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About the Chiral Stability of Germacrene B and the Biomimetic Synthesis of Guaiane Sesquiterpenes

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The planar chirality of 15-hydroxygermacrene B (2) has been examined by means of the asymmetric Sharpless epoxidation, performed as a kinetic resolution. 1H NMR experiments with Eu(hfc)3 demonstrate that the recovered 2 is racemic. Consequently, 2 and most likely also germacrene B (1) are not enantiomerically stable at room temperature. The formation of the optically active dis-fused guaiane 4 of high ee with limited Sharpless reagent shows that the asymmetric epoxidation of 2 proceeds highly enantioselectively. The Sharpless epoxidation methodology applied on the (E,Z)-germacrene 3 results in the formation of the stable optically active epoxide 5. Acid-induced cyclization of 5, leading to a mixture of guaianes, probably proceeds via the trans-fused carbocatonic intermediate A.

Introduction

Transannular cyclization reactions of (E,E)-germacranes and their monoepoxides have attracted much attention in connection with sesquiterpene biosynthesis. It has been shown1 that a concerted mechanism in combination with a fixed conformation of the cycloeca-1(10),4-diene ring system2 of (E,E)-germacranes, at least in the transition state, accounts for the regio- and stereospecificity of these reactions. The 10-membered ring system of (E,E)-germacranes can adopt four principal conformations in which the Me(14) and Me(15) group3 are located at both sides of the ring. These conformers have either a crossed or parallel relation of the double bonds and are interconvertible by rotation of each of the double bonds.4 Independently, the C(7) substituent of (E,E)-germacranes may have two possible orientations, which in turn are related via C(7)–C(8) inversion.5 In addition, (E,E)-germacranes display planar chirality6 because the two endocyclic double bonds are approximately perpendicular to the plane of the 10-membered ring.

For germacrene B (1),7 a widespread naturally occurring (E,E)-germacrene with sp2 hybridization at C(7), the interconversion operations described above count for eight low-energy conformers: four diastereomers and their respective enantiomers. According to MNDO8 and MM29 calculations on 1, the crown conformation in which the endocyclic double bonds possess the crossed orientation with both Me(14) and Me(15) at the same side of the molecule is energetically most favorable. The preference of 1 for the crown conformation is supported by X-ray analysis of the 1:1 adduct of 1 with AgNO3.10 This X-ray analysis also revealed the presence of both the enantiomers (S,S)-1 and (R,R)-1 (1:1 ratio) in the adduct (Scheme 1).11 In another calculation study on the conformational aspects of 1, the suggestion has been made that resolution of (S,S)-1 and (R,R)-1 should be possible but that the racemization process should be quite facile.12 It was therefore challenging to study the chiral stability of 1 and related compounds13 in more detail, all the more so because the in vivo formation of 1 is assumed enantioreactive.14

The successful synthesis of 15-hydroxygermacrene B (2)15 permitted the use of the asymmetric Sharpless epoxidation, performed as a kinetic resolution,16 as a direct method for studying the chiral stability of this type of (E,E)-germacranes17 through determination of the ee of recovered 218 by means of the enantiopure shift reagent Eu(hfc)3.19 Additionally, it was expected that transannular cyclization of the asymmetric epoxidation product product

