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

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Received February 7, 1996

The enantiomer of (+)-allohedycaryol, a germacran 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 bourbon 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 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. 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. 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. 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 germacran alcohol (+)-hedycaryol (2), the name allohedycaryol was proposed for 1.

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. 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, allogermacranes are the most likely precursors of bourbonanes, a small class of sesquiterpenes possessing the cyclobuta[1,2,3]diene system. In contrast to the synthesis of trans,trans-germacrane sesquiterpenes and their double bond stereoisomers, little attention has been paid to the synthesis of the regioisomeric allogermacrane.

Because of our interest in biogenetic-like cyclization reactions of germacrane, 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. The synthesis of 4 in turn was planned starting from (+)-α-cyperone (5) via a

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(5) J. org. Chem. 1994, 59, 4755, respectively.
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number of conversions with the introduction of an equatorial hydroxyl group at C(1) 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) has been widely used as a starting material for the synthesis of various other fused-ring sesquiterpenes. Whereas (-)-10-epi-α-cyperone can be easily synthesized from (+)-dihydrocarvone, the synthetic methods leading to 5 are either rather laborious or give low yields.

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.

The key step in this synthesis was based on the deacemizing alkylation of chiral imines derived from racemic cyclanones. It was shown that in the alkylation of imine 7 derived from 6 with methyl vinyl ketone (MVK) the inherent preference for axial alkylation 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 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.

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. 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 NH₄Cl gave an unstable deconjugated ketone which was directly reduced with NaBH₄ in the presence of CaCl₂ to afford the stable allyl 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 (J₃,4) 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. 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 were performed with 12, but the results were poor. We therefore focused our attention on the stereocontrolled Sharpless epoxidation of the C(1)−C(2) double bond in 12. It was found in the literature that treatment of a β-allylic alcohol structur-
ally related to 12 with t-BuOOH catalyzed by vanadyl acetylacetonate (VO(acac)) 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 first29 (Scheme 4). In the 1H 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 H2O2 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 bond30 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.

Because reduction of the mesylate ester of 12 only gave elimination products, the removal of the C(3) hydroxy group of 12 was performed via reduction of its phosphorodiamidate with Li in EtNH2.32 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-dialixial 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 diaxial 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 1H 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 BH3/THF and NaOMe in MeOH. After purification by aqueous AgNO3 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 ([α]D −192°) was opposite to that ([α]D +181°) reported for

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26) Recently, a similar result has been found during the t-BuOOH/VO(acac)3 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 with t-BuOOH/VO(acac)3 gave selectively the corresponding α epoxide.
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.
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.34

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32) We thank Prof. Dr. G. Appendino for supplying copies of the NMR spectra of natural allohedycaryol.
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 \(\text{ent}-\)configuration,\(^3\) which is remarkable because ent-sesquiterpenes are rarely found in higher plants.\(^3\) 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.\(^4\)

The conformation of allohedycaryol was also investigated. It has been demonstrated\(^1\) that a trans,trans-cyclodec-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.\(^2\) Cyclodec-1,6-diene ring systems in which one of the double bonds bears a Me group show the same preference.\(^\text{ib}\) 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 \(\lambda = 260\) nm shows strong tailing toward the red (260 nm). This tailing indicates that both double bonds are lying parallel and close to each other.\(^1\) 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 conversion 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 \(\text{C}(4)\) 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.\(^4\)

Experimental Section 44

Materials. All reagents were purchased from Aldrich or Janssen except for N,N,N',N'-tetramethylephosphorodiamidic chloride which was purchased from Fluka. The compounds 5,\(^17\) 9,\(^16\) and 10,\(^16\) have been characterized before.

(\(+\))-\(\alpha\)-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 0 °C for 3.0–25 min, a solution of 0.2M 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, 11.0 g (11%) of 6 and 6.74 g (47%) of 5: \(\alpha\)-2: +92.2° (c 2.04) (lit.\(^4\) +91.1°). The spectroscopic data for 5 were identical with those reported in the literature.\(^17\) 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-\(\alpha\)-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 room temperature 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: \(\alpha\)-2: +161.5° (c 1.37) (lit.\(^4\) +149.0°); mp 50–51 °C (from pentane).\(^5\) Anal. Calcd for C\(_6\)H\(_{10}\)O: C, 88.42; H, 9.24. Found: C, 88.33; H, 9.47.

The spectroscopic data for 10 were identical with those reported in the literature.\(^17\)

(4aS-cis)-5,6,7,8-Tetrahydro-1,4a-dimethyl-7-(2-methylloxiranyl)-2(4aH)-naphthalenone (11). To a stirred solution of 1.195 g (9.03 mmol) of 10 in 120 mL of a 1:1 mixture of CH\(_2\)Cl\(_2\) 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 stirred at 0 °C for 3.5 h and then treated with an excess of saturated aqueous Na\(_2\)S\(_2\)O\(_3\) and saturated aqueous NaHCO\(_3\) for 20 min. The mixture was extracted with CH\(_2\)Cl\(_2\), 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: \(^1\)C NMR \(\delta 10.52\) (q), 18.08 (q), 18.51 (q), 22.75 (t), 23.25 (t).

