

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

**Photolysis of 17 $\beta$ -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.

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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; 17 $\beta$ -hydroxy-5(10)-estren-3-one, 1089-78-7; 17 $\beta$ -hydroxyestra-4,9-dien-3-one, 6218-29-7.

## A Stereoselective Total Synthesis of ( $\pm$ )-Muzigadial

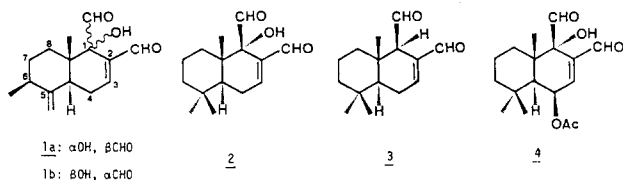
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A stereoselective, 14-step, total synthesis of ( $\pm$ )-muzigadial (1a, 11% overall yield), starting from the commercially available Wieland-Miescher ketone (5), via intermediate ketone 13, is described. The two additional chiral centers in 13 were 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 tetroxide 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,<sup>1</sup> aromatic steroids,<sup>2</sup> quinones,<sup>2d,3</sup> germacranes sesquiterpenes,<sup>4</sup> clerodanes,<sup>5</sup> and iridoids.<sup>6</sup> A series of "drimane" sesquiterpenes, isolated from the bark of the East African plants *Warburgia ugandensis* and *W. stuhlmanii* (Canellaceae), i.e., muzigadial<sup>7a,b</sup> (1a), warburganal<sup>7c</sup> (2), polygodial<sup>7d</sup> (3), and ugandensidial<sup>7e</sup> (cinnamodial,<sup>7f</sup> 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<sub>50</sub> = 5 ppm within 24 h), and *Lymnaca natalensis* (LD<sub>50</sub> = 10 ppm within 24 h).<sup>7a</sup>



Total syntheses of warburganal (2) and polygodial (3) have been accomplished by several groups, starting from 2,6,6-trimethyl-1-vinylcyclohex-1-ene,<sup>8a-c</sup> isodrimenin,<sup>8d</sup> 1-abietic acid,<sup>8e</sup> or 5,5,9-trimethyl-*trans*-1-decalone<sup>8f,g</sup> or through an ingenious metathesis/transannular ene se-

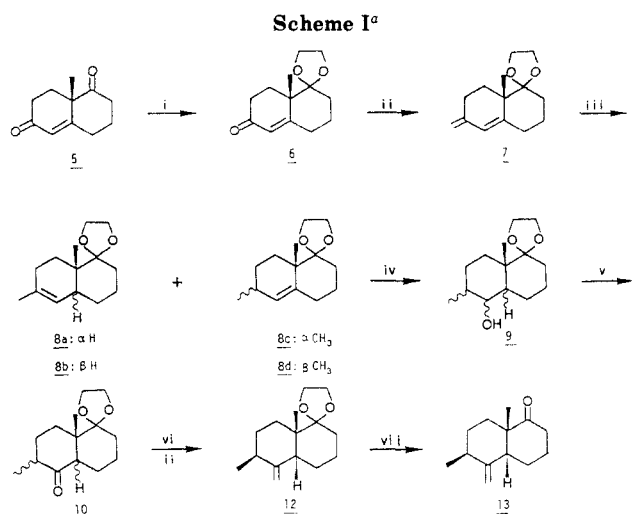
quence to the required *trans*-fused decalin derivative.<sup>8h</sup> On the other hand, to our knowledge, the synthesis of muzigadial has not been heretofore reported in the literature. Nevertheless, 1a clearly provides a challenging target to synthetic organic chemists, since it possesses an exomethylene 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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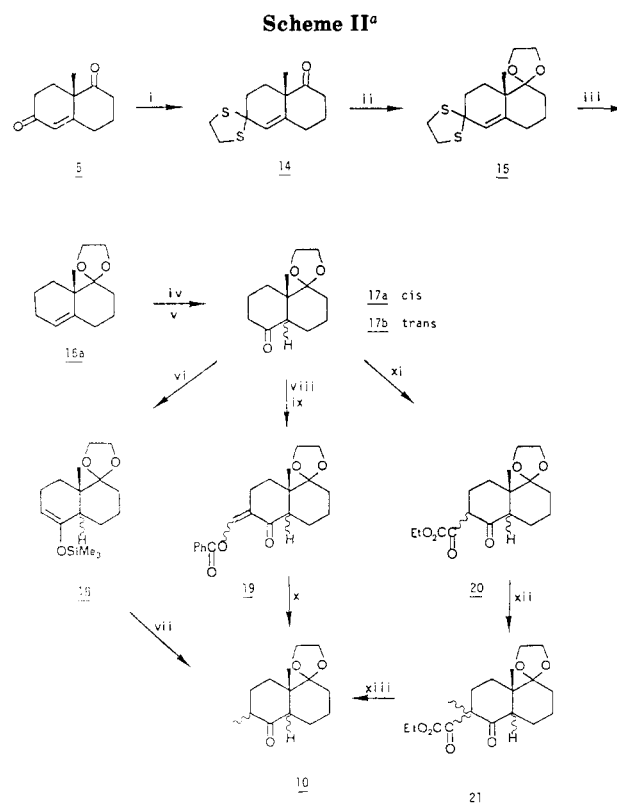
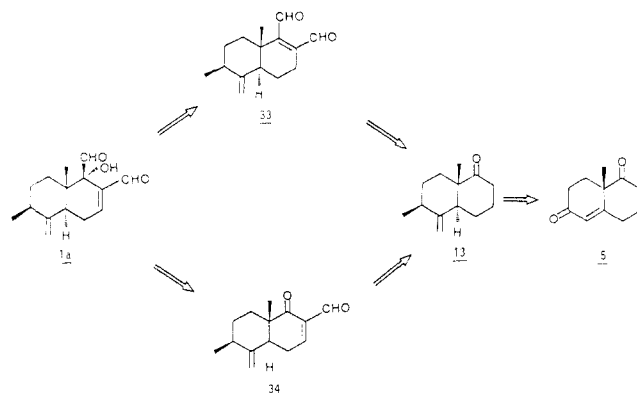
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<sup>a</sup> Reagents: (i) MED, (CH<sub>2</sub>OH)<sub>2</sub>; (ii) CH<sub>2</sub>=PPh<sub>3</sub>; (iii) Li, NH<sub>3</sub>; (iv) BH<sub>3</sub>·THF, H<sub>2</sub>O<sub>2</sub>/NaOH; (v) CrO<sub>3</sub>·Py; (vi) NaOMe/MeOH; (vii) 1 N HCl-AcOH-THF (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



