Pergamon

Tetrahedron 54 (1998) 6767–6780

TETRAHEDRON

The Synthesis of Pentacyclic Steroidal Polyesters in Consecutive Heck- and Diels-Alder Reactions

György Jeges [a], Rita Skoda-Földes [a], László Kollár [a,b], Judit Horváth [c] and Zoltán Tuba [c]

a) University of Veszprém, Department of Organic Chemistry, H-8201 Veszprém, P. O. Box 158, Hungary

b) Janus Pannonius University, Department of Inorganic Chemistry, H-7624 Pécs, P. O. Box 266, Hungary

c) Chemical Works of Gedeon Richter Ltd., H-1103 Budapest, Hungary

Received 22 January 1998; revised 15 April 1998; accepted 20 April 1998

Abstract: Steroidal alkenyl iodides (17-iodo-androsta-16-ene and 17-iodo-4-methyl-4-aza-androsta-16-ene-3-one) were reacted with conjugated unsaturated esters (ethyl acrylate, diethyl fumarate, diethyl maleate, diethyl acetylene dicarboxylate) in Heck-reaction and consecutive Diels-Alder reaction resulting in facile formation of pentacyclic derivatives. All steroidal esters possessing two, three and four ester functionalities on the E-ring were formed by the α-side addition of the dienophile.

Introduction

There are many examples of pentacyclic steroidal derivatives of pharmacological and biological importance. Most of these compounds possess an E-ring, which contains heteroatoms like nitrogen or oxygen.[1]

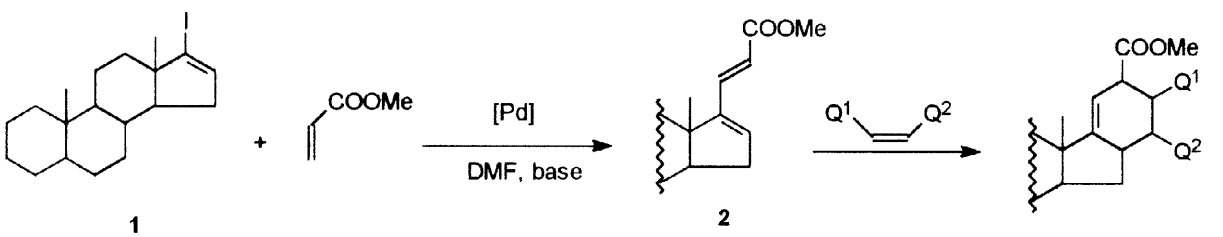
However, only a few carbocyclic steroidal derivatives containing cyclohexene (or cyclohexane) ring fused to A, B or D-ring are known.[2] Due to extreme reaction conditions and low selectivities these reactions are of low synthetic value.

0040-4020/98/$19.00
PII: S0040-4020(98)00361-5

Recently we have found [3] that various pentacyclic steroids can be synthesized by a one-pot reaction of a steroidal alkenyl iodide, vinyltributyltin and a dienophile in the presence of a palladium-catalyst. The diene, formed in Stille-coupling [4] as an intermediate, undergoes Diels-Alder reaction in the presence of the dienophile. Here we report on the synthesis of novel pentacyclic androstane derivatives by a Heck-reaction [5] — Diels-Alder reaction sequence carried out in one-pot. This methodology has been used by de Meijere *et al.* [6] for the synthesis of bicyclic systems. However, in our case the olefin that is used as a coupling partner in the Heck-reaction can compete with the dienophile both in the coupling and in the cycloaddition step. The effect of reaction conditions on chemo-, regio- and stereoselectivity of the two-step procedure has been investigated.

