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SELECTIVE FORMATION OF CHIRAL GLYCEROL ETHERS: A SYNTHESIS OF INTERMEDIATES OF A PLATELET-ACTIVATING FACTOR (C_{18}-PAF)

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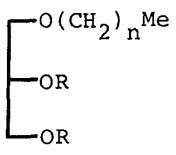
Some chiral glycerol ethers serving as key synthetic intermediates of platelet-activating factors (PAF) have been prepared in a selective manner from the acetals, obtained from chiral glycerol derivatives, employing the reductive cleavage reaction of the acetal bond with diisobutylaluminum hydride.

KEYWORDS———naturally occurring glycerol ether; platelet-activating factor; hydrogenolysis; diisobutylaluminum hydride; chiral synthesis; site selective acetal cleavage; chirality inversion

Some hexadecyl and octadecyl ethers of glycerol are found in animals. Thus, simple 1-hexadecyl and 1-octadecyl ethers, 1 and 2, and their dipalmitates, 3 and 4, are produced in certain marine invertebrates such as Gorgonians,[1] while their 2-O-acetyl-3-O-cholinylphosphoryl derivatives, 5 and 6, occur in the blood cells of various higher mammals including man, rabbits, rats, and pigs.[2] Although the

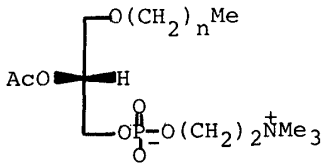


1 : R=H, n=15

2 : R=H, n=17

3 : R=$C(CH_2)_{14}Me$, n=15

4 : R=$C(CH_2)_{14}Me$, n=17



5 : n=15 "C_{16}-PAF"

6 : n=17 "C_{18}-PAF"

Chart 1

four compounds in the former group do not exhibit any particular physiological activities, the latter two possess potent biological effects in physiological processes and are called platelet-activating factors (PAF) as their interaction with rabbit platelets induce aggregation and secretion of granular constituents.[3] Recently, chiral synthesis of the latter two compounds has become of interest,[4),5),6),7)] because these natural enantiomers have been reported to have important terapeutic effects:[8),9)] antihypertensive,[10)] vasodilating,[11)] and tumor-cytotoxic.[12)] We report here the selective synthesis of some optically active glycerol ethers which serve as synthetic intermediates for the above mentioned natural products, especially the natural enantiomer of C_{18}-PAF 6, employing the hydrogenolytic cleavage of acetals using diisobutylaluminum hydride.[13)]

First, the known (R)-glycerol benzyl ether 7,[14)] obtained from D-mannitol via the glycerol acetonide 8, was converted into an epimeric mixture of the acetal 9 in 71% yield by reaction with stearylaldehyde in the presence of p-toluenesulfonic acid. When the mixture was treated with 3.0 M eq of diisobutylaluminum hydride in toluene at 0°C- room temperature for 5 h, site selective cleavage did not occur to give a mixture of reduction products which were separated by a silica gel column to afford the known 3-benzyl ether (R)-10,[6)] $[\alpha]_D$ + 1.82° (c=7.022, benzene) (lit.[6)] $[\alpha]_D$ + 1.63° (c=10, benzene)), and the 2-benzyl ether 11, $[\alpha]_D$ + 4.38° (c=13.566, benzene) (lit.[6)] $[\alpha]_D$ + 4.60° (c=5, benzene)), in 55 and 43% yields. The former has already been converted into natural 1-O-octadecyl-2-O-acetyl-sn-glycero-3-phosphocholine 6 (C_{18}-PAF) by Hirth and Barner.[6)] On the other hand, the acetal 9 was catalytically debenzylated under neutral conditions to give the primary alcohol 12, quantitatively, which on treatment with 5 M eq of diisobutylaluminum hydride in toluene at 0°C- room temperature for 24 h afforded 1-O-octadecyl-2,3-propanediol (S)-13, $[\alpha]_D$ - 2.49° (c=2.654, THF) (lit.[6)] $[\alpha]_D$ - 2.41° (c=7.0, THF)), selectively, in 85% yield as a sole product. This compound was also converted into C_{18}-PAF 6 by Hirth and Barner.[6)] The exclusive formation of 13 may be rationalized in terms of initial formation of the aluminum alkoxide