<sup>a</sup> Reagents: (i) (CH<sub>2</sub>SH)<sub>2</sub>, AcOH, *p*-TsOH; (ii) (CH<sub>2</sub>OH)<sub>2</sub>, *p*-TsOH; (iii) Na, NH<sub>3</sub>; (iv) BH<sub>3</sub>·THF, 30% H<sub>2</sub>O<sub>2</sub>/NaOH; (v) CrO<sub>3</sub>·Py; (vi) LDA/(CH<sub>3</sub>)<sub>3</sub>SiCl; (vii) *n*-BuLi/CH<sub>3</sub>I; (viii) HCO<sub>2</sub>Et/NaOEt; (ix) PhCOCl/Py; (x) PtO<sub>2</sub>/EtOH; (xi) (CO<sub>2</sub>Et)<sub>2</sub>/NaH; (xii) MeI/K<sub>2</sub>CO<sub>3</sub>; (xiii) NaOEt/EtOH.

Wittig reaction of 6 with methylenetriphenylphosphorane<sup>11</sup> 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).<sup>12</sup>

Fractionation of a portion of this monoene mixture on AgNO<sub>3</sub> 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 <sup>1</sup>H 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).<sup>13</sup> The second isolated compound exhibited a 21.91 ppm secondary methyl signal in the <sup>13</sup>C NMR spectrum, which agrees with expectations for a pseudoequatorial conformation for this group, as shown in 8d.<sup>14,15</sup> 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.<sup>16</sup>

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)<sup>9</sup> 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.<sup>10a,b</sup>

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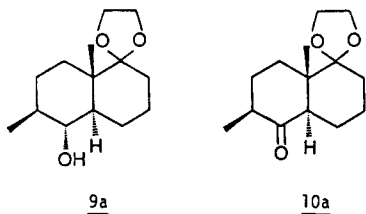
(15) A 7% NOE was obtained for the vinyl proton upon irradiation of the secondary methyl group in 8d, but in the absence of the isolated diastereomer 8c with an  $\alpha$ -oriented methyl, this result was not a conclusive proof for the assignment. (b) For application of NOE, see: Barrett, M. W.; Farrant, 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**.

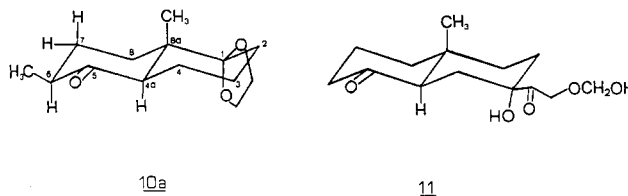
The mixture of monoenes **8a-d**, from the reduction of **7** with lithium in ammonia, was subjected to oxidative hydroboration<sup>17</sup> to provide a mixture of diastereomeric alcohols, **9**, in 81% yield, along with a mixture (10%) of unreacted olefins **8c** and **8d**.<sup>18</sup> In these olefins, syn addition of  $\text{BH}_3\cdot\text{THF}$  complex<sup>19</sup> was expected to take place preferentially, if not exclusively, from the less hindered  $\beta$  face of the molecule, i.e., cis to the angular methyl group,<sup>20</sup> due to the anticipated effective blocking of the  $\alpha$  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  $\alpha$  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  $\text{CHOH}$  absorption at  $\delta$  2.93, in the  $^1\text{H}$  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.<sup>21</sup> 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  $\text{Me}_4\text{Si}$ ,  $\Delta W = 0.9$  Hz, is fully in the range of the expected value for a trans-fused decalin system.<sup>13</sup>



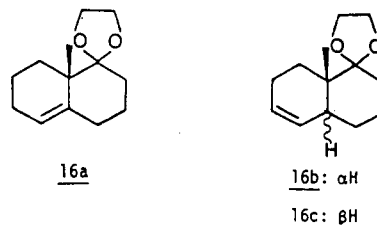
As shown in Scheme I, the mixture of isomeric alcohols **9** was oxidized with chromium trioxide in pyridine to afford a 77% yield of a stereomeric mixture of decalones **10**, in a 6:53:41 ratio, as revealed by GLC analysis. The major isomer obtained was decalone **10a**, the oxidation product of **9a**, as demonstrated after epimerization of the mixture under basic conditions ( $\text{NaOMe}$  in  $\text{MeOH}$ ). 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  $^1\text{H}$  NMR spectrum, including selected homonuclear decoupling experiments. Thus, the

apparent septet of doublets at  $\delta$  2.38 of  $\text{H}_{6\alpha}$  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  $J_{6\alpha,\text{CH}_3}$  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  $\delta$  2.62 of  $\text{H}_{4a}$ , 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  $\text{H}_{4a\alpha}-\text{H}_{4\beta}$ , as required for a trans-fused decalin. These spectroscopic data are in perfect agreement with those reported for protons  $\text{H}_{4a\alpha}$  and  $\text{H}_{6\alpha}$  in compound **11**, a dioxo derivative of the sweet potato phytoalexin 7-hydroxycostol.<sup>22</sup>



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  $\text{Me}_2\text{SO}$  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  $\text{HCl}$ -glacial  $\text{AcOH}$ - $\text{THF}$  mixture,<sup>23</sup> giving intermediate decalone **13**<sup>24</sup> 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<sup>25</sup> 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<sup>26</sup> gave olefin **16a** stereoselectively as the only isolable product, in 74% yield.



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

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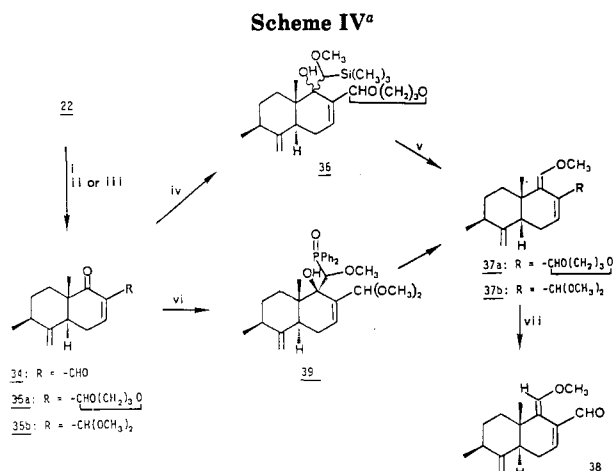
(18) Longer reaction times or larger excess of borane, in order to ensure complete reaction, produced acetal cleavage products, as determined by MS analysis. See ref 19.