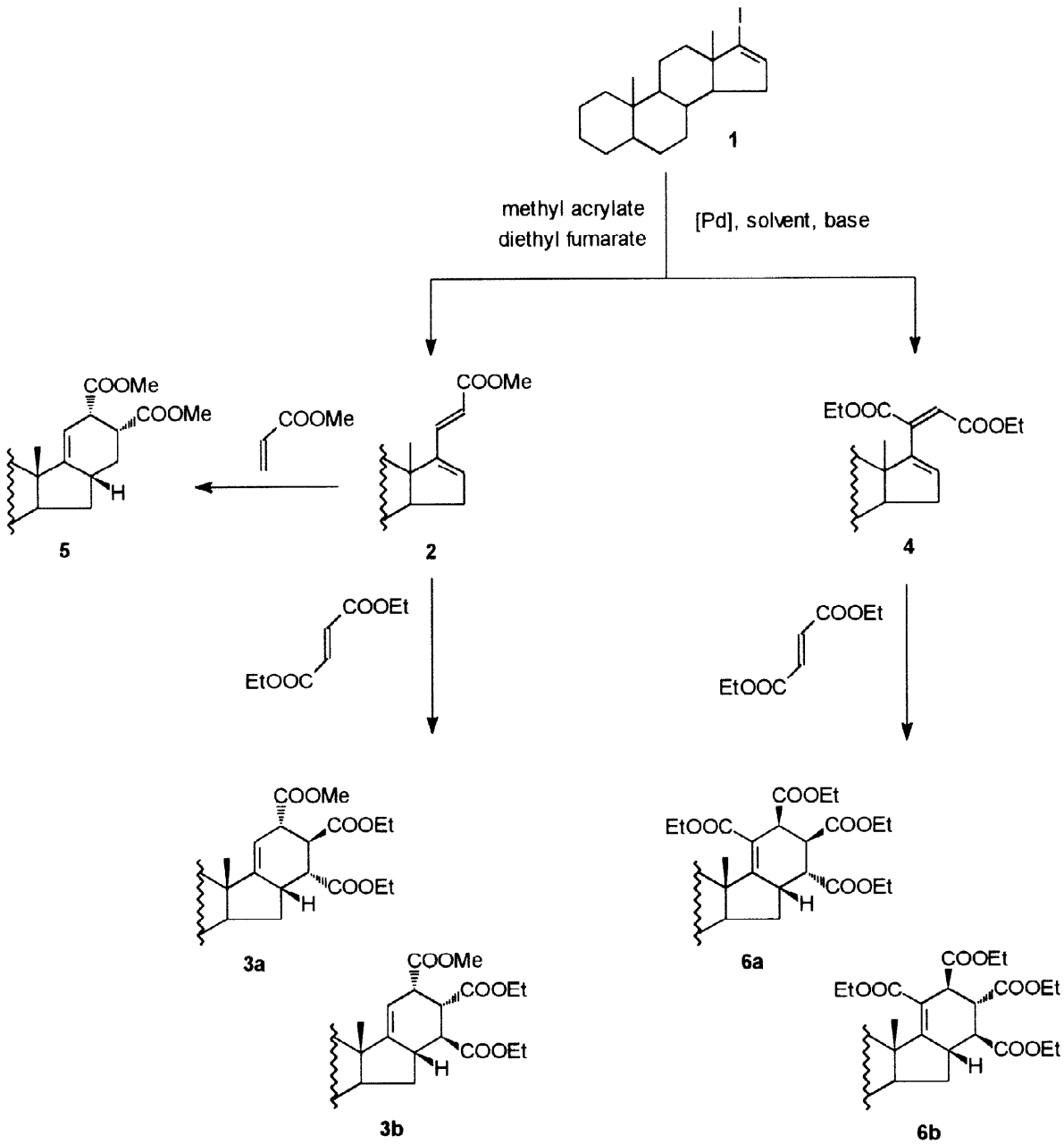
Results

The synthesis of steroid epimers possessing functionalized E-ring was carried out in two routes. *i)* 20-Methoxycarbonyl-pregna-16,20-diene (**2**) was synthesized by Heck-coupling reaction of 17-iodo-androst-16-ene and methyl acrylate.[7] The isolated diene was reacted with dienophiles resulting in pentacyclic steroids possessing a six-membered carbocyclic E-ring (Scheme 1).



Scheme 1.

ii) 17-Iodo-androst-16-ene (**1**) was converted to the ring-closed products by a one-pot reaction using methyl acrylate and diethyl fumarate, both reagents are able to act both as dienophile in Diels-Alder reaction and activated olefin suitable for Heck reaction (Scheme 2). Other pentacyclic derivatives were also produced by this method, using allyl alcohol or allyl acetate as olefin in coupling reaction and diethyl fumarate as the dienophile.



Scheme 2.

Reactions with methyl acrylate and diethyl fumarate

The steroidal derivatives with trisubstituted E-ring (**3a** and **3b**) are easily accessible from the 'preformed' diene (**2**) and diethyl fumarate in Diels-Alder reactions (Table 1). The use of elevated reaction times results in practically complete conversion of the substrate both in toluene and DMF. The ratio of the two stereoisomers is affected by the temperature, reaction time and solvent. In toluene the 1'α,2'β,3'α-triester (**3a**) predominates over 1'β,2'α,3'α-triester (**3b**) throughout the reaction (entry 1). Carrying out the reaction in good donor

solvent, DMF, and short reaction times **3a** is the major product (entry 2). However, in longer reaction times the formation of **3b** is favoured (entry 3). It should be noted that **3a** could be produced selectively with 69 % yield (GC) at 60 °C in 3.5 hours. The isolated 1'α,2'β,3'α-triester (**3a**) can be partly converted into the 1'β,2'α,3'α-derivative (**3b**) on heating in DMF in the absence of the dienophile.

The use of a 'preformed' Pd(0) catalyst ($Pd_2(dba)_3$) does not influence the conversion thoroughly. The **3a**/**3b** ratio is similar to that obtained without catalyst in a short reaction time (entry 4). Surprisingly, although some increase in the amount of **3b** can be observed in a longer reaction time, **3a** is still predominating (entry 5).

Table 1. Reaction of 20-methoxycarbonyl-pregna-16,20-diene (**2**) with diethyl-fumarate [a]

entry	r. time [h]	solvent	catalyst	conv. [b] [%]	ratio of isomers [b]	
					3a	**3b**
1	26	toluene	—	100	67	33
2	6.5	DMF	—	88	59	41
3	30	DMF	—	100	22	78
4	6.5	DMF	$Pd_2(dba)_3$	87	66	34
5	26	DMF	$Pd_2(dba)_3$	97	54	46

a: Reaction temperature: 100 °C, mol diethyl fumarate/ mol steroid: 1/1

b: Determined by GC.

The one-pot reaction of 17-iodo-androst-16-ene (**1**) with methyl acrylate and diethyl fumarate in the presence of various Pd precursors gave moderate to high yields of ring-closed products (Scheme 2, Table 2). At 100°C complete conversion was obtained both with $Pd_2(dba)_3$ and $Pd(OAc)_2$ catalytic precursors (entries 8, 10). Although methyl acrylate and diethyl fumarate compete in Heck-coupling at higher temperatures, at low temperature methyl acrylate reacts almost exclusively (entries 1-4). The addition of a strong base (K_2CO_3) instead of Et_3N resulted in lower conversion (entries 5,6). Diene **4** was produced in larger amount only when the methyl acrylate/diethyl fumarate ratio was changed from 2/1 to 1/1 and 1/2 (entries 12 and 13).

Table 2 Reaction of 17-iodo-androsta-16-ene (**1**) with methyl acrylate and diethyl fumarate in the presence of Pd catalysts [a]

entry	catalyst [b]	r. time [h]	methyl acrylate/ diethyl fumarate/**1**	conv. [c] [%]	Heck products [c]		Diels-Alder products [c]				
					2	**4**	**3a**	**3b**	**6a**	**6b**	**5**
1 [d]	A	4.5	2/1/1	24	18	—	3	2	—	—	1
2 [d]	A	27	2/1/1	58	20	2	11	18	—	—	7
3 [d]	A	4.5	1/1/1	34	15	1	9	7	—	—	2
4 [d]	A	27	1/1/1	51	12	3	8	21	—	—	7
5 [e]	A	4.5	2/1/1	23	10	—	6	1	—	—	6
6 [e]	A	27	2/1/1	43	2	—	16	24	—	—	11
7	A	4.5	2/1/1	30	11	3	8	13	—	—	5
8	A	27	2/1/1	97	4	5	16	57	2	3	10
9	B	4.5	2/1/1	75	15	5	13	32	—	—	10
10	B	27	2/1/1	100	—	5	14	64	—	3	14
11	B	4.5	2/2/1	80	8	8	18	37	—	—	9
12	B	27	2/2/1	100	—	8	15	63	2	7	5
13	B	4.5	1/2/1	100	3	19	14	55	—	2	7
14	B	50	—/2/1	100	—	50	—	—	9	41	—

[a]: Reaction conditions: solvent: DMF, reaction temperature: 100 °C, base: Et_3N. [b]: Catalyst A: $Pd_2(dba)_3$, catalyst B: $Pd(OAc)_2$. [c]: Determined by GC. [d]: Reaction temperature: 60 °C. [e]: Base: K_2CO_3.

