added. The resulting suspension was heated under reflux for 15 min, and then it was cooled and poured into 3% aqueous HCl. The product was isolated with $CHCl_3$ and the crude material (90 mg) was chromatographed on a SiO_2 column (5 g, hexane–acetone, 93:7) to give compound **1b** (81 mg, 84%), mp 194–197 °C. A sample recrystallized from acetone–hexane had: mp 196.5–197.5 °C (reported[12] mp 195–197 °C); ν_{max} (KBr) 1790, 1750, and 1630 (lactone moiety), 1750 and 1240 (acetate) cm^{-1}; ^1H NMR 0.66 (s, 3 H, 18-CH_3), 1.04 (s, 3 H, 19-CH_3), 2.1 (s, 3 H, $OCOCH_3$), 4.75 and 4.83 (2 d, 2 H, J = 18 Hz, 21-H), 5.13 (m, 1 H, 3-H), 5.89 (br s, 1 H, 22-H).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.87; H, 9.13.

Acknowledgment. We thank Dr. David M. Piatak and Dr. Marcel Gut for helpful discussions and for their assistance in the preparation of the manuscript.

Registry No. **1b**, 6564-57-4; **2b**, 14414-50-7; **3**, 853-23-6; **3** ethylene ketal, 17921-59-4; **4**, 5615-32-7; **4** (4-ene), 1044-89-9; **4**-ol, 5717-77-1; **5**, 4820-41-1; **5**-ol, 571-31-3; (*E*)-**6**, 87393-39-3; (*Z*)-**6**, 87372-91-6; **7a** (isomer 1), 87372-92-7; **7a** (isomer 2), 87393-40-6; **7b**, 87372-93-8; **8**, 87372-94-9; **8** acetate, 87372-95-0; **9**, 87372-96-1; **9** (deTHP), 87372-97-2; **10**, 87420-82-4; **11**, 87372-98-3; **12**, 87372-99-4; **12** diacetate, 87373-00-0; **13**, 87373-01-1; **14**, 87393-41-7; ethyl cyanoacetate, 105-56-6; dihydropyran, 110-87-2; triethyl phosphonoacetate, 867-13-0.

Acid Cyclization and Other Products of the Germacranolide Epoxide Lipiferolide[1]

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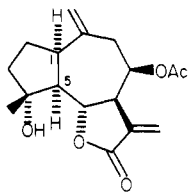
A comparison was made of the products generated from lipiferolide (**2**) upon treatment with $SOCl_2$, HCl, and BF_3·Et_2O. $SOCl_2$ formed three epoxide-opened compounds, chlorohydrin **3** and two allylic alcohols, **4** and **5**, three cyclization products of the guaianolide type, chloro compound **9** and olefins **1** and **10**, as well as three novel bicyclo[6.2.0]decanes, **6**, **7**, and **8**. HCl generated the epoxide-opened substances **3**, **4**, and **5** and guaianolides **1**, **9**, and **10**, but no cyclobutane products. BF_3·Et_2O gave the fluorohydrin **11** as the major component and ketone **12**, xanthanolide **13**, and epitulipinolide (4,5-deoxylipiferolide) as compounds not observed from the other reagents, along with small yields of allylic alcohol **4** and guaianolides **1** and **10**.

Cyclizations of germacranolides and their derivatives have been of significant value in structure elucidation studies,[2] because the bicyclic products are more rigid and overcome the flexibility and conformational uncertainty of the ten-membered ring. As a result, application of spectral methods to these derivatives, particularly ^1H NMR, can provide useful stereochemical information. From spectral data, the structure of β-cyclolipiferolide[3] (**1**)



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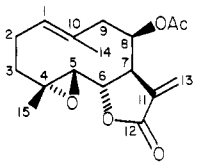

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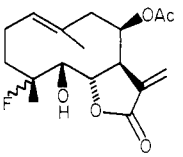

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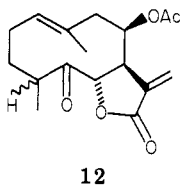

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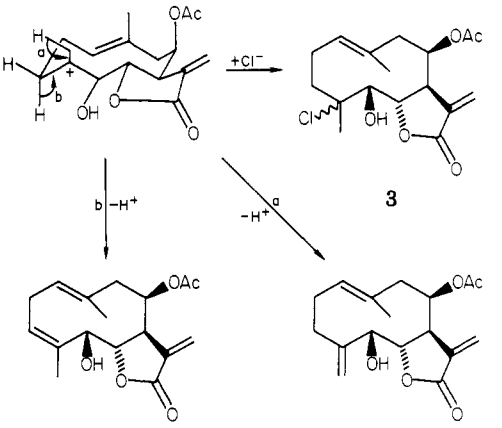
Scheme I



5 **4**

appeared to be a cyclized product of lipiferolide[4] (**2**), and treatment of lipiferolide (**2**) with $SOCl_2$ as a cyclizing reagent[5] gave, indeed, the natural product **1**. However, the yield was only 9% and TLC analyses showed the reaction mixture to contain many more substances than would be expected from a single epoxide ring opening followed by a cyclization between C(1) and C(5). This report is on the nature of those compounds, their yields, and a comparison study of the products formed by two other cyclization reagents, HCl and BF_3·Et_2O.

Nine pure products were obtained from the $SOCl_2$ cyclization after careful chromatography and accounted for

(1) Taken in part from the Ph.D. Dissertation of J.H.W. that was accepted in Aug. 1982 by the Graduate School, The Ohio State University.

