

Constitution and Stereochemistry of the Diels-Alder Products from the Reaction of 1-Methylpyrano[3,4-*b*]indol-3-one with Cyclic Dienophiles

Ulf Pindur* and Houshang Erfanian-Abdoust

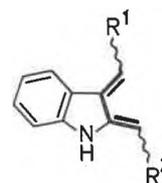
Abstract: From the Diels-Alder reactions of 1-methylpyrano[3,4-*b*]indol-3-one (**4**) with *N*-phenylmaleimide or maleic anhydride, single and double [4 + 2]-cycloadducts have been isolated. The constitutions and relative configurations of the carbazole derivatives obtained have been analyzed for the first time by means of 1D- and 2D-NMR spectroscopy.

Indolo-2,3-quinodimethanes **1**, generated in situ, are synthetically attractive 4 π -components for Diels-Alder reactions aimed at the construction of [*b*]annellated

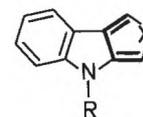
indole systems^[1-4] and pharmacologically active indole alkaloids^[5]. Particular interest has been focused on stable cyclic synthetic equivalents of **1** containing annellated pyrrolo-, thieno-, selenolo-, and furo-moieties **2**^[6-9]. The pyrano[3,4-*b*]indol-3-ones **3** represent further stable and readily accessible members of the above series^[2, 10, 11].

* Correspondence: Prof. Dr. U. Pindur
Institut für Pharmazie
Fachbereich Chemie und Pharmazie der Universität
Saarstrasse 21, D-6500 Mainz 1
(Bundesrepublik Deutschland)

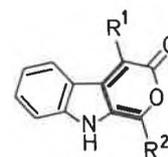
Although the preparation and Diels-Alder reactivity of this class of compounds **3** have been known for a long time^[2, 10, 11], only few systematic studies have been carried out with the objective



