Regiospecific Functionalization of the Monoterpene Ether 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane (1,8-Cineole). Synthesis of the Useful Bridged γ-Lactone 1,3-Dimethyl-2-oxabicyclo[2.2.2]octan-3→5-olide

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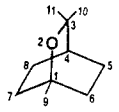
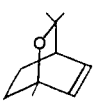
The regiospecific functionalization at C-5 and difunctionalization at C-5/C-8 and C-5/C-10 of the monoterpene 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane (1) is described. Chromyl acetate oxidation of 1 afforded 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-one (6) in 60% yield along with 28% of unreacted 1 and minor amounts of *exo*-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-ol acetate (9), 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane-5,8-dione (13), *exo*-8-acetoxy-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-one (16), 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane-5,7-dione (14), and orcinol (15). On digestion with oxalic or phthalic acid, ketone 6 was converted into a mixture of piperitenone (20), 3-methyl-2-cyclohexenone (22), acetone, and traces of isopiperitenone (21), while 60% sulfuric acid at room temperature yielded 20 as the sole reaction product. Oxidation of 6 with chromyl acetate yielded diketone 13, which decomposed into orcinol (15) on digestion with either boiling water or a 2.5% sodium bicarbonate solution. Sodium borohydride or lithium aluminum hydride reduction of 6 gave stereospecifically *exo*-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-ol (7) while reduction with sodium–ethanol or aluminum isopropoxide in isopropyl alcohol (equilibrium conditions) yielded a 3:2 mixture of the alcohols 7 and 8, respectively. Treatment of 7 with phosphoryl chloride produced 1,3,3-trimethyl-2-oxatricyclo[2.2.2.$0^{5,8}$]octane (25) together with minor amounts of the chlorocineoles 10 and 11. Pyrolysis of the methyl xanthate of 7 yielded 1,3,3-trimethyl-2-oxabicyclo[2.2.2]oct-5-ene (2). Photolysis of 7 in the presence of mercuric oxide and iodine or iodosylbenzene diacetate and iodine gave the tricyclic diether 29, which was quantitatively converted into the bridged γ-lactone 30 by oxidation with ruthenium tetraoxide. Oxidation of 29 with chromyl acetate yielded a 1:1 mixture of 30 and the formate lactone 31. Lithium aluminum hydride reduction of 30 produced diol 37, which was converted into menthofuran (44) in five steps.

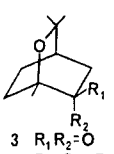
Although 1,8-cineole (1) (hereafter referred to as cineole) is widely distributed in the plant kingdom, only a few naturally occurring derivatives of 1 have been reported. The unsaturated analogue 2 was isolated from the essential oil of *Laurus nobilis*,[1] ketone 3 and alcohols 4 and 5 were reported as metabolites arising from the microbiological oxidation of cineole by a bacterium of the genus *Pseudomonas*,[2] and recently a sesquiterpene ketone with the 2-oxabicyclo[2.2.2]octane skeleton has been isolated from *Heterotropa curvistigma*.[3]



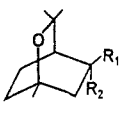
1



2



3 R_1R_2=O
4 R_1=OH;R_2=H
5 R_1=H;R_2=OH

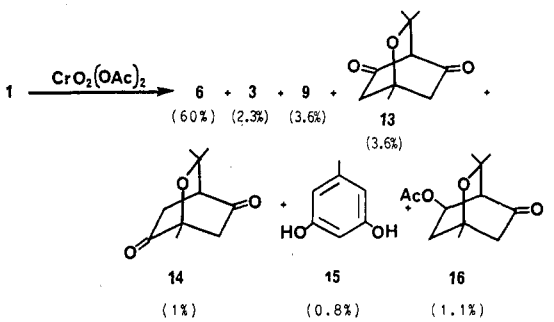


6 R_1R_2=O
7 R_1=OH;R_2=H
8 R_1=H;R_2=OH
9 R_1=AcO;R_2=H
10 R_1=Cl;R_2=H
11 R_1=H;R_2=Cl

12

Cineole is chemically rather inert since there are no activated C–H bonds in the molecule. Consequently, the literature on the chemistry of this monoterpene is scarce and mostly related to the cleavage of the ether bridge to obtain *p*-menthane derivatives. Hot aqueous acids,[4] pyrolysis over different supports,[5-7] and hydrogenolysis over supported platinum and palladium catalysts[8] have been used to open the ether linkage of 1. On the other hand, free-radical reactions such as photochlorination yield a complex mixture of products[9,10] from which all seven possible monochlorocineoles have been isolated.[10] As a consequence, most synthetic derivatives of 1 have been prepared by using α-terpineol[11,12] or pinol[13,14] as ultimate starting materials.

Scheme I



(1) Hogg, J. W.; Terhune, S. J.; Lawrence, B. M. *Phytochemistry* **1974**, *13*, 868.
(2) McRae, I. C.; Alberts, V.; Carman, R. M.; Shaw, I. M. *Aust. J. Chem.* **1979**, *32*, 917.
(3) Niwa, M.; Sugie, Y.; Yamamura, S. *Phytochemistry* **1981**, *20*, 1137.
(4) Matsuura, T.; Komae, H.; Saito, K. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 990. For a review on the early chemistry of 1, including the reaction with hydrohalic acids, see: Simonsen, J. L. *The Terpenes*; Cambridge: 1953; Vol. I, pp 423–432.
(5) Nomura, M.; Fujihara, Y. *Yukagaku* **1983**, *32*, 444.
(6) Ishidate, M. *Yakugaku Zasshi* **1928**, *48*, 20. Fujita, Y. *Nippon Kagaku Kaishi (1921–47)* **1930**, *51*, 260. Ikeda, T.; Fujita, Y. *Nippon Kagaku Kaishi (1921–47)* **1930**, *51*, 184. Waki, T. *Nippon Kagaku Zasshi* **1960**, *81*, 131.
(7) Hayashi, S. *Nippon Kagaku Zasshi* **1959**, *80*, 933.
(8) Hugel, H. M.; Jackson, W. R.; Kachel, C. D.; Rae, I. D. *Aust. J. Chem.* **1977**, *30*, 1287.
(9) Gandini, A. *Gazz. Chim. Ital.* **1933**, *63*, 151 and **1934**, *64*, 118. Bignardi, G.; Munari, S. *Farmaco, Ed. Sci.* **1962**, *17*, 222. Delaby, R.; Billuart, A. *Bull. Soc. Chim. Fr.* **1943**, *10*, 567.
(10) Carman, R. M.; Fletcher, M. T. *Aust. J. Chem.* **1983**, *36*, 1483. Copies of the MS of all seven monochlorocineoles were kindly supplied by Dr. R. M. Carman.
(11) Cusmano, G.; Linari, A. *Gazz. Chim. Ital.* **1912**, *42*, 1. Cusmano, G.; *Gazz. Chim. Ital.* **1919**, *49*, 26. **1923**, *53*, 195; **1925**, *55*, 149; **1942**, *72*, 68.
(12) Minardi, G.; Schenone, P.; Bignardi, G. *Farmaco, Ed. Sci.* **1967**, *22*, 1077.
(13) Wolinski, J.; Hutchins, R. O.; Thorstenson, J. H. *Tetrahedron* **1971**, *27*, 753.
(14) Cocker, W.; Crowley, K. J.; Srinivasan, K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1971.

