in the 2000–2400-cm^{-1} region; the NMR spectrum was identical with that of the original hydrazonium salt, and seven integration sweeps showed 8.97 methyl protons to 10.0 phenyl protons (indistinguishable from the original salt).

Registry No. **1a**·BF_4, 114595-46-9; **1a**·I, 13134-23-1; **1b**, 114583-43-6; **1c**, 13134-25-3; **1d**, 114583-47-0; **1e**, 114583-42-5; **1f**, 13134-24-2; **10** (Ar = *p*-ClC_6H_4, R = CH_2CH_3), 114583-46-9; *p*-$ClC_6H_4CH{=}NN^+(CH_3)(CH_2)_5$, 16994-36-8; $(p\text{-}H_3CC_6H_4)_2C{=}NN(CH_2)_5$, 114583-48-1; $(p\text{-}ClC_6H_4)_2C{=}NN(CH_2)_5$, 13134-22-0; $Ph_2C{=}NN(CH_2)_5$, 13134-20-8; *p*-$ClC_6H_4CH{=}NN(CH_2)_5$, 13134-29-7; $C_{10}H_{21}MgBr$, 17049-50-2; C_3H_7MgBr, 927-77-5; $Ph_2C{=}O$, 119-61-9; $Ph_2C{=}NN(CH_3)_2$, 24398-55-8; $Ph_2C{=}NH$, 1013-88-3; $H_3CN(CH_2)_5$, 626-67-5; $(p\text{-}ClC_6H_4)_2C{=}O$, 90-98-2; $(p\text{-}H_3CC_6H_4)_2C{=}O$, 611-97-2; $(p\text{-}H_3COC_6H_4)_2C{=}O$, 90-96-0; $(p\text{-}H_3COC_6H_4)_2C{=}CHCH_3$, 4663-13-2; Ph_2CHNH_2, 91-00-9; $(C\text{-}H_3)_2CHMgCl$, 1068-55-9; *t*-C_4H_9MgCl, 677-22-5; decane-*d*, 71941-72-5; decane, 124-18-5; 1-decane, 872-05-9; eicosane, 112-95-8; benzophenone *N*,*N*-pentane-1,5-diylhydrazone, 13134-20-8; acetonitrile, 75-05-8; benzophenone *N*-methyl-*N*-(5-cyanopentyl)hydrazone, 114583-44-7; benzophenone *N*-methyl-*N*-(5-azidopentyl)hydrazone, 114583-45-8.

Transannular Cyclization of Glaucolide A†

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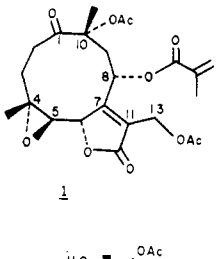
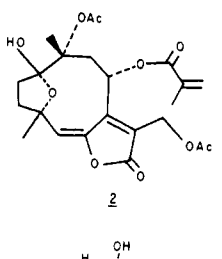
Treatment of glaucolide A with boron trifluoride etherate yielded 10-acetyl-8α-(methacryloyloxy)-2-epivernomargolide 1,4-semiacetal and 8α-(methacryloyloxy)vernomargolide 1,4-semiacetal as a result of a transannular cyclization reaction. Their structures were deduced from spectral data and X-ray diffraction analysis of 5,10-diacetyl-8α-(methacryloyloxy)-2-epivernomargolide 1,4-semiacetal. The 8α-(tigloyloxy)-2-epivernomargolide 1,4-semiacetal had been previously isolated from *Vernonia marginata*.

