A Stereoselective Total Synthesis of (+/−)-Muzigadial

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K-10 Montmorillonite Clay catalyst powder failed to isomerize 8.

Photolysis of 17β-Hydroxyestra-4,9,11-trien-3-one (9). Trienone **9** (10 mg) in 10 mL of solvent, was irradiated as described above. The reaction was monitored by TLC until **9** had all reacted. A variety of solvents including methanol, ethyl acetate, ether, acetone, dioxane, benzene, and isopropyl alcohol led to the formation of a polymeric solid, mp >300 °C, which precipitated out of solution.

Acknowledgment. We are grateful to Dr. J. W. Raynal of Roussel Uclaf for a generous sample of 17β-hydroxyestra-4,9,11-trien-3-one, Dr. R. Rees of Wyeth Laboratories for a generous sample of norgestrel, Mr. L. Killmer and Mr. G. Zuber both of Smith Kline and French Laboratories, for the mass spectra and FT-IR spectra, respectively, Mr. Hassan El-Okdah for experimental assistance, and the NIH for financial support.

Supplementary Material Available: Table of anisotropic thermal parameters of **8** (8 pages). Ordering information is given on any current masthead page.

Registry No. **1a**, 434-22-0; **1b**, 797-63-7; **2a**, 42028-18-2; **2b**, 100021-05-4; **3a**, 1434-85-1; **3b**, 78088-19-4; **4a**, 100021-06-5; **4b**, 100021-07-6; **5a**, 100044-89-1; **5b**, 100021-08-7; **6**, 100021-09-8; **7**, 53303-85-8; **8**, 100021-10-1; **9**, 10161-33-8; 17β-hydroxy-5(10)-estren-3-one, 1089-78-7; 17β-hydroxyestra-4,9-dien-3-one, 6218-29-7.

A Stereoselective Total Synthesis of (±)-Muzigadial

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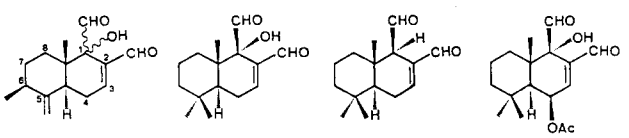
A stereoselective, 14-step, total synthesis of (±)-muzigadial (**1a**, 11% overall yield), starting from the commercially available Wieland–Miescher ketone (**5**), via intermediate ketone **13**, is described. The two additional chiral centers in **13** were incorporated by equilibration of the mixture of stereoisomeric ketones **10** to the most favorable isomer, **10a**. The key step for introducing the necessary functionality at C-1 involved the regio- and stereoselective cis hydroxylation of enol ether **37b** with osmium tetraoxide in the presence of *tert*-butyl hydroperoxide.

Much recent effort has been devoted to developing new biorational methods for insect control. In this context, the application of natural antifeedants is of potential value due to their specificity of action and their nontoxic character. Naturally occurring antifeedants include glycosides of steroidal alkaloids,[1] aromatic steroids,[2] quinones,[2d,3] germacrane sesquiterpenes,[4] clerodanes,[5] and iridoids.[6] A series of "drimane" sesquiterpenes, isolated from the bark of the East African plants *Warburgia ugandensis* and *W. stuhlmanii* (Canellaceae), i.e., muzigadial[7a,b] (**1a**), warburganal[7c] (**2**), polygodial[7d] (**3**), and ugandensidial[7e] (cinnamodial,[7f] **4**) have shown highly potent antifeedant activity against the African army worms *Spodoptera littoralis* and *S. exempta*. In addition, compounds **1a** and **2** exhibit a broad antibiotic spectrum, as well as helicocidal activity against the schistosome-transmitting snails *Biomphalaria glabratus*, *B. pfeifferi* (LD_{50} = 5 ppm within 24 h), and *Lymnaca natalensis* (LD_{50} = 10 ppm within 24 h).[7a]



1a: αOH, βCHO
1b: βOH, αCHO
2
3
4

Total syntheses of warburganal (**2**) and polygodial (**3**) have been accomplished by several groups, starting from 2,6,6-trimethyl-1-vinylcyclohex-1-ene,[8a-c] isodrimenin,[8d] 1-abietic acid,[8e] or 5,5,9-trimethyl-*trans*-1-decalone[8f,g] or through an ingenious metathesis/transannular ene sequence to the required trans-fused decalin derivative.[8h] On the other hand, to our knowledge, the synthesis of muzigadial has not been heretofore reported in the literature. Nevertheless, **1a** clearly provides a challenging target to synthetic organic chemists, since it possesses an exomethylene group at C-5 and the chiral center at C-6 not found in warburganal. To avoid confusion and allow direct comparison between spectral and stereochemical data, the numbering system of muzigadial has been used throughout the discussion. One plausible retrosynthetic analysis of **1a** would require dialdehyde **33**, which we hoped would

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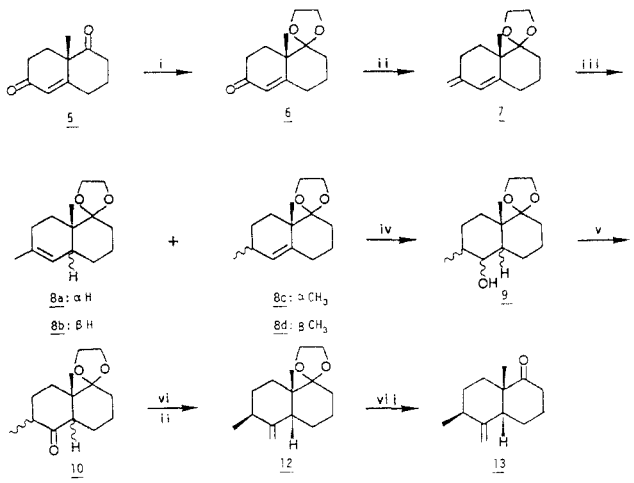
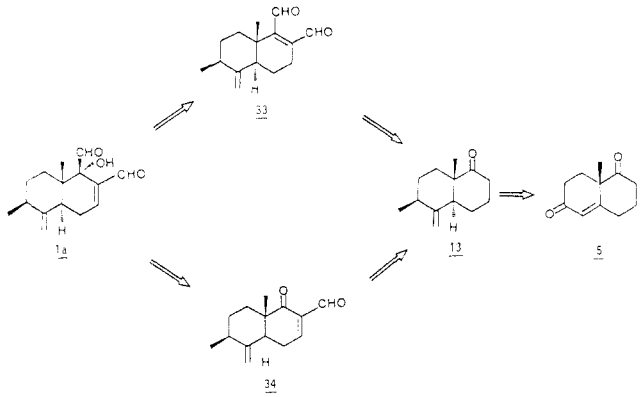
Scheme I[a]



[a] Reagents: (i) MED, $(CH_2OH)_2$; (ii) $CH_2{=}PPh_3$; (iii) Li, NH_3; (iv) BH_3·THF, H_2O_2/NaOH; (v) CrO_3·Py; (vi) NaOMe/MeOH; (vii) 1 N HCl–AcOH–THF (1:2:3).

afford muzigadial by regioselective epoxidation of the tetrasubstituted double bond, followed by a base-promoted ring-opening reaction of the epoxide. Alternatively, keto



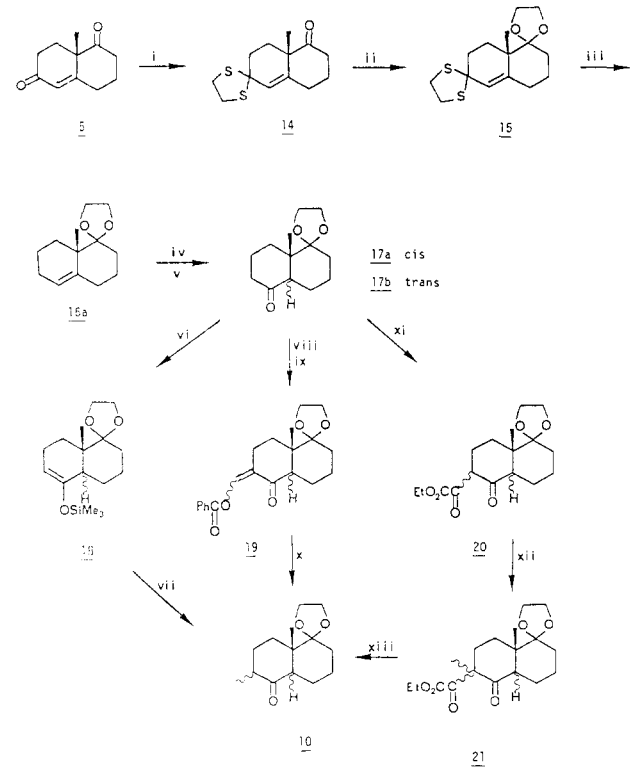
aldehyde **34** might provide the required functionality at C-1 through the regio- and stereoselective cis hydroxylation of the derived enol ether, **37b**. Both intermediate aldehydes could be derived from the versatile intermediate ketone **13**, prepared in turn from the commercially available Wieland–Miescher ketone (**5**). On the basis of this analysis, we describe herein the first, stereoselective total synthesis of (±)-muzigadial (**1a**) from **5**, in 14 steps, with an overall yield of 11%.

The two new chiral centers in **13** have been introduced through stereoselective hydrogenation of diene **7**, which yields predominantly *trans*-decalin **8a**, and by equilibration of the stereoisomeric mixture of ketones **10** to the most favorable isomer (**10a**).

Results and Discussion

Access to intermediate **13** has been accomplished by two different approaches, both starting from ketone **5** (Schemes I and II). In the first of these, selective protection of the nonconjugated carbonyl group by trans-acetalization with 2-methyl-2-ethyl-1,3-dioxolane (MED)[9] yielded 95% of the monoacetal **6**, along with only 2% of the corresponding diacetal, markedly improving the results of the conventional acid-catalyzed treatment with ethylene glycol.[10a,b]

Scheme II[a]



[a] Reagents: (i) $(CH_2SH)_2$, AcOH, *p*-TsOH; (ii) $(CH_2OH)_2$, *p*-TsOH; (iii) Na, NH_3; (iv) BH_3·THF, 30% H_2O_2/NaOH; (v) CrO_3Py; (vi) LDA/$(CH_3)_3SiCl$; (vii) *n*-BuLi/CH_3I; (viii) HCO_2Et/NaOEt; (ix) PhCOCl/Py; (x) PtO_2/EtOH; (xi) $(CO_2Et)_2$/NaH; (xii) MeI/K_2CO_3; (xiii) NaOEt/EtOH.

Wittig reaction of **6** with methylenetriphenylphosphorane[11] afforded diene **7** in 83% yield. Subsequent reduction with lithium in ammonia yielded (97%) a mixture of monoenes **8a**, **8c**, and **8d** in a 58:23:19 ratio. (The presence of **8b** was not detected after careful purification by column chromatography and subsequent capillary GLC analysis).[12]

Fractionation of a portion of this monoene mixture on $AgNO_3$ impregnated silica gel led to the isolation of **8a** and **8d**. Structure **8a** was assigned to the major isomer, on the basis of the characteristic width at half height (0.82 Hz) of its angular methyl ^1H NMR absorption, which is characteristically broader in *trans*-decalins than in *cis*-decalins ($\Delta W_{h/2}$ trans 0.80 ± 0.20; cis 0.25 ± 0.11).[13] The second isolated compound exhibited a 21.91 ppm secondary methyl signal in the ^{13}C NMR spectrum, which agrees with expectations for a pseudoequatorial conformation for this group, as shown in **8d**.[14,15] Assignment of structure **8c** to the third isomer observed in GLC was based on the assumption that the alternative choice **8b** should be formed in negligible amounts in a lithium/ammonia reduction, which would be expected to provide almost exclusively the thermodynamically more stable trans-fused decalin.[16]

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(14) Vierhapper, F. W.; Willer, R. L. *Org. Magn. Reson.* **1977**, *9*, 13.
(15) A 7% NOE was obtained for the vinyl proton upon irradiation of the secondary methyl group in **8d**, but in the absence of the isolated diastereomer **8c** with an α-oriented methyl, this result was not a conclusive proof for the assignment. (b) For application of NOE, see: Barrett, M. W.; Farrant, F. D.; Kirk, D. N.; Mersh, J. D.; Sanders, J. K. M.; Duax, W. L. *J. Chem. Soc., Perkin Trans 2* **1982**, 105.
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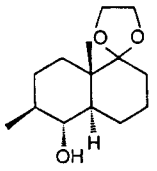
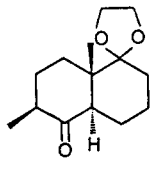
This assumption was confirmed by the result of a subsequent homogeneous catalytic hydrogenation (see below). Several unsuccessful attempts were made to improve the selectivity of this reduction to favor the formation of **8a**, the most reactive isomer in the hydroboration reaction required in the next step of our sequence. Thus, reductions with sodium in ammonia or lithium in *N*-methylaniline furnished mixtures of **8a** and **8d** ranging from 1:1 to 1:2 ratios, whereas homogeneous catalytic hydrogenation in the presence of tris(triphenylphosphine)rhodium chloride, afforded a 1:1 mixture of **8c** and **8d**.

The mixture of monoenes **8a–d**, from the reduction of **7** with lithium in ammonia, was subjected to oxidative hydroboration[17] to provide a mixture of diastereomeric alcohols, **9**, in 81% yield, along with a mixture (10%) of unreacted olefins **8c** and **8d**.[18] In these olefins, syn addition of BH_3·THF complex[19] was expected to take place preferentially, if not exclusively, from the less hindered β face of the molecule, i.e., cis to the angular methyl group,[20] due to the anticipated effective blocking of the α side by the axial oxygen of the acetal group. Conversely, as revealed from inspection of molecular models, hydroboration of the major isomer, **8a**, should proceed from the α face, as a result of the steric effect of the angular methyl group.

