Synthesis of Pentacyclic Steroids via Tandem Stille Coupling and Diels−Alder Reactions

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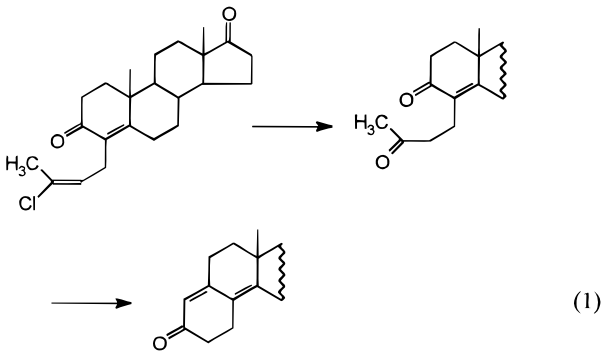
Tandem Stille coupling and Diels−Alder reaction of steroidal iodoalkenyl substrates [17-iodoandrosta-16-ene (**2**), 17-iodo-3-keto-4-methyl-4-azaandrosta-16-ene (**10**), and 17-iodo-3-keto-4-azaandrosta-16-ene (**11**)] were examined in the presence of vinyltributyltin, a dienophile (diethyl maleate, methyl acrylate, dimethyl acetylenedicarboxylate, diethyl fumarate, (−)-di[(1*R*)-menthyl] fumarate, maleic anhydride), and a palladium catalyst. The yields of novel pentacyclic steroids and the stereochemical outcome of the cycloaddition reaction were investigated under different reaction conditions. In some cases mixtures of isomers were formed, but with dimethyl acetylenedicarboxylate, diethyl fumarate, (−)-di[(1*R*)-menthyl] fumarate, and maleic anhydride the products could be produced in good yields with high stereoselectivity. The unequivocal assignment of stereoisomers was carried out by various NMR techniques including $^1H-^1H$ COSY and NOE experiments.

Introduction

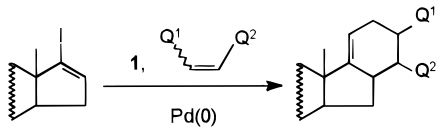
Pentacyclic steroids possessing a heterocycle annelated to the ring D are of high practical interest. A substituted tetrahydrofuran or pyrrolidine ring is a characteristic moiety of steroidal saponins or alkaloids, respectively.[1] Little is known on the synthesis of carbocycles attached to a steroidal skeleton. A cyclohexenone ring annelated to carbon-3 and carbon-4 of the androsta-4-ene-3,17-dione was synthesized by coupling and condensation reactions (eq 1).[2] Steroids were mainly used as dienophiles[3] in



(1)

Diels−Alder reactions resulting in pentacyclic products. The aim of our work was to develop a methodology for the synthesis of novel pentacyclic steroids possessing a carbocycle as E ring.

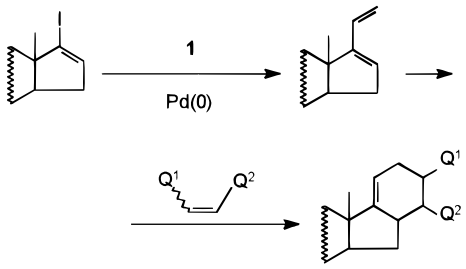
As we have shown previously,[4] Pd(0) catalysts can effectively be used for the coupling reaction of steroidal alkenyl iodides with organostannanes. The iodoalkenyl derivatives can be prepared easily from the corresponding ketone via the hydrazone[5] and give clean reactions compared to those of the steroidal triflates.[6] Furthermore, the unsaturated side chain formed during the coupling enables the introduction of new functionalities in the steroidal skeleton.[4a,7] Recently we have found[8] that various pentacyclic steroids can be synthesized by a one-pot reaction of a steroidal alkenyl iodide, vinyltributyltin (**1**), and a dienophile in the presence of a homogeneous catalyst containing palladium (eq 2). In this reaction the



(2)

diene formed by Stille coupling[9] undergoes a Diels−Alder reaction in the presence of an olefin or acetylene possessing electron-withdrawing groups.

Although this method was applied successfully for a number of dienophiles, in some cases their presence slowed down or completely stopped the vinylation step. Here the desired products could be produced in good yields in a two-step synthesis with or without isolation of the diene (eq 3).



(3)

Here we report on the scope and limitations of the one-pot synthesis of pentacyclic steroids via tandem Stille

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(4) (a) Skoda-Földes, R.; Kollár, L.; Heil, B.; Gálik, Gy.; Tuba, Z.; Arcadi, A. *Tetrahedron: Asymmetry* **1991**, *2*, 633−634. (b) Skoda-Földes, R.; Csákai, Z.; Kollár, L.; Horváth, J.; Tuba, Z. *Steroids* **1995**, *60*, 786.

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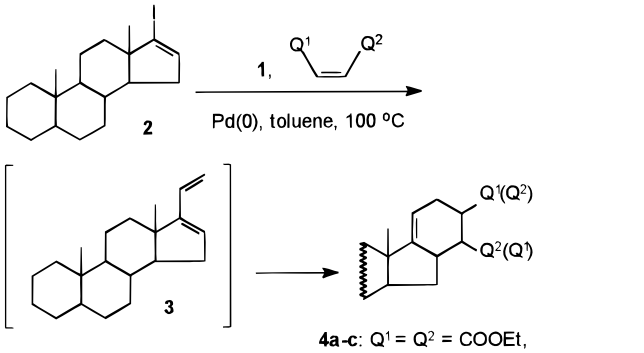
coupling and Diels−Alder reaction, as well as the effects of varying the reaction conditions.

