HETEROCYCLES, Vol. 29, No. 7, 1989

INTRAMOLECULAR CYCLOADDITIONS WITH ISOBENZOFURANS -VIII[1]

SYNTHESIS OF PRECURSORS VIA AN OPPÉ REACTION

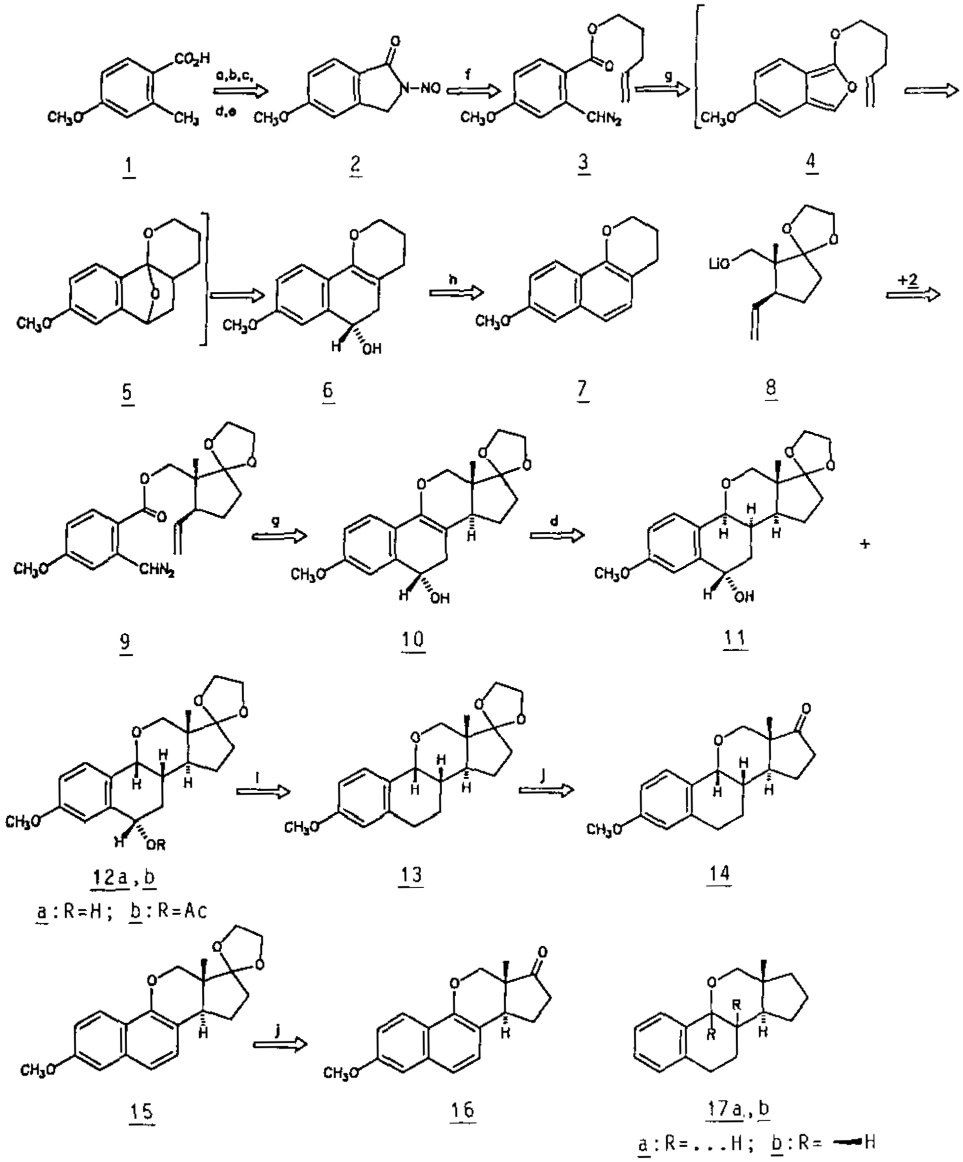
Knut Hildebrandt and Willy Friedrichsen*

Institut für Organische Chemie der Universität Kiel,

Olshausenstraße 40-60, D-2300 Kiel, FRG

Abstract - The diazoesters 3 and 9 were prepared via an Oppé reaction. Generation of isobenzofurans (e.g. 4) and subsequent intramolecular Diels-Alder reaction yields polycyclic systems (6, 10). Compound 10 *can be transformed into an* 11-oxasteroid 14.

