Tetrahedron Vol 32, pp. 1335 to 1338. Pergamon Press 1976 Printed in Great Britain

CYCLIZATION OF METHYL 6,7-EPOXYCITRONELLATE TO METHYLCYCLOPENTANE DERIVATIVES

ALKOXIDE INDUCED CONVERSION OF γ-LACTONES TO γ,δ-UNSATURATED ACIDS[1]

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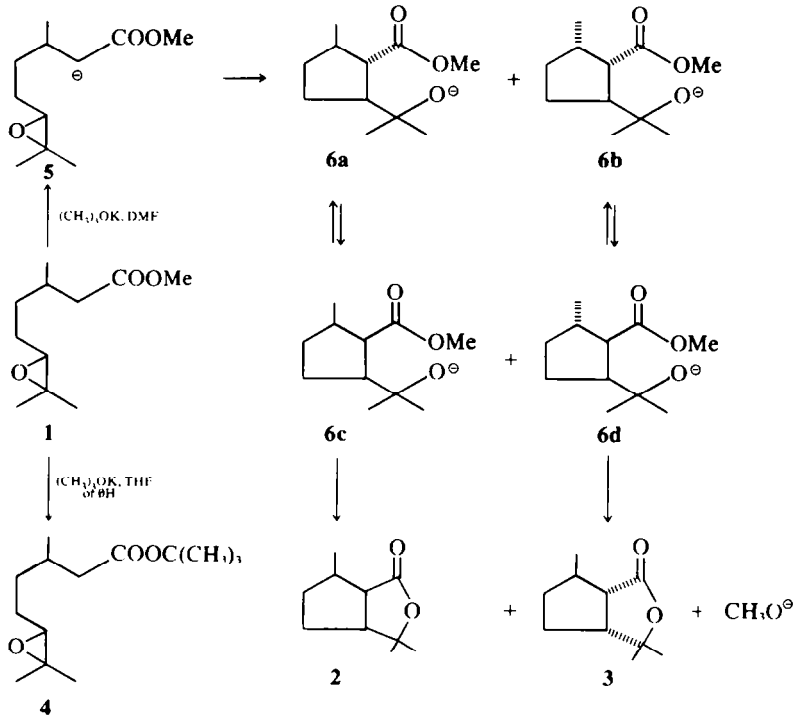
(*Received in USA* 8 *September* 1975; *Received in UK for publication* 16 *January* 1976)

Abstract—The reaction of sodium hydride or potassium t-butoxide with methyl epoxycitronellate (**1**) in dimethylformamide affords a mixture of *cis,cis*-puleganolide (**2**) and *cis,trans*-puleganolide (**3**) in high yield. When the cyclization is conducted at 110°, the isomeric 2-isopropenyl-5-methylcyclopentanecarboxylic acids (**8a-d**) become the major products. It is demonstrated that γ-lactones undergo alkoxide-induced elimination to afford γ,δ-unsaturated acids.

In the present work we consider the question of whether monoterpene epoxides might serve as synthetic intermidiates for methylcyclopentane monoterpenes (iridoids).[4] Since the action of acids on various epoxides derived from citral, geraniol, and methyl geranate[2] failed to give methylcyclopentane derivatives, we turned our attention to a study of the base-catalyzed cyclization of methyl 6,7-epoxycitronellate (**1**).

occured to afford t-butyl 6,7-epoxycitronellate (**4**) as the sole product.

Cyclization of anion **5** should lead to the four alkoxyesters **6a-d**. In the case of **6c** and **6d** intramolecular transesterification accompanied by loss of methoxide ion generates lactones **2** and **3**. The higher strain energy in the *trans*-lactones which might conceivably be derived from **6a** and **6b** preclude their formation. Alkoxides **6a** and **6b**



Methyl 6,7-epoxycitronellate (**1**) was transformed, in 80–85% isolated yield, to a mixture of *cis,cis*-puleganolide[7] (**2**; *ca.* 53%) and *cis,trans*-puleganolide[7] (**3**; *ca.* 47%) when treated with sodium hydride or potassium t-butoxide in DMF at 25° for 20 hr. Sodium methoxide in DMF at ambient temperature had no effect on epoxide **1**, and even at 60° cyclization to the mixture of lactones **2** and **3** was slow. Cyclization did not occur with potassium t-butoxide in benzene or THF. Instead, transesterification

