visible, consisting of anhydro isomers (R_f 0.6) and cyanobacterin (R_f = 0.4). Each band is rechromatographed with CCl_4/acetone (9:1) on silica gel plates. Final purification is accomplished by normal-phase HPLC with gradient elution (2.5–6.3% EtOAc/CCl_4) and detection at 280 nm. Note: If hexane is used as the nonpolar solvent, partial dehydration of 1 occurs during rotary evaporation: For 1: yield ~200 mg/100 g wet weight of cells; UV (CH_3OH) 266 nm (ϵ 1.2 × 10^4); $[\alpha]_D^{30}$ ($CHCl_3$) +102°; IR (CCl_4) 3580, 2970, 1812, 1680, 1605, 1510, 1500, 1485, 1430, 1255, 1050, and 1040 cm^{-1}; IR (KBr) 3490, 2970, 1805, 1735, 1680, 1610, 1512, 1500, 1480, 1430, 1253, 1180, 1050 cm^{-1}; MS (20 eV), *m/z* (relative intensity) 432 (2.7) and 430 (10.8) (M^+), 414 (25), 412 (77), 371 (7.5), 369 (16), 220 (12), 171 (37), 169 (100), 148 (33), 135 (14), 121 (77). Anal. Calcd: C, 64.11; H, 5.38; Cl, 8.23. Found: C, 64.13; H, 5.51; Cl, 8.43.

The yield of the anhydro isomers is approximately 30 mg/100 g wet weight of cells. MS (20 eV), *m/z* (relative intensity) 412 (100) and 414 (36) (M^+), 369 (22), 371 (7), 148 (11), 121 (14). UV spectra are obtained as the separated isomers elute from an RP-8 analytical column in 85% MeOH/H_2O: isomer A 360 nm (λ_{max}), 243 (0.61 λ_{max}), 286 (0.39 λ_{max}); isomer B 357 nm (λ_{max}), 245 (0.64 λ_{max}), 276 (0.53 λ_{max}). Anal. Calcd: C, 66.91; H, 5.13; Cl, 8.59. Found: C, 66.70; H, 5.33; Cl, 8.80.

3-(6-Chloropiperonyl)dihydro-2(3*H*)-furanone (2). This compound was prepared according to a published procedure by condensation of γ-butyrolactone and 6-chloropiperonal in benzene with $NaOCH_3$.[7] Dehydration of the benzyl alcohol was accomplished with 10% H_2SO_4, and hydrogenation of the resulting olefin (PtO_2, 1 atm of H_2) yielded the desired product. The crude product was purified by preparative TLC on silica gel (ethyl ether; R_f 0.7) and crystallized from CCl_4 to give slightly yellow prisms; mp 103–104 °C (uncorrected); ^1H NMR (270 MHz, $CDCl_3$) δ 1.93–2.32 (m, 2 H, CH_2CH_2O), 2.81 (dd, 1 H, *J* = 18, 8.7 Hz, Ar–CH_a), 2.90 (m, 1 H, Ar–CH_2CH), 3.33 (dd, 1 H, *J* = 18, 5.4 Hz, Ar–CH_b), 4.09–4.37 (m, 2 H, CH_2OC=O), 5.97 (s, 2H, OCH_2O), 6.74 (s, 1 H, 2-Ar), 6.84 (s, 1 H, 5-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3 (s, C=O), 147.2 and 146.9 (2 s, 3- and 4-Ar), 125.7 (s, 6-Ar), 129.1 (s, 1-Ar), 110.3 and 109.9 (2 d, 2- and 4-Ar), 101.7 (t, OCH_2O), 66.3 (t, C–O), 40.0 (d, CH–C–O), 33.2 (t, Ar–CH_2), 28.0 (t, C–C–O); MS, *m/z* (relative intensity) 254 (21) and 256 (7), 219 (23), 191 (16), 171 (31), 169 (100). Anal. Calcd: C, 56.59; H, 4.35; Cl, 13.92. Found: C, 57.24; H, 4.44; Cl, 13.23.

3-(5-Chloro-3,4-dimethoxybenzyl)dihydro-2-(3*H*)-furanone (3). Vanillin was chlorinated according to the procedure of Raiford and Tichty to yield 5-chlorovanillin.[8] Reaction of this product (186 mg, 1.00 mmol) with excess diazomethane in ether produced the dimethoxy compound in quantitative yield. The carbanion of γ-butyrolactone (86.1 mg, 1.00 mmol) was preformed at -78 °C in dry THF (10 mL) under a nitrogen atmosphere by using lithium diisopropylamide (1.1 mmol of diisopropylamine and 1.0 mmol of *n*-butyllithium, 1.3 M in hexane). A solution of the aldehyde in THF (5 mL) was added via syringe over a 5-min period while the temperature was maintained at -78 °C. After 10 min, 25% H_2SO_4 (10 mL) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was extracted with ether (3 × 20 mL) and dried (Na_2SO_4), and the solvent was removed at reduced pressure. The residual oil was dissolved in ethyl acetate (25 mL) and reduced with PtO_2 (20 mg) under 1 atm of H_2. The reaction mixture was filtered and evaporated to yield a pale yellow oil. This mixture was purified by isochratic HPLC (35% ethyl acetate/hexane) on a preparative silica gel column (Du Pont, Zorbax, 1 × 20 cm, 5 mL/min): yield 163 mg (60%); colorless oil; t_R = 8.40 min; ^1H, NMR (361 MHz, $CDCl_3$) δ 1.99 (m, 1 H, CH_a–C–O), 2.29 (m, 1 H, CH_b–C–O), 2.71 (dd, 1 H, *J* = 13.81 8.90, Ar–CH_a), 2.83 (m, 1 H, CH–C=O), 3.14 (dd, 1 H, *J* = 13.81, 4.25, Ar–CH_b), 3.85 (s, 3 H, 4-OMe), 3.86 (s, 3 H, 3-OMe), 4.17 (dt, 1 H, *J* = 9.12, 6.63, CH_a–O), 4.23 (dt, 1 H, *J* = 9.12, 2.74, CH_b–O), 6.69 (d, 1 H, *J* = 1.93, 2-ArH), 6.80 (d, 1 H, *J* = 1.93, 6-ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3 (s, C=O), 153.7 and 144.0 (2 s, 3- and 4-Ar), 134.9 (s, 1-Ar), 128.0 (s, 5-Ar), 121.9 (d, 6-Ar), 111.6 (d, 2-Ar), 66.5 (t, C–O), 60.6 and 56.1 (2 q, 3- and 4-OMe), 40.9 (d, C–C=O), 35.6 (t, Ar–C), 27.9 (t, C–C–O); MS (70 eV), *m/z* (relative intensity) 270 (35) and 272 (11), 185 (100) and 187 (31). Anal. Calcd: C, 57.68; H, 5.59; Cl, 13.10. Found: C, 57.50; H, 5.68; Cl, 13.31.