From the expected mixture of the five possible alcohols **9**, the major isomer was isolated in 58% yield and characterized as **9a**. This assignment was based on the appearance of a shielded C*H*OH absorption at δ 2.93, in the ^{1}H NMR spectrum, in agreement with the reported deshielding effect of −0.31 ppm promoted by an equatorial methyl group on the chemical shift of a vicinal axial hydrogen.[21] Furthermore, the multiplicity of the signal (doublet of doublets, J = 11.0 and 8.0 Hz) required two trans 1,3-diaxial couplings and, therefore, a trans,trans relationship for the three methine protons at C-4a, C-5, and C-6 in the preferred chair–chair conformation. The angular methyl group peak width compared with that of Me_4Si, ΔW = 0.9 Hz, is fully in the range of the expected value for a trans-fused decalin system.[13]

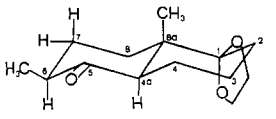


9a

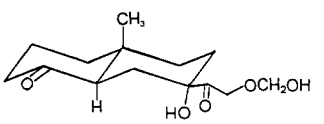


10a

As shown in Scheme I, the mixture of isomeric alcohols **9** was oxidized with chromium trioxide in pyridine to afford a 77% yield of a stereomeric mixture of decalones **10**, in a 6:53:41 ratio, as revealed by GLC analysis. The major isomer obtained was decalone **10a**, the oxidation product of **9a**, as demonstrated after epimerization of the mixture under basic conditions (NaOMe in MeOH). Epimerization occurred, as expected, at both asymmetric centers adjacent to the carbonyl group, to provide crystalline decalone **10a**. Stereochemical assignment of decalone **10a** at C-6 and C-4a was secured by its 200-MHz ^{1}H NMR spectrum, including selected homonuclear decoupling experiments. Thus, the apparent septet of doublets at δ 2.38 of $H_{6\alpha}$ was rationalized as a doublet of quintuplets of doublets, since irradiation of the secondary methyl group collapsed the signal into a doublet of doublets of doublets, pointing out the equal values of the coupling constants $J_{6\alpha,CH_3}$ and $J_{6\alpha,7\alpha}$ = 6.7 Hz, and exactly the double of this value for the 1,3-trans diaxial coupling $J_{6\alpha,7\beta}$ = 13.4 Hz. The remaining multiplicity (doublet) was attributed to a long range coupling $J_{6\alpha,4a\alpha}$ of 1.5 Hz, confirmed by selective irradiation at δ 2.62 of H_{4a}, which in turn appeared as a doublet of doublets of doublets ($J_{4a,4\beta}$ = 10.0 Hz, $J_{4a,4\alpha}$ = 4.0 Hz, $J_{4a,6\alpha}$ = 1.5 Hz), showing the large coupling constant expected for a 1,3-trans diaxial system $H_{4a\alpha}$–$H_{4\beta}$, as required for a trans-fused decalin. These spectroscopic data are in perfect agreement with those reported for protons $H_{4a\alpha}$ and $H_{6\alpha}$ in compound **11**, a dioxo derivative of the sweet potato phytoalexin 7-hydroxycostol.[22]



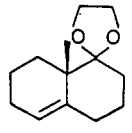
10a



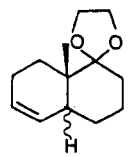
11

Having devised an efficient route to introduce the chiral centers with the right stereochemistry, the two remaining steps toward intermediate ketone **13** were straightforward. Thus, Wittig reaction of **10a** with methylenetriphenylphosphorane in Me_2SO led to the isolation of exomethylene acetal **12** in 95% yield. Acid hydrolysis of the acetal group, avoiding migration of the exocyclic double bond, was effected by treatment with a 1:2:3 1 N HCl–glacial AcOH–THF mixture,[23] giving intermediate decalone **13**[24] in 30% overall yield from **5**. Ketone **13**, with the required stereochemistry at C-4a, C-6, and C-8a, appeared to be a suitable synthon to introduce the remaining functionalities at C-1 and C-2 of the target molecule **1a**.

An alternative approach to **10a** is outlined in Scheme II. Selective thioacetalization of the conjugated carbonyl group[25] in **5** yielded ketone **14** in almost quantitative yield. Protection of the remaining carbonyl as the corresponding ethylene acetal afforded compound **15** in 96% overall yield from **5**. Desulfurization of **15** by treatment with W-2 Raney Ni in absolute ethanol resulted in the partial concomitant migration of the double bond, affording a mixture of olefins **16a–c**, in a 71:16:13 ratio, respectively (60% yield). However, reduction of **15** with sodium in ammonia[26] gave olefin **16a** stereoselectively as the only isolable product, in 74% yield.



16a



16b: αH

16c: βH

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(18) Longer reaction times or larger excess of borane, in order to ensure complete reaction, produced acetal cleavage products, as determined by MS analysis. See ref 19.

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(24) Ketone **13** has been fully characterized by its melting point, IR, ^{1}H NMR, ^{13}C NMR, and MS spectra, thus completing the scarce data (mp and ^{1}H NMR) reported in the literature (De Groot, A. E.; Broekhuysen, M. P.; Doddema, L. L.; Vollering, M. C.; Westerbeck, J. M. M. *Tetrahedron Lett.* **1982**, *23*, 4831).

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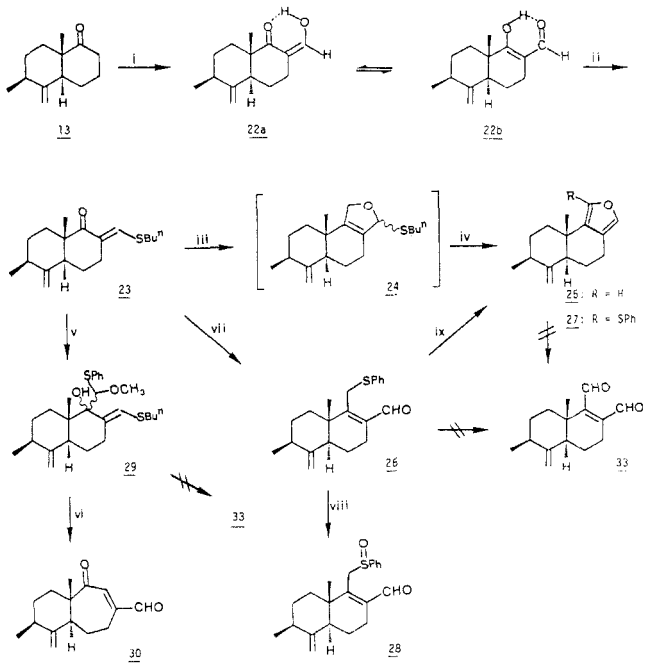
Scheme III[a]



[a] Reagents: (i) HCO_2Et, NaOEt; (ii) TsCl/Py, *n*-BuSH; (iii) *n*-BuLi, $(CH_3)_3S^+BF_4^-$; (iv) $HgSO_4$; (v) $PhSCH_2OCH_3$, *n*-BuLi; (vi) $HgCl_2$, HCl; (vii) $PhSCH_3$, DABCO/$HgCl_2$, HCl; (viii) NCS, H_2SO_4/CH_3OH; (ix) NCS/CCl_4.

Hydroboration of **16a**, followed by oxidation of the resulting diastereomeric alcohols, yielded a mixture of *cis*- and *trans*-decalones **17a** and **17b** in 6:94 ratio in 59% overall yield from **5**. Stereochemistry of the ring junction was inferred from the half band width difference between the angular methyl and the reference (Me_4Si) signals (see above).

Methylation of **17** at C-6 turned out to be a more troublesome task than expected. In this context, the less highly substituted lithium enolate of **17**, obtained through a kinetically controlled deprotonation with LDA, allowed the preparation of the corresponding trimethylsilyl enol ether **18** in 85% yield.[27a] However, subsequent reaction of the enolate derived therefrom with methyl iodide, provided only a 2:1 mixture of methylated product **10** and unreacted ketone **17** in 80% yield. Other attempts, involving direct alkylation of this enolate, failed to improve this result. Therefore, an alternative three-step sequence had to be applied to achieve stereoselective methylation in good yield. Formylation of **17** (HCO_2Et/NaOEt),[27b] followed by benzoylation produced compound **19**, which, subjected to a hydrogenolysis in the presence of PtO_2,[28] furnished **10a** in a modest 39% overall yield. A better yield was obtained through the sequence reported by F. Sondheimer et al.[29] Condensation of **17** with ethyl oxalate in the presence of sodium hydride afforded compound **20**, which was readily methylated with CH_3I/K_2CO_3 to yield the keto ester **21**, which in turn was treated with NaOEt/EtOH to effect removal of the keto ester group. The thermodynamically more stable stereoisomer, **10a**, along with the unexpected **10c** ($\alpha H,\alpha CH_3$) in 2:1 ratio, were obtained in 54% yield from **17**. Overall, the approach depicted in Scheme I was considered more convenient for multigram scale preparation of **10a**.

At this point, having developed an efficient synthesis of **13**, we attempted the required modification of ring B to give muzigadial (**1a**), through dialdehyde **33**. As shown in Scheme III, introduction of the enal functionality at C-2 was effected by treatment of **13** with HCO_2Et/NaH[30] to yield hydroxymethylene derivative **22** (97%), which exists in the two tautomeric forms, **22a**, and **22b**, as inferred from its spectroscopic features[31] (singlets at δ 8.55 and 14.65, corresponding to the vinyl hydrogen of **22a** in equilibrium with the aldehyde proton of **22b** and to the hydroxylic hydrogen of both forms, respectively).

Protection of the aldehyde function as the (*n*-butylthio)methylene derivative **23**[32] (78% overall yield from **13**), followed by reaction with dimethylsulfonium methylide,[33] prepared in situ from trimethylsulfonium tetrafluoroborate[34] and *n*-butyllithium in DME, provided the expected dihydrofuran **24**, which upon treatment with $HgSO_4$ was cleanly converted into furan **25**, isolated in 72% yield after column chromatography. Compound **25**, unreported so far in nature, is structurally related to euryfuran,[35,36a] which has been recently isolated from the sponges *Dysidea herbacea* and *Eurysongia sp.* and the nudibranchs *Hypselodoris californensis* and *H. porterae*. Unfortunately, efforts to oxidize **25** to dialdehyde **33** were unsuccessful.[36b]

On the other hand, reaction of (*n*-butylthio)methylene ketone **23** with [(phenylthio)methyl]lithium,[37] followed by dehydration of the resulting tertiary alcohol with $HgCl_2$, yielded (phenylthio)methyl aldehyde **26**[38] in 72% yield (from **23**). Treatment of **26** with *N*-chlorosuccinimide (NCS) in CCl_4 did not give the expected chloro sulfide,[39] but afforded instead the (thiophenyl)furan **27** along with unreacted starting material, whereas the use of NCS in H_2SO_4/MeOH yielded sulfoxide **28**. Other attempts to effect the transformation $CH_2SPh \rightarrow CH_2OH$ gave unsatisfactory results. In addition, when **23** was treated with [methoxy(phenylthio)methyl]lithium,[40] a mixture of stereomeric alcohols, **29**, was obtained in almost quantitative yield. However, treatment of this mixture with $HgCl_2$ did not lead to the expected dialdehyde **33** after dehydration but to the seven-membered ring keto aldehyde **30**, in agreement with the ring expansion approach to α-methylene δ-lactones reported by Trost et al.[40] Under careful control of the experimental conditions, it was possible to isolate the diastereomeric methoxy derivatives **31** or hydroxy aldehyde **32**, although, unfortunately, all our

(27) (a) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361. (b) Reaction of the hydroxymethylene derivative of **17** with Pd/C in *p*-TsOH (House, H.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502) resulted in the corresponding hydroxymethyl ketone instead of the expected hydrogenolysis product.

(28) Astill, B. D.; Boekelheide, V. *J. Am. Chem. Soc.* **1955**, *77*, 4079.

(29) Sondheimer, F.; Elad, D. *J. Am. Chem. Soc.* **1958**, *80*, 1967.

(30) Welch, S. C.; Hagan, C. P.; White, D. H.; Fleming, W. P.; Trotter, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 549.

(31) The ^1H NMR data are in agreement with those described for an analogous hydroxymethylene derivative: Spencer, T. A.; Weaver, T. D.; Villarica, R. M.; Friary, R. J.; Posler, J.; Schwartz, M. A. *J. Org. Chem.* **1968**, *33*, 712.

(32) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615.

(33) Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250.

(34) Preparation of the salt was accomplished by the Fukui method (Fukui, H.; Kanai, K.; Kitano, H. *Nippon Kagaku Zasshi* **1961**, *82*, 178). A more recent procedure by Hasimoto et al. (Hasimoto et al. *Nippon Kagaku Zasshi* **1968**, *89*, 810) gave inferior results in our hands.

(35) Dunlop, R. W.; Kazlauskas, R.; March, G.; Murphy, P. T.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 95.

(36) (a) Hochlowski, J. E.; Walker, R. P.; Ireland, C.; Faulkner, D. J. *J. Org. Chem.* **1982**, *47*, 88. (b) Reaction of **25** with singlet oxygen (Wassermann, H. H.; Ives, J. L. *Tetrahedron* **1981**, *37*, 1825) or bromine in methanol did not result in the expected **33**. After this approach had been abandoned, Ley et al. (Ley, S. V.; Mahon, M. *J. Chem. Soc., Perkin Trans 1* **1983**, 1379) reported the formation of butenolides from *gem*-dimethyldecalones isomeric to **13**, following similar procedures.

