Relative and Absolute Configuration of Allohedycaryol. Enantiospecific Total Synthesis of Its Enantiomer

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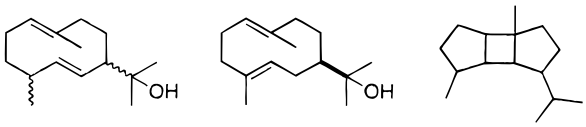
The enantiomer of (+)-allohedycaryol, a germacrane alcohol isolated from giant fennel (*Ferula communis* L.), has been synthesized, thereby elucidating the relative and absolute stereochemistry of the natural product. The synthesis of (−)-allohedycaryol started from (+)-α-cyperone (**5**) which was available in relatively large quantities via alkylation of imine **7** derived from (+)-dihydrocarvone and (*R*)-(+)-1-phenylethylamine. In a number of steps **5** was converted into the mesylate **4** with a regio- and stereoselective epoxidation as the key step. A Marshall fragmentation of **4** was used to prepare the *trans,trans*-cyclodeca-1,6-diene ring present in allohedycaryol. The conformation of synthetic (−)-allohedycaryol was elucidated via photochemical conversion into a bourbonane system. The synthesis of (−)-allohedycaryol also showed that natural (+)-allohedycaryol has the opposite absolute stereochemistry to that normally found in higher plants.

Introduction

Through the ages, plant species belonging to the genus *Ferula* (Umbelliferae) have been used in folk medicine[1] and are now known as rich sources of secondary metabolites. A long list of sesquiterpene alcohols and lactones as well as coumarins has been reported.[2] Recently, a new main component has been isolated from the essential oil obtained from the roots of *F. communis* L. (giant fennel), a plant toxic to livestock and widespread in the Mediterranean area.[3] The compound was originally thought to be a bisabolane sesquiterpene alcohol but through synthesis of this alcohol, it turned out that the proposed bisabolane structure was incorrect.[4] Then the germacradiene structure **1** with unknown relative and absolute stereochemistry was assigned to this new natural product (Chart 1). Being a double bond regioisomer of the germacrane alcohol (+)-hedycaryol (**2**),[5] the name allohedycaryol was proposed for **1**.[3]

Germacrane sesquiterpenes, structurally characterized by a *trans,trans*-cyclodeca-1,5-diene ring system, are widespread in nature and probably act as intermediates in the biosynthetic pathways towards eudesmanes, guaianes, and other types of sesquiterpenes.[6] Allogermacranes, in which a *trans,trans*-cyclodeca-1,6-diene ring system is present, are not very abundant in nature and may play a different role in the biosynthesis of sesquiterpenes. Since the *trans,trans*-cyclodeca-1,6-diene unit is known to undergo a smooth photochemical [2 + 2] cycloaddition,[7] allogermacranes are the most likely precursors of bourbonanes, a small class of sesquiterpenes possessing the cyclobuta[1,2:3,4]dicyclopentene skeleton **3**.[8] In contrast to the synthesis of *trans,trans*-germacrane sesquiterpenes and their double bond stereoisomers,[9] little attention has been paid to the synthesis of the regioisomeric allogermacranes.[10]

Chart 1



allohedycaryol (**1**) (+)-hedycaryol (**2**) **3**

Because of our interest in biogeneticlike cyclization reactions of germacranes,[11] and because the relative and absolute stereochemistry of allohedycaryol was unsettled, we decided to investigate its enantiospecific synthesis following the strategy outlined in Scheme 1. The key step in this approach is the conversion of mesylate **4** into allohedycaryol by means of a Marshall fragmentation reaction in which both double bonds are regio- and stereospecifically formed.[12] The synthesis of **4** in turn was planned starting from (+)-α-cyperone (**5**) via a

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(1) Gunther, R. T. In *The Greek Herbal of Dioscorides*; University Press: Oxford, 1934; p 323.

(2) For an extensive review, see: Gonzalez, A. G.; Barrera, J. B. *Prog. Chem. Org. Nat. Prod.* **1995**, *64*, 1.

(3) Valle, M. G.; Appendino, G.; Nano, G. M.; Picci, V. *Phytochemistry* **1987**, *26*, 253.

(4) Kreiser, W. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; Vol. 8, pp 39−61.

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

(6) Banthorpe, D. V. In *Natural Products: Their Chemistry and Biological Significance*; Longman Scientific & Technical: Harlow, 1994; Chapter 5.

(7) Heathcock, C. H.; Badger, R. A.; Starkey, R. A. *J. Org. Chem.* **1972**, *37*, 231.

(8) (a) Yoshihara, K.; Ohta, Y.; Sakai, T.; Hirose, Y. *Tetrahedron Lett.* **1969**, 2263. (b) Raldugin, V. A.; Salenko, V. L.; Gamov, N. S.; Titova, T. F.; Khan, V. A.; Pentegova, V. A. *Chem. Nat. Compd. (Engl. Transl.)* **1980**, 154.

(9) For example, all stereoisomers of (±)-**2** have been synthesized, see: (a) Kodama, M.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1976**, 1121. (b) Kodama, M.; Yokoo, S.; Yamada, H.; Itô, S. *Tetrahedron Lett.* **1978**, 3121. It is of interest to note that during the synthesis of (±)-**2** a by-product was formed to which structure **1** was assigned.[9a]

(10) (a) Kodama, M.; Shimada, K.; Takahashi, T.; Kabuto, C.; Itô, S. *Tetrahedron Lett.* **1981**, *22*, 4271. (b) Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971.

(11) (a) Piet, D. P.; Minnaard, A. J.; van der Heijden, K. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1995**, *51*, 243. (b) Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1995**, *51*, 6303.

(12) (a) Marshall J. A. *Synthesis* **1971**, 229. The fragmentation has also been used for the synthesis of (±)- and (+)-hedycaryol, see: (b) Wharton, P. S.; Sundin, C. E.; Johnson, D. W.; Kluender, H. C. *J. Org. Chem.* **1972**, *37*, 34 and (c) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1994**, *50*, 4755, respectively.