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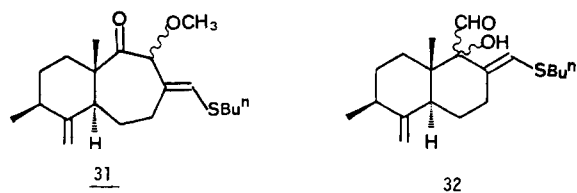
(21) Dannels, D.; Anteunis, M. *Org. Magn. Reson.* 1974, 6, 617.





<sup>a</sup> Reagents: (i) PhSeCl/Py, 30% H<sub>2</sub>O<sub>2</sub>; (ii) HO(CH<sub>2</sub>)<sub>3</sub>OH, H<sub>2</sub>SO<sub>4</sub>; (iii) HC(OMe)<sub>3</sub>, MeOH, *p*-TsOH; (iv) (CH<sub>3</sub>)<sub>3</sub>SiCH<sub>2</sub>OCH<sub>3</sub>, *sec*-BuLi; (v) KH/THF; (vi) Ph<sub>2</sub>P(O)CH<sub>2</sub>OCH<sub>3</sub>, LDA; (vii) Florisil.

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



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)<sup>41</sup> 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,<sup>42</sup> to furnish the corresponding  $\alpha$ -phenylselenenyl ketone, which was oxidized with 30% H<sub>2</sub>O<sub>2</sub> at 0 °C to produce, after syn elimination of the selenoxide, the  $\alpha,\beta$ -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.

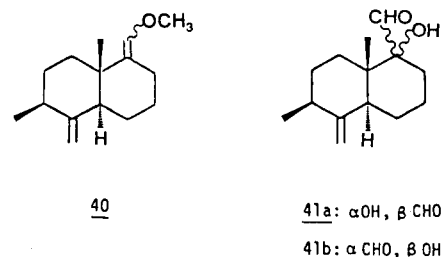
Homologation of ketones to  $\alpha$ -hydroxy aldehydes is a well-known procedure.<sup>43</sup> However, in our case, direct nucleophilic reaction of a suitable masked acyl anion should result in attack from the less hindered  $\alpha$  side of the carbonyl group of 35a, giving rise to the undesired epimer of muzigadial, 1b. Analogous results would be obtained if the  $\alpha$ -hydroxy aldehyde were generated from cleavage of an  $\alpha,\beta$ -epoxy sulfone.<sup>44</sup> The high degree of steric hindrance in 35a presented an additional difficulty to circumvent. Thus, reaction of encumbered ketones with Ph<sub>3</sub>P=CHOCH<sub>3</sub>, Ph<sub>3</sub>P=CH<sub>2</sub>, (EtO)<sub>2</sub>P(O)CHOCH<sub>3</sub>,<sup>45</sup> Me<sub>3</sub>SiCHCl,<sup>46</sup> or (RO)<sub>2</sub>P(O)CHN<sub>2</sub><sup>47</sup> have generally pro-

ceeded with unsatisfactory yields. Nevertheless, nucleophilic acylation of ketone 35a could be carried out successfully by treatment with methoxy(trimethylsilyl)methyl lithium,<sup>48,49</sup> at -78 °C in THF, to afford a mixture of diastereomeric alcohols, 36, in 79% yield.

Surprisingly, extrusion of Me<sub>3</sub>SiOH 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,<sup>49</sup> 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.<sup>50-52</sup> 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  $\delta$  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.<sup>5f</sup>

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 tetroxide oxidation of 40 provided hydroxy aldehydes 41a and 41b in 65% yield. This configurational assignment was based on the nuclear Overhauser effect (NOE) measurements.<sup>53</sup>



Introduction of the remaining hydroxyl group into 37b,  $\alpha$  to the angular methyl, would require the use of a bulky electrophilic reagent to secure attack from the  $\alpha$  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,

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 (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<sub>3</sub> absorptions of 41a ( $\delta$  1.037) and 41b ( $\delta$  0.815) show that the former is clearly influenced by the deshielding zone of the aldehyde carbonyl group, whereas the latter is not.

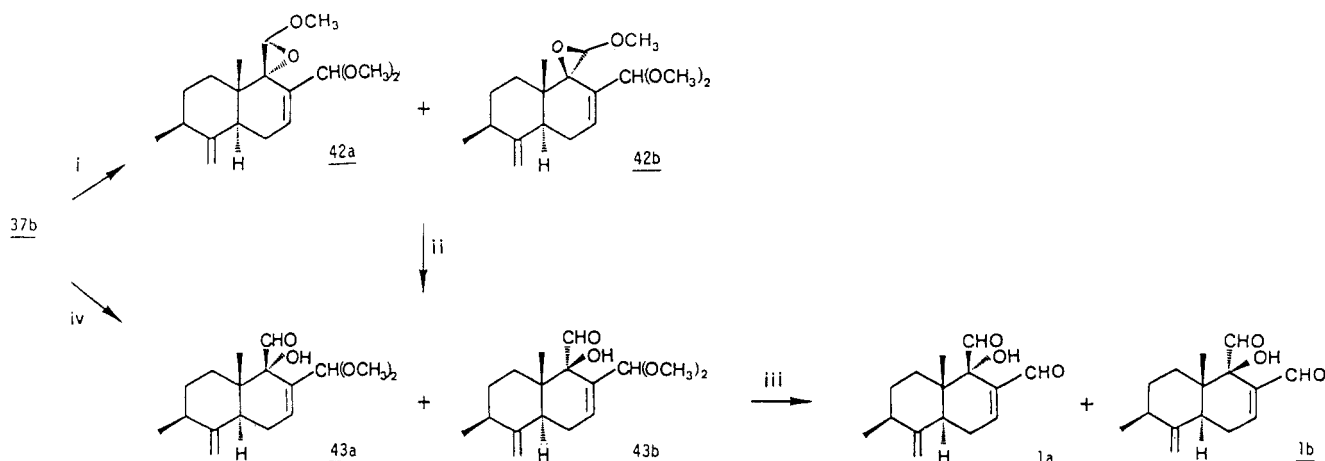
(41) (a) Meyer, W. L.; Manning, R. A.; Schindler, E.; Schroeder, R. J.; Craig, D. *J. Org. Chem.* 1976, 41, 1005. (b) Meyer, W. L.; Clemans, G. B.; Manning, R. A. *J. Org. Chem.* 1975, 40, 3686.

