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THE CONFORMATIONAL CONTROLLED STEREO- AND REGIO-SELECTIVE SYNTHESIS OF CYCLOPROPANE DERIVATIVES OF 8-HYDROXY-GERMACRENE B

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Abstract—On the basis of the known preferential conformations of 8-oxo-germacrene B **7** it was possible to predict the resulting configurations at the chiral centres upon $LiAlH_4$-reduction and cyclopropanation. Further analysis of 8-hydroxy-germacrene B, **1** and the cyclopropane derivatives of **7**, **8** and **9** afforded the prediction that the ultimate product distribution of the 4,5- and 1,10-cyclopropane derivatives of **1** (i.e. **2–5**) will be essentially independent of the reaction sequence. The prediction was vindicated by the observation of stereo- and regio-selective formation of **2–5**, on reaction of **7** with the Simmons–Smith reagent and $LiAlH_4$. Assignment of the relative configurations at the three chiral centres in each of the products **2–5** could be achieved by combining the two reaction routes. This assignment was based on an earlier performed conformational analysis of **1**.

During our investigations on the photochemistry of allylic substituted germacrene B derivatives it was found that the photochemical behaviour of these derivatives is mainly determined by the endocyclic 1,5-diene fragment. Irradiation of 8-hydroxy-germacrene B **1** leads to an exclusive [1,3]-OH shift.[1] In particular, the 1,10-double bond is thought to be important as its orientation is favourable for homo-allylic anchimeric assistance. In order to obtain further insight with respect to the mechanism, we prepared the corresponding compounds **2–5** in which either the 4,5- or the 1,10-double bond is replaced by a cyclopropane ring.

The introduction of a cyclopropane group leads to the formation of two new, coupled, chiral centres on either the C atoms 4 and 5 or 1 and 10. It is to be expected that the stereoselectivity of the cyclopropanation will depend on the conformational equilibrium of **1**, thus controlling the configuration at the chiral centres. A correspondence between ground state conformation and product structure was shown before.[2] In order to evaluate relative stabilities of the conformers in the ground state, force field calculations have been carried out.[3] For germacrene B **6** it was found that the crossed orientation of the endocyclic double bonds is the most stable conformation. However, the orientation of the exocyclic double bond was not predicted correctly. Therefore Fransen *et al.*[4] performed quantum-chemical calculations with the semi-empirical MNDO-method on **1** thus including the effect of the OH-substituent. These calculations led to a correct outcome of the most stable conformer (Fig. 1).

For 8-oxo-germacrene B **7** the crossed orientation of the endocyclic double bonds and the preferential location of the exocyclic double bond in the plane of the

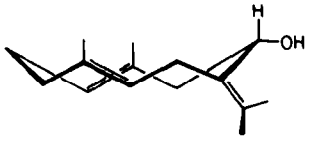

Fig. 1. Most stable conformer of (*S*)-8-hydroxy-germacrene B **1**.

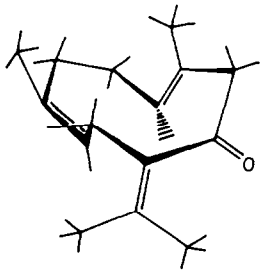

Fig. 2. Preferential conformation of 8-oxo-germacrene B **7**.

CO group, in order to permit optimal conjugation, will result in a conformation as depicted in Fig. 2.

Comparison of the Figs 1 and 2 warrants the conclusion that in both cases cyclopropanation of one of the endocyclic double bonds will lead to the same preferential configuration on either C-4 and C-5 or C-1 and C-10. Furthermore, Dreiding molecular models show that upon cyclopropanation of 8-oxo-germacrene B **7**, a molecule will be formed with a similar preferential crossed orientation of the remaining double bond and the substituted one. Thus in both cases, upon $LiAlH_4$-reduction, hydride-attack is more likely to occur from the front-side. We can now predict that changing the sequence in which the cyclopropanation and the $LiAlH_4$-reduction are carried out will only have a slight effect on the ultimate product distribution.

RESULTS AND DISCUSSION

In Fig. 3 the two reaction routes for the synthesis of the compounds **2–5**, starting from 8-oxo-germacrene B **7**, are shown.