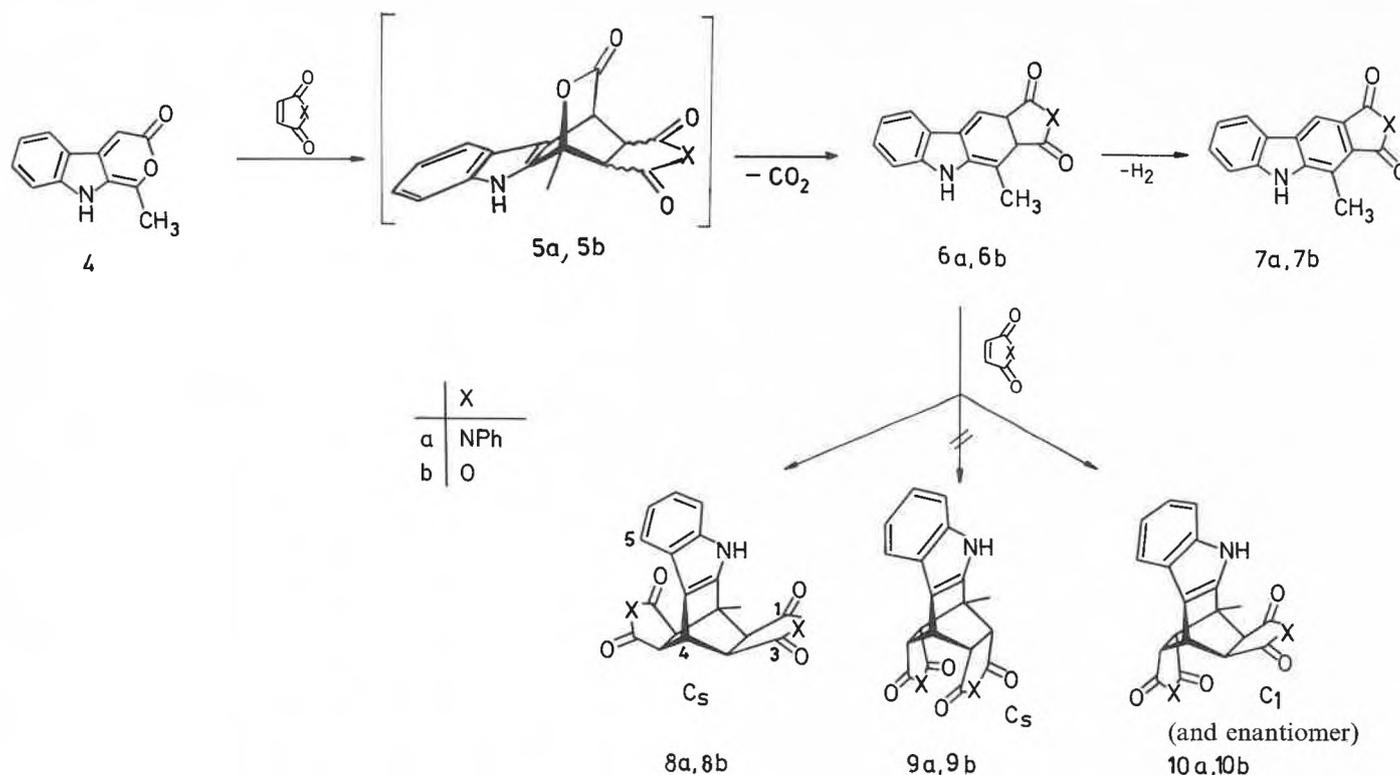
1



2



3



of probing the synthetic potential of these compounds with regard to carbon- and hetero-Diels-Alder reactions. Thus, a comprehensive knowledge of the regio- and stereochemistry of the reactions of **3** with dienophiles is still lacking.

In the present communication, we report first on new results concerning the product spectrum obtainable from the cycloaddition reactions of **4** with *N*-phenylmaleimide and maleic anhydride. These reactions were first carried out by

Plieninger et al.^[10]. In addition to the constitutional analysis, we were able to clarify the stereochemistry of the double Diels-Alder adduct for the first time.

In dependence on the solvent, the reaction temperature, and the reaction time,

Table 1. Cycloadducts **7**, **8**, and **10**. NMR spectra: Bruker AC 300 and WM 400 (δ scale); mass spectra (70 eV): Varian CH 7A; «flash»-chromatography: silica gel 60, Merck, particle size 0.040–0.063 mm.

