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TWO SESQUITERPENE LACTONES FROM *TRICHOGONIA GARDNERI*

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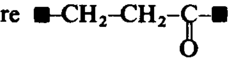
Key Word Index—*Trichogonia gardneri*; Compositae; Eupatorieae; sesquiterpene lactones; germacranolide; chloroguaianolide.

Abstract—The structures and stereochemistries of two sesquiterpene lactones from *Trichogonia gardneri* were established as (6*R*,7*S*,8*S*,9*S*,10*R*)-4*E*-9,10-dihydroxy-8-tigloxygermacr-4-en-6,12-olide) and (5*R**,6*R**,7*S**,8*S**,9*R**)-14-acetoxy-3-chloro-9-hydroxy-2-oxo-8-tigloxyguia-1(10),3-dien-6,12-olide by a combination of NMR spectrometry and X-ray diffraction. The results show that the structures of several sesquiterpene lactones which were isolated previously from related species require revision.

INTRODUCTION

Recent reports on the chemistry of some South American *Trichogonia* species [1, 2] and their close relative *Trichogoniopsis* [3] (Compositae, tribe Eupatorieae, subtribe Gyptidinae [4, 5]) indicate that highly oxygenated germacranolides and their transformation products are characteristic secondary metabolites of these genera. One *Trichogonia* species also furnished highly oxygenated guaianolides seemingly more typical of certain other members of the subtribe [2]. We now describe the isolation from a previously uninvestigated species, *Trichogonia gardneri* A. Gray, of new representatives, **1a** and **2a**, of each structural type. Structural determination of each compound by X-ray analysis showed that the formulae of some sesquiterpene lactones reported earlier from this subtribe require revision.*

RESULTS AND DISCUSSION

The presence of the α-methylene-α,β-unsaturated lactone function in substance **1a**, $C_{20}H_{26}O_7$ (high-resolution MS), mp 224–226°, was indicated by the usual ^{1}H NMR and ^{13}C NMR criteria (Tables 1 and 2). Irradiation at the frequency of H-13a and H-13b enabled the signal of H-7 to be located at δ2.84; further sequential decoupling delineated H-6 as the locus of lactone ring closure, H-8 as the point of attachment of an ester moiety identified as a tiglate by mass and NMR spectrometry, and H-9 as the hydrogen under a secondary hydroxyl which adjoined a carbon carrying a tertiary hydroxyl group (singlet at δ80.46). Irradiation at the frequency of H-6 also identified vinylic H-5, allylically coupled to a vinylic methyl on neighboring C-4 (singlet at δ144.57). The remaining three carbon atoms were represented by the partial structure  $\blacksquare{-}CH_2{-}CH_2{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}\blacksquare$ (carbon singlet at δ215.71, triplets at δ38.22 and 36.08, with the protons accounting for the two triplets being spin-coupled to each other). Since the IR spectrum and the chemical shifts of H-5 and the carbonyl carbon showed that **1a** was not an α,β-unsaturated ketone, this grouping had to be inserted between C-10 and C-4 as shown in the formula.

With regard to stereochemistry, the absence of an NOE involving H-5 and H-15 showed that the 4,5-double bond was *E*, from which it followed, by considering the coupling constants and Dreiding models, that the lactone ring was *trans*, with H-6β, H-8α and H-9α in the configuration indicated in the formula. However, the stereochemistry of C-10 remained questionable although it seemed likely, on biogenetic grounds, that the hydroxyl group was α if C-10 is depicted as apical.

To settle this point and to continue our study of the conformation of medium-sized rings in sesquiterpene lactones, an X-ray analysis of **1a** was undertaken. The crystal data are listed in the Experimental. Figure 1 is a stereoscopic drawing of the molecule which shows that the conclusions drawn from the NMR data are correct and that the C-10 hydroxyl group is α. The molecule suffered from disorder in the tiglyl ester side chain and an attempt to account for the disorder in the manner described in the Experimental met with only limited success.