As it was impossible to get a complete separation of the resulting mixtures and since no information concerning the relative abundances of the cyclopropane derivatives of **7** (**8** and **9**) was available, the determination of the relative configurations of **2–5** could only be accomplished by combining the two routes. By carrying out route A it could be established that in case of the products **2** and **3** the 4,5-double bond

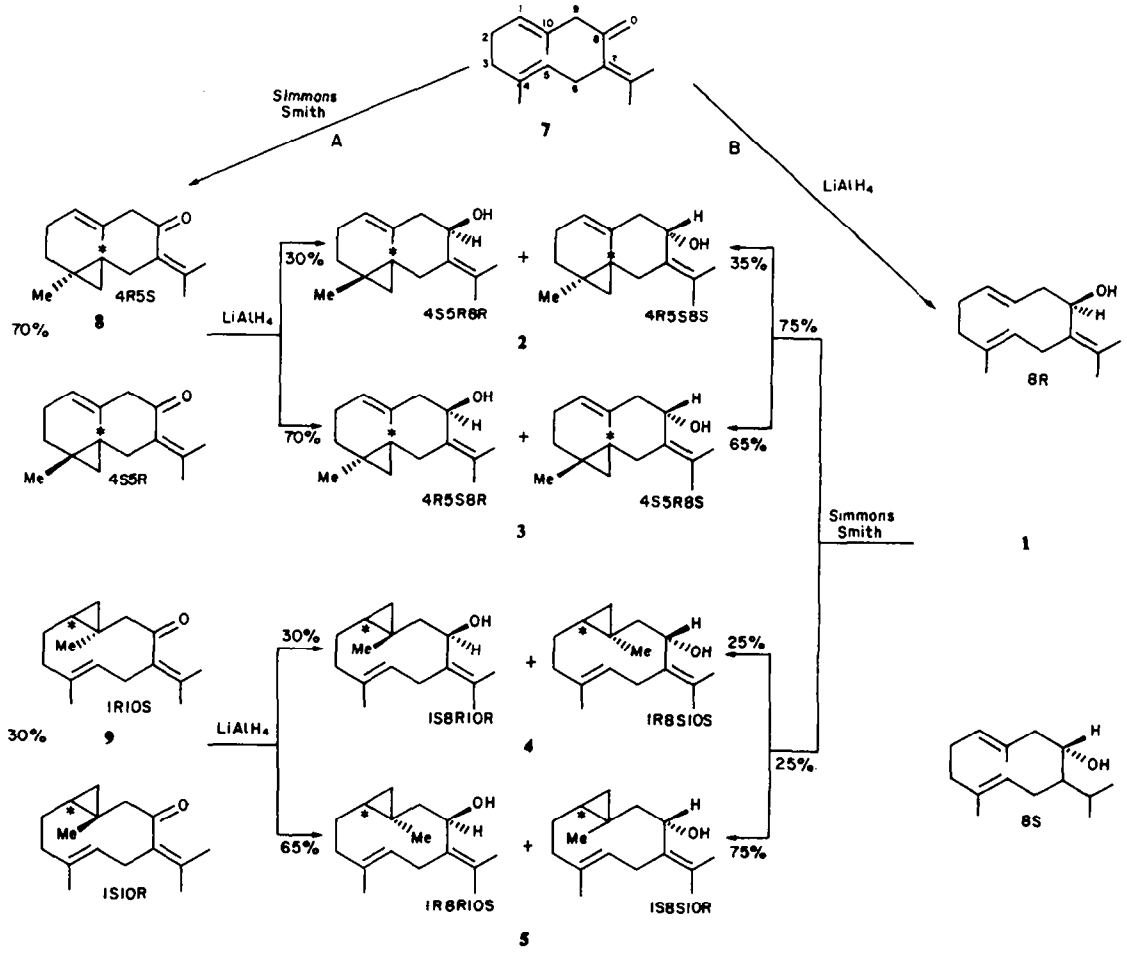

Fig. 3. Two possible reaction routes for the synthesis of 4,5- and 1,10-cyclopropane-8-hydroxy-germacrene B (2–5) from 8-oxo-germacrene B (7).

is replaced by a cyclopropane group, whereas in case of the products **4** and **5** the same happened to the 1,10-double bond. Thereupon, route B offered the possibility to use the results of earlier performed conformational calculations on **1**[4] to make an unambiguous assignment of the relative configurations to the compounds **2–5**.

Reaction route A

A commonly used method for the synthesis of cyclopropane derivatives from olefins is the one that makes use of the Simmons–Smith reagent.[5,6] This reagent consists of an iodomethylzinc iodide complex that reacts regioselectively in a *cis* fashion. Reaction of 8-oxo-germacrene B **7** with the Simmons–Smith reagent led to the formation of 2 products. GLC indicated that the products, which were identified as racemic mixtures of 4,5- and 1,10-cyclopropane-8-oxo-germacrene B (**8** and **9** respectively), were formed in a ratio of 70 : 30. No 7,11-cyclopropane derivatives could be detected. This difference in reactivity of the double bonds was noted before[4,7] and may be attributed to differences in sp^2–sp^2 and sp^2–sp^3 torsional strain.