(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.; Reibenspies, J. H.; Anderson, O. P. *J. Org. Chem.* 1984, 49, 1378 and references cited therein.

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Scheme V<sup>a</sup>

<sup>a</sup> Reagents: (i) *m*-CPBA, KF, NaF/CH<sub>2</sub>Cl<sub>2</sub>; (ii) SiO<sub>2</sub>/Et<sub>2</sub>O; (iii) H<sub>2</sub>SO<sub>4</sub>/(CH<sub>3</sub>)<sub>2</sub>CO; (iv) OsO<sub>4</sub>, TBHP, Et<sub>4</sub>NOH/*t*-BuOH.

we deemed it worthwhile to try the reaction with our new epoxidation reagent (*m*-CPBA/KF/NaF).<sup>54</sup> 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 <sup>1</sup>H NMR spectra (**43b**, δ<sub>CHO</sub> 9.51; **43a**, δ<sub>CHO</sub> 9.60) but were clearly differentiated by further hydrolysis (H<sub>2</sub>SO<sub>4</sub>/acetone) to *epi*-muzigadial (**1b**) [δ<sub>CHO</sub> (in CDCl<sub>3</sub>) 9.35 and 9.92] and muzigadial (**1a**) [δ<sub>CHO</sub> (in CDCl<sub>3</sub>) 9.46 and 9.66], respectively, in a 4:1 ratio.

The undesired stereoselectivity was dramatically reversed by the use of osmium tetroxide. In this case, the bulky intermediate osmate ester produced in the *cis* hydroxylation of olefins,<sup>55,56</sup> 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<sub>4</sub> in dioxane, followed by brief exposure to H<sub>2</sub>S, resulted in concomitant hydroxylation of the enol ether and the exo-methylene group. Similar results were obtained by using OsO<sub>4</sub> in catalytic amount with 1 mol of *N*-methylmorpholine *N*-oxide,<sup>57</sup> to regenerate the catalyst. Successful hydroxylation was finally achieved by using *tert*-butyl hydroperoxide as the oxidant in the presence of Et<sub>4</sub>NOH/*t*-BuOH, which has proved to be suitable to effect hydroxylation of tri- and tetrasubstituted olefins.<sup>58</sup> 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.<sup>59</sup> 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, <sup>1</sup>H NMR, MS) are in good agreement with those reported.<sup>7a,b,60</sup>

The stereochemistry of (±)-muzigadial (**1a**) and its epimer **1b** was confirmed by NOE differences in the corresponding <sup>1</sup>H 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. <sup>1</sup>H and <sup>13</sup>C NMR spectra were run in CDCl<sub>3</sub>; chemical shifts are reported in δ relative to Me<sub>4</sub>Si in the <sup>1</sup>H NMR and to CDCl<sub>3</sub> at 77.0 ppm in the <sup>13</sup>C NMR. Assignments in the <sup>13</sup>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<sub>4</sub>, and evaporation of the solvent was carried out under vacuum using a rotatory evaporator.

**5,5-(Ethylenedioxy)-4αβ-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.<sup>10b</sup> mp 66–67 °C). Alternatively, the procedure reported by Corey<sup>10b</sup> 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<sub>4</sub>) 1670, 1625, 1080 cm<sup>-1</sup>; UV (MeOH) λ<sub>max</sub> 238 nm (ε 21.490); <sup>1</sup>H NMR (80.13 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (20.15 MHz, CDCl<sub>3</sub>) δ 198.77 (C-2), 167.51 (C-8a), 125.34 (C-1), 112.13 (C-5), 65.12, 64.82 (CH<sub>2</sub>O), 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<sup>+</sup>, 8), 100 (5.4), 99 (100), 91 (5.2), 77 (5.6), 55 (16), 41 (5.5).

**5,5-(Ethylenedioxy)-4αβ-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

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(59) It was essential for the success of the reaction to free the solvent (*t*-BuOH) from isobutylene by treatment with KMnO<sub>4</sub>; otherwise the OsO<sub>4</sub> 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  $\text{Me}_2\text{SO}$  (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  $\text{Me}_2\text{SO}$  (220 mL), was added and the mixture stirred for 30 min. The ketone acetal **6** (32 g, 144 mmol) in  $\text{Me}_2\text{SO}$  (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  $\times$  100 mL), and the organic extracts were combined, washed with 1:1  $\text{H}_2\text{O}$ -DMSO (3  $\times$  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 ( $\text{CCl}_4$ ) 3080, 1640, 1080  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  236 nm ( $\epsilon$  29.042);  $^1\text{H}$  NMR (80.13 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  144.86 (C-8a), 143.04 (C-2), 124.86 (C-1), 112.77 (C-5), 108.66 (=CH<sub>2</sub>), 65.07, 64.71 ( $\text{CH}_2\text{O}$ ), 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 ( $\text{M}^+$ , 13), 159 (6), 134 (100), 119 (69), 105 (14), 91 (18), 77 (11), 43 (12), 41 (12). Anal. Calcd for  $\text{C}_{14}\text{H}_{20}\text{O}_2$ : C, 76.33; H, 9.15. Found: C, 76.02; H, 9.18.

**5,5-(Ethylenedioxy)-2,4a $\beta$ -dimethyl-trans-3,4,4a,5,6,7,8,8a-octahydronaphthalene (8a).** **5,5-(Ethylenedioxy)-2,4a $\beta$ -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  $\text{N}_2$ , water was added, and the mixture was extracted with ether (5  $\times$  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  $\text{AgNO}_3$ -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  $\times$  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 ( $\text{CCl}_4$ ) 3040, 2940, 1675, 1442, 1060, 910  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (80.13 MHz,  $\text{CDCl}_3$ )  $\delta$  0.92 (s, 3 H), 1–1.25 (14 H), 1.65 (s), 3.90 (s, 4 H), 5.02 (br s, 1 H);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  132.41 (C-2), 125.25 (C-1), 112.97 (C-5), 65.20 ( $\text{CH}_2\text{O}$ ), 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 ( $\text{M}^+$ , 2), 161 (2), 145 (3), 119 (16), 99 (100), 81 (2), 55 (3).

