Mechanism of the Formation of Herbertene from *trans*-Didehydrobicyclofarnesol

Georg Fráter* and Urs Müller

Givaudan Research Co. Ltd., CH-8600 Duebendorf, Switzerland

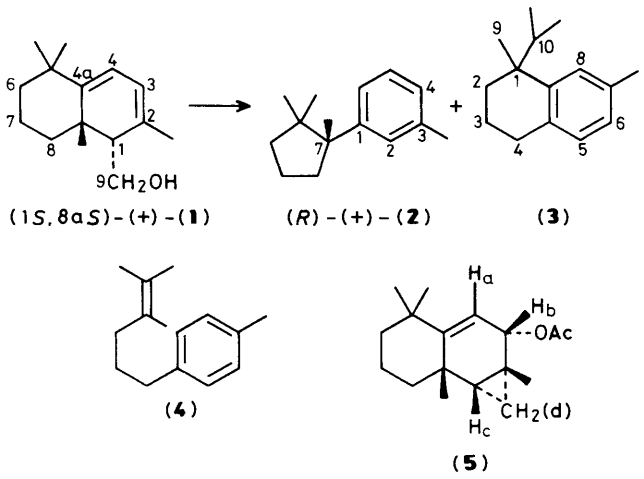
Product and ^{13}C labelling studies of the rearrangement of *trans*-didehydrobicyclofarnesol (+)-(**1**) to partly racemised herbertene [(+)-(**2**)] have led us to propose a mechanism for the reaction.

Several years ago we reported[1] the unexpected formation of herbertene[2] (**2**) from *trans*-didehydrobicyclofarnesol (**1**).† We have now studied the mechanism of this acid-catalysed rearrangement. Six key experiments have led to a better founded mechanistic proposal than before.[1]

(1) The by-product has now been identified as 1,2,3,4-tetrahydro-1-isopropyl-1,7-dimethylnaphthalene (**3**). The position of the CH_3 group on the aromatic ring was confirmed by double resonance and differential nuclear Overhauser experiments, revealing the relationship of H-4 (m, δ 2.65—2.59) and H-5 (δ 6.8, d, $J_{5,6}$ *ca.* 8, $J_{5,4}$ *ca.* 0.5 Hz). Moreover compound (**4**)‡ has been cyclised quantitatively to (**3**) under the conditions of the rearrangement (HCO_2H, 0.02 M $HClO_4$, 5—10 min reflux). Cyclisation of (**1**) in CF_3CO_2D (cat. amount H_2SO_4) yielded (**3**) with complete deuteriation at C-10; this also points to (**4**) as an intermediate.

† This structure can also be regarded as didehydro-*epi*-drimenol or (as numbered in the formula) a hexahydronaphthalene derivative.

‡ Compound (**4**) is available in four steps from 2-(4-methylphenyl)-ethanol by bromination, alkylation with t-butyl acetoacetate, decarboxylation, and Wittig reaction of the resulting ketone with isopropyltriphenylphosphonium bromide.



