Photochemistry of 4,5-dihydro-8-hydroxygermacrene B

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Photochemistry of 4,5-dihydro-8-hydroxygermacrene B

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Abstract. Irradiation of two racemates of 4,5-dihydro-8-hydroxygermacrene B (**2**, **3**) results, in addition to *E–Z* isomerization, in the occurrence of a [1,3]-C shift. Conformational differences between the diastereoisomers are reflected in a highly stereospecific photoreaction.

Introduction

Our investigations into the photochemistry of 8-hydroxygermacrene B (**1**) have demonstrated the occurrence of an exclusive photochemical [1,3]-OH shift[1]. In particular, the 1,10-double bond is thought to be important in that its orientation is favourable for homo-allylic anchimeric assistance. This prompted us to investigate the photochemistry of 4,5-dihydro-8-hydroxygermacrene B (**2**, **3**), which was obtained by reduction of **1** with diimide resulting in two racemates of 4,5-dihydro-8-hydroxygermacrene B: (4*SR*,8*SR*)-**2** and (4*SR*,8*SR*)-**3** in the ratio 6/4. The regioselectivity of the reduction was attributed to differences in sp^2–sp^3 torsional strain between the endocyclic double bonds (see Fig. 1).

Upon $LiAlH_4$ reduction of a racemate of 4,5-dihydro-8-oxogermacrene B (**4**), obtained by oxidation of a mixture of **2** and **3**, a ratio of 9/1 for **2** and **3**, respectively, was realized[2]. This implies that the *S(R)*-configuration on C-4 results in a preferential hydride-attack yielding predominantly *S(R)*-configuration on C-8. Thus, almost complete asymmetric induction occurs, which is somewhat unexpected, in view of the large spatial distance between the chiral centre and the location of hydride attack. It would appear that the conformation of **4** is determined by the preferential location of the exocyclic double bond in the plane of the carbonyl group, which permits optimal conjugation together with the location of the methyl group on the chiral centre.

Results

Irradiation of 4,5-dihydro-8-hydroxygermacrene B

The title compound, 4.5-dihydro-8-hydroxygermacrene B (**2**, **3**), prepared by reduction of **1** with diimide[2], comprises two chiral centres and thus exists in two racemates: (4*SR*,8*SR*)-**2** and (4*RS*,8*SR*)-**3**. The ^{1}H NMR spectra and the results of experiments employing shift reagents *(vide infra)* indicate that the conformation in both pairs is markedly different. As expected, this difference in conformation is reflected in the photochemical behaviour of the compounds (see Fig. 2).

Irradiation of (4*SR*,8*SR*)-**2** led to the formation of three products: the *Z*-isomer **5** and two pairs of enantiomers **6** and **7**. All three products were formed at comparable rates. After *ca.* 3 h, **2** was completely converted. Prolonged irradiation yielded a large number of secondary products. Irradiation of (4*RS*,8*SR*)-**3** yielded two primary photoproducts: the *Z*-isomer **8** and product **9**, which is a diastereoisomer of **6** and **7**. The secondary photoproduct **10** was formed after a relatively short irradiation period.

[1] *H. R. Fransen* and *H. M. Buck*, J. Chem. Soc., Chem. Commun. 786 (1982).

[2] *H. R. Fransen, G. J. M. Dormans* and *H. M. Buck*, Tetrahedron **39**, 2981 (1983).