Upon $LiAlH_4$-reduction of **8** the racemic mixtures **2** and **3** (4*SR*; 5*RS*; 8*RS* and 4*RS*; 5*SR*; 8*RS*) were formed in a ratio of 30 : 70 (as indicated by GLC). $LiAlH_4$-reduction of **9** led to the formation of the racemic mixtures **4** and **5** (1*SR*; 8*RS*; 10*RS* and 1*RS*; 8*RS*; 10*SR*) in a ratio of 35 : 65.

Reaction route B

GLC indicated that on cyclopropanation of $LiAlH_4$-reduced 8-oxo-germacrene B **7** the same products **2–5** were formed as in the case of route A. The racemic mixtures **2** and **3** were formed in a ratio of 35 : 65 respectively, whereas the ratio **4** : **5** was 25 : 75. The total amount of 4,5-cyclopropane-8-hydroxy-germacrene B (= **2** and **3**) versus the total amount of 1,10-cyclopropane-8-hydroxy-germacrene B (= **4** and **5**) was 75 : 25.

Assignment of the relative configurations

Upon substitution of either the 4,5- or the 1,10-double bond by a cyclopropane group, two new, coupled chiral centres are created. The configuration at these C atoms is determined by the conformation of the double bond in the substrate since reaction of the Simmons–Smith reagent takes place at the sterically least hindered side of the double bond. As can be seen from Fig. 4 we can predict that on the one hand the *R*(*S*)-conformation of the 4,5-double bond will result in a *R*(*S*)-configuration on C-4 and a *S*(*R*)-configuration on C-5, while on the other hand upon substitution of the 1,10-double bond the *R*(*S*)-conformation will result in a *S*(*R*)-configuration on C-10 and a *R*(*S*)-configuration on C-1.

8-Hydroxy-germacrene B **1** incorporates three double bonds. Each of them can adapt the *S* or *R* orientation according to Prelog's rule for planar

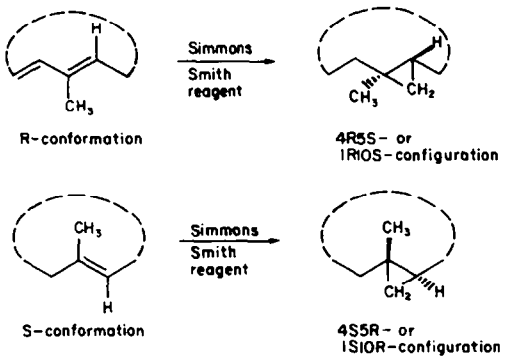

Fig. 4. Relation between the substrate conformation of the double bond and the product configuration upon reaction with the Simmons–Smith reagent.

Table 1. Calculated heats of formation and relative populations at 30° of all stable conformers of (*S*)-8-hydroxy-germacrene B 1[4]

Conformation	ΔH_f (kcal.mol^{-1})	n_i^r (%)
SSS	-13.24	76.3
SSR	-9.14	0.1
SRS	-9.41	0.1
SRR	-10.32	0.6
RSS	-12.00	9.7
RSR	-10.37	0.7
RRS	-11.91	8.4
RRR	-11.48	4.1

chirality,[8] thus resulting in eight possible conformations for both configurations on C-8. In Table 1 the heats of formation and the relative populations at a reaction temperature of 30° of all stable conformers of (*S*)-8-hydroxy-germacrene B **1** are shown.[9]

From this Table it can be seen that at 30°, 77.1% of the conformers possess the *S*-conformation for the 4,5-double bond. This leads to the assignment of the configuration 4*RS*; 5*SR*; 8*RS* to the product with the highest yield (**3**). Similarly, since 86.8% of the conformers possess the *S*-conformation for the 1,10-double bond we can assign the configuration 1*RS*; 8*RS*; 10*SR* to **5**.

Structure elucidation

The structure elucidation of the several products could be accomplished by ^{13}C- and ^{1}H-NMR spectroscopy including the use of shift reagents. The ^{13}C-NMR spectra of **8** and **9** show four olefinic signals: three singlets and one doublet. The appearance in the ^{1}H-NMR spectra of the characteristic resonance of a cyclopropane ring at about 0 ppm shows that in both compounds one endocyclic double bond is replaced by a cyclopropane group. In order to distinguish the 4,5- and 1,10-cyclopropane derivatives, ^{1}H-NMR Eu(fod)$_3$ shift experiments were carried out.