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Scheme II

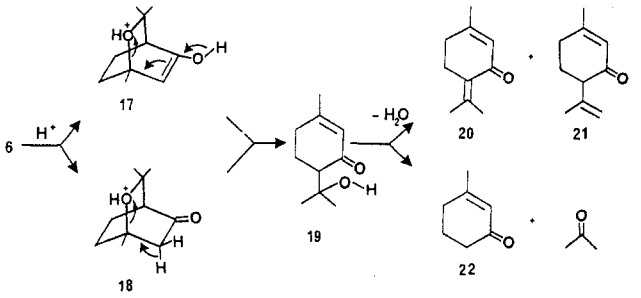


Table I. Reduction of Ketone 6

reducing agent	product composition, % 7	8
$NaBH_4$, MeOH	99.5	
$LiAlH_4$, ether	99.0	traces
H_2–Pt, AcOH, 60 psi[a]	99.0	
$Al(i\text{-}PrO)_3$, i-PrOH[b]	56	44
Na–EtOH	60	40

[a] Incomplete reduction; minor amounts of at least three unidentified hydrogenolysis products were also formed. [b] Equilibrating conditions.

In this paper we complete and extend our previous report[15] on the regioselective functionalization of **1**, which constitutes a new and easy access to many 2-oxabicyclo[2.2.2]octane and *p*-menthane derivatives, as will be shown below.

In a previous paper,[15] we reported that chromyl acetate attacks the unactivated C-5 (or C-8) methylene group of **1** in a highly regiospecific way, producing the interesting ketone 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-5-one (**6**) (all compounds described in this paper are racemic mixtures). This ketone was prepared in 1980 by Bondavalli et al.[16] through a multistep synthesis from α-terpineol.

After the best experimental conditions for our one-step procedure were selected, ketone **6** was obtained in 60% yield by using a 1:3 molar ratio of cineole–chromyl acetate[17] at 0 °C. As shown in Scheme I, minor amounts of several byproducts are also formed, but **6** is readily isolated by fractional or spinning-band distillation of the reaction mixture.

The ether linkage of ketone **6** is easily cleaved by acids under mild conditions. On boiling **6** with aqueous phthalic or oxalic acid, a mixture consisting of piperitenone (**20**) (major product), 3-methyl-2-cyclohexenone (**22**), acetone, and isopiperitenone (**21**) was obtained (Scheme II). The reaction can be visualized as involving either the enolic form of the ketone (**17**) or the protonated species (**18**), or both, yielding the key intermediate (**19**),[18] which on dehydration produces **20** along with traces of **21**.[19] Competitively, a retroaldol decomposition of **19** affords **22** and acetone.[20] Interestingly, piperitenone (**20**) was the sole reaction product when **6** was treated at room temperature with 60% sulfuric acid.[21]

Table II. Chemical Shifts of the Methyl Groups in Cineole Derivatives[a]

no.	9-Me	10-Me	11-Me	others
1	1.00	1.20	1.20	
3[b]	1.02 (0.96)	1.19 (0.34)	1.33 (0.28)	
4	1.26 (0.51)	1.09 (0.40)	1.26 (0.20)	C_6-H, 3.51 (1.41)[26]
5	1.10 (0.45)	1.29 (0.15)	1.20 (0.13)	C_6-H, 3.75 (1.11)[26]
6	1.23 (0.31)	1.14 (0.67)	1.31 (0.37)	*d*
7[b]	1.01 (0.34)	1.33 (1.08)	1.15 (0.43)	C_5-H, 4.00[c] (2.03)
8	1.06 (0.21)	1.28 (0.10)	1.23 (0.08)	C_5-H, 4.40 (1.30)
9	1.11	1.34	1.23	C_5-H, 4.91[c]
13	1.42	1.24	1.24	

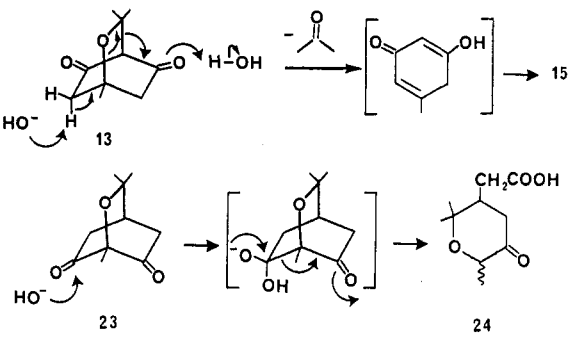
[a] The values within parentheses are the shifts (in δ units) induced after addition of $Eu(fod)_3$. [b] In CCl_4. [c] ddd with J_1 = 10 Hz, J_2 = 6 Hz, and J_3 = 2 Hz. [d] See Experimental Section.

Table III. ^{13}C NMR Spectral Data[a] of Compounds 6, 13, 30, and 31

C atom	1[b]	6	13	30	31
1	69.6	72.8	75.5	71.2	80.5
3	73.5	72.8	73.6	74.4	172.5
4	32.9	51.1	74.3	38.3	39.7
5	22.8	211.6	202.2	76.3	69.6
6	31.5	48.4	49.0	37.8	39.7
7	31.5	29.7	49.0	31.2	30.2
8	22.8	17.6	202.2	14.1	19.4
9	27.5	26.3	24.9	26.1	24.6
10	28.8	29.9	28.8	175.8	159.7
11	28.8	25.6	28.8	17.4	

[a] Solvent: $CDCl_3$. [b] See ref 34.

Scheme III



The oxidation of **6** with chromyl acetate also proceeded regiospecifically, yielding the symmetrical diketone **13**, whose structure was evident from the ^1H NMR spectrum. The *gem*-dimethyl group, the bridgehead methyl, and the C_4-H proton appeared as singlets at 1.24, 1.42, and 3.10 ppm, respectively. At 60 MHz, the methylene groups at C-6 and C-7 displayed a typical AA'BB' pattern, which simplified into an AB quartet centered at 2.64 and 2.36 ppm with J_{gem} = −18 Hz in a 100-MHz spectrometer. According to the Barfield–Grant equation,[22] the very high value for J_{gem} indicates that the C=O groups of **13** dissect the H—C—H angle of the neighboring CH_2 groups symmetrically, as is observed from a Dreiding stereomodel of **13**. The symmetry of **13** was also evident from the ^{13}C NMR data, which are listed in Table III.

Diketone **13** is far more sensitive than ketone **6**, decomposing into orcinol (**15**) on digestion with boiling water or

(15) de Martinez, M. V.; de Venditti, F. G.; de Fenik, I. J. S.; Catalán, C. A. N. *An. Asoc. Quím. Argent.* **1982**, *70*, 137.

(16) Bondavalli, F.; Schenone, P.; Ranise, A.; Lanteri, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2626.