Transannular cyclization reactions of 1(10),4-germacradienolides and their epoxide derivatives have been studied by several groups.[1] The in vitro transformations of these compounds into eudesmanolides, elemanolides, guaianolides, and cadinolides strongly suggest that cyclodeca-1,5-diene derivatives are biogenetic precursors of a number of sesquiterpene lactones.[1-3]

Glaucolides and hirsutinolides are common sesquiterpene constituents of plants of the genus *Vernonia*[4] (Compositae, tribe Vernonieae). These lactones are characterized by a 7(11)-double bond and an oxygen function at C-13. The biogenetic relation between glaucolides (A, **1**) and hirsutinolides (**2**) has been proposed.[5] Recently, the isolation of cadinanolides **3a,b** from plants of the *Vernonia* genus has been reported. The formation of cadinanolides on treatment of a methanolic solution of glaucolide A (**1**) with silica gel suggests that they could be artifacts.[6] This paper deals with the boron trifluoride catalyzed transannular cyclization of glaucolide A (**1**).



1



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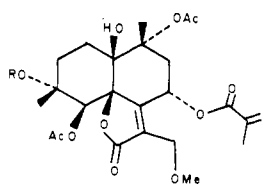
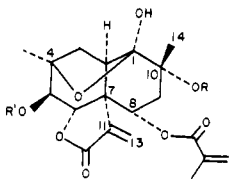


3a, R = H
3b, R = Ac



4a, R = R' = H
b, R = Ac, R' = H
c, R = H, R' = Ac
d, R = R' = Ac

†Contribution No. 898 of the Instituto de Química, UNAM.

Results and Discussion

Treatment of glaucolide A (**1**) with boron trifluoride etherate in dichloromethane yielded a mixture of products **4a** and **4b** in a ratio that varied with reaction conditions (see Experimental Section). The structures of products **4a** and **4b** were deduced from spectral data.

Product **4b** had a molecular weight of 422 by chemical ionization mass spectrometry. Its IR spectrum showed bands due to hydroxyl groups (3540 cm^{-1}), the α,β-unsaturated γ-lactone function (1770 cm^{-1}), and ester carbonyl (1735 cm^{-1}). The ^{1}H NMR spectrum (Table I) indicated the presence of a new exocyclic methylene conjugated to the carbonyl group of a γ-lactone function (δ 5.65 and 6.43 as sharp singlets, H-13 and H-13′), and the absence of coupling of these signals indicated that C-7 must be quaternary. This was confirmed by the ^{13}C NMR spectrum (Table II), in which a singlet at δ 50.69 could be assigned to C-7 by comparison with the ^{13}C NMR spectra for similar structures.[4,5] The chemical shift found for C-7 indicated that this carbon atom is not bound to oxygen. The ^{1}H NMR spectrum of **4b** also showed a signal due to an acetoxy methyl group (δ 1.96, s, 3 H), which must be bound to a fully substituted carbon atom as there is no signal in the spectrum that can be attributed to a proton geminal to this ester group; therefore it should be bound to C-10. A triplet (J = 3 Hz) observed at δ 4.8 is assigned to the proton geminal to the methacrylate function, H-8. The proton bound to the γ-lactone closure, H-6, is observed as a doublet (J = 5 Hz) at δ 4.28; double-resonance experiments showed that it is coupled to H-5, which appears as a doublet (J = 5 Hz) at δ 3.52, a chemical shift

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Table I. ^{1}H NMR Spectral Data of Compounds 4a–d and 4c + TAI[a]

	4a	4b	4c	4d	4c + TAI[b]
H-2	2.76 d (4)	2.81 d (4)	2.83 d (4)	2.87 d (d)	2.90 d (4)
H-3	2.51 dd (12.1; 4)	2.57 dd (12.2; 4)	2.58 dd (12.2; 4)	2.63 dd (12.2; 4)	2.70 dd (12.2; 4)
H-3′	1.50 d (12.2)	1.50 d (12.2)	1.65 d (12.2)	1.67 d (12.2)	1.66 d (12.2)
H-5	3.49 d (5)	3.52 d (5)	4.85 d (5)	4.90 d (5)	4.88 d (5)
H-6	4.27 d (5)	4.28 d (5)	4.37 d (5)	4.37 d (5)	4.38 d (5)
H-8	4.92 t (3)	4.8 t (3)	4.91 t (3)	4.82 t (3)	4.88 t (3)
H-9		3.28 dd (17.2; 3)		3.30 dd (17.2; 3)	3.37 dd (17.2; 3)
H-9′	2.18 d (3)	2.15 dd (17.2; 3)	2.24 d(3)	2.11 dd (17.2; 3)	2.22 dd (17.2; 3)
H-13	5.63 s	5.65 s	5.61 s	5.68 s	5.64 s
H-13′	6.40 s	6.43 s	6.41 s	6.47 s	6.42 s
Me-14	1.31 s	1.66 s	1.30 s	1.67 s	1.74 s
Me-15	1.46 s	1.47 s	1.32 s	1.32 s	1.35 s
Meacr[c]					
Me	1.93 m	1.93 m	1.93 m	1.92 m	1.89 m
H	5.63 m	5.62 m	5.63 m	5.63 m	5.53 m
H	6.08 m	6.04 m	6.07 m	6.07 m	5.95 m
*Me*COO-C-5			2.16 s	2.17 s	2.17 s
*Me*COO-C-10		1.96 s		1.98 s	8.35 s (NH)