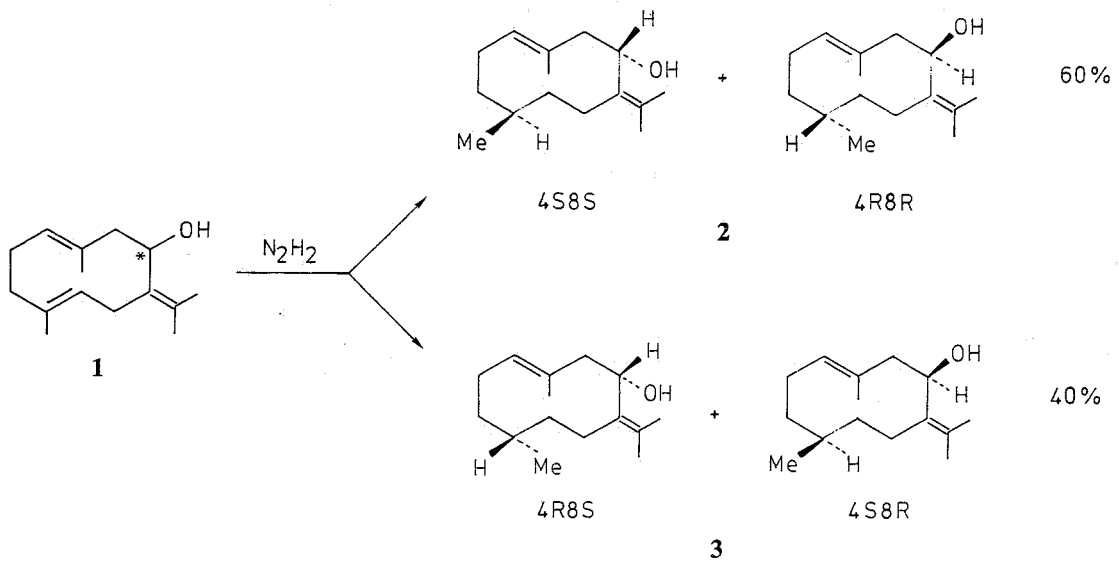


Fig. 1. Regiospecific reduction of 8-hydroxygermacrene B (**1**).

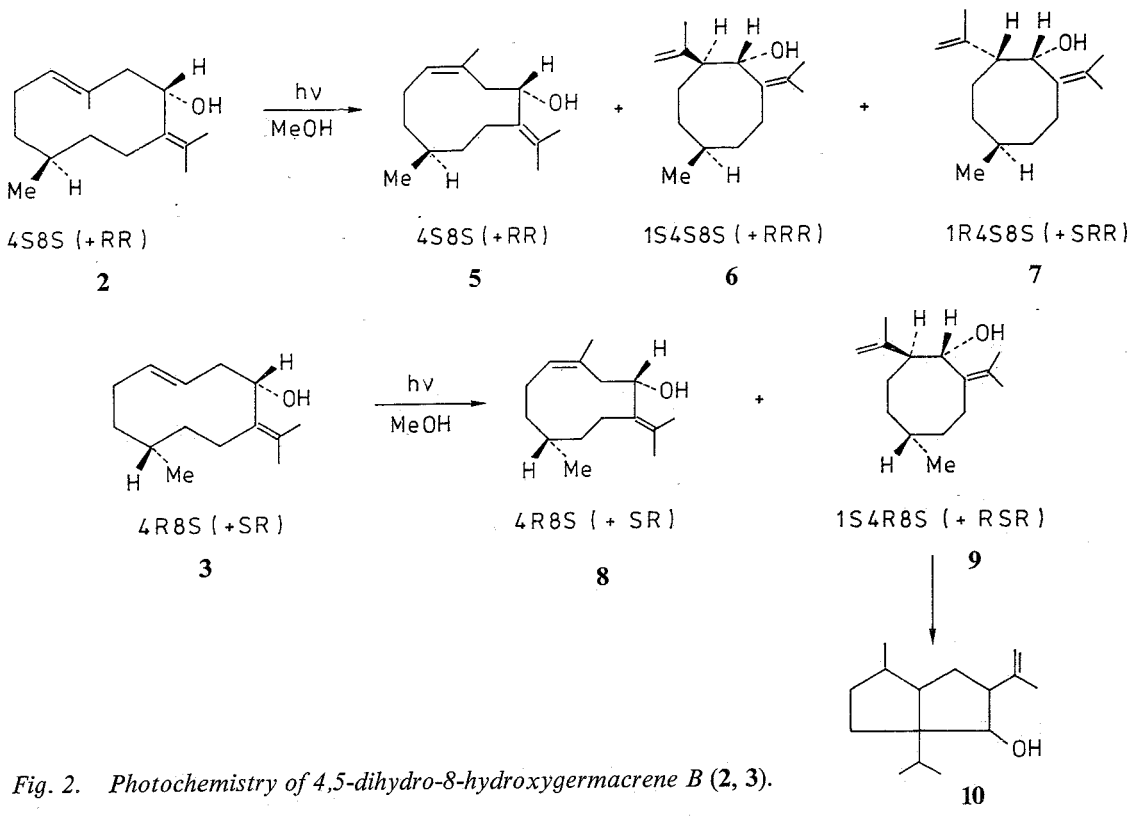


Fig. 2. Photochemistry of 4,5-dihydro-8-hydroxygermacrene B (**2**, **3**).

