

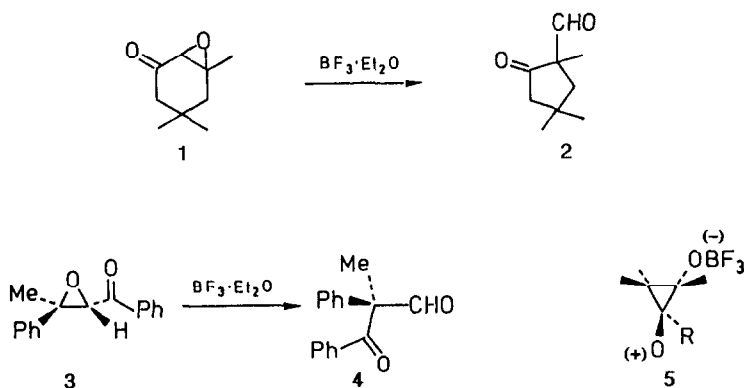
ON THE STEREOCHEMISTRY OF THE BF_3 -CATALYZED REARRANGEMENT OF (+)-ISOPHORONE OXIDE

Franz Kunisch, Kurt Hobert, and Peter Welzel*

Fakultät für Chemie der Ruhr-Universität
Postfach 102148, D-4630 Bochum (FRG)

Abstract - The title reaction proceeds with partial or extensive racemization depending on the solvent used.

1,2-Shifts of electron-withdrawing groups (COR, COOR, COSR, CONR_2 , etc.) towards electron-deficient centres are well established.¹ For example, isophorone oxide (1) undergoes a rearrangement to give 2 when treated with BF_3 etherate in an inert solvent (benzene² or CH_2Cl_2 ³). Under proper experimental conditions the yield of 2 is as high as 97%.^{3,4,7} In the open-chain 1,3-diphenyl-2,3-epoxybutan-1-ones (cf. 3) the 1,2-acyl migration proceeds with inversion of configuration at the migration terminus and without loss of optical purity as shown by Domagala and Bach.⁸ Bach has suggested that in these cases the reaction involves neighbouring group participation by the carbonyl carbon and proceeds via a transition state of type 5.^{9,10,11}



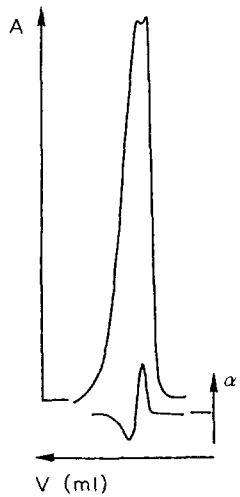
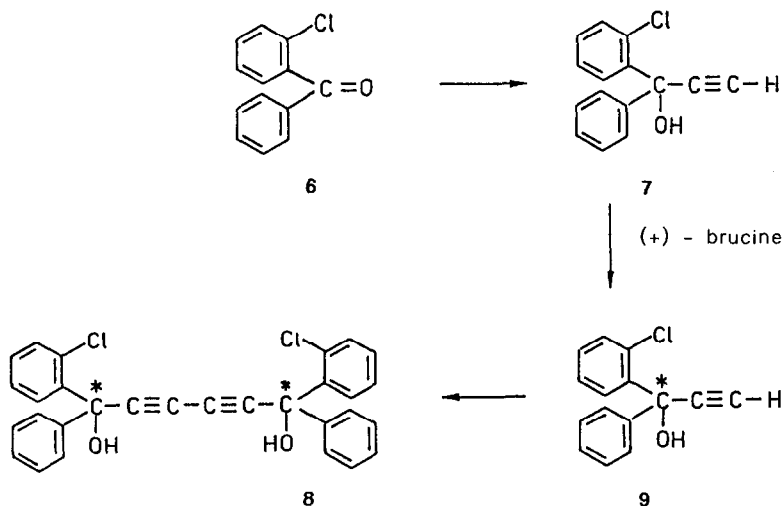
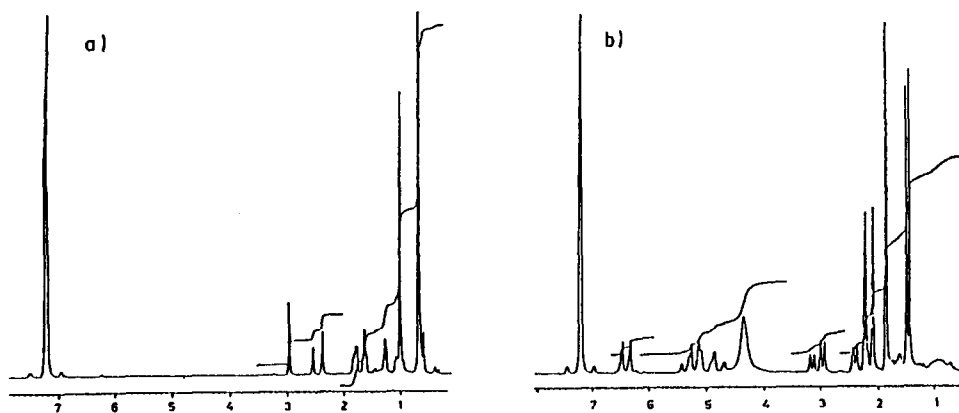