[a] Run using $CDCl_3$ as solvent and TMS as internal standard. Coupling constants in hertz are in parentheses. Chemical shifts are in δ values. [b] TAI = trichloroacetyl isocyanate. [c] Meacr represents the methacryl protons.

Table II. ^{13}C NMR Data for 4a–d[a]

C	4a	4b	4c	4d
1	105.38 s	104.05 s	106.10 s	104.79 s
2	43.18 d	44.37 d	43.89 d	44.62 d
3	35.86 t	36.47 t	36.41 t	36.53 t
4	82.85 s	83.53 s	82.69 s	82.97 s
5	79.16 d	79.89 d	80.50 d	80.31 d
6	87.32 d	88.19 d	83.77 d	84.16 d
7	50.41 s	50.69 s	50.90 s	50.81 s
8	70.10 d	70.43 d	70.28 d	70.05 d
9	35.20 t	30.77 t	35.26 t	31.05 t
10	69.75 s	81.05 s	70.55 s	81.48 s
11	137.75 s	137.78[b] s	137.10[b] s	136.83[b] s
12	168.51 s	168.48 s	168.14 s	167.71 s
13	126.02 t	125.05[c] t	125.59[c] t	125.50[c] t
14	23.95 q	22.70 q	23.69 q	22.64 q
15	21.81 q	22.00 q	21.90 q	21.94 q
Meacr[d]	165.61 s	165.52 s	165.80 s	165.51 s
	135.82 s	136.13[b] s	136.09[b] s	136.37[b] s
	124.82 t	125.38[c] t	126.08[c] t	125.99[c] t
	17.81 q	18.16 q	18.16 q	18.27 q
Me*C*OO		169.82 s	169.82 s	169.89 s
*Me*COO-C-10		18.98 q		19.26 q
*Me*CO-C-5			20.72 q	20.71 q

[a] Recorded at 20 MHz; as $CDCl_3$ solution (**4d**), $CDCl_3$ + DMSO-d_6 solution (**4b**, **4c**), and DMSO-d_6 solution (**4a**). Chemical shifts in δ values from TMS. [b,c] Values in any vertical column may be interchanges. [d] Meacr represents the methacryl carbon atoms.

appropriate for a proton geminal to a hydroxy group. Singlets observed at δ 1.47 and 1.66 (3 H each) are ascribed to methyl groups bound to fully substituted carbon atoms bearing oxygen functions.

The ^{13}C NMR spectrum of **4b** (Table II) confirmed the presence of all those groups. A singlet at δ 104.05 is attributed to an acetal carbon atom and is assigned to C-1; no signal due to a keto group is observed in the ^{13}C NMR spectra of **4b**.