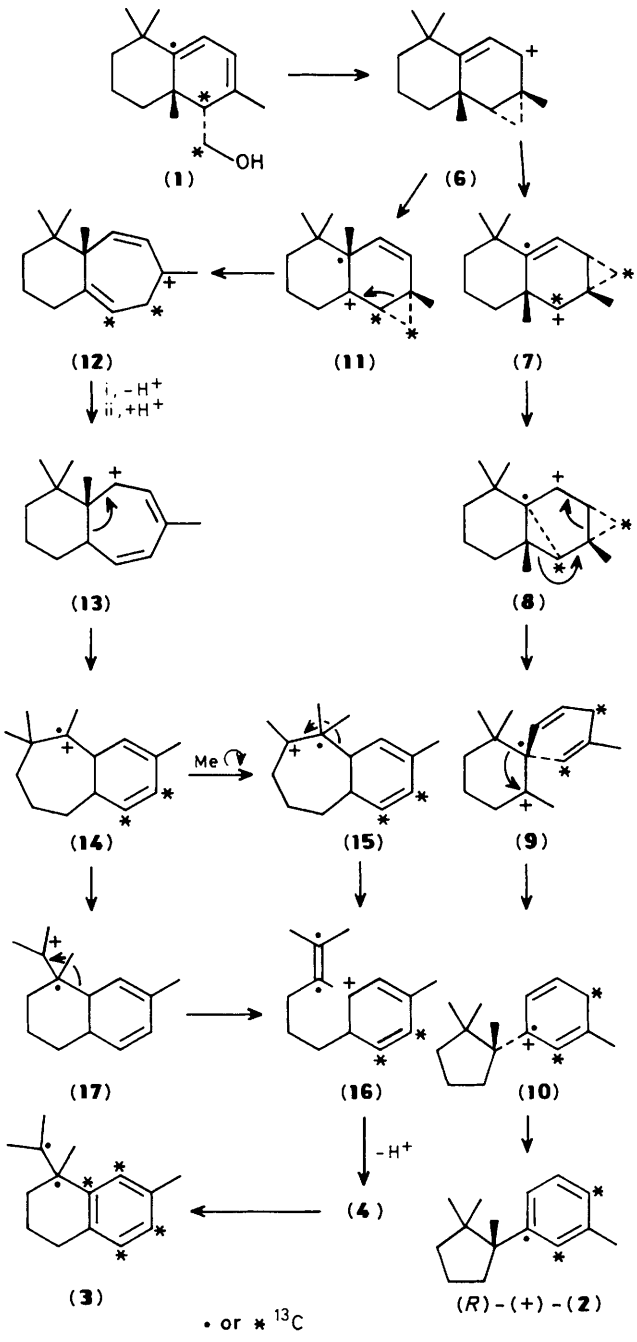
(2) Optically pure§ [(1S, 8a*S*)¶] (+)-(**1**) {$[\alpha]_D^{20}$ + 517° ($CHCl_3$, *c* 1.4), +505° (EtOH, *c* 1.2); Δε (271 nm, n-hexane) +18.8)} was prepared by hydrolysis of its recrystallized camphanoate (m.p. 107 °C). Its rearrangement furnished (+)-(**2**) {$[\alpha]_D^{20}$ + 50.2° ($CHCl_3$, *c* 1.5)} and *rac*-(**3**) {$[\alpha]_D^{20}$ 0° ($CHCl_3$, *c* 0.4)}. The optical rotation value found for (+)-(**2**) implies partial racemisation, since natural herbertene {(*S*)-(−)-(**2**), $[\alpha]_D$ −48.3° ($CHCl_3$, *c* 1.3)} after ozonolysis gave rise to (*S*)-(−)-camphonanic acid with $[\alpha]_D$ −13.2°;[2] *cf.* (*R*)-(+)-camphonanic acid with $[\alpha]_D$ + 20° derived from (*R*)-(+)-cuparene.[4]

(3) [9-$^2H_2$]-(**1**) was prepared by reduction of the corresponding ethyl ester[5] with $LiAlD_4$. Rearrangement of this material furnished [4-^{2}H]-(**2**) with *ca.* 80% deuterium [mass spectroscopic evidence and n.m.r. (δ 7.1—6.98 CH-4)].

(4) [1,9-$^{13}C_2$]-(**1**) (7% ^{13}C) was synthesised from β-ionone and doubly-labelled Horner reagent (prepared from [1,2-$^{13}C_2$]bromoacetic acid), by thermal cyclisation of the corresponding ester,[5,6] and reduction of the resulting ester. The doubly labelled (**1**) showed $J(^{13}C,^{13}C)$ 35 Hz [δ 61.5 (C-9, t) and 53.8 (C-1, d)]. Rearrangement of this material yielded (**2**) with ^{13}C-labels on C-2 (d, δ 127.8) and C-4 (d, δ 126.1), *i.e.* the vicinal ^{13}C labels were separated during the rearrangement. In (**3**) the labels have been randomised on C-5, C-6, and C-8 and -8a [C-8a, s, δ 145.1; C-8, d, δ 127.2; *J* (^{13}C-8a, ^{13}C-8) 58.4 Hz; C-5, d, δ 128.7; C-6, d, δ 125.7; *J* (^{13}C-5, ^{13}C-6) 57.2 Hz.

(5) [4a-^{13}C]-(**1**) (4% ^{13}C) was prepared in ten steps from 6-methylhept-5-en-2-one and [2-^{13}C]bromoacetic acid by well known synethic procedures. Herbertene (**2**) derived from [4a-^{13}C]-(**1**) carried the label on C-(**1**), whereas in (**3**) the label was randomised on C-1 (s, δ 39.6) and C-10 (d, δ 37.1).

