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OXIDATIVE DECARBOXYLATION; FACILE ROUTE TO 18-NOR STEROIDS

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Previous methods for the preparation of 18-nor-steroids have either involved total synthesis,[1-3] cleavage and regeneration of the D ring,[4,5] transformation of natural product[6] or elaboration of the 18,20-hemiketal moiety.[7,8] We wish to report here an alternate shorter and more efficient route, incorporating decarboxylation of the keto acid (3) as the key reaction.

Treatment of 3β-methoxy-5-pregnen-20β-ol[9] with Pb (O Ac)$_4$ I_2/hν followed by chromic acid oxidation of the crude product,[10] gave the lactone (2) in 42% yield: ir (cm^{-1}) 1755; Anal ($C_{22}H_{32}O_3$) C,H. Alternatively, hydrolysis (K_2CO_3,MeOH, room temperature, 4h) and methylation (MeI,NaH,DME, 60°, 4h) of the readily available acetoxy lactone (1)[10] afforded (2) in 75% yield Vigorous hydrolysis (30% KOH, MeOH, reflux, 4h) of (2) and subsequent oxidation,[11] yielded 83% of the keto acid (3) which exists mainly as the corresponding lactol (4)[12]: ir (cm^{-1}) 3400, 1780; Anal ($C_{22}H_{32}O_4$) C,H.

Decarboxylation of (3) with lead tetraacetate in the presence of cupric acetate,[13] afforded the 18-nor-steroids (5) and (6) in yields very dependent on the solvent used. When the reaction was conducted in benzene, (5) was isolated in 57% yield: ir (cm^{-1}) 1700; NMR ($CDCl_3$, δ) 1.0 (s,3H-CH_3), 2.1 (s,3H,CH_3-C=O), 3.4 (s,3H,CH_3-O), 5.4 (m,1H,C=CH-); Anal (C_{21},H_{30},O_2) C,H, and (6) in 11% yield. Use of HMPA as solvent however, gave (6) 50-58% ir (cm^{-1}) 1675, 1655, 1615; NMR ($CDCl_3$, δ) 1.0 (s,3H,CH_3-), 2.2 (s,3H,CH_3-C=O), 3.4 (s,3H,CH_3-O), 5.4 (1H,M,C=CH-); uv (EtOH,λ) 257,ε10,900; high resolution mass spectrum M$^+$.314.2247 (Calcd for $C_{21}H_{30}O_2$ 314.2246) and 5-10% yield of (5). Other solvents evaluated included DMF,DMSO and DME. Attempted isomerization of (5)→(6) under acidic or basic conditions proved unsuccessful in accord with previous investigations in the bicyclo {4.3.0} nonane system.[14]

The 18-nor-steroid (6) is a potentially important precursor for future isotopic labelling experiments at C-18 via 1,4-addition routes.

Procedure for (3)→(6). Lead tetraacetate (200 mg, 0.45 mmol) and cupric acetate (10 mg, 0.05 mmol) were added to a degassed solution of (3) (100 mg, 0.28 mmol) in HMPA (1 ml) and pyridine (0.1 ml), followed by stirring at 80° for 4 h. The mixture was then diluted with heptane : ethyl acetate (1.5 ml, 3:1 v/v) and filtered through Sephadex LH20 (4g), preswollen in the same solvent system. Further purification by preparative TLC (silica, light petroleum : ether 3:2 v/v) yielded (6) (50 mg, 57%) as an oil, which slowly solidified on standing at 0°. The white solid m.p. 78-80° was >97% pure (GC).

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References and Notes

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12. This equilibrium is readily reversible e.g. treatment of (4) with diazomethane smoothly affords the respective methyl ester of (3).
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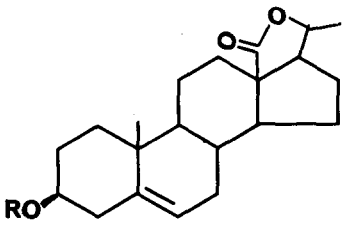
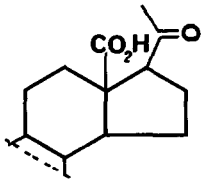


(1) R = CH_3CO

(2) R = CH_3



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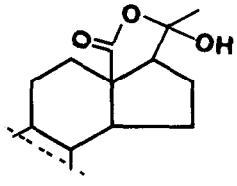

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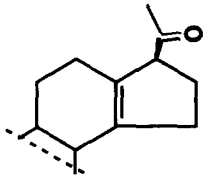
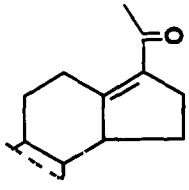


(5)



(6)