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A GENERAL METHOD FOR THE STEREOSELECTIVE CONSTRUCTION OF DES-AB-CHOLESTANES. A FIRST TOTAL SYNTHESIS OF (+)-8α-PHENYLSULFONYL-DES-AB-CHOLESTANE

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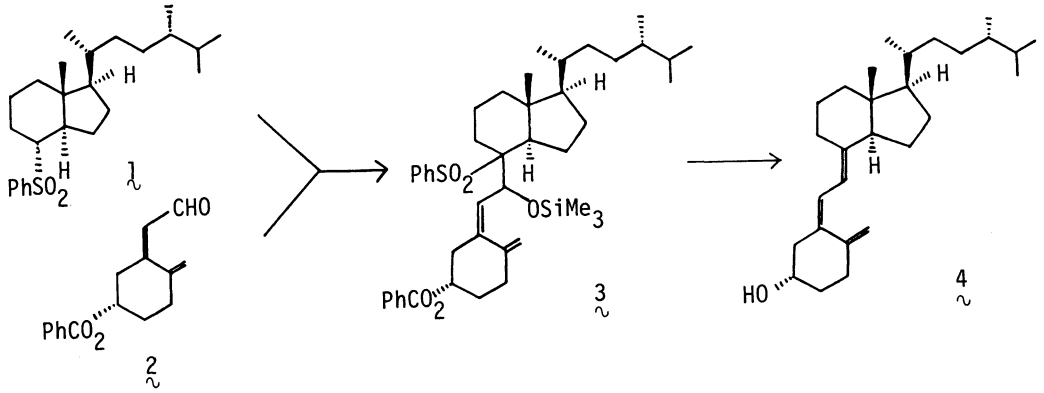
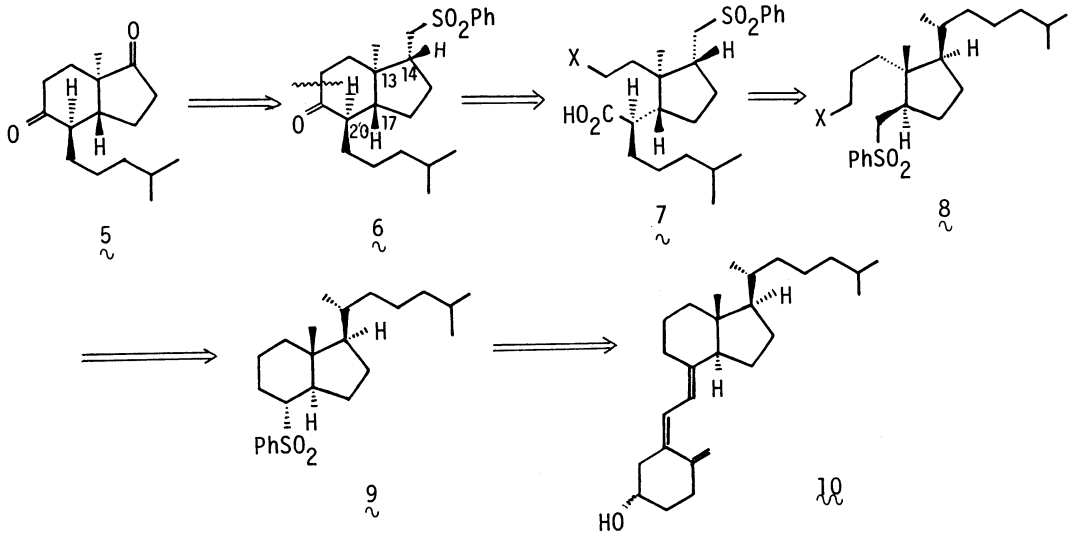
(+)-8α-Phenylsulfonyl-des-AB-cholestane, a potential intermediate of vitamin D_3, was stereoselectively synthesized from (-)-indanone derivative possessing the required chiralities, at the C_{13}, C_{14}, C_{17}, and C_{20} positions of steroidal skeleton.

