Correction of the Structure of a New Sesquiterpene from *Cistus creticus* ssp. *creticus*

Konstantinos Hatzellis,[†] Georgia Pagona,[†] Apostolos Spyros,[†] Costas Demetzos,*[,‡] and Haralambos E. Katerinopoulos*[,†]

Department of Chemistry, University of Crete, Heraklion 71409, Crete, Greece, and School of Pharmacy, Department of Pharmaceutical Technology, University of Athens, Panepistimiopolis Zografou 15771, Athens, Greece

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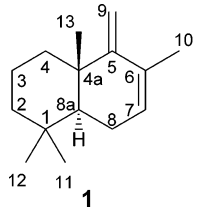
In an attempt to identify the structure of a sesquiterpene from *Cistus creticus* ssp. *creticus* proposed in the literature as 1,1,4a,6-tetramethyl-5-methylene-1,2,3,4,4α,5,8,8α-octahydronaphthalene, the synthesis of its *cis* isomer **2** was carried out in 11 steps and 9.5% yield. Comparison of the spectra of **2** and those reported earlier for the synthetic *trans* isomer **1** with the spectral profile of the isolated natural product indicated that the latter was not compatible with either **1** or **2**. The correct structure was assigned, by detailed spectroscopic analysis of the natural product, as 6-isopropenyl-4,4a-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (**3**).

Cistus creticus ssp. *creticus* (L.) Greuter et Burdet [syn. *Cistus incanus* ssp. *creticus* (L.) Heywood; *Cistus creticus* (L.)] (Cistaceae) is a perennial shrub that grows in the Mediterranean area, especially in Crete.[1−3] During hot summer days its leaves secrete a thick, aromatic resin, called by the locals "ladano".[2,3] The resin has been used in folkloric medicine as an anticancer agent since ancient times.[4] This traditional use was supported by a recent study[5] indicating that its major labdane-type components extracted from the plant exhibited strong cytotoxic activity. Another major component was isolated from the essential oil of the resin and assigned the structure of a new drimane-type sesquiterpene,[6] namely, 1,1,4a,6-tetramethyl-5-methylene-1,2,3,4,4a,5,8,8a-octahydronaphthalene (drima-7,9(11)-diene, following drimane carbon framework numbering).



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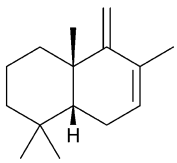

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The stereochemistry at the fusion of the decalin ring was tentatively assigned as *trans*. However, subsequent publications reported the isolation of the *trans* isomer **1** as a byproduct in the synthesis of structurally related natural products.[7−9] The spectral (^{1}H and ^{13}C NMR) characteristics of synthetic **1** were clearly different than those of the natural product.[6] We therefore undertook the total synthesis of the *cis* compound **2** with the purpose of comparing its spectral profile with that of the natural product and studying its cytotoxic activity. From the synthetic point of view, the project also led to the development of a flexible synthetic pathway toward the target molecule which, upon simple synthetic modifications, would lead to both *cis*/*trans* isomers. Asymmetric synthesis of the target was not considered necessary at that point given that the spectral data of the racemic mixture were sufficient to indicate structural differences of the synthetic and natural product.

Results and Discussion

The synthetic pathway, depicted in Scheme 1, involves initial selective protection of the (±) Wieland-Miescher ketone (**4**) to monoketal **5**. Although a number of conditions have been, even recently, reported in the literature,[10−14] we performed the reaction in benzene using 1 equiv of PTSA, and 10 equiv of ethylene glycol at 60 °C for 4 h. The use of a Dean−Stark trap was not necessary under these conditions, which gave **5** in 84−88% yield. Subsequent C-1 dimethylation[15] using *t*-BuOK/*t*-BuOH and MeI (0 °C, 75 min) produced **6** in 74% yield. Huang−Minlon reduction of the ketone group[14] ($H_2NNH_2 \cdot H_2O$, DEG, 120 °C, 2.5 h, then KOH 170−245 °C, 4 h, 94%) followed by hydrolysis of ketal **7** (PPTS, EtOH/H_2O, 9:1, 99%) furnished **8**,[16] as the common intermediate to both *cis* and *trans* decalin systems. It was realized that the problem of the ring fusion stereochemistry should be dealt with at this early stage of the synthesis. Given that the decalin framework was already present in the starting material, stereoselective cyclization[17−20] was not a feasible alternative, and therefore the *cis* or *trans* disposition of the decalin system would be arranged via face-selective reactions, possibly through the reduction of similar-structure substrates incorporating the $\Delta^{4,4a}$ olefinic moiety.

On the basis of the rationale put forth above the olefinic bond in **8** was catalytically reduced (H_2, 10%Pd/C, EtOH, 3.5 h), yielding, as expected from literature precedents,[21] *cis* decalone **9** as the major product (90%) together with 8% of the *trans* isomer **12**. It was anticipated that exposure of the hindered face of the $\Delta^{4,4a}$ double bond in **8** would be achieved through relief of the additional strain imposed by the carbonyl moiety, i.e., by altering the sp^2 hybridization in C-1 to sp^3. Indeed, carbonyl reduction in **8** ($NaBH_4$) furnished the corresponding alcohol **10**[22] in 88% yield. Catalytic reduction of **10b** under identical conditions as mentioned above yielded compound **11**[22] (95%), which was transformed by Jones oxidation to the desired *trans* decalone **12**[22,23] (91%), containing only 1.5% of the inseparable *cis* isomer **9**. MS as well as NMR spectra confirmed the difference in stereochemistry in structures **9** and **12**. A clear

* To whom correspondence should be addressed. (H.E.K.) Tel: +30 2810 393 626. Fax: +30 2810 393 601. E-mail: kater@chemistry.uoc.gr, and (C.D.) Fax: +301-210-7274596. E-mail: demetzos@pharm.uoa.gr.
[†] University of Crete.
[‡] University of Athens.

