New Synthesis of 18-Norestradiol

by **Alexander Kuhl**[a]), **Heiko Karels**[b]), and **Wolfgang Kreiser**[a])*

[a]) Naturstoffchemie, Universität Dortmund, D-44221 Dortmund
[b]) *Schering AG*, Chemical Process Development, D-59179 Bergkamen

The partial synthesis of 18-norestradiol (**1**) *via Wittig-Schöllkopf* cyclization of an appropriately functionalized *D-seco*-steroid **9**, obtained in nine steps from estrone, (**2**) is described. The crucial hydration of the C(13)=C(17) bond in an *anti-Markovnikov* sense was achieved *via* a diastereoselective hydroboration procedure.

1. Introduction. – The known literature procedures directed towards the synthesis of 18-norsteroids [1] [2c] [4] generally suffer from lack of stereocontrol at the C(13) atom[1]), leading to mixtures of both *cis*- and *trans*-fused D-rings at the perhydrophenanthrene moiety. In most cases, this problem may be attributed to the formation of 17-oxo-18-nor intermediates which are prone to epimerization [2] at C(13) *via* the requisite enol derivatives. Moreover, since there is some ambiguity[2]) about 18-norestradiol in the literature, we now wish to introduce an alternative approach *via Wittig-Schöllkopf* cyclization [3] for the partial synthesis of 18-norestradiol (**1**) [5].

During the course of our investigations [6] *Beckmann* fragmentation had proven to be the best method for the functionalization of the angular methyl group Me(18). Therefore, estrone (**2**) – after protection as 3-methyl ether – was transformed [7] (*Scheme 1*) into the corresponding oxime in nearly quantitative yield. According to a procedure published by *Moffat* and coworkers [8], subsequent treatment with dicyclohexylcarbodiimide (DCC) and CF_3COOH in a solution of DMSO and benzene led to *seco*-nitrile **3**. However, upscaling using the above procedure failed. Due to a remarkable pH dependency of this cleavage reaction [8], we found, that CF_3COOH had to be added in aliquots to a cooled solution of the oxime in DMSO and CCl_4 giving – after column chromatography – a 66% yield of **3** at best.

Early attempts to degrade the exocyclic C=C bond of **3** by either ozonolysis [9], RuO_4-catalyzed oxidation [10], or *cis*-hydroxylation (OsO_4) and subsequent glycol cleavage [11] by $NaIO_4$ resulted in only 39–50% yield.

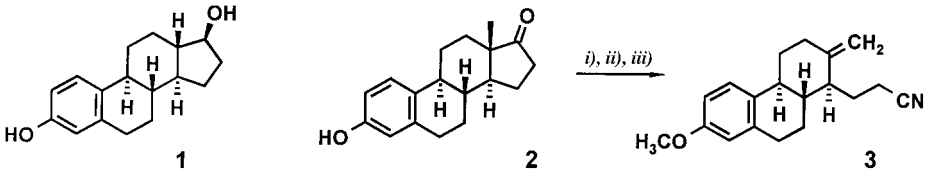
We, therefore, decided to take advantage of the exocyclic C=C bond as a protecting group for the requisite oxo function which could be liberated at a later stage during the synthesis of 18-norestradiol (**1**). In fact this strategy payed off.

---

[1]) In the case of 18-norestrone, equilibrium values from 70:30 to 55:45 in favor of the *cis*-fused epimer have been reported [2]; in general, *cis*-configuration of perhydroindenes is thermodynamically favored by far.

[2]) The 18-norestradiol (**1**) has been synthesized *via* a *retro*-pinacol rearrangement of estradiol 3-methyl ether in 12 steps in *ca.* 0.01% total yield [4].

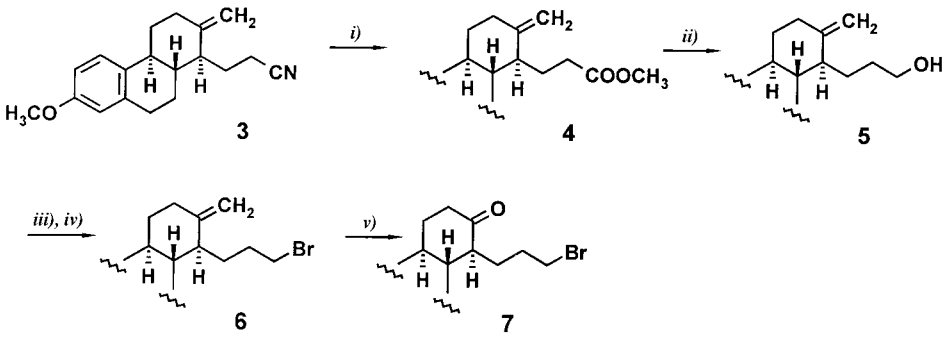
Scheme 1



i) Me_2SO_4, K_2CO_3, Me_2CO, Δ; 99%. *ii*) $NH_2OH \cdot HOAc$, EtOH, Δ; 98%. *iii*) Dicyclohexylcarbodiimide (DCC), CF_3COOH, DMSO, CCl_4, 0°, 66%.