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(2) The numbering system as given in structure 1 will be followed throughout the text of this paper.
(3) In most naturally occurring (E,E)-germacranes, C(14) and C(15) are Me groups. (E,E)-Geranocaranes in which C(14) or C(15) is oxidized are also frequently found in nature, see: Connolly, J. D.; Hill, R. A. Dictionary of Terpenoids; Chapman & Hall: London, 1991; Vol. 1, Mono- and Sesquiterpenoids.
(4) During the rotation of a double bond, the vinylidene hydrogen passes through the ring.
(11) Prefixes like 5,5 denote the chirality associated with the C(1)—C(10) and the C(4)—C(5) double bond, respectively, see: Cahn, R. S.; Ingold, C.; Prelog, V. Angew. Chem. 1966, 78, 413.
(15) See preceding paper.
(17) It was assumed that replacement of a Me(15) hydrogen atom by a hydroxyl group would have no effect on the conformational behavior.18
(18) It is obvious that this ee will depend on the racemization rate of 2.
(19) (+)-Eu(hfc)3 stands for europium tris[3-(heptafluoropropyl-hydroxymethylene)-(+-)camphorate].
It is well-known that, with few exceptions, transannular cyclizations of \((E,E)\)-germacranes, or more likely their respective 1,10- and 4,5-epoxides, give eudesmane and guaiane sesquiterpenes.\(^{20,21}\) On the other hand, knowledge of the possible transannular cyclizations of the geometric isomers of \((E,E)\)-germacranes, i.e., \((Z,E)\)-germacranes (melampolides) and \((E,Z)\)-germacranes (heliangolides), appears to be limited to a few studies.\(^{22,23}\) and the accumulated results do not permit any generalization. With the heliangolide 3 available,\(^{15}\) it was obvious to investigate the cyclization behavior of the 4,5-epoxide of 3 too. From this cyclization study, it was expected that new information about the possible role of heliangolides in the biosynthesis of sesquiterpenes would be obtained.

**Results and Discussion**

The conformational behavior and enantiomer composition of 2 was studied first. Information about its conformational behavior was obtained from \(^1H\) NMR measurements at room and lower temperatures. The signals in the \(^1H\) NMR spectrum of 2 recorded at room temperature were broadened but singular.\(^{24}\) At low temperature, the number of signals increased, indicating the presence of more than one conformer. Although these observations do not necessarily imply that 2 racemizes at room temperature, they indicate that an averaged \(^1H\) NMR spectrum is obtained at room temperature.

The enantiopure shift reagent \((-)\)-Eu(hfc)\(_3\) was used to determine the enantiomer composition of 2. In the normal \(^1H\) NMR spectrum of 2, the carbinyl protons at C(15) appeared as an AB quartet (\(J = 11.7\) Hz, \(\Delta \nu_J = 5.4\)). After addition of \((-)\)-Eu(hfc)\(_3\), the signals of these protons were strongly shifted and doubled, which points to the racemic nature of 2.\(^{25}\)

As mentioned in the Introduction, a direct way to establish the chiral stability of 2 involves the asymmetric Sharpless epoxidation, performed as a kinetic resolution. Since 2 probably exists in a single (crown) conformation (vide supra), it is expected that the epoxidation of 2 will only occur from the outer face because the \(\pi\) lobe of the C(4)–C(5) double bond at the interior of the 10-membered ring is effectively shielded and not available for reaction.\(^{26}\) Consequently, only one enantiomer can undergo reagent preferred epoxidation and none of the diastereomeric epoxy alcohol would be expected to form. The Sharpless epoxidation of 2 was carried out following well-described procedures with \((+)\)-diethyl tartrate (DET) as the chiral ligand.\(^{27}\) The reaction was designed as a kinetic resolution using 0.55 equiv of tert-butyl hydroperoxide (t-BuOOH) and stoichiometric amounts of titanium isopropoxide (Ti(OiPr)\(_4\)) at \(-23^\circ\)C. Under these circumstances, the asymmetric epoxidation of 2 produced the optically active guaiane 4 \((\alpha_\beta, -52^\circ)\) in 17\% yield, together with small amounts of unidentified products (Scheme 2). The ee of 4 was found to be 92\% through chiral GC analysis.\(^{28}\) Aqueous AgNO\(_3\) extraction and chromatographical purification were applied to regain unreacted 2 (46\%). \(^1H\) NMR experiments with Eu(hfc)\(_3\) showed that this recovered 2 was racemic.\(^{29}\) This result suggests that the unreacted 2 racemizes either during the epoxidation reaction at \(-23^\circ\)C or as it warms from \(-23^\circ\)C to room temperature during the isolation process. Whatever the case may be, 2 is not enantiomerically stable at room temperature. Assuming that replacement of the hydroxyl group in 2 by a hydrogen atom has no influence on the racemization rate, germacrene B (1) will also be enantiomerically unstable at room temperature. Therefore, these compounds cannot be added to the list of enantiomerically stable \((E)\)-cycloalkenes.\(^6\) When the asymmetric epoxidation of 2 was performed with 1.1 equiv of t-BuOOH, 4 of 56\% ee was formed in 36\% chemical yield. This finding indicates that during epoxidation at \(-23^\circ\)C with a full equivalent of Sharpless reagent, racemization of 2 occurs slowly relative to the asymmetric epoxidation, so the more reactive enantiomer is not constantly replenished, and, hence, the less reactive enantiomer is epoxidized as well.