Results and Discussion

Reaction Conditions. The main goal of our recent work was to find optimal reaction conditions for various substrates and dienophiles in the one-pot reaction. Three different homogeneous catalytic systems containing palladium were tested in the vinylation of steroidal alkenyl iodides[4b] and were found to be active also in the tandem reaction. $Pd(PPh_3)_4$ proved to be superior to other catalysts examined in the one-pot reaction of 17-iodoandrosta-16-ene (**2**) with vinyltributyltin (**1**) and diethyl maleate or methyl acrylate (eq 4, Table 1, entries 1−8).



4a-c: $Q^1 = Q^2$ = COOEt, three stereoisomers

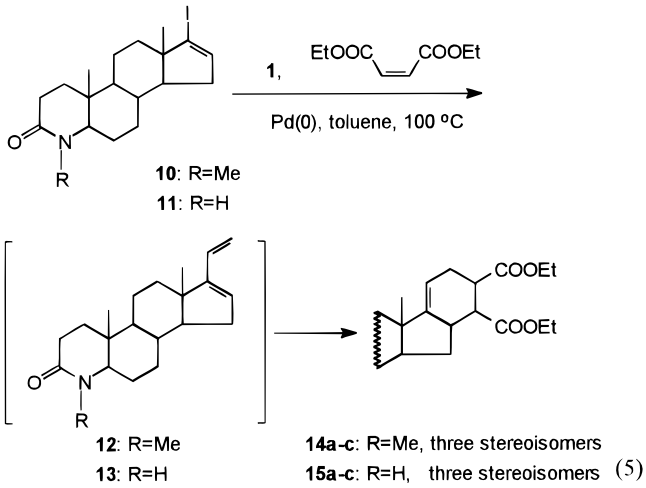
5a-e: Q^1 = H, Q^2 = COOMe, five stereoisomers (4)

However, different catalytic activity of these systems are surprising because the palladium-catalyzed Stille reaction of **2** with vinyltributyltin (without dienophile!) does not show great differences in the activities of the same catalysts.[4b] The explanation of this may be as follows. The first step of the one-pot reaction is a Stille coupling that results in the formation of the steroidal diene **3**. The common mechanism of a transition metal-catalyzed cross-coupling reaction between organometallic reagents and electrophiles involves sequential oxidative addition, transmetalation, and reductive elimination. It is known that the oxidative addition of iodobenzene to the Pd(0) species formed "in situ" from $Pd(dba)_2 + 4PPh_3$ is less facile than to $Pd(PPh_3)_4$.[10] Also, as $AsPh_3$ has lower donor strength for soft metal centers,[11] the palladium becomes less electron rich, which hinders oxidative addition. But as transmetalation was usually found to be the rate-determining step of vinylation,[12] different rates of oxidative addition to the various precursors may have little effect on the yield of the diene in the Stille coupling (without dienophile). However, in the one-pot reaction under the conditions given in Table 1, the coordination of the dienophile to palladium may slow down the oxidative addition which in this case may become the rate-determining step and so cause differences in the activity of the catalysts.

While the presence of diethyl maleate in the reaction mixture only slightly affected the rate of the vinylation step[13] (entry 4), methyl acrylate considerably decreased the yield of the diene (entry 8), presumably due to the facile coordination of the dienophile to the palladium catalyst. Although the yield of the Diels−Alder product was moderate using 1 equiv of the dienophile, an increase in the amount of diethyl maleate (entries 2 and 5) or methyl acrylate (entry 7) greatly enhanced the rate of the cycloaddition. The nature of the catalyst did not significantly affect the yield of this second step.

The conditions optimized above were found to be effective also for other dienophiles. However, pentacyclic steroids were obtained in good yields even in the presence of only 1 equiv of dimethyl acetylenedicarboxylate (entry 9), diethyl fumarate (entry 10) and (−)-di[(1*R*)-menthyl] fumarate (entry 11). In the case of dimethyl acetylenedicarboxylate the excellent yield can be explained by the fact that this compound is a better dienophile than diethyl maleate or methyl acrylate. At the same time this compound only slightly affected the Stille coupling due to its less coordinative ability to Pd(0) compared to that of methyl acrylate. Esters of fumaric acid were found not to decrease the rate of the vinylation step, possibly because these dienophiles coordinate less readily to the palladium(0) complex. These compounds were also found very reactive in the cycloaddition compared to diethyl maleate. This great difference can probably be explained by different steric hindrance in the transition states (see below).

The other two steroidal substrates possessing lactam functionality in ring A (**10** and **11**, eq 5) were found to be less reactive in the one-pot reaction (Table 2, entries 2 and 3). The same order of reactivity was observed



14a-c: R=Me, three stereoisomers

15a-c: R=H, three stereoisomers (5)

before during vinylation.[4b] In order to compare the reactivity of the different skeletons in the Diels−Alder reaction, the three cycloaddition products were also synthesized according to procedure B from the dienes **3**, **12**, and **13** (entries 4−6). Here the same order of reactivity was observed, so both the different rates of the vinylation step and those of the consecutive cycloaddition cause the different reactivities in the one-pot reaction of the various steroidal alkenyl iodides.

Stereoselectivity of Cycloaddition. With diethyl maleate, according to GC−MS and ^{1}H-NMR investigations, three isomeric products (**4a**−**c**) were formed by both routes (procedures A and B) examined[14] (Table 3). There were no large differences in the selectivities of products between procedures A and B (entries 1 and 2),

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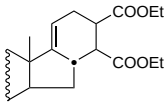
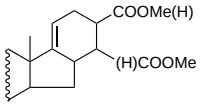
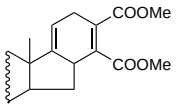
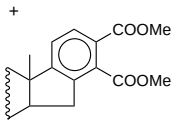
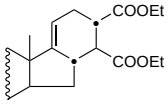
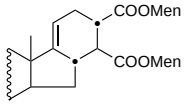
(12) Farina, V.; Krishnan B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(13) During the vinylation of **2**, 95% of **3** was produced with $Pd(PPh_3)_4$ in 4.5 h under the same conditions.

