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Access to 11β-ethynyl-androst-5-ene

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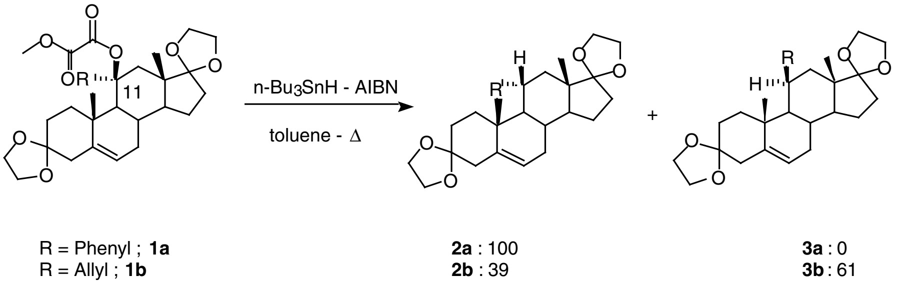
Abstract—11β-Hydroxy-11α-alkynyl-steroids were prepared from a protected adrenosterone. The use of the radical deoxygenation of an oxalate moiety gave access to 11β-ethynyl-androst-5-ene with 100% de.

The introduction of chirality in radical reactions can be achieved by the use of chiral auxiliaries, chiral Lewis acids or, more recently, by retention of the stereochemical information.[1] The radical reduction of oxalate moieties is an efficient method for the mild deoxygenation of alcohols, especially in the case of hindered systems.[2] Our group has used that method for the diastereoselective preparation of position C-11 modified androst-5-enes,[3] which are valuable precursors for the determination of the structure–activity relationships of modified testosterones as potentially new selective androgen receptor modulators.[4]

Both the mechanism and the stereochemical outcome of that reaction remain unclear since no systematical study has been undertaken to date. Reflecting the absolute configuration at C-11, one or two diastereomers could be obtained (Scheme 1).[3] The phenyl substituted androst-5-ene **1a** led exclusively to the deoxygenated steroid **2a** with relative retention of configuration, while the allyl substituted androst-5-ene **2a** led to a 39/61 mixture of **2b** and **3b** in the same conditions.

Taking into account these preliminary results, a mechanism was thus postulated, on the basis of the well-known radical deoxygenation of xanthate derivatives, which involved the production of a radical centre at the C-11 position.[5] Radicals produced at a stereogenic centre exist under two configurations with a low inversion barrier ⩽0.5 kcal/mol (Scheme 2).[6] For steric reasons in the case of a substitution by a bulky group (such as a phenyl), that equilibrium is shifted towards the left, thus producing exclusively the retention product **2** after the abstraction step. When a less steric demanding group is used (such as an allyl), both the configurations exist and the abstraction step can proceed from the



Scheme 1.

Keywords: Steroids; Radical reactions; Alkynes.

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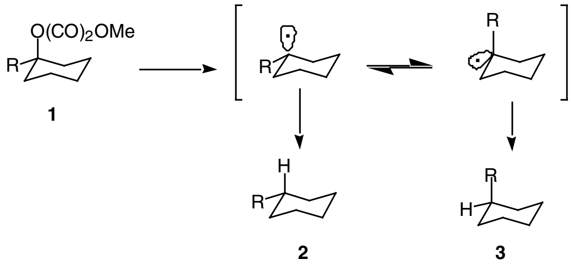


Scheme 2.

two faces yielding both **2** and **3**. The inversion product **3** is nevertheless favoured as the corresponding radical is more accessible, and thus more reactive.

The product distribution could be easily modulated by substituting our steroid with a non-steric demanding group, such as an alkynyl derivative, which can also stabilise the radicals. In that case, if the abstraction step becomes much slower than the equilibration, one can expect exclusively the formation of the interesting inversion product bearing the substituent on the β face.

The propargyl alcohols **6c**–**f** were produced by addition of the lithium or sodium alkynyl derivatives **5c**–**f** to the protected adrenosterone **4** (Scheme 3). None of the other available methods of the literature was successful (amongst other, the use of potassium *tert*-butoxide[7] or caesium hydroxide as bases,[8] the system Et_3N/zinc triflate[9] or triton B®[10] in polar solvents).

Some of the results obtained are presented in Table 1.

The addition of the lithium derivatives **5c**–**e** (M = Li) and the sodium derivative **5f** (M = Na) to the keto steroid **4** proceeded with moderate conversion (43–15%) in THF at room temperature (Table 1, entries 1–4). The addition proceeds always from the least hindered α face as observed in relative cases[11] and determined by NMR methods.[12] This reaction was in competition with the classical enolisation reaction, which after hydrolysis can lead to an epimerisation in the position 9 giving the product **7**. The steroid **7** was previously observed and described for addition of aryllithiums to the ketosteroid **4**.[13]

Other attempts (not documented here) have shown that the enolisation reaction was favoured by very polar medium (DMF), in the presence of a chelating agent (eda or tmeda) or when the reaction time was increased, as indicated by the presence of the epimer **7** after hydrolysis.

