Å and in interbond angles are less than 0.2°.

The structure of the $[Cu_2(OH)(ClO_4)\subset A]^{2+}$ cation is shown in Figure 1. Two copper atoms are coordinated to the two diethylenetriamine poles of the macrocycle as found previously[4,5] for $[Cu_2(im)(imH)_2\subset A]^{3+}$ and $[Cu_2(im)(MeIm)_2\subset A']^{3+}$. A single hydroxide ion bridges the two metal centers at D_{2d} distorted square-planar coordination sites. The resulting Cu–O bonds (av, 1.916 Å) and the Cu–O–Cu angle of 143.7 (2)° may be compared with Cu–O distances of 1.90–1.93 Å and Cu–O–Cu angles of 96–104° observed in di-μ-hydroxo bridged dicopper(II) complexes[9] and corresponding values of 1.930 (5) Å and 141.6 (3)° for another structurally well-characterized monohydroxo bridged dicopper(II)

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(6) Elemental analysis. Anal. Calcd for $Cu_2C_{17}H_{40}N_6O_{15}Cl_6$: C, 22.48; H, 4.44; N, 9.25; Cl, 23.42. Found: C, 22.68; H, 4.62; N, 9.39; Cl, 24.15. Infrared spectrum (Nujol mull) N–H stretches, 3288, 3264 cm^{-1}; O–H stretch, 3472 cm^{-1}. The assignment of this band to the O–H stretching mode is supported by its absence in $[Cu_2(im)(imH)_2\subset A](ClO_4)_3$.[4] Optical spectrum (aqueous solution) λ_{max} (ϵ, M^{-1} cm^{-1}): 637 (240), 330 (1800, sh), 265 (9300) nm.

(7) The compound crystallizes in the space group $P2_1/c$ with four formulas in a unit cell of dimensions $a = 14.487$ (2), $b = 15.282$ (2), $c = 15.573$ (2) Å; $\beta = 91.79$ (1)°; $\rho_{calcd} = 1.751$, $\rho_{obsd} = 1.754$ (2) g cm^{-3}. The copper atom positional parameters were determined by direct methods and the other atoms were located on difference Fourier maps. When 4305 unique reflections [$3° \leq 2\theta \leq 50°$, $F_o > 4\sigma(F_o)$] collected at 26° by diffractometer using Mo Kα radiation were used, the structure was refined to a current value of 0.054 for the discrepancy index $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. Full details, including the best model used to fit two disordered perchlorate anions, will be reported at a later date.

(8) Supplementary material.

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