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(24) In the NMR spectra of 1, similar effects were observed.


(26) A similar reasoning has been made for the biological epoxidation of \((E,E)\)-germacranes, see: Fischer, N. H. Rech. Latinoamer. Quim. 1978, 9, 41.


(28) A gas chromatograph equipped with a Supelco 30 m BETADEXWh fused silica capillary column, 0.25 mm i.d. and 0.25 \(\mu\)m film thickness, was used. \(H_2\) was the carrier gas. Peaks were partly resolved and integrated manually.

(29) In different runs the optical rotation did not exceed 5\%. 

Initially, the elucidation of the relative stereochemistry of 4 was troublesome because of overlapped signals in its $^1H$ NMR spectrum recorded in CDCl$_3$ and C$_6$D$_6$. The use of a 1:1:1 mixture of CDCl$_3$, C$_6$D$_6$, and C$_3$D$_3$N, however, resulted in unobscured signals for both the bridgehead protons H-1 and H-5. NOE-difference experiments showed a clear NOE between these two protons, thereby establishing the cis fusion of the guaiane skeleton. The NOE observed between H-1 and the 2-propoxy group ascertained the stereochemistry at C(10). Because the C(15) carbinol group and H-5 necessarily possess the trans orientation, the stereochemistry of 4 is as depicted in Scheme 2. Structure 4 also reflects the absolute configuration. The assignment is based on the enantioselectivity principles of the asymmetric Sharpless epoxidation according to which epoxidation of 2 will preferentially take place from the S,S-conformation.  

The formation of cis-fused ($-\rightarrow$)-4 must proceed via the resolved epoxide alcohol, initially formed in the Sharpless epoxidation of 2 (see Scheme 2). Under the reaction conditions employed, this epoxide alcohol immediately reacts further by way of epoxide ring opening, probably induced by titanium species acting as Lewis acids, transannular cyclization, and incorporation of 2-propanol present in the reaction medium to afford ($-\rightarrow$)-4. Although other stereochemical courses for the cyclization of (E,E)-germacranes cannot be excluded, the formation of ($-\rightarrow$)-4 provides strong evidence for the involvement of (E,E)-germacrane epoxides in the biosynthesis of cis-fused guaianes.  

Beside guaianes possessing a cis-fused ring system, a number of trans-fused guaianes has been found in nature. In most of these trans-fused guaianes, H-5 and C(15) are located at different sides of the molecule. It has been postulated that the biosynthesis of these trans-guaianes proceeds via the 4,5-epoxides of melampolides. The isolation of guaianes possessing a syn relationship between H-5 and C(15), on the other hand, suggests the involvement of heliandolides in guaiane biosynthesis. In order to test the latter hypothesis, the heliandolide alcohol 3 was converted into its 4,5-epoxide and subjected to cyclization conditions. 

The Sharpless epoxidation of 3 was performed with excess t-BuOOH and afforded, after workup and purification, the stable epoxide 5 ($\Delta 15$-$\rightarrow$-145°) in 52% yield (Scheme 3). The sharp signals and couplings in the $^1H$ NMR spectrum suggest that 5 probably exists in one conformation at room temperature. Upon treatment of 5 with acid, a fast reaction was observed which resulted in a mixture of essentially four guaianic products in a 1:1:1:4 ratio as judged by GC. Separation of this product mixture appeared to be troublesome, and only after repeated chromatography on silica gel, one of the minor compounds, 8, could be obtained in almost pure form. A more successful separation of the remaining product mixture was achieved with AgNO$_3$-impregnated silica gel. In this way, the main product 6 ($\Delta 15$, +48°) and another minor compound, 7, contaminated with small amounts of 8, were obtained. The fourth product, most likely the C(9)-C(10) double bond isomer of 6 and 7, was lost during the latter purification step. The absence of olefinic signals in the $^1H$ NMR spectrum of 6 and the appearance of four olefinic singlets in its $^{13}C$ NMR spectrum are consistent with the assigned structure. The presence of an exocyclic double bond in 7 follows from the appearance of a broad two-proton singlet at $\delta$ 4.72 ($^1H$) and an olefinic triplet at $\delta$ 107.23 ($^{13}C$) in its NMR spectra. The vinyllic one-proton doublet ($J = 0.9$ Hz) and the three-proton doublet ($J = 7.0$ Hz) at $\delta$ 5.32 and 1.02, respectively, in the $^1H$ NMR spectrum of 8 are typical and, together with the other $^1H$ and $^{13}C$ NMR data, in full agreement with the assigned structure. 

