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INTRAMOLECULAR DIELS-ALDER REACTION WITH FURAN DIENE.[1] A NEW SYNTHESIS OF 11-KETO STEROIDS

Luc A. Van Royen, Roelant Mijngheer and Pierre J. De Clercq[2*]
Department for Organic Chemistry, State University of Ghent
Laboratory for Organic Synthesis,
Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

ABSTRACT

A novel D → BCD → ABCD route to 11-keto steroids is reported involving a high yield stereoselective intramolecular Diels-Alder reaction of furan-diene 5a in water as a key-step. The dienophilic side chain is readily introduced starting from 2 via a sequence involving alkylation with ethyl 4-iodo-3-ethoxycrotonate, reduction and acid hydrolysis. The reduced adduct 8a, obtained in 24 % overall yield from 2-methyl-1,3-cyclopentanedione, is converted into (±)-adrenosterone (16) via base-opening to 9 and further transformation to 13, the dienediolate equivalent of which is a known intermediate in corticosteroid synthesis.

A feature of recent syntheses of 11-keto steroids has been the inclusion of the 11-oxygen function early in the synthesis[3]. In this context we report here on a novel D → BCD → ABCD route in which a functionalized BC ring system is directly obtained via intramolecular Diels-Alder reaction of a furan diene (cf. 5 to 6). Following this scheme the reduced adduct 8a is obtained in 24 % overall yield from 2-methyl-1,3-cyclopentanedione, and its potential in corticosteroid synthesis is further exemplified by its 10-step conversion into (±)-adrenosterone (16)[3b].

Crucial for the success of the sequence were the following findings : (1) the 3-ethoxy-2-butenoate side chain (cf. 3) can serve as a direct precursor of the required dienophilic enone 5, (2) the |4+2| cycloaddition reaction of 5a, when performed in water, yields selectively adduct 6a in high yield and pure form, and (3) hydroxyenone 9, obtained by base treatment of 8, is readily converted to 13, the dienediolate equivalent of which is an adequate intermediate for the stereoselective appendage of the A ring[3b,4].

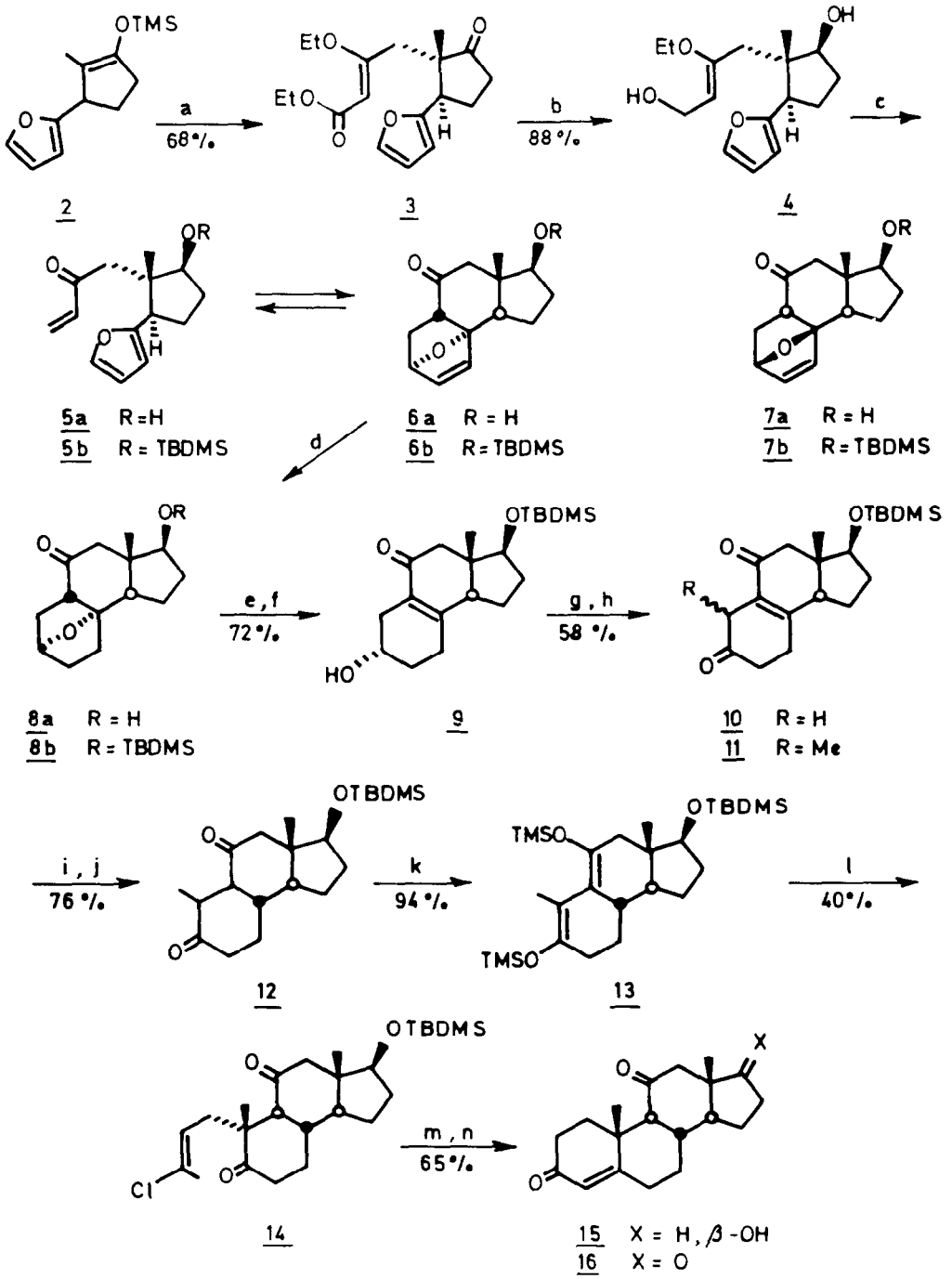
Alkylation of the enolate derived from 2[1a] with ethyl 3-ethoxy-4-iodocrotonate[5] in hexamethylphosphoramide gave after chromatography on silica pure 3 (mp 76°C)[6] in 68 % yield next to 13 % dialkylated product. Lithium aluminum hydride reduction of keto ester 3 led to diol 4 (mp 84-86°C; 88 % yield after purification on florisil)[6], which on exposure to Danishefsky's dilute acidic conditions[7] gave enone 5a (quantitative)[6]. In contrast to this efficient sequence our previous synthesis of 5b required 6 steps from 2, which is obtained via dissolved metal reduction of 3-furyl-2-methyl-2-cyclopentenone (1)[1a].

