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INTRAMOLECULAR DIELS-ALDER REACTION WITH FURAN-DIENE. TOTAL SYNTHESIS OF (±)-11-KETOTESTOSTERONE AND (±)-ADRENOSTERONE.

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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 12 in water as a key-step. The dienophilic side chain is readily introduced starting from 8 via a sequence involving alkylation with ethyl (E)-3-ethoxy-4-iodo-2-butenoate, reduction and acid hydrolysis. The reduced adduct 14 is further converted into (±)-adrenosterone (6) via 24, the dienediolate equivalent of which is a known intermediate in corticosteroid synthesis.

Steroids, and in particular corticosteroids, are challenging targets for total synthesis, not only due to their biological importance, but also because they constitute a rich area for the development of novel strategies in synthesis[1,2]. In a previous report we have described a novel approach to the BCD-ring system of 11-keto steroids based on the intramolecular Diels-Alder reaction of furan-enone 1 (scheme 1)[3]. The following conclusions could be drawn from this exploratory study. Among the investigated dienophilic side chains the unsubstituted enone 1 is, at the same time, a suitable substrate for cycloaddition and of further potential interest for corticosteroid synthesis. Depending on the reaction conditions either adduct 2 (kinetic control) or 3 (thermodynamic control) is formed predominantly, albeit in low yield (~40-50 %). After the hydrogenation of the double bond in 2, the opening of the oxygen bridge is readily effected with base yielding enone 4; however, the more forceful conditions required for the opening of the product obtained by hydrogenation of adduct 3 cause epimerization at C-14 leading to the cis-fused enone 5.

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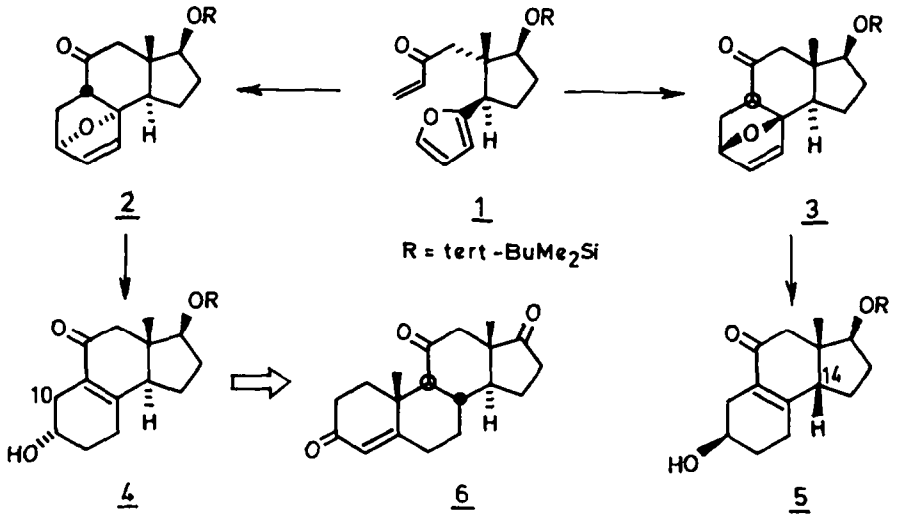


SCHEME 1

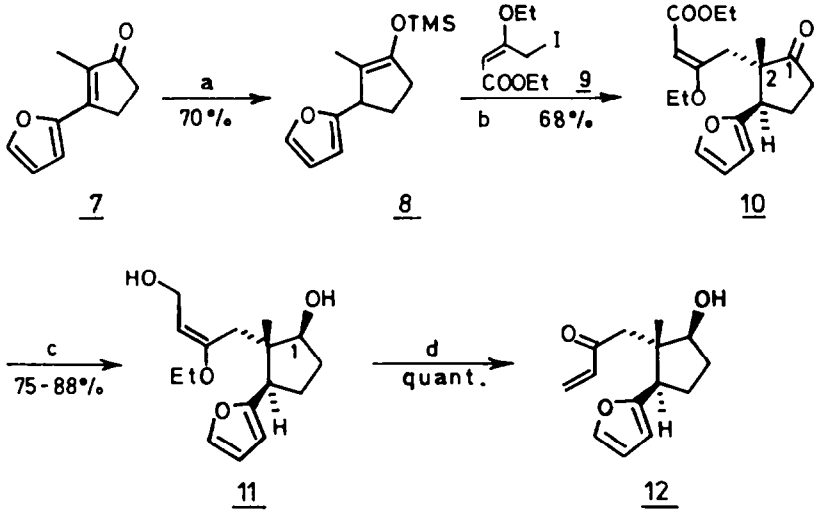
In view of the above results an efficient synthesis of 11-keto steroids along the proposed Diels-Alder strategy still requires : (1) the development of a short and direct route to enone 1; (2) the finding of appropriate conditions upon which the Diels-Alder reaction would proceed stereoselectively and in high yield to 2; (3) the stereoselective appendage of the A-ring with an angular methyl group at C-10. In the present paper we report a solution to these problems which eventually led to a 16-step synthesis of (±)-adrenosterone (6)[4,5].

The synthesis of enone 12 (scheme 2).

Our previous synthesis of 1 required six steps from the trimethylsilyl enol ether 8, which is readily available from cyclopentenone 7 in 69 % yield via reduction with lithium in liquid ammonia followed by trapping with trimethylsilyl chloride[3]. Not unexpectedly, the direct introduction of the 2-oxo-3-butenyl side chain by alkylation of the enolate anion derived from 8 (methyllithium) failed; various experiments with 1-iodo-3-buten-2-one[6] in tetrahydrofuran involving variations in temperature, the presence of hexamethylphosphoramide and the mode of addition only led to complex reaction mixtures. In view of the kinetic preference of ß-alkoxy allylic alcohols (as in 11) to yield the corresponding enone in acid[7], we decided to use a 3-alkoxy-4-halo-2-butenoate ester as the electrophile[8] for the introduction of the enone side chain in masked form. Thus, alkylation of the enolate anion derived from 8 (methyllithium) with ethyl (E)-3-ethoxy-4-iodo-2-butenoate (9)[9] in tetrahydrofuran-hexamethylphosphoramide gave the desired trans-ketone 10 in 68 % yield next to 13 % of 2,5-dialkylated product (undefined stereochemistry at C-5). The trans-stereochemistry of 10 is inferred from the shielded angular methyl resonance (cis with furyl group) in the ^{1}H NMR spectrum (δ 0.75); no cis-product was isolated in this experiment [10]. We should note here that the double bond configuration in 10 and 11, which

eventually originates from ethyl (E)-3-ethoxy-2-butenoate[9c], has been misassigned in our preliminary report[4,11].

