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A-RING AROMATIC 9,10-SECOSTEROIDS BY RADICAL-INDUCED FRAGMENTATION OF 3-OXO-1,4-DIENE DERIVATIVES

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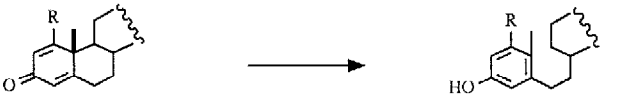
Summary. For nine steroid representatives in the 3-oxo-1,4-diene series, the majority of which bears a methyl substituent at C(1), it is shown that both tri-*n*-butyltin hydride and tris(trimethylsilyl)silane promote C(9)-C(10) bond cleavage in the presence of a radical-chain initiator to afford A-ring aromatic 9,10-secosteroids in moderate to good yield. A possible mechanism for this transformation is discussed.

Among the secosteroids, those in the vitamin D series command considerable attention because of their prominent role in a number of biological processes.[1] Well-established synthetic routes to this particular class of compounds, and to 9,10-secosteroids in general, join A- and CD-ring synthons via a two-carbon tether[2] or mimic the biosynthetic route to the D-vitamins by electrocyclic ring opening of an appropriate 5,7-diene precursor.[3]

A-ring aromatic 9,10-secosteroids, which constitute an interesting subclass containing potential intermediates for vitamin D synthesis[4] and also naturally occurring, biologically active representatives,[5] have been obtained chemically by fragmentation reactions of certain C(11)-substituted 3-oxo-1,4-diene derivatives[6] or during microbial degradation of steroids of various structural types.[7]

In this communication, we introduce a new protocol for the production of A-ring aromatic 9,10-secosteroids by a mild, radical-induced fragmentation reaction of 3-oxo-1,4-diene steroids, I→II (R= H, CH_3, CH_2OH).



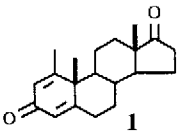
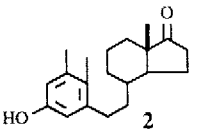
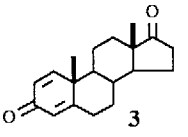
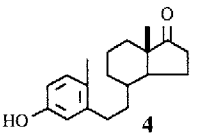
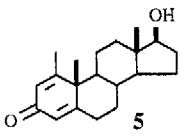
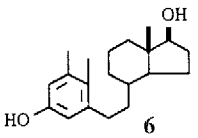
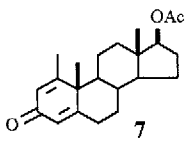
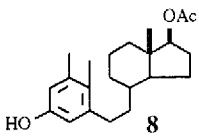
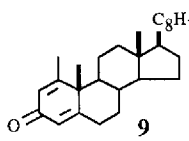
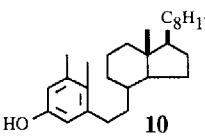
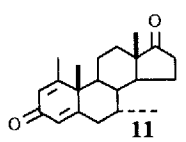
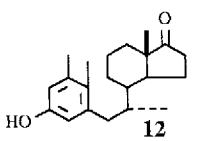
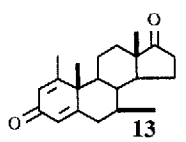
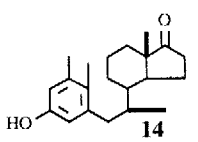
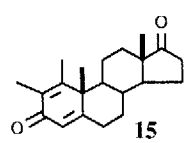
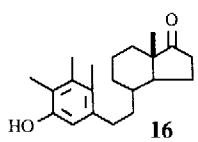
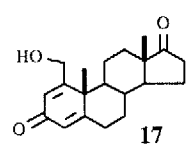
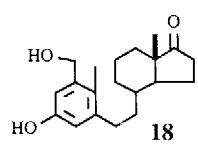
I II

Typical examples for this process are compiled in the Table below.

