A New Secotrinervitane Diterpene Isolated from Soldiers of the Madagascan Termite Species, *Nasutitermes canaliculatus*

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Reported herein is the X-ray crystallographic structure of a novel 10-oxygenated secotrinervitane diterpene, 3α,10α-diacetoxy-7,16-secotrinervita-7,11,15(17)-triene (**4**), from soldiers of the endemic Madagascan termite *Nasutitermes canaliculatus*, which was compared with an energy-minimized structure obtained by computer molecular modeling. We also report ^{1}H- and ^{13}C-NMR and MS data for this new diterpene.

One-quarter of the 2000 or so known species of the family Termitidae are in the subfamily Nasutitermitinae. In many species of this subfamily, particularly those of the genera *Nasutitermes* and *Trinervitermes*, the soldier castes have evolved large frontal glands and nozzle-like cephalic structures from which they eject irritating, entangling secretions to disable their foes.[1–6] Nearly all the many cembrane-based diterpenes isolated from the defensive secretions of these and other advanced nasute genera have had tricyclic[7–11,18–24] or tetracyclic[9,12,13,17,20,22–24] structures. Three notable exceptions, the bicyclic structures **1** and **2**, were reported by Braekman *et al.*[13,15,19] and **2** and **3** by Goh *et al.*,[22] from one species each of the genera *Nasutitermes* and *Longipeditermes*, respectively. Such bicyclic structures had been proposed earlier by Prestwich *et al.* as likely biosynthetic intermediates to the tricyclic ("trinervitane") and tetracyclic ("kempane" or the methyl-shifted "rippertane"[13]) classes.[16] Kato and co-workers have demonstrated the chemical conversion of an epoxyneocembrene-A to the secotrinervitane **3**[25,26] and its further chemical conversion to the related trinervitane.[27] They pointed out that the secotrinervitane structures are unique natural products in having a cyclohexane chair with a bridging 10-carbon chain, 1,4-*trans*-diequatorially oriented.[27]

We report here the isolation of a new diterpene diacetate from the Madagascan termite *Nasutitermes canaliculatus* Wasmann, and the assignment to it of the 3α,10α-diacetoxy-7,16-secotrinervita-7,11,15(17)-triene structure (**4**) by X-ray crystallographic analysis. We also report complete ^{1}H- and ^{13}C-NMR and EIMS data for **4** and a comparison of the X-ray structure with an
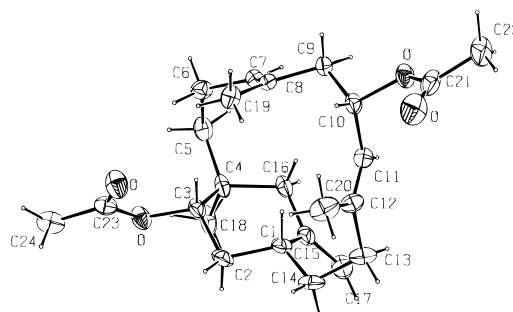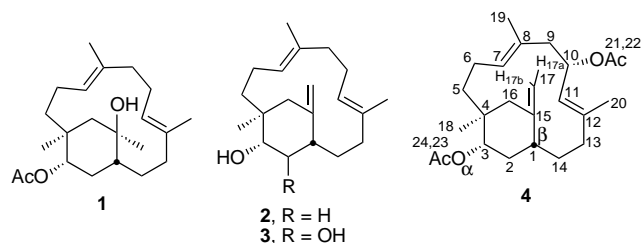

Figure 1. Stereo drawing (PLATON)[29] of the X-ray structure of the Madagascan termite diterpene **4**.

energy-minimized structure obtained by computer molecular modeling.

2, R = H
3, R = OH

The computed structure is generated from the X-ray diffraction data and depicts in Figure 1 and structure **4**, a configuration of the diterpene, arbitrarily chosen to agree with the structures of the related trinervitanes,[7,18] kempanes,[9,12] or 3α-hydroxy-15-rippertene,[13] whose absolute configurations have been determined directly by X-ray analysis of heavy atom-containing derivatives or by using combined X-ray crystallography and CD spectra. Relative configurations of **1**[14] and a trinervitane 3,8-oxide[19] have also been determined by X-ray analysis.