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Registry No. 1, 80902-00-7; 2, 87174-76-3; 3, 87174-77-4; 7, 87174-78-5; 8, 87183-65-1; 6-chloropiperonal, 15952-61-1; γ-butyrolactone, 96-48-0; 5-chlorovanillin, 19463-48-0; 3-chloro-4,5-dimethyoxybenzaldehyde, 18268-68-3; 3-[(3-chloro-4,5-dimethoxyphenyl)carbonyl]dihydro-2(3*H*)-furanone, 87174-79-6.

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Crystal Structure and Stereochemistry of Achalensolide, a New Guaianolide from *Stevia achalensis*[1]

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Structure and stereochemistry of achalensolide, a new guaianolide, and its 11,13-dihydro derivative, both isolated from *Stevia achalensis*, were deduced by a combination of NMR spectroscopy, X-ray diffraction, and chemical transformations.

Discovery of the intensely sweet diterpene glycoside stevioside in leaves of *Stevia rebaudiana* Bertoni some years ago[2] initiated a study of other representatives of this large American genus. Since then, sweet glycosides have been isolated only from *S. rebaudiana*, *S. paniculata*, and *S. ovata*,[3,4] while other diterpenoids and various sesqui-

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Table I. ^{1}H NMR Spectra[a]

	1[b,d]	1[c,d]	2[b,e]	2[b,f]	3[b,f]	3[c,f]	4[c,g]
H-1	2.99 m	in 1.95 c	2.96 m	2.07 m	3.13 m	2.20 m	3.10 dd br
2a	2.40 dd	in 1.95 c	2.43 dd	in 2c	2.29[i]	1.92 d br	2.46 dd br
2b	in 2.25 c	in 1.95 c	2.04 dd	and	2.29[i]	2.03 dd	2.04 dd
6α	2.93 dd	2.00 dd	2.86 d br	1.6c	2.67 d br	in 1.73 c	3.07 d br
6β	2.68 dd br	1.78 dd br	in 2.6 m		2.43 dd br	1.59 dd br	3.94 d
7	3.51 m	2.48 m	in 2.6 m	1.67 c	in 3.00 c	in 1.73 c	
8	4.97 ddd	4.10 ddd	4.60 ddd	3.78 ddd	4.83 ddd	3.96 ddd	4.80 dd br
9α	in 2.25 c	1.68 m	1.63 dd br	1.04 dd br	in 2.27 c	1.78 dd br	1.93 dd br
9β	1.48 ddd	0.98 ddd	1.29 m	0.62 ddd	1.39 ddd	0.84 ddd	1.26 ddd
10	in 2.25 c	1.39 m	2.10 m	1.20 ddd br	in 2.27 c	1.41 c	2.30 ddd br
11			2.22 dq	1.65 dq	in 3.00 c	in 2.22 c	
13	6.39 d	6.21 d	1.31 d[h]	0.96 d[h]	1.26 d[h]	0.87 d[h]	1.92 br[h]
	5.71 d	4.96 d					
14	0.75 d	0.24 d	1.03 d	0.47 d	0.73 d	0.30 d	1.09 d
15[h]	1.73 t	1.52 t	1.71 d	1.41 d	1.71 m1	1.49 m	1.75 d