The formation of the two predominating cyclization products (**3a**, **3b**) is based on the Heck-product with methyl acrylate which undergoes consecutive Diels-Alder reaction with diethyl fumarate (Scheme 2.). At low temperature (entries 1-4) and in the presence of K_2CO_3 base (entries 5,6) these steroid stereoisomers possessing trisubstituted E-rings are the major products. A further derivative (diester **5**) was also formed as minor product, indicating that methyl acrylate can react both as activated olefin in Heck-reaction and as dienophile in Diels-Alder reaction.[3b]

The dependence of the **3a/3b** ratio on the reaction time is similar to that obtained with 'preformed' diene (**2**) in Diels-Alder reaction. In longer reaction times the ratio is shifted towards **3b** in all cases (compare entries

5 and 6 or 7 and 8, etc) . The most pronounced effect of the reaction time on **3a/3b** ratio was observed in the presence of K_2CO_3 .

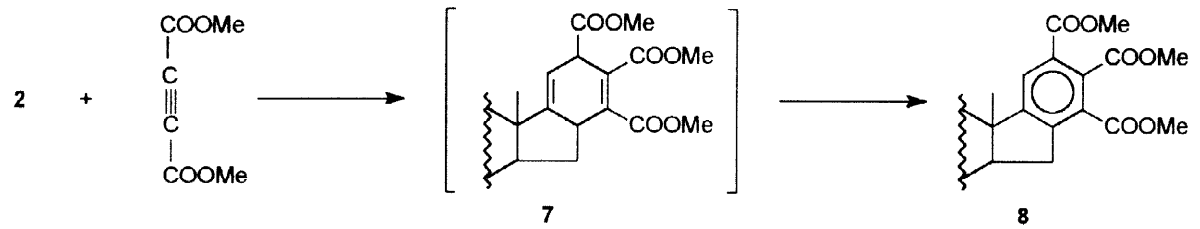
The formation of tetraesters (**6a** and **6b**) in isolable amount takes place only when diethyl fumarate is the only activated olefin present in the reaction mixture (entry 14). Although the full conversion of 17-iodo-androsta-16-ene (**1**) to coupling product **4** and cyclisation products (**6a** and **6b**) needs longer reaction time than that in the presence of methyl acrylate, the major cyclisation product **6b** could be synthesized in moderate yield and characterised.[8] Heck-product with diethyl fumarate (**4**) could also be isolated from the reaction mixture with 25 % yield.

Reactions with methyl acrylate and various dienophiles

Diethyl maleate was found to be a poor dienophile in the Diels-Alder reaction of steroidal dienes without functional groups at the C-20 carbon.[3b] This observation has been explained sterically. In the case of **2**, the presence of an electron-withdrawing group in the diene decreases its reactivity. So it is not surprising that in the one-pot reaction of 17-iodo-androsta-16-ene (**1**), methyl acrylate and diethyl maleate the main product was **5**, and the four stereoisomers of pentacyclic triesters were formed in *ca.* 40%. Diels-Alder reaction of isolated **2** with diethyl maleate resulted in 54 % conversion in 24 hours and the same four isomers could be detected in approximately equal amounts.[9]

Steroidal triester (**8**) was produced by the reaction of the isolated diene (**2**) with dimethyl acetylenedicarboxylate in moderate yield (Scheme 3). Cycloaddition product (**7**) was transformed (aromatised) spontaneously into the compound with aromatic E-ring (**8**) even in the absence of a palladium catalyst. (Aromatization of the cycloaddition product of dimethyl acetylenedicarboxylate and pregna-16,20-diene had been observed before only in the presence of palladium catalysts.[3])

The one-pot reaction with dimethyl acetylenedicarboxylate as dienophile failed. In the presence of the palladium catalyst a cyclic trimer was formed from the dienophile. Although the formation of hexamethyl benzenehexacarboxylate (detected by GC—MS) can be suppressed by using phosphine ligands, it predominates over cycloaddition even in the presence of palladium—phosphine systems under the conditions of the one-pot reaction. In THF no Heck-products, and consequently, no Diels-Alder products could be detected.

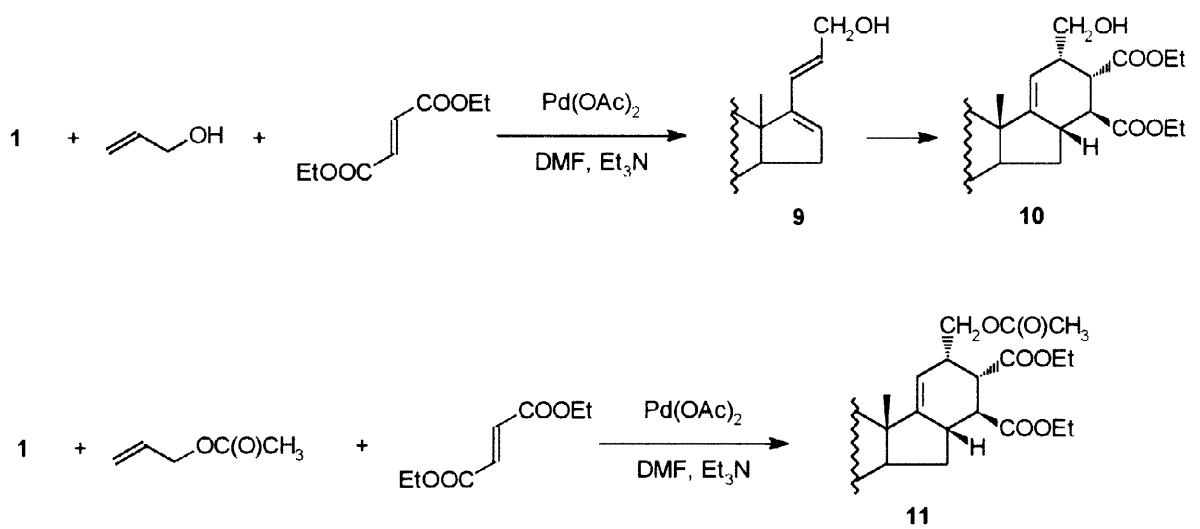


Scheme 3.

