Total Synthesis of Neohedycaryol. Its Possible Role in the Biosynthesis of Eudesmane Sesquiterpenes

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The total synthesis of neohedycaryol (**4**), the C(9)−C(10) double bond regioisomer of the germacrane sesquiterpene hedycaryol, was accomplished in 10 steps from the known dione **6**. A Marshall fragmentation of the intermediate mesylate **14** was used to prepare the *trans*,*trans*-cyclodeca-1,6-diene ring present in neohedycaryol. During the synthesis of **14**, a pronounced example of through-bond interactions (TBI) was observed. The preferred elongated chair conformation of neohedycaryol was demonstrated spectroscopically and by chemical conversion into α-, *β*-, and *γ*-eudesmol. These findings indicate that the occurrence of neohedycaryol as a precursor in the biosynthesis of *epi*-eudesmanes as proposed in the literature is unlikely. The preference of neohedycaryol for the elongated chair conformation further shows that the compound occupies the meso form. This implies that neohedycaryol may act as a precursor in the biosynthesis of both *ent*- and usual eudesmanes.

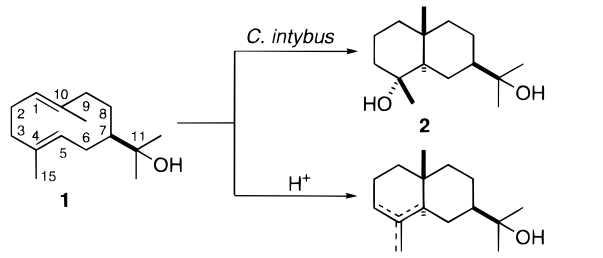
Introduction

Germacrane sesquiterpenes, structurally characterized by a *trans*,*trans*-cyclodeca-1(10),4-diene unit,[1] and their 1,10-monoepoxides are generally considered as direct precursors of eudesmane sesquiterpenes.[2] Strong evidence for the involvement of these monocyclic compounds in the biogenetic formation of eudesmanes comes from enzyme- and acid-mediated cyclization reactions. For instance, incubation of (+)-hedycaryol (**1**) with a root suspension of chicory (*Cichorium intybus*) gave selectively cryptomeridiol (**2**),[3] while a mixture of α-, *β*-, and *γ*-eudesmol (**3a**, **3b**, and **3c**, respectively) was obtained upon treatment of **1** with acid[4] (Scheme 1). The formation of these eudesmanes can easily be explained by enzymatic or chemical protonation of the C(1)−C(10) double bond followed by cyclization (formation of the C(5)−C(10) bond) and subsequent incorporation of water (in case of **2**) or proton loss (in case of **3a**, **3b**, and **3c**).

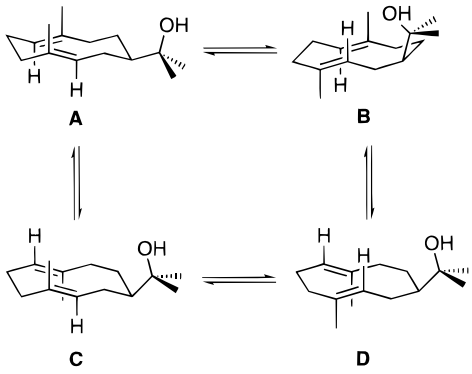
The stereochemical aspects of these cyclization reactions are also important. Although ^{1}H NMR experiments clearly show that **1** exists in at least three different conformations at room temperature,[5] cyclization of **1** only affords the trans-fused eudesmane skeleton with a syn relationship between the C(10) Me group and the C(7) side chain. Because the different conformers are interconverting at room temperature as depicted in Scheme 2, it is obvious that **1** only cyclizes via the conformer **A** in which both vinylic Me groups are on the *β*-face.[6]

The greater part of the eudesmanes isolated from higher plants possesses the same relative and absolute configuration as present in the structures **2** and **3**.[7] A small number of eudesmanes, however, has an aberrant configuration at C(5) and/or C(10).[8] These so-called *epi*-eudesmanes have been found in plant species together with the usual eudesmanes.[9]

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1997.

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(4) Jones, R. V. H.; Sutherland, M. D. *J. Chem. Soc., Chem. Commun.* **1968**, 1229.

(5) (a) Wharton, P. S.; Poon, Y. C.; Kluender, H. C. *J. Org. Chem.* **1973**, *38*, 735. (b) Minnaard, A. J. Unpublished.

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(8) The 7-*epi*-eudesmanes are the antipodes of 5-*epi*-10-*epi*-eudesmanes and, consequently, possess the *ent*-configuration. For example, see: van Beek, T. A.; Kleis, R.; Posthumus, M. A.; van Veldhuizen, A. *Phytochemistry* **1989**, *28*, 1909.

(9) For some representative examples, see: (a) Prudent, D.; Perineau, F.; Bessiere, J. M.; Michel, G.; Bravo, R. *J. Essent. Oil Res.* **1993**, *5*, 255. (b) Cañigueral, S.; Vila, R.; Vicario, G.; Tomas, X.; Adzet, T. *Biochem. Syst. Ecol.* **1994**, *22*, 307.