[a] Run at 270 MHz using Me_4Si as internal standard. [b] In $CDCl_3$. [c] In C_6D_6. [d] Coupling constants: $J_{1,2a} = 6$ Hz; $J_{1,2b} = 2$ Hz; $J_{1,10} = ?$, $J_{1,15} = 1.5$ Hz; $J_{2a,2b} = 18$ Hz; $J_{6\alpha,6\beta} = 18$ Hz, $J_{6\alpha,7} = 3$ Hz; $J_{6\beta,7} = 12$ Hz; $J_{6\beta,10} = 1$ Hz; $J_{6\beta,15} = 1.5$ Hz; $J_{7,8} = 8$ Hz; $J_{7,13a} = 3$ Hz; $J_{7,13b} = 2.8$ Hz; $J_{8,9\alpha} = 3$ Hz; $J_{8,9\beta} = 11.5$ Hz; $J_{9\alpha,9\beta} = 4$ Hz; $J_{9\alpha,10}$ small; $J_{9\beta,10} = 12$ Hz; $J_{10,14} = 7$ Hz. [e] $J_{1,2a} = 6$ Hz; $J_{1,2b} = 4$ Hz; $J_{1,10} \sim 5$ Hz; $J_{1,15} = 2$ Hz; $J_{2a,2b} = 18$ Hz; $J_{6\alpha,6\beta} = 18$ Hz; $J_{6\alpha,7}$ small; $J_{6\beta,7}$?; $J_{7,8} = 8$ Hz; $J_{7,11} = 11$ Hz; $J_{8,9\alpha} = 3.5$ Hz; $J_{8,9\beta} = 12.5$ Hz; $J_{9\alpha,9\beta} = 14$ Hz; $J_{9\alpha,10} = 2$ Hz; $J_{9\beta,10} = 13$ Hz; $J_{10,14} = 7$ Hz; $J_{11,13} = 7$ Hz. [f] $J_{1,2a} = 1$ Hz; $J_{1,2b} = 6$ Hz, $J_{1,10}$?; $J_{2a,b} = 18$ Hz; $J_{6\alpha,\beta} = 17$ Hz; $J_{6\alpha,7} = 3$ Hz; $J_{6\beta,7} = 12.5$ Hz; $J_{6\beta,15} = 1.5$ Hz; $J_{7,8} = 8$ Hz; $J_{7,11} = 10$ Hz; $J_{8,9\alpha} = 4$ Hz; $J_{8,9\beta} = 12$ Hz; $J_{9\alpha,9\beta} = 12$ Hz; $J_{9\alpha,10}$ small; $J_{9\beta,10} = 10$ Hz; $J_{10,14} = 7$ Hz; $J_{11,14} = 7$ Hz. [g] $J_{1,2a} = 6$ Hz; $J_{1,2b} = 4$ Hz; $J_{1,10} = 6$ Hz; $J_{1,15} = 2$ Hz; $J_{2a,b} = 18$ Hz; $J_{6\alpha,6\beta} = 13$ Hz; $J_{6\alpha,13} = 2$ Hz; $J_{8,9\alpha} = 5$ Hz; $J_{8,9\beta} = 12$ Hz; $J_{9\alpha,9\beta} = 15$ Hz; $J_{9\alpha,10} = 1.5$ Hz; $J_{9\beta,10} = 10$ Hz; $J_{10,14} = 7$ Hz. [h] Intensity three protons. [i] Center of AB system.

terpenoids, mainly of the longipinene variety, have been reported from 14 additional *Stevia* species.[5] However, sesquiterpene lactones that are characteristic secondary metabolites of many genera within Compositae have so far been found in only 6 of the 17 species studied.[5f,6-9] In the present report we describe the isolation and structure determination of two new guaianolides from the previously uninvestigated Argentinian species *S. achalensis* Hieron.

The major constituent achalensolide (1), $C_{15}H_{18}O_3$, mp 176–177 °C, was obtained in yields as high as 0.79% of dried plant material. Presence of the α-methylenen-α,β-unsaturated γ-lactone function (IR bands at 1770 and 1640 cm^{-1}) was indicated by the usual ^{1}H and ^{13}C NMR criteria (see Tables I and II). By irradiating at the frequencies of H-13a and H-13b, the signal of H-7 was located at δ 3.51 (in $CDCl_3$); this signal was split so as to indicate the presence of three vicinal protons. The chemical shifts of two of these, H-6a and H-6b at δ 2.93 and 2.68, which constituted the AB part of an ABX system, suggested that they were allylic; the third, H-8 at δ 4.97, and hence the proton under the lactone oxygen, was additionally coupled to two protons (H-9a and H-9b), one of which, buried in a three-proton multiplet near δ 2.25, was rendered visible by conducting the spin–decoupling experiments in C_6D_6. H-9a and H-9b were in turn coupled to another proton (H-10, superimposed on H-9a in $CDCl_3$, but neatly separated in C_6D_6), irradiation at whose frequency caused collapse of a methyl doublet (H-14) to a singlet as well as simplification of a three-proton multiplet near δ 1.95 (in C_{D6}). That this multiplet consisted of the system $-CH_2-CH-$, where the methinyl carbon represents C-1 and the methylene carbon C-2, was more satisfactorily seen in

Table II. ^{13}C NMR Spectra[a]

	1	2	3	4
C-1	42.74 d*	46.81 d*	41.62 d*	46.69 d
2	38.03	37.15 t*	38.36 t*	37.16 t
3	207.91	207.41	208.22	206.80
4	138.13[b]	140.41	138.26	139.32
5	168.27[c]	168.28	169.09	166.26[d]
6	31.98 t*	26.13 t*	25.72 t*	27.40 t
7	38.46 d*	44.66 d	38.22 d[b]	157.21
8	77.96 d*	79.98 d*	78.87 d	82.98 d
9	36.63 t*	33.38 t*	37.54 t*	33.87 t
10	30.07 d	27.49 d*	30.16 d*	28.82 d
11	138.39[b]	36.49 d	37.79 d[b]	123.16
12	168.96[c]	178.01	177.95	173.63[d]
13	123.46 t	13.68 q*	15.28 q*	8.94[c]
14	14.88 q*	19.58 q*	10.82 q	19.80
15	8.21 q	8.61 q	8.12 q	8.35[c]

[a] Run at 67.89 MHz in $CDCl_3$ using Me_4Si as internal standard. Signals of unspecified multiplicity are singlets. Assignments of signals marked with an asterisk were established by selective decoupling. [b,c] Assignments may be interchanged. [d] As the C-5 signal is always more intense than the C-12 signal, the frequency at δ 166.26, more intense than the frequency at δ 173.63, is tentatively assigned to C-5.