Reduction of keto-ester 10 with lithium aluminum hydride in ether and alkaline work-up[12] gave diol 11 as a single diastereomer[10] in yields ranging from 75 to 88 % depending on the scale. The assigned ß-orientation of the hydroxyl group at C-1 is in accord with the observed resonance for H-1 which exhibits a triplet pattern with a coupling constant value of 9.5 Hz[3b]. Further exposure of 11 to Danishefsky's dilute acid conditions (0.005 N hydrochloric acid-tetrahydrofuran, 1:4)[13] led quantitatively to enone 12 which is further used without purification. Alternatively, 12 can be produced in two steps from cyclopentenone 7. A reductive alkylation sequence involving lithium in liquid ammonia followed by the in situ addition of iodide 9 gave ester 10 in 34 % yield after HPLC purification (next to 7 % of dialkylated product)[14]; subsequent lithium aluminum hydride reduction and acid work-up (dilute sulfuric acid)[15] led directly to enone 12 isolated in 41 % yield after chromatography on florisil.



[a]Li, NH_3, t-BuOH, THF; NH_3↑; Me_3SiCl, Et_3N, THF; [b]MeLi, THF-ether; 9, HMPA; [c]$LiAlH_4$, ether; H_2O-NaOH; [d]0.005 N HCl-THF (1:4).

SCHEME 2

The Diels-Alder reaction of enone 12 (scheme 3)

Previously, we had observed the predominant formation of adduct 2 upon treatment of enone 1 in methylene chloride at room temperature for six days (^1H NMR; 61 % conversion; ratio 8:1 of 2 and 3, respectively)[3]. In contrast, under the same conditions only minor amounts of the desired adduct 13 (< 10 %) were obtained from the corresponding alcohol 12. This lack of reactivity (compared to 1) can be ascribed to an intramolecular hydrogen bond[16] between the 17-hydroxyl group (cf. steroid numbering) and the dienophilic side chain (cf. 15) making the latter spatially unavailable for the cycloaddition reaction[17]. This is revealed by comparison of the H-12 resonances in the ^1H NMR spectrum (360 MHz, $CDCl_3$) of 1 (2H : 2.61

ppm, singlet) [3b] and 12 (^{1}H : 3.34 ppm, doublet; ^{1}H : 2.42 ppm, doublet; ^2J = 17 Hz). A further indication is provided by the results of the cycloaddition of 12 in chloroform-d, (dimethyl sulfoxide)-d_6 and water-d_2 (table). In the dipolar aprotic DMSO, where the alcohol should be completely hydrogen-bonded to the solvent[16], a similar reactivity is noticed as in the case of the protected hydroxy-enone 1. Most notably, however, after dissolving enone 12 in deuterium oxide (10 min; ultrasonic assistance) immediate and complete conversion to adduct 13 is observed. Undiluted enone 12 has also been found to yield the desired adduct 13 upon standing at -20°C for prolonged periods of time.

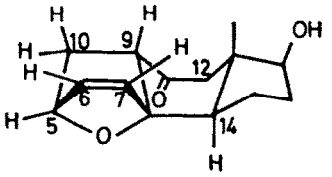
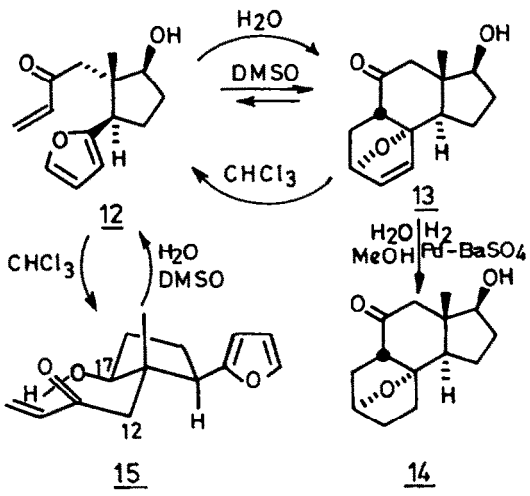


TABLE : Diels-Alder reaction of 12

Conditions	Ratio (%)[a] 12	13
$CDCl_3$, 25°C, 3d[b]	>90	<10
$(CD_3)_2SO$, 25°C, 3d[b]	50	50
D_2O, 25°C, 10 min[c]	-	>95
neat, -20°C, >2 months		>95

[a]From ^{1}H NMR; [b]Same ratio's after 6 days; [c]Dissolution assisted by Ultrasonic vibration.



SCHEME 3

For preparative purposes enone 12 is shaken vigorously in water (~0.07 M) for 15-30 min at room temperature. The resulting milky emulsion, which by TLC contains only the desired adduct, is separated by decantation from undissolved starting material and unidentified side products which remain as an oily film. Interestingly, upon isolation of 13 by extraction from the aqueous phase, the gradual formation of enone 12 is observed indicating a facile cycloreversion in the organic phase. Therefore, adduct 13 is kept in the aqueous phase and, after the addition of methanol, directly hydrogenated (Pd-$BaSO_4$; 2.2 bar). In this way pure reduced adduct 14 is obtained in overall yields of up to 85 % (from diol 11). Lower yields, typically 50-60 %, are observed when the cycloaddition is performed on larger scales (see experimental) or in more concentrated solution; in these cases vigorous mechanical stirring or ultrasonic assistance did not give rise to any reproducible yield improvement. Also, retreating the oily residue (vide supra) in the manner as described above does not lead to substantial amounts of more 14.

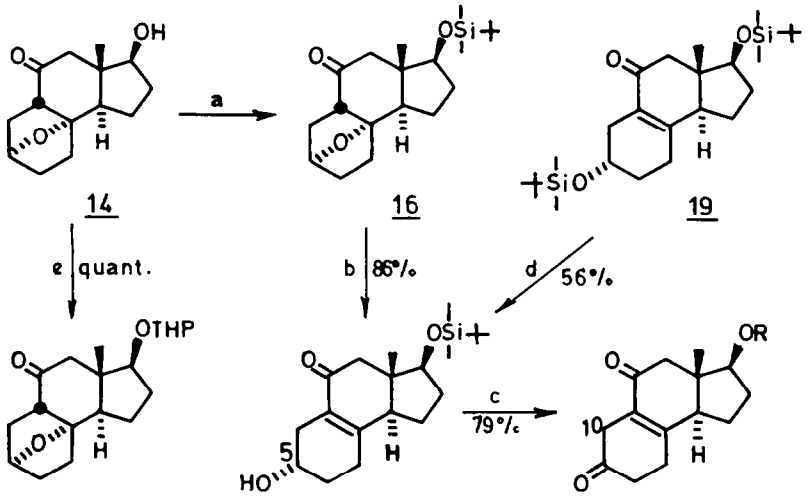
As in the case of adduct 2[3b], the stereochemistry of 13 is inferred from the following ^{1}H NMR spectral data ($CDCl_3$) : (i) a doublet of doublets coupling pattern (11.5 and 8.0 Hz) for

the at high field resonating ß-hydrogen at C-10 (1.42 ppm), typical of an exo-type adduct (oxygen bridge and H-9 trans)[18]; (ii) a large geminal coupling constant value for the H-12 protons (18.5 Hz) in accord with a boat-type conformation for ring C with a small endocyclic torsion angle at the 11,12-bond[19]; (iii) a diagnostic long range coupling between H-6 and H-14 (0.75 Hz)[20]. Eventually, the structure 13 was fully confirmed by an X-ray diffraction study of the reduced adduct 14[21]. The preferred formation of the exo-adduct with an ∝-oriented bridge (cf. 2 and 13) under kinetic conditions has been discussed previously[3b].

