

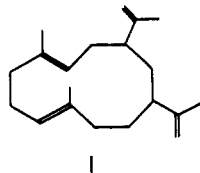
- (19) Analysis of the $(m + 1)$ and $(m + 2)$ ions is consistent with the assignment from the $(m + 3)$ ion shown here.
- (20) Corrected for the enantiomer excess of the propanediol, the cross-contamination of 'syn' and 'anti' diastereoisomers, and the natural abundance of ^{13}C and ^2H . The largest contribution to the error is in the estimate of the cross-contamination of the 'syn' and 'anti' isomers; the metastable ion spectra are precise to $\pm 3\%$.
- (21) Methods of ring closure other than that reported here have been less satisfactory, giving apparent values for the enantiomer excess of 9% (using thermal closure of the open dimethyl triester) and 40% (using dipyrlydyl disulfide/triphenylphosphine in dioxane, on 3).

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Cubitene: An Irregular Twelve-Membered-Ring Diterpene from a Termite Soldier

Sir:

The oily defensive secretions released from the frontal glands of *Cubitermes* soldiers (Isoptera: Termitidae: Termitinae) are known to contain uncharacterized diterpene hydrocarbons.¹ These compounds are used in conjunction with attacks by the termites' mandibles,² a characteristic mode of defense used by *soldats faucheurs* ("reaping soldiers").³ Although the defensive effectiveness of these *Cubitermes* secretions has not been studied in detail, a possible role of another nontoxic hydrocarbon mixture has been suggested in the case of a *Macrotermes* soldier, which possesses analogous defensive behavior.⁴ In this communication, we report the structure of cubitene, one of the major constituents of the frontal gland secretion of soldiers of the East African termite *Cubitermes umbratus* Williams.⁵ Cubitene (**1**)⁶ proved to possess a novel cyclododeca-1,5-diene skeleton resulting from an irregular joining of isoprene units.



Cubitene was isolated from the hexane extract of *C. umbratus* soldier heads ($\sim 75 \mu\text{g}/\text{soldier}$) by chromatography over Florisil followed by preparative GLC.⁷ Its low resolution EI mass spectrum exhibited major fragments at m/e 67, 68, 81, and 93; the CI-MS (CH_4 reagent gas) showed a weak $(M + 1)^+$ peak at m/e 273. High resolution mass spectroscopy indicated the molecular formula of cubitene to be $\text{C}_{20}\text{H}_{32}$ (M^+ , m/e 272.2496; calcd, 272.2504). Catalytic hydrogenation of 0.5 mg of cubitene (Pd/C) gave a mixture of at least three perhydro derivatives. The CI mass spectra of each of these showed $(M - 1)^+$ peaks at m/e 279, consistent with their formulation as substituted cycloalkanes of the composition $\text{C}_{20}\text{H}_{40}$. Cubitene is therefore a monocyclic hydrocarbon, with four centers of unsaturation. The ^1H NMR spectral data revealed the presence of two 1,1-disubstituted double bonds (δ 4.75, br s, 4 H) and two additional olefinic protons (4.95, br m, 2 H). Four methyl groups attached to double bonds were observed at δ 1.55 (s, 3 H), 1.56 (s, 3 H), 1.64 (s, 3 H), and 1.77 (s, 3 H). No other diagnostically useful signals appeared in the ^1H NMR spectrum. However, the ^{13}C NMR spectrum of cubitene allowed the recognition of two trisubstituted double bonds (δ 134.4, 132.5, 127.5, 123.1) and confirmed the presence of two terminal methylene groups (δ 150.0, 149.4, 110.7, 109.0). The remaining twelve resonances (δ 40.9, 40.7, 39.9,

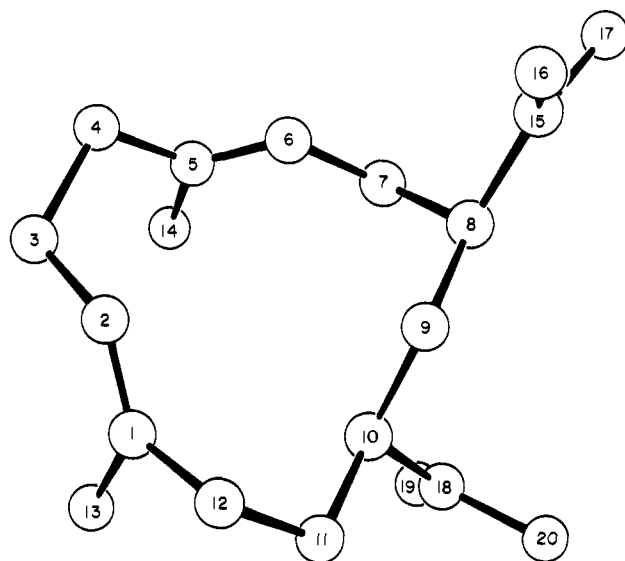


Figure 1. A computer-generated perspective drawing of cubitene (1). Hydrogens are omitted for clarity.