Reactions with electron deficient olefines and diethyl fumarate

Pentacyclic derivatives were also produced by the reaction of 17-iodo-androsta-16-ene (**1**) with allyl alcohol and diethyl fumarate in the presence of palladium catalysts. Heck-reaction of steroidal alkenyl iodides with allyl alcohol had been found to lead to the 21-formyl derivatives exclusively.[7] This can be explained either by the rapid isomerization of the unsaturated alcohol produced in the first step or by the decomposition of a palladium—alkyl intermediate of the catalytic cycle, *i.e.* by the favoured β-elimination of the proton adjacent to the alcohol functionality.[10]

Product **10** bearing both alcohol and ester functionalities was formed as the main product from the cycloaddition of 21-hydroxymethyl-pregna-16,20-diene (**9**) and diethyl fumarate. This supports the first of the two explanations mentioned above: the unsaturated alcohol is formed during the Heck-reaction and this compound can be partly trapped by the dienophile before isomerization could occur. In this case allyl alcohol could be used in fivefold excess. Since it is a poor dienophile, it did not compete with diethyl fumarate in the cycloaddition step. Under these conditions no Heck-coupling of diethyl fumarate was observed.

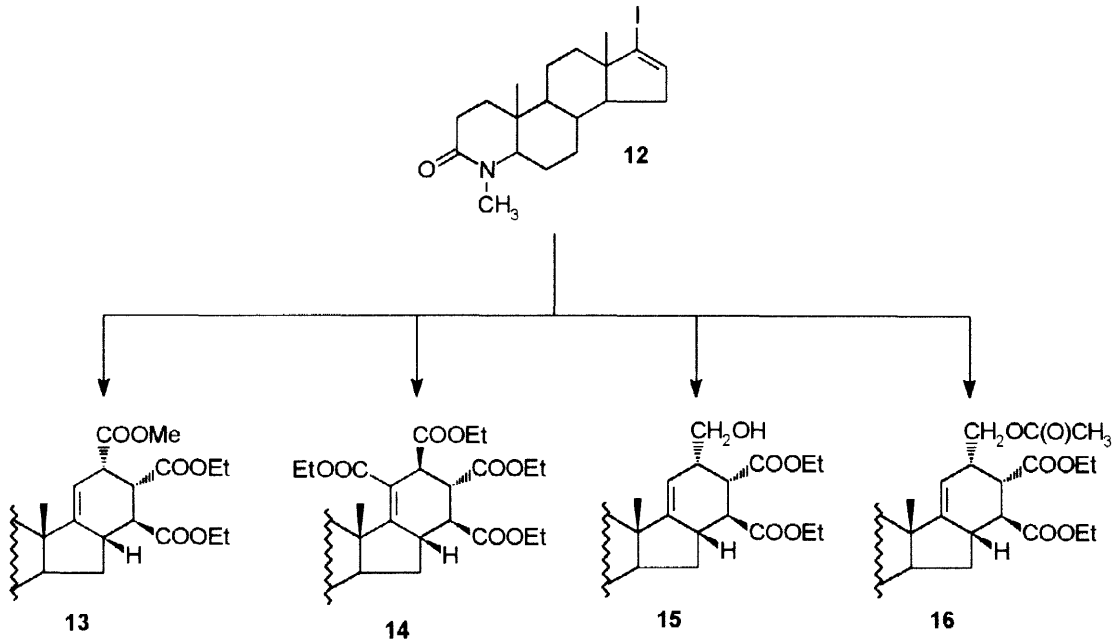


Scheme 4

Unexpectedly selective formation of **11** was observed using allyl acetate instead of allyl alcohol as the coupling partner.

The functionalization of a skeleton of pharmacological importance (by using 12 as substrate)

Pentacyclic derivatives **13-16** (Scheme 5) were also produced with moderate to high yields by using the above procedures starting with steroidal alkenyl iodide (**12**). Diethyl fumarate served as the dienophile in all reactions. Methyl acrylate, diethyl fumarate, allyl alcohol and allyl acetate were reacted as olefins in Heck-reactions resulting in the intermediates of ring-closure products, **13**, **14**, **15** and **16**, respectively.



Scheme 5

Discussion

i) Characterisation of the stereoisomers (3a, 3b, etc.) by NMR

Exact structures of the main products were determined after isolation by NMR (^{1}H-^{1}H-COSY and NOE experiments). Each pentacyclic steroid proved to be the 16β-H isomer: saturation of the ^{1}H-NMR signal of the 16-H (determined by ^{1}H-^{1}H-COSY experiments) resulted in an increase of the intensity of the 18-CH_3 signal in each case.

When the resonance of 16-H (2.80 ppm) of steroidal triester **3b** is saturated, the intensity of 2'-H at 3.32 ppm (and that of 18-CH_3 at 0.79 ppm) increases. At the same time no effect was observed at 2.30 ppm (3'-H).

Irradiation of the sample at 3.32 ppm (2'-H) caused an increase in the intensity of the signal at 3.48 ppm (1'-H). That means that the position of the protons at the new stereogenic centers are 16β, 1'β, 2'β, 3'α. This corresponds to an α-side approaching and a *syn* addition of the dienophile to the steroidal skeleton. Saturation of the resonance of the 16-H (2.63 ppm) of the other isomer **3a** resulted in the increase of the signal of 3'-H (3.03 ppm) and 18-CH_3 (0.82 ppm) and there was no effect on 2'-H (3.70 ppm). Supposing a *syn*-addition, this isomer has the protons in 16β, 1'β, 2'α and 3'β positions.

