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SIMPLE PREPARATION OF A USEFUL C/D-RING FRAGMENT FOR THE CONSTRUCTION OF 11-KETO STEROIDS

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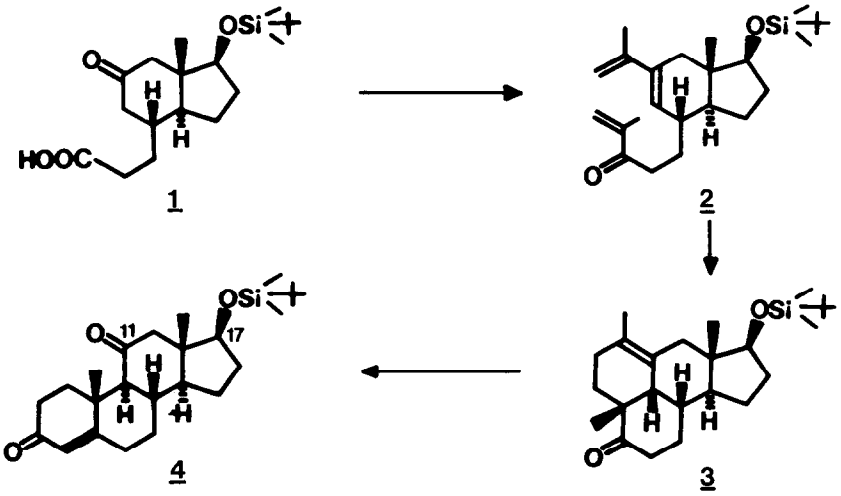
Summary: Starting with the readily available enol-lactone 5 the indanone-propionic acid 1 is prepared in few steps with 33% overall yield.

We have recently shown that 11-keto steroids (e.g. 4) can be constructed by an intramolecular Diels-Alder reaction 2 ⟶ 3, starting with the C/D-ring fragment 1[2)].

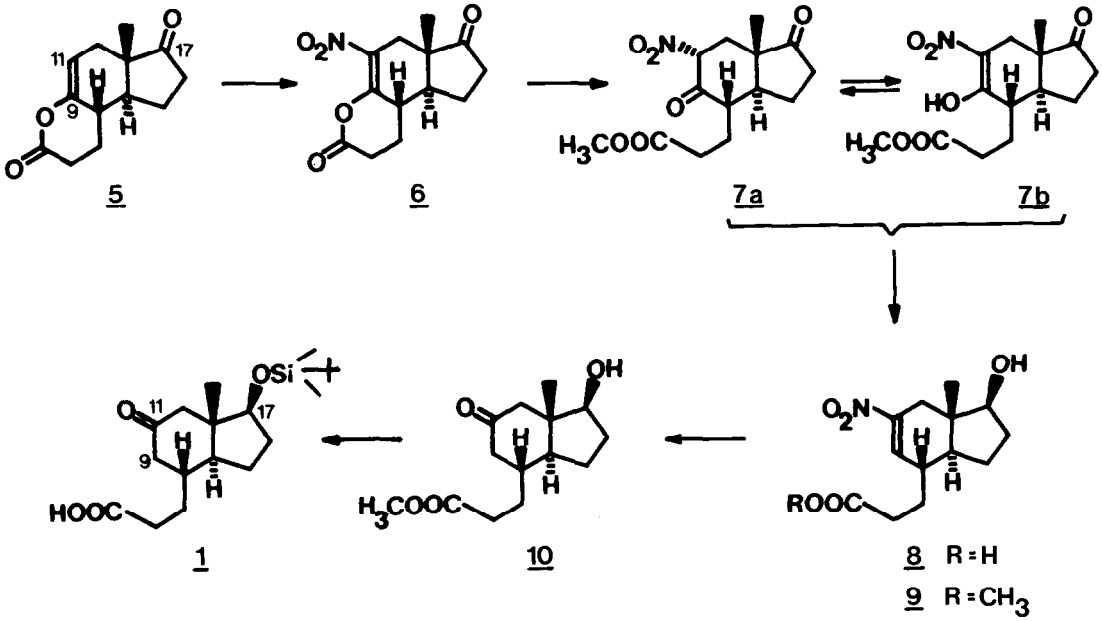


1 2 3 4

The ongoing interest in the field of 11-keto steroid synthesis[3)4)5)] prompts us to disclose our approach to the preparation of the keto acid 1.

Our starting material, the enol-lactone 5, is readily available in optically active form by microbial degradation of cheap β-sitosterol[6)7)].