(17) Although the stoichiometry of the reaction requires a 3:4 molar ratio of cineole–chromyl acetate, an excess of oxidant is necessary in order to obtain good yields of **6** since the highly reactive intermediate species of Cr(V) and/or Cr(IV) formed during the reaction are competitively reduced by the solvent, i.e., acetic anhydride. See, for instance: Enqvist, J. *Ann. Acad. Sci. Fenn., Ser. A2*, **1977**, *183*, 1 and ref 15.

(18) Recently we have isolated and characterized this compound, which slowly decomposes at room temperature, yielding mainly piperitenone (**20**) (ref 21).

(19) Naves, Y. R., *Riv. Ital. Essenze, Profumi, Piante Off., Aromi, Saponi, Cosmet., Aerosol* **1976**, *58*, 128 and references therein.

(20) The decomposition of **20** into **22** and acetone on digestion with formic acid has been reported: Naves, Y. R.; Papazian, G. *Helv. Chim. Acta* **1942**, *25*, 1023.

(21) de Fenik, I. J. S.; de Martínez, M. V.; de Venditti, F. G.; Catalán, C. A. N., in preparation.

(22) Barfield, M.; Grant, D. M. *J. Am. Chem. Soc.* **1963**, *85*, 1899.

by heating with 2.5% sodium bicarbonate solution at 100 °C for 3 min. This fact accounts for the presence of **15** among the reaction products of cineole (**1**) with chromyl acetate (Scheme I). The antiperiplanar arrangement of the activated *endo*-C_6-H or the *endo*-C_7-H and the C_1-O permits a facile β-elimination, which is followed by a retroaldol decomposition leading to acetone and orcinol as shown in Scheme III. It is interesting to note that under identical conditions the isomeric diketone **23** yields 2,2,6-trimethyl-5-oxotetrahydropyran-3-acetic acid (**24**).[14] The only viable path available for the reaction of **23** with base involves a reverse Claisen condensation, as shown in Scheme III.

In agreement with a previous report, lithium aluminum hydride[16] or sodium borohydride reduction of **6** yielded exclusively the *exo*-alcohol **7** as a result of a highly stereospecific attack by the hydride from the less hindered side of the carbonyl group. On seeking a route for the *endo*-alcohol **8**, we tried some other reducing agents. The results are summarized in Table I.

On the basis of steric considerations, the *endo*-alcohol **8** should be the more stable isomer and therefore the major product of an equilibrated mixture. However, Meerwein–Ponndorf–Verley reduction of **6** under equilibrating conditions led to a mixture containing 44% of **8** and 56% of **7**. It was not possible to increase the amount of **8** above this figure. Reduction with sodium in ethanol[23] gave a similar result: 40% of **8** and 60% of **7**.

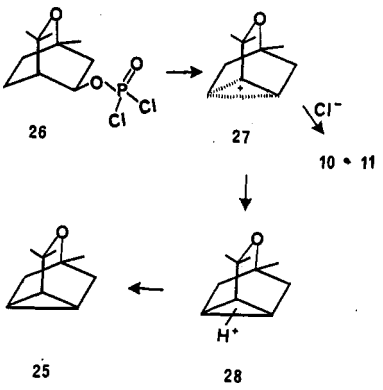
At present, the best access to the *endo*-alcohol **8** is the lithium aluminum hydride reduction of the *endo*-epoxide **12**,[16] which is easily prepared by epoxidation of **2** with a peracid.

The stereochemistry of the alcohols was assigned by studying the paramagnetic shifts induced[25] by $Eu(fod)_3$. The *exo*-alcohol **7** showed a marked downfield shift for the C-10 methyl group, in agreement with its close proximity to the OH function, while the *endo*-isomer **8** exhibited weak ΔEu values for all three methyl groups (Table II). The mass spectra of the alcohols were practically identical except for the significantly lower intensity of the molecular ion of **7**, a characteristic feature[24] of the more crowded isomer.

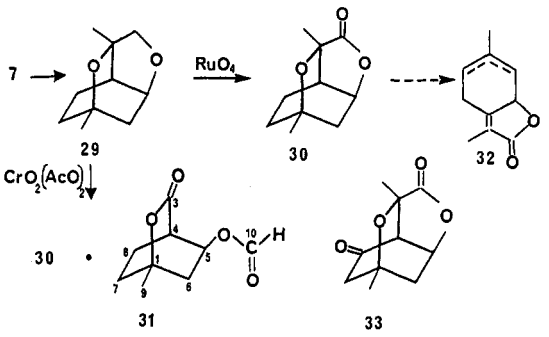
In all asymmetrically substituted cineole derivatives listed in Table II, we noted that the two singlets corresponding to the *gem*-dimethyl group were shorter than that belonging to the bridgehead methyl due to a small long-range coupling of about 0.3 Hz. This fact may be used for the assignment of the methyl groups in other cineole derivatives.

Treatment of **7** with phosphoryl chloride in pyridine yielded a mixture containing three major products in the ratio 70:18:12, which were separated by preparative GC. The two minor components were readily identified as the chlorocineoles **10** and **11**[10] by their MS and ^{1}H NMR spectra. The main product showed a weak molecular ion at m/z 152 and significant fragments at m/z 137 (base peak), 109, 97, 95, 93, 81, 79, 67, and 43. The protonic spectrum displayed two singlets at 1.17 ppm (3 H) and 1.25 ppm (6 H) and a complex multiplet of three protons between 0.70–1.05 ppm, suggesting the presence of a cyclopropane ring. The only structure compatible with the above data is the symmetrical tricyclic ether 1,3,3-trimethyl-2-oxatricyclo[2.2.2.0^{5,8}]octane (**25**).

Scheme IV



Scheme V



The formation of **25** can be explained as follows: The first step in the reaction of **7** with phosphoryl chloride must involve the hydroxyl group to afford intermediate **26**. Ionization of the phosphate ester bond, probably assisted by the favorable anti disposition of the C-4–C-8 bond, generates cation **27** (or its classical counterparts), which equilibrates with the protonated[27] cyclopropane **28**, whose further deprotonation yields **25**. Alternatively, cation **27** can be attacked by chloride ion to give a mixture of **10** and **11** as shown in Scheme IV.

Considering the syn-periplanar disposition of the *exo*-C_6–H and C_5–O bonds of **7**, we prepared the methyl xanthate of the alcohol, which cleanly produced cineolene[28] (**2**) by pyrolysis at 180 °C.

Another useful feature of **7** is that the hydroxyl group is close enough to the 10-Me group (C-10···OH distance measured on a Dreiding stereomodel = 2.6 Å) to bring about selective intramolecular hydrogen abstraction.[29] This feature provides a convenient method for functionalizing the unactivated C-10 methyl group. Thus, on treating **7** with mercuric oxide and iodine,[30] the tricyclic diether **29** was obtained in 53–60% yield. Better results were obtained with the recently described iodosylbenzene diacetate–iodine system,[31] which led to **29** in 82% yield. (Scheme V.)