As has been described in previous papers[1,2] intramolecular cycloadditions[3] with isobenzofurans[4] offer an attractive route for the preparation of polycyclic systems. For the generation of isobenzofurans (e.g. 4) several methods are available; inter alia diazoesters (e.g. 3) may act as convenient precursors[5]. We have found that diazo compounds of this type can be prepared via an Oppé reaction[6]. The starting material 2 (mp 178-9°C; ir(KBr): 1755 cm^{-1}, 1740; uv(MeCN): λ_{max} (logϵ)=242 nm (4.009), 280 (sh, 3.965), 285 (sh, 4.000), 300 (4.092), 414 (1.927), 434 (1.956); ^{1}H-nmr($CDCl_3$/DMSO-d_6): δ=3.93 (s, 3H), 4.72 (s, 2H), 7.00-7.20 (m, 2H), 7.97 (d, J=8.1 Hz, 1H)) was prepared from 4-methoxy-2-methylbenzoic acid[7] (1) in 5 steps in an overall yield of 50%. Treatment of nitrosamide 2 with lithium 4-penten-1-olate according to the Oppé conditions yields 3 (85%, oil; ir(film): 2070 cm^{-1}, 1700; ^{1}H-nmr ($CDCl_3$): δ=1.72-2.00 (m, 2H), 2.07-2.33 (m, 2H), 3.82 (s, 3H), 4.24 (t, J=6.0 Hz, 2H), 4.90-5.17 (m, 2H), 5.63-6.10 (m, 1H), 6.43-6.62 (m, 2H), 6.77 (s, 1H), 7.98 (d, J=8.7 Hz, 1H)). The generation of 4 and subsequent ring opening to 6 (42%, mp 106°C; ir(KBr): 3485 cm^{-1}, 1660; uv(MeCN): λ_{max} (logϵ)=202 nm (4.570), 223 (4.097), 278 (4.214); ^{1}H-nmr($CDCl_3$): δ=1.77-2.30 (m, 5H), 2.37-2.57 (m, 2H), 3.79 (s, 3H), 4.03-4.23 (m, 2H), 4.55-4.82 (m, 1H), 6.80 (dd, J_1=2.7 Hz, J_2=8.4 Hz, 1H), 6.94 (d, J=2.7 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H)) was accomplished *with copper(II) bishexafluoroacetylacetonate*[8]. The alcohol 6 showed to be sensitive against acids; in the presence of a catalytic amount of p-TsOH 7 was obtained (52% [from 3], mp 80°C). In an extension of this study nitrosamide 2 was reacted with lithium alcoholate 8[9] giving diazo ester 9 (90%, oil; ir(film): 2065 cm^{-1}, 1700; ^{1}H-nmr(CCl_4): δ=0.97 (s, 3H), 1.13-1.97 (m, 4H), 2.45-2.80 (m, 1H), 3.70-3.90 (m, 7H), 4.02, 4.10 (AB-q, J_{AB}=11.3 Hz, 2H), 4.85-5.13 (m, 2H), 5.47-6.00 (m, 1H), 6.33-6.53 (m, 2H), 6.88 (s, 1H), 7.89 (d, J=8.7 Hz, 1H)). Under the same conditions as described for the genera-