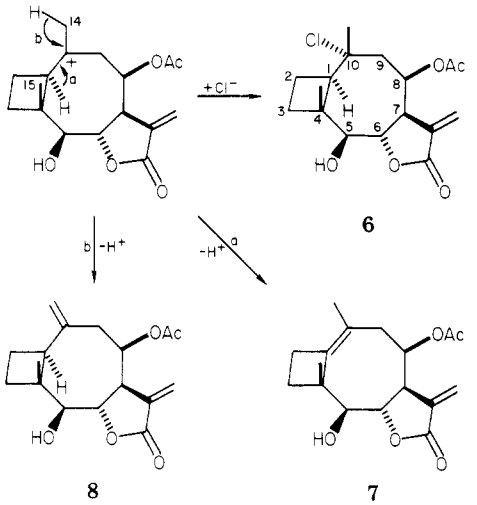
(2) A summary and list of references to studies with a variety of acidic reagents and sesquiterpenes are given by Fischer, N. H.; Olivier, E. J.; Fischer, H. D. "The Biogenesis and Chemistry of Sesquiterpene Lactones" in "Progress in the Chemistry of Organic Natural Products"; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, pp 105–110.

(3) Doskotch, R. W., Wilton, J. H.; Harraz, F. M.; Fairchild, E. H.; Huang, C.-T.; El-Feraly, F. S. *J. Nat. Prod.*, in press.

(4) Doskotch, R. W.; Keely, Jr., S. L.; Hufford, C. D.; El-Feraly, F. S. *Phytochemistry* **1975**, *14*, 769.

0022-3263/83/1948-4251$01.50/0

Scheme II



a total yield of 83%. The remainder of the material was composed of very minor components and tars. For discussion, the compounds are gathered into three groups according to the manner of their formation, i.e., the direction of the epoxide bond breaking and participation of the olefinic bond.

Bond cleavage at C(4)–O of **2** with subsequent loss of a proton from, or addition of a chloride to, the carbocation intermediate[6] (Scheme I) results in products **3**, **4**, and **5**. The chlorohydrin **3**, mp 197.0–197.5 °C, showed spectral characteristics of an α,β'-unsaturated γ-lactone, an acetate, and a trisubstituted olefin. The NMR features are recorded in Tables I and II. Of note is the lack of spin coupling between H(5) and H(6) implying that the dihedral angle must be near 90° and underscoring a major change in conformation from that of the starting material. Stereochemical designation at C(4) is withheld for lack of concrete evidence but is most probably *R* (Cl placed α in expression **3**) as a consequence of a S_N1 mechanism. Attempts at regenerating lipiferolide (**2**) from the chlorohydrin **3**, under a variety of basic conditions, were unsuccessful as might be expected from the *R* isomer.

Exocyclic allylic alcohol **4**, mp 107.5–108.0 °C, was assigned the structure from spectral data, in particular NMR, with double-resonance experiments aiding the assignments. At ambient temperature (~25 °C) the molecule is conformationally flexible and gives an uninterpretable ^1H NMR spectrum consisting of broadened peaks. At about 70 °C, however, the spectrum becomes sharpened to a single clear set of peaks, and at −30 °C two distinct patterns are observed in a ratio of 54:46. The standard free energy was calculated to be 77 cal/mol.

Endocylic allylic alcohol **5**, mp 174.5–175.5 °C, was given a unique structure from analysis of spectral data. The ^1H NMR spectrum was interpreted with the aid of extensive double-irradiation experiments, which will not be detailed here. The cis nature of the C(3)–C(4) double bond was established by nuclear Overhauser effect (NOE) difference studies[7] at 300 MHz in $CDCl_3$. Irradiation at H(15) resulted in an enhancement of 11% for H(3) in accord with a cis relationship, while irradiation at H(14) showed no effect on H(1); however, H(6) was increased by 13%. This would suggest a conformation for **5** in which H(14) and H(6) are syn and in close proximity.

The second group of three products (Scheme II) can be viewed as arising from cleavage of the C(4)–O bond with the cyclobutane ring generated from the C(1)–C(10) double bond and subsequent conversion of the carbocation to products **6**, **7**, and **8**. The chlorobicyclo[6.2.0]decane **6**, mp 154–155 °C, did not show a molecular ion in the electron impact MS (only M − H_2O), but the chemical ionization MS (with isobutane) did give a pseudomolecular ion corresponding to the molecular formula $C_{17}H_{23}O_5Cl$. The ^{35}Cl to ^{37}Cl ratio of the pseudomolecular ions was 3:1. The IR and ^1H NMR (Table I) spectra supported the presence of hydroxyl, acetate, and α,β'-unsaturated γ-lactone groups.

Spin-decoupling studies at 300 MHz, which are not detailed here, were begun by location of H(7) through irradiation of H(13) and followed by sequential irradiation of all other interacting protons. In this manner H(5) through H(9) were identified and found to correspond to the arrangement in the starting material lipiferolide (**2**). Also H(5) and H(9) were most probably adjacent to carbons C(4) and C(10) without hydrogens since further coupling of those protons was not observed. Five additional multiplicities for five protons formed another interacting unit. For example, a double doublet at 3.16 ppm (in $(CD_3)_2CO$) when irradiated collapsed one-proton multiplicities at 1.97 and 2.20 ppm, while irradiation of a nonfirst-order pattern at 1.63 ppm altered the latter pair and a multiplicity at 1.82 ppm. This sequence supported the arrangement of H(1) through H(3) as in **6** and, with a need for an additional double-bond equivalent, as required by the molecular formula, a cyclobutane ring. Other ways of accomodating the formula were not supported by the spectra data. Furthermore, the carbon–hydrogen coupling constants for C(1), C(2), and C(3) were measured from the ^{13}C NMR spectrum at 75 MHz, as determined by a gated decoupling technique, and found to be 138, 132, and 135 Hz, respectively, while the value for C(9) was 126 Hz. These figures are in agreement with published values for cyclobutane and larger ring compounds.[8]

The ring junction in **6** would be expected to have H(1) and C(15) placed trans on mechanistic grounds. Irradiation of H(1) in a NOE difference study at 300 MHz in $CDCl_3$ produced a signal enhancement for H(5) and H(7) of 7% and 23%, respectively, thereby placing H(1) on the α-side of the molecule. Irradiation of H(15) gave an increase of 11% for H(6) which located C(15) on the β-side and confirmed the trans ring junction. Furthermore, a 2% increase for H(14) established the stereochemistry at C(10) as *R*, and an increase for H(9β) of 10% located its position at 2.08 ppm.