Table 1. Addition of different alkynyl derivatives to the 11-keto steroid **4**

Entry[a]	Reagent	*t* (min)	Conversion (%)[b]			Yield (%)[c] of **6**
			6c–**f**	**7**	**4**	
1	**5c** (M = Li)	90	43	1	56	34
2	**5d** (M = Li)	90	34	9	57	23
3	**5e** (M = Li)	90	25	0	75	11
4	**5f** (M = Na)	180	15	44	41	6

[a] The reactions were performed by addition of a solution of **4** in THF or toluene to the organometallic derivatives prepared as described in the literature, at room temperature.

[b] Conversion by ^1H NMR of crude mixtures.

[c] Isolated yields.

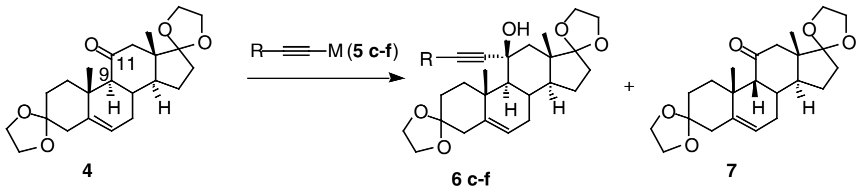
The reactivity of those alkynyl derivatives towards the keto steroid **4** was thus generally low to moderate as it is well known when working on hindered and enolisable ketones.[14] The retro-addition[15] and the enolisation reactions can be diminished by working at lower temperature and in some cases, the use of sodium derivatives enhances the nucleophilicity of the organometallic derivatives.

The preparation of the alkynyl oxalate **1c**[16] was quantitatively done by deprotonation of the corresponding tertiary alcohol **6c**[17] followed by addition of the commercially available methyl chlorooxoacetate. We were pleased to observe that the deoxygenation of **1c** under radical conditions yielded exclusively the inversion product **3c**[18] (20% isolated yield, 100% de) and elimination product **8**[19] (49% isolated yield, Scheme 4).

No reaction occurred at room temperature (using air/Et_3B as radical initiator). The enyne **8** was formed by thermolysis of the oxalate **1c** during the course of the reaction as shown by a control experiment: **1c** was refluxed in toluene for 2 h yielding exclusively **8**.

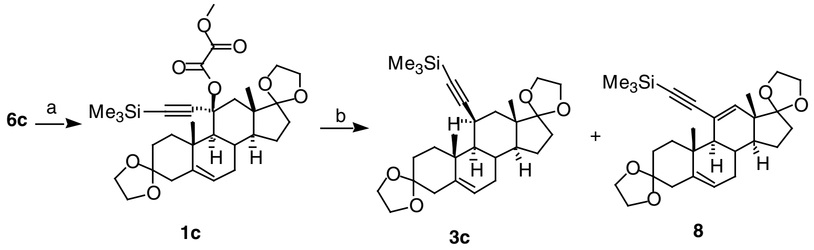
After deprotection of the alkynyl moiety using a TBAF solution in THF, the configurations of C-9 and C-11 in **9**[20] were determined by cross-peaks observed in the NOESY spectrum between H-11 and H-9 and between H-ethynyl and H-19 and H-18 (Scheme 5).

The 100% diastereoselective preparation of 11β substituted androst-5-enes is now possible by radical deoxy-

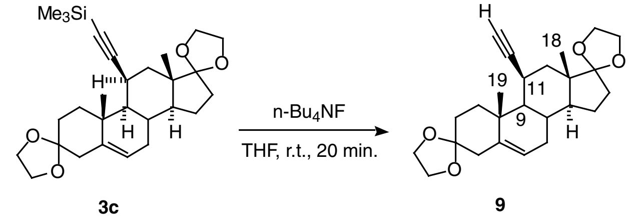


R = **c** Me_3Si- ; **d** $CH_3(CH_2)_2$- ; **e** Cp_2Fe- ; **f** Ph

Scheme 3.



Scheme 4. Reagents and conditions: (a) *n*-BuLi −70 °C, then Cl(CO)$_2$OMe −70 °C to rt, 2h. (b) Ph$_3$SnH, AIBN, toluene, 80 °C, 2 h.



Scheme 5.

genation of hindered tertiary 11β-hydroxy-11α-alkynyl-androst-5-ene derivatives. The stereochemistry of that reaction was successfully controlled by increasing the stability of the intermediate radical so as to slow down the following abstraction reaction. The operation can be interpreted as an overall racemisation/kinetic resolution process on radical species. That may constitute a new way of introducing chirality in radical reactions. As an application, those compounds could now give access to coupling products with, for example, organometallic moieties.