a: CH_3OH, H_2SO_4; b: NBS, AIBN; c: NaN_3, toluene, H_2O, $Bu_4N^+HSO_4^-$; d: $Pd/C-H_2$, CH_3OH; e: $NaNO_2$, AcOH, H_2O; f: 4-penten-1-ol/CH_3Li, CO_2; g: $Cu(CF_3COCHCOCF_3)_2$, toluene; h: p-TsOH, toluene; i: Pd/C-H_2, EtOH/Et_3N=9/1; j: p-TsOH, acetone, rt tion of 6 diazo ester 9 gives 10 (40%, mp 132°C; ir(KBr): 3500 cm^{-1}, 3480, 1648; uv(MeCN): λ_{max} (logϵ)=202 nm (4.434), 227 (3.959), 282 (4.108); ^{1}H-nmr($CDCl_3$): δ=0.95 (s, 3H), 1.17-2.25 (m, 5H), 2.40-2.58 (m, 2H), 2.73-3.07 (m, 1H), 3.63-4.03 (m, 4H), 3.78 (s, 3H), 4.02, 4.22 (AB-system, J_{AB}=9.6 Hz, 2H, 12-H), 4.53-4.82 (m, 1H), 6.80 (dd, J_1=2.7 Hz, J_2=8.7 Hz, 1H), 6.96 (d, J=2.7 Hz, 1H), 7.42 (d, J=8.7 Hz, 1H)). Catalytic hydrogenation of 10 (Pd/C in methanol) yields 11 (18.4%, mp 146°C; ir(KBr): 3460 cm^{-1}; ^{1}H-nmr($CDCl_3$): δ=1.08 (s, 3H, 18-CH_3), 1.53-2.63 (m, 9 H), 3.62-4.05 (m, 6 H, 12-H, O-CH_2-CH_2-O), 3.80 (s, 3 H, ar-OCH_3), 4.19 (d, J=3.0 Hz, 1 H, 9-H), 4.73-4.90 (m, 1 H, 6-H), 6.80-7.00 (m, 2 H, 2-H, 4-H), 7.35 (d, J=8.7 Hz, 1 H, 1-H) and 12a (67.4%, mp 160°C; ir(KBr): 3510 cm^{-1}; ^{1}H-nmr($CDCl_3$): δ=1.07 (s, 3 H, 18-CH_3), 1.27-2.30 (m, 9 H), 3.30-3.93 (m, 6 H, 12-H, O-CH_2-CH_2-O), 3.78 (s, 3 H, ar-OCH_3), 4.53-4.72 (m, 1 H, 6-H), 4.79 (d, J=4.8 Hz, 1 H, 9-H), 6.80-6.97 (m, 2 H, 2-H, 4-H), 7.50 (d, J=8.4 Hz, 1 H, 1-H)[11]. Detailed ^{1}H-nmr investigations reveal J(8-H,9-H)=3.2 Hz, J(8-H,14-H)=5.0 Hz (for 11) and J(8-H,9-H)=5.6 Hz, J(8-H,14-H)=12.0 Hz (for 12a, steroid numbering). From computed geometries (AM1[12] with full geometry optimization) for the model systems 17a (fig.1) and 17b (fig.2) J(8-H,9-H)=7.85 Hz, J(8-H,14H)=7.43 Hz (for 17a) and J(8-H,9-H)=8.60 Hz, J(8-H,14H)=12.68 Hz (for 17b) are obtained[13]. The elimination of the hydroxy function was accomplished via the acetate 12b (from 12a with Ac_2O, Et_3N, and DMAP in dichloromethane, mp 192°C; ir(KBr): 1732 cm^{-1}). Catalytic hydrogenation of 12b with Pd/C-H_2 in a mixture of ethanol/triethylamine=9/1 gives 13 (82%, mp 90°C). Deacetalisation of 13 yields 11-oxa-9ß-estrone methyl ether (14) (90%, mp 107°C; ir(KBr): 1745 cm^{-1}; ^{1}H-nmr($CDCl_3$): δ=1.15 (s, 3H), 1.56-2.87 (m, 10H), 3.32, 3.59 (AB-system, J_{AB}=11.1 Hz, 2H, 12-H), 3.77 (s, 3H, ar-OCH_3), 4.95 (d, J=5.4 Hz, 1H, 9ß-H), 6.60 (d, J=2.7 Hz, 1H, 4-H), 6.78 (dd, J_1=2.7 Hz, J_2=8.7 Hz, 1H, 2-H), 7.46 (d, J=8.7 Hz, 1H, 1-H)). Final deprotection of the carbonyl group gives 11-oxaequilenin methyl ether (16; 94%, mp 152°C; ir(KBr): 1735 cm^{-1}; uv(MeCN): λ_{max} (logϵ)=224 nm (4.797), 246 (4.607), 251 (sh, 4.575), 273 (3.672), 285 (3.697), 298 (3.596), 321 (3.464), 337 (3.529); ^{1}H-nmr($CDCl_3$): δ=0.93 (s, 3H), 1.73-2.93 (m, 4H), 3.23 (dd, J_1=6.0 Hz, J_2=12.0 Hz, 1H, 14-H), 3.87 (s, 3H, ar-OCH_3), 4.34, 4.47 (AB-system, J_{AB} = 10.4 Hz, 2H, 12-H), 7.00-7.35 (m, 4H), 8.06 (d, J=10.2 Hz, 1H, 1-H)). Overall the reactions described in this paper offer a convenient way for the preparation of 11-oxasteroids and derivatives thereof[14].