As can be seen from Fig. 5, one of the four Me-groups displays hardly any shift. Dreiding molecular models show that this is possible only for the C-15 Me since the Me-groups 12, 13 and 14 are much closer to the CO group. By comparing the resonance of the four Me-groups in the original ^{1}H-NMR spectra it can be concluded that **8** is a racemic mixture of 4,5-cyclopropane-8-oxo-germacrene B, while **9** must be a racemic mixture of 1,10-cyclopropane-8-oxo-germacrene B. In the case of compound **8**: δH_{12} = 1.81 ppm, δH_{13} = 1.81 ppm, δH_{14} = 1.75 ppm and δH_{15} = 0.83 ppm. This means that C-15 Me is an aliphatic Me-group whereas C-12, C-13 and C-14 Me are three olefinic groups. In the case of compound **9**: δH_{12} = 1.77 ppm, δH_{13} = 1.67 ppm, δH_{14} = 1.02 ppm and δH_{15} = 1.56 ppm. Thus C-15 Me is an olefinic Me-group, whereas C-12, C-13 and C-14 Me form one aliphatic and two olefinic Me-groups.

The structure determination of the LiAlH$_4$-reduced products **2**–**5** could be accomplished by comparing the resonances of C-8 in the ^{13}C-NMR spectra. The shift of this resonance from a value of about 200 ppm (singlet)

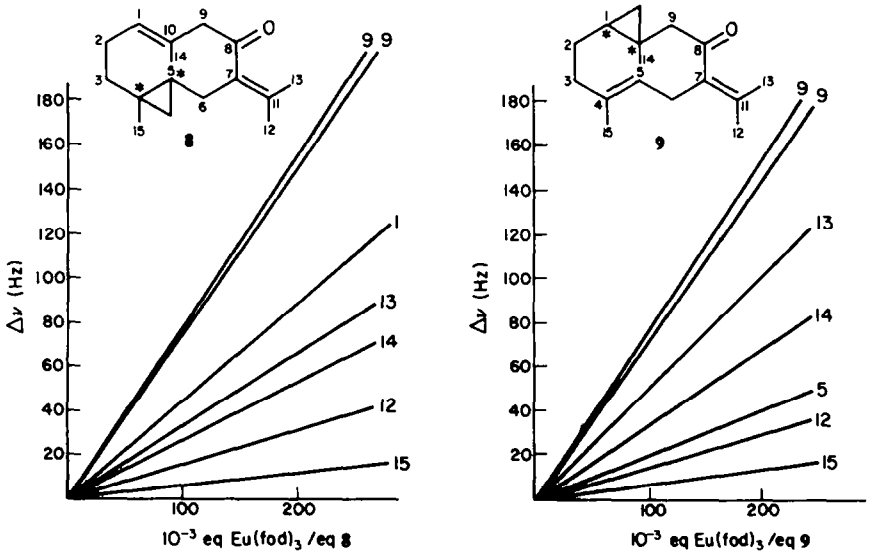

Fig. 5. The induced chemical shift, Δν, versus the amount of added shift reagent for protons of **8** and **9**.

to a value of about 75 ppm (doublet) shows unambiguously that the CO group is reduced to an OH group.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian EM-360 A (60 MHz) spectrometer with TMS as an internal reference ($\delta = 0$). ^{13}C-NMR spectra were recorded on a Bruker HX-90 R spectrometer equipped with a Digilab FTS-NMR-3. Gaschromatograms were recorded with a Kipp Analytica 8200 equipped with a flame-ionization detector. Columns used were Chrompack fused silica wall, open tubular columns with CP Wax 51 as liquid phase (25 m × 0.23 mm). Preparative HPLC separations were accomplished on a Jobin Yvon Miniprep LC using silica H (type 60, Merck). Argentation chromatography was performed using impregnated silica, prepared by evaporating to dryness of a slurry of silica (type 60, Merck) and 10% $AgNO_3$ in CH_3CN. 8-Hydroxy-germacrene B 1 was prepared according to literature.[10]

4,5- and 1,10-Cyclopropane-8-oxo-germacrene B (8 and 9)[11]

A mixture of Zn (1.32 g, 20.2 mmol) and CuCl (2 g, 20.2 mmol) in 30 ml dry ether was refluxed under N_2 pressure for 30 min. Compound 7 (1 g, 4.58 mmol) was added, followed by CH_2I_2 (2.7 g, 10.1 mmol). The resulting mixture was stirred for 24 hr at a temp of 30° and then filtered. The filtrate was washed with satd NH_4Cl aq and brine, dried on $MgSO_4$ and evaporated. Separation of the mixture was performed with repeated argentation chromatography using hexane–acetone 95:5 as eluent.

