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NOVEL AND STEREOSELECTIVE SYNTHESIS OF 1α-HYDROXYLATED VITAMIN D METABOLITES STEREOCONTROLLED SYNTHESIS OF (24R)-1α,24,25-TRIHYDROXYCHOLESTEROL

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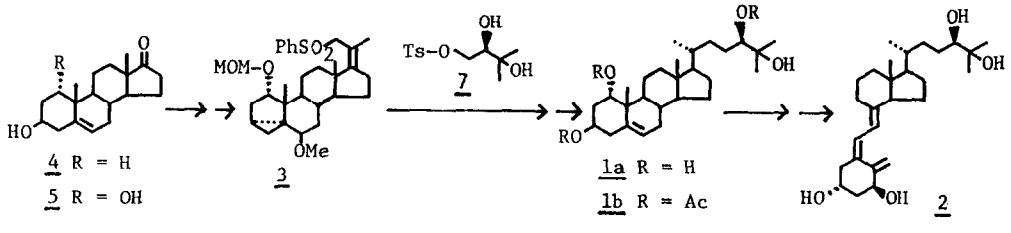
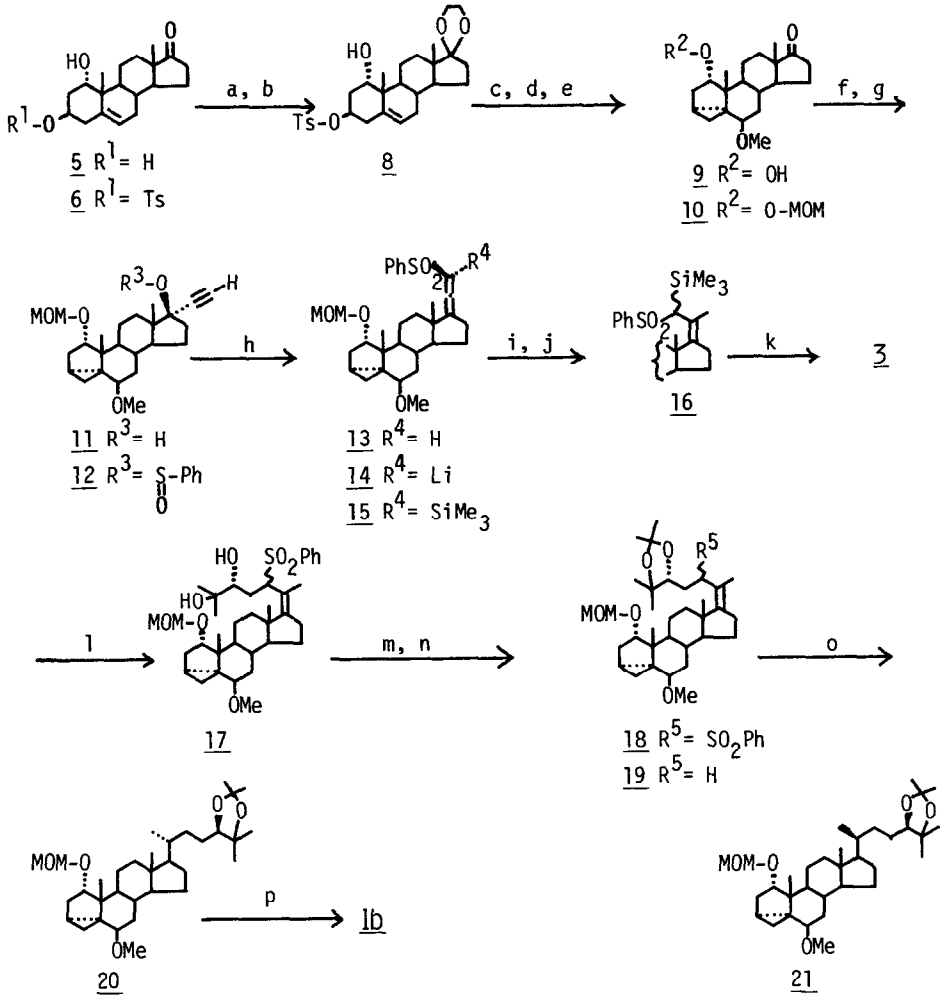
Summary: Stereoselective synthesis of (24R)-1α,24,25-trihydroxycholesterol (1a) from 1α-hydroxydehydroepiandrosterone (5) was described, in which the C-20(R) and C-17(R) configurations were introduced by stereoselective conjugate addition of $LiCuMe_2$ to sulfonylallene (15) followed by stereoselective reduction of 17(20)-dehydrosterol (19) and functionalities on the side chain were introduced by using chiral synthon (7).