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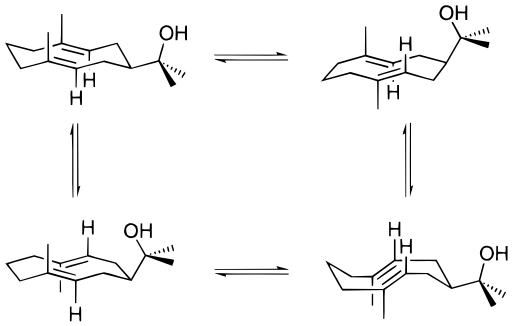
Several hypotheses have appeared in the literature to unravel the biosynthesis of *epi*-eudesmanes. In the most straightforward explanation, both the *epi*- and usual eudesmanes are formed from *trans*,*trans*-germacranes.[10] From the conformations of **1** depicted in Scheme 2, it can easily be deduced that cyclization of the conformations **B**, **C**, and **D** will lead to 5-*epi*-, 10-*epi*-, and 5-*epi*-10-*epi*-eudesmanes, respectively. In the literature, two examples are known in which *trans*,*trans*-germacranes yielded *epi*-eudesmanes.[11,12] In both cases, however, the *trans*,*trans*-cyclodeca-1(10),4-diene ring bears a β substituent at C(6) as a result of which conformation **A** will be less favorable.

A second explanation for the biosynthesis of *epi*-eudesmanes assumes the cyclization of double bond stereoisomers of *trans*,*trans*-germacranes.[13] It has been shown that acid-catalyzed cyclizations of *cis*,*trans*-isomers of **1** do give *epi*-eudesmanes.[11,14] A serious drawback of this hypothesis is the fact that the double bond stereoisomers of simple *trans*,*trans*-germacranes have not been found in nature.[15]

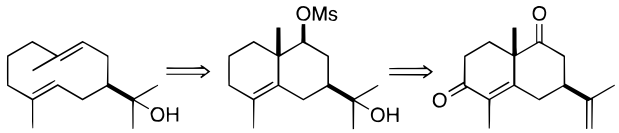
In a third explanation, the one we will concentrate on, the cyclization of a double bond regioisomer of *trans*,*trans*-germacranes has been proposed. It was already recognized in 1959 by Hendrickson that cyclization of the C(9)−C(10) double bond regioisomer of hedycaryol, subsequently named neohedycaryol (**4**), might give an eudesmane.[16] This suggestion was picked up by McSweeney *et al*. who reasoned that cyclization to both *epi*- and usual eudesmanes would proceed via different conformations of **4**.[17] Experimental information, however, failed to appear because **4** was not available. Some years later, a route toward agarofurans based on **4** was postulated.[18] Since then, **4** has been mentioned several times in connection with the biosynthesis of *epi*-eudesmanes,[19] eremophilanes,[20] and agarofurans.[21]

Although recently two C(5)−C(6) double bond regioisomers of hedycaryol have been isolated from higher plants,[22,23] **4** has not been found in nature. This does not imply that **4** does not exist. It may have escaped isolation due to its supposed instability; the ten-membered ring should be prone to cyclization because the double bonds

Scheme 3



Scheme 4



are close to each other and cyclization can occur via stable tertiary carbocations. In this context, it is important to note that examination of a three-dimensional model of **4** revealed several interesting stereochemical aspects. The *trans*,*trans*-cyclodeca-4,9-diene system of **4** can be considered as a cyclohexane ring elongated with two double bonds (Scheme 3). There are two conformations in which the double bonds are lying parallel (comparable with the chair and boat conformation of cyclohexane) and two conformations in which the double bonds are crossed (the twist conformations of cyclohexane).[24] It also appeared that in the parallel conformations, **4** has on the average a symmetry plane, and this means that the compound occupies a meso form. The two crossed forms are enantiomers of each other.

Because of our interest in the biogenetic-like cyclization reactions of germacrane sesquiterpenes[3,25] and their analogues,[26] we decided to synthesize neohedycaryol. As with hedycaryol,[3] it was expected that the acid-catalyzed cyclization of **4** would provide more information about its possible role in the biosynthesis of eudesmanes.

In our synthetic approach to **4**, the known dione **6**[27] was used as the starting material (Scheme 4). A number of apparently simple reactions was needed to prepare the mesylate **5** from **6**. The key step in this approach, the conversion of **5** into neohedycaryol, involved a Marshall fragmentation reaction in which both double bonds are regio- and stereospecifically formed.[28]

Results and Discussion

Following the procedure described by Agami *et al*.,[29] the synthesis of **6** started with the addition of ethyl vinyl

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(16) Hendrickson, J. B. *Tetrahedron* **1959**, *7*, 82.
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(24) Only the interconversion of the conformations by rotation of the double bonds is considered.
(25) Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1995**, *51*, 6303.
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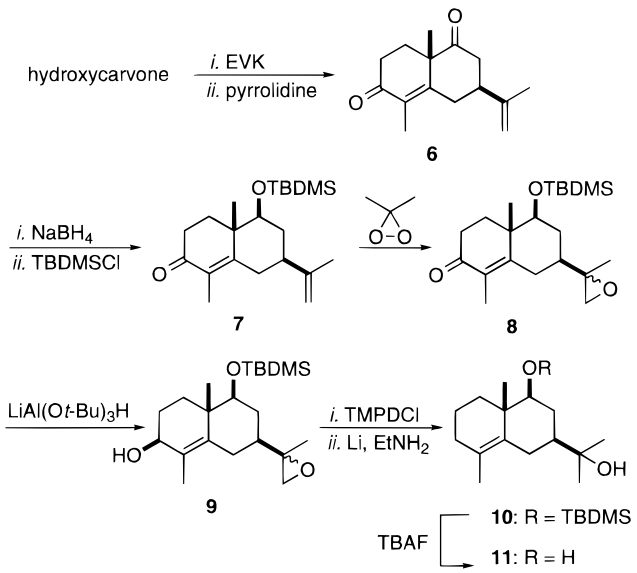
Scheme 5



ketone (EVK) to hydroxycarvone which was easily prepared from (*R*)-(−)-carvone.[27] In our hands, both the reported enantioselective[30] and the acid-catalyzed ring closure[31] of the addition product, a 3:2 mixture of two triketones, did not yield any workable result. It was then decided to achieve cyclization with a substoichiometric amount of pyrrolidine in refluxing benzene. In this way, racemic **6** was obtained in 38% yield (Scheme 5). Reduction of the C(9) carbonyl group of **6** with $NaBH_4$ and protection of the resulting alcohol as its TBDMS ether gave **7** in good yield. Selective epoxidation of the double bond in the side chain of **7** was effected with dimethyldioxirane and afforded **8** as a diastereomeric 1:1 mixture.