The same stereoselectivity of cycloaddition was observed in the case of the steroidal tetraesters **6a** and **6b**. Irradiation at 2.78 ppm (16-H of **6b**) resulted in an increase in 2'-H (3.44 ppm), and no effect was observed on 1'-H (2.46 ppm). Saturation of 1'-H caused an increase in 3'-H (4.05 ppm). According to these observations, the main isomer is the16β-H, 2'α-H, 3'β-H, 4'α-H derivative. The other stereoisomer (**6a**) was proved to have the protons in the 16β, 2'α, 3'α, 4'β positions: saturation of 3'-H (3.65 ppm) resulted in an increase on 2'-H (3.17 ppm).

The structural characterisation of **8**, **10**, **11**, **13**, **14**, **15** and **16** has been carried out by similar NMR methods as discussed above.

ii) Influence of the reaction conditions on chemo- and stereoselectivities of the cyclization reactions

The formation of both **3a** and **3b** is due to the approach of diethyl fumarate from the less hindered α-side, its COOEt substituent close to 21-COOMe putting "outwards" and "towards" the steroidal skeleton, respectively (Figure 1).

The surprisingly low reactitvity of diethyl maleate could be a consequence of the presence of 21-COOMe substituent because of two reasons: first, it could sterically hinder the formation of the *endo* transition state (both from α- or β-side) favoured by orbital overlapping, and second, it reduces the reactivity of the steroidal diene as an electron withdrawing group.

The existence of a retro-Diels-Alder/Diels-Alder reaction sequence leading to the formation of a thermodynamically more stable product (**3b**) in longer reaction times could be deduced from the catalytic results. Derivative **3a** could be considered as a kinetically controlled product formed *via* less crowded transition state (Figure 1). This is supported by the fact that **3a** was formed selectively at lower temperatures, and isolated **3a** could be converted into **3b** on heating it in DMF at higher temperature for 24 hours in 70 % yield. The greater stability of **3b** can be explained by the equatorial 3'β position of the COOEt group (instead of its axial position in **3a**) resulting in smaller sterical congestion between this substituent and the D-ring.

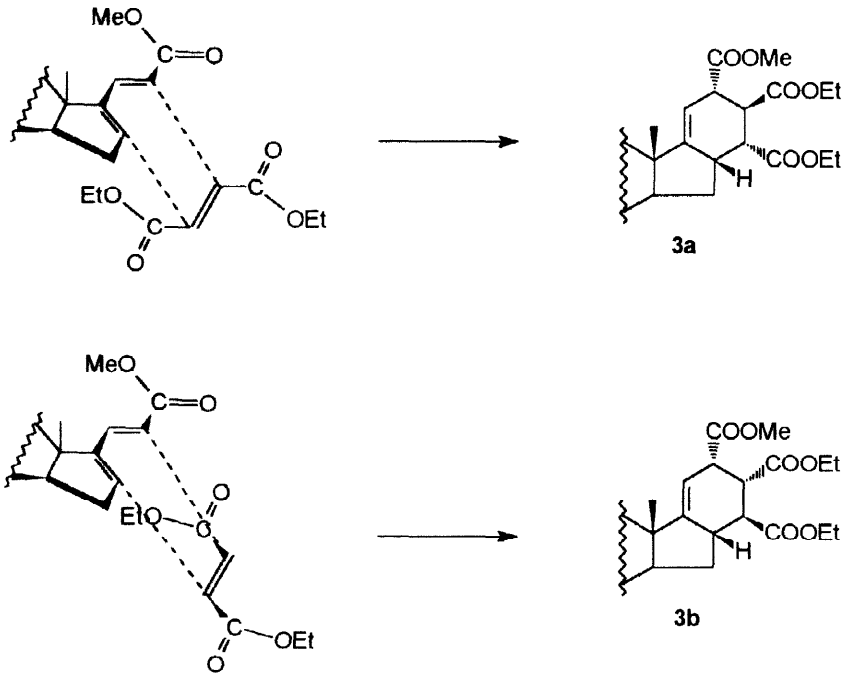


Figure 1

The retro-Diels-Alder reaction in DMF seems to be hindered by Pd(0) catalysts probably by coordination of a Pd species to the unsaturated functionalized E-ring of **3a**.

As a conclusion it can be stated, that key-intermediates of potential 5α-reductase inhibitors of increased hydrophilic character can be synthesised in a facile one-pot procedure involving palladium-catalysed Heck-reaction and Diels-Alder reaction.

Experimental

All experiments were carried out under an argon atmosphere. Solvents were dried over sodium and distilled under argon.

Palladium Catalysts. $Pd(PPh_3)_4$ and $Pd_2(dba)_3.CHCl_3$ (dba=dibenzylideneacetone) were prepared as described previously.[11,12]

Dienophile Reagents. Dimethyl acetylenedicarboxylate were Aldrich-products, diethyl maleate, diethyl fumarate, methyl acrylate were purchased from Fluka.

General Procedure for the Synthesis of the Cycloaddition Products.

0.02 mmol of $Pd_2(dba)_3.CHCl_3$ and 1 mmol of steroid were added to a flask equipped with a reflux condenser and a septum inlet. The flask was flushed with argon and charged with 10 ml of DMF. 2 mmol of

methyl acrylate (or 5 mmol of allyl alcohol or allyl acetate), 2 mmol of diethyl fumarate and 5 mmol of triethylamine were injected through the septum inlet. The mixture was stirred at 100 °C for 30 hours. The solvent and all unreacted volatile materials were removed *in vacuo*. The residue was dissolved in 20 ml of $CHCl_3$, washed with two portions of 20 ml 5 % HCl, 20 ml of saturated aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. Isolation was carried out by column chromatography (eluent: hexane/ethyl acetate: 80/20 for **3a**, **3b** and **6b**, 70/30 for **11**, 50/50 for **10**; chloroform/methanol: 98/2 for **13** and **14**, 95/5 for **15**, 90/10 for **16**). All products have been obtained as solides.

