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

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A TOTAL SYNTHESIS OF VITAMIN D₃

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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-phenylsulfonyle-DES-AB-cholestane (1). Further this product was converted into vitamin D₃ (4).

In the preceding paper,¹ we described a first total synthesis of (+)-8α-phenylsulfonyle-DES-AB-cholestane (1) which could be a potential intermediate for vitamin D₃ (4) either by Julia's synthesis²,³ via β-hydroxyphenylsulfonyle derivative (2) or other types of reaction via Grundmann's ketone (3). The studies on the synthesis of vitamin D₃ (4) via 1 through 2 have been limited in contrast with that⁴ via 3.

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Scheme 1
Scheme 2
partially because of the difficulty of obtaining 1. So, we have undertaken the studies on exploring the facile synthesis of (+)-8a-phenylsulfonyl-des-AB-cholestan-1 (1) and here wish to report its alternative synthesis and its conversion into vitamin D₃.

Epoxidation (Me₃Si, n-BuLi, THF, 0°C, 1.5 h) of the aldehyde (5) gave the oxirane (6) [m/z; 265 (M⁺SO₂Ph)] which was subjected to the intramolecular cyclization (LDA, THF, -78°C, 30 min) giving the alcohols (8a) [m/z; 265 (M⁺SO₂Ph)] and (7a) [m/z; 265 (M⁺SO₂Ph)] in 50% and 30% yields respectively. In the ¹H-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 a 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 (11) in 70% overall yield via the mesylate (8b) and olefins (9) by a successive treatment (MsCl, pyridine, 0°C, 1 h; LiBr, Li₂CO₃, DMF, 150°C, 4 h; H₂, Pd-C, AcOEt, room temperature, 10 h). The compound (1) thus obtained was identical with the authentic sample prepared previously 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 (MnO₂, THF, room temperature) of corresponding allyl alcohol (10). 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-Bu₄NF, THF, room temperature, 2 h) gave vitamin D₃ (4) in 51% overall yield. The 3,5-dinitrobenzoate of the synthetic vitamin D₃ (mp 129 - 130°C, [a]²⁰D +95.9°) was identical with authentic vitamin D₃ 3,5-dinitrobenzoate (lit. mp 128 - 129°C, lit., [a]²⁰D +97°) in mp and spectral (IR and ¹H-NMR) comparisons.

Thus, we could disclose an alternative route for the synthesis of (+)-8α-phenylsulfonyl-des-AB-cholestan-1. Furthermore, such the compound (1) was converted into vitamin D₃ (4) by Juria's olefin synthesis.

REFERENCES AND NOTES


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