Recently Breslow[22] has reported important rate accelerations of some intermolecular Diels-Alder reactions when performed in water (also in the presence of cyclodextrins), the principal effect being ascribed to hydrophobic association of the diene with the dienophile[23,24]. In view of the intramolecular mode of our reaction, the observed rate enhancement in water compared to dimethyl sulfoxide (cf. table) was unexpected[25]. Finally, the enhanced stability of adduct 13 in water compared to organic solvents is also noteworthy and will be the subject of further study.

The synthesis of (±)-11-ketotestosterone (27) and (±)-adrenosterone (6)

Our next objective required the opening of the oxygen bridge of the reduced adduct. This would release the hydroxyl group at C-5 and, after oxidation, provide for a BCD-ring system correctly functionalized for the introduction at C-10 of the 19-methyl group and of the necessary side chain for the construction of the A-ring (scheme 4).

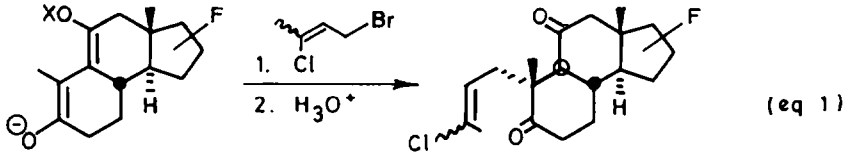


[a]see text; [b]NaOMe, MeOH, 2 h, r.t.; [c]$SO_3.C_5H_5N$, Et_3N, DMSO, r.t.; [d] 1M HF in CH_3CN, C_6H_6, 30 min, r.t.; [e]DHP, p-TsOH, CH_2Cl_2.

SCHEME 4

We have previously described the ready conversion of 16 (obtained from 2 via catalytic hydrogenation) into hydroxy-enone 17 (sodium methoxide in methanol, 2 h at room

temperature; 86 % yield) and the subsequent oxidation to 18 (sulfur trioxide pyridine complex in triethylamine-dimethyl sulfoxide[26]; 79 % yield)[3b]. The protection of the hydroxyl group in 14 with tert-butyldimethylsilyl chloride-imidazole[27] (ratio 2:1; 10 equiv) in dimethylformamide at room temperature offered no problem on a small scale but required a large excess of reagent (83 % yield of 16). Enlarging the scale, however, gave rise to the formation of ring opened product 17 next to protected 16; e.g. on a 3g-scale, a 89 % yield of 16 and 17 (ratio 4:1, respectively) was obtained (see experimental). On still larger scales substantial amounts of the disilyl ether 19 were also formed. Although the latter may be recycled via selective mono-desilylation to 17 with 1 M hydrogen fluoride in acetonitrile (56 % yield)[28], we examined a variety of alternative conditions for converting alcohol 14 into protected 16 in a reproducible way. However, the investigated methods led either to the recovery of starting material or to the formation of varying amounts of opened 17 and disilylated 19 next to the desired 16 (see experimental)[29]. Lewis acid catalysis is probably responsible for the facile bridge opening since 16 was found unaffected by triethylamine alone. In contrast with the above result, protection of the hydroxyl group in 14 as the tetrahydropyranyl ether 20 occurs smoothly and in quantitative yield. Although 20 can be converted in a similar way to the corresponding keto-enone 21 (60 % overall yield), we preferred to use the silylated derivative 18 in the final sequence for reasons of stereohomogeneity.

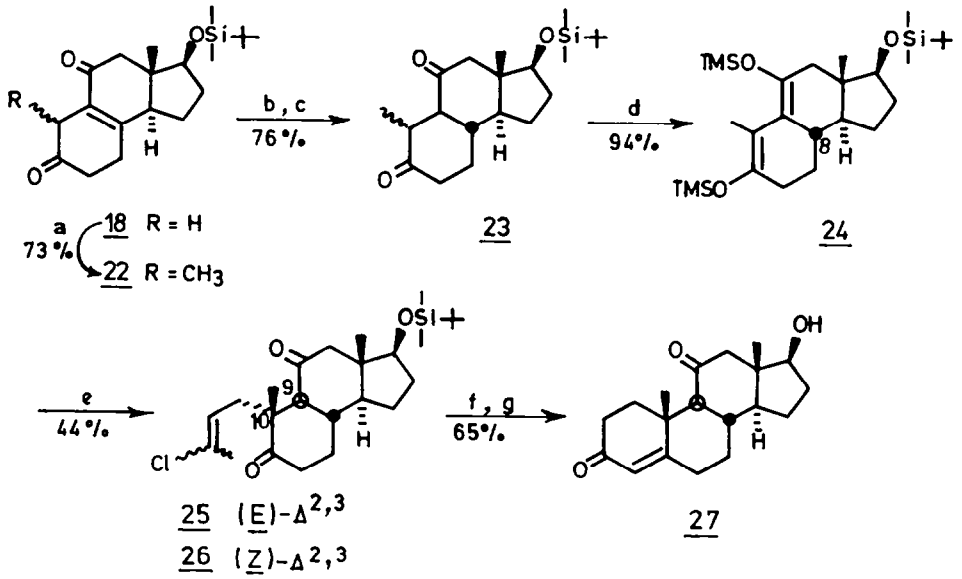


i X = Li^+ or Me ii (eq 1)

Although the unsaturated diketone 18 offers in principle diverse possibilities for steroid synthesis[30], we have so far been mainly concerned with its conversion into a classical corticosteroid derivative. This necessitates both the reduction of the $\Delta^{8,9}$-double bond to the requisite trans-BC-ring junction and the timely introduction of the angular 19-methyl group and of the side chain for eventual appendage of the A-ring. Crucial to the choice of our further strategy was the finding of Stork[2d,f] that, upon alkylation of 11-oxygen substituted $\Delta^{9,11}$,$\Delta^{5,10}$-dienolates i, the electrophile is introduced from the α-face leading to the derivative ii with the group in equatorial position (equation 1).

