for recording the ^1H NMR spectra; to Dr. Rodger L. Foltz, Batelle High Resolution Mass Spectrometer Center, Pittsburgh, Pa., for the mass spectrum; to Mr. A. W. Spang, Ann Arbor, Mich., for the microanalyses; and to Dr. Miklos Bodanszky for the use of the polarimeter.

Registry No.—**1b,** 1914-30-3; **2b,** 2270-04-4; **3d,** 56665-84-0; **3e,** 56665-85-1; **3f,** 56665-86-2; **4d,** 56665-87-3; **4e,** 56665-88-4; **4f,** 56665-89-5; **6b,** 56665-90-8; **7a** isomer 1, 56665-91-9; **7a** isomer 2, 56665-92-0; **7b** isomer 1, 56665-93-1; **7b** isomer 2, 56665-94-2; **7c** isomer 1, 56665-95-3; **7c** isomer 2, 56665-96-4; **8a,** 56665-97-5; **8c,** 31751-19-6; **9b,** 56665-98-6; **10b,** 56665-99-7; **11b,** 56666-00-3; **12b,** 56666-01-4; **13d,** 56666-02-5; **13e,** 56666-03-6; **13f,** 56666-04-7; **14e,** 56666-05-8; **14f,** 56666-06-9; **15b,** 56666-07-0; 17α,20β-epoxy-5α-pregnan-3β-yl acetate, 56666-08-1; diborane, 18099-45-1; *p*-toluenesulfonyl chloride, 98-59-9; 3β,17aβ-dihydroxy-17a-methyl-*D*-homo-5α-androstan-17-one, 3751-01-7; *m*-chloroperbenzoic acid, 937-14-4; 17α,17aα-epoxy-17a-methyl-*D*-homo-5α-androstan-3β-yl acetate, 56666-09-2.

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Synthesis of α-Methylene Lactones by Reductive Amination of α-Formyl Lactones. Scope and Limitations

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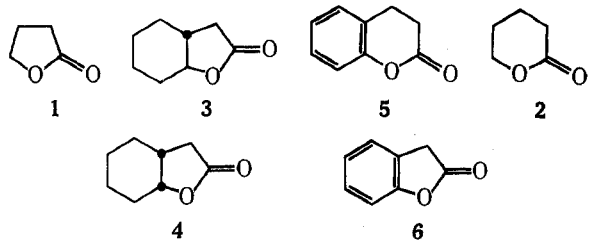
The synthesis of α-methylene lactones by reductive amination of α-formyl lactones with sodium cyanoborohydride and dimethylamine is described with regard to its scope and limitations. The α-methylene lactones α-methylene-δ-valerolactone (**10**), α-methylene-*trans*-2-hydroxycyclohexaneacetic acid γ-lactone (**13**), α-methylene-*cis*-2-hydroxycyclohexaneacetic acid γ-lactone (**16**), and 3-methylene-3,4-dihydrocoumarin (**23**) are prepared from their α-formyl lactones. The α-methylene lactone of 2-coumaranone could not be synthesized by this procedure.

As a counterpart to our development of a synthesis of α-methylene-γ- or -δ-lactones by reductive amination of the corresponding α-formyl lactones,[3a] which enabled an efficient synthesis of tulipalin A and pentaacetyl tuliposide A,[3b] we decided to examine the scope and limitations of this method. In view of the continued great interest in synthetic methods for construction of α-methylene-γ- and -δ-lactone units,[4] which are found in a variety of biologically active natural products,[5] such a study was felt to be necessary to truly define the generality of our synthetic approach. We now report the successes and failures of our investigation.

Results

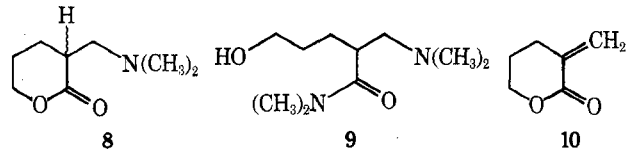
Our general synthetic format for the preparation of α-methylene-γ- and -δ-lactones is shown in Scheme I. Since it involves the addition of an α-methylene unit to a preformed γ- or δ-lactone, we investigated the "α-methylenation" of lactones 1–4 as representative of the α-methylene lactone systems found in certain natural products,[5] and 5 and 6, whose "α-methylenation" had been attempted by



Martin et al.[6] but with unsuccessful results using an α-methylation method based on methyl methoxymagnesium carbonate carboxylation of lactones. For comparative purposes we chose to look at our reductive amination method as comprised of three basic steps: I, lactone formylation; II, reductive amination; and III, quaternization and elimination, although the latter was a trivial distinction.

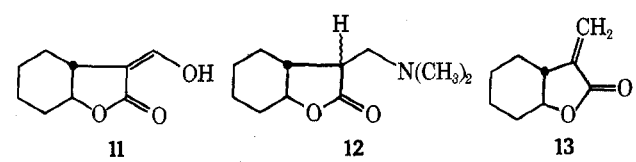
The synthesis of tulipalin A, the α-methylene analog of 1, has been described.[3a,b] Since steps I and III of its synthesis were carried out essentially quantitatively whereas the yield of α-dimethylaminomethyl-γ-butyrolactone (7)[3b] in step II of the reaction sequence appeared to be variable, a brief study of the effect of experimental conditions on the yield of 7 was undertaken. The results of this study are shown in Table I. Control of the *initial* pH of the reaction mixture between 5 and 7 by addition of absolute methanolic HCl favorably affected the yield of 7 and lessened the amount of the principal by-product, 2-dimethylaminomethyl-4-hydroxybutanoic acid dimethylamide (formed in less than ca. 10% yield[7]), whereas the ratio of dimethylamine to α-formyl butyrolactone and the reaction solvent seemed to be somewhat less critical.

The synthesis of α-methylene-δ-valerolactone[3a] (10) could be achieved in only a 41% overall yield from 2. As with 1, the lowest yield was obtained in step II of the reaction sequence. A similar study (vide supra) of the yield of α-dimethylaminomethyl-δ-valerolactone (8) was done; the

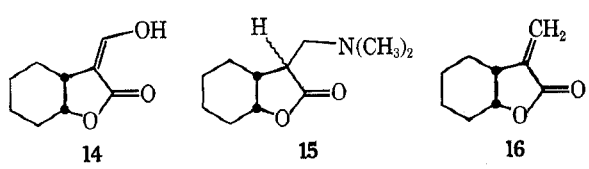


results are shown in Table II. The amount of dimethylamide by-product (9) always represented a greater percentage of the consumed α-formyl-2 than with 1, appearing with 8 in a 1:1 ratio when the reaction solvent was DME. Although the methiodide of 8 could not be obtained crystalline, step III of the reaction sequence could be carried out to give an 80–85% yield of 10.