The formation of 6, 7, and 8 presumably proceeds via the intermediate A. This tertiary carbocation can undergo proton loss to give the isomeric guaianes 6 and 7, but can also react further by way of two consecutive 1,2-H shifts (C(1) -> C(10) and C(5) -> C(11)) to afford another tertiary carbocational intermediate (B). Proton loss leading to a conjugated diene system accounts for the formation of 8 from B. Because tandem 1,2-H shifts are suprafacial and occur most likely via a concerted process, the ring junction in the initially formed intermediate A is probably trans. Combined with the syn relationship between H-5 and C(15), this has led to the stereochemistry depicted in the structures 6, 7, and 8 (Scheme 3).

(30) With (+)-DET as the chiral ligand, (R,R)-2 remains largely unoxidized, see ref 27a, pp 104–108. 
(34) The possible role of melampolides in guaiane biosynthesis is currently studied at our department. To be published.  
(35) Chiral GC could not be used to establish the ee of 5 because of its thermal instability.  
(36) Because only a single peak was observed, the ee of 6 could not be determined with chiral GC. In this respect, it should be noted that the enantioselectivity of the Sharpless epoxidation of allylic alcohols almost invariably approaches 100%. See reference 27a, p 104.  
(37) The presence of this isomer was deduced from the appearance of a broad triplet at $\delta$ 5.52 in the $^1H$ NMR spectrum of the crude product mixture.  
The reaction outcome of the cyclization of 5 reinforces our hypothesis that heliandrogens can act as precursors for guaianes with H-5 and C(15) in a syn arrangement. The formation of 8 from 5, in which probably 1,2-H shifts are involved, further suggests that the biosynthesis of naturally occurring guaianes with a C(5)-C(6) double bond and a syn relationship between H-1 and C(14)\(^{39}\) probably proceeds in the same way. Similar 1,2-H shifts have also been proposed for the biosynthesis of pseudoguaianes,\(^{40}\) but in that case a C(4) → C(5) shift of C(15) instead of proton loss follows the 1,2-H shifts. It is obvious that the syn orientation of H-5 and C(15), as in intermediate A, prevents a concerted 1,2-C shift.

Concluding Remarks

The question whether germacrene B (1) would be enantiomerically stable could be answered by the asymmetric Sharpless reagents show that the asymmetric epoxidation of e with limited Sharpless reagents.

Experimental Section\(^{42}\)

Materials. All reagents were purchased from Aldrich or Janssen. The compounds were prepared as described.\(^{33,39}\)

