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**Title:** Synthesis of a versatile (S)-3-(hydroxymethyl)butane-1,2,4-triol building block and its application for the stereoselective synthesis of N-homoceramides

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Synthesis of a Versatile (S)-3-(Hydroxymethyl)butane-1,2,4-triol Building Block and its Application for the Stereoselective Synthesis of N-Homoceramides

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ABSTRACT

A versatile (S)-3-(hydroxymethyl)butane-1,2,4-triol building block has been synthesized starting from D-isoascorbic acid, a common food preservative. The key transformation in this approach was the introduction of branching through a high yield and fully regioselective epoxide opening. This flexible synthon has been elaborated to a new class of (dihydro)-N-homo(phyto)ceramides.

The development and availability of reliable and efficient methods for the construction of chiral building blocks are crucial for the synthesis of many pharmaceutical agents and complex natural products. These chiral building blocks can be derived from the chiral pool or by chemical/enzymatic means from achiral or racemic starting material.

(S)-3-(Hydroxymethyl)butane-1,2,4-triol is a flexible, multivalent scaffold with defined stereochemical features which can be exploited by judicious selection of appropriate protecting groups. Some examples of the synthetic potential of this intermediate are summarized in Figure 1. Indeed, sugar derivatives (S,S)-4-(hydroxymethyl)pyrrolidine-3-ol,1 the enantiomer of the common precursor of second-generation purine phosphorylase inhibitors2 and oxetanocin A, a known antibacterial,2 (a) Tyler, P. C; Clinch, K. PCT Int. Appl. WO 2005033076, 2005. (b) Karlsson, S.; Hogberg, H.-E. Tetrahedron: Asymmetry 2001, 12, 1977-1982.

antitumoral and antiviral natural product, are readily accessible through a limited number of steps. Moreover, ceramide analogues with an inversed amide functionality could provide useful biochemical tools for assessment of ceramide interaction with a myriad of clinically relevant enzymes. Finally, simple elaboration of the other primary alcohol (C4-OH) to the amide part (C) gives access to D-threo-PDMP homologues (D-threo-1-phenyl-2-amino decanoyl-3-morpholinopropanol), an inhibitor of glucosyl ceramide synthase which is a potential target in the treatment of cancer.

Figure 1. Synthetic potential of key intermediate (S)-3-(hydroxymethyl)butane-1,2,4-triol: A) (aza)sugar analogues; B) ceramides and phytoceramides with an inversed amide functionality; C) PDMP homologues; D) N-(dihydro)homo(phyto)ceramides.

Here, we wish to demonstrate the usefulness of the (aza)sugar derivatives; B) ceramides and phytoceramides with an inversed amide functionality; C) PDMP homologues; D) N-(dihydro)homo(phyto)ceramides.

Figure 2. General structures of O1-homoceramides (1) and N-(dihydro)homo(phyto)ceramides (2-5).

Homologation is a classical tool in medicinal chemistry to alter biological properties of endogenous compounds. Salbutamol, for instance, a widely used bronchodilator with agonistic properties for β2-receptors, consists of a 4-hydroxy-3-hydroxymethylphenyl moiety instead of the catechol ring, which is present in (nor)adrenaline. Recently, our group reported an expedient route for the synthesis of D-erythro-OH-homoceramides. An alternative synthetic procedure for this class of non-natural ceramide analogues was later proposed by Ogino and coworkers. The authors found that several representatives exhibited considerable apoptotic activities. Recently, Schmidt and coworkers presented the synthesis of O2-homophosphoginosine-phosphate starting from D-galactose.

References:

N-acyl chain and C2 (Figure 2; 2-4). