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Synthetic Approaches to Pentacyclic Triterpenes of the Arborane Family

II[1] - Tetracyclic intermediates

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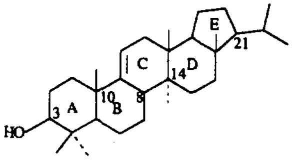
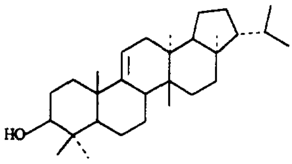
Abstract: Diels-Alder condensation of the bicyclic diene **1** with 2,6-dimethylbenzoquinone **2** under thermal and Lewis acid-catalyzed conditions gives the diastereomers **3**, **4**, **5** and **8**; their structures are demonstrated by NMR analysis, in full agreement with the conformations deduced from molecular mechanics.

Introduction:

In the first paper of this series,[1] we have presented the general approach we are studying, for the synthesis of isoarborinol A and of analogues, which we wished to compare with cholesterol in their condensing effect on phospholipid membranes.[2] We had described the synthesis of chiral fragments representing A/B and D/E moieties, derived from the antipodal forms of the Wieland-Miescher ketone and of its hydrindane analogue. In the mean time, the first evaluation of the interaction of isoarborinol itself with dimyristoyl-phosphocholine (DMPC) has shown that they do not behave at all like the DMPC/cholesterol classical system, or the other DMPC/cholesterol-surrogates systems which we had studied;[3] this negative result may be due to a wrong choice of phospholipid (a choice which cannot be improved, as the bacterial origin of sedimentary isoarborinol[4] is still hypothetical), and anyway it rather reinforces our interest in analogues of A, in particular demethylated ones available only by synthesis.



A



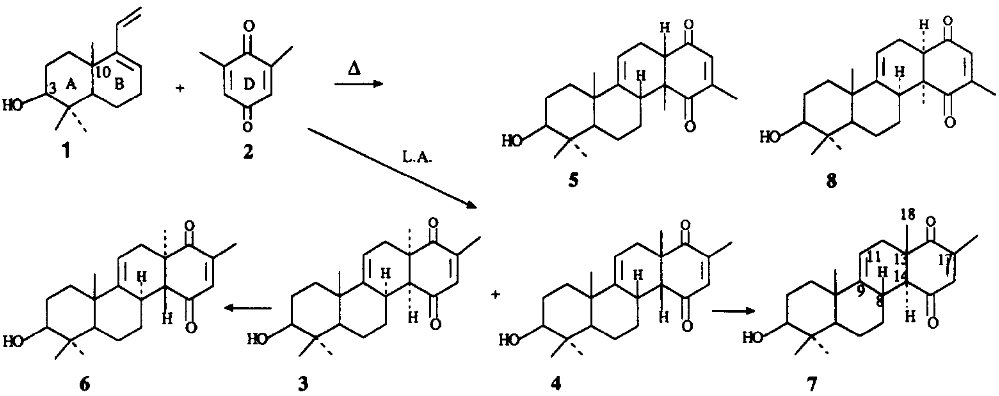
B

We now describe the interesting course of the efficient Diels-Alder reactions, Lewis acid-catalyzed or thermal, of the A/B diene **1** with a very reactive dienophile, 2,6-dimethyl-benzoquinone **2**. This study was required to define proper conditions for the A/B + D/E -> ABCDE route, and furthermore because some of the tetracyclic products obtained could be converted later into the desired pentacyclic derivatives.

A similar route had been studied in a synthesis of estrone (and therefore without methyl groups in the A/B rings) by Das et al.[5]

The Lewis Acid-Catalyzed Diels-Alder Reaction.