Further irradiation again yielded a plethora of over-irradiation products.

Mechanistic considerations

In contrast to **1**, the compounds **2** and **3** display a [1,3]-C shift upon irradiation, yielding **6**, **7** and **9** with the *Z*-isomers **5** and **8**. The formation of the latter isomers is to be expected, since geometrical isomerization is the principal photochemical reaction of alkenes. The [1,3]-C shift involves a C-8 migration over the allylic fragment C-9,C-10,C-1 towards C-1, leading to an additional chiral centre on C-1. The number of chiral carbon atoms then increases to three which means that both the compounds **2** and **3** should each produce two racemates. However, only three pairs of enantiomers were formed. An explanation for this result is to be found in the conformation of the starting compounds (see Fig. 3). The conformations depicted here were derived from the ^{1}H NMR data regarding the multiplet structure of the proton signal of H_A (hydrogen at C-8), which results from coupling with the neighbouring protons H_B and H_C (both attached to C-9). Protons B and C are chemically inequivalent (**2**: δ_{BC} = 18 Hz, **3**: δ_{BC} = 16.8 Hz and J_{BC} = 12–13 Hz). Since the chemical shift difference between B and C is larger than J_{BC}, the coupling constants J_{AB} and J_{AC} can be derived from the ^{1}H NMR spectra by considering the resonance of proton A as the X-part of a first-order ABX spin system[3], *i.e.* **2**: $J_{AB} = J_{AC}$ = 3.6 Hz and **3**: J_{AB} = 7.2 Hz, J_{AC} = 5.5 Hz. The relationship between the vicinal coupling constant J and the dihedral angle ϕ between the protons is given by the *Karplus* equations[4]:

$$J_{H,H} = 8.5 \cos^2 \phi - 0.28 \quad \text{for} \quad 0° \leq \phi \leq 90°$$

$$J_{H,H} = 9.5 \cos^2 \phi - 0.28 \quad \text{for} \quad 90° \leq \phi \leq 180°$$

It should be mentioned, however, that the above represents the most simple form of this particular equation. Studies by *Haasnoot* and *Altona*[5] yielded expressions in which, for example, the influence of electronegative substituents is included. Since we are not interested in exact angles, a simplified version was employed. For **2** it is evident that H_A lies between H_B and H_C. Application of the *Karplus* equation to **3** reveals that the OH group is now situated between H_B and H_C. The approximate dihedral angles, $\phi(H_A,C\text{-}8,C\text{-}9,H_B)$ and $\phi(H_A,C\text{-}8,C\text{-}9,H_C)$, are 41° and 155°, respectively. The dihedral angles calculated in this way result in the conformations shown in Fig. 3. Further

