# Thermal and Photochemical Rearrangement of 3-Substituted 2-Methylbenzofuran Epoxides and Their Valence-Isomeric Quinone Methides

**Waldemar Adam*, Günther Käb[+], and Markus Sauter**

*Institut für Organische Chemie der Universität Würzburg,*
Am Hubland, D-97074 Würzburg, Germany

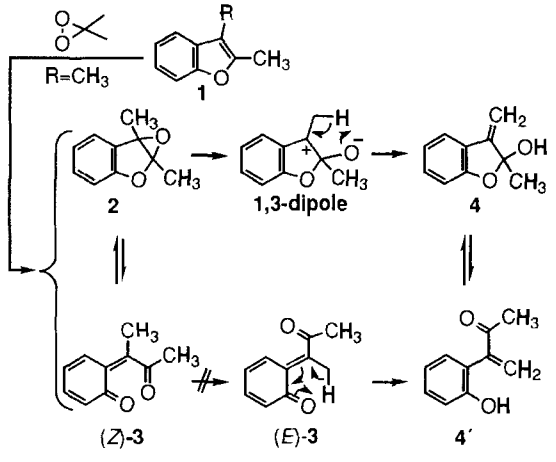
Received September 23, 1993

**Key Words:** Epoxidation / Dioxirane, dimethyl- / Benzofurans, 2-methyl- / Benzofuran epoxides / Quinone methides / Photoisomerization / Chromenes / 3-Benzofuranones

The dimethyldioxirane oxidation of the 3-substituted 2-methylbenzofurans **1** [**1a**: 3(*E*)-styryl, **1b**: 3-acetoxy, **1c**: 3-(*tert*-butyldimethylsilyloxy)] is reported. Only quinone methide **3a**, none of the benzofuran epoxides **2a–c**, could be detected by $^1$H- and $^{13}$C-NMR spectroscopy at low temperature (−30°C), which on photoisomerization led to chromene **7a**. The benzofuran-3-ones **5b**, **c** and the α-diketone **6c** are presumably formed by thermal isomerization of the transient benzofuran epoxides **2b**, **c** and quinone methide **3c**.

Benzofuran epoxides **2** and their valence-isomeric quinone methides **3**, both readily accessible by dimethyldioxirane oxidation of benzofurans **1**, have been shown to be very reactive compounds[1]. Thus, the epoxides **2** and quinone methides **3** rearrange thermally above −20°C to the allylic alcohols **4** and their tautomeric phenols **4'** (Scheme 1).

Scheme 1




Due to the fact that the allylic alcohols **4** and their ring-opened tautomeric phenols **4'** interconvert[1a,f], it has been difficult to establish rigorously, whether these derive from the epoxides **2** or their valence-isomeric quinone methides **3**. However, the 1,5-sigmatropic shift in the rearrangement **3** → **4** (Scheme 1) requires isomerization of (*Z*)-**3** to (*E*)-**3**, which usually is promoted photochemically. It was our interest, therefore, to examine benzofuran epoxides **2** and their corresponding quinone methides **3** with substituents which cannot rearrange to the allylic alcohols **4** and/or their phenol tautomers **4'** (Scheme 1) to provide mechanistic insight into their mode of formation. For this reason, the benzofurans **1a–c** were selected as model compounds, and their dimethyldioxirane oxidation was examined. We report presently on the chemical fate of the transient benzofuran epoxides **2** and their valence-isomeric quinone methides **3**.

