# Isolation and Structural Elucidation of Zoapatanol and Montanol, Novel Oxepane Diterpenoids from the Mexican Plant Zoapatle (*Montanoa tomentosa*)

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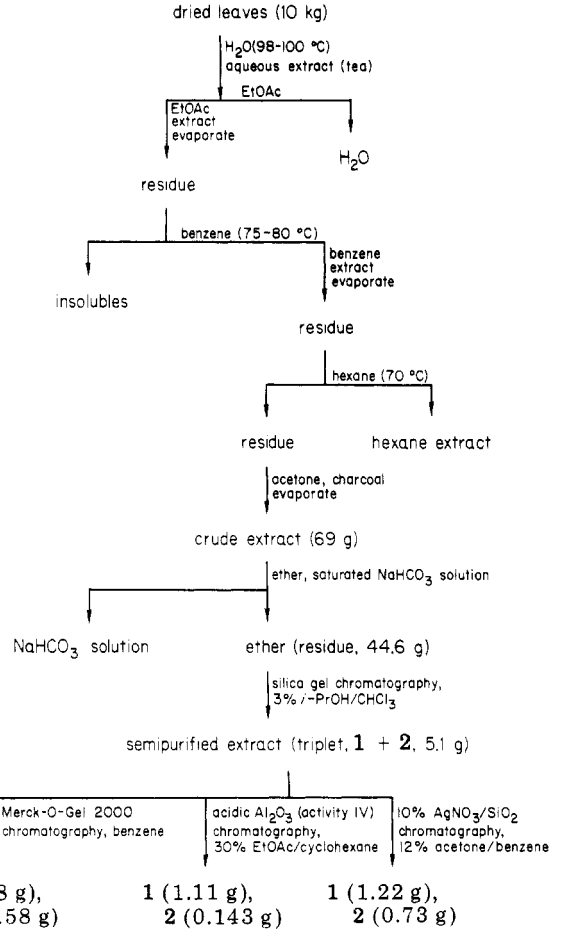
Two novel biologically active oxepane diterpenoids, zoapatanol (1) and montanol (2), have been isolated from the leaves of zoapatle (*Montanoa tomentosa*). A tea prepared from the plant has been used in Mexico for the past four centuries to induce menses and labor. The isolation of 1 and 2 via a variety of chromatographic and chemical procedures is described. The two title diterpenoids and related oxepanes were characterized by a variety of spectroscopic methods and chemical degradation. The structure of the major component 1 was confirmed by X-ray analysis of a 3,8-dioxabicyclo[3.2.1]octane derivative.

Zoapatanol (1) and montanol (2) are biologically active, novel oxepane diterpenoids isolated[1] from the Mexican plant *Montanoa tomentosa* (zoapatle, Family Compositeae). This plant has been used during the past four centuries by Mexican women to induce menses and labor. In fact, leaves of the plant are still sold today in the

Scheme I. Isolation of Zoapatanol (1) and Montanol (2) from *Montanoa tomentosa*




(1) (a) Wachter, M. P.; Kanojia, R. M. U.S. Patent 4 086 358, Apr 25, 1978. (b) *Ibid.* 4 130 556, Dec 19, 1978.
(2) Levine, S. D.; Hahn, D. W.; Cotter, M. L.; Greenslade, F. C.; Kanojia, R. M.; Pasquale, S. A.; Wachter, M. P.; McGuire, J. L. *J. Reprod. Med.* **1981**, 524-528.
(3) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C. J.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L., Noriega, L.; Guzman, A.; Mijarez, A.; Tover, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404-3405.
(4) Hahn, D. W.; Ericson, E. W.; Lai, M. T.; Probst, A. *Contraception* **1981**, *23*, 133-140.
(5) Geissman, T. A.; Griffin, T. S. *Rev. Latinoam. Quim.* **1971**, *2*, 81-83.
(6) Caballero, Y.; Walls, F. *Bol. Inst. Quim. Univ. Nac. Auton. Mex.* **1970**, *22*, 79-102.
(7) Mateos, J. L.; Noriega, L.; Huettemann, R. E.; Kanojia, R. M., U.S. Patent 3 996 132, Dec 7, 1976.
(8) Kanojia, R. M.; Huettemann, R. E. U.S. Patent 3 986 952, Oct 19, 1976.
(9) Kanojia, R. M.; Levine, S. D. U.S. Patent 4 061 739, Dec 6, 1976.
(10) Kanojia, R. M. U.S. Patent 4 046 604, Sept 6, 1977.
(11) Chen, R. H. K.; Kanojia, R. M. U.S. Patent 4 127 651, Nov 28, 1978.
(12) Chen, R. H. K. U.S. Patent 4 122 079, Sept 5, 1978.
(13) Kanojia, R. M. U.S. Patent 4 060 604, Nov 29, 1977.
(14) Shaw, C. J.; Chen, R. H. K.; Cotter, M. L.; Kanojia, R. M.; Wachter, M. P. *Org. Mass. Spectrom.* **1981**, *16*, 281-282.
(15) Cotter, M. L. *Org. Magn. Reson.* **1981**, *17*, 14-17.
(16) Dart, M. C.; Henbest, H. B. *J. Chem. Soc.* **1960**, 3563-3570.
(17) Ohloff, G.; Giersch, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 401-402.
(18) Eschinazi, H. E. *J. Org. Chem.* **1961**, *26*, 3072-3076.
(19) Maurit, M. E.; Smirnova, G. V.; Parfenov, E. A.; Sarycheva, I. K.; Preobrazhenskii, N. A. *Dokl. Akad. Nauk. SSSR* **1961**, *140*, 1330-1333.
(20) Jackman, L. M.; Wiley, R. H. *J. Chem. Soc.* **1960**, 2881-2886.
(21) Nakanishi, K. "Infrared Absorption Spectroscopy"; Holden-Day: San Francisco, 1961; p 165 and references cited therein.
(22) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616-5617.
(23) Tumlinson, J. H.; Gueldner, R. C.; Hardee, D. D.; Thompson, A. C.; Hedin, H.; Minyard, J. P. *J. Org. Chem.* **1971**, *36*, 2616-2621. Bedoukian, R. H.; Wolinsky, J. *Ibid.* **1975**, *40*, 2154-2156.
(24) Chen, R.; Rowand, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 6609-6611.
(25) Kane, V. V.; Doyle, D. L. *Tetrahedron Lett.* **1981**, *22*, 3027-3030, 3031-3034.
(26) Nicolaou, K. C.; Claremon, D. A.; Barnett, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611-6612.
(27) The stereochemistry of the chiral center $\alpha$ to the ketone in 1 has not been determined in the natural product. Although we assume it to be of the *R* configuration on the basis of the X-ray crystallographic determination of **38**, it is possible that this center epimerized during isolation and/or chemical modification of natural 1.

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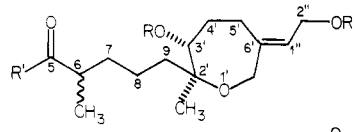
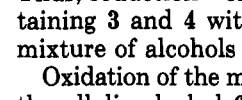
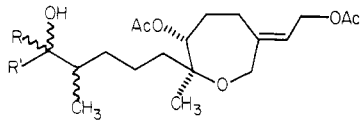
markets of Mexico City. An account[2] of the status of this plant in reproductive medicine has recently appeared. Following our preliminary disclosure[3] of the isolation and characterization of 1 and 2, a description of the biological



1, R = H; R′ = $(CH_3)_2C{=}CHCH_2$
2, R = H; R′ = $(CH_3)_2CHC(CH_3){=}CH$
3, R = Ac; R′ = $(CH_3)_2C{=}CHCH_2$
4, R = Ac; R′ = $(CH_3)_2CHC(CH_3){=}CH$]



8, R = Ac; R′ = $(CH_3)_2C{-}CHCH_2$
9, R = *p*-$BrC_6H_4CO$; R′ = $(CH_3)_2C{=}CH{-}CH_2$
10, R = *p*-$BrC_6H_4CO$; R′ = $(CH_3)_2CHC(CH_3){=}CH$



5, R = H; R′ = $(CH_3)_2C{=}CHCH_2$
6, R = H; R′ = $(CH_3)_2CHC(CH_3){=}CH$
7, R = CN; R′ = $(CH_3)_2C{=}CHCH_2{-}$

test system utilized to follow the progress of the isolation work has also been reported.[4] This paper provides a complete account of our chemical efforts leading to the unraveling of the structures of 1 and 2.

## Isolation

Earlier studies with zoapatle have led to the isolation of the sesquiterpene lactone tomentosin,[5] the diterpene lactone zoapatlin,[6] and monoginoic acid,[6] but none of these compounds was responsible for the biological activity. Our studies began with the preparation of a folkloric "tea" by hot aqueous extraction of dried leaves. Following a filtration, the aqueous layer was processed with a series of organic solvents as depicted in Scheme I to provide the crude extract. After the removal of acidic components by a $NaHCO_3$ wash, the material was chromatographed on a silica gel column. Elution with *i*-PrOH/$CHCl_3$ (3:97) afforded a biologically active material that appeared homogeneous in several TLC systems but was found to be a mixture of three components[7] upon GC examination.

Gel-permeation chromatography of this triplet mixture on a polyvinyl acetate column utilizing benzene as the eluting solvent resulted in the ultimate separation of 1 and 2 as oils. The third component which appeared as a slight shoulder on 2 in the GC has yet to be identified. Difficulties encountered during attempts to scale-up the gel-permeation chromatography led to the investigation of other physical and chemical methods. Among the chromatographic methods that met with some degree of success were the use of $AgNO_3$-impregnated silica gel[8] and deactivated acidic alumina.[9] The latter provided a reasonable way to separate appreciable amounts of 1 from the triplet mixture, whereas the former became more useful as an analytical TLC method to monitor the separation and estimate the purity of 1 and 2.

It was recognized early in our structure elucidation efforts that both 1 and 2 possessed two hydroxy groups and that 1 contained a $\beta,\gamma$-unsaturated ketone whereas 2 had an $\alpha,\beta$-enone system (vide infra). Our first attempted chemical separation involved acetylation[10] of the triplet mixture to form a mixture of the diacetate derivatives 3 and 4. These were separated in low yields by silica gel chromatography and then hydrolyzed back to 1 and 2 with aqueous $K_2CO_3$ in MeOH. The preparation of a variety of other diacyl derivatives including the benzoates, *p*-bromobenzoates, *p*-nitrobenzoates, and $\beta,\beta,\beta$-trichloroethyl carbonates did not lead to improved separation upon chromatography. We then focused on chemical methods that would differentiate between the two enone systems. Thus, reduction[11] of the acetylated triplet mixture containing 3 and 4 with $NaBH_4$ in MeOH at 0 °C gave a mixture of alcohols 5 and 6.

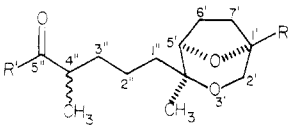
Oxidation of the mixture with $MnO_2$ regenerated 4 from the allylic alcohol 6 and left the homoallylic alcohol 5 unaffected. Following chromatographic separation, 5 was treated with Jones reagent to give 3, which was hydrolyzed to 1 with tetra-*n*-butylammonium hydroxide. The need for the $MnO_2$ oxidation in this sequence was obviated by carrying out the $NaBH_4$ reduction of 3 and 4 at a lower temperature (−15 to −10 °C) for about 10 min. This led to the almost selective reduction of 3 to 5. The difference in reactivity of the carbonyl groups was also exploited upon reaction with HCN.[12] Treatment of the mixture of 3 and 4 led to the cyanohydrin 7 and unchanged 4. After chromatographic separation, 7 was converted to 1 by treatment with $AgNO_3$ followed by hydrolysis. Selective epoxidation[13] with MCPBA afforded epoxide 8, leaving 4 unchanged. Chromatographic separation followed by deoxygenation of 8 with a Zn/Cu couple and hydrolysis gave 1. These chemical methods thus provided additional means of obtaining 1 and 2 for subsequent work.