(23) For a discussion on the reduction of ketones with alkali metals and alcohols, see: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: 1972; pp 145–158 and references therein.
(24) Biemann, K.; Seibl, J. *J. Am. Chem. Soc.* **1959**, *81*, 3149.
(25) Sanders, J. K. M.; Williams, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 641. Sanders, J. K. M.; Williams, D. H. *J. Chem. Soc. D* **1970**, *7*, 422. Hinckley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 5160.
(26) Gandini, A.; Bondavalli, F.; P. Schenone, P.; Bignardi, G. *Ann. Chim. (Rome)* **1972**, *62*, 188.
(27) The transient existence of protonated cyclopropanes is well-documented. See, for instance: Attina, M.; Cacace, F.; Giacomello, P. *J. Am. Chem. Soc.* **1980**, *102*, 4768. Dymersky, P. P.; Prinstein, R. M.; Bente, P. F.; McLafferty, F. W. *J. Am. Chem. Soc.* **1976**, *98*, 6834. Prolingheuer, E. C. *Chem. Ber.* **1980**, *113*, 104.
(28) Bondavalli, F.; Schenone, P.; Lanteri, S.; Ranise, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 430.
(29) Carruthers, W. *Some Modern Methods of Organic Synthesis*, 2nd ed.; Cambridge: 1978; pp 231–260 and references therein.
(30) Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1964**, *86*, 1528.
(31) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953.

The protonic spectrum of **29** showed the methyl groups at 1.11 and 1.27 ppm. The C-10 methylene protons appeared as an AB quartet at 3.55 and 3.67 ppm with J_{gem} = −8.5 Hz; the C_5-H proton appeared at 4.30 ppm as a poorly resolved multiplet. The MS showed the molecular ion at m/z 168 (19%) and fragments at m/z 150 (26; M − 18), 138 (15; M − CH_2O), 135 (11; 150 − 15), 123 (28; 138 − 15), 110 (base peak; 138 − C_2H_4), 95 (80; 110 − 15), and 43 (54; $C_2H_3O^+$).

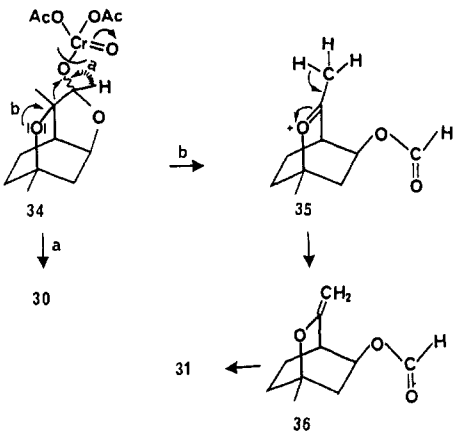
Ruthenium tetraoxide oxidation[32,33] of **29** gave the bridged γ-lactone **30** in nearly quantitative yield. The protonic spectrum of **30** displayed two methyl groups as singlets at 1.16 and 1.36 ppm and the C-5 proton as a dt centered at 4.78 ppm with $J_1 = J_2$ = 5.2 Hz and J_3 = 2.2 Hz. The IR spectrum (KBr) showed a splitting of the carbonyl absorption, with bands at 1785 and 1772 cm^{-1}. Final confirmation of the structure was obtained from the ^{13}C NMR spectrum. The assignments are shown in Table III, where the values for cineole[34] are included for comparison.

Two attempts at breaking the ether bridge of **30** with hydrogen bromide in glacial acetic acid or boron trifluoride etherate in 1,2-dichloroethane were unsuccessful. We expected to obtain the *p*-menthadien-8→3-olide **32** since the sequence **1** → **7** → **29** → **30** → **32** could be a possible biomimetic simile for the metabolic detoxication of cineole in the koala.[35]

An attempt to prepare the tricyclic keto diether **33** by chromyl acetate oxidation of **29** was unsuccessful. This reaction yielded two products in nearly equal amounts. The first one was identified as the lactone **30** on the basis of its physical and spectroscopic properties while the second one, rather surprisingly, gave a molecular formula of $C_9H_{12}O_4$, indicating that a carbon atom had been eliminated in the reaction. The mass spectrum, besides showing a molecular ion at m/z 184, displayed fragments at m/z 155 (M − CHO), 139 (M − HCO_2), and 138 (M − HCO_2H), which are indicative of a formate residue. The IR spectrum (KBr) displayed carbonyl absorptions at 1748 (δ-lactone), 1720, and 1710 cm^{-1} (formate). The protonic spectrum exhibited a single methyl group at 1.45 ppm (s, 9-Me),[36] a complex 5-H multiplet between 2.10 and 1.55 ppm, a dd of an ABX system at 2.29 ppm with J_1 = 15.2 Hz and J_2 = 9.6 Hz (*endo*-C_6-H), a ddd at 2.92 ppm with $J_1 = J_2 = J_3$ = 3.1 Hz (C_4-H), a dt at 5.24 ppm with J_1 = 9.6 Hz and $J_2 = J_3$ = 3.1 Hz (C_5-H), and a singlet at 8.04 ppm (formate proton). Irradiation at 5.24 ppm simplified the signals at 2.92 and 2.29 ppm into a dd ($J_1 = J_2$ = 3.0 Hz) and a d (J = 15.2 Hz), respectively. These data are consistent with the structure **31**. Finally, the ^{13}C NMR spectrum confirmed structure **31**.[36] The assignments are shown in Table III.

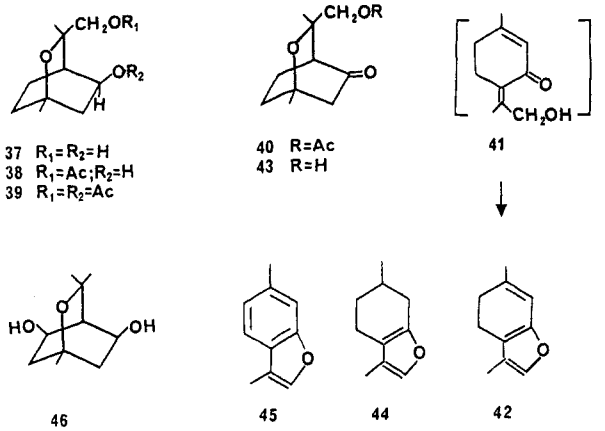
At this point, we speculated that **31** might originate by oxidation of **30**. However, chromyl acetate oxidation of **30** under identical conditions to those employed to oxidize **29** did not produce **31**. Probably both **30** and **31** are derived from a common intermediate such as the chromium(V) ester **34** (or a similar species), which, depending on the stereochemistry of the chromium ester residue, would lead to **30** or **31**. Thus, for an endo configuration, the reaction would follow a normal decomposition (path a),

Scheme VI



producing **30**. However, an exo configuration would allow the cleavage of the C-3–C-10 bond due to the anchimeric assistance by the bridged ether oxygen, giving the stabilized cation **35** (path b). Elimination of a proton from **35** would give the vinyl ether **36**, whose further oxidation would yield **31** as shown in Scheme VI.