Reduction of **8** with lithium tri-*tert*-butoxyaluminohydride ($LiAl(Ot\text{-}Bu)_3H$) provided **9** also as a diastereomeric 1:1 mixture in 87% yield. Since the $LiAl(Ot\text{-}Bu)_3H$ reduction of a system comparable to **8** proceeds selectively from the α-side,[32] the orientation of the C(3) hydroxyl group of **9** is probably β. In order to remove the oxygen function at C(3), the phosphordiamidate of **9** was reduced with Li in $EtNH_2$.[33] In this way, not only the C(3)−O bond was reduced but also the epoxide ring was opened to give almost pure **10** in high yield. Cleavage of the C(9) Si−O bond with TBAF in hot DMSO afforded the diol **11** in pure form after recrystallization from EtOH.

In order to apply the Marshall fragmentation reaction, the C(9) hydroxyl group of **11** had to be converted into a mesylate group, and here we encountered a curious problem. Despite many attempts, we were not able to produce the desired mesylate **5**. For instance, treatment of **11** with MsCl in dry pyridine at −10 °C showed the complete disappearance of the starting material on TLC, but workup and purification only afforded a small amount of a compound which contained Cl as deduced from its mass spectrum. In its ^1H NMR spectrum,[34] a one-proton signal appears as a double doublet at δ 3.74 with couplings of 4.4 and 12.2 Hz, indicating the replacement of the C(9) hydroxyl group by Cl with retention of configuration. In sharp contrast with this unexpected result, no problems were reported for the mesylation of a homoallylic alcohol similar to **11** but lacking the C(7) substituent.[35] It was therefore assumed that the difficulties encountered with the mesylation of **11** were due to the presence of the C(7) 2-propanol group.[36] Strong support for this assumption came from our previous studies on *trans*-fused perhydronaphthalene-[37] and norbornane-1,4-diol monosulfonate esters.[38] It has been demonstrated that deprotonation of the alcohol function of these compounds leads to a strongly enhanced leaving group ability of the sulfonate ester group, almost certainly as a result of long-range orbital interactions through the four σ-bonds between the alcoholate anion (electron donor) and the sulfonate ester bond (electron acceptor). The extent of these through-bond orbital interactions (TBI)[39] depends on the geometry of the σ-relay (the intervening σ-framework) and is maximized for an all-trans arrangement.[40] From examination of a molecular model of **5**, it appeared that the σ-relay between the tertiary hydroxyl group at C(11) and the mesylate group at C(9) possesses such an all-trans arrangement. This should mean that deprotonation of the C(11) hydroxyl group strongly enhances the leaving group ability of the mesylate group. Because the synthesis of mesylate **5** requires the use of pyridine,[41] hydrogen bond formation between pyridine and the C(11) alcohol function will lead to partial negative charge on the C(11) oxygen, thereby increasing the leaving group ability of the mesylate group. Consequently, the mesylate group of **5** will be very susceptible to nucleophilic replacement as the reaction outcome of our initial mesylation experiments clearly showed (vide supra).

Having thus explained the anomalous behavior of mesylate **5**, the solution was obvious: protection of the C(11) hydroxyl function as its acetate to prevent hydrogen bond formation. In order to confirm this hypothesis, **10** was treated with Ac_2O and a catalytic amount of DMAP in Et_3N[42] to afford **12** in 82% yield (Scheme 6). After removal of the TBDMS protecting group, treatment of the resulting alcohol **13** with MsCl in pyridine now proceeded without any problems and gave the mesylate **14** in 89% yield. The NMR and mass spectral data of **14** are fully consistent with the assigned structure.

The Marshall fragmentation reaction of mesylate **14** was expected to complete the synthesis of neohedy-

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(34) ^1H NMR δ 1.04 (s, 3 H), 1.15 (s, 6 H), 1.65 (br s, 3 H), 1.1−2.1 (m, 11 H), 2.55 (ddd, J = 2.2, 2.2, 12.5 Hz, 1 H), 3.74 (dd, J = 4.4, 12.2 Hz, 1 H); ^{13}C NMR δ 18.76 (q), 18.84 (t), 19.85 (q), 25.52 (t), 26.87 (q), 27.27 (q), 33.17 (t), 34.37 (t), 37.36 (t), 40.68 (s), 48.98 (d), 72.28 (s), 72.69 (d), 128.58 (s), 133.01 (s); MS *m/z* (relative intensity) 258 (M^+ + 2, 3), 256 (M^+, 9), 240 (33), 238 (100), 225 (7), 223 (21), 197 (20), 195 (60), 187 (34), 159 (36), 59 (48).
(35) Bundy, G. L. *Synthesis of Cyclodecadienes from Decalylborane Derivatives*; Ph.D. Thesis, Northwestern University, Evanston, Illinois, 1968.
(36) Initially, it was thought that just the presence of the homoallylic double bond frustrated the mesylation of **11**, see: Shoppee, C. W.; Summers, G. H. R. *J. Chem. Soc.* **1952**, 3361.
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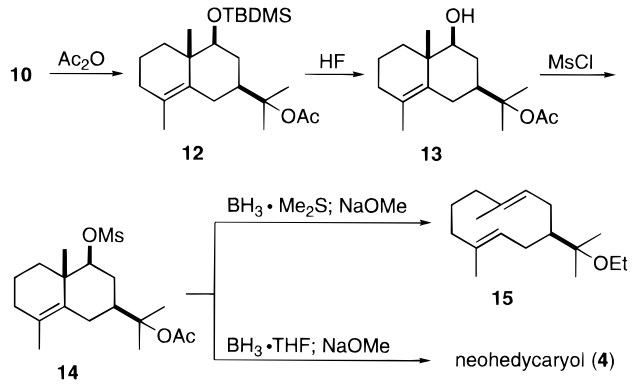
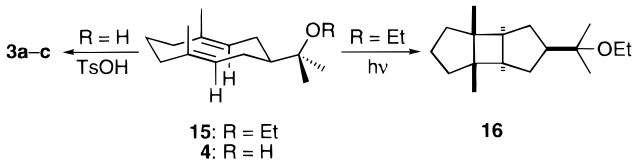
Scheme 6