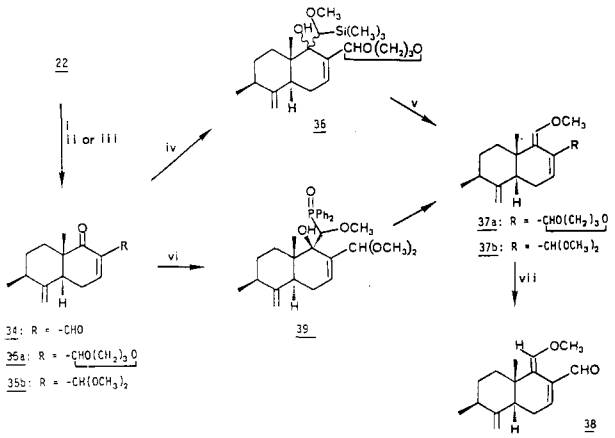
(37) Sowerby, R. L.; Coates, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 4758.

(38) This compound has been prepared as a suitable intermediate for the synthesis of colorata-4(13),8-dienolide (see ref 24).

(39) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1977**, *42*, 2362.

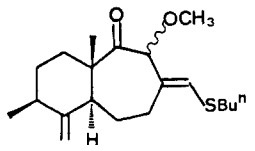
(40) Trost, B. M.; Miller, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 7182.

Scheme IV[a]

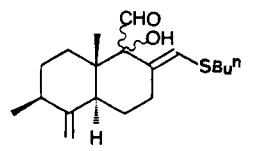


[a] Reagents: (i) PhSeCl/Py, 30% H_2O_2; (ii) $HO(CH_2)_3OH$, H_2SO_4; (iii) $HC(OMe)_3$, MeOH, *p*-TsOH; (iv) $(CH_3)_3SiCH_2OCH_3$, *sec*-BuLi; (v) KH/THF; (vi) $Ph_2P(O)CH_2OCH_3$, LDA; (vii) Florisil.

attempts to transform this intermediate aldehyde into the target dialdehyde **33** were unsuccessful.



31



32

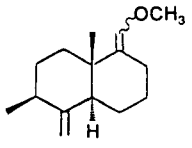
The second approach to muzigadial via keto aldehyde **34** was much more rewarding (Scheme IV). Dehydrogenation of **22** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[41] afforded keto aldehyde **34** in a modest 53% yield, which could not be improved despite extensive efforts. Considerably better results were obtained by selenenation with phenylselenenyl chloride in pyridine,[42] to furnish the corresponding α-phenylselenenyl ketone, which was oxidized with 30% H_2O_2 at 0 °C to produce, after syn elimination of the selenoxide, the α,β-unsaturated keto aldehyde **34** in 95% yield. Selective protection of the aldehyde moiety of **34** as the trimethylene acetal afforded ketone **35a** in 91% yield. This ketone proved to be a suitable intermediate for completion of the required functionalization at C-1.

Homologation of ketones to α-hydroxy aldehydes is a well-known procedure.[43] However, in our case, direct nucleophilic reaction of a suitable masked acyl anion should result in attack from the less hindered α side of the carbonyl group of **35a**, giving rise to the undesired epimer of muzigadial, **1b**. Analogous results would be obtained if the α-hydroxy aldehyde were generated from cleavage of an α,β-epoxy sulfone.[44] The high degree of steric hindrance in **35a** presented an additional difficulty to circumvent. Thus, reaction of encumbered ketones with $Ph_3P{=}CHOCH_3$, $Ph_3P{=}CH_2$, $(EtO)_2P(O)\bar{C}HOCH_3$,[45] $Me_3Si\bar{C}HCl$,[46] or $(RO)_2P(O)\bar{C}HN_2$[47] have generally proceeded with unsatisfactory yields. Nevertheless, nucleophilic acylation of ketone **35a** could be carried out successfully by treatment with methoxy(trimethylsilyl)methyl lithium,[8f,48] at −78 °C in THF, to afford a mixture of diastereomeric alcohols, **36**, in 79% yield.

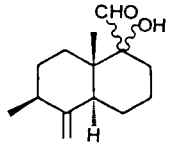
Surprisingly, extrusion of Me_3SiOH from **36** with KH at 0 °C gave only a poor yield (22%) of the desired enol ether **37a**. Similarly, the use of (methoxymethyl)diphenylphosphine in *sec*-butyllithium at −90 °C, followed by quaternization with MeI,[49] yielded a complex mixture from which only a very small amount of enol ether **37a** could be isolated.

Much more encouraging, though, was the reaction of ketone **35b**, less sterically hindered than the corresponding **35a**, with the lithium salt of (methoxymethyl)diphenylphosphine oxide.[50-52] This reaction required a large excess of the anion (20 equiv), formed in LDA at −75 °C, to provide in almost quantitative yield the corresponding adduct **39**, which decomposed under the reaction conditions to afford enol ether **37b**, with *Z* configuration, in 75% yield. This assignment was inferred from the vinyl proton NMR absorption at δ 6.07, exhibited by aldehyde **38**, which resulted from selective hydrolysis of **37b** on Florisil, in agreement with that reported for a similar intermediate in a synthesis of warburganal.[8f]

The almost complete absence of the corresponding (*E*)-**37b** isomer indicated the stereoselective formation of the *erythro* diastereomer, **39**, in the Wittig reaction of ketone **35b** with the lithium salt of (methoxymethyl)diphenylphosphine oxide, in contrast with the poor stereoselectivity observed under the same reaction conditions for model ketone **13**, which afforded a 2:1 mixture of enol ethers **40** in 75% yield. Osmium tetraoxide oxidation of **40** provided hydroxy aldehydes **41a** and **41b** in 65% yield. This configurational assignment was based on the nuclear Overhauser effect (NOE) measurements.[53]



40



41a: αOH, β CHO

41b: α CHO, β OH

Introduction of the remaining hydroxyl group into **37b**, α to the angular methyl, would require the use of a bulky electrophilic reagent to secure attack from the α face of the methoxymethylene group, in order to achieve the correct configuration at C-1 in **1a**. Although the use of peroxy acids appeared not to be promising for this purpose,

(41) (a) Meyer, W. L.; Manning, R. A.; Schindler, E.; Schroeder, R. J.; Craig, D. *J. Org. Chem.* **1976**, *41*, 1005. (b) Meyer, W. L.; Clemans, G. B.; Manning, R. A. *J. Org. Chem.* **1975**, *40*, 3686.

(42) (a) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H.S., III. *J. Org. Chem.* **1981**, *46*, 2920. (b) Reich, H. J.; Chow, F.; Shah, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 6638.

(43) For a review of homologation reactions, see: Martin, S. F. *Synthesis* **1979**, 633.

(44) Adamczyk, M.; Dolence, E. K.; Watt, D. S.; Christy, M. R.; Reinbenspies, J. H.; Anderson, O. P. *J. Org. Chem.* **1984**, *49*, 1378 and references cited therein.

(45) Cooke, F.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1977**, 513.

(46) Gilbert, J. C.; Weerasooriya, V. *J. Am. Chem. Soc.* **1983**, *105*, 448.

(47) (a) Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553. (b) Cunico, R. F.; Gill, H. S. *Organometallics* **1982**, *1*, 1.

(48) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.

(49) Wender, P. A., personal communication.

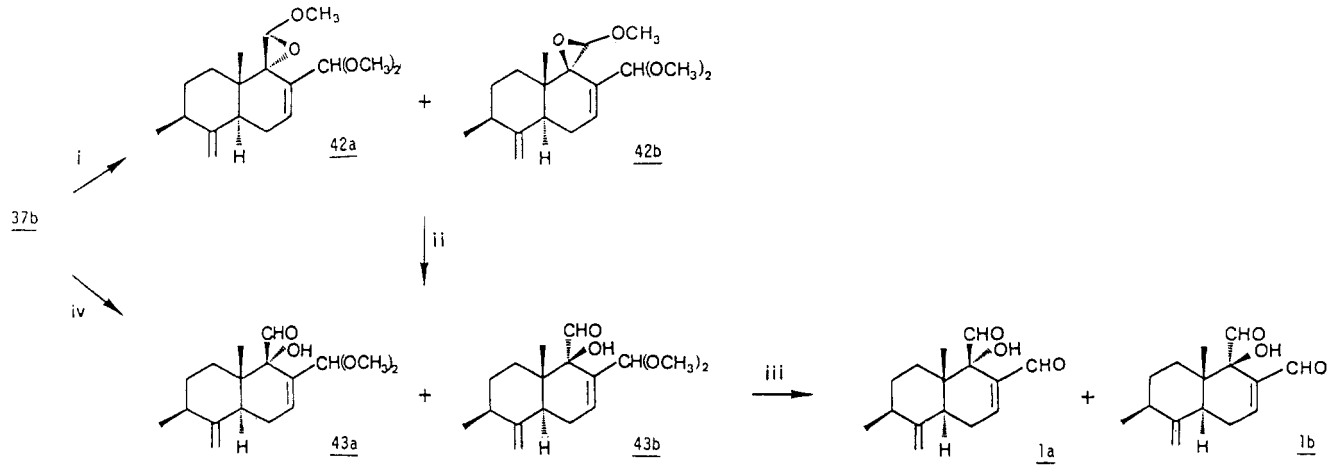
(50) The use of ketone **35a** afforded only a 12% yield of enol ethers **37a**.

(51) (a) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans 1* **1979**, 3099. (b) Torr, R.S.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1173.

(52) Optimization of stereochemistry of this Wittig–Horner reaction has been reported: Buss, A. D.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 3931.

(53) Irradiation of the angular methyl group in **41a** resulted in a 9% increase of the aldehyde signal, whereas no significant difference was found in **41b**, thus demonstrating the closer approach of both groups in **41a**. In addition, the CH_3 absorptions of **41a** (δ 1.037) and **41b** (δ 0.815) show that the former is clearly influenced by the deshielding zone of the aldehyde carbonyl group, whereas the latter is not.

Scheme V[a]



[a] Reagents: (i) *m*-CPBA, KF, NaF/CH_2Cl_2; (ii) SiO_2/Et_2O; (iii) $H_2SO_4/(CH_3)_2CO$; (iv) OsO_4, TBHP, Et_4NOH/t-BuOH.

we deemed it worthwhile to try the reaction with our new epoxidation reagent (*m*-CPBA/KF/NaF).[54] As shown in Scheme V, this reaction was stereoselective in the undesired sense, affording a mixture of epoxides **42a** and **42b**. Unambiguous assignment of configuration **42b** to the major isomer followed from selective hydrolysis with silica gel to provide the hydroxy aldehydes **43a** and **43b**. These compounds presented similar aldehyde absorptions in their ^1H NMR spectra (**43b**, δ_{CHO} 9.51; **43a**, δ_{CHO} 9.60) but were clearly differentiated by further hydrolysis (H_2SO_4/acetone) to *epi*-muzigadial (**1b**) [δ_{CHO} (in $CDCl_3$) 9.35 and 9.92] and muzigadial (**1a**) [δ_{CHO} (in $CDCl_3$) 9.46 and 9.66], respectively, in a 4:1 ratio.

The undesired stereoselectivity was dramatically reversed by the use of osmium tetraoxide. In this case, the bulky intermediate osmate ester produced in the cis hydroxylation of olefins,[55,56] was expected to be formed preferentially by the attack from the α face of the vinyl ether **37b**. This turned out to be the case, although only after several discouraging attempts. Thus, reaction of **37b** with 0.9 equiv of OsO_4 in dioxane, followed by brief exposure to H_2S, resulted in concomitant hydroxylation of the enol ether and the exo-methylene group. Similar results were obtained by using OsO_4 in catalytic amount with 1 mol of *N*-methylmorpholine *N*-oxide,[57] to regenerate the catalyst. Successful hydroxylation was finally achieved by using *tert*-butyl hydroperoxide as the oxidant in the presence of Et_4NOH/t-BuOH, which has proved to be suitable to effect hydroxylation of tri- and tetrasubstituted olefins.[58] When this reaction was carried out at 0 °C, a mixture of hydroxy aldehydes **43a** and **43b**, in a 10:1 ratio, was obtained in 85% yield.[59] This mixture was subjected to acid hydrolysis to yield (±)-muzigadial (**1a**) in 76% yield along with (±)-*epi*-muzigadial (**1b**) in 7% yield, after column chromatography on silica H. The overall yield of **1a** from the Wieland–Miescher ketone **5** was 11%, and the spectroscopic properties of the synthetic material (IR, UV, ^1H NMR, MS) are in good agreement with those reported.[7a,b,60]

The stereochemistry of (±)-muzigadial (**1a**) and its epimer **1b** was confirmed by NOE differences in the corresponding ^1H NMR spectra. Thus, whereas **1a** showed a 14% increase of the aldehyde signal when the angular methyl group was irradiated, compound **1b** showed no significant enhancement.

The biological activities of synthetic racemic **1a** and its epimer **1b** are currently under investigation; the results will be described in due course.

Experimental Section

Melting points were determined on a Reichert Kofler apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were run in $CDCl_3$; chemical shifts are reported in δ relative to Me_4Si in the ^1H NMR and to $CDCl_3$ at 77.0 ppm in the ^{13}C NMR. Assignments in the ^{13}C NMR are based on chemical shifts of model compounds and single-frequency off-resonance decouplings. Gas chromatographic analyses were performed on Carlo Erba Models 2350 and 4130 instruments, equipped with a FID detector, using respectively a 3% OV-101 on Chromosorb W glass column 2 m × 3.17 mm i.d. and a SE-54 fused silica capillary column 50 m × 0.32 mm i.d. Reaction mixtures were routinely dried over $MgSO_4$, and evaporation of the solvent was carried out under vacuum using a rotatory evaporator.