Lithium aluminum hydride reduction of **30** afforded **37**, which is a valuable starting point for preparing a plethora of difunctionalized derivatives of cineole and *p*-menthane. Thus, treatment of **37** with 1.05 equiv of acetic anhydride in pyridine yielded a mixture of monoacetate **38**, diacetate **39**, and unreacted starting diol **37**. Oxidation of **38** with pyridinium chlorochromate[37] yielded ketone **40**, which was converted by hydrochloric acid into 3,6-dimethyl-4,5-dihydrobenzofuran (**42**) through the intermediate **41**.[38] Though the yield of this last step was low (ca. 20%), we did not try to seek the best experimental conditions to perform the reaction, owing to the small amount of **40** available. It is likely that the keto alcohol **43** is a much better alternative for preparing **42**. Partial hydrogenation of **42** using Adams' catalyst gave menthofuran (**44**) along with a minor amount of **45**. Likewise, the diol **46**, readily obtained by sodium borohydride reduction of **13**, can be used to prepare evodone.[21,39]



Experimental Section

General. Melting points were determined on an E. Leitz 350 microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 421 spectrometer. ^1H NMR spectra were taken

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(33) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 814.
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(36) Systematic name for **31**: (1*RS*,4*SR*,5*RS*)-1-methyl-2-oxabicyclo-[2.2.2]octan-5-ol-3-one formate.
(37) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(38) A synthesis of menthofuran (**44**) that probably proceeds via a dihydro derivative of **41** has been reported: Sato, T.; Tada, M.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3129.
(39) Masaki, Y.; Sakuma, K.; Hashimoto, H.; Kaji, K. *Chem. Lett.* **1981**, 1283 and references cited therein.

on a Varian EM 360 or XL-100 spectrometer in $CDCl_3$ as solvent unless otherwise stated. Mass spectra were determined with a MAT 112 S spectrometer at an ionizing voltage of 70 eV. Gas chromatographic analyses and separations were carried out on a Perkin-Elmer F 21 preparative chromatograph using the following columns: column A, 6.7 mm × 2.7 m stainless steel column packed with 5% Carbowax 20 M on Chromosorb G; column B, 6.7 mm × 1.8 m stainless steel column packed with 5% XE 60 on Chromosorb G. All samples gave a satisfactory elemental analysis.

Oxidation of 1,8-Cineole (1) with Chromyl Acetate. Preparation of 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octan-5-one (6). a. Preparation of Chromyl Acetate. Chromic anhydride (75 g, 750 mmol; dried at 120 °C and finely powdered; 98.3% pure) was added over 2 h to a stirred solution of acetic anhydride (375 mL) and glacial acetic acid (180 mL) cooled at 0 °C. The oxidant was prepared just before use.

b. Oxidation Procedure. To a stirred solution of 1 (38.55 g, 250 mmol; 99.91% pure) in glacial acetic acid (60 mL) cooled at 0–5 °C was added dropwise over 3 h the above solution of chromyl acetate. The mixture was kept below 10 °C for 10 h and then overnight at room temperature with continuous stirring. After 24 h, the green mixture was poured into three times its volume of ice–water and thoroughly extracted with ether. The organic layer was treated with a concentrated solution of sodium carbonate until cessation of CO_2 evolution, washed with water, dried (Na_2SO_4), filtered, and evaporated to give a reddish yellow oil (32.8 g), which was analyzed by GC (column A) and showed the following composition: **1**, 26.1%; **6**, 59.8%; **3**, 2.3%; **9**, 3.6%; **13** 3.6%; **14**, 1.0%; **16**, 1.1%; and **15** 0.8%. Fractional distillation of this mixture through a short column yielded four fractions: I, 7.74 g, bp 52–57 °C (10 mm), constituted by **1** (96.2%), **6** (2.5%), and traces of other components; II, 14.34 g, bp 64–66 °C (2.2–2.5 mm), consisting of **1** (4.3%), **6** (92.1%), **3** (1.3%), **9** (1.7%), and traces of two other components; III, 3.72 g, bp 69–72 °C (2.2 mm), consisting of **1** (0.4%), **6** (87.8%), **3** (2.8%), **9** (7.9%), **13** (0.6%), and traces of other compounds; IV, residue, 6.07 g, which was subsequently distilled to give 1.55 g of a yellow oil, bp 70–111 °C (1–2 mm), consisting of **6** (5.2%), **3** (5.0%), **9** (17.7%), **13** (40.4%), **14** (14.7%), **16** (10.5%), and **15** (6.5%). After this fraction was allowed to stand for 48 h at 4 °C, it crystallized partially, yielding 153 mg of essentially pure **13**.

A careful fractional or spinning-band distillation of fractions II and III gave 11.1–11.9 g (overall) of racemic **6** (purity: >99% by GC), bp 61 °C (1.5 mm). A specimen purified by preparative GC (column A, 130 °C had the following: mp 13–14 °C; $n^{26}{}_D$ 1.4655; $d_{26}{}^{26}$ 1.018; IR (film) 1730 cm^{-1} (C=O); MS, *m/z* (rel int) 168 (M^+, 9), 153 (36), 140 (6), 126 (7), 125 (28), 111 (38), 83 (34), 82 (68), 67 (27), 55 (49), 43 (100), and 41 (28). ^1H NMR (100 MHz, $CDCl_3$): δ 1.14 (s, 10-Me), 1.23 (s, 9-Me), 1.31 (s, 11-Me), 2.15 (br t, J = 2.8 Hz, C_4-H), 2.23 (d, J = −19 Hz, *endo*-C_6-H), and 2.35 (br d, J = −19 Hz, *exo*-C_6-H) (assignments based on LIS[25,40] and DR experiments).

The **semicarbazone** derivative of **6** showed the following: mp 216 °C (from 75% ethanol), λ_{max} (EtOH) 228 nm, log ϵ = 4.20. 2,4-DNPH: mp 128 °C. For structural identification of compounds **3**, **9**, **14**, and **16**, see ref 15.

1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane-5,8-dione (13). The crystals separated from the distilled fraction IV (153 mg) were crystallized twice from hexane to give an analytical sample (89 mg) of **13**, mp 93 °C. IR: 1755 and 1720 cm^{-1} (1,3-dicarbonyl compound). ^1H NMR: discussed in the text. MS: *m/z* (rel int) 182 (M^+, 16), 167 (25), 164 (20), 140 (14), 136 (5), 125 (63), 98 (14), 85 (27), 83 (100), 82 (64), 69 (31), 59 (16), 55 (39), and 43 (54).

Diketone **13** can be prepared from **6** (0.84 g, 5 mmol) by oxidation according to the general procedure described above by using a molar ratio of 1:1.5 **6**–chromyl acetate. The isolated product (0.563 g) showed the following composition (column B): **13**, 32%; unreacted **6**, 58%; **15**, 5%, and small amounts of other unidentified products. A total of 0.151 g of diketone **13** was isolated from this mixture by CC on silica gel (27 g) using hexane–ethyl acetate, 4:1, as eluting solvent (R_f on TLC with this solvent mixture: **6**, 0.49; **13**, 0.31, and **15**, 0.15).

Acid Cleavage of 6. a. With Phthalic Acid. A mixture of **6** (0.39 g), phthalic acid (1.5 g), and water (15 mL) was steam distilled, and the distillate was extracted with ether. The organic layer was dried (Na_2SO_4), filtered, and evaporated, and the residue (0.32 g) was analyzed by GC (column A): acetone, 0.5% (a significant amount of acetone is lost during workup due to its volatility and water solubility); **22**, 9%; **6**, 28.6%; **21**, 0.4%, and **20**, 61.2% (the quantitative composition of the mixture depended on the speed of distillation). The compounds were identified by co-injection with authentic samples and mass spectrometry.