The method of Newman and Vanderwerf[8] was used to obtain *trans*-2-hydroxycyclohexaneacetic acid γ-lactone (3). This was converted in 90% yield to its α-formyl derivative (11, sodium salt) when diethyl ether was the reaction solvent in step I, and 73% yield when DME was used. Step II of the reaction sequence was shown to be much less variable than for 1 or 2; the yield of 12 ranged from 43% (MeOH) to 57% (DME). Step III was carried out in high yield to give α-methylene-*trans*-2-hydroxycyclohexaneacetic acid γ-lactone (13) in an overall yield of 48% from 3.

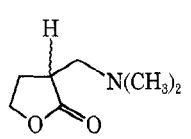


cis-2-Hydroxycyclohexaneacetic acid γ-lactone (4) was prepared according to Klein.[9] Formylation of 4 was accomplished in either diethyl ether or DME as the reaction solvent to give 14 in a 97–100% yield. Two C-2 epimers of 15



were obtained in step II of the reaction sequence in a combined yield of 33–50% when the sodium enolate of 14 was used as starting material to 57% when 14 itself was used. Although the chromatographically separable epimers of 15

Table I
Reductive Amination of Sodium α-Formyl-γ-butyrolactone



Expt	Ratio of $(CH_3)_2NH$ to Na enolate[b]	Initial pH	Solvent	Time, hr	Yield of 7, %
1	7:1	*c*	MeOH	96	50
2[a]	6:1	*c*	THF–MeOH (3:1)	96	69
3	1:1	~4	MeOH	1	42
4	2:1	~4	MeOH	1	32
5	2:1	~4	MeOH	18	68
6	2:1	~6	MeOH	18	64
7	2:1	*c*	DME	18	68
8	2:1	~6	DME	24	81
9	2:1	*c*	DME–HMPA (9:1)	18	66
10	2:1	~6	DME–MeOH (15:1)	18	63

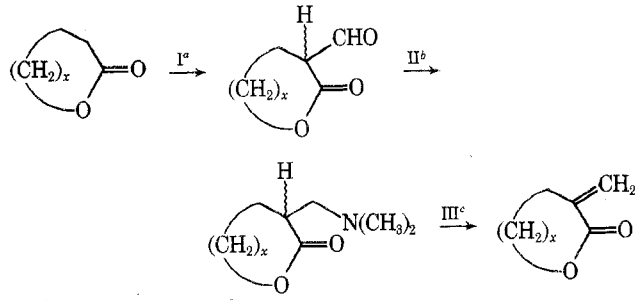
[a] Using purified $NaCNBH_3$;[16] all other runs were done with the commercially available $NaCNBH_3$ used as received. [b] $NaCNBH_3$ always was used in at least 50% excess molar equiv. [c] Initial pH not adjusted.

Table II
Reductive Amination of Sodium α-Formyl-γ-valerolactone

Expt	Ratio of $(CH_3)_2NH$ to Na enolate[a]	Initial pH	Solvent	Time, hr	Yield of 8,[c] %
1	6:1	*b*	MeOH	96	64
2	5:1	*b*	MeOH	24	30
3	2:1	*b*	MeOH	24	35
4	2:1	~6	MeOH	20	49
5	2:1	*b*	DME	24	32
6	2:1	~6	DME–MeOH (10:1)	20	33

[a] $NaCNBH_3$ always was used in at least 50% excess molar equiv. [b] Initial pH not adjusted. [c] Accompanied by varying amounts of 9 (10–20%), which appeared in significant amounts (~32%) in run 5.

Scheme I



[a] Base, $HCO_2C_2H_5$. [b] $NaCNBH_3$, $(CH_3)_2NH$. [c] CH_3I, aqueous $NaHCO_3$.

gave distinctly different methiodides (Experimental Section), their structural distinction spectroscopically was not done largely owing to the close proximity of the resonances from the carbocyclic ring to those of the C-2 hydrogen in the 100-MHz NMR spectra. Each of the epimers of **15**, or their mixture, was carried through step II to give **16** in an overall yield of 50% from **14**.

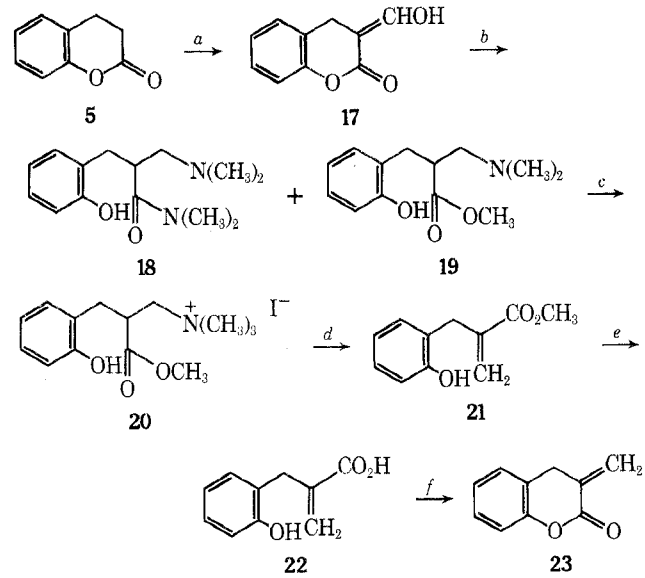
3-Formyl-3,4-dihydrocoumarin (**17**) was prepared in 45% yield essentially as described by Korte and Büchel,[10] although several alternative approaches were examined. Numerous bases and formylating reagents were examined in the hope of finding a combination which would favor the formation of **17** rather than ring-opened products. The combination of lithium 2,2,6,6-tetramethylpiperidide and acetic–formic anhydride[11] produced a 30% yield of **17**. The same base with formic–pivalic anhydride gave only a 27% yield of **17**. Sodium hydride and lithium diisopropylamide produced less satisfactory results. Numerous uncharacterized products were formed in all instances.