## Structure and Chemistry

Although zoapatanol (1) had an apparent $[M]^{+\cdot}$ 320 (EI mass spectrum) and an empirical formula of $C_{20}H_{32}O_3$ (high-resolution mass spectrum, *m/e* 320.2370), it became clear from the preparation of a variety of derivatives that the true $[M]^{+\cdot}$ was *m/e* 338 ($C_{20}H_{34}O_4$), and this was later confirmed by CI mass spectroscopy.[14] Twenty carbon atoms were observed by $^{13}C$ NMR[15] for 1, and the $^1H$ NMR assignments for 1 and 2 are listed in Table I. Hydroxyl (2.91 μm) and carbonyl (5.88 μm) absorption bands in the IR and a lack of significant UV absorbance indicated that 1 was a nonconjugated hydroxy ketone. Acylation of 1 with acetic anhydride or *p*-bromobenzoyl chloride in pyridine afforded the noncrystalline diacetate 3 and bis(*p*-bromobenzoate) 9, respectively, and both lacked hydroxyl bands in the IR.

Moreover, the characteristic downfield shifts observed in the NMR for the conversion of 1 [δ 4.14 ($CH_2OH$) and 3.53 (CHOH)] to 3 (δ 4.60 and 4.80) were indicative of the presence of primary and secondary alcohol groups in 1. Observation of a $[M]^{+\cdot}$ of *m/e* 422 for 3 confirmed for the first time the true $[M]^{+\cdot}$ *m/e* 338 for 1. Reaction of 1 with *N,O*-bis(trimethylsilyl)acetamide led to the observation of a tris(trimethylsilyl) derivative by mass spectroscopy, suggesting the presence of an enolizable ketone group in the molecule as well. Our early hopes of carrying out an X-ray structure determination on a close derivative of 1 were frustrated by our inability to prepare a crystalline compound despite reaction of the hydroxyl and ketone groups with numerous reagents. We thus turned our attention toward more classical degradative methods.

Treatment of 1 with $MnO_2$ in $CH_2Cl_2$ at room temperature gave the saturated bicyclic aldehyde 11 ($[M]^{+\cdot}$, *m/e* 336). The absence of hydroxyl absorption in the IR spectrum of 11 and the observation of a one-hydrogen triplet at δ 9.73 (CHO) coupled to a two-hydrogen doublet at δ 2.60 (*J* = 2 Hz, $CCH_2CHO$) in the NMR spectrum suggested an intramolecular addition of the secondary

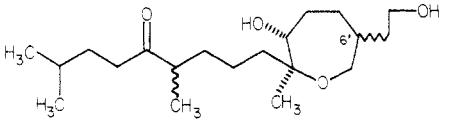


11, R = $CH_2CHO$; R' = $(CH_3)_2C{=}CHCH_2$
12, R = $CH_2CHO$; R' = $(CH_3)_2CHC(CH_3){=}CH$
13, R = $CH{=}CH_2$; R' = $(CH_3)_2C{=}CHCH_2$
14, R = $CH{=}CH_2$; R' = $(CH_3)_2CHC(CH_3){=}CH$

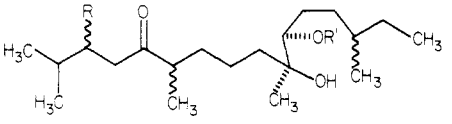
hydroxyl group to the initially formed $\alpha,\beta$-unsaturated aldehyde. Further, the $\delta$ 4.08 methylene signal in **1** was replaced by an AB quartet at $\delta$ 3.29 and 3.76 ($J$ = 11 Hz) in **11**. These data were consistent with the assigned structure **11**.

Treatment of **1** with *p*-TsOH in benzene afforded dehydration product **13** (37%, $C_{20}H_{32}O_3$, $[M]^+\cdot$ at $m/e$ 320) which like aldehyde **11** lacked any hydroxyl function (IR). Apart from the new vinylic signals at $\delta$ 5.0–6.2 (3 H, OCC**H**=C**H**$_2$), the rest of the NMR spectrum was nearly identical with that of **11**, indicating that a similar type of intramolecular reaction had taken place.

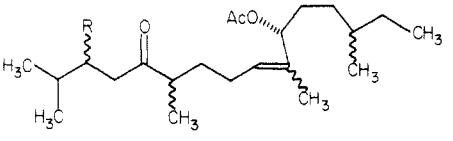
Hydrogenation of **1** over $PtO_2$ containing traces of $NaNO_2$[16] resulted in the uptake of 2 equiv of hydrogen and saturation of two double bonds, affording a 1:1 mixture of isomers **15** and **16**, which were separable by chroma-



15, 6'*R*
16, 6'*S*



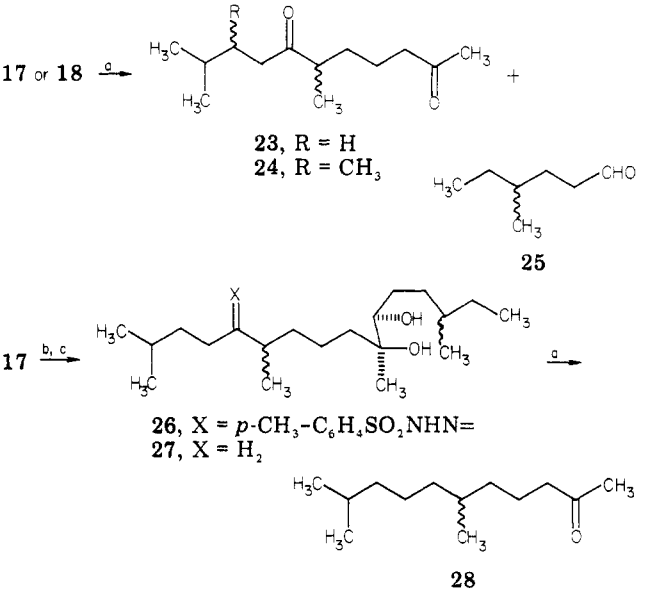
17, R = H; R' = H
18, R = $CH_3$; R' = H
19, R = H; R' = Ac
20, R = $CH_3$; R' = Ac



21, R = H
22, R = $CH_3$

tography on silica gel. Additional valuable structural information was gained by hydrogenation of **1** over Pd/C in EtOH. Under these conditions, the major product obtained was **17** in which both double bonds were saturated as evidenced by the absence of vinylic protons in the NMR spectrum, and the secondary hydroxyl function was still intact [$\delta$ 3.26 (m, 1 H, C**H**OH); 2.91 $\mu$m]. The uptake of 4 equiv of hydrogen without the loss of any carbon atom indicated that the primary allylic alcohol function and the allylic ether bridge in **1** must share a common double bond in a cyclic ether structure. This is consistent with 2 equiv of hydrogen being used for the hydrogenolytic cleavage of the allylic oxygen functions to form an acyclic structure and the other 2 mol being used in saturating the two C=C bonds. Furthermore, the oxepane nature of the ether ring, its formation upon a quaternary carbon atom, and the vicinal or $\alpha$ attachment of the allylic ether bridge with

Scheme II[a]



23, R = H
24, R = $CH_3$

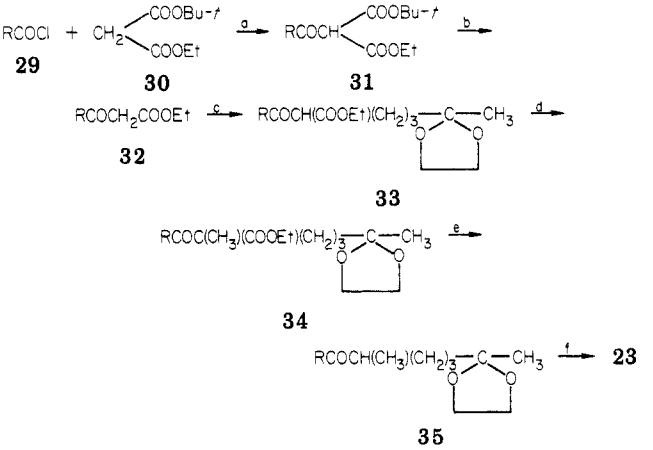
25

26, X = *p*-$CH_3$-$C_6H_4SO_2NHN{=}$
27, X = $H_2$

28

[a] (a) $MnO_2$, $CH_2Cl_2$, room temperature; (b) $TsNHNH_2$, EtOH, $\Delta$; (c) $NaBH_4$, MeOH, $\Delta$.

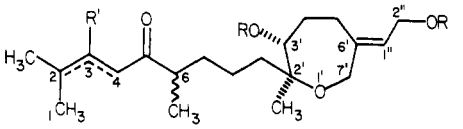
Scheme III[a,b]



[a] (a) Mg, EtOH/ether; (b) *p*-TsOH, $C_6H_6$, $\Delta$; (c) NaH, DMF, $Cl(CH_2)_3$-$C(OCH_2)_2$-$CH_3$; (d) NaH, DMF, $CH_3I$; (e) NaOH, EtOH, $\Delta$; (f) *p*-TsOH, acetone/$H_2O$, $\Delta$. [b] R = $(CH_3)_2CH(CH_2)_2$-.

respect to the secondary hydroxyl function on the ring all became apparent when the following experiments suggested structure **17** for the hydrogenolysis product of **1**. Acetylation of **17** with $Ac_2O$ in pyridine at room temperature gave monoacetate **19** containing a tertiary hydroxyl group (2.87 $\mu$m) which had been generated by hydrogenolysis of the allylic ether bridge. The secondary nature of the acetoxy group in **19** was also indicated by an NMR signal appearing at $\delta$ 4.83 (C**H**OAc). Dehydration of the tertiary carbinol **19** with $POCl_3$ in pyridine at room temperature gave a product characterized as the $\gamma$-methyl allylic acetate **21** on the basis of its NMR spectrum ($CH_3C{=}CHCHOAc$ signals at $\delta$ 1.59 and 5.1, respectively). These data were consistent with the vicinal glycol structure **17** and, when considered in light of the generally expected isoprenoid methyl substitution pattern, led us to propose oxepane structure **1** for zoapatanol. More rigorous support for the proposed structure then rested on an unequivocal structural proof of **17**. The aldehyde **25** and the diketone **23** obtained after $MnO_2$ cleavage of **17** (Scheme II) were separated by chromatography as the major products of the

Table I. $^1$H NMR Data for Zoapatanol (1), Montanol (2), and Their Acyl Derivatives (3, 9 and 4, 10, respectively)[a]



| compd | chemical shift | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1-$H_3$ and 2-$CH_3$ | 3-H | 3-$CH_3$ | 4-H | 6-$CH_3$ | 2'-$CH_3$ | 3'-H | 7'-$H_2$ | 1''-H | 2''-H |
| 1 ($\Delta^2$, R = R' = H) | 1.62 (s, 3 H), 1.75 (s, 3 H) | 5.47 (t, $J$ = 7) | | 3.12 (d, $J$ = 7, 2 H) | 1.08 (d, $J$ = 7) | 1.14 (s) | 3.53 (dd, $J$ = 4, 8) | 4.08 (s) | 5.29 (t, $J$ = 7) | 4.14 (d, $J$ = 7) |
| 2 ($\Delta^3$, R = H; R' = $CH_3$) | 1.08 (d, $J$ = 7, 6 H) | | 2.08 (d, $J$ = 2) | 6.07 (br s) | 1.08 (d, $J$ = 7) | 1.13 (s) | 3.53 (br t) | 4.10 (s) | 5.43 (m) | 4.13 (d, $J$ = 7) |
| 3 ($\Delta^2$, R = Ac, R' = H) | 1.60 (s, 3 H), 1.70 (s, 3 H) | 5.1-5.55 (m) | | 3.11 (d, $J$ = 7, 2 H) | 1.06 (d, $J$ = 7) | 1.14 (s) | 4.80 (m) | 4.08 (s) | 5.1-5.55 (m) | 4.60 (d, $J$ = 7) |
| 4 ($\Delta^3$, R = Ac, R' = $CH_3$) | 1.07 (d, $J$ = 7, 6 H) | | 2.03 (br s) | 6.07 (br s) | 1.07 (d, $J$ = 7) | 1.13 (s) | 4.78 (m) | 4.10 (s) | 5.40 (br s) | 4.58 (d, $J$ = 7) |
| 9 ($\Delta^2$, R = $p$-$BrC_6H_4CO$, R' = H) | 1.61 (s, 3 H), 1.75 (s, 3 H) | 5.60 (m) | | 3.10 (d, $J$ = 7) | 1.04 (d, $J$ = 7) | 1.25 (s) | 5.0 (m) | 4.23 (s) | 5.60 (m) | 4.87 (d, $J$ = 7) |
| 10 ($\Delta^3$, R = $p$-$BrC_6H_4CO$, R' = $CH_3$) | 1.06 (d, $J$ = 7, 6 H) | | 2.08 (br s) | 6.09 (br s) | 1.06 (d, $J$ = 7) | 1.26 (s) | 5.0 (m) | 4.22 (s) | 5.60 (br m) | 4.87 (d, $J$ = 7) |

