Tetrahedron Vol 39, No 18, pp 2981 to 2987, 1983
Printed in Great Britain

0040-4020/83 $3.00 + .00

CONFORMATIONAL DEPENDENT REGIO- AND STEREO-SELECTIVITY IN TRANSFORMATIONS OF GERMACRENES

A THEORETICAL AND EXPERIMENTAL APPROACH

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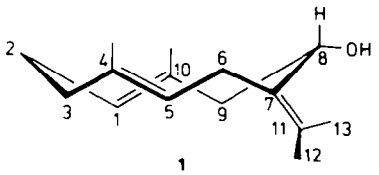
(*Received in UK 6 January* 1983)

Abstract—Conformational calculations on 8-hydroxy-germacrene B **1** with the MNDO method led to a correct prediction of the most stable conformer. Reaction of **1** with diimide resulted in regio-selective reduction which leads to the formation of two racemic mixtures of 4,5-dihydro-8-hydroxy-germacrene B (**2** + **3**). The ratio of **2** and **3** could be predicted by conformational analysis. The regioselectivity of the reduction may be attributed to differences in sp_2–sp_3 torsional strain between the endocyclic double bonds. Upon $LiAlH_4$ reduction of 4,5-dihydro-8-oxo-germacrene B **10** conformational induced asymmetric induction results in a highly stereospecific process in which **2** and **3** are formed in a ratio of 9·1.

During our investigations on the photochemistry of rigid 1,5-dienes it was found that irradiation of 8-hydroxy-germacrene B **1** leads to an exclusive [1,3]–OH shift.[1] As



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a part of the mechanism it was suggested that the endocyclic double bonds play an essential role. In particular the 1,10-double bond is thought to be important as its orientation is favourable for homo-allylic anchimeric assistance. Therefore the synthesis of 4,5-dihydro-8-hydroxy-germacrene B **2** + **3** was carried out. The introduction of a new chiral centre on C_4 leads to the formation of two racemic mixtures. It is to be expected that the stereoselectivity of the reduction will depend on the conformational equilibrium of **1** thus controlling the configuration at C_4 in **2** and **3**. Conformation of 10-membered ring sesquiterpenes analogue to **1** has been studied extensively, in connection with the biosynthesis of many other types of sesquiterpenes.[2] Frequently a correspondence was shown between ground state conformations and product structure.[3] Molecular mechanics calculations have been carried out often to evaluate relative stabilities of the conformers in the ground state.[4] For germacrene B **4** it was found that the crossed orientation of the endocyclic double bonds is the most stable conformation. This is in agreement with the experimental results.[5] However the orientation of the exocyclic double bond was not predicted correctly. So we 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.

Studies concerning the chemistry of important biosynthetic precursors as germacrenes and humulenes have been aimed mainly at conformational dependent transannular cyclization reactions.[6] As far as addition reactions with the double bonds of germacrene-derivatives are concerned only catalytic hydrogenation[7] of 8-oxo-germacrene B **5**, resulting in formation of a tetrahydro derivative **6**, and epoxidation of **4** and **5**[8] has been reported. A difference in reactivity of the double bonds was observed in the epoxidation reactions: 4,5 > 1,10 ≫ 7,11. These differences were thought to originate from sp_2–sp_2 torsional strain in the double bonds. This is based on the results of X-ray molecular structure analysis of the germacrene–silvernitrate (1:1) adduct (Allen, Rogers[5]). Our MNDO calculations clearly predict the preferential reactivity of the 4,5-double bond as a result of sp_2–sp_3 torsional strain.

Conformational analysis. Compound **1** incorporates one exocyclic and two endocyclic double bonds. Each of these double bonds has two possible orientations leading to a stable conformer. These orientations which can be defined with Prelog's rules for planar chirality,[9] result in eight stable conformations for both configurations on C_8.† These conformers are interconverted by single or multiple rotations of the planes of the double bonds. The starting geometry for one of the conformers was estimated from a Dreiding molecular model. The steric energy of this conformer was minimized by means of MMI-calculations.[10] Starting from this optimized structure the initial geometries of the other conformers were found by a single rotation of 170° around the 4,5- and, or 1,10-double bond. The change in conformation of the exocyclic double bond can be brought about by a change of the dihedral angle (5, 6, 7, 8) by 140° resulting in flipping of the C_6-methylene and the exocyclic double bond. Values for the angle variations used were estimated from Dreiding models. The resulting structures were optimized to a fully relaxed geometry. Coordinates found in this way were used as starting values for the MNDO calculations.[11] In order to reduce the computer time needed the geometries were optimized with respect to 48 of the 114 internal coordinates. Bond lengths, angles and dihedral angles of the hydroxyl function and

†Calculations were carried out on conformers with (S)8-configuration.

