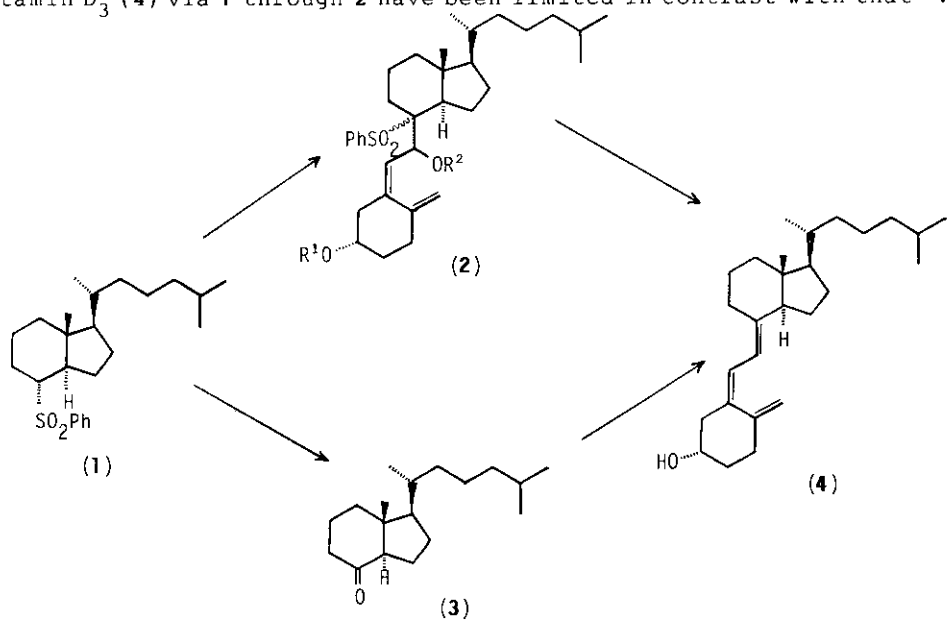
A MODIFIED SYNTHESIS OF THE (+)-8α-PHENYLSULFONYL-DES-AB-CHOLESTANE VIA AN INTRAMOLECULAR NUCLEOPHILIC ATTACK TO EPOXIDE ——— A TOTAL SYNTHESIS OF VITAMIN D_3