2'β,3'α-bis(ethoxycarbonyl)-1'α-methoxycarbonyl-androstano-[16α,17-d]-cyclohex-5'-ene (3a): Synthesized in 60 % yield. ^{1}H-NMR δ 5.17(m, 1H, 6'-H); 4.15(m, 4H, OC***H***$_2$CH$_3$); 3.7(s, 1H, 1'β-H); 3.7(m, 1H, 2'α-H); 3.6(s, 3H, OC***H***$_3$); 3.03(m, 1H, 3'β-H); 2.63(m, 1H, 16β-H); 1.49(m, 1H, 15α-H); 0.70-1.9(m, 21H, ring protons); 1.22(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.19(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 0.82(s, 3H, 18-H$_3$); 0.8(s, 3H, 19-H$_3$); ^{13}C-NMR δ: 175.9(CO), 172.85(CO), 172.15(CO), 155.82(C-17), 103.15(C-6'), 60.65(O*C*H$_2$), 60.62(O*C*H$_2$), 55.01, 52.56, 51.91, 47.07, 44.25, 44.04, 43.14, 40.29, 38.66, 36.42, 34.50, 35.40, 31.67, 30.39, 29.69, 29.01, 27.70, 26.76, 22.16, 20.50, 17.18, 14.23, 14.00, 12.23. MS *m/e* 514 (M$^+$)/0.2, 482/10, 468/20, 425/50, 381/60, 217/60, 151/100, 109/90. IR (cm^{-1}) 1730(ν(C=O)) Anal. Calcd for $C_{31}H_{46}O_6$ (514.33): C, 72.33; H, 9.01. Found: C, 72.41; H, 9.18.

2'α,3'β-bis(ethoxycarbonyl)-1'α-methoxycarbonyl-androstano-[16α,17-d]-cyclohex-5'-ene (3b): Synthesized in 72 % yield. ^{1}H-NMR δ 5.15(m, 1H, 6'-H); 4.12(m, 4H, OC***H***$_2$CH$_3$); 3.68(s, 3H, OC***H***$_3$); 3.48(td, J_{AB}=J_{BA}=26Hz, 11.5Hz, 1H, 1'β-H); 3.32(t, J_{AB}=J_{BA}=12.2Hz, 1H, 2'β-H); 2.8(m, 1H, 16β-H); 2.3(t, J_{AB}=J_{BA}=11.5 Hz, 1H, 3'α-H); 1.50(m, 1H, 15α-H); 0.70-1.9(m, 21H, ring protons); 1.20(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.18(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 0.79(s, 3H, 18-H$_3$); 0.78(s, 3H, 19-H$_3$); ^{13}C-NMR δ: 173.93(CO), 173.42(CO), 173.13(CO), 154.83(C-17), 108.12(C-6'), 60.98(O*C*H$_2$), 60.64(O*C*H$_2$), 55.16(C-1') (52.56,52.19)(C-2',C-3'), 48.37, 47.06, 45.40, 44.98, 44.24, 38.67, 38.67, 36.41, 35.39, 34.98, 31.67, 29.01, 28.88, 28.23, 26.76, 22.15, 20.28, 17.15(C-18), 14.21(OCH$_2$*C*H$_3$), 14.00(OCH$_2$*C*H$_3$), 12.24(C-19); MS *m/e* 514 (M$^+$)/0.4, 482/6, 468/57, 425/78, 381/100, 335/19. IR (cm^{-1}) 1730(ν(C=O)) Anal. Calcd for $C_{31}H_{46}O_6$ (514.33): C, 72.33; H, 9.01. Found: C, 72.46; H, 9.21.

1'β,2'α,3'β,4'-tetrakis(ethoxycarbonyl)-androstano-[16α,17-e]-cyclohex-4'-ene (6b): Synthesized in 35 % yield. ^{1}H-NMR δ 4.15(m, 8H, OC***H***$_2$CH$_3$); 4.05(m, 1H, 3'α-H); 3.44(dd, 7.5Hz, 11.2Hz, 1H, 2'β-H); 2.78(m, 1H, 16β-H); 2.46(t, J_{AB}=J_{BA}=11.2Hz, 1H, 1'α-H); 1.50(m, 1H, 15α-H); 0.60-1.7(m, 21H, ring

protons); 1.23(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 1.22(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 1.20(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 1.19(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 0.96(s, 3H, 18-H_3); 0.76(s, 3H, 19-H_3); ^{13}C-NMR δ: 173.49(CO), 172.67(CO), 171.68(CO), 171.56(CO), 158.04(C-17), 117.77(C-4'), 61.37(OCH_2), 61.26(OCH_2), 60.82(OCH_2), 60.52(OCH_2), 54.35, 52.98, 48.00, 46.86, 46.74, 46.49, 45.11, 39.89, 38.57, 36.20, 35.16, 34.26, 31.61, 28.93, 28.13, 26.74, 22.10, 20.64, 16.31, 14.22 14.07(OCH_2CH_3), 14.04(OCH_2CH_3), 14.02(OCH_2CH_3), 14.02(OCH_2CH_3), 12.13(C-19); MS *m/e* 509(M^+-EtOH-OEt)/44, 453/78, 407/100, 342/8, 203/12. FAB-MS: 601 $(M+H)^+$. IR (cm^{-1}) 1730(ν(C=O)). Anal. Calcd for $C_{35}H_{52}O_8$ (600.37) C, 69.97; H, 8.72. Found: C, 70.08; H, 8.85.

1',2',3'-dimethyl-androstano-[16,17-d]-phthalate (8): Synthesized in 62 % yield. ^{1}H-NMR δ 7.75(s, 1H, 6'-H); 3.90(s, 3H, OCH_3); 3.87(s, 3H, OCH_3); 3.86(s, 3H, OCH_3); 3.04(dd, 6 Hz, 16.5 Hz, 1H, 5α-H); 2.65(dd, 12 Hz, 16.5 Hz, 1H, 5β-H); 0.9-2.20 (m, 20H, ring protons); 0.88(s, 3H, 18-H_3); 0.81(s, 3H, 19-H_3); MS *m e* 482(M^+)/2, 467/31, 450/82, 435/100, 286/15. Anal. Calcd for $C_{29}H_{38}O_6$ (482.62) C, 72.17; H, 7.44. Found: C, 71.88; H, 7.51.