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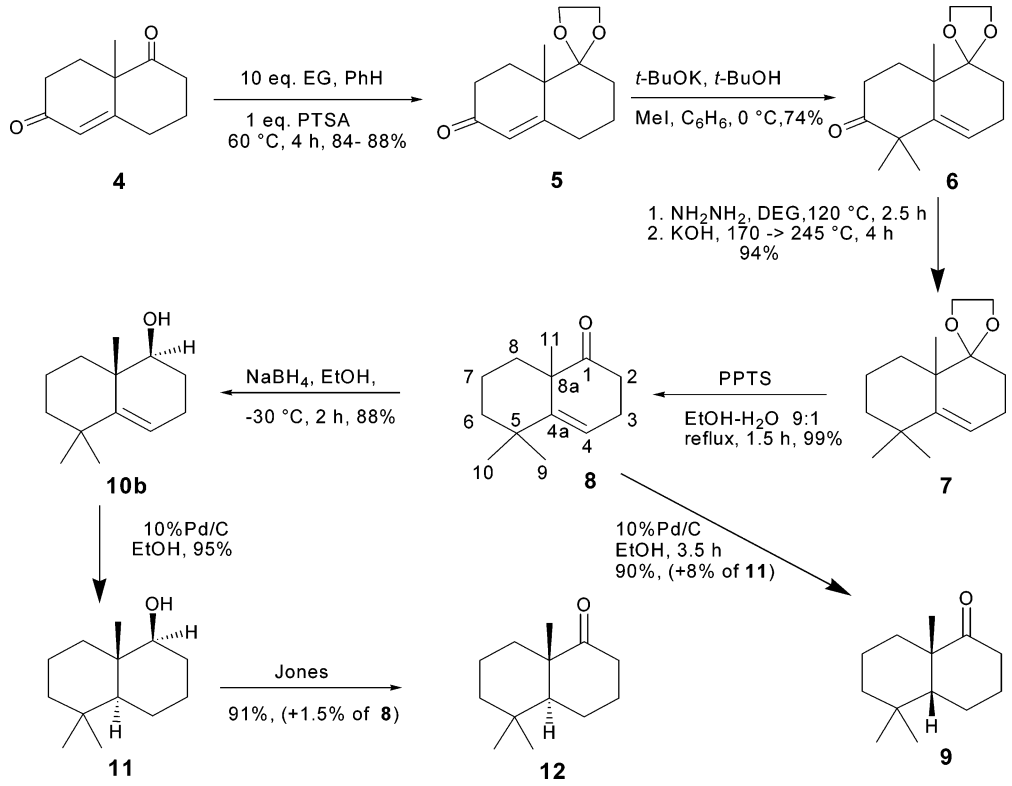
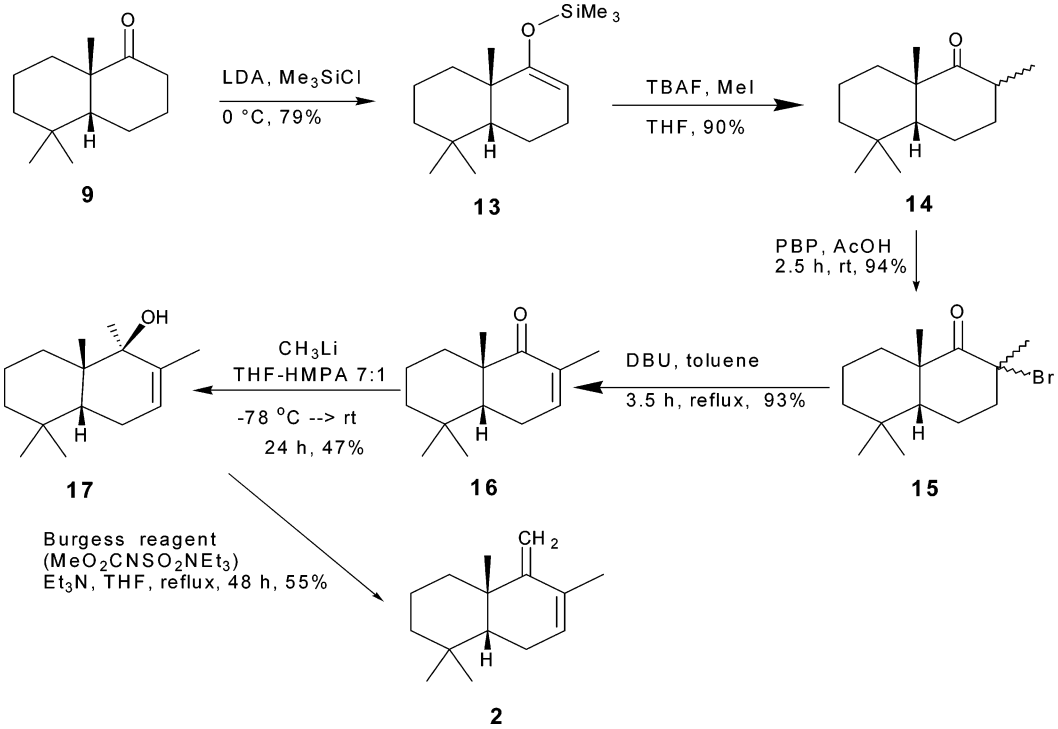
Scheme 1. Synthetic Pathway to *cis, trans* Isomers **9** and **12**



Scheme 2. Synthetic Pathway to *cis* Drimane Sesquiterpene **2**



indication of the *cis* fusion of the decalin rings in **9** came from its NOESY spectrum, which shows an interaction between the C-4a methine and the C-11 methyl protons; such an interaction is absent in the corresponding spectrum of **12**.