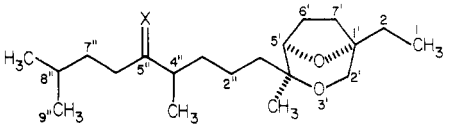
[a] All the $^1$H NMR spectra were recorded at 60 MHz in $CDCl_3$ except for that of 1 which was at 220 MHz. Chemical shifts are expressed in parts per million relative to $Me_4Si$ as an internal standard; coupling constants are given in hertz. Protons are numbered according to the carbon atoms to which they are attached.

oxidation reaction, and together they accounted for the 20-carbon backbone structure of **17**. Their structures were verified by independent synthesis. The known aldehyde **25**[18] was prepared from 4-methyl-1-hexene upon treatment with 9-BBN followed by oxidation of the intermediate alcohol ($CrO_3$, pyridine, $CH_2Cl_2$). The synthesis (Scheme III) of the diketone **23** was initiated by treatment of ethyl *tert*-butylmalonate **30** with 4-methylvaleryl chloride **29** to afford the mixed diester **31**, which without isolation was refluxed with *p*-TsOH in benzene to give the β-keto ester **32** (40%). Condensation of **32** with the ethylene ketal of 5-chloro-2-pentanone gave a mixture of O- and C-alkylated products. The desired C-alkylated isomer **33** (26%) was separated by column chromatography and methylated with methyl iodide (NaH/DMF) to give the desired 13-carbon precursor **34** (71%). Ester hydrolysis and decarboxylation of the resulting β-keto acid in ethanolic NaOH followed by removal of the ketal protecting group (TsOH, aqueous acetone) gave **23**, which was identical in all respects with the diketone obtained from $MnO_2$ cleavage of **17**. An alternate structure proof for **17** was obtained by its conversion to tosylhydrazone **26** and subsequent reduction with $NaBH_4$ to deoxo vicinal diol **27** which upon treatment with $MnO_2$ as above gave the identical aldehyde **25** and a monoketone, **28**,[19] identified as hexahydropseudoionone by comparison with an authentic sample prepared by hydrogenation of pseudoionone (Scheme III).

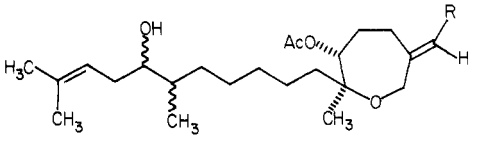
The structure of montanol (**2**, $C_{21}H_{36}O_4$) was established by a similar degradative scheme. Spectral comparison (Table I) and derivatization of **2** indicated the presence of an additional methyl group and an α,β-enone system [UV 239 nm (ε 8500)] in place of the β,γ-enone system of **1**. Thus **18**, the hydrogenolysis product derived from **2**, was acetylated to give **20**, which afforded the allylic acetate **22** upon treatment with $POCl_3$/pyridine. Oxidative cleavage of the vicinal diol **18** with $MnO_2$ gave **25**, the same aldehyde obtained in the zoapatanol series, and a diketone **24**. This differed from the zoapatanol-derived diketone **23** by the presence of an additional methyl group and thus placed the extra methyl group on the side chain.

It was evident from spectral data that the extra methyl group in **2** (δ 2.06) was located either α or β to the ketone. Evaluation of NMR data for several model compounds[20] suggested that the β-position cis to the carbonyl group was more likely. The IR spectrum of **2** possessed a strong C=C absorption at 6.2 μm relative to the C=O absorption at 5.95 μm, indicative of an s-cis conformation for the α,β-enone system bearing a β-methyl substituent as in mesityl oxide.[21] In addition, the mass spectrum of diketone **24** exhibited a strong $m/e$ of 156 indicative of a McLafferty rearrangement, while if the methyl group were α to the carbonyl, a fragment of $m/e$ 170 would have been expected.

Determination of the absolute stereochemistry at C-2',C-3' of zoapatanol was obtained via X-ray analysis of the *p*-toluenesulfonylhydrazone (**38**) of bicyclic derivative



**36**, X = O
**37**, X = $NNHSO_2C_6H_4$-*p*-Br
**38**, X = $NNHSO_2C_6H_4$-*p*-$CH_3$



**39**, R = $CH_2OH$
**40**, R = CHO
**41**, R = $CO_2CH_3$

**36** obtained by hydrogenation (Pd/C/EtOH) of **13**. The *p*-bromobenzenesulfonylhydrazone **37** was initially prepared but proved to be unsuitable for X-ray analysis due to the very small size of the crystals. Crystal data for **38** are given in the Experimental Section. Selected torsion angles describing the spatial arrangement of the molecule

Table II. Torsion Angles (deg) in 38[a]

| | | | |
|---|---|---|---|
| $C2_\phi$-$C1_\phi$-S-O1′ | −30 | C1″-C1-O2-C3 | 71 |
| $C2_\phi$-$C1_\phi$-S-O2′ | −162 | C1′-C1-O2-C3 | −167 |
| $C2_\phi$-$C1_\phi$-S-N1 | 88 | C1-O2-C3-C4 | 52 |
| $C1_\phi$-S-N1-N2 | −74 | O2-C3-C4-C5 | 50 |
| S-N1-N2-C5′ | 172 | O2-C3-C4-$C4_1$ | −177 |
| N1-N2-C5′-C6′ | 1 | O2-C3-C4-O8 | −65 |
| N1-N2-C5′-C4′ | 179 | C3-C4-C5-C6 | −91 |
| C1-C1′-C2′-C3′ | 172 | C4-C5-C6-C7 | 6 |
| C1′-C2′-C3′-C4′ | −169 | C5-C6-C7-C1 | 83 |
| O2-C3-C4-$C4_1$ | 172 | C6-C7-C1-O2 | −54 |
| C2′-C3′-C4′-C5′ | −65 | C6-C7-O8-C4 | 48 |
| C3′-C4′-C5′-N2 | 117 | C7-O8-C4-C5 | −46 |
| C3′-C4′-C5′-C6′ | −65 | O8-C4-$C4_1$-$C4_2$ | 174 |
| C4′-C5′-C6′-C7′ | −102 | C7-C1-O2-C3 | −47 |
| C5′-C6′-C7′-C8′ | 180 | C5-C6-C7-O8 | −33 |
| C6′-C7′-C8′-C9′ | −171 | C7-O8-C4-$C4_1$ | −168 |
| C6′-C7′-C8′-C10′ | 72 | C7-C1-C1′-C2′ | −177 |

[a] Estimated standard deviations for these angles are on average ±3°.

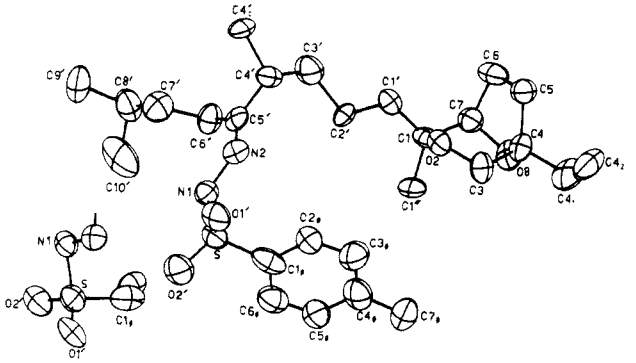
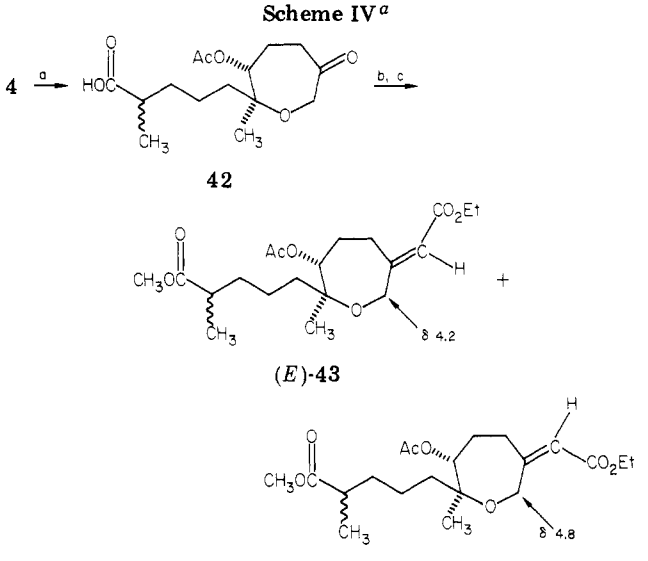


Figure 1. ORTEP drawing of 38.

are listed in Table II. The absolute configuration of the molecule as determined by the X-ray data is illustrated in Figure 1. Tables III–V listing final atomic coordinates, anisotropic thermal parameters, bond lengths and bond angles are available as supplementary material. All intramolecular distances and angles are in agreement with those expected. The proton on N1 appears to be involved in a weak hydrogen bond with O1′ of a neighboring molecule. The N1–O1′ distance is 3.31 Å. This appears to be the only intermolecular interaction of consequence, aside from van der Waals contacts. The formation of the bicyclic derivatives did not alter the stereochemistry at C-2′,C-3′ and so the 2′*S*,3′*R* relationship present in **38** is also true for zoapatanol. A point that still remained to be established, however, was the geometry of the hydroxyethylidine group at C-6′. This was achieved by converting **2** to **41** by the following sequence.

Selective hydrolysis ($K_2CO_3/H_2O/MeOH$) of diacetate **5** afforded the primary alcohol **39** which upon oxidation with $MnO_2$ gave the aldehyde **40**. Oxidation ($NaCN/MnO_2/MeOH$)[22] of **40** gave the desired carboxylic ester **41**. The NMR spectrum of **41** showed a signal at δ 4.17 for the 7′-$CH_2$, while the corresponding signal in several related primary alcohols appeared at δ 4.11. This difference in chemical shift was consistent with the 6′*E* configuration, since a downfield shift of 0.4–0.6 ppm would be anticipated for a methylene group in close proximity (6′*Z*) to the anisotropic ester carbonyl.[23] That this anticipated downfield shift was indeed the case was demonstrated by the following series of transformations (Scheme IV). Treatment of **4** with $OsO_4$ and $NaIO_4$ gave the 6′-keto ester **42**. The Wittig reaction of triethyl phosphonoacetate with **42** followed by esterification with diazomethane gave an approximately 3:2 ratio of *E*/*Z* isomers **43** and **44**, respectively, with a chemical shift of δ 4.2 for the 7′-$CH_2$ of **43** and of δ 4.8 for the 7′-$CH_2$ of **44**. Since the chemistry involved in the conversion of **2** to **41** was stereoretentive and the chemical shifts of the closely related *E*/*Z* isomers **43** and **44** were demonstrated to have a value of 0.6 ppm, we have assigned the stereochemistry of the double bond as *E* in zoapatanol (**1**) and montanol (**2**). Finally, the recently reported total syntheses of zoapatanol (**1**) from these laboratories[24,25] as well as by others[26] have verified[27] its structure.

Scheme IV[a]



[a] (a) $OsO_4$, $NaIO_4$; (b) $(EtO)_2POCH^-Na^+CO_2Et$; (c) $CH_2N_2/Et_2O$.