Recently, considerable efforts heve been directed to synthesis in the vitamin D series[1] due, in part, to the physiological importance[2] of 1-hydroxy-vitamin D. It has been shown[3] that the reductive elimination of β-silyloxy-sulfone (3), which was derived from a condensation between 8α-phenylsulfonyl-des-AB-ergostane (1) and the benzoyloxy-aldehyde (2), followed by the removal of the protecting group, gave vitamin D_4 (4) stereoselectively.



Although this observation shows that sulfone (1) is a promising synthon for vitamin D_4 (4), it is not readily available (requiring several steps from the corresponding 8-keto derivative).[3,4] These facts stimulated us to develop a direct and effective method for the stereoselective synthesis of 8α-phenylsulfonyl-des-AB-

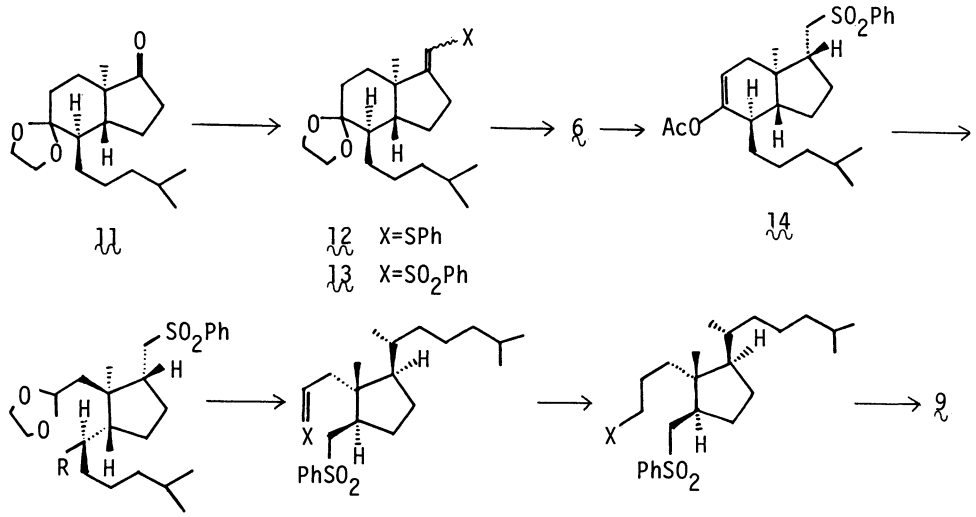
cholestane (9) as a potential synthon for vitamin D_3 (10), and here we describe a first total synthesis of sulfone (9) in its optically pure form. In our synthetic plan, the most remarkable feature is that the chiral centers at C_{13}, C_{14}, C_{17}, and C_{20} (steroid numbering) in compound 9 have been incorporated in the keto sulfone (6) as one of the most stable isomers which could be prepared easily from the diketone (5).[5] Cyclopentane (8) is then formed by a bond scission in 6, followed by a reduction of the carboxyl group and a one-carbon homologation of 7. Cyclization gives the initial target compound (9).



5 6 7 8 9 10

Thus, the monoketal (11) ($[\alpha]_D$ -74.3°),[6] obtained by a selective ketalization of diketone (5) (HO⌒OH, cat. p-TsOH, benzene, reflux, 2 h) (85%) was subjected to a Wittig reaction ($PhSCH_2\overset{O}{\overset{\|}{P}}(OEt)_2$, NaH, THF, reflux, 5 h) affording vinyl sulfide (12) (95%) as a mixture of E/Z isomers. Oxidation (MCPBA, CH_2Cl_2, aq. $NaHCO_3$, room temperature, 10 h) gave the corresponding vinyl sulfone (13) (80%). Hydrogenation (H_2, 5 atm, 10% Pd-C, cat. 10% HCl, MeOH, room temperature, 5 h) of 13 afforded the keto sulfone (6) ($[\alpha]_D$ -26.0°) (72%) stereoselectively, enol acetylation (⟩— OAc, cat. p-TsOH, reflux, 10 h) of which furnished the enol acetate (14) ($[\alpha]_D$ -0.38°) (98%). Successive reactions of 14, namely, ozonolysis (O_3, CH_2Cl_2, -78 °C, 30 min), hydrolysis (LiOH, THF : H_2O — 5 : 1, room temperature, 2 h) and then acetalization (HO⌒OH, cat. CSA, benzene, reflux, 2 h) formed the acid acetal (15) ($[\alpha]_D$ +0.79°) (73%). The alcohol (16) ($[\alpha]_D$ +0.88°), obtained (72%) by reduction ($LiAlH_4$, THF, room temperature, 9 h) of 15, was then converted into the methyl derivative (18) ($[\alpha]_D$ -12.0°) (95%) via tosylation (p-TsCl, pyridine, DMAP, room temperature, 5 h) followed by reduction ($LiAlH_4$, THF, reflux, 3 h). The final stage of this synthesis involved a one-carbon homologation and an intramolecular alkylation. To accomplish this, acetal (18) was hydrolyzed (10% HCl,