The problem of the diastereoselective synthesis of the ketone intermediates being solved, and given that the spectral profile of the *trans* drimanediene **1** was known,[7–9] we focused on the synthesis of the *cis* diastereomer (Scheme 2). Following a literature procedure,[22b] the methylation of **9** was carried out by initial silylation of the corresponding enolate **13** (THF, LDA, Me_3SiCl, 79%). It is worth noting that at this point the diastereomeric *trans* impurity was separable and the synthesis was continued with the pure *cis* isomers in hand. Deprotection[22b] of the enolate by anhydrous $C_6H_5CH_2N(CH_3)_3F$ in the presence of MeI in THF furnished a diastereomeric mixture of the α-methylated ketones **14** in 90% yield. Bromination (pyridinium bromide perbromide (PBP), AcOH, rt, 2.5 h, 94%) and subsequent dehydrohalogenation[22b,24] (DBU, toluene, 110

Table 1. NMR Data for Compound **3**[a]

position	proton[b]	δ^1H	COSY	NOESY	δ^{13}C	HBMC
1	H-1	1.64 (m)	H-2, H-2′, H-12	H-7, H-8	38.71	H-2, H-2′, H-8′, H-13
2	H-2	1.49 (m)	H-1, H-2′, H-3′		31.40	H-12
	H-2′	1.39 (m)	H-1, H-2, H-3, H-3′	H-13		
3	H-3	1.76 (m)	H-3′, H-4′		29.26	H-2′, H-4′
	H-3′	1.28 (m)	H-2, H-2′, H-3, H-4, H-4′			
4	H-4	1.90 (m)	H-3′, H-4′	H-5	32.30	H-3, H-5
	H-4′	2.17 (m)	H-3, H-3′, H-4	H-13		
4a					146.39	H-13, H-1, H-3, H-3′, H-4, H-4′, H-6, H-6′, H-8′
5	H-5	5.33 (brd, 6.0)	H-6, H-6′	H-4	117.90	H-4, H-4′, H-6, H-6′, H-8′
6	H-6	1.98 (m)	H-5, H-6′, H-7		31.50	H-8, H-8′, H-5
	H-6′	1.84 (m)	H-5, H-6, H-7			
7	H-7	2.12 (brd, 13.0)	H-6, H-6′, H-8′	H-1	37.71	H-5, H-8′, H-10
8	H-8	1.90 (brd, 13.0)	H-8	H-12	39.65	H-7, H-13
	H-8′	1.11 (dd, 13.0,13.0	H-7, H-8	H-13		
8a					39.43	H-1, H-5, H-13
9					150.29	H-7, H-8, H-8′, H-10, H-11
10	H-10	1.72 (s)	H-11	H-11	21.09	H-7, H-11
11	H-11	4.70 (bs)	H-10	H-10	108.26	H-7, H-10
	H-11′	4.71 (bs)	H-10	H-10		
12	H-12	0.78 (d,7.0)	H-1	H-13, H-8	20.77	H-1, H-2, H-2′
13	H-13	0.91 (s)		H-12S, H-2′, H-4′, H-8	15.76	H-1, H-8

[a] All spectra were recorded on a Bruker AMX 500, in $CDCl_3$. Chemical shifts are expressed in ppm, and J values in parentheses are in Hz. [b] In proton numbering, protons at pseudoaxial positions are denoted with prime symbol (′).

°C, 3.5 h) of the resulting α-bromoketones **15** yielded α,β-unsaturated ketone **16** in 93% yield.

Conversion of **16** to the desired diastereomer **2** was troublesome[25] since a number of attempts using Wittig-type reaction[26−30] conditions either failed or gave the product in small yields together with a number of inseparable byproducts (data not shown). A dimethyltitanocene methylenation reaction[31,32] was also fruitless. A two-step sequence involving attack of the carbonyl function by methyllithium (MeLi, THF/HPMA, 7:1, −78 °C → rt, 24 h) and dehydration of tertiary alcohol **17** using the Burgess reagent[33,34] ($MeO_2CNSO_2NEt_3$, THF, Et_3N, 65 °C, 48 h) gave **2** in 26% yield from **16**. A small amount of an isomeric impurity was detected by GC/MS analysis after workup of the reaction mixture. Studies of the spectral profile of **2** indicated that mass spectra as well as ^{1}H NMR and ^{13}C NMR data showed clear and distinct differences from those of the natural product.[6,35] We were therefore prompted to reinvestigate the structure of the natural product in greater detail by means of NMR and mass spectra analysis.

Following the published procedure[6] we were able to isolate from the methanol extract of the resin a 10 mg sample of the natural product, whose mass spectrum was identical to that reported in the literature.[6,35] The molecular ion at *m/z* 204 suggested a molecular formula of $C_{15}H_{24}$. Analysis of the ^{1}H NMR spectrum of the compound revealed the presence of three methyl groups appearing as two singlets at 1.72 and 0.91 ppm and a doublet at 0.78 ppm, indicating that the latter is connected to a tertiary carbon atom. In earlier ^{1}H NMR studies,[6] overlap of the doublet at 0.78 ppm with an aliphatic proton peak of an unidentified impurity, still present as a trace in our samples, gave the erroneous impression of the presence of two methyl groups. In agreement with the initial report, two olefinic-proton resonances were observed, with one an exocyclic methylene occurring as two broad singlets at 4.71 and 4.70 ppm, and the second, apparently of an endocyclic double bond, as a broad doublet at 5.33 ppm. These assignments were verified by the ^{13}C NMR spectrum showing the corresponding carbons at 108.26 and 117.90 ppm, respectively. Analysis of the ^{13}C DEPT subspectra indicated that the former carbon was secondary, with the latter being tertiary. Two more (quaternary) olefinic carbons appeared in the ^{13}C NMR spectrum at 150.29 and 146.39 ppm. With an unsaturation degree of 4, the structure was suggested to contain two rings and two double bonds. In total, the ^{13}C NMR spectrum along with the DEPT experiments indicated the presence of three quaternary, three methine, six methylene, and three methyl carbons. Using the above-mentioned information as well as the data from the COSY, HMQC, ^{1}H−^{1}H NOESY, NOE enhancement, and ^{1}H−^{13}C HMBC long-range coupling NMR spectra presented in Table 1, we assigned the structure of the new natural product as an eremophilene isomer, namely, 1,8a-dimethyl-7-(1-methylethenyl)-1,2,3,4,6,7,8,8a-octahydronaphthalene (**3**) (Figure 1) in the following manner. The third quaternary carbon (39.43 ppm) was assigned as C-8a, a ring fusion carbon connected to the C-13 methyl. The tertiary carbon, connected to the second (C-12) methyl group, was assigned as C-1. This carbon also exhibited a strong long-range coupling with the H-13 protons, indicating the proximity of the two methyl groups. Long-range interaction of the third methyl carbon (C-10) with the exocyclic methylene C-11 protons as well as the C-7 methine proton suggested the presence of an isopropenyl substituent, with C-9 being one of the quaternary olefinic carbons. The second quaternary olefinic carbon, with a strong long-range coupling with the H-13 methyl protons, was therefore assigned as C-4a, the second ring fusion carbon. Results from the COSY experiment were in agreement with this assignment, establishing the presence of two isolated ring systems, namely, H-1−(2,2′)−(3,3′)−(4,4′) and H-5−(6,6′)−7−(8,8′). The use of 1D NOE spectra was instrumental in differentiating the overlapping H-4 and H-8 protons.