Prominent features of the ^{1}H-NMR spectrum (500 MHz, CDCl₃, Table 1) of **4** were three methyl signals at δ 0.88 (CH₃-18), 1.74 (CH₃-19), and 1.76 (CH₃-20) (the

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Table 1. NMR Spectral Data for Compound **4**

carbon	$\delta_C{}^a$	hydrogen	$\delta_H{}^b$(mult., J)
1	37.5	1	1.91 (m, 13.1 + others)
2	36.4	$2\beta^e$	1.69 (dd, 13.4, < 1)
		2α	1.33 (ddd, 12.5, 10.7, 10.7)
3	74.9	3	4.95 (dd, 10.4, 4.9)
4	38.8		
5	36.9	5β	1.54 (dt, 14.3, 4.0)
		5α	1.30 (ddd, 14.3, 12.8, 4.3)
6	24.7	6β	2.49 (dddd 15.3, 12.7, 12.2, 3.6)
		6α	1.99 (m)
7	129.4	7	5.26 (dd, 11.9, $\approx$1)
8	129.5		
9	45.5	$9\beta,9\alpha$	2.59 (bd, 13.5), 2.30 (dd 13.4, 11.3)
10	69.3	10	5.80 (ddd 11.3, 10.0, 4.3)
11	125.8	11	4.84 (d, 10.0)
12	142.0		
13	37.0	$13\alpha,13\beta$	2.12 (td, 13.1, 3.6), 2.03 (m)
14	25.7	$14\beta,14\alpha$	1.74 (m), 1.23 (tdd, 13.4, 3.7, 1.6)
15	147.7		
16	47.4	$16\beta,16\alpha$	2.95 (d, 13.5), 1.69 (d, 13.6)
17	103.8	$17a,17b^e$	4.67 (d, 1.5), 4.56 (d, 1.5)
18	22.3	18	0.88 (s)
19	15.0	19	1.74 (d, 2)
20	15.9	20	1.76 (d, 2)
21^c	170.2		
22^c	21.3	22	2.02 (s)
23^d	170.6		
24^d	21.4	24	1.98 (s)

^{a} Measured at 125 MHz in CDCl$_3$. CDCl$_3$ was used as an internal reference (77 ppm). ^{b} In ppm downfield from tetramethylsilane in CDCl$_3$ (measured at 500 MHz). ^{c,d} The assignments for the pair 21/22 may be interchanged with the assignments for the pair 23/24 in structure **4**. ^{e} α and β and 17a/b hydrogens are indicated on structure **4**.

first, a quaternary methyl; the other two suggesting allylic methyls) and two acetoxyl methyls at δ 1.98 and 2.02. Signals compatible with an exomethylene group were observed as broad singlets at δ 4.56 and 4.67 (H-17a,b), and two pairs of vinyl hydrogen signals were seen: one, a doublet at δ 4.84 (H-11, J = 9.9 Hz), the other a dd signal at δ 5.26 (H-7, J = 11.9, ca. 1 Hz). Assignments of these and other protons were made from analysis of COSY and TOCSY spectra. The vinyl hydrogen, H-7, exhibited two principal cross peaks with H-6α (δ 2.49 m), H-6β (δ 1.99, m), and a weak allylically coupled cross peak with CH$_3$-19 (δ 1.74). Proton H-7 also showed long-range correlation with protons at CH$_3$-19 and C-5 in a TOCSY spectrum, thus establishing a network involving C-19 to C-5. The other vinyl proton (H-11) showed a strong cross peak with H-10 (δ 5.80) and a weak cross peak with the slightly more downfield allylic methyl (CH$_3$-20) in a COSY spectrum. H-11 also showed major cross peaks with both H-9 protons, and both H-6 and H-9 showed cross peaks with CH$_3$-19 in a TOCSY spectrum. A TOCSY spectrum also established H-3 to H-1 and H-14 connectivities and H-10 and H-11 to CH$_3$-20. The exomethylene H-17 hydrogens were weakly coupled to one another, but both were strongly coupled to H-16β at δ 2.95, weakly coupled with H-1, and not coupled to H-16α. The computer-measured dihedral angle of the exomethylene plane with H-16α was approximately 0°. H-16β was also coupled to the quaternary CH$_3$-18. Identification of the protons of the methylene groups were made from the COSY and HMQC spectra, which showed correlation of geminal methylene protons to single carbons. The most downfield signals, a ddd at δ 5.80 (J = 11.3, 10.0, 4.3 Hz) and a dd (J = 10.4, 4.9 Hz) at δ 4.95 were assigned to protons H-10 and H-3, respectively, on acetoxyl-bearing