Product ^{a)}	<i>m.p.</i> [°C]	Yield [%]	¹ H-NMR	¹³ C-NMR
7a	297–298 (methanol)	4	DMSO- <i>d</i> ₆ : 2.90 (s, 3H, CH ₃), 7.28 (t, ³ <i>J</i> = 7.5 Hz, 1H, 6- or 7-H), 7.45 (m, 3H, aromatic), 7.52 (m, 3H, aromatic), 7.61 (d, ³ <i>J</i> = 8.2 Hz, 1H, 8-H), 8.34 (d, ³ <i>J</i> = 7.9 Hz, 1H, 5-H), 12.12 (s, 1H, NH), 8.62 (s, 1H, 4-H).	DMSO- <i>d</i> ₆ : 12.10 (CH ₃), sp ² -C: 111.83, 114.57, 120.17, 121.46, 121.54, 121.86, 122.56, 124.38, 125.32, 127.26 (2'-C, 6'-C or 3'-C, 5'-C), 127.38, 127.56, 128.62 (3'-C, 5'-C or 2'-C, 6'-C), 132.26, 141.04, 142.50, 167.13 (CO), 167.97 (CO)
8a	315 ^[10] (acetone/ <i>n</i> -hexane)	80	acetone- <i>d</i> ₆ : 2.27 (s, 3H, CH ₃), 3.47 (d, ³ <i>J</i> _{10a,3a} = ³ <i>J</i> _{11,12} = 8 Hz, 2H, 10a-H, 11-H), 3.72 (dd, ³ <i>J</i> _{3a,10a} = ³ <i>J</i> _{12,11} = 8 Hz, ³ <i>J</i> _{3a,4} = ³ <i>J</i> _{12,4} = 3.2 Hz, 2H, 3a-H, 12-H), 4.60 (t, ³ <i>J</i> _{4,3a} = ³ <i>J</i> _{4,12} = 3.2 Hz, 1H, 4-H), 6.43 (m, 4H, 2',6'-phenyl-H), 7.04 (t, ³ <i>J</i> = 7.1 Hz, ³ <i>J</i> = 7.9 Hz, 1H, 6-H or 7-H), 7.10 (t, ³ <i>J</i> = 8.0 Hz, ³ <i>J</i> = 7.1 Hz, 1H, 7-H or 6-H), 7.17 (m, 6H, 3',4',5'-phenyl-H), 7.38 (d, ³ <i>J</i> = 8.0 Hz, 1H, 8-H), 7.49 (d, ³ <i>J</i> = 8.0 Hz, 1H, 5-H), 10.7 (s, 1H, NH)	DMSO- <i>d</i> ₆ : 15.85 (CH ₃), 33.07 (4-C), 40.68 (10-C), 45.06 and 49.03 (3a-C, 10a-C, 11-C, 12-C), 111.52, 117.09, 119.30, 120.73 (5-C, 6-C, 7-C, 8-C), 126.30, 128.50 (2'-C, 3'-C, 5'-C, 6'-C), 128.08 (4'-C), 131.74 (1'-C), 107.19, 124.68, 135.89, 136.73 (4a-C, 5a-C, 8a-C, 9a-C), 175.03, 175.96 (2 × CO)
10a^{b)}	–	–	DMSO- <i>d</i> ₆ : 2.11 (s, 3H, CH ₃), 3.18 (dd, ³ <i>J</i> = 7.3 Hz, ³ <i>J</i> = 3.8 Hz, 2H, 3a-H, 12-H), 3.25 (d, ³ <i>J</i> = 7.6 Hz, 2H 10a-H, 11-H), 4.38 (t, ³ <i>J</i> ≈ 3.25 Hz, 1H, 4-H), 6.14 (d, ³ <i>J</i> = 7.6 Hz, 2H, 2,6-phenyl-H), 11.5 (s, 1H, NH)	DMSO- <i>D</i> ₆ : 16.22 (CH ₃), 32.42 (4-C), 40.00, 43.19, 46.75, 47.00, 50.14, (10-C, 3a-C, 10a-C, 11-C, 12-C), 174.96, 175.49, 175.89, 176.22 (CO)
7b	318	4	DMSO- <i>d</i> ₆ : 2.49 (s, 3H, CH ₃), 7.31 (t, ³ <i>J</i> = 7.3 Hz, ³ <i>J</i> = 7.2 Hz, 1H, 6-H or 7-H), 7.57 (t, ³ <i>J</i> = 7.6 Hz, ³ <i>J</i> = 7.2 Hz, 1H, 7-H or 6-H), 7.63 (d, ³ <i>J</i> = 8.1 Hz, 1H, 8-H), 8.37 (d, ³ <i>J</i> = 7.84 Hz, 1H, 5-H), 8.73 (s, 1H, 4-H), 12.31 (s, 1H, NH)	
8b	317 ^[10] (THF/ <i>n</i> -hexane)	41	DMSO- <i>d</i> ₆ : 2.05 (s, 3H, CH ₃), 3.63 (d, ³ <i>J</i> _{10a,3a} = ³ <i>J</i> _{11,12} = 8.4 Hz, 2H, 10a-H, 11-H), 3.88 (dd, ³ <i>J</i> _{3a,4} = ³ <i>J</i> _{12,4} = 3.2 Hz, ³ <i>J</i> _{3a,10} = ³ <i>J</i> _{12,11} = 8.4 Hz, 2H, 3a-H, 12-H), 4.32 (t, ³ <i>J</i> _{4a,3} = ³ <i>J</i> _{4,12} = 3.2 Hz, 1H, 4-H), 7.02 (t, ³ <i>J</i> = 7.1 Hz, ³ <i>J</i> = 7.7 Hz, 1H, 6-H or 7-H), 7.09 (t, ³ <i>J</i> = 7.3 Hz, ³ <i>J</i> = 7.4 Hz, 1H, 7-H or 6-H), 7.35 (d, ³ <i>J</i> = 8.0 Hz, 1H, 8-H), 7.40 (d, ³ <i>J</i> = 7.8 Hz, 1H, 5-H), 11.6 (s, 1H, NH)	DMSO- <i>d</i> ₆ : 14.75 (CH ₃), 25.01 (4-C), 32.24 (10-C), 46.13, 49.46 (3a-C, 10a-C, 11-C, 12-C), 111.99, 117.19, 119.75, 121.34 (5-C, 6-C, 7-C, 8-C), 107.24, 124.12, 135.83 and 136.14 (8a-C and 4b-C), 170.50, 171.59 (CO)