Table 1. Reaction of 17-Iodoandrosta-16-ene with Vinyltributyltin and Various Dienophiles in the Presence of Pd(0) Catalysts[a]

entry	dienophile	catalyst	reaction time (h)	dienophile/ substrate ratio	main product	conv (%)	product distribution (%)[b] **3**	product distribution (%)[b] Diels−Alder product
1	diethyl maleate	$Pd_2(dba)_3 + 8PPh_3$	4.5	1	 **4a**	76	76	24
2		$Pd_2(dba)_3 + 8PPh_3$	4.5	2		75	45	55
3		$Pd_2(dba)_3 + 8AsPh_3$	4.5	1		55	71	29
4		$Pd(PPh_3)_4$	4.5	1		85	80	20
5		$Pd(PPh_3)_4$	4.5	2		84	64	36
6	methyl acrylate	$Pd_2(dba)_3 + 8PPh_3$	4.5	1	 **5**	49	80	16[c]
7		$Pd_2(dba)_3 + 8PPh_3$	4.5	2		53	53	38[c]
8		$Pd(PPh_3)_4$	4.5	1		64	88	10[c]
9	dimethyl acetylenedicarboxylate	$Pd(PPh_3)_4$	4.5	1	 **6** +  **7**	87	29	71
10	diethyl fumarate	$Pd(PPh_3)_4$	4.5	1	 **8a**	99	2	98
11	dimenthyl fumarate	$Pd(PPh_3)_4$	4.5	1	 **9a**	95	5	95

[a] Reactions of 17-iodoandrosta-16-ene (1 mmol), vinyltributyltin (1.1 mmol), and the dienophile (quantity as indicated in the table) were carried out in 10 mL of toluene at 100 °C, steroid/Pd = 50. [b] Determined by GC. [c] Formation of **18** as byproduct was also observed.

so here the stereoselectivity of the cycloaddition step seemed not to be greatly influenced by the presence of palladium. The same product distribution was found in the cases of the other two steroidal substrates (**10** and **11**).[15]

Selective cycloaddition reactions were observed using esters of fumaric acid as dienophiles (entries 3−5).

(14) The main product could not be isolated as a pure substance, but as a 63:23:14 mixture of the three isomers. Stereochemistry of the two major isomers was determined by $^1H-^1H$ COSY and NOESY experiments (see below). Selected spectroscopic data for the two major isomers are as follows: **1′*β*,2′*β*-Bis(ethoxycarbonyl)androstano-[16α,17-*c*]cyclohex-4′-ene (4a)**: ^{1}H-NMR δ 5.1 (m, 1H), 4.12 (m, 4H), 3.22 (m, 1H), 2.85 (m, 1H), 2.52 (m, 1H), 2.29 (m, 1H), 2.25 (m, 1H), 1.1−1.75 (m, 22H), 1.2 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 0.8 (s, 3H), 0.77 (s, 3H); MS *m/e* 456 (2), 441 (38), 382 (39), 367 (58), 105 (45), 91 (96), 67 (84), 55 (100). **1′α,2′α-Bis(ethoxycarbonyl)androstano[16α,17-*c*]cyclohex-4′-ene (4b)**: ^{1}H-NMR δ 5.23 (m, 1H), 4.12 (m, 4H), 3.28 (m, 1H), 2.92 (m, 1H), 2.76 (m, 1H), 2.55 (m, 1H), 2.35 (m, 1H), 1.1−1.75 (m, 22H), 1.2 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 079 (s, 3H), 0.77 (s, 3H); MS *m/e* 411 (15), 410 (32), 395 (40), 382 (21), 367 (100), 105 (40), 91 (76), 67 (79), 55 (92). For the minor component **(4c)**: ^{1}H-NMR δ 5.31 (m, 1H, 5′-H); MS *m/e* 456 (1), 382 (23), 256 (73), 131 (34), 105 (40), 91 (79), 67 (93), 55 (100).

Table 2. Reactivity of Various Iodovinyl Steroids in the One-Pot Reaction (Procedure A) and That of Steroidal Dienes in the Diels−Alder Reaction (Procedure B) Using Diethyl Maleate as Dienophile

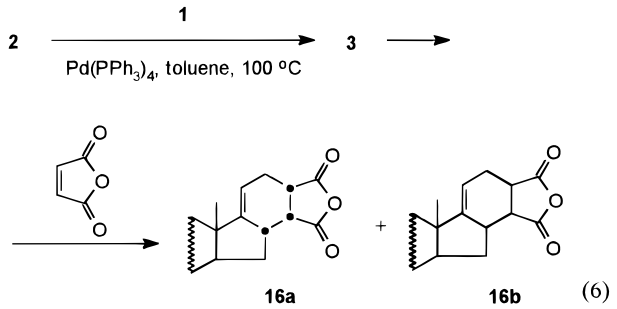
entry	substrate	procedure[a]	reaction time (h)	yield of Diels−Alder products (%)[b]
1	**2**	A	22	83 (**4a−c**)
2	**10**	A	22	46 (**14a−c**)
3	**11**	A	22	29 (**15a−c**)
4	**3**	B	10	70 (**4a−c**)
5	**12**	B	10	51 (**14a−c**)
6	**13**	B	10	10 (**15a−c**)

[a] Procedure A: Reaction of 17-iodoalkenyl substrates (**2**, **10**, and **11**, 1 mmol) with vinyltributyltin (1.1 mmol) and diethyl maleate (1 mmol) was carried out in the presence of $Pd(PPh_3)_4$ (0.02 mmol) in 10 mL of toluene at 100 °C. Procedure B: Reaction of steroidal dienes (**3**, **12**, and **13**, 1 mmol) with diethyl maleate (1 mmol) was carried out in 10 mL of toluene at 100 °C. [b] Determined by GC. Compound numbers in parentheses.