Product **4a** showed a molecular weight of 380 as determined by CIMS. Its IR spectrum in $CHCl_3$ is very similar to that of **4b** with a lower intensity of the ester carbonyl band (1720 cm^{-1}). The ^{1}H NMR spectrum of **4a** (Table I) is almost identical with that of **4b** but it lacks the acetoxy methyl singlet (δ 1.96) present in the spectrum of **4b**; the singlet due to Me-14 is shifted upfield to δ 1.31. The spectral data found for **4a** are close to those described for 8α-(tigloyloxy)-2-epivernomargolide 1,4-cyclosemiacetal isolated from *Vernonia marginata*[7] with the exception of the signals due to the tigloyl moiety (methacryloyl in **4a**).

When 1 was treated with boron trifluoride etherate in the presence of acetic anhydride, the 5-monoacetyl derivative **4c** was obtained. Its ^{1}H NMR spectrum (Table I) shows H-5 as a doublet (J = 5 Hz) at δ 4.85 coupled to H-6 (δ 4.37, d, J = 5 Hz). Time-dependent changes were observed in the ^{1}H NMR spectrum of **4c** ($CDCl_3$), which could indicate a possible equilibrium between the cyclic semiacetal form and the opened ketone isomer. The ^{1}H NMR spectrum of the material recovered on elimination of the solvent was identical with the initial spectrum.

The 5-monoacetyl derivative **4c** was also obtained on acetylation of **4a**.

Acetylation of **4b** gave the 5,10-diacetyl derivative **4d**, which showed a hydroxyl absorption in the IR spectrum at 3540 cm^{-1} and an acetal carbon at δ 104.79 (s) in the ^{13}C NMR spectrum (Table II). The acetoxy groups at C-5 and C-10 are responsible for singlets (3 H each) observed at δ 2.17 and 1.98, respectively (Table I). In the ^{13}C NMR spectrum both acetoxy carbonyl groups appear at δ 169.89 (s) and the corresponding methyl groups appear as quartets at δ 19.24 and 20.71.

The formation of products **4a–c** can be envisaged as a nucleophilic attack of C-2 on C-7 with concomitant loss of the allylic acetoxy group bound to C-13. This attack is only possible if the epoxy group in glaucolide A (**1**) is opened prior to the transannular cyclization as observed with molecular models.[8] The ketalization between the hydroxy group at C-4 and the C-1 ketone is only possible in a *cis*-decalin skeleton and is favored by the acidic conditions used in the reaction.

Although there is no agreement with respect to the relative and absolute stereochemistry of glaucolides and hirsutinolides,[9-11] we have assumed as correct the stereo-

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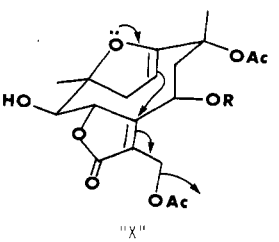
(8) One of the reviewers suggested X as the key intermediate in the formation of the products **4a–c**. A molecular model of X reveals a great rigidity of the system and the impossibility of the attack C-2 → C-7, which could only occur in an open system.



"X"

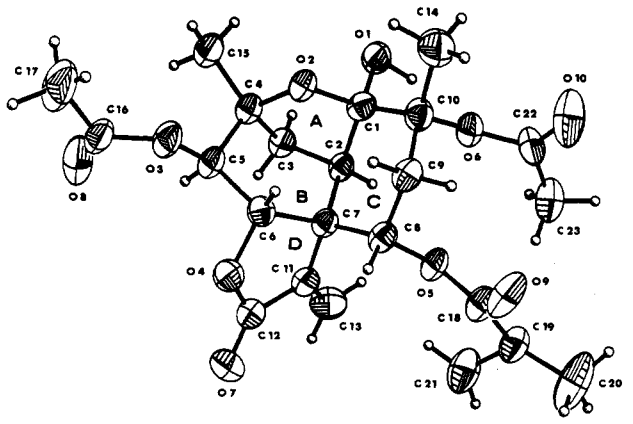


Figure 1. Molecular conformation of 5,10-diacetyl-8α-methacryloyl-2-epivernomargolide 1,4-semiacetal, showing atom numbering. The thermal ellipsoids are drawn at the 50% probability level.

chemistry shown in **1** for glaucolide A,[12-14] that is, 4*R*,5*R*,6*S*,8*S*,10*R*. The stereochemistry shown in **4a–d** was deduced from the coupling constants found for the ^{1}H NMR signals (Table I), especially the coupling constants of H-2 (J = 4 Hz) with H-3 (J = 12.2 and 4 Hz) and H-3′ (J = 12.2 Hz), which are adequate for an equatorial–equatorial (dihedral angle $\simeq$ 60°) and equatorial–axial (dihedral angle $\simeq$ 90°) interaction as observed from molecular models.