**8d:** IR ( $\text{CCl}_4$ ) 3040, 2930, 1675, 1452, 1060, 925  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  140.46 (C-8a), 128.79 (C-1), 113.17 (C-5), 65.19, 64.8 ( $\text{CH}_2\text{O}$ ), 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 ( $\text{M}^+$ , 0.1), 178 (3.4), 163 (3.1), 145 (3.6), 121 (6.1), 99 (100), 55 (10). Anal. Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_2$ : 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  $\text{BH}_3\cdot\text{THF}$  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,  $\text{H}_2\text{O}$  was added (35 mL), followed by 3 N NaOH (200 mL) and 30%  $\text{H}_2\text{O}_2$  (200 mL), and the mixture stirred for 6 h. The reaction mixture was diluted

with water and extracted with ether (5  $\times$  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 ( $\text{CCl}_4$ ) 3640, 1455, 1195, 960  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (80.13 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  112.65 (C-5), 76.19 (C-1), 65.15, 64.99 ( $\text{CH}_2\text{O}$ ), 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 ( $\text{M}^+$ , 3), 222 (2.5), 178 (6.4), 155 (12), 100 (57), 99 (100), 77 (19), 55 (97). Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{O}_3$ : C, 69.96; H, 10.07. Found: C, 70.10; H, 10.02.

**5,5-(Ethylenedioxy)-2 $\beta$ ,4a $\beta$ -dimethyl-trans-perhydronaphthalen-1-one (10a).** To a cold solution of  $\text{CrO}_3$  (37.5 g, 0.374 mol), anhydrous pyridine (62 mL, 0.749 mol), and anhydrous  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$ , 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 ( $\text{CCl}_4$ ) 1710, 1452  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $J_{6\alpha,\text{CH}_2}$  =  $J_{6\alpha,7\alpha}$  = 6.7 Hz,  $J_{6\alpha,4\alpha}$  = 1.5 Hz, 1 H), 2.62 (ddd,  $J_{4\alpha,4\beta}$  = 10.0 Hz,  $J_{4\alpha,4\alpha}$  = 4.0 Hz,  $J_{4\alpha,6\alpha}$  = 1.5 Hz, 1 H), 3.98 (c, 4 H);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  200.49 (C-1), 111.66 (C-5), 65.49, 64.98 ( $\text{CH}_2\text{O}$ ), 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 ( $\text{M}^+$ , 12), 223 (3), 207 (3), 178 (5), 112 (100), 99 (82), 86 (52), 55 (22). Anal. Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_3$ : C, 70.56; H, 9.30. Found: C, 70.48; H, 9.56.

**5,5-(Ethylenedioxy)-2 $\beta$ ,4a $\beta$ -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  $\text{Me}_2\text{SO}$  (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 ( $\text{CCl}_4$ ) 3095, 1645, 1450, 1095, 890  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (80.13 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  154.58 (C-1), 113.11 (C-5), 103.73 (=CH<sub>2</sub>), 65.31, 65.13 ( $\text{CH}_2\text{O}$ ), 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 ( $\text{M}^+$ , 36), 221 (11), 181 (20), 174 (40), 161 (16), 112 (86), 99 (100), 86 (58), 55 (72), 41 (85). Anal. Calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_2$ : C, 76.23; H, 10.24. Found: C, 76.18; H, 10.08.

**6 $\beta$ ,8a $\beta$ -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  $\text{NaHCO}_3$  saturated solution. The aqueous layer was extracted with ether (5  $\times$  40 mL), and the combined organic phases were washed with a saturated  $\text{NaHCO}_3$  solution (2  $\times$  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.<sup>24</sup> mp 47–48 °C): IR (CCl<sub>4</sub>) 3095, 1705, 1645, 1450, 895 cm<sup>-1</sup>; <sup>1</sup>H NMR (80.13 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (20.15 MHz, CDCl<sub>3</sub>) δ 215.16 (C-1), 152.18 (C-5), 105.18 (=CH<sub>2</sub>), 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<sup>+</sup>, 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<sub>13</sub>H<sub>20</sub>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<sub>3</sub> solution, and water, and dried to yield ketone 14 (8.31 g, 99.1%): IR (KBr) 2910, 1705, 1640 cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) 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<sub>3</sub> 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<sub>4</sub>) 2930, 1645, 1440, 1280 cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) 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 thioacetol 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<sub>4</sub>) 2930, 1645, 1450 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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<sup>25</sup> 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<sub>3</sub>·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<sub>2</sub>O<sub>2</sub> (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<sub>4</sub>) 1710, 1450 cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) 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<sub>3</sub> 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<sub>4</sub>) 3040, 2940, 1670, 1255 cm<sup>-1</sup>; <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) 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<sub>3</sub>I (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<sub>3</sub>I.** 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<sub>3</sub>I (0.13 mL, 2.1 mmol) was added and the mixture stirred for 30 min. After quenching with NaHCO<sub>3</sub> 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<sub>3</sub>), 5.70; 10b (β-H, β-CH<sub>3</sub>), 5.40; 10c (α-H, α-CH<sub>3</sub>), 5.25; 10a, (α-H, β-CH<sub>3</sub>), 5.17.

**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<sub>2</sub>SO<sub>4</sub> (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 <sup>1</sup>H NMR: <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) 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<sub>3</sub> 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: <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) 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<sub>2</sub> (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<sub>3</sub> 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  $^1\text{H}$  NMR: IR ( $\text{CCl}_4$ ) 1730, 1720, 1705  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (90 MHz,  $\text{CCl}_4$ )  $\delta$  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),  $\text{CH}_3\text{I}$  (0.4 mL), anhydrous  $\text{K}_2\text{CO}_3$  (71 mg), and dry acetone (5 mL) under Ar during 16 h. After this time 0.3 mL more of  $\text{CH}_3\text{I}$  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  $\text{Na}_2\text{S}_2\text{O}_3$  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  $\times$  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)-6 $\beta$ ,8 $\alpha\beta$ -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  $^\circ\text{C}$  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  $^\circ\text{C}$ . 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  $^\circ\text{C}$  and at room temperature overnight. The reaction was quenched with a saturated  $\text{NH}_4\text{Cl}$  solution, extracted with ether (4  $\times$  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 ( $\text{CCl}_4$ ) 1645, 1630, 1580, 890  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (80.13 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  192.20 (C-1), 187.19 (=CHOH), 152.56 (C-5), 105.74 (=CH<sub>2</sub>), 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]-6 $\beta$ ,8 $\alpha\beta$ -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  $^\circ\text{C}$ , was added *p*-toluenesulfonyl chloride (0.345 g, 1.81 mmol). The mixture was stirred for 1 h at 0  $^\circ\text{C}$ , and then 1-butanethiol (0.19 mL, 1.81 mmol) was added via syringe. The reaction mixture was stirred 1 h at 0  $^\circ\text{C}$  and left standing in the refrigerator (5  $^\circ\text{C}$ ) overnight. The mixture was poured into 1 N NaOH (20 mL) and extracted with ether (5  $\times$  30 mL). The organic phase was washed with 4 N KOH, 2 N  $\text{H}_2\text{SO}_4$ , 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 ( $\text{CCl}_4$ ) 3090, 1665, 1640, 895  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (80.13 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  201.24 (C-1), 152.91 (C-5), 142.41 (=CS), 128.79 (C-2), 104.96 (=CH<sub>2</sub>), 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 ( $\text{M}^+$ , 18), 235 (100), 203 (89.6), 175 (8.5), 161 (33), 55 (36.7), 41 (86.9). Anal. Calcd for  $\text{C}_{18}\text{H}_{28}\text{OS}$ : C, 73.93; H, 9.65. Found: C, 74.06; H, 9.85.

