INTRAMOLECULAR CYCLOADDITIONS WITH ISOBENZOFURANS I

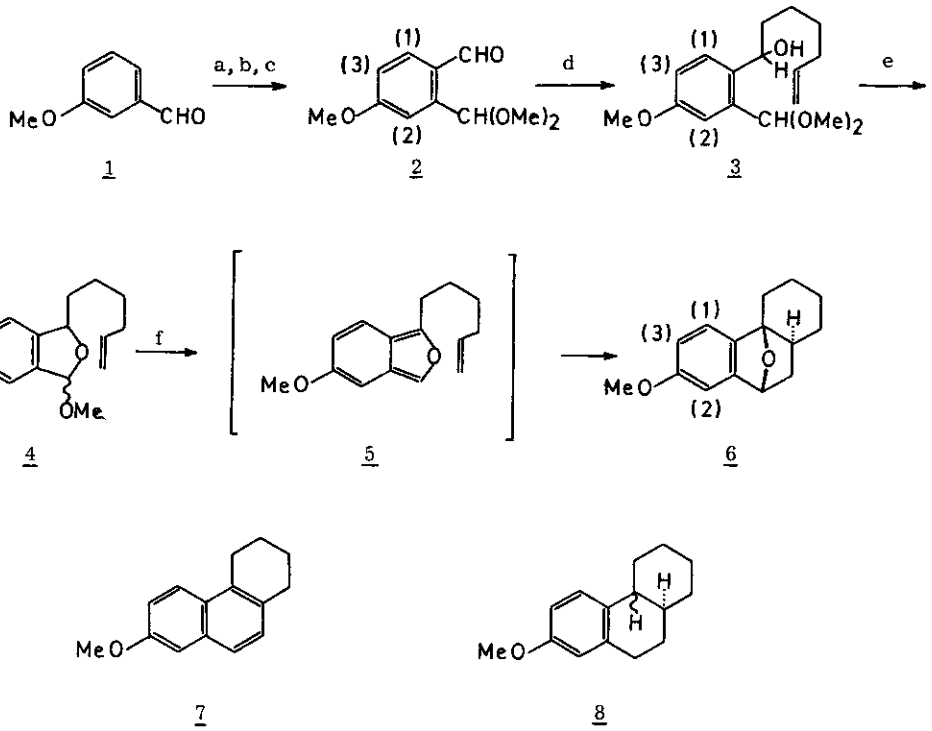
Willy Friedrichsen[+a], B.-Michael König[a], Knut Hildebrandt[a],
and Tony Debaerdemaeker[b]

[a]Institut für Organische Chemie der Universität Kiel
Olshausenstraße 40-60, D-2300 Kiel, FRG

[b]Sektion für Röntgen- und Elektronenbeugung der Universität Ulm
Oberer Eselsberg, D-7900 Ulm, FRG

Abstract - Intramolecular Diels-Alder reactions with isobenzofurans (5, 12) offer an attractive route for the preparation of polycyclic systems (6, 13).

Intramolecular Diels-Alder reactions[1,2] are frequently encountered procedures for the preparation of complicated ring systems. Especially o-quinodimethanes generated in situ either from benzocyclobutenes[2,3] or from silyl-substituted precursors[2,4] have been used extensively for this purpose. In their elegant synthesis of resistomycin Rodrigo et al. have shown[5] that isobenzofurans[6] may offer an attrative alternative to the o-quinodimethane route. In this paper we want to describe two examples which underline the significance of their approach. - The precursor (4) of the isobenzofuran 5 was prepared as outlined in Scheme 1. 3-Methoxybenzaldehyde (1) was transformed to the acetal 2 (oil, bp 101-104°C/5·10^{-4} Torr; IR(film): 1684 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ =3.40 (s, 2 OCH_3), 3.88 (s, ar-OCH_3), 5.92 (s, 1 H), 6.94 (dd, 1 H, H(3), J_1 = 8.7 Hz, J_2 = 2.7 Hz), 7.21 (d, 1 H, H(2), J = 2.7 Hz), 7.87 (d, 1 H, H(1), J = 8.7 Hz), 10.25 ppm (s, C<u>H</u>O)). The reaction of 2 with hexenylmagnesium bromide gave carbinol 3 (oil, IR(film): 3430, 2925 cm^{-1} ; ^{1}H-NMR($CDCl_3$): δ = 1.2-2.2 (m, 8 H), 2.55 (bs, O<u>H</u>), 3.32 (s, OCH_3), 3.35 (s, OCH_3), 3.80 (s, ar-OCH_3), 4.8-5.1 (m, 3 H, $C\underline{H}_2$═CH-, C<u>H</u>OH), 5.50 (s, $CH(OCH_3)_2$), 5.55-6.05 (m, 1 H, CH_2═C<u>H</u>-), 6.87 (dd, 1 H, H(3), J_1 = 8.7 Hz, J_2 = 2.7 Hz), 7.09 (d, 1H, H(2), J = 2.7 Hz), 7.41 ppm (d, 1 H, H(1), J = 8.7 Hz)) which on treatment with acetic acid in methanol (reflux) yielded a mixture of epimeric dihydrobenzo[c]furans (4, trans/cis = 1/1 to 1.4/1). The preparation and trapping of isobenzofurans from precursors of type 4 under a variety of conditions has been extensively documented[8,11]. Treatment of the epimeric mixture 4 with acetic acid