The configuration (*R*) at C-10 was maintained in all the products **4a–d**. This was deduced for **4c** from the downfield shift suffered by Me-14 when its ^{1}H NMR spectrum (Table I) was run in the presence of trichloroacetyl isocyanate (TAI). The conservation of chirality at C-10 in **4a** and **4c** could be explained by an anchimeric assistance of the ketal hydroxyl group at C-1. The stereochemistry at C-5 could not be deduced from the ^{1}H NMR data since the coupling constant observed for this proton (J = 5 Hz) is not sufficient to discern between the two possible configurations.

This problem was finally solved by X-ray diffraction analysis of the 5,10-diacetyl derivative **4d**.

The molecular structure of **4d** determined from the X-ray data is illustrated in Figure 1. The carbon skeleton of the molecule comprises a system of two six-membered rings (B and C), a five-membered ring (A) formed by the C(1) to C(4) atoms and the bridgehead acetal system [C(1)–O(2)–C(4)], and a γ-lactone ring [D] fused at C(6) and C(7).

The conformation of rings A and D may be described by the puckering parameters Δ and ϕ_m[15] where Δ is the phase angle of pseudorotation and ϕ_m is the maximum angle of torsion. The A and D rings have Δ and ϕ_m values of 33.6, 50.9° and 7.2, 23.9°, indicating a β-envelope and a conformation intermediate between a half-chair and a β-envelope, respectively.

Both the B ring and the C ring adopt a deformed chair conformation. At the B/C and B/D cis-ring junctions, the torsion angles C(3)–C(2)–C(7)–C(6), C(1)–C(2)–C(7)–C(8), C(5)–C(6)–C(7)–C(2), and O(4)–C(6)–C(7)–C(11) are −42.6 (4), −53.2 (4), 24.7 (4), and 23.9 (4)°, respectively. In the B ring the acetoxy and methyl groups are in equatorial positions whereas in the C ring, the acetoxy and methacryloxy groups are axial and the hydroxyl and methyl groups occupy equatorial sides.

The crystal structure contains an intramolecular hydrogen bond between the O(1)–H hydroxyl group and the O(9) carbonyl group of an adjacent molecule [O(1)···O(9) (−1 + x, −y, z) = 2.914 (4) Å] and the intermolecular approaches <3.4 Å, C(13)···O(10) (x, y, −1 + z) = 3.22 (1) and C(17)···O(7) (−1 − x, 0.5 + y, −z) = 3.24 Å, which play an important role in the stabilization of the molecule in the crystal.

The isolation of sesquiterpene lactones with the carbon skeleton found for the products **4a–d** from "old extracts" of plants of the *Vernonia* species[7] could be the result of acid-catalyzed transformation of a natural product with a glaucolide type of structure.

Experimental Section

General Methods. Melting points are uncorrected. The IR spectra were recorded in chloroform solutions. Mass spectra were obtained by direct inlet or chemical ionization at 70 eV. ^{1}H NMR spectra were recorded at 80 MHz in $CDCl_3$ solutions unless stated otherwise, with TMS as internal standard. The ^{13}C NMR spectra were recorded at 20 MHz, with TMS as internal standard. Assignments of ^{13}C NMR chemical shifts were made with the aid of APT[16] and gated-decoupling ^{13}C NMR spectra.