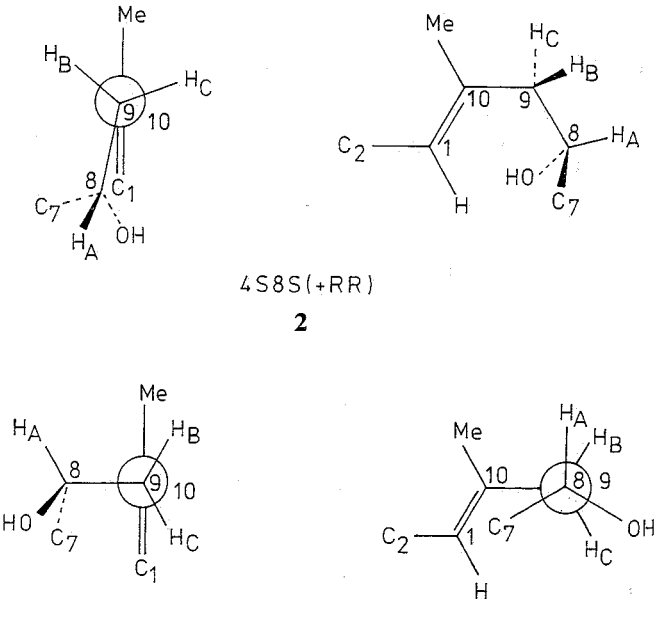


Fig. 3. Conformation of **2** *and* **3**.

[3] *D. H. Williams* and *I. Fleming*, "Spectroscopic methods in organic chemistry", McGraw-Hill, London, 1980.

[4] *M. Karplus*, J. Am. Chem. Soc. **85**, 2870 (1963).

evidence was provided by ^{1}H NMR Eu(fod)$_3$ shift experiments (see Fig. 4). Both the chemical shift of the protons attached to C-9 (H_B and H_C) and the shift of the proton attached to C-1 confirm the proposed conformations of **2** and **3** as depicted in Fig. 3.

It is now clear that for **2** the C-8,C-9 bond, which is involved in the shift, lies approximately in the same plane as the allyl fragment C-1,C-10,C-9. As a result, C-8 may shift at both sides of the plane with equal probability, leading to the formation of both possible configurations at C-1. GLC analysis of the reaction mixture confirms that products **6** and **7** are formed at comparable rates. Compound **3**, however, displays a stereospecific photoreaction. The C-8,C-9 bonding is almost perpendicular to the plane formed by C-1, C-10 and C-9. A shift at the front of the molecule is far more favourable than at the rear. Thus, one configuration will result and only (1*SR*,4*RS*,8*SR*)-**9** is formed. Secondary photoproduct **10** originates from **9** and its formation can be explained by a radical reaction in which a hydrogen of C-3 moves to C-11 by a 1,6-H abstraction in a favourable transition state. This type of reaction, the so called olefin type II[6], is often found in large cycloalkenes.

Structural assignment of photoproducts

Identification of *Z*-isomers **5** and **8** was accomplished by comparison with the spectral data of the corresponding starting compounds. All spectra show only small differences; in the ^{13}C spectra, all multiplicities of the signals remain unchanged. A confirmation of the *Z*-configuration of the double bond is obtained by considering C-9. It is known from the literature[7] that, in the case of *Z*-alkenes, the resonances of the allylic atoms are upfield compared to the corresponding *E*-isomers, as is shown in the spectra of **5** and **8**. (**2**: $\delta_{C\text{-}9}$ 46.35 ppm, **5**: 39.96 ppm; **3**: $\delta_{C\text{-}9}$ 46.37 ppm, **8**: 39.16 ppm). The spectra of compounds **6**, **7** and **9** are very similar, indicating that these three compounds are stereoisomers. As far as **6** is concerned, the ^{13}C spectra show the presence of four olefinic signals, *i.e.* three singlets and one triplet, indicating that two double bonds are still present. The singlet olefinic signals at 132.4 and 133.0 ppm and the position of the methyl signals in the ^{1}H NMR spectra (1.7–1.8 ppm) reveal the presence of the isopropylidene function. The appearance of the ^{13}C doublet at 72.1 ppm (C–OH), combined with an ^{1}H doublet (1H) at 4.22 ppm, indicates that the allyl alcohol fragment has remained unchanged. The olefinic signal with triplet multiplicity at 113.1 ppm indicates the presence of an exocyclic vinylic double bond, which is confirmed by comparison of the relevant ^{13}C resonances with those of isopulegol (**11**) and pulegol (**12**) (see Table I)[8]. These

[5] *C. A. G. Haasnoot, F. A. A. M. de Leeuw* and *C. Altona*, Tetrahedron **36**, 2783 (1980).
[6] *Y. Inoue, S. Takamuku* and *H. Sakurai*, Can. J. Chem. **54**, 3117 (1976).
[7] *J. W. de Haan* and *L. J. M. van de Ven*, Org. Magn. Reson. **5**, 147 (1973); *P. A. Couperus, A. D. H. Clague* and *J. P. C. M. van Dongen*, Org. Magn. Reson. **8**, 426 (1976).
[8] *L. F. Johnson* and *W. C. Jankowski*, "Carbon 13 NMR spectra", John Wiley, New York, 1972.

