Erigerol, a New Labdane Diterpene from *Erigeron philadelphicus*

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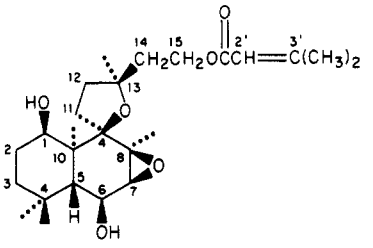
A new, highly oxygenated labdane diterpene, erigerol (1), has been isolated from *Erigeron philadelphicus* and its structure assigned on the basis of spectral data and X-ray crystallographic analysis. Erigerol is a 1,6-dihydroxy-7,8-epoxydihydrogrindelyl ester of 3,3-dimethylacrylic acid.

Introduction

Plants of the genus *Erigeron* (Compositae; tribe Astereae) have a history of folk medicine applications. In particular, the leaves of *E. canadensis* have been reportedly used to prepare a tonic efficient in the treatment of diarrhea, diabetes, and hemorrhages.[1,2] Early American settlers packed dried flower heads of *E. strigosus* into linens to repel fleas,[3] and, in fact, the roots of *E. affinis* contain an aliphatic amide possessing insecticidal properties.[4] Furthermore, an aqueous extract of *E. annuus* has been shown to lower blood sugar in experimental animals.[5] A related species, *Erigeron philadelphicus* L. (fleabane), has been shown to contain matricaria ester[6] and several common fatty acids.[7] This latter plant has not been extensively studied and came to our attention as a potential source of new bioactive compounds. In this paper, we report the isolation of a new labdane-class[8] diterpene from *E. philadelphicus*.

Results and Discussion

The methylene chloride extract of *E. philadelphicus*, upon further fractionation and silica gel chromatography, provided a 0.00033% yield of a crystalline compound, erigerol (1), mp 159–161 °C. Compound 1, $C_{25}H_{40}O_6$, *m/z*



1

436.277 ($M^{+}\cdot$), showed IR absorption at 3575, 3400 (OH), 1710 (ester carbonyl), and 1648 cm^{-1} (C=C), while its UV spectrum displayed intense end absorption near 210 nm. The mass spectrum of erigerol indicated a molecular ion at *m/z* 436 and major fragment ions at *m/z* 418 (M^{+} – H_2O), 295, 267, 254, and 83 (base peak). The base peak at *m/z* 83 is characteristic of the $^{+}O{=}CCh{=}C(CH_3)_2$ ion in dimethyl acrylate esters.[9] Minor fragment ions at *m/z* 336 ($M^{+}\cdot$ – $HOOCCH{=}C(CH_3)_2$) and 349 ($M^{+}\cdot$ – $O{=}CCH{=}C(CH_3)_2$) support this assignment. Erigerol forms a dihydro derivative having a corresponding mass spectrum: *m/z* 438 ($M^{+}\cdot$), 420($M^{+}\cdot$ – H_2O), 297, 269, 256, and 85 (base peak). The presence of at least one hydroxyl group was confirmed by the conversion of 1 into a monotrimethylsilyl derivative: *m/z* 508 ($M^{+}\cdot$), 368, 339, 83 (base peak). The complex nature of erigerol was further indicated by its ^{13}C NMR spectrum, which showed signals for all 25 carbon atoms grouped as follows: 193.5 ppm (C=O); 116 (C=C); 90.1, 84.9, 73.2, 68., 64.4, 64.2, 61.0 (CO); 45.5, 43.3, 41.8, 38.6, 36.1, 35.5, 33.9, 29.9, 28.1, 27.3, 26.7, 24.7, 23.5, 21.0, 18.9 (shielded C).