Scheme 7



caryol.[43] However, successive treatment of **14** with BH_3•Me_2S and NaOMe in MeOH gave, instead of expected **4**, the corresponding ethyl ether **15** as the sole product in moderate yield (36%). Apparently, the C(11) acetate group was reduced to the corresponding ethyl ether.[44] In order to minimize the reduction of the acetate group, **14** was treated with BH_3•THF at 0 °C for only a relatively short time. In this way, after treatment with NaOMe in MeOH, a complex mixture of **4** and several unidentified products was obtained. Fortunately, isolation of pure **4** from this mixture was easily effected with aqueous $AgNO_3$ extraction.[45] Although the yield of **4** was poor (11%),[46] all spectral and chromatographic data including the Kováts indices[47] could be obtained.

The ^{1}H NMR spectrum of **4** points to the preference for one distinct conformation. From its ^{13}C NMR spectrum, it follows that **4** possesses a symmetry plane which means that the crossed conformations (see Scheme 3) can be excluded. The UV spectrum of **4**, in which the absorption maximum at <200 nm shows strong tailing toward the red (270 nm), is in line with this conclusion.[48] The formation of a 1:2:1 mixture of α-, β-, and γ-eudesmol, respectively, upon treatment of **4** with TsOH in CH_2Cl_2 proved that **4** reacts exclusively from the elongated chair conformation (Scheme 7).[49] The NMR data and the almost quantitative formation of **16** upon irradiation (3.5 h) of **15** in MeCN solution with a low-pressure Hg lamp indicate that **15** also exists in the elongated chair conformation.[50]

Concluding Remarks

These findings show that neohedycaryol (**4**) preferentially exists in the elongated chair conformation at room temperature. Consequently, its cyclization can only result in the usual stereochemistry of eudesmanes found in higher plants as confirmed by the formation of α-, β-, and γ-eudesmol upon acid treatment. For this reason, **4** is a less likely precursor in the biosynthesis of *epi*-eudesmanes and probably also of agarofurans.

The preferred elongated chair conformation further indicates that **4** occupies the meso form. As a consequence, **4** can only produce racemic eudesmanes under nonenzymatic circumstances, while pure enantiomers may be generated enzymatically. If both pathways are followed in biosynthesis, then enantiomeric mixtures of eudesmanes with one enantiomer in excess will be formed. The cooccurrence of both enantiomers of eudesmanes in the same plant supports this hypothesis.[51] It is therefore tempting to consider the possibility that **4** may be a direct *in vivo*-formed precursor[52] of both *ent*- and usual eudesmanes and not, as argued above, of *epi*-eudesmanes.

Experimental Section[53]

Materials. All reagents were purchased from Aldrich or Janssen except for *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidic chloride (TMPDCl) which was purchased from Fluka. 2-Methyl-5-(1-methylethenyl)-1,3-cyclohexanedione[27] and compound **6**[29,54] have been characterized before.

2-Methyl-5-(1-methylethenyl)-1,3-cyclohexanedione. Epoxycarvone (46 g, 277 mmol) was treated with 1 M aqueous NaOH at 65 °C for 65 min following a previously described procedure.[27] After workup, the remaining residue was dried in a vacuum desiccator on P_2O_5 overnight to give 44 g (96%) of 2-methyl-5-(1-methylethenyl)-1,3-cyclohexanedione (GC purity 98%). Its spectroscopic data corresponded with those reported in the literature.[27]

***cis*-(±)-3,4,8,8a-Tetrahydro-5,8a-dimethyl-3-(1-methylethenyl)-1,6-(2*H*,7*H*)-naphthalenedione (6).** A 3:2 mixture of two epimeric triketones was prepared in 81% yield from 2-methyl-5-(1-methylethenyl)-1,3-cyclohexanedione and EVK as described.[29] To a solution of 17.3 g (69.2 mmol) of this mixture in 125 mL of benzene was added 0.81 mL (9.8 mmol) of pyrrolidine. The reaction mixture was heated at reflux and, after 7 and 18 h, two other 0.81 mL portions of pyrrolidine were added. The total reflux time amounted to 4 d. The mixture was allowed to come to rt, poured into water, and extracted with petroleum ether (bp 40−60 °C). The combined organic layers were washed successively with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. After drying and evaporation, the remaining residue was flash chromatographed [15% EtOAc in petroleum ether (bp 40−60 °C)] to give 6.1 g (38%) of **6**. The spectroscopic data of **6** corresponded with those reported in the literature.[29,54]

(43) It was expected that the use of NaOMe in the Marshall fragmentation reaction would lead to cleavage of the acetate ester bond.