acetone, room temperature, 6 h) to aldehyde (19) ($[\alpha]_D$ -19.3°) (95%), which was then subjected to Peterson's olefin synthesis (Me_3SiCH_2MgCl, Et_2O, room temperature, 1.5 h; NaH, THF, reflux, 12 h), affording olefin (20) ($[\alpha]_D$ -12.6°) (81%). The alcohol (21) ($[\alpha]_D$ -4.8°), obtained (92%) by hydroboration-oxidation ($BH_3 \cdot SMe_2$, hexane, 1.5 h; 30% H_2O_2, 10% NaOH, 1.5 h) of 20 was first mesylated (MsCl, pyridine, 0 °C, 1 h) to give mesylate (22) ($[\alpha]_D$ -0.42°) (98%) and then subjected to intramolecular alkylation (LDA, THF, -78 °C then room temperature) to furnish the initial target compound (9)[7] ($[\alpha]_D$ +0.06°) (84%).



Thus, a direct method for the synthesis of 8α-phenylsulfonyl-des-AB-cholestane (9) in an optically pure form has been achieved, and this methodology could be applied to the synthesis of a wide range of des-AB-steroids which have a phenylsulfonyl group at the C-8 position.

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References

1) M. L. Hammond, A. Mouriño, and W. H. Okamura, J. Am. Chem. Soc., 100, 4907 (1978); B. M. Trost, P. R. Bernstein, and P. C. Funfschilling, ibid., 101, 4378 (1979); P. A. Grieco, T. Takigawa, and D. R. Moore, ibid., 101, 4380 (1979); P. M. Wovkulich, E. G. Baggiolini, B. M. Hennessy, M. R. Uskoković, E. Mayer, and A. W. Norman, J. Org. Chem., 48, 4433 (1983); A. D. Batcho,

D. E. Berger, and M. R. Uskoković, J. Am. Chem. Soc., 103, 1293 (1981); H. Nemoto, K. Suzuki, M. Tsubuki, K. Minemura, K. Fukumoto, T. Kametani, and H. Furuyama, Tetrahedron, 39, 1123 (1983); H. Nemoto, X. -M. Wu, H. Kurobe, M. Ihara, K. Fukumoto, and T. Kametani, Tetrahedron Lett., 24, 4257 (1983); 25, 3095 (1984); S. R. Wilson, M. S. Haque, A. M. Venkatesan, and P. A. Zucker, ibid., 25, 3151 (1984).

2) For a review, see W. H. Okamura, A. W. Norman, and R. M. Wing, Proc. Natl. Acad. Sci. U. S. A., 71, 4194 (1974).

3) P. J. Kocienski, B. Lythgoe, and S. Ruston, J. Chem. Soc., Perkin Trans. I, 1979, 1290.

4) P. S. Littlewood, B. Lythgoe, and A. K. Saksena, J. Chem. Soc., C, 1971, 2955.

5) H. Nemoto, H. Kurobe, K. Fukumoto, and T. Kametani, Tetrahedron Lett., 25, 4669 (1984).

6) Satisfactory IR, NMR, and mass spectral data have been obtained for all new substances described and all optical rotations have been obtained at 20 °C in chloroform.

7) Although the structure of 9 could be easily deduced from its spectral data and previous study,[5] the conversion of 9 into vitamin D_3 and Grundmann's ketone is now under way.

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