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Allylsilane addition on C-13 of 11-methoxycarbonyl-17-acetyl-1,3,5(10),13(17)-gonatetraenes: a straightforward route to introduce an 18α-methyl group

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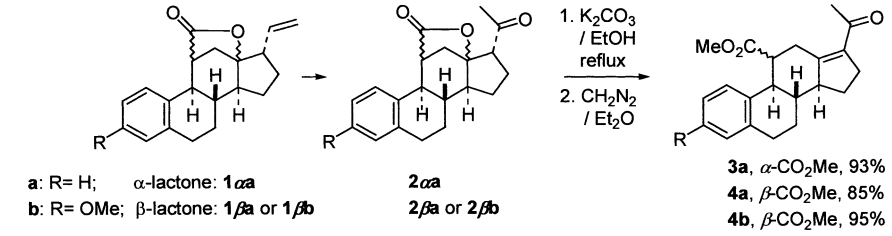
Abstract—The conjugate addition of allylsilane (Sakurai reaction) to 11-methoxycarbonyl-17-acetyl-1,3,5(10),13(17)-gonatetraenes provided 13α-allyl steroids. Ozonolysis followed by a decarbonylation affords steroids exhibiting the 18α-methyl group. This new steroid is an estrone derivative.

Generally, steroids are formed by hemisyntheses and consequently bear the natural 18-methyl group. In totally synthetic steroids, the introduction of a methyl group at C-13 represents a challenge. In the course of a program directed toward developing novel steroids matching various functionalities and especially at C-13, we have recently reported a very short synthesis of steroids **1**.[1] Steroids **1** were readily oxidised by the Wacker process into the corresponding ketones **2**.[2] In order to introduce various substituents at C-13 via conjugate additions, an unsaturation was created between C-13 and C-17. Actually, reaction of steroid **2**α or **2**β with K_2CO_3 in ethanol followed by treatment with diazomethane led to the corresponding α,β-unsaturated ketones **3a** or **4**, respectively, in good yields.

In order to introduce the 18-methyl group, we have investigated two kinds of reactions.

Initially, we carried out the addition of diazomethane to unsaturated steroid **3a**. This stereoselective process has been widely used for the preparation of a number of natural products.[3] As expected, the reaction of steroid **3a** with diazomethane afforded pyrazoline **5** in 68% yield.

Photolysis of steroid **5** led to a mixture of both epimers **6** and **7** in 95% yield.[4] The configuration of **6** and **7** was determined by NOESY experiments. The absence of a cross peak between H(18) and H(8) accounts for the *cis* C/D ring junction. According to NMR, C-11 has been partially epimerised during the reaction. Thus, the addition of diazomethane took place stereoselectively on the α-face of the steroid moiety. Curiously, only few 13,17-methylene steroids are reported in the literature.[5] It is interesting to note that thermolysis of **5** provided the unexpected D-homo-steroid **8** in 73% yield as a mixture of two inseparable epimers.



a: R= H; α-lactone: **1**α**a**
b: R= OMe; β-lactone: **1**β**a** or **1**β**b**

2α**a**
2β**a** or **2**β**b**

3a, α-CO_2Me, 93%
4a, β-CO_2Me, 85%
4b, β-CO_2Me, 95%

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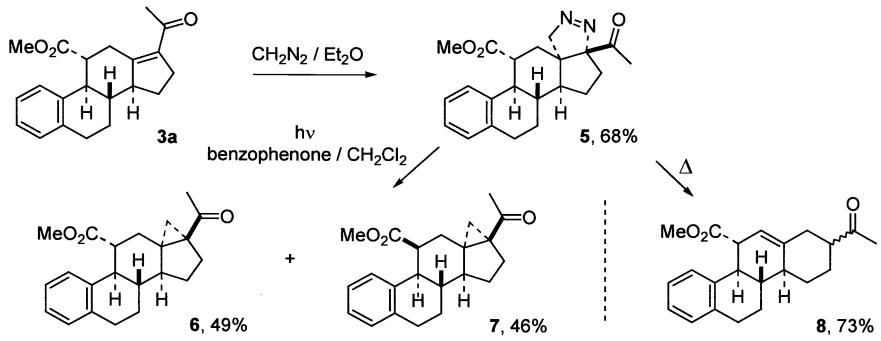
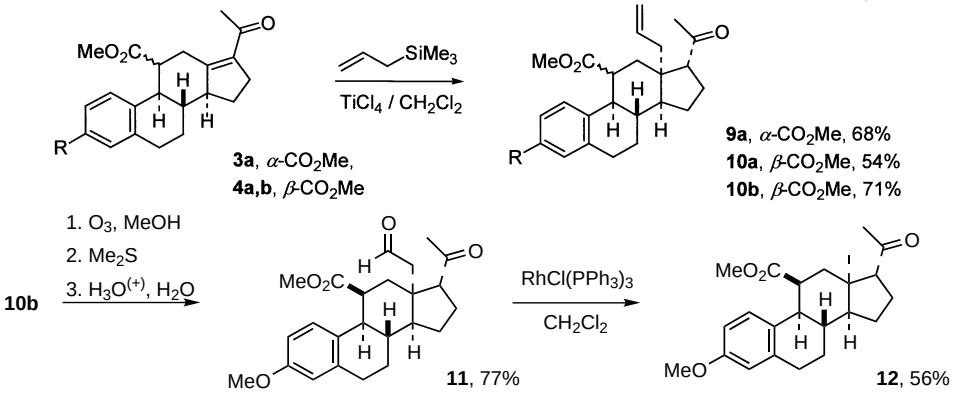