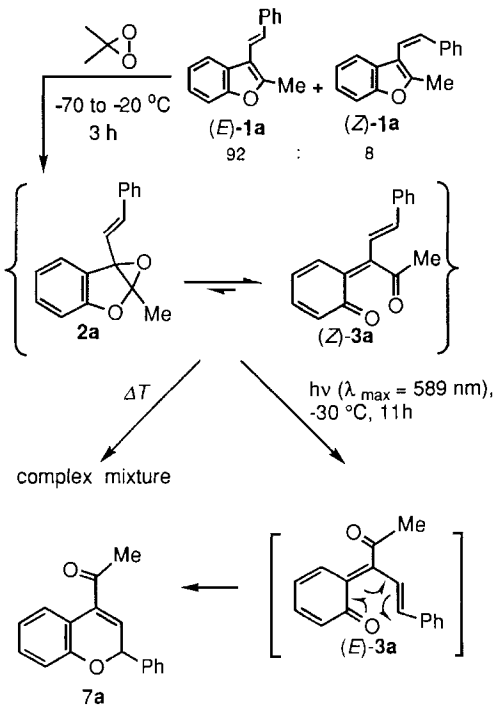
## Results and Discussion

The dimethyldioxirane[2] oxidation of a 92:8 mixture of the 3-styrylbenzofurans (*E*)-**1a**/(*Z*)-**1a** gave exclusively the (*E*)-styryl-substituted quinone methide (*Z*)-**3a** (Scheme 2), which could be isolated at −20°C as a dark-red solid, while benzofuran (*Z*)-**1a** was not oxidized under these conditions, as revealed by NMR data. At temperatures above 0°C dimethyldioxirane oxidized both, the isomers (*E*)-**1a** and (*Z*)-**1a**. However, at this elevated temperature decomposition or overoxidation took place, which resulted in a complex mixture, even if one equivalent of dimethyldioxirane was employed. Attempted separation and purification of that mixture by column chromatography (silica gel, ether) at −30°C failed. The most characteristic signals in the $^{13}$C-NMR spectrum of quinone methide (*Z*)-**3a** are the acetyl methyl group at δ = 29.8, the carbonyl carbon atoms of the cyclohexadienone at δ = 186.1, and the acetyl group at δ = 204.8. These data are in accord with those of known quinone methides[3a]. The (*E*) configuration for the styryl group of the quinone methide **3a** was ascertained by the coupling constant $J$ = 16.1 Hz of the two styryl protons at δ = 6.91 (d) and 7.35 (d), which is characteristic for (*E*) configuration. Further, **3a** shows in the UV spectrum in acetone $\lambda_{max}$ at 384 and 407 nm and a strong tailing up to 590

[+] Undergraduate research participant, March 1992.

  0009–2940/94/0202–0433 $ 10.00+.25/0

Scheme 2

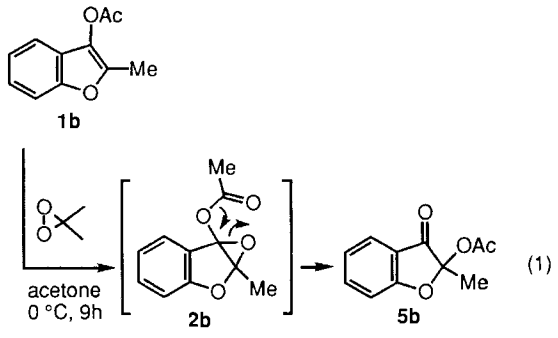



nm; these data constitute another support for the quinone methide structure of **3a**[3b].

The preferential formation of quinone methide (*Z*)-**3a** versus epoxide **2a** can be explained in terms of a stabilization of the (*Z*)-**3a** valence isomer by conjugation by the styryl group. Additionally, the styryl substituent facilitates carbon-oxygen bond heterolysis of the furan epoxide ring by stabilizing the incipient cation center at the 3-position by delocalization.