Table 3 lists selected torsion angles for **1a** (tables listing final atomic and final anisotropic thermal parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Centre). The ten-membered ring is highly contorted, with the C(4)–C(5) bond twisted out of the plane by 29°. Its conformation resembles that of the melampolides enhydrin [9] and melampodin [10]

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*Dr. K. S. Brown, Jr. has found [6] that fresh flowers of *T. gardneri* as well as flowers of eight *Eupatorium* and three *Adenostemma* species yielded dehydropyrrolizidine alkaloids which were also isolated from butterflies feeding on these taxa. The highest concentration of alkaloids was in the flower heads and especially the nectaries of the *Eupatorium* species. This raises the possibility that the dehydropyrrolizidine alkaloids which were isolated earlier [7] by extraction of the above-ground parts of *Conoclinium coelestinum*, another member of subtribe Gyptidinae, and from *Eupatorium* species [7, 8] may have been concentrated in the flower heads.

Table 1. ^{1}H NMR spectral data (270 MHz, $CDCl_3$) of sesquiterpene lactones

H	**1a**	**2a**	**2b***	**2c**†
2α	2.26 *td* (3, 13.5)	—	—	—
2β	3.55 *dt* (3, 13.5)	—	—	—
3α	2.94 *ddd* (13.5, 12, 3)	—	—	—
3β	2.16 *td* (3, 12)	—	—	—
5	4.91 *dbr* (10)	3.63 *dbr* (10)	3.70 *dbr*	3.62 *dbr* (10)
6	5.10 *dd* (10, 8)	4.04 *t* (10)	4.05 *t*	4.00 *dd* (10, 10)
7	2.84 *dddd* (8, 3.5, 3, 2.5)	3.35 *dddd* (10, 3.5, 3, 1.5)	3.40 *dddd*	3.35 *dddbr* (10, 3, 3)
8	5.82 *dd* (4, 2.5)	5.88 *dd* (1.5, 1)	5.97 *dbr*	5.84 *br*
9	4.34 *d* (4)	4.86 *br*	5.90 *br*	4.91 *br* (1)
13a	6.23 *d* (3.5)	6.30 (3.5)	6.27 *d*	6.29 *d* (3)
13b	5.51 *d* (3)	5.64 *d* (3)	5.63 *d*	5.64 *d* (3)
14	1.49‡	5.55 *d* (11)	5.50 *d*	4.98 *dbr* (12)
		5.26 *dbr* (11)	5.35 *d*	4.77 *dbr* (12)
15‡	1.85	2.42 *d* (1.5)	2.42 *d*	2.42 *br*
3′	6.79 *qq* (7, 1.5)	6.76 *qq* (7, 1.5)	6.79 *qq*	6.75 *qbr* (7)
4′‡	1.81 *dq* (7, 1.5)	1.80 *dq* (7, 1.5)	1.79 *dq*	1.78 *dbr* (7)
5′‡	1.80 *quint* (1.5)	1.77 *quint* (1.5)	1.78 *quint*	1.75 *br*
OAc‡	—	1.96	1.94, 2.11	

Coupling constants (*J* in Hz) are given in parentheses.
J*'s same as for **2a.
†Taken from ref. [15] (400 MHz).
‡Intensity of three protons.

Table 2. ^{13}C NMR spectral data (67.89 MHz, $CDCl_3$) of sesquiterpene lactones*

C	**1a**	**2a**
1	215.71	162.10
2	38.22 *t*	185.69
3	36.08 *t*	137.40
4	144.57	147.70
5	129.19 *d*	50.75 *d*†
6	79.67 *d*	77.85 *d*†
7	49.43 *d*	52.85 *d*†
8	70.52 *d*	71.26 *d*†
9	75.31 *d*	75.09 *d*†
10	80.46	131.85
11	135.40	133.29
12	169.66	168.14
13	121.64 *t*	121.79 *t*
14	26.22 *q*	57.21 *t*
15	18.94 *q*	17.61 *q*
1′	166.29	167.49
2′	127.78	127.34
3′	139.00 *d*	140.45 *d*
4′	14.51 *q*	14.65 *q*
5′	12.17 *q*	12.14 *q*
OAc	—	171.41
		20.70 *q*