Diels−Alder products **8a** and **9a** were formed with 86 and 85% selectivity with diethyl[16] and (−)-di[(1*R*)-menthyl] fumarate,[17] respectively. Following procedure B slightly better results could even be achieved. The

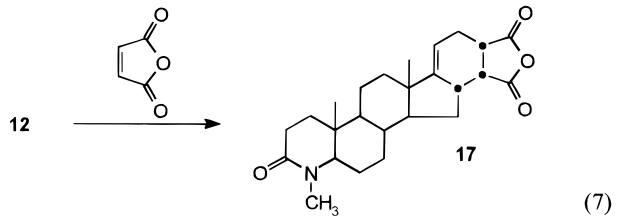
stereoselectivity of cycloaddition seems not to be influenced by the chiral moiety of the dienophile.

Selective formation of **16a** was observed in the Diels−Alder reaction of **3** with maleic anhydride. Although this compound could not be produced by a one-pot reaction, it can be synthesized from **2** in two steps, without isolation of the diene (procedure C, eq 6). In this case,



(6)

palladium was present during the cycloaddition, which was found to alter the stereoselectivity of this step. Instead of the selective formation of **16a**, two isomeric derivatives (**16a** and **16b**) were produced in 38 and 62% yield, respectively. In the reaction of **12** with maleic anhydride, **17** could be synthesized selectively (eq 7).



(7)

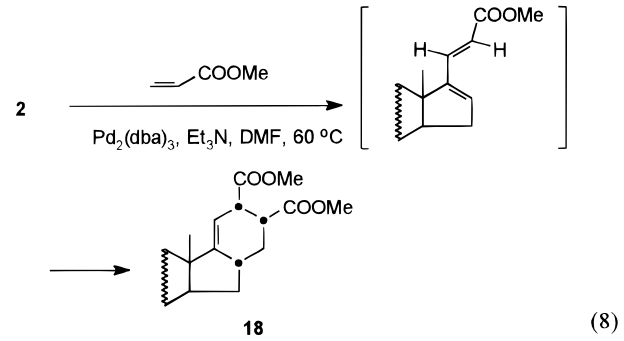
In all of the reactions mentioned above, only the formation of the Diels−Alder products was observed; no side reaction took place. From that point of view, reactions with methyl acrylate or dimethyl acetylenedicarboxylate were different.

The formation of five isomeric Diels−Alder products of pregna-16,20-diene and methyl acrylate (**5a**−**e**, eq 4)[18] and a byproduct (**18**) was observed in the one-pot reaction using methyl acrylate as dienophile (under standard reaction conditions). Compound **18** is produced in 20% selectivity beside 80% of the five Diels−Alder products. A possible explanation for the formation of this pentacyclic derivative is as follows. A Heck product (21-(methoxycarbonyl)pregna-16,20-diene)[19] was formed in the reaction of **2** and methyl acrylate (eq 8), the latter

Table 3. Selectivity of Cycloaddition in the Presence and in the Absence of a Palladium Catalyst

entry	dienophile	procedure[a]	ratio of isomers
1	diethyl maleate	A	53:27:20[b]
2		B	53:29:18[b]
3	diethyl fumarate	A	86:7:7[c]
4		B	93:5:2[c]
5	(−)-di[(1*R*)-menthyl] fumarate	A	85:15[b]
6	maleic anhydride	B	97:3[c]
7		C	38:62[c]

[a] Procedure A: Reaction of 17-iodoandrosta-16-ene (**2**, 1 mmol) with vinyltributyltin (1.1 mmol) and a dienophile (1 mmol) was carried out in the presence of $Pd(PPh_3)_4$ (0.02 mmol) in 10 mL of toluene at 100 °C for 10 h. Procedure B: Reaction of pregna-16,20-diene (**3**, 1 mmol) with a dienophile (1 mmol) was carried out in 10 mL of toluene at 100 °C for 2 h. Procedure C: Reaction of 17-iodoandrosta-16-ene (**2**, 1 mmol) with vinyltributyltin (1.1 mmol) was carried out in the presence of $Pd(PPh_3)_4$ (0.02 mmol) in 10 mL of toluene at 100 °C for 4.5 h; 1 mmol of maleic anhydride was then added, and the reaction mixture was heated at 100 °C for 2 h. [b] Determined by ^{1}H-NMR. [c] Determined by GC.



(8)

reacting by its trans β-olefinic hydrogen. The second molecule of methyl acrylate reacted with the Heck intermediate with high regioselectivity resulting mainly in **18** possessing the two ester functionalities in vicinal position.

Compound **18** was synthesized as main product with 90% selectivity and in good yield[20] in the reaction of **2** with a large excess of methyl acrylate in the presence of triethylamine and a palladium catalyst in DMF.

Great differences in the selectivities of procedures A and B were observed with dimethyl acetylenedicarboxylate as the dienophile. In procedure B **6** was produced selectively, but in the one-pot reaction aromatization of **6** took place and **7** was formed in 46%, presumably due to the presence of the palladium catalyst.[21,22] This is supported by the fact that **6** can be partially converted into **7** using $Pd(PPh_3)_4$.