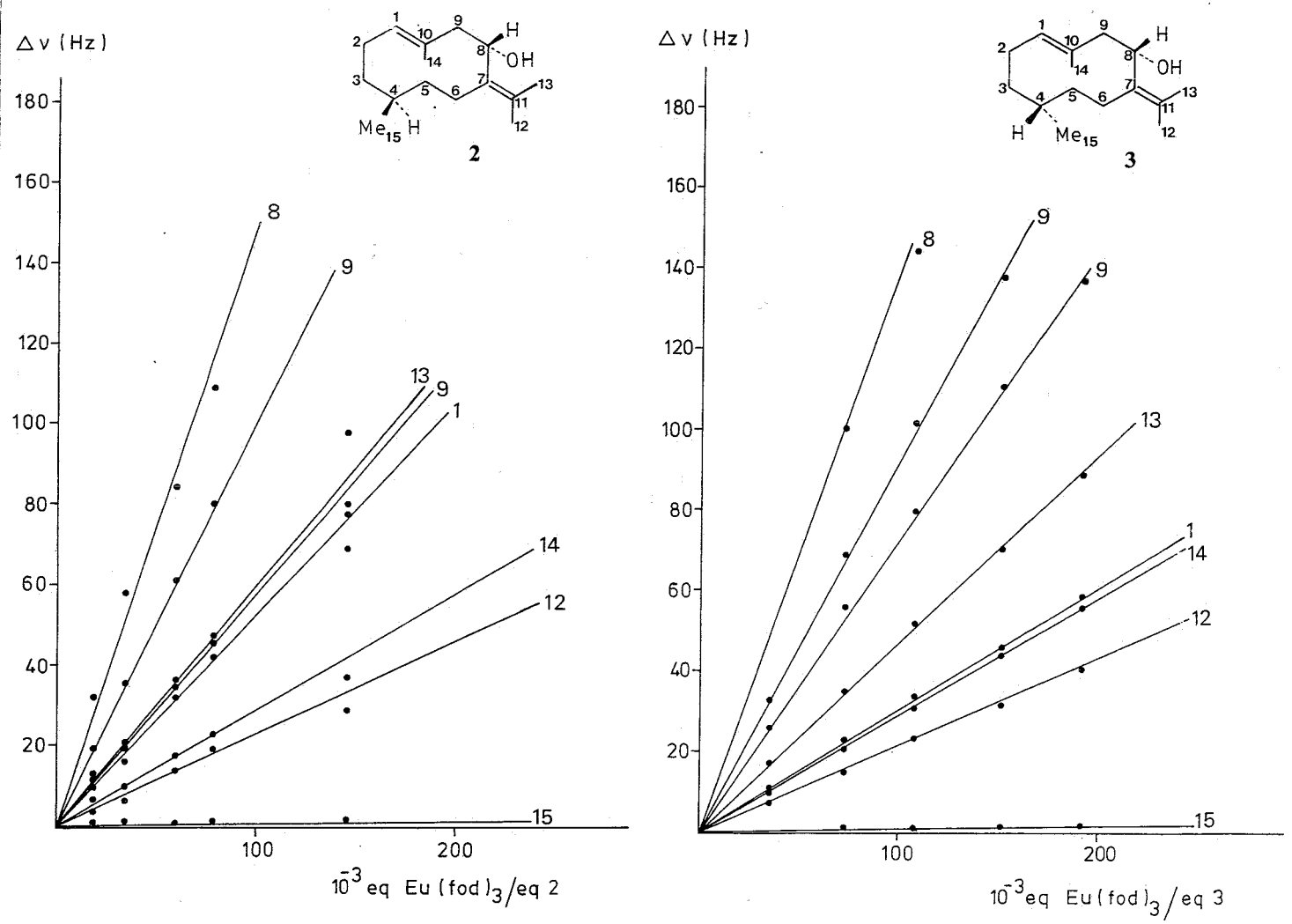
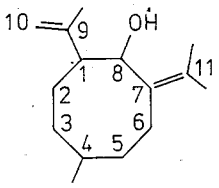
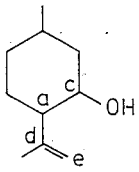


Fig. 4. Plot of the induced chemical shifts, Δν, versus *the amount of added shift reagent, for protons of* **2** *and* **3**.