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16. Compound **1c**: ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 0.13 (9H, s, CH$_3$–Si), 0.88 (3H, s, CH$_3$-18), 0.90 (1H, m), 1.26–1.36 (2H, m), 1.38 (3H, s, CH$_3$-19), 1.44–1.59 (2H, m), 1.64–1.89 (7H, m), 1.93–2.20 (5H, m), 2.55–2.60 (1H, m), 2.65 (1H, dq, J = 14.3, 2.5 Hz), 2.91 (1H, d, J = 15.1 Hz), 3.81–4.03 (8H, m, H-ketals), 3.87 (3H, s, O–CH$_3$), 5.31 (1H, m, H-6). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 0.0, 15.3, 21.8, 23.6, 31.2, 32.7, 34.8, 38.2, 40.5, 42.1, 42.3, 44.9, 51.6, 53.9, 58.7, 64.7, 64.9, 65.1, 65.6, 77.7, 81.5, 109.4, 119.7, 121.2, 141.8, 155.4, 159.1. IR (KBr) (cm^{-1}) 2953, 2878, 1771, 1751.
17. Compound **6c**: ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 0.13 (9H, s, Si–CH$_3$), 0.88 (1H, m), 1.06 (3H, s, CH$_3$), 1.29 (2H, m), 1.36 (3H, s, CH$_3$), 1.46–2.05 (13H, m), 2.10 (2H, dd, J = 3.1, 14.7 Hz), 2.21 (1H, d, J = 14.1 Hz), 2.64 (2H, m), 3.81–4.03 (8H, m, ketals), 2.29 (1H, m, H-6). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 0.0 (C-Si), 16.0 (CH$_3$), 21.8 (CH$_3$), 23.5, 31.0, 32.6, 34.4, 37.8, 40.2, 41.7, 44.9, 49.9, 51.2, 56.6, 64.4, 64.6, 64.8, 65.4, 71.7 (C-11), 88.2 (C-alcyne), 109.3, 114.5 (C-alcyne), 119.7, 121.1 (C-6), 141.8(C-5). MS (EI 70 eV) *m/z* 486 [M$^{+\bullet}$] (4), 99 (100).
18. Compound **3c**: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.10 (9H, s, CH$_3$–Si), 1.17 (3H, s, CH$_3$-18), 1.20–1.36 (5H, m), 1.42 (3H, s, CH$_3$-19), 1.62–2.05 (10H, m), 2.11 (1H, dd, J = 3.2, 14.7 Hz), 2.59 (1H, dq, J = 14.5, 3.2 Hz), 3.12 (1H, dt, J = 2.0, 5.9 Hz, H-11), 3.79–3.96 (8H, m, H-ketals), 5.20 (1H, m, H-6). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 0.0, 16.7, 20.8, 23.1, 26.4, 30.0, 31.2, 31.6, 34.5, 35.9, 37.4, 37.7, 41.2, 46.1, 52.5, 53.1, 64.5, 64.7, 64.8, 65.4, 88.9, 109.5, 113.9, 119.7, 121.1 (C-6), 141.5 (C-5). MS (ICP/NH$_3$) *m/z* 488 [M + NH$_4^+$] (20), 471 [M+H$^+$] (100).
19. Compound **8**: ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.11 (9H, s, CH$_3$–Si), 0.80–0.86 (3H, m), 0.92 (3H, s, CH$_3$-18), 1.14 (3H, s, CH$_3$-19), 1.21–1.48 (6H, m), 1.64–1.79 (6H, m), 2.04 (1H, m), 2.12 (1H, dd, J = 3.0, 13.9 Hz), 2.51 (1H, br d, J = 14.7 Hz), 3.21 (1H, dt, J = 13.6, 3.6 Hz), 3.87–3.97 (8H, m, H-ketals), 5.45 (1H, m, H-6), 6.41 (1H, d,

$J = 2.3$ Hz, H-12). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 17.8, 18.0, 21.9, 30.6, 31.2, 32.7, 35.0, 36.8, 40.1, 42.6, 46.2, 48.1, 55.0, 64.1, 64.5, 64.6, 65.6, 93.4, 109.5, 109.9, 118.3, 119.3, 122.2, 122.5 (C-6), 141.7 (C-5), 145.9 (C-12). MS (ICP/NH_3) *m*/*z* 486 [$M + NH_4{}^+$] (38), 469 [$M+H^+$] (100).

20. Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.85–0.90 (2H, m), 1.17 (3H, s, CH_3-18), 1.21–1.39 (4H, m), 1.43 (3H, s, CH_3-19), 1.62–2.15 (15H, m), 2.59 (1H, dq, $J = 14.5$, 2.5 Hz), 3.16 (1H, m, H-11), 3.80–3.97 (8H, m, H-ketals), 5.21 (1H, br s, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.0, 20.4, 22.8, 24.9, 29.8, 30.8, 31.4, 34.1, 35.4, 37.0, 37.4, 40.8, 45.7, 51.7, 52.6, 64.2, 64.4, 64.5, 65.1, 72.6, 90.3, 109.1 (C-3), 119.4 (C-17), 120.7 (C-6), 141.2 (C-5).