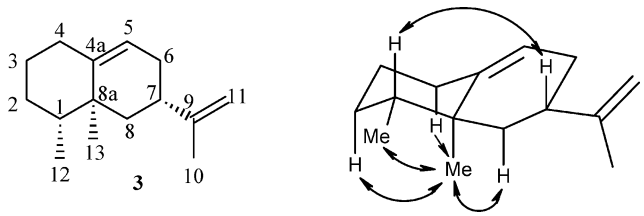


Figure 1. Structure of eremophilene isomer **3** and its key NOE correlations.

The relative configuration of the three substituents was deduced by the following observations. The resonance of axial proton H-8′ appears as a pseudotriplet (doublet of doublets) due to J-coupling with protons H-8 and H-7 with $^2J_{8,8'} = {}^3J_{7,8'} = 13$ Hz. The latter value corresponds to a

trans-diaxial conformation for H-8′ and H-7 and suggests a pseudoequatorial orientation for the isopropyl group, positioning it on the same side with H-8′. The observation is in agreement with dihedral angle values from theoretical calculations.[36] The strong NOE observed between methyl protons H-12 and H-13 established the proximity of the two methyl groups in space. Since H-8′ showed a strong NOE effect with H-13, it was concluded that H-13 is pseudoaxial, and all three substituents adopt a *syn* configuration. The observation of a strong H-7/H-1 NOE interaction verified that the proposed structure of **3** is correct, since this is the only configuration that brings H-1 and H-7 in close proximity.

The relative configuration being established, we were able to define absolute configuration of **3** using literature data. The proposed structure has been mentioned in the literature as synthetic intermediate in reactions involving the known eremophilane carbon framework.[37,38] Although the ^{1}H NMR data were incomplete, ^{13}C NMR values reported by Itokawa et al.[38] were in perfect agreement with our data. A value of $[\alpha]^{25}_D$ +12.5° (*c* 2.5, $CHCl_3$) compared to the reported $[\alpha]^{25}_D$ −11.1° (*c* 0.18, $CHCl_3$)[38] suggests that **3** is the enantiomer of the compound reported by Itokawa et al.

Prompted by the fact that major, labdane-type components extracted from *Cistus creticus* ssp. *creticus* exhibited strong cytotoxic activity, we investigated the cytotoxic activity of sesquiterpene **3** in three human cancer cell lines—MCF7 (breast cancer), H460 (non small cell lung cancer), and SF268 (central nervous system)—and in resting or activated normal human peripheral blood mononuclear cells (PBMCs) isolated from healthy human donors. Compound **3** exhibited low activity, reducing the growth rate of MCF7 and H460 to 93.6% and 80.8%, respectively, compared to the untreated cells after a 48 h continuous incubation and was found not toxic against SF268 and PBMCs at concentrations as high as 100 μM.

In conclusion, in this report we presented the total synthesis of *cis*-drima-7,9(11)-diene (**2**), proposed as a component from *Cistus creticus* ssp. *creticus*. We also developed a common synthetic pathway, using an "unfolding of structure" approach that could eventually lead to both *cis* (**2**) and *trans* (**1**) isomers of this drimane sesquiterpene, as well as numerous *cis*/*trans* analogues. Excluding, by both synthetic means and literature data, the possibility that the natural product is either **1** or **2**, we were also able to assign its correct structure **3** via spectroscopic analysis. Compound **3** exhibited limited cytotoxic activity when tested against three human cancer cell lines.

Experimental Section

General Experimental Methods. Solvents were dried and freshly distilled under argon before use. All reactions were performed under argon atmosphere. Thin-layer chromatography was performed on precoated TLC plates (silica gel). Flash chromatography was carried out with silica gel 60 (particle size 0.040−0.063 mm). Melting points are uncorrected. NMR spectra were recorded at 500 MHz on a AMX 500 Bruker instrument. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in parts per million downfield from TMS as an internal standard. GC/MS spectra were recorded on a Schimadzu GC/MS-QP5050A instrument.