(15) Selected spectroscopic data for compounds formed in the one-pot reaction as main products using **10** and **11** as starting material are as follows: **1′*β*,2′*β*-Bis(ethoxycarbonyl)(3-keto-4-methyl-4-azaandrostano)[16α,17-*c*]cyclohex-4′-ene (14a)**: ^{1}H-NMR δ 5.15 (m, 1H), 4.02−4.24 (m, 4H), 3.28 (m, 1H), 3.00 (dd, J = 5.1 Hz, 12.3 Hz), 2.92 (s, 3H), 2.84 (m, 1H), 2.58 (m, 1H), 2.44 (m, 2H), 2.34 (m, 1H), 2.31 (m, 1H), 1.10−2.10 (m, 15H), 1.23 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 0.85 (s, 3H), 0.8 (s, 3H); MS *m/e* 485 (4), 470 (15), 411 (65), 396 (67), 338 (62), 124 (100), 91 (90), 70 (55), 29 (35). **1′*β*,2′*β*-Bis(ethoxycarbonyl)-3-keto-4-azaandrostano)[16α,17-*c*]cyclohex-4′-ene (15a)**: ^{1}H-NMR δ 5.54 (brs, 1H), 5.15 (m, 1H), 4.02−4.24 (m, 4H), 3.28 (m, 1H), 3.00 (dd, J = 5.2 Hz, 12.5 Hz), 2.90 (m, 1H), 2.58 (m, 1H), 2.39 (m, 2H), 2.32 (m, 1H), 2.29 (m, 1H), 1.10−2.00 (m, 15H), 1.23 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 0.90 (s, 3H), 0.82 (s, 3H).

(16) For the spectral data of the main component (**8a**) see Experimental Section. The minor, isomeric products were detected by ^{1}H-NMR and GC−MS: (**8b**) ^{1}H-NMR δ 5.15 (m, 1H); MS *m/e* 410 (20), 367 (100), 91 (70), 67 (65), 55 (82); (**8c**) ^{1}H-NMR δ 5.28 (m, 1H); MS *m/e* 410 (18), 367 (55), 91 (93), 67 (82), 55 (100).

(17) For the spectral data of the main component (**9a**) see Experimental Section. The minor, isomeric product (**9b**) was detected by ^{1}H-NMR: δ 5.28 (m, 1H), 4.72−4.84 (m, 2H).

(18) The five isomers were detected by GC−MS and gave almost identical mass spectra: (**5a**) MS *m/e* 370 (17), 355 (25), 93 (100), 67 (71), 55 (83); (**5b**) MS *m/e* 355 (24), 217 (24), 145 (33), 121 (31), 91 (79), 67 (89), 55 (100); (**5c**) MS *m/e* 370 (3), 355 (89), 311 (55), 145 (30), 131 (33), 91 (68), 67 (77), 55 (100); (**5d**) MS *m/e* 370 (7), 355 (100), 145 (33), 131 (38), 91 (64), 67 (69), 55 (85); (**5e**) MS *m/e* 370 (1), 355 (100), 145 (31), 131 (29), 91 (59), 67 (60), 55 (81).

(19) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985; pp 214−222.

(20) For the spectral data of the main component (**18**) see Experimental Section. The minor, isomeric product was detected by GC−MS: MS *m/e* 428 (1), 413 (100), 396 (28), 381 (36), 369 (50), 353 (77), 91 (72), 55 (65).

(21) This compound was detected by GC−MS: MS *m/e* 342 (12), 327 (25), 178 (38), 91 (61), 67 (78), 55 (100).

(22) Six-membered alicyclic rings can be aromatized e.g. in the presence of hydrogenation catalysts like platinum, palladium, and nickel. For a review, see: Rylander, P. N. *Organic Synthesis with Noble Metal Catalysts*; Academic Press: New York, 1973; pp 1−59.

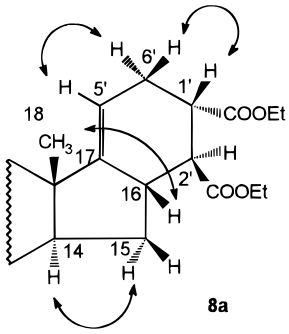


Figure 1. NOE effects observed during the NMR investigation of **8**.

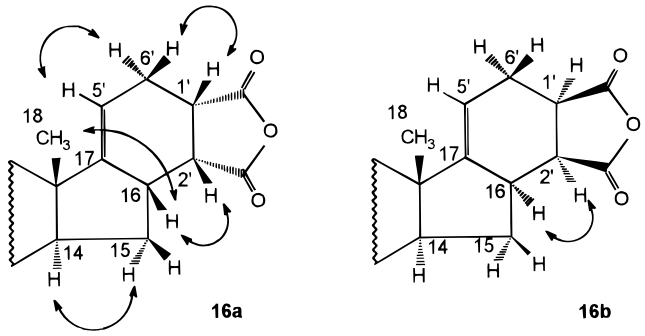


Figure 2. NOE effects observed during the NMR investigation of the two isomeric products **16a** and **16b**.

Determination of the Structure of Stereoisomers of the Cycloaddition Products. Exact structures of the main products were determined by NMR (^{1}H−^{1}H COSY and NOE experiments) in almost every case after isolation.