37.0, 31.3, 30.9, 28.0, 24.8, 22.6, 18.3, 15.1, and 14.3) were unassigned.

To further characterize cubitene, a small sample (0.1 mg) was ozonized⁸ in CH_2Cl_2 at -78°C . After reduction of the ozonide with triphenylphosphine, GC-MS analysis of the product mixture allowed the identification of 4-oxopentanal.⁹ The mass spectrum of the product of highest molecular weight did not contain sufficient detail to permit an unambiguous structure assignment. Fortunately, at this stage in the investigation it was found that cubitene could be obtained crystalline (mp $33.5\text{--}34^\circ\text{C}$) from cold methanol, permitting a single-crystal x-ray diffraction analysis.

Cubitene crystallized in the monoclinic crystal class with $a = 15.963$ (5), $b = 6.799$ (2), $c = 17.038$ (5) Å; $\beta = 96.69$ (2)°. Systematic extinctions combined with the known optical activity ($[\alpha]_{\text{MeOH}}^{20} + 128^\circ$ (c 0.76)) required space group $C2$. The limited amount of sample precluded a density measurement, but four molecules of composition $\text{C}_{20}\text{H}_{32}$ in this unit cell gave a reasonable hydrocarbon density of $\sim 1.0 \text{ g}/\text{cm}^3$. All unique reflections with $\theta \leq 57^\circ$ were collected on a four-circle diffractometer with graphite monochromated $\text{Cu K}\alpha$ (1.54178 Å) x-rays. After correction for Lorentz, polarization, and background effects, 1058 (74%) reflections of the 1422 surveyed were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$). The angular dependence of the scattering was removed as the reflection data were converted to normalized structure factors and solution via a multisolution weighted tangent formula approach attempted.^{10,11} A plausible eight-atom fragment was located and the structure extended by tangent formula refinement.¹² Full-matrix least-squares refinements with anisotropic carbons and isotropic hydrogens have currently converged to a standard residual of 0.062 for the observed reflections.¹³ A computer-generated perspective drawing is presented in Figure 1.

As can be seen from Figure 1, cubitene (**1**) is (1*E*,5*E*,8*S**,10*R**)-1,5-dimethyl-8,10-bis(isopropenyl)cyclododeca-1,5-diene, a structure in which one isoprene unit is irregularly joined to three others. It appears to be the first example of a diterpene hydrocarbon based on a twelve-membered carbocyclic ring, and its biosynthesis poses interesting problems. One possibility would involve the initial coupling of farnesyl pyrophosphate to dimethylallyl pyrophosphate to give an irregular, acyclic diterpenoid, cyclization of which could lead directly to **1**.¹⁴ A second, more indirect possibility is suggested by the observation that **1** co-occurs in *C. umbratus* with two cembrene derivatives.¹⁵ In this context, the co-occurrence of the cembrene-related β -4,8,13-duvatriene-1,3-diol (**2**) and its frag-

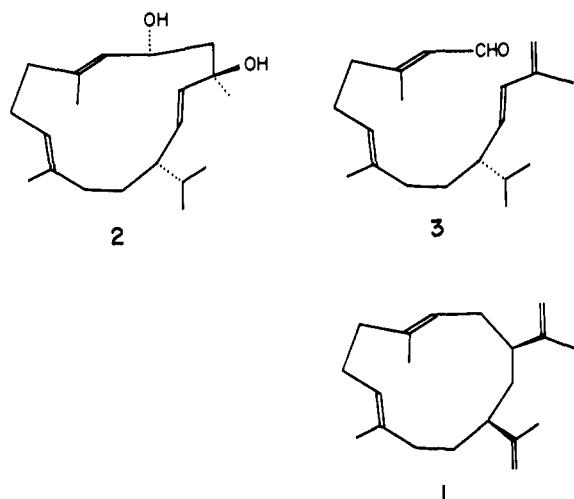


Figure 2. Cubitene and structurally related diterpenoids.

mentation product **3** in tobacco plants^{16,17} is intriguing; the joining of C(1) to C(12) in an intermediate related to **3** would give rise to the cubitene skeleton (see Figure 2).