Since the diazomethane procedure did not allow the introduction of the 18-methyl group, we decided to investigate next the Sakurai addition of allyltrimethylsilane to **3a** and **4a**,**b**.[6] In both cases, the stereoselective addition occurred on the α-face of the steroid providing compounds **9a** and **10a**,**b**, respectively, exhibiting a *cis* C/D ring junction and the 17-acetyl group on the α-face.[7] The relative configuration of the steroids was determined by a series of 1D NMR, COSY and NOESY experiments (400 MHz).

Rigorous establishment of the C-13 configuration was secured by the X-ray crystallographic analysis of steroid **10a** (Fig. 1). The X-ray crystal structure reveals the *trans-anti-syn* structure, chair conformation of cycle C and a half-chair conformation for the cycle D. The D-ring is directed to the β-side and exhibits a strongly restricted pseudorotation similarly to natural 13β-estra-1,3,5(10)-trienes.[8] The phase angle Δ, a parameter for the pseudorotation,[9] has a value of +0.5° corresponding to a 13α,14β-half-chair.

To the best of our knowledge, there was only one 13-allyl steroid reported in the literature before.[10]

13α-Allylgonatrienes can be transformed into estrane derivatives in two steps: ozonolysis leading to 13α-(2-oxoethyl)gonatrienes[11,12] followed by a rhodium-(I)-



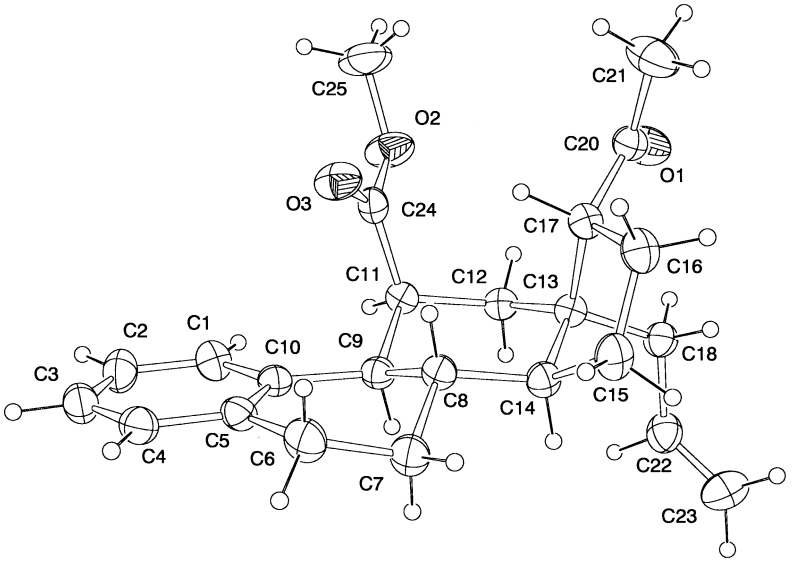


Figure 1. Structure of compound **10a** showing 30% probability displacement ellipsoids.

catalysed decarbonylation.[13] This strategy has been illustrated by the conversion of **10b** into **12**.[14] Actually, the hard problem of the introduction of the 18-methyl group can be solved in three steps.[15]

In conclusion, the conjugate addition of allyltrimethylsilane to enones **3** and **4a**,**b** allowed the introduction of the 18α-methyl group.