The starting diene (10S)-(+)-**1** has been obtained as described earlier[1] from the (10S)-Wieland-Miescher ketone, using the Cohen-Valenta modification in the step involving the dehydration.[6] It reacted smoothly with 2,6-dimethyl-benzoquinone **2** at -78°C in dichloromethane, in the presence of $AlCl_3$, to give in 80% yield two adducts **3** (m.p. 198-200°C, $[\alpha]_D$ −29) and **4** (m.p. 178-182°C, $[\alpha]_D$ -10), as a 1/1.4 mixture separable by silicagel flash chromatography. No trace of any other condensation product was detectable in the 400 MHz spectrum of the crude reaction mixture. We shall show below that both **3** and **4** result from the required attack placing the methyl groups in the isoarborinol-like 13 and 17 positions. Their structure results from the NMR analysis described below; that of **4** could make it a precursor of isoarborinol, while **3** can be considered as a potential intermediate in a synthesis of the isomeric fern triterpene fernenol **B**.



The 1/1.4 ratio obtained with aluminium trichloride is of course unfavourable. It could be somewhat improved by a change of reaction conditions, as indicated in Table 1: the reaction was fast with titanium or tin tetrachlorides in acetonitrile; moreover, the yield was high (81 - 83 %), and the selectivity more improved (3/4 = 1/4.2 - 1/5), in favour of the potential precursor of our primary goal, isoarborinol. With titanium tetrachloride in dichloromethane, at -78°C, the yield was a little lower (70 %) and the selectivity somewhat higher (1/8).

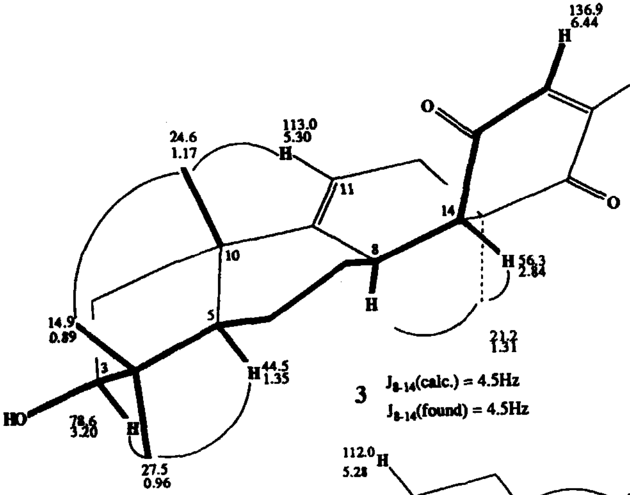
The Thermal and the $Eu(fod)_3$-Catalysed Diels-Alder Reactions.

The thermal reaction of **1** and **2**, when run in boiling benzene, was very clean, affording in nearly quantitative yield a single product **5**, m.p.190-197°C, $[\alpha]_D$ +4. In this case also, the structure was deduced from the NMR studies described below.

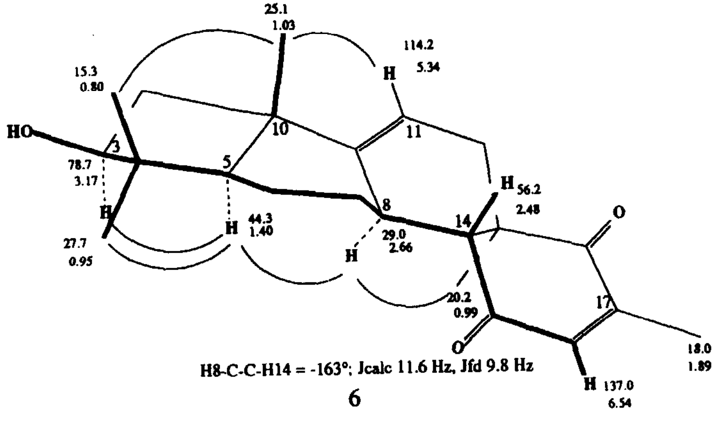
The decalin derivatives **3** and **4**, with a *cis* ring junction, should be unstable with respect to their *trans* epimers, and position 14 should be enolizable; this is indeed the case, and a simple treatment with sodium bicarbonate in methanol gave the *trans* (14α) diastereomers **6** and **7**.