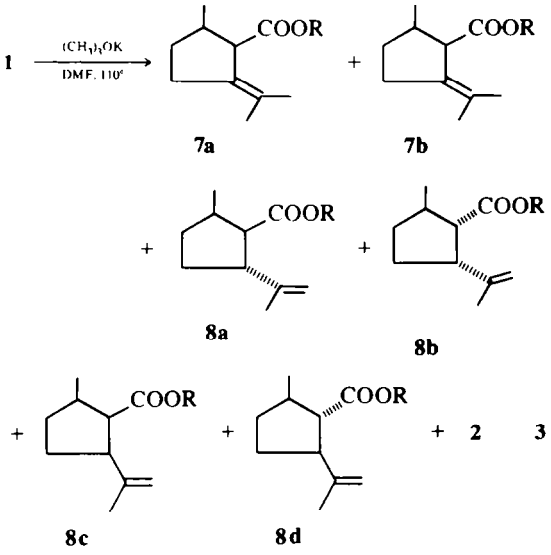
can, however, undergo epimerization to **6c** and **6d**, respectively, which in turn convert to **2** and **3**.

A surprisingly different array of products was obtained when epoxide **1** was heated at 110° with potassium t-butoxide in DMF. The yield of neutral lactones **2** and **3** dropped to 25%, with the proportion of **2** rising to 73% and that of **3** dropping to 27%. In addition, a mixture of unsaturated acids **7a-b**[7] and **8a-d**[8] was obtained in 70–73% isolated yield (Table 1). Since the acids showed a

Table 1. Cyclization of epoxyester 1. Effect of base and temperature

Base	Time (temp.)	Cyclization products Yield	Neutrals	Acids	2	3	7a	7b	8a	8b	8c	8d
KOtBu	20 hr (25°)	82%	100%	0	52.7	47.3	0	0	0	0	0	0
NaH	24 hr (25°)	85%	100%	0	52.1	47.9	0	0	0	0	0	0
KOtBu	1 hr (110°)	94%	25%	75%	73.2	26.8	3.8	3.3	0.8	58.5	30.5	3.1
NaH	2 hr (140°)	32%	89%	11%	53.1	46.9	2.6	4.2	3.2	44.2	32.9	12.8

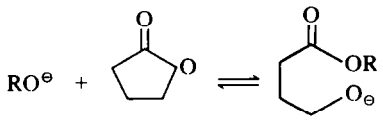
tendency to lactonize to **2** and **3**, it was advantageous to esterify the crude acid fraction with diazomethane and carry out separations and analyses with the stable methyl esters. It should be noted that the overall yield of methylcyclopentane monoterpenes in this cyclization is well over 90%.

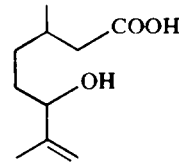


Cyclization of **1** with sodium hydride in DMF at 140° proved to be even more complicated; in addition to the neutral and acidic products mentioned above, the allylic alcohol **9** and at least six other unidentified products were formed. The marked difference in behavior of sodium hydride at elevated temperature is attributed to its reaction with DMF affording carbon monoxide and sodium dimethylamide.[9] Sodium diethylamide is known to convert epoxides to allylic alcohols.[10]

Unsaturated acids **7a, 7b** and **8a-8d** are formed in the reactions conducted at higher temperature by the action of alkoxides[11] on lactones **2** and **3**. The utility of this elimination reaction has been demonstrated by the

†Transesterification must also occur with lactones, however, the alkoxy esters (i) should readily reconvert to the original lactone which can eventually undergo an irreversible elimination reaction to give the salt of an unsaturated acid.





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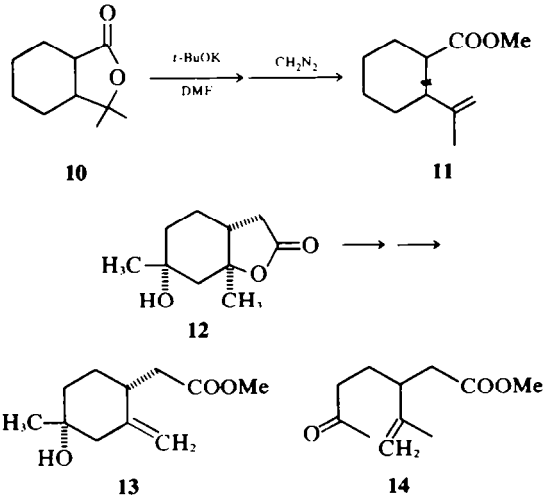
conversion of lactones **2** and **3** into unsaturated acids **8c** and **8b**, respectively, in high yield, and the further conversion of these unsaturated acids into dihydronepetalactones.[12] In order to obtain a clean stereochemical result[13] it is essential to avoid the use of an excess of alkoxide (see Table 2) since the excess base not only promotes epimerization (**8b** converting to **8a** and **8c** converting to **8d**), but also results in double bond migration to afford the pulegenic acids **7a** and **7b**.