Reference 14, p 636

(44) For a general description of the experimental procedures employed in this research, see: Kesselsmans, R. P. W.; Wijnberg, J. B. P. A.; Minnaard, A. J. J.; Walinga, R. E.; de Groot, A. J. J. Org. Chem. 1991, 56, 7237. NMR spectra were recorded at 200 MHz (\(\text{H}\)) and at 50 MHz (\(\text{13C}\)) 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.\(^15\),\(^17\)

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\(^3\) Reference 14, p 636

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(45) Previously, compound 10 was reported as an oil.\(^15\),\(^17\)
To a stirred solution of 3.60 g (17.0 mmol) of 12 in 30 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 2 h. The excess LAH was destroyed by careful addition of 2 mL of water at 0 °C. After stirring at 0 °C for 1 h, 100 mL of 10% KOH solution was added and the reaction mixture was extracted with 3 x 75 mL of ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO3 and water, dried over Na2SO4, and evaporated. The residue was purified by column chromatography (2:1 to 1:2 petroleum ether (bp 40–60 °C)/EtOAc) to afford 0.938 g (62%) of 13.

**13NMR (60 MHz, CDCl3, δ, J, ppm):**
- 1.06 (d, J = 6.7 Hz, 3 H), 1.24 (m, 1 H), 1.81 (m, 1 H), 2.68 (br q, J = 7.2 Hz, 1 H), 3.18 (s, 1 H), 3.54 (br s, 1 H), 3.57 (br d, J = 7.2 Hz, 1 H), 3.63 (s), 5.59 (s), 5.59 (s), 6.35 (t), 75.60 (d), 118.14 (d), 119.05 (d), 127.97 (d), 128.06 (d), 138.01 (s), 144.85 (s), 145.01 (s).
- MS m/z (relative intensity) 234 (M⁺, 100), 219 (45), 193 (64), 123 (67), 122 (43), 110 (46), 107 (45), 95 (49), 59 (100), 43 (54).
- HRMS calcd for C16H20O (M⁺) 252.1725, found 252.1725.

**1H NMR (700 MHz, CDCl3, δ, J, ppm):**
- 1.48 (s, 3 H), 1.49 (s, 3 H), 1.57 (m, 1 H), 1.91 (d, J = 9.0 Hz, 3 H), 1.92 (s, 3 H), 1.93 (s, 3 H), 1.96 (m, 1 H), 2.24 (s, 3 H), 2.25 (s, 3 H), 2.40 (m, 1 H), 2.50 (m, 1 H), 2.52 (s, 3 H), 2.56 (s, 3 H), 2.66 (br q, J = 7.2 Hz, 1 H), 3.16 (s), 3.18 (s), 3.53 (br s, 1 H), 3.58 (br s, 1 H), 3.61 (s), 5.59 (s), 5.59 (s), 6.35 (t), 75.60 (d), 118.14 (d), 119.05 (d), 127.97 (d), 128.06 (d), 138.01 (s), 144.85 (s), 145.01 (s).
- MS m/z (relative intensity) 234 (M⁺, 100), 219 (45), 193 (64), 123 (67), 122 (43), 110 (46), 107 (45), 95 (49), 59 (100), 43 (54).
- HRMS calcd for C16H20O (M⁺) 252.1725, found 252.1725.

**13C NMR (125 MHz, CDCl3, δ, ppm):**
- 17.23 (q), 20.20 (t), 22.63 (q), 25.71 (q), 26.77 (d), 27.87 (q), 30.88 (d), 36.43 (s), 36.74 (t), 45.49 (d), 49.20 (d), 72.93 (s), 120.02 (d), 124.75 (d), 125.50 (d), 126.01 (d), 130.67 (d), 133.42 (d), 139.15 (d), 143.49 (s), 147.94 (s); MS m/z (relative intensity) 421 (M⁺, 1), 219 (7), 161 (100), 159 (10), 145 (21), 119 (17), 105 (16), 69 (19), 59 (45); HRMS calcd for C16H18NO5Se (M⁺) 421.156, found 421.157.
1.11 (s, 3 H), 1.18 (s, 3 H), 1.22 (m, 11 H), 2.30 (m, 1 H), 2.98 (s, 3 H), 4.29 (dd, 7.2 Hz, 3 H), 0.86 (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); 13C 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) 228 (M+ 1), 161 (8), 149 (13), 140 (8), 122 (11), 107 (14), 95 (8), 82 (100), 67 (18), 59 (40); HRMS calcd for C15H26O5 (M+ 1) 222.1983, found 221.1984.

**Acknowledgment.** We thank A. van Veldhuizen for recording 1H and 13C NMR spectra and H. Jongejan for mass spectral data and elemental analyses.

**Supporting Information Available:** 1H 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.


J. O9602534