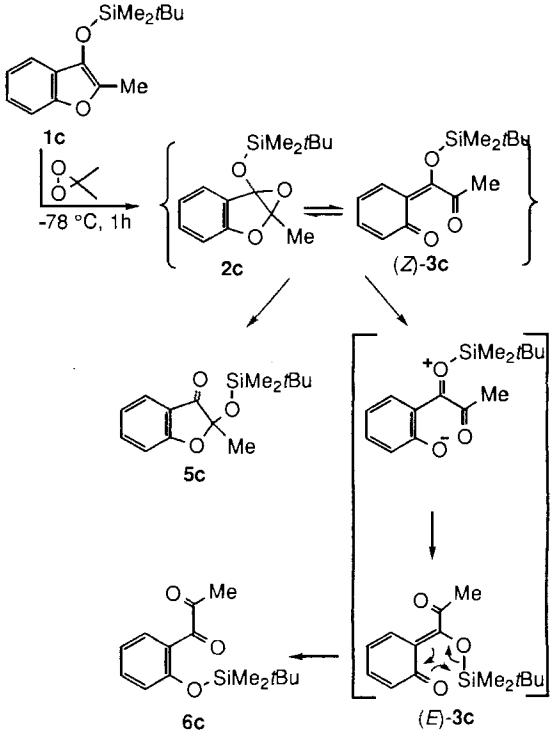
On warming to room temperature, quinone methide (*Z*)-**3a** gave a complex, intractable product mixture. However, on irradiation at −30°C, **3a** yielded the hitherto unknown chromene **7a** as colorless needles (Scheme 2). The formation of **7a** can be rationalized in terms of an (*Z*)/(*E*) isomerization of quinone methide (*Z*)-**3a** and cyclization of the latter to **7a** leading to aromatization. **7a** shows a characteristic absorption at $\tilde{\nu}$ 1680 $cm^{-1}$ in the IR spectrum for the α,β-unsaturated carbonyl bond. Furthermore, chromene **7a** exhibits a signal at δ = 76.1 (d) for the C-2 carbon atom; these data definetely speake for structure **7a** versus the corresponding isomer 4-acetyl-2-phenyl-4*H*-chromene, which could be formed by acid catalysis during silica gel chromatography. Since quinone methide (*Z*)-**3a** requires photochemical excitation for isomerization to (*E*)-**3a**, it is more likely that in Scheme 1 the allylic alcohols **4** and their tautomers **4′** are formed by rearrangement of the epoxides **2** rather than the quinone methides (*Z*)-**3**.

Quite different were our experiences in the dioxirane oxidation of 3-acetoxy-2-methylbenzofuran (**1b**), carried out at 0°C, since at lower temperatures the reaction was extremely slow (Eq. 1). Instead of the expected epoxide **2b** or the quinone methide **3b**, directly the benzofuran-3-one **5b** was observed and isolated quantitatively in analytically pure form as a colorless solid. Consequently, acetyl group migration in the benzofuran epoxide **2b** to form the 3-furanone **5b** is so facile that the labile epoxide **2b** could not be detected. Related isomerizations of epoxides to α-acetoxy ketones have been reported[4].




The oxidation of the known[5] silyloxy-substituted benzofuran **1c** with dimethyldioxiran at −78°C afforded within 1 h quantitatively the benzofuranone **5c** and the diketone **6c** (monitored by TLC) in a ratio of 17:83 (Scheme 3), as revealed by the integration of the crude product NMR spectrum. This result is in agreement with the dimethyldioxirane oxidation of the more sensitive 2-methyl-3-(trimethylsiloxy)benzofuran[6]. By column chromatography both products **5c** and **6c** were separated. An isomerization of **5c** to **6c** or vice versa was not observed. Benzofuran-3-one **5c** is formed by silyl migration in the epoxide **2c** analogous to 3-acetoxybenzofuran **1b**.

Scheme 3



Remarkable is the formation of diketone **6c** since prior to the intramolecular rearrangement **3c** → **6c** a (*Z*)/(*E*) isomerization would be necessary. The latter isomerization might be promoted from the dipolar mesomeric structure of (*Z*)-**3c** in Scheme 3, which would allow free rotation.

In conclusion, the styryl-substituted quinone methide (*Z*)-**3a** requires photochemical (*Z*)/(*E*) isomerization to afford the chromene **7a** by electrocyclization of (*E*)-**3a**. This fact constitutes evidence in support that the thermal rearrangement of the 3-alkyl-substituted benzofuran epoxides **2** and their valence-isomeric quinone methides **3** in Scheme 1 to the corresponding alcohols **4** and **4'** proceeds via the epoxides **2**. In contrast, the α-diketone **6c** formed in the oxidation of the 3-silyloxy-substituted benzofuran **1c** appears to involve thermal (*Z*)/(*E*) isomerization of the quinone methide (*Z*)-**3c**, promoted by stabilization of the intermediary 1,5 dipole by the electron-donating silyloxy group and phenoxy resonance.