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(45) Southwell, I. A. *Phytochemistry* **1970**, *9*, 2243.

(46) The Marshall fragmentation reaction of a mesylate similar to **14** but lacking the C(7) substituent also proceeded in low yield (25%), see reference 35.

(47) The Kováts indices in combination with GC-MS may be very helpful to detect **4** in complex mixtures of natural origin.

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(52) A simple double bond isomerization from (+)-hedycaryol (**1**) to neohedycaryol (**4**) can occur with negligible steric complaint.[16]

(53) For a general description of the experimental procedures employed in this research, see: Kesselmans, R. P. W.; Wijnberg, J. B. P. A.; Minnaard, A. J.; Walinga, R. E.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 7237. NMR spectra were recorded at 200 MHz (^{1}H) and 50 MHz (^{13}C) in $CDCl_3$, unless otherwise reported. Kováts indices were determined on a gas chromatograph equipped with a J&W DB-1 column (60 m × 0.25 mm i.d., film thickness 0.25 μm) and a Restek Stabilwax column (60 m × 0.25 mm i.d., film thickness 0.25 μm). Split ratio 1:100, carrier gas H_2, inlet pressure 20 psi, linear velocity 35 cm/s; temperature program 50 °C (0 min hold) to 238 °C (8 min hold) at 4 °C/min; injector temperature 220 °C; detector temperature 260 °C; FID detection. Column chromatography was performed using Baker neutral alumina (activity grade III).

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(±)-(4aα,5α,7α)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-7-(1-methylethenyl)-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-2(3*H*)-naphthalenone (7). After reduction of **6** with $NaBH_4$ following a previously described procedure,[30] the resulting alcohol (8.82 g, 37.7 mmol) was added to a solution of 6.42 g (94.4 mmol) of imidazole and 7.08 g (46.9 mmol) of TBDMSCl in 50 mL of DMF. The mixture was stirred at rt for two d and then poured into 200 mL of water. After extraction with petroleum ether (bp 40−60 °C), the combined organic layers were washed with brine and dried. Flash chromatography [5% EtOAc in petroleum ether (bp 40−60 °C)] gave 10.53 g (80%) of **7** as an oil: ^{1}H NMR δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 1.13 (s, 3 H), 1.76 (br s, 6 H), 1.6−1.8 (m, 3 H), 1.99−2.08 (m, 3 H), 2.36−2.44 (m, 2 H), 2.66 (dd, J = 1.6, 9.7 Hz, 1 H), 3.40 (dd, J = 5.1, 10.7 Hz, 1 H), 4.77 (br s, 2 H); ^{13}C NMR δ −4.91 (q), −3.91 (q), 11.30 (q), 16.00 (q), 17.00 (s), 20.41 (q), 25.78 (3q), 32.34 (t), 33.55 (t), 33.89 (t), 35.58 (t), 41.55 (d), 41.97 (s), 78.57 (d), 109.71 (t), 130.21 (s), 147.97 (s), 160.11 (s), 199.10 (s); MS m/z (relative intensity) 291 (M^+ − 57, 100), 211 (39), 75 (20), 73 (27); HRMS calcd for $C_{17}H_{27}O_2Si$ (M^+ − 57) 291.1780, found 291.1780.

(±)-(4aα,5α,7α)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(2-methyloxiran-2-yl)-2(3*H*)-naphthalenone (8). To a stirred solution of 10.5 g (30.2 mmol) of **7** in 360 mL of a 1:1 mixture of CH_2Cl_2 and acetone were added 0.755 g (2.86 mmol) of 18-crown-6 and a solution of 11.5 g (137 mmol) of $NaHCO_3$ in 200 mL of water. The mixture was cooled to 0 °C, and a solution of 20.7 g (33.6 mmol) of Oxone in 100 mL of water was added dropwise. The reaction mixture was vigorously stirred at 0 °C for 3 h and then treated with an excess of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ for 20 min. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried, and evaporated to afford 11.0 g of crude **8**, which was used directly for the next step. A sample (0.125 g, 0.34 mmol) of crude **8** was flash chromatographed [10% EtOAc in petroleum ether (bp 40−60 °C)] to give 0.115 g (93%) of **8** as a 1:1 mixture of diastereomers: ^{1}H NMR δ 0.01 (s, 3 H), 0.04 (s, 3 H), 0.86 (s, 9 H), 1.10 (s, 3 H), 1.30 (s, 3 H), 1.75 (br s, 3 H), 1.2−2.1 (m, 6 H), 2.35−2.42 (m, 2 H), 2.57−2.72 (m, 3 H), 3.34 (dd, J = 4.7, 10.7 Hz, 1 H); ^{13}C NMR δ −4.93 (q), −3.90 (q), 11.32 (q), 15.93 (q), 17.87 (q), 17.97 (s), 18.12 (q), 25.77 (3q), 28.87 (t), 29.33 (t), 32.26 (t), 32.75 (t), 33.49 (t), 33.81 (t), 40.35 (d), 40.57 (d), 42.06 (s), 53.13 (t), 53.32 (t), 58.49 (s), 78.12 (d), 130.40 (s), 130.66 (s), 159.04 (s), 198.86 (s); MS m/z (relative intensity) 307 (M^+ − 57, 46), 249 (98), 227 (35), 215 (40), 204 (44), 86 (52), 75 (94), 73 (100); HRMS calcd for $C_{17}H_{27}O_3Si$ (M^+ − 57) 307.1730, found 307.1731.