Biosynthetic studies will be necessary to determine whether either of these schemes is correct. The even more basic question of whether termite soldiers synthesize cubitene at all, or whether they simply sequester it (or a closely related precursor) from their food, also remains a topic for future research.

Acknowledgments. We are grateful to Dr. R. M. C. Williams (Centre for Overseas Pest Research) for identification of the termite species, Mr. I. Miura and Professor K. Nakanishi (Columbia University) for the ¹³C NMR spectrum of cubitene, and Ms. B. A. Solheim (Iowa State University) for collection of the x-ray diffraction data. Partial support of this work by the NIH (Grant No. AI 12020 and Fellowship Awards AI 05076 (G.D.P.) and CA 05646 (D.F.W.)) is acknowledged with pleasure.

Supplementary Material Available: A table of fractional coordinates of cubitene (2 pages). Ordering information is given on any current masthead page.

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- (7) *Cubitermes umbratus* Williams was collected from 1–3-ft-high columnar mounds in the Shimba Hills Forest (Kwale, Kenya). The termite soldiers were individually removed from the excavated mounds, cooled to 0 °C, and decapitated, and the heads were crushed under hexane. Approximately 130 mg of crude extract was obtained from 400 individuals. Chromatography of this crude material over Florisil (100–120 mesh) with hexane afforded 92 mg of a mixture of four diterpene hydrocarbons which could be separated by preparative GLC on 6% Carbowax 20M or 3% FFAP columns (both on 100/120 Gas Chrom Q, 240 cm × 0.2 cm, 150 °C). Cubitene (**1**), the component of shortest retention time, represented 23% of the diterpene mixture. Temperature-programmed GLC (Carbowax, 60–250 °C) and TLC analysis of the secretion obtained directly from the frontal gland with a microcapillary indicated that the diterpene hydrocarbons accounted for the total secretion. The experiments reported here were performed on a total of 7 mg of pure **1**.
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A Stereocontrolled General Synthesis of C-Nucleosides¹

Sir:

C-Nucleosides, having a carbon to carbon ribosidic linkage, constitute the class of compounds that possess important antibiotic properties as well as potent anticancer and antiviral activities.² Most of the synthetic approaches reported so far have utilized carbohydrate precursors.^{2c} In this communication, we wish to disclose a stereocontrolled entry starting from noncarbohydrate materials.³ Here the ribose skeleton has been constructed using the polybromo ketone/iron carbonyl reaction⁴ as the key method.

The starting material is the bicyclic ketone **1**, which is prepared easily by the Fe₂(CO)₉-promoted cyclocoupling reaction of α,α,α',α'-tetrabromoacetone and furan followed by Zn/Cu couple reduction.⁵ When the unsaturated ketone **1** was allowed to react with 35% H₂O₂ (1.5 equiv) and a catalytic amount of OsO₄ (20:1:1 acetone-ether-*tert*-butyl alcohol, 30–35 °C, 4 h) and then with 70% HClO₄ (25 °C, 6 h), the oxygen functions were introduced with perfect stereoselectivity to afford in 65% yield a single acetonide **2**, mp 119–121 °C, having α stereochemistry.⁶ Subsequent Baeyer–Villiger oxidation of **2** to the lactone **3**, mp 146–147 °C,⁷ was achieved by CF₃CO₂H⁸ (2 equiv, room temperature, 1 h) in 92% yield. Thus the ketone **1** was transformed without any complication to **3** that has an adequate C-β-glycoside structure.

The optical resolution required for the natural product synthesis was accomplished through cinchonidine salt of the hydrolyzed product **6**, mp ~80 °C, [α]_D²⁶ –75° (c 0.47, C₂H₅OH). Heating of the resolved material with acetic anhydride/pyridine (reflux, 12 h) gave back the optically pure lactone, mp 161–163 °C, [α]_D²⁶ +84° (c 0.63, CHCl₃).

Reaction of the lactone **3** and [(CH₃)₂N]₂CHOC(CH₃)₃⁹ (excess, DMF, 40–45 °C, 2 h) gave the dimethylaminometh-