While tin hydride reagents, like $(n\text{-Bu})_3SnH$ or Ph_3SnH, have been employed to reduce α,β-unsaturated carbonyl compounds regioselectively in 1,4-fashion to the corresponding saturated carbonyl derivatives,[8] the 3-oxo-1,4-diene functionality in steroids seems to be quite resistant toward these reagents. In fact, $(n\text{-Bu})_3SnH$ has been successfully utilized to reductively remove halogen substituents in steroids containing this entity.[9]

Surprisingly, when 1-methylandrosta-1,4-diene-3,17-dione (**1**)[10] was refluxed for 2 h in tetrahydrofuran (THF) solution under an atmosphere of argon in the presence of $(n\text{-Bu})_3SnH$ and a radical-chain initiator, like azobisisobutyronitrile (AIBN), a very clean transformation occurred, the product **2** of which was obtained in high yield after chromatography on silica gel (methylene chloride-ethyl acetate, 9:1) and recrystallization from acetone-hexane. The structure proposed for this reaction product is based on spectroscopic measurements, the ^{13}C NMR spectrum in combination with a DEPT-type variant being particularly informative.[11] Thus, four out of six olefinic-aromatic downfield resonances originate from quaternary carbon

Table. (n-Bu)$_3$SnH-Promoted C(9)-C(10) Bond Cleavage in 3-Oxo-1,4-diene Steroid Derivatives.

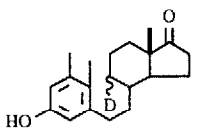
Entry	Substrate	Product	Yield	Physical Data[a,b]
1	 **1**	 **2**	85%	mp 158-160°C $[\alpha]_D^{22}$ +55.6° (c 0.50)
2	 **3**	 **4**	60%	mp 117-119°C $[\alpha]_D^{22}$ +54.2° (c 0.54)
3	 **5**	 **6**	82%	mp 184-185°C $[\alpha]_D^{22}$ -32.8° (c 0.53)
4	 **7**	 **8**	80%	mp 136-138°C $[\alpha]_D^{22}$ -17.6° (c 0.52)
5	 **9**	 **10**	85%	amorphous $[\alpha]_D^{22}$ + 8.6° (c 2.50)
6	 **11**	 **12**	78%	mp 154-155°C $[\alpha]_D^{22}$ +68.0° (c 0.51)
7	 **13**	 **14**	75%	mp 162-164°C $[\alpha]_D^{22}$ +65.9° (c 0.53)
8	 **15**	 **16**	79%	mp 133-135°C $[\alpha]_D^{22}$ +56.0° (c 0.51)
9	 **17**	 **18**	72%	mp 164-166°C $[\alpha]_D^{22}$ +53.3° (c 0.51)

[a]Solid products were recrystallized from acetone-hexane. [b]Rotations were recorded in $CHCl_3$.

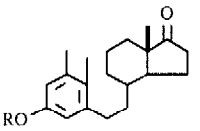
atoms, while the remaining two show methine status. In the aliphatic region, the required number of methyl, (3), methylene, (7), methine, (2), and quaternary carbon atoms, (1), was also readily identified. Moreover, by means of a 2-D INADEQUATE experiment,[11] the complete ^{13}C NMR spectrum could be assigned unambiguously. To overcome the reluctance of androsta-1,4-diene-3,17-dione (**3**) towards fragmentation, the reaction of this compound was run in toluene solution at 80-90 °C for 6 h, adding small amounts of initiator repeatedly. Under these conditions, a range of unidentified by-products lowers the yield of the desired secosteroid **4**[7b] to some extent. The substrates depicted in Entries 3-9 were transformed in close analogy to **1**.

Evidence in support of a free-radical pathway for the fragmentation **1**→**2** is provided by the fact that no secosteroid could be detected in the absence of initiator. As expected for a radical process, the presence of hydroxyl or ester/ketone carbonyl groups at C(17) did not interfere with fragmentation unfavorably. Complete inhibition of this reaction was not observed, however, upon addition of a typical radical scavenger like 2,6-di-*t*-butyl-4-methylphenol. Further mechanistic insight accumulated by exposing **1** to the action of the deuterated tin reagent $(n\text{-Bu})_3SnD$. In this instance, a mixture of the labeled secosteroids **19/20** (3:1) was formed. The stereoselective incorporation of the deuterium isotope in the α-position at C(9) was deduced from a careful comparison of ^1H, ^2H, and ^{13}C NMR spectra of **2** and **19/20**, respectively.