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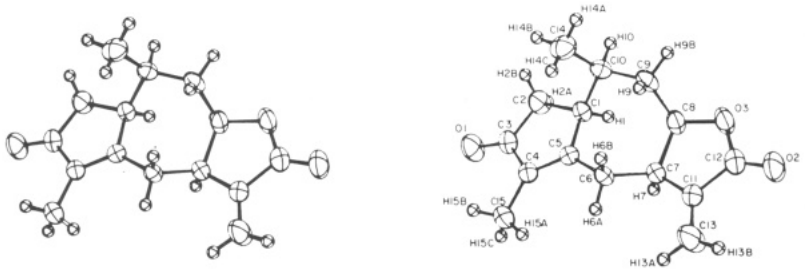

Figure 1. Stereoscopic view of achalensolide molecule with ellipsoids of thermal motion.

C_6D_6 solution and was verified by selective decoupling of the ^{13}C NMR spectrum where irradiation at the frequency of H-1 at δ 2.99 collapsed an otherwise unassigned doublet at δ 42.74 to a singlet and where irradiation at the frequency of H-2a at δ 2.40 (coupled to a nearby proton, i.e., H-2b, in the δ 2.25 multiplet) collapsed an otherwise unassigned triplet at δ 38.03 to a doublet. Thus, the carbon chain from C-6 through C-10 and thence to C-2 was established.

That the remaining four carbons were part of a 2-methylcyclopentenone chromophore of the type found in acetylisophotosantonic acid lactone (**5a**),[10] cyclotagitinin (**5b**),[10] and mikanokryptin (**6**)[11] and had to be inserted between C-2 and C-6 was evident from the IR frequency at 1690 cm^{-1}, the ^1H NMR spectrum in which H-1 and H-6b were long-range coupled to H-15, and the ^{13}C NMR spectrum, which exhibited the requisite frequencies for C-3, C-4, and C-5 near δ 208, 138, and 168, respectively. Consequently, the gross structure of achalensolide was **1** (Chart I).

As to stereochemistry, the CD curve, like the curves of **5a**,[10] **5b**[10] and 6-deoxy-11,13-dihydromikanokryptin (**7**)[11a] exhibited a negative Cotton effect in the n,π^* region and a positive Cotton effect in the π,π^* region of the α,β-unsaturated cyclopentenone chromophore, the additional presence of the α,β-unsaturated lactone chromophore seemingly being responsible for a slight dip in the 260-nm region. Hence, H-1 was α if the absolute stereochemistry is H-7α[12] as is true of all sesquiterpene lactones for which the absolute stereochemistry has been established with certainty.

While the coupling constants involving H-7, H-8, and H-9 were very similar to those recently reported[13b] for xerantholide (**8**), a guaianolide with a trans-fused lactone ring closed toward C-8 and a very similar melting point of 175–177 °C,[13] the chemical shift of H-8, for one, was markedly different, and a direct comparison of the two lactones established their nonidentity.[14] Consequently it seemed likely that the lactone ring was cis fused. Moreover, the sign of what appeared to be a weak lactone Cotton effect superimposed on the cyclopentenone CD was negative, which again supported cis fusion of the lactone ring if the empirical Stöcklin–Waddell–Geissman rule[15] were to hold in the case of achalensolide. However, the superposition of signals in the high-field region interfered with accurate determination of the value of $J_{1,10}$ and hence with assignment of the C-10 stereochemistry, especially since cis fusion of the lactone ring makes for considerable greater conformational flexibility of the seven-membered ring than in the relatively rigid trans-fused guaianolides and pseudoguaianolides.

An X-ray analysis of achalensolide was undertaken to assure assignment of stereochemistry and to shed further light on the various conformations assumed by guaiano-

Chart I

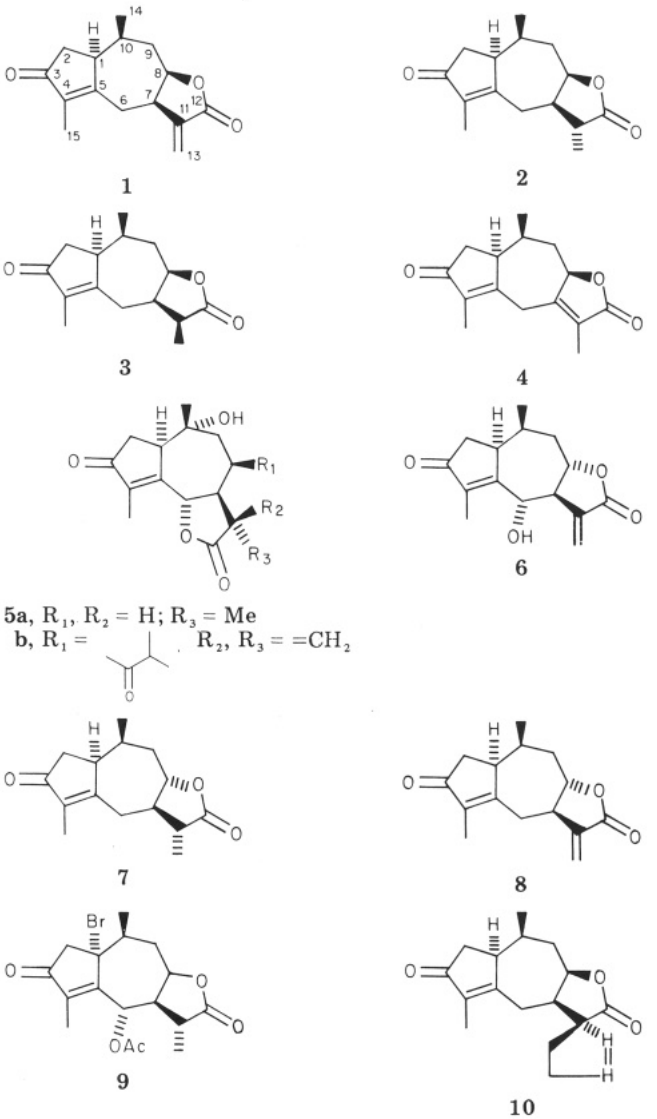

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Table VII. Selected Torsion Angles (deg) in 1[a]