ACKNOWLEDGEMENT
Support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Kultusministerin des Landes Schleswig-Holstein is gratefully acknowledged.

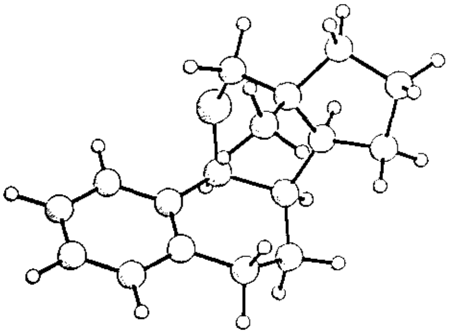


fig.1: 17a (AM1 calculation)

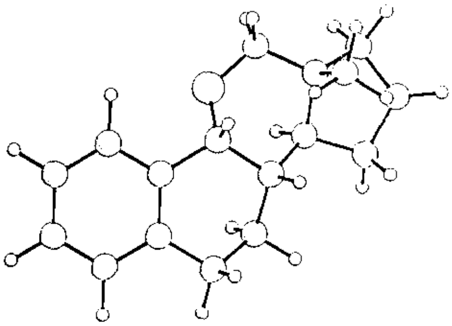


fig.2: 17b (AM1 calculation)

REFERENCES

1. VII: A.Schöning and W.Friedrichsen, Z.Naturforsch., 1989, in press.
2. VI: L.Aßmann and W.Friedrichsen, Heterocycles, 1989, 29, 1003.
3. Review: M.S.Salakhov and S.A.Ismailov, Russ.Chem.Rev., 1986,55, 2008.
4. 3a. B.Rickborn,"Adv.Theoret.Interest.Molecules", ed. by R.P.Thummel, JAI Press, Conn., in press. - 3b. R.Rodrigo, Tetrahedron, 1988, 44, 2093. - 3c. W.Friedrichsen, Adv.Heterocycl.Chem., 1980, 26, 135.
5. M.Hamaguchi and T.Ibata, Chem.Lett., 1976, 287.
6. A.Oppé, Ber., 1913, 46, 1095.
7. 7a. J.Houben and W.Fischer, Ber., 1927, 60, 1768. - 7b. G.Grethe, H.L.Lee,M.Uskokovic, and A.Brossi, J.Org.Chem., 1968, 33, 494.
8. 8a. A.Saba, Synthesis, 1984, 268. - 8b. W.Friedrichsen,B.-M.König, K.Hildebrandt, and T.Debaerdemaeker, Heterocycles, 1986, 24, 297. - 8c. J.A.Bertrand and R.I.Kaplan, Inorg.Chem., 1966, 5, 489.
9. Obtained from (±)-trans-7-ethenyl-6-methyl-1,4-dioxaspiro[4.4]nonan-6-methanol[10] with MeLi in ether.
10. K.Hildebrandt,T.Debaerdemaeker,and W.Friedrichsen, Tetrahedron Lett., 1988, 29, 2045.
11. Conformations of cis-syn-trans and cis-anti-trans steroids: T.Terasawa, Y.Yoshimura, and K.Tori, J.Chem.Soc.,Perkin Trans., 1, 1983, 903.
12. 12a. M.J.S.Dewar, E.G.Zoebisch, E.F.Healy, and J.J.P.Stewart, J.Am.Chem. Soc., 1985, 107, 3902. - 12b. J.J.P.Stewart, QCPE Bulletin, 1984, 6, 24a.
13. PCMODEL (Serena Software, Bloomington, Indiana).
13. See also: H.Suginome and J.B.Wang, Bull.Chem.Soc.Jpn., 1988, 62, 193.

Received, 17th April, 1989