Table I. Dihedral Angles (deg) between Least-Squares Planes[a]

	1	2	3	4	5	6
1	0					
2	32.3	0				
3	28.1	45.7	0			
4	51.6	60.3	23.8	0		
5	78.4	75.0	89.2	74.3	0	
6	87.8	58.8	80.1	70.6	16.5	0

[a] The numbers in the table refer to the following planes: 1, all heavy atoms; 2, C(15), O(12A), C(1A), O(11A), C(2A), C(3A), C(4A), C(5A); 3, C(9), C(11), C(12), C(13), O(9); 4, C(7), C(8), O(7); 5, C(5), C(6), C(7), C(8), C(9), C(10); 6, C(1), C(2), C(3), C(4), C(5), C(10).

For determination of the complete molecular structure and sterochemistry of 1, a single-crystal X-ray structure determination was carried out. The results indicate that the compound is a new diterpene ester of the labdane[8] series. The crystal conformation, nomenclature used in the X-ray work, and bond lengths are shown in Figure 1 (ORTEP[10] drawing). The bond angles and some torsion angles are shown in Figure 2. The esd's of bond lengths are in the range 0.007–0.010 Å and esd's of bond angles are less than 0.5°. A table of least squares planes is given as Table I. The conformation of the diterpene moiety is as might be expected from the chemical structure with considerable distortion from ideal torsion angles for six-membered rings, but the C(1), C(2), C(3), C(4), C(5), C(10) ring is definitely in the chair conformation. The other ring is in the monoplanar conformation that Bucourt[11] indicates

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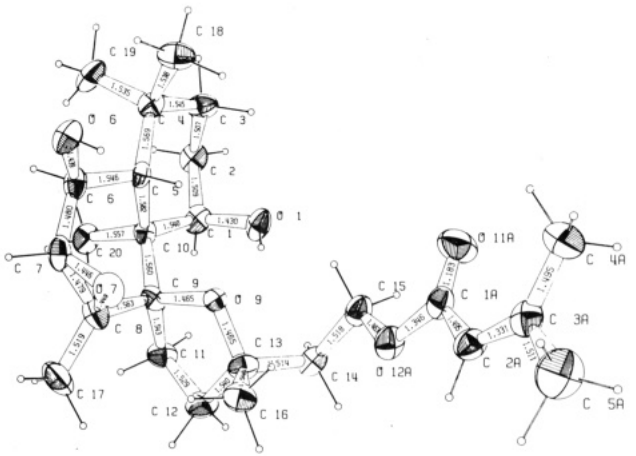
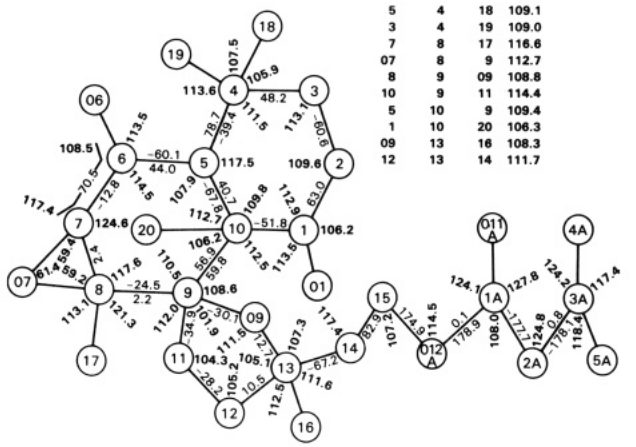


Figure 1. ORTEP[10] drawing showing crystal conformation, X-ray nomenclature, and bond lengths; esd's of lengths are in the range 0.07–0.01 Å. Absolute configuration is not implied.