*Unmarked signals are singlets.
†Assignments made by selective decoupling.

which also contain a *trans*-fused lactone ring closed to C-6, and that of the melampolide schkuhriolide [11] with a *cis*-fused γ-lactone closed to C-8, but is unlike that of frutescin, a melampolide with a trans-fused γ-lactone closed to C-8 [12]. The lactone ring is a slightly distorted envelope with C-6 as the flap and relatively flat, the sum $\Sigma|\omega|$ derived from its endocyclic torsion angles being 52°. The sign of the O(3)–C(12)–C(11)–C(13) torsion angle (ω_2) is paired with the sign of the O(2)–C(6)–C(7)–C(11) torsion angle (ω_3) [13] and corresponds to the sign of the negative Cotton effect associated with the n–π^* transition of the α,β-unsaturated lactone which **1a** exhibits in solution. Hence Fig. 1 represents the absolute configuration of the molecule (6*R*,7*S*,8*S*,9*S*,10*R*).

The ^{1}H NMR signals of **1a** are essentially identical (if differences in the side chains are taken into account) with two lactones from *Trichogonia prancii* and *T. salviaefolia* to which structures **3a** and **3b** were assigned recently [2]. It is clear that these formulae must be revised to **1b** and **1c**. Likewise, the structures of lactones **3c**–**3e** from *Trichogonia* species [2] should be changed to **1d**–**1f**†.

A second crystalline lactone from *T. gardneri*, mp 184–185°, had the empirical formula $C_{22}H_{23}O_8Cl$. The IR, ^{1}H NMR and ^{13}C NMR spectra (Tables 1 and 2) and the chemical shifts observed on acetylation quickly established that the substance was a guaianolide of type A or B, the stereochemistry being based on the observed coupling constants and on NOE difference spectrometry. Thus irradiation at the frequency of H-5α produced enhancements in the strength of the H-7α (10%) and H-9α signals (5.8%); irradiation at the frequency of H-7α enhanced H-7α (8.5%), H-8α (7.2%), and H-9α (13.2%); and irradiation at the frequency of H-9α enhanced H-5α (8.1%), H-7α (14.9%) and H-8α (6.4%). Of the various possibilities represented by A and B, those with a tiglate at C-8 seemed *a priori* more likely than the others in view of the structure of **1a** and other lactones in related species,

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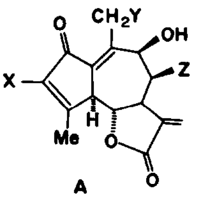
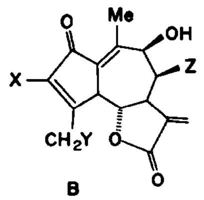
†Analogously, the bejaranolides from *Bejaranoa semistriata* [14] and the trichomoriolides from *Trichogoniopsis morii* [3] possess formulae **4a**–**4d** and **5a**–**5c**, respectively.



A



B

X,Y,Z = Cl,OAc,OTig

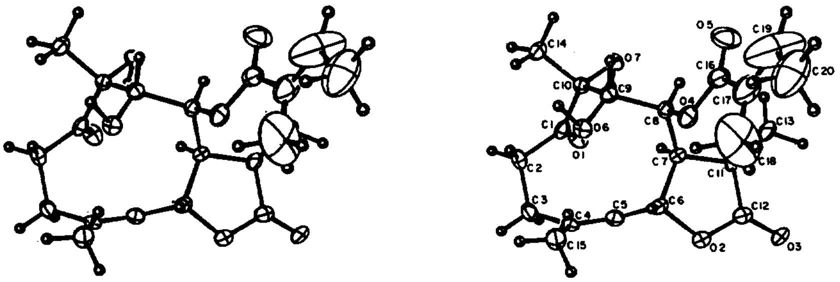


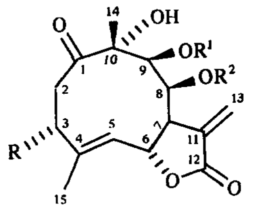
Fig. 1. Stereoscopic view of **1a** with ellipsoids of thermal motion shown at the 25 % probability level. For clarity, only one orientation of the disordered side chain is shown.