By using diethyl maleate as dienophile, the main product (**4a**) could not be isolated as a pure substance, but as a 63:23:14 mixture of the three isomers **4a**−**c**. According to the NOESY experiment, saturation of the 16-H signal (2.85 ppm) of **4a** resulted in the increase in the signals at 1.79 ppm (15β-H) and at 0.80 ppm (18-CH_3). Also, the saturation of the 16-H signal (2.92 ppm) of **4b** caused an increase in the signals at 3.28 ppm (2′-H), 2.76 ppm (1′-H), 1.52 ppm (15β-H), and 0.79 ppm (18-CH_3). That means that both of the abovementioned components have the 16-H protons in the β position and **4b** is the isomer which has 1′β and 2′β protons. Supposing a *syn* addition, the main component (**4a**) is the isomer with 1′α and 2′α protons. This is also supported by the fact that irradiation of 1′-H of **4a** (3.22 ppm) and **4b** (2.76 ppm) resulted in an increase in the multiplets of 6′α-H (2.52 ppm) and 6′β-H (2.35 ppm), respectively. So during the Diels−Alder reaction of diethyl maleate, the dienophile approaches the steroid mainly from the most favorable α-side, but the formation of the major isomer occurs through an *exo* transition state.

The new steroidal derivative (**6**) with a cyclohexadiene E ring, prepared in the reaction of **2** and dimethyl acetylenedicarboxylate, proved to possess 16-H in the β position: saturation of the ^{1}H-NMR signal at 3.46 ppm (16-H) resulted in an increase in the intensity of the 18-CH_3 singlet at 0.84 ppm. The formation of this 16β-H product also supports the fact that in the transition state the dienophile is favorably disposed on the α-side of the steroidal skeleton. The presence of an aromatic E ring in the other product (**7**) obtained with dimethyl acetylenedicarboxylate using procedure A is supported by the appearance of the aromatic proton doublets at 7.17 and 7.77 ppm.

The multiplets assigned to the protons of the steroidal skeletons were identical in the ^{1}H-NMR spectra of the main products obtained using diethyl (**8a**) or (−)-di[(1*R*)-menthyl] fumarate (**9a**). The stereochemistry of these compounds was clarified by NOE experiments (Figure 1). If the resonance of 16-H at 2.67 ppm is saturated, the intensity of 1′-H at 2.9 ppm and that of 18-CH_3 at 0.8 ppm increases. In the same time, no effect was observed at 2.29 ppm (2′-H). That means that the position of the protons at the new stereogenic centers are 16β, 1′β, and 2′α.

Characterization of **16a** has been reported elsewhere.[8] Although the other isomer (**16b**) could not be isolated as a pure substance, its structure was proved by the NMR investigation of the mixture of **16a** and **16b** (Figure 2). Only small differences of shifts of corresponding protons of the two compounds were observed and the multiplicity of the corresponding signals were found to be identical due to the almost identical coupling constants. That means that the relative positions of the protons are the same in both products. As **16a** was proved to have 16β, 1′β, and 2′β protons, this requirement is only fulfilled if all of 16, 1′, and 2′ hydrogens of **16b** are in α-positions. This is also supported by the results of NOE experiments. Irradiation of the 16-H signal of **16b** at 2.51 ppm resulted in an increase in the intensity of the multiplet at 3.46 ppm (2′-H), so the position of these protons are identical. With maleic anhydride only a *syn* addition can take place, which means that 1′-H and 2′-H must also have the same position. According to these considerations 16-H, 1′-H, and 2′-H have all α- or all β-positions. The compound with 16β, 1′β, and 2′β hydrogens is **16a**, so **16b** has 16α, 1′α, and 2′α protons. Compound **16b** can be formed through an *endo* transition state, as **16a**, but by the dienophile approaching the steroid from the sterically unfavorable β-side. The explanation of this may be as follows. The steroidal diene coordinates to the palladium with the metal disposed on the sterically favorable α-side of the skeleton. In this case the dienophile can approach the diene only from the β-side, which leads to the formation of **16b**.

At the same time **16a** can be partially converted into **16b** on heating in toluene at 100 °C in the presence of $Pd(PPh_3)_4$. However, no conversion could be observed on prolonged heating of **16a** in the absence of a palladium catalyst. This isomerization can take place through a tandem retrograde Diels−Alder reaction−Diels−Alder reaction supposing that cycloreversion of **16a** is faster than that of **16b**.

Both poor reactivity and selectivity of diethyl maleate were surprising but can be explained by steric factors. As it was observed before, the most favorable approach of the dienophile to the diene is from the α-side of the steroidal skeleton, because of β-disposition of the 18-methyl group. In the case of *cis*-substituted dienophiles the most probable reaction usually takes place via an *endo* transition state, which can be explained by a favorable secondary overlap between the orbitals of carbonyl carbons of the dienophile and internal carbons of the diene. In this transition state the ethoxy group of

(23) Dehydrogenation of alkanes and alkenes via oxidative addition can take place in the presence of transition metal complexes. See: Crabtree, R. H.; Habib, A. Oxydation by Chemical Methods. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1993; Vol. 7, pp 4−7.

diethyl maleate gets too close to the D ring of the skeleton. Because of the steric hindrance, the rate of the cycloaddition is slower. Furthermore, in the usually less favorable *exo* transition state the ethoxy groups point away from the D ring, so there is no steric hindrance between the diene and the dienophile and the major isomer can be formed through this transition state. There is no such effect with maleic anhydride, probably because of the planarity and rigidity of this molecule. The main product using fumarate esters as dienophiles is formed through the approach of the dienophile from the α-side of the steroidal skeleton, with the ethoxy group pointing away from D ring. There is much less steric hindrance in this transition state, because there is no interaction between the ethoxy group and the skeleton, so the reaction rate is higher and selectivity is also better than those using diethyl maleate.