Consequently, we set out to study the conversion of 18 into a derivative as i. This was readily accomplished as follows (scheme 5). Alkylation of the enolate anion derived from 18 (lithium diisopropylamide, tetrahydrofuran) with methyl iodide in hexamethylphosphoramide gave 22 as a 1:1 diastereomeric mixture in 73 % yield. Subsequent reduction with lithium in

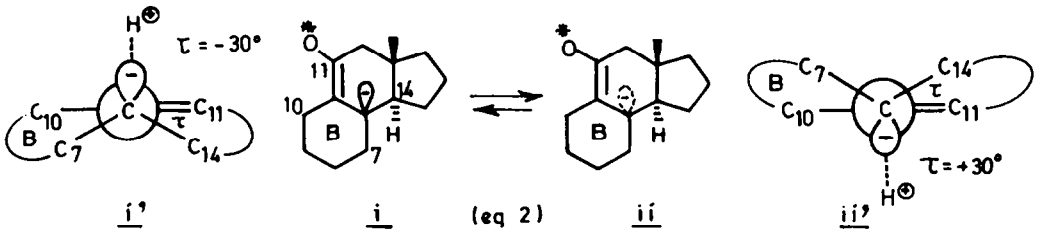
liquid ammonia in the presence of tert-butanol, directly followed by Jones oxidation, led to a mixture of diketone 23 (76 % yield) in which two diasteromers predominate (^{1}H NMR). Treatment of this mixture with trimethylsilyl iodide and hexamethyldisilazane in methylene chloride[31] followed by fast elution on florisil finally yielded a single dienedioldisilylether 24 (94 % yield) with the required stereochemistry at C-8 as substantiated by the further synthesis of (±)-adrenosterone (6). This crucial stereochemical outcome results from the dissolved metal-ammonia reduction of enone 22. It is of interest here to analyze the possible pathways for reduction with the results obtained with the microcomputer program for systematic conformational analysis (SCA) that has been recently reported by one of us[32].



[a](i-Pr)$_2$NLi, THF; CH_3I, HMPT; [b]Li,NH_3, THF, t-BuOH; [c]Jones, acetone; [d]Me_3SiI, $(Me_3Si)_2NH$, CH_2Cl_2; [e]CH_3Li, THF; $ICH_2CHC(CH_3)Cl$, HMPT; [f]70 % $HClO_4$-HCOOH; [g] 2 N HCl-THF

SCHEME 5

Assuming that the stereochemical outcome of the enone reduction at C-8 is dictated by the thermodynamic stability of the intermediates i and ii[33], the SCA program computes a free energy difference ΔG° 16 kJ/mol (1 cal = 4.186 J) for the equilibrium i ⇌ ii, in line



i' i ii ii'

with the observed result (equation 2). On the other hand, consideration of the minimum energy transition states in which overlap of the developing p-orbital on C-8 with the $\Delta^{9,11}$-

bond of the enolate system is maintained during protonation[34], leads ideally to 1' (β-protonation at C-8) or 11' (α-protonation at C-8) with a torsion angle at C-8, C-9 in the C-ring of -30° and +30°, respectively. In view of the deduced possible basic conformations[32] for the C-ring of 1, i.e., 13+/HC, 13+/E and 14-/E with torsion angles at C-8,C-9 of -16°, 0°, and -29°, respectively, and of 11, i.e. 13+/HC and 13+/E with torsion angles of -16° and 0°, respectively, only in the former case can the stereoelectronic requirements for preferred protonation be accommodated. Hence, also on this basis would the observed β-configuration at C-8 be expected.

The eventual annelation of the A-ring proceeded via Wichterle's[35] method[2d,f]. In view of the reported enhanced reactivity towards nucleophiles of (E)-1,3-dichloro-2-butene, compared with the (Z)-derivative, we decided to study the alkylation with both pure isomers[36]. Treatment of the dienediolate generated from 24 (methyllithium) with both (E)- and (Z)-1-iodo-3-chloro-2-butene[37] in hexamethylphosphoramide led, however, in both cases to a disappointing 44 % yield of the expected isomers 25 and 26, respectively[38]. The assigned configuration at C-9 and C-10 in both compounds mainly follows from the observed ^{1}H NMR coupling pattern of H-9 (d, J = 12-12.5 Hz) and from the low field resonance[39] of the 19-methyl group (1.32-1.37 ppm). This preference for undergoing alkylation leading to equatorial products (cf. 24 to 25 and 26; eq. 2) has been rationalized before[2f,39]. Finally the full steroid nucleus was realized according to the modified Wichterle's conditions (perchloric acid-formic acid)[40], directly followed by acidic hydrolysis of the intermediate formate to (±)-11-ketotestosterone (27) in 65 % yield. Final confirmation was obtained through oxidation[26] to (±)-adrenosterone (6; mp 185-186°C)[41], whose spectral properties (IR, 360 ^{1}H NMR) and TLC behavior were identical with those of an authentic sample[42].

Previous corticosteroid syntheses have often introduced the 11-oxygen function at a late stage[1a,c,d,2a,b,d]. In contrast, in the present synthesis the same function plays a central role throughout the sequence. In masked form it served to activate the electrophile 9 upon alkylation of the enolate anion derived from 8 and to unravel the enone moiety in 12 upon hydrolysis of 11. It was found essential in activating the dienophile for the key Diels-Alder reaction to adduct 13[3]. It further served as a handle for the opening of the oxygen bridge (cf. 16 to 17) and enabled the obtention of the desired C-8 stereochemistry via dissolved metal reduction of enone 22. Eventually, it allowed for the generation of a dienediolate (cf. 24) and, hence, for the stereoselective introduction of the modified Wichterle reagent, necessary for the appendage of the A-ring. Finally we note that in this 16-step sequence the 19 carbon atoms of the steroid originated from furan, 2-methyl-1,3-cyclopentanedione, methyl iodide and 2 moles of acetoacetic ester.

EXPERIMENTAL

IR Spectra were recorded on a Beckmann IR 4230 or a Unicam SP 1000 spectrometer, mass spectra on a AEI MS-50 spectrometer. The ^{1}H NMR spectra were recorded at 90 MHz (Varian EM-390) or at 360 MHz (WH-Brucker) with TMS as internal standard. Rf values are

quoted for Merck silica gel 60 GF_{254} plates of thickness 0.25 mm. HPLC separations were performed on Waters LC/System 500 or Waters 6000 A, both with RI-detection. M.ps. are uncorrected.