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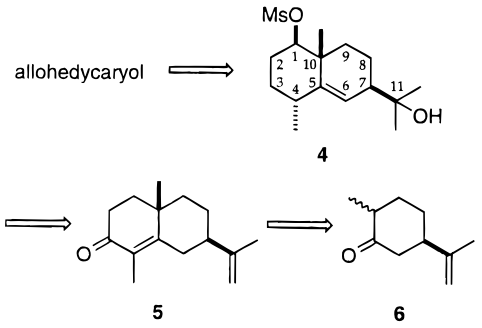
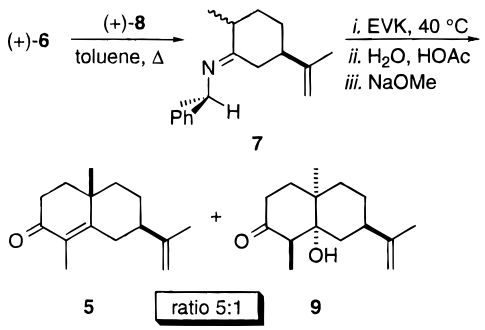
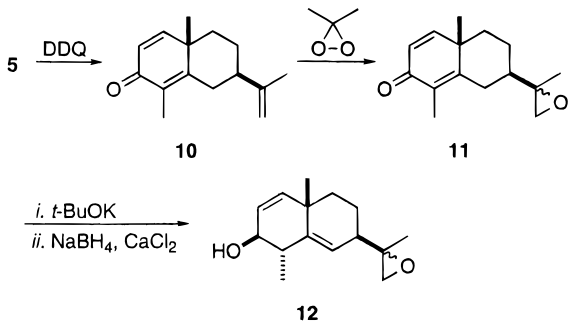
Scheme 1



Scheme 2



Scheme 3



number of conversions with the introduction of an equatorial hydroxyl group at C(1)[13] as the most challenging step. An easy access to (+)-α-cyperone was therefore needed, and a simple procedure for the synthesis of **5** starting from (+)-dihydrocarvone (**6**) was developed.

Since the absolute and relative stereochemistry of natural allohedycaryol was unknown, we realized that the synthetic route depicted in Scheme 1 might lead to the formation of the enantiomer or, at worst, to the formation of a diastereomer of allohedycaryol. We have opted for an equatorial Me group at C(4) and the absolute stereochemistry around C(7) as present in (+)-hedycaryol (**2**). This absolute stereochemistry is normally found in higher plants (vide infra).

Results and Discussion

(+)-α-Cyperone (**5**)[14] has been widely used as a starting material for the synthesis of various other fused-ring sesquiterpenes.[15] Whereas (−)-10-*epi*-α-cyperone can be easily synthesized from (+)-dihydrocarvone,[16] the synthetic methods leading to **5** are either rather laborious or give low yields.[17] Because relatively large quantities of **5** were needed for our study, we were looking for a more efficient method for the preparation of this compound.

Recently, an improved synthesis of homochiral naphthalenones was reported.[18] The key step in this synthesis was based on the deracemizing alkylation of chiral imines derived from racemic cyclanones.[19] It was shown that in the alkylation of imine **7** derived from **6** with methyl vinyl ketone (MVK) the inherent preference for axial alkylation[15a] was largely overruled by the chiral induction of the imine substituent. We realized that this method could also be used for a short and efficient synthesis of (+)-α-cyperone, simply by replacing MVK by ethyl vinyl ketone (EVK). The synthesis of **5**[20] started with the azeotropic imination of **6** and (*R*)-(+)-1-phenylethylamine (**8**), both commercially available, to afford the imine **7** (Scheme 2). The alkylation of **7** was performed in THF at 40 °C with a slight excess EVK. After hydrolysis of the imine, the product was dissolved in MeOH and treated with NaOMe at room temperature to give an easily separable mixture of **5** and the ketol **9** in a ratio of ca. 5:1, respectively. Flash chromatography afforded pure **5** in 47% overall yield from (+)-dihydrocarvone.[21]

With easy access to **5**, we could start with our synthetic route toward allohedycaryol (Scheme 3). Dehydrogenation of **5** with DDQ in dry dioxane afforded (−)-1,2-dehydro-α-cyperone (**10**) in good yield.[15c] Selective epoxidation of the isopropenyl side chain in **10** produced **11** as a 1:1 mixture of diastereomers. Treatment of **11** with *t*-BuOK in dry DMSO and quenching of the resulting enolate with aqueous NH_4Cl gave an unstable deconjugated ketone which was directly reduced with $NaBH_4$ in the presence of $CaCl_2$[22] to afford the stable allylic alcohol **12**. In the ^1H NMR spectrum of **12**, also a 1:1 diastereomeric mixture, the coupling constant between α H-3 and β H-4 ($J_{3,4}$) was found to be 8.8 Hz, which indicates that the Me group at C(4) and the hydroxyl group at C(3) possess an equatorial α and β orientation, respectively.[23] Together with the other NMR data, this observation unequivocally establishes the identity of **12**.

In order to achieve an oxygen function at C(1), some allylic rearrangement experiments[23,24] were performed with **12**, but the results were poor. We therefore focused our attention on the stereoselective Sharpless epoxidation of the C(1)−C(2) double bond in **12**. It was found in the literature[25] that treatment of a β-allylic alcohol structur-

(13) The numbering system as given in structure **4** will be followed throughout the text of this paper.

(14) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids, p 326.

(15) For some representative examples, see: (a) Ho, T.-L. *Enantioselective Synthesis, Natural Products from Chiral Terpenes*; Wiley Interscience: New York, 1992; pp 132−135. (b) Li, Y.; Chen, X.; Shao, S.; Li, T. *Synth. Commun.* **1993**, *23*, 2457. (c) Liu, L.; Xiong, Z.; Nan, F.; Li, T.; Li, Y. *Bull. Soc. Chim. Belg.* **1995**, *104*, 73.

(16) Howe, R.; McQuillin, F. J. *J. Chem. Soc.* **1955**, 2423.

(17) (a) Reference 15a, pp 198−200 and 272−273. (b) Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1992**, *48*, 3121. (c) Agami, C.; Kadouri-Puchot, C.; Le Guen, V. *Tetrahedron: Asymm.* **1993**, *4*, 641.