The thermal reaction of **1** and **2** run in dichloromethane at room temperature was of course slow, and even after one week the yield did not exceed 58 %. Furthermore, it gave not the pure product **5** described

Figure 1
Minimized Energy Conformations of Adducts
Lewis Acid Catalyzed Reactions
The numerical values indicate the ^{1}H and ^{13}C NMR assignments; the arcs indicate observed n.O.e's.

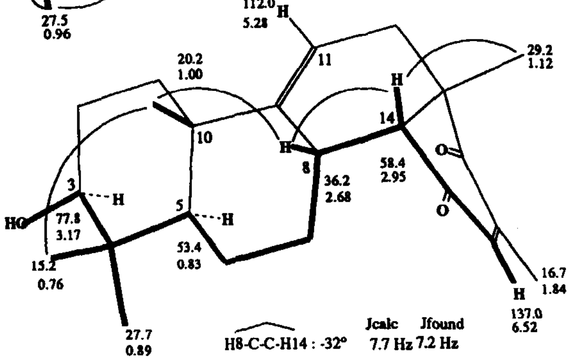


3 $J_{8\text{-}14}$(calc.) = 4.5Hz
$J_{8\text{-}14}$(found) = 4.5Hz



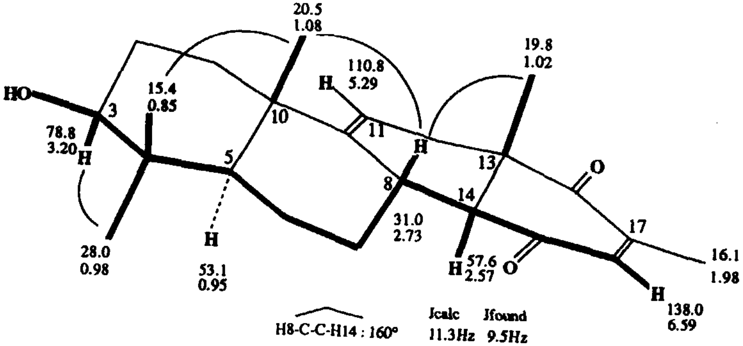
H8-C-C-H14 = -163°; Jcalc 11.6 Hz, Jfd 9.8 Hz

