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STEREOSELECTIVE SYNTHESIS OF STEROID SIDE CHAIN AND CD-RINGS. A ROUTE TO (±)-DE-AB-CHOLESTA-8(14),22-DIEN-9-ONE

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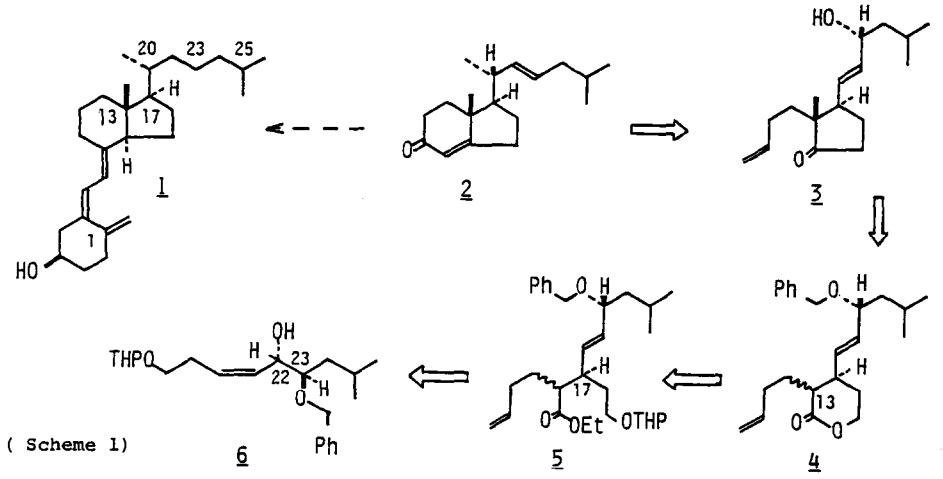
Summary: The stereoselective synthesis of (±)-de-AB-cholesta-8(14),22-dien-9-one from (±)-erythro-6-benzyloxy-5-hydroxy-8-methyl-1-tetrahydropyranyloxy-3(Z)-nonene by two Claisen rearrangements as a precursor of vitamin D_3 is presented.

With the recent isolation of new sterols possessing novel side chains from marine and animal sources, new methods for the attachment of side chains onto the naturally occurring steroids have been the subject of investigation by several groups.[1] Furthermore, the recent discoveries of many physiologically active vitamin D_3 metabolites have focused attention on developing stereocontrolled methods for the elaboration of steroidal CD rings and functionalized side chains.[2] We describe here the stereoselective synthesis of (±)-de-AB-cholesta-8(14),22-dien-9-one (**2**) as a precursor of vitamin D_3 (**1**).[3]

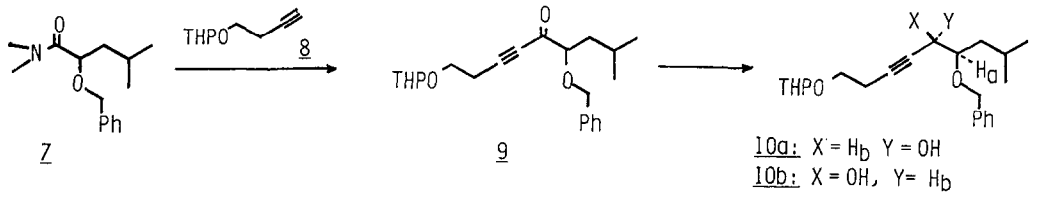
In our synthetic plan (Scheme 1), the required relative stereochemistry between C(17) and C(20) (steroidal numbering) is introduced from the relative stereochemistry at C(22) and C(23) of the triol **6** by two Claisen rearrangements; the first one to introduce the asymmetric center at C(17) as well as the butenyl chain corresponding to the C ring and the second Claisen rearrangement of the resultant allyl alcohol **3** and decarbonylation of the aldehyde **17** promoted by a rhodium complex to introduce C(20)methyl (21-methyl). Methylation