(18) Tenius, B. S. M.; de Oliveira, E. R.; Ferraz, H. M. C. *Tetrahedron: Asymm.* **1993**, *4*, 633.

(19) (a) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. Review: (b) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymm.* **1992**, *3*, 459.

(20) The well-described procedure was followed: Revial, G.; Pfau, M. *Org. Synth.* **1992**, *70*, 35.

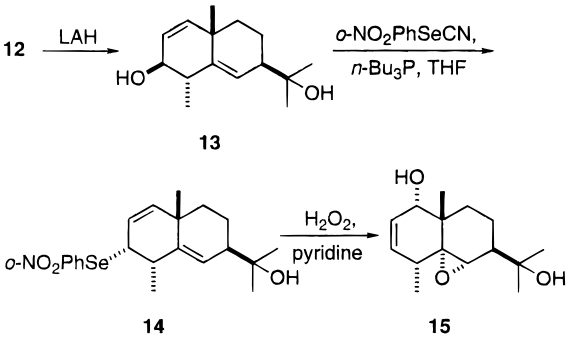
(21) The use of (*S*)-(−)-1-phenylethylamine resulted in a selective formation of (−)-10-*epi*-α-cyperone in 67% overall yield from (+)-dihydrocarvone.

(22) Krieg, R.; Schönecker, B. *Liebigs Ann. Chem.* **1994**, 1025.

(23) Ando, M.; Akahane, A.; Takase, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 283.

(24) (a) Narasaka, K. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Science: London, 1994; pp 17−36.

Scheme 4



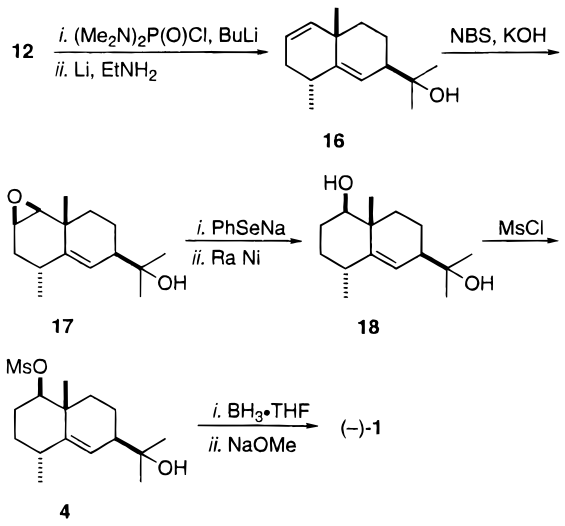
ally related to **12** with *t*-BuOOH catalyzed by vanadyl acetylacetonate ($VO(acac)_2$) resulted in the formation of the corresponding β *cis*-epoxy alcohol in reasonable yield. With **12**, however, the *t*-BuOOH/$VO(acac)_2$ reaction only showed oxidation to the corresponding enone.[26] Apparently, the equatorial β hydroxyl group in **12** is not properly positioned for assistance in the epoxidation reaction, and oxidation of the alcohol function will be preferred.[27]

Another possibility for introducing a hydroxyl function at C(1) involves the stereospecific [2,3] sigmatropic rearrangement of secondary allylic selenoxides.[28] To determine the applicability of the above [2,3] sigmatropic rearrangement to the 3β-allylic alcohol system in **12**, the epoxide ring in the side chain had to be reduced first[29] (Scheme 4). In the ^{1}H NMR spectrum of the resulting diol **13**, $J_{3,4}$ was found to be 8.5 Hz which confirmed the equatorial α orientation of the Me group at C(4).[23] Treatment of diol **13** with *o*-nitrophenyl selenocyanate in the presence of tri-*n*-butylphosphine afforded the α selenide **14** in 91% yield. Oxidation of **14** with H_2O_2 in the presence of pyridine at −30 °C proceeded smoothly, but gave, in addition to the expected rearrangement, also α epoxidation of the C(5)−C(6) double bond[30] to give **15** as the sole product in 86% yield.[31]

Because none of the above approaches yielded a workable result, we were forced to develop an alternative route for the conversion of **12** into the mesylate **4**.

From examination of molecular models, it appeared that the C(5)−C(6) double bond in **12** is sterically more shielded than the C(1)−C(2) double bond. It was therefore expected that the selective epoxidation of the C(1)−C(2) double bond without participation of the hydroxyl group at C(3) would be possible. Based on these considerations, a synthetic pathway was devised in which the hydroxyl group at C(3) of **12** was removed prior to the epoxidation of the C(1)−C(2) double bond.

Scheme 5



Because reduction of the mesylate ester of **12** only gave elimination products, the removal of the C(3) hydroxyl group of **12** was performed via reduction of its phosphordiamidate with Li in $EtNH_2$.[32] This reaction proceeded smoothly and was attended with reductive opening of the epoxide ring in the side chain to provide the diene **16** in about 60% overall yield from **12** (Scheme 5).

At this stage, we had to introduce an epoxide ring at the sterically less favored β side of the C(1)−C(2) double bond. For this purpose, we chose a strategy based on the *trans*-diaxial bromohydrin formation.[33] Treatment of **16** with *N*-bromosuccinimide (NBS) in aqueous dioxane followed by ring closure with methanolic KOH afforded the β epoxide **17** as the sole product in 61% yield. As expected (vide supra), epoxidation of the C(5)−C(6) double bond did not take place.

The regioselective opening of the epoxide ring in **17** was the next step. Normally, nucleophilic attack on an epoxide ring gives rise to diaxial ring opening,[34] but in case of the β epoxide **17** it was found that the diequatorial ring opening prevailed when sodium phenylselenide was used as the nucleophile.[35] After reductive cleavage of the Se−C(2) bond with Raney nickel, the resulting β C(1)-alcohol **18** was treated with MsCl in pyridine to afford the desired mesylate **4** in 92% overall yield from **17**. In the ^{1}H NMR spectrum of **4** a one-proton double doublet (J = 11.0, 5.3 Hz) appears at δ 4.29, which is consistent with the presence of an equatorial mesylate group at C(1).