The reductive amination of **5** (Scheme II) was carried out more successfully than with **2–4** in that the yield of the α-dimethylaminomethyl derivative was as high as 72%. It is unfortunate that the amino lactone was not the reaction product. In all cases the ring-opened methyl ester (**19**) was obtained as the major product, with the corresponding dimethylamide (**18**) as a minor product. In one instance when DME was used as the solvent a nearly 1:1 mixture of **18** and **19** was obtained, **19** arising from initial acidification of the reaction mixture with methanolic hydrogen chloride.

Conversion of **19** to its methiodide (**20**) resulted in the formation of a yellow, amorphous solid. TLC analysis of the reaction mixture after 5 min at room temperature in the dark indicated the presence of unreacted **19** as well as **20**. Two other spots were observed which were not amines, one corresponding to **21**. Treatment of the mixture by shaking with 5% aqueous sodium bicarbonate gave a 62% isolated yield of the α-methylene ester (**21**) based on **17**. Hydrolysis with barium hydroxide and neutralization with 1 *N* sulfuric acid afforded **22**, which was lactonized with *p*-toluenesulfonic acid in refluxing toluene to 3-methylene-3,4-dihydrocoumarin (**23**). A 55% overall yield of **23** was obtained from **17**.

The structure given as **23** was assigned on the basis of the following spectral and analytical data. The ir spectrum contained a strong peak at 1740 cm^{-1}. When compared with the 1773-cm^{-1} peak observed with **5** it was seen that the observed shift of carbonyl absorption corresponded to that observed between other α,β-unsaturated esters and lactones when compared to their saturated analogs.[12] Peaks at 1639 and 810 cm^{-1} suggest a vinylidene group. The NMR spectrum (60 MHz) contained a four-proton multiplet at δ 6.9–7.4 for the aromatic system. A pair of finely split multiplets at δ 5.77 and 6.40 represented the α-methylene protons which were split by the two β protons and by

Scheme II



[a] $Mg[N(i\text{-}Pr)_2]_2$, $HCO_2C_2H_5$. [b] $NaCNBH_3$, $(CH_3)_2NH$, $(CH_3)_2NH_2Cl$. [c] CH_3I. [d] Aqueous $NaHCO_3$. [e] $Ba(OH)_2$. [f] *p*-TSA, Δ.

the magnetically nonequivalent vinylogous twin. Both *J* values are <1 Hz. Finally, the two β methylene protons at δ 3.75 occurred as a triplet (*J* = <1 Hz), being split by the vinylogous protons equally. The two-proton singlet appearing at δ 7.97 in the NMR spectrum of **22** was absent in the spectrum of **23** providing further evidence for the lactonization. High-resolution mass spectrometric analysis on the parent ion of **23** resulted in a value of 160.0527 for the molecular weight. The calculated value of 160.0524 agreed well with the observed value. A satisfactory combustion analysis could not be obtained for this compound.

Attempts to synthesize the α-methylene analog of 2-coumaranone (**6**) uniformly were unsuccessful owing to our inability to formylate it, although the use of several reagents and reaction conditions was explored.[13] It was found that **6**, unlike **5**, could not be deuterated at C-3 by anion formation at −78° in THF with lithium 2,2,6,6-tetramethylpiperidide and subsequent quenching with deuteriotrifluoroacetic acid. On exposure to these conditions **6** was recovered unchanged, whereas **5** easily was converted to its monodeuterio derivative. The use of higher reaction temperatures led to low recovery of **6**, undeuterated, plus the formation of many decomposition products. These results obviated the use of formic–acetic or formic–pivalic anhydride to formylate **6**.

Discussion

The lactone α-formylation reaction generally was quite satisfactory. Excellent yields of the α-formyl lactones of **1–4** were obtained and the compounds, as their sodium enolates, were stable, although hygroscopic, compounds. For the cases where this procedure led to only moderate yields (**5**) or was inapplicable (**6**), we felt that the ethoxide anion generated in the reaction was precipitating the problems. It would be expected to nucleophilically attack **5** and **6** forming their corresponding ethyl esters,[10] thereby leading to greatly diminished yields of the α-formyl derivatives. Since acetate would not be expected to have this drawback nor to lead to reversal of the formylation reaction, we attempted to formylate **5** and **6** by quantitative generation of their lithium enolates at low temperatures using lithium 2,2,6,6-tetramethylpiperidide followed by acylation with formic–acetic[11] or formic–pivalic anhydride. However, this approach did not prove to be very efficient for **5**, nor success-

ful for **6**. In the latter case, the lithium enolate of **6** appeared to be very unstable above −78° and unreactive at this temperature.

Although the reductive amination of aldehydes and ketones can be achieved under a variety of conditions,[15] the experimentally most suitable method herein was felt to be that of Borch et al.,[16] since aldehydes are reduced at pH 3–4 by sodium cyanoborohydride whereas the optimum pH range for reductive amination is 6–8. In our hands, Borch's reductive amination method proved to be experimentally convenient although its use lead to somewhat variable yields of the resulting α-dimethylaminomethyl lactones (Tables I and II). The use of the sodium enolates of the α-formylated lactones required the addition of 1 equiv of acid to form the protonated α-formyl lactone, enabling nucleophilic addition of dimethylamine to form the intermediate carbinolamine.[16] This was accomplished by the addition to the reaction of either solid dimethylamine hydrochloride or anhydrous methanolic HCl until a preselected pH was reached. In those instances where the α-formyl lactone itself was utilized, it was found that very poor yields were obtained if dimethylamine hydrochloride was present as the only amine source. This is to be expected on the basis of the reaction's mechanism[16] because of the involvement of the unshared electrons in imminium ion formation.

The variability in yields of the α-dimethylaminomethyl lactones recovered from the reductive amination appears to be sensitive to pH, reaction time, and choice of solvent. During the course of the reaction the pH always increased to a value of 9 or 10 if additional acid was not introduced to lower it. The high pH did not deter the formation of the α-dimethylaminomethyl lactone and in some instances actually increased the yield of it. This was most likely due to a more favorable equilibrium between amine and aldehyde to produce the carbinolamine. A lower pH would result in a more rapid protonation of the resulting enamine[16] but would not favor the carbinolamine formation.

An increased reaction time usually resulted in somewhat increased yields of α-dimethylaminomethyl lactone but the incidence of side reactions also increased. Dimethylamides were most frequently observed after prolonged reactions, especially when δ-lactones were involved. Solvolytic ring opening became important with dihydrocoumarin but did not appear to be time dependent, for its ethyl ester was recovered from all reactions that were attempted. Borch et al.[16] suggested that distilled water could be utilized as the solvent in such cases, which would have eliminated the formation of esters. This was prevented by the insolubility of most of the compounds that were investigated in this study, however.

