Tetrahedron Letters,Vol.26,No.35,pp 4243-4244,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

THE CONVENIENT ROUTE TO CD FRAGMENT FOR THE SYNTHESIS OF VITAMIN D_3 RELATIVES

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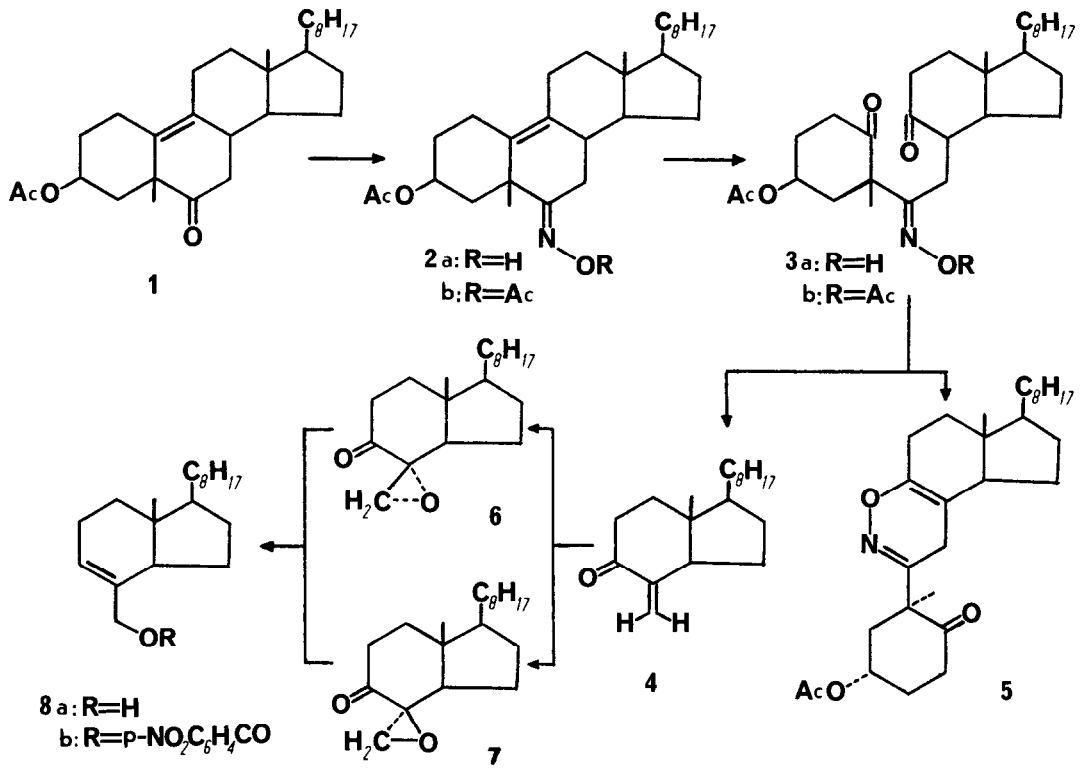
Abstract: *The efficient degradation of 1 to the α-methylene ketone 4 is described. Compound 4 was then converted to the allylic alcohol 8a - the precursor of vitamin D_3 relatives.*

The synthesis of A-ring modified vitamin D relatives involves the general synthetic concept of coupling independently prepared A and CD fragments. The suitable CD fragment can be obtained either by total synthesis or by degradation of cholesterol. The degradative approach is usually more convenient and was chosen by Lythgoe[1] in his synthesis of 8-hydroxymethyl--des-AB-cholest-8-ene (8a). This compound was then successfully converted to 1α-hydroxy-vitamin D_3.[2] We propose an alternative, shorter route to the compound 8a. The readily available keton 1[3] was transformed into the oxime 2a. The double bond $C_{(9)}$-$C_{(10)}$ in the protected oxime 2b was subjected to ozonolysis. The selective hydrolysis ($NaHCO_3$/MeOH) of the product afforded the mono-oxime of triketone 3a. Its fragmentation is the crucial step of our synthesis. It is known[4] that δ-keto-ketoximes undergo a heterolytic 5-centre fragmentation to the α,β-unsaturated ketones and nitriles. A similar fragmentation to the α-methylene ketone 4 ($[\alpha]_D^{25}$ +45°; m/e: 276 (M^+; 10 %), 163 ($M^+ - C_8H_{17}$; 100 %); δ: 6.15 and 5.21 (2 x m, 2 x 1H, H_2C=), 0.73 (s, 3H, 18-H); $\nu_{max}^{CHCl_3}$: 1692 (C=O), 1626 cm^{-1} (C=C); λ_{max}: 234 nm (ε = 4100)) occured when compound 3a was treated with $POCl_3$/Py. The A-ring fragment is probably water soluble as we did not find it in benzene extract of the reaction products. Compound 4 was obtained in about 50 % yield in addition to a small amount of oxazine 5. The α-methylene ketone 4 may be used to the synthesis of vitamin D_3 relatives either directly or after being converted to the allylic alcohol 8a in the following way. The hydrogen peroxide/NaOH/MeOH oxidation of 4 led to a mixture of epoxyketones 6 and 7. Each of them reduced with hydrazine at room temperature[5] afforded the same compound 8a. Physical



constants and spectral properties of its p-nitro-benzoil derivative 8b (m.p. 103-104°C; $[\alpha]_D^{25}$+16.5°; m/e: 427 (M^+; 2 %), 260 (M^+ - p-$NO_2C_6H_4COOH$; 48 %), 147 (M^+ - p-$NO_2C_6H_4COOH$ - C_8H_{17}; 100 %); δ: 8.22 (m, 4H, arom-H), 5.70 (m, 1H, 9-H), 4.75 (s, 2H, -CH_2-OR), 0.71 (s, 18-H); ν_{max}^{KBr}: 1725 (C=O), 1531, 1353 (-NO_2), 1291 cm^{-1}) proved to be almost identical with the data given for this compound in the literature.[1] The overall yield of 8 from 1 was slightly lower than that reported by Lythgoe (47 %) but it is expected to be improved after the optimization of the reactions parameters.

We thank the Polish Academy of Sciences for financial support.

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(Received in UK 27 June 1985)