(±)-(2α,4aα,5α,7α)-2,3,4,4a,5,6,7,8-Octahydro-1,4a-dimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(2-methyloxiran-2-yl)-2-naphthalenol (9). To a stirred solution of 8.34 g (32.8 mmol) of Li(*t*-BuO)$_3$AlH in 100 mL of THF was added dropwise a solution of 3.27 g (8.98 mmol) of **8** in 60 mL of THF at 0 °C. After being stirred at rt for 1.5 h, the reaction mixture was quenched with 13.5 g of $Na_2SO_4 \cdot 10H_2O$ followed by the addition of 2 mL of water and excess $MgSO_4$. The mixture was stirred for an additional 0.5 h and filtered. The filtrate was evaporated, and the remaining residue was purified by flash chromatography [15% EtOAc in petroleum ether (bp 40−60 °C)] to give 2.85 g (87%) of **9** as a 1:1 mixture of diastereomers: ^{1}H NMR δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 0.99 (s, 3 H), 1.28 (br s, 3 H), 1.0−2.4 (m, 12 H), 2.35−2.62 (m, 3 H), 3.24 (dd, J = 4.7, 10.7 Hz, 1 H), 3.94 (m, 1 H); ^{13}C NMR δ −4.90 (q), −3.88 (q), 15.55 (q), 18.02 (q), 18.15 (s), 18.29 (q), 25.81 (3q), 26.96 (t), 27.45 (t), 28.39 (t), 31.74 (t), 32.76 (t), 33.25 (t), 41.31 (s), 41.74 (d), 41.91 (d), 53.43 (t), 58.87 (s), 70.90 (d), 76.99 (d), 79.42 (d), 129.88 (s), 129.96 (s), 137.00 (s); MS m/z (relative intensity) 309 (M^+ − 57, 5), 291 (40), 227 (89), 177 (46), 159 (51), 75 (65), 73 (100); HRMS calcd for $C_{17}H_{29}O_3Si$ (M^+ − 57) 309.1886, found 309.1884.

(±)-(2α,4α,4aα)-1,2,3,4,4a,5,6,7-Octahydro-α,α,4a,8-tetramethyl-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-naphthalenemethanol (10). To a stirred solution of 0.746 g (2.04 mmol) of **9** in a mixture of 16 mL of THF and 4 mL of TMEDA was added 2.84 mL of BuLi (1.6 M in hexane) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, and then 2.4 mL (16.0 mmol) of TMPDCl was added. After stirring at −78 °C for another 5 min, the reaction mixture was allowed to come to rt and stirred for an additional 1 h. The reaction mixture was then slowly added, via syringe, to a solution of 0.90 g (129 mmol) of Li in 50 mL of $EtNH_2$ at 0 °C. After stirring at 0 °C for 1 h, 20 mL of saturated aqueous NH_4Cl was added and $EtNH_2$ was allowed to evaporate by standing at rt overnight. The remaining layer was extracted with ether, and the combined organic layers were washed with brine, dried, and evaporated. Flash chromatography [10% EtOAc in petroleum ether (bp 40−60 °C)] gave 0.63 g (88%) of **10**:[55] ^{1}H NMR δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.88 (s, 9 H), 0.94 (s, 3 H), 1.18 (s, 6 H), 1.60 (br s, 3 H), 1.2−2.0 (m, 11 H), 2.54 (ddd, J = 2.4, 2.4, 13.4 Hz, 1 H), 3.26 (dd, J = 4.6, 10.8 Hz, 1 H); ^{13}C NMR δ −4.83 (q), −3.87 (q), 14.08 (s), 18.02 (2q), 18.86 (t), 19.72 (q), 25.59 (t), 25.87 (3q), 26.79 (q), 32.36 (t), 33.14 (t), 36.72 (t), 41.52 (s), 46.71 (d), 72.26 (s), 79.44 (d), 126.88 (s), 133.51 (s); MS m/z (relative intensity) 352 (M^+, 1), 293 (52), 229 (31), 203 (100), 161 (51), 147 (31), 73 (61), 59 (12); HRMS calcd for $C_{21}H_{40}O_2Si$ (M^+) 352.2798, found 352.2795.

(±)-(2α,4α,4aα)-1,2,3,4,4a,5,6,7-Octahydro-4-hydroxy-α,α,4a,8-tetramethyl-2-naphthalenemethanol (11). To a stirred solution of 0.62 g (1.76 mmol) of **10** in 10 mL of DMSO was added 4 mL of TBAF (1 M in THF). The reaction mixture was placed in an oil bath of 100 °C and stirred for 45 min. The resulting brown mixture was cooled to rt and poured into 120 mL of water. The mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried, and evaporated. Flash chromatography [30% EtOAc in petroleum ether (bp 40−60 °C)] and crystallization from EtOH gave 0.310 g (74%) of pure **11**: mp 147 °C; ^{1}H NMR δ 0.98 (s, 3 H), 1.27 (s, 6 H), 1.62 (br s, 3 H), 1.27−2.0 (m, 12 H), 2.58 (ddd, J = 2.6, 2.6, 13.8 Hz, 1 H), 3.32 (dd, J = 4.5, 10.9 Hz, 1 H); ^{13}C NMR δ 17.68 (q), 18.77 (q), 19.81 (t), 25.58 (t), 26.86 (q), 27.28 (q), 31.70 (t), 33.02 (t), 36.20 (t), 40.06 (s), 46.89 (d), 72.38 (s), 79.31 (d), 127.51 (s), 132.93 (s); MS m/z (relative intensity) 238 (M^+, 100), 223 (47), 195 (50), 187 (33), 159 (40), 147 (33), 145 (30), 105 (39), 59 (34). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.55; H, 11.21.