The amounts of amides as by-products increased with solvent changes from protic to aprotic. This was probably due to decreased solvation of the amine in solution allowing a much closer approach to the carbonyl as well as an increased nucleophilicity. Both of these factors would tend to increase the formation of such by-products.

In order to circumvent the problem with the reductive amination of **5** two other approaches were examined: (1) a direct enamine synthesis by treatment of **5** with dimethylformamide diethyl acetal,[17] and (2) the formation of the enamine from **17** and diethylamine in refluxing benzene with removal of water. Subsequent reduction was anticipated to lead to the desired α-dimethylaminomethyl lactone. Following the addition of dimethylformamide diethyl acetal to dihydrocoumarin and heating, the only product isolated in reasonable yield was ethyl 2-hydroxyphenylpropanoate. No nitrogen-containing compounds other than dimethylformamide were found in any of the reaction mixtures. Similar results were obtained with **1** and **6**.

Borch et al.[16] have reported that enamines and especially their imminium salts are readily reduced to the corresponding amine by $NaCNBH_3$. α-Formyl-γ-butyrolactone[3b] gave a good yield of its diethylenamine when treated with diethylamine in refluxing benzene with constant water removal. Reduction of this diethylenamine in methanol at an initial pH of ca. 3 with sodium cyanoborohydride resulted in a fairly good yield of **7**. Treatment of **17** with diethylamine under the same conditions also resulted in a good yield of its diethylenamine. Attempted reduction of this enamine using $NaCNBH_3$ resulted in hydrolysis of the enamine and very little reduced α-dimethylaminomethyl lactone was obtained. The imminium salt of this diethylenamine could not be isolated by addition of acid or by the method of Leonard and Paukstelis,[18] so this route was subsequently abandoned.

The failures of the reductive amination were not as serious as those found in the formylation step. Although several by-products were obtained in certain instances, these could be lessened by proper choices of solvent and reaction time. If the optimum conditions for the formation of the imminium systems could be met, the reduction could be performed in very high yield making the complete sequence attractive as a synthetic tool.

Throughout the syntheses described in this paper, the quaternization of the α-dimethylaminomethyl lactones using CH_3I in methanol and the subsequent elimination using 5% aqueous $NaHCO_3$ were carried out in 90% or greater yields. The methiodides, when crystalline, proved to be unstable to recrystallization, which always resulted in the formation of small amounts of the corresponding α-methylene lactones.

It is interesting to note the elimination of dimethylamine from **15** during chromatography on silica gel to give **16**. This was undoubtedly the effect of the equilibrium between the Michael adduct—the dimethylaminomethyl lactone—and the Michael acceptor—the α-methylene lactone—being affected by the acidic nature of the silica gel. Dalton and Elmes[19] have suggested that the methylene lactone predominates under acidic conditions and that the Michael adduct is formed under neutral or basic conditions. If this is true in all cases, then the possibility exists that during the work-up of the reductive amination products, a portion of the dimethylaminomethyl lactone may be lost during the acidic wash used to remove neutral compounds. No α-methylene lactones were observed in some of these extracts (TLC) but a careful examination of each was not done.

Experimental Section

General. γ-Butyrolactone, δ-valerolactone, dihydrocoumarin, 2,2,6,6-tetramethylpiperidine, pivaloyl chloride, and miscellaneous organic chemicals were purchased from Aldrich Chemical Co., Cedar Knolls, N.J. Sodium cyanoborohydride, *n*-butyllithium (22% in hexane), and sodium hydride (57% mineral oil dispersion) were purchased from Alfa Inorganics, Beverley, Mass. Deuterium oxide was purchased in 99.8 mol % from Bio-Rad Laboratories, Richmond, Calif. Dimethylamine was purchased from Matheson Gas Products, East Rutherford, N.J.

Adsorbents for preparative and thin layer chromatography (silica gel GF_{254} and silica gel PF_{254}) were purchased from VWR Scientific, Boston, Mass. All solvents for chromatography were distilled prior to use. 1,2-Dimethoxyethane, tetrahydrofuran, and diethyl ether were distilled from lithium aluminum hydride prior to use as reaction solvents. Anhydrous methanol and anhydrous (super-dry) ethanol were prepared according to the method of Vogel.[20]

Nuclear magnetic resonance spectra (60 MHz) were obtained on a Hitachi Perkin-Elmer R-24 spectrometer with deuteriochloroform as solvent. Chemical shifts are reported relative to a Me_4Si internal standard. Infrared spectra were obtained on a Perkin-

Elmer Model 21 spectrophotometer and the wavenumbers are corrected to a polystyrene reference. Mass spectra were obtained on a AEI Scientific, Inc., MS 902 mass spectrometer. Melting points were obtained on either a Kofler hot stage or a Thomas-Hoover Uni-Melt apparatus and are corrected. Gas chromatography was done on a Varian 90-75 gas chromatograph utilizing a thermal conductivity detector and helium as the carrier gas. Refractive indices were obtained on a Bausch and Lomb Abbe 3L refractometer at ambient temperature. In vacuo refers to water aspirator pressures, all evaporations being conducted on a rotary flash evaporator at 25–40°C.

Sodium α-Formyl-δ-valerolactone. A mineral oil dispersion of sodium hydride (57%, 1.1 g, 26 mmol) was placed in a dry 100-ml three-neck round-bottom flask which had been previously evacuated and flushed with dry nitrogen. The mineral oil was removed by washing with petroleum ether (3 × 10 ml) and decanting under nitrogen. The sodium hydride was then suspended in 50 ml of anhydrous diethyl ether by magnetic stirring.

A mixture of **2** (2.5 g, 25 mmol) and ethyl formate (1.85 g, 25 mmol) in 3 ml of diethyl ether was added dropwise to the stirred suspension. Absolute ethanol (0.2 ml) was added to initiate the reaction. Stirring was continued at room temperature for 18 hr, and the resulting mixture was filtered with suction, washed with 15 ml of diethyl ether, and dried under vacuum in a desiccator to yield sodium α-formyl-δ-valerolactone as a light tan powder, 3.8 g (100%).