5	4	18	109.1
3	4	19	109.0
7	8	17	116.6
07	8	9	112.7
8	9	09	108.8
10	9	11	114.4
5	10	9	109.4
1	10	20	106.3
09	13	16	108.3
12	13	14	111.7

Figure 2. Bond angles and torsion angles; esd's are <0.5° and <0.7°, respectively.

as most likely for a cyclohexene ring. The five-membered ring is a fairly good half-chair with conformational parameters[12] Φ_m of 35.71° and 4.11°. The observed conformation allows a close approach of O(1) to O(9) in the five-membered ring, and an intramolecular hydrogen bond is formed, perhaps accounting for the band at 3575 cm^{-1} in the IR. The appropriate dimensions are O(1)···O(9) 2.620 (5) Å, H(9)···O(1) 1.95 (5) Å, and O(1)–H(O1)···O(9) 146°. The two six-membered rings are trans fused and somewhat flatter than ideal as may be seen from the torsion angles. Most bond lengths are as might be expected with some long bonds at quaternary C atoms. The shortening of the bonds C(7)–C(6) and C(8)–C(17) is consonant with the partial sp^2 hydridization expected in a three-membered ring, but the normal stretching at a quaternary C atom appears to govern the C(8)–C(9) length. There can be no doubt that the C(2A)–C(3A) bond is a double bond. It is apparent from the structure that all of the oxygen functions are clustered on one side of the ring system, and this may have biological implications.

The molecular packing is shown in Figure 3 and appears to be fairly efficient. The most important factor seems to be the linking of the molecules along the *b* screw axis by an O(6)–H(O6)···O(1) hydrogen bond [O(6)···O(1) 2.819 (7) Å, H(O6)···O(1) 2.06 (5) Å, and O(6)–H(O6)···O(1) 146°]. Other interatomic distances correspond to van der Waals interactions.[13]

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Table II. 360-MHz Proton NMR Spectrum of Erigerol (1) ($CDCl_3$)

assignment	δ (Me_4Si)	J, Hz
H-1	3.89 br d	
1-OH	5.44	
H-2, H-3	2.0–2.4 complex	
4-CH_3	1.05, 0.86	
H-5	1.78 d	10
H-6	4.08	4.5, 10, 12
6-OH	1.67 d	12
H-7	3.19 d	4.5
8-CH_3	1.45	
10-CH_3	1.16	
H-11, H-12	1.5–1.7 br	
13-CH_3	1.49	
H-14	2.05 complex	
H-15	4.18 complex	
H-2′	5.68 complex	
4′-CH_3	2.18 d	1.5
5′-CH_3	1.90 d	1.5

The intramolecular hydrogen bond revealed in the crystal structure between the 1-OH and the tetrahydrofuran oxygen may account for the failure of **1** to form a bis(trimethylsilyl) ether derivative as discussed above. Indeed, in flavonoid natural products, phenolic hydroxyls involved in strong intramolecular hydrogen bonds react at reduced rates with silylating reagents.[14]

With the structure and relative stereochemistry of erigerol defined by X-ray analysis, the 360-MHz proton NMR spectrum ($CDCl_3$) becomes interpretable and is summarized in Table II. Upon addition of D_2O, the hydroxyl signals at δ 5.44 and 1.67 disappear and the δ 4.08 multiplet (H-6) simplifies to a doublet of doublets as expected for coupling to H-5 and H-7. These relationships are further revealed by spin-decoupling experiments. Irradiation at the 6-OH frequency does not affect the H-7 or H-5 doublets but causes the H-6 multiplet to become a doublet of doublets. The dimethylacrylate moiety responds normally toward spin decoupling; the 4′- and 5′-CH_3 doublets become singlets upon irradiation at the H-2′ frequency and the H-2′ multiplet becomes a quartet upon irradiation at either the 4′- or 5′-CH_3 frequency. Irradiation at δ 2.05 (14-CH_2) causes the complex 15-CH_2 signal at δ 4.18 to become an AB quartet.