2'α,3'β-bis(ethoxycarbonyl)-1'α-hydroxymethyl-androstano-[16α,17-d]-cyclohex-5'-ene (10): Synthesized in 51 % yield. ^{1}H-NMR δ 5.05(m, 1H, 6'-H); 4.46(t, $J_{AB}=J_{BA}$=8.8 Hz, 1H, $C\boldsymbol{H_2}OH$); 4.11(m, 4H, $OC\boldsymbol{H_2}CH_3$); 3.9(t, $J_{AB}=J_{BA}$=8.8 Hz, 1H, $C\boldsymbol{H_2}OH$); 3.25(m, 1H, 1'β-H); 3.05(dd, 8Hz, 12Hz, 1H, 2'β-H); 2.76(m, 1H, 16β-H); 2.25(m, 1H, 3'α-H); 1.54(m, 1H, 15α-H); 1.22(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 1.20(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 0.67-1.8(m, 22H, ring protons); 0.78(s, 3H, 18-$C\boldsymbol{H_3}$); 0.76(s, 3H, 19-$C\boldsymbol{H_3}$) MS *m e* 486(M^-)/4, 422/63, 394/45, 379/100, 257/50, 217/19, 171/24, 131/29, 91/43, 81/34, 29/24. IR (cm^{-1}) 3400(ν(OH)), 1720(ν(C=O)). Anal. Calcd for $C_{30}H_{46}O_5$(486.69): C, 74.04; H, 9.53. Found: C, 74.32; H, 9.39.

1'α-acethoxymethyl-2'α,3'β-bis(ethoxycarbonyl)-androstano-[16α,17-d]-cyclohex-5'-ene (11): Synthesized in 77 % yield. ^{1}H-NMR δ 5.08(dd, 3Hz, 3Hz, 1H, 6'-H); 4.13(m, 4H, $OC\boldsymbol{H_2}CH_3$); 3.90(d, 6Hz, 1H, $C\boldsymbol{H_2}COCH_3$); 3.91(d, 6Hz, 1H, $C\boldsymbol{H_2}COCH_3$); 3.08(dd, 6Hz, 11.25Hz, 1H, 2'-βH); 2.92(m, 1H, 1'β-H); 2.64(m, 1H, 16β-H); 2.41(t, $J_{AB}=J_{BA}$=11.25Hz, 1H, 3'α-H); 1.99(s, 3H, $COC\boldsymbol{H_3}$); 1.72(m, 1H, 15α-H); 1.5(m, 1H, 15β-H); 1.23(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 1.22(t, 7.1Hz, 3H, $OCH_2C\boldsymbol{H_3}$); 0.80-1.8(m, 20H, ring protons); 0.8(s, 3H, 18-H_3); 0.79(s, 3H, 19-H_3); ^{13}C-NMR δ: 175.38(CO), 173.16(CO), 170.58(CO), 155.08(C-17), 110.71(C-6'), 64.91(CH_2OCH_3), 60.57(OCH_2), 60.48(OCH_2), 55.18, 53.23, 47.05, 45.69, 44.05, 43.87, 40.17, 38.63, 36.41, 36.02, 35.49, 35.09, 31.67, 29.00, 28.88, 27.76, 27.15, 26.75, 20.87, 20.24, 17.12, 14.26(OCH_2CH_3), 14.09(OCH_2CH_3), 12.24; MS *m/e* 482(M^+-EtOH)/2, 467/1, 379/28, 349/25,

281/11, 217/10, 149/37, 145/12, 117/14, 91/36, 67/38, 43/100. IR (cm^{-1}) 1720(ν(C=O)), 1685(ν(C=O)), Anal. Calcd for $C_{32}H_{48}O_6$(528.73): C, 72.69; H, 9.15. Found: C, 72.80; H, 9.38.

2'α,3'β-bis(ethoxycarbonyl)-1'α-methoxycarbonyl-(3-keto-4-aza-4-methyl-androstano)-[16α,17-d]-cyclohex-5'-ene (13): Synthesized in 67 % yield. ^{1}H-NMR δ 5.18(m, 1H, 6'-H); 4.15(m, 4H, OC***H***$_2$CH$_3$); 3.62(s, 3H, OC***H***$_3$); 3.48(m, 1H, 1'β-H); 3.35(m, 1H, 2'β-H); 2.91(s, 3H, N-C***H***$_3$); 2.82(m, 1H, 16'β-H); 2.41(m, 2H, 2α-H, 2β-H); 2.3(m, 1H, 3'α-H); 1.50(m, 1H, 15α-H); 0.8-1.9(m, 15H, ring protons); 1.21(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.20(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 0.82(s, 3H, 18-H$_3$); 0.79(s, 3H, 19-H$_3$); MS *m/e* 482(M^+-EtOH -CH$_3$). Anal. Calcd for $C_{31}H_{45}O_7N$ (543.32): C, 68.47; H, 8.35; N, 2.58. Found: C, 68.32; H, 8.51, N, 2.62.

1'β,2'α,3'β,4'-tetrakis(ethoxycarbonyl)-(3-keto-4-aza-4-methyl-androstano)-[16α,17-e]-cyclohex-4'-ene (14): Synthesized in 48 % yield. ^{1}H-NMR δ 4.15(m, 8H, OC***H***$_2$CH$_3$); 4.05(m, 1H, 3'α-H); 3.44(dd, 7.5Hz, 11.2Hz, 1H, 2'β-H); 2.91(s, 3H, N-C***H***$_3$); 2.78(m, 1H, 16β-H); 2.46(t, J_{AB}=J_{BA}=11.2Hz, 1H, 1'α-H); 2.41(m, 2H, 2α-H, 2β-H); 1.50(m, 1H, 15α-H); 0.60-1.7(m, 15H, ring protons); 1.23(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.22(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.20(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.19(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.00(s, 3H, 18-H$_3$); 0.85(s, 3H, 19-H$_3$). MS *m/e* 629(M^+)/5, 584/29, 538/35, 526/15, 482/82, 480/10, 436/100, 84/92, 49/46. Anal. Calcd for $C_{35}H_{51}O_9N$ (629.79): C, 66.75; H, 8.16; N, 2.22. Found: C, 67.02; H, 8.01, N, 2.11.