Similar results were obtained when oxalic acid was used.

b. With Sulfuric Acid. To 2 mL of 60% H_2SO_4 was added 100 mg of **6**, and the mixture was stirred for 1.5 h at room temperature. The mixture was neutralized with aqueous sodium carbonate, extracted with ether, dried, and evaporated to give 62 mg of essentially pure piperitenone (**20**) (94.7% by GC).

Decomposition of Diketone 13 into Orcinol (15). Diketone **13** (50 mg) was heated for 3 min at 100 °C with sodium bicarbonate solution (2.5%, 10 mL) prepared with freshly boiled water. The solution was extracted with ethyl acetate (2 × 5 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to yield 35 mg of **15** (partially as monohydrate) that was essentially pure by TLC and NMR. A similar result was obtained on boiling **13** in water for 2 h.

***exo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octan-5-ol (7) and *endo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octan-5-ol (8). a. Reduction of 6 with Sodium Borohydride.** A solution of **6** (0.505 g, 3 mmol) in MeOH (5 mL) was added dropwise to a recently prepared solution of sodium borohydride (0.228 g, 6 mmol) in 10 mL of MeOH and kept at room temperature for 2 h, refluxed for 3 h, and then acidified with acetic acid. The solution was concentrated (ca. 1.5 mL), diluted with a 5% sodium carbonate solution (4 mL), and thoroughly extracted with ethyl acetate. After drying and solvent evaporation, the oily residue (0.461 g, 92%) was shown to be essentially pure **7** on both GC and TLC. To obtain an analytical sample, the residue was chromatographed on silica gel and eluted with hexane–ethyl acetate, 3:1; the alcohol crystallized after several weeks in the refrigerator, mp 40 °C (reported[16] for the (+)-isomer: 90–91 °C). The NMR spectum is described in Table II. MS, *m/z* (rel int) 170 (M^+, 2.7), 155 (41), 153 (2), 152 (1), 142 (1.5), 141 (3), 137 (15), 127 (14), 108 (23), 93 (48), 87 (24), 85 (32), 71 (20), 69 (28), 59 (37), 43 (100).

The acetate **9** had mp 42–43 °C. The NMR spectrum is described in Table II.

b. Reduction of 6 with Lithium Aluminum Hydride. A solution of **6** (0.505 g; 3 mmol) in ether (5 mL) was added dropwise to a stirred suspension of LAH (0.228 g) in ether (20 mL) and then refluxed for 3 h. The mixture was cooled at 0 °C and treated with water (0.25 mL), 4 M sodium hydroxide (0.25 mL), and water (0.5 mL). The precipitate was filtered and extracted twice with ether. The ethereal extracts were dried (Na_2SO_4) and evaporated to leave an oily residue (0.450 g, 90%), which when analyzed by GC (column B, programmed from 100 °C to 130 °C at 2 deg/min) was shown to be composed of **7** (99%) and traces of **6** and **8**.

c. Catalytic Reduction of 6. A mixture of **6** (0.505 g), glacial acetic acid (5 mL), Adams' catalyst (25 mg), and a drop of concentrated hydrochloric acid was hydrogenated in a Parr apparatus at room temperature and 60 psi of hydrogen pressure for 7 h. The mixture was filtered, carefully neutralized with a 30% sodium hydroxide solution, and extracted with ether. The ethereal phase was washed with brine, dried, and evaporated, leaving 0.461 g (91%) of residue. GC showed the following composition: **6**, 47.2%; **7**, 29.8%; and three unidentified hydrogenolysis products of shorter retention time than **6** with percentages, by elution order, 6.0%, 1.9%, and 14.1%.

d. Reduction with Aluminum Isopropoxide. Thirty milliliters of a 1 M solution of aluminum isopropoxide in isopropyl alcohol[41] and 0.505 g of **6** were placed in a 50-mL flask provided with a distillation head and a cold finger condenser at the top. The apparatus was protected against moisture, and the mixture was slowly distilled. When the acetone test on the distillate was weakly positive, a sample was analyzed by GC (column B, 110 °C), giving the following composition: **6**, 3.3%; **8**, 19.6%; and **7**, 77.1%. Then heating was continued under total reflux, and the

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equilibration was monitored by GC (time in hours followed by the percentages of **6**, **8**, and **7**, respectively): 10 h, 3, 30, 67; 30 h, 3, 35, 62; 50 h, 2.5, 38.5, 59; 70 h, 3, 41, 56; 90 h, 2, 43, 55; 110 h, 3, 42, 55; 130 h, 2, 43, 55. The reaction mixture was evaporated in vacuo, diluted with water, neutralized with dilute hydrochloric acid, and extracted with ether. After drying and solvent evaporation, 409 mg of a mixture consisting of **6** (traces), **8** (44%), and **7** (56%) was obtained. Alcohol **8** was isolated as a colorless oil (96.1% pure) by preparative GC (column B, 110 °C) (reported[16] for the (−)-isomer: mp 68–69 °C). NMR spectrum: see Table II. MS: *m/z* (rel int) 170 (M^+, 13), 155 (12), 153 (1.5), 152 (1.5), 142 (2), 141 (4), 137 (12), 127 (12), 108 (26), 93 (32), 87 (36), 85 (29), 71 (26), 69 (34), 59 (23), 43 (100).

e. Reduction with Sodium–Ethanol. Sodium (0.51 g) in small pieces was added to a stirred solution of **6** (0.505 g) in anhydrous ethanol (7 mL). The reaction mixture was then diluted with anhydrous ethanol (5 mL) and refluxed until the sodium was completely dissolved. The mixture was diluted with water (40 mL) and extracted with ether (4 × 30 mL), and the combined ethereal extracts were washed with brine. After drying and solvent evaporation, 0.24 g (47%) of a reddish oily residue was obtained that showed the following composition: **6**, traces; **7**, 59.7%; and **8**, 40.3%.

1,3,3-Trimethyl-2-oxatricyclo[2.2.2.0^{5,8}]octane (25), *exo*-5-Chloro-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane (10), and *endo*-5-Chloro-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane (11). Phosphoryl chloride (15.35 g, 100 mmol) was added dropwise at 0 °C to a solution of **7** (4.25 g, 25 mmol) in anhydrous pyridine (40 mL). The mixture was stirred at room temperature for 48 h, cooled at 0 °C, treated dropwise with water (20 mL), and extracted with ether (4 × 50 mL). The ethereal extracts were washed with 5% hydrochloric acid (3 × 60 mL), a saturated solution of $CuSO_4 \cdot 5H_2O$ (2 × 20 mL), and brine, then dried, filtered, and evaporated to leave an oily residue (1.74 g). GC analysis showed three major compounds in the ratio 70:18:12 corresponding to **25**, **11**, and **10**, respectively, which were separated by preparative GC. Compound **25** was a colorless oil. The NMR spectrum is discussed in the text. MS: *m/z* (rel int) 152 (M, 1), 137 (100), 134 (7), 109 (26), 97 (28), 95 (47), 93 (33), 81 (25), 67 (35), 43 (46). The chlorocineoles **10** and **11** were isolated as pale yellow oils whose spectroscopic data (MS, ^{1}H NMR) were practically identical with those reported.[10]

1,3,3-Trimethyl-2-oxabicyclo[2.2.2]oct-5-ene (2). To a stirred suspension of sodium hydride (0.86 g, 36 mmol) in dry ether (25 mL) was added dropwise a solution of alcohol **7** (5.1 g, 30 mmol) in dry ether (5 mL), and the mixture was refluxed for 3 h. Carbon disulfide (2.62 g, 34 mmol) was added, the reflux was continued for 3 h, and then methyl iodide (4.83 g, 34 mmol) was added and the mixture refluxed for 3 h. The mixture was diluted with water, the organic layer was separated, dried, and filtered, and the solvent was evaporated to give the crude xanthate (7.45 g, 95%).