Completion of the synthesis of allohedycaryol was accomplished by successive treatment of **4** with excess fresh BH_3•THF and NaOMe in MeOH. After purification by aqueous $AgNO_3$ extraction,[36] allohedycaryol was obtained as a colorless oil in 68% yield. The synthetic material was spectroscopically identical to the natural product isolated from *F. communis*.[37] However, the specific rotation obtained for our synthetic product ($[\alpha]_D$ −192°) was opposite to that ($[\alpha]_D$ +181°) reported for

(25) Yamakawa, K.; Nishitani, K.; Tominaga, T. *Tetrahedron Lett.* **1975**, 2829.

(26) Recently, a similar result has been found during the *t*-BuOOH/$VO(acac)_2$ epoxidation of a steroidal allylic alcohol: Kocovsky, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1759.

(27) In contrast to **12**, treatment of its C(3) epimer[46] with *t*-BuOOH/$VO(acac)_2$ gave selectively the corresponding α epoxide.

(28) Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebiro, A. A. *J. Org. Chem.* **1985**, *50*, 2981.

(29) It was expected that ring opening of the side-chain epoxide in **12** would occur during the formation of the allylic selenide. For example, see: Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049.

(30) The epoxidation of olefinic bonds, probably due to the formation of arylperoxyseleninic acid, is a known problem in the selenoxide chemistry, see: (a) Grieco, P. A.; Yokoyama, Y.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 2034. (b) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689.

(31) The observation that the use of pyridine did not prevent the epoxidation of the C(5)−C(6) double bond suggests an intramolecularly directed process.[28]

(32) (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668.

(33) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1959**, 4136.

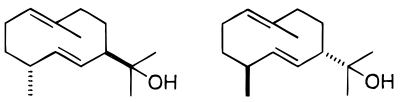
(34) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 165.

(35) Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1993**, *58*, 7204.

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

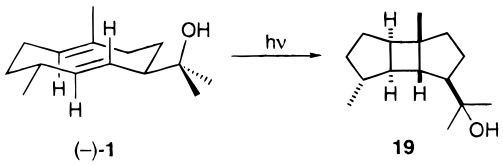
(37) We thank Prof. Dr. G. Appendino for supplying copies of the NMR spectra of natural allohedycaryol.

Chart 2



synthetic (–)-**1** natural (+)-**1**

Scheme 6



(–)-**1** **19**

natural allohedycaryol,[3] which meant that we had synthesized the antipode of the natural product as structure (−)-**1** illustrates (Chart 2). Consequently, structure (+)-**1** represents the relative and absolute configuration of natural allohedycaryol. This also means that natural (+)-**1** possesses the *ent*-configuration,[38] which is remarkable because *ent*-sesquiterpenes are rarely found in higher plants.[39] In addition, the possibility that (+)-hedycaryol (**2**) acts as a direct precursor of (+)-**1** can be ruled out because the *ent*-form of **2** has not been found in nature.[40]

The conformation of allohedycaryol was also investigated. It has been demonstrated[41] that a *trans,trans*-cyclodeca-1,6-diene ring preferably adopts an "elongated chair" conformation. This is not surprising because such a conformation is essentially Pitzer-strain free, and all the Van der Waals radii are respected.[42] Cyclodeca-1,6-diene ring systems in which one of the double bonds bears a Me group show the same preference.[41b] It is most likely that allohedycaryol also will exist in the elongated chair conformation all the more so because in this conformation both the C(4) methyl group and the C(7) 2-propanol group adopt the pseudoequatorial orientation as the three-dimensional structure (−)-**1** in Scheme 6 indicates. The preference for one distinct conformation was supported by the NMR spectra of our synthetic (−)-**1**. Further information about the conformation of allohedycaryol was obtained from the UV spectrum of (−)-**1**, in which the absorption maximum at <190 nm shows strong tailing toward the red (260 nm). This tailing indicates that both double bonds are lying parallel and close to each other.[41b] The rather close proximity of the double bonds in (−)-**1** was further proved by irradiation of (−)-**1** in MeCN solution with a low-pressure Hg lamp. This resulted in a smooth convertion of **1** into **19** in almost quantitative yield. The structure of **19** was established with ^{1}H NMR spectroscopy using Eu(fod)$_3$ as a shift reagent. With increasing concentration of the shift reagent, the angular Me group shifted markedly to lower field ($\Delta\delta = 0.56$ ppm) which proves a *syn* relationship between the 2-propanol group and the angular Me group. The doublet of the α C(4) Me group was hardly shifted by varying the concentration of the shift reagent. It is of interest to note that most of the naturally occurring bourbonane sesquiterpenes possess the same relative stereochemistry as found for **19**.[43]

Experimental Section[44]

Materials. All reagents were purchased from Aldrich or Janssen except for *N,N,N′,N′*-tetramethylphosphorodiamidic chloride which was purchased from Fluka. The compounds **5**,[17b] **9**,[16] and **10**[17b] have been characterized before.

(+)-α-Cyperone (5). To a solution of 10.0 g (65.8 mmol) of (+)-dihydrocarvone (**6**) in 70 mL of dry toluene was added 9.3 mL (72.2 mmol) of (*R*)-(+)-1-phenylethylamine (**8**). The reaction mixture was refluxed under Dean−Stark conditions until completion (14 h) and concentrated under reduced pressure. The remaining crude imine **7** was dissolved in 75 mL of dry THF, and 7.9 mL (79 mmol) of EVK was added. After stirring in the dark at 40 °C for 3 d, 25 mL of 10% aqueous AcOH was added. The reaction mixture was vigorously stirred for 1 h and then poured into 50 mL of brine. After extraction with five portions of petroleum ether (bp 40−60 °C), the combined organic layers were washed successively with 0.2 M aqueous HCl, saturated aqueous NaHCO$_3$, and brine. The solution was dried and evaporated. The remaining residue was dissolved in 100 mL of MeOH, and 4 mL of 1 M NaOMe in MeOH was added dropwise. The reaction mixture was stirred at rt for 30 h, diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Flash chromatography (50:1 petroleum ether (bp 40−60 °C)/EtOAc) gave, in order of elution, 1.10 g (11%) of **6** and 6.74 g (47%) of **5**: $[\alpha]_D$ +92.2° (*c* 2.04) (lit.[17b] +91.1°). The spectroscopic data for **5** were identical with those reported in the literature.[17b] Further elution (2:1 petroleum ether (bp 40−60 °C)/EtOAc) gave 1.4 g (9%) of the known ketol **9**.[16]