Table 1. Heats of formation and relative populations (at 60°) of all stable conformers of (S)-8-hydroxy-germacrene B 1

Conformer	ΔH_f (kcal.mol^{-1})	relative populations (%)
SSS	-13.238	72.0
SSR	- 9.143	0.1
SRS	- 9.406	0.2
SRR	-10.138	0.9
RSS	-12.004	11.1
RSR	-10.369	1.0
RRS	-11.914	9.7
RRR	-11.478	5.0

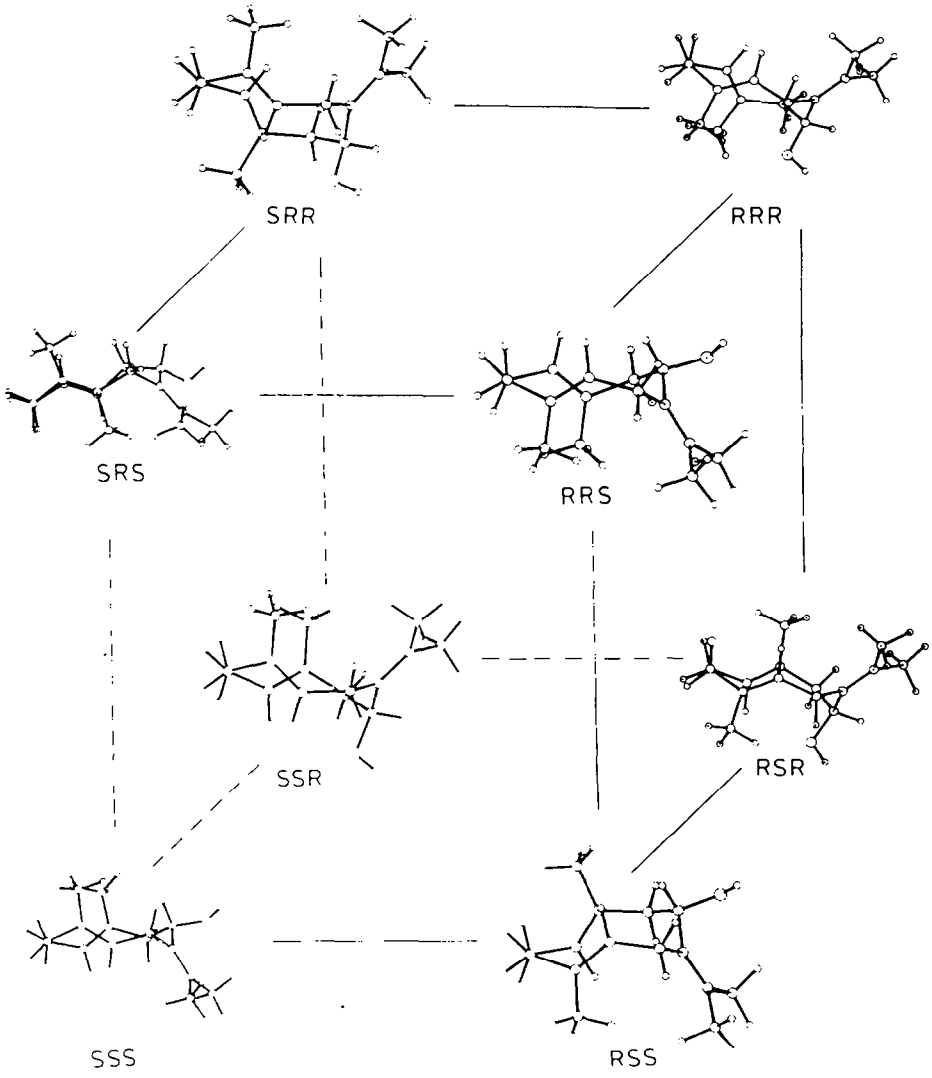
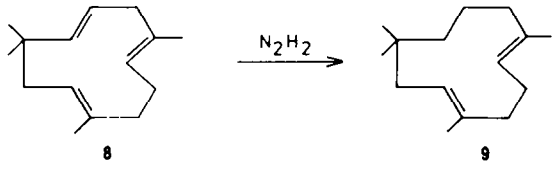