6



H8-C-C-H14 : -32° Jcalc Jfound 7.7 Hz 7.2 Hz

4



H8-C-C-H14 : 160° Jcalc Jfound 11.3Hz 9.5Hz

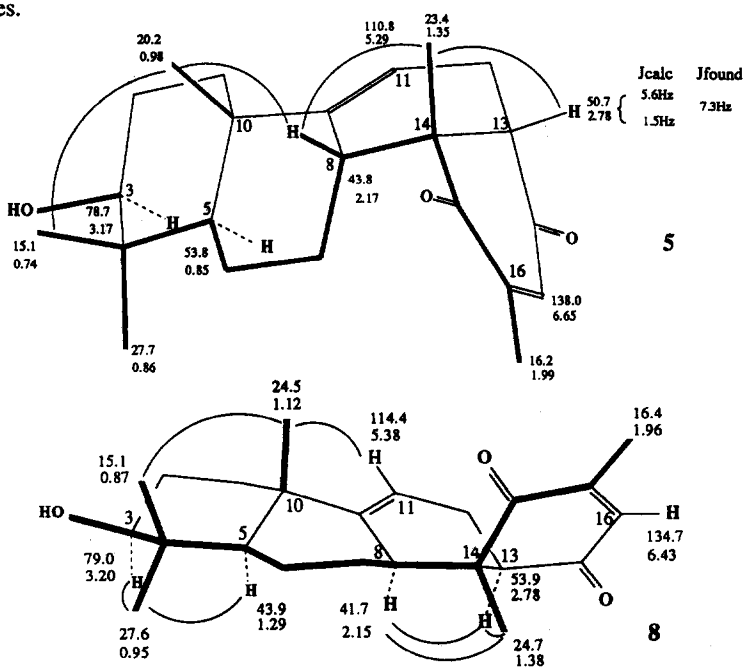
7

above, but this was accompanied by an unexpected isomer, characterized (by NMR again) as the 8α,13α,14α-epimer **8** of **5**, resulting from the same regioselectivity, but from the attack of the dienophile **2** on the opposite β-side of the diene **1**, (**5**/**8**: 3/1). We have no interpretation for this change in direction of addition.

However, these results tally with those of the Eu(fod)$_3$-catalysed reaction: in agreement with previous observations in unrelated series[7], this was found to accelerate markedly the reaction in dichloromethane at room temperature, (see Table), but still to give mixtures of the two diastereomers **5** and **8**. Furthermore, the facial selectivity was reversed.

Structural Assignments (Fig. 1 & 2)

Despite their high melting points, the tetracyclic products obtained did not give crystals suitable for X-ray analysis. We have therefore relied entirely on NMR studies, which have provided a complete picture of the structures.



5

8

Minimized Energy Conformations of Thermal and Eu(fod)$_3$ Catalyzed Adducts

(The arcs indicate observed nuclear Overhauser effects)

Figure 2

Assignment of all methyl and ring proton signals was straightforward using ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectroscopy (including long-range homo- and heterocoupling experiments). In the 600 MHz, resolution-enhanced spectra of **3** - **7**, in CDCl$_3$, the signals of the angular methyl groups are well separated from each other and from most of those of the ring protons; this allowed to study methyl-to-methyl, methyl-to-methylene, and methyl-to-methyne nuclear Overhauser enhancements, with the results indicated on the structural formulas.

The case of the thermal adducts **5** and **8** warrants additional comments. First, for **5**, presaturation of the signal of the angular methyl group at C-14 (δ 1.34 ppm) revealed a *cis* relationship with H-13 (CD rings *cis* fused as expected), and an enhanced peak due to H-8. Irradiation of the signal of H-8 (2.17 ppm) enhances the peaks due to both methyl groups at C-10 and C-14, whilst irradiation of the C-10 angular methyl group enhances the peaks due to H-8 (confirming the bottom-side attack) and the axial methyl group at C-4. No nOe was observed upon irradiation of either H-8 or H-13 on each other: this is in complete agreement with the detailed conformation of lowest energy defined by molecular mechanics. Similarly, in all the cases including the other thermal adduct **8**, excellent agreement was observed between the measured coupling constants and those deduced from the conformations of lowest energy conformers defined by the molecular mechanics calculations.

Discussion

It had been assumed initially that the Diels-Alder condensation on diene **1** would take place by attack from the less hindered α side, the one not protected by the β-axial methyl groups at C-4 and C-10. This is effectively what has taken place for the major isomer **4** produced in the Lewis acid-catalyzed condensations and for the single product of the thermal reaction, **5**. The extent of β-attack, to give **3**, is however relatively important in the Lewis acid-catalyzed reaction, especially with aluminium trichloride.

In all cases, the expected cis-addition results in a C/D-cis ring junction; this is of course not a problem, since conversion to isoarborinol would eventually require methylation at C-14, a center accessible to enolisation as is shown by the alkaline epimerisation of **3** and **4** to their C/D trans epimers **6**, $[\alpha]_D$ + 5, oil, and **7**, m.p. 185-186°C, $[\alpha]_D$ -17, the NMR of which are in agreement with their assigned structures. Methylation at C-14 would certainly occur mostly by the α-face, as required, at any rate for **4** which carries two β-axial methyl groups.