Compound **8**; ^{1}H-NMR ($CDCl_3$): δ 0.35––0.12 (br, 3H), 0.83 (s, 3H), 1.25 (m), 1.75 (s, 3H), 1.81 (s, 6H), 2.23 (m, 2H), 2.70 (br), 3.19 (m, 2H), 5.20 (br, 1H). ^{13}C-NMR ($CDCl_3$): δ 205.71 (s), 140.01 (s), 132.13 (2x, s+d), 125.82 (s), 56.39 (t), 40.95 (dd), 31.66, 26.52 (2x), 23.28, 22.35, 21.04, 19.55 (2x).

Compound **9**; ^{1}H-NMR ($CDCl_3$): δ 0.37––0.11 (br, 3H), 1.02 (s, 3H), 1.17 (m), 1.56 (s, 3H), 1.67 (s, 3H), 1.77 (s, 3H), 2.06 (m), 2.89 (br), 3.05 (dd, 2H), 4.99 (br, 1H). ^{13}C-NMR ($CDCl_3$): δ 211.52 (s), 140.09 (s), 134.78 (s), 128.31 (s), 123.91 (d), 56.55 (dd), 40.12 (t), 30.58, 25.86, 24.51, 22.70, 20.46, 19.38, 19.14, 18.31, 16.32.

$LiAlH_4$-reduction of **8**

To a stirred suspension of 0.1 g of $LiAlH_4$ (3 mmol) in 10 ml of anhydrous ether was added dropwise, at 0°, a soln of 1 g of **8** (4.3 mmol) in 10 ml of ether. After 0.5 hr additional stirring the mixture was allowed to warm up to room temp. After decomposition of the aluminates, usual work-up afforded 1 g (100%) of **2** and **3**. GLC showed this mixture to consist of 30% **2** and 70% **3**. Despite several attempts, using column chromatography, argentation chromatography and preparative HPLC, it was impossible to separate the mixture.

Compounds **2** and **3**; ^{1}H-NMR ($CDCl_3$): δ 0.38––0.17 (m), 0.70 (s), 1.72 (s), 1.84 (s), 1.86 (s), 2.83–0.53 (m), 3.45 (m), 4.20 (m), 4.59 (m), 5.07 (m). ^{13}C-NMR ($CDCl_3$): δ 139.06, 132.18, 131.44, 130.23, 129.76, 128.95, 128.41, 78.46, 74.41, 48.05, 46.37, 40.71, 40.44, 33.70, 28.30, 26.15, 25.94, 23.25, 22.98, 22.57, 22.24, 20.38, 19.74, 19.34, 18.93.

$LiAlH_4$-reduction of **9**

The same procedure was used as for reduction of **8**. GLC showed the mixture to consist of 35% **4** and 65% **5**. The mixture was separated by column chromatography (hexane–ether, 1:1).

Compound **4**; ^{1}H-NMR ($CDCl_3$): δ 0.31––0.21 (br, 3H), 0.85 (s, 3H), 1.56 (s, 3H), 1.74 (s, 3H), 1.86 (s, 3H), 3.43–0.42 (br), 4.36 (dd, 1H), 5.29 (t, 1H). ^{13}C-NMR ($CDCl_3$): δ 136.30 (s), 135.56 (s), 130.23 (d), 124.43 (s), 72.39 (d), 49.20 (dd), 40.23 (t), 31.67 (t), 28.44, 23.72, 22.91, 22.81, 22.24, 20.15, 19.27, 18.19.

Compound **5**; ^{1}H-NMR ($CDCl_3$): δ 0.26––0.17 (br, 3H), 1.02 (s, 3H), 1.67 (s, 3H), 1.72 (s, 3H), 1.82 (s, 3H), 3.21–0.67 (br), 4.05 (dd, 1H), 4.79 (dd, 1H). ^{13}C-NMR ($CDCl_3$): δ 139.06 (s), 134.21 (s), 129.02 (d), 125.51 (s), 73.81 (d), 52.91 (dd), 40.77 (t), 34.57 (dd), 26.21, 22.84, 22.37, 21.97, 19.20, 19.07, 18.80, 18.46, 16.91.

Cyclopropanation of **1**

The same procedure was used as for the cyclopropanation of **7**. GLC indicated that the products **2–5** were formed in ratios of 35:65 (**2**:**3**) and 25:75 (**4**:**5**).

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