Preparation of 1,1-Ethylenedioxy-8a-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene (5). In a two-neck 250 mL round-bottomed flask were placed compound **4** (2.0 g, 11.23 mmol), benzene (100 mL), and ethylene glycol (8.5 mL, 152.3 mmol) followed by PTSA·H_2O (2.13 g, 11.23 mmol). The solution was heated at 60 °C for 3.5 h. A saturated solution of $NaHCO_3$ was added to the system, and the organic solvent was removed in vacuo. Diethyl ether (50 mL) was added to the system, the aqueous layer was separated and extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with water (3 × 20 mL) and saturated NaCl solution (2 × 10 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo to give 2.45 g (98%) of the crude product, which was purified by flash chromatography (ether/pet. ether, 20−60%). The yield of the pure product was 2.1 g (84%): ^{1}H NMR data of **5** ($CDCl_3$) δ 1.36 (3H, s), 1.67−1.73 (3H, m), 1.78−1.80 (1H, m), 1.87−1.93 (1H, m), 2.26−2.36 (2H, m), 2.39−2.46 (3H, m), 3.94−4.00 (4H, O−CH_2CH_2−O, m), 5.81 (1H, C=C−H, s); MS *m/z* 222 $[M]^+$.

Preparation of 1,1-Ethylenedioxy-5,5,8a-trimethyl-1,2,3,5,6,7,8,8a-octahydro-6-oxonaphthalene (6). In a two-neck 250 mL round-bottomed flask were placed benzene (60 mL), *t*-BuOH (40 mL), and *t*-BuOK (5.04 g, 45 mmol), and the system was cooled to 0 °C. To this mixture was added, under vigorous stirring, compound **5** (2.0 g, 9.0 mmol) dissolved in a minimum amount of BuOH. The system was stirred at 0 °C for 0.5 h, and then MeI (5.6 mL, 90 mmol) was added dropwise. After 70 min further stirring the reaction was quenched via addition of water, the organic solvent was removed in vacuo, and diethyl ether (50 mL) was added to the system. The aqueous phase was separated and extracted with diethyl ether (4 × 15 mL), and the combined organic layers were washed with water (3 × 20 mL) and saturated NaCl solution (15 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, yielding 2.0 g (89%) of a yellow oil, which was purified by flash chromatography (AcOEt/pet. ether, 5−20%) to give 1.66 g (74%) of white solid product: ^{1}H NMR data of **6** ($CDCl_3$) δ 1.15 (3H, s), 1.29 (6H, s), 1.69−1.76 (2H, m), 1.90−1.96 (1H, m), 2.25−2.32 (3H, m), 2.49−2.55 (1H, m), 2.61 (1H, ddd, J_1 = 18.1 Hz, J_2 = 8.0 Hz, J_3 = 2.2 Hz), 3.95−4.08 (4H, O−CH_2CH_2−O, m), 5.61 (1H, dd, C=C−H, $J_1 = J_2$ = 3.4 Hz); MS *m/z* 250 $[M]^+$.

Preparation of 1,1-Ethylenedioxy-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene (7). In a two-neck 50 mL round-bottomed flask were placed compound **6** (0.62 g, 2.48 mmol) and diethylene glycol (12.5 mL), followed by hydrazine hydrate, and the mixture was stirred at 120 °C for 2.5 h. To this mixture was then added KOH pellets (0.93 g, 18.1 mmol), and the system was gradually heated to 170 °C to distill off water and hydrazine. The system was heated under reflux for 4 h, then cooled to room temperature, and diluted with pet. ether (30 mL) and water (30 mL). The aqueous phase was separated and extracted with ether (2 × 10 mL), and the combined organic layers were washed with water (2 × 20 mL) and saturated NaCl solution (2 × 10 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, yielding 0.55 g (94%) of pure **7**, a yellowish oil, which was used in the next step without further purification. ^{1}H NMR data for **7** ($CDCl_3$) δ 1.13 (3H, s), 1.15 (3H, s), 1.32−1.37 (1H, m), 1.35 (3H, s), 1.43−1.49 (2H, m), 1.53−1.57 (1H, m), 1.62−1.69 (2H, m), 1.73−1.79 (1H, m), 1.91−1.97 (1H, m), 2.13−2.18 (1H, m), 2.25−2.31 (1H, m), 3.92−4.04 (4H, O−CH_2CH_2−O, m), 5.52 (1H, C=C−H, bs); MS *m/z* 236 $[M]^+$.

Preparation of 3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethylnaphthalene-1(2H)-one (8). In a 10 mL round-bottomed flask were placed compound **7** (0.1 g, 0.42 mmol), a 4 mL solution of EtOH/H_2O (9:1), and PPTS (0.013 g, 0.052 mmol). The system was heated under reflux for 1.5 h, then cooled to room temperature, and the organic solvent was removed in vacuo. The remaining solution was extracted with 10 mL of ether, and the organic layer was washed with water (3 × 10 mL) and saturated NaCl solution (10 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to yield 0.081 g (99%) of pure **8**, which was used in the next step without further purification. ^{1}H NMR data for **8** ($CDCl_3$) δ 1.13 (3H, s), 1.19 (3H, s), 1.23−1.29 (1H, m), 1.37 (3H, s), 1.45−1.48 (2H, m), 1.57−1.61 (1H, m), 1.75−1.79 (2H, m), 2.28−2.33 (1H, m), 2.39−2.42 (1H, m), 2.44−2.48 (1H, m), 2.69−2.75 (1H, m), 5.73 (1H, C=C−H, bs); ^{13}C NMR ($CDCl_3$) δ 18.33 (CH_2, C-7), 25.23 (CH_3, C-9), 22.56 (CH_2, C-3), 30.59 (CH_3, C-11), 32.70 (CH_3, C-10), 34.21 (CH_2, C-8), 35.61 (CH_2, C-2), 36.52 (C, C-5), 41.06 (CH_2, C-6), 48.18 (C, C-8a), 119.19 (CH, C-4), 149.67 (C, C-4a), 216.44 (C=O, C-1); MS *m/z* 192 $[M]^+$.