Fig. 1. Resolution of 7

Stationary phase: 7 μ m cellulose triacetate

Eluent: ethanol - water 96:4

A: Absorbance (254 nm)

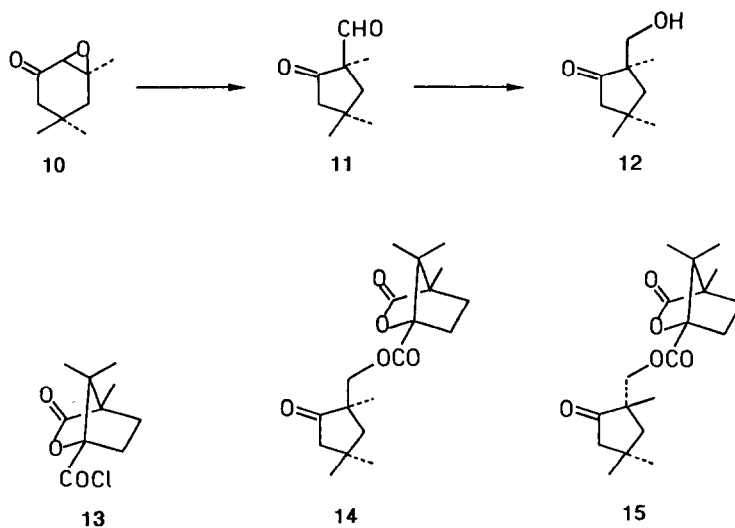
 α : Optical rotationFig. 2. ^1H NMR spectra (80 MHz, C_6D_6)a) (\pm) - 1 ; b) (\pm) - 1 + 0.5 equiv $\text{Eu}(\text{hfbc})_3$

Recently, discussing the rearrangement of some cyclic α,β -epoxy ketones Bach and Klix attributed the facility of acyl migration in certain cases also to neighbouring group participation by the carbonyl group and the ability of the molecule to assume a transition state geometry resembling **5**.³ According to Bach and Klix, **1** should rearrange along this reaction path. One would expect, therefore, optically active isophorone oxide to rearrange without loss of optical purity.

It is the purpose of this communication to demonstrate that the situation may not be as simple as that, for results obtained in a study of the BF_3 -catalyzed rearrangement of (+)-isophorone oxide seem to contradict the view put forward by Bach and Klix.³

(+)-Isophorone oxide (**10**) was prepared taking advantage of Toda's recently introduced resolution technique which utilizes complexation of racemic isophorone oxide (**1**) with optically active 1,6-bis(o-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**8**).¹² Several features of this procedure merit comment. The synthesis of **8** from **6** via **7** and **9** involves itself a resolution step. **7** is resolved by a three-step procedure including a) complexation with (+)-brucine, b) crystallization, and c) cleavage of the complex with dilute HCl.¹³ We were unable to achieve complete resolution of **7** by just one cycle. Inconveniently, 3 cycles had to be performed to obtain **9** with more than 90% optical purity. At the end of this work we found that resolution of **7** by liquid chromatography using cellulose triacetate as stationary phase was possible (see Fig. 1). Tanaka and Toda have reported that they were unable to determine the % e.e. of **10** by NMR analysis using the chiral shift reagents $\text{Eu}(\text{tfc})_3$ and $\text{Eu}(\text{hfbc})_3$ in CDCl_3 solution.¹² As figures 2a and 2b demonstrate this determination can be readily performed using $\text{Eu}(\text{hfbc})_3$ ¹⁴ in C_6D_6 solution. According to this method our sample of **10** had an e.e. > 90%.¹⁵