Treatment of Glaucolide A (1) with Boron Trifluoride Etherate. Glaucolide A (1; 500 mg) in dry methylene chloride (10 mL) was treated with freshly distilled boron trifluoride etherate (0.5 mL). The reaction was started at −78 °C and the temperature was allowed to rise to room temperature (1 h). After 15 min the formation of a precipitate was observed. The reaction mixture was poured into cold sodium bicarbonate aqueous solution, extracted with ethyl acetate, washed with brine, and dried over anhydrous sodium sulfate, and the solvent was removed. The semisolid mixture was crystallized from acetone–hexane to yield **4b** (180 mg). Chromatography of the mother liquors on silica gel yielded **4b** (100 mg) and **4a** (100 mg) (**4a** and **4b** were obtained in a 1:3 proportion).

When the reaction was left for 1 h at room temperature (total reaction time 2 h), **4a** and **4b** were obtained in a 2:1 proportion.

4a: mp 175–178 °C; IR ($CHCl_3$) 3530, 1770, 1720, 1635, 910 cm^{-1}; ^{1}H NMR (Table I); MS m/z 362 (M^+ − 18), 344, 293, 276, 259, 81, 69 (67%), 43 (100%); CIMS m/z 381 (M^+ + 1, 8%) (calcd for $C_{19}H_{24}O_8$: M^+ at m/z 380).

4b: mp 208–210 °C; UV 205 nm (16 430); IR 3540, 3500, 1770, 1720, 1630, 1120, 1070, 960, 940, 910 cm^{-1}; ^{1}H NMR (Table I); ^{13}C NMR (Table II); MS m/z 362 (M^+ − 60), 344, 293, 276, 189, 69 (53%), 43 (100%); CIMS m/z 423 (M^+ + 1, 10%) (calcd for $C_{21}H_{26}O_9$: M^+ at m/z 422). Anal. Calcd: C, 59.71; H, 6.20. Found: C, 59.56; H, 5.98.

Treatment of Glaucolide A (1) with Boron Trifluoride Etherate and Acetic Anhydride. To a solution of glaucolide A (1; 250 mg) in dry methylene chloride (5 mL) were added at 0 °C acetic anhydride (0.5 mL) and freshly distilled boron trifluoride etherate. The reaction mixture was allowed to reach room temperature (1 h), poured into ice, and extracted with ethyl acetate. The organic solution was washed with aqueous sodium bicarbonate solution and brine and dried, and the solvent was removed. The solid product obtained (200 mg) was crystallized from acetone–hexane to yield **4c**: mp 212–214 °C; IR ($CHCl_3$) 3580, 1774, 1736, 1637, 1234, 1125, 1100, 956, 922, 854 cm^{-1}; ^{1}H NMR (Table I); ^{13}C NMR (Table II); CIMS m/z 423 (M^+ + 1), 405 (100%), 345 (73.8%), 277 (31%), 259 (58.8%). Anal. Calcd for $C_{21}H_{26}O_9$: C, 59.71; H, 6.20. Found: C, 59.06; H, 6.00.

Acetylation of **4a** under the usual conditions (Ac_2O, py, room temperature, overnight) gave **4c**.

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Acetylation of **4b** (Ac_2O, py, room temperature, overnight) gave **4d**: mp 205–208 °C; IR ($CHCl_3$) 3540, 1770, 1735, 1630, 1600, 1240, 1120, 1100, 950, 910 cm^{-1}; ^1H NMR (Table I); ^{13}C NMR (Table II); CIMS m/z 465 ($M^+ + 1$) (Calcd for $C_{23}H_{28}O_{10}$: M^+ m/z at 464).