The directions of attack observed, as well as the interpretation of the NMR results used to define the tetracyclic products obtained, imply for the diene **1** and for the tetracyclic products **3-5** particular conformations which had to be justified by molecular mechanics. The accumulation of sp^2 centers renders first-level modelling, for instance with Dreiding models, rather futile, and we have studied the outcome of molecular mechanics calculations, using Still's Macromodel programme, with Allinger's basic MM2 force field. The lowest energy conformations are fully compatible with the observed n.O.e.s and with the calculated H-C-C-H dihedral angles deduced from Karplus' equation, with the additional constraint of ^3J's when observed. In the case of **8**, a manifold of near-lowest energy conformers was found, and we have calculated the average minimized conformation by 500 steepest descent steps in a 10ps simulation from 500 K, using the Discover™ module of Insight-II™.

We shall describe later further extensions of this work for the synthesis of pentacyclic systems, towards isoarborinol and analogues; we may also study later, as suggested by one of the referees, the influence of the 3-hydroxyl group on the selectivities reported here; this would however lead us away from our goal, and for the time being we intend to concentrate on the synthesis of the pentacyclic systems carrying this hydroxyl.

Experimental Section:

Optical rotations were measured on a Perkin-Elmer 243 polarimeter in chloroform. **IR spectra** were recorded on a Nicolet 205 FTIR instrument, in chloroform. **^{1}H NMR spectra** were obtained on Bruker AM 400 and AM600 instruments at 400 MHz and 600 MHz. Nuclear Overhauser enhancements by the NOEDIFF[6] method were obtained with the aid of the Aspect microprograms, which allow direct accumulations of difference FID's. NOe's were successfully obtained with extremely low irradiating power levels (40 dB); 320 transients were acquired in nOe experiments, and an exponential line broadening of 0.3 Hz was used. **^{13}C NMR data** were obtained at 62 and 100 MHz using Bruker AC250 or AM400-wide bore instruments. ^{13}C resonances were assigned by the SEFT method.[8] The COSY ^1H-^1H spectra were recorded with the 90°-t_1-90° (and/or 45°) sequence (matrix size 512 x 1024 pts, zero filled to 1024 x 1024 before FT). Heteronuclear shift correlation spectra were obtained using the pulse sequence:

$$\text{delay-}\pi/2\text{-}(^1H)\text{-}t_{1/2}\text{-}\pi(^{13}C)\text{-}t_{1/2}\text{-}\Delta_1\text{-}\pi/2(^1H),\ \pi/2(^{13}C)\text{-}\Delta_2;$$

acquisition with broad band decoupling[9]. A 1 s delay time was used with delay times $\Delta_1 = 1/2\ J = 3.8$ ms and $\Delta_2 = 1/4\ J = 1.9$ ms. In the F2 and F1 domains, 2048 and 1024 points were used respectively. **Mass spectra** were recorded on an AEI MS-50 spectrometer (EI spectra), or a Kratos MS-50 spectrometer (HR spectra). **Molecular mechanics calculations** were run using Still's Macromodel program version 3.1[10] operated on a Silicon Graphics work-station. Structures were constructed by means of the interactive graphics input and then subjected to the MM2 minimization using the Monte Carlo option of the program for the search of all conformers and the evaluation of their energy (indicated solvent: chloroform).

Lewis acid catalyzed Diels-Alder reactions

2,6-Dimethylbenzoquinone **2** (300 mg, 2.2 mmol) was dissolved at -20°C in dichloromethane (6 mL); aluminimum chloride (348 mg, 2.6 mmol) was added. After 30 min stirring, the mixture was cooled to -70°C and the bicyclic diene **1** (440 mg, 2 mmol) in chloromethane (7 mL) was added. Stirring was continued for 2 hrs at -70°C, excess water was added; dichloromethane extraction was followed by drying with brine and magnesium sulphate, and vacuum evaporation (crude: 750 mg). Silicagel flash chromatography (ethyl acetate:heptane 1:4) separated the adducts **3** (244 mg) and **4** (326 mg) in 80% overall yield. In other experiments, the adducts could be isolated more simply by trituration of the crude reaction product in ether: the less soluble, more polar, adduct **4** can thus be obtained pure; flash chromatography of the dissolved part completed the separation.