Fig. 1. Correlation diagram among eight stable conformers of (S)-8-hydroxy-germacrene B 1, depicted as their ORTEP-drawings.

all carbon atoms except the methyl groups were optimized. In addition the dihedral angles of all atoms linked directly to the ring or the exocyclic methylene function were optimized. The heats of formation of the eight conformers are given in Table 1. ORTEP-drawings of the optimized structures are depicted in Fig. 1 in a conformation-correlation diagram.† Conformers are interconvertible along each edge of the cube by a single rotation of one of the double bonds.‡

Our MMI calculations on **1** resulted in the SSR-conformer as the most stable one, in agreement with the published results for **4**.[4a,b] MNDO calculations lead to the SSS-conformer as the most stable one. The preference for the SSS-conformer with the latter calculation is supported by the X-ray analysis of a germacrene–silver nitrate adduct.[5]

Diimide reductions. It has been reported[7] that hydrogenation of **5** in a selective way, leading to a tetrahydro derivative, asks for a seven day reaction time with Pt as a catalyst. A difference in reactivity between both endocyclic double bonds was observed upon epoxidation and is in agreement with the theoretical predictions (*vide supra*). Efforts to carry out the catalytic hydrogenation of **5** with uptake of one equivalent of H_2, under varying conditions (Pd/$BaSO_4$, Ni_2B and Pt/C–Pd/C) were not successful. In the case of reduction of **1** also poor results were obtained. Reduction with 5% Pt/C in ethanol yielded about 10% of 4,5-dihydro derivative **2**. Apparently in all cases isomerization of the double bond occurs. A highly selective reducing agent was found in diimide. It is known that this reagent reacts regioselectively in a *cis* fashion.[12] Diimide could be conveniently prepared by reaction of hydroxylamine with ethylacetate.[13] The reduction of **1** by diimide has been carried out at moderate temperatures (60–70°). At lower temperatures disproportionation of diimide is too fast while at higher temperatures the substrate is converted to the Cope-rearranged product. Reduction in this way appeared to proceed in a highly regioselective way. GLC indicated that two products were formed in a ratio of 6:4, which were identified as racemic mixtures of 4,5-dihydro-8-hydroxy-germacrene B: 4S8S + 4R8R (**2**) and 4S8R + 4R8S (**3**) respectively. No 1,10- or 7,11-dihydro derivatives could be detected. Long reaction times resulted in formation of 1,10,4,5-tetrahydro-8-hydroxy-germacrene B **7** but careful control of reaction time enables complete conversion of **1** with only a small yield of 7. In order to test the regioselectivity of diimide, the closely related sesquiterpene humulene **8** was subjected to reduction. In this case steric factors appear to play a predominant role. Diimide reduces exclusively the least hindered 4,5-double bond, although this is the least reactive one,[14] yielding 4,5-dihydro-humulene **9**.



8 **9**

Upon reaction of racemic **1** with diimide a second chiral centre is created (C_4). The configuration at this C atom is determined by the conformation of the 4,5-double bond in the substrate. The reaction with diimide proceeds by a simultaneous transfer of both H atoms from the least hindered side of the double bond.[12] As shown in Fig. 2 we can predict now that the S(R)-configuration is formed from an S(R)-conformation in the substrate. The relative populations of the diverse conformers as calculated from the heats of formation show that at 60° (reaction temp) about 75% possesses the S-conformation for the 4,5-double bond (Table 1). This leads to the assignment of the configuration 4S8S and (4R8R) to the product with the highest yield, (**2**).

Conformational controlled asymmetric induction. Reducing the 4,5-double bond of **1** yielded **2** and **3** in a ratio of 6 : 4 as dependent on the conformation

†A similar correlation diagram was used previously in Ref. [2b].

‡Prefixes like SSS denote planar chirality of the three double bonds 4,5–1,10 and 7,11 respectively.