## Experimental Section

NMR spectra were obtained on either a Varian A-60 or a T-60A spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard unless specified otherwise, and the values are expressed in parts per million (δ). IR spectra were recorded neat on a Beckman IR-8 infrared spectrophotometer unless specified otherwise, and the values are expressed in micrometers. UV spectra were measured on a Cary Model 15 recording spectrophotometer in EtOH. Optical rotations were determined on a Rudolph Model 70 polarimeter attached to a Model 200 photoelectric unit. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Symbols of elements refer to microanalyses with results within 0.4% of calculated values. EI/CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph via a glass jet separator. Data acquisition and reduction were performed on line by the 6100 data system. Separation was achieved with a 5-ft glass column ($^1/_8$-in. i.d.) packed with 3% OV-1 on Gas Chrom Q (80–100 mesh). The column was temperature programmed from 190 to 250 °C at 15 °C/min, after an initial hold of 30 s. EI spectra were obtained at 70 eV, and CI spectra were recorded at 100 eV with methane and isobutane as reagent gases. All evaporations were carried out in vacuo. TLC analyses were performed on Uniplate SilicAR 7GF plates (Analtech), and preparative TLC was carried out on Quantagram PQIF plates (1000 μm). Column chromatographies were performed on Mallinckrodt SilicAR-CC7 unless otherwise specified.

**Isolation of Zoapatanol (1) and Montanol (2). Preparation of Semipurified Extract or Triplet Mixture (1 + 2).** Dried zoapatle leaves (10 kg) and $H_2O$ (30 gal) were added to a 100-gal steam-jacketed stainless-steel tank. The mixture was heated at 98–100 °C for 2.5 h with periodic stirring. The hot mixture was filtered through gauze to afford a clear dark tea (about 25 gal). The solid residue in the tank was washed with hot water (4 gal) and filtered, and the filtrate was combined with the tea. The combined aqueous extracts were extracted with EtOAc (30 gal). The mixture was stirred vigorously and allowed to settle. The

top frothy layer was siphoned off to break the emulsion, and as much EtOAc was separated as possible. Additional EtOAc (20 gal) was added to the mixture, and the above process was repeated. The combined EtOAc extracts were evaporated at 50 °C. The residue was extracted with three portions of hot (75–80 °C) benzene (10 L total). The benzene extracts were evaporated at 50 °C, and the residue was washed three times with refluxing hexane (a total of 8 L). The hexane-washed residue was dissolved in acetone (2 L), Nuchar (10 g) was added, and the mixture was stirred 1 h at room temperature. The charcoal was removed by filtration, and the filtrate was evaporated by distillation at 30 °C to afford the crude extract (69 g).

The crude extract (50 g) was dissolved in ether (5 L), and the resulting solution was filtered and washed with saturated $NaHCO_3$ (500 mL). The ether was dried ($Na_2SO_4$), filtered, and concentrated to dryness to afford a light yellow oil (44.6 g). This oil was dissolved in $CHCl_3$ (400 mL) and the solution added to a column of neutral silica gel (2.5 kg) packed in $CHCl_3$. The column was eluted with $CHCl_3$ and $CHCl_3$–*i*-PrOH mixtures, and the collected fractions were evaporated to dryness at a temperature below 40 °C. The column was eluted as follows [fraction, volume (mL), eluent (ratio)]: 1–7, 650, $CHCl_3$; 8–30, 500, *i*-PrOH/$CHCl_3$ (1:41.7); 31–60, 500, *i*-PrOH/$CHCl_3$ (1:33.3); 61–105, 500, *i*-PrOH/$CHCl_3$ (1:28.6); 106–110, 500, *i*-PrOH/$CHCl_3$ (1:25).

The composition of the fractions was monitored by TLC [silica gel, 2-propanol–$CHCl_3$ (1:12.5)] and by GC [3% OV-17 column with a programmed run (150–250 °C)]. Fractions 78–84 were combined, and the solvent was evaporated to afford an oily residue of the semipurified material (5.1 g) which contained at least three components as indicated by GC (Triplet).

**Gel-Permeation Chromatography of Triplet Mixture To Isolate Zoapatanol (1) and Montanol (2).** The triplet mixture (3.2 g) was dissolved in benzene (50 mL) and the solution added to a column packed with OR-PVA Merck-O-Gel 2000 (2 kg; a vinyl acetate copolymer, E. M. Merck, Inc.) prepared in benzene. The column was eluted with benzene and the compostion of the fractions monitored by TLC and GC.

The initial eluting fractions (no. 50–54, 750 mL) were combined to give montanol (**2**, 375 mg) as a pale yellow oil: IR 2.90, 5.96, 6.21; GC/MS, *m/e* 334 ($M^+ - 18$), 225, 140, 111 (BP), 95, 81, 69; UV (EtOH) 239 nm ($\epsilon$ 8500); CI mass spectrum, *m/e* 353 ($M^+ + H$). Anal. ($C_{21}H_{36}O_4$) C, H.

Subsequent fractions (no. 66–74, 1.35 L) were combined to give zoapatanol (**1**, 740 mg) as a pale yellow oil: IR 2.91, 5.88; GC/MS, *m/e* 320 ($M^+ - 18$), 251, 233, 221, 171, 143, 141, 137, 125, 113, 97, 95, 81, 69 (BP); CI mass spectrum, *m/e* 339 ($M^+ + H$).

**Acidic $Al_2O_3$ Chromatography of Triplet Mixture To Isolate Zoapatanol (1) and Montanol (2).** An acidic alumina (1.5 kg, activity IV) column was prepared in cyclohexane, and a solution of the triplet mixture (10 g) in benzene (25 mL) was applied followed by additional benzene (about 15 mL). The column was eluted with an increasing proportion of EtOAc in cyclohexane, collecting fractions as follows [fraction, volume (mL), EtOAc/cyclohexane eluent ratio)]: 1–5, 1000, 10:90; 6–10, 1000, 15:85; 11–15, 1000, 20:80; 16–35, 1000, 25:75; 36–113, 250, 30:70.

The fractions were monitored by TLC on 20% $AgNO_3$-impregnated silica gel GF plates (acetone/benzene, 1:1) and also by GC.

Fractions 45–47 were evaporated to give **2** as an oil (280 mg, 2.8%), and fractions 68–98 were evaporated to afford **1** as an oil (2.18 g, 22%).

**$AgNO_3$–Silica Gel Chromatography of Triplet Mixture To Isolate Zoapatanol (1) and Montanol (2).** The triplet mixture (505 mg) in benzene (2 mL) was added to a column of silicic acid impregnated with 10% $AgNO_3$ (25 g) prepared in benzene. The column was eluted under a low pressure of nitrogen (7 psi) with increasing proportions of acetone in benzene. A total of 71 fractions (25 mL each) was collected as follows (fraction number, acetone/benzene eluent ratio): 1–18, 5:95; 19–28, 7:93; 29–38, 10:90; 39–71, 12:88.

The composition of the fractions was monitored by TLC and by GC. Fractions 33–39 were evaporated to give **2** (73.3 mg, 14.5%), and fractions 46–56 were evaporated to give **1** (122.7 mg, 24.2%).

**Silica Gel Chromatography of Triplet Acetate Mixture To Isolate Zoapatanol Diacetate (3) and Montanol Diacetate (4).** The triplet mixture (0.5 g) was dissolved in pyridine (6 mL) and treated with stirring at room temperature with $Ac_2O$ (3 mL) under an atmosphere of $N_2$ for 18 h. The pyridine was evaporated, and the residue was treated with methanol. The residue (0.522 g) obtained following evaporation of the methanol was chromatographed on a column of silica gel (50 g) packed in cyclohexane. The column was eluted with an increasing gradient of EtOAc in cyclohexane, collecting 25-mL fractions and following the separation by TLC and GC. Diacetate **4** (63 mg) was isolated as the less polar substance (1:1 EtOAc/cyclohexane) and **3** (100 mg) as the more polar substance (60:40 EtOAc/cyclohexane), both having spectral data identical with those of **3** and **4** obtained from purified zoapatanol (**1**) and montanol (**2**) (vide infra).

**Hydrolysis of Zoapatanol Diacetate (3) and Montanol Diacetate (4) To Regenerate Zoapatanol (1) and Montanol (2).** Diacetate **3** (38 mg, 0.09 mmol) in MeOH (10 mL) was stirred at room temperature with 10% $K_2CO_3$ (0.6 mL) under $N_2$ for 19 h. After removal of the solvent, the residue was extracted with $CH_2Cl_2$, dried ($Na_2SO_4$), and evaporated to afford an oily residue which after preparative TLC purification (10:90 *i*-PrOH/$CHCl_3$) gave purified **1** (15 mg, 50%).

Diacetate **4** (60 mg, 0.13 mmol) was similarly hydrolyzed with 10% $K_2CO_3$ to afford **2** (33 mg, 70%).

**Nonselective $NaBH_4$ Reduction of the Triplet Acetate Mixture To Give 5 and 6.** A solution of the triplet acetate mixture (crude **3** and **4**, 1.2 g) in MeOH (100 mL) was treated wtih $NaBH_4$ (400 mg) at 0 °C under $N_2$. After 5 min, the mixture was treated with saturated $NH_4Cl$ (100 mL) and then extracted with $CH_2Cl_2$ (3 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a yellow, oily mixture of **5** and **6** (1.1 g), which was used directly for the $MnO_2$ treatment.

**$MnO_2$ Treatment of the Mixture of 5 and 6.** The crude mixture of **5** and **6** (1.1 g) as obtained above was treated with $MnO_2$ (4 g) in $CH_2Cl_2$ (100 mL) at room temperature for 16 h. The mixture was then filtered through a pad of Celite and the solvent evaporated to give a yellow oily residue. This was chromatographed on a silica gel column (20 g) packed in petroleum ether. The keto derivative **4** (243 mg) was eluted with ether/petroleum ether (1:3), and the hydroxy derivative **5** (754 mg) was eluted with ether/petroleum ether (3:1).

**$NaBH_4$ Treatment of the Triplet Acetate Mixture To Reduce Selectively Zoapatanol Diacetate (3) to Homoallylic Alcohol 5.** A stirred solution of the triplet acetate mixture (crude **3** and **4**, 12 g) in MeOH (500 mL) cooled to −15 to −10 °C was treated wtih $NaBH_4$ (2.7 g), added in small portions over a period of 10 min. The reaction mixture was then treated with acetone (10 mL) for 1 min followed by saturated $NH_4Cl$ (~300 mL). The mixture was extracted with $CH_2Cl_2$, the combined organic extracts were washed with brine and water and dried ($Na_2SO_4$), and the solvent was removed to afford a viscous residue (~11.5 g). The residue was dissolved in benzene (~50 mL) and added to a column of silica gel (Baker, 1 kg) packed in cyclohexane. The column was eluted with an increasing gradient of EtOAc in cyclohexane, and 250-mL fractions were collected. On the basis of TLC monitoring (40:60 EtOAc/cyclohexane), fractions 33–58 (10–15% EtOAc in cyclohexane) were combined to afford, after the removal of the solvent, unreduced **4** (0.74 g). Similarly, fractions 74–122 (15% EtOAc in cyclohexane) were combined to afford **5** (4.68 g).

**Jones Oxidation of Homoallylic Alcohol 5 To Regenerate Zoapatanol Diacetate (3).** The diacetate **5** (0.333 g, 0.77 mmol) was dissolved in acetone (5 mL) and treated slowly with Jones reagent (2 mmol) at 0 °C under $N_2$. The resulting mixture was stirred for 7 min and then treated with ether and $H_2O$. The organic layer was separated and the aqueous layer reextracted with ether. The combined organic layer was washed with $H_2O$, dried ($MgSO_4$), and evaporated to give **3** as an oil (0.301 g, 90%).

**Tetra-*n*-butylammonium Hydroxide Hydrolysis of Zoapatanol Diacetate (3) and Montanol Diacetate (4) To Regenerate Zoapatanol (1) and Montanol (2).** Crude **3** (161 mg, 0.35 mmol) as obtained above was dissolved in THF (5 mL) and $H_2O$ (5 mL) and treated with tetra-*n*-butylammonium hydroxide (1 mL of 20% MeOH solution) with stirring under $N_2$ for 40 h. The mixture was extracted with ether, and the organic layer was washed with 10% HCl, dried ($MgSO_4$), and evaporated to give an oil. Chromatography on a column of silica gel (5 g) with ether as the eluent gave **1** (81.8 mg, 62%).