(±)-(2α,4α,4aα)-[1,2,3,4,4a,5,6,7-Octahydro-α,α,4a,8-tetramethyl-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-naphthalenyl]methyl Acetate (12). To a stirred solution of 0.324 g (0.93 mmol) of **10** in 3 mL of Et_3N was added 0.26 mL (2.80 mmol) of Ac_2O followed by 0.010 g (0.08 mmol) of DMAP at 0 °C. The mixture was allowed to come to rt, stirred for two d, and then poured into water. After extraction with EtOAc, the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. Flash chromatography [2% EtOAc in petroleum ether (bp 40−60 °C)] gave 0.303 g (82%) of **12** as an oil: ^{1}H NMR δ 0.00 (s, 6 H), 0.87 (s, 9 H), 0.92 (s, 3 H), 1.40 (s, 3 H), 1.42 (s, 3 H), 1.58 (br s, 3 H), 1.1−1.7 (m, 7 H), 1.8−2.05 (m, 3 H), 2.02 (s, 3 H), 2.42 (ddd, J = 2.3, 2.3, 10.5 Hz, 1 H), 3.26 (dd, J = 4.7, 10.8 Hz, 1 H); ^{13}C NMR δ −4.79 (q), −3.91 (q), 18.06 (q), 18.06 (s, obscured), 18.90 (t), 19.71 (q), 22.43 (q), 23.43 (q), 23.47 (q), 25.50 (t), 25.92 (3q), 32.15 (t), 33.18 (t), 36.67 (t), 40.68 (s), 43.63 (d), 79.18 (d), 84.49 (s), 127.28 (s), 133.10 (s), 170.34 (s); MS m/z (relative intensity) 334 (M^+ − 60, 34), 277 (100), 229 (24), 211 (20), 203 (80), 161 (29), 75 (27), 73 (32); HRMS calcd for $C_{21}H_{38}OSi$ (M^+ − 60) 334.2692, found 334.2689.

(±)-(2α,4α,4aα)-[1,2,3,4,4a,5,6,7-Octahydro-4-hydroxy-α,α,4a,8-tetramethyl-2-naphthalenyl]methyl Acetate (13). To a stirred solution of 0.349 g (0.89 mmol) of **12** in 4 mL of MeCN was added two drops of 40% aqueous HF every hour over a period of 6 h. After this time, the reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. After drying and evaporation, the remaining residue was flash chromatographed [30% EtOAc in petroleum ether (bp 40−60 °C)] to give 0.193 g (78%) of **13** as an oil: ^{1}H NMR δ 0.98 (s, 3 H), 1.44 (s, 6 H), 1.60 (br s, 3 H), 1.98 (s, 3 H), 1.2−2.1 (m, 11 H), 2.47 (br d, J = 13.2 Hz, 1 H), 3.33 (dd, J = 4.3, 11.3 Hz, 1 H); ^{13}C NMR δ 17.67 (q), 18.72 (t), 19.69 (q), 22.44 (q), 23.41 (2q), 25.31 (t), 31.27 (t), 32.96

(55) GC analysis revealed the presence of a small amount (<10%) of another compound, probably a double bond isomer of **10**.

(t), 36.12 (t), 40.07 (s), 44.03 (d), 78.96 (d), 84.25 (s), 127.72 (s), 132.46 (s), 170.50 (s); MS *m/z* (relative intensity) 220 (M^+ − 60, 100), 202 (19), 187 (23), 177 (23), 173 (16), 159 (22), 107 (16), 69 (30), 43 (16); HRMS calcd for $C_{15}H_{24}O$ (M^+ − 60) 220.1827, found 220.1829.

(±)-(2α,4α,4aα)-[1,2,3,4,4a,5,6,7-Octahydro-α,α,4a,8-tetramethyl-4-[(methylsulfonyl)oxy]-2-naphthalenyl]methyl Acetate (14). To a stirred solution of 0.089 g (0.32 mmol) of **13** in 2 mL of pyridine was added 0.037 mL (0.48 mmol) of MsCl at 0 °C. The mixture was allowed to come to rt, stirred for 50 min, and poured into water. After extraction with petroleum ether (bp 40−60 °C), the combined organic layers were washed with brine, dried, and evaporated. Removal of residual pyridine by azeotropic distillation with toluene afforded 0.101 g (88%) of almost pure **14**: ^{1}H NMR (C_6D_6) δ 1.09 (s, 3 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.54 (br s, 3 H), 1.72 (s, 3 H), 1.2−2.3 (m, 10 H), 2.31 (s, 3 H), 2.44 (br d, J = 13.2 Hz, 1 H), 4.42 (dd, J = 4.8, 11.2 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 18.42 (q), 18.65 (t), 19.48 (q), 21.56 (q), 23.03 (2q), 24.99 (t), 29.91 (t), 32.75 (t), 36.01 (t), 37.67 (q), 39.64 (s), 44.12 (d), 82.76 (s), 88.29 (d), 128 (s, obscured), 131.00 (s), 169.5 (s); MS *m/z* (relative intensity) 298 (M^+ − 60, 2), 203 (63), 202 (92), 187 (100), 160 (29), 159 (91), 145 (38), 105 (26), 43 (47); HRMS calcd for $C_{16}H_{26}O_3S$ (M^+ − 60) 298.1603, found 298.1603.

