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FACILE AND SELECTIVE METALATION OF 7-DEHYDRO-CHOLESTEROL (PRO-VITAMIN D_3)

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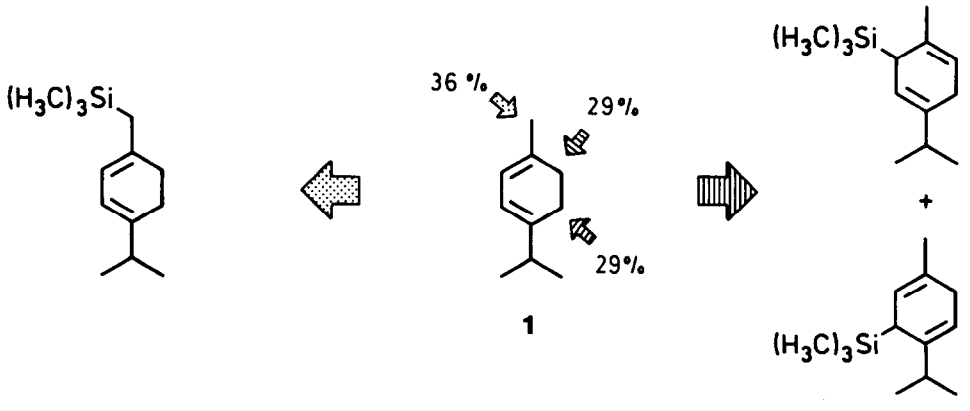
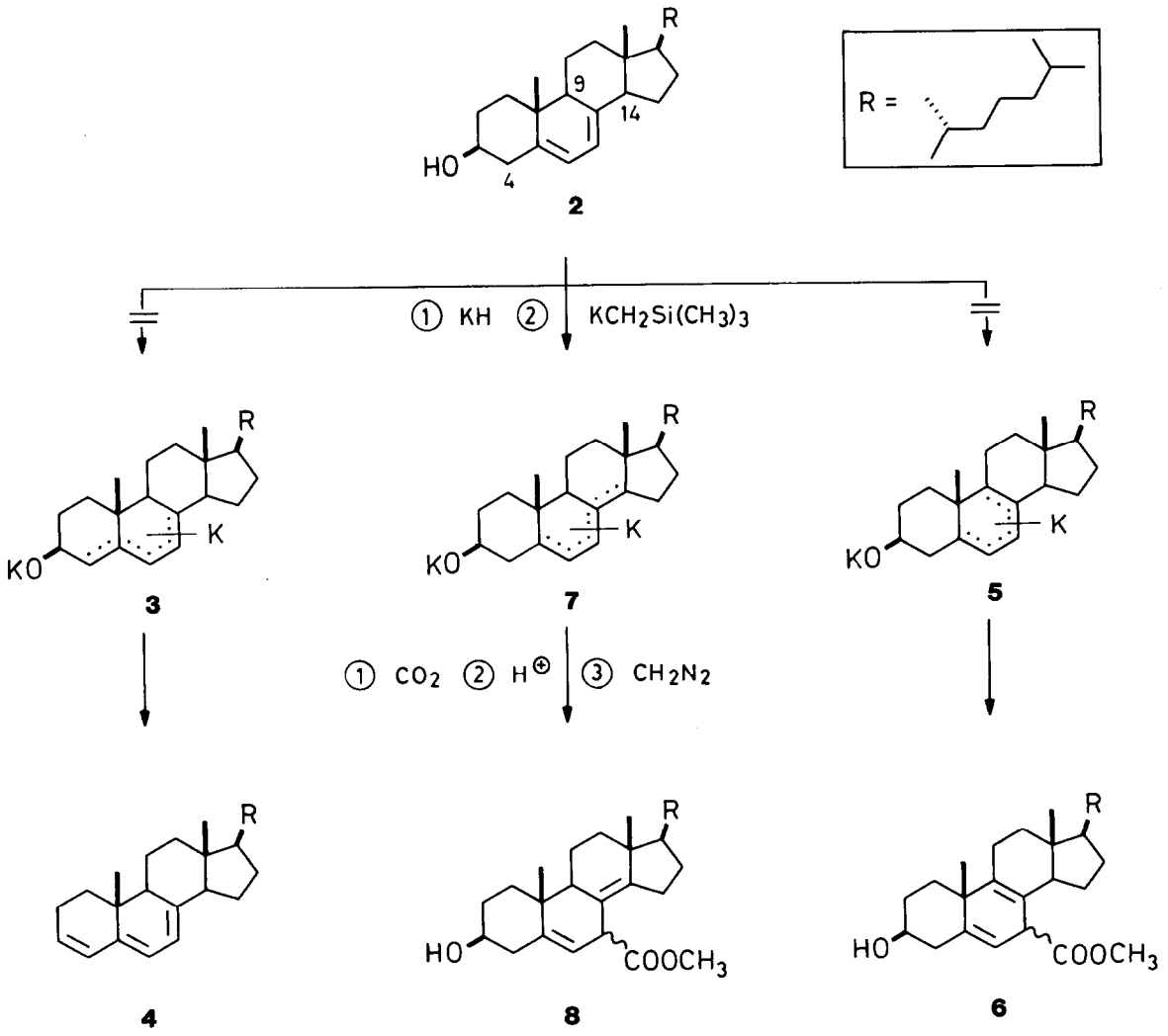
Summary: Subsequent treatment of 7-dehydrocholesterol with trimethylsilylmethylpotassium in tetrahydrofuran, dry ice, mineral acid and diazomethane gives a regioisomerically pure, homo-conjugated ester as a diastereomeric mixture, the minor component of which turns out to be thermodynamically more stable than a conjugated isomer.