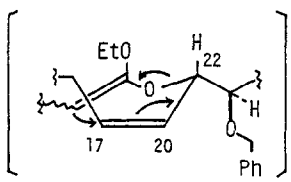
(Scheme 1)

at C(13) of **4** and the conversion of the six-membered lactone to the cyclopentanone by applying the protected cyanohydrin method afford **3**. Palladium-catalyzed oxidation of the terminal olefin of **3** to the methyl ketone and its intramolecular aldol condensation provide the C-ring. This methodology, if successful, can offer a solution to the chiral synthesis of **2** starting from the optically active erythro triol **6** with (22S) and (23R) configurations.[4)]

Thus (±)-erythro-6-benzyloxy-5-hydroxy-8-methyl-1-tetrahydropyranyloxy-non-3(Z)-ene (**6**) was our initial synthetic target and easily prepared from 3-butynyl 2-tetrahydropyranyl ether (**8**) and (±)-2-benzyloxy-N,N,4-trimethyl-pentanamide (**7**) in the following ways. The coupling reaction of **8** and **7** by a modification of Yamaguchi method[5)] gave the alkynyl ketone **9** in 60% yield; IR 2200 and 1670 cm^{-1}. The reduction of **9** with zinc borohydride[6)] gave an easily separable mixture of *erythro product* **10a** and *threo product* **10b** in 75% yield, as a 95 : 5 ratio of diastereomers[7)], respectively (**10a**: Rf=0.41, **10b**: Rf=0.45, 2 : 1 ether-n-hexane). The partial hydrogenation of the triple bond of **10a** to the cis olefin (5%-Pd/$BaSO_4$ in MeOH, trace of quinoline) gave **6** in 90% yield.

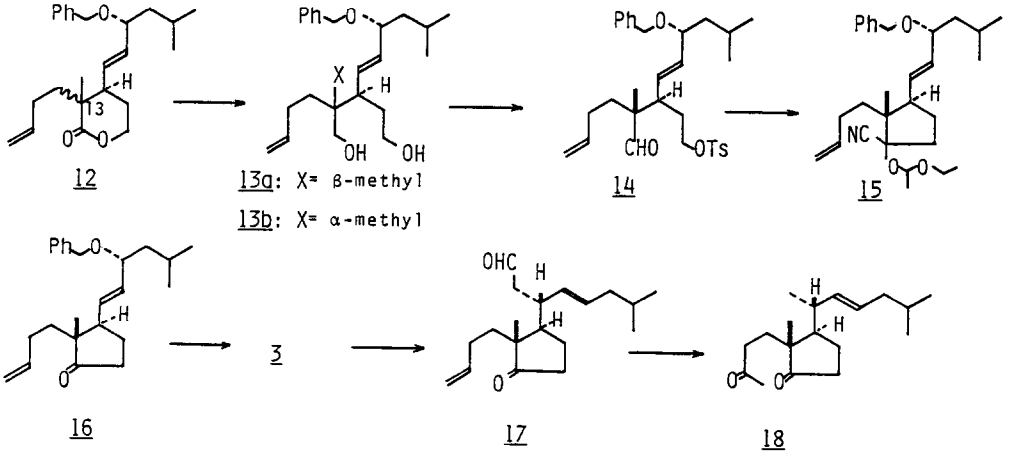


The Johnson Claisen rearrangement of the erythro derivative **6** to the ester **5** was carried out. Thermal treatment of **6** with two equiv. of triethyl orthohexenate (**11**)[8] at 140 °C for one hour in the presence of heptanoic acid gave the ester **5** in 70% yield. This rearrangement should proceed via the transition state A (Fig. 1) which leads to the stereoselective transfer of the C-O chirality at C(22) to the nonadjacent C-C chirality at C(17) as well as the (20)-E-olefin, while the butenyl chain is not controlled. This expectation was confirmed in the following ways. The ester **5** was converted to the lactone **4** in three steps (p-TsOH in MeOH, 30% aqueous KOH in EtOH, $EtO_2CN{=}NCO_2Et/PPh_3$ in toluene at 0 °C; overall yield 90%). HPLC of a mixture of diastereomeric lactones **4** showed two peaks in roughly 1 : 1 ratio. Base treatment of a mixture of diastereomers **4** (LDA at 0 °C), followed by kinetic protonation of the lactone enolate gave the α-butenylated lactone **4** and β-isomer as a ratio of 10 : 1.