^{a)} Compounds **7** and **8** gave satisfactory elemental analyses. All compounds exhibited correct molecular ion peaks in their mass spectra. The structure of **10a** was confirmed by FAB-mass spectrometry and by NMR spectroscopy.

^{b)} As a mixture with product **7a**; clearly separated signals are reported here.

differing product ratios can be recognized on monitoring the course of the reaction by time-dependent, thin-layer chromatography. Thus, in tetrahydrofuran at room temperature for 25 h, **4** reacts with *N*-phenylmaleimide to furnish preferentially the double Diels-Alder product **8a** (80% yield), the simultaneously formed [b]annellated carbazole derivative **7a** is a minor product (2%, by TLC analysis). When, in contrast, the reaction of **4** with *N*-phenylmaleimide is performed in bromobenzene at 150°C for 13 h under an inert gas atmosphere, **8a** is again formed as the major product; however, **7a** can be isolated from this reaction in 4% yield by a single, flash-chromatographic separation of the product mixture. The 400 MHz ¹H- and ¹³C-NMR spectra (*J*-modulated spin-echo ¹³C-NMR spectrum) show, however, that the carbazole **7a** iso-

lated from this reaction is contaminated with about 25% of the cycloadduct **10a**. The latter is isomeric with **8a**. The ¹³C-NMR data are of decisive diagnostic value for analysis of the constitution and configuration of **10a**^[12]. Thus, as a consequence of the C_s symmetry, four signals at 174.96, 175.49, 175.89, and 176.22 ppm are observed for the CO groups of **10a**. In addition, 21 other structurally significant resonances for sp²- and sp³-hybridized carbon atoms are present and are clearly different from the corresponding ¹³C-NMR chemical shifts of the C_s symmetrical double Diels-Alder product **8a** (Table 1). By means of further flash-chromatographic separations, compounds **7a** and **10a** can be completely separated and the structurally relevant NMR spectroscopic assignments thus confirmed (Table 1).

In principle, all three cycloadducts **8a**, **9a**, and **10a** should be expected from the double Diels-Alder reaction (reaction route **4**→**8**, **9**, **10**) since, according to considerations of Büchi-Dreiding models (approach of reactants to transition state), they should be formed with about the same probabilities. Since the ¹H- and ¹³C-NMR spectra reflect C_s symmetry for the pure, isolated double Diels-Alder major product, the two diastereoisomeric alternatives **8a** and **9a** are feasible. In addition to the analysis of the *J*-modulated spin-echo ¹³C-NMR spectrum, the decision in favor of the *exo-cisoid-exo* **8a** product was based mainly on ¹H{¹H}-NOED measurements which were performed as 1D and 2D experiments (Fig. 1), this being the most informative NMR technique. Among others, the positive NOE's a-e that are of high diagnostic value for clari-