5,5-(Ethylenedioxy)-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-one (6). A mixture of the Wieland–Miescher ketone (**5**) (30.8 g, 0.173 mol), 2-methyl-2-ethyl-1,3-dioxolane (109 g, 0.942 mol), ethylene glycol (2.4 g, 0.039 mol), and *p*-toluenesulfonic acid monohydrate (2.4 g, 0.013 mol) was stirred at room temperature for 30 h. The reaction was quenched by careful neutralization with triethylamine, diluted with 300 mL of benzene, washed with water, and dried. Evaporation of the solvent furnished crude monoacetal **6** (36.5 g, 95%). This product was used without further purification for the next step. Recrystallization of an analytical sample from ethyl acetate gave a mp of 60–62 °C (lit.[10b] mp 66–67 °C). Alternatively, the procedure reported by Corey[10b] afforded a mixture of monoacetal **6**, the corresponding diacetal, and unchanged **5** in a 78:10:12 ratio by GLC analysis: bp 130 °C (0.5 torr); IR (CCl_4) 1670, 1625, 1080 cm^{-1}; UV (MeOH) λ_{max} 238 nm (ϵ 21.490); ^1H NMR (80.13 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.5–2.0 (6 H), 2.1–2.5 (4 H), 3.96 (s, 4 H), 5.80 (d, J = 1.4 Hz, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 198.77 (C-2), 167.51 (C-8a), 125.34 (C-1), 112.13 (C-5), 65.12, 64.82 (CH_2O), 44.82 (C-4a), 33.74 (C-3), 31.26 (C-8), 29.86 (C-4), 26.71 (C-6), 21.56 (C-7), 20.35 (Me); MS, m/z (relative intensity) 222 ($M^{+\cdot}$, 8), 100 (5.4), 99 (100), 91 (5.2), 77 (5.6), 55 (16), 41 (5.5).

5,5-(Ethylenedioxy)-4aβ-methyl-2-methylene-2,3,4,4a,5,6,7,8-octahydronaphthalene (7). In a three-necked round-bottomed 500-mL flask equipped with magnetic stirrer, nitrogen inlet, a reflux condenser, and rubber stopper was placed

(54) Camps, F.; Coll, J.; Messeguer, A.; Pujol, F. *Chem. Lett.* **1983**, 971.
(55) Schroeder, M. *Chem. Rev.* **1980**, *80*, 187.
(56) Vankheenen, V.; Kelly, R. L.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
(57) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986.
(58) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.
(59) It was essential for the success of the reaction to free the solvent (*t*-BuOH) from isobutylene by treatment with $KMnO_4$; otherwise the OsO_4 solution in *t*-BuOH was found to be unstable (Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936**, *58*, 1302).
(60) An authentic sample of natural muzigadial was not available for comparison (Nakanishi, K., personal communication).

sodium hydride (9.42 g, 0.216 mol) as a 55% dispersion in oil which was washed with pentane. To the dry hydride was added anhydrous Me_2SO (108.4 mL), and the slurry was heated at 70–80 °C until evolution of hydrogen ceased (45 min). After the mixture was cooled to room temperature, methyltriphenylphosphonium bromide (77.56 g, 0.216 mol), previously dried at 100 °C (0.5 torr), in Me_2SO (220 mL), was added and the mixture stirred for 30 min. The ketone acetal **6** (32 g, 144 mmol) in Me_2SO (74 mL) was then added and the reaction mixture heated at 55–60 °C for 15 h with stirring. The cooled reaction mixture was poured into 400 mL of ice–water and the triphenylphosphine oxide filtered and washed with the pentane. The aqueous phase was extracted with pentane (4 × 100 mL), and the organic extracts were combined, washed with 1:1 H_2O–DMSO (3 × 125 mL) and brine, and dried. The solvent was stripped off, and the resulting crude diene **7** was chromatographed on alumina I, with hexane as eluent, to yield pure **7** (26.5 g, 83.6%): bp 75–80 °C (0.6 torr); IR (CCl_4) 3080, 1640, 1080 cm^{-1}; UV (MeOH) λ_{max} 236 nm (ϵ 29.042); ^1H NMR (80.13 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.2–1.8 (6 H), 1.9–2.4 (4 H), 3.8 (s, 4 H), 4.58 (s, 2 H), 5.8 (s, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 144.86 (C-8a), 143.04 (C-2), 124.86 (C-1), 112.77 (C-5), 108.66 (=CH_2), 65.07, 64.71 (CH_2O), 44.03 (C-4a), 30.81, 30.41 (C-8, C-4), 28.16 (C-3), 26.81 (C-6), 22.57 (C-7), 21.39 (Me); MS, m/z (relative intensity) 220 (M^+·, 13), 159 (6), 134 (100), 119 (69), 105 (14), 91 (18), 77 (11), 43 (12), 41 (12). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.02; H, 9.18.

5,5-(Ethylenedioxy)-2,4aβ-dimethyl-*trans*-3,4,4a,5,6,7,8,-8a-octahydronaphthalene (8a). 5,5-(Ethylenedioxy)-2,4aβ-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (8c,d). Ammonia (560 mL) was condensed in a three-necked round-bottomed flask, previously cooled in a dry ice–acetone bath. Lithium wire (1.92 g, 278 mmol), cut into small pieces, was added, and after the mixture was stirred for 30 min, diene **7** (20.01 g, 90.95 mmol), dissolved in anhydrous THF (340 mL) and anhydrous *t*-BuOH (7 mL), was added to the system. The stirring was continued for 90 min, and the reaction mixture was quenched by adding ethanol until the blue color was discharged. Ammonia was distilled off under a stream of N_2, water was added, and the mixture was extracted with ether (5 × 75 mL). After the mixture was dried and the solvent stripped off, a mixture of monoenes **8a,c,d** (19.60 g, 97%) was obtained in a 58:23:19 ratio on GLC analysis.

A sample (150 mg) was chromatographed on $AgNO_3$-impregnated silica gel with hexane–ether (95:5) as eluent, to provide pure samples of **8a** (65 mg) and **8d** (71 mg). The former had a retention time of 15.2 min and the latter of 13.6 min (SE-54 50 m × 0.32 mm i.d. fused silica capillary column, column temperature programmed from 150 to 200 °C at a rate of 2 °C/min). Since the relative amount obtained of both olefins did not fit with the analysis of the crude, an internal equilibration on the column was inferred.

Mixture of monoenes: bp 78–80 °C (0.6 torr).

8a: IR (CCl_4) 3040, 2940, 1675, 1442, 1060, 910 cm^{-1}; ^1H NMR (80.13 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1–1.25 (14 H), 1.65 (s), 3.90 (s, 4 H), 5.02 (br s, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 132.41 (C-2), 125.25 (C-1), 112.97 (C-5), 65.20 (CH_2O), 41.10 (C-4a), 40.90 (C-8a), 30.93 (C-4), 28.05 (C-3), 27.29, 26.85 (C-8, C-6), 23.26 (C-7), 23.02 (Me-4a), 13.66 (Me-2); MS, m/z (relative intensity) 222 (M^+·, 2), 161 (2), 145 (3), 119 (16), 99 (100), 81 (2), 55 (3).

8d: IR (CCl_4) 3040, 2930, 1675, 1452, 1060, 925 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, J = 7 Hz, 3 H), 1.18 (d, J = 0.88 Hz, 3 H), 1.22–1.82 (8 H), 1.9–2.35 (3 H), 3.88 (4 H), 5.26 (q, J = 1.6 Hz, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 140.46 (C-8a), 128.79 (C-1), 113.17 (C-5), 65.19, 64.8 (CH_2O), 43.85 (C-4a), 30.96, 30.53 (C-8, C-4), 28.63 (C-3), 28.24 (C-6), 23.16 (C-7), 22.52 (Me-2), 21.91 (Me-4a); MS, m/z (relative intensity) 222 (M^+·, 0.1), 178 (3.4), 163 (3.1), 145 (3.6), 121 (6.1), 99 (100), 55 (10). Anal. Calcd for $C_{14}H_{22}O_2$: C, 76.63; H, 9.97. Found: C, 75.71; H, 10.08.

5,5-(Ethylenedioxy)-2,4a-dimethylperhydronaphthalen-1-ol (9). Into a dry three-necked flask provided with stirrer, dropping funnel, and septum inlet, was placed a solution of monoenes **8** (26.05 g, 0.117 mol) in anhydrous THF (257 mL) and cooled with an ice bath. Then a BH_3·THF solution (105 mL, 0.117 mol) was slowly added and the reaction kept at 0 °C for 3 h and overnight at room temperature. Afterwards, H_2O was added (35 mL), followed by 3 N NaOH (200 mL) and 30% H_2O_2 (200 mL), and the mixture stirred for 6 h. The reaction mixture was diluted with water and extracted with ether (5 × 100 mL). The organic extracts were washed with brine and dried, yielding on solvent removal 27.9 g of crude alcohol **9**.

Purification through a silica gel column (115 g) using hexane–EtOAc (85:15) of a 0.917-g aliquot led to isolate 10% of starting monoenes **8c,d** and 0.75 g of the partially separated mixture of alcohols **9**. The major compound **9a** was isolated and crystallized from pentane–EtOAc in 58% yield: mp 93–96 °C; IR(CCl_4) 3640, 1455, 1195, 960 cm^{-1}; ^1H NMR (80.13 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 0.98 (d, J = 4.64 Hz, 3 H), 1.2–2 (13 H), 2.94 (dd, J = 11, 8 Hz, 1 H), 3.89 (c, 4 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 112.65 (C-5), 76.19 (C-1), 65.15, 64.99 (CH_2O), 43.83 (C-4a), 43.40 (C-8a), 40.61 (C-2), 30.40 (C-4), 29.46, 28.93 (C-6, C-8), 22.65, 22.47 (C-7, C-3), 18.98 (Me-4a), 15.03 (Me-2); MS, m/z (relative intensity) 240 (M^+·, 3), 222 (2.5), 178 (6.4), 155 (12), 100 (57), 99 (100), 77 (19), 55 (97). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.10; H, 10.02.

5,5-(Ethylenedioxy)-2β,4aβ-dimethyl-*trans*-perhydronaphthalen-1-one (10a). To a cold solution of CrO_3 (37.5 g, 0.374 mol), anhydrous pyridine (62 mL, 0.749 mol), and anhydrous CH_2Cl_2 (886 mL) previously stirred at 0 °C for 30 min was added a mixture of alcohols **9** (15.0 g, 0.624 mol) dissolved in anhydrous CH_2Cl_2 (150 mL). Stirring was continued for 1 h and the solvent evaporated off. The crude material was filtered through a neutral alumina IV column by eluting with CH_2Cl_2, to yield a mixture of decalones **10** (11.59 g, 77%), which was directly subjected to epimerization conditions without further purification. Thus, a solution of ketones **10** (11.59 g, 48.93 mol) in anhydrous MeOH (258 mL) was added to a 3% NaOMe in MeOH (86 mL), and the reaction mixture was stirred for 5 h at room temperature under Ar. Methanol was removed under reduced pressure and the residue taken up in ether (900 mL), washed with water and brine, and dried. Removal of the solvent furnished crude **10a** (95% recovery), which was purified by column chromatography on silica gel eluting with hexane–ether mixtures, to yield pure crystalline ketone **10a** (9.04 g, 78%): bp 135 °C (0.3 torr); mp 49–50 °C; IR (CCl_4) 1710, 1452 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, J = 0.6 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 1.3–1.9 (6 H), 1.95–2.2 (2 H), 2.38 (d quint d, $J_{6\alpha,7\beta}$ = 13.4 Hz, $J_{6\alpha,CH_3}$ = $J_{6\alpha,7\alpha}$ = 6.7 Hz, $J_{6\alpha,4a\alpha}$ = 1.5 Hz, 1 H), 2.62 (ddd, $J_{4a,4\beta}$ = 10.0 Hz, $J_{4a,4\alpha}$ = 4.0 Hz, $J_{4a,6\alpha}$ = 1.5 Hz, 1 H), 3.98 (c, 4 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 200.49 (C-1), 111.66 (C-5), 65.49, 64.98 (CH_2O), 54.34 (C-8a), 47.77 (C-4a), 44.08 (C-2), 31.19 (C-4), 29.77, 29.19 (C-8, C-6), 21.18 (C-7), 19.63 (C-3), 15.2 (Me-4a), 14.11 (Me-2); MS, m/z (relative intensity) 238 (M^+·, 12), 223 (3), 207 (3), 178 (5), 112 (100), 99 (82), 86 (52), 55 (22). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.48; H, 9.56.

5,5-(Ethylenedioxy)-2β,4aβ-dimethyl-1-methylene-*trans*-perhydronaphthalene (12). The same procedure as described for **7** was applied. Thus, starting from ketone **10a** (8.50 g, 35.82 mmol) trimethyltriphenylphosphonium bromide (33.5 g, 93.8 mmol), NaH (4.07 g, 93.8 mmol), and Me_2SO (127 mL), acetal **12** was obtained as an oil (8.07 g, 95%). An analytical sample was prepared by column chromatography on alumina I eluting with pentane–ether mixtures: mp 38–40 °C; bp 75 °C (0.8 torr); IR (CCl_4) 3095, 1645, 1450, 1095, 890 cm^{-1}; ^1H NMR (80.13 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 1.20 (d, J = 6 Hz, 3 H), 1.2–2.4 (12 H), 3.82 (s, 4 H), 4.56 (d, J = 1 Hz, 1 H), 4.72 (d, J = 1 Hz, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 154.58 (C-1), 113.11 (C-5), 103.73 (=CH_2), 65.31, 65.13 (CH_2O), 47.53 (C-8a), 44.93 (C-4a), 38.50 (C-2), 32.46 (C-4), 30.54, 30.53 (C-8, C-3), 24.00 (C-6), 22.63 (C-7), 18.50 (Me-4a), 14.84 (Me-2); MS, m/z (relative intensity) 236 (M^+·, 36), 221 (11), 181 (20), 174 (40), 161 (16), 112 (86), 99 (100), 86 (58), 55 (72), 41 (85). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.18; H, 10.08.