Table 3. Selected torsion angles (°) in sesquiterpene lactone **1a**

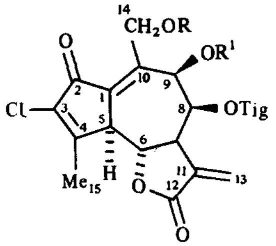
Atom 1	Atom 2	Atom 3	Atom 4	Angle
C-1	C-2	C-3	C-4	63.9
C-2	C-3	C-4	C-5	−86.4
C-3	C-4	C-5	C-6	151.4
C-4	C-5	C-6	C-7	−116.0
C-5	C-6	C-7	C-8	97.6
C-6	C-7	C-8	C-9	−62.5
C-7	C-8	C-9	C-10	−58.8
C-8	C-9	C-10	C-11	14.3
C-8	C-9	C-10	C-1	83.1
C-9	C-10	C-1	C-2	70.3
C-10	C-1	C-2	C-3	−132.8
O-1	C-1	C-2	C-3	55.4
O-1	C-1	C-10	C-9	−117.9
C-6	O-2	C-12	C-11	−7.1
O-2	C-12	C-11	C-7	−3.6
C-12	C-11	C-7	C-6	12.0
C-11	C-7	C-6	O-2	−15.3
C-7	C-6	O-2	C-12	14.4
C-6	O-2	C-12	O-3	176.5
O-3	C-12	C-11	C-7	172.4
O-3	C-12	C-11	C-13	−11.6
C-13	C-11	C-7	C-6	−163.7
O-4	C-16	C-17	C-18	1.0
O-5	C-16	C-17	C-19	10.8
C-16	C-17	C-19	C-20	165.6

but it was difficult to decide between the four possibilities that remained.

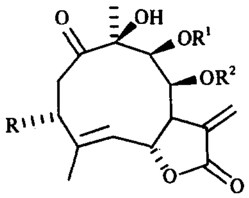
To resolve this matter, X-ray crystallography was again employed. The crystal data are listed in the Experimental. Figure 2 is a stereoscopic view of the molecule which shows that formula **2a** (relative configuration 5*R**,6*R**,7*S**,8*S**,9*R**) is correct. Table 4 lists selected torsion angles for **2a** (tables listing final atomic and final anisotropic thermal parameters, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Centre). The cyclopentenone ring is essentially planar, the sum $\Sigma|\omega|$ of its internal torsion angles being 10°, as compared with 4° for the very similar guianolide lactucin (**6**) [15]. The seven-membered ring is a slightly distorted chair with the C(1)–C(10) double bond twisted out of the plane by 9° and Σ_s [13] = 43°, the corresponding values for lactucin being 6° and $\Sigma_s = 33°$. But while the lactone ring of **6** approximates to an envelope with C-6 as the flap, the lactone ring of **2a** is better described as a half-chair with C-6 below and C-7 above a plane defined by C-11, C-12 and O-5, due to one somewhat smaller and three somewhat larger internal torsion angles. The signs of ω_2 and ω_3 [13] are paired and, in the configuration represented by Fig. 2, negative, but this in itself provides no clue to the absolute configuration of **2a** as the n,π^*-Cotton effect of the lactone chromophore is obscured or possibly reinforced by what appears to be a strongly negative Cotton effect associated with the π,π^*-transition of the cross-conjugated dienone chromophore ($[\theta]_{265} - 35000$). The sign of the dienone n,π^*-transition is positive ($[\theta]_{332} + 855$). However, the presence of the α-chloro substituent in **2a** renders invalid any attempt to deduce its absolute configuration by comparing its CD curve with the CD curves of lactucin (**6**), hydroxyachillin (**7a**) and acetoxyachillin (**7b**) of known absolute configuration. In these compounds, the dienone π,π^*-transition gives rise to a positive Cotton effect; the sign of the n,π^*-transition of **6** is negative and for obscure reasons opposite to the sign of this transition in **7a** and **7b**.