We thank the *Deutsche Forschungsgemeinschaft* (SFB 172 "Molekulare Mechanismen kanzerogener Primärveränderungen") and the *Fonds der Chemischen Industrie* for generous funding.

## Experimental

Melting points: Reichert Thermovar hot stage apparatus. – IR: Perkin Elmer 1420. – $^1$H and $^{13}$C NMR: Bruker AC 200 (200 MHz), AC 250 (250 MHz) or WM 400 (400 MHz). Chemical shifts refer to $CDCl_3$, $CD_2Cl_2$, or [$D_6$]acetone. – MS: Varian 8200 Finnigan Mat. – Elemental analyses: Analytical Division of the Institute of Inorganic Chemistry (University of Würzburg). – All solvents were purified by following standard literature methods. Dimethyldioxirane (as acetone solution) was prepared according to the published procedure[2]; its peroxide content was determined by oxidation of methyl phenyl sulfide to its sulfoxide, the latter quantitated by $^1$H-NMR analysis. The dimethyldioxirane solutions were stored over molecular sieves at −20°C. All reactions were carried out under nitrogen; room temperature was ca. 20°C.

*2-Methyl-3-[(E)-styryl]benzofuran* [(*E*)-**1a**] *and 2-Methyl-3-[(Z)-styryl]benzofuran* [(*Z*)-**1a**]: To a flame-dried, three-necked, round-bottomed flask, equipped with a reflux condenser, mechanical stirrer and dropping funnel, was added 224 mg (9.22 mmol) of magnesium turnings (activated by a few crystals of $I_2$) and 10 ml of THF, followed by slow addition of 1.04 ml (8.09 mmol) of a 85:15 mixture of (*E*)- and (*Z*)-β-bromostyrene[7] under reflux for 30 min. The reaction mixture was cooled to room temp., and a solution of 1.01 g (6.82 mmol) of 2-methylbenzofuran-3(2*H*)-one[8] in 5 ml of THF was added slowly. The resulting reaction mixture was stirred at room temp. for 2 d and then refluxed 2 h after adding 15 ml of 1 N $H_2SO_4$. The solvent was removed at reduced pressure (ca. 20°C/20 Torr), and the residue was partitioned between dichloromethane (20 ml) and water (20 ml). The combined organic phases were washed with a saturated, aqueous $NaHCO_3$ solution (20 ml) and water (20 ml) and finally dried with $MgSO_4$. The solvent was removed in a rotary evaporator (ca. 20°C/20 Torr), and the crude product was purified by double column chromatography (silica gel), first dichloromethane and second *n*-pentane as eluent to yield 476 mg (30%) of a 92:8 mixture of (*E*)- and (*Z*)-**1a** as colorless needles, m.p. 47–49°C ($Et_2O$). – (*E*)-**1a**/(*Z*)-**1a**: IR ($CCl_4$): $\tilde{\nu}$ = 3015 cm$^{-1}$, 3005, 1620, 1565, 1455, 1435, 1235, 1180, 990, 930, 900, 685. – $^1$H NMR (200 MHz, [$D_6$]acetone): δ = 2.19 (s, 3H, *Z*), 2.60 (s, 3H, *E*), 7.02–7.55 (m, 16H), 7.61–7.70 (m, 4H), 7.97–8.06 (m, 2H). – (*E*)-**1a**: $^{13}$C NMR (50 MHz, [$D_6$]acetone): δ = 12.5 (q), 111.5 (d), 114.5 (s), 120.0 (d), 121.3 (d), 123.8 (d), 124.7 (d), 126.9 (d), 127.8 (s), 128.0 (d), 129.2 (d), 129.5 (d), 138.9 (s), 155.0 (s), 155.2 (s). – (*Z*)-**1a**: $^{13}$C NMR (50 MHz, [$D_6$]acetone): δ = 13.0 (q), 111.3 (d), 113.9 (s), 119.9 (d), 121.0 (d), 123.1 (d), 124.3 (d), 127.2 (d), 128.8 (s), 129.0 (d), 129.5 (d), 130.2 (d), 138.4 (s), 153.1 (s), 154.9 (s). – (*E*)-**1a**/(*Z*)-**1a**: $C_{17}H_{14}O$ (234.3): calcd. C 87.15, H 6.02; found C 87.48, H 6.39.