**MCPBA Treatment of the Triplet Acetate Mixture To Epoxidize Selectively Zoapatanol Diacetate (3) to Epoxide 8.** *m*-Chloroperoxybenzoic acid (85%, 0.08 g) in $CH_2Cl_2$ (2 mL) was slowly added to the triplet acetate mixture (crude **3** and **4**, 0.139 g) in $CH_2Cl_2$ (2 mL) at 0–5 °C, and the mixture was stirred at that temperature for an additional 2.5 h. The solution was then washed sequentially with 5% $NaHSO_3$ and 5% $NaHCO_3$, dried ($Na_2SO_4$), and evaporated to dryness to give a residue (0.130 g). This was purified by preparative TLC using EtOAc/cyclohexane (30:70) as the eluent. The principal UV absorbing band ($R_f$ 0.7–0.8) was unreacted **4**. The principal non-UV-absorbing band ($Rf$ 0.5–0.6) gave, after extraction with EtOAc/cyclohexane (1:1), epoxide **8**: 0.080 g; IR 5.75, 5.85; NMR 1.05 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 1.1, 1.2, 1.32 (each s, each 3 H, 1-H, 2-$CH_3$, 2′-$CH_3$), 2.0 (s, 6 H, $OCOCH_3$), 2.68 (d, $J$ = 5 Hz, 2 H, 4-H), 3.07 (t, $J$ = 5 Hz, 1 H, 3-H), 4.07 (s, 2 H, 7′-H), 4.53 (d, $J$ = 7 Hz, 2″-H), 4.72 (m, 1 H, 3′-H), 5.33 (m, 1 H, 1″-H); GC/MS, $m/e$ 420 ($M^+$ – 18).

**Deoxygenation of Epoxide 8 with Zn–Cu Couple To Regenerate Zoapatanol Diacetate (3).** Epoxide **8** (45 mg, 0.1 mmol) in EtOH (30 mL) was refluxed with Zn–Cu couple (1.0 g) under $N_2$ for 2 days. The solid metallic residue was removed by filtration and the filtrate evaporated to dryness to give **3** (40 mg, 92%).

**HCN Treatment of the Triplet Acetate Mixture To Form Selectively Cyanohydrin 7.** The triplet acetate mixture (**3** and **4**, 20 mg) in THF (4.5 mL) and $H_2O$ (0.5 mL) was treated at 0 °C in a stoppered test tube with KCN (10 mg) and concentrated HCl (0.2 mL). The mixture was stirred at room temperature for 48 h. The test tube was carefully opened and the mixture treated with ether and $H_2O$. The organic phase was separated, dried ($MgSO_4$), and evaporated to give an oily residue. This was chromatographed on a column of silica gel (3 g) to first elute unreacted **4** (8 mg) with ether/petroleum ether (20:80) followed by **7** (10 mg) with 30:70 ether/petroleum ether. Compound **7**: IR ($CCl_4$) 2.8, 4.7, 5.75; NMR 1.1 (s, 3 H, 2′-$CH_3$), 1.75 and 1.82 (each s, each 3 H, 1′-H, 2-$CH_3$), 2.1 (s, 6 H, $OCOCH_3$), 4.02 (br s, 2 H, 7′-H), 4.44 (d, $J$ = 6 Hz, 2 H, 2″-H), 5.2 (m, 2 H, 1″-H and 3′-H).

**$AgNO_3$ Treatment of Cyanohydrin 7 To Regenerate Zoapatanol Diacetate (3).** A portion of the cyanohydrin **7** (2 mg), as isolated above, in THF (2 mL) and $H_2O$ (0.2 mL) was treated with $AgNO_3$ (2 mg) and the mixture stirred at room temperature for 5 min under $N_2$. Ether and $H_2O$ were added, and the organic layer was separated, dried ($MgSO_4$), and evaporated to give **3** (1.6 mg).

**9-[(2′*S*,3′*R*)-3′-Acetoxy-6′-[(*E*)-2″-acetoxyethylidene]-2′-methyl-2′-oxepanyl]-2,6-dimethyl-2-nonen-5-one (Zoapatanol Diacetate, 3).** Zoapatanol (**1**; 500 mg, 1.48 mmol) in pyridine was treated with $Ac_2O$ (3.0 mL) at room temperature under $N_2$ for 18 h. Pyridine was removed under high vacuum, and MeOH was added to destroy excess $Ac_2O$. The solvent was removed, and the residue (600 mg, 94%) was purified on a column of silica gel (30 g in cyclohexane) and eluted with EtOAc/cyclohexane (4–5.5:96–94.5) to give purified **3**: 200 mg (31.3%); IR 5.75, 5.83; NMR 1.06 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 1.14 (s, 3 H, 2′-$CH_3$), 1.60 and 1.70 (each s, each 3 H, 1-H, 2-$CH_3$), 2.03 (s, 6 H, $OCOCH_3$), 3.11 (d, $J$ = 8 Hz, 2 H, 4-H), 4.08 (s, 2 H, 3-H); GC/MS, $m/e$ 422 ($M^+$).

**(*E*)-9-[(2′*S*,3′*R*)-3-Acetoxy-6′-[(*E*)-2″-acetoxyethylidene]-2′-methyl-2′-oxepanyl]-2,3,6-trimethyl-3-nonen-5-one (Montanol Diacetate, 4).** Montanol diacetate (**4**) was similarly prepared from montanol (**2**): IR 5.75, 5.95, 6.21; NMR 1.07 (d, $J$ = 7 Hz, 6 H, 1-H, 6-$CH_3$), 1.13 (s, 3 H, 2′-$CH_3$), 2.03 (br s, 9 H, 3-$CH_3$, $OCOCH_3$), 4.10 (s, 2 H, 7′-H), 4.58 (d, $J$ = 7 Hz, 2 H, 2″-H), 4.78 (m, 1 H, 3′-H), 5.40 (br s, 1 H, 1″-H), 6.07 (br s, 1 H, 4-H); GC/MS, $m/e$ 376 ($M^+$ – 60).

**(1′*R*,4′*S*,5′*R*)-4′-(4″,8″-Dimethyl-5″-oxo-7″-nonenyl)-4′-methyl-3′,8′-dioxabicyclo[3.2.1]octane-1-acetaldehyde (11).** Zoapatanol (**1**; 1.0 g, 2.96 mmol) in $CH_2Cl_2$ (250 mL) was stirred with $MnO_2$ (2.2 g, 25 mmol) at room temperature under $N_2$ for 17 h. The inorganic solids were filtered and washed with $CH_2Cl_2$, and the solvent was removed to give a yellow oil (850 mg) which was purified by preparative TLC (80:20 EtOAc/$CHCl_3$) to give aldehyde **11**: 690 mg (69%); IR 3.63, 5.80; NMR 1.06 (d, $J$ = 7 Hz, 3 H, 4″-$CH_3$), 1.30 (s, 3 H, 4′-$CH_3$), 1.63 and 1.75 (each s, each 3 H, 8″-H, 9″-H), 2.60 (d, $J$ = 2 Hz, 2 H, 2-H), 3.13 (d, $J$ = 8 Hz, 2 H, 6″-H), 3.29 and 3.73 (each d, $J$ = 11 Hz, 2 H, 2′-H), 3.81 (br s, 1 H, 5′-H), 5.25 (m, 1 H, 7″-H), 9.78 (t, $J$ = 2 Hz, 1 H, 1″-H); GC/MS, $m/e$ 336 ($M^+$).

**(1′*R*,4′*S*,5′*R*)-4′-(4″,7″,8″-Trimethyl-5″-oxo-6″-nonenyl)-4′-methyl-3′,8′-dioxabicyclo[3.2.1]octane-1-acetaldehyde (12).** Montanol (**2**; 50 mg, 0.14 mmol) when treated as above with $MnO_2$ in $CH_2Cl_2$ gave aldehyde **12**: IR 3.64, 5.80, 5.95, 6.2; UV (EtOH) 238 nm ($\epsilon$ 12 460); NMR 1.08 (d, $J$ = 7 Hz, 9 H, 4″-$CH_3$, 8″-$CH_3$, 9″-H), 1.32 (s, 3 H, 4′-CH), 2.11 (d, $J$ = 1 Hz, 3 H, 7″-$CH_3$), 2.63 (d, $J$ = 2.5 Hz, 2 H, 2-H), 3.34 and 3.78 (each d, $J$ = 11 Hz, 2 H, 2′-H), 3.87 (br m, 1 H, 5′-H), 6.13 (br s, 1 H, 6″-H), 9.78 (t, $J$ = 2 Hz, 1-H); GC/MS, $m/e$ 350 ($M^+$).

**(1′*R*,4′*S*,5′*R*)-1′-Ethenyl-4′-(4″,8″-dimethyl-5″-oxo-7″-nonenyl)-4′-methyl-3′,8′-dioxabicyclo[3.2.1]octane (13).** Zoapatanol (**1**; 701 mg, 2 mmol) was dissolved in benzene (40 mL), *p*-TsOH·$H_2O$ (181 mg) was added, and the resulting suspension was stirred at room temperature for 24 h. The benzene solution was decanted, the residue washed with benzene and the combined benzene layers evaporated to dryness at 35 °C. The resulting reddish brown residue (605 mg) was chromatographed on silica gel (90 g), eluting with chloroform and collecting 10-mL fractions. The fractions were monitored by TLC (1:10 EtOAc/cyclohexane). Fractions 33–54 were combined and evaporated to dryness to give **13** (235 mg, 37%) as a yellow oil: $R_f$ 0.47 (4:1 cyclohexane/EtOAc); IR 5.85; NMR 1.04 (d, $J$ = 7 Hz, 3 H, 4″-$CH_3$), 1.31 (s, 3 H, 4′-$CH_3$), 1.63 and 1.76 (each s, each 3 H, 9″-H, 8″-$CH_3$), 3.51 (AB q, $J$ = 11 Hz, 2′-H), 3.89 (br m, 1 H, 5-H), 5.0–6.2 (m, 4 H, 1-$CH_2$, 2-CH, 7″-H); GC/MS, $m/e$ 320 ($M^+$).

**(1′*R*,4′*S*,5′*R*)-1′-Ethenyl-4′-(4″,7″,8″-trimethyl-5″-oxo-6″-nonenyl)-4′-methyl-3′,8′-dioxabicyclo[3.2.1]octane (14).** Montanol (**2**; 65 mg, 0.18 mmol) when treated as above with *p*-TsOH·$H_2O$ in benzene gave **14**: 30 mg (49%); IR 5.96, 6.22; NMR 1.07 (d, $J$ = 7 Hz, 9 H, 4″-$CH_3$, 8″-$CH_3$, 9″-H), 1.31 (s, 3 H, 4′-$CH_3$), 2.10 (d, $J$ = 1.5 Hz, 3 H, 7″-$CH_3$), 3.52 (AB q, $J$ = 11 Hz, 2H, 2′-H), 3.90 (br m, 1 H, 5′-H), 5.0–6.2 (m, 4 H, 1-$CH_2$, 2-CH, 6″-H); GC/MS, $m/e$ 334 ($M^+$).

**9-[(2′*S*,3′*R*,6′*R*- and -2′*S*,3′*R*,6′*S*)-3′-Hydroxy-(2″-hydroxyethyl)-2′-methyl-2′-oxepanyl]-2,6-dimethylnonan-5-one (15 and 16).** Zoapatanol (**1**; 96 mg, 0.28 mmol) in EtOH (20 mL) was hydrogenated in the presence of $PtO_2$ (35 mg) and a trace amount of $NaNO_2$ (0.4 mg in 1 drop of $H_2O$) at atmospheric pressure for 1.5 h. The reaction mixture was filtered through a pad of Celite, and the solvent was removed to give an oily residue (99 mg), which was purified by preparative TLC (1:9 *i*-PrOH/$CHCl_3$) to give a 50:50 mixture of **15** and **16**: 78 mg (81%); IR 2.90, 5.89; NMR 0.88 (d, $J$ = 5 Hz, 6 H, 1-H, 2-$CH_3$), 1.07 and 1.08 (both s, 3 H, 2′-$CH_3$), 2.40 (t, $J$ = 6 Hz, 2 H, 4-H), 3.05–3.80 (m, 5 H, 7′-H, 3′-H, 2″-H); GC/MS, single peak obtained for the underivatized sample, $m/e$ 342 ($M^+$) not observed. The mass spectrum for the $Me_3Si$ derivative was as follows: $m/e$ 486 ($M^+$) not observed, 415 ($M^+$ – 71, $C_5H_{11}$), 381 ($M^+$ – TMSOH – $CH_3$), 325 (415$^+$ – TMSOH), 317 ($M^+$ – side chain $C_{11}H_{21}O$), 285, 227 (317$^+$ – TMSOH), 213 (317$^+$ – TMSOH – $CH_3$), 169 (213$^+$ – $CH_3CHO$), 155 ($C_{10}H_{19}O$, BP), 147 [$(Me_3Si)_2$], 129, 116, 103 ($Me_3SiOCH_2$). Anal. ($C_{20}H_{38}O_4$) C, H.