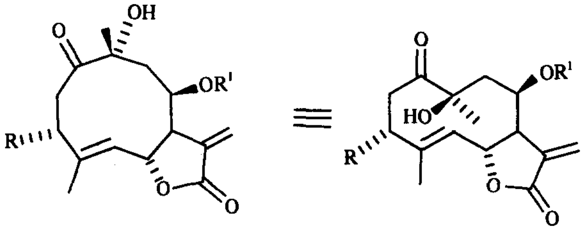
1a R,R^1=H, R^2=Tig
1b R,R^1=H, R^2= iVal
1c R,R^1=H, R^2= Ang
1d R=H, R^1= Ac, R^2= iVal
1e R = OH, R^1 = H, R^2= Ang
1f R = OH, R^1 = Ac, R^2= Ang



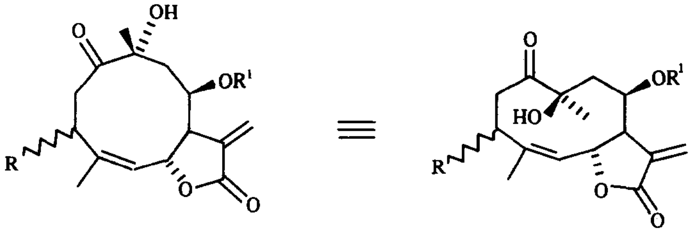
2a R= Ac, R^1 =H
2b R, R^1 = Ac
2c R, R^1 = H



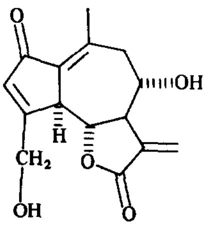
3a R,R^1= H, R^2= iVal
3b R,R^1= H, R^2= Ang
3c R = H, R^1=Ac, R^2= iVal
3d R = OH, R_1 = H, R^2= Ang
3e R = OH, R^1=Ac, R^2 = Ang



4a R = H,R =Tig
4b R = OH, R^1= Tig
4c R = H, R^1 = Ang



5a R = αOH, R^1= Tig
5b R = βOH, R^1= Tig
5c R = βOH, R = Ang



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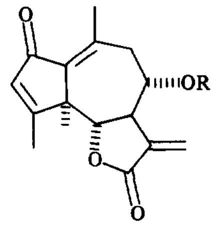
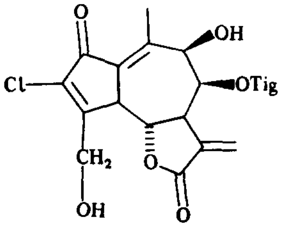


7a R = H
7b R = Ac



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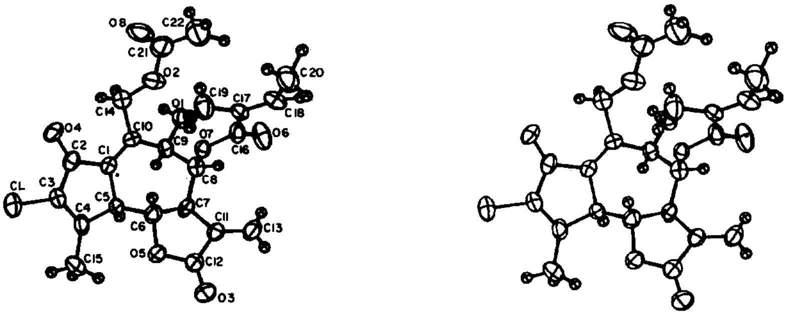

Fig. 2. Stereoscopic view of **2a** with ellipsoids of thermal motion shown at the 25% probability level.