α-Dimethylaminomethyl-δ-valerolactone (8). The sodium enolate from above (1.5 g, 10 mmol) was dissolved in 30 ml of anhydrous methanol. To this was added a solution of dimethylamine (2.7 g, 4 ml, 60 mmol) and methanolic hydrogen chloride (3 *N*, 10 ml, 30 mequiv). Sodium cyanoborohydride (440 mg, 7 mmol) and 1.5 g of Linde 3A molecular sieves were then introduced and the mixture was stirred at room temperature fitted with a drying tube for 3 days. The reaction mixture was filtered with suction through Celite and the solid remaining on the Celite was washed with methanol (100 ml). The combined filtrates were acidified (pH 2) with concentrated hydrochloric acid, and the methanol was removed in vacuo. The resulting residue was redissolved in distilled water (100 ml) and extracted with CH_2Cl_2 (2 × 100 ml). $NaHCO_3$ was added to the aqueous phase to bring its pH to 8 and the resulting solution was extracted with CH_2Cl_2 (4 × 100 ml). The aqueous solution then was adjusted to ca. pH 10 with Na_2CO_3 and reextracted with EtOAc (4 × 100 ml). The combined basic organic extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4), and the solvent was removed in vacuo to give **8** as a viscous yellow liquid: 1.01 g (64%); ir (neat) 1740 cm^{-1} (lactone); NMR (60 MHz) δ 1.65 (m, 2 H), 2.23 (s, 6 H), 2.7 (m, 2 H), 4.1 (t, J = 7 Hz, 2 H); vapor phase chromatography (VPC), 3% SE-30, 160°, 60 ml/min, crude amine showed greater than 95% one component, retention time 1.9 min. Reaction by-products were isolated and characterized by ir and NMR spectroscopy. α-Dimethylaminomethyl-δ-hydroxyvaleric acid dimethylamide (**9**) and δ-hydroxyvaleric acid dimethylamide were found in the reaction mixture: ir (neat) 3400 (hydroxyl), 1630 (amide I), 1510 (amide II), 1410 cm^{-1} (ν C–N); NMR (60 MHz) δ 3.05 (d, J = 5 Hz, 6 H, dimethylamide).

α-Methylene-δ-valerolactone (10).[21] The tertiary amine (**8**, 300 mg, 2 mmol) was dissolved in 4 ml of methanol and 1.5 ml of methyl iodide was added. No crystals were observed after standing in the dark at room temperature for 24 hr or following the addition of 5 ml of diethyl ether to the solution. The yellow oil that separated after the addition of diethyl ether was isolated by removing the solvent in vacuo; however, all attempts at crystallization were fruitless. The oil was transferred to a separatory funnel containing 10 ml of 5% sodium bicarbonate solution and 20 ml of dichloromethane. After shaking the mixture for 15 min, the aqueous phase was extracted with dichloromethane (6 × 25 ml), the extracts were dried with sodium sulfate, and the solvent was removed in vacuo to yield **10** as a yellowish liquid, 175 mg (81%). The crude product was purified by preparative TLC on silica gel using chloroform–methanol (4:1): ir (neat) 1730 (lactone), 1630 and 814 cm^{-1} (C=CH_2); NMR (60 MHz) δ 2.00 (m, 2 H), 2.71 (m, 2 H), 4.38 (t, J = Hz, 2 H), 5.57 (dd, J_{AB} = $J_{A'B'}$ = 1 Hz, 1 H), 6.40 (dd, J_{AB} = $J_{A'B'}$ = 1 Hz, 1 H); mass spectrum m/e (rel intensity) 112 (M^+, 100), 82 (M − CH_2O, 58), 54 (M − C_3H_6O, 94).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.26.

***trans*-2-Hydroxycyclohexaneacetic acid γ-lactone (3)** was prepared according to Newman and Vanderwerf:[8] colorless liquid, bp 71.5–72.5° (0.25 mm) [lit.[8] bp 118–119° (6 mm)].

Sodium α-Formyl-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone (11). The trans lactone **3** (1.40 g, 10 mmol) and ethyl formate (740 mg, 10 mmol) dissolved in 5 ml of anhydrous diethyl ether was added dropwise to a suspension of oil-free sodium hydride (252 mg, 10.5 mmol) in 50 ml of diethyl ether in a 100-ml three-neck flask. Absolute ethanol (0.1 ml) was introduced to initiate the reaction. After stirring for 15 hr at room temperature the mixture was filtered, washed with ether, and dried in a desiccator under vacuum to give **11** as its sodium enolate, 1.71 g (90%).

α-Dimethylaminomethyl-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone (12). The sodium enolate **11** (380 mg, 2 mmol) was suspended in 15 ml of 1,2-dimethoxyethane. To this was added dimethylamine hydrochloride (325 mg, 4 mmol), sodium cyanoborohydride (130 mg, 2 mmol), and 300 mg of Linde 3A molecular sieves. The mixture was stirred at room temperature for 40 hr and filtered through Celite. After extraction of the acidified (pH 2) solution with dichloromethane, the solution was made basic (pH 8) with sodium bicarbonate and again extracted with dichloromethane (5 × 30 ml). The basic extracts were dried over magnesium sulfate and the solvent was removed to obtain **12** as a colorless liquid: 225 mg (57%); ir (neat) 1775 cm^{-1} (lactone); NMR (60 MHz) δ 1.2–2.6 (m, 10 H), 2.25 (s, 6 H), 2.63 (t, J = 6 Hz, 2 H), 3.4–3.8 (m, 1 H); picrate, recrystallized from ethanol, mp 210–211.5°.

Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.96; H, 5.15; N, 13.13.

α-Trimethylaminomethyl-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone Iodide. The tertiary amine **12** (279 mg, 1.4 mmol) was dissolved in 2 ml of anhydrous methanol and 1 ml of methyl iodide was added. White crystals were observed after 5 min and the solution was left in the dark at room temperature overnight. The crystals were filtered, washed with diethyl ether, and dried in vacuo to obtain the methiodide: 460 mg (96%); mp 215–216° dec.

α-Methylene-*trans*-2-hydroxycyclohexaneacetic Acid γ-Lactone (13).[22] A portion of the methiodide salt (170 mg, 0.5 mmol) was placed in a separatory funnel with 5 ml of 5% aqueous sodium bicarbonate solution and 10 ml of dichloromethane. After complete dissolution of the salt, the aqueous layer was extracted with dichloromethane (6 × 10 ml) and the combined extracts were dried over sodium sulfate. Evaporation of the solvent yielded **13** as a crystalline solid: 76 mg (99%); mg 38.5–39° (lit.[22] 40–41°); ir ($CHCl_3$ solution) 1770 (lactone), 1675 and 814 cm^{-1} (C=CH_2); NMR (60 MHz) δ 1.1–2.7 (m, 9 H), 3.5–4.0 (m, 1 H), 5.40 (d, J = 3 Hz, 1 H), 6.07 (d, J = 3 Hz, 1 H); mass spectrum m/e (rel intensity) 152 (M^+, 9.5), 124 (M − CO, 100).