The problem was thus restricted to finding a concise route for the C(9)-C(11)[8] carbonyl transposition (5 ⟶ 1)[9]. After some experimentation we found that nitration[10)12)] of 5 with concentrated nitric acid in acetic anhydride led to the crystalline nitro enol-lactone 6 in 92% yield. (For the reaction conditions and some properties of the compounds 1 and 6-10 see the accompanying table).



The direct reduction of 6 to the nitro-olefin 8 turned out to be a rather difficult task[11)], which could not be achieved in a single step. Therefore the enol-lactone 6 was converted to the nitro-ester 7 (91% yield) by simple solvolysis in methanol. Inspection of the ^{1}H-NMR-spectrum indicated a 1:1-mixture of the keto-form 7a and the enol-form 7b. The crude mixture 7a/7b was reduced with sodium borohydride in the presence of $CeCl_3 \cdot 7H_2O$[13)] to give the desired 17β-hydroxy-nitro-olefin 9 (60% yield after flash chromatography[16)]). Upon treatment of 9 with an aqueous solution of titanium trichloride, buffered by addition of ammonium acetate[14)], the 17β-hydroxy-keto-ester 10 was obtained in 77% yield. Finally, protection of the free hydroxyl group of 10 by formation of the t-butyl-dimethyl-silyl-ether[15)] followed by saponification of the methyl ester produced the desired indanone propionic acid 1 in 79% yield.

Table. Reaction conditions for the preparation of the compounds 1 and 6-10 together with some characteristic spectroscopic data. The ^{1}H-NMR-spectra were run at 270 MHz. (δ-values in ppm with $SiMe_4$ as internal standard)

6	from 5, 1.1 mol-equiv. 70% HNO_3, acetic anhydride, -20°C to room temperature overnight, followed by removal of solvents at 70°C/ 1 Torr; IR ($CHCl_3$): 1780, 1740, 1520, 1330 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.10 (s, 3H).
7a/ 7b	from 6, CH_3OH, catalytic amount of p-toluenesulfonic acid, room temperature overnight; IR ($CHCl_3$): 1730, 1560 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.00 and 1.30 (2 s, together 3H), 3.75 (s, 3H), 5.45 (dxd, J=5 and 12 Hz, 0.5H), 14.40 (s, 0.5H); MS: 298 (M^++1).
9	from 7a/7b, 2 mol-equiv. $NaBH_4$, 3 mol-equiv. $CeCl_3 \cdot 7H_2O$, EtOH, 2 h at room temperature; IR ($CHCl_3$): 3640, 1735, 1520, 1340 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.79 (s, 3H), 3.69 (s, 3H), 3.89 (t, J=7 Hz, 1H), 7.19 (br.s, 1H).
10	from 9, 6 mol-equiv. $TiCl_3$ in H_2O/CH_3OH 1:1 in the presence of NH_4OAc; IR ($CHCl_3$): 3640, 1730, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.72 (s, 3H), 3.67 (s, 3H), 3.88 (t, J=8.5 Hz, 1H).
1	from 10, Me_2t-BuSiOSO_2CF_3, 2,6-lutidine, CH_2Cl_2, -70°C followed by hydrolysis with KOH, CH_3OH, room temperature; IR ($CHCl_3$): 3300-2400 (br), 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.02 (s, 6H), 0.70 (s, 3H), 0.87 (s, 9H), 3.80 (t, J=8 Hz, 1H): m.p. 127-129° C.

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7) We thank the Upjohn Company for a generous gift of 5.

8) Steroid numbering.

9) For a review of 1,2-carbonyl transposition methods see e.g. V.V.Kane, V.Singh, A.Martin, D.L.Doyle, Tetrahedron 39, 345 (1983).

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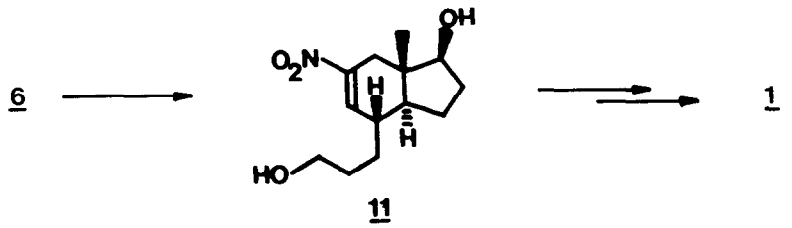
11) Treatment of 6 with a large excess of sodium borohydride led to the formation of the diol 11[12] (84% yield), which could also be converted to 1 by a different route, although much less efficiently than described above.



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12) A related result was observed by A.Hassner, J.M.Larkin, J.E.Dowd, J.Org.Chem. 33, 1733 (1968).

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