Erigerol (**1**) is a 1,6-dihydroxy-7,8-epoxydihydrogrindelyl ester of 3,3-dimethylacrylic acid and is related to the grindelane diterpene acids, many of which show significant activity as feeding deterrents toward aphids.[15] The occurrence of a grindelane diterpene in *Erigeron* is taxonomically consistent with the recent isolation of other members of this natural product class from other Compositae of the tribe Astereae.[16]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Column chromatography was done on Baker Analyzed Reagent silica gel, 40–140 mesh. Eastman chromatogram sheets (Kodak 13179 silica gel) were used for thin-layer chromatography. The TLC solvent system was 20% acetone in chloroform, and chromatograms were visualized by UV light and iodine. Mass spectra were obtained by direct insertion probe on an LKB-9000 spectrometer (source 270 °C, 70 eV, 50

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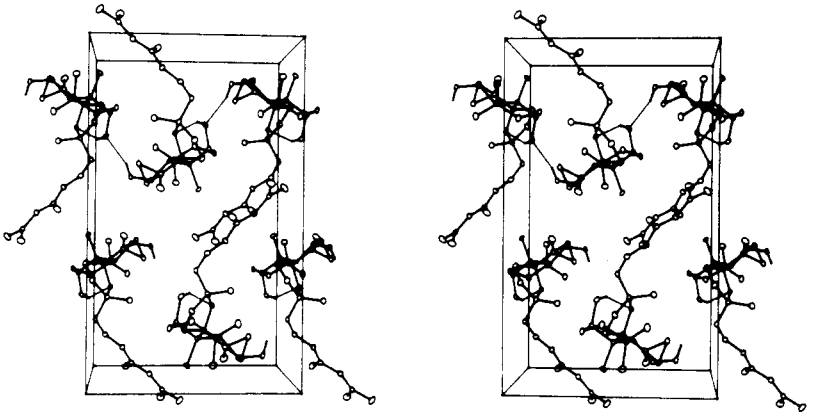

Figure 3. ORTEP[10] drawing showing crystal packing and hydrogen bonds.

μamp ionizing current). Infrared spectra were run in $CDCl_3$ with a Perkin-Elmer Model 1420 spectrometer. NMR were run on a Nicolet-NTC-360 wide-bore spectrometer using a Nicolet 1180 computer and 293B pulse programmer. ^1H spectra were run in $CDCl_3$ with using Me_4Si internal reference at 361.045 MHz with a pulse of 10 μs (90 flip) with a s delay between pulses. Quadrature detection was employed with sweep width ±1923 Hz and exponential filtering giving a line broadening factor of 0.2 Hz.

Plant Material. *Erigeron philadelphicus* L. (Compositae) was collected in April 1972, on Signal Mountain, Tn, and stored dry. This plant was identified by Dr. Gene S. Van Horn, Department of Biology, UT–Chattanooga, and a voucher specimen (no. EP-SM472-TW) is on file in the UTC herbarium, Chattanooga, Tn.

Extraction of *E. philadelphicus*. A 1.50-kg portion of the dried, aerial parts of *E. philadelphicus* was ground in a Wiley mill (Model 4) fitted with a 2-mm screen. The powdered plant material was extracted with methylene chloride for 3 days by using a Soxhlet apparatus, and the extract was evaporated to dryness in vacuo, leaving a dark green tar. This extract was dissolved in 150 mL of hot ethanol, whereupon 375 mL of hot water was added. The resulting mixture was stirred for 15 min at 75 °C and refrigerated. After 7 days, the mixture was filtered through Celite and the clear amber solution was extracted with five 150-mL portions of chloroform. The combined chloroform extract was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness in vacuo to give 3.5 g of a dark, amber oil.

This extraction procedure has been shown to concentrate sesquiterpene lactones,[17] which are common in many Compositae genera.[18] In the present study, the final *E. philadelphicus* extract lacked the characteristic γ-lactone infrared absorption, indicating the absence of significant quantities of sesquiterpene lactones.