carbons. This was confirmed by an HMQC experiment, where these signals were correlated with ^{13}C-NMR signals at 69.3 and 74.9 ppm, respectively. Also in the ^{1}H-NMR spectrum of **4**, H-16β is evidently deshielded by 1.2 ppm relative to H-16α. A deshielding effect on an adjacent hydrogen by an exomethylene bond has been reported by Prestwich *et al.*[8] in a trinervitane diterpene. It appears likely also that H-13β is deshielded relative to H-6β by the anisotropy of the exomethylene bond. The exomethylene H-17 protons were assigned by long-range ^{1}H-^{13}C couplings (COLOC program). The signal at δ 4.67 (H-17a) was coupled with C-1 and that at δ 4.55 (H-17b) was coupled with C-16. Proton H-17b was also seen to be coupled with H-1 in an ^{1}H–^{1}H-COSY spectrum; the H-17a–H-1 cross peak, on the other hand, was very weak. A 2D NOESY spectrum indicated H-17a–H-13β and H-17b–H-16α cross peaks permitting the assignment of H-17a and H-17b as indicated in structure **4**. Additional cross peaks were seen for H-6β and CH$_3$-19; H-7 with H-9α and also with H-16β; H-10 with CH$_3$-20; H-11 with H-1; H-11 with H-9β; H-11 with H-16α, and finally, H-16β with H-5α.

A total of 24 ^{13}C-NMR resonances (Table 1) were detected and the quaternary carbons C-8 and C-12 as well as the two pairs of acetoxyl carbons could be assigned with COLOC spectra. The C-15 carbon, for which a COLOC correlation could not be obtained, was assigned by default. The C-18 methyl protons were correlated with carbons 4 and 5; the C-19 methyl protons with C-8, C-9, and, very probably, C-7, while the C-20 methyl protons were correlated with C-11, C-12, and C-13. The acetoxyl methyl hydrogens of CH$_3$-22 were correlated with the C-21 carbonyl at 170.2 ppm and those of CH$_3$-24 with the C-23 carbonyl carbon at 170.6 ppm; however, the C-21, C-22 and the C-23, C-24 pairs in structure **4** could be interchanged. One other long-range coupling was detected, that of the H-9α (δ 2.59) with the vinylic carbons C-7 and C-11. Note that the ^{13}C-NMR signals of methylenes at C-6 and C-14 were considerably upfield of the others, probably by virtue of a γ-effect exerted by CH$_3$-18/CH$_3$-19 and CH$_3$-20, respectively.

Computer molecular modeling with an MM2-based program (Chem 3D for the Macintosh) yielded a single energy-minimized structure that is nearly identical to that of Figure 1. It should be stressed that the crystal structure of **4** contained two molecules in somewhat differing environments, yet both possessed the same conformation by X-ray analysis. Thus, this conformation, which results from either observation or modeling, is strongly supported as a global energy minimum.

The computed conformation for **4** had a calculated minimized energy of 37.8 kcal/mol. The largest contributions to this energy were 20 kcal/mol of 1,4 van der Waals' interactions and 13 kcal/mol of angle deformations. In Table 2 are listed the computer-calculated H–H dihedral angles (θ) for comparison with observed θ values from the X-ray data and ^{1}H-NMR coupling constants (J). In nearly every instance, where the X-ray crystallographic θ deviated significantly from the computed value, the computed θ was less. In one case, that of $\theta_{14\alpha-1}$, the computed θ was greater. Dihedral angles measured in mol. 1 were a slightly better match with calculated values than the angles of mol. 2. The

Table 2. Computed and Observed (X-ray) Dihedral Angles ($\theta°$) for **4**[a]

C−C bond	H−H dihedral angle	comp ($\theta°$)	X-ray ($\theta°$)	¹H-NMR (J, Hz)
1−2	1−2α	171	172,[b] 170[c]	13.1
	1−2β	71	68, 69	
2−3	2α−3β	174	178, 177	10.6
	2β−3β	56	62, 63	5.0
5−6	5α−6α	56	60, 64	4.3
	5α−6β	169	178, 178	13.3
	5β−6α	58	58, 53	4.0
	5β−6β	55	60, 65	4.0
6−7	6α−7	62	70, 73	≈1
	6β−7	176	172, 170	11.9
9−10	9α−10β	176	172, 177	11.3
	9β−10β	60	70, 67	4.3
10−11	10β−11	158	174, 170	10.0
13−14	13α−14α	60	60, 59	3.6
	13α−14β	176	178, 180	13.1
	13β−14α	55	59, 60	
	13β−14β	60	60, 61	
14−1	14α−1	178	168, 165	
	14β−1	66	72, 77	

[a] See structure **4** for designation of α and β. [b] θ, mol. 1 of unit cell. [c] θ, mol. 2 of unit cell. The standard deviation of θ measurements is ± 3−4°.

dihedral angles that showed significant differences (> ± 6°) between the observed and computed values, were θ_{2-3}, θ_{5-6}, θ_{6-7}, θ_{9-10}, θ_{10-11}, and θ_{14-1}.