Table 4. Selected torsion angles (°) in sesquiterpene lactone **2a**

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C-1	C-2	C-3	C-4	−3.0
C-2	C-3	C-4	C-5	3.1
C-3	C-4	C-5	C-1	−1.8
C-4	C-5	C-1	C-2	−0.0
C-5	C-1	C-2	C-3	1.7
C-1	C-5	C-6	C-7	−82.5
C-5	C-6	C-7	C-8	75.6
C-6	C-7	C-8	C-9	−63.6
C-7	C-8	C-9	C-10	74.5
C-8	C-9	C-10	C-1	−69.3
C-10	C-1	C-2	C-3	−175.6
C-9	C-10	C-1	C-2	−173.7
C-6	C-7	C-11	C-12	26.1
C-7	C-11	C-12	O-5	−9.4
C-11	C-12	O-5	C-6	−12.4
C-12	O-5	C-6	C-7	29.0
O-5	C-6	C-7	C-11	−32.9
O-3	C-12	C-11	C-13	−11.2
C-8	C-7	C-11	C-13	−25.4
C-6	O-5	C-12	O-3	168.3
Cl	C-3	C-2	O-4	−1.1
Cl	C-3	C-4	C-15	1.3
C-10	C-1	C-5	C-6	54.9
C-9	C-10	C-1	C-5	9.6

Nevertheless, it seems highly probable that **2a** possesses the same absolute configuration as **1a** and indeed that of all other sesquiterpene lactones from higher plants with established absolute configuration.

As the only solvents used in the isolation of **2a** were hexane and ethyl acetate, this unusual chlorine-containing guaianolide does not appear to be an artefact. If the presence of the extra acetate is taken into account, the ^{1}H NMR data of **2a** parallel those reported for a non-crystalline chlorine-containing guaianolide from *Lasiolaena morii*, also in subtribe Gyptidinae, to which formula **8** was assigned without discussion of possible alternatives [17]. On the basis of the data in Table 1, we think that the *Lasiolaena* lactone is **2c**.

EXPERIMENTAL

Extraction of Trichogonia gardneri. Aerial parts of *T. gardneri* A. Gray, harvested by W. V. and K. S. Brown, Jr. in June 1983 in Amarais, Campinas, S. P., Brazil, on the Fazenda Elisa, Centro Experimental do Istituto Agronómico de Campinas, (UNICAMP herbarium voucher No. 14294), wt 2.1 kg, were extracted with hexane–EtOAc (5:1) to give 45 g crude extract, which was dissolved in 500 ml EtOH, diluted with 500 ml H_2O, allowed to stand, and filtered. The filtrate was thoroughly extracted with $CHCl_3$. Evapn of the dried extract furnished 5.5 g residue. A 2.5 g portion was chromatographed over 50 g silica gel, 80 ml fractions being eluted as follows: 1–5 (hexane–EtOAc, 3.5:1), 6–10 (hexane–EtOAc, 3:1), 11 (hexane–EtOAc, 2.8:1), 12–15 (hexane–EtOAc, 2.5:1), 16–21 (hexane–EtOAc, 2.2:1), 22–24 (hexane–EtOAc, 1.6:1), 25–30 (EtOAc) and 31–33 (EtOH).

The solid material from fractions 6–8 was recrystallized from Et_2O–$CHCl_3$ (8:1) to give 68 mg **1a**, mp 224–226°; IR ν^{KBr} cm^{-1}: 3450 br, 1740, 1705, 1695 and 1650; CD curve (MeOH) $[\theta]_{259}$ −7500 (sh), $[\theta]_{239}$ −8420 (neg. max), $[\theta]_{220}$ 0, $[\theta]_{215}$ +4200 (last reading); MS *m/z* (rel. int.): 378 (0.1), 278 (1.1), 260 (1.5), 83 (100). [Calc. for $C_{20}H_{26}O_7$: MW, 378.1676. Found: MW (MS), 378.1684.]