a: Br_2 - $CHCl_3$ - RT, 94% (55%)[7]; b: MeOH - $HC(OMe)_3$ - Dowex 50WX2[8], 99.6%; c: n-BuLi - DMF, 90%; d: hexenylmagnesium bromide[9], 96%; e: MeOH - AcOH, 97%; f: AcOH - toluene, 84%

Scheme 1

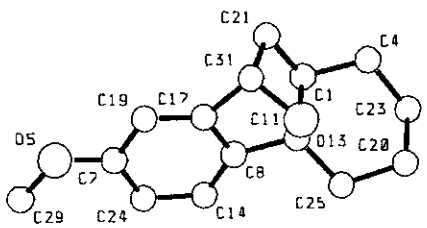
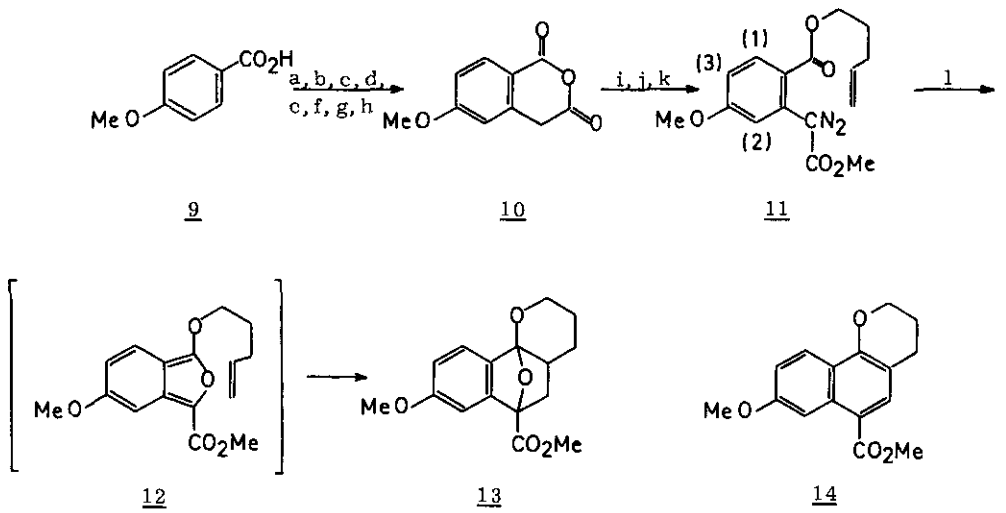


FIG. 1 : Model of compound 6 (determined by x-ray crystallography)

in refluxing toluene yielded 6 as colourless crystals with mp 64°C (IR(KBr): 1591, 1622, 2925 cm^{-1}; ^{1}H-NMR(acetone-d_6): δ = 1.10-2.35 (m, 11 H), 3.74 (s, ar-OCH_3), 5.18 (m, 1 H, C<u>H</u>-O),

6.64 (dd, 1 H, H(3), J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.80 (d, 1 H, H(2), J = 2.4 Hz), 7.02 ppm (d, 1 H, H(1), J = 8.4 Hz)). As it seemed difficult to determine the stereochemistry of 6 unequivocally by NMR-spectroscopy even at 500 MHz[12] we undertook an x-ray analysis. The result[13] is shown in Figure 1; as in comparable cases the exo-stereochemistry is favoured in the Diels-Alder reaction[4a,14]. - Expectedly, compound 6 showed to be sensitive against strong acids; on treatment with p-TsOH 7 was obtained (81%, mp 56-57°C). The reductive elimination of the oxygen bridge in 6 was achieved[15] with Pd-C/H_2 in ethanol[16]; using this method methoxy-octahydrophenanthrene 8 was obtained in 88% yield (mixture of isomers, cis/trans = 9/1 (tent. assigned)).