(Fig. 1) A

Methylation of diastereomeric lactones **4** in THF with excess iodomethane in the presence of $KN(SiMe_3)_2$ at -25 °C gave a mixture of diastereomers **12** in 80% yield. NMR spectrum of the crude diastereomers **12** [C(13)-β-methyl, δ 1.12, C(13)-α-methyl δ 1.25] showed at least a 4.3 : 1 ratio in favor of the desired β-methylated lactone **12**. The diastereomeric lactones **12** were converted, without separation, to an easily separable mixture of diols **13a** and **13b** (i-Bu_2AlH in THF at 0 °C, 90% yield). The desired diol **13a** showed C(13)-methyl at 0.77 in NMR spectrum, whereas the minor isomer **13b** showed C(13)-methyl at 0.87. Selective monotosylation of the diol **13a** (five equiv. of p-TsCl in pyridine at -20 °C), and oxidation of the residual alcohol (pyridinium chlorochromate in CH_2Cl_2) gave the aldehyde **14** in 64% overall yield. The cyanohydrin formation of **14** (excess $NaHSO_3$ and NaCN in H_2O at 0 °C, ethyl vinyl ether/p-TsOH in benzene), cyclization[9] of the resultant protected cyanohydrin [excess $NaN(SiMe_3)_2$ in THF at 40 °C; 90% yield] and conversion of the cyclized product **15** to the cyclopentanone (p-TsOH in MeOH, 2% aqueous KOH) gave the benzyl ethyl **16** in 59% overall yield [mass spectrum m/e 354 (M^+); NMR δ 0.88 C(13)-methyl; IR 1740 cm^{-1}]. Protection of the carbonyl group [$HC(OMe)_3$/p-TsOH], removal of the benzyl group (Na in liq. NH_3 at -40 °C) and hydrolysis of the ketal group (1N-HCl in THF) gave the ketone **3** in 64% overall yield. The stereoselective introduction of the methyl group at C(20) and the formation of C-ring were carried out in the following way. The formation of vinyl ether of **3** [CH_2=CHOEt, $Hg(OAc)_2$, 78% yield], and Claisen rearrangement of the resultant vinyl ether at 160 °C in collidine gave the single product **17** in quantitative yield. Oxidation ($PdCl_2/CuCl/O_2$[10] in aqueous DMF; 60% yield) of the terminal olefin of **17** to the methyl ketone and decarbonylation[3b] of the aldehyde with $Rh(PPh_3)_3Cl$ in refluxing benzene for one hour gave the diketone **18** in 80% yield. The base catalyzed aldol condensation (NaOMe, refluxing in MeOH for 30 min) of **18** gave the enone **2** [high resolution mass spectrum, calcd for $C_{18}H_{28}O$, m/e=260.2140, found m/e=260.2159; NMR 1.10 (d, J=7.8Hz, C(20)-methyl, 1.13



(s, C(13)-methyl); IR 1675 cm^{-1}] which was identical in all respects (NMR, IR, HPLC) with an authentic sample.[3b)]

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7) On the other hand the reduction of 9 with K-selectride gave a mixture of 10a and 10b in a 10:90 ratio of diastereomers. The erythro- and threo-stereochemistry was comfirmed by mechanistic considerations cyclic-chelated model for ($Zn(BH_4)_2$) and open-chain model for (K-Selectride) as well as the NMR technique after removal of the THP group. The coupling constant (J_{ab}=3.33Hz) of the diol from 10a was much smaller than that (J_{ab}=5.09) of the diol from 10b.

8) The orthoester **11** was prepared with pentenyl nitrile (dry HCl/EtOH/Et_2O, 2 days, at 0 °C, followed by dry EtOH/Et_2O, 3 days, at 25 °C) by a modification of Stork method [G. Stork, S. Raucher, J. Am. Chem. Soc., **98**, 1583 (1976)].

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