Experimental Section

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 $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone) were prepared as described previously.[24,25]

Dienophile Reagents. Maleic anhydride and dimethyl acetylenedicarboxylate were Aldrich products; diethyl maleate, diethyl fumarate, and (−)-di[(1*R*)-menthyl] fumarate were purchased from Fluka.

General Procedure for the Synthesis of the Cycloaddition Products. Procedure A. Palladium catalyst (0.02 mmol) and the steroid possessing 17-iodo 16-ene functionality (1 mmol) 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 toluene. Vinyltributyltin (1.1 mmol) and 1 mmol of the dienophile were added by means of a hypodermic syringe through the septum inlet (during the synthesis of **9a** (−)-di[(1*R*)-menthyl] fumarate was added previously to the flask together with the steroidal substrate and the catalyst). The mixture was stirred at 100 °C. The reaction was followed by GC. After completion of the reaction an aqueous solution of 1.5 mmol KF was added, and the mixture was stirred overnight. The organic layer was separated and dried over Na_2SO_4. The product was purified after removal of the solvent by column chromatography on silica gel with hexane/ethyl acetate 60/40 (**4a**, **6**, **7**, **8a**, and **9a**) and hexane/ethyl acetate 40/60 (**14a**, **15a**, **16a**, and **17**).

Procedure B. Palladium catalyst (0.02 mmol) and the steroid (1 mmol) 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 toluene. Vinyltributyltin (1.1 mmol) was added by means of a hypodermic syringe through the septum inlet. The mixture was stirred at 100 °C. The reaction was followed by GC. After completion of the vinylation an aqueous solution of 1.5 mmol KF was added, and the mixture was stirred overnight. The organic layer was separated and dried over Na_2SO_4. The product was purified after removal of the solvent by recrystallization from methanol (**2**) or hexane (**12** and **13**).

Then 1 equiv of the dienophile was reacted with the isolated diene in toluene until the cycloaddition reaction was completed. The final workup of the products was the same as indicated for procedure A.

Procedure C. The vinylation was carried out as in procedure B. After completion of the vinylation 1 mmol of the dienophile was added under argon without isolation of the diene and the mixture was stirred further until the cycloaddition was completed. The final workup of the products was the same as indicated for procedure A.

The compounds prepared by the above procedures are as follows.

1′,2′-Bis(methoxycarbonyl)androstano[16α,17-*c*]cyclohexa-1′,4′-diene (6) was synthesized according to procedure B in 96% yield: ^{1}H-NMR δ 5.3 (m, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.46 (m, 1H), 3.14 (ddd, J = 6 Hz, 12 Hz, 21 Hz, 1H), 2.81 (ddd, J = 2 Hz, 12 Hz, 20 Hz, 1H), 0.9−1.9 (m, 22H), 0.84 (s, 3H), 0.79 (s, 3H); ^{13}C-NMR δ 169.35, 167.40, 150.48, 141.74, 129.99, 108.42, 55.02, 52.64, 52.11, 51.99, 46.95, 43.15, 38.56, 37.48, 36.34, 35.27, 34.92, 31.54, 29.00, 28.96, 28.81, 27.84, 26.70, 22.10, 20.19, 16.54, 12.20; MS *m/e* 426 (14), 411 (11), 394 (24), 379 (100); IR (cm^{-1}) 1720 (ν(C=O)), 1620 (ν-(C=C)). Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.18; H, 8.87.

1′,2′-Dimethylandrostano[16,17-*c*]phthalate (7) was synthesized according to procedure A in 40% yield: ^{1}H-NMR δ 7.77 (d, J = 7.9 Hz), 7.17 (d, J = 7.9 Hz), 3.87 (s, 3H), 3.92 (s, 3H), 0.9−1.9 (m, 22H), 0.90 (s, 3H), 0.79 (s, 3H); MS *m/e* 424 (4), 409 (22), 392 (24), 377 (54), 213 (23), 128 (17), 109 (13), 67 (71), 55 (100). Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.29; H, 8.46.

1′α,2′β-Bis(ethoxycarbonyl)androstano[16α,17-*c*]cyclohex-4′-ene (8a) was synthesized by procedure B in 91% yield: ^{1}H-NMR δ 5.11 (m, 1H), 4.11 (m, 4H), 2.9 (qd, $J_{AB} = J_{BA}$ = 12.2 Hz, 6.5 Hz, 1H), 2.67 (m, 1H), 2.48 (m, 1H), 2.29 (t, $J_{AB} = J_{BA}$ = 12.2 Hz, 1H), 2.1 (m, 1H), 1.1−1.75 (m, 22H), 1.22 (t, J = 7.1 Hz, 3H), 1.2 (t, J = 7.1 Hz, 3H), 0.76 (s, 3H), 0.75 (s, 3H); ^{13}C-NMR δ 175.28, 174.66, 152.44, 109.53, 60.46, 60.33, 55.25, 52.76, 47.54, 47.08, 43.74, 43.18, 39.14, 38.67, 36.40, 35.47, 35.07, 31.66, 29.01, 28.91, 28.17, 28.04, 26.76, 22.15, 20.29, 17.23, 14.24, 14.11, 12.21; MS *m/e* 410 (15), 382 (26), 367 (88), 143 (55), 105 (56), 91 (74), 67 (100), 55 (72). Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.36; H, 9.83.