Table 2. Potential energy contributions resulting from strain of 4,5- and 1,10-double bonds as calculated from the geometry of the SSS-conformer of **1**.

$C_4=C_5$			$C_1=C_{10}$		
angle (deg)		E (kcal.mol^{-1})	angle (deg)		E (kcal.mol^{-1})
a (3,4,5)	119.08	0.149	a (9,10,1)	119.99	0.071
b (4,5,6)	130.56	1.281	b (10,1,2)	130.30	1.206
c (19,3,4,15)	140.09	1.496	c (24,9,10,14)	155.55	0.713
d (20,3,4,15)	29.37	1.033	d (25,9,10,14)	42.00	0.412
e (2,3,4,15)	98.97	1.453	e (8,9,10,14)	82.18	0.602
f (22,6,5,21)	172.97	0.067	f (18,2,1,16)	163.02	0.370
g (23,6,5,21)	71.51	0.176	g (17,2,1,16)	46.39	0.243
h (7,6,5,21)	49.97	0.135	h (3,2,1,16)	73.38	0.236
w (2,3,4,5)	18.12	2.625	w (2,1,10,9)	18.54	2.750
	E_{tot}	8.415		E_{tot}	6.603

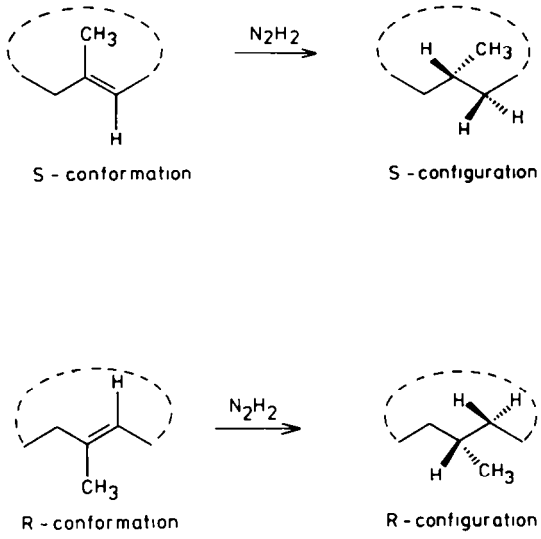
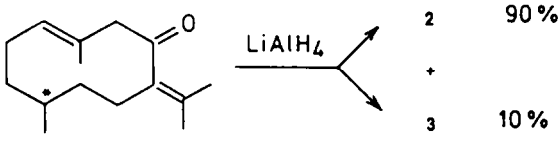


Fig. 2. Substrate conformation of the 4,5-double bond determines product configuration upon reaction with diimide.

of **1** in the ground state. Upon $LiAlH_4$-reduction of a racemic mixture of 4,5 - dihydro - 8 - oxo - germacrene B **10**, **2** and **3** were formed in a ratio of 9:1. This means



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that the S(R)-configuration on C_4 results in a preferential hydride-attack yielding predominantly the S(R)-configuration on C_8. Thus nearly complete asymmetric induction occurs, which is rather unexpected in view with the large spatial distance between the chiral centre and the location of hydride-attack. An explanation of this phenomenon is based on the conformation of the substrate. This conformation will be determined by two factors: preferential location of the exocyclic double bond in the plane of the CO group in order to permit optimal conjugation and the position of the Me-group on the chiral centre. This results in a conformation as depicted in Fig. 3. From this it is evident that hydride-attack is much easier from the front-side.

Strain-reactivity correlation. As mentioned before the reaction of **1** with diimide results in a regiospecific 4,5-double bond reduction. Difference in reactivity of the double bonds was noted previously upon epoxidation of **4** resulting in a product distribution of 65:35:0 (4,5:1,10:7,11).[8b] The explanation was based on the geometry of **4** as determined in the silver nitrate adduct. The greater reactivity of the 4,5-double bond was attributed to a larger sp_2–sp_2 torsion around this double bond. It should be realized however that complexation with Ag^+ may have invoked changes in geometry. MMI-calculations on humulene **8** showed that the sp_2–sp_2 torsion is much less important as might be concluded from the X-ray data of its silver nitrate adduct.[4c] On the basis of our MNDO calculations we tried to find a correlation between the regioselective behaviour of **1** and differences in strain between the double bonds. Garbisch[15] demonstrated that the major factors contributing to reactivity differences in reactions of alkenes with diimide are torsional strain and bond angle bending strain, thereby assuming that steric factors are of the same order. Making the assumption that the transition states are analogue for reduction of the 4,5- and 1,10-double bonds the ratio of the rateconstants for reduction of the double bonds ($k_{4,5}$ and $k_{1,10}$) can be expressed as:

$$-RT \ln(k_{4,5}/k_{1,10}) = \Delta E_\phi + \Delta E_\omega + \Delta E_\alpha.$$