GC−MS yielded a chromatogram with two peaks, one (30−40%) an evident thermal decomposition product whose retention time and amount were injector-temperature dependent, while the main peak (which could also be a decomposition peak, despite its constant retention time) gave as the highest mass a fragment at m/z 269 corresponding to the molecular ion minus HOAc and OAc. A direct-probe instrument (see Experimental Section) with ammonia chemical ionization did reveal (M + NH₄)⁺ at m/z 406 (13%), but major fragment ions were seen also for loss of HOAc from the (M + NH₄)⁺ and (M + H)⁺ ions, and the base peak at m/z 269 indicated the loss of two HOAc from (M + H)⁺. FABMS also indicated peaks (40−60%) corresponding to the loss of two HOAc from the molecular ion. A major loss of both acetoxyl groups under these mild conditions is unexpected.

The present work, in addition to providing a fourth reported structure of the uncommon bicyclic 7,16-secotrinervitane class of termite diterpenes provides the first example of oxygenation at C-10 in any of the known bicycles, tricycles, or tetracycles. Braekman and co-workers have reported a pair of epimeric C-11 acetoxytrinervitane tetraacetates from a New Guinean *Nasutitermes* sp.[19] The usual position of oxygenation, outside of C-2, C-3, and C-15, is C-9[7,8,15,18−24] or C-13;[10,11,15,18,20,21,23,24] examples of C-6[12] or C-14[9,17,24] oxygenation also exist. The diterpene **4** should be a useful chemosystematic character, as proposed by Prestwich,[1−6] for studying the evolution of and relationships among termite genera and species.

Prestwich has hypothesized that intermolecular hydrogen-bonding in termite diterpenes forming dimers may help account for their viscous, adhesive properties.[28] He noted furthermore that all the termite tricyclic and tetracyclic diterpenes whose structures have been studied by X-ray crystallography were dome-shaped with a largely hydrophobic cavity and had most polar substituents on the convex face. The diterpene **4**

does have both its polar substituents on the same face, but, as it lacks a hydroxyl group, it cannot associate through H-bonding. No evidence was seen by X-ray diffraction of any unusual intermolecular association between the two molecules occupying the unit cell. It should be noted that many of the termite diterpenes so far characterized are ketoacetates,[9,12,15,16,18,20,23,24] diacetates,[9,10,16,24] triacetates,[10,15,20,22−24] tripropionates,[18] or tetraacetates[21] and likewise lack even the one hydroxyl group required for H-bonding.

Experimental Section

General Experimental Procedures. ¹H- and ¹³C-NMR spectra were recorded at 500 and 125 MHz, respectively, with a Varian VXR-500S spectrometer and standard Varian programs were used for COSY and NOESY spectra. A Brucker AC-300 spectrometer and Brucker standard programs were used for some homonuclear and heteronuclear COSY spectra and COLOC experiments. GC−MS used a Finnigan Model 800 ion-trap mass detector with a Varian 3400 gas chromatograph fitted with a Restek RTX-5 Amine 30-m fused silica column, programmed from 100 to 280 °C at 10°/min; in some cases, the injector was programmed from 80 to 280 °C at 100°/min. GC−CIMS (NH₃ reagent gas) and direct-probe EIMS employed a Finnigan model 4500 mass spectrometer. The HRMS measurement was done with a JEOL SX102 instrument fitted with a 15-m × 0.20-mm HP-5 column. FAB spectra were run in glycerol and nitrobenzyl alcohol matrixes and used the JEOL instrument.

Animal Material. The termite soldiers were collected in 1993 at Mahatsara in northeastern Madagascar near Fénérive-Est.

Extraction and Isolation. Soxhlet extraction of 4500 ground-up *Nasutitermes canaliculatus* termite soldiers with CH₂Cl₂ yielded 688 mg (3.86% w/w) of a mixture of at least eight major components as detected by GC. Chromatography of 271 mg of this mixture on a silica gel column (17 cm × 2.5 cm, Merck Silica-gel 40, 70−230 mesh) yielded several fractions. An initial EtOAc-cyclohexane fraction on recrystallization from *n*-hexane−CH₂Cl₂ yielded 20 mg (7.4% w/w) of colorless, orthorhombic, prismatic crystals (mp 109.5 °C, [α]²⁰_D −0.30°, *c* 0.004, CHCl₃) suitable for a single-crystal X-ray diffraction analysis. ¹H- and ¹³C-NMR data are reported in Table 1. Three other substances in the extract were also purified by chromatography.

