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Facile, High-yielding Synthesis of Novel Pentacyclic Steroids

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

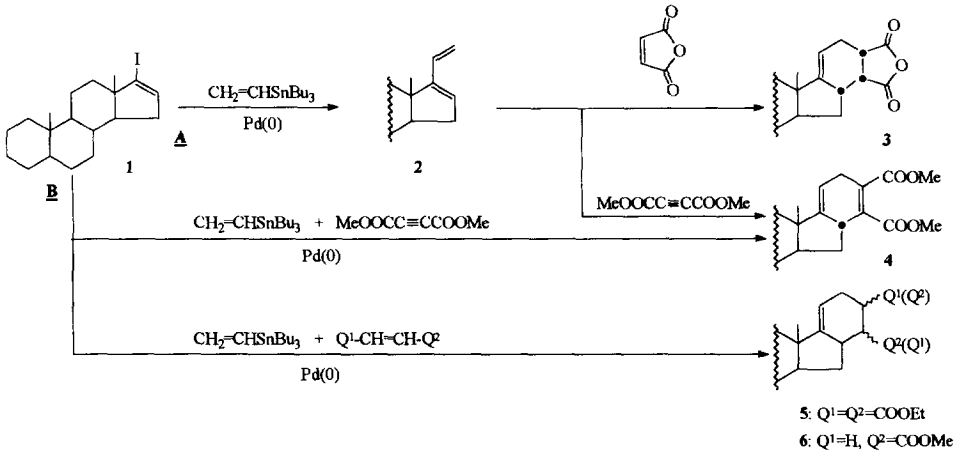
a) University of Veszprém, Department of Organic Chemistry, H-8201 Veszprém, P.O.Box 158, Hungary

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

Abstract: Novel androstane-based skeletons were synthesized in a facile one-pot reaction of 17-iodo-androsta-16-ene, vinyltributylstannane and functionalised olefins. The palladium-catalysed coupling reaction was followed by Diels-Alder reaction resulting in the formation of an unsaturated six-membered E-ring.

There are many examples for 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. In this paper the synthesis of some conformationally highly stable, androstane-based pentacyclic derivatives representing a principally novel skeleton will be described.



Scheme 1.

The pentacyclic steroidal derivatives (**3-6**, Scheme 1) were synthesized in two routes in 'one-pot' reactions, using a Stille-type coupling [3] followed by Diels-Alder reaction. In one of the methods, the substrate (17-iodo-androsta-16-ene, (**1**)) was coupled with vinyltributylstannane in the presence of $Pd(PPh_3)_4$. The pentacyclic products (**3-6**) were produced by adding the dienophile to the reaction mixture (route **A**). Thus, the pregna-16,20-diene (**2**) formed in the first step, reacted with the dienophile. The second method involves the reaction of the three components (17-iodo-androsta-16-ene, vinyltributylstannane and the dienophile) in the presence of the palladium catalyst (route **B**).

In a typical reaction (route **B**) 115.2 mg (0.3 mmol) **1** was reacted with 97.5 μl (0.33 mmol) vinyltributylstannane and 0.3 mmol dimethyl acetylenedicarboxylate (or 0.6 mmol diethyl maleate or methyl acrylate) in the presence of 0.006 mmol $Pd(PPh_3)_4$ in 3 ml toluene under argon at 100 °C. The reaction was followed by GC. After 14 hours the Bu_3SnI was removed as Bu_3SnF by washing the reaction mixture with the water solution of 0.4 mmol KF, followed by filtration. The organic layer was dried on Na_2SO_4 and after removal of the solvent in vacuo the product was purified by column chromatography using n-hexane/ethyl acetate=40/60 eluent.

Using maleic anhydride as dienophile, **3** could not be produced by the second method (route **B**) because of catalyst decomposition possibly caused by trace amounts of maleic acid, and because of coordination of the anhydride to the metal [4], which decreases the number of active palladium species. Thus, the first step, the Stille-type coupling of the steroidal alkenyl iodide and the organostannane did not take place. When the dienophile was added to the reaction mixture after completion of the Stille-coupling, the product (**3**) was synthesized in high yield (92 %) after 1 hour.