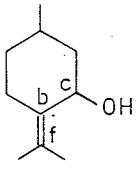
Table I Comparison of some relevant ^{13}C resonances of photoproducts **6**, **7** *and* **9** *with the reference compounds* **11** *and* **12**. *Chemical shifts in ppm, relative to TMS.*



6,7,9



11



12

	6	7	9		11	12
1	55.2	50.2	49.2	a	54.1	
7	133.0	133.3	134.5	b		133.7
8	72.1	68.7	71.2	c	70.4	69.2
9	149.9	150.9	149.2	d	146.7	
10	113.1	110.6	114.2	e	112.4	
11	132.4	127.3	131.4	f		127.2

data lead to the structural assignment of compounds **6**, **7** and **9**. The considerations mentioned above showed **9** to be the (1*SR*,4*RS*,8*SR*). The main differences between compounds **6**, **7** and **9** lie in the configuration on C-1 and C-8, which is reflected in the coupling between the protons corresponding with these atoms. For **6**, the coupling is 10 Hz, **7** has a coupling of 14 Hz, while for (1*SR*,4*RS*,8*SR*)-**-9**, the coupling is 10 Hz.

This leads to the conclusion that the C-1,C-8 configuration of **6** is probably (1*SR*,8*SR*), which results in the assignment of (1*SR*,4*SR*,8*SR*) for **6** and (1*RS*,4*SR*,8*SR*) for **7**.

Comparison of the ^{13}C spectra of **10** and **9**, from which the former compound is obtained, shows the absence of one double bond in **10**. Only one singlet and one triplet signal remain (146.7 and 112.3 ppm, respectively). Doublets at 79.47 and *ca.* 55 ppm confirm that the fragment C-8, C-1, C-9, C-10 is also incorporated into **10**. Since the spectrum of **10** shows the presence of fifteen C-atoms, an intramolecular reaction involving the 7,11-double bond must have occurred. The two olefinic signals are now replaced by a singlet at 59.4 ppm and a doublet at 54.9 ppm. The singlet suggests an addition to the 7,11-double bond, resulting in formation of a bicyclic system. The ^1H spectrum shows C-7 to be quaternary since there is no extra coupling for the proton at C-8 (compared to the spectrum of **9**). In comparison with compound **9**, one triplet was formed from a doublet. This means that the hydrogen atom must originate from C-2, C-3 or C-5 and, since no cyclopropane or cyclobutane rings are present, it must, in fact, come from C-3, leading to the assigned structure for **10**.

Discussion

Irradiation of **2** and **3** results in a highly stereospecific [1,3]-C shift which is determined by the conformation of the substrate. Since no [1,3]-OH shift was found, one may presume that both endocyclic double bonds are needed to initiate the [1,3]-OH shift in 8-hydroxygermacrene B (**1**)[1]. It was suggested that the 1,10-double bond is of great importance in providing favourable homo-allylic anchimeric assistance. Model studies suggest that the absence of the 4,5-double bond introduces more flexibility into the germacrene skeleton, which results in an unfavourable conformation for a [1,3]-OH shift. It therefore appears likely that both endocyclic bonds are operating co-operatively in generating a [1,3]-OH shift.

Experimental

^1H NMR spectra were recorded on a Varian EM-360A (60 MHz) spectrometer with Me_4Si as internal reference ($\delta = 0$). ^{13}C NMR spectra were obtained using 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). Gas chromatograms were recorded using a Kipp Analytica 8200 equipped with a flame-ionization detector. The column used was a Chrompack fused, silica wall coated, open tubular column with as liquid phase CPWax 51 (25 m × .23 mm).