2. Results and Discussion. – Thus, we continued the synthesis of **1** by transforming the CN function of **3** (*Scheme 2*). Smooth hydrolysis[3]) of **3** proceeded under pressure with NaOH in $EtOH/H_2O$ at 135°. Treatment of the crude acid with diazomethane resulted in ester **4**, which was reduced by $LiAlH_4$ in quantitative yield. The preparation of bromide **6** succeeded *via* mesylation of **5** and was followed by displacement with LiBr [12]; we preferred the methanesulfonate of **5** to the corresponding less reactive tosylate for this purpose, since the former could be conveniently purified by crystallization from abs. MeOH[4]). In contrast to nitrile **3**, the exocyclic C=C bond of bromide **6** could readily be oxidized with 1 equiv. of ozone at −78° in a solution of abs. CH_2Cl_2 and MeOH [9], leaving the aromatic ring A unaffected[5]). Subsequent reductive workup with dimethyl sulfide gave 80% of ketone **7** (after column chromatography) apart from unchanged starting material, based on a 93% conversion. No epimerization of the side chain at C(14) was observed under these conditions, since ^{1}H- and ^{13}C-NMR spectra of **7** displayed a single set of signals.

Scheme 2



i) NaOH, H_2O, EtOH, 135°, then CH_2N_2 in Et_2O, 0°; 80%. *ii*) $LiAlH_4$, THF, r.t. then Δ; 98%. *iii*) Et_3N, MesCl, CH_2Cl_2, 0°; 83%. *iv*) LiBr, acetone; 100%. *v*) O_3, CH_2Cl_2, MeOH, −78°, then Me_2S, r.t.; 80%.

---

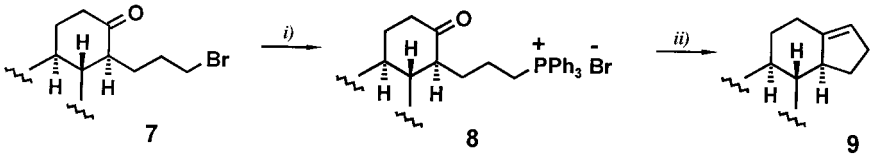
[3]) Nitrile **3** was quantitatively reduced to the corresponding imine with DIBAH in benzene. However, hydrolysis with dil. H_2SO_4 solution led mainly to polymerization and only in modest yield to the desired aldehyde.

[4]) The herein described secosteroids were isolated as oils, with the exception of the mesylate from **5** and the phosphonium salt **8**.

[5]) Introduction of O_3 until complete consumption reduced the yield by the formation of by-products resulting from attack at the steroidal ring A.

The preparation of the corresponding phosphonium salt from **7** turned out to be a crucial step in this synthesis, since various commonly applied methods to substitute the primary bromide by PPh_3 failed. In solvents like benzene, toluene [13] or Et_2O at elevated temperature (general method for the synthesis of (oxoalkyl)triphenylphosphonium bromide [14]), only tarry materials were recovered. However, melting at 85° a neat mixture of bromide **7** and PPh_3 (prepared by dissolving both components in abs. $CHCl_3$ and evaporating *in vacuo*) led to a quantitative yield of the glassy phosphonium salt **8** which further on proved a suitable intermediate for the intramolecular *Wittig* reaction [3] (*Scheme 3*). Best results were observed by single-batch addition of **8** in abs. DMSO to a solution of dimsyl sodium ($MeSOCH_2Na$) [15] prepared from 1.1 equiv. of NaH and DMSO. The alkene **9** was obtained after column chromatography as a colorless oil in 80% yield, along with minor amounts (10%) of its 14β-epimer[6]).

Scheme 3



i) PPh_3, 85°; 100%. *ii*) H_3CSOCH_2Na, DMSO, r.t., then 75°; 80%.