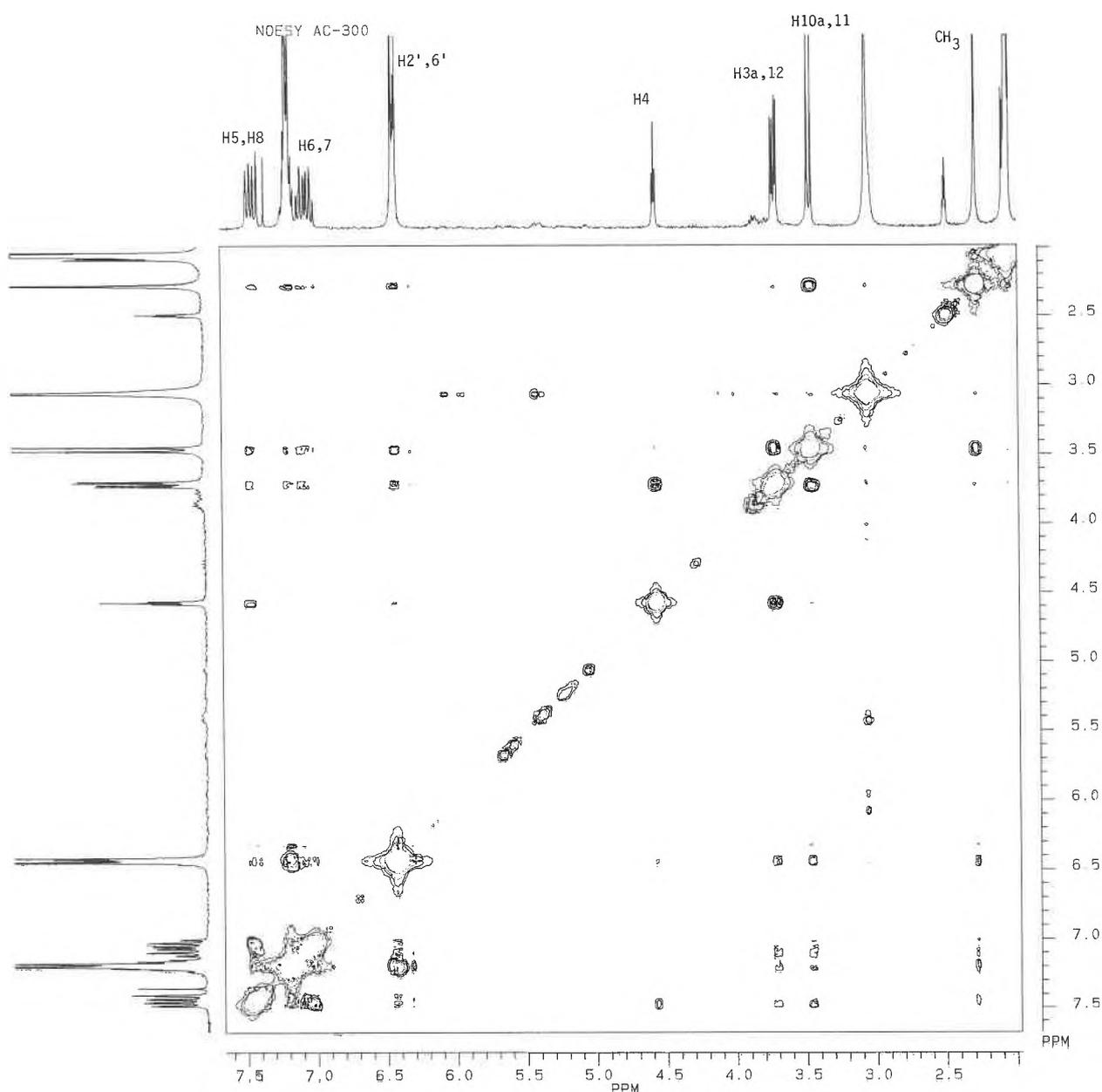
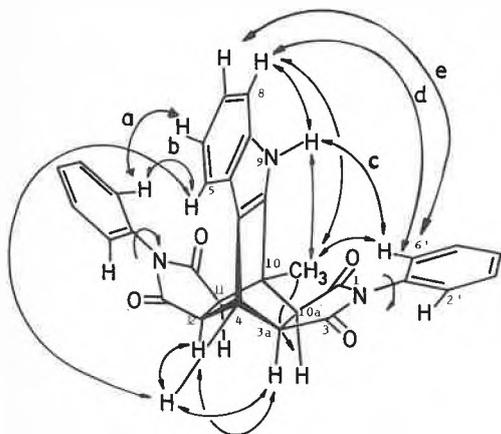


Fig. 1. ¹H{¹H}-NOESY spectrum of compound **8a** in [D₆]dimethyl sulfoxide/[D₆]acetone. The normal spectrum is visualized along the diagonal (bottom left to top right) and off-diagonal peaks (cross-peaks) indicate NOE's and therefore reflect the spatial proximities of the ¹H nuclei.