*3-Acetoxy-2-methylbenzofuran* (**1b**): In a 50-ml flask were placed 1.82 ml (13.0 mmol) of diisopropylamine in 15 ml of THF, and while stirring at −78°C was added 8.12 ml (13.0 mmol) of 1.60 M *n*BuLi solution in hexane within 3 min. After 30 min stirring at −78°C a solution of 1.90 g (12.8 mmol) of 2-methylbenzofuran-3(2*H*)-one[8] in 5 ml THF was added dropwise over 5 min. The reaction mixture was stirred for 45 min and treated with a solution of 1.40 ml (19.6 mmol) of acetyl chloride in 5 ml THF, stirred for 4 h at −78°C, and then allowed to warm up to room temp. overnight. The solvent was removed under reduced pressure (ca. 20°C/20 Torr), the residue digested with saturated, aqueous $NaHCO_3$ solution (25 ml), and extracted with *n*-pentane (3 × 20 ml). The combined organic phases were dried and purified by chromatography (silica gel, dichloromethane) to afford 1.18 g (53%) of **1b** as a colorless liquid. – IR ($CCl_4$): $\tilde{\nu}$ = 3060 cm$^{-1}$, 2820, 1780, 1765, 1640, 1585, 1450, 1365, 1250, 1200, 1000, 740. – $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.38 (s, 3H), 7.20–7.26 (m, 4H). – $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 11.2 (q), 20.5 (q), 111.3 (d), 117.8 (d), 122.7 (d), 123.2 (s), 123.8 (d), 129.8 (s), 144.2 (s), 152.1 (s), 168.4 (s). – $C_{11}H_{10}O_3$ (190.2): calcd. C 69.46, H 5.30; found C 69.35, H 5.14[9].

*6-[(E)-1-Acetyl-3-phenylpropenylidene]-2,4-cyclohexadien-1-one* (**3a**): To a cold (−78°C) solution of 90.0 mg (0.385 mmol) of benzofuran (*E*)-**1a**/(*Z*)-**1a** (92:8) in 2 ml of anhydrous $CH_2Cl_2$ was rapidly added while stirring under $N_2$ 9 ml (0.486 mmol) of a cold (−78°C) solution of dimethyldioxirane in acetone (0.054 M). The stirring was continued for 3 h until complete consumption of **1a** (monitored by TLC), while the reaction temp. was allowed to rise to −20°C. The solvent was evaporated (−20°C/0.01 Torr, 1–2 h) to yield quinone methide **3a** quantitatively as a dark-red solid, which deteriorated rapidly on standing at 20°C. – $^1$H NMR (400 MHz, $CD_2Cl_2$, −30°C): δ = 2.30 (s, 3H), 6.27 (d, *J* = 9.6 Hz, 1H), 6.40 (dd, $J_1$ = 9.6, $J_2$ = 7.1 Hz, 1H), 6.91 (d, *J* = 16.1 Hz, 1H), 7.01–7.29 (m, 5H), 7.35 (d, *J* = 16.1 Hz, 1H), 7.41–7.45 (m, 2H). – $^{13}$C NMR (100 MHz, $CD_2Cl_2$, −30°C): δ = 29.8 (q), 119.7 (d), 124.2 (d), 127.0 (d), 128.1 (d), 129.1 (d), 131.0 (d), 132.6 (s), 135.2 (s), 140.2 (d), 144.4 (d), 158.1 (s), 186.1 (s), 204.8 (s). – UV (acetone): $\lambda_{max}$ = 384 nm, 407. Exact extinction coefficients could not be obtained because of decomposition.