To achieve a regioselective hydration of the C(13)=C(17) bond yielding the anticipated *trans*-fused alcohol **11** (*Scheme 4*), we examined several hydroboration procedures with regard to yield and diastereoselectivity. The use of *in situ* prepared [16] B_2H_6 or $BH_3 \cdot Me_2S$ in THF [17] at 0° led, after oxidative workup, to a 2:1 mixture[7]) in favor of the undesired *cis*-fused gonane **10** in 59 and 60% yield, respectively; in both cases, concomitant hydrogenation of **9** to *ca.* 30% was observed. Application of substituted boranes like catecholborane [18] or 9-borabicyclo[3.3.1]nonane (9-BBN) [19] under standard conditions failed as well. Apart from the expected **10** and **11**, the formation of several different secondary alcohols was noticed, as by-products of suspected borane rearrangements [20]. We noticed that this process did not occur when powdered $LiBH_4$ was added[8]). Best results were achieved when a solution of **9** in abs. benzene was treated with 2.5 equiv. of freshly prepared [22] catecholborane and 10 mol-% of $LiBH_4$ under reflux for 24 h. Oxidative workup and purification by column chromatography gave a 1:2 mixture of **10** and **11** in 67% yield.

The undesired *cis*-fused **10**[9]) was easily separated by fractional crystallization from MeOH and the 4-chlorobenzoate derivative of **10** was subjected to X-ray analysis [23]. The latter was taken as an independant proof of the relative and absolute configuration.

---

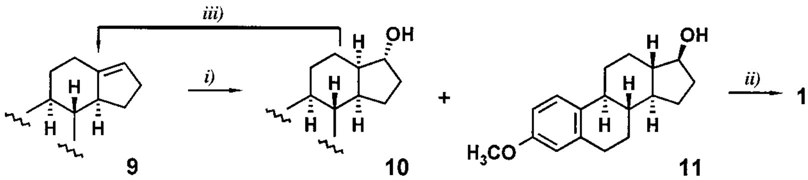
[6]) Ratio established by the chemical-shift difference of the olefinic H–C(17) in the ^{1}H-NMR spectrum (400.13 MHz, $CDCl_3$; 14α-isomer **9** at 5.29 ($J = 1.7$ Hz) and 14β-isomer (minor) at 5.42 ppm ($J = 1.7$ Hz)).

[7]) The diastereoselectivity was determined by integration of the ^{13}C-NMR signals ($CDCl_3$) of C(17) (17α-isomer **10** at 73.9 and 17β-isomer **11** at 77.7 ppm) since the *m* of H_α–C(17) in the ^{1}H-NMR spectrum of **11** was partly overlapped by the *s* of MeO–C(3).

[8]) A promoting effect of $LiBH_4$ on hydroboration with catecholborane in THF at 0° was reported [21].

[9]) Data of **10**: M.p. 144–145°. $[\alpha]_D^{20} = +22$ ($c = 1.03$, $CHCl_3$).

Scheme 4



i) Catecholborane (CB), $LiBH_4$, C_6H_6, Δ; EtOH, NaOH, H_2O_2, 0°, 67% *ii*) DIBAH, C_6H_6, Δ; 99%. *iii*) $POCl_3$, py, 0°; 45%.

For the isolation of the configurational isomer **11**[10]) in pure form, the alcohol mixture **10**/**11** was separated by prep. reversed-phase HPLC. Subsequent removal of the 3-methyl ether group of **11** proceeded readily with an excess of DIBAH [24] in abs. benzene under reflux and led after one crystallization from AcOEt to **1**[11]) in 12 steps, overall. Moreover, it was possible to transform the by-product of the hydroboration, alcohol **10**, back into the starting alkene **9** by dehydration with $POCl_3$ in abs. pyridine [25], thus increasing the total yield of this synthesis of **1** from 12 to 13%.