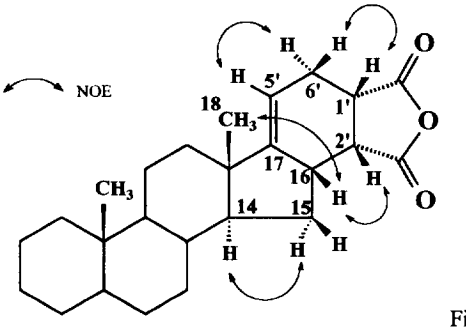


Fig.1

The stereochemistry of the pentacyclic derivative (1'α,2'α-(dicarboxylic anhydride)-androstano-[16α,17-c]-cyclohex-1'-ene, Fig. 1) was clarified by various spectroscopic methods (^{1}H-, ^{13}C-NMR, ^{1}H-^{1}H COSY and NOE) [5]. The differential NOE experiments showed that saturation of 18-CH_3 at 0.78 ppm resulted in the enhancement of the multiplet at 2.67 ppm (16-H) and irradiation of the sp^2 proton signal at 3.42 ppm (2'-H) caused an increase of the same signal (16-H). That means that the positions of 18-CH_3, 16-H and 2'-H are the same, they all have β-position. Supposing a *syn*-addition, 1'-H has also β position.

Considering the mechanism of Diels-Alder reaction (Fig. 2) this 16β,1'β,2'β isomer (the numbers indicate the position of hydrogens) is formed through an *endo* transition state, which is usually favoured in Diels-Alder reactions, and by the dienophile approaching the steroid from the sterically favourable α side.

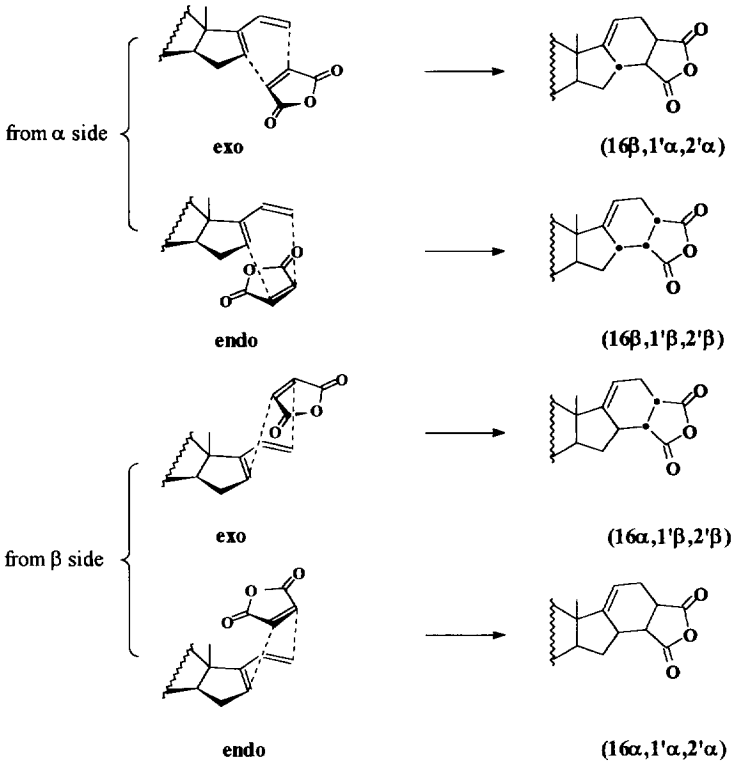


Fig. 2

With dimethyl acetylenedicarboxylate the reaction could be carried out on both **A** and **B** routes (Scheme 1). The product was proved to be again the 16β epimer according to GC-MS, ^{1}H-, ^{13}C-NMR and NOE measurements [6]. Isolated yields for **4**: 90% and 40% [7] in the absence and in the presence of Pd, respectively.