Irradiation procedure

Irradiations were performed using a 500 Watt medium pressure mercury lamp (Hanau TQ 718) through quartz. Cooling of the lamp and the reaction vessel was accomplished by means of a closed circuit filled with methanol. The temperature in the reaction vessel was maintained at ±0°C. A 6×10^{-3} molar solution of the various compounds in methanol (p.a. Merck, 3 Å Molsieves) was used. Before and during irradiation, the reaction mixture was purged by a stream of dry nitrogen in order to remove all traces of oxygen. The solvent was removed on a rotary evaporator after TLC or GLC had indicated that the reaction was complete. The crude reaction mixture was separated by means of column chromatography.

4,5-Dihydro-8-hydroxygermacrene B (**2**,**3**)

The preparation and NMR spectra of 4,5-dihydro-8-hydroxygermacrene B (**2** and **3**) are described in ref. 2.

Irradiations were carried out using the general irradiation procedure described above. Products were separated by preparative HPLC. Spectral data for the various products are given below.

5; ^1H NMR ($CDCl_3$) δ .92 (s, 3H), 1.65 (s, 6H), 1.77 (s, 3H), 4.90 (m, 1H), 4.93 (dd, 1H).
^{13}C NMR ($CDCl_3$) δ 133.26 (s, 2×), 132.12 (s), 126.99 (d), 70.17 (d), 39.96 (t), 36.39 (t), 32.68 (t), 26.62, 25.88, 24.86, 24.46, 23.92, 23.18, 22.17.

6; ^1H NMR ($CDCl_3$) δ .90 (s, 3H), 1.70 (s, 6H), 1.80 (s, 3H), 4.22 (d, 1H), 4.72 (s, 2H).
^{13}C NMR ($CDCl_3$) δ 149.91 (s), 132.99 (s), 132.39 (s), 113.11 (t), 72.12 (d), 55.20 (d), 39.36, 35.51, 33.29, 31.60, 26.14, 24.26, 22.71, 21.16, 19.67.

7; ^1H NMR ($CDCl_3$) δ .93 (s, 3H), 1.75 (s, 3H), 1.78 (s, 3H), 1.89 (s, 3H), 4.72 (d, 1H), 4.77 (s, 2H).
^{13}C NMR ($CDCl_3$) δ 150.87 (s), 133.34 (s), 127.34 (s), 110.63 (t), 68.69 (d), 50.52 (d), 36.13 (t), 33.51 (t), 27.64 (d), 25.42, 24.07, 23.46, 22.64, 20.90, 19.48.

8; ^1H NMR ($CDCl_3$) δ .93 (s, 3H), 1.67 (s, 6H), 1.82 (s, 3H), 4.66 (dd, 1H), 5.12 (m, 1H).
^{13}C NMR ($CDCl_3$) δ 137.51 (s), 131.91 (s), 131.51 (s), 129.96 (d), 72.27 (d), 39.16, 37.87, 37.40, 35.65, 29.04, 25.81, 24.39, 22.91, 21.36.

9; ^1H NMR ($CDCl_3$) δ .92 (s, 3H), 1.36 (s, 3H), 1.75 (s, 6H), 4.38 (d, 1H), 4.84 (s, 2H).
^{13}C NMR ($CDCl_3$) δ 149.24 (s), 134.54 (s), 131.44 (s), 114.19 (t), 71.24 (d), 49.20 (d), 38.55 (t), 33.90, 33.09, 31.00, 27.09, 26.68, 22.37, 21.19, 20.21.

10; ^1H NMR ($CDCl_3$) δ .87 (s, 3H), .98 (s, 6H), 1.74 (s, 3H), 3.63 (d, 1H), 4.80 (s, 2H).
^{13}C NMR ($CDCl_3$) δ 146.68 (s), 112.30 (t), 79.47 (d), 59.45 (s), 54.86 (d), 53.31 (d), 44.68 (d), 37.67 (d), 36.26 (t), 32.48 (t), 30.12 (t), 21.02 (q), 20.55 (q, 2×), 18.93 (q).

Acknowledgement

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