***cis*-2-Hydroxycyclohexaneacetic acid γ-lactone (4)** was prepared according to Klein[9] as a colorless liquid: bp 95–100° (0.8 mm) [lit.[9] bp 150–155° (20 mm)]; ir 1775 cm^{-1} (lactone).

Sodium α-Formyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (14). A solution of **4** (1.40 g, 10 mmol) and ethyl formate (740 mg, 10 mmol) in 5 ml of anhydrous diethyl ether was added dropwise to a suspension of oil-free sodium hydride (252 mg, 10.5 mmol) in 25 ml of diethyl ether in a 100-ml three-neck round-bottom flask. Absolute ethanol (0.1 ml) was added by pipette to initiate the reaction. After stirring at room temperature for 22 hr the mixture was filtered, washed once with 20 ml of diethyl ether, and dried in a desiccator under vacuum to obtain **14** as a dark grayish brown solid, 1.85 g (97%).

α-Formyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (14). The sodium enolate of **14** (1.0 g, 5.25 mmol) was slowly added to 10 ml of 2 *N* hydrochloric acid which had been previously cooled in an ice bath. The resulting mixture was extracted with diethyl ether (6 × 15 ml), and the extracts were washed with 10 ml of saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent in vacuo afforded the α-formyl lactone **14** as a light yellow liquid, 890 mg (100%).

α-Dimethylaminomethyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (15). The slurry of the sodium enolate of **14** (760 mg, 4 mmol) in 20 ml of methanol was treated with dimethylamine hydrochloride (650 mg, 8 mmol) and sodium cyanoborohydride (195 mg, 3 mmol). Linde 3A molecular sieves (500 mg) was added and the mixture was stirred at room temperature for 18 hr. The mixture was filtered through Celite and the filtrate was acidified (pH 2) with concentrated hydrochloric acid. The methanol was removed in vacuo and 35 ml of distilled water was added. The aqueous acidic mixture was extracted with dichloromethane (3 × 20 ml) and then made basic (pH 8) with sodium bicarbonate. Extraction of the basic solution with dichloromethane (6 × 20 ml) and drying the combined extracts with sodium sulfate yielded **15** as a pale yellow liquid following the evaporation of the solvent in vacuo, 395 mg (50%). TLC analysis on silica gel with chloroform–methanol

(9:1) showed the presence of two amines in a ratio of about 3:2.

Preparative TLC on silica gel with chloroform–methanol (9:1) was used to separate the two amines into relatively pure fractions. A second chromatographic run using the same system with each fraction resulted in the two chromatographically pure amines.

Amine **15a:** R_f 0.47; ir (neat) 1775 cm^{-1} (lactone); NMR (100 MHz) δ 1.37–1.75 (m, 9 H), 2.17 (s, 6 H), 2.45 (br s, 2 H), 2.25–2.6 (m, 1 H), 4.46 (q, J = 6 Hz, 1 H); picrate, recrystallized from ethanol, mp 193–195°.

Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.60; H, 5.33; N, 13.16.

Amine **15b:** R_f 0.63; ir (neat) 1775 cm^{-1} (lactone); NMR (100 MHz) δ 1.30–1.60 (m, 9 H), 2.15 (s, 6 H), 2.44 (d, J = 8 Hz, 2 H), 2.4–2.7 (m, 1 H), 4.31 (q, J = 6 Hz, 1 H); picrate, recrystallized from ethanol, mp 144–145.5°.

Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 48.00; H, 5.40; N, 13.19.

α-Trimethylaminomethyl-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone Iodide. A. A sample of mixed isomers of **15** (228 mg, 1.16 mmol) was dissolved in 1 ml of anhydrous methanol. To this was added 1.5 ml of methyl iodide and the mixture was allowed to stand in the dark at room temperature overnight. The mixture was then cooled to 4° for 1 hr after which the colorless crystals were filtered and washed with diethyl ether to obtain the mixed methiodides, 302 mg (77%). The crystals melted over a wide range.

B. Amine **15a** (91 mg, 0.46 mmol) was dissolved in 1 ml of methanol and 0.5 ml of methyl iodide was added. After standing at room temperature in the dark for 2 hr the colorless crystals were isolated by filtration, washed with diethyl ether, and dried to obtain the methoidide of amine A as shiny plates: 136 mg (87%); mp 228°.

C. Amine **15b** (65 mg, 0.33 mmol) was dissolved in 1 ml of methanol and 0.5 ml of methyl iodide was added. The solution was kept at 4° for 1 hr and then at 25° overnight. The colorless crystals were recovered by filtration, washed with diethyl ether, and dried to yield the methiodide of amine B: 98 mg (88%); mp 215–215.5°.

α-Methylene-*cis*-2-hydroxycyclohexaneacetic Acid γ-Lactone (16).[22] Each sample of the methiodides above was treated separately by shaking with 5% aqueous sodium bicarbonate and dichloromethane and extracting with dichloromethane (5 × 10 ml). After drying the extracts with magnesium sulfate and evaporating the solvent in vacuo, **16** was obtained as a pale yellow liquid from each sample. The following yields were realized.

Methiodide salt of	α-Methylene lactone (16)
Amine mixture, 15 (300 mg)	93 mg (70%)
Amine 15a (100 mg)	40 mg (88%)
Amine 15b (90 mg)	40 mg (99%)

Spectral data: ir (neat) 1774 (lactone), 1670 and 817 cm^{-1} (C=CH_2); NMR (60 MHz) δ 1.1–2.1 (m, 8 H), 2.8–3.2 (m, 1 H), 4.4–4.75 (m, 1 H), 5.52 (d, J = 3 Hz, 1 H), 6.17 (d, J = 3 Hz, 1 H); mass spectrum m/e (rel intensity) 152 (M^+, 14), 124 (M − CO, 100). These values agree with the data given in the literature for *cis*-**16**.[22]

Preparative TLC on silica gel with chloroform–methanol (9:1) of the mixed amines of **15** resulted in the recovery of a small amount of **16** identical with that obtained through the methiodide salts (NMR).