Mass Spectral Analyses. Ion-trap mass detector: m/z 269 (5, M − HOAc −OAc), 268 (7, M − 2 HOAc), 253 (12), 239−241 (8), 227 (8), 225 (9), 213 (8), 199 (20), 197 (20), 185 (20), 173 (18), 171 (18), 161 (16), 159 (40), 157 (57), 145 (32), 133 (15), 131 (27), 129 (12), 121 (20), 119 (35), 117 (15), 109 (15), 107 (23), 105 (50), 95 (40), 93 (20), 91 (45), 81 (32), 79 (45), 69 (15), 67 (35), 57 (15), 55 (25), 53 (21), 43 (100), 41 (50). Accompanied by a decomposition product whose amount and retention time (less than the main peak and variable) is dependent upon the injector temperature. CIMS (NH₃): m/z 406 (13, M + NH₄⁺), 346 (37, M + NH₄⁺ − HOAc), 329 (45, M + H⁺ − HOAc), 269 (100, M + H⁺ − 2 HOAc) accompanied by ca. 10% of a congener with fragments at m/z 422, 362, 285, evidently corresponding to a C₂₄H₃₆O₅ formula. Direct-probe EIMS: m/z 328 (10), 268 (8), 253 (5), 197 (5), 185 (10), 173 (8), 159 (15), 157

(20), 145 (10), 133 (12), 121 (10), 119 (18), 109 (10), 107 (13), 105 (15), 97 (12), 95 (16), 93 (18), 84 (10), 83 (10), 81 (13), 79 (13), 69 (10), 67 (10), 55 (18), 43 (100). FAB spectra in nitrobenzyl alcohol and glycerol exhibited weak ($\sim$5−10%) peaks at m/z 460 and 461, respectively, for M + 3 H$^+$ + 3 Na$^+$ and M + 4 H$^+$ + 3 Na$^+$. Major peaks (40−60%) in the nitrobenzyl alcohol matrix indicated losses of 2 HOAc. HRMS on the direct probe EI fragment at m/z 328, calculated for $C_{22}H_{32}O_2$ (M$^+$ − HOAc), m/z 328.2402; found, 328.2417.

X-ray Analysis. Following are the X-ray experimental data: crystal size, $0.5 \times 0.2 \times 0.2$ mm; space group, $P2_12_12_1$ (No. 19); $a = 13.165(1)$ Å, $b = 14.151(2)$ Å, $c = 24.803(2)$ Å; V = 4670.7 Å^3; Z = 8; $D_{calc} = 1.117$ g cm^{-1}; radiation = CuKα, $\lambda = 1.54184$ Å; $\mu = 6.2$ cm^{-1}; $F(000)$ = 1696; $T = 23 \pm 1°$; diffractometer, Enraf-Nonius CAD4; corrections, Lorentz-polarization; extinction (coefficient = 1.52×10^{-6}); maximum 2θ; 148.0°; hkl ranges, $h = 0$:16; $k = 0$:17; $l = 0$:30; number of measured unique reflections, 5196.[30]

Phase Solution. The density suggested a molecular weight either twice that of the assumed related seco-trinervitane[14] or else two molecules in the asymmetric unit. MolEN (basically MULTAN) produced two nearly identical fragments, suggesting the latter choice was correct and all missing atoms were readily obtained in a preliminary refinement.

Least-squares refinement: program, XTAL 3.2 (MolEN cannot refine a moderately large structure, such as **4**); 3440 reflections with $F_o^2 > 3.0\ \sigma(F_o^2)$; hydrogen atoms, riding on C atoms; parameters refined, 506; R, 0.058; R_w, 0.062; esd of observation of unit weight, 2.72; convergence, largest shift, 0.001 σ; minimization function, $\sum w(|F_o| - |F_c|)^2$; least-squares weights, $4F_o^2/\sigma(F_o^2)$; instrumental instability factor, 0.040; highest value in final difference map, 0.41e/Å^3; lowest value, −0.36 e/A^3. The asymmetric unit consists of two molecules of essentially identical conformation. A determination of absolute stereochemistry was not considered feasible given the O:C ratio of 1:6 in **4**.

Computer programs used: CAD4 and MolEN (Enraf-Nonius, Delft, 1990); XTAL 3.2 (S. R. Hall, H. D. Flack, and J. M. Stewart, Universities of Western Australia, Geneva and Maryland, 1992, adapted for the IBM PC by D. Grossie, Wright State University, Dayton OH).

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(30) X-ray data for the structure enantiomeric to that shown in Figure 1 have been deposited at the Cambridge Crystallographic Center, UK.