In another run 821 mg (2.43 mmol) of **1** was similarly hydrogenated to give 846 mg (crude) of a mixture of **15** and **16**, which was separated by column chromatography on silica gel (45 g) in cyclohexane. The column was eluted with increasing proportions of EtOAc in cyclohexane, collecting 30–50-mL fractions. The less polar isomer [283 mg, fractions 18–20, EtOAc/cyclohexane (2:3)] displayed a relatively downfield 2′-$CH_3$ ($\delta$ ~1.08) compared to the more polar isomer [268 mg, fractions 22–25, EtOAc/cyclohexane (1:1), $\delta$ ~1.07].

**(10*S*,11*R*)-10,11-Dihydroxy-2,6,10,14-tetramethylhexadecan-5-one (17).** Zoapatanol (**1**; 732 mg, 2.17 mmol) in EtOH (300 mL) was hydrogenated over 10% Pd/C (450 mg) at atmospheric pressure for 1 h. The reaction mixture was filtered through Celite and the solvent removed. The oily residue (673 mg, 94.5%) was purified by preparative TLC (20% EtOAc/$CHCl_3$) to give diol **17**: 295 mg (41%); IR 2.87, 5.85; NMR 0.88 (d, $J$ = 5 Hz, 9 H, 1-H, 2, 14-$CH_3$), 0.88 (t, 3 H, 16-H), 1.07 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 1.12 (s, 3 H, 10-$CH_3$), 1.93 (br s, 2 H, OH), 2.38 (m, 2 H, 4-H), 3.26 (m, 1 H, 11-H); GC/MS, $m/e$ 292 ($M^+$ – $2H_2O$); for bis(trimethylsilyl) derivative (due to enolization of C=O) $m/e$ 457 ($M^+$ – $CH_3$). Anal. ($C_{20}H_{40}O_3$) C, H.

**(10*S*,11*R*)-10-Hydroxy-11-acetoxy-2,6,10,14-tetramethylhexadecan-5-one (19).** The diol **17** (50 mg, 0.15 mmol) in pyridine (0.6 mL) was treated with $Ac_2O$ (0.2 mL) at room temperature for 17 h and then evaporated to dryness. The residue was purified by preparative TLC (20% EtOAc/cyclohexane) to give monoacetate **19**: 50 mg (89%); IR 2.8, 5.75, 5.85; NMR 0.88 (d, $J$ = 5 Hz, 9 H, 1-H, 2, 14-$CH_3$), 0.88 (t, $J$ = 6 Hz, 3 H, 16-H), 1.07 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 1.11 (s, 3 H, 10-$CH_3$), 2.09 (s, 3 H, $OCOCH_3$), 2.45 (t, 2 H, $J$ = 7 Hz, 4-H), 4.83 (m, 1 H, 11-H).

**(11*R*)-11-Acetoxy-2,6,10,11-tetramethyl-9-hexadecen-5-one (21).** Monoacetate **19** (44.5 mg, 0.12 mmol) in pyridine (0.3 mL) was treated at −5 °C with $POCl_3$ (0.1 mL) and stirred at room temperature for 3 days. After treatment with ice–water, the mixture was extracted with ether. The organic layer was washed with 5% $KHSO_4$ and 5% $NaHCO_3$, dried ($Na_2SO_4$), and evaporated to give the oily product **21**: 37 mg (87%); IR 5.75, 8.5, 8.05; NMR 0.88 (d, $J$ = 5 Hz, 9 H, 1-H, 2, 14-$CH_3$), 0.88 (t, $J$ = 7 Hz, 3 H, 16-H), 1.07 (d, $J$ = 7 Hz, 6-$CH_3$), 1.59 (br s, 3 H, 10-$CH_3$), 2.02 (s, 3 H, $OCOCH_3$), 2.43 (t, 2 H, $J$ = 7 Hz, 4-H), 5.1 (m, 1 H, 11-H), 5.3 (m, 1 H, 9-H); GC/MS, $m/e$ 292 ($M^+$ − HOAc).

**(10*S*,11*R*)-10,11-Dihydroxy-2,3,6,10,14-pentamethylhexadecan-5-one (18).** Montanol (**2**; 54.1 mg, 0.154 mmol) in EtOH (25 mL) was hydrogenated over 10% Pd/C (50 mg) at atmospheric pressure for 10 min, and the crude product was purified by preparative TLC to give **18** (31 mg, 59%) as a colorless oil: IR 2.77, 5.87; NMR 0.80, 0.82, 0.85, 0.87, 0.90 (m, various $CHCH_3$), 1.08 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 1.13 (s, 3 H, 10-$CH_3$), 3.33 (br m, 1 H, 11-H).

**(10*S*,11*R*)-10-Hydroxy-11-acetoxy-2,3,6,10,14-pentamethylhexadecan-5-one (20).** Diol **18** (41 mg, 0.12 mmol) was acetylated with $Ac_2O$ (0.2 mL) in pyridine (0.2 mL) at room temperature to give monoacetate **20**: 40 mg (87%); IR 2.85, 5.75, 5.85, 8.08; NMR 0.78–0.92 (m, 15 H, 16-H, 1,2,3,14-$CH_3$), 1.06 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 1.11 (s, 3 H, 10-$CH_3$), 2.08 (s, 3 H, $OCOCH_3$), 2.39 (t, 2 H, $J$ = 7 Hz, 4-H), 4.81 (m, 1 H, 11-H).

**(11*R*)-11-Acetoxy-2,3,6,10,14-pentamethyl-9-hexadecen-5-one (22).** Monoacetate **20** (37 mg, 0.096 mmol) in pyridine (0.4 mL) at −5 °C was treated with $POCl_3$ (0.1 mL) and stirred at room temperature for 17 h. Following the usual workup, the dehydration product **22** was isolated as an oil: 31 mg (88%); IR 5.75, 5.85, 8.05; NMR 0.78–0.92 (m, 15 H, 16-H, 1,2,3,14-$CH_3$), 1.06 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 1.11 (s, 3 H, 10-$CH_3$), 2.08 (s, 3 H, $OCOCH_3$), 2.37 (t, $J$ = 7 Hz, 2 H, 4-H), 5.1 (m, 1 H, 11-H), 5.3 (m, 1 H, 9-H); GC/MS, $m/e$ 306 ($M^+$ − HOAc).

**Oxidative Cleavage of Diol 17 with $MnO_2$ To Give 23 and 25.** Compound **17** (210 mg, 0.66 mmol) was stirred at room temperature with activated $MnO_2$ (1.13 g) in $CH_2Cl_2$ (50 mL) for 45 min. The suspension was filtered to remove $MnO_2$, and the solids were washed well with $CH_2Cl_2$. The combined filtrate and washings were distilled at atmospheric pressure. GC/MS analysis of the residue revealed the presence of aldehyde **25** ($M^+$, $m/e$ 114) and diketone **23** ($M^+$, $m/e$ 212). Aldehyde **25** was recovered pure from the mixture by preparative GC on a 4-ft glass column packed with 3% OV-17 on Gas Chrom Q (100–120 mesh). This aldehyde **25** and its 2,4-DNP derivative [mp 90 °C (lit.[18] mp 91 °C); mass spectrum, $m/e$ 294 ($M^+$); $R_f$ 0.41 (EtOAc/hexane, 1:4)] were identical in all respects with those obtained via hydroboration of 4-methyl-1-hexene with 9-BBN followed by oxidation of the intermediate alcohol with $CrO_3$/pyridine/$CH_2Cl_2$.

In order to obtain pure **23**, the reaction was repeated as follows. Compound **17** (187 mg, 0.58 mmol) was treated with $MnO_2$ as described above. The combined washings and filtrate were evaporated to give a mixture (115 mg, 95%) containing the diketone **23**, which was chromatographed on preparative plates (EtOAc/cyclohexane, 1:4). The band with $R_f$ 0.45–0.55 was eluted with the same solvent to give **23** (83 mg, 68%) as a yellow oil: IR 5.86; NMR 0.89 (d, 6 H, $J$ = 7 Hz, 10-$CH_3$, 11-H), 1.09 (d, 3 H, 6-$CH_3$), 1.2–1.8 (m, 7 H, 4,5,9-$CH_2$, 10-H), 2.12 (s, 3 H, 1-H), 2.4 (m, 5 H, 3-$CH_2$, 8-$CH_2$, 6-H); GC/MS, $m/e$ 212 ($M^+$). Di-2,4-DNP derivative of **23**: yellow solid; mp 128–131 °C; NMR 1.01 (d, 6 H, $J$ = 7 Hz, 10-$CH_3$, 11-H), 1.25 (d, 3 H, $J$ = 7 Hz, 6-$CH_3$), 2.1 (s, 3 H, 1-H), 7.8–9.2 (aromatic H); mass spectrum, $m/e$ 572 ($M^+$).

**6,9,10-Trimethyl-2,7-undecanedione (24).** Treatment of **18** (134 mg, 0.38 mmol) in $CH_2Cl_2$ (35 mL) with $MnO_2$ (807 mg, 9.3 mmol) at room temperature for 2 h gave, after the usual workup, an oil (130 mg, 98%) which showed the presence of aldehyde **25** ($M^+$ 114) and diketone **24** in the GC/MS. The diketone was isolated pure (52 mg, 59%) by preparative TLC (EtOAc/cyclohexane, 1:4): IR 5.83; NMR 0.88, 0.93, and 1.01 (each d, $J$ = 6 Hz, 9 H, 9-$CH_3$, 10-$CH_3$, 11-H), 1.06 (d, $J$ = 7 Hz, 3 H, 6-$CH_3$), 2.11 (s, 3 H, 1-H); GC/MS, $m/e$ 226 ($M^+$), MOX derivative $m/e$ 253 ($M^+$ − 31). Anal. ($C_{14}H_{26}O_2$) C, H. Di-2,4-DNP derivative, mp 90–95 °C. Anal. ($C_{26}H_{35}N_8O_8$) C, H, N.

**(10*S*,11*R*)-10,11-Dihydroxy-5-(*p*-toluenesulfonylhydrazino)-2,6,10,14-tetramethylhexadecane (26).** Diol **17** (99 mg, 0.3 mmol) in EtOH (0.6 mL) was refluxed with tosylhydrazide (68.5 mg, 0.36 mmol) for 22 h. The solvent was removed, and the waxy tosylhydrazone **26** (75 mg, 50%) was isolated by preparative TLC (EtOAc/cyclohexane, 3:7): IR 2.82, 3.08, 6.21; NMR 0.87 (d, $J$ = 7 Hz, 9 H, 1-H, 2, 14-$CH_3$), 0.88 (t, $J$ = 6 Hz, 3 H, 16-H), 1.06 (s, 3 H, 10-$CH_3$), 1.08 (d, $J$ = 6 Hz, 3 H, 6-$CH_3$), 2.41 (s, 3 H, Ar $CH_3$), 3.43 (br m, 1 H, 11-H), 7.30 and 7.85 (each d, $J$ = 16 Hz, 1 H, Ar H); GC/MS; $m/e$ 481 ($M^+$ − $CH_3$), 479, 461, 411, 381.

**(10*S*,11*R*)-10,11-Dihydroxy-2,6,10,14-tetramethylhexadecane (27).** Tosylhydrazone **26** (60 mg, 0.12 mmol) in $CH_3OH$ (1 mL) and cyclohexane (0.3 mL) was slowly treated with $NaBH_4$ (60 mg, 1.58 mmol) and the mixture refluxed for 22 h under $N_2$. The solvent was removed, and the residue was treated with $H_2O$ and extracted with ether. The ether layer was dried ($Na_2SO_4$) and evaporated, and the residue (38 mg) was purified by preparative TLC (EtOAc/cyclohexane, 9:46) to give the oily deoxo compound **27**: 18 mg (47%); IR 2.9; NMR 0.88 (d, $J$ = 5 Hz, 15 H, 1-H, 16-H, 2,6,14-$CH_3$), 1.17 (s, 3 H, 10-$CH_3$), 3.36 (br m, 1 H, 11-H); GC/MS ($Me_3Si$ derivative), $m/e$ 443 ($M^+$ − $CH_3$).