The second cyclobutane product **7**, mp 153–154 °C, was characterized by spectral data. The ^1H NMR spectrum was similar to that of compound **6** except that an olefinic methyl replaced the 3-proton singlet for Me(14) and H(1) was absent; this confirms the molecular formula of $C_{17}H_{22}O_5$, which was supported by MS data and is that of the chlorocyclobutane **6** less HCl. The ^{13}C NMR spectrum supported the presence of a tetrasubstituted double bond with singlet peaks at 125.3 and 141.5 ppm. Results of extensive decoupling experiments were used in assigning ^1H and ^{13}C NMR peaks.

(5) (a) Doskotch, R. W.; El-Feraly, F. S. *J. Org. Chem.* **1970**, *35*, 1928. (b) Tada, H.; Takeda, K. *Chem. Pharm. Bull.* **1976**, *24*, 667.

(6) These intermediates are used for illustrative purposes only and do not imply an established mechanism.

(7) (a) Müllen, K.; Pregosin, P. S. "Fourier Transform NMR Techniques: A Practical Approach"; Academic Press: New York, 1976; pp 80–1. (b) Noggle, J. H.; Schirmer, R. E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1971.

(8) Stothers, J. B. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1972; p 333. Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish. *Tetrahedron* **1965**, *21*, 2749. Browne, C. E.; Ruehle, P. H.; Dobbs, T. K.; Eisenbraum, E. J. *Org. Magn. Reson.* **1979**, *12*, 553. Hansen, P. E.; Led, J. J. *Ibid.* **1981**, *15*, 288.

Table I. ^{1}H NMR Spectral Data of Products from Lipiferolide (2)[a]

compd	H(1)	H(5)	H(6)	H(7)	H(8)	H(9)	H(13)	H(14)	H(15)	miscellaneous
2[b]	5.32 br m	2.84 d (8.2)	4.40 t (8.2)	3.18 m	5.72 m		6.38 d (3.6); 5.73 d (3.2)	1.77 br s	1.38 s	2.07 s (Ac)
3[c]	5.75 br t (~7, 0.9)	4.43 ABd (7.0)	4.68 d (3.2)	3.34 m (3.2, 2.6, 2.2, 1.7)	5.34 dt (3.2, 3.2, 1.7)		6.11 d (2.6); 5.75 d (2.2)	1.85 d (0.9)	1.59 s	4.34 ABd (7.0, OH); 1.98 s (Ac)
4[d]	5.02 br t (~7, 1.0)	3.62 br d (8.6)	4.55 br dd (8.6, 1.2, 0.5)	2.67 m (2.6, 1.9, 1.5, 1.2)	5.17 dt (6.2, 6.1, 2.6)		6.15 dd (1.9, 0.5); 5.15 d (1.5)	1.37 d (1.0)	4.81 m	1.69 s (Ac)
5[c]	5.92 br t (~8)	5.09 d (8.3)	4.43 d (3.7)	3.38 m (3.7, 2.8, 2.4, 1.6)	5.39 dt (3.4, 3.4, 1.6)	2.5-2.6 br d	6.13 d (2.8); 5.75 d (2.4)	1.69 br s	1.77 m	2.05 s (Ac) 2.6-2.9 m H(2); 5.28 m H(3)
6[e]	2.97 dd (10.7, 8.3)	3.57 dd (9.9)	4.49 dd (9.9, 6.6)	3.49 m (6.6, 3.4, 3.3, 2.9)	5.77 ddd (10.5, 5.5, 3.4)	2.37 dd (15.1, 5.5); 2.08 dd (15.1, 10.5)	6.39 d (3.3); 5.71 d (2.9)	1.70 s	1.31 s	1.98 s (Ac)
6[f]	3.16 dd (11.0, 8.1)	3.72 d (10.3)	4.51 dd (10.1, 6.4)	3.71 m (6.4, 3.7, 3.1, 2.9)	5.72 ddd (10.5, 5.5, 3.7)	2.37 dd (15.3, 5.3); 2.21 dd (15.3, 10.5)	6.25 (3.1); 5.67 (2.9)	1.72 s	1.33 s	1.96 s (Ac); 2.20 m H(2); 1.97 m H(2); 1.82 m H(3); 1.63 m H(3)
7[e]		3.73 d (9.9)	4.63 dd (9.9, 6.6)	3.22 m (6.6, 3.7, 3.3, 2.9)	5.43 m (11.4, 6.3, 3.3)	2.38 dd (12.8, 11.4); 2.27 dd (12.8, 6.3)	6.35 d (3.7); 5.59 d (2.9)	1.60 dd (1.8, 1.8)	1.36 s	1.98 s (Ac); 2.57 t, H(2), (8.4); 2.10 m, H(3a), 1.87 m, H(3b)
8[e]	2.88 dd (8.9, 8.9)	3.70 d (9.9)	4.59 dd (9.9, 7.3)	3.31 m (7.3, 3.3, 2.9, 2.6)	5.38 m (9.1, 4.4, 2.6)	2.65 dd (14.3, 9.1); 2.49 dd (14.3, 4.4)	6.36 d (3.3); 5.65 d (2.9)	5.05 br s; 4.84 br s	1.22 s	2.01 s (Ac)
9		2.38 dd (11.8, 9.1)	4.58 dd (11.8, 9.5)	3.35 m (9.5, 3.5, 3.2, 2.9)	5.64 dt (4.9, 4.9, 2.9)	2.6-2.4 m	6.31 d (3.5); 5.53 d (3.2)	1.71 s	1.46 s	2.04 s (Ac)
10[e]		2.78 br d (10.8)	4.38 dd (10.8, 10.6)	2.98 m (10.6, 3.4, 3.0, 1.6)	5.58 dt (3.7, 3.7, 1.6)	2.50-2.51 m	6.26 d (3.4); 5.57 d (3.0)	1.66 br s	1.38 s	2.04 s (Ac)
11[e]	5.63 br t (7.4)	4.38 dd (11.8, 7.4)	4.56 t (~3, 2.2)	3.19 m (~3, 2.6, 2.2, ~1.5)	5.34 m (3.4, 3.1, 1.5)	2.60 dd (14.4, 3.4); 2.45 dd (14.1, 3.1)	6.34 d (2.6); 5.71 d (2.2)	1.78 s	1.39 d (22.4)	2.03 s (Ac); 2.17 d, OH (7.4)
12[e]	5.03 br d (5.9)		5.22 d (4.8)	3.67 m (4.8, 3.3, 2.6, 2.3)	5.46 m (3.7, 2.4, 2.3)	2.58 dd (14.3, 3.7); 2.27 dd (14.3, 2.4)	6.38 d (3.3); 5.75 d (2.6)	1.83 br s	1.34 d (7.4)	2.06 s (Ac)
13[e]		5.76 dd (2.2, 1)	5.28 dd (10.2, 2.2)	2.90 dq (10.2, 3.6, 3.2, 2.4)	5.74 ddd (4.8, 3.7, 2.4)	2.04 ddd (15.5, 3.7, 3.7); 1.90 ddd (15.5, 4.8, 4.8)	6.22 d (3.6); 5.50 d (3.2)	1.21 d (7.7)	2.18 s	2.04 s (Ac); 2.42 m, H(10); 2.34 m, H(2); 2.57 m, H(3)