The terms on the r.h.s. are the differences in potential energy contributions between both double bonds of respectively sp_3–sp_2 torsion, sp_2–sp_2 torsion and bond angle bending strain (Fig. 4).

Our MNDO calculations for the most stable conformation of **1** indicate that sp_2–sp_2 torsion is considerable but nearly the same for both endocyclic double bonds (Table 2). For the exocyclic double bond this torsion is negligible thus explaining the lack of reactivity of this bond. The degree of bond angle bending is also comparable for both types of double bonds. A considerable difference however is found for the sp_3–sp_2 strain contributions. The calculated differences in strain energy result in a difference in reactivity of 94:6, which is completely in agreement with our experimental results. Therefore we conclude that sp_2–sp_2 torsion explains the difference in reactivity between the endocyclic double bonds and the exocyclic double bond. The regioselective reactions with the 4,5-double bond are caused by the greater sp_3–sp_2 torsion. Apparently the geometry of **4** in a silver nitrate adduct is influenced to some extent by Ag^+.

Structure elucidation. The structure determination of **2** and **3** could be accomplished by ^{13}C and ^1H NMR spectroscopy including the use of shift reagents. ^{13}C NMR spectra revealed that both **2** and **3** have two double bonds left, a tri- and a tetrasubstituted one (**2**: doublet 129.06 ppm, singlets 137.93, 133.37 and 129.56 ppm; **3**: doublet 128.41 ppm; singlets 136.97, 132.59 and 130.97 ppm). The secondary OH function conjugated with a double bond is still intact (**2**: doublet 76.46 ppm; **3**: doublet 75.49 ppm).

In order to distinguish the 4,5- and 1,10-dihydro derivatives ^1H NMR $Eu(fod)_3$ shift experiments were carried out. The results show clearly (Fig. 5) that the signal of the aliphatic Me-group does not display any shift at all. Molecular models show unambiguously that this is possible only for the C_{15}-Me since C_{14} is much closer to the OH function and certainly would shift upon addition of $Eu(fod)_3$. Also both **2** and **3** must be stereoisomers of the 4,5-dihydro derivative of **1**. This was confirmed by separate oxidation of both products by

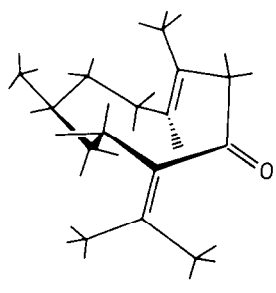


Fig. 3. Preferential conformation of **10**.

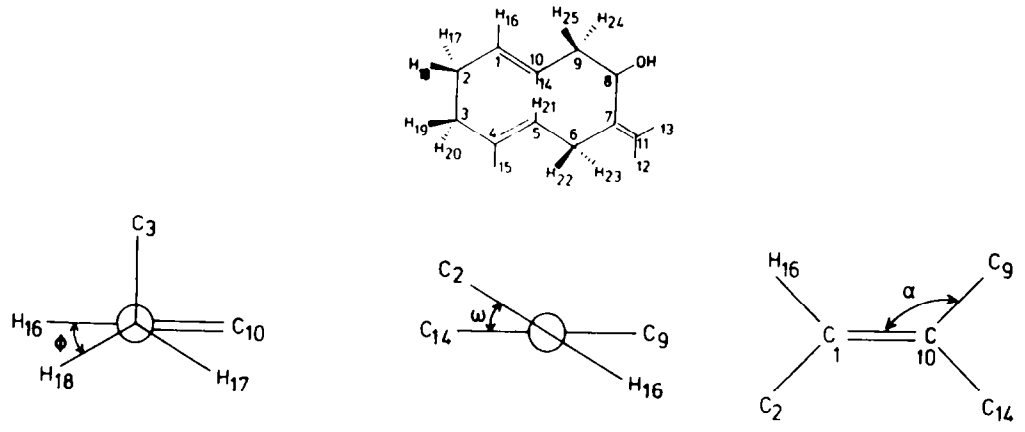


Fig. 4. Various types of strain around the 1,10-double bond.

pyridine dichromate, resulting in formation of the same compound, 4,5-dihydro-8-oxo-germacrene B **10**. (Scheme 4).