REFERENCES

[1] K. H. Loke, E. J. D. Watson, G. F. Marrian, *J. Biochem.* **1959**, *71*, 230; M. M. Coombs, C. W. Vose, *J. Chem. Soc., Chem. Commun.* **1974**, 602; J. C. Chapman, J. T. Pinhey, *Aust. J. Chem.* **1974**, *27*, 2421; M. Han, D. F. Covey, *J. Org. Chem.* **1996**, *61*, 7614.
[2] a) W. F. Johns, *J. Am. Chem. Soc.* **1958**, *80*, 6456; b) N. A. Allinger, R. B. Hermann, C. Djerassi, *J. Org. Chem.* **1958**, *25*, 922; c) W. L. Meyer, D. D. Cameron, W. S. Johnson, *ibid.* **1962**, *27*, 1130.
[3] K. B. Becker, A. F. Boschung, C. A. Grob, *Helv. Chim. Acta* **1973**, *56*, 2733.
[4] W. F. Johns, *J. Org. Chem.* **1961**, *26*, 4583; W. F. Johns, *ibid.* **1963**, *28*, 1856; W. F. Johns, *ibid.* **1968**, 33, 109.
[5] A. Kuhl, H. Karels, W. Kreiser, presented at the '17th Conference on Isoprenoids', Cracow, 1997.
[6] A. Kuhl, W. Kreiser, *Helv. Chim. Acta* **1998**, *81*, 2264.
[7] R. Anliker, M. Müller, J. Wohlfahrt, H. Heusser, *Helv. Chim. Acta* **1955**, *38*, 1404.
[8] A. H. Fenselau, E. H. Hamamura, J. G. Moffat, *J. Org. Chem.* **1970**, *35*, 3546.
[9] P. L. Stotter, J. B. Eppner, *Tetrahedron Lett.* **1973**, 2417.
[10] P. H. J. Carlson, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, 46, 3936.
[11] R. Pappo, D. S. Allen. Jr., R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **1956**, *21*, 478.
[12] J. W. Wilt, S. N. Massie, R. B. Dabek, *J. Org. Chem.* **1970**, *35*, 2803.
[13] K. Sasse, in '*Houben-Weyl*, Methoden der org. Chemie', 4th edn., Thieme Verlag, Stuttgart, 1963, pp. 78.
[14] K. B. Becker, *Helv. Chim. Acta* **1977**, *60*, 68.
[15] R. Greenwald, M. Chaykovsky, E. J. Corey, *J. Org. Chem.* **1963**, *28*, 1128.
[16] M. Nussim, Y. Mazur, F. Sondheimer, *J. Org. Chem.* **1964**, *29*, 1120.
[17] C. F. Lane, *J. Org. Chem.* **1974**, *39*, 1437.
[18] H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.* **1975**, *97*, 5249.

---

[10]) Data of **11**: M.p. 153–155° (Et_2O). $[\alpha]_D^{20} = +74$ ($c = 0.99$, $CHCl_3$).

[11]) Data of **1**: M.p. 222–225°. $[\alpha]_D^{20} = +69$ ($c = 0.90$, MeOH). IR (KBr; in cm^{-1}): 3410 (OH, arom.), 3232 (OH); 1618, 1582, 1497 (C=C(arom)). ^{1}H-NMR (300.13 MHz, CD_3OD; δ in ppm, J in Hz): 2.89–2.95 (*m*, 2 H–C(6)); 3.87–3.95 (*m*, H–C(17)); 6.63 (*d*, $^4J = 2.6$, H–C(4)); 6.68–6.72 (*dd*, $^3J = 8.3$, $^4J = 2.6$, H–C(2)), 7.26 (*d*, $^3J = 8.3$, H–C(1)); 8.01 (*s*, OH(arom.)). ^{13}C-NMR (CD_3OD): 25.3 (*t*, C(15)); 26.4 (*t*, C(11)); 27.8 (*t*, C(7)); 28.7 (*t*, C(6)); 29.8 (*t*, C(16)); 31.2 (*t*, C(12)); 42.1 (*d*, C(8)); 45.4 (*d*, C(9)); 46.8 (*d*, C(14)); 52.2 (*d*, C(13)); 76.1 (*d*, C(17)); 111.6 (*d*, C(2)); 113.8 (*d*, C(4)); 125.4 (*d*, C(1)); 130.2 (*s*, C(10)); 136.7 (*s*, C(5)); 153.7 (*s*, C(3)). MS (*m/z* (%)): 258 (100, $M^{+\cdot}$), 240(12), 225(2), 211(17), 183(5), 159(9). HR-MS: 258.1619 ($C_{17}H_{22}O_2^+$; calc. 258.16199).

[19] H. C. Brown, E. F. Knights, C. G. Scouten, *J. Am. Chem. Soc.* **1974**, *96*, 7765.
[20] H. C. Brown, in 'Hydroboration', W. A. Benjamin, New York, 1962, pp. 136.
[21] A. Arase, Y. Nunokawa, Y. Masuda, M. Hoshi, *J. Chem. Soc., Chem. Commun.* **1991**, 205.
[22] C. F. Lane, G. W. Kabalka, *Tetrahedron* **1976**, *22*, 981.
[23] A. Kuhl, D. Schollmeyer, M. Schürmann, H. Preut, W. Kreiser, *Acta. Crystallogr., Sect. C* **1998**, *54*, 521.
[24] E. Winterfeldt, *Synthesis* **1975**, 617.
[25] S. Bernstein, R. Littell, *J. Org. Chem.* **1961**, *26*, 3610.

Received September 4, 1998