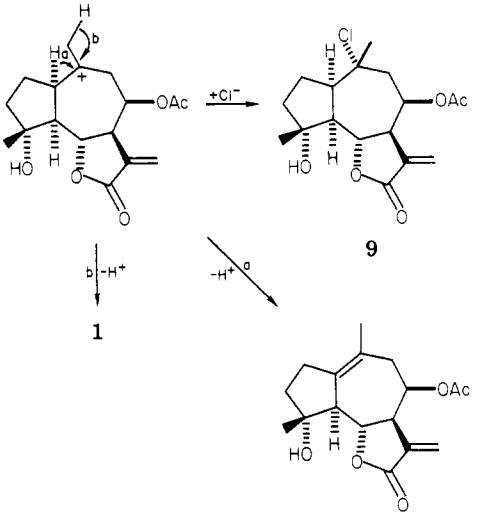
[a] Taken at 90 MHz in $CDCl_3$ with Me_4Si as internal standard, unless stated otherwise, with computer resolution of 0.3 Hz/point, and reported in ppm with coupling constants in Hz. Multiplicities are designated by the symbols: s = singlet, d = doublet, m = multiplet, q = quartet, t = triplet, and br = broad signal. [b] Reported in ref 13. [c] In $(CD_3)_2CO$. [d] In C_6D_6 at 70 °C and 80 MHz. [e] At 300 MHz in $CDCl_3$ and D_2O exchanged. [f] At 300 MHz in $(CD_3)_2CO$.

Table II. ^{13}C NMR Spectral Data of Products from Lipiferolide (2)[a]

carbon	2[b]	3[c]	4[f]	5[i]	6[c,k]	7[c]	8[c]	9[c]	10[c]	11[c,l]	12[c,k]	13[c]
1	129.1 d	129.7 d	131.7 d	130.5 d[j]	50.1 d[e]	125.3[d]	44.8 d	49.0 d	125.6[d]	130.0 d	131.8 d	145.4
2	24.5 t	22.7 t	27.7 t[h]	27.7 t	20.9 t	23.8 t[e]	23.7 t	26.8 t	30.2 t[g]	21.0 t	24.8 t	32.5 t[d]
3	36.4 t	40.3 t	28.0 t[h]	122.0 d[j]	32.8 t	30.8 t	33.0 t[e]	38.7 t	38.3 t[g]	36.1 t (24)	36.1 t	36.0 t[d]
4	61.8	79.3	130.3[g]	140.5	45.1	47.3	43.7	80.7	80.4	99.5 (171)	43.1 d	207.4
5	66.8 d	79.7 d[e]	76.8 d[d]	74.3 d[j]	83.2 d[e]	80.2 d[e]	83.4 d[e]	57.9 d	58.8 d	77.4 d (24)	209.2	125.2 d
6	76.4 d	74.6 d[e]	80.5 d[d]	82.5 d[j]	77.8 d	79.1 d[e]	79.1 d	76.5 d	77.7 d	75.0 d (11)	75.8 d[d]	75.6 d[g]
7	49.4 d	49.4 d[e]	44.2 d	49.0 d	44.1 d[e]	44.8 d	45.5 d[e]	51.9 d	52.0 d	49.2 d	46.9 d	50.2 d
8	74.5 d	79.5 d[e]	79.8 d[d]	79.3 d[j]	69.4 d[e]	69.7 d[e]	70.8 d[e]	66.7 d	65.0 d	79.7 d	73.7 d[d]	68.5 d[g]
9	44.0 t	43.8 t	43.8 t	43.6 t[j]	43.6 t[e]	35.0 t[e]	41.5 t	47.0 t	39.3 t[g]	43.9 t	43.4 t	42.0 t[d]
10	132.0	136.1[d]	148.0[g]	138.5[d]	69.8	141.5[d]	142.6	74.4	132.9[d]	136.1[d]	135.0[g]	36.6 d
11	137.9	135.5[d]	138.0	134.4[d]	134.5	135.4	136.4	134.3	134.9	135.5[d]	135.5[g]	135.8
12	169.1	170.0	169.1	169.9	168.5	168.8	168.3	168.8	169.1	170.0	168.6	169.3
13	121.9 t	123.6 t	122.5 t	122.2 t[j]	124.0 t	123.3 t	123.2 t	122.1 t	121.1 t	123.9 t	124.3 t	120.6 t
14	19.7 q	19.3 q[e]	17.0 q	18.2 q[j]	32.7 q	18.4 q	116.5 t	31.3 q	22.8 q	19.3 q	19.1 q	19.1 q
15	17.2 q	25.5 q[e]	117.1 t	18.5 q[j]	13.7 q	18.1 q[e]	14.5 q	24.9 q	24.5 q	19.9 q (25)	15.4 q	30.0 q
MeCO	20.6 q	21.1 q	20.2 q	20.6 q	20.7 q	21.1 q	20.8 q	20.9 q	21.1 q	21.0 q	21.2 q	21.0 q
MeCO	169.9	170.0	169.5	169.9	169.6	170.5	169.9	170.0	170.5	170.0	169.9	170.1