**7 $\beta$ ,9 $\alpha\beta$ -Dimethyl-6-methylene-trans-4,5,5a,6,7,8,9,9a-octahydronaphtho[1,2-*c*]furan (25)**. To a solution of trimethylsulfonium tetrafluoroborate<sup>34</sup> (0.560 g, 3.4 mmol), in anhydrous DME (20 mL), cooled to -35  $^\circ\text{C}$ , 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  $^\circ\text{C}$ . (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  $\times$  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  $\text{HgSO}_4$  (0.10 g, 0.33 mmol) for 2 h at room temperature. The

liquid was decanted and the solid washed with  $\text{CHCl}_3$ . 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  $^\circ\text{C}$  (0.1 torr); IR ( $\text{CCl}_4$ ) 1645, 1445, 1245, 860  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  225 nm ( $\epsilon$  2570);  $^1\text{H}$  NMR (80.13 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  153.79 (C-6), 136.98, 136.26 (C-1, C-3), 134.34 (C-9b), 119.91 (C-3a), 104.10 (=CH<sub>2</sub>), 49.21 (C-5a), 39.35 (C-4), 38.66 (C-7), 35.29 (C-9a), 32.72 (C-9) (Me-9a), 21.99 (C-8), 19.87 (C-5), 18.35 (Me-7); (relative intensity) MS,  $m/z$  216 ( $\text{M}^+$ , 100), 201 (99), 159 (41), 145 (33), 131 (53), 119 (30), 91 (63), 77 (41). Anal. Calcd for  $\text{C}_{15}\text{H}_{20}\text{O}$ : C, 82.30; H, 9.87. Found: C, 82.65; H, 9.69.

**6 $\beta$ ,8 $\alpha\beta$ -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 thioanisole (0.21 mL, 1.77 mmol) in anhydrous THF (5 mL), cooled to 0  $^\circ\text{C}$ , was added 0.95 mL of 2.07 M BuLi in hexane (1.94 mmol) under Ar. The solution was stirred at 0  $^\circ\text{C}$  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  $\times$  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),  $\text{CH}_3\text{CN}$  (25 mL), and  $\text{HgCl}_2$  (0.6 g, 2.21 mmol) at 70  $^\circ\text{C}$  for 4.5 h. Then solid  $\text{NaHCO}_3$  was added and the mixture filtered through Celite. The cake was washed with ether and the filtrate with 5 M  $\text{NH}_4\text{AcO}$  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 ( $\text{CCl}_4$ ) 1670, 1650, 1615, 1585  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR (80 MHz,  $\text{CDCl}_3$ )  $\delta$  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<sub>2</sub>), 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<sub>2</sub>S), 18.79, 17.88 (Me-6, Me-8a).

**7 $\beta$ ,9 $\alpha\beta$ -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  $\text{CCl}_4$  (3.5 mL) was refluxed for 32 h under Ar. The solid was filtered and washed with  $\text{CCl}_4$ . 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  $\alpha$ -chlorination to the phenylthio group,<sup>39</sup> was not detected. IR ( $\text{CHCl}_3$ ) 3040, 1645, 1602, 1580, 900  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{CuCl}_2/\text{CuO}$ , starting material **26** was recovered unchanged.<sup>61</sup>

**6 $\beta$ ,8 $\alpha\beta$ -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%  $\text{H}_2\text{SO}_4$  in methanol (6 mL) was stirred at 0  $^\circ\text{C}$  for 30 min. The reaction mixture was quenched with solid  $\text{NaHCO}_3$  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 ( $\text{CHCl}_3$ ) 1665, 1610, 1045, 905  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  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<sub>3</sub>) 1667, 1610, 1048, 905 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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,8αβ-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<sub>2</sub>/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<sub>3</sub>CN (4 mL). To the solution were added HgCl<sub>2</sub> (228 mg, 0.84 mmol), 3% HCl (3 mL), and CH<sub>3</sub>CN (11 mL). The mixture was stirred at 80 °C for 4 h, quenched with solid NaHCO<sub>3</sub>, and diluted with ether. The ethereal solution was washed with NH<sub>4</sub>AcO 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<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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<sub>2</sub>/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<sub>3</sub>) 1710, 1640, 1105, 890 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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<sub>3</sub>) 1710, 1645, 1110, 905 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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<sub>2</sub>/HgO at Room Temperature.** **2-[(Butylthio)methylene]-1-hydroxy-6β,8αβ-dimethyl-5-methylene-*trans*-perhydronaphthalene-1-carboxaldehyde (32).** A mixture of crude A (108.4 mg), HgCl<sub>2</sub> (241.4 mg, 0.889 mmol), red HgO (96.3 mg, 0.444 mmol), and 80% CH<sub>3</sub>CN in water (10 mL) was stirred at room temperature for 3.5 h. After this period of time, 5 M NH<sub>4</sub>AcO (6 mL) was added, the mixture stirred for 10 min more and filtered through Celite, and the cake washed with hexane-CHCl<sub>3</sub> (1:1). The filtrate was decanted and the organic layer washed with 5 M NH<sub>4</sub>AcO 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<sub>4</sub>) 3460, 2840, 1705, 1641, 890 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) 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<sub>2</sub> (41.5 mg, 0.153 mmol), CH<sub>3</sub>CN (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<sub>3</sub> solution and filtered through Celite after 5 M NH<sub>4</sub>AcO (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,8αβ-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<sub>3</sub> (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<sub>3</sub> (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 <sup>1</sup>H NMR spectrum.