We have previously described the intramolecular Diels-Alder reaction of 5b to a 8:1 mixture of 6b and 7b, respectively (methylene chloride, room temperature, 61 % conversion after 6 days), and shown 6b to be the kinetically preferred adduct[1a]. However, under identical conditions no substantial adduct formation is observed in the case of 5a (< 10 % of 6a by NMR), presumably due to hydrogen bonding between the hydroxyl and carbonyl groups[8]. Attempts at realizing a high conversion rate with the exclusive formation of 6a led us to find that 5a, when shaken in cold water for 10 min without cosolvent, yields the desired 6a (mp 88-90.5°C)[6] as the only solute product (> 75 %; no isomeric adduct 7a is detected) next to a residual oil which mainly consists of enone 5a. No isolation is required at this stage : routinely, the aqueous phase is decanted and after addition of 50 vol % of methanol directly hydrogenated (palladium on barium sulphate) to 8a (85 % yield from diol 4)[6,9]. Next to prohibiting any intramolecular hydrogen bonding in 5a the promoting effect of water in this particular reaction presumably originates from a hydrophobic acceleration[10].

Treatment of the corresponding t-butyldimethylsilyl ether[11] 8b (mp 92-92°C)[6] with sodium methoxide in methanol for 2 h at room temperature effects bridge opening to 9 (mp 111-115°C)[6] in 72 % isolated yield from 8a. The recent report by Stork[4] on the pronounced preference of dienediolates of the type as derived from 13 for undergoing alkylation leading to equatorial products (cf. 14) led us to convert 9 into 13 via the following sequence : (1) oxidation to enedione 10 (mp 96-99°C)[6] with dimethyl sulfoxide-triethylamine-sulfur trioxide pyridine complex[12] (79 % yield), (2) kinetic alkylation with methyl iodide to a 1:1 diastereoisomeric mixture 11 (73 % yield), (3) lithium-liquid ammonia reduction followed by Jones oxidation to a mixture of diketones 12 (76 % yield), and (4) reaction with trimethylsilyl iodide-hexamethyldisilazane in methylene chloride[13] followed by fast elution on florisil to pure 13 (94 % yield).

Treatment of the dienediolate generated from 13 with 1-iodo-3-chloro-2-butene[14] in hexamethylphosphoramide led to the expected stereoisomer 14 in 40 % yield. Eventually the full steroid nucleus was realized according to the modified Wichterle's conditions[4b,15] directly followed by acidic hydrolysis of the intermediate formate to (±)-11-ketotestosterone (mp 192-195°C) in 65 % yield. Final confirmation was obtained through oxidation[12] to (±)-adrenosterone (mp 185-186°C)[3b], whose spectral properties (IR, 360 ^{1}H NMR) and TCL behavior were identical with those of an authentic sample.