[a] Taken at 20.12 MHz or as stated in indicated solvent. Unmarked signals are singlets. [b] Taken from ref 13 in C_5D_5N with a change for C(2) and C(9) according to ref 14. [c] In $CDCl_3$. [d,g,h] Assignments may be interchanged. [e] Assignments made by selective single-frequency decoupling. [f] Taken in C_6D_6 at 70 °C. [i] In $(CD_3)_2CO$. [j] Assignments made by graphing off-resonance data, ref 15. [k] At 75 MHz. [l] Multiplicities exclusive of ^{19}F coupling. J_{CF} values in Hz given in parentheses.

Scheme III



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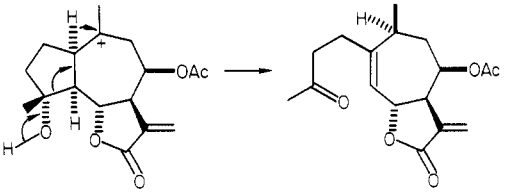
Scheme IV



13

The third cyclobutane product **8**, mp 122–123 °C, was similarly characterized by spectral data recorded in the Tables and in the Experimental Section. In addition, further support for the cyclobutane ring came from the carbon–hydrogen coupling constants[8] of 142 and 137 Hz for C(2) and C(3), respectively, as determined from the ^{13}C NMR spectrum run at 75 MHz under gated decoupling conditions.

The third group of the three products (Scheme III), the guaianolides **9**, **10**, and **1**, are formed from lipiferolide (**2**) by epoxide opening at C(5) and bond formation between C(1) and C(5). The chloroguaianolide **9** and α-cyclolipiferolide (**10**) were characterized from spectral data including extensive spin decoupling of the ^1H NMR spectra and by comparison of their spectra with spectra of β-cyclolipiferolide (**1**).[3]

Cyclization of lipiferolide (**2**) with dry HCl in an aprotic solvent system gave a mixture of compounds from which were isolated the three ten-membered ring products **3**, **4**, and **5** (Scheme I) and the three guaianolides **1**, **9**, and **10** (Scheme III) for a total recovered yield of 93%. Of these, the guaianolides were formed in a yield of over 75%. The cyclobutane products (Scheme II), on the other hand, were not detected. However, with BF_3·Et_2O the major product (69%) was the fluorohydrin **11** whose structure was established from spectral data, and the ^{13}C NMR peak assignments were aided by ^{13}C–^{19}F spin–spin coupling values.[9] In addition, three other ten-membered ring products were obtained, the deoxygenated germacranolide epitulipinolide,[5a] ketone **12**, and allylic alcohol **4**, for a total yield of only 3.2%. The guaianolides, α-(**10**) and β-cyclolipiferolide (**1**), were formed in 2.6% and 1.7%, respectively. The second most abundant product, the xantholide **13** (6.3%) represents a type not observed in the previous

(9) Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 2361. Penk, T.; Lippmaa, E. *Org. Magn. Reson.* **1971**, *3*, 679.

reactions. Its formation can be rationalized as in Scheme IV and represents a laboratory analogy for xanthanolide formation.

Results of this comparison study underscore the difference in the nature of the cyclization reagents, in that they are not interchangeable, at least when applied to lipiferolide (2) as an example of a germacranolide 4,5-epoxide. Thionyl chloride made available in reasonable yields not only the expected guaianolide products but several unusual germacranolides and the novel cyclobutanes. Undoubtedly many of these will in time be discovered as natural products. Hydrochloric acid would be a reagent of choice for the guaianolides, while $BF_3{\cdot}Et_2O$ is to be avoided unless a fluorohydrin is desired.

Experimental Section[10]

Treatment of Lipiferolide (2) with $SOCl_2$. To 2.5 g of lipiferolide (2) in 55 mL of C_6H_6 and 25 mL of Et_2O under N_2 was added 2.0 mL of $SOCl_2$ while stirring at room temperature. After 2 h, 20 mL of 3% aqueous $NaHCO_3$ was added and when gas evolution stopped, the organic layer was separated, washed with 100 mL of 3% $NaHCO_3$ and 3 × 25 mL of H_2O. The organic phase gave, upon evaporation at reduced pressure, 2.4 g of a dark yellow viscous oil, which was flash chromatographed[11] on 110 g of silica gel 60 (230–400 mesh) by using 500 mL each of EtOAc–hexane in the ratios 7:13, 3:2, and 4:1 and EtOAc. Fractions (Al through A15) were formed by combining effluent residues after TLC analysis with EtOAc–hexane (7:11 and 3:2).

