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Horner-Wittig Reaction of Dimethyl 2,3-O-Isopropylidene-D-glyceroylmethylphosphonate and Its Application to the Formal Synthesis of D-erythro-C_{18}-Sphingosine

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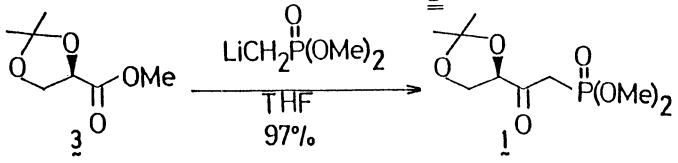
Dimethyl 1,2-O-isopropylidene-D-glyceroylmethylphosphonate was found to react with aldehyde in the presence of cesium carbonate in isopropyl alcohol. Using this reaction the formal synthesis of D-erythro-C_{18}-sphingosine was achieved.

Recently polyfunctional compounds became the interesting target molecule in the organic synthetic chemistry. In order to synthesize these compounds many efficient synthetic methods have been reported. In this letter we wish to describe the Horner-Wittig reaction of dimethyl 2,3-O-isopropylidene-D-glyceroylmethylphosphonate(**1**) as novel chiral synthon, and its application to the synthesis of D-erythro-C_{18}-sphingosine(**2**).

Compound **1** was synthesized from commercially available methyl 2,3-O-isopropylidene-D-glycerate(**3**) and dimethyl methylphosphonate(**4**) by the following procedure; to a stirred dry tetrahydrofuran(THF) solution(15 cm^3) of **4**(2.14 g, 17.3 mmol) was added a 1.6 M (1 M=1 $mol \cdot dm^{-3}$) hexane solution of butyllithium(10.7 cm^3, 17.3 mmol) at -78 °C under argon. After stirring for 10 min, a THF solution (2 cm^3) of **3**(2.37 g, 15 mmol) was added to it and the resulting solution was allowed to warm to room temperature overnight. The solution was quenched by the addition of a 5% citric acid solution and extracted with ethyl acetate. The aqueous layer was extracted with ethyl acetate for several times. The organic extracts were combined and washed with water and dried over sodium sulfate, and evaporated in vacuo. The residue was purified by means of silica-gel column chromatography to give a colorless oil **1**($[\alpha]_D^{30}$+77.6° (c 1.6, $CHCl_3$)) in 97% yield.



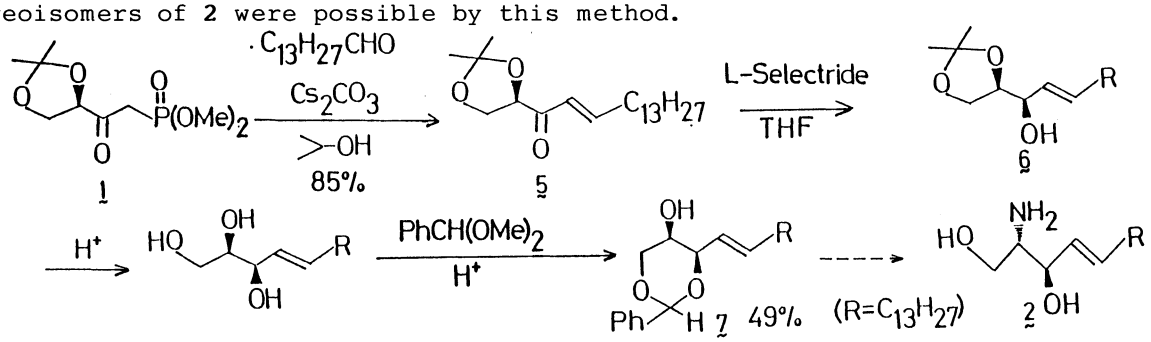
3 **1**

First we tried the reaction of **1** and butylaldehyde using sodium hydride as base in THF and found surprisingly the only starting material was detected by silica-gel thin-layer chromatography(TLC). The use of triethylamine-lithium chloride[1] gave the desired olefin in poor yield. On the other hand, in the case of cesium carbonate in isopropyl alcohol[2] the reaction was proceeded vigorously

and we finally found the use of 1 equiv. of cesium carbonate in isopropyl alcohol at 0 °C effective to promote this reaction specifically. A general procedure is as follows: To a stirred suspension of Cs_2CO_3(163 mg, 0.46 mmol) and **1**(115 mg, 0.46 mmol) in isopropyl alcohol(0.55 cm^3), an isopropyl alcohol(0.2 cm^3) solution of aldehyde(0.51 mmol) was added at 0 °C. The resulting mixture was allowed to warm to room temperature overnight with stirring and quenched by the addition of a 5% aqueous citric acid solution and extracted with ether. The organic extract was washed with a 5% aqueous citric acid solution and water and dried over sodium sulfate, and evaporated in vacuo. The residue was purified by the usual manner to give the corresponding (E)-olefin in high yield. It should be noted that (Z)-olefin could not be detected by TLC, ^1H and ^{13}C NMR.

Next, we applied the compound **1** to the synthesis of D-erythro-C_{18}-sphingosine(**2**), which is one of the essential constituent of sphingoglycolipids. Recently many reports for the synthesis of sphingosine have been published.[3)]

The reaction of **1** and tetradecylaldehyde by the similar manner described above gave the desired (E)-olefin(**5**) in 85% yield. Next diastereoselective reduction of ketone in (E)-olefin(**5**) was attempted and found the reaction with L-Selectride (Li-s-Bu_3BH) in THF at -78 °C gave the desired threo-alcohol(**6**) and erythro-isomer in 80, 8% yield, respectively.[4)] Further, the deprotection of isopropylidene group of **6** and the following benzylidenation in usual manner gave the benzylidene derivative(**7**) in 49% yield from **6** as shown in following equation. The synthesis of sphingosine **2** from compound **7** have already been reported.[5)] Thus, the formal synthesis of sphingosine **2** was completed, and the syntheses of stereoisomers of **2** were possible by this method.



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References

1) M. W. Rathke and M. Nowak, J. Org. Chem., 50, 2624(1985).

2) The Noguchi Institute, Jpn. Kokai Tokkyo Koho 62-258342(1987); T. Yamanoi, H. Itoh, and T. Inazu, to be published.

3) M. Kiso, A. Nakamura, Y. Tomita, and A. Hasegawa, Carbohydr. Res., 158, 101(1986); K. Koike, M. Numata, M. Sugimoto, Y. Nakahara, and T. Ogawa, ibid., 158, 113(1986); P. Garner, J. M. Park, and E. Malecki, J. Org. Chem., 53, 4395(1988), and references cited therein.

4) Details of these asymmetrical reduction of **5** will be published separately. No epimer of **6** could be detected by ^{13}C NMR of (+)-MTPA ester of **6**.

5) K. Ohashi, Y. Yamagiwa, T. Kamikawa, and M. Kates, Tetrahedron Lett., 29, 1185(1988).

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