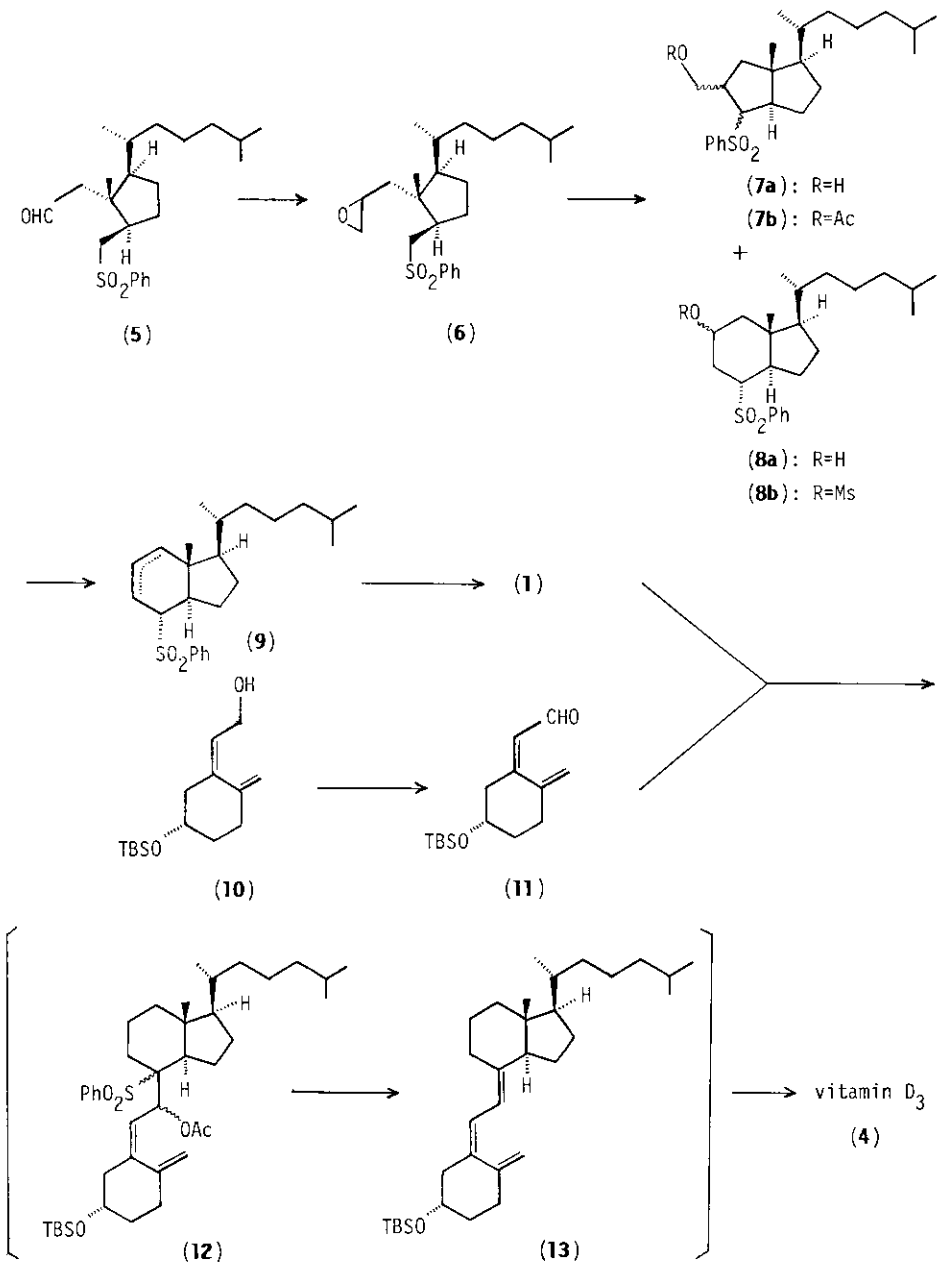
Hideo Nemoto, Hiroshi Kurobe, and Keiichiro Fukumoto*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Tetsuji Kametani
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract —— An intramolecular alkylation of the phenylsulfonyl epoxide (**6**), which was readily obtained from the aldehyde (**5**), gave a separable mixture of the alcohols (**7a**) and (**8a**). The alcohol (**8a**) was then dehydrated via the corresponding mesylate (**8b**) to afford the olefin (**9**) which on hydrogenation furnished (+)-8α-phenylsulfonyl-des-AB-cholestane (**1**). Further this product was converted into vitamin D_3 (**4**).

In the preceeding paper,[1] we described a first total synthesis of (+)-8α-phenylsulfonyl-des-AB-cholestane (**1**) which could be a potential intermediate for vitamin D_3 (**4**) either by Julia's synthesis[2,3] via β-hydroxyphenylsulfonyl derivative (**2**) or other types of reaction via Grundmann's ketone (**3**). The studies on the synthesis of vitamin D_3 (**4**) via **1** through **2** have been limited in contrast with that[4] via **3**



Scheme 1


OHC
H
SO2Ph
(5)
O
(6)
RO
PhSO2
(7a): R=H
(7b): R=Ac
+
(8a): R=H
(8b): R=Ms
(9)
(1)
OH
TBSO
(10)
CHO
(11)
PhO2S
OAc
(12)
(13)
vitamin D3
(4)

Scheme 2

partially because of the difficulty of obtaining 1. So, we have undertaken the studies on exploring the facile synthesis of (+)-8α-phenylsulfonyl-des-AB-cholestane (**1**) and here wish to report its alternative synthesis and its conversion into vitamin D_3.