Preparation of *cis*-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalene-1(2H)-one (9). In a two-neck 50 mL round-bottomed flask were placed compound **8** (0.15 g, 0.78 mmol), ethanol (12 mL), and 10% Pd/C (0.039 g), and the system was hydrogenated for 3.5 h. Addition of CH_2Cl_2 (1 mL) was followed by filtration through Celite, and removal of solvent gave 0.15 g (97%) of a mixture of the *cis* isomer **9** (91% by GC/MS) and its *trans* isomer **12** (9% by GC/MS). The two isomers were separated as their enolate trimethylsilyl ethers as described below. ^{1}H NMR data for **9** ($CDCl_3$) δ 0.82 (3H, s), 0.78−0.84 (1H, m), 0.94 (3H, s), 1.12−1.17 (1H, m), 1.24 (3H, s), 1.25−1.30 (1H, m), 1.31−1.36 (1H, m), 1.48−1.58 (2H, m), 1.81−1.90 (2H, m), 2.00−2.09 (2H, m), 2.17−2.25 (2H, m), 2.56−2.63 (1H, m); ^{13}C NMR ($CDCl_3$) δ 19.09, 20.12, 23.53, 24.72, 29.69, 32.06, 34.68, 34.78, 36.37, 43.24, 48.17, 54.09, 216.76; MS *m/z* 194 $[M]^+$.

Preparation of *trans*-1,2,3,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalen-1-ol (10). Into a 25 mL round-bottomed flask were placed compound **8** (0.11 g, 0.57 mmol) and anhydrous ethanol (5 mL). The system was cooled to −30 °C, and $NaBH_4$ (0.02 g, 0.9 mmol) was added under vigorous stirring. The system was then stirred at 0 °C for 2 h, when acetone (5 mL) was added, and stirring was continued at room temperature for 1 h. The solvents were removed in vacuo, and the residue was diluted with ether (30 mL) and washed consequently with 1 M NaOH solution (2 × 15 mL), water (2 × 10 mL), and saturated NaCl solution (10 mL). The ether layer was dried over $MgSO_4$ and the solvent was removed in vacuo, yielding 0.11 g of an epimeric mixture of **10a** and **10b** in a ratio of 1:9. The epimers were separated by flash chromatography using AcOEt/pet. ether (2−5%) as eluent. The yield of white crystalline **10b** was 0.098 g (88%): ^{1}H NMR data for **10b** ($CDCl_3$) δ 1.02 (3H, s), 1.09 (3H, s), 1.10 (3H, s), 1.19−1.25 (1H, m), 1.41−1.51 (3H, m), 1.62−1.77 (3H, m), 1.84−1.87 (1H, m), 2.04−2.20 (2H, m), 3.41 (1H, dd, J_1 = 11.6 Hz, J_2 = 4.4 Hz) 5.38 (1H, dd, J_1 = 3.9, J_2 = 3.45 Hz); ^{13}C NMR ($CDCl_3$) δ 18.13, 19.47, 24.61, 26.06, 30.33, 32.25, 35.24, 37.58, 39.14, 41.05, 78.27, 117.79, 148.69; MS *m/z* 194 $[M]^+$.

Preparation of *trans*-1,2,3,4,4a,5,6,7,8,8a,-Decahydro-5,5,8a-trimethylnaphthalen-1-ol (11). In a two-neck 25 mL round-bottomed flask were placed compound **10b** (0.045 g, 0.23 mmol), hexane (5.0 mL), and 10% Pd/C (0.025 g), and the system was hydrogenated for 3.5 h. Addition of CH_2Cl_2 (1 mL) was followed by filtration through Celite, and removal of solvent gave 0.043 g (97%) of a mixture of **11** (98% by GC/MS) and 2% of a diastereomeric side product. ^{1}H NMR data for **11** ($CDCl_3$) δ 0.77−0.80 (1H, m), 0.82 (3H, s), 0.84 (3H, s), 0.87 (3H, s), 0.93−0.99 (1H, m), 1.10−1.30 (4H, m), 1.34−1.63 (5H, m), 1.72−1.79 (2H, m), 3.13 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.27 Hz); ^{13}C NMR ($CDCl_3$) δ 12.04, 18.29, 20.83, 21.70, 24.44, 30.09, 32.79, 33.23, 37.48, 39.41, 42.05, 52.28, 80.79; MS *m/z*196 $[M]^+$.

Preparation of *trans*-3,4,4a,5,6,7,8,8a-Octahydro-5,5,-8a-trimethylnaphthalene-1(2H)-one (12). Into a 25 mL round-bottomed flask was placed a solution of compound **11** (0.042 g, 0.21 mmol, including the 2% isomer) in acetone (3 mL), and Jones reagent was added dropwise under vigorous stirring until the red color of the reagent persisted. The excess reagent was quenched by addition of isopropyl alcohol, the solution was diluted with ether (15 mL), washed successively with water (2 × 10 mL) and saturated $NaHCO_3$ (2 × 15 mL), and dried over $MgSO_4$, and the solvent was removed in vacuo, yielding 0.038 g (92%) of colorless liquid containing **12** and **9** in 98.5% and 1.5% yield, respectively, as indicated by GC/MS. The two isomers were separated as their enolate trimethylsilyl ethers as described below. ^{1}H NMR data for **12** ($CDCl_3$) δ 0.86 (3H, s), 0.90 (3H, s), 1.12 (3H, s), 1.08−1.14 (2H, m), 1.35−1.38 (1H, m), 1.44−1.63 (6H, m), 1.70−1.73 (1H, m) 2.01−2.03 (1H, m), 2.14−2.17 (1H, m), 2.51−2.57 (1H, m); ^{13}C NMR ($CDCl_3$) δ 17.97, 18.47, 20.84, 21.95, 26.21, 32.93, 33.02, 34.04, 37.50, 41.49, 48.98, 53.38, 215.80; MS *m/z* 194 $[M]^+$.