A further approach to the generation of a reactive isobenzofuran is based on an intramolecular reaction of a diazo compound with a carbonyl group[17]. 6-Methoxyisochromane-1,3-dione (10, Scheme 2)[18] was prepared from anisic acid (9) in 8 steps in an overall yield of 50%. The solvo-



a: $SOCl_2$, 97%; b: 2-amino-2-methyl-1-propanol - CH_2Cl_2, 96%; c: $SOCl_2$, 90%; d: n-BuLi - MeI, 92%; e: MeI - MeCN, 92%; f: 2n NaOH - MeOH, 96%; g: 4 equiv. LDA - $OC(OEt)_2$, 83%; h: AcCl, 89%; i: MeOH - H_2SO_4, 93%; j: N-hydroxypyridone - DCC - 4-penten-1-ol, 89%; k: TsN_3 - DBU - MeCN, 75%; l: Cu(hexafluoroacetylacetonate)$_2$ - dichloroethane, 90%

Scheme 2

lytic cleavage[19] of the anhydride 10 with methanol yielded 2-methoxycarbonylmethyl-4-methoxybenzoic acid, mp 154°C (157-158°C)[19], which was transformed to methyl 5-methoxy-2-(4-pentenoxycarbonyl)-phenylacetate (IR(film): 1645, 1710, 1745 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ = 1.70-1.97 (m, 2 H, $-CH_2-C\underline{H}_2-CH_2-$), 2.05 - 2.30 (m, 2 H, $-C\underline{H}_2-CH=CH_2$), 3.68 (s, CO_2CH_3), 3.83 (s, OCH_3), 3.99 (s, 2 H, $-CH_2-CO_2CH_3$), 4.24 (t, 2 H, $-CO_2-C\underline{H}_2-CH_2-$, J = 6.3 Hz), 4.90 - 5.17 (m, 2 H, $-CH=C\underline{H}_2$), 5.62 - 6.07 (m, 1 H, $-C\underline{H}=CH_2$), 6.73 - 6.90 (m, 2 H, ar-H), 8.02 ppm (d, 1 H, J = 9 Hz, ar-H) by employing the elegant but obviously seldom used method proposed by Paquette[20]. The introduction of a diazo group was quite easily accomplished by the Regitz procedure[21]. In this way the diazoester 11 (mp 42 - 43°C; IR(KBr) : 1645, 1690, 1710, 2120 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ = 1.72 - 1.97 (m, 2 H, $-CH_2-C\underline{H}_2-CH_2-$), 2.07 - 2.30 (m, 2 H, $-C\underline{H}_2-CH=CH_2$), 3.80 (s, CO_2CH_3), 3.84 (s, OCH_3), 4.27 (t, 2 H, J = 6 Hz, $-CO_2-CH_2-$), 4.90 - 5.13 (m, 2 H, $-CH=C\underline{H}_2$), 5.62 - 6.07 (m, 1 H, $-C\underline{H}=CH_2$), 6.88 (dd, 1 H, J_1 = 9 Hz, J_2 = 3 Hz, H(3)), 7.03 (d, 1 H, J = 3 Hz, H(2)), 8.00 ppm (d, 1 H, J = 9 Hz, H(1))) was obtained from 10 in an overall yield of 62%. A number of methods have been described for the preparation of a carbene (carbenoid)[22] from a precursor of type 11. Whereas dirhodiumtetraacetate[23] and copper(II)bisacetylacetonate[19, 22a, 24] proved to be less suitable treatment of 11 with copper(II) bishexafluoroacetylacetonate[25] gave 13 in 90% yield. Expectedly, the ketal 13 is unstable under acidic conditions; on treatment with p-TsOH the oxa-phenanthrene derivative 14 is obtained in 77% yield.

The methods depicted in Scheme 1 and in Scheme 2 seem to be well suited for the preparation of a great variety of polycyclic systems. Work is in progress to confirm this expectation.

ACKNOWLEDGEMENT

Thanks are due to the Verband der Chemischen Industrie - Fonds der Chemischen Industrie - for continuous support.

REFERENCES

1. K. Alder and M. Schumacher in Fortschritte der Chemie organischer Naturstoffe, Vol. 10, p. 1, Springer-Verlag, Wien 1953.