(−)-1,2-Dehydro-α-cyperone (10). A mixture of 1.33 g (6.10 mmol) of **5** and 1.93 g (8.50 mmol) of DDQ in 50 mL of dry dioxane was refluxed for 24 h. The reaction mixture was allowed to come to rt and filtered. The filtrate was evaporated under reduced pressure, and the remaining residue was purified by column chromatography (5:1 petroleum ether (bp 40−60 °C)/EtOAc) to give 1.01 g (76%) of **10**: $[\alpha]_D$ −161.5° (*c* 1.37) (lit.[17b] −149.0°); mp 50−51 °C (from pentane).[45] Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.31; H, 9.47. The spectroscopic data for **10** were identical with those reported in the literature.[17b]

(4a*S-cis*)-5,6,7,8-Tetrahydro-1,4a-dimethyl-7-(2-methyloxiranyl)-2(4a*H*)-naphthalenone (11). To a stirred solution of 1.95 g (9.03 mmol) of **10** in 120 mL of a 1:1 mixture of CH_2Cl_2 and acetone was added 0.240 g (0.91 mmol) of 18-crown-6 followed by a solution of 3.6 g (43 mmol) of NaHCO$_3$ in 48 mL of water. The mixture was cooled to 0 °C, and a solution of 6.6 g (10.7 mmol) of Oxone in 30 mL of water was added dropwise. The reaction mixture was vigorously stirred at 0 °C for 3.5 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 1.98 g (94%) of **11** as a 1:1 diastereomeric mixture: ^{13}C NMR δ 10.52 (q), 18.08 (q), 18.51 (q), 22.75 (t), 23.25 (t),

(38) The conventions proposed for describing germacrane sesquiterpenes are followed: Rogers, D.; Moss, G. P.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 142.

(39) Prof. Dr. G. Appendino attended us to an article in which the isolation of α-ferulene, another *ent*-sesquiterpene from *F. communis*, has been reported: Carboni, S.; Da Settimo, A.; Malaguzzi, V.; Marsili, A; Pacini, P. L. *Tetrahedron Lett.* **1965**, 3017.

(40) In the *Chemical Abstracts*, the *S*-configuration is erroneously assigned to (+)-hedycaryol (**2**) probably because a corrigendum of reference 5 has been overlooked: *J. Chem. Soc., Chem. Commun.* **1970**, 892. Recently, the *R*-configuration of natural (+)-**2** has been ascertained through its synthesis starting from (−)-guaiol of known absolute configuration.[12c]

(41) (a) White, D. N. J.; Bovill, M. J. *Tetrahedron Lett.* **1975**, *27*, 2239. (b) Neykov, G. D.; Ivanov, P. M.; Orahovats, A. S. *J. Mol. Struct.* **1987**, *153*, 147.

(42) Dale, J.; Moussebois, C. *J. Chem. Soc. (C)* **1966**, 264.

(43) Reference 14, p 636.

(44) 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 at 50 MHz (^{13}C) in $CDCl_3$. The ^{1}H NMR experiments using Eu(fod)$_3$ as a shift reagent were performed at 400 MHz. Optical rotations were measured in $CHCl_3$ solutions. Column chromatography was performed using Merck silica gel 60 (70−230 mesh). Product solutions were dried over $MgSO_4$, unless otherwise reported.

(45) Previously, compound **10** was reported as an oil.[15c,17b]

23.45 (d), 29.36 (t), 29.78 (t), 37.30 (d), 40.15 (s), 45.07 (d), 45.37 (d), 53.11 (t), 53.44 (t), 58.74 (s), 126.16 (d), 129.48 (s), 156.32 (d), 156.37 (d), 158.56 (s), 186.26 (s). The ^{1}H NMR and mass spectral data for **11** corresponded with those reported in the literature.[15c]

[1R-(1α,2*β*,4a*β*,7*β*)-1,2,4a,5,6,7-Hexahydro-1,4a-dimethyl-7-(2-methyloxiranyl)-2-naphthalenol (12). To a stirred solution of 1.98 g (8.53 mmol) of **11** in 50 mL of dry DMSO was added 3.0 g (24.6 mmol) of *t*-BuOK. The reaction mixture was stirred at rt for 45 min and then poured into ice−water containing 5.0 g of NH_4Cl. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried over Na_2SO_4, and evaporated. The so-obtained crude deconjugated ketone was used directly for next step reaction. A solution of 1.94 g (17.5 mmol) of anhydrous $CaCl_2$ in 40 mL of dry EtOH was added dropwise to a stirred solution of 1.1 g (29.1 mmol) of $NaBH_4$ in 40 mL of dry EtOH at −25 °C. The solution was stirred at this temperature for 30 min, and then a solution of the crude deconjugated ketone in a mixture of 20 mL of dry EtOH and 10 mL of dry THF was added. After stirring at −25 °C for an additional 1.5 h, the reaction mixture was treated with 10 mL of acetone and allowed to come to rt. The solution was concentrated under reduced pressure, diluted with water, and then treated with AcOH until a clear solution was formed. After extraction with CH_2Cl_2, the combined organic layers were washed with water, dried, and evaporated. The residue was purified by flash chromatography (5:1 petroleum ether (bp 40−60 °C)/EtOAc) to afford 1.35 g (67%) of **12** as a 1:1 diastereomeric mixture:[46] ^{1}H NMR (major peaks) δ 2.54−2.61 (m, 2 H), 3.60 (d, J = 8.8 Hz, 1 H), 5.25, 5.46 (br s, br s, 1:1 ratio, 1 H), 5.43 (br d, J = 10.0 Hz, 1 H), 5.50 (br d, J = 10.0 Hz, 1 H); ^{13}C NMR δ 13.78 (q), 17.32 (q), 18.53 (q), 20.85 (t), 20.96 (t), 26.61 (q), 35.81 (t), 35.88 (t), 36.31 (s), 39.82 (d), 42.21 (d), 43.91 (d), 52.47 (t), 53.26 (t), 59.50 (s), 59.55 (s), 60.35 (t), 75.60 (d), 118.14 (d), 119.05 (d), 127.97 (d), 128.06 (d), 138.01 (d), 144.85 (s), 145.01 (s); MS m/z (relative intensity) 234 (M^+, 36), 201 (90), 177 (62), 159 (98), 143 (100), 131 (70), 119 (86), 105 (83), 91 (73), 43 (69); HRMS calcd for $C_{15}H_{22}O_2$ (M^+) 234.1620, found 234.1619.