(6) Finally, the very labile tosylate from (**1**) (m.p. 67—69 °C) was solvolysed (HOAc/NaOAc, 25 °C, 30 min) to give the acetate (**5**) (70% yield).‖ Acidic treatment of (**5**) (HCO_2H, cat. $HClO_4$, reflux, 5 min) yielded (**2**) and (**3**) in the ratio 3.5 : 1. This suggests that the cation corresponding to (**5**) might be a common intermediate for both (**2**) and (**3**).



Scheme 1

In Scheme 1 we have tried to accommodate all the foregoing findings in a mechanistic proposal. The intermediacy of (**6**) is made probable through the isolation of (**5**) [experiment (**6**)]. From here the reaction branches. A cyclopropylcarbinyl rearrangement (**6**) → (**7**) is the reason for the separation of the vicinal ^{13}C labels in experiment (4). The vinylcyclopropylcarbinyl → biscyclopropylcarbinyl rearrangement (**7**) → (**8**) is followed by the formation of the spirobicyclic intermediate (**9**) or by a synchronous process (**8**) → (**10**). In step (**9**) → (**10**) one would expect partial or total racemisation [see experiment (2)]. Loss of a proton in (**10**) yields the partially racemised (*R*)-(+)-(**2**).

§ Optical purity was proven by g.l.c. analysis of the derivatives of (±)-(**1**) and (+)-(**1**) with (*R*)(+)-Mosher acid (baseline separation).

¶ The strongly positive c.d. allows us to deduce[3] the absolute configuration of (+)-(**1**) as 1*S*,8a*S*.

‖ The structure and stereochemistry of (**5**) can be deduced unequivocally from n.m.r. spectra, *i.e.* ^{1}H n.m.r., ^{13}C n.m.r., ^{1}H, ^{13}C-2D, ^{13}C-INADEQUATE, and differential nuclear Overhauser experiments: H_b δ 5.7 (br. s), H_a δ 5.14 (d, J_{ab} *ca.* 2 Hz), H_c δ 0.5 (dd, *J ca.* 5.5 Hz), H_d δ 0.72 and 0.22 (each dd, J_{gem} *ca.*, 8 Hz).

On the other hand migration of the angular CH_3 group in (**6**) gives (**11**), which through ring enlargement yields (**12**). The latter furnishes (**13**) by deprotonation–protonation, which is followed by ring enlargement/ring contraction and gives (**14**). Here the reaction again branches [experiment (5)]: either CH_3 migration (**14**) → (**15**) or methylene migration (**14**) → (**17**) takes place. Both intermediates (**15**) and (**17**) acquire stability by rearrangement to (**16**), which is a protonated form of (**4**). The symmetrical intermediate (**4**) cyclises to (**3**) with randomation of the labels in the aromatic ring [experiment (4)].

We thank Dr. E. Billeter and Mr. J. Maerki (n.m.r.), Dr. K. Noack (c.d. spectra), Dr. M. Vecchi, Dr. M. Hrivnac, and Mr. F. Etzweiler (g.l.c.), Dr. J. Schmid (mass spectrometry), for help as indicated, and Professors D. Arigoni and A. Eschenmoser for discussions.

Received, 3rd May 1989; Com. 8/01721B

References

1 G. Fráter, *J. Chem. Soc., Chem. Commun.*, 1982, 521.
2 A. Matsuo, S. Yuki, M. Nakayama, and S. Hayashi, *J. Chem. Soc., Chem. Commun.*, 1981, 864; A. Matsuo, S. Yuki and M. Nakayama, *J. Chem. Soc., Perkin Trans. 1*, 1986, 701.
3 M. J. Rougier, in 'Stereochemistry: Fundamentals and Methods,' ed. H. Kagan, vol. 2, Thieme, Stuttgart, 1982.
4 C. Enzell and H. Erdtman, *Tetrahedron*, 1958, **4**, 361.
5 G. Fráter, *Helv. Chim. Acta*, 1974, **57**, 2446.
6 G. Fráter and U. Müller, *Helv. Chim. Acta.*, 1988, **71**, 808.