Preparation of *cis*-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-1-trimethylsiloxynaphthalene (13). To a 50 mL round-bottomed flask was placed a solution of the mixture of **9** and **12** in a ratio of 91:9 (1.94 g, 10.0 mmol) in 10 mL of THF, the system was cooled to 0 °C, and a solution of LDA (10 mmol) in THF (6 mL) was added dropwise. After 2 h stirring at 0 °C, Me_3SiCl (1.36 mL, 10.0 mmol) was added, and the system was stirred at room temperature for 2 h. The reaction was then quenched via addition of saturated Na_2CO_3 solution (10 mL), and the aqueous layer was separated and washed with ether (3 × 15 mL). The combined organic fractions were washed with saturated NaCl solution (2 × 10 mL) and dried over $MgSO_4$, and the solvents were removed in vacuo to give 2.6 g of a mixture of enol ethers. Flash chromatography using petroleum ether as eluent gave pure fractions of **13** (2.1 g, 79%) as a colorless oil, and its *trans* isomer. Analytical samples of the two products were hydrolyzed to yield pure **9** and **12**, respectively, which were characterized by their ^{1}H NMR, ^{13}C NMR, and mass spectra. All spectral data were identical to those taken from **9** or **12** as mixtures with their respective minor components, mentioned above. ^{1}H NMR data for **13** ($CDCl_3$) δ 0.17 (9H, s), 0.97 (3H, s), 1.01 (3H, s), 1.17 (3H, s), 1.10−1.24 (3H, m), 1.28−1.41 (3H, m), 1.57−1.63 (1H, m), 1.78−1.89 (2H, m), 1.94−2.01 (1H, m), 2.06−2.11 (1H, m), 4.62−4.61 (1H, m); ^{13}C NMR ($CDCl_3$) δ 0.31, 19.52, 19.69, 23.43, 27.01, 29.13, 32.29, 34.14, 34.52, 38.64, 40.49, 50.44, 101.13, 156.35; MS *m/z* 266 $[M]^+$.

^{1}H NMR data for the minor *trans* isomer of **13** ($CDCl_3$) δ 0.14 (9H, s), 0.82 (3H, s), 0.86 (3H, s), 1.02 (3H, s), 1.01−1.19 (3H, m), 1.30−1.46 (3H, m), 1.49−1.62 (2H, m), 1.76−1.78 (1H, m), 1.94−2.02 (2H, m), 4.50−4.51 (1H, m); ^{13}C NMR ($CDCl_3$) δ 0.31, 18.43, 18.65, 19.52, 21.48, 24.28, 33.01, 33.07, 35.21, 39.14,. 41.80, 51.53, 99.73, 158.87; MS *m/z* 266 $[M]^+$.

Preparation of *cis*-3,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethylnaphthalene-1(2H)-one (14). In a 20 mL round-bottomed flask were placed $BnMe_3NF$ (0.6 g, 4.0 mmol), predried in vacuo at 65 °C for 24 h, molecular sieves (2 g), and THF (20 mL), and the system was stirred at room temperature for 24 h. To this mixture was added MeI (1.2 mL, 10 mmol). After 15 min stirring, a solution of compound **13** (0.84 g, 4.0 mmol) in THF (6 mL) was added dropwise, and the mixture was stirred for 1 h, then diluted with ether and filtered through Celite. The solvent was removed in vacuo to give 0.65 g of a yellow oil, which was purified by flash chromatography using 1% ether/pet. ether as eluent. The yield of **14** as a mixture of diastereomers was 0.59 g (90%). A small amount (0.025 g) of starting material was also recovered. ^{1}H NMR data for **14** ($CDCl_3$) δ 0.72 (3H, s), 0.84 (3H, s), 0.91 (3H, s), 0.95 (3H, d, J = 6.4 Hz), 1.00 (3H, d, J = 6.6 Hz), 1.04 (3H, s), 1.24 (3H, s), 1.25 (3H, s), 1.19−1.98 (20H, m), 2.16−2.27 (2H, m), 2.51−2.59 (1H, m), 2.72−2.74 (1H, m); ^{13}C NMR ($CDCl_3$) δ 15.37, 16.19, 18.79, 19.17, 20.35, 23.29 24.27, 24.53, 29.96, 30.62, 31.07, 32.23, 32.37, 32.72, 33.43, 33.64, 34.64, 35.45, 36.57, 38.61, 40.12, 43.75, 48.05, 49.72, 52.32, 54.81, 217.38. 218.10; MS *m/z* 208 $[M]^+$.

Preparation of *cis*-2-Bromo-3,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalene-1(2H)-one (15). In a two-neck 100 mL round-bottomed flask were placed compound **14** (0.4 g, 1.8 mmol), CH_3COOH (25 mL), and pyridinium bromide perbromide (0.75 g, 2.34 mmol), and the mixture was stirred at room temperature for 2.5 h. Water (50 mL) was then added, and the resulting solution was extracted with ether (4 × 75 mL). The combined organic fractions were washed with saturated $NaCO_3$ solution (4 × 50 mL) and dried over $MgSO_4$, and the solvent was removed in vacuo, yielding 0.55 g of a yellow oil, which was purified by flash chromatography using 2% ether/pet. ether as eluent. The yield of the diastereomeric bromides **15** was 0.52 g (94%): ^{1}H NMR data for **15** ($CDCl_3$) δ 0.75 (3H, s), 0.92 (3H, s), 0.96 (3H, s), 1.14 (3H, s), 1.32 (3H, s), 1.63 (3H, s), 1.79 (6H, s), 1.15−2.06 (14H, m), 2.24−2.46 (8H, m); ^{13}C NMR ($CDCl_3$) δ 18.28, 18.65, 18.67, 21.13, 25.56, 26.53, 30.43, 30.93, 31.03, 31.48, 32.01, 33.21, 34.07, 35.68, 35.72, 36.23, 40.65, 41.87, 42.23, 48.22, 50.53, 51.69, 52.17, 59.33, 62.45, 209.62, 210.60; MS *m/z* 288 $[M]^+$.