Since optical rotation is zero for both components it may be concluded that **2** and **3** are racemic mixtures (4S8S + 4R8R and 4S8R + 4R8S) as is confirmed by addition of a chiral shift reagent† which results in splitting up of the ^{1}H NMR signals.

†Tris(3 - heptafluoropropylhydroxymethylene) - d - camphorato) europium (III) derivative.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian EM-360 A (60 MHz) spectrometer with Me_4Si as an internal reference (δ = 0). ^{13}C NMR spectra were taken on a Bruker HX-90 R spectrometer equipped with a Digilab FTS-NMR-3. Preparative HPLC separations were accomplished on a Jobin Yvon Miniprep LC using silica H (type 60, Merck). 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 for separation of germacrene-derivatives and CP Sil 5 for humulenes (25 m × 0.23 mm and 25 m × 0.25 mm resp.) Argentation chromatography was performed using impregnated silica, prepared by

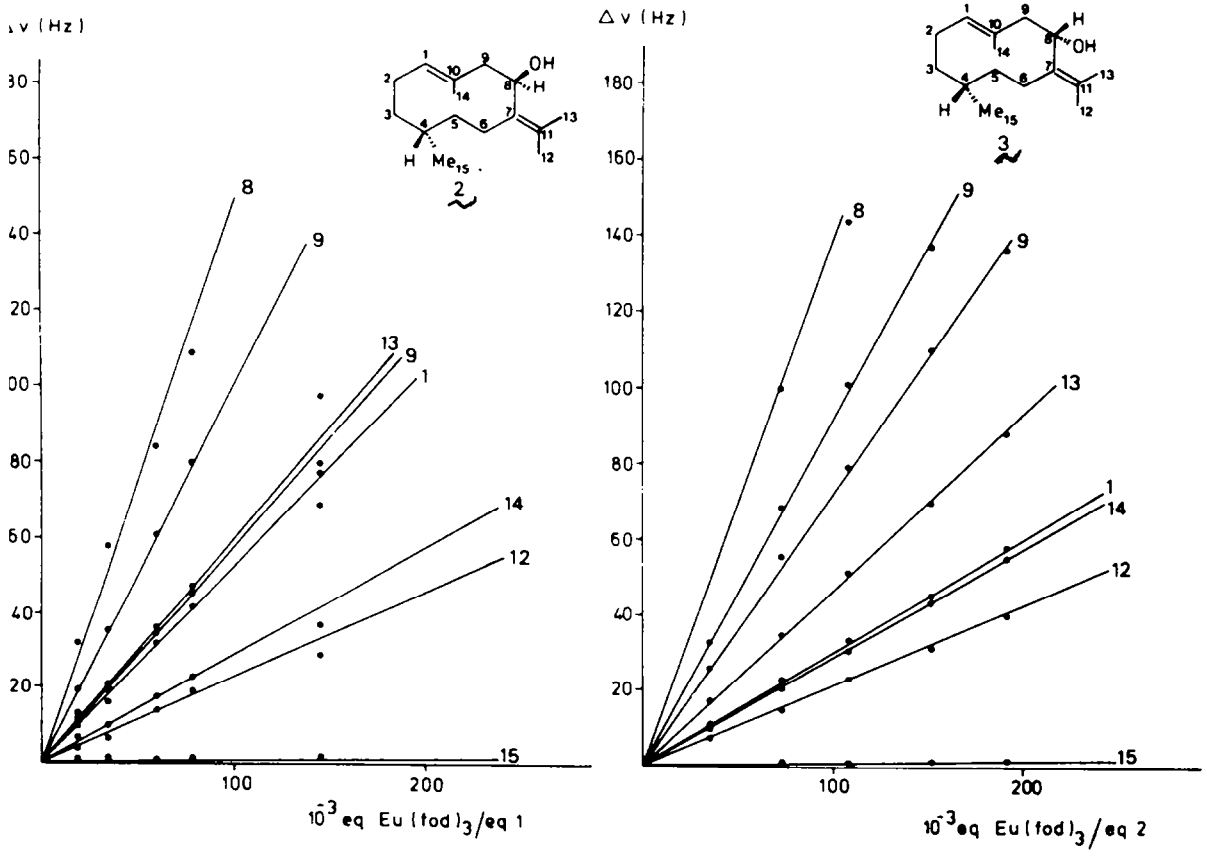
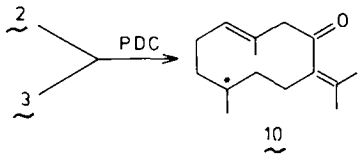
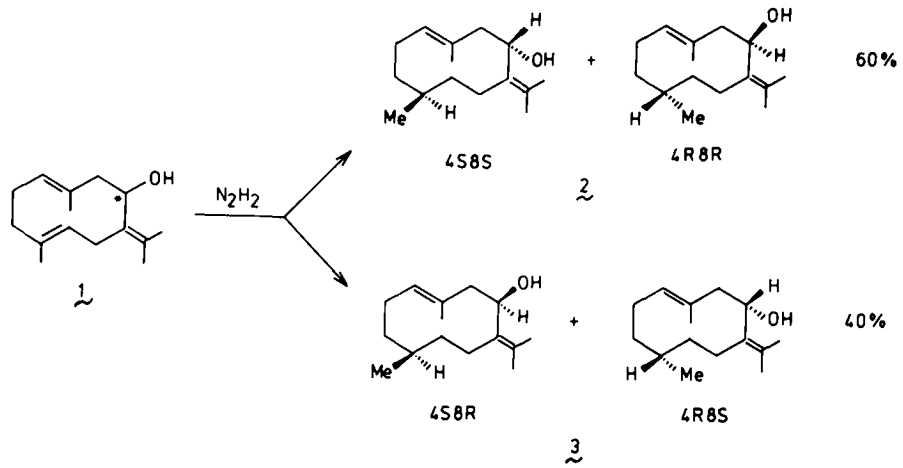