Trimethylsilylmethyl potassium or the "super-basic" butyllithium/potassium *tert*-butoxide mixture react with homo-conjugated [1, 2] and even conjugated dienes [1, 3] to produce pentadienyl-type organometallic compounds without noticeable polymerization. Systems having a U-shaped area of delocalization are generated with particular ease [3]. The tendency of forming such a η^5-organo-potassium compound is strong enough to outrival the natural preference for attack of the metalation agent at a methyl rather than methylene group. When α-terpinene (1-isopropyl-4-methyl-1,3-cyclohexadiene, 1) was consecutively treated with butyllithium in the presence of potassium *tert*-butoxide [4] and chlorotrimethylsilane, the exocyclic methyl group underwent substitution only to the extent of 36% while substitution at one of the endo-cyclic methylene groups totaled 58% [3].



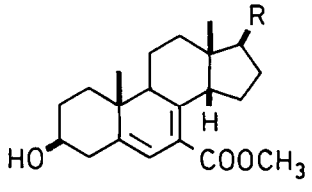
The regioselectivity of alkene metalation, however, depends on subtle factors and may change after minor structural modifications. Pro-vitamin D_3 (7-dehydro-cholesterol, 2) has three different allylic, hence activitated positions. Position 4 is occupied by a methylene group,

which according to a rule of thumb [5] should turn out to be more reactive than any competing methine group. Hydrogen/metal exchange involving this center must lead to an S(sickle)-shaped pentadienylpotassium compound 3 which presumably would eliminate potassium oxide [6] to give the triene 4. Alternatively one may expect position 9 to be deprotonated, the lower reactivity of a methine center possibly being overcompensated by the advantage of forming a U-shaped η^5-pentadienylpotassium compound 5. After carboxylation and treatment with diazomethane it should afford either diastereoisomer of ester 6 or both of them. The last remaining possibility looks the least attractive : metalation at the C-14 methine group to generate again an S-shaped organometallic intermediate 7 from which a diastereomeric mixture of esters 8 could be derived. Actually it is this pathway which is followed.



Solutions of 5 mmol trimethylsilylmethylpotassium [5] and 5 mmol of the potassium alcoholate of 5,7-cholestadien-3β-ol (1.92 g), both in 12.5 mL tetrahydrofuran, were mixed at -75°C and kept 24 h at -55°C. The reaction mixture was then poured on dry ice, acidified with dilute hydrochloric acid, extracted with 20 mL *tert*-butyl methyl ether, washed with brine and evaporated. Fractional crystallization of the residue (2.3 g) from acetone and acetone/hexane mixtures gave 0.93 g of acids (43%) and 0.2 g (10%) of recovered starting material (soluble in hexane, crystallized from methanol). Recrystallization of the acid fraction afforded two steroid acids, mp. 215 - 216°C and 245,5 - 246,5°C [7]. Quantitative esterification with diazomethane converted the former acid into a glass and the latter into a crystalline material with mp. 117 - 118°C. After a fraction of the crude residue had been treated with diazomethane, these two esters were found to be present in an approximate ratio of 2 : 1 and were accompanied by traces (3%) of a third, still unidentified ester (6 ?). According to mass spectra (*m/e* = 428, M^+), uv, ^{1}H-nmr (only one olefinic H, 5.26 and 5.35 ppm, respectively, *d x d*, *J* = 4.5 and 2.5 Hz) and ^{13}C-nmr the two principal products must be the two diastereoisomers of 8.

Upon base-catalyzed isomerization ($NaOCH_3/HOCH_3$, same result after 16 h or 72 h at 70°C) the non-crystalline ester disappeared almost completely (< 3%). The equilibrium mixture contained a new, non crystalline ester 9 (one olefinic H, 5.49 ppm, *d* = 2.5 Hz; λ_{max} = 256 nm, lg ε = 3.84) [7] together with the previously isolated one, mp. 117 - 118°C, in the ratio of 1 : 5. Since Dreiding models reveal the α-diastereomer of 8 to be sterically less hindered, we assign this structure to the latter product. The same 1 : 5 mixture of 9 and α-8 was obtained when a pure sample of 9 was submitted to the conditions of base-catalyzed isomerization (72 h).



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Why is the metalation favored at position 14 rather than at 4 or 9 ? The methylene group at position 4 is deactivated by the electronic effect and steric bulk (aggregate formation !) of the alcoholate center. The methine group at position 9 is located in a congested area and hence again not readily accessible. Moreover, the planar cyclohexadienyl ring would impose much angle deformation on the neighboring A and B rings in 5 . The attack on the C-14 methine group and the resulting organometallic intermediate 7 are free of such handicaps.

Several features of the present work merit attention. For the first time a steroidal diene, more heavily congested than any previous substrate and carrying an unprotected hydroxyl group [8], has been successfully metalated. Thus, a new entry into the pharmacologically promising [9] class of 7-substituted steroids has been opened [10]. Finally, the homo-conjugated ester which resulted from metalation, carboxylation and esterification was found to be favored compared with the corresponding conjugated isomers under equilibrium conditions.

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[7] All new products gave satisfactory elemental analyses.

[8] For other examples of alkenol metalations see : (a) Ref. 6; (b) E. Moret, thèse de doctorat, Université de Lausanne, 1980 .

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[10] Also other electrophiles such as methyl iodide, oxirane, acetic anhydride and fluorodimethoxyborane [11] preferentially attack at the 7-position (E. Moret, unpublished).

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