Kinetic Resolution/Asymmetric Epoxidation of 2. To a stirred solution of 0.134 mL (0.45 mmol) of Ti(OiPr)\(_4\) in 2 mL of dry CH\(_2\)Cl\(_2\) was added 0.00 mL (0.52 mmol) of (+)-DET at −23 °C. The solution was stirred for 5 min, and then a solution of 0.100 g (0.45 mmol) of 2 in 2 mL of CH\(_2\)Cl\(_2\) was added. After stirring at −23 °C for an additional 30 min, 0.045 mL (≈ 0.25 mmol) of t-BuOOH (5–6 M in dioxane) was added. Stirring was continued at −23 °C for 1 h, and then a mixture of 8 mL of acetone and 0.5 mL of water was added. After being stirred at −23 °C for another 30 min and at 0 °C for 3 h, the reaction mixture was filtered, and the filtrate was washed with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried, and evaporated at rt. The remaining residue was dissolved in 10 mL of tert-butyl methyl ether and added to a mixture of 5 mL of brine and 0.2 g of NaOH at 0 °C. The two-phase mixture was stirred at 0 °C for 1 h. After separation and drying, the organic layer was evaporated at rt to afford 0.115 g of the crude product mixture. This mixture was dissolved in 10 mL of tert-butyl methyl ether and extracted with five portions of 20% aqueous AgNO\(_3\). The combined aqueous layers were washed with tert-butyl methyl ether and cooled to 0 °C. After addition of 15 mL of 25% aqueous NH\(_3\), the aqueous layer was extracted with tert-butyl methyl ether. The combined organic layers were washed with brine, dried, and evaporated at rt to afford 0.037 g (37%) of the starting material 2. The tert-butyl methyl ether solution remaining after aqueous AgNO\(_3\) extraction was washed with brine, dried, and evaporated. Flash chromatography (3:1 to 3:2 petroleum ether (bp 40–60 °C)/tert-butyl methyl ether) gave, in order of elution, an additional 0.009 g (9%) of 2 and 0.022 g (17%) of (1R,1aS,4aR,8aS)-4-dehydro-1-hydroxymethyl-4-methyl-7-(1-methylthio)-4-azulenol (4): [\(\alpha\)\(_D\)]\(^{22}\) = −52.3° (c 0.38), 92% ee.\(^{39}\) \(^1\)H NMR \(\delta^{13}\) (70, 147) 236 (70), 218 (28), 205 (100), 187 (46), 147 (25), 122 (67), 107 (27), 43 (32); HRMS calc. for C\(_{19}\)H\(_{27}\)O\(_2\) (M\(^{+}\)) 296.2351, found 296.2355. This procedure was used by using 0.062 g (0.28 mmol) of 2 and 0.062 g (≈ 0.31 mmol) of t-BuOOH (5–6 M in dioxane), except that the AgNO\(_3\) extraction was omitted.

Flash chromatography (3:1 to 3:2 petroleum ether (bp 40–60 °C)/tert-butyl methyl ether) afforded 0.004 g (6%) of unreacted 2 and 0.029 g (36%) of 4: [\(\alpha\)\(_D\)]\(^{22}\) = −35.5° (c 0.69), 56% ee. (1R,2S,5S)-7-Methyl-4-(1-methylthielylenide)-(1,2-b)oxiranyl-7-cyclodecenemethanol (5). The procedure used for the epoxidation of 2 was employed by using 0.123 g (0.56 mmol) of 3 and 0.28 g (≈ 1.40 mmol) of t-BuOOH (5–6 M in dioxane). The reaction mixture was stored at −20 °C in the refrigerator overnight and worked up as described. Flash chromatography (2:1 petroleum ether (bp 40–60 °C)/tert-butyl methyl ether) afforded 0.067 g (52%) of 5: [\(\alpha\)\(_D\)]\(^{22}\) = −145° (c 0.70); \(^1\)H NMR \(\delta^{13}\) 1.31 (ddd, \(J_1 = 4.8, 13.5, 13.5\) Hz, 1 H), 1.65 (s, 6 H), 1.73 (s, 3 H), 1.80–2.30 (m, 8 H), 2.51 (m, 1 H), 2.83 (br d, \(J = 15.0\) Hz, 1 H), 3.07 (br d, \(J = 6.0, 13\) Hz, 1 H), 3.78 (dd, \(J = 6.0, 8.0\) Hz, 1 H), \(^{13}\)C NMR \(\delta^{13}\) 17.02 (q), 20.63 (q), 21.53 (q), 22.78 (t), 27.99 (t), 33.82 (t), 34.18 (t), 38.63 (t), 60.60 (d), 64.07 (t), 64.73 (s), 122.83 (d), 129.11 (s), 129.92 (s), 135.88 (s); MS m/z (relative intensity) 236 (M\(^+\)), 221, 205, 170 (70), 147 (100), 135 (94), 121 (73), 107 (96), 93 (87), 55 (80); HRMS calc. for C\(_{11}\)H\(_{20}\)O\(_2\) (M\(^+\)) 236.1776, found 236.1772. The \(^1\)H NMR spectrum of 5 revealed the presence of a small amount of 2.