Fractions 15–16 also solidified and were recrystallized from Et_2O–$CHCl_3$ (6:1) and hexane–EtOAc to give 100 mg **2a**, mp 184–185°; IR ν^{KBr} cm^{-1}: 3420 br, 1785, 1720, 1710, 1695, 1650 and 1615; CD (MeOH) $[\theta]_{332}$ +855 (max), $[\theta]_{304}$ 0, $[\theta]_{265}$ −35640 (neg. max), $[\theta]_{235}$ 0, $[\theta]_{220}$ +35600 (last reading); MS *m/z* (rel. int.): 453 (2.0), 451 (5.4), 410 (2.1), 408 (5.6), 392 (6.1), 390 (14.2), 292 (9.2), 290 (25.2) and 83 (100). The positive CIMS showed $[M+1]^+$ peaks at *m/z* 495 (3.9) and 493 (7.1). [Calc. for $C_{22}H_{24}O_8{}^{37}Cl$ and $C_{22}H_{24}O_8{}^{35}Cl$: MW + 1, 453.1130 and 451.1160. Found: MW + 1 (MS), 453.1130 and 451.1169]. Acetylation of a small amount of **2a** in the usual manner (Ac_2O–pyridine) afforded **2b**, whose ^{1}H NMR spectrum is reported in Table 1; MS (positive CI): 495 and 493 $[M+1]^+$.

X-Ray analyses. (a) Single crystals of **1** were grown by slow crystallization from EtOAc–$CHCl_3$. They were orthorhombic, space group $P2_12_12_1$, with $a = 10.759(4)$, $b = 12.327(7)$, $c = 15.365(4)$ Å and $d_{calc.} = 1.234$ g/cm^3 for $Z = 4$ ($M_r = 378.43$). The intensity data were measured on a CAD4 Enraf-Nonius diffractometer (Mo radiation, monochromated, θ–2θ scans). The size of the crystal used for collection was approximately 0.3 × 0.3 × 0.3 mm^3. No absorption correction was necessary ($\mu = 0.867$). A total of 2662 reflections was measured for $\theta \leqslant 27.5°$, of which 1534 were considered to be observed [$I \geqslant 2\sigma(I)$]. The structure was solved by direct methods using MULTAN 78 [18] and refined by full-matrix least-squares methods.

Severe disorder and large thermal amplitudes of vibration in the tiglyl residue became apparent during the early stages of the solution and limited the accuracy of the refined structure. The nature of this disorder, best described by a 180° rotation about the C(16)–C(17) bond, placed atoms C-18 and C-19 (Table 1) too close together to refine individually. Their electron density was best accommodated by refining these two sites at unit multiplicities. The disordered methyl group was refined as C-20 and C-21, assuming multiplicities of 0.5 for each fragment (based upon equal peak intensities of difference Fourier maps).

In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms. Methyl and hydroxyl atoms, with the exception of the disordered fragment, were located from a difference Fourier map; the remaining hydrogen atom parameters were calculated assuming idealized geometry. Hydrogen atom contributions were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were $R = 7.6$ and $R_w = 7.8$ for the 1534 observed reflections. The final difference Fourier map was essentially featureless; the highest residual peaks were in the vicinity of the disordered site chain and had densities of 0.3 e A^{-3}.

(b) Single crystals of **2a** were grown by slow crystallization from $CHCl_3$–EtOH. They were monoclinic, space group $P2_1$, with $a = 11.382(2)$, $b = 7.896(1)$, $c = 11.960(1)$ A, $\beta = 91.61(1)°$, and $d_{calc.} = 1.397$ g/cm^3 for $Z = 2$ ($M_r = 450.87$). The procedure used was the same as that in the preceding paragraph (except for the absence of disorder), with a crystal of approximately 0.3 × 0.3 × 0.4 mm^3 and 2780 reflections of which 2225 were considered to be observed. No absorption correction was necessary ($\mu = 2.19$). The final discrepancy indices were $R = 4.9$ and $R_w = 5.2$ for the 2225 observed reflections. The final difference Fourier map was essentially featureless with no peaks greater than 0 3 e A^{-3}.

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