Chlorohydrin 3. Fractions A5 and A6 (517 mg) were flash chromatographed[11] on 55 g of silica gel 60 with EtOAc–hexane (42:58) to give fractions B1 through B4, of which B2 and B3 afforded 125 mg (8.6%) of chlorohydrin 3 from EtOAc–hexane as colorless needles: mp 197.0–197.5 °C; TLC R_f 0.36 with EtOAc–hexane (1:1), violet; $[\alpha]^{22}_D$ −177° (c 0.24, MeOH); CD (c 3.24 × 10^{-3} M, MeOH) $[\theta]_{300}$ 0, $[\theta]_{262}$ + 2960, $[\theta]_{249}$ 0, $[\theta]_{212}$ −35 700; UV (MeOH) λ_{max} 210 nm (log ϵ 4.18); IR ($CHCl_3$) ν_{max} 3590 (OH), 3030 (C=CH), 1772 (lactone), 1748 (ester), 1670 (C=C), 1260–1210 cm^{-1} (COC); and MS, m/z 342 (0.9%, M^+), 282 (7, M − AcOH), 264 (3, M − AcOH − H_2O), 246 (11), 177 (7), 117 (8), and 43 (100, Ac); calcd. for $C_{17}H_{23}O_5\,^{35}Cl$, M_r 342.1234; found, M_r (MS) 342.1239.

Allylic Alcohol 4. Fraction A7 (396 mg) was separated by flash chromatography[11] on 55 g of silica gel 60 by using EtOAc–hexane (42:58) to give fractions B1 through B5 of which B3 and B4 were rechromatographed on silica gel 60 (6% H_2O) with EtOAc–hexane (45:55). A 275-mg fraction gave from EtOAc–hexane 145 mg (9.8%) of compound 4: mp 107.5–108.0 °C; TLC R_f 0.43 with EtOAc–hexane (6:4), dark blue with p-anisaldehyde reagent and red with H_2SO_4–Et_2O (1:9); $[\alpha]^{22}_D$ −246° (c 0.16, MeOH); CD (c 5.07 × 10^{-3} M, MeOH) $[\theta]_{310}$ 0, $[\theta]_{260}$ + 4740, $[\theta]_{248}$ 0, $[\theta]_{200}$ −131 000 (last reading); UV (MeOH) λ_{max} 210 nm (log ϵ 4.07); IR ($CHCl_3$) ν_{max} 3580 (OH), 3020 (C=CH), 1775 (lactone), 1747 (ester), 1672 and 1645 cm^{-1} (C=C); and MS, m/z 306 (2%, M^+), 264 (2, M − CH_2CO), 246 (34, M − AcOH), 228 (7), 217 (6), 177 (10), and 43 (100); calcd for $C_{17}H_{22}O_5$, M_r 306.1467; found, M_r (MS) 306.1461.

Allylic Alcohol 5. From Fraction A7, 78 mg (4.5%) of compound 5 crystallized from Et_2O–hexane as needles: mp 174.5–175.5 °C; TLC R_f 0.25 with EtOAc–hexane (1:1), blue; $[\alpha]^{22}_D$ −163° (c 0.195, MeOH); CD (c 9.07 × 10^{-3} M, MeOH) $[\theta]_{290}$ 0, $[\theta]_{270}$ + 580, $[\theta]_{262}$ 0, $[\theta]_{200}$ − 80 500 (last reading); UV (MeOH) log ϵ_{210} 4.28; IR ($CHCl_3$) ν_{max} 3585 (OH), 1770 (lactone), 1748 (ester), 1668 cm^{-1} (C=C); MS, m/z 306 (1.3%, M^+), 288 (2, M − H_2O), 264 (2, M − CH_2CO), 246 (16, M − AcOH), 150 (13), 117 (32), and 43 (100); calcd for $C_{17}H_{22}O_5$, M_r 306.1467; found, M_r (MS) 306.1458.

Chlorobicyclo[6.2.0]decane 6. The mother liquor residue, after isolation of compound 3, from Fraction B3 was separated on 55 g of silica gel 60 with EtOH–hexane (2:8) to give Fraction C1 through C5. Fraction C3 crystallized from EtOAc–hexane to give 150 mg (10.8%) of the chlorocyclobutane product 6: mp 154–155 °C; TLC R_f 0.25 with EtOAc–$CHCl_3$ (2:8), blue; $[\alpha]^{22}_D$ −6.3° (c 0.16, MeOH); UV (MeOH) log ϵ_{220} 4.13; IR ($CHCl_3$) 3595 (OH), 3020 (C=CH), 1772 (lactone), 1748 (ester), 1660 cm^{-1} (C=C); MS (CI, i-BuH), m/z 345 (1.7%, MH^+ with ^{37}Cl), 343 (4.6%, MH^+ with ^{35}Cl), 307 (36, MH − HCl), 289 (10), 283 (3), 265 (5), 247 (62), and 229 (100), calcd for $C_{17}H_{21}O_4Cl$ (M − H_2O), fragment weight 324.1129; found, (MS) 324.1139.

Bicyclo[6.2.0]dec-1(10)-ene 7. Chromatography of Fraction A4 on 30 g of silica gel 60 with 4% MeOH in $CHCl_3$ gave Fractions B1 through B4. Fractions B1 and B2 crystallized from EtOAc–hexane to give 18 mg (0.85%) of compound 7: mp 153–154 °C; TLC R_f 0.27 with 6% MeCN in $CHCl_3$, blue; $[\alpha]^{22}_D$ −74 (c 0.17, MeOH); UV (MeOH) log ϵ_{220} 4.14; IR ($CHCl_3$) ν_{max} 3590 (OH), 1770 (lactone), 1740 (ester), 1655 (C=), 1200–1250 cm^{-1} (COC); MS, m/z 306 (13%, M^+) 246 (33, M − AcOH), 231 (6), 213 (6), 200 (18), 176 (44), and 43 (100); calcd for $C_{17}H_{22}O_5$, M_r 306.1467; found, M_r (MS) 306.1472.