Extensive studies on the metabolism of vitamin D have revealed that the vitamin D_3 must be metabolized to active metabolite, 1α,25-dihydroxyvitamin D_3, before expression of its biological activity and more than twenty metabolites have been identified.[1,2] Among them, (24R)-24,25-dihydroxyvitamin D_3 is one of the major metabolite of vitamin D_3, but the biological role of the hydroxylation at C-24 has remained unclear.[1] Furthermore, much attention has been focused on the action of the active metabolite in inhibiting proliferation and inducing differentiation of human myeloid leukemia cells (HL-60).[3a] Among several derivatives of vitamin D_3 tested,[3b] the derivatives with 1α-hydroxyl group, such as 1α,25-dihydroxyvitamin D_3 and 1α,24-dihydroxyvitamin D_3 are much more potent in inducing the differentiation than the ones without 1α-hydroxyl group. In the course of our studies on the syntheses of vitamin D metabolites, we have established facile and stereoselective method[5a-c] for syntheses of the metabolites having chiral center(s) on the side chains and a new stereoselective method[5d] for introducing steroidal side chains onto 17-oxosteroid. Expanding our studies, we now established a novel and stereoselective synthesis of 1α-hydroxylated metabolites. In this communication, we wish to report a stereoselective synthesis of a key intermediate (3) for 1α-hydroxylated metabolites[4,6] from 1α-hydroxylated 17-oxosteroid (5) readily available in single step from microbial hydroxylation of dehydroepiandrosterone (4),[7]



and subsequent transformation to the title compound (1a), an intermediate for (24R)-1α,24,25-trihydroxyvitamin D_3 (2).[8] Synthesis of 1a formally constitutes first stereoselective synthesis of 2.



Reagents (a) 1.5 eq. Tos-Cl, pyridine, 82%; (b) $HOCH_2CH_2OH$, PPTS, C_6H_6, refl., 98%; (c) MeOH, KOAc, refl., 53%; (d) PPTS, MeOH, refl., 76%; (e) CH_3OCH_2Cl, $EtN(i\text{-}Pr)_2$, 90%; (f) LiC≡CH, THF, 98%; (g) PhS(=O)Cl, pyridine, 86%; (h) PhCl, Li_2CO_3, refl., 89%; (i) MeLi, THF, -78°C then TMS-Cl; (j) $LiCuMe_2$, 0°C, 96% from 13; (k) n-Bu_4NF, EtOH, 0°C, 91%; (l) 2 eq. 7, $HN(i\text{-}Pr)_2$, THF, -20°C then 6 eq. n-BuLi, 93%; (m) 2,2-dimethoxypropane, PPTS, r.t., 93%; (n) Li, $EtNH_2$, -78°C, 84%; (o) H_2, 5% Pt-C, AcOEt, 0°C; (p) 1) H_2SO_4, aq. acetone, 2) H_2SO_4, aq. MeOH, 3) Ac_2O, pyridine, 73%