1′α,2′β-Bis((1″*R*)-menthoxycarbonyl)androstano[16α,-17-*c*]cyclohex-4′-ene (9a) was synthesized by procedure A in 81% yield: ^{1}H-NMR δ 5.11 (m, 1H), 4.64 (td, J = 10 Hz, 3.7 Hz, 1H), 4.6 (td, J = 10 Hz, 3.7 Hz, 1H), 2.94 (qd, $J_{AB} = J_{BA}$ = 12 Hz, 6.75 Hz, 1H), 2.68 (m, 1H), 2.53 (m, 1H), 2.31 (t, $J_{AB} = J_{BA}$ = 12 Hz, 1H), 2.1 (m, 1H), 0.67−1.75 (m, 58H), 0.87 (s, 3H), 0.78 (s, 3H); ^{13}C-NMR δ 175.21, 174.43, 152.64, 109.54, 74.56, 74.46, 52.77, 55.28, 47.08, 47.71, 46.94, 46.77, 43.8, 43.38, 40.43; 40.76, 39.19, 38.69, 36.41, 35.43, 35.17, 34.32, 34.34, 31.52, 31.41, 31.41, 29.04, 29.00, 28.51, 28.11, 26.79, 26.01, 25.75, 23.22, 22.90, 22.19, 22.07, 22.04, 20.83, 20.95, 20.36, 17.30, 15.68, 16.00, 12.24; IR (cm^{-1}) 1720 (ν(C=O)), 1260 (ν(C−O−C)). Anal. Calcd for $C_{45}H_{72}O_4$: C, 79.82; H, 10.73. Found: C, 79.70; H, 10.64.

1′α,2′α-(Oxydicarbonyl)androstano[16α,17-*c*]cyclohex-4′-ene (16a) was synthesized according to procedure B in 98% yield: ^{1}H-NMR δ 5.5 (m, 1H), 3.42 (m, 1H), 3.38 (m, 1H), 2.74 (ddd, J = 2.3 Hz, 6.3 Hz, 15 Hz, 1H), 2.67 (m, 1H), 2.37 (dd, J = 6 Hz, 13.5 Hz, 1H), 2.15 (m, 1H), 0.9−1.8 (m, 21H), 0.78 (s, 3H), 0.76 (s, 3H); ^{13}C-NMR δ 174.51, 172.16, 157.43, 111.74, 54.67, 54.08, 46.79, 43.30, 42.75, 41.07, 38.52, 36.31, 35.64, 35.20, 34.92, 31.57, 28.97, 28.82, 26.70, 26.37, 23.79, 22.11, 20.27, 18.99, 12.11; IR (cm^{-1}) 1760 (ν(C=O)), 1820 (ν(C=O)); MS *m/e* 382 (11), 367 (7), 354 (13), 217 (100), 161 (12), 135 (28), 91 (34), 67 (19), 55 (30), 41 (19), 28 (36). Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.57; H, 8.84.

1′β,2′β-(Oxydicarbonyl)androstano[16β,17-*c*]cyclohex-4′-ene (16b) was isolated by recrystallization of the crude product synthesized by procedure C from hexane as a 35/65 mixture of **16a** and **16b**: ^{1}H-NMR δ 5.53 (m, 1H), 3.46 (m, 1H), 3.41 (m, 1H), 2.76 (ddd, J = 3.7 Hz, 6.6 Hz, 15.5 Hz, 1H), 2.51 (m, 1H), 2.15 (m, 1H), 0.9−1.8 (m, 22H), 0.8 (s, 3H), 0.67 (s, 3H); MS *m/e* 382 (14), 367 (76), 354 (6), 295 (21), 257 (19), 242 (17), 217 (100), 163 (24), 135 (37), 91 (66), 67 (31), 55 (31), 41 (25).

1′α,2′α-(Oxydicarbonyl-3-keto-4-methyl-4-azaandrostano)[16α,17-*c*]cyclohex-4′-ene (17) was synthesized by procedure B in 96% yield: ^{1}H-NMR δ 5.5 (m, 1H), 3.42 (m, 1H), 3.39 (m, 1H), 3.1 (dd, J = 5.2 Hz, 12.4 Hz), 2.91 (s, 3H), 2.78 (m, 1H), 2.65 (m, 1H), 2.41 (m, 2H), 2.39 (m, 1H), 2.11 (m,

(24) Coulson, D. R. *Inorg. Synth.* **1970**, *13*, 121.
(25) Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253−266.

1H), 0.9−2.08 (m, 14H), 0.85 (s, 3H), 0.8 (s, 3H); MS *m/e* 411 (27), 396 (14), 124 (15), 76 (100), 57 (30). Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.85; H, 8.26; N, 3.32.

1′α,2′α-Bis(methoxycarbonyl)androstano[16α,17-*c*]cyclohex-3′-ene (18). $Pd_2(dba)_3$·$CHCl_3$ (0.02 mmol) and 1 mmol of **2** 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. Methyl acrylate (10 mmol) and 3 mmol of triethylamine were added by means of a hypodermic syringe through the septum inlet. The mixture was stirred at 60 °C for 20 h. 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 of 5% HCl, 20 mL of saturated aqueous $NaHCO_3$, and brine; and dried over Na_2SO_4. Isolation by chromatography on silica gel with hexane/ethyl acetate 85/15 gave the cycloadduct in 85% yield: ^{1}H-NMR δ 5.16 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.52 (td, J = 2.5 Hz, 7.5 Hz, 1H), 3.01 (ddd, J = 5.1 Hz, 7.5 Hz, 13.1 Hz, 1H), 2.58 (m, 1H), 2.30 (m, 1H), 0.8−1.8 (m, 23H), 0.77 (s, 3H), 0.75 (s, 3H); MS *m/e* 428 (2), 413 (80), 396 (42), 353 (62), 91 (70), 67 (84), 55 (100). Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.52; H, 9.32.

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Supporting Information Available: ^{1}H-NMR spectra of **16a** and the mixture of **16a** and **16b** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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