3-Formyl-3,4-dihydrocoumarin (17). A. 17 was prepared from ethyl formate and **5** using $MgN(i\text{-}Pr)_2$ according to Korte and Büchel[10] as a yellowish powder: 2.4 g (45%); mp 138–142° [lit.[10] 140–141°]; ir (KBr) 1700 cm^{-1} (lactone); NMR (acetone-d_6) δ 3.6 (brs, 2 H), 7.2 (m, 4 H), 7.9 (t, J = 2 Hz, 1 H), 9.9 (s, 1 H).

B. From Acetic-Formic Anhydride. 2,2,6,6-Tetramethylpiperidine (141 mg, 1 mmol) was mixed with 15 ml of anhydrous tetrahydrofuran in a dry nitrogen-flushed flask. The mixture was cooled to −15° in an ice–acetone bath and n-butyllithium (2.05 M, 0.5 ml, 1.02 mmol) was introduced. After stirring at −15° for 10 min, the flask was cooled to −78° in a Dry Ice–acetone bath and a mixture of **5** (148 mg, 1 mmol) and acetic–formic anhydride[24] (130 mg, 1.5 mmol) in 5 ml of anhydrous tetrahydrofuran was added dropwise. The mixture was stirred at −78° for 10 min and was then warmed to −15°, at which time 50 ml of 0.2 N hydrochloric acid was introduced. The acidic solution was extracted with dichloromethane (3 × 40 ml), the extracts were dried with sodium sulfate, and the solvent was evaporated in vacuo to afford a yellow liquid which was approximately 30% **17** by TLC analysis on silica gel using chloroform–methanol (50:1).

C. From Formic–Pivalic Anhydride. A solution of 2,2,6,6-tetramethylpiperidine (141 mg, 1 mmol) in 10 ml of anhydrous THF was treated with n-butyllithium (2.05 M, 0.5 ml, 1.02 mmol) at −15°. After stirring for 10 min the mixture was cooled to −78° and **5** (148 mg, 1 mmol) dissolved in 3 ml of anhydrous THF was added slowly. This solution was stirred for 5 min at −78° and then formic–pivalic anhydride[25] dissolved in 1,2-dimethoxyethane (0.5 ml, 1.25 mmol) was added. After 10 min the mixture was warmed to −15°, poured into 50 ml of 0.1 N hydrochloric acid, and extracted with dichloromethane (3 × 40 ml). The combined extracts were dried with sodium sulfate and the solvent was removed in vacuo to obtain an oily residue which was chromatographed on silica gel with chloroform–methanol (50:1). Isolation of the band corresponding to **17** yielded 43 mg (27%) of a yellowish solid, mp 140–142°.

Methyl α-Dimethylaminomethyl-β-(2-hydroxyphenyl)propanoate (19). A solution of **17** (350 mg, 2 mmol) was prepared in 4 ml of 1,2-dimethoxyethane and a solution of dimethylamine (880 mg, 1.2 ml, 20 mmol) and methanolic hydrogen chloride (3 N, 3 ml, 9 mequiv) in 4 ml of anhydrous methanol was added. The pH was adjusted with methanolic hydrogen chloride to the transition point of Bromthymol Blue (pH 6) and then sodium cyanoborohydride (130 mg, 2 mmol) and 400 mg of Linde 3A molecular sieves were introduced. The pH was maintained near 6 by the repeated dropwise addition of 3 N methanolic HCl for 2 hr and the mixture was then stirred at room temperature for 15 hr. After filtering through Celite the solution was acidified (pH 2) with concentrated hydrochloric acid and extracted with dichloromethane (3 × 15 ml). The aqueous phase was then treated with sodium bicarbonate (pH 8) and extracted with dichloromethane (5 × 20 ml). After the combined basic extracts were dried with sodium sulfate and the solvent was removed in vacuo, **19** was obtained as a greenish liquid: 340 mg (72%); ir (neat) 3300, 1200 (phenol), 1733 (ester), 1167 cm^{-1} (tertiary amine); NMR δ 2.31 (s, 6 H), 2.5–3.0 (m, 5 H), 3.69 (s, 3 H), 6.6–7.3 (m, 4 H), 9.2 (br s, 1 H); δ 0.2 peak disappeared on addition of D_2O; mass spectrum m/e (high resolution) calcd for $C_{13}H_{19}NO_3$, 237.1360; found, 237.136.

The amide by-product (**18**) was obtained by preparative TLC of crude amine mixture on silica gel with chloroform–methanol (9:1). It was obtained as a pale yellow liquid: NMR δ 2.32 (s, 6 H), 2.47–3.2 (m, 5 H), 2.99 (d, J = 3 Hz, 6 H), 6.7–7.3 (m, 4 H), 8.95 (br s, 1 H). The absence of a three-proton singlet at δ 3.6 negated the presence of a methyl ester and the appearance of the δ 2.99 doublet strongly suggested the presence of a dimethylamide group; mass spectrum m/e (high resolution) calcd for $C_{14}H_{22}N_2O_2$, 250.1676; found, 250.1674.

Methyl α-Methylene-β-(2-hydroxyphenyl)propanoate (21). A solution of **19** (155 mg, 0.63 mmol) in 1 ml of anhydrous methanol was treated with 1 ml of methyl iodide and the solution was placed in the dark at room temperature for 48 hr. The solvent was removed in vacuo and the residue was triturated with ether to give **20** as a yellowish, amorphous solid, 224 mg (94%).

The crude methiodide salt (**20**) was placed in a separatory funnel, 5 ml of 5% sodium bicarbonate solution and 10 ml of dichloromethane were added, and the mixture was agitated for 5 min. The solution was extracted with dichloromethane (6 × 10 ml), the combined extracts were dried with magnesium sulfate, and the solvent was removed in vacuo to obtain **21** as a white solid: 97 mg (91%); mp 32.5–33° (following preparative TLC on silica gel with chloroform–methanol, 50:1); ir (film) 3380, 1220 (phenol), 1724 (ester), 1631, 818 cm^{-1} (C=CH_2); NMR δ of 3.60 (s, 2 H), 3.76 (s, 3 H), 5.79 (s, 1 H), 6.25 (s, 1 H), 6.7–7.3 (m, 4 H); mass spectrum m/e (rel intensity) 192 (M^+, 32), 160.0523 (M − CH_3OH, 98; calcd for $C_{10}H_8O_2$, 160.0522), 131.0497 (M − H, HCO_2CH_3 100, calcd for C_9H_7O, 131.0495).