*2-Acetoxy-2-methylbenzofuran-3(2H)-one* (**5b**): To a stirred solution of 100 mg (0.526 mmol) of benzofuran **1b** in 2 ml of dichloromethane was added 8 ml (0.733 mmol) of a solution of dimethyldioxirane in acetone (0.092 M) at 0°C. Stirring was continued for 9 h at this temp., and removal of the solvent in a rotary evaporator (ca. 20°C/20 Torr) afforded 108 mg (99%) of analytical pure **5b** as a colorless solid, m.p. 83.5–85°C. The same result was obtained, when the reaction temp. was increased up to 20°C. – IR ($CCl_4$): $\tilde{\nu}$ = 2940 cm$^{-1}$, 1770, 1745, 1705, 1470, 1330, 1255, 1155, 1090. – $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.61 (s, 3H), 2.09 (s, 3H), 7.00–7.25 (m, 2H), 7.57–7.71 (m, 2H). – $^{13}$C NMR (63 MHz, $CDCl_3$): δ = 20.5 (q), 21.0 (q), 102.1 (s), 112.7 (d), 119.9 (d), 122.5 (d), 124.6 (d), 138.0 (d), 168.3 (s), 168.4 (s), 196.4 (s). – MS (70 eV), *m/z* (%): 207 (1) [$M^+$ + 1], 206 (9) [$M^+$], 163 (74), 121 (100), 93 (8), 43 (26). – $C_{11}H_{10}O_3$ (206.2): calcd. C 64.07, H 4.89; found C 63.74, H 5.05.

*2-(tert-Butyldimethylsilyloxy)-2-methylbenzofuran-3(2H)-one* (**5c**) *and 1-[2-(tert-Butyldimethylsilyloxy)phenyl]-1,2-propanedione* (**6c**): To a stirred solution of 200 mg (0.762 mmol) of benzofuran **1c**[6] in 2 ml of dichloromethane was added rapidly 11 ml (0.825 mmol) of a solution of dimethyldioxirane in acetone (0.075 M) at −78°C. Stirring was continued for 1 h at −78°C, and the solvent was removed by destillation in a rotary evaporator (ca. 20°C/20 Torr). Chromatography (silica gel, ether/pentane, 1:4) of the crude product (a 17:83 mixture of **5c** and **6c**, determined by $^1$H-NMR spectroscopy) gave 158 mg (74%) of **5c** as a colorless oil and 28 mg (13%) of **6c** as a pale yellow oil. When the reaction temp. was increased to −30°C, **5c** and **6c** were obtained in the same ratio as above of about 20:80. − **5c**: IR ($CCl_4$): $\tilde{\nu}$ = 2975 cm$^{-1}$, 2945, 2870, 1740, 1620, 1470, 1330, 1260, 1205, 830. − $^1$H NMR (200 MHz, $CDCl_3$): δ = −0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.57 (s, 3H), 7.00−7.09 (m, 2H), 7.64−7.69 (m, 2H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = −3.6 (q), −3.3 (q), 17.8 (q), 23.1 (q), 25.5 (s), 104.4 (s), 113.2 (d), 118.9 (s), 122.0 (d), 125.2 (d), 138.7 (d), 169.6 (s), 199.4 (s). − $C_{15}H_{22}OSi_3$ (278.4): calcd. C 64.71, H 7.96; found C 65.16, H 8.27. − **6c**: IR ($CCl_4$): $\tilde{\nu}$ = 2980 cm$^{-1}$, 2960, 2880, 1730, 1678, 1610, 1490, 1465, 1280, 855. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.29 (s, 6H), 0.96 (s, 9H), 2.45 (s, 3H), 6.62−7.70 (m, 4H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = −4.0 (q), 18.8 (q), 25.5 (q), 26.0 (s), 119.2 (d), 121.3 (d), 125.4 (s), 131.0 (d), 135.1 (d), 138.6 (s), 156.4 (s), 194.6 (s), 199.4 (s). − $C_{15}H_{22}OSi_3$ (278.4): calcd. C 64.71, H 7.96; found C 64.55, H 8.19.