C(1)-C(2)-C(3)-C(4)	4.5
C(1)-C(2)-C(3)-O(1)	-176.7
C(2)-C(3)-C(4)-C(5)	-1.6
O(1)-C(3)-C(4)-C(5)	179.7
O(1)-C(3)-C(4)-C(15)	1.5
C(3)-C(4)-C(5)-C(1)	-2.2
C(3)-C(4)-C(5)-C(6)	179.0
C(15)-C(4)-C(5)-C(6)	-3.0
C(4)-C(5)-C(1)-C(2)	4.9
C(1)-C(5)-C(6)-C(7)	-40.2
C(5)-C(6)-C(7)-C(8)	63.6
C(6)-C(7)-C(8)-C(9)	13.4
C(7)-C(8)-C(9)-C(10)	-75.2
C(8)-C(9)-C(10)-C(1)	24.2
C(9)-C(10)-C(1)-C(5)	58.9
C(10)-C(1)-C(5)-C(6)	-48.4
C(6)-C(7)-C(11)-C(12)	-132.3
C(6)-C(7)-C(11)-C(13)	46.5
C(6)-C(7)-C(8)-O(3)	131.7
C(7)-C(11)-C(12)-O(3)	3.1
C)8)-C(7)-C(11)-C(12)	-7.3
C(11)-C(12)-O(3)-C(8)	2.9
C(12)-O(3)-C(8)-C(7)	-7.5
O(3)-C(8)-C(7)-C(11)	8.7
O(3)-C(8)-C(9)-C(10)	167.1
O(2)-C(12)-O(3)-C(8)	-176.5
O(2)-C(12)-C(11)-C(13)	3.6
C(2)-C(1)-C(10)-C(14)	55.7
C(5)-C(1)-C(10)-C(14)	-65.5
C(8)-C(9)-C(10)-C(14)	150.8

[a] Estimated standard deviation is 0.3°.

lides. Crystal data are listed in the Experimental Section. Figure 1 is a stereoscopic drawing of the molecule that not only shows that the lactone ring is indeed cis fused and that the C-10 methyl group is β-orientated but also represents the absolute configuration because of the sign of the cyclopentenone Cotton effect referred to earlier.

Tables III–VI listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles are available as supplementary material. Table VII lists selected torsion angles. These and Figure 1 show that the cycloheptane ring is a twist-boat whose two-fold axis of symmetry passes through C-5 and the midpoint of the C-8,C-9 bond. Σ_2, the deviation of the ring from C_2 symmetry, is 23°, and $\Sigma_2/(\Sigma_s + \Sigma_2)$ is 0.13.[16] This conformation is quite different from that adopted by the trans-fused guaian-8,12-olides mikanokryptin (**6**) and xerantholide (**8**), which in the solid state approximate a chair.[11b,13b] It is also different from that of acetylbromogeigerin (**9**), the only other exomethylenecycloheptane cis-fused guaian-8,12-olide examined by X-ray crystallography,[16,17] whose conformation approximates a twist-chair with the C_2 axis through C-1,[16] possibly because of the halogen atom on C-1 and the extra substituent on C-6. Other guaian-8,12-olides or pseudoguaian-8,12-olides with a cis-fused lactone ring, but less obviously related to achalensolide, for which X-ray data are available[18-22] adopt boat or twist-boat conformations different from that found for achalensolide.[23]

The cyclopentenone ring of **1** is almost planar as is the γ-lactone ring, the sum of whose internal torsion angles is only 29°. The sign of the small C=C—C=O torsion angle (ω_2) is positive (+3.6°) and is paired with the sign of the O-3—C-8—C-7—C-11 torsion angle (ω_3 = +8.7°). This correlation applies widely in sesquiterpene lactones,[16,25] although a few exceptions have been noted in cis-fused γ-lactones.[18,24,26] However, if the lactone Cotton effect were indeed weakly negative as indicated when the CD curves of **2** or **3** (vide infra) are subtracted from the CD curve of **1**, neither Beecham's generalization[27] that it is controlled by the chirality of the C=C—C=O chromophore nor the later suggestion[28] that it correlates with the sign of ω_3 would hold. Since the lactone Cotton effect could not be observed directly and is at best very weak and since the lactone ring conformation in solution may depart somewhat from that determined in the crystal, speculation on the apparent discrepancy is probably not warranted at this time.

A second lactone, $C_{15}H_{20}O_3$, mp 122–124 °C, obtained in somewhat smaller amount (up to 0.35% of dried plant) had spectral properties (Tables I and II and Experimental Section) that will not be discussed in detail but were commensurate with its being an 11,13-dihydro derivative of achalensolide, a supposition confirmed by $NaBH_4$ reduction of **1**, which furnished the minor lactone in low yield after reoxidation (MnO_2) of the simultaneously introduced hydroxyl group on C-2.[29] The 11β-H configuration **2** assigned to this lactone is best discussed in connection with that of a C-11 epimer **3**, which was the predominant product formed on catalytic reduction of **1**. Reduction of **1** in the presence of the homogeneous catalyst $(Ph_3P)RhCl$ proceeded very sluggishly, affording only minor amounts of **2**, a somewhat larger quantity of the achalensolide double-bond isomer **4** whose structure was obvious from its ^1H and ^{13}C NMR spectra (Tables I and II), and, as the main product, a new lactone **3**, which in spite of its very similar melting point (121–123 °C) could be differentiated easily from **2** by its ^1H and ^{13}C NMR spectra (Tables I and II). Heterogeneous catalytic reduction ($Pd/CaCO_3$) was much more rapid and gave only **2** and **3**, approximately in the ratio 1:3.