Ethyl(±)-(2'α,3'β)-3-ethoxy-4-(3'-(2"-furyl)-2'-methylcyclopentan-1'-on-2'-yl)-2(E)butenoate (10). Method a : Cyclopentenone 7 (6 g; 37 mmol) is reduced with lithium (0.778 g; 0.111 mol) in liq ammonia (200 mL) containing tert-butanol (2.8 mL; 29.6 mmol) and THF (40 mL), as previously described[36]. After addition of isoprene the mixture is diluted with THF (100 mL) and treated in one portion with a soln of iodide 9 (31.6 g; 0.111 mol) in THF (60 mL). After stirring for 2.5 hrs at r.t., the reaction mixture is poured into a satd NH_4Cl soln. After usual work-up the residue is purified by HPLC with 15 % EtOAc-hexane as eluent, yielding 4.0 g of 10 (33.7 %) next to 1.3 g of 2,5-dialkylated product (7.4 %). Method b : To a cooled (0°C) soln of enol ether 8 (28.4 g; 0.12 mol) in dry THF (1 L) is added dropwise a soln of methyllithium in ether (103.4 mL of a 1.16 M soln). After completion of the reaction (TLC) a soln of iodide 9 (104 g; 0.367 mol) in HMPA (182 mL) is added. After stirring for 3 hrs at r.t. the reaction mixture is poured into a satd NH_4Cl soln (700 mL). After the usual extractive (ether) work-up the residue (160 g) is dissolved in ether-hexane (1:1, 1.5 L) and the organic phase washed with water (4 x 75 mL). After drying ($MgSO_4$) and concentration in vacuo, the residue (100 g) is purified by HPLC with 20 % EtOAc-hexane as eluent, yielding 26 g of 10 (67.5 %) next to 7.4 g of 2,5-dialkylated product (13 %). For ester 10 : m.p. 76°C (EtOAc-hexane). Rf 0.19 (20 % EtOAc-isooctane). UV(MeOH) : λ_{max} 220-240 nm. IR (KBr) : 3110, 1740, 1710, 1700, 1620 cm^{-1}. NMR (360 MHZ, $CDCL_3$) : 7.31 (1H, dd : 2, 1 Hz), 6.30 (1H, dd : 3, 2 Hz), 6.06 (1H, dt : 3, 0.5 Hz), 5.10 (1H, s), 4.15 (2H, q : 7. Hz), 3.80 (2H, m), 3.68 (1H, d : 15 Hz), 3.36 (1H, dd : 11, 6.5 Hz), 2.88 (1H, dd : 15, 1 Hz), 2.5-2.0 (4H, m), 1.29 (3H, t : 7 Hz), 1.28 (3H, t : 7 Hz), 0.75 (3H, s) ppm. MS : m/z 320 ($M^{+\cdot}$, 2), 276 (4), 275 (20), 164 (26), 163 (100), 162 (43), 158 (23). Exact mass. calcd for $C_{18}H_{24}O_5$: 320.1624. Found : 360.1612. For the dialkylated derivative : Rf 0.22 (20 % EtOAc-isooctane). IR (film) : 1745, 1715, 1620 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 7.28 (1H, dd : 2, 1 Hz), 6.27 (1H, dd : 3, 2 Hz), 6.02 (1H, brd : 3 Hz), 5.12 (1H, s), 5.05 (1H, s), 4.13 (4H, m), 3.95-3.77 (4H, m), 3.55 (1H, t : 7.5 Hz), 3.43 (1H, d : 14.5 Hz), 3.33 (1H, dd : 13.5, 11.5 Hz), 2.98 (1H, d : 14.5 Hz), 3.04 (1H, dd : 13.5, 4 Hz), 2.3-2.0 (3H), 1.33 (3H, t : 7 Hz), 1.31 (3H, t : 7 Hz), 1.28 (3H, t : 7 Hz), 1.24 (3H, t : 7 Hz), 0.83 (3H, s) ppm. MS : m/z 185 (15), 178 (14), 163 (10), 162 (15), 84 (58), 79 (30), 77 (20), 75 (100).

(±)-(1'β,2'α,3'β)-3-Ethoxy-4-(3'-(2"-furyl)-1'-hydroxy-2'-methylcyclopentan-2'-yl)-2(E)-butenol (11). A soln of ester 10 (15.67 g; 49 mmol) in ether (155 mL) is added dropwise to a suspension of LAH (6.5 g; 0.17 mol) in ether (190 mL). After reflux for 1 h the suspension is cooled to 0°C and treated consecutively with water (6.5 mL), NaOH (15 % soln; 6.5 mL) and water (19.5 mL). After stirring for 30 min at r.t. the precipitate is filtered and thoroughly washed with ether. After concentration in vacuo the residue is purified by HPLC (55 % EtOAc-hexane) yielding 10.33 g of crystalline diol 11. Typical yields are in the range 75-88 %. M.p. 84-86°C (EtOAc-isooctane). Rf 0.28 (60 % EtOAc-isooctane). IR (KBr) : 3600-3200, 1640, 1620 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 7.36 (1H, dd : 2, 1 Hz), 6.33 (1H, dd : 3, 2 Hz), 6.11 (1H, dt : 3, 0.5 Hz), 4.87 (1H, t : 8 Hz), 4.07 (2H, m), 4.0 (1H, brt : 9.5 Hz), 3.78 (2H, m), 3.47 (1H, br s), 3.07 (1H, t : 9.8 Hz), 2.50 (1H, d : 14 Hz), 2.23 (1H, d : 14 Hz), 2.13-1.60 (5H, m), 1.33 (3H, t : 7 Hz), 0.64 (3H, s) ppm. MS : m/z 262 ($M^{+\cdot}$-H_2O, 38), 217 (24), 205 (24), 55 (100).

(±)-(1'β,2'α,3'β)-4-(3'-(2"-Furyl)-1'-hydroxy-2'-methylcyclopentan-2'-yl)-1-buten-3-one (12). Method a : A soln of diol 11 (10.33 g; 36.9 mmol) and dil HCl (60 mL; 0.005 N) in THF (240 mL) is stirred at r.t. for 4 hrs. The reaction mixture is diluted with ether, washed with a satd $NaHCO_3$ soln and dried over $MgSO_4$. After the usual work-up enone 12 (8.63 g) is obtained in quantitative yield and further used without purification. Pure enone is best obtained via chromatography on florisil using 20-30 % EtOAc-isooctane. Method b : A soln of ester 10 (100 mg; 0.3 mmol) in ether (1.5 mL) is added dropwise to a suspension of LAH (38 mg; 1 mmol) in ether (1.5 mL). After reflux for 30 min, the suspension is cooled to r.t. and treated with water (38 µL) and dil sulfuric acid (2 N) until a clear aqueous phase is obtained. After ether extraction the organic phase is washed with $NaHCO_3$ soln and dried ($MgSO_4$). After the usual work-up the residue is purified by column chormatography on florisil with 25 % EtOAc-isooctane as eluent yielding 30 mg (41 %) of enone 12. Rf 0.46 (60 % EtOAc-isooctane). IR (film) : 3430, 1685, 1660, 1610 cm^{-1}. IR ($CHCl_3$ soln) : 3420, 1710-

1685, 1665, 1610 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 7.35 (1H, dd : 2, 0.8 Hz), 6.38 (1H, ABd : 17.5, 10.5 Hz), 6.33 (1H, dd : 3, 2 Hz), 6.25 (1H, ABd : 17.5, 1 Hz), 6.09 (1H, br d : 3 Hz), 5.85 (1H, dd : 10, 1.5 Hz), 4.56 (1H, br d : 1 Hz), 4.12 (1H, br t : 8.5 Hz), 3.34 (1H, d : 17 Hz), 2.86 (1H, dd: 11.5, 8.5 Hz), 2.42 (1H, d : 17 Hz), 2.21-1.76 (4H, m), 0.70 (3H, s) ppm. MS : m/z 234 ($M^{+\cdot}$; 2), 216 (4), 183 (15), 164 (54), 149 (87), 94 (100). Exact mass. Calcd for $C_{14}H_{18}O_3$: 234.1255. Found : 234.1110.