3β-Hydroxy 4,4,17-trimethyl (8α,13α,14α)D-homoandrosta-9(11),16-diene 15,17a-dione (3)

m.p. 198-200°C (MeOH). $[\alpha]_D$ −29 (c = 0.9). **IR**: 3450, 1680, 1630, 1379, 1182, 1083, 1031, 975. **^{1}H-NMR**: δ 0.89, 0.96, 1.17, 1.31 (all 3H, s), 1.94 (1H, dt, J = 3.5, 13.5), 1.95 (3H, d, J = 1.5), 2.35 (1H, dt, J = 2, 17.5), 2.50 (1H, dt, J = 9.5, 12.5), 2.55 (1H, m), 2.84 (1H, d, J = 4.5), 3.20 (1H, 1H, dd, J=5.6, 10), 5.30 (1H, q, J = 3.5), 6.44 (1H, d, J = 1.5). **^{13}C-NMR**: δ 14.9, 16.0, 19.3, 21.2, 22.2, 24.6, 27.5, 28.0, 31.8, 34.1, 38.2, 38.5, 39.5, 44.5, 48.9, 56.3, 78.6, 113.0, 136.9, 146.0, 150.3, 199.7, 202.8. **EIMS**: 357 (M+1, 27), 356 (M, 100), 246 (14), 201 (27), 91 (59).

3β-Hydroxy 4,4,17-trimethyl (14β)D-homoandrosta-9(11),16-diene 15,17a-dione (4)

m.p. 178-182°C MeOH). $[\alpha]_D$ -10 (c = 1.1). **IR**: 3500, 1674, 1625, 1377, 1265, 1229, 1027, 909. **^{1}H-NMR**: δ 0.76, 0.89, 1.00, 1.28 (all 3H, s), 2.00 (3H, d, J = 1.5), 2.68 (1H, m), 2.95 (2H, m), 3.17 (1H, dd, J = 5, 11), 5.28 (1H, br.d, J = 4.5), 6.52 (1H, q, J = 1.5). **^{13}C-NMR**: δ 15.2, 16.7, 20.2, 22.5, 27.7, 27.8, 29.2, 31.1, 34.1, 34.8, 36.2, 39.2, 40.0, 46.2, 53.4, 58.4, 77.8, 112.0, 137.0, 147.2, 148.9, 202.2. **EIMS**: 357 (M+1, 22), 356 (M, 100), 201 (14), 138 (31), 137 (31), 105 (36).

Anal. Calcd for $C_{23}H_{32}O_3$: C 77.53, H 8.99. Fd: C 77.2, H 9.0.

Thermal Diels-Alder Reaction in Benzene:

The bicyclic diene **1** (220 mg, 1 mmol) and 2,6-dimethylbenzoquinone **2** (136 mg, 1 mmol) were dissolved in anhydrous benzene (6 mL) and heated to reflux during 2.5 hrs. The volume of solvent was reduced to ca. 4 mL, and reflux was continued overnight. After evaporation *in vacuo*, silicagel flash chromatography (ethyl acetate:heptane 1:2) gave 340 mg (96 %) of the single adduct **5**.