It is of interest to note that these side reactions pose a greater problem in the *cis,cis*-series, apparently due to the more facile approach of base to the non-shielded *alpha* hydrogen.

The base-induced elimination of γ-lactones to γ,δ-unsaturated carboxylic acids appears to be a general synthetic transformation[14,15] and is illustrated by the conversions of **10** to **11** and of **12** to a mixture of **13** and **14**. In the latter example, elimination competes with a Grob type fragmentation.



The action of potassium t-butoxide on terpinyl acetate, 2-octyl acetate and 2-octyl mesitoate resulted in transesterification and the formation of α-terpineol and 2-octanol, suggesting that the reaction is limited to lactones.† A more detailed survey of the scope of the

Table 2. Reaction of puleganolides 2 and 3 with alkoxides. Effect of excess base

Base (lactone)	Base/lactone ratio	Material balance	Recov'd. lactone	Unsat'd. acids	Product distribution, acidic fraction (%)[a] 7a	7b	8a	8b	8c	8d	Unidentified
KOtBu (2)	0.88	97.9	29	71	8.9	1.5	0	0	86.1	3.5	0
KOtBu (2)	1.00	94.4	15	85	14.6	11.8	0	0	63.4	10.2	trace
KOtBu (2)	1.20	92.8	0	100	9.8	43.9	0	0	1.4	28.2	16.7
NaOMe (3)	1.02	93.7	38	62	1.6	2.8	3.2	90.3	0	0	2.1
NaOMe (3)	1.23	97.9	10	90	2.1	7.2	16.6	72.8	0	0	1.2
KOtBu (3)	0.97	93.6	21	79	1.1	4.5	0.5	92.5	0	0	1.4
KOtBu (3)	1.20	93.5	0	100	2.9	20.8	3.6	72.7	0	0	trace

elimination reaction of lactones will be presented in a later publication.

In summary, it has been shown that the cyclization of epoxyesters[16] provides a simple and convenient method for the construction of iridoids. The epoxide cyclization presents a viable alternative to the currently accepted "Robinson" biosynthetic pathway to iridoids. We hope to test this hypothesis in the future.

EXPERIMENTAL

B.ps are uncorrected. All solvents were dried by distillation from calcium hydride. All reactions were conducted under a N_2 atmosphere. IR spectra were recorded with a Perkin–Elmer infracord. NMR spectra were determined at 60 MHz with a Varian Associates A-60A spectrometer. Mass spectra were measured on a Hitachi RMU-6A spectrometer employing an ionization energy of 70 eV, an inlet temp. of *ca.* 185°, and a source temperature of 160°. Microanalyses were performed by Dr. C. S. Yeh and associates.

Methyl 6,7-epoxycitronellate (**1**). A soln of 29.96 g (0.163 mol) of methyl citronellate in 50 ml of methylene chloride was added dropwise to a stirred ice-chilled soln of 37 g (0.182 mol) of *m*-chloroperbenzoic acid (85%) in 500 ml methylene chloride. The mixture was stirred for 24 hr and the precipitated *m*-chlorobenzoic acid was removed by filtration. The methylene chloride soln was washed with 10% Na_2SO_3aq until the organic layer gave a negative test with starch-iodide paper. The soln was then extracted with sat $NaHCO_3$aq until no ppt was produced upon acidification of the extract. The soln was dried ($MgSO_4$), and evaporated to give 31.5 g (96.7%) of **1**, b.p. 73–75° (0.40 mm): IR (neat) 5.72 μ NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 6 Hz, CH_3CH–), 1.25 and 1.28 (2s, 6 H, CH_3–C–CH_3), 1.37–1.77 (m, 4 H), 1.77 – 2.4 (m, 3 H), 2.5–2.8 (m, 1 H) and 3.65 ppm (s, 3 H, –OCH_3). Examination of the crude epoxyester via GLC (5′ × 1/4″, 20%SE-30, column at 135°, injector temp. 150°) showed a single component with retention time of 8.5 min. (Decomposition of the epoxyester occurred when a higher (210°) injector temp. was used.)(Found: C, 65.75; H, 10.29. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%).