Bicyclo[6.2.0]dec-10(14)-ene 8. Mother liquor residue of C3 and subfractions C4 and C5 from initial fractions A5 and A6 were combined and chromatographed on 65 g of silica gel 60 with EtOAc–$CHCl_3$ (1:4) to give fractions D1 through D3, of which D3 was rechromatographed twice more. Crystallization from EtOAc–$CHCl_3$ gave 75 mg (5.1%) of compound 8: mp 122–123 °C; TLC R_f 0.19 with 15% EtOAc in hexane, purple; $[\alpha]^{22}_D$ −65° (c 0.10, MeOH); UV (MeOH) log ϵ_{220} 4.21; IR ($CHCl_3$) ν_{max} 3590 (OH), 1770 (lactone), 1747 (ester), 1663 and 1644 (C=C), 1255–1210 cm^{-1} (COC); MS (EI), m/z 306 (1.1%, M^+), 264 (29, M − CH_2CO), 246 (23, M − AcOH), 188 (25), 176 (80), 147 (58), 129 (52), 91 (100); CI (i-BuH), m/z 307 (7%, MH^+); calcd for $C_{15}H_{20}O_4$ (M − CH_2CO); fragment weight 264.1361; found, fragment weight (MS) 264.1368.

Chloroguaianolide 9. Fraction A10 (309 mg) crystallized from EtOAc–hexane to give 87 mg of chloroguainolide 9 (overall yield 9%): mp 148–149°; TLC R_f 0.31 with EtOAc–hexane (3:2), lavender; $[\alpha]^{22}_D$ −48° (c 0.12, MeOH); CD (c 3.45 × 10^{-3} M, MeOH) $[\theta]_{290}$ 0, $[\theta]_{255}$ −1190, $[\theta]_{230}$ 0, $[\theta]_{210}$ −2320; UV (MeOH) λ_{max} 212 nm (log ϵ 3.86); IR ($CHCl_3$) ν_{max} 3595 and 3520 (OH), 1775 (lactone), 1748 (ester), 1670 (C=C), 1240–1210 (COC), 1178 cm^{-1} (CO of alcohol); MS (CI, i-BuH), m/z 345 (0.7%, MH^+ with ^{37}Cl), 343 (1.7, MH^+ with ^{35}Cl), 325 (1.8, M − H_2O), 307 (6, M − HCl), 289 (13), 283 (5), 247 (34), 229 (100); calcd for $C_{16}H_{20}O_5\,^{35}Cl$ (M − Me), fragment weight 327.0999; found, (MS) 327.1006.

α-Cyclolipiferolide (10). The mother liquor residue from Fraction A10 and column fractions of similar composition with a total weight of 853 mg were chromatographed on silica gel 60 (6% H_2O) with EtOAc–hexane (1:1) to give fractions B1 through B10. Fraction B4 was pure α-cyclolipiferolide (10): unstable oil[12]; TLC R_f 0.19

(10) For information on instruments, adsorbents, and reagents, see reference 3 and others therein. The color designation following the TLC data is from visualization by the spray reagent, 5% (v/v) p-anisaldehyde in 5% H_2SO_4 (v/v) in EtOH, after the plates were heated at 110 °C for 5–10 min.

(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

with EtOAc–hexane (1:1), turquoise; $[\alpha]^{22}_D$ −88° (*c* 0.71, MeOH); UV (MeOH) log ϵ_{220} 3.66; IR ($CDCl_3$) ν_{max} 3590 and 3500 (OH), 1775 (lactone), 1740 (ester), 1675 (C=C), 1260–1210 cm^{-1} (COC); MS (EI), *m/z* 306 (1.1%, M^+), 288 (7, M − H_2O), 246 (9, M − AcOH), 228 (100, M − H_2O − AcOH); calcd for $C_{15}H_{18}O_3$ (M − AcOH), fragment weight 246.1256; found, fragment weight (MS) 246.1302.

β-Cyclolipiferolide (1). Fraction A2 crystallized from EtOAc–hexane to give 113 mg (9.1%) of β-cyclolipiferolide (1) as needles which were identical (mp, TLC, $[\alpha]_D$, IR, UV, ^1H NMR, and MS) with the natural product from the leaves of *L. tulipifera*.[3]

Treatment of Lipiferolide (2) with HCl. Dry HCl gas was passed through a solution of 203 mg of lipiferolide (2) in 12 mL of C_6H_6–Et_2O (1:1) for 10 min. The reaction mixture was stirred for 12 h in a closed system under slight HCl pressure, then concentrated to a small volume at reduced pressure (no heat), and dissolved in 25 mL of $CHCl_3$. Extraction of the solution with H_2O (3 × 15 mL) and evaporation of the $CHCl_3$ left 227 mg of a pale yellow oil, that was separated on 3 20 × 40 cm silica gel G plates (0.75 mm thick) with 15% EtOAc in hexane (3 times) and 30% EtOAc in hexane. Seven bands were scraped off as indicated by short UV light examination and color detection at the plate edges with *p*-anisaldehyde spray reagent. Band 4 on chromatography over 25 g of silica gel 60 with EtOAc–hexane (1:3) afforded 34 mg of unreacted lipiferolide (2), 14 mg (7.6%) of chlorohydrin **3**, 7 mg (4.1%) of allylic alcohol **4**, and 103 mg (60.7%) of α-cyclolipiferolide (**10**). Chromatography of bands 5 and 6 on 25 g of silica gel with EtOAc–hexane (7:13) gave 10 mg (5.6%) of allylic alcohol **5**, 11 mg (5.9%) of chloroguaianolide **9**, and 15 mg (9%) of β-cyclolipiferolide (1). No cyclobutane products were detected.