[1S-(2α,4aα,7α,8*β*)]-2,3,4,4a,7,8-Hexahydro-7-hydroxy-α,α,4a,8-tetramethyl-2-naphthalenemethanol (13). A mixture of 1.30 g (5.56 mmol) of **12** and 0.60 g (15.8 mmol) of LAH in 25 mL of dry THF was stirred at rt for 1 h. The excess LAH was destroyed by careful addition of 2 mL of water at 0 °C. After addition of 5.0 g of $MgSO_4$, the mixture was stirred at rt for 5 min and then filtered. The filtrate was evaporated to give 1.20 g (91%) of **13**: $[\alpha]_D$ = −43.1° (*c* 0.07); ^{1}H NMR δ 1.07 (s, 3 H), 1.10 (s, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.16 (s, 3 H), 1.29−1.72 (m, 6 H), 2.08 (m, 1 H), 2.24 (m, 1 H), 3.64 (dd, J = 8.5, 4.8 Hz, 1 H), 5.35−5.47 (m, 3 H); ^{13}C NMR δ 13.87 (q), 20.16 (t), 25.75 (q), 26.52 (q), 28.02 (q), 36.30 (t), 36.30 (s), 40.13 (d), 47.58 (d), 73.05 (s), 75.95 (d), 119.15 (d), 127.67 (d), 138.74 (d), 144.93 (s); MS m/z (relative intensity) 178 (M^+ − 58, 41), 163 (18), 160 (39), 149 (13), 145 (100), 135 (12), 121 (10), 105 (10), 91 (8), 59 (41); HRMS calcd for $C_{14}H_{21}O_2$ (M^+ − 15) 221.1542, found 221.1545.

[1aS-(1aα,2*β*,4a*β*,5α,8aαR*)]-1a,2,4,4a,5,8-Hexahydro-5-hydroxy-α,α,4a,8-tetramethyl-3*H*-naphth[1,8a-*b*]oxirene-2-methanol (15). To a solution of 236 mg (1.0 mmol) of **13** and 342 mg (1.5 mmol) of *o*-nitrophenyl selenocyanate in 10 mL of dry THF was added 0.40 mL (1.61 mmol) of tri-*n*-butylphosphine. The mixture was allowed to stand at rt for 20 h and then concentrated at reduced pressure. The concentrate was purified by column chromatography (20:1 to 5:1 petroleum ether (bp 40−60 °C)/EtOAc) to give 397 mg (91%) of α selenide **14**: $[\alpha]_D$ = −409° (*c* 0.30); ^{1}H NMR δ 1.10 (s, 3 H), 1.14 (s, 3 H), 1.18 (d, J = 6.8 Hz, 3 H), 1.21 (s, 3 H), 1.25−1.75 (m, 5 H), 2.24 (m, 1 H), 2.92 (m, 1 H), 4.03 (dd, J = 5.3, 4.3 Hz, 1 H), 5.43 (d, J = 9.5 Hz, 1 H), 5.49 (br s, 1 H), 5.87 (dd, J = 9.5, 5.5 Hz, 1 H), 7.24 (dt J = 8.1, 1.3 Hz, 1 H), 7.45 (dt, J = 8.2, 1.5 Hz, 1 H), 7.67 (dd, J = 8.1, 1.1 Hz, 1 H), 8.12 (dd, J = 8.2, 1.5 Hz, 1 H); ^{13}C NMR δ 16.71 (q), 20.01 (t), 25.63 (q), 26.36 (q), 28.08 (q), 35.20 (d), 35.90 (q), 36.90 (s), 47.25 (d), 49.20 (d), 72.93 (s), 120.02 (d), 124.75 (d), 125.50 (d), 126.01 (d), 130.81 (d), 133.07 (d), 133.42 (s), 139.15 (d), 143.49 (s), 147.94 (s); MS m/z (relative intensity) 421 (M^+, 1), 219 (7), 201 (9), 161 (100), 159 (10), 145 (21), 119 (17), 105 (16), 69 (19), 59 (45); HRMS calcd for $C_{21}H_{27}NO_3Se$ (M^+) 421.1156, found 421.1157. To a solution of 390 mg (0.926 mmol) of **14** and 0.3 mL of pyridine in 25 mL of THF was added dropwise 2.4 mL (25 mmol) of 35% H_2O_2 at −30 °C. The reaction mixture was stirred at −30 °C for 1 h and then allowed to come to rt. After addition of water, the reaction mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated. The remaining residue was purified by column chromatography (2:1 to 1:2 petroleum ether (bp 40−60 °C)/EtOAc) to afford 202 mg (86%) of **15**: $[\alpha]_D$ = +9.4° (*c* 2.06); ^{1}H NMR δ 0.83 (d, J = 7.2 Hz, 3 H), 1.02 (m, 1 H), 1.08 (s, 3 H), 1.19 (s, 3 H), 1.24 (m, 1 H), 1.26 (s, 3 H), 1.81−2.23 (m, 4 H), 2.68 (br q, J = 7.2 Hz, 1 H), 3.18 (s, 1 H), 3.54 (br s, 1 H), 5.53 (dd, J = 10.0, 2.0 Hz, 1 H), 5.90 (ddd, J = 10.0, 5.1, 2.8 Hz, 1 H); ^{13}C NMR δ 12.83 (q), 18.86 (t), 20.97 (q), 25.28 (q), 27.46 (t), 28.81 (q), 30.75 (d), 36.76 (s), 45.49 (d), 53.66 (d), 63.92 (s), 72.26 (s), 73.33 (d), 127.55 (d), 133.18 (d); MS m/z (relative intensity) 252 (M^+, 10), 219 (45), 193 (64), 123 (67), 122 (43), 110 (46), 107 (45), 95 (49), 59 (100), 43 (54); HRMS calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1725.