6β,8aβ-Dimethyl-5-methylene-*trans*-perhydronaphthalen-1-one (13). A mixture of acetal **12** (7.5 g, 31.76 mmol), THF (161 mL), glacial acetic acid (108 mL), and 1 N HCl (54 mL) was stirred at room temperature overnight and then diluted with 300 mL of ether and neutralized with a $NaHCO_3$ saturated solution. The aqueous layer was extracted with ether (5 × 40 mL), and the combined organic phases were washed with a saturated $NaHCO_3$ solution (2 × 50 mL) and brine and dried. Evaporation of the solvent gave ketone **13** as an oil, which was purified by column chromatography on alumina III eluting with hexane, to afford ketone **13** (5.16 g, 85%) as a solid, mp 46–48

°C, from pentane–ether (lit.[24] mp 47–48 °C): IR (CCl_4) 3095, 1705, 1645, 1450, 895 cm^{-1}; ^1H NMR (80.13 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.09 (d, J = 6 Hz, 3 H), 1.57–2.8 (12 H), 4.70 (d, J = 1 Hz, 1 H), 4.82 (d, J = 1 Hz, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 215.16 (C-1), 152.18 (C-5), 105.18 (=CH_2), 51.51 (C-4a), 50.45 (C-8a), 38.15 (C-6), 37.21 (C-2), 32.94 (C-8), 31.84 (C-4), 25.58 (C-3), 23.68 (C-7), 18.14 (Me-6), 16.72 (Me-8a); MS, (relative intensity) m/z 192 (M^+, 66), 177 (15), 159 (13), 137 (100), 135 (38), 121 (67), 109 (77), 93 (65), 77 (33), 55 (50), 41 (72). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.15; H, 10.33.

6,6-(Ethylenedithio)-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-one (14). To a solution of Wieland–Miescher ketone (**5**) (5.87 g, 33.0 mmol) in glacial acetic acid (14 mL) were added 1,2-ethanedithiol (3.41 g, 36.3 mmol), *p*-toluenesulfonic acid (2.94 g), and glacial acetic acid (34 mL). The mixture was stirred at room temperature for 5 h, poured into water, and stirred for 15 min more. The white solid was filtered off, washed successively with water, a dilute $NaHCO_3$ solution, and water, and dried to yield ketone **14** (8.31 g, 99.1%): IR (KBr) 2910, 1705, 1640 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.3 (s, 3 H), 1.35–2.9 (10 H), 3.2–3.4 (4 H), 5.69 (s, 1 H).

5,5-(Ethylenedioxy)-2,2-(ethylenedithio)-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (15). A mixture of ketone **14** (8.30 g, 32.7 mmol), ethylene glycol (20.46 g, 330 mmol), anhydrous benzene (91 mL), and a small amount of *p*-toluenesulfonic acid was refluxed in a Dean–Stark apparatus for 15 h. The reaction was quenched with a saturated $NaHCO_3$ solution, the benzene layer was decanted, and the aqueous layer was extracted with ether (4 × 40 mL). The organic solutions were combined, washed with brine, and dried to give compound **15** (9.47 g, 96.3% overall yield from **5**): IR (CCl_4) 2930, 1645, 1440, 1280 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.19 (s, 3 H), 1.3–2.7 (10 H), 3.2–3.4 (4 H), 3.95 (br s, 4 H), 5.60 (br s, 1 H).

5,5-(Ethylenedioxy)-4aβ-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (16a). A solution of thioacetal **15** (9.46 g, 31.7 mmol) in anhydrous ether (100 mL) and anhydrous DME (6 mL) was cooled in a dry ice/acetone bath. A stream of dry ammonia was passed through the flask until ca. a 500-mL volume was condensed. To this solution was added sodium (11.68 g, 0.51 mol) in small pieces and the mixture allowed to reflux for 1 h. The reaction was quenched by careful addition of ethanol (25 mL) until the color was discharged. The ammonia was allowed to evaporate and ether–water (1:1, 100 mL) added. The aqueous solution was extracted with ether, and the organic layers were combined, washed with brine, and dried. Evaporation of the solvent left a colorless liquid, which was purified on silica gel by eluting with hexane–ether (100:2), to afford pure olefin **16a** (4.82 g, 73.8%), as determined by GLC analysis on a FFAP column (3% on GCQ): IR (CCl_4) 2930, 1645, 1450 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.2–2.4 (12 H), 3.85 (s, 4 H), 5.30 (br s, 1 H).

The reaction of **15** with W-2 Raney Ni (7 equiv) in absolute ethanol[25] gave a mixture of olefins **16a–c** (60%), in a 71:16:13 ratio on GLC analysis.

5,5-(Ethylenedioxy)-4aβ-methylperhydronaphthalen-1-one (17). To a solution of olefin **16a** (4.6 g, 22.3 mmol) in anhydrous THF (100 mL), previously cooled at 0 °C, was added 30.8 mL of 1 M BH_3·THF solution (30.8 mmol). The reaction mixture was maintained at 0 °C for 3 h and at room temperature overnight. Oxidation of the borane was carried out by adding 3 N NaOH (6.9 mL) and 30% H_2O_2 (6.9 mL) and stirring the reaction mixture for 4 h more. The mixture was diluted with ether, washed with brine, and dried. Evaporation of the solvent afforded a mixture of the corresponding alcohols, which was oxidized as described above to yield a mixture of decalones **17** (3.80 g, 82.7%) after purification by column chromatography on silica gel. GLC analysis of the purified product on a OV-1 column 3% on GCQ revealed **17** to be an isomeric mixture of *trans*-17 (**17b**) and *cis*-17 (**17a**) in a 94:6 ratio: IR (CCl_4) 1710, 1450 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.05–2.05 (10 H), 2.05–2.6 (3 H), 3.85 (s, 4 H).

Methylation of Ketone 17 via Enol Ether 18. A solution of diisopropylamine (60 mg, 0.594 mmole) in anhydrous THF (4 mL) was cooled to 0 °C and treated with 0.30 mL of 1.9 M BuLi in hexane (0.59 mmol). The amide was stirred for 25 min at 0 °C, and after this period decalone **17** (121 mg, 0.54 mmol) in anhydrous THF (3 mL) was slowly added and the mixture stirred for 15 min more. Meanwhile, a mixture of triethylamine (34 μL), anhydrous THF (2 mL), and trimethylsilyl chloride (0.11 mL) was centrifuged to remove the insoluble chloridate. The decanted solution was added to the enolate and the mixture stirred for 2.5 h. The reaction was quenched with a saturated $NaHCO_3$ solution and extracted with pentane and the organic layer washed with brine. Evaporation of the solvent furnished the enol ether **18** (135 mg, 84.8%), which was used without further purification in the next step: IR (CCl_4) 3040, 2940, 1670, 1255 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.20 (9 H), 0.90 (s, 3 H), 1.1–2.3 (10 H), 3.87 (s, 4 H), 4.50 (t, J = 4.0 Hz, 1 H).

To a solution of **18** (68 mg, 0.229 mmol) in anhydrous THF (1.5 mL) was added 0.14 mL of 1.9 M BuLi (0.275 mmol) at room temperature. The solution was stirred for 30 min and, after addition of CH_3I (43 μL, 0.687 mmol), further stirred for 15 min. The mixture was quenched with water, extracted with pentane, washed with brine, and dried to afford a mixture of *cis*- and *trans*-β-methyldecalones **10** and nonmethylated ketone **17** in a 2:1 ratio, after GLC analysis (55 mg, 80%).

Direct Methylation of 17 with LDA/CH_3I. A solution of 0.6 mL of 1.77 M MeLi (1.07 mmol) in anhydrous DME (8 mL) was cooled to 4 °C. Diisopropylamine (0.15 mL, 1.07 mmol) was then added and the solution stirred for 20 min. Ketone **17** (50 mg, 0.268 mmol) in anhydrous DME (6 mL) was slowly added to the base in 19 min. The reaction was allowed to occur for 15 min more at 4 °C and then warmed to 35 °C. At this moment, CH_3I (0.13 mL, 2.1 mmol) was added and the mixture stirred for 30 min. After quenching with $NaHCO_3$ saturated solution, the usual workup gave a mixture of *cis*- and *trans*-β-methyldecalones **10** and nonmethylated ketone **17** in a 1:1 ratio. On OV-1 column 3% on GCQ at 190 °C (column temperature) ketones **10** and **17** had the following relative retention values in cm: **17a**, 4.95; **17b**, 5.35; **10d** (β-H, α-CH_3), 5.70; **10b** (β-H, β-CH_3), 5.40; **10c** (α-H, α-CH_3), 5.25; **10a**, (α-H, β-CH_3).

Methylation of Ketone 17 via Enol Benzoate 19. Sodium hydride (376 mg, 8.93 mmol) as a 55% dispersion in oil was washed with pentane and cooled to 0 °C under Ar. A mixture of ketone **17** (503 mg, 2.23 mmol), freshly distilled ethyl formate (9 mL) and anhydrous methanol (2 drops) were added, and the reaction was stirred 40 min at 0 °C. Then anhydrous THF (13 mL) was added, and the reaction mixture was allowed to warm up to room temperature and further stirred for 10 h. After being poured into 1 N H_2SO_4 (20 mL) at 0 °C, the hydroxymethylene derivative was rapidly extracted with ether (4 × 20 mL), washed with brine, and dried to give the expected keto aldehyde (535 mg, 95.2%), spectroscopically pure by ^1H NMR: ^1H NMR (60 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 0.95 (s, 3 H), 1.05–2.8 (11 H), 3.9 (s, 4 H), 7.9 (s, 1 H), 8.05 (s, 1 H), 8.59 (s, 1 H).

To a solution of this hydroxymethylene ketone (102 mg, 0.41 mmol) in anhydrous pyridine (5 mL) at 0 °C was added benzoyl chloride (63 mg, 0.45 mmol). The mixture was stirred for 30 min and quenched with a saturated $NaHCO_3$ solution, extracted with ether, washed with brine, and dried. Evaporation of the solvent furnished benzoate **19** (138 mg, 95.5%), which was subjected to a hydrogenolysis reaction without further purification: ^1H NMR (60 MHz, $CDCl_3$) δ 1.05 (s, 3 H), 1.1–3.1 (11 H), 3.92 (s, 2 H), 3.96 (s, 2 H), 7.1–8.7 (6 H).

A mixture of **19** (138 mg), ethanol (5.5 mL), and PtO_2 (50 mg) was hydrogenated at atmospheric pressure. When the theoretical amount of hydrogen had been uptaken, the mixture was filtered and the catalyst washed with ether. The filtrate was washed with a saturated $NaHCO_3$ solution and brine and dried. After removal of the solvent, the residue was chromatographed on silica gel to afford the required **10a** (37 mg, 39%). For spectroscopic properties of **10a**, see above.

Methylation of 17 via Keto Ester 20. Sodium hydride (56 mg, 2.33 mmol) as a 55% dispersion in oil was washed with pentane, suspended in anhydrous benzene (5.5 mL), and allowed to react with a mixture of ketone **17** (92.8 mg, 0.41 mmol), diethyl oxalate (257 mg, 1.76 mmol), and anhydrous benzene (2 mL). The mixture was stirred at room temperature overnight, quenched with water, and extracted with ether. The organic layer was thoroughly washed with NaOH dilute solution, and the aqueous layers were combined and acidified with glacial acetic acid in an ice bath. Extraction with ether and the usual workup gave keto

ester **20** (118 mg, 89.2%), homogeneous by TLC and ^{1}H NMR: IR (CCl_4) 1730, 1720, 1705 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 0.96 (s, 3 H), 1.40 (t, J = 6.5 Hz, 3 H), 1.15–2.0 (8 H), 2.0–2.85 (4 H), 3.95 (s, 4 H), 4.37 (q, J = 6.5 Hz, 2 H).

Methylation was effected by reflux of a mixture of **20** (104 mg, 0.32 mmol), CH_3I (0.4 mL), anhydrous K_2CO_3 (71 mg), and dry acetone (5 mL) under Ar during 16 h. After this time 0.3 mL more of CH_3I in dry acetone (3 mL) was added and the reflux continued for 4 h. The reaction mixture was quenched with 1 N NaOH (3 mL), extracted with ether, washed with a $Na_2S_2O_3$ solution and brine, and dried. Evaporation of the solvent afforded a solid **21**, which was dissolved in a mixture of NaOEt (85 mg) and absolute ethanol (6 mL) and refluxed for 7 h. After the mixture was allowed to stand overnight, water and pentane were added, and the aqueous layer was extracted with pentane (3 × 20 mL). The organic phases were combined, washed with brine, and dried to yield, after removal of the solvent, a mixture of decalones **10a** and **10c** (46 mg, 54.6% overall yield from *17*) in a 2:1 ratio, according to GLC analysis (OV-1 column 3% on GCQ).