The Diels-Alder reaction of enone 12. (±)-(1α,2α,5β,6β,9β,11α)-5-Hydroxy-6-methyl-14-oxatetracyclo/7.4.1^{1,11}.0^{2,6}/tetradecan-8-one (14). A suspension of crude enone 12 (4.28 g; 18 mmol), obtained from diol 11 (5.04 g), in water (240 mL) is shaken vigorously for 30 min. At this stage the adduct can be isolated in pure form by decanting the milky emulsion from the oily residue and extracting the aqueous phase with ether. When kept into the organic phase the adduct 13 reverts to enone 12 within hours. Usually, however, the milky emulsion is transferred to a hydrogenation vessel (1 L) and diluted with methanol (120 mL). After addition of palladium on barium sulfate (180 mg) the mixture is hydrogenated at 2.2 bar. After 2 hrs the catalyst is filtered and washed with methanol. After concentration of the filtrate in vacuo, the residue is salted out with solid sodium chloride and extracted with ether. After usual work-up ($MgSO_4$) the solid residue is recrystallized from EtOAc-hexane (3:2) yielding 2.23 g of alcohol 14. Typical overall yields from diol 11 are dependent on the scale and range from 53 % (this procedure) to 85 % (small scale). For adduct 13 : m.p. 88-90.5°C. Rf 0.10 (60 % EtOAc-isooctane). IR (KBr) : 3400, 1700, 1635, 1615 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 6.47 (1H, AB : 5.8 Hz), 6.43 (1H, AB dd : 5.8, 1.5, 0.75 Hz), 4.93 (1H, dd : 4.5, 1.5Hz), 3.90 (1H, t : 8.5 Hz), 2.59 (1H, AB : 18.5 Hz), 2.57 (1H, dd : 8.0, 4.5 Hz), 2.33 (1H, dt : 11.5, 4.5 Hz), 2.31 (1H, br AB : 18.5 Hz), 2.29-2.19, 2.05-1.87, 1.74-1.66 (5H, m), 1.42 (1H, dd : 11.5, 8.0 Hz), 1.22 (3H, s) ppm. MS : m/z 234 ($M^{+\cdot}$, 5), 216 (7), 164 (72), 149 (100), 134 (17), 121 (25), 94 (57), 55 (80), 43 (75). For alcohol 14 : m.p. 120° C (sublimation). Rf 0.12 (60 % EtOAc-isooctane). IR (KBR) : 3500, 1680 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 4.48 (1H, t : 5.0 Hz), 3.86 (1H, td : 8.75, 5.5 Hz), 2.62 (1H, dd : 9.0, 6.0 Hz), 2.54 (1H, AB : 19.0 Hz), 2.23 (1H, AB : 19.0 Hz), 2.25-2.05, 1.95-1.54 (11H, m), 1.64 (1H, dd : 12.3, 9.0 Hz), 1.13 (3H, s) ppm. MS : m/z 236 ($M^{+\cdot}$,80), 218 (22), 208 (60), 207 (18), 180 (100), 179 (30). Exact mass. Calcd for $C_{14}H_{20}O_3$: 236.1412. Found : 236.1445.

(±)-(1α,2α,5β,6β,9β,11α)-5-tert-Butyldimethylsilyloxy-6-methyl-14-oxatetracyclo /7.4.1^{1,11}.0^{2,6}/tetradecan-8-one (16). To a soln of tert-butyldimethylsilyl chloride (18.9 g; 0.126 mol) in dry DMF (22.5 mL) is added a soln of alcohol 14 (3 g; 12.6 mmol) and imidazole (4.3 g; 63 mmol) in DMF (30 mL) in one portion. After completion of the reaction (TLC) the mixture is diluted with n-hexane (60 mL) and poured into a satd NH_4Cl soln. The aqueous phase is extracted with hexane and ether. After usual work-up of the combined organic phases ($MgSO_4$) the residue is purified by gradient elution on silica gel (10 g/g product) yielding the desired 16 (3.2 g; 72 %) with 3 % ether-benzene and the opened alcohol 17 (0.75 g; 17 %) with 50 % EtOAc-hexane. Remaining traces of tert-butyldimethylsilyl alcohol are removed in vacuo (0.05 mm Hg/70°C). On larger scales varying amounts of the corresponding disilyl ether 19 are also formed (vide infra). The base opening of pure silyl ether 16 to the corresponding enone 17 has been described before. For the spectral data of 16 and 17, see reference 3b. For the disilyl ether 19 : m.p. 112°C. Rf 0.85 (60 % EtOAc-hexane). IR (KBr) : 1645, 1620 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 3.9 (2H, m), 2.59 (1H, d : 16.0 Hz), 2.10 (1H, dd : 16.0, 1.0 Hz), 0.87 (9H, s), 0.86 (9H, s), 0.76 (3H, d : 1.0 Hz), 0.055 (3H, s), 0.050 (3H, s), 0.024 (3H, s), 0.018 (3H, s) ppm. MS : m/z 449 ($M^{+\cdot}$-15, 10), 407 (77), 71 (100).No reaction was observed when using a small excess of tert-butyldimethylsilyl chloride (TBDMCS)) imidazole in DMF, e.g., ratio 2.2/1.1, 3/1.5, 2/4, 3/6 (equivalents, respectively). More recent methods involving TBDMCS (7.5 equiv) and HMPA[29a], TBDMCS (6.6 equiv) and Et_3N (30 equiv) in THF[29b], TBDMCS (1.5 equiv) and Et_3N (3.0 equiv)/DMAP (0.15 equiv) in methylene chloride[29c], TBDMCS and lithium sulfide in acetonitrile[29d], TBDMCS (6 equiv) and diisopropylethylamine (3 equiv) in methylene chloride[29e], tert-butyldimethylallylsilane and p-toluene sulfonic acid in acetonitrile[29f], tert-butyldimethylsilyl perchlorate and pyridine in acetonitrile[29g], TBDMCS (1.0 equiv) and aliquat 336 or 18-Crown-6, potassium carbonate[29h], also led to the recovery of strating material. The desired silyl ether 16, next to varying amounts of 17 and 19 (TLC), was formed using a large excess of TBDMCS and imidazole in DMF (vide supra), TBDMCS and 3,5-dimethylpyrazole in DMF (ratio 1/1, 2/1 or 2/2, respectively), tert-

butyldimethylsilyl cyanide (1.0 equiv) in DMF at 25°C or 80°C,[29i] and TBDMCS/diisopropylethylamine in DMF[29e].