2'α,3'β-bis(ethoxycarbonyl)-1'α-hydroxymethyl-(3-keto-4-aza-4-methyl-androstano)-[16α,17-d]-cyclohex-5'-ene (15): Synthesized in 55 % yield. ^{1}H-NMR δ 5.05(m, 1H, 6'-H); 4.46(t, J_{AB}=J_{BA}=8.8 Hz, 1H, C***H***$_2$OH); 4.11(m, 4H, OC***H***$_2$CH$_3$); 3.9(t, J_{AB}=J_{BA}=8.8 Hz, 1H, C***H***$_2$OH); 3.25(m, 1H, 1'β-H); 3.05(m, 1H, 2'β-H); 2.91(s, 3H, N-C***H***$_3$); 2.76(m, 1H, 16β-H); 2.41(m, 2H, 2α-H, 2β-H); 2.25(m, 1H, 3'α-H); 1.54(m, 1H, 15α-H); 1.22(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.20(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 0.67-1.8(m, 16H, ring protons); 0.78(s, 3H, 18-C***H***$_3$); 0.76(s, 3H, 19-C***H***$_3$). MS *m/e* 515(M^+)/2, 497/4, 500/4, 482/8, 269/30, 158/30, 112/40, 70/80, 41/100. IR (cm^{-1}) 3400(ν(OH)), 1720(ν(C=O)). Anal. Calcd for $C_{30}H_{45}NO_6$(515.69): C, 69.87; H, 8.80; N, 2.72 Found: C, 69.56; H, 8.92, N, 2.80.

1'α-acethoxymethyl-2'α,3'β-bis(ethoxycarbonyl)-(3-keto-4-aza-4-methyl-androstano)-[16α,17-d]-cyclohex-5'-ene (16): Synthesized in 71 % yield. ^{1}H-NMR δ 5.09(dd, 2.9Hz, 2.9Hz, 1H, 6'-H); 4.13(m, 4H, OC***H***$_2$CH$_3$); 3.90(d, 6.1Hz, 2H, C***H***$_2$COCH$_3$); 3.08(dd, 6Hz, 11.25Hz, 1H, 2'β-H); 2.92(m, 1H, 1'β-H); 2.91(s, 3H, N-C***H***$_3$); 2.64(m, 1H, 16β-H); 2.41(m, 2H, 2α-H, 2β-H); 2.41(m, 1H, 3'α-H); 1.99(s, 3H, COC***H***$_3$); 1.72(m, 1H, 15α-H); 1.5(m, 1H, 15β-H); 1.23(t, 7.1Hz, 3H, OCH$_2$C***H***$_3$); 1.22(t, 7.1Hz, 3H,

OCH_2CH_3); 0.80-1.8(m, 14H, ring protons); 0.8(s, 3H, 18-H_3); 0.79(s, 3H, 19-H_3); MS *m/e* 511(M^+-EtOH)/1, 312/33, 286/58, 158/20, 127/83, 124/44, 99/63, 70/50, 43/100. FAB-MS: 558 $(M+H)^+$. Anal. Calcd for $C_{32}H_{47}NO_7$(557.73): C, 68.91; H, 8.49; N, 2.51 Found: C, 69.98; H, 8.65, N, 2.63.

Acknowledgements: The authors thank the Hungarian National Science Foundation for financial support (OTKA T023525 and F023532) and the Ministry of Education for grant FKFP 0818 and 0803. The help of G. Czira (Gedeon Richter Ltd.) for FAB MS analysis is kindly acknowledged.

References and Notes

1. Pinder, A.R. Steroidal Alkaloids in *Rodd's Chemistry of Carbon Compounds;* Coffey, S. Ed.; Elsevier, Amsterdam, **1986**, Vol. IV, p 381.
2. (a) Lenz, G.R. *J. Org. Chem.* **1979**, *44*, 4299. (b) Levina, I.S.; Kulikova, L.E.; Kamernicki, A.V.; Elyanov, B.S.; Gonikberg, E.M. *Izv. Akad. Nauk., Ser. Khim.* **1992**, *7*, 1622.
3. (a) Skoda-Földes, R.; Jeges, Gy.; Kollár, L.; Horváth, J.; Tuba Z. *Tetrahedron Lett.* **1996**, *37*, 2085. (b) Skoda-Földes, R.; Jeges, Gy.; Kollár, L.; Horváth, J.; Tuba Z. *J. Org. Chem.* **1997**, *62*, 1326.
4. Stille, J.K. *Angew. Chem., Int.Ed. Engl.* **1986**, *25*, 508.
5. Heck, R.F. *Org. React.* **1982**, *27*, 345.
6. (a) Meyer, F.E.; Ang, K.H.; Steinig, A.G.; de Meijere A. *Synlett*, **1994**, 191. (b) Bräse, S.; de Meijere, A. *Angew. Chem.* **1995**, *107*, 2741.
7. Skoda-Földes, R.; Bodnár, M.; Kollár, L.; Horváth, J.; Tuba Z. *Steroids* **1998**, *63*, 93.
8. **6a** (1'α,2'β,3'β,4'-tetrakis(ethoxycarbonyl)-androstano-[16α,17-e]-cyclohex-4'-ene) could not be isolated as a pure substance, it was characterised by the NMR-spectrum of a **6a**+**6b** mixture. ^{1}H-NMR of **6a**: δ 4.15(m, 8H, OCH_2CH_3); 3.65(m, 1H, 3'β-H); 3.17(m 1H, 2'α-H); 2.9(m, 1H, 1'β-H); 2.3(m, 1H, 16β-H); 1.35(m, 1H, 15α-H); 0.60-1.7(m, 21H, ring protons); 1.24(t, 7.1Hz, 3H, OCH_2CH_3); 1.22(t, 7.1Hz, 3H, OCH_2CH_3); 1.22(t, 7.1Hz, 3H, OCH_2CH_3); 1.20(t, 7.1Hz, 3H, OCH_2CH_3); 0.98(s, 3H, 18-H_3); 0.78(s, 3H, 19-H_3).
9. MS spectra of the four isomers detected in the reaction of diene **2** with diethyl maleate: *i)* 514(M^+)/2, 468/20, 381/32, 283/28, 217/60, 191/28, 163/65, 105/100, 81/95. *ii)* 514(M^+)/2, 483/10, 469/20, 380/15, 283/45, 217/55, 149/58, 105/100. *iii)* 483(M^+-OMe)/22, 468/37, 425/70, 381/100, 335/45, 271/42, 191/60, 81/62. *iv)* 468(M^+-EtOH)/20, 425/50, 382/45, 335/55, 191/70, 81/100.
10. Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121.
11. Coulson, D.R. *Inorg. Synth.* **1970**, *13*, 121.
12. Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253.