[2R-(2α,4aα,8*β*)]-2,3,4,4a,7,8-Hexahydro-α,α,4a,8-tetramethyl-2-naphthalenemethanol (16). To a stirred solution of 8.77 g (37.5 mmol) of **12** in a mixture of 40 mL of dry THF and 10 mL of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was added dropwise 20 mL of BuLi (2.5 M in hexane) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, and then 7.5 mL (52 mmol) of *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidic chloride was added. After stirring at −78 °C for 5 min, the cooling bath was removed and the reaction mixture was allowed to come to rt and stirred for an additional 1 h. The reaction mixture was then added, via syringe, to a solution of 3.0 g (428 mmol) of Li in 200 mL of $EtNH_2$ at 0 °C. After stirring at 0 °C for 1 h, 100 mL of saturated aqueous NH_4Cl was added and $EtNH_2$ was allowed to evaporate by standing at rt overnight. Addition of water to the remaining layer was followed by extraction with EtOAc. After drying and evaporation of the combined organic layers, column chromatography (4:1 petroleum ether (bp 40−60 °C)/EtOAc) afforded 5.60 g (68%) of **16** (GC purity >85%):[47] ^{1}H NMR δ 1.06 (d, J = 6.6 Hz, 3H), 1.10 (s, 3H), 1.16 (s, 3H), 1.22 (s, 3H), 1.38−1.74 (m, 6 H), 2.10−2.24 (m, 2 H), 2.42 (m, 1 H), 5.31 (dd, J = 10.0, 2.3 Hz, 1 H), 5.37 (br s, 1 H), 5.50 (ddd, J = 10.0, 5.2, 2.3 Hz, 1 H); ^{13}C NMR δ 17.70 (q), 20.29 (t), 25.85 (q), 27.27 (q), 27.98 (q), 30.88 (d), 36.43 (s), 36.74 (t), 37.14 (t), 47.71 (d), 73.07 (s), 116.11 (d), 123.33 (d), 137.72 (d), 148.47 (s); MS m/z (relative intensity) 205 (M^+ − 15, 2), 162 (66), 161 (9), 147 (100), 133 (14), 119 (11), 105 (17), 91 (12), 81 (12), 59 (51); HRMS calcd for $C_{14}H_{21}O$ (M^+ − 15) 205.1592, found 205.1593.

[1aR-(1aα,3*β*,5α,7aα)]-1a,2,3,5,6,7,7a,7b-Octahydro-α,α,3,-7a-tetramethyl-5-naphth[1,2-*b*]oxirenemethanol (17). To a stirred solution of 5.43 g (24.7 mmol) of **16** in a mixture of 200 mL of dioxane and 40 mL of water was added dropwise a solution of 5.21 g (29.3 mmol) of NBS in 50 mL of dioxane at 0 °C. The reaction mixture was stirred at 5−10 °C for 30 min, and then 8.0 g (143 mmol) of KOH in 50 mL of MeOH was added. After stirring at rt for another 1 h, the reaction mixture was diluted with EtOAc, washed with water, dried, and evaporated. Flash chromatography of the remaining residue (9:1 to 3:1 petroleum ether (bp 40−60 °C)/EtOAc) gave 3.55 g (61%) of **17** as white crystals: mp 148−149 °C (from EtOH); $[\alpha]_D$ = −99.8° (*c* 0.46); ^{1}H NMR δ 0.96 (d, J = 6.6 Hz, 3 H), 1.10 (s, 3 H), 1.15 (s, 3 H), 1.19 (s, 3 H), 1.24−1.39 (m, 2 H), 1.49−1.77 (m, 4 H), 2.08−2.36 (m, 3 H), 2.75 (d, J = 3.8 Hz, 1 H), 3.22 (br d, J = 3.8 Hz, 1 H), 5.27 (br s, 1 H); ^{13}C NMR δ 17.23 (q), 20.20 (t), 22.63 (q), 25.71 (q), 26.77 (d), 27.87 (q), 33.64 (s), 35.33 (t), 36.43 (t), 47.25 (d), 54.20 (d), 61.34 (d), 72.90

(46) This reaction also gave a small amount (ca. 5%) of the C(3) epimer of **12** [^{1}H NMR (main peaks) δ 2.49−2.61 (m, 2 H), 3.82 (dd, J = 5.1, 3.6 Hz, 1 H), 5.22−5.52 (m, 2 H), 5.72 (m, 1 H)].

(47) In a smaller scale experiment using freshly distilled TMEDA, the yield of **16** was 82%. The same reduction procedure applied on the C(3) epimer of **12**[46] yielded **16** in 95%.

(s), 116.30 (d), 146.96 (s); MS *m/z* (relative intensity) 218 (M^+ − 18, 25), 178 (100), 163 (70), 145 (54), 134 (49), 121 (81), 119 (45), 105 (48), 93 (30), 59 (88); HRMS calcd for $C_{15}H_{22}O$ (M^+ − 18) 218.1671, found 218.1669.