(±)-(2.3β,3aβ,6.7α,8.9.9bα)-Octahydro-3-tert-butyldimethylsilyloxy-7-hydroxy-3a-methyl-1H-benz[e]indene-5(4H)-one (17). To a soln of ether 19 (140 mg; 0.3 mmol) in benzene (2 mL) is added a soln of 1 M hydrogen fluoride in acetonitrile (300 µl of a 5 % soln of 40 % HF in CH_3CN). After 25 min (TLC) solid $NaHCO_3$ is added and the mixture extracted with ether. After the usual work-up the residue is purified by column chromatography on silica gel yielding the alcohol 17 (59 mg; 56 %) next to disilyl ether 19 (20 mg; 14 %).

(±)-(1α,2α,5β,6β,9β,11α)-6-Methyl-5-tetrahydropyranyloxy-14-oxatetracyclo /7.4.1^{1,11}.0^{2,6}/tetradecan-8-one (20). A soln of alcohol 14 (3.91 g; 16.6 mmol), p-toluenesulfonic acid (20 mg) and dihydropyran (2.08 g; 24.9 mmol) in methylene chloride (70 mL) is stirred for 30 min at 30°C. After the addition of K_2CO_3 the mixture is diluted with methylene chloride, filtered and washed with a satd Na_2CO_3 soln. Usual work-up gave crude crystalline ether 20 (5.3 g; 100 %) sufficiently pure for further work. Rf 0.37 (60 % EtOAc-isooctane). IR (KBr) : 1695 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 4.60 (1H, m), 4.47 (1H, t : 5.0 Hz), 3.92-3.78 (2H, m), 3.49 (1H, m), 1.16 and 1.13 (3H, 2 s) ppm. MS : m/z 302 (M$^{+\cdot}$-18, 22), 218 (10), 180 (10), 85 (100).

(±)-(2.3β,3aβ,8.9.9bα)-Hexahydro-3a-methyl-3-tetrahydropyranyloxy-1H-benz[e]indene-5.7-(4H.6H)-dione (21). A soln of crude ether 20 (5.3 g; 16.6 mmol) and sodium methoxide (0.894 g; 16.6 mmol) in methanol (250 mL) is stirred under nitrogen at 20°C for 3 hrs. After concentration in vacuo, water is added and the soln extracted with ether. After drying ($MgSO_4$) and further work-up the residue is purified via column chromatography on silica gel (70 % EtOAc-hexane) yielding 4.5 g (85 %) of hydroxy enone (cf. 17) that is subsequently oxidized as described for the conversion of 17 into 18[3b]. The corresponding diketone 21 (3.13 g) is obtained in 70 % yield. Rf 0.2 (50 % EtOAc-isooctane). IR (KBr) : 1720, 1665, 1625 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 4.63 (1H, m), 3.99 (1H, m), 3.88 (1H, m), 3.51 (1H, m), 3.14(1H, br AB : 21.5 Hz), 3.03 (1H, br AB : 21.5 Hz), 0.87 and 0.85 (3H, d : 1.0 Hz).

(±)-(2.3β,3aβ,8.9.9bα)-Hexahydro-3-tert-butyldimethylsilyloxy-3a.6-dimethyl-1H-benz[e]-indene-5.7(4H.6H)-dione (22). To a cooled soln (0°C) of lithium diisopropylamide, prepared from diisopropylamine (0.905 g; 8.96 mmol) in dry THF (54 mL) and n-butyllithium (6.48 mL of a 1.33 M soln in hexane), is added dropwise a soln of enone 18 (3.0 g; 8.62 mmol) in THF (82 mL). After stirring for 30 min at 0°C HMPA (11 mL), followed by methyl iodide (10.03 g; 70.6 mmol), are added. After completion of the reaction (TLC) the mixture is poured into a satd NH_4Cl soln and extracted with ether. After the usual work-up the residue is purified by HPLC with 10 % EtOAc-hexane as eluent, yielding a 1:1 mixture of diastereomeric 22 (2.27 g; 73 %). Rf 0.36 (30 % EtOAc-isooctane). UV (MeOH) : λ_{max} 254 nm. IR (KBr) : 1710, 1655, 1615 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 3.92/3.89 (1H, t : 8.5 Hz), 3.35/3.29 (1H, br q : 7.5 Hz), 1.24/1.23 (3H, d : 7.3 Hz), 0.89/0.88 (9H, s), 0.82/0.76 (3H, d : 0.8 Hz), 0.06 (6H, s).

(±)-(2.3β,3aβ,5a,8.9.9aβ,9bα)-Octahydro-3-tert-butyldimethylsilyloxy-3a.6-dimethyl-1H-benz[e]indene-5.7(4H.6H)-dione (23). To a soln of lithium (71 mg; 10 mmol) in liquid ammonia (20 mL; distilled from sodium) is added slowly a soln of enone 23 (618 mg; 1.7 mmol) in THF (13 mL) and tert-butanol (0.13 g; 1.7 mmol). After stirring for 45 min at -33°C the reaction is quenched with NH_4Cl. After evaporation of the ammonia, the residue is dissolved in water and extracted with ether. After the usual work-up, the residue is dissolved in acetone (50 mL) and treated at 0°C with Jones reagent. After completion of the reaction (TLC), excess reagent is destroyed with isopropanol and solid sodium carbonate added. After stirring for 15 min the mixture is filtered, the precipitate washed with ether and acetone, and the combined organic phases concentrated in vacuo. The residue is dissolved in water and extracted with ether. After the usual work-up the residue is purified by column chormatography with 10 % EtOAc-isooctane as eluent yielding 469 mg of 23 (76 %) as a diastereomeric mixture in which 2 isomers (NMR) predominate. Rf 0.20, 0.25 (20 % EtOAc-isooctane). IR (KBr) : 1710 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 3.83/3.79 (1H, t : 8.5 Hz), 1.19/1.05 (3H, d : 7.0/6.5 Hz), 0.87 (9H, s), 0.75/0.73 (3H, d : 0.5/1.0 Hz) ppm. MS : m/z 307 (M$^{+\cdot}$-57, 100), 289 (10), 231 (26), 75 (98). Exact mass. Calcd for $C_{21}H_{36}O_3Si$: 364.2434. Found : 364.2294.