Attempted cyclization of (**1**)

(a) *Potassium t-butoxide in refluxing benzene.* A soln of 1.11 g (9.94 mmol) of t-BuOK and 1.10 g (5.48 mmol) of **1** in 35 ml dry benzene was heated at reflux for 2 hr. After cooling to room temp. the mixture was poured into 30 ml ice-cold 5% HCl covered with 50 ml ether. The organic layer was separated and the aqueous layer was extracted with ether. The ether solution was washed with 10 ml water, dried ($MgSO_4$) and evaporated to give 1.08 g of yellow liquid. Examination of this liquid by GLC (5′ × 1/4″, 20% SE-30, 160° col., 160° inj.) indicated a mixture of 8.2% recovered epoxyester **1** and 91.8% (76% yield) of **4**. An analytical sample **4** was obtained by GLC and displayed IR (neat) 5.77 μ; NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 6 Hz, CH_3–CH–), 1.27 and 1.31 (2 s, 6 H, CH_3–C–CH_3), 1.45 (s, 9 H, $(CH_3)_3C$–), 1.4–1.9 (broad, m, 2 H), 1.9–2.3 (m, 4 H), and 2.3–2.8 ppm (broad m, 2 H); MS *m/e* (relative intensity) 184 (1), 123 (25), 57 (100). (Found: C, 69.62; H, 11.00. Calcd for $C_{14}H_{26}O_3$: C, 69.39; H, 10.81%.)

(b) *Potassium t-butoxide in THF at* 25°. When a soln of 821 mg (7.33 mmol) of t-BuOK and 1.46 g (7.29 mmol) of **1** in 35 ml dry THF was kept for 5 hr at 25° and then worked up as described above there was obtained 1.45 g of yellow liquid. Analysis by NMR and GLC indicated the presence of 34.2% of **1** and 65.8% of **4**.

Cyclization of methyl 6,7-epoxycitronellate (**1**)

(a) *Potassium t-butoxide at room temp.* To a soln of 1.01 g (9.02 mmol) of t-BuOK in 35 ml dry DMF was added 1.184 g (5.92 mmol) of **1** at room temp. The soln immediately turned a cloudy yellow. Stirring was continued for 20 hr and the reaction was quenched by pouring into 30 ml ice-cold 5% HCl covered with 50 ml ether. The ether was separated and the aqueous layer extracted with ether. The ether soln was washed with water, dried ($MgSO_4$) and evaporated to give 811 mg of crude product (82%): IR (neat) 5.65 μ; NMR ($CDCl_3$) δ 1.38 (s, –O–$C(CH_3)_2$), 1.15 (d, J = 6.5 Hz, CH_3CH– in **3**) and 1.20 ppm (d, J = 7.0 Hz, CH_3CH– in **2**). GLC comparison with authentic samples[7] established that the product was a mixture of 52.7% *cis,cis*-**2**, and 47.3% *cis,trans*-**3**.

(b) *Potassium t-butoxide in DMF at* 110° A soln of 556 mg (4.97 mmol) of t-BuOK and 1.03 g (5.15 mmol) of **1** in 35 ml dry DMF was stirred for 1 hr at 25° and then heated at 110° for 1 hr. The mixture was cooled to 0° and then quenched by pouring into ice-cold 5% HCl covered with 50 ml ether. The ether was removed and the aqueous phase extracted with ether. The ether was washed with water, dried ($MgSO_4$) and evaporated to give 811 mg of crude product (94%). Examination by NMR indicated a mixture of **2** and **3** and unsaturated acids **7a**, **7b**, **8a-d** (R = H) (Signals at 1.39, 4.71–4.88 and 10.65 ppm). Integration of the –COOH signal (10.65 ppm) and the –O–$C(CH_3)_2$ signal (1.39 ppm) suggested the presence of a mixture composed of 75% acids and 25% lactones. Further comparison of the integration of the –COOH signal with the $=CH_2$ signal (4.71–4.88 ppm) suggested that of the unsaturated acids present approximately 90% contained a terminal methylene group.