2-(Hydroxymethylene)-6β,8aβ-dimethyl-5-methylene-*trans*-perhydronaphthalen-1-one (22). Sodium hydride (2.17 g, 49.9 mmol) as a 55% dispersion in oil was washed with pentane and cooled to 0 °C in an ice–salt bath. Ethyl formate (67.2 mL, 0.828 mol) was then added and the mixture stirred for 1 h at 0 °C. After this period of time, the methylene ketone **13** (2.40 g, 12.48 mmol) in anhydrous DME (67.2 mL) and a few drops of ethanol were added, and the mixture was stirred for 30 min at 0 °C and at room temperature overnight. The reaction was quenched with a saturated NH_4Cl solution, extracted with ether (4 × 100 mL), and dried. Evaporation of the solvent furnished keto aldehyde **22** (2.66 g, 97%) as an oil. Due to the labile nature of **22**, it was carried on to the next step without further purification: IR (CCl_4) 1645, 1630, 1580, 890 cm^{-1}; ^{1}H NMR (80.13 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 1.04 (d, J = 6.4 Hz, 3 H), 1.2–2.7 (10 H), 4.58 (br s, 1 H), 4.78 (br s, 1 H), 8.55 (s, 1 H), 14.65 (br s, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 192.20 (C-1), 187.19 (=CHOH), 152.56 (C-5), 105.74 (=CH_2), 104.93 (C-2), 47.46 (C-4a), 43.20 (C-8a), 38.19 (C-6), 33.86 (C-3), 31.80 (C-8), 23.24 (C-4), 21.23 (C-7), 18.39, 18.08 (Me-6, Me-8a); MS, m/z (relative intensity) 219 (1), 191 (20), 177 (19), 147 (66), 107 (70.3), 91 (97.7), 77 (70), 69 (28), 67 (39.7), 55 (100), 41 (70.3).

2-[(Butylthio)methylene]-6β,8aβ-dimethyl-5-methylene-*trans*-perhydronaphthalen-1-one (23). To a solution of formyl decalone **22** (0.33 g, 1.5 mmol) in anhydrous pyridine (6.6 mL), cooled to 0 °C, was added *p*-toluenesulfonyl chloride (0.345 g, 1.81 mmol). The mixture was stirred for 1 h at 0 °C, and then 1-butanethiol (0.19 mL, 1.81 mmol) was added via syringe. The reaction mixture was stirred 1 h at 0 °C and left standing in the refrigerator (5 °C) overnight. The mixture was poured into 1 N NaOH (20 mL) and extracted with ether (5 × 30 mL). The organic phase was washed with 4 N KOH, 2 N H_2SO_4, and brine and dried. The oily residue was purified by column chromatography on silica gel to provide [(*n*-butylthio)methylene]decalone **23** (0.35 g, 80%): IR (CCl_4) 3090, 1665, 1640, 895 cm^{-1}; ^{1}H NMR (80.13 MHz, $CDCl_3$) δ 0.93 (t, J = 8 Hz, 3 H), 1.08 (d, J = 6.4 Hz, 3 H), 1.2–2.7 (14 H), 2.85 (t, J = 8.0 Hz, 2 H), 4.68 (s, 1 H), 4.84 (s, 1 H), 7.54 (c, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 201.24 (C-1), 152.91 (C-5), 142.41 (=CS), 128.79 (C-2), 104.96 (=CH_2), 47.76 (C-8a), 47.46 (C-4a), 37.99 (C-6), 34.20 (C-8, C-3), 32.54 (C-1′), 31.92 (C-4), 26.62 (C-3′), 21.52 (C-7), 20.97 (C-2′), 18.08 (Me-6), 16.94 (Me-8a), 13.43 (C-4′); MS, m/z (relative intensity) 292 (M$^+$·, 18), 235 (100), 203 (89.6), 175 (8.5), 161 (33), 55 (36.7), 41 (86.9). Anal. Calcd for $C_{18}H_{28}OS$: C, 73.93; H, 9.65. Found: C, 74.06; H, 9.85.

7β,9aβ-Dimethyl-6-methylene-*trans*-4,5,5a,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan (25). To a solution of trimethylsulfonium tetrafluoroborate[34] (0.560 g, 3.4 mmol), in anhydrous DME (20 mL), cooled to −35 °C, was added 3.35 mL of 1 M BuLi in hexane (3.35 mmol). The ylide was stirred at this temperature for 30 min and then cooled to −78 °C. (Butylthio)methylene derivative **23** (0.10 g, 0.34 mmol) in anhydrous DME (2.5 mL) was then added and the mixture stirred for 1 h. After being quenched with water (25 mL) and extracted with ether (5 × 25 mL), the organic phase was washed with brine and dried to yield dihydrofuran **24** (0.110 g).

A solution of **24** in anhydrous DME (2 mL) was allowed to react with $HgSO_4$ (0.10 g, 0.33 mmol) for 2 h at room temperature. The liquid was decanted and the solid washed with $CHCl_3$. The organic solutions were combined and washed with brine to give 0.098 g of crude material, which was chromatographed on Florisil by eluting with pentane to afford furan **25** (0.055 g, 72%): bp 110–115 °C (0.1 torr); IR (CCl_4) 1645, 1445, 1245, 860 cm^{-1}; UV (MeOH) λ_{max} 225 nm (ϵ 2570); ^{1}H NMR (80.13 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.08 (d, J = 8.0 Hz, 3 H), 2.4–4.4 (10 H), 4.68 (s, 1 H), 4.85 (s, 1 H), 7.05 (dd, J = 2.0, 1.0 Hz, 1 H), 7.07 (dd, J = 2.0, 1.0 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.79 (C-6), 136.98, 136.26 (C-1, C-3), 134.34 (C-9b), 119.91 (C-3a), 104.10 (=CH_2), 49.21 (C-5a), 39.35 (C-4), 38.66 (C-7), 35.29 (C-9a), 32.72 (C-9), 22.57 (Me-9a), 21.99 (C-8), 19.87 (C-5), 18.35 (Me-7); (relative intensity) MS, m/z 216 (M$^+$·, 100), 201 (99), 159 (41), 145 (33), 131 (53), 119 (30), 91 (63), 77 (41). Anal. Calcd for $C_{15}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.65; H, 9.69.

6β,8aβ-Dimethyl-5-methylene-1-[(phenylthio)methyl]-*trans*-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (26). To a solution of freshly sublimed DABCO (198 mg, 1.77 mmol) and thioanisol (0.21 mL, 1.77 mmol) in anhydrous THF (5 mL), cooled to 0 °C, was added 0.95 mL of 2.07 M BuLi in hexane (1.94 mmol) under Ar. The solution was stirred at 0 °C for 70 min and ketone **23** (0.323 g, 1.10 mmol) dissolved in anhydrous THF (3 mL) added. The bath was removed and the mixture stirred for 16 h at room temperature. The reaction was quenched with water and extracted with ether (5 × 15 mL) and the organic solution washed with brine and dried. Removal of the solvent afforded the intermediate alcohol, which was treated with a mixture of 1 N HCl (7 mL), CH_3CN (25 mL), and $HgCl_2$ (0.6 g, 2.21 mmol) at 70 °C for 4.5 h. Then solid $NaHCO_3$ was added and the mixture filtered through Celite. The cake was washed with ether and the filtrate with 5 M NH_4AcO and brine and dried. After the solvent was stripped off, the residue was chromatographed on silica gel by eluting with hexane–ether mixtures to give aldehyde **26** (0.260 g, 72.3%): IR (CCl_4) 1670, 1650, 1615, 1585 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 1.05 (d, J = 6.0 Hz, 3 H), 1.15–2.75 (10 H), 3.75 (d, J = 10.5 Hz, 1 H), 4.15 (d, J = 10.5 Hz, 1 H), 4.65 (s, 1 H), 4.82 (s, 1 H); ^{13}C NMR (80 MHz, $CDCl_3$) δ 191.93 (CHO), 158.64 (C-1), 153.22 (C-5), 136.08 (C-2), 134.91 (C-1′), 130.03 (C-2′), 129.0 (C-3′, C-13, C-15, and C-16), 126.94 (C-4′), 104.99 (=CH_2), 48.27 (C-4a), 42.04 (C-8a), 37.93 (C-6), 35.67 (C-8), 31.83 (C-7), 30.42 (C-4), 23.34 (C-3), 20.06 (CH_2S), 18.79, 17.88 (Me-6, Me-8a).

7β,9aβ-Dimethyl-6-methylene-1-(phenylthio)-*trans*-4,5,5a,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan (27). A mixture of aldehyde **26** (35.6 mg, 0.109 mmol), recrystallized NCS (32.8 mg, 0.246 mmol), and anhydrous CCl_4 (3.5 mL) was refluxed for 32 h under Ar. The solid was filtered and washed with CCl_4. Evaporation of the solvent afforded a residue, which was purified by preparative TLC on silica gel to furnish thiophenyl furan **27** (15.5 mg, 43.9%). The expected chloro sulfide, resulting from α-chlorination to the phenylthio group,[39] was not detected. IR ($CHCl_3$) 3040, 1645, 1602, 1580, 900 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.05 (d, J = 6.0 Hz, 3 H), 1.2–3.0 (10 H), 4.65 (s, 1 H), 4.80 (s, 1 H), 7.1 (1 H), 7.1–7.5 (5 H).

When the reaction was carried out in the presence of $CuCl_2$/CuO, starting material **26** was recovered unchanged.[61]

6β,8aβ-Dimethyl-5-methylene-1-[(phenylsulfinyl)methyl]-*trans*-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxaldehyde (28). A mixture of aldehyde **26** (31.6 mg, 0.097 mmol), recrystallized NCS (28.4 mg, 0.214 mmol), and 2% H_2SO_4 in methanol (6 mL) was stirred at 0 °C for 30 min. The reaction mixture was quenched with solid $NaHCO_3$ and partitioned between ether and water. Workup as usual gave, after purification by preparative TLC on silica gel, a mixture of the two possible diastereomeric sulfoxides **28** (15.6 mg, 47.3%), which were cleanly separated on preparative TLC eluting twice with hexane–ether (2:1).

Major diastereomer: 6.7 mg; IR ($CHCl_3$) 1665, 1610, 1045, 905 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 1.1 (d, J = 6.0 Hz, 3 H), 1.15–2.6 (10 H), 3.60 (d, J = 12.0 Hz, 1 H), 4.28 (d, J = 12.0 Hz, 1 H), 4.65 (s, 1 H), 4.81 (s, 1 H), 7.45–7.82 (5 H), 9.95 (s, 1 H).

(61) When the same process was applied to the dimethyl acetal of **26**, nucleophilic substitution of the phenylthio group by chlorine was observed.

Minor diastereomer: 5.1 mg; IR ($CHCl_3$) 1667, 1610, 1048, 905 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.15–2.8 (10 H), 3.85 (d, J = 12.0 Hz, 1 H), 4.15 (d, J = 12.0 Hz, 1 H), 4.61 (s, 1 H), 4.81 (s, 1 H), 7.35–7.70 (5 H), 9.64 (s, 1 H).

2-[(Butylthio)methylene]-6β,8aβ-dimethyl-5-methylene-1-[(phenylthio)methoxymethyl]-*trans*-perhydronaphthalen-1-ol (29). To a solution of methoxymethyl phenyl sulfide (158.4 mg, 1.027 mmol) in anhydrous THF (3 mL), cooled to −35 °C, was added under Ar 0.49 mL of 2.07 M BuLi (1.027 mmol). The solution was stirred at −35 °C for 50 min, and ketone **23** (61.4 mg, 0.210 mmol), dissolved in anhydrous THF (3 mL), was then added. The reaction mixture was stirred at −35 °C over 1 h, quenched with water, extracted with ether, washed with brine, and dried. Evaporation of the solvent afforded a mixture of diastereomeric alcohols **29** and the excess of the sulfide (crude A) (183.9 mg), which was directly subjected to hydrolysis without further purification.

Attempts of Hydrolysis of 29 to Dialdehyde 33. 1. With $HgCl_2$/HCl at 80 °C. 1β,9β-Dimethyl-8-methylene-2-oxo-*trans*-bicyclo[5,4,0]undec-3-ene-4-carboxaldehyde (30). A third of the previous crude (61.3 mg) was dissolved in CH_3CN (4 mL). To the solution were added $HgCl_2$ (228 mg, 0.84 mmol), 3% HCl (3 mL), and CH_3CN (11 mL). The mixture was stirred at 80 °C for 4 h, quenched with solid $NaHCO_3$, and diluted with ether. The ethereal solution was washed with NH_4AcO and brine and dried. Removal of the solvent left a residue, which was purified by preparative TLC to yield the formyl cycloheptenone **30** (14.4 mg, 88.6% overall yield from **23**): IR (neat) 2710, 1690, 1645, 1080, 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.06 (s, 3 H), 1.10 (d, J = 6.0 Hz, 3 H), 1.2–2.9 (10 H), 4.75 (s, 1 H), 4.94 (s, 1 H), 6.7 (s, 1 H), 9.60 (s, 1 H).

2. With $HgCl_2$/HCl at Room Temperature. 4-[(Butylthio)methylene]-3-methoxy-1β,9β-dimethyl-8-methylene-*trans*-bicyclo[5,4,0]undecan-2-one (31). When the same reaction described above was run at room temperature for 4 h, the two diastereomers **31**, intermediates of aldehyde **30**, were isolated after preparative TLC in 54% overall yield from **23**.

Major diastereomer: 7.8 mg; IR ($CHCl_3$) 1710, 1640, 1105, 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3 H), 0.89 (s, 3 H), 0.90 (d, J = 6.0 Hz, 3 H), 1.0–2.5 (14 H), 2.57 (t, J = 7.5 Hz, 2 H), 3.21 (s, 3 H), 4.23 (s, 1 H), 4.55 (s, 1 H), 4.70 (s, 1 H), 6.05 (s, 1 H).