Treatment of Lipiferolide (2) with Bf_3·Et_2O and Isolation of Fluorohydrin 11 and Epitulipinolide. Lipiferolide (1.44 g) was dissolved in 150 mL of dry Et_2O at 0 °C and treated with 6 mL of distilled BF_3·Et_2O for 2.5 h while stirring under N_2. H_2O (50 mL) was added and after 10 min the reaction mixture was evaporated to remove the Et_2O. Extraction of the remaining aqueous layer with $CHCl_3$ (4 × 30 mL) and evaporation of the $CHCl_3$ left 1.83 g of a residue that yielded 1.05 g (69%) of fluorohydrin (**11**) from EtOAc–hexane (3:7) as prisms: mp 194.5–195.0 °C dec (from $CHCl_3$); TLC R_f 0.14 with EtOAc–hexane (2:3); $[\alpha]^{22}_D$ −166° (*c* 0.30, MeOH); UV (MeOH) log ϵ_{220} 4.72; IR ($CHCl_3$) ν_{max} 3580 and 3490 (OH), 3020 (C=CH), 1765 (lactone), 1747 (ester), 1663 (C=C), 1260–1200 (COC), 1100 cm^{-1} (COH); MS, *m/z* 326 (0.5%, M^+), 306 (0.5, M − HF), 284 (2, M − CH_2CO), 266 (26, M − AcOH), 246 (28, M − HF − AcOH), 109 (8), 81 (11), 43 (100, CH_3CO); calcd for $C_{17}H_{23}FO_5$, M_r 326.1529; found; M_r (ms) 326.1537.

The mother liquor residue (0.88 g) from recrystallization of fluorohydrin **11** was chromatographed on 55 g of silica gel 60 with EtOAc–hexane (3:7) to give Fractions A1 through A20. Fraction A1 (13.6 mg) was separated by preparative TLC developed with EtOAc–hexane (1:3) once and (1:9) twice. Crystallization of the eluted band (detection by short UV light) from EtOH–hexane gave 8.2 mg (0.6%) of epitulipinolide:[5a] mp 91–92 °C; TLC R_f 0.51 with EtOAc–hexane (9:11); TLC, IR, and ^1H NMR spectra identical with an authentic sample.

α-Methyl Ketone 12. Fractions A3 and A4 (41 mg) from the BF_3·Et_2O-generated mixture crystallized from EtOAc–hexane to give 24 mg (1.7%) of ketone **12** as needles: mp 128.5–129.0 °C; TLC R_f 0.49 with EtOAc–hexane (9:11), pink; $[\alpha]^{22}_D$ −140° (*c* 0.19, MeOH); UV (MeOH) log ϵ_{220} 4.86; IR ($CHCl_3$) ν_{max} 3030 (C=CH), 1773 (lactone), 1748 (ester), 1712 (ketone), 1665 (C=C), 1260–1210 cm^{-1} (COC); MS, *m/z* 306 (1.6%, M^+), 246 (17), 218 (6), 148 (9), 98 (9), 81 (18), 43 (100); calcd for $C_{17}H_{22}O_5$, M_r 306.1467; found, M_r (ms) 306.1474.

Xanthanolide 13. Fraction A10 from the BF_3·Et_2O-generated products yielded 34 mg of crystalline **13** from EtOAc–hexane. The mother liquor residue along with fractions A8 and A9 were combined (215 mg) and chromatographed on 55 g of silica gel 60 (6% H_2O) with 0.5% MeOH in $CHCl_3$ to give fractions B1 through B3. Fraction B3 afforded 56 mg of xanthanolide **13** (6.3% total yield): mp 101.0–101.5 °C; TLC R_f 0.35 with 1% MeOH in $CHCl_3$, pink; positive iodoform test; $[\alpha]^{22}_D$ −52° (*c* 0.12, MeOH); UV (MeOH) log ϵ_{220} 4.68; IR ($CHCl_3$) ν_{max} 3020 (C=CH), 1770 (lactone), 1740 (ester), 1720 (ketone), 1670 (C=C), 1250–1210 (COC), 815 cm^{-1} (C=CH); MS, *m/z* 264 (1.2%, M − CH_2CO), 248 (29, M −Me_2CO), 228 (3), 188 (40) 91 (11), 77 (8), 43 (100); calcd for $C_{14}H_{16}O_4$ (M − Me_2CO), fragment weight 248.1049; found, (MS) 248.1063.

Allylic Alcohol 4, α-10, and β-Cyclolipiferolide (1). BF_3·Et_2O-generated fraction B3 of A8, A9, and mother liquors of A10 crystallized from EtOAc–hexane to give 13.5 mg (0.9%) of allylic alcohol **4**. Fraction A16 crystallized from EtOAc–hexane to give 25 mg (1.7%) of β-cyclolipiferolide (1). α-Cyclolipiferolide (37.5 mg, 2.6%) was obtained after chromatography of fractions A11 through A13 on 25 g of silica gel 60 with EtOAc–hexane (7:13).

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Registry No. 1, 87308-17-6; 2, 41059-80-7; 3, 87282-29-9; 4, 87282-30-2; 5, 87282-31-3; 6, 87282-32-4; 7, 87282-33-5; 8, 87282-34-6; 9, 87282-35-7; 10, 87308-18-7; 11, 87282-36-8; 12, 87282-37-9; 13, 87282-38-0; $SOCl_2$, 7719-09-7; HCl, 7647-01-0; BF_3·Et_2O, 109-63-7; epitulipinolide, 24164-13-4.

(12) Because this compound could not be crystallized and decomposed above 15 °C especially during evaporation to dryness, special precautions were required in collecting the physical data. Handling of the concentrated solutions above 5 °C resulted in rapid loss, although dilute solutions at ambient temperature if manipulated quickly could be used to collect standard spectral data. An accurate estimation of yield for compound 10 was not possible but 26% was isolated in pure form. The MS was a dynamic measurement on a Kratos MS-30 instrument via direct inlet probe.

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