***trans,trans*-α,α,4,8-Tetramethyl-3,8-cyclodecadiene-1-methanol Ethyl Ether (15).** To a stirred solution of 0.101 g (0.28 mmol) of **16** in 3 mL of THF was added 0.75 mL of BH_3·S-$(CH_3)_2$ (2 M in THF) at 0 °C. The reaction mixture was stirred at rt overnight. The resulting white cloudy mixture was cooled to 0 °C, and 1 mL of MeOH was added dropwise, immediately followed by 3 mL of NaOMe (2 M in MeOH). The reaction mixture was allowed to come to rt and stirred overnight. After addition of water, the mixture was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine, dried, and evaporated. Column chromatography (10% *tert*-butyl methyl ether in hexane) gave 0.025 g (36%) of **15**: ^{1}H NMR (C_6D_6) δ 1.13 (s, 6 H), 1.16 (t, J = 6.9 Hz, 3 H), 1.65 (br s, 6 H), 0.9−1.85 (m, 3 H), 2.1−2.56 (m, 8 H), 3.30 (q, J = 6.9 Hz, 2 H), 5.16 (br d, J = 10.8 Hz, 2 H); ^{13}C NMR (C_6D_6) δ 15.86 (2q), 16.13 (q), 17.22 (t), 23.17 (2q), 30.13 (2t), 42.21 (2t), 46.97 (d), 55.60 (t), 76.28 (s), 130.90 (2d), 131.32 (2s); MS *m/z* (relative intensity) 250 (M^+, 14), 204 (72), 189 (51), 175 (25), 161 (75), 96 (62), 87 (100), 59 (70); HRMS calcd for $C_{17}H_{30}O$ (M^+) 250.2297, found 250.2292.

***trans,trans*-α,α,4,8-Tetramethyl-3,8-cyclodecadiene-1-methanol (4).** To a stirred solution of 0.062 g (0.17 mmol) of **14** in 2 mL of THF was added 0.86 mL of BH_3·THF (1 M in THF) at 0 °C. The mixture was allowed to come to rt and stirred for 2 h. After cooling to 0 °C, 1 mL of MeOH was added dropwise and immediately followed by 3 mL of NaOMe (2 M in MeOH). The mixture was allowed to come to rt and stirred overnight. After addition of water, the mixture was extracted with petroleum ether (bp 40−60 °C). The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in 3 mL of *tert*-butyl methyl ether and extracted four times with 2 mL of 20% aqueous $AgNO_3$. The combined aqueous layers were washed with 1 mL of *tert*-butyl methyl ether and cooled to 0 °C. After addition of 10 mL of 25% aqueous NH_3, the mixture was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine, dried, and evaporated to give 0.004 g (11%) of **4**: UV (MeCN) λ_{max} < 200 nm, tail to 270 nm; Kováts indices: 2341 (Stabilwax) and 1689 (DB-1); ^{1}H NMR (C_6D_6) δ 1.07 (s, 6 H), 1.64 (br s, 6 H), 0.75−1.75 (m, 4 H), 2.0−2.55 (m, 8 H), 5.14 (br d, J = 10.8 Hz, 2 H); ^{13}C NMR (C_6D_6) δ 15.84 (2q), 17.13 (t), 27.16 (2q), 30.27 (2t), 42.20 (2t), 50.39 (d), 74.4 (s), 130.67 (2d), 131.33 (2s); MS *m/z* (relative intensity) 222 (M^+, 15), 204 (62), 189 (36), 161 (100), 119 (40), 107 (35), 105 (54), 96 (73), 81 (80), 59 (63), 43 (34); HRMS calcd for $C_{15}H_{26}O$ (M^+) 222.1984, found 222.1977.

(2α,3a*β*,3bα,6aα,6b*β*)-Decahydro-α,α,3b,6a-tetramethylcyclobuta[1,2:3,4]dicyclopentene-2-methanol Ethyl Ether (16). A solution of 0.008 g (0.03 mmol) of **15** in 4 mL of MeCN placed in a sealed quartz cuvet was irradiated for 3.5 h using a CAMAG Universal UV-lamp 29230. The reaction progress was monitored by GC. After completion, the solvent was evaporated to give 0.007 g (90%) of **16** (GC purity >96%): ^{1}H NMR δ 0.87 (s, 6 H), 1.15 (t, J = 7.0 Hz, 3 H), 1.17 (s, 6 H), 0.9−2.05 (m, 13 H), 3.38 (q, J = 7.0 Hz, 2 H); ^{13}C NMR δ 16.24 (q), 18.79 (2q), 23.43 (t), 23.76 (2q), 28.84 (2t), 42.96 (2t), 43.24 (2d), 45.40 (2s), 51.50 (d), 56.00 (t), 75.58 (s); MS *m/z* (relative intensity) 204 (M^+ − 46, 31), 189 (13), 161 (20), 96 (36), 87 (100), 81 (16), 59 (39), 43 (11); HRMS calcd for $C_{16}H_{27}O$ (M^+ − 15) 235.2062, found 235.2057.

α-, *β*-, and *γ*-Eudesmol (3a, 3b, and 3c). To a stirred solution of 0.001 g (0.005 mmol) of **4** in 1 mL of CH_2Cl_2 was added a small crystal of TsOH·H_2O. After stirring at rt for 7 min, the mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, and dried. After evaporation, the remaining residue was analyzed by GC and GC-MS. The product mixture consisted of α-eudesmol (**3a**), *β*-eudesmol (**3b**), and *γ*-eudesmol (**3c**) in a ratio of 1:2:1, respectively.[56] Kováts indices on Stabilwax and DB-1, respectively: **3a** 2224 and 1643; **3b** 2233 and 1638; **3c** 2171 and 1620.

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Supporting Information Available: ^{1}H NMR spectra for compounds **4**, **7**−**10**, and **12**−**16** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(56) Reference 8, van Beek *et al.*