[2R-(2α,4aα,5α,8*β*)]-2,3,4,4a,5,6,7,8-Octahydro-5-hydroxy-α,α,4a,8-tetramethyl-2-naphthalenemethanol (18). To an ethanolic solution of NaOEt, prepared from 75 mg (3.26 mmol) of Na and 20 mL of dry EtOH, were successively added 500 mg (3.18 mmol) of benzeneselenol and 318 mg (1.35 mmol) of **17**. The reaction mixture was refluxed for 7 h, allowed to come to rt, and then treated with 5.0 g of Raney nickel for 1 h. After filtration of the solid material, the filtrate was concentrated under reduced pressure, dissolved in $CHCl_3$, and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. Flash chromatography (5:1 to 2:1 petroleum ether (bp 40−60 °C)/EtOAc) afforded 300 mg (93%) of **18**: $[\alpha]_D = -71.7°$ (*c* 0.06); ^{1}H NMR δ 0.97 (d, J = 6.8 Hz, 3 H), 0.99 (s, 3 H), 1.11 (s, 3 H), 1.18 (s, 3 H), 1.22−1.40 (m, 2 H), 1.50−2.20 (m, 10 H), 3.21 (dd, J = 11.0, 4.6 Hz, 1 H), 5.41 (br s, 1 H); ^{13}C NMR δ 17.80 (q), 18.43 (q), 20.33 (t), 25.66 (q), 27.87 (q), 30.45 (t), 32.30 (d), 33.27 (t), 36.64 (t), 40.27 (s), 47.74 (d), 72.96 (s), 80.14 (d), 119.57 (d), 147.16 (s); MS *m/z* (relative intensity) 223 (M^+ − 15, 1), 180 (31) 162 (100), 147 (48), 133 (14), 123 (35), 105 (23), 91 (15), 81 (13), 59 (51); HRMS calcd for $C_{14}H_{23}O_2$ (M^+ − 15) 223.1698, found 223.1697.

[2R-(2α,4aα,5α,8*β*)]-2,3,4,4a,5,6,7,8-Octahydro-5-[(methylsulfonyl)oxy]-α,α,4a,8-tetramethyl-2-naphthalenemethanol (4). To a stirred solution of 298 mg (1.25 mmol) of **18** in 6 mL of pyridine was added a solution of 300 mg (2.63 mmol) of MsCl in 3 mL of pyridine at 0 °C. After stirring at 0 °C for 1 h, saturated aqueous $NaHCO_3$ was added dropwise. The reaction mixture was stirred for an additional 5 min and then extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and evaporated. After removal of the residual pyridine by azeotropic distillation with toluene, 392 mg (99%) of **4** was obtained: $[\alpha]_D$ −25.2° (*c* 0.47); ^{1}H NMR δ 0.99 (d, J = 6.4 Hz, 3 H), 1.08 (s, 3 H), 1.10 (s, 3 H), 1.18 (s, 3 H), 1.25−2.30 (m, 11 H), 2.98 (s, 3 H), 4.29 (dd, J = 11.0, 5.3 Hz, 1 H), 5.51 (br s, 1 H); ^{13}C NMR δ 18.15 (q), 18.86 (q), 20.08 (t), 25.54 (q), 27.97 (q), 28.75 (t), 32.01 (d), 32.75 (t), 36.64 (t), 38.82 (q), 39.83 (s), 47.64 (d), 72.74 (s), 90.88 (d), 121.53 (d), 145.06 (s); MS *m/z* (relative intensity) 258 (M^+ − 58, 2), 204 (7), 162 (100), 147 (40), 133 (11), 120 (11), 119 (11), 105 (18), 91 (12), 59 (28); HRMS calcd for $C_{15}H_{25}O_4S$ (M^+ − 15) 301.1474, found 301.1472.

(−)-Allohedycaryol (1). To a stirred solution of 385 mg (1.22 mmol) of **4** in 5 mL of dry THF was added 8 mL of 1 M BH_3·THF at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and additionally at rt for 2 h. After cooling to 0 °C, 1.5 mL of MeOH was added dropwise, immediately followed by 16 mL of NaOMe (2 M in MeOH). The reaction mixture was allowed to come to rt and stirred overnight. After addition of 20 mL of saturated aqueous NH_4Cl and 10 mL of 25% ammonia to the cooled reaction mixture, petroleum ether (bp 40−60 °C), was added. Stirring was continued for an additional 30 min after which the two-phase mixture was separated. The aqueous layer was extracted with petroleum ether (bp 40−60 °C) and the combined organic layers were dried over Na_2SO_4 and evaporated. The remaining residue was dissolved in a mixture of 15 mL of hexane and 5 mL of *tert*-butyl methyl ether and extracted with 20% aqueous $AgNO_3$. The combined aqueous layers were washed with *tert*-butyl methyl ether and then cooled to 0 °C. After addition of 25% ammonia, the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation gave 185 mg (68%) of pure **1**: $[\alpha]_D = -192°$ (*c* 0.92) (lit.[3] +181°); UV (CH_3CN) λ_{max} <190 nm, tail to 260 nm. The NMR and mass spectral data for (−)-**1** corresponded with those reported for natural (+)-**1**.[3]

[1R-(1α,3aα,3b*β*,6*β*,6a*β*,6bα)]-Decahydro-α,α,3a,6-tetramethyl-1-cyclobuta[1,2:3,4]dicyclopentenemethanol (19). A solution of 26 mg (0.12 mmol) of (−)-**1** in 4 mL of MeCN placed in a sealed quartz cuvet was irradiated for 14 h using a CAMAG Universal UV-lamp 29230. The reaction progress was monitored by GC. After completion, the solvent was evaporated under reduced pressure to give 25 mg (96%) of **19** (GC purity >98%): $[\alpha]_D = -1.3°$ (*c* 0.95); ^{1}H NMR δ 0.75 (d, J = 7.2 Hz, 3 H), 0.86 (s, 3 H), 1.13 (s, 6 H), 1.24 (br s, OH), 1.39−1.66 (m, 7 H), 1.73−1.96 (m, 5 H), 2.28 (ddd, J = 6.3, 6.3, 2.8 Hz, 1 H); ^{13}C NMR δ 20.28 (q), 20.57 (q), 24.55 (t), 28.27 (q), 28.48 (q), 28.84 (t), 33.31 (t), 38.57 (d), 43.19 (s,t), 44.84 (d), 50.39 (d), 51.70 (d), 61.93 (d), 71.81 (s); MS *m/z* (relative intensity) 222 (M^+, 1), 161 (8), 149 (13), 140 (8), 122 (11), 107 (14), 95 (8), 82 (100), 67 (18), 59 (40); HRMS calcd for $C_{15}H_{26}O$ (M^+) 222.1984, found 222.1983.

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Supporting Information Available: ^{1}H NMR spectra for compounds **4** and **12**−**19** (9 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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