Acknowledgements

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4. **6**, White crystals, mp 128°C; IR 1732, 1679, 1437, 1276, 1153, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (3H, m), 6.98 (1H, m), 3.68 (3H, s), 2.83 (1H, t, $J=11.4$ Hz), 2.70 (2H, m), 2.22 (3H, s), 2.09 (7H, m), 1.42 (4H, m), 1.39 (1H, d, $J=4.4$ Hz), 1.03 (1H, d, $J=4.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 207.4 (s), 176.6 (s), 140.1 (s), 139.4 (s), 127.4 (d), 126.2 (d), 125.9 (d), 123.5 (d), 52.1 (q), 47.2 (d), 45.6 (d), 42.2 (s), 41.8 (s), 39.9 (d), 30.5 (t), 29.2 (q), 28.5 (t), 28.2 (t), 27.5 (t), 24.3 (t), 21.9 (t); **7**, white crystals, mp 140°C; IR 1730, 1679, 1430, 1275, 1150, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (4H, m), 3.42 (1H, t, $J=5.9$ Hz), 3.38 (3H, s), 2.92 (1H, m), 2.84 (1H, m), 2.69 (1H, dd, $J=11.4$, 5.9 Hz), 2.40 (1H, m), 2.39 (1H, dd, $J=14.9$, 1.9 Hz), 2.27 (1H, dd, $J=14.9$, 5.9 Hz), 2.21 (3H, s), 2.17 (1H, dq, $J=11.4$, 2.2 Hz), 2.06 (1H, m), 1.95 (1H, dd, $J=11.9$, 7.6 Hz), 1.72 (1H, d, $J=7.6$ Hz), 1.68 (1H, dd, $J=7.6$, 2.8 Hz), 1.37 (1H, m), 1.29 (1H, m), 1.26 (1H, d, $J=4.7$ Hz), 0.99 (1H, d, $J=4.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 209.2 (s), 173.8 (s), 138.1 (s), 137.3 (s), 129.4 (d), 125.8 (d), 124.7 (d), 51.1 (q), 46.4 (d), 44.2 (d), 41.9 (s), 41.8 (s), 40.8 (d), 35.9 (d), 30.3 (t), 29.8 (q), 28.9 (t), 28.2 (t), 27.9 (t), 23.6 (t), 22.8 (t).
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7. **9a**: IR 1730, 1710, 1450, 1360, 1150, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (1H, d, $J=7.7$ Hz), 7.11 (2H, m), 7.01 (1H, d, $J=7.7$ Hz), 5.60 (1H, m), 4.95 (2H, m), 3.42 (3H, s), 3.01 (1H, td, $J=11.5$, 4.2 Hz), 2.86 (1H, t, $J=11.5$ Hz), 2.54 (1H, m), 2.53 (1H, t, $J=9.0$ Hz), 2.45 (1H, m), 2.17 (1H, m), 2.14 (1H, dd, $J=14.1$, 4.1 Hz), 2.06 (1H, m), 2.06 (1H, m), 2.01 (1H, td, $J=14.1$ Hz), 1.83 (1H, m), 1.83 (3H, s), 1.61 (2H, m), 1.50 (1H, dd, $J=10.7$, 6.7 Hz), 1.37 (1H, m), 1.12 (2H, m); ^{13}C NMR ($CDCl_3$) δ 209.6 (s), 175.2 (s), 140.8 (s), 138.7 (s), 133.2 (d), 127.8 (d), 126.0 (d), 125.8 (d), 123.4 (d), 118.8 (t), 54.7 (q), 52.1 (d), 50.1 (d), 48.1 (s), 42.1 (d), 41.8 (d), 39.4 (t), 38.2 (d), 34.7 (t), 31.9 (q) 28.6 (t), 28.2 (t), 25.3 (t), 23.3 (t); **10a**: white crystals, mp 99–100°C; IR 1731, 1706, 1438, 1356, 1158, 914 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (4H, m), 5.73 (1H, ddt, $J=17.0$, 10.0, 7.4 Hz), 5.08 (1H, d, $J=10.0$ Hz), 5.03 (1H, d, $J=17.0$ Hz), 3.51 (1H, ddd, $J=7.2$, 5.8, 5.2 Hz), 3.45 (3H, s), 2.92–2.82 (2H, m), 2.78 (1H, 1/2AB, m, $J=14.6$), 2.66 (1H, dd, $J=11.1$, 5.8 Hz), 2.31 (1H, 1/2AB, d, $J=14.6$, 5.2 Hz), 2.20 (1H, 1/2AB, d, $J=14.6$, 7.2 Hz), 2.12 (3H, s), 2.16–1.8 (6H, m), 1.59 (2H, m), 1.20 (2H, m); ^{13}C NMR ($CDCl_3$) δ 210.4 (s), 175.5 (s), 138.2 (s), 137.4 (s), 134.4 (d), 129.2 (d), 125.8 (d), 125.6 (d), 125.3 (d), 118.7 (t), 58.3 (d), 51.3 (d), 50.2 (q), 47.4 (s), 42.5 (d), 41.2 (d), 40.8 (t), 36.5 (d), 33.9 (t), 31.9 (q), 30.3 (t), 28.4 (t), 26.7 (t), 25.5 (t); **10b**: ^1H NMR ($CDCl_3$) δ 6.99 (1H, d, $J=8.6$ Hz), 6.63 (1H, dd, $J=8.6$, 2.5 Hz), 6.57 (1H, d, $J=2.5$ Hz), 5.73 (1H, ddt, $J=17.3$, 9.8, 7.3), 5.03 (2H, m), 3.73 (3H, s), 3.46 (3H, s), 3.46 (1H, m), 2.87 (2H, m), 2.73 (1H, dd, $J=16.4$, 2.3 Hz), 2.60 (1H, dd, $J=11.4$, 6.0 Hz), 2.26 (1H, dd, $J=14.5$, 5.1 Hz), 2.16 (1H, dd, $J=14.5$, 7.5 Hz), 2.11 (3H, s), 1.97 (5H, m), 1.58 (2H, m), 1.15 (3H, m); ^{13}C NMR ($CDCl_3$) δ 210.2 (s), 175.4 (s), 157.1 (s), 138.6 (s), 134.2 (d), 130.2 (s), 126.1 (d), 118.5 (t), 113.6 (d), 11.9 (d), 58.1 (d), 55.0 (q), 51.2 (q), 50.0 (d), 47.2 (s), 41.8 (d), 41.0 (d), 40.6 (t), 36.4 (d), 33.6 (t), 31.8 (q), 30.4 (t), 29.4 (t), 26.5 (t), 25.4 (t).
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12. **11**: Oil; ^1H NMR ($CDCl_3$) δ 9.74 (1H, s), 6.99 (1H, d, $J=8.5$ Hz), 6.63 (1H, dd, $J=8.5$, 2.7 Hz), 6.58 (1H, d, $J=2.7$ Hz), 3.72 (3H, s), 3.42 (4H, m), 2.83 (3H, m), 2.78 (2H, s), 2.68 (1H, dd, $J=12.1$, 5.6 Hz), 2.43 (1H, dd, $J=14.6$, 5.8 Hz), 2.13 (1H, m), 2.12 (3H, s), 1.99 (3H, m), 1.59 (2H, m), 1.23 (3H, m); ^{13}C NMR ($CDCl_3$) δ 210.6 (s), 201.9 (d), 175.2 (s), 157.2 (s), 138.5 (s), 129.8 (s),