The crude product was heated under reflux at 170–180 °C for 10 h, and the residue was distilled at 30 mm through a short column, yielding 2.39 g (55%) of essentially pure **2** (>95% pure by GC). The mass and ^{1}H NMR spectra were as reported.[1,28]

Preparation of the Tricyclic Diether 29. a. Alcohol **7** (3.80 g) in dry carbon tetrachloride (760 mL) was stirred with mercuric oxide (6.84 g) and iodine (8.13 g) under gentle reflux (8 h). The progress of the reaction was monitored by TLC (solvent, hexane–ethyl acetate, 85:15; R_f (**29**) 0.40). The mixture was then filtered, washed with aqueous sodium thiosulfate, and dried and the solvent removed in vacuo. The residue was chromatographed on silica gel using hexane–ethyl acetate, 9:1, as eluting solvent to give 1.99 g (53%, 98.7% pure) of **29** as a pale yellow oil. The mass and ^{1}H NMR spectra are discussed in the text. The experiment was repeated under irradiation using a high-pressure mercury lamp,[30] yielding 2.25 g (60%) of **29** and 53 mg of **6**.

b. Alcohol **7** (510 mg, 3 mmol) in cyclohexane (300 mL) containing iodine (762 mg) and iodosylbenzene diacetate (1.015 g, 3.15 mmol) was heated at 40–45 °C for 1.5 h while being irradiated with a 100-W tungsten-filament lamp.[31] The mixture was poured into water and extracted with ether. The ethereal extracts were processed as above to give 414 mg (82%) of **29**.

1,3-Dimethyl-2-oxabicyclo[2.2.2]octan-3→5-olide (30). To a solution of 923 mg (5.5 mmol) of **29** in carbon tetrachloride (12 mL) was added RuO_2 (130 mg) followed by 16 mL of a 5.16% aqueous solution of sodium hypochlorite[42] (household bleach). The two-phase mixture was magnetically stirred at 0 °C and the reaction monitored by TLC (silica gel; hexane–ethyl acetate, 75:25; R_f(**30**) 0.43, R_f(**29**) 0.66). When the oxidation was complete (ca. 12 h), the yellow carbon tetrachloride layer was separated and the aqueous layer extracted with CCl_4 (4 × 10 mL). The combined organic extracts were treated with 5 drops of methanol to destroy the excess of RuO_4. The precipitated RuO_2 was filtered, and the filtrate was evaporated in vacuo to give 930 mg (92%) of a crystalline residue, which was essentially pure **30**, mp 79 °C (hexane). IR (KBr): 1785 and 1772 cm^{-1} (γ-lactone), 1380, 1290, 1250, 1127, 1095, 1060, 990, 930, 831, and 622 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra: discussed in the text and Table III, respectively. MS: *m/z* (rel int) 182 (M, 2.2), 138 (M − CO_2, 23), 123 (14), 111 (7), 109 (10), 108 (6), 95 (43), 93 (14), 80 (34), 71 (27), 55 (13), 43 (100).

Chromyl Acetate Oxidation of 29. The diether **29** (900 mg, 5.36 mmol) in acetic anhydride (1.6 mL) was treated with 12 mL of chromyl acetate solution prepared as previously described (this volume is equivalent to ca. 15 mmol of chromyl acetate) and processed as described for the oxidation of 1,8-cineole (**1**). In this way, a partially crystallized residue (680 mg) was obtained, which showed two major spots on TLC, with R_f 0.50 and 0.32, respectively (hexane–ethyl acetate, 7:3). The compounds were separated by column chromatography (silica gel; hexane–ethyl acetate, 7:3). The product with R_f 0.50 was obtained as a crystalline solid (259 mg), mp 76–77 °C, which was identical with lactone **30** (^{1}H NMR, IR, mmp). The compound with R_f 0.32 was a crystalline solid (350 mg), mp 68.5 °C (hexane–ethyl acetate), and was identified as the formate lactone **31**. ^{1}H NMR and ^{13}C NMR spectra: discussed in the text and Table III. IR (KBr): 1748 (δ-lactone), 1720 and 1710 (formate), 1383, 1232, 1210, 1170, 1083, 1060, and 970 cm^{-1}. MS: *m/z* (rel int) 184 (M, 0.6), 155 (1.5), 139 (4), 138 (2), 111 (10), 110 (10), 94 (48), 84 (19), 79 (21), 57 (42), 43 (100).

***exo*-5-Hydroxy-1,3-dimethyl-2-oxabicyclo[2.2.2]oct-3-anemethanol (37).** A solution of **30** (195 mg, 1.06 mmol) in ether (2 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (300 mg) in anhydrous ether (3 mL) and the mixture refluxed for 5 h. After the usual workup, the diol **37** (5,10-dihydroxycineole) was obtained as a crystalline solid (187 mg, 94%), mp 113 °C (heptane–ethyl acetate). ^{1}H NMR: δ 1.13 (s, 3 H), 1.21 (s, 3 H), 3.54 (br s, 2 H), 3.93 (m, 1 H), and 4.75 (br, 2 H); on exchange with D_2O, the broad singlet at 3.54 ppm was transformed into an AB quartet centered at 3.47 and 3.61 ppm with J_{gem} = −11.5 Hz; the multiplet at 3.93 ppm was transformed into a ddd with J_1 = 10 Hz, J_2 = 6 Hz, and J_3 = 2 Hz, and the broad signal at 4.75 ppm disappeared. MS: *m/z* (rel int) 156 (M − CH_2O; 25), 155 (M − CH_2OH; 22), 137 (24), 93 (66), and 43 (100).

***exo*-5-Hydroxy-1,3-dimethyl-2-oxabicyclo[2.2.2]oct-3-anemethanol Monoacetate (38) and Diacetate (39).** A solution of **37** (376 mg, 2 mmol) in anhydrous pyridine (6 mL) was treated with acetic anhydride (217 mg = 0.20 mL; 2.10 mmol) and allowed to react for 5 h at room temperature. The mixture was treated with 10% hydrochloric acid (30 mL) and thoroughly extracted with chloroform. The chloroform extracts were washed with a saturated solution of $CuSO_4$ and dried, and the solvent was evaporated to yield 414 mg of residue. GC analysis indicated the following composition: **38**, 64%; **39**, 20%; and **37**, 16%. Column chromatography of the mixture (silica gel; ethyl acetate–chloroform, 25:75, as eluting solvent) yielded 70 mg of pure **39**, 241 mg of pure **38**, and 38 mg of **37**.