I: $^1\text{H}\{^1\text{H}\}$ -NOED

fication of the configuration are shown in the structural formula I. These are also in agreement with the H,H distances estimated in the Dreiding model. An additionally measured $^1\text{H},^1\text{H}$ -COSY spectrum of **8a** supports the assignments of the protons of the bicyclic moiety.

The compound **6a** shown as an intermediate in the reaction scheme can be detected by thin-layer chromatography (subsequent oxidation to **7a** with chloranil) but could not be isolated on account of the small amount formed and its insufficient stability (lability to oxidation).

In the reaction of **4** with maleic anhydride, the analogous product spectrum could be identified. In addition to the previously only constitutionally known double Diels-Alder adduct **8b**^[10], product **7b** was also isolated. In spite of several attempts under varying experimental conditions, thin-layer chromatographic analyses indicated that the cycloaddition of **4** with maleic anhydride produced only extremely small amounts of **10b** and **6b**. The assignments of the NMR signals of **7b** and **8b** were made in analogy to those of the confirmed structures from the reaction of **4** with *N*-phenylmaleimide (Table 1).

Further experiments have shown that other pyranoindolones of the type **3** such as, for example, the previously not reported 1-phenyl derivative and the known 1,4-dimethyl derivative gave rise to a related product spectrum in analogy to the reaction with **4**. Work is in progress in our laboratory to extend the synthetic scope of this reaction principle, in particular by use of heterodienophiles and by clarification of regiochemistry.

Reaction Conditions and Work-up:

7a, 10a: **4** + *N*PhMI (1:2), BrPh, N_2 , reflux, 13 h; FC (acetone/ CHCl_3 1:12).

8a: **4** + *N*PhMI (1:2), THF, RT, 25 h.

7b: **4** + MA (1:1), BrPh, N_2 , reflux, 18 h; FC (petrol ether/ethyl acetate 6:4).

8b: **4** + MA (1:2), THF, N_2 , reflux, 3 h; RT, 24 h.

Received: March 14, 1988 [FC 136]

- [1] E. R. Marinelli, *Tetrahedron Lett.* 23 (1982) 2745.
- [2] C. J. Moody, *J. Chem. Soc. Perkin Trans. I* (1985) 2505, and references cited therein.
- [3] B. Saroja, P. C. Srinivasan, *Tetrahedron Lett.* 25 (1984) 5429.
- [4] P. Magnus, T. Gallagher, P. Brown, P. Pappalardo, *Acc. Chem. Res.* 17 (1984) 35, and references cited therein.
- [5] Anionic equivalents: T. Kurihara, M. Hanakawa, S. Harusawa, R. Yoneda, *Chem. Pharm. Bull.* 34 (1986) 4545.
- [6] W. M. Welch, *J. Org. Chem.* 41 (1976) 2031.
- [7] C.-K. Sha, K.-S. Chuang, J.-J. Young, *J. Chem. Soc. Chem. Commun.* (1984) 1552; C.-K. Sha, K.-S. Chuang, S.-J. Wey, *J. Chem. Soc. Perkin Trans. I* (1987) 977; R. P. Kreher, G. Dyker, *Z. Naturforsch. B* 42 (1987) 473.
- [8] A. Shafiee, S. Sattari, *J. Heterocycl. Chem.* 19 (1982) 227.
- [9] M. G. Saulnier, G. W. Gribble, *Tetrahedron Lett.* 24 (1983) 5435; G. W. Gribble, M. G. Saulnier, *J. Chem. Soc. Chem. Commun.* (1984) 168.
- [10] H. Plieninger, W. Müller, K. Weinerth, *Chem. Ber.* 97 (1964) 667.
- [11] N. S. Narasimhan, S. M. Gokhale, *J. Chem. Soc. Chem. Commun.* (1985) 86.
- [12] Structurally related carbazoles: L. Peuffer, U. Pindur, *Helv. Chim. Acta* 70 (1987) 1419; 71 (1988) 467.