Minor diastereomer: 4.9 mg; IR ($CHCl_3$) 1710, 1645, 1110, 905 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 3 H), 0.90 (s, 3 H), 1.0 (d, J = 6.0 Hz, 3 H), 1.1–2.7 (14 H), 2.65 (t, J = 7.5 Hz, 2 H), 4.65 (s, 1 H), 4.76 (s, 1 H), 4.84 (s, 1 H), 6.20 (s, 1 H).

3. With $HgCl_2$/HgO at Room Temperature. 2-[(Butylthio)methylene]-1-hydroxy-6β,8aβ-dimethyl-5-methylene-*trans*-perhydronaphthalene-1-carboxaldehyde (32). A mixture of crude A (108.4 mg), $HgCl_2$ (241.4 mg, 0.889 mmol), red HgO (96.3 mg, 0.444 mmol), and 80% CH_3CN in water (10 mL) was stirred at room temperature for 3.5 h. After this period of time, 5 M NH_4AcO (6 mL) was added, the mixture stirred for 10 min more and filtered through Celite, and the cake washed with hexane–$CHCl_3$ (1:1). The filtrate was decanted and the organic layer washed with 5 M NH_4AcO and brine and dried. Purification of the residue by preparative TLC yielded hydroxy aldehydes **32** (24.6 mg, 45%) along with a mixture of diastereomers **31** (17.3 mg, 30.4%): IR (CCl_4) 3460, 2840, 1705, 1641, 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 0.91 (t, J = 7.5 Hz, 3 H), 1.05 (d, J = 7.5 Hz, 3 H), 1.15–2.6 (14 H), 2.7 (t, J = 7.5 Hz, 2 H), 3.65 (d, J = 1.5 Hz, 1 H), 4.65 (s, 1 H), 4.82 (s, 1 H), 6.30 (s, 1 H), 10.1 (d, J = 1.5 Hz, 1 H).

Attempted Hydrolysis of 32 to Dialdehyde 33. A solution of hydroxy aldehydes **32** (24 mg, 0.076 mmol), $HgCl_2$ (41.5 mg, 0.153 mmol), CH_3CN (6 mL), and 3% HCl (1.5 mL) was stirred at 75 °C for 65 min. The reaction mixture was quenched with a saturated $NaHCO_3$ solution and filtered through Celite after 5 M NH_4AcO (5 mL) was added to precipitate the mercuric salts. The filtrate was extracted with ether, washed with brine, and dried to yield keto aldehyde **30** (17.2 mg, 97%) instead of the expected dialdehyde **33**.

6β,8aβ-Dimethyl-5-methylene-1-oxo-*trans*-1,4,4a,5,6,7,8,-8a-octahydronaphthalene-2-carboxaldehyde (34). A solution of freshly distilled phenylselenenyl chloride (2.9 g, 15.18 mmol) in anhydrous $CHCl_3$ (180 mL) was cooled at 0 °C. Anhydrous pyridine (1.3 mL) was added to the solution and the mixture stirred for 30 min. Then, hydroxymethylene **22** (2.04 g, 9.24 mmol) in anhydrous $CHCl_3$ (27 mL) was added and the mixture allowed to react at 0 °C for 8 h and washed with 10% HCl (3 × 30 mL). At this stage, an analytical sample was taken and shown to lack the δ 8.55 absorption of **22** in the ^1H NMR spectrum.

The crude was treated at 0 °C with 30% H_2O_2 (2.94 mL) in four portions at 10-min intervals. Then, water (42 mL) was added and the reaction mixture stirred at 0 °C for 10 min. The organic phase was separated, and the aqueous layer was extracted with $CHCl_3$ (5 × 20 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (3 × 20 mL) and brine and dried. Evaporation of the solvent gave unstable keto aldehyde **34** (1.93 g, 95%), pure enough to proceed forward with the synthetic scheme. An analytical sample was chromatographed on silica gel with pentane as eluent: bp 95 °C (0.7 torr); IR (CCl_4) 3095, 1705, 1680, 1650, 900 cm^{-1}; ^1H NMR (80.13 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1.095 (d, J = 6 Hz, 3 H), 1.26 (q, J = 0.2 Hz, 1 H), 1.3–2.3 (3 H), 2.57 (d, J = 0.8 Hz, 1 H), 2.59 (d, J = 3.4 Hz, 1 H), 4.78 (s, 1 H), 4.96 (s, 1 H), 7.80 (dd, J = 3.4, 0.8 Hz, 1 H), 10.08 (s, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 202.92 (C-1), 189.67 (CHO), 154.94 (C-5), 151.21 (C-2), 132.47 (C-3), 106.26 (=CH_2), 47.13 (C-8a), 46.48 (C-4a), 38.00 (C-6), 32.62 (C-8), 31.73 (C-7), 26.68 (C-4), 18.19 (Me-6), 15.05 (Me-8a); (relative intensity) MS, m/z 218 ($M^{+\cdot}$, 80), 190 (100), 175 (30.4), 134 (72.3), 133 (97.6), 115 (24), 107 (55.7), 91 (68), 77 (30.4). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.98; H, 8.20.

6β,8aβ-Dimethyl-5-methylene-2-[(trimethylenedioxy)methyl]-*trans*-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-one (35a). To a 25-mL dry THF solution of keto aldehyde **34** (1 g, 4.58 mmol) were added 1,3-propanediol (0.348 g, 4.58 mmol), 0.62 g (4.58 mmol) of anhydrous calcium sulfate (with humidity indicator), and concentrated H_2SO_4 (50 μL, 0.94 mmol) at 0 °C, and the mixture was stirred overnight at room temperature. To the decanted solution was added 170 mg of solid $NaHCO_3$, followed by 15 mL of water and the resulting mixture extracted with CH_2Cl_2 (5 × 25 mL). The joined organic extracts were washed with a saturated solution of $NaHCO_3$ (3 × 25 mL) and brine and dried, and the solvent was removed in vacuo to afford 1.21 g of crude residue. This residue was flash chromatographed on Florisil (15 g) by eluting with CH_2Cl_2 to yield 1.17 g (91%) of keto acetal **35a**, mp 56–58 °C (from pentane–ether): IR (CCl_4) 3095, 1680, 1645 cm^{-1}; ^1H NMR (80.13 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 1.03 (d, J = 6 Hz, 3 H), 1.14–2.3 (8 H), 2.44 (br s, 2 H), 3.7–4.2 (4 H), 4.69 (s, 1 H), 4.86 (s, 1 H), 5.38 (s, 1 H), 7.21 (br s, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 202.24 (C-1), 151.87 (C-5), 145.53 (C-3), 134.35 (C-2), 105.47 (=CH_2), 95.92 (OCHO), 67.33 (CH_2O), 46.68 (C-4a, C-8a), 37.38 (C-6), 32.77 (C-8), 31.75 (C-7), 25.71, 25.64 (CH_2CO, C-4), 18.06 (Me-6), 15.02 (Me-8a); MS, m/z (relative intensity) 276 ($M^{+\cdot}$, 10), 261 (96), 233 (9), 218 (18), 217 (96), 175 (98), 133 (23), 122 (40), 107 (40), 87 (100). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.80; H, 8.75. Found: C, 73.61; H, 8.84.

2-(Dimethoxymethyl)-6β,8aβ-dimethyl-5-methylene-*trans*-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-one (35b). A mixture of keto aldehyde **34** (0.15 g, 0.68 mmol), MeOH (16 mL), trimethyl orthoformate (2 mL), and a few crystals of *p*-TsOH was stirred 24 h at room temperature. Then, solid $NaHCO_3$ was added, the MeOH removed in vacuo, 15 mL of H_2O added, and the mixture extracted with diethyl ether (4 × 25 mL). The ether extracts were washed with brine and dried, and the solvent was evaporated in vacuo to yield 170 mg of crude residue. This residue was purified on a 20 g alumina IV column (98:2 hexane–ethyl acetate), yielding 150 mg (85%) of keto acetal **35b**: bp 135–140 °C (0.9 torr); IR (CCl_4) 3095, 1685, 1680, 1645, 1595, 900 cm^{-1}; ^1H NMR (80.13 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.06 (d, J = 6.3 Hz, 3 H), 1.2–2.3 (6 H), 2.47 (br s, 2 H), 3.31 (s, 3 H), 3.36 (s, 3 H), 4.73 (s, 1 H), 4.88 (s, 1 H), 5.18 (s, 1 H), 7.10 (c, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 203.07 (C-1), 152.02 (C-5), 144.61 (C-3), 133.41 (C-2), 105.60 (=CH_2), 99.03 (OCHO), 54.48, 53.91 (CH_3O), 46.97 (C-8a), 46.92 (C-4a), 37.93 (C-6), 32.93 (C-8), 31.91 (C-7), 25.71 (C-4), 18.19 (Me-6), 15.22 (Me-8a); MS CI (NH_3), m/z (relative intensity) 299 (2), 282 (28), 265 (3), 218 (100). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.49; H, 9.02.

(*Z*)-1-(Methoxymethylene)-6β,8aβ-dimethyl-5-methylene-2-[(trimethylenedioxy)methyl]-*trans*-

1,4,4a,5,6,7,8,8a-octahydronaphthalene (37a). To a solution of (methoxymethyl)trimethylsilane (0.245 g, 2.07 mmol) in anhydrous THF (3 mL) was added, at −78 °C under Ar, 2.45 mL of 0.89 M *sec*-BuLi (2.07 mmol). The reaction mixture was stirred at −78 °C for 35 min and at −30 °C for 55 min. The ketone **35a** (44 mg, 0.18 mmol) in anhydrous THF (0.7 mL) was then added and the reaction stirred at −25 °C for 30 min and at −10 °C for 30 min. After quenching with a saturated NH_4Cl solution (20 mL), the mixture was extracted with ether and washed with brine and dried. After removal of the solvent, purification of the residue on Florisil yielded a mixture of diastereomeric alcohols **36** (49 mg, 79%), which was directly subjected to the extrusion reaction as follows. Potassium hydride (60 mg, 0.74 mmol) as 50% dispersion in oil, was washed with pentane under Ar and diluted with anhydrous THF (0.5 mL). Then, the mixture of alcohols **36** (44 mg, 0.11 mmol) in anhydrous THF (2 mL) was added and the reaction mixture stirred at room temperature for 5 h. After this period of time, a saturated NH_4Cl solution (20 mL) was added and the organic material extracted with CH_2Cl_2, washed with brine, and dried. Purification of the crude on Florisil gave enol ether **37a** (7.3 mg, 22%): IR (CCl_4) 1645, 1620, 1210, 1120, 980, 890 cm^{-1}; UV (MeOH) λ_{max} 251 nm; ^1H NMR (80 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 0.92 (d, J = 7.5 Hz, 3 H), 1.1–2.3 (10 H), 3.56 (s, 3 H), 3.6–4.3 (4 H), 4.58 (s, 1 H), 4.72 (s, 1 H), 4.58 (s, 1 H), 4.16 (br s, 1 H); MS, m/z (relative intensity) 304 (M^+·, 22), 273 (25), 205 (10), 131 (20), 105 (30), 87 (100), 69 (36), 57 (64). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.86; H, 9.15.

(*Z*)-2-(Dimethoxymethyl)-1-(methoxymethylene)-6β,8aβ-dimethyl-5-methylene-*trans*-1,4,4a,5,6,7,8,8a-octahydronaphthalene (37b). Hydrolysis to 38. To a solution of diisopropylamine (1.36 mL, 10.37 mmol) in anhydrous THF (29 mL) under Ar was added 9.6 mL of a 1 M BuLi (9.6 mmol) and the mixture stirred at 0 °C for 1 h. After the mixture was cooled to −78 °C, (methoxymethyl)diphenylphosphine oxide (4.04 g, 16.42 mmol) in anhydrous THF (24 mL) was added over 30 min and the mixture kept for 45 min under stirring. Ketone **35b** (0.16 g, 0.58 mmol) in anhydrous THF (9 mL) was then added and the reaction maintained at −78 °C for 2 h and at room temperature for 2.5 h. Water was added, and the aqueous mixture was extracted with pentane (5 × 25 mL). The pentane extracts were washed with brine and dried to leave, after the solvent was stripped off, a crude from which was isolated enol ether **37b** (137 mg, 75%) by crystallization from pentane at low temperature. Selective hydrolysis of **37b** by column chromatography on Florisil led to aldehyde **38**, whose spectral data confirmed the *Z* configuration of the enol ether.

37b: IR (CCl_4) 1635, 1615, 1200, 1120, 950, 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.79 (s, 3 H), 1.06 (d, J = 6.5 Hz, 3 H), 1.3–2.5 (6 H), 2.18 (br s, 2 H), 3.24 (s, 3 H), 3.42 (s, 3 H), 3.62 (s, 3 H), 4.68 (s, 1 H), 4.79 (s, 1 H), 5.91 (s, 1 H), 5.49 (s, 1 H), 6.13 (br s, 1 H); MS, (relative intensity) m/z 292 (M^+·, 16), 261 (24), 213 (11), 185 (11), 171 (14), 157 (12), 155 (16), 143 (16), 141 (12), 131 (10), 129 (18), 115 (17), 105 (16), 91 (24), 77 (15), 75 (100), 55 (10), 41 (23).

38: IR (CCl_4) 3045, 1695, 1635, 1600, 1220, 1140, 1100, 890 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.78 (s, 3 H), 1.10 (d, J = 6.5 Hz, 3 H), 1.35–2.7 (8 H), 3.63 (s, 3 H), 4.70 (s, 1 H), 4.85 (s, 1 H), 6.07 (s, 1 H), 6.53 (br s, 1 H), 9.75 (s, 1 H); MS CI (NH_3), m/z (relative intensity) 247 (M^+· + 1, 100).