Isolation of Erigerol (1). The foregoing dark amber oil (3.5 g) was chromatographed on a column of silica gel (2.5 × 33 cm), eluting sequentially with 1:1 chloroform–hexane (300 mL), chloroform (460 mL), 1:9 acetone–chloroform (360 mL), and 1:5 acetone–chloroform (280 mL). Fractions of 20 mL each were collected and combined according to TLC analysis. Combined fractions 23–43 deposited crystalline erigerol (1), 5 mg, mp 159–161 °C, after recrystallization from ethanol. Compound 1 showed a single, circular spot on TLC: R_f 0.80; IR ($CHCl_3$) 3575, 3400, 1710, 1648, 1448, 1422, 1380, 1350, 1230, 1150, 1100, 1080, 1015, 1000, 860 cm^{-1}; MS, *m/z* (relative intensity) 436, (1.8, $M^{+\cdot}$), 418 (4), 349 (1.0), 336 (1.0), 295 (17), 267 (7), 254 (7), 185 (8), 172 (7), 167 (8), 151 (8), 139 (9), 127 (7), 123 (8), 111 (9), 109 (11), 95 (9), 85 (9), 83 (100), 82 (10), 81 (17), 69 (11), 55 (17), 43 (21), 41 (9). The NMR spectra of 1 are described in the Results and Discussion section and in Table II.

Dihydroerigerol. Approximately 50 μg of erigerol was dissolved in 100 μL of ethanol; about 0.5 mg of platinum oxide was added and hydrogen bubbled through the suspension for 10 min. The solution was then filtered with a micropipette and the ethanol evaporated: mp 110–111 °C; MS, *m/z* (relative intensity) 438 (9, $M^{+\cdot}$), 420 (22, $M^{+\cdot} - 18$), 405 (1), 297 (48), 269 (36), 256 (39), 185 (52), 172 (41), 167 (42), 151 (33), 139 (50), 127 (62), 123 (35), 111 (54), 109 (55), 97 (33), 95 (40), 85 (100), 81 (75), 69 (62), 57 (66), 55 (41), 43 (96), 41 (45).

Table III. Atomic Parameters for the Heavier Atoms[a]

atom	*x*	*y*	*z*	*U*
C(1)	5281 (5)	5869 (5)	6947 (3)	40 (2)
O(1)	5454 (4)	5647 (4)	7671 (2)	49 (2)
C(2)	3931 (6)	6211 (5)	6868 (3)	41 (2)
C(3)	3099 (5)	5254 (5)	7098 (3)	44 (2)
C(4)	3276 (5)	4167 (4)	6663 (2)	35 (2)
C(5)	4693 (5)	3861 (4)	6581 (2)	25 (2)
C(6)	4926 (5)	2985 (4)	5998 (3)	37 (2)
O(6)	4277 (4)	1934 (3)	6102 (2)	42 (2)
C(7)	6259 (6)	2734 (5)	5866 (3)	42 (2)
O(7)	6998 (4)	2333 (3)	6447 (2)	46 (1)
C(8)	7313 (5)	3415 (5)	6133 (3)	47 (2)
O(9)	7086 (3)	4078 (3)	7341 (1)	29 (1)
C(9)	6998 (5)	4442 (4)	6614 (2)	32 (2)
C(10)	5644 (5)	4870 (4)	6474 (2)	30 (2)
C(11)	8008 (6)	5371 (5)	6578 (3)	44 (2)
C(12)	9031 (6)	4957 (6)	7070 (3)	48 (2)
C(13)	8354 (4)	4222 (4)	7613 (3)	40 (2)
C(14)	8246 (6)	4820 (5)	8308 (3)	39 (2)
C(15)	7359 (6)	4318 (5)	8841 (3)	47 (2)
C(16)	8951 (6)	3038 (6)	7693 (4)	49 (2)
C(17)	8514 (7)	3377 (8)	5714 (4)	69 (3)
C(18)	2617 (6)	3219 (6)	7070 (4)	52 (3)
C(19)	2590 (8)	4303 (8)	5967 (4)	59 (3)
C(20)	5640 (7)	5335 (6)	5716 (3)	45 (2)
C(1A)	7393 (6)	2921 (5)	9721 (3)	46 (2)
O(11A)	6380 (4)	3199 (4)	9897 (2)	59 (2)
O(12A)	8026 (3)	3402 (3)	9193 (2)	46 (1)
C(2A)	8176 (6)	1986 (5)	10010 (3)	44 (2)
C(3A)	7835 (6)	1308 (5)	10529 (3)	44 (2)
C(4A)	6593 (8)	1354 (9)	10882 (5)	72 (3)
C(5A)	8757 (10)	433 (8)	10784 (5)	84 (4)