1α-hydroxydehydroepiandrosterone (5) was transformed into 3,5-cycloandrostane (9) via its ethylene ketal (8).[9] Methoxymethyl ether (10) of 9 was converted to sulfonylallene (13) in three steps by the known method involving sulfinate ester rearrangement.[10] Reaction of 13 with $LiCuMe_2$ proceeded stereoselectively[11] to give only (Z)-allylsulfone (3), however the yield of 3 was 40% and about 50% of starting material (13) was recovered even when the reaction was carried out in the presence of large excess of $LiCuMe_2$. The recovery of 13 in the presence of excess reagent suggests a competitive reaction to form 21-lithio derivative (14) in which $LiCuMe_2$ acts as base to abstract an allenic proton at C-21 of 13. To avoid the undesirable deprotonation, the allenic proton was protected with trimethylsilyl group before the conjugate addition was carried out. Thus, 21-trimethylsillylated sulfonylallene (15) generated in situ from 13 by the reaction with Me_3SiCl in the presence of MeLi was treated with $LiCuMe_2$[12] to give corresponding (Z)-allylsulfone (16) in nearly quantitative yield with exclusive stereoselectivity. Desilylation[13] of 16 gave the desired allylsulfone (3) in 91% yield. The allylsulfone (3) thus obtained was coupled with chiral tosylate (7)[5a] under the same condition as reported previously in the stereoselective synthesis of (24R)-24, 25-dihydroxyvitamin D_3 to afford dihydroxysulfone (17) in 93% yield. The vicinal hydroxyl groups in 17 were protected[14] and then the phenylsulfonyl group was removed under Birch condition to give (Z)-17(20)-dehydrosterol (19). Hydrogenation of 19 over 5% Pt-C proceeded in highly stereoselective manner[15] to afford a desired cyclocholestane derivative (20) in high yield (73% of 20 and 4% of 21). Rearrengment of 20 in aqueous acetone followed by removal of the hydroxyl protective groups gave the desired trihydroxycholesterol (1a) which was isolated as triacetate (1b) in 73% yield from 20. Structure of 1a was confirmed by comparison of its physical properties with those reported by Ikekawa et al.[8] Thus, stereoselective synthesis of (24R)-1α,24,25-trihydroxyvitamin D_3 (2) was formally achieved.

Synteses of other metabolites and related compounds from the key intermediate (3) are now in progress.

Acknowledgement: We are grateful to Dr. Kiyoshige Ochi of Chugai Pharmaceutical Co. for a gift of 1α-hydroxydehydroepiandrosterone.

References and Notes

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6) 1α-hydroxyl group is essential for the expression of the biological activity of vitamin D_3. See ref. 1)

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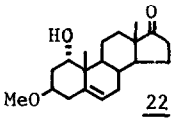
9) Cycloconvertion of the 3-tosylate (6) to 9 in satisfactory yield was possible only when the 17-oxo group was protected. All other attempts to convert 3-tosylate (6) directly to 9 was unsuccessful. For example, reactions under ordinary conditions, e.g. methanolysis in the presence of buffer (AcOK, pyridine, etc.,), resulted in complex mixture, the yields of the desired product (9) being less than 15%. Some components of the mixture were 9, 22, and 23. Methanolysis after protection of the 1α-hydroxyl group of 6 with acetyl, tetrahydropyranyl, and methoxymethyl also gave complex mixture.



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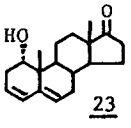

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10) (a) W. R. Benn, U. S. Patent, 1972, 3,639,435. (b) idem., ibid., 1970, 3,499,013.

11) C-18 methyl group of 13 directs the attack of the reagent to opposite face of the sulfonylallene group, as shown in Fig. I.

12) Reaction of the sillylated sulfonylallene (15) with MeLi also gave the desired product (16), but the yield of 16 was somewhat lower (53%) than that (96%) of the reaction with the cuprate reagent.

13) Direct trapping of the intermediate sulfone α-carbanion corresponding to 16 with the chiral synthon (7) gave unsatisfactory result, because of the steric congestion on the anionic carbon.

14) The use of a protected synthon (24) in place of 7 was also examined. Because of steric bulkness of four methyl groups on the dioxolan ring, 24 gave no coupling product even with sterically less crowded sulfone derivatives (25)[5a]. Lewbart et al. reported that a pregnane derivative (26) having the same partial structure as 24b was unreactive under several substitution conditions examined. M. L. Lewbart and J. J. Schneider, J. Org. Chem., 1969, 34, 3505.

15) Because of steric bulk of C-18 methyl group of 19, the catalyst must approach the double bond from the less hindered α side of the molecule (Fig. II).

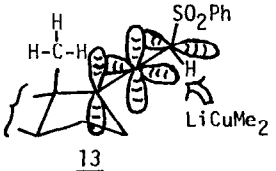

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Fig. I

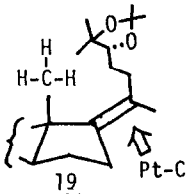

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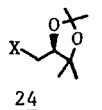
Fig. II



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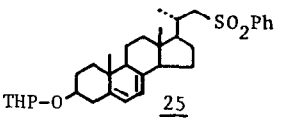
a X = Ts-O
b X = Br



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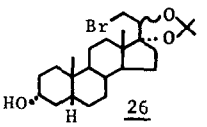

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