(*Z*,*E*)-1-(Methoxymethylene)-6β,8aβ-dimethyl-5-methylene-*trans*-perhydronaphthalene (40). Similarly prepared was a mixture of enol ethers **40** from diisopropylamine (0.55 mL, 4.16 mmol), anhydrous THF (22 mL), 5.1 mL of 0.8 M BuLi (4.1 mmol), (methoxymethyl)diphenylphosphine oxide (1.28 g, 5.2 mmol), and ketone **13** (0.160 g, 0.52 mmol). After purification on Florisil, pure enol ethers **40** (86 mg, 75%) were obtained in 2:1 ratio: bp 135–140 °C (0.1 torr); IR (CCl_4) 1650, 1635, 1245, 1140, 882 cm^{-1}; MS, m/z (relative intensity) 220 (M^+·, 59), 205 (100), 173 (51), 138 (60), 131 (46), 119 (31), 91 (49), 77 (47), 55 (40), 41 (62). Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.51; H, 11.04. Major isomer: ^1H NMR (80 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 1.2–2.4 (12 H), 3.58 (s, 3 H), 4.54 (s, 1 H), 4.78 (s, 1 H), 5.74 (d, J = 1.2 Hz, 1 H). Minor isomer: ^1H NMR (80 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1.04 (d, J = 6.5 Hz, 3 H), 1.2–2.4 (12 H), 3.48 (s, 3 H), 4.54 (s, 1 H), 4.74 (s, 1 H), 5.68 (d, J = 1.0 Hz, 1 H).

1-Hydroxy-6β,8aβ-dimethyl-5-methylene-*trans*-perhydronaphthalene-1-carboxaldehyde (41a,b). The mixture of enol ethers **40** was dissolved in a mixture of dioxane–water (2:1, 1 mL) and cooled to 0 °C. To the solution was added osmium tetraoxide (33 mg, 0.129 mmol) and the reaction mixture stirred for 5 h. Hydrogen sulfide was then bubbled through the solution over 45 min, and the precipitate was filtered and washed with ether. The ethereal washings were concentrated under vacuum to yield a crude, which was chromatographed on silica gel to furnish hydroxy aldehydes **41a** and **41b** (19 mg, 67%) in a 4:1 ratio.

41a: mp 44–45 °C; bp 75–80 °C (0.8 torr); IR (CCl_4) 3400, 1735, 1640, 1160, 890 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.019 (d, J = 6.2 Hz, 3 H), 1.037 (s, 3 H), 1.07–2.35 (12 H), 3.36 (d, J = 1.0 Hz, 1 H), 4.60 (d, J = 1.66 Hz, 1 H), 4.79 (d, J = 1.66 Hz, 1 H), 9.69 (d, J = 1.0 Hz, 1 H); ^{13}C NMR (20.15 MHz, $CDCl_3$) δ 205.51 (CHO), 153.93 (C-5), 104.91 (=CH_2), 81.17 (C-1), 44.61 (C-4a), 43.23 (C-8a), 38.54 (C-6), 33.17 (C-8), 32.07 (C-7), 28.56 (C-3), 24.07 (C-4), 20.40 (C-2), 18.27 (Me-6), 15.37 (C-9); MS, m/z (relative intensity) 222 (M^+·, 10), 194 (18), 193 (100), 175 (73), 135 (35), 119 (46), 107 (51), 93 (51), 55 (8). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.41; H, 9.69.

41b: mp 103–105 °C; IR (CCl_4) 3400, 1715, 1645, 1160, 895 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.815 (s, 3 H), 0.987 (d, J = 6.4 Hz, 3 H), 1.3–2.1 (12 H), 3.48 (d, J = 1.0 Hz, 1 H), 4.65 (s, 1 H), 4.79 (s, 1 H), 10.33 (d, J = 1.0 Hz, 1 H) MS, m/z (relative intensity) 222 (M^+·, 14), 204 (5), 193 (49), 175 (57), 135 (100), 119 (60), 107 (81), 93 (90), 91 (94), 55 (41). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.49; H, 9.75.

The NOE between the angular methyl and the aldehyde group was 9% for hydroxy aldehyde **41a** and null for **41b**, thus confirming the configurational assignment shown (see text).

1-Hydroxy-2-(dimethoxymethyl)-6β,8aβ-dimethyl-5-methylene-*trans*-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxaldehyde (43a,b). To a mixture of NaF (3.2 mg, 0.077 mmol), KF (1.5 mg, 0.025 mmol), and *m*-CPBA (10.6 mg, 0.051 mmol) in CH_2Cl_2 (0.3 mL), cooled to 0 °C and under Ar, was added enol ether **37b** (16 mg, 0.054 mmol) in CH_2Cl_2 (0.4 mL). The reaction mixture was stirred at 0 °C for 1 h, and more KF (4.5 mg, 0.077 mmol) was added. The stirring was kept at this temperature for 1 h more, the precipitated NaF/KF/*m*-CBA complex was filtered off and washed with ether, and the organic extracts were dried and evaporated to yield a mixture of epoxides **42a** and **42b** (18 mg). Attempted purification on neutral alumina (activity IV) resulted in partial hydrolysis to the corresponding aldehydes **43a** and **43b**.

The mixture of epoxides **42** (6 mg, 0.019 mmol) was treated with activated silica gel (1 g) in ether (5 mL) for 5 h under stirring. After filtering, the solid was thoroughly washed with ether, and the ethereal washings were combined and dried. Evaporation of the solvent yielded a mixture of aldehydes **43a** and **43b** (4 mg) in a 1:4 ratio, which was readily separated by preparative TLC on alumina to furnish **43b** (1.5 mg) and **43a** (0.4 mg).

43b: IR (CCl_4) 3435, 1715, 1680, 1640, 1260, 1090, 892 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.74 (s, 3 H), 1.10 (d, J = 5.6 Hz, 3 H), 1.2–2.5 (8 H), 3.43 (s, 3 H), 3.63 (s, 3 H), 4.47 (s, 1 H), 4.67 (s, 1 H), 4.84 (s, 1 H), 5.55 (s, 1 H), 6.90 (dd, J = 4.9, 2.9 Hz, 1 H), 9.51 (s, 1 H); MS CI (NH_3), m/z (relative intensity) 295 (M^+· + 1, 2), 280 (40), 263 (18), 248 (100), 231 (5).

43a: IR (CCl_4): 3325, 1725, 1680, 1640, 1260, 910 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.76 (s, 3 H), 1.10 (d, J = 6.2 Hz, 3 H), 1.2–2.5 (8 H), 3.46 (s, 3 H), 3.57 (s, 3 H), 4.55 (s, 1 H), 4.70 (s, 1 H), 4.87 (s, 1 H), 5.30 (s, 1 H), 6.82 (br s, 1 H), 9.60 (s, 1 H); MS CI (NH_3), m/z (relative intensity) 295 (M^+· + 1, 12), 280 (100), 263 (18), 248 (53), 231 (2).

(±)-Muzigadial (1a) and (±)-*epi*-Muzigadial (1b). To a solution of enol ether **37b** (74 mg, 0.253 mmol) in *t*-BuOH (50 μL) (distilled from $KMnO_4$) were added Et_4NOH (90 μL), 80% *tert*-butyl hydroperoxide (51 μL), and 25 μL of a 2 × 10^{-5} M OsO_4 solution in *t*-BuOH at 0 °C under Ar. The mixture was stirred for 3 h and at room temperature overnight. Then, ether and 5% $NaHSO_3$ (255 μL) were added, and stirring was continued for 45 min. The solvent was removed, brine was added, and the aqueous mixture was extracted with ether (5 × 15 mL). After drying, removal of the solvent yielded a mixture of aldehyde acetals **43a** and **43b** (63 mg, 85%) in a 10:1 ratio, which was directly subjected to hydrolysis without further purification.

A solution of **43a** and **43b** (63 mg, 0.214 mmol) in a mixture of acetone (4.4 mL), water (14 μL), and concentrated H_2SO_4 (21 μL) was stirred at room temperature for 30 min. Solid $NaHCO_3$ was added, the solvent was removed, and the residue was extracted with ether (5 × 15 mL), washed with brine, and dried. Removal of the solvent yielded a crude (51 mg), which was purified by medium-pressure column chromatography on silica H to afford pure (±)-muzigadial **1a** (40 mg, 76%) and (±)-*epi*-muzigadial **1b** (4 mg, 7%).

1a: mp 115–118 °C (lit.[7a] mp 122–124 °C); IR (CCl_4) 3480, 3095, 1725, 1690, 1638, 1260, 905, 892 cm^{-1}; UV (MeOH) λ_{max} 223.4 nm (ε 5340) [lit.[7a] λ_{max} 223 nm (ε 5300)]; ^1H NMR (80 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.09 (d, J = 6.4 Hz, 3 H), 1.3–2.3 (6 H), 2.55 (d, J = 3.0 Hz, 2 H), 4.06 (s, 1 H), 4.77 (s, 1 H), 4.95 (s, 1 H), 7.34 (dd, J = 3.2, 2.4 Hz, 1 H), [in $(CD_3)_2CO$] 9.46 (s, 1 H), 9.66 (s, 1 H); MS, m/z (relative intensity) 230 (3), 219 (100), 177 (12), 159 (13), 145 (10), 135 (26), 131 (12), 117 (12), 107 (23), 105 (17), 93 (14), 91 (29), 77 (15), 43 (11); MS CI (isobutane), m/z (relative intensity) 249 (M^+· + 1, 100), 231 (20), 219 (5); exact mass calcd for $C_{15}H_{20}O_3$ 248.141235, found 248.141235.

1b: mp 104–105 °C; IR (CCl_4) 3440, 1710, 1680, 1635, 1260, 895 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 1.08 (d, J = 6.4 Hz, 3 H), 1.4–2.4 (6 H), 2.52 (d, J = 2.4 Hz, 2 H), 3.54 (s, 1 H), 4.75 (s, 1 H), 4.93 (s, 1 H), 7.16 (dd, J = 4.8, 2.8 Hz, 1 H), 9.35 (s, 1 H), 9.92 (s, 1 H); MS, m/z (relative intensity) 219 (100), 177 (11), 135 (22), 107 (13), 91 (17), 77 (13), 55 (11), 43 (15); MS CI (isobutane), m/z (relative intensity) 249 (M^+· + 1, 100), 231 (20), 219 (8), 203 (8).

As expected, the NOE between the angular methyl and the nonconjugated aldehyde group was 14% for (±)-muzigadial (**1a**) and null for its epimer **1b**.

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Neviotine-A, a New Triterpene from the Red Sea Sponge *Siphonochalina siphonella*

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The structure of a new triterpene neviotine-A (**3**) from the Red Sea sponge *Siphonochalina siphonella* was elucidated by chemical transformations and mainly on the basis of an INADEQUATE 2D NMR experiment. Neviotine-A possesses a new pentacyclic skeleton related to the sipholanes and siphonellanes previously isolated from the same sponge.

The Red Sea sponge *Siphonochalina siphonella* contains an unusually large amount of secondary metabolites,[1-3] the majority of which are triterpenoids of four new types. Structures of two of these, the sipholanes (e.g., **1**)[1,2] and siphonellanes (e.g., **2**),[3] have already been described by us (Figure 1). The structure of a compound belonging to the third type, and designated neviotine-A after the place of collection (Nevi'ot), is the subject of this report. All four new groups have in common the perhydrobenzoxepine moiety.

Neviotine-A (**3**) was purified by repeated chromatography on silica gel and Sephadex LH-20 columns (0.27%, dry weight) and finally by crystallization from acetone–benzene. Neviotine-A revealed the following physicochemical properties: mp 231–233 °C; α_D −50° (c 4.0, $CHCl_3$); MS, (CI) m/e (relative intensity) 507 (M^+) + 1, $C_{30}H_{50}O_6$, 2), (HREI) 488.3513 ($M^+ - H_2O$, $C_{30}H_{48}O_5$, 6.8); IR ν_{max} 3370 (OH), 1705 (CO) cm^{-1}. The ^1H NMR spectrum of **3** disclosed the presence of seven methyl groups (five singlets and two doublets) and five downfield protons, two of which were exchangeable (two additional OH protons are out of sight), while the ^{13}C NMR spectrum revealed seven CH_3's, nine CH_2's, seven CH's, and seven C atoms, thus accounting altogether for 30 carbons and 46 protons out of 50 (see Table I). Addition of trichloracetyl isocyanate (TAI) to a solution of **3** in $CDCl_3$ caused the appearance of four NH singlets at δ 9.18, 8.79, 8.22, and 8.20,[4] thus proving that the remaining four protons of the empirical formula belonged to OH groups. The downfield shift of two signals at δ 4.19 and 5.05 to 5.17 and 5.71 on addition of TAI and the formation of a diacetate **4** indicated that two of the hydroxyls were secondary. In purified $CDCl_3$, these two signals appeared as doublets coupled to two OH doublets at δ 3.42 (d, J = 8 Hz) and 3.48 (d, J = 4 Hz) and collapsed to singlets on addition of D_2O. The appearance of two NH signals on addition of TAI to a solution of **4** in $CDCl_3$ revealed, as expected, the presence of two tertiary hydroxyls which quite rapidly underwent elimination: the 19-OH in 10 min, to give exclusively the 19(20) double bond (vide infra), and the 15-OH after 3.5 h, to give all three possible isomeric olefins.

The location of the two secondary hydroxyls of **3** in positions α and α′ to a ketone, was suggested by the results of a $NaBH_4$ reduction which resulted in the two epimeric

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(4) Addition of TAI to a solution of sipholenol-A in $CDCl_3$ has shown NH signals at δ_H 8.18 (s) and 8.25 (s).

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