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Synthesis and preliminary odour evaluation of 5α-androst-16-en-7-one: a new androstenone analogue

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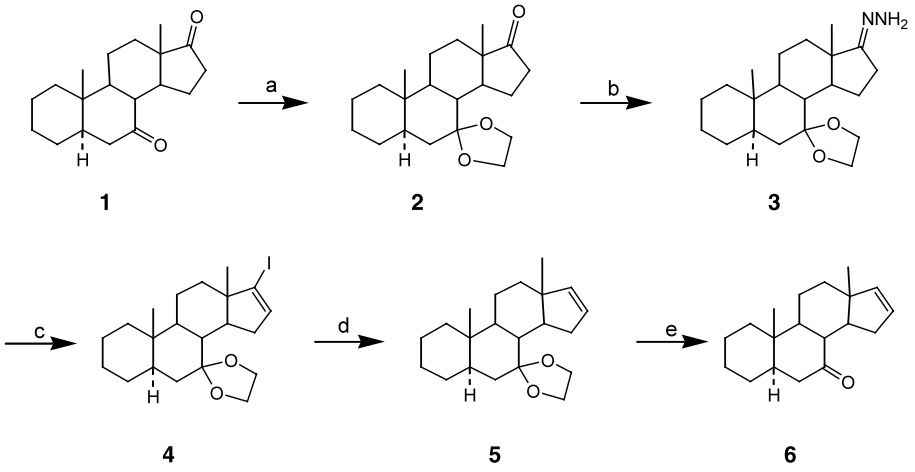
Abstract—5α-Androst-16-en-3-one has been prepared from 5α-androstane-7,17-dione in a five-step sequence, via selective ketalisation at C-7 with bis-trimethylsilyloxyethane and trimethylsilyl triflate as the key step, followed by introduction of the Δ^{16} bond by reaction of the 17-hydrazone with iodine to give the vinyl iodide, and deiodination with sodium in ethanol, with acid-catalysed deprotection of the 7-oxo group as the final step. The compound has a mild sandalwood odour. © 2002 Elsevier Science Ltd. All rights reserved.

The pungent odour of steroid ketones such as 5α-androst-16-en-3-one (androstenone) is well known.[1] The similar strong odour of the macrocyclic ketone, civetone, is ascribed to its ability to adopt a steroid-like conformation with the carbonyl group at one end of the molecule and the double bond at the other.

Androstenone analogues having the carbonyl group at other positions in ring A retain some or all of this 'steroid-type' scent, but the odour characteristics of ring B analogues of androstenone have not been studied. We report here on the synthesis and properties of the analogue having the carbonyl group at C-7.

The synthetic route (Scheme 1) starts from 5α-androstane-7,17-dione **1**, which is readily prepared from 3β-hydroxyandrost-5-en-17-one by acetylation, allylic oxidation, elimination of acetic acid, and catalytic hydrogenation of the resulting androsta-3,5-dien-7,17-dione.[2] The overall yield of the dione **1** is 62%, reflecting the poor yield obtained on the oxidation stage.



Scheme 1. *Reagents and conditions*: (a) $(CH_2OTMS)_2$, CF_3SO_3TMS, DCM, −78°C; (b) $NH_2NH_2{\cdot}H_2O$, Et_3N, EtOH, 78°C; (c) I_2, Et_3N, THF, 25°C; (d) Na, EtOH, Et_3N, 78°C; (e) aq. MeOH, HCl, 65°C.

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Selective protection of the 7-oxo group was then required in order to allow introduction of the double bond in ring D. Initial attempts at direct preparation of the 7-monoketal **2** using ethane-1,2-diol (0.7–1.2 equiv.) in the presence of toluene-*p*-sulphonic acid suggested that some degree of selectivity was attainable, but extensive chromatography was needed to obtain a pure product (30–35% yield). Similar results were obtained with an ion-exchange resin[3] as catalyst (40% yield of the monoketal). Use of the bulkier bis-trimethylsilyloxyethane and trimethylsilyl triflate at low temperature[4] proved to be a much better method, giving the 7-monoketal **2** as the sole product in 82% yield [^{13}C NMR **2**: δ 221.7 (C-17 C=O), 110.8 (C-7 O–C–O), 64.1 and 62.5 (O–CH_2–CH_2–O), 51.6, 48.2, 45.1, 42.4, 41.7, 38.4, 37.6, 36.0, 35.9, 31.2, 28.5, 25.4, 24.3, 22.0, 20.4, 13.9, 11.5, *m*/*z* 332 (M^+, 45%), 317 (11), 125 (100)].