Fig. 5. Plot of the induced chemical shift, $\Delta\nu$, vs the amount of added shift reagent for protons of **2** and **3**.



137.38 (s), 134.14 (s), 126.12 (d), 125.31 (d), 40.57, 39.76, 38.75 (2x), 34.91, 30.06 (2x), 26.41, 24.12, 18.73, 16.77.

[4,5]-*Dihydro - 8 - oxo - germacrene B* (**10**). A soln of **2** or **3** (3 g, 13.5 mmol) was added, under N_2, to a stirred suspension of pyridine dichromate[16] (7.6 g, 20 mmol) in 50 ml CH_2Cl_2 at room temp. TLC ($CHCl_3$) indicated that reaction was complete after



evaporation to dryness of a slurry of silica (type 60, Merck) and 10% $AgNO_3$ in MeCN. Mps were determined on a Fisher–Johns block and are uncorrected. Germacrol **1** was prepared according to literature.[2a]

4,5-Dihydro-8-hydroxy-germacrene B (**2+3**)[13]. Powdered KOH (25.2 g) was added to a stirred soln of hydroxylamine hydrochloride (31.3 g, 0.45 mol) in 100 ml dimethylformamide at 25–35°, under N_2. The resulting mixture was stirred for another 10 min and then filtered under N_2 pressure. The filtrate was cooled in an ice-bath and EtOAc (17.65 g, 0.198 mol) was added. The resulting soln was dropped quickly into a soln of 2 g of **1** (0.009 mol) in 25 ml of DMF at a temp of 60–70°. GC indicated that after 3 hr reaction was complete. The mixture was poured into water and extracted with pentane. The organic layer was washed with water, dried on $MgSO_4$ and evaporated. Separation of the mixture was performed with preparative HPLC using hexane/ether 1:1 as eluent, yielding three components, **2**, **3** and **7** in yields of 50%, 35% and 5% respectively. If the second component, **3**, was contaminated with unreacted **1** this could be removed by argentation chromatography (hexane/ether 1:1). Compound **2**; ^{1}H NMR($CDCl_3$): δ 0.82 (s, 3H), 0.89 (m), 1.39 (m), 1.68 (s, 3H), 1.70 (s, 3H), 1.85 (s, 3H), 2.0 (m), 2.24*† (dd, 1H), 2.54* (dd, 1H), 2.57* (br, 1H), 4.80 (t, 1H), 5.43 (t, 1H). ^{13}C NMR ($CDCl_3$): δ 137.93 (s), 133.37 (s), 129.56 (s), 129.06 (d), 76.46 (d), 46.35 (t) 35.64, 33.82 (2x), 26.69, 23.70 (2x), 22.62, 21.46, 20.79. Compound **3**; ^{1}H NMR ($CDCl_3$): δ 0.87 (s, 3H), 0.92 (m), 1.35 (br m), 1.68 (s, 3H), 1.80 (s, 3H), 1.85 (s, 3H), 2.0 (m), 2.29* (dd, 1H), 2.57* (dd, 1H), 4.44 (dd, 1H) 5.27 (t, 1H). ^{13}C NMR ($CDCl_3$): δ 136.97 (s), 132.59 (s), 130.97 (s), 128.41 (d), 75.49 (d), 46.37 (t), 36.80, 35.11, 31.47, 29.72, 25.54, 23.18 (x2), 22.10, 19.74. Compound **7**; ^{1}H NMR ($CDCl_3$): δ 0.92 (m), 1.33 (m), 1.40 (s, 3H), 1.70 (s, 6H), 2.33 (br m), 4.75 (dd, 1H). ^{13}C NMR ($CDCl_3$): δ 134.41 (s), 131.85 (s), 70.97 (d), 41.25 (t), 37.07, 36.59, 32.89, 29.72, 28.91, 24.80, 24.12, 22.98, 21.70.

