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SYNTHESIS OF D-*ERYTHRO*-SPHINGOSINES [1]

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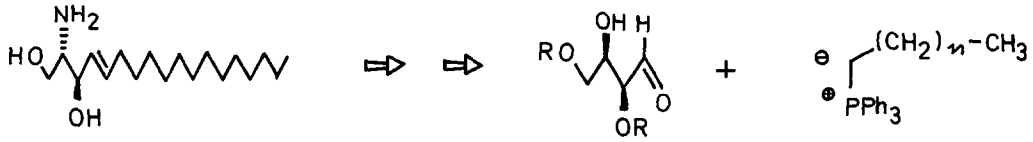
Abstract: *2,4-Di-O-protected D-threose, readily available from D-galactose, is a versatile intermediate for D-erythro-sphingosine syntheses via trans-selective Wittig reaction, azide introduction at the unprotected hydroxylic group, and subsequent azide reduction.*

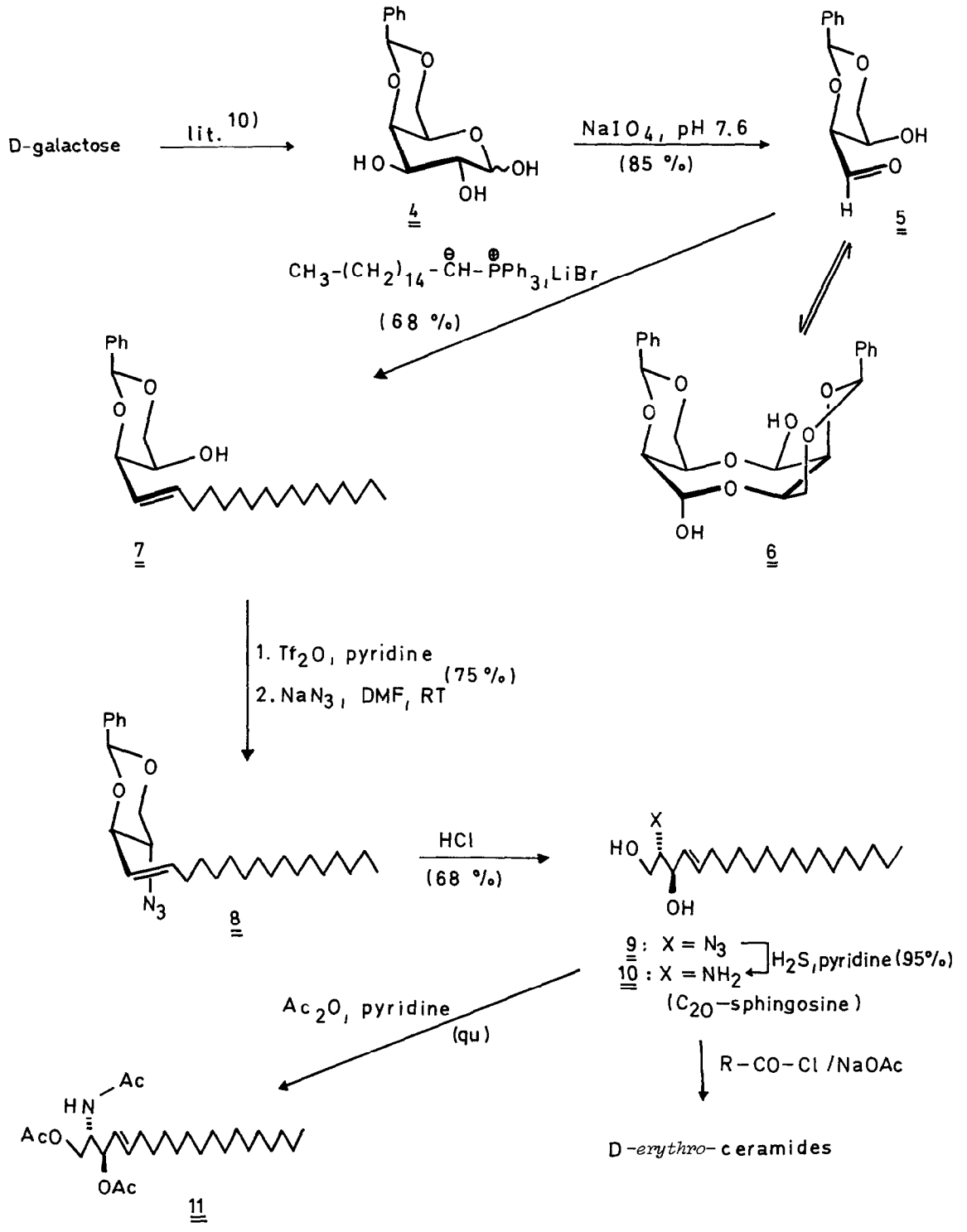
The synthesis of glycosphingolipds, which are major membrane constituents, has gained increasing interest because of the aim to understand the role and function of biological membranes [2]. Several syntheses for the required sphingosines (mainly C_{18}- and C_{20}-sphingosine; structure 1 and 10, respectively) have been reported recently [3-8]. We have developed via an *erythro*-specific aldol reaction of N,O-silylated glycine with α,β-unsaturated aldehydes a two-step synthesis of racemic sphingosines, which are easily resolved on the ceramide or cerebroside stage [5]. Bernet and Vasella have exemplified a six-step synthesis of D-*erythro*-C_{18}-sphingosine (1) starting from pentadecyne and using the Sharpless asymmetric epoxidation [6]. Garigipati and Weinreb developed a ten-step synthesis of racemic sphingosine 1 via intramolecular Diels-Alder cycloaddition of N-sulfinyl-carbamates [7]. Ogawa and coworkers converted 1,2:5,6-di-O-isopropylidene-D-glucofuranose as carbohydrate template in a ten- to eleven-step synthesis into D-*erythro*-C_{18}-sphingosine (1) [8]. In this synthesis carbon atoms C-2 to C-5 of D-glucose become part of the sphingosine molecule this way requiring two separate CC-bond cleavage reactions.