The crude was treated at 0 °C with 30% H<sub>2</sub>O<sub>2</sub> (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<sub>3</sub> (5 × 20 mL). The combined organic phases were washed with a saturated NaHCO<sub>3</sub> 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<sub>4</sub>) 3095, 1705, 1680, 1650, 900 cm<sup>-1</sup>; <sup>1</sup>H NMR (80.13 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (20.15 MHz, CDCl<sub>3</sub>) δ 202.92 (C-1), 189.67 (CHO), 154.94 (C-5), 151.21 (C-2), 132.47 (C-3), 106.26 (=CH<sub>2</sub>), 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<sup>+</sup>, 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<sub>14</sub>H<sub>18</sub>O<sub>2</sub>: C, 77.03; H, 8.31. Found: C, 76.98; H, 8.20.

**6β,8αβ-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<sub>2</sub>SO<sub>4</sub> (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<sub>3</sub>, followed by 15 mL of water and the resulting mixture extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 25 mL). The joined organic extracts were washed with a saturated solution of NaHCO<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub> to yield 1.17 g (91%) of keto acetal **35a**, mp 56–58 °C (from pentane-ether): IR (CCl<sub>4</sub>) 3095, 1680, 1645 cm<sup>-1</sup>; <sup>1</sup>H NMR (80.13 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (20.15 MHz, CDCl<sub>3</sub>) δ 202.24 (C-1), 151.87 (C-5), 145.53 (C-3), 134.35 (C-2), 105.47 (=CH<sub>2</sub>), 95.92 (OCHO), 67.33 (CH<sub>2</sub>O), 46.68 (C-4a, C-8a), 37.38 (C-6), 32.77 (C-8), 31.75 (C-7), 25.71, 25.64 (CH<sub>2</sub>CO, C-4), 18.06 (Me-6), 15.02 (Me-8a); MS, *m/z* (relative intensity) 276 (M<sup>+</sup>, 10), 261 (96), 233 (9), 218 (18), 217 (96), 175 (98), 133 (23), 122 (40), 107 (40), 87 (100). Anal. Calcd for C<sub>17</sub>H<sub>24</sub>O<sub>3</sub>: C, 73.80; H, 8.75. Found: C, 73.61; H, 8.84.

**2-(Dimethoxymethyl)-6β,8αβ-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<sub>3</sub> was added, the MeOH removed in vacuo, 15 mL of H<sub>2</sub>O 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<sub>4</sub>) 3095, 1685, 1680, 1645, 1595, 900 cm<sup>-1</sup>; <sup>1</sup>H NMR (80.13 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (20.15 MHz, CDCl<sub>3</sub>) δ 203.07 (C-1), 152.02 (C-5), 144.61 (C-3), 133.41 (C-2), 105.60 (=CH<sub>2</sub>), 99.03 (OCHO), 54.48, 53.91 (CH<sub>2</sub>O), 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<sub>3</sub>), *m/z* (relative intensity) 299 (2), 282 (28), 265 (3), 218 (100). Anal. Calcd for C<sub>18</sub>H<sub>24</sub>O<sub>3</sub>: C, 72.69; H, 9.15. Found: C, 72.49; H, 9.02.

**(Z)-1-(Methoxymethylene)-6β,8αβ-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  $-78\text{ }^{\circ}\text{C}$  under Ar, 2.45 mL of 0.89 M *sec*-BuLi (2.07 mmol). The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 35 min and at  $-30\text{ }^{\circ}\text{C}$  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  $-25\text{ }^{\circ}\text{C}$  for 30 min and at  $-10\text{ }^{\circ}\text{C}$  for 30 min. After quenching with a saturated  $\text{NH}_4\text{Cl}$  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  $\text{NH}_4\text{Cl}$  solution (20 mL) was added and the organic material extracted with  $\text{CH}_2\text{Cl}_2$ , washed with brine, and dried. Purification of the crude on Florisil gave enol ether **37a** (7.3 mg, 22%): IR ( $\text{CCl}_4$ ) 1645, 1620, 1210, 1120, 980, 890  $\text{cm}^{-1}$ ; UV (MeOH)  $\lambda_{\text{max}}$  251 nm;  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 22), 273 (25), 205 (10), 131 (20), 105 (30), 87 (100), 69 (36), 57 (64). Anal. Calcd for  $\text{C}_{19}\text{H}_{28}\text{O}_3$ : C, 74.96; H, 9.27. Found: C, 74.86; H, 9.15.

**(Z)-2-(Dimethoxymethyl)-1-(methoxymethylene)-6 $\beta$ ,8a $\beta$ -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  $0\text{ }^{\circ}\text{C}$  for 1 h. After the mixture was cooled to  $-78\text{ }^{\circ}\text{C}$ , (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  $-78\text{ }^{\circ}\text{C}$  for 2 h and at room temperature for 2.5 h. Water was added, and the aqueous mixture was extracted with pentane ( $5 \times 25$  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 ( $\text{CCl}_4$ ) 1635, 1615, 1200, 1120, 950, 890  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (90 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 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 ( $\text{CCl}_4$ ) 3045, 1695, 1635, 1600, 1220, 1140, 1100, 890  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{NH}_3$ ),  $m/z$  (relative intensity) 247 ( $\text{M}^+ + 1$ , 100).

**(Z,E)-1-(Methoxymethylene)-6 $\beta$ ,8a $\beta$ -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  $^{\circ}\text{C}$  (0.1 torr); IR ( $\text{CCl}_4$ ) 1650, 1635, 1245, 1140, 882  $\text{cm}^{-1}$ ; MS,  $m/z$  (relative intensity) 220 ( $\text{M}^+$ , 59), 205 (100), 173 (51), 138 (60), 131 (46), 119 (31), 91 (49), 77 (47), 55 (40), 41 (62). Anal. Calcd for  $\text{C}_{15}\text{H}_{24}\text{O}$ : C, 81.76; H, 10.98. Found: C, 81.51; H, 11.04. Major isomer:  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ )  $\delta$  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:  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ )  $\delta$  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-6 $\beta$ ,8a $\beta$ -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  $0\text{ }^{\circ}\text{C}$ . To the solution was added osmium tetroxide (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  $^{\circ}\text{C}$ ; bp 75–80  $^{\circ}\text{C}$  (0.8 torr); IR ( $\text{CCl}_4$ ) 3400, 1735, 1640, 1160, 890  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  (20.15 MHz,  $\text{CDCl}_3$ )  $\delta$  205.51 (CHO), 153.93 (C-5), 104.91 (=CH<sub>2</sub>), 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 ( $\text{M}^+$ , 10), 194 (18), 193 (100), 175 (73), 135 (35), 119 (46), 107 (51), 93 (51), 55 (8). Anal. Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_2$ : C, 75.63; H, 9.97. Found: C, 75.41; H, 9.69.