Introduction of the double bond into ring D was carried out using the vinyl iodide route.[5,6] This involved treatment of the monoketal **2** with hydrazine to give the 17-hydrazone **3** [mp 111–114°C, selected ^{1}H NMR δ 0.81 (19-Me), 0.78 (18-Me), ^{13}C NMR δ 167.1 (C-17 C=N), 111.9 (C-7 O–C–O), 65.2, 63.6 (O–CH_2–CH_2–O), 52.8, 48.0, 45.7, 43.6, 42.8, 39.5, 38.8, 37.1, 35.0, 29.6, 27.5, 26.7, 25.6, 23.1, 21.8, 18.1, 12.5]. Reaction of the hydrazone **3** with iodine using Barton's inverse addition method[5] gave the vinyl iodide **4** [mp 180–182°C, selected ^{1}H NMR δ 6.08 (16-olefinic H), 0.79 (19-Me), 0.69 (18-Me), ^{13}C NMR δ 139.5, 113.1, 111.8, 65.1, 63.7, 52.4, 51.6, 49.1, 43.9, 42.4, 39.3, 38.6, 37.14, 37.14, 37.06, 29.6, 27.5, 23.1, 21.8, 16.1, 12.4]. Deiodination of the vinyl iodide **4** was readily achieved by dissolving sodium in boiling ethanol to give the alkene **5** [mp 115–117°C, selected ^{1}H NMR δ 5.74 and 5.65 (16- and 17-olefinic H), 3.93 (O–CH_2–CH_2–O), 0.80 (19-Me), 0.72 (18-Me), ^{13}C NMR δ 142.9, 129.9, 110.9, 64.1, 62.7, 51.9, 49.2, 46.3, 42.9, 41.0, 38.3, 37.8, 36.2, 35.6, 34.3, 28.6, 26.5, 22.1, 21.0, 16.9, 11.4, *m*/*z* 316 (M^+, 28%), 301 (14), 235 (96), 153 (60), 125 (100)].

Finally, the protecting group was removed under mildly acidic conditions to give the target compound, 5α-androst-16-en-7-one, **6** [mp 94–96°C, selected ^{1}H NMR δ 5.75 and 5.70 (16- and 17-olefinic H), 1.03 (19-Me), 0.72 (18-Me), ^{13}C NMR δ 213.5 (C-7 C=O), 143.3, 131.4, 57.7, 50.3, 49.8, 49.7, 47.4, 46.8, 39.2, 37.9, 36.1, 34.3, 30.2, 27.5, 22.8, 22.1, 18.0, 12.7, *m*/*z* 272 (M^+, 5%), 257 (20), 239 (15), 191(100), 147 (20), 95 (42), 91 (50)]. The overall yield of the androstenone analogue **6** from the diketone **1** was 35%.

The odour of the ketone **6** was quite different to that of androstenone, and very much less intense, with tests indicating only a mild sandalwood odour. This is of interest in connection with the reported ability of certain sandalwood aroma chemicals, bearing a structural relationship to androstenol, to be able partially to stimulate the androstenol receptor.[7] The iodoketone obtained by deprotection of the vinyl iodide **4** was odourless.

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References

1. Ohloff, G.; Maurer, B.; Winter, B.; Giersch, W. *Helv. Chim. Acta* **1983**, *66*, 192–217.
2. Clegg, A. S.; Denny, W. A.; Jones, E. R. H.; Kumar, V.; Meakins, G. D.; Thomas, V. E. M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 492–498.
3. Jones, E. R. H.; Meakins, G. D.; Pragnell, J.; Muller, W. E.; Wilkins, A. L. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2376–2380.
4. Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3946–3948.
5. Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron Lett.* **1983**, *24*, 1605–1608.
6. Turner, A. B.; van Leersum, P. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1653–1657.
7. Brunke, E.-J., Klein, E. In *Fragrance Chemistry: The Science of the Sense of Smell*, Theimer, E. T., Ed.; Academic Press: New York, 1982; Chapter 11, pp. 426–429.