Subjecting **10** to the BF_3 -catalyzed rearrangement in CH_2Cl_2 solution under the conditions reported by Bach,³ led to **11** in 93% yield. The stereochemical outcome of this rearrangement was studied



as follows. Selective reduction of the aldehyde group of **11** with lithium tri-*t*-butoxyaluminum hydride (1.06 equiv) in THF (5.5 h at -65°C , then H_2O quench and aqueous work-up) followed by chromatographic separation (silica gel, hexane-ethyl acetate 9:1) furnished **12** in 59% yield. Esterification with an excess (3 equiv) of the acid chloride **13** of (-)-camphanic acid¹⁶ in pyridine solution (22 h at 20°C) led to a 73.9:26.1 mixture of **14** and **15** (GC comparison¹⁷ with authentic samples of **14** and **15**¹⁸). Rearrangement of **10** in benzene solution² followed by reduction and esterification as described above gave a 56.7:43.3 mixture of **14** and **15**.

In conclusion, our results provide evidence that the mechanism of the rearrangement of **10** has a carbocationic component causing partial or extensive racemization depending on the solvent used.¹⁹

Acknowledgements - We thank K.Hohgardt for initial studies on this project. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

- 1) For leading references, see D.Berner, D.Ph.Cox, and H.Dahn, *Helv.Chim.Acta* **65**, 2061 (1982).
- 2) H.O.House and R.L.Wasson, *J.Am.Chem.Soc.* **79**, 1488 (1957).
- 3) R.D.Bach and R.C.Klix, *Tetrahedron Lett.* **26**, 985 (1985).
- 4) The acid-catalyzed isomerization of α,β -epoxy ketones to 1,3-dicarbonyl compounds was first observed by Weitz and Scheffer⁵ and later investigated in many laboratories.^{3,6}
- 5) E.Weitz and A.Scheffer, *Ber.Dtsch.Chem.Ges.* **54**, 2344 (1921).
- 6) a) H.O.House and G.D.Ryerson, *J.Am.Chem.Soc.* **83**, 979 (1961), b) J.M.Coxon, M.P.Hartshorn, and D.N.Kirk, *Tetrahedron* **20**, 2531 (1964); c) V.Tortorella, L.Toscano, C.Vetuschi, and A.Romeo, *J.Chem.Soc.(C)* 2422 (1971); d) A.C.Brouwer, L.Thijs, and B.Zwanenburg, *Tetrahedron Lett.* 807 (1975); and references cited therein.
- 7) Labeling studies established the rearrangements of open-chain α,β -epoxy ketones to be intramolecular: H.O.House, *J.Am.Chem.Soc.* **78**, 2298 (1956).
- 8) J.M.Domagala and R.D.Bach, *J.Am.Chem.Soc.* **100**, 1605 (1978).
- 9) R.D.Bach and J.M.Domagala, *Tetrahedron Lett.* 4025 (1976); J.M.Domagala and R.D.Bach, *J.Am.Chem.Soc.* **101**, 3118 (1979).
- 10) It was also taken into account that for the epoxides derived from substituted *E*-benzalacetophenones the rate of isomerization was accelerated by electron-donating and retarded by electron-withdrawing substituents on either benzene ring. The ρ -values were found to be approximately -1 in both cases.^{6a}
- 11) Dahn has explained the preferred migration of the COOH group in a related case by the fact that if an alkyl group migrated the rearranged ion would bear a positive charge next to the CO group which is avoided when the carboxyl group itself migrates.¹
- 12) K.Tanaka and F.Toda, *J.Chem.Soc., Chem.Comm.* 1513 (1983).
- 13) F.Toda and K.Tanaka, *Tetrahedron Lett.* **22**, 4669 (1981), *J.Am.Chem.Soc.* **105**, 5151 (1983).
- 14) Tris [3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato] europium(III), purchased from Aldrich.
- 15) $[\alpha]_{\text{D}} = +12.0$ (c 0.26 in CH_3OH) (lit.,¹² $[\alpha]_{\text{D}} = +13.5$ (c 0.15 in CH_3OH)).
- 16) H.Gerlach, *Helv.Chim.Acta* **61**, 2773 (1978), and references therein.
- 17) 10m x 0.28 mm glas capillary column (OV 17, ca. 3.5×10^4 theoretical plates), 180°C , carrier gas: H_2 . **14** and **15** were base-line separated, retention times: 44 min for **15**, 49 min for **14**.
- 18) F.Kunisch, K.Hobert, and P.Welzel, submitted for publication in *Tetrahedron Lett.*
- 19) Relevant to these observations are results by Tsankova et al.²⁰ on the BF_3 -catalyzed reactions of α,β -epoxy-artemisia ketone.
- 20) E.Tsankova, V.Enev, and S.Simova, *Tetrahedron* **40**, 2435 (1984).