**41b:** mp 103–105  $^{\circ}\text{C}$ ; IR ( $\text{CCl}_4$ ) 3400, 1715, 1645, 1160, 895  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{M}^+$ , 14), 204 (5), 193 (49), 175 (57), 135 (100), 119 (60), 107 (81), 93 (90), 91 (94), 55 (41). Anal. Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_2$ : 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)-6 $\beta$ ,8a $\beta$ -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  $\text{CH}_2\text{Cl}_2$  (0.3 mL), cooled to  $0\text{ }^{\circ}\text{C}$  and under Ar, was added enol ether **37b** (16 mg, 0.054 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.4 mL). The reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  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 ( $\text{CCl}_4$ ) 3435, 1715, 1680, 1640, 1260, 1090, 892  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{NH}_3$ ),  $m/z$  (relative intensity) 295 ( $\text{M}^+ + 1$ , 2), 280 (40), 263 (18), 248 (100), 231 (5).

**43a:** IR ( $\text{CCl}_4$ ) 3325, 1725, 1680, 1640, 1260, 910  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ )  $\delta$  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 ( $\text{NH}_3$ ),  $m/z$  (relative intensity) 295 ( $\text{M}^+ + 1$ , 12), 280 (100), 263 (18), 248 (53), 231 (2).

**( $\pm$ )-Muzigadial (1a) and ( $\pm$ )-epi-Muzigadial (1b).** To a solution of enol ether **37b** (74 mg, 0.253 mmol) in *t*-BuOH (50  $\mu\text{L}$ ) (distilled from  $\text{KMnO}_4$ ) were added  $\text{Et}_3\text{NOH}$  (90  $\mu\text{L}$ ), 80% *tert*-butyl hydroperoxide (51  $\mu\text{L}$ ), and 25  $\mu\text{L}$  of a  $2 \times 10^{-5}$  M  $\text{OsO}_4$  solution in *t*-BuOH at  $0\text{ }^{\circ}\text{C}$  under Ar. The mixture was stirred for 3 h and at room temperature overnight. Then, ether and 5%  $\text{NaHSO}_3$  (255  $\mu\text{L}$ ) were added, and stirring was continued for 45 min. The solvent was removed, brine was added, and the aqueous mixture was extracted with ether ( $5 \times 15$  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  $\mu$ L), and concentrated H<sub>2</sub>SO<sub>4</sub> (21  $\mu$ L) was stirred at room temperature for 30 min. Solid NaHCO<sub>3</sub> was added, the solvent was removed, and the residue was extracted with ether (5  $\times$  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 ( $\pm$ )-muzigadial **1a** (40 mg, 76%) and ( $\pm$ )-*epi*-muzigadial **1b** (4 mg, 7%).

**1a**: mp 115–118 °C (lit.<sup>7a</sup> mp 122–124 °C); IR (CCl<sub>4</sub>) 3480, 3095, 1725, 1690, 1638, 1260, 905, 892 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\max}$  223.4 nm ( $\epsilon$  5340) [lit.<sup>7a</sup>  $\lambda_{\max}$  223 nm ( $\epsilon$  5300)]; <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>3</sub>)<sub>2</sub>CO] 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<sup>+</sup> + 1, 100), 231 (20), 219 (5); exact mass calcd for C<sub>15</sub>H<sub>20</sub>O<sub>3</sub> 248.141235, found 248.141235.

**1b**: mp 104–105 °C; IR (CCl<sub>4</sub>) 3440, 1710, 1680, 1635, 1260, 895 cm<sup>-1</sup>; <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>)  $\delta$  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<sup>+</sup> + 1, 100), 231 (20), 219 (8), 203 (8).

As expected, the NOE between the angular methyl and the nonconjugated aldehyde group was 14% for ( $\pm$ )-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 sipholanans and siphonellanes previously isolated from the same sponge.

The Red Sea sponge *Siphonochalina siphonella* contains an unusually large amount of secondary metabolites,<sup>1-3</sup> the majority of which are triterpenoids of four new types. Structures of two of these, the sipholanans (e.g., **1**)<sup>1,2</sup> and siphonellanes (e.g., **2**),<sup>3</sup> 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;  $\alpha_D$  -50° ( $c$  4.0, CHCl<sub>3</sub>); MS, (CI)  $m/e$  (relative intensity) 507 (M<sup>+</sup> + 1, C<sub>30</sub>H<sub>50</sub>O<sub>6</sub>, 2), (HREI) 488.3513 (M<sup>+</sup> - H<sub>2</sub>O, C<sub>30</sub>H<sub>48</sub>O<sub>5</sub>, 6.8); IR  $\nu_{\max}$  3370 (OH), 1705 (CO) cm<sup>-1</sup>. The <sup>1</sup>H 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 pro-

tons are out of sight), while the <sup>13</sup>C NMR spectrum revealed seven CH<sub>3</sub>'s, nine CH<sub>2</sub>'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 trichloroacetyl isocyanate (TAI) to a solution of **3** in CDCl<sub>3</sub> caused the appearance of four NH singlets at  $\delta$  9.18, 8.79, 8.22, and 8.20,<sup>4</sup> thus proving that the remaining four protons of the empirical formula belonged to OH groups. The downfield shift of two signals at  $\delta$  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<sub>3</sub>, these two signals appeared as doublets coupled to two OH doublets at  $\delta$  3.42 (d,  $J$  = 8 Hz) and 3.48 (d,  $J$  = 4 Hz) and collapsed to singlets on addition of D<sub>2</sub>O. The appearance of two NH signals on addition of TAI to a solution of **4** in CDCl<sub>3</sub> 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  $\alpha$  and  $\alpha'$  to a ketone, was suggested by the results of a NaBH<sub>4</sub> reduction which resulted in the two epimeric

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(4) Addition of TAI to a solution of sipholenol-A in CDCl<sub>3</sub> has shown NH signals at  $\delta_H$  8.18 (s) and 8.25 (s).