Epoxidation ($Me_3\overset{+-}{S}I$, n-BuLi, THF, 0°C, 1.5 h) of the aldehyde (**5**)[1] gave the oxirane (**6**) [m/z; 265 (M^+-SO_2Ph)] which was subjected to the intramolecular cyclization (LDA, THF, -78°C, 30 min) giving the alcohols (**8a**) [m/z; 265 (M^+-SO_2Ph)] and (**7a**) [m/z; 265 (M^+-SO_2Ph)] in 50 % and 30 % yields respectively. In the ^{1}H-NMR spectrum, the signals observed at 3.55 - 3.76 ppm as multiplet due to methylene protons of hydroxymethylene moiety in the compound (**7a**) was shifted to 3.80 - 4.21 ppm in its acetoxy derivative (**7b**). The α configuration of a phenylsulfonyl group at C-8 in (**8a**) was deduced from the coupling constants (3.02 ppm, d,d,d, J=12, 12, 4 Hz) of C-8 H in the NMR spectrum. This was eventually confirmed by a conversion of (**8a**) into (**1**). Then, the compound (**8a**) was converted into the target compound (**1**) in 70 % overall yield via the mesylate (**8b**) and olefins (**9**) by a succesive treatment (MsCl, pyridine, 0 °C, 1 h; LiBr, Li_2CO_3, DMF, 150°C, 4 h; H_2, Pd-C, AcOEt, room temperature, 10 h). The compound (**1**) thus obtained was identical with the authentic sample prepared previously[1] in all aspects including optical rotation. The metallated sulfone (1) was condensed (LDA, THF, -78°C) with the ring A component (**11**), obtained by oxidation (MnO_2, THF, room temperature) of corresponding allyl alcohol (**10**).[5] Treatment of the reaction mixture with acetyl chloride gave a mixture of diastereoisomeric β-acetoxy-sulfones (**12**). This was reduced (5 % Na-Hg, MeOH-THF, -20 °C ~ room temperature, 7 h) to the triene (**13**), whose desilylation ($n\text{-}Bu_4\overset{+-}{N}F$, THF, room temperature, 2 h) gave vitamin D_3 (**4**) in 51 % overall yield. The 3,5-dinitrobenzoate of the synthetic vitamin D_3 (mp 129 - 130°C, $[\alpha]_D^{20}$ +95.9°) was identical with authentic vitamin D_3 3,5-dinitrobenzoate (lit.[6], mp 128 - 129 °C, lit.[7], $[\alpha]_D^{20}$ +97°) in mp and spectral (IR and ^{1}H-NMR) comparisons.

Thus, we could disclose an alternative route for the synthesis of (+)-8α-phenylsulfonyl-des-AB-cholestane (**1**). Furthermore, such the compound (**1**) was converted into vitamin D_3 (**4**) by Juria's olefin synthesis.

REFERENCES AND NOTES

1. H. Nemoto, H. Kurobe, K. Fukumoto, and T. Kametani, Chem. Lett., in press.
2. P. J. Kocienski, B. Lythgoe, and S. Ruston, J. Chem. Soc. Perkin Trans. I, **1979**, 1290.
3. P. J. Kocienski and B. Lythgoe, ibid., **1980**, 1400.
4. For recent works on the synthesis of vitamin D_3 via Grundmann's ketone, see H. Nemoto, K. Suzuki, M. Tsubuki, K. Minemura, K. Fukumoto, T. Kametani, and H. Furuyama, Tetrahedron, 1983, **39**, 1123; H. Nemoto, X.-M. Wu. H. Kurobe, M. Ihara, K. Fukumoto, and T. Kametani, Tetrahedron Lett., 1984, **25**, 3095 and references cited therein.
5. H. T. Toh and W. H. Okamura, J. Org. Chem., 1983, **48**, 1414.
6. A. Windaus, F. Schenck, and F. V. Werder, Z. Physiol. Chem., 1936, **241**, 100.
7. L. Velluz, G. Amiard, and A. Petit, Bull. Soc. Chim. France, **1949**, 501.

Received, 25th December, 1984