NMR criteria that are generally used to assign stereochemistry to C-11 epimers of sesquiterpene lactones include the value of $J_{7,11}$, which depends on the dihedral angle between H-7 and H-11, and the solvent shift of the C-11 methyl signal, the shift exhibited by a pseudoaxial methyl group supposedly being considerably greater than

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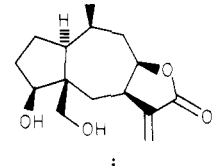
(23) We have described[24] rudmollin (i) as a boat, but it can equally well be interpreted as a twist-boat with the C_2 axis passing through C-10 and the middle of the C-7,C-8 bond.



i

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that of a pseudoequatorial methyl group.[30] The former method seems reasonably reliable in the case of relatively rigid trans-fused lactone systems but has not been tested adequately for cis-fused lactones whose conformational flexibility interferes with deciding on the basis of models what the dihedral angle should be. The second method, originally proposed for eudesmanolides,[30] has been found inapplicable to helenanolides;[31] it is presumably only valid if the conformation of the system to which it is applied is sufficiently well-known or if both epimers are available and exhibit significantly different solvent shifts. In the present instance, $\Delta\delta$ H-13's for **2** and **3** were 0.35 and 0.39, respectively, a result that offered no basis for a decision, while the values of $J_{7,11}$ (13 Hz for **2**, 10 Hz for **3**[32]), although suggesting that the naturally occurring isomer had an α-orientated 11-methyl group, was sufficiently ambiguous to inspire discomfort.

More satisfactory evidence in favor of **2** for the naturally occurring isomer was eventually provided as follows. Reaction of diazomethane with achalensolide afforded mainly one pyrazoline contaminated by small amounts of a second isomer (TLC evidence), which was removed by one recrystallization. As the CD curve of the pure pyrazoline exhibited a very strong positive maximum at 322 nm, its configuration was **10**,[33] formed by approach from the α-side. It is reasonable to assume that catalytic hydrogenation that affords **3** predominantly is subject to the same steric constraints as reaction with diazomethane; consequently, the synthetic 11,13-dihydroacholensolide isomer should be **3** and the naturally occurring isomer should be **2**.

Inspection of Table II indicates that the ^{13}C NMR spectra of **2** and **3** differ significiantly more than would a priori be expected for C-11 epimers (compare the shifts of C-1, C-9, C-10, and C-14). The ^1H NMR spectra of **2** and **3** suggest that the conformations in solution differ somewhat; however, models offer no ready explanation for the observation that β-orientation of the 11-methyl (which remains relatively far from C-14) produces a significant diamagnetic shift of the H-14 signal which is paralleled in the ^{13}C NMR spectrum by a diamagnetic shift of the C-14 signal of nearly 9 ppm. Attempts to prepare crystals of **2** and **3** suitable for X-ray crystallography to shed light on this phenomenon have so far been unsuccessful.[34]

Experimental Section

Isolation of Constituents of *Stevia achalensis*. (A) Air-dried aerial parts of *S. achalensis* Hieron (0.90 kg), collected in Feb 1982 in Copina, Córdoba, Argentina, and identified by Professor Luis Ariza Espinar, Museo Botanico, Córdoba, were extracted with petroleum ether. Evaporation of the solvent furnished 41 g of residue, which was dissolved in 150 mL of EtOH. A solution of lead acetate in 150 g of H_2O was added. After 24 h at room temperature, the insoluble material was filtered and the filtrate concentrated in vacuo to remove the alcohol. Extraction of the remaining aqueous solution with $CHCl_3$ followed by drying, filtration, and evaporation of the $CHCl_3$ extract gave a residue, which was dissolved in MeOH, diluted with ether, and allowed to stand overnight. A white solid (1) was obtained, which after filtration weighed 1.5 g. The mother liquor after standing 48 h produced new crops, total yield of crude achalensolide (1) 2.90 g (0.32%). Column chromatography over silica gel and recrystallization from MeOH–ether gave pure **1**: mp 176–177 °C; $[\alpha]_D$ +226.8° (*c* 0.34, $CHCl_3$); CD curve (MeOH) $[\theta]_{310}$ −4100 (negative max), $[\theta]_{264}$ −1650 (sh), $[\theta]_{256}$ 0, $[\theta]_{229}$ + 31 300 (max), $[\theta]_{208}$ +15 000 (last reading); λ_{max} (MeOH) 241 nm (ϵ 10 000); IR ($CHCl_3$) 1770, 1690, 1640, 1160 cm^{-1}; (KBr) 1755, 1695, 1650, 1480, 1420, 1390, 1365, 1345, 1320, 1280, 1205, 1162, 1135, 1080, 1060, 1000, 970, 920, 890, 830, 810 cm^{-1}; ^1H and ^{13}C NMR spectra in Tables I and II; M_r calcd for $C_{15}H_{18}O_3$, 246.1255, found (MS), 246.1272.