**2,6-Dimethyl-10-undecanone (Hexahydropseudoionone, 28).** Deoxo diol **27** (65 mg, 0.21 mmol) in $CH_2Cl_2$ (13 mL) was treated with $MnO_2$ (390 mg, 4.5 mmol) at room temperature under $N_2$ for 1 h. After the removal of $MnO_2$ by filtration, the solvent was evaporated in the cold. The GC/MS analysis of the crude residue revealed the presence of aldehyde **25** [$m/e$ 114 ($M^+$)] as well as the ketone **28** [$m/e$ 198 ($M^+$)]. Purification by preparative TLC (EtOAc/cyclohexane, 5:95) gave the purified ketone **28**: 23.2 mg (59%); IR 5.80; NMR 0.86 (d, $J$ = 5 Hz, 9 H, 1-H, 2, 6-$CH_3$), 2.11 (s, 3 H, 11-H), 2.58 (t, $J$ = 5 Hz, 2 H, 9-H); GC/MS, $m/e$ 198 ($M^+$). Anal. ($C_{13}H_{26}O$) C, H. These data were identical with those of an authentic sample of **28** prepared by hydrogenation of pseudoionone.

**Synthesis of 6,10-Dimethylundecane-2,7-dione (23). Ethyl *tert*-Butyl (4-Methylvaleroyl)malonate (31).** Magnesium (7.75 g, 0.32 mol) was added to a solution of $CCl_4$ (0.7 mL) and absolute EtOH (5 mL) in a 1-L flask under $N_2$. A vigorous reaction occurred, the reaction mixture was cooled and $Et_2O$ (130 mL) added, and the reaction mixture was heated to reflux temperature. Ethyl *tert*-butyl malonate (**30**; 60 g, 0.32 mol) in EtOH (100 mL) was added dropwise over 15 min, and the resulting solution was refluxed for 3 h. 4-Methylvaleroyl chloride (**29**; 31.6 g, 0.325 mol) in $Et_2O$ (40 mL) was then added at reflux over 15 min, and reflux was continued for 1 h. After the mixture cooled, $H_2O$ was added, and the solution was acidified with 10% $H_2SO_4$ and extracted with $Et_2O$. The organic layer was dried ($Na_2SO_4$), filtered, and evaporated to give crude **31** (91 g) as a pale yellow liquid, which was used as such in the next step.

**Ethyl 6-Methyl-3-oxoheptanoate (32).** The crude **31** (91 g) was treated with *p*-TsOH·$H_2O$ (1.4 g) in benzene (200 mL) at reflux for 2 h in a flask equipped with a Dean–Stark trap. The reaction was then cooled and treated with a saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and evaporated to give a yellow liquid (98 g). Distillation afforded pure **32**: bp 87–89 °C (1.5 mm); 40% yield; NMR 0.9 (d, 6 H, 6-$CH_3$, 7-H), 1.5–1.75 (m, 6 H, alkyl H), 2.58 (br t, 2 H, 4-$CH_2$), 3.42 (s, 2 H, 2-$CH_2$), 4.25 (q, 2 H, $OCH_2CH_3$).

**6-Carbethoxy-2,2-ethylenedioxy-10-methyl-7-oxoundecane (33).** Compound **32** (7.84 g, 34 mmol) was added via syringe to sodium hydride (1.88 g, 39 mmol) in DMF (20 mL) at room temperature under $N_2$. After evolution of $H_2$ ceased, 5-chloro-2-pentanone ethylene ketal (7.1 g, 43 mmol) was added via syringe and the reaction mixture heated at 100 °C for 16 h. The reaction mixture was cooled, diluted with $H_2O$, and extracted with $Et_2O$/petroleum ether (1:1). The organic extract was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and distilled to give semipurified product: 5.8 g; bp 147–149 °C (0.25 mm). Chromatography of

a portion of this product (4.2 g) on silica gel (250 g) with EtOAc/hexane (1:20) gave pure **33** (2.75 g, 26%) as a pale yellow liquid: NMR 0.9 (d, 6 H, 10-$CH_3$, 11-H), 1.1–2.1 (m, 15 H, alkyl H), 2.54 (br t, 2 H, 8-$CH_2$), 3.46 (br t, 1 H, 6-H), 3.91 (s, 4 H, $OCH_2CH_2O$), 4.24 (q, 2 H, $OCH_2CH_3$).

**6-Carbethoxy-6,10-dimethyl-2,2-ethylenedioxy-7-oxoundecane (34).** Compound **33** (2.5 g, 7.96 mmol) was added via syringe to sodium hydride (0.382 g, 7.96 mmol) in DMF (15 mL) at room temperature under $N_2$. After evolution of $H_2$ ceased, methyl iodide (3.4 g, 23.9 mmol) was added and the reaction mixture heated at 100 °C for 18 h. The reaction mixture was cooled, diluted with $H_2O$, and extracted with $Et_2O$/petroleum ether (1:1). The combined organic extracts were washed with $H_2O$ and brine, dried ($Na_2SO_4$), filtered, and evaporated to give the crude product (2.63 g), which was chromatographed on silica gel (125 g) with EtOAc/hexane (5:95) as the eluent to give **34** as a yellow oil: 1.84 g (71%); NMR 0.9 (d, 6 H, 10-$CH_3$, 11-H), 1.1–2.1 (m, 18 H, alkyl H), 2.43 (br t, 2 H, 8-$CH_2$), 3.91 (s, 4 H, $OCH_2CH_2O$), 4.24 (q, 2 H, $OCH_2CH_3$).

**6,10-Dimethyl-2,2-ethylenedioxy-7-oxoundecane (35).** Compound **34** (1.19 g, 3.64 mmol) was dissolved in 8% NaOH (20 mL) and 95% EtOH (10 mL) and refluxed for 1 h. The reaction mixture was cooled and extracted with $Et_2O$. The organic layer was washed with $H_2O$, dried ($Na_2SO_4$), filtered, and evaporated to give crude **35** (820 mg, 88%) as a yellow oil, which was used as such for the next step.

**6,10-Dimethyl-2,7-dioxoundecane (23).** Compound **35** (377 mg, 1.47 mmol), acetone (20 mL), $H_2O$ (2 mL), and *p*-TsOH·$H_2O$ (50 mg) were refluxed for 0.5 h, cooled, poured into $H_2O$, and extracted with $Et_2O$. The combined organic layer was washed with $H_2O$ and saturated $NaHCO_3$, dried ($Na_2SO_4$), filtered, and evaporated to give crude **23** (282 mg) as a pale yellow liquid. Preparative TLC chromatography with EtOAc/cyclohexane (1:4) as the eluent gave pure **23** (230 mg, 74%). The di-2,4-DNP derivative was a yellow solid, mp 128–131 °C. Compound **23** and its 2,4-DNP derivative were identical by NMR, mass, and IR spectra with those derived from **17** via $MnO_2$ cleavage.

**(1′*S*,4′*S*,5′*R*)-1′-Ethyl-4′-(4″,8″-dimethyl-5″-oxononyl)-4′-methyl-3′,8′-dioxabicyclo[3.2.1]octane (36).** Compound **13** (235 mg, 0.73 mmol) was dissolved in absolute EtOH (200 mL), 10% Pd/C (200 mg) was added, and the resulting suspension was hydrogenated at 25 psi of $H_2$ for 1 h. The Pd/C was filtered and the filtrate evaporated to give **36** as a yellow oil: 237 mg (99%); $R_f$ 0.46 (cyclohexane/EtOAc, 4:1); IR 5.85; NMR 0.8–1.35 (m, $CH_3$, $CH_2$, 1-CH), 2.38 (br m, 3 H, 4″-H, 6″-$CH_2$), 3.51 (AB q, 2 H, J = 11 Hz, 2′-H), 3.82 (br m, 1 H, 5′-H).

**(*p*-Bromobenzenesulfonyl)hydrazone (37) of 36.** Compound **36** (237 mg, 0.73 mmol) was dissolved in absolute EtOH (10 mL), *p*-bromobenzenesulfonylhydrazide (300 mg) and 1 drop of HCl were added, and the resulting solution was stirred for 18 h at room temperature. The solvent was evaporated, and the residue was dissolved in $CH_2Cl_2$, filtered to remove unreacted hydrazide, and chromatographed on preparative plates with cyclohexane/EtOAc (4:1). The major band was eluted with EtOAc, filtered, and evaporated to give a white solid (226 mg), which gave a single spot with $R_f$ 0.39 (cyclohexane/ethyl acetate, 4:1). The white solid was triturated with hexane (3 mL), filtered, and dried to give a crystalline white solid: 184 mg; mp 105–109 °C; IR (KBr) 3.06; NMR 0.85–1.3 ($CH_3$, $CH_2$, CH), 3.52 (AB q, 2 H, $J$ = 11 Hz, 2′-H), 7.5–8.1 (aromatic H). This solid (43 mg) was recrystallized from $Et_2O$ to give white needles: 27 mg; mp 109–111 °C. Further recrystallization from $Et_2O$ gave compound **37** as white needles, mp 110–112 °C. Anal. ($C_{26}H_{41}BrN_2O_4S$): C, H, N.

***p*-Toluenesulfonylhydrazone (38) of 36.** Compound **36** (108 mg, 0.33 mmol) was dissolved in EtOH (3 mL), *p*-toluenesulfonylhydrazide (92 mg) and 1 drop of HCl were added, and the resulting solution was stirred for 18 h at room temperature. The solvent was evaporated, and the residue was dissolved in $CH_2Cl_2$ and chromatographed on preparative plates with cyclohexane/EtOAc (4:1). The major band was slurried in EtOAc, filtered, and evaporated to give an oily residue, which was triturated with hexane. Recrystallization from isopropyl ether or hexane gave **38**, mp 100–101 °C. Anal. ($C_{27}H_{44}N_2O_4S$): C, H, N.

**9-[(2′*S*,3′*R*)-3′-Acetoxy-6′-[(*E*)-2″-acetoxyethylidene]-2′-methyl-2′-oxepanyl]-2,6-dimethyl-2-nonen-5-ol (5).** Diacetate **3** (507 mg, 1.2 mmol) in $CH_3OH$ (25 mL) under $N_2$ at 0 °C was treated with excess $NaBH_4$ (84 mg, 2.2 mmol). The reaction mixture was stirred for 10 min, treated with saturated $NH_4Cl$ (20 mL), dried ($MgSO_4$), and evaporated. The oily residue was purified by chromatography on a silica gel column [10 g, ether/petroleum ether (1:1)] to give **5**: 407 mg (81%); colorless oil: $R_f$ 0.7 (EtOAc/benzene, 3:7); IR 2.86, 5.76; NMR 0.88 (d, $J$ = 6 Hz, 3 H, 6-H), 1.13 (s, 3 H, 2′-$CH_3$), 1.63 and 1.73 (both s, 3 H each, 1-H, 2-$CH_3$), 2.03 (s, 6 H, $OCOCH_3$), 3.48 (br m, 1 H, 5-H), 4.08 (s, 2 H, 7′-H), 4.55 (d, $J$ = 6 Hz, 2 H, 2″-H), 4.7–4.9 (m, 1 H, 3′-H), 4.97-5.53 (br m, 2 H, 3-H, 1″-H).

**9-[(2′*S*,3′*R*)-3′-Acetoxy-6′-[(*E*)-2″-hydroxyethylidene]-2′-methyl-2′-oxepanyl]-2,6-dimethyl-2-nonen-5-ol (39).** Diacetate **5** (940 mg, 2.36 mmol) in $CH_3OH$ (36 mL) was treated with aqueous $K_2CO_3$ (489 mg in 24 mL of $H_2O$, 3.54 mmol) under $N_2$ at 0 °C for 5 h. After being diluted with $H_2O$, the mixture was extracted with $Et_2O$, the organic layer was dried ($Na_2SO_4$) and evaporated, and the oily residue (725 mg, 86%) was purified by preparative TLC (EtOAc/hexane, 3:2) to give monoacetate **39** as a colorless oil, 553 mg (65%).