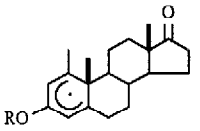
Occasional difficulties in the removal of traces of organotin impurities from reaction products and a growing awareness for toxicological issues posed by tin compounds have spurred the search for alternative reagents devoid of these shortcomings. Recently, tris(trimethylsilyl)silane (TTMSS) has been reported to serve as an excellent substitute for $(n\text{-Bu})_3SnH$ in numerous reactions of the latter.[12] Indeed, upon replacement of $(n\text{-Bu})_3SnH$ by TTMSS, **1** was converted into the stable, protected secosteroid **21**, which could be isolated in 84% yield as crystalline material following chromatographic purification. Treatment of a methanolic solution of the crude cleavage product **21** with dilute aqueous hydrochloric acid[13] at room temperature for 30 minutes led to **2** in 72% overall yield for the two steps after chromatography. Given the ready reduction of ketones by TTMSS in the presence of a radical-chain initiator,[14] it is noteworthy that hydrosilylation of the carbonyl group at C(17) cannot compete with the analogous reaction at C(3)/C(9) in this example.



19 α-D
20 β-D



21 R=$(TMS)_3Si$
2 R=H



22 R=$(n\text{-Bu})_3Sn$
23 R=$(TMS)_3Si$

These findings combine to a mechanistic picture in which a tin- or silicon-centered radical adds to the steroid carbonyl oxygen atom at C(3) to furnish pentadienyl radicals **22** or **23**. Subsequent homolytic C(9)-C(10) bond cleavage leaves an aromatic A-ring and a secondary radical center at C(9), which regenerates the chain-propagating heteroatom-centered radical by abstraction of a hydrogen atom from the reducing agent. A bulky substituent at C(1) supports C(9)-C(10) bond rupture substantially, probably because it destabilizes the ground state in radicals **22/23** by severe steric interaction with nearby atoms on the C-ring relative to the corresponding C(1)-unsubstituted intermediates, the latter, therefore, proceeding to secosteroids under more forcing conditions.[15]

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15. Spectroscopic data for secosteroids **2** and **18** are as follows.
2: IR (KBr) 3320, 2936, 1715, 1610, 1595, 1486, 1470, 1455, 1442, 1315, 1309, 1142, 858, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (m, 2H), 4.96 (s, 1H), 2.24 (s, 3H), 2.12 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.0 (C(17)), 153.1 (C(3)), 142.4 (C(5)), 138.3 (C(1)), 126.2 (C(10)), 114.6 (C(2)), 113.4 (C(4)), 50.8 (C(14)), 48.3 (C(13)), 36.3 (C(8)), 35.5 (C(16)), 34.8 (C(7)), 32.5 (C(9)), 31.8 (C(12)), 31.4 (C(6)), 22.3 (C(15)), 21.3 (C(11)), 20.8 (C(1')), 14.2 (C(19)), 13.7 (C(18)). **18**: IR (KBr) 3400, 2930, 2870, 1744, 1595, 1470, 1405, 1312, 1298, 990, 866 cm^{-1}; ^1H NMR (300 MHz, C_5D_5N) δ 11.14 (s, 1H), 7.67 (d, J= 2.6 Hz, 1H), 7.16 (d, J= 2.6 Hz, 1H), 6.85 (t, J= 5.5 Hz, 1H), 5.08 (d, J= 5.5 Hz, 2H), 2.37 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, C_5D_5N) δ 219.5, 156.5, 142.7, 142.6, 123.3, 115.2, 112.8, 62.8, 50.3, 47.8, 35.8, 35.1, 34.9, 32.3, 31.9, 30.9, 22.1, 21.2, 13.3, 13.0.

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