3β-Hydroxy 4,4,14,16-tetramethyl (14β)D-homo-18-nor-androsta-9(11),16-diene 15,17a-dione (5)

m.p. 190-197°C (MeOH). $[\alpha]_D$ + 4 (c = 2.2). **IR**: 3500, 1700, 1600. **^{1}H-NMR**: δ 0.74, 0.86, 0.98, 1.35, (all 3H, s), 1.99 (3H, d, J = 1.5), 2.03 (1H, dd, J = 2.7, 13), 2.17 (1H, br. d, J = 13), 2.78 (1H, d, J = 7), 2.93 (1H, d, J = 5.5, 18), 3.17 (1H, dd, J = 2.7, 13), 5.29 (1H, br. d, J = 5), 6.65 (1H, br. s). **^{13}C-NMR**: δ 15.1, 16.2, 19.9, 20.2, 22.9, 23.4, 27.7, 34.6, 34.8, 39.4, 40.2, 43.8, 49.8, 53.8, 78.7, 110.8, 138.0, 147.2, 149.7, 204.3. **EIMS**: 357 (M+1, 25), 356 (M, 100), 328 (8), 323 (5), 313 (10), 260 (10), 151 (60), 105 (90), 91 (95).

Anal. Calcd for $C_{23}H_{32}O_3$: C 77.53, H 8.99. Fd: C 77.7, H 9.1.

Alkaline Epimerisation of the Adducts 3 and 4.

The adduct **3** (1.068 g, 3 mmol) and sodium bicarbonate (200 mg) were stirred in refluxing methanol (50 mL) under nitrogen for 1-2 h (TLC monitoring). After vacuum evaporation, brine was added and the resulting purple mixture was extracted as usual with dichloromethane. The residue was submitted to silicagel flash chromatography (ethyl acetate:heptane 1:4).

The same procedure was followed for the alkaline epimerisation of the isomeric adduct **4**.

3β-Hydroxy 4,4,14-trimethyl (8α,13α,14β)D-homo-androsta-9(11),16-diene 15,17a-dione (6)

Oil. $[\alpha]_D$ + 5 (c = 1.2). **IR**: 3600, 1681, 1626, 1377, 1216, 1027. **^{1}H-NMR**: δ 0.80, 0.95, 0.99, 1.03 (all 3H, s), 0.90 - 1.80 (10H, m), 1.89 (3H, d, J = 1.5), 2.15 (1H, m), 2.36 (1H, br.d, J = 18), 2.48 (1H, d, J=9.8), 2.66 (1H, m), 3.17 (1H, dd, J = 6.2, 9.4), 5.34 (1H, m), 6.54 (1H, q, J = 1.5). **^{13}C-NMR**: δ 15.3, 16.0, 18.0, 20.2, 25.1, 25.3, 27.7, 27.9, 29.0, 33.4, 37.8, 38.9, 39.2, 44.3, 47.6, 56.2, 78.7, 114.2, 137.0, 146.3, 149.7, 200.1, 204.0. **EIMS**: 357 (M+1, 24), 356 (M, 100), 338 (14), 323 (18), 271 (10), 203 (12), 202 (10), 201 (16), 187 (37); **HREIMS**: calcd for $C_{23}H_{32}O_3$: 356.2351, fd: 356.2339.

3β-Hydroxy 4,4,14-trimethyl D-homo-androsta-9(11),16-diene 15,17a-dione (7)

m.p. 185 - 186°C (MeOH). $[\alpha]_D$ −17 (c = 1.2). **IR**: 3600, 3450, 1680, 1626, 1377, 1291, 1183, 1067, 1029, 975. **^{1}H-NMR**: δ 0.85, 0.98, 1.02, 1.08, (all 3H, s), 0.75 - 1.85 (10 H, m), 1.98 (3H, d, J = 1.5), 2.20 (1H, ddd, J = 1, 6, 17.5), 2.40 (1H, m), 2.60 (1H, d, J = 9.5), 2.72 (1H, m), 3.22 (1H, dd, J = 5, 10.5), 5.29 (1H, m), 6.59 (1H, q, J = 1.5). **^{13}C-NMR**: δ 15.4, 16.1, 19.8, 20.5, 21.4, 27.7, 28.1, 31.0, 33.0, 35.0, 35.5, 39.2, 47.7, 53.1, 57.6, 78.8, 110.8, 138.0, 146.9, 148.2, 199.8, 204.1. **EIMS**: 357 (M + 1, 26), 356 (M, 100), 341 (25), 271 (15), 203 (16), 187 (42). **HREIMS**: calcd for $C_{23}H_{32}O_3$: 356.2351, fd: 356.2343. Anal. calcd for $C_{23}H_{32}O_3$: C 77.53, H 8.99, fd: C 77.2, H 8.9.