**9-[(2′*S*,3′*R*)-3′-Acetoxy-6′-[(*E*)-2″-oxoethylidene]-2′-methyl-2′-oxepanyl]-2,6-dimethyl-2-nonen-5-ol (40).** Monoacetate **39** (553 mg, 1.45 mmol) in $CH_2Cl_2$ (100 mL) was stirred with $MnO_2$ (1.0 g) at room temperature under $N_2$ for 66 h. The mixture was filtered, the solids were washed with $CH_2Cl_2$, and the combined filtrate and washings were evaporated to give an oily residue (500 mg). Purification by preparative TLC (EtOAc/hexane, 3:2) gave aldehyde **40** as a colorless oil: 296 mg (60%); IR 2.85, 3.63, 5.75, 5.98; NMR 0.89 (d, $J$ = 7 Hz, 3 H, 6-H), 1.16 (s, 3 H, 2′-$CH_3$), 1.64 and 1.74 (both s, 3 H each, 1-H, 2-$CH_3$), 2.03 (s, 3 H, $OCOCH_3$), 3.48 (m, 1 H, 5-H), 4.28 (s, 2 H, 7′-H), 4.92 (m, 1 H, 3′-H), 5.15 (m, 1 H, 3-H), 5.78 (d, $J$ = 8 Hz, 1 H, 1″-H), 9.98 (d, $J$ = 8 Hz, 1 H, 2″-H).

**9-[(2′*S*,3′*R*)-3′-Acetoxy-6′-[(*E*)-2″-(carboxymethyl)-ethylidene]-2′-methyl-2′-oxepanyl]-2,6-dimethyl-2-nonen-5-ol (41).** Aldehyde **40** (936 mg, 1.04 mmol) in $CH_3OH$ (100 mL) was treated with NaCN (229 mg, 4.67 mmol), AcOH (94 mg, 1.57 mmol), and $MnO_2$ (1.81 g, 33 mmol) for 19 h at room temperature under $N_2$. The $MnO_2$ was filtered through a pad of Celite and washed with $CH_2Cl_2$, and the filtrate and washings were evaporated to give an oily residue (352 mg), which upon preparative TLC purification (EtOAc/hexane, 3:2) gave **41**: 145 mg (34%); IR 2.92, 5.75, 5.80, 6.15; NMR 0.90 (d, $J$ = 6 Hz, 3 H, 6-$CH_3$), 1.15 (s, 3 H, 2′-$CH_3$), 1.63 and 1.73 (both s, 3 H each, 1-H, 2-$CH_3$), 2.03 (s, 3 H, $OCOCH_3$), 3.45 (m, 1 H, 5-H), 3.68 (s, 3 H, $COOCH_3$), 4.20 (s, 2 H, 7′-H), 4.80 (m, 1 H, 3-H), 5.17 (m, 1 H, 3″-H), 5.65 (br s, 1 H, 1″-H), GC/MS, $m/e$ 341 ($M^+$ − 69).

**5-[(2′*S*,3′*R*)-3′-Acetoxy-6′-oxo-2′-methyl-2′-oxepanyl]-2-carboxypentane (42).** To a mixture of **4** (1.2 g, 2.7 mmol), HOAc (40 mL), water (10 mL), and $OsO_4$ (10 mg) was slowly added an excess of $NaIO_4$ (2.5 g, 23 mmol). The resulting mixture was stirred at room temperature for 16 h, and the solvent was removed to give a white solid, which was treated with water and EtOAc. The organic layer was separated, dried ($MgSO_4$), and evaporated to give an oil. This oil was redissolved in ether and extracted with 5% $K_2CO_3$. The aqueous phase was combined and acidified at 0 °C to pH 2–3 with concentrated HCl. The mixture was extracted with ether, and the extract was dried ($Na_2SO_4$) and evaporated to give **42**: 410 mg (51%); IR 2.78–4.0 (br), 5.78, 5.86; NMR 2.02 (s, 3 H, $OCOCH_3$), 4.02 (s, 2 H, 7′-H), 4.9 (dd, $J_1$ = 8 Hz, $J_2$ = 4 Hz, 1 H, 3′-H), 9.0 (br, 1 H, $CO_2H$).

**5-[(2′*S*,3′*R*)-3′-Acetoxy-6′-[(*E*,*Z*)-2″-(carboxyethyl)-ethylidene]-2′-methyl-2′-oxepanyl]-2-(carbomethoxy)pentane (43 and 44).** A mixture of **42** (46 mg, 0.15 mmol), $(EtO)_2POCHNaCO_2Et$ (generated from triethyl phosphonoacetate and sodium hydride, 4 mmol), and benzene (10 mL) was refluxed under $N_2$ for 1.5 h. The resulting mixture was cooled to 0 °C and treated with saturated $NH_4Cl$ (5 mL). The mixture was extracted with ether, the combined organic layer was dried ($MgSO_4$), and the solvent was removed to give an oil. This was redissolved in ether (30 mL), and an excess of $CH_2N_2$ in ether was added at 0 °C. The resulting mixture was quenched with HOAc (5 mL). This was washed with saturated $Na_2CO_3$ and then dried ($MgSO_4$). The solvent was removed, and the residue was purified by column chromatography on silica gel [10 g, ether/petroleum ether (1:4)] to give a pale yellow oil as a mixture of **43** and **44**: 32 mg (54%);

IR 5.78; NMR 1.99 (s, 3 H, $OCOCH_3$), 3.62 (s, 3 H, $CO_2CH_3$), 4.2 (overlapping s and q, 7′(*E*)-H, $OCH_2CH_3$), 4.8 (overlapping m, 7′(*Z*)-H, 3′-H), 5.6 (br s, 1 H, 1″-H); GC/MS, two components in a 3:2 (**43**/**44**) ratio with identical fragmentations.

**X-ray Analysis of 38.** This compound crystallized as small monoclinic needles from *n*-hexane. The following crystallographic data were measured for these crystals: $a$ = 5.378 (7) Å, $b$ = 18.973 (18) Å, $c$ = 14.182 (17) Å, $\beta$ = 102.68(10)°, and space group $P2_1$ with 2 molecules in the unit cell.

Intensity data were collected by the stationary crystal–stationary counter method with Cu K$\alpha$ radiation monochromatized by balanced nickel and cobalt filters on a GE XRD-6 diffractometer. A total of 1706 reflections were measured ($2\theta < 100°$) with 588 having intensities which were weak and considered unobserved. Corrections were applied to the data for $\alpha_1$–$\alpha_2$ splitting and Lorentz polarization effects.

All nonhydrogen atoms were located by a combination of tangent formula refinement[29] and Fourier methods. The structure was refined by the block diagonal least-squares method with anisotropic thermal parameters assigned to all the nonhydrogen atoms. The absolute configuration of the molecule was determined by statistical comparison of the converged structure factors for each enantiomorph. The refined $R$ values were 0.087 and 0.092 for the correct and incorrect configurations, respectively.

(29) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

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**Registry No.** **1**, 71117-51-6; **2**, 71117-50-5; **3**, 71117-49-2; **4**, 80629-31-8; **5**, 67441-42-3; **6**, 80572-59-4; **7**, 69493-28-3; **8**, 80572-60-7; **9**, 80572-61-8; **10**, 80572-62-9; **11**, 67441-49-0; **12**, 80572-63-0; **13**, 67441-47-8; **14**, 68688-88-0; **15**, 67441-46-7; **15** bis(TMS), 80572-64-1; **16**, 67463-69-8; **16** bis(TMS), 80629-32-9; **17**, 71092-34-7; **18**, 80572-65-2; **19**, 80572-66-3; **20**, 80572-67-4; **21**, 71092-35-8; **22**, 80572-68-5; **23**, 80572-69-6; **23** di-2,4-DNP, 80572-70-9; **24**, 80572-71-0; **24** di-2,4-DNP, 80572-72-1; **25**, 41065-97-8; **25** 2,4-DNP, 14093-70-0; **26**, 80572-73-2; **27**, 71092-37-0; **28**, 1604-34-8; **29**, 38136-29-7; **30**, 32864-38-3; **31**, 80572-74-3; **32**, 57689-16-4; **33**, 80572-75-4; **34**, 80572-76-5; **35**, 80572-77-6; **36**, 67441-48-9; **37**, 80629-33-0; **38**, 80629-34-1; **39**, 80572-78-7; **40**, 80572-79-8; **41**, 80572-80-1; **42**, 80583-30-8; **43**/**44**, 80572-81-2; 5-chloro-2-pentanone ethylene ketal, 5978-08-5; triethyl phosphonoacetate, 867-13-0.

**Supplementary Material Available:** Tables III–V containing atomic coordinates, anisotropic thermal parameters, bond distances, and bond angles (3 pages). Ordering information is given on any current masthead page.

# Observations on the Chemistry of $\alpha$-Azido Esters. Efficient Synthesis of a Potently Sweet Homoserine–Dihydrochalcone Conjugate

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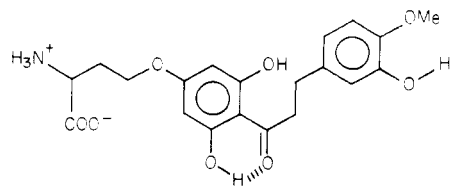
An efficient preparation of methyl 2-azido-4-bromobutyrate (**6**) has been developed. This reagent undergoes an alkylation reaction with the trihydroxyflavanone hesperetin (**2**) with complete regiospecificity to give only the 7-substitution product **3**. Hydrogenation of **3** in aqueous alkali yields the potent dihydrochalcone sweetener **1** in nearly quantitative yield. Azido ester **6** was found to undergo intramolecular alkylation to yield 1-(carbomethoxy)-1-azidocyclopropane (**9**) on treatment with base. This represents the *first* observation of base-promoted aliphatic azide alkylation. 4-[3-Azido-3-(carbomethoxy)propoxy]acetophenone (**8**), formed on alkylation of 4-hydroxyacetophenone (**7**) with **6**, undergoes oxidative nitrogen elimination on treatment with base to yield the unstable 4-[3-(carbomethoxy)-3-oxopropoxy]acetophenone (**11**). Keto ester **11** undergoes facile 1,2-elimination of **10** to yield **7**, thus explaining the fragmentation of **3** to **2**. Azido ester **6** alkylates **2**, a strongly acidic phenol [$(pK_a)_{rel}$ = 0.0], in high yield and **7**, a less acidic phenol [$(pK_a)_{rel}$ = 1.6], in poor yield, and fails to alkylate phenol, a weakly acidic phenol [$(pK_a)_{rel}$ = 3.0]. This result is explained in terms of the high basicity of the weak acid–phenol conjugate bases. Thus the more basic phenolate anions act as bases in promoting 1,3-elimination in **6** to yield **9**. This rationale is extended to explain the complete regiospecificity in the alkylation of **2**.

The interesting observations of Jarvis and Nicholas[1] on the base-promoted decomposition of $\alpha$-azido nitriles and sulfones as well as related work by Rathke and Manis[2] on $\alpha$-azido esters prompt us to report some observations of a related nature encountered in the development of a large-scale economical synthesis of the potent dihydrochalcone sweetener 1.[3] In order to apply the previously developed methodology for synthesis of 4-O-substituted hesperetin dihydrochalcones (**4**) outlined in Scheme I,[4] we required an inexpensive alkylating agent RX for the introduction of the homoserine side chain.




1

One possible candidate was methyl 2-azido-4-bromobutyrate (**6**). This compound was readily available from methyl 2,4-dibromobutyrate (**5**) by reaction with sodium azide in dimethylformamide (DMF). In earlier work we described an efficient synthesis of dibromide **5**.[5] The preparation of $\alpha$-azido ester **6** is illustrated in Scheme II.

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(1) Jarvis, B. J.; Nicholas, P. E. *J. Org. Chem.* **1979**, *44*, 2951–2952.
(2) Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952–4954.
(3) DuBois, G. E.; Crosby, G. A.; Lee, J. F.; Stephenson, R. A.; Wang, P. C. *J. Agric. Food Chem.* **1981**, *29*, 1269–1276.
(4) DuBois, G. E.; Crosby, G. A.; Saffron, P. *Synth. Commun.* **1977**, *7*, 49–56.
(5) DuBois, G. E.; Crosby, G. A.; Stephenson, R. A. *J. Med. Chem.* **1981**, *24*, 408–428.

0022-3263/82/1947-1319$01.25/0 