*4-Acetyl-2-phenyl-2H-chromene* (**7a**): A solution of **3a** (28.0 mg, 0.110 mmol) in 10 ml of acetone was placed into a 50-ml test tube and externally irradiated by two 250-W sodium lamps (λ > 366 nm) for 11 h at −30°C until complete decoloration of the red solution was observed. The solvent was removed in a rotary evaporator (ca. 20°C/20 Torr), and purification by column chromatography (silica gel, ether/pentane, 1:1) afforded 21.0 mg (76%) of **7a** as colorless needles, m.p. 71−72°C (ether). − IR ($CCl_4$): $\tilde{\nu}$ = 3060 cm$^{-1}$, 3030, 1680, 1595, 1475, 1455, 1370, 1340, 1240, 1220, 1170, 695. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 2.48 (s, 3H), 5.91 (d, $J$ = 3.8 Hz, 1H), 6.61 (d, $J$ = 3.8 Hz, 1H), 6.88 (dd, $J_1$ = 7.8, $J_2$ = 1.3 Hz, 1H), 6.79 (ddd, $J_1$ = 7.8, $J_2$ = 7.8, $J_3$ = 1.3 Hz, 1H), 7.20 (ddd, $J_1$ = 7.8, $J_2$ = 7.8, $J_3$ = 1.6 Hz, 1H), 7.36−7.52 (m, 5H), 7.91 (dd, $J_1$ = 7.8, $J_2$ = 1.6 Hz, 1H). − $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 22.8 (q), 76.1 (d), 116.7 (d), 118.7 (s), 121.6 (d), 126.8 (d), 127.0 (d), 128.8 (d), 128.9 (d), 130.2 (d), 133.4 (d), 134.2 (s), 139.0 (s), 153.4 (s), 198.1 (s). − $C_{17}H_{14}O_2$ (250.3): calcd. C 81.58, H 5.64; found C 81.86, H 5.55.

[1] [1a] W. Adam, L. Hadjiarapoglou, T. Mosandl, C. R. Saha-Möller, D. Wild, *J. Am. Chem. Soc.* **1991**, *113*, 8005−8011. − [1b] W. Adam, L. Hadjiarapoglou, T. Mosandl, C. R. Saha-Möller, D. Wild, *Angew. Chem.* **1991**, *103*, 187−189; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 200−202. − [1c] W. Adam, J. Bialas, L. Hadjiarapoglou, M. Sauter, *Chem. Ber.* **1992**, *125*, 231−234. − [1d] W. Adam, M. Sauter, *Liebigs Ann. Chem.* **1992**, 1095−1096. − [1e] W. Adam, L. Hadjiarapoglou, K. Peters, M. Sauter, *Angew. Chem.* **1993**, *105*, 769−770; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 735−736. − [1f] W. Adam, L. Hadjiarapoglou, K. Peters, M. Sauter, *J. Am. Chem. Soc.* **1993**, *115*, 8603−8608.

[2] W. Adam, J. Bialas, L. Hadjiarapoglou, *Chem. Ber.* **1991**, *124*, 2377.

[3] [3a] M. Benson, L. Jurd, *Org. Magn. Reson.* **1984**, *22*, 86−89. − [3b] L. Jurd, *Tetrahedron* **1977**, *33*, 163−168.

[4] R. N. McDonald in *Mechanisms of Molecular Migrations* (Ed.: B. S. Thyagarajan), Wiley-Interscience, New York, **1971**, v. 3, p. 67−107.

[5] W. Adam, L. Hadjiarapoglou, X. Wang, *Tetrahedron Lett.* **1991**, *32*, 1295−1298.

[6] W. Adam, E. Kades, X. Wang, *Tetrahedron Lett.* **1990**, *31*, 2259−2262.

[7] E. Grovenstein Jr, D. E. Lee, *J. Am. Chem. Soc.* **1953**, *75*, 2639−2644.

[8] L. J. Powers, M. P. Mertes, *J. Med. Chem.* **1970**, *13*, 1102−1105.

[9] A pure sample was provided by Dr. *M. Schulz*, University of Würzburg.

[320/93]