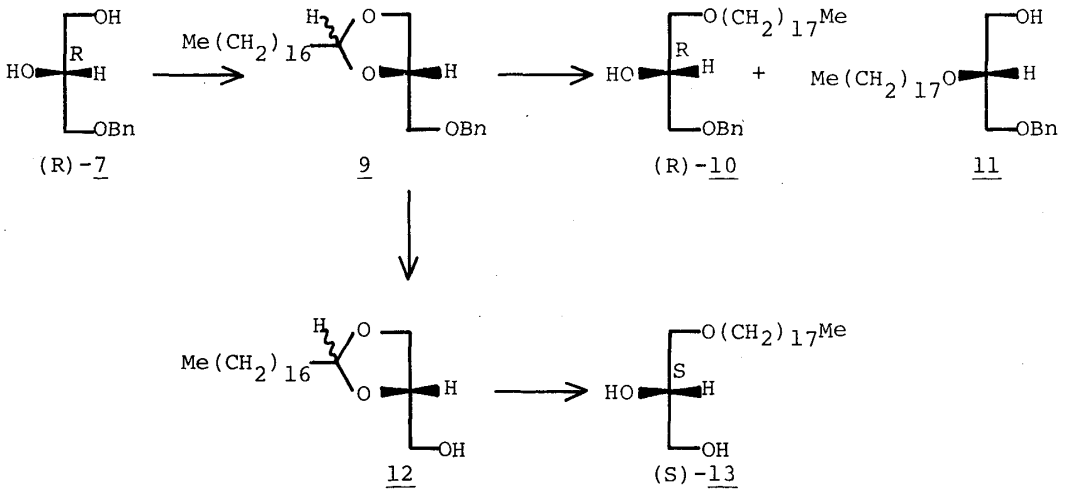


Chart 2

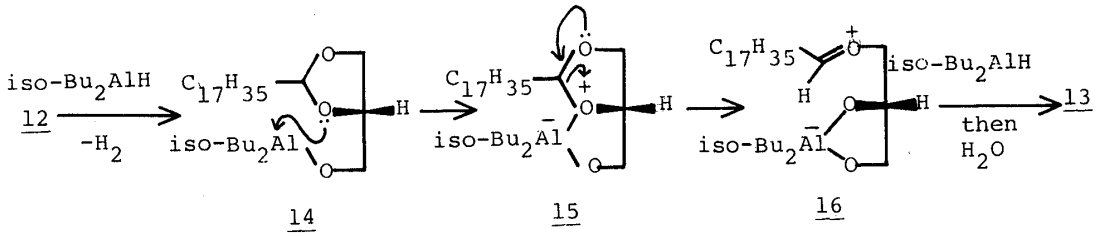


Chart 3

14, the aluminum atom of which acts as Lewis acid to coordinate the neighboring oxygen allowing site selective cleavage of the acetal ring to give the oxonium betaine 16 via 15 which then was reduced with another hydride reagent to give the vic-glycol (S)-13 as shown in chart 3.

Second, 1-O-octadecyl glycerol acetonide 17, $[\alpha]_D$ + 9.27° (c=1.144, $CHCl_3$) (lit.[6] $[\alpha]_D$ + 8.1° (c=20, $CHCl_3$)), prepared from the acetonide 8, was directly converted, by heating with benzaldehyde in toluene in the presence of a catalytic amount of p-toluenesulfonic acid, into the benzylidene acetal 18 in 84% yield as a mixture of epimers. Treatment of the mixture with 3.0 M eq of diisobutylaluminum hydride at 0°C for 20 min afforded a mixture of two products which could be separated by silica gel column chromatography to give the derivatives 3-O-benzyl-(S)-10, $[\alpha]_D$ - 1.42° (c=3.656, benzene) (lit.[6] $[\alpha]_D$ - 1.77° (c=10, benzene)) in 67% yield, and 2-O-benzyl- 19, $[\alpha]_D$ + 9.47 (c=1.584, benzene) (lit.[6] $[\alpha]_D$ + 8.7° (c=5, benzene)) in 22 % yield. These compounds have already been shown to be convertible into C_{18}-PAF 6 with inversion of their chiralities.[6]

Chirality inversion of the (R)-1,2-glycol (R)-13 was also carried out efficiently by applying the method which we developed recently.[15] Thus, the

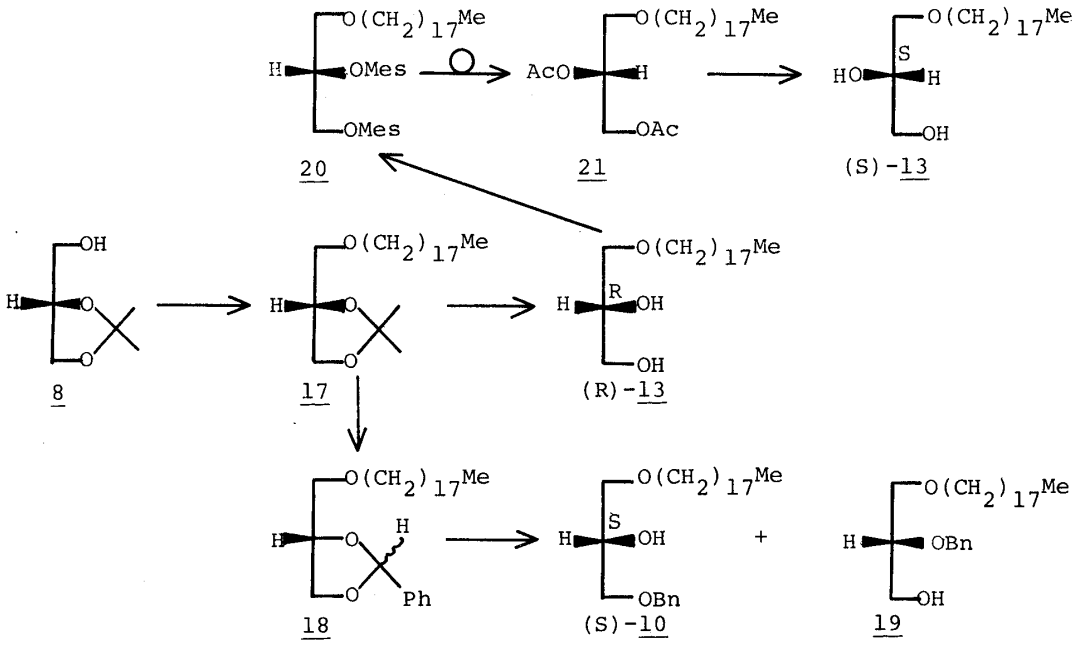


Chart 4

(R)-glycol (R)-13, $[\alpha]_D$ + 2.59° (c=3.240, THF) (lit.[6] $[\alpha]_D$ + 2.36° (c=7, THF)), obtained from the acetonide 17 by acid hydrolysis, was first converted into the dimethanesulfonate 20 which was then treated with 5.0 M eq of potassium acetate in boiling acetic anhydride to give the diacetate 21 with inversion of the chirality. Removal of the acetyl groups with methanol in the presence of potassium carbonate gave the (S)-vic-glycol (S)-13, $[\alpha]_D$ - 2.46° (c=7.078, THF), in 70% overall yield.

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