The 1H NMR spectrum of 5 revealed the presence of a small amount of 2. This spectrum was recorded in a 1:1:1 mixture of CDCl\(_3\), CD\(_3\)OD, and D\(_2\)O.
\(^1\)H NMR \(\delta\) 1.56 (br s, 3 H), 1.60 (br s, 6 H), 1.55–2.60 (m, 13 H), 3.46 (d, AB system, \(J = 11.0\) Hz, 1 H), 3.65 (d, AB system, \(J = 11.0\) Hz, 1 H); \(^{13}\)C NMR \(\delta\) 20.33 (2 q), 22.21 (q), 28.82 (t), 29.47 (t), 31.94 (t), 35.17 (t), 36.07 (t), 47.35 (d), 68.49 (t), 83.12 (s), 122.71 (s), 128.99 (s), 132.07 (s), 137.40 (s); MS m/z (relative intensity) 236 (M\(^+\), 46), 218 (20), 205 (100), 187 (30), 149 (15), 123 (10), 105 (16), 97 (39); HRMS calcld for C\(_{15}\)H\(_{24}\)O\(_2\) (M\(^+\)) 236.1776, found 236.1778.

\[\{(1R,3a,8a\,\parallel)\}\}-Decahydro-1-hydroxymethyl-4-methylidene-7-(1-methylethylidene)-1-azulenol (7): \(^1\)H NMR \(\delta\) 1.20 (ddd, \(J = 3.8,\, 11.7,\, 11.7\) Hz, 1 H), 1.55–2.15 (m, 5 H), 1.60 (br s, 2 OH), 1.65 (br s, 3 H), 1.67 (br s, 3 H), 2.25–2.65 (m, 6 H), 3.50 (dd, AB system, 5.3, 10.7 Hz, 1 H), 3.62 (dd, AB system, 3.2, 10.7 Hz, 1 H), 4.72 (br s, 2 H); \(^{13}\)C NMR \(\delta\) 20.25 (2 q), 26.68 (t), 30.96 (t), 31.69 (t), 36.35 (t), 36.62 (t), 49.08 (d), 53.34 (d), 69.58 (t), 82.10 (s), 107.23 (t), 124.87 (s), 130.62 (s), 152.58 (s); MS m/z (relative intensity) 236 (M\(^+\), 15), 218 (17), 206 (15), 205 (100), 187 (37), 145 (11), 131 (12), 105 (11), 91 (14); HRMS calcld for C\(_{15}\)H\(_{23}\)O\(_2\) (M\(^+\)) 236.1776, found 236.1777.

\[\{(1R,3a,8a\,\parallel)\}\}-Octahydro-1-hydroxymethyl-4-methyl-7-(1-methylethylidene)-1-azulenol (8): \(^1\)H NMR \(\delta\) 1.02 (d, \(J = 7.0\) Hz, 3 H), 1.20 (m, 1 H), 1.60 (br s, 2 OH), 1.68 (br s, 3 H), 1.71 (br s, 3 H), 1.60–2.70 (m, 9 H), 3.61 (dd, AB system, \(J = 4.8,\, 10.6\) Hz, 1 H), 3.72 (br d, AB system, \(J = 10.6\) Hz, 1 H), 5.32 (br s, 1 H); \(^{13}\)C NMR \(\delta\) 20.19 (q), 20.66 (q), 20.77 (q), 29.93 (t), 30.52 (t), 33.30 (t), 35.47 (d), 42.80 (t), 51.01 (d), 69.30 (t), 83.55 (s), 120.06 (d), 124.44 (s), 132.31 (s), 152.68 (s); MS m/z (relative intensity) 236 (M\(^+\), 57), 218 (54), 205 (100), 187 (86), 149 (30), 145 (32), 131 (30), 121 (32), 91 (32), 55 (33), 41 (30); HRMS calcld for C\(_{15}\)H\(_{23}\)O\(_2\) (M\(^+\)) 236.1776, found 236.1776.

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Supporting Information Available: \(^1\)H NMR spectra for compounds 4–8 (5 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.