X-ray Analysis of 4d. Crystals of the title compound were obtained by slow evaporation from acetone–hexane. These crystals are monoclinic. Data were collected by using a single crystal (0.20 × 0.28 × 0.40 mm) mounted on top of a glass fiber. Systematic absences established the space group $P2_1$. Intensities were collected on a Nicolet R3m diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.7107 Å). Lattice constants were determined from the setting angles of 25 machine-centered reflections with $5.0 < 2\theta < 19.1°$: a = 7.222 (2) Å, b = 17.194 (5) Å, c = 9.423 (4) Å, β = 97.63 (3)°, V = 1160 (1) Å^3, $F(000)$ = 492, T = 293 K, D_{calcd} = 1.33 g cm^{-3}, Z = 2, and μ(Mo Kα) = 0.98 cm^{-1}. Reflections in two octants of reciprocal space were measured with an index range of $h \pm 8$, k 0→19, l 0→11, using the $2\theta/\theta$ scan mode, a variable scan speed, a scan width of 1.0 (°θ), and two standard reflections ($\bar{1}1\bar{2}$; $\bar{1}00$) monitored every 50 measurements. The intensities were corrected for Lorentz and polarization effects but no absorption corrections were applied. Of the 2135 reflections within the 2θ range of 3–50° collected, 1798 had values of $|F_o|^2 > 2.5\sigma(I)$ and were used in the final refinement of structural parameters. The data were adjusted to an approximately absolute scale and an overall U value of 0.050 Å^2. The crystal structure was solved by combination of direct methods and partial structure expansion by an iterative E-Fourier procedure using the SHELXTL[17] system of programs. The trial structure was refined by a blocked cascade least-squares procedure with anisotropic temperature factors for the non-H atoms. The H atoms of the CH, CH_2, and CH_3 groups were allowed to ride on bonded C. The H atom attached to the O(1) atom was found on a difference Fourier map at an advanced stage of the anisotropic refinement, and all H atoms had a fixed isotropic temperature factor, U = 0.06 Å^2. The function minimized was $\sum\omega(\Delta F)^2$ with a statistical weight of the form $\omega = \{\sigma^2(F_o) + 0.001(F_o)^2\}^{-1}$, where σ is the standard deviation of the observed amplitudes based on counting statistics. The final conventional R factor was 0.044 and R_ω = 0.047; the isotropic extinction parameter X = 0.0012 and the goodness-of-fit value S = 1.19. Atomic scattering factors for C, O, and H atoms were from the *International Tables for X-ray Crystallography*.[18] The final difference map had a $\Delta\rho$ from −0.18 to 0.19 e Å^{-3}. All computations were performed on a Nova 4S computer, and plots were drawn on a Tektronix plotter with the SHELXTL system of programs.

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Supplementary Material Available: Tables of final atomic coordinates for the non-hydrogen atoms, bond distances and angles, final hydrogen coordinates, and thermal parameters for **4d** (4 pages). Ordering information is given on any current masthead page.

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Enantioselective Construction of Heterocycles: Synthesis of (*R*,*R*)-Solenopsin B

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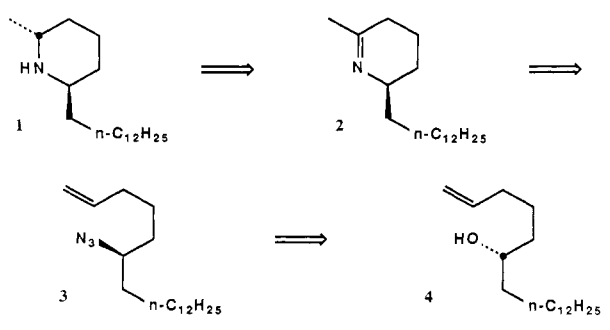
An enantioselective route to solenopsin B (**1**), the major saturated component of the alkaloid mixture isolated from the venom of the fire ant, *Solenopsis invicta*, is reported. The key transformation in this synthesis is the smooth thermolytic cyclization of alkenyl azide **3**. The precursor to **3**, alcohol **4**, is prepared by stereoselective reduction of an enantiomerically pure β-keto ester.

The fire ant, *Solenopsis invicta*, is a ubiquitous pest in the southeastern United States.[1] The 2,6-*trans*-dialkylpiperidine derivative solenopsin B (**1**), the major saturated component of a closely related family of alkaloids isolated from the ant,[2] has been shown to have both vesicant and hemolytic activity and to cause histamine release from mast cells.[3] Other, more complex alkaloids containing this same 2,6-dialkylpiperidine nucleus have been shown to have diverse physiological activity.[4] We have developed

Scheme I



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