To a solution of 0.1 g of **1** in 8 mL of THF was added a solution of diazomethane in ether until the solution remained yellow. After 24 h in the refrigerator, the residue remaining after removal of solvent was recrystallized from ether–acetone to give 122 mg of the pyrazoline **10**: mp 135–136 °C; IR bands; ^1H NMR δ 5.53 ddd (H-8, $J_{7,8}$ = 6.5 Hz, $J_{8,9a}$ = 4 Hz, $J_{8,9b}$ = 12 Hz), 4.88 and 4.69 (AB system of H-16a,b), 3.17 m (H-1, $J_{1,2a}$ = 4 Hz, $J_{1,2b}$ = 4 Hz, J = 13 Hz and H-7), 2.57 d br and 2.53 d (J = 13 Hz, H-6a and H-6b), 2.47 m (H-9a), 2.33 (center of AB system of H-2a,b superimposed on H-10), 2.13 ddd (H-13a, $J_{13a,b}$ = 12 Hz, $J_{13a,16a}$ = 4 Hz, $J_{13a,16b}$ = 8 Hz), 1.69 (finely split, H-15), 1.65 m (partially obscured, H-13b), 1.48 m (H-9b), 0.76 d (J = 7 Hz, H-14); CD (MeOH) $[\theta]_{322}$ +26 800 (max), $[\theta]_{284}$ 0 (min), $[\theta]_{228}$ + 21 600 (max), $[\theta]_{198}$ 0 (last reading); MS, *m/z* (relative percent) 288 (M^+, 1), 260 (89), 245 (13), 242 (5), 232 (5), 231 (4), 227 (8), 218 (9), 217 (7), 215 (10), 214 (8), 213 (5), 203 (10), 199 (13), 189 (13), 187 (11), 175 (18), 174 (12), 173 (17), 171 (11), 162 (15), 161 (57), 79 (100).

(B) In a second run, 160 g of air-dried plant was extracted with $CHCl_3$ and worked up in the usual fashion. The crude gum (7.65 g) was chromatographed over 200 g of silica gel, 50-mL factions being collected as follows: fractions 1–12 (benzene), 13–25 (benzene–acetone, 49:1), 26–37 (benzene–acetone, 24:1), 38–52 (benzene–acetone, 23:2). Fractions 38–44 yielded 0.568 g (0.35%) of lactone **2**, fractions 45 and 46 gave a mixture of **1** and **2** and fractions 47–52 gave 1.273 g (0.79%) of **1**. Compound **2** on recrystallization from methanol–ether: mp 122–124 °C; $[\alpha]_D$ +109.5° (*c* 0.338, MeOH); CD curve (MeOH) $[\theta]_{307}$ −3400 (negative max), $[\theta]_{271}$ −250 (sh), $[\theta]_{268}$ 0, $[\theta]_{235}$ +38750 (max); IR (KBr) 1772, 1760, 1700, 1645, 1462, 1395, 1365, 1330, 1190, 1158, 1100, 1060, 1050, 1008, 1000 cm^{-1}; M_r calcd for $C_{15}H_{20}O_3$, 248.1411, found (MS) 248.1398.

$NaBH_4$ Reduction of Achalensolide. To a solution of 0.1 g of **1** in 25 mL of dry MeOH was added 0.015 g of $NaBH_4$ in portions with stirring at room temperature. After 30 min, the mixture was acidified with dilute HCl, diluted with H_2O, and extracted with $CHCl_3$. The washed and dried extract was evaporated at reduced pressure. Preparative TLC (C_6H_6–EtOAc, 1:1) of the residue (0.08 g) gave several bands; NMR analysis indicated that the first band contained a substance with a saturated γ-lactone ring, while the later bands contained more highly reduced material. The product from the first band (0.02 g) was dissolved in dry $CHCl_3$ and stirred with activated MnO_2 for 12 h and filtered. The combined filtrate and $CHCl_3$ washings were dried, evaporated, and purified by preparative TLC (C_6H_6–EtOAc, 2:3). The band with the highest R_f value yielded 8 mg of lactone **2**.

Catalytic Hydrogenation of Achalensolide. (A) A solution of 0.08 g of achalensolide in 20 mL of anhydrous benzene containing 0.015 g of tris(triphenylphosphine)rhodium chloride was hydrogenated at atmospheric pressure and room temperature for 6 days at which time TLC indicated complete disappearance of starting material. Removal of solvent and prepatative TLC (C_6H_6–EtOAc, 1:1, multiple development) yielded three fractions. The most mobile fraction (8 mg) was identical with **2**. The second substance (**4**, 15 mg) could not be induced to crystallize: IR (film) 1755, 1705, 1650, 1455, 1390, 1345, 1328, 1105, 1060 and 1030 cm^{-1}; $[\alpha]_D$ +57.3° (*C* 0.122, MeOH); CD curve (MeOH) $[\theta]_{304}$ +5050 (max), $[\theta]_{268}$ 0, $[\theta]_{256}$ −3200 (negative max), $[\theta]_{250}$ 0, $[\theta]_{234}$ +22 900 (max); ^1H and ^{13}C NMR spectra in Tables I and II; mass spectrum, *m/z* (relative intensity) 246 (M^+, 75.6) 228 (6.4), 219 (9.1), 218 (6.4), 217 (6.5), 213 (6.7), 200 (5.3), 191 (5.1), 189 (8,8), 176 (14.5), 175 (56.6), 173 (11.7), 162 (7.5), 161 (17.9), 160 (10.9), 159 (7.2),

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(34) Note Added in Proof. Achalensolide appears to be identical with one of the constituents of *Decachaeta thieleana* described in a recent article.[35]
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150 (16.5), 149 (10.1), 148 (17.7), 147 (30.0), 145 (8.0), 138 (15.3), 137 (100), 136 (12.8), 135 (24.8), 134 (7.3), 133 (17.6), 132 (13.1), 131 (14.9), 129 (7.7); M_r calcd for $C_{15}H_{18}O_3$ 246.1251, found, (MS) 246.1253.