Preparation of *cis*-4,4a,5,6,7,8,-Hexahydro-2,5,5,8a-tetramethylnaphthalene-1(8aH)-one (16). In a 200 mL round-bottomed flask were placed a solution of compound **15** (0.84 g 2.92 mmol), in toluene (45 mL), and DBU (0.57 mL, 3.8 mmol). The solution was heated under reflux for 3.5 h, then cooled to room temperature, diluted with ether (120 mL), and washed

successively with water (2 × 30 mL), 3 N HCl solution (2 × 30 mL), and saturated NaCl solution (2 × 40 mL). The organic fraction was dried over $MgSO_4$, and the solvents were removed to give 0.59 g of product, which was purified by flash chromatography (5% AcOEt/pet ether). The yield of **16** was 0.56 g (93%) as a yellowish oil: ^{1}H NMR data for **16** ($CDCl_3$) δ 0.55 (3H, s), 0.77−0.83 (1H, m), 0.83 (3H, s), 1.08 (3H, s), 1.12−1.17 (1H, m), 1.26−1.38 (3H, m), 1.69 (1H, d, J = 6.8 Hz), 1.66−1.67 (3H, m, CH_3), 2.23−2.35 (2H, m), 2.52−2.58 (1H, m), 6.37−6.38 (1H, m); ^{13}C NMR ($CDCl_3$) δ 16.06, 19.12, 23.32, 23.80, 28.56, 31.25, 34.13, 34.40, 42.22, 44.97, 51.86, 133.80, 141.11, 203.43; MS *m/z* 206 $[M]^+$.

Preparation of *cis*-1,4,4a,5,6,7,8,8a-Octahydro-1,5,5,8a-tetramethylnaphth-1-ol (17). In a two-neck 100 mL round-bottomed flask was placed a solution of compound **16** (0.19 g, 0.92 mmol), in HMPA/THF, 1:7 (3.37 mL), the system was cooled at −78 °C, and a 1.4 M solution of MeLi in hexane (0.92 mL, 1.29 mmol) was added dropwise. The system was then stirred at room temperature for 24 h, and the reaction was quenched via addition of a trace of water, with the solution extracted with ether (3 × 10 mL). The organic fractions were washed successively with water (3 × 10 mL), saturated NH_4-Cl solution (2 × 15 mL), and saturated NaCl solution (10 mL). The organic fraction was dried over $MgSO_4$, the solvents were removed in vacuo, and the crude product was purified by flash chromatography using 1−2% AcOEt/pet. ether as eluent to give 0.1 g (47%) of **17** as a yellowish oil: ^{1}H NMR data for **17** ($CDCl_3$) δ 0.82 (3H, s), 1.10 (3H, s), 1.09−1.13 (1H, m), 1.14 (3H, s), 1.16 (3H, s), 1.22−1.30 (2H, m), 1.38−1.44 (1H, m), 1.47−1.52 (2H, m), 1.60−1.65 (1H, m), 1.68−1.70 (3H, m, CH_3), 1.88−1.93 (1H, m), 1.94−1.96 (1H, m), 5.26−5.28 (1H, m); ^{13}C NMR ($CDCl_3$) δ 18.13, 18.83, 21.49, 23.42, 26.09, 26.64, 30.53, 31.21, 32.87, 34.28, 40.82, 45.38, 77.20, 121.25, 136.29; MS *m/z* 222 $[M]^+$, *m/z* 204 $[M^+ - 18]$.

Preparation of *cis*-1,1,4a,6-Tetramethyl-5-methylene-1,2,3,4,4a,5,8,8a-octahydronaphthalene (2). In a 25 mL round-bottomed flask were placed compound **17** (0.1 g, 0.45 mmol), THF (2 mL), triethylamine (0.7 mL, 5.0 mmol), and Burgess reagent (0.12 g, 0.5 mmol), and the solution was heated under reflux for 48 h. The system was then cooled to room temperature, water (3 mL) and ether (10 mL) were added to the solution, and the organic phase was washed successively with water (3 × 10 mL) and saturated NaCl solution (2 × 10 mL). The organic fraction was dried over $MgSO_4$, and the solvents were removed in vacuo to afford a crude product. GC/MS analysis of this crude mixture indicated the presence of the dehydration product **2**, a small amount of a side product, and unreacted starting material, which was removed by flash chromatography using 1−3% AcOEt/pet. ether as eluent to give 0.036 g (36%) of **17** and 0.037 g of a yellowish oil (55% yield, 74% conversion). ^{1}H NMR data for **2** ($CDCl_3$) δ 0.70 (3H, s, H-12), 0.83 (3H, s, H-11), 1.02 (3H, s, H-13), 1.10−1.17 (1H, m), 1.21−1.37 (3H, m), 1.61−1.68 (2H, m), 1.77−1.78 (3H, m, CH_3), 2.12−2.17 (2H, m, H-8), 2.34−2.38 (1H, m, H-8a), 4.91 (1H, bs, H-9), 4.92 (1H, bs, H-9), 5.48−5.49 (1H, m); ^{13}C NMR ($CDCl_3$) δ 18.73 (CH_2, C-3), 20.40 (CH_3, C-10), 21.51 (CH_3, C-13), 23.68 (CH_2, C-8), 32.26 (CH_3, C-12), 33.02 (CH_3, C-11), 34.23 (C, C-1), 37.57, (CH_2, C-4), 37.82 (C, C-4a), 43.78 (CH_2, C-2), 49.81 (CH, C-8a), 104.91 (CH_2, C-9), 125.26 (CH, C-7), 131.70 (C, C-6), 150.20(C, C-5); MS *m/z* 204 $[M]^+$.

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Supporting Information Available: Copies of ^{1}H and ^{13}C 1D and 2D NMR spectra of compounds **9**, **10b**, **11**, **12**, **2**, and **3**, as well as mass spectra of compounds **9**, **12**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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