The crude product was dissolved in ether and extracted with $NaHCO_3$aq. The residual ether soln was dried ($MgSO_4$) and evaporated to give 189 mg of neutral material. GLC analysis (12′ × 3/8″, 15% Carbowax 20M TPA, 165° column) established that the neutrals consisted of 73.2% **2** and 26.8% **3**.

The $NaHCO_3$ extracts from above were chilled to 0°, covered with 50 ml of ether, and acidified by the dropwise addition of ice-cold 5% HCl until pH 1 was reached. The aqueous phase was extracted with ether and the combined ether extracts were dried ($MgSO_4$) and evaporated to give 589 mg of acidic material; NMR ($CDCl_3$) δ 1.07 (d, CH_3CH–), 1.78 (m, CH_2=C–CH_3 and $=C(CH_3)_2$), 4.70–4.88 (m, $=CH_2$) and 11.10 ppm (s, –COOH).

The acids were treated with excess diazomethane in ether and

the methyl esters **7a**, **7b**, **8a-d** (R = CH_3) were analyzed on a 150' × 0.01" I.D. OS-138 column at 120°. Results of this analysis are given in Table 1.

(c) *Sodium hydride in DMF at* 25°. Epoxyester **1** (1.298 g, 6.49 (mmol)) was added dropwise to a stirred slurry of 297 mg (12.38 mmol) of NaH in 35 ml dry DMF. The mixture was stirred for 20 hr at room temp. and then quenched by pouring into 30 ml ice-cold 5% HCl covered with 50 ml ether. Extraction of the aqueous phase with ether followed by drying and evaporation of the solvent gave 924 mg crude product (85%). NMR analysis indicated a mixture of lactones **2** and **3** plus a trace of unreacted **1**. GLC ananylis (15%Carboxwax 20 M column at 165°) indicated the presence of 51.1% **2** and 47.9% **3**.

(d) *Sodium hydride in DMF at* 140°. A slurry of 582.6 mg (24.3 mmol) of NaH in 25 ml dry DMF was heated to 140° and 2.51 g (12.5 mmol) of **1** dissolved in 15 ml DMF was added dropwise. Initially the temp. rose above 140° but eventually stabilized in the range 134–138°. The mixture was stirred for 2 hr and then worked up in the usual manner. The ether soln was extracted with sat $NaHCO_3$aq and the ether was dried ($MgSO_4$) and evaporated to give 600 mg neutral material. Examination by IR (5.65 μ) and GLC comparison with authentic samples established that the neutral fraction consisted of 53.1% *cis,cis*- **2** and 46.9% *cis,trans*- **3**.

The $NaHCO_3$- extracts were covered with ether, chilled to 0°, and brought to pH 1 by dropwise addition of 5% HCl from a buret. The aqueous phase was extracted with ether and the ether extracts were dried ($MgSO_4$) and evaporated to give 1.136 g acidic material (IR: broad 3–4 μ and 5.85 μ). The acids were converted to the methyl esters with excess ethereal diazomethane. Analysis by GLC (20% DC-200 column at 205°) showed a complex mixture containing 38.8% of **9** and 7.9% of a mixture of **7a**, **7b**, **8a-d** (R = CH_3).

9 showed a retention time of 11.5 min, IR (neat) 2.95, 5.77, 6.08 and 11.2 μ; NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 6.5 Hz, CH_3CH–), 1.72 (m, 3 H), 3.65 (s, 3 H, $-OCH_3$), 4.03 (t, 1 H, J = 6 Hz, $-CH_2-CH-$) and 4.8–5.0 ppm (m, 2 H, $C=CH_2$).

A sample of the mixture of **7a**, **7b**, **8a-d** was collected via GLC on DC-200. This mixture was successfully separated on a 150' × 0.01" I.D. OS-138 column at 120°. Results of this analysis are given in Table 1.

Reaction of puleganolides **2** *and* **3** *with alkoxides in DMF.* The lactone (1.0–1.3 g, 5.95–7.73 mmol) in 5 ml of DMF was added to hot DMF containing 0.88–1.23 equivalent of alkoxide (Table 2). The mixture was heated at 140–144° for 4 hr, cooled to room temp., and quenched by pouring into 50 ml ice covered with 50 ml ether. The ether was removed and the aqueous phase extracted with ether. The ether was washed, dried ($MgSO_4$) and evaporated to give a neutral fraction consisting only of recovered lactone.