The monoacetate **38** was a colorless oil. ^{1}H NMR: δ 1.12 (s, 3 H), 1.28 (s, 3 H), 2.08 (s, 3 H), 4.20 and 4.45 (AB q, J = 11 Hz, 10-CH_2), 4.25 (m, 1 H, C_5-H). IR (film): 3350 (OH) and 1735 cm^{-1} (acetate). MS: *m/z* (rel int) 155 (M − CH_2OAc; 6), 137 (155 − H_2O; 12), 95 (2), 93 (155 − CH_2=CHOH; 36), 55 (1.5), 45 (6.5), 43 (100). The diacetate **39** was a colorless oil, which crystallized after several days in the refrigerator, mp 55–56 °C. ^{1}H NMR: δ 1.10 (s, 3 H), 1.26 (s, 3 H), 1.97 (s, 3 H), 2.02 (s, 3 H), 3.90 and 4.10 (AB q, J = 11 Hz, 10-CH_2), 4.91 (ddd, J_1 = 10.5 Hz, J_2 = 7 Hz, and J_3 = 2 Hz, C_5-H). IR (film): 1740 cm^{-1} (acetate). MS: *m/z* (rel int) 197 (M − CH_2OAc; 12), 137 (197 − AcOH; 24), 109

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(2.5), 95 (3), 93 (45), 55 (1.5), 45 (8), 43 (100).

Preparation of the Keto Acetate 40. Monoacetate **38** (233 mg) in CH_2Cl_2 (3 mL) was added dropwise to a suspension of pyridinium chlorochromate[37] (330 mg) in CH_2Cl_2 (3 mL) at room temperature. The mixture was stirred for 2 h and diluted with anhydrous ether (6 mL), the supernatant decanted, and the gummy residue extracted with ether (3 × 6 mL). After solvent evaporation, the residue (249 mg) was chromatographed through a short silica gel column ($CHCl_3$) to yield **40** (198 mg, 86%) as a colorless oil. ^1H NMR: δ 1.25 (s, 3 H), 1.29 (s, 3 H), 2.01 (s, 3 H), 3.75 and 3.97 (AB q, J = 11.5 Hz, 10-CH_2). IR (film): 1730–1750 cm^{-1} (acetate and carbonyl). MS: m/z (rel int) 153 (M – CH_2OAc; 62), 111 (153 – CH_2=C=O; 51), 109 (10), 71 (5.5), 67 (6), 57 (6), 55 (16), 43 (100).

3,6-Dimethyl-4,5-dihydrobenzofuran (42) and Menthofuran (44). The keto acetate **40** (100 mg) in benzene (3 mL) was magnetically stirred at 50 °C under an N_2 atmosphere with 2 M hydrochloric acid (10 mL) for 4 h. The benzene layer was separated, and the aqueous layer was further extracted with ether (3 × 10 mL). The organic extracts were washed with aqueous sodium hydrogen carbonate solution and brine, dried, and evaporated in vacuo, giving a residue, which was chromatographed on a Florisil column (4 g). Elution with pentane afforded **42** (13 mg, 20%) as a pale yellow oil, sensitive to air and light. ^1H NMR: δ 1.82 (br s, 3 H), 1.88 (br s, 3 H), 6.69 (m, 1 H), and 7.25 (m, 1 H). This compound, dissolved in pentane (2 mL) and cooled at 0 °C, was subjected to a microhydrogenation for 15 min using Adams' catalyst (4 mg). After solvent evaporation, the residue was analyzed by GC, showing the following composition: **44**, 82%; **45**, 12%; and minor amounts of other unidentified products. Compounds **44** and **45** were identified by comparison with authentic samples on three different GC columns. The protonic spectrum of the mixture clearly showed the signals corresponding to **44**.[43]

***exo,exo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane-5,8-diol (46).** Diketone **13** (1.023 g) in methanol (25 mL) was treated with sodium borohydride (230 mg), and the mixture was stirred at room temperature for 27 h. The solution was neutralized with glacial acetic acid, then alkalized to pH 8 with sodium carbonate solution, and thoroughly extracted with ethyl acetate. After solvent evaporation, the residue was chromatographed on a silica gel column with chloroform–acetone, 7:3, to give **46** (1.003 g, 96%) as plates, mp 165–165.5 °C (ethyl acetate–heptane). IR (KBr): 3430–3180 (OH), 1370, 1355, 1250, 1220, 1115, 1030, and 970 cm^{-1}. ^1H NMR ($CDCl_3$ + Me_2SO-d_6): δ 1.08 (s, 3 H, 9-Me), 1.41 (s, 6 H, 10-Me and 11-Me), 3.80 (m, 4 H, 2 OH, C_5-H and C_8-H). MS: m/z (rel int) 171 (M – Me; 74), 142 (6), 131 (3), 127 (23), 125 (7), 109 (16), 100 (10), 93 (92), 87 (24), 85 (53), 73 (63), 43 (100).

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Total Synthesis and Absolute Configuration of the Natural Dipeptide γ-Glutamylmarasmine

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The natural dipeptide γ-glutamylmarasmine (**1**) and its sulfoxide epimer **22** have been synthesized in optically active form starting from L-glutamic acid and L-cystine. In a convergent approach, the amine **14** and the anhydride **15** were synthesized and subsequently coupled by amide formation. After separation of the epimeric sulfoxides **16** and **17** and subsequent removal of the amino and carboxyl protecting groups (→ **20** and **21**), the chlorine atom was substituted by SMe by reaction with NaSMe in liquid ammonia to yield **1** and **22**, respectively. By comparison of ^3J and [α] values it was concluded that **1** is identical with γ-glutamylmarasmine. The absolute configuration of **1** was determined by CD spectroscopy; the sign of the Cotton effect was employed in the assignment of the configuration of the sulfoxide–sulfur atom. γ-Glutamylmarasmine was thus assigned the $S_cR_cS_s$ configuration.

Introduction

During the last 25 years, a large number of γ-glutamyl derivatives of amino acids and amines have been isolated from plants including mushrooms (Basidiomycetes).[1] Among these are eighteen γ-glutamyl derivatives of sulfur or selenium containing non-protein amino acids.[1] One of these is γ-glutamylmarasmine (**1**) an *N*-γ-L-glutamyl *S*-substituted L-cysteine derivative.

This dipeptide has been isolated[2] from the Basidiomyceteous mushrooms *Marasmius alliaceus*, *M. scorodonius*, and *M. prasiosmus* which are known for their garlic like odor.[3] In aqueous solution it gradually decomposes with the formation of the typical odor of the parent mushrooms.[2] This odor has been ascribed to products derived from the sulfenic acid $MeSCH_2SOH$ formed from **1** by an acid-catalyzed β-elimination[4] reaction with concomitant formation of γ-glutamyldehydroalanine. In the mushroom itself a similar degradation takes place catalyzed by the fungal C–S lyase.[2,5] However, this β-elimination reaction takes place at higher pH (8.5) and only after cleavage of the amide bond of **1** by γ-glutamyl transpeptidase.[6,7] This

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