[a] Positional parameters are multiplied by 10^4 and thermal parameters by 10^3. The *U* value quoted is the geometric mean of the diagonal terms of the vibration tensor.

Erigerol mono(trimethylsilyl) ether was prepared from 50 μg of erigerol, using an excess of bis(trimethylsilyl)trifluoroacetamide as solvent. After heating (sealed vial at 100 °C for 15 min), part of the solution was transferred to the direct insertion probe of the mass spectrometer and excess reagent evaporated in the vacuum housing prior to insertion into the ion source. Only a monotrimethylsilyl derivative formed; MS, *m/z* (relative intensity) 508 (43, $M^{+\cdot}$) 493, ($M - CH_3$), 368 (12), 339 (33), 267 (12), 242 (7), 239 (9), 227 (11), 221 (10), 185 (9), 159 (24), 143 (14), 139 (12), 109 (14), 83 (100), 81 (20), 75 (15), 73 (35), 69 (14), 55 (17), 43 (22).

X-ray Structure Determination of Erigerol. Crystallographic data: $C_{25}H_{40}O_6$, M_r 436.56; space group, $P2_12_12_1$; diffractometer, Enraf-Nonius CAD-4; radiation, Cu Kα (graphite monochromator); wavelength 1.5418 Å; cell dimensions from least-squares refinement of ±θ data, a = 10.714 (1) Å, b = 11.821 (1) Å, c = 19.216 (2) Å, V = 2433.7 Å^3; D_x = 1.191 g/cm^3; Z = 4;

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sin $/\lambda$(max), 0.6225 Å^{-1}; 2788 reflections (761 with $I < \sigma(I)$); function minimized, $\sum w\Delta^2$; R, 0.076.

The amount of erigerol available was very small, and it was not possible to prepare large crystals. The only crystal of any practical size (prepared by slow evaporation of a chloroform solution) had dimensions 0.3 × 0.1 × 0.03 mm, and this was used for all X-ray measurements. Since it could not be determined whether radiation damage would cause problems and finding another suitable crystal would be difficult, the intensity data were collected rapidly, allowing a constant time of 30 s for each reflection. In retrospect, a longer counting time would have been possible since there was no evidence of radiation damage, but the data proved adequate for structure solution and refinement. The remainder of the sample was used for spectroscopic experiments, and thus the crystal density was not measured.

The phase problem was solved by the use of programs of MULTAN78[19] and was conducted in parallel by means of the standard convergence method and also by a Monte Carlo method similar to that described by Yao.[20] In contrast to Yao's prescription, all phases generated randomly were given the same weight, and, to avoid prejudicing the course of the calculation, neither the origin nor the enantiomorph were directly specified. As a result of this structure determination and several others, we find ourselves in opposition to Hall and Subramanian[21] who recently stated "it is particularly important that the Monte-Carlo aspects of the multisolution approach are minimized".

The model was refined by using the programs of XRAY72,[22] and all hydrogen atoms were visible in a difference map. The final R factor, using anisotropic parameters, $\exp(-2\pi^2(\sum_i\sum_j U_{ij}a_i^*a_j^*h_ih_j))$, for the heavier atoms and isotropic parameters for the H atoms, was 7.6%. The R factor is quite satisfactory considering the less-than-optimum X-ray intensity data, and, although the esd's of the H atom thermal parameters are fairly large, the results are quite adequate. The atomic parameters for the heavier atoms are given in Table III, and the observed and calculated structure factors were submitted to the referees and may be obtained from J.V.S.