The third fraction (**3**, 42 mg) was recrystallized from benzene–EtOAc: mp 121–123 °C; IR (KBr) 1778, 1752, 1740, 1642, 1190, 1020, 1002, 960 cm^{-1}; ^1H and ^{13}C NMR spectra in Tables I and II; $[\alpha]_D$ +147.9° (*c* 0.126, MeOH); CD curve (MeOH) $[\theta]_{310}$ −3760 (negative max), $[\theta]_{288}$ 0, $[\theta]_{235}$ +20500 (max), mass spectrum, *m/z* (relative intensity) 248 (M^+, 92.0), 233 (4.1), 220 (5.7), 219 (8.9), 203 (4.7), 202 (5.0), 192 (4.4), 190 (4.8), 187 (5.5), 177 (9.3), 176 (17.7), 175 (100), 174 (40.9), 173 (8.4), 161 (19.5), 160 (7.4), 159 (20.3), 157 (9.0), 150 (15.5), 194 (21.1), 148 (50.9), 147 (53.0), 146 (24.9), 145 (21.4), 137 (8.3), 136 (15.3), 135 (27.4), 134 (14.7), 133 (54.9), 132 (14.7), 131 (28.9); M_r calcd for $C_{15}H_{20}O_3$ 248.1412, found, (MS) 248.1434.

(B) A solution of 25 mg of achalensolide in 15 mL of acid-free EtOAc containing 10 mg of 5% $Pd/CaCO_3$ catalyst was hydrogenated at atmospheric presure for 2 h, at which time reduction was complete. Filtration, removal of solvent at reduced pressure, and preparative TLC of the residue (C_6H_6–EtOAc, 1:1, multiple development) afforded as the first band 5 mg of lactone **4** and as the second band 13 mg of lactone **3**.

X-Ray Analysis of Achalensolide. Single crystals of **1** were prepared by slow crystallization from benzene–EtOAc. The crystals were orthorhombic, space group $P2_12_12_1$ with a = 7.449 (5) Å, b = 7.574 (3) Å, c = 22.44 (1) Å, and d_{calcd} = 1.292 g cm^{-3} for Z = 4 ($C_{15}O_3H_{18}$, M_r = 246.3). The intensity data were measured on a CAD4 diffractometer (Mo radiation, monochromated, θ–2θ scans). The size of the crystal used for data collection was approximately 0.3 × 0.3 × 0.3 mm^3. No absorption correction was necessary (μ = 0.829). A total of 1331 reflections were measured for $\theta \leq 25.0°$, of which 1115 were considered to be observed [$I \geq 3\sigma$]. The structure was solved by direct methods using MULTAN 78[36] and refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms. Methyl hydrogen atoms 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 = 4.1 and R_w = 4.3% for the 1115 observed reflections. The final difference Fourier map was essentially featureless with no peaks greater than 0.3 e A^{-3}.

Registry No. **1**, 87302-42-9; **2**, 13447-58-0; **3**, 87206-13-1; **4**, 87174-96-7.

Supplementary Material Available: Tables III–VI listing final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compound **1** (5 pages). Ordering information is given on any current masthead page.

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Chemistry of Four-Membered Cyclic Nitrones. 5. Synthesis and Oxidation of 1-Hydroxyazetidines

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1-(Benzyloxy)azetidines **9** are prepared by reductive cyclization of the corresponding *O*-benzyl oximes (**6**) that have a leaving group at the β-position. Reduction of the unprotected oxime **6a** with sodium cyanoborohydride in acetic acid affords 3,4,4-trimethylisoxazolidine (**8**) in a yield of 61%. The azetidines **9** are catalytically debenzylated with Pd/C, H_2 in acetic acid to give the 1-hydroxyazetidines **10a** and **10b** in yields of 71% and 61%, respectively. A study of the nitrogen inversion process in azetidines **9b** and **10b** shows that the barrier is dependent on both the substituent at oxygen and the solvent. Oxidation of 1-hydroxyazetidine **10a** with active lead(IV) oxide quantitatively gives a mixture of the two isomeric nitrones, **11a** and **11b**, and oxidation of **10b** affords four-membered cyclic nitrone **12**, which is characterized by reaction with dimethyl acetylenedicarboxylate. Reaction of 1-hydroxyazetidine **10a** with 3 equiv of lead tetraacetate gives 1,4-bis(acetyloxy)-3,3,4-trimethyl-2-azetidinone (**19**) in a yield of 71%, whereas oxidation of **10b** with lead tetraacetate results in a mixture of the 1,4-bis(acetyloxy)-2-azetidinone **22** and the 1,4,4-tris(acetyloxy)-2-azetidinone **25**.

Introduction

Recently we have described the synthesis of four-membered cyclic nitrones by reaction of 1-nitroalkenes and 1-aminoacetylenes (ynamines).[1] Since four-membered cyclic nitrones are structural isomers of β-lactams, we have studied a number of reactions under which nitrones are converted into amides. Reactions with both nucleophiles[2] and electrophiles[3] failed in this respect, but reaction with lead tetraacetate resulted in the formation of 1-acetyloxy β-lactams.[3]

Since in addition to the aforementioned nitrones only two other four-membered cyclic nitrones have been reported[4,5] by using synthetic methods that have also a very limited scope, a wider application of this novel β-lactam synthesis requires a more general synthesis of four-membered cyclic nitrones.

In the course of our studies on the reactivity of four-membered cyclic nitrones with nucleophiles we obtained 1-hydroxyazetidines, and we have shown that these compounds can be oxidized to the corresponding four-membered cyclic nitrones with yellow mercury(II) oxide.[2] Furthermore, it revealed that 1-hydroxyazetidines that are unsubstituted at C-4 can be oxidized with *2 equiv* of lead tetraacetate to the corresponding 1-(acetyloxy)-2-azetidinones via the in situ generated four-membered cyclic nitrones. This result, viz., the oxidation of 1-hydroxy-

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