1 (C_{18} – sphingosine) 2 3 ($n = 12$)

Inspection of the sphingosine structure indicates that a 2,4-di-O-protected D-threose 2 (and a simple Wittig reagent 3) is required for an efficient D-*erythro*-specific synthesis of these unsaturated aminodiols. A compound of this structure should be readily accessible from 4,6-O-benzylidene-D-galactose 4 by cutting off carbon atoms 1 and 2 [9]. Compound 4 is available in a one-step procedure from D-galactose [10]. Sodium metaperiodate treatment at pH 7.6 provides directly the desired 2,4-O-benzylidene-D-threose 5 in high yield. This compound was in equilibrium with a dimer, possessing according to ^{1}H NMR data structure 6. Wittig reaction of this material with hexadecanylidene triphenylphosphorane in presence of an excess of lithium bromide [11] affords practically exclusively the *trans*-eicosentriol derivative 7. Activation of the hydroxy group with the trifluoromethane sulfonyl (Tf) moiety gives better yields in the azide introduction than activation by mesylation or tosylation. Isolation of the trifluoromethane sulfonate is not required, it can be converted with sodium azide in DMF at room temperature directly to the azide 8 in 75 % overall yield. Acid treatment provides the deprotected azide 9 (mp. 56-57°C), which was smoothly reduced to the D-*erythro*-C_{20}-sphingosine (10) (mp. 70-72°C) with hydrogen sulfide as reducing agent. The corresponding D-*erythro*-C_{18}-sphingosine (1) is obtained via this route in identical yields; the method is also successful in larger scale preparations [12].

For structural proof compound 10 was transformed into the known tri-acetyl-sphingosine 11 [$[\alpha]_D^{21}$ -22.3° (c = 2; HOAc); lit. [13]: $[\alpha]_D^{21}$ -22.86° (3 % in HOAc); mp. 104°C; lit. [13]: mp. 106-107°C]. Compound 10 was also converted in one-step procedures to different D-*erythro*-ceramides [12,14].


D-galactose
lit. 10)
NaIO4, pH 7.6
(85 %)
4
5
CH3-(CH2)14-CH-PPh3, LiBr
(68 %)
7
6
1. Tf2O, pyridine
2. NaN3, DMF, RT (75 %)
8
HCl
(68 %)
9: X = N3
10: X = NH2
H2S, pyridine (95%)
(C20-sphingosine)
Ac2O, pyridine
(qu)
R-CO-Cl /NaOAc
11
D-erythro-ceramides

1) Synthesis of Sphingosines, Part 2. - This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. - Part 1, see ref. 5.

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5) R.R. Schmidt and R. Kläger, Angew.Chem. 94, 215 (1982); Angew.Chem.Int.Ed.Engl. 21, 210 (1982); Angew.Chem.Suppl. 1982, 393.

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8) K. Koike, Y. Nakahara, and T. Ogawa, Glycoconjugate J. 1, 107 (1984). - The di-O-protected sphingosine 1 was directly converted to the corresponding ceramide.

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