(±)-(2.3β,3aβ,4.8,9.9aβ,9bα)-Octahydro-3-tert-butyldimethylsilyloxy-3a,6-dimethyl-5,7-ditrimethylsilyloxy-1H-benz[e]indene (24). To a cooled (-20°C) soln of diketone 23 (0.369 g; 1.01 mmol) in dry methylene chloride (18 mL) is added consecutively hexamethyldisilazane (0.512 mL; 2.43 mmol) and iodotrimethylsilane (0.317 mL; 2.23 mmol) under nitrogen. After stirring for 15 min at -20°C and for 2 hrs at 25°C, the reaction mixture is diluted with methylene chloride (20 mL) and the organic phase washed with $NaHCO_3$ soln (5 mL). After the usual work-up, the residue is purified rapidly over florisil (20 g; 1 % acetone-hexane as eluent) yielding 484 mg of a colourless viscous oil (94 %). Rf 0.96 (20 % EtOAc-hexane). IR (film) : 1610 cm^{-1}. NMR (360 MHz, CCl_4) : 3.68 (1H, t : 8.5 Hz), 2.06 and 1.97 (2H, br AB : 16 Hz), 1.84 (3H, t : 1.8 Hz), 0.89 (9H, s), 0.79 (3H, s) ppm.

(±)-(2.3β,3aβ,5aα,8.9,9aβ,9bα)-Octahydro-3-tert-butyldimethylsilyloxy-6α-(3'-chlorobut-2'(E)-en-1'-yl)-3a,6β-dimethyl-1H-benz[e]indene-5,7(4H,6H)-dione (25). To a cooled soln (0°C) of freshly prepared ether 24 (439 mg; 0.86 mmol) in dry THF (20 mL) is added dropwise methyllithium (1.56 mL of a 1.11 M soln in ether). After completion of the reaction (TLC) the reaction mixture is cooled to -40°C and treated with (E)-1-iodo-3-chloro-2-butene (186 mg; 0.86 mmol) in HMPA (3 mL; 17 mmol) in one portion. After 20 min at 20°C the mixture is poured into water and extracted with ether. After the usual work-up the residue is purified by HPLC (5 % EtOAc-hexane) yielding 168 mg of diketone 25 (43 %). Rf 0.40 (20 % EtOAc-isooctane). IR (film) : 1710, 1660 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 5.41 (1H, ddq : 10.0, 6.25 and 1.25 Hz), 3.79 (1H, t : 8.5 Hz), 2.70 (1H, dd : 14.0, 10.0 Hz), 2.63 (1H, ddq : 14.0, 6.25 and 1.0 Hz), 2.56 (1H, td : 14.5, 6.25 Hz), 2.34 (1H, d : 12.5 Hz), 2.33 (1H, ddd : 15.0, 4.75, 2.5 Hz), 2.21 (1 H, AB : 11.5 Hz), 1.96 (3H, br s : $\Delta^{1/2}$ 4 Hz), 1.32 (3H, s), 0.87 (9H, s), 0.73 (3H, br s), 0.008 (6H, s) ppm. MS : m/z 452 ($M^{+\cdot}$, 4), 395 (35), 225 (17), 161 (18), 145 (20), 135 (17), 75 (100). Exact mass. Calcd for $C_{25}H_{41}O_3SiCl^{35}$: 452.2513. Found : 452.2513.

The (Z)-isomer 26. Using (Z)-1-iodo-3-chloro-2-butene, there was obtained from ether 24 (429 mg) the corresponding diketone 26 (169 mg; 44 % yield) in the same manner as described for the synthesis of 25. Rf 0.39 (20 % EtOAc-isooctane). IR (film) : 1705 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 5.39 (1H, ddq : 9.5, 5.5 and 1.25 Hz), 3.79 (1H, t : 8.25 Hz), 2.89 (1H, dd : 14.5, 9.5 Hz), 2.54 (2H, m), 2.35 (1H, d : 12.0 Hz), 2.31 (1H, ddd : 15.0, 4.5, 2.5 Hz), 2.21 (1H, AB : 11.5 Hz), 2.04 (3H, br s), 1.37 (3H, s), 0.86 (9H, s), 0.73 (3H, br s), 0.08 (6H, s) ppm. MS : m/z 452 ($M^{+\cdot}$, 32), 417 (22), 395 (30), 223 (17), 207 (75), 75 (100).

(±)-11-ketotestosterone (27) and (±)-adrenosterone (6). A soln of the chloride 25 or 26 (or a mixture of both; 71 mg; 0.16 mmol) in formic acid (7.2 mL) and 70 % perchloric acid (0.7 mL) is stirred at 80°C under nitrogen until no starting material is visible on TLC. After concentration in vacuo the residue is diluted with EtOAc (10 mL) and a satd Na_2CO_3 soln (3 mL) and further treated with solid $NaHCO_3$ until the evolution of CO_2 has ceased. After separation of the organic phase, the aqueous phase is extracted with ethyl acetate. After usual work-up (Na_2SO_4) the residue is diluted with THF (5 mL) and 2 N hydrochloric acid (1.4 mL). After stirring for 35 min at reflux the solution is diluted with an equal volume of ether and further treated consecutively with a satd $NaHCO_3$ soln (1.5 mL) and solid $NaHCO_3$. The aqueous phase is extracted with ether and the combined organic phases dried over Na_2SO_4. After the usual work-up the residue is purified by HPLC (60% EtOAc-hexane as eluent) yielding 31 mg (65%) of (±)-11-ketotestosterone (27). M.p. 192-195°C (EtOAc). Rf 0.20 (60 % EtOAc-hexane). UV (MeOH) : λ_{max} 238 nm. IR ($CHCl_3$ soln) : 3450 (br), 1710, 1670, 1620 cm^{-1}. NMR (360 MHz, $CDCl_3$) : 0.76 (3H, d : 0.75 Hz), 1.43 (3H, s), 2.77 (1H, ddd : 13.75, 5.0, 3.25 Hz), 3.87 (1H, t : 8.5 Hz), 5.73 (1H, br s) ppm. MS : m/z 302 ($M^{+\cdot}$, 20), 274 (14), 258 (16), 243 (18), 181 (40), 161 (38), 122 (100). For the purpose of structural confirmation a sample of (±)-11-ketotestosterone (27) is oxidized with sulfur trioxide pyridine complex in dimethyl sulfoxide[26] to give, after purification on HPLC (60 % EtOAc-hexane), (±)-adrenosterone (6). M.p. 185°-186°C (EtOAc). Rf 0.21 (60 % EtOAc-hexane). IR ($CHCl_3$ soln) : 1745, 1710, 1665, 1620 cm^{-1}. UV (MeOH) : λ_{max} 236 nm. NMR (360 MHz, $CDCl_3$) : 0.89 (3H, d : 0.75 Hz), 1.44 (3H, s), 2.77 (1H, ddd : 13.75, 5.0, 3.25 Hz), 5.75 (1H, br s). MS : m/z 300 ($M^{+\cdot}$, 20), 285 (5), 282 (4), 257 (10), 256 (10), 228 (10), 161 (16), 122 (100).

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