Table 1 'One-pot' reaction of 17-iodo-androsta-16-ene with vinyltributylstannane and dienophiles

Entry	Catalyst	Dienophile	Dienophile/ diene	Product distribution[a] [%]		
				1	**2**	Diels-Alder product (**5** or **6**)
1	$Pd_2(dba)_3$+8PPh_3	—	—	22	78	—
2	$Pd_2(dba)_3$+8PPh_3	diethyl maleate	1	24	58	18
3	$Pd_2(dba)_3$+8PPh_3	diethyl maleate	2	25	34	41
4	$Pd_2(dba)_3$+8$AsPh_3$	diethyl maleate	1	45	39	16
5	$Pd_2(dba)_3$+8PPh_3	methyl acrylate	1	50	41	9
6	$Pd_2(dba)_3$+8PPh_3	methyl acrylate	2	47	28	25

[a] Determined by GC after 4.5 hours

Diethyl maleate and methyl acrylate gave moderate results in the 'one pot' reaction with 89% (after 14 hours) and 66 % (after 20 hours) yields, respectively (Scheme 1). According to GC-MS measurements at least 3 isomers of **5** and 6 isomers of **6** were produced. The effect of the reaction conditions on both steps was investigated with these dienophiles (Table 1). With methyl acrylate the yield of the Stille-coupling was lower presumably because of coordination of the dienophile to the palladium. Diethyl maleate had little effect on the first step. Using the dienophile in excess resulted in the acceleration of the Diels-Alder reaction. The catalyst with $AsPh_3$ ligands gave lower yield than that with PPh_3.

In conclusion, D-E *trans*-fused androstane-based pentacyclic compounds can be produced with moderate to high yields in 'one pot' synthesis via tandem Stille-coupling and Diels-Alder reaction.

References and Notes

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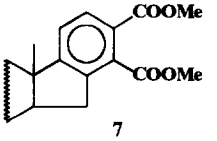
5. Selected spectroscopic data for **3**: ^{1}H-NMR(δ,$CDCl_3$): 5.5(m, 1H, 5'-H); 3.42(m, 1H, 2'β-H); 3.38(m, 1H, 1'β-H); 2.74(ddd, 2.3Hz, 6.3Hz, 15Hz, 1H, 6'α-H); 2.67(m, 1H, 16β-H); 2.37(dd, 6Hz, 13.5Hz, 1H, 15α-H); 2.15(m, 1H, 6'β); 0.9-1.8(m, 21H, ring protons); 0.78(s, 3H, 18-H_3); 0.76(s, 3H, 19-H_3); ^{13}C-NMR(δ,$CDCl_3$):174.51(CO); 172.16(CO); 157.43(C-17); 111.74(C-5'); 54.67(C-2'); 54.08(C-1'); 18.99(C-18); 12.11(C-19); IR(KBr,ν(cm^{-1})): 1760(ν (C=O)); 1820(ν(C=O)); MS(m/z): 382(M^+).
6. Selected spectroscopic data for **4**: ^{1}H-NMR(δ,$CDCl_3$): 5.3(m, 1H, 5'-H);, 3.81(s, 3H, OCH_3); 3.75(s, 3H, OCH_3); 3.46(m, 1H, 16β-H); 3.14 (ddd, 6Hz, 12Hz, 21Hz, 1H,6'α-H); 2.81(ddd, 2Hz, 12Hz, 20Hz, 1H, 6'β-H); 0.9-1.9(m, 22H, ring protons); 0.84(s, 3H, 18-H_3); 0.79(s, 3H, 19-H_3); ^{13}C-NMR(δ,$CDCl_3$): 169.35(CO); 167.40(CO); 150.48(C-17); (141.74,129.99) (C-1',C-2'); 108.42(C-5'); 16.54(C-18); 12.20(C-19); IR(KBr,ν(cm^{-1})): 1720(ν (C=O)); 1620(ν (C=C)); MS(m/z): 426(M^+).
7. In the presence of the palladium catalyst the formation of another, aromatic derivative, **7** (MS(m/z): 424(M^+); ^{1}H-NMR(δ,$CDCl_3$): 7.77 (d, 7.9Hz, 6'-H), 7.17 (d, 7.9 Hz, 5'-H)) could also be observed.



7

Reacting the isolated diene (**2**) with the dienophile, only the expected product (**4**) formed almost quantitatively in 1 hour. In the presence of $Pd(PPh_3)_4$ **4** could be converted to **7** with 46 % yield.

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