Acknowledgment. This paper is dedicated to Dr. Ulrich Weiss, NIADDK, NIH, on the occasion of his 75th birthday. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. We are grateful to Dr. Robert Highet for valuable discussions regarding NMR spectra.

Registry No. 1, 87462-32-6; dihydroerigerol, 87462-33-7; erigerol trimethylsilyl ether, 87507-93-5.

Supplementary Material Available: Tables of atomic parameters for all atoms of erigerol (2 pages). Ordering information is given on any current masthead page.

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General Method of Synthesis of Cyclopentanoid Terpenic Acids. Stereocontrolled Total Syntheses of (±)-Isocomenic Acid and (±)-Epiisocomenic Acid

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(4β,8α)-1α,2,4β-Trimethyl-9α-carboxytricyclo[6.3.0.0^{4,8}]undec-2-ene (**1**, isocomenic acid) and (4β,8α)-1α,2,4β-trimethyl-9β-carboxytricyclo[6.3.0.0^{4,8}]undec-2-ene (**28**, epiisocomenic acid) were prepared in 10 steps from ester **13**. The internal cyclopropanation of exocyclic acrylates and the subsequent vinylcyclopropane–cyclopentene rearrangement were used in an efficient synthesis of a key intermediate, triquinane **23**, containing all of the contiguous quaternary centers. The utilization of abnormal Reformatsky reaction of 4-bromocrotonates with keto esters served in the preparation of important precursors to the cyclopentene annulation sequence, the lactone **15**, and the dienic acid **19**. Hydrogenation of **23** produced the keto ester **25a**, which was converted in three steps to *either 1 or 28* with complete control of stereochemistry. Carbon-13 data are reported for all intermediates. A total of eight natural products are accessible in a stereocontrolled fashion from keto ester **25a**. The generality of this method is thus addressed in the context of system-oriented design of synthesis of cyclopentanoid terpenes.

Introduction

Terpenoid carboxylic acids containing at least one cyclopentane ring are being isolated in increasing numbers from sources within either the plant or the animal kingdom. Among the better known examples are gibberellic and gascardic acids, zizanoic acid (**2**), retigeranic acid (**3**), and hirsutic acid (**4**). With the exception of sesterterpene **3**, all of these acids became available through the chemical synthesis shortly after their isolation.[2]

We pursued the design of a method that could be applied not only to the synthesis of all or most of the cyclopentanoid acids but also to the parent hydrocarbon

(1) (a) Fellow of the Alfred P. Sloan Foundation, 1981–3. (b) Work done at I.I.T. Chicago, by J. M. R., on leave from the University of Grenoble, France.

(2) See the following for representative syntheses. **Gibberellic Acid**: Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Grass, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8034. Lombardo, L.; Mander, L. N.; Turner, J. V. *Ibid.* **1980**, *102*, 6626. Hook, J. M.; Mander, L. N.; Urech, R. *Ibid.* **1980**, *102*, 6628. **Gascardic Acid**: Boeckman, R. K., Jr.; Blum, D. M.; Arthur, S. D. *Ibid.* **1979**, *101*, 5060. **Zizanoic acids/khusane-type terpenes**: Oppolzer, W.; Pitteloud, R. *Ibid.* **1982**, *104*, 6478. Liu, H. J. *Can. J. Chem.* **1982**, *60*, 1081. Vettel, P. R.; Coates, R. M. *J. Org. Chem.* **1980**, *45*, 5430. Piers, E.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 1138. **Retigeranic acid**: The triquinane portion of this molecule has been synthesized. See ref 5 also for compliation of isolation and structure retermination.

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