Thermal Diels-Alder Reaction in Dichloromethane.

The diene **1** (300 mg, 1.36 mmol) and the quinone **2** (230.1 mg, 1.7 mmol) were stirred at room temperature in dichloromethane (5mL) under an inert atmosphere. TLC monitoring showed no further evolution after 7 days. The solvent was evaporated under reduced pressure and silicagel flash chromatography (AcOEt:heptane 1:2) gave 307 mg (58%) of a mixture of **5** and **8**, not separated by silicagel column chromatography but separated by HPLC (inverse phase, methanol:water 65:35): **5**:**8**: 74:26.

Eu(fod)$_3$-catalyzed Diels-Alder condensations.

Same procedure as above. The work-up was done as follows: the reaction mixture was poured into a cold aqueous solution of sodium hydrogen carbonate and extracted with dichloromethane. The **5**:**8** ratios were determined by 400 ^{1}H-NMR and also by HPLC as above. Yields and ratios are indicated on Table 1.

3β-Hydroxy 4,4,14-trimethyl (14β)D-homo-androsta-9(11),16-diene 15,17a-dione (8)

Oil. $[\alpha]_D$ - 40 (c = O.8). **IR**: 3500, 1680, 1625, 1377. **^{1}H-NMR**: δ 0.87, 0.95, 1.12, 1.38 (all 3H, s), 1.30 (2H, m), 1.82 (1H, dt, J = 13.3, 3.4), 1.96 (3H, d, J = 1.5), 2.15 (1H, m), 2.26 (1H, m), 2.42 (1H, m), 2.78 (1H, dd, J = 6.8, 7.2), 3.20 (1H, dd, J = 5, 10), 5.38 (1H, m), 6.43 (1H, d; J = 1.5). **^{13}C-NMR**: δ 15.1, 16.4, 19.2, 21.3, 24.5, 24.7, 25.4, 27.6, 28.0, 38.5, 39.5, 41.9, 44.1, 51.0, 54.1, 79.0, 114.4, 134.7, 149.0, 150.0, 200.5. **EIMS**: 356 (M, 100), 328 (31), 313 (23), 260 (38), 229 (31), 195 (46), 91 (54).

TABLE 1:

Catalyst	**Solvent***	**Temp.°C**	**Time**	**Total yield**	**Product ratio 3/4**	**5**	**8**
$AlCl_3$	DCM	-70	2 h	80	1/1.4	-	
$EtAlCl_2$	"	-78 / -10	a	79	1/3	-	
BF_3,Et_2O	"	-78 / RT	b	76	1/2.7	-	
$SnCl_4$	"	-78 / 0	c	80	1/2.3	-	
	MeCN	-50 / 0	d	83	1/5	-	
$TiCl_4$	MeCN	-50	1 h	81	1/4.2	-	
	"	-78	3 h	70	1/8		
$Eu(fod)_3$; 0.2 eq.	DCM	RT	13 d	56	-	60	40
1 eq.	DCM		4 d	80	-	36	64
2 eq.	DCM		1 d	73	-	42	58
			UNCATALYZED REACTION:				
None	DCM	RT	7 d	58	-	74	26
	C_6H_6	Reflux	20 h	96	-	100	

a - d (reaction/time sequences; reactions followed by tlc) : **a** -78 (3h), then -70 to -10 (3h); **b** -78, 2h, then 0 (3h), then +4 (24 h), then RT (24h); **c** -78 (1h), then 0 (4h); **d** -50 (1h), then 0 (3h).

* DCM = CH_2Cl_2.

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