2. Reviews: 2a. D. Taub in The Total Synthesis of Natural Products (J. ApSimon), Vol. 6. Wiley, New York 1984. - 2b. D. F. Taber, Intramolecular Diels-Alder and Alder Ene Reactions. Reac-

tions. Reactivity and Structure. Concepts in Organic Chemistry, Vol. 18, Springer-Verlag, Berlin 1984. - 2c. A.G. Fallis, Canad. J. Chem., 62, 183 (1984). - 2d. E. Ciganek, Org. React. 32, 1 (1984). - 2e. S. M. Weinreb, Acc. Chem. Res., 18, 16 (1985).

3. 3a. T. Kametani, Pure Appl. Chem., 51, 747 (1979). - 3b. W. Oppolzer, Heterocycles, 14, 1615 (1980).
4. 4a. Y. Ito, M. Nakatsuka and T. Saegusa, J. Am. Chem. Soc., 104, 7609 (1982). - 4b. S. Djuric, T. Sarkar and P. Magnus, J. Am. Chem. Soc., 102, 6885 (1980).
5. B. A. Keay and R. Rodrigo, J. Am. Chem. Soc., 104, 4725 (1982).
6. Reviews: 6a. W. Friedrichsen, Adv. Heterocycl. Chem., 26, 135 (1980). - 6b. U. E. Wiersum, Aldrichimica Acta, 14, 53 (1981).
7. I. Fleming and M. Woolias, J. Chem. Soc., Perkin Trans. I, 1979, 829.
8. B. A. Keay, H. P. Plaumann, D. Rajapaksa and R. Rodrigo, Canad. J. Chem., 61, 1987 (1983).
9. Hexenylbromide was prepared from hexenol and triphenylphosphine/pyridine/Br_2 in dichloromethane (86%, bp 47-49°C/15 Torr, n_D^{25} 1.4630 (1.4630)[10]).
10. G. B. Butler and G. D. Price, J. Org. Chem., 24, 1092 (1959).
11. 11a. K. Naito and B. Rickborn, J. Org. Chem., 45, 4061 (1980). - 11b. R. J. Moss and B. Rickborn, J. Org. Chem., 49, 3694 (1984).
12. Thanks are due to Dr. Formacek, Bruker-Physik, Karlsruhe for measuring these spectra.
13. Space group: B2/b; a = 22.584, b = 18.438, c = 5.756, γ = 90.99; Z = 8.
14. K. P. C. Vollhardt in Strategies and Tactics in Organic Synthesis (Th. Lindberg). Academic Press, New York 1984.
15. Discussions with Prof. Dr. C. H. Eugster, Zürich on this point are gratefully acknowledged.
16. This method has been found independently by Dr. R. Rodrigo and coworkers (G. Weeratunga, D. Rajapaksa and R. Rodrigo, J. Org. Chem., submitted). We thank Dr. R. Rodrigo for bringing these results to our knowledge (10th Int. Congr. Het. Chem., Waterloo, Ontario 1985).
17. M. Hamaguchi and T. Ibata, Chem. Lett., 1976, 287.
18. G. A. Swan, J. Chem. Soc., 1950, 1534.
19. N. K. Bose and D. N. Chaudhury, J. Indian Chem. Soc., 66, 854 (1969).
20. L. A. Paquette, J. Am. Chem. Soc., 87, 5186 (1965), footnote 27.
21. M. Regitz, Chem. Ber., 98, 1210 (1965).
22. 22a. D. S. Wulfman and B. Poling in Reactive Intermediates (R. A. Abramovitch), Vol. 1.

Plenum Press, New York 1980. - 22b. M. Orchin, F. Kaplan, R. S. Macomber, R. M. Wilson and H. Zimmer, The Vocabulary of Organic Chemistry. Wiley, New York 1980.

23. P. Legzdins, R. W. Mitchell, G. L. Rempel, J. D. Ruddick and G. Wilkinson, J. Chem. Soc. A, 1970, 3322.

24. M. Hamaguchi and T. Nagai, J. Chem. Soc., Chem. Comm., 1985, 726. - See also K. T. Potts in 1, 3-Dipolar Cycloaddition Chemistry (A. Padwa), Vol. 2, p. 1, footnote 97. Wiley, New York 1984 and W. Friedrichsen and W.-D. Schröer, Liebigs Ann. Chem., 1890, 1836.

25. 25a. A. Saba, Synthesis, 1984, 268. - 25b. J. A. Bertrand and R. I. Kaplan, Inorg. Chem., 5, 489 (1966).

Received, 24th September, 1985