[4,5]-*Dihydrohumulene* (**9**). The same procedure was used as for reduction of **1**. Reaction of 3 g of **8** yielded after HPLC-separation (hexane) 2.25 g (75%) of **9**. ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 6H), 1.22, 1.43, 1.53, 1.8, 2.07, 4.8 (t, 2H). ^{13}C NMR ($CDCl_3$): δ

†Positions of signals marked by * were determined from shift experiments by extrapolation to 0 mg Eu(fod)$_3$.

2 hr. The mixture was diluted with ether, filtered and separated by column chromatography ($CHCl_3$, silica 60). Evaporation yielded 2.7 g (90%) of **10**, m.p. 53°. ^{1}H NMR (CCl_4): δ 0.85 (m), 0.92 (s, 3H), 1.21 (br m), 1.63 (s, 3H), 1.68 (s, 3H), 1.73 (s, 3H), 2.12 (br t, 4H), 3.1 (AB-q, $_A$2.97, $_B$3.23, J_{AB} = 3.6 Hz, 2H), 5.33 (t, 1H). ^{13}C NMR ($CDCl_3$): δ 207.71 (s), 139.43 (s), 132.87 (d), 131.88 (s), 126.49 (s), 56.80 (t), 34.98, 34.48, 30.75, 28.34, 26.10, 23.70, 22.62, 21.54, 18.22.

Reduction of **10** *by* $LiAlH_4$. To a stirred suspension of 0.1 g of $LiAlH_4$ (0.003 mol) in 10 ml dry ether was added dropwise, at 0°, a soln of 1 g of **10** (0.005 mol) in 10 ml of ether. After 0.5 hr additional stirring the mixture was allowed to warm to room temp. After decomposition of the aluminates, usual work-up afforded 0.9 g (90%) of **2+3**. GC showed this mixture to consist of 90% of **2** and 10% of **3**.

Catalytic reduction of **1**. A mixture of 1 g of **1** in 20 ml EtOH and 100 mg catalyst was stirred under H_2 at atmospheric pressure for 48 hr or until one equivalent of H_2 had been consumed. The mixture was filtered and the solvent evaporated. 5% Pd/C and 5% Pt/C yielded complex mixtures of isomerized and reduced products. The mixture resulting by reduction with the Pt catalyst yielded after repeated HPLC-separations (hexane/ether 1:1) 10% of **2**. Nickel boride (P2), Pd/$BaSO_4$ and Lindlar catalyst yielded no reaction at all. All catalysts used were commercially available, except nickelboride which was prepared according to lit.[17]

Acknowledgements—This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

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