126.4 (d), 113.6 (d), 112.0 (d), 57.8 (d), 55.1 (q), 52.0 (d), 51.3 (q), 50.1 (t), 50.1 (t), 46.0 (s), 41.4 (d), 41.0 (d), 36.8 (d), 33.9 (t), 31.3 (q), 30.4 (t), 28.4 (t), 27.3 (t), 26.8 (t).

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14. **12**: Oil; ^{1}H NMR ($CDCl_3$) δ 7.00 (1H, d, $J=8.7$ Hz), 6.64 (1H, dd, $J=8.7$, 2.6 Hz), 6.57 (1H, d, $J=2.6$ Hz), 3.74 (3H, s), 3.47 (1H, m), 3.43 (3H, s), 2.83 (4H, m), 2.32 (1H, dd, $J=14.2$, 6.8 Hz), 2.16 (1H, m), 2.10 (3H, s), 2.02 (2H, m), 1.96 (1H, m), 1.39 (2H, m), 1.26 (3H, m), 0.92 (3H, s); ^{13}C NMR ($CDCl_3$) δ 209.2 (s), 174.5 (s), 156.1 (s), 137.7 (s), 125.5 (d), 112.6 (d), 110.9 (d), 59.0 (d), 54.0 (q), 53.9 (d), 50.2 (q), 42.5 (s), 40.4 (d), 40.3 (d), 36.4 (d), 30.9 (t), 29.4 (t), 27.4 (t), 28.7 (q), 27.0 (t), 24.7 (t), 13.1 (q).
15. We tried to introduce the angular 18-methyl group by the use of Me_2CuLi or derivatives. Unfortunately, all attempts were unsuccessful and enones **3a** and **4a** were recovered unchanged. We also observed a 1,2-addition of MeMgCl on enone **3a** in presence of $Ti(OiPr)_4$ and $Ni(acac)_2$ in spite of the fact that this method was reputed to lead to conjugate addition even in the case of sterically hindered enones, see: Flemming, S.; Kabbara, K.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron Lett*. **1994**, *35*, 6075–6078.