The aqueous phase from above was covered with ether, chilled to 0°, and brought to pH 5 with 5% HCl. The aqueous phase was extracted with ether and the ether extracts washed, dried ($MgSO_4$) and evaporated to give an acidic fraction consisting of a mixture of **7a-b** and **8a-d** (R = H), IR (neat) broad 3–4, 5.86, 6.08 and 11.2 μ; NMR ($CDCl_3$) δ 4.78 ($=CH_2$) and 11.67 ppm (–COOH).

The acids were treated with excess ethereal diazomethane and **7a-b** and **8a-d** (R = CH_3) were analyzed on a 150' × 0.01" I.D. OS-138 column at 120°. Results of these analyses are given in Table 2. Spectral properties of esters **8a-d** are given in Table 3.

Methyl 2-isopropenylcyclohexanecarboxylate (**11**). A soln of 1.0 g (6 mmol) of **10**[17] and 1.0 g (9 mmol) of t-BuOK in 30 ml dry DMF was refluxed for 1 hr and poured into 200 ml sat. salt soln. The mixture was extracted with ether and the ether soln was dried ($MgSO_4$) and evaporated to give 74 mg of an oil which appeared to be largely unaltered lactone.

The original aqueous soln was acidified with 10% HCl and extracted with ether. The ether soln was dried ($MgSO_4$) and evaporated to give 847 mg of unsaturated acid; IR 5.82, 6.05 and 11.10 μ; NMR δ 4.71 ($C=CH_2$) and 11.80 ppm –COOH); containing a small amount of lactone (weak 5.65 μ peak). The oil was treated with an excess of ethereal diazomethane and a pure sample of **11** was obtained by GLC: IR (CCl_4) 5.75, 6.09 and 11.12 μ; NMR (CCl_4) δ 3.55 (s, 3 H, $-OCH_3$) and 4.65 ppm (s, 2 H, $-C=CH_2$); mass spectrum, molecular ion at *m/e* 182.

Reaction of 2,4 - *dihydroxy* - 2,4 - *dimethylcyclohexane* - 1 - *acetic acid,* γ - *lactone* (**12**) *with potassium t* - *butoxide.* The reaction of 1.0 g (5.4 mmol) of **12** with 1.0 g (9 mmol) of t-BuOK in 30 ml DMF at reflux for 1 hr was worked up in the usual manner and gave no neutral products. The acid fraction (481 mg) was esterified with an excess of ethereal diazomethane. GLC analysis and separation indicated the presence of 55% of **14** whose identity was established by comparison with an authentic sample,[18] and 45% of **13** IR (CCl_4) 2.80, 5.72, 6.08 and 11.02 μ; NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3–C–OH), 1.50–1.90 (m, 4 H, $-CH_2CH_2-$), 2.15–2.85 (m, 6 H), 3.70 (s, 3 H, $-OCH_3$) and 4.75 and 4.85 ppm (s, 2 H, $-C=CH_2$); mass spectrum, molecular ion at *m/e* 198.

Table 3. Major NMR spectral features[a] of esters **8a-d**, (δ, pp)

	8a	8b	8c	8d
CH_3—CH	0.93	1.04	1.00	1.05
C=C—CH_3	1.72	1.74	1.78	1.71
—OCH_3	3.68	3.59	3.59	3.68
=CH_2	4.74	4.73	4.76	4.73

[a] NMR spectra determined in $CDCl_3$ using tetramethylsilane as an internal standard.

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[1a] The initial stages of this work were supported by a grant from The National Science Foundation. [b] Presented in part at the 151*st National Meeting of the American Chemical Society*, Los Angeles, Calif. (Spring, 1971).

[2] Abstracted in part from the thesis submitted by P.H. in partial fulfillment of the requirements for the Ph.D. degree, Purdue University (June 1970).

[3] David Ross Research Fellow (1971–73); Sohio Research Fellow (1973–74).

[4] See *Cyclopentanoid Terpene Derivatives* (Edited by W. I. Taylor and A. R. Battersby). Marcel Dekker, New York (1969) for a general review of iridoids. Among the most interesting members of this family are iridomyrmecin and the dihydronepetalactones which are powerful attractants to felines[5] and loganin which is a key intermediate in indole alkaloid biosynthesis.[6]

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