TBDMS = tert-butyldimethylsilyl. (a) CH_3Li, THF, 0°C; $ICH_2C(OEt)CHCOOEt$ (3.3 equiv), HMPT, 3 h at rt. (b) LAH, ether, 1 h at reflux; 15 % NaOH in H_2O. (c) 0.005 N HCl-THF (1:4), 4 h at rt. (d) H_2O, 10 min at 10°C; CH_3OH, Pd-$BaSO_4$, H_2. (e) t-$BuMe_2SiCl$ (10 equiv), imidazole (5 equiv), DMF, rt. (f) $NaOCH_3$ (1 equiv), CH_3OH, 2 h at rt. (g) $SO_3.C_5H_5N$ (7 equiv), Et_3N, DMSO, 20 min at rt. (h) $(i\text{-}Pr)_2NLi$ (1 equiv), THF, 0°C; CH_3I (6 equiv), HMPT. (i) Li (6 equiv), liq NH_3, THF, t-BuOH (1 equiv), 45 min at reflux. (j) Jones reagent, acetone, 0°C. (k) Me_3SiI (2.2 equiv),



$(Me_3Si)_2NH$ (2.4 equiv), CH_2Cl_2, 15 min at -20°C, then 2 h at rt. (l) CH_3Li (2 equiv), THF, 0°C; $ICH_2CHC(CH_3)Cl$ (1 equiv), HMPT, 20 min at -40°C. (m) 70 % $HClO_4$-HCOOH (1:10), reflux. (n) 2 N HCl-THF (1:3.6), 35 min at reflux.

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6. Satisfactory spectral data were obtained for all compounds. Relevant ^{1}H NMR data (360 MHz, δ downfield from Me_4Si, $CDCl_3$) : 3 : 0.75 (s,3H), 1.28 (t, J=7 Hz, 3H), 1.29 (t, J=7 Hz, 3H), 3.80 (m,2H), 4.15 (q, J=7 Hz, 2H), 5.10 (s,1H), 6.06 (dt, J=3, 0.5 Hz, 1H), 6.30 (dd, J=3, 2 Hz, 1H), 7.31 (dd, J=2, 1 Hz, 1H); 4 : (90 MHz) 0.65 (s,3H), 1.32 (t, J=7Hz, 3H), 3.61-4.14 (6H), 4.86 (t, J=8 Hz, 1H), 6.08 (d, J=3 Hz, 1H), 6.28 (dd, J=3, 2 Hz, 1H), 7.32 (dd, J=2, 1 Hz, 1H); 5a : 0.70 (s,3H), 4.12 (bt, J=8.5 Hz, 1H), 4.56 (bd, J=1.0 Hz, 1H), 5.85 (dd, J=10, 1 Hz, 1H), 6.09 (d, J=3 Hz, 1H), 6.25 (ABd, J=17.5, 1 Hz, 1H), 6.33 (dd, J=3, 2 Hz, 1H), 6.38 (ABd, J=17.5, 10 Hz, 1H), 7.35 (dd, J=2, 1 Hz, 1H); 6a : 1.22 (s,3H), 1.42 (dd, J=8, 11.5 Hz, 1H), 2.31 (AB, J=18.5 Hz, 1H), 2.33 (dt, J=11.5, 4.5 Hz, 1H), 2.57 (dd, J=8, 4.5 Hz, 1H), 2.59 (AB, J=18.5 Hz, 1H), 3.90 (t, J=8.5 Hz, 1H), 4.93 (dd, J=4.5, 1.5 Hz, 1H), 6.43 (bAB, J=6 Hz, 1H), 6.46 (AB, J=5.8 Hz, 1H); 8a : 1.13 (s,3H), 2.23 and 2.54 (AB, J=19 Hz, 2H), 3.86 (dt, J= 5.5, 8.5 Hz, 1H), 4.48 (t, J=5 Hz, 1H); 8b : 0.88 (s,9H), 1.08 (s,3H), 2.14 and 2.46 (AB, J= 18.5 Hz, 2H), 3.76 (t, J=8.5 Hz, 1H), 4.46 (t, J=5 Hz, 1H); 9 : 0.76 (bs,3H), 0.88 (s,9H), 2.08 and 2.60 (AB, J=15.5 Hz, 2H), 3.88 (dd, J=9, 7.5 Hz, 1H), 3.99 (m, ΣJ=24 Hz, 1H); 10 : 0.79 (bs,3H), 0.88 (s,9H), 2.14 and 2.66 (AB, J=16 Hz, 2H), 3.03 and 3.13 (bAB, J≈21 Hz, 2H), 3.93 (dd, J=8.5, 7.5 Hz, 1H); 11 : 0.76/0.82 (d, J≈0.8 Hz, 3H), 0.88/0.89 (s,9H), 1.23/1.24 (d, J=7.3 Hz, 3H), 3.29/3.35 (bq, J≈7.5 Hz, 1H), 3.89/3.92 (t, J=8.5 Hz, 1H); 13 : (CCl_4) 0.79 (s,3H), 0.89 (s,9H), 1.84 (t, J=1.8 Hz, 3H), 1.97 and 2.06 (bAB, J=16 Hz, 2H), 3.68 (t, J=8.5 Hz, 1H); 14 : 0.73 (bs,3H), 0.87 (s,9H), 1.32 (s,3H), 1.96 (bs,3H), 3.79 (t, J=8.4 Hz, 1H), 5.41 (ddq, J=10, 6, 1.3 Hz, 1H); 15 : 0.76 (d, J=0.8 Hz, 3H), 1.43 (s,3H), 3.87 (t, J=8.5 Hz, 1H), 5.73 (bs, 1H); 16 : 0.89 (d, J=0.5 Hz, 3H), 1.44 (s,3H), 5.75 (bs, 1H).
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