α-Methylene-β-(2-hydroxyphenyl)propanoic Acid (22). The methyl ester **21** (148 mg, 0.77 mmol) was dissolved in 8 ml of methanol and 4.1 ml of saturated aqueous barium hydroxide was added. The solution was purged with nitrogen and stirring was continued at room temperature for 18 hr. The solution was acidified (Methyl Red) with 1 N sulfuric acid and 10 ml of distilled water was added. The methanol was removed in vacuo and the remaining aqueous mixture was extracted with dichloromethane (4 × 15 ml). The mixture was adjusted to pH 2 with 1 N sulfuric acid and was extracted with dichloromethane (3 × 15 ml). The combined extracts were dried with sodium sulfate and the solvent was removed in vacuo to obtain **22** as a white solid: 123 mg (90%); mp 79–81°; ir ($CHCl_3$) 3300 (phenol), 1700 (carboxylic acid), 1631 and 823 cm^{-1} (C=CH_2); NMR δ 3.54 (s, 2 H), 5.76 (s, 1 H), 6.31 (s, 1 H), 6.7–7.4 (m, 4 H), 7.97 (s, 2 H). An elemental analysis was not obtained.

3-Methylene-3,4-dihydrocoumarin (23). A solution of **22** (123

mg, 0.69 mmol) in 60 ml of toluene was treated with 50 mg of *p*-toluenesulfonic acid. The flask was fitted with a Dean-Stark constant water separator and the mixture was heated at reflux for 10 min. After removal of the toluene in vacuo the residue was chromatographed on silica gel with benzene–ethyl acetate (8:1) and the band corresponding to **23** was isolated to obtain the product as a crystalline solid: 108 mg (98%); mp 67.5–68° (sublimation and then recrystallization from ether–pentane); ir ($CHCl_3$) 1740 (lactone), 1639 and 810 cm^{-1} (C=CH_2); NMR (60 MHz) δ 3.75 (t, J = <1 Hz, 2 H), 5.77 (dt, J = <1 Hz, 1 H), 6.40 (dt, J = <1 Hz, 1 H), 6.9–7.4 (m, 4 H); mass spectrum *m/e* (high resolution) calcd for $C_{10}H_8O_2$, 160.0524; found, 160.0527; *m/e* (rel intensity) 160 (M^+, 83), 131 (M − CHO, 100). A satisfactory elemental analysis for this compound could not be obtained despite repeated crystallizations form diethyl ether–pentane and sublimation (60°, 0.06 mm). The mass spectrum showed the presence of traces of higher molecular weight material in the purified compound which may have arisen via polymerization during the purification.

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Registry No.—**2,** 542-28-9; **3,** 27345-71-7; **4,** 24871-12-3; **8,** 56783-31-4; **10,** 42023-19-8; **11,** 56783-32-5; **12,** 55643-46-4; **12** MeI, 56783-33-6; **12** picrate, 56783-45-0; **13,** 3727-53-5; **14,** 56783-34-7; **15a,** 56783-35-8; **15a** MeI, 56783-36-9; **15a** picrate, 56783-46-1; **15b,** 56783-37-0; **15b** MeI, 56783-38-1; **15b** picrate, 56783-47-2; **16,** 16822-06-3; **17,** 56783-39-2; **18,** 56783-40-5; **19,** 56783-41-6; **21,** 56783-42-7; **22,** 56783-43-8; **23,** 56783-44-9; sodium α-formyl-δ-valerolactone, 53761-41-4; ethyl formate, 109-94-4; dimethylamine, 124-40-3; acetic–formic anhydride, 2258-42-6; 2,2,6,6-tetramethylpiperidine, 768-66-1; formic–pivalic anhydride, 10535-67-8.

References and Notes

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(25) Sodium formate (750 mg, 11 mmol), finely powdered and dried at 125° for 4 hr was mixed with pivaloyl chloride (1.20 g, 10 mmol) and 3 ml of anhydrous 1,2-dimethoxyethane in a tightly stoppered flask. The flask was heated at 47° for 45 min and then stirred overnight at room temperature. The mixture was filtered and used without further purification: NMR (60 MHz) δ 1.31 (s, 10 H), 9.07 (s, 1 H). Distillation of the anhydride at 18 mmHg, ambient temperature, resulted in decarbonylation and recovery of pivalic acid.

New Germacranolide Sesquiterpene Dilactones from the Genus *Melampodium* (Compositae)

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The isolation of four germacranolide sesquiterpene dilactones from the three white-rayed *Melampodium* species is reported. Melampodin B (**1a**) is found in all three species, and 4(5)-dihydromelampodin B (**4a**) only in *M. cinereum* DC. Cinerenin (**2a**) occurs in both, *M. cinereum* and *M. argophyllum* (A. Gray ex Robinson) Blake, and melampodin C (**3a**) is typical of the latter species. Artemetin is a common constituent of *M. cinereum* and *M. argophyllum*. The structures, configurations, and conformations of the new dilactones were determined by chemical transformations, correlations, and spectral methods.

In connection with our biochemical systematic study of the white-rayed complex of the genus *Melampodium* (Compositae, Heliantheae)[1] we have analyzed multiple populations of *M. cinereum* DC. and *M. argophyllum* (A. Gray ex Robinson) Blake for their sesquiterpene lactone content. In this communication we describe the isolation and structure elucidation of four closely related germacranolide type sesquiterpene dilactones, which we named melampodin B (**1a**), cinerenin (**2a**), melampodin C (**3a**), and 4(5)-dihydromelampodin B (**4a**). The flavonoid artemetin[2] is a common constituent in both *M. cinereum* and *M. argophyllum*.

Melampodin B and Derivatives. Melampodin B (**1a**), $C_{17}H_{18}O_7$, mp 226–228°, the major, most polar constituent, was present in most populations of *M. cinereum* and *M. argophyllum* and was also found in several west Texas populations of *M. leucanthum*.[3] The structure of melampodin B has been described in a previous communication[4] and was mainly deduced on the basis of correlations of 25.5-MHz ^{13}C and 300-MHz ^1H NMR spectra obtained in acetone-d_6 and pyridine-d_5. The ^{13}C NMR data were obtained under proton noise decoupled (PND) and single-frequency off-center decoupled (SFOCD) conditions.[5] The ^1H NMR spectral data of **1a**, which included extensive double resonance experiments, are tabulated in Table I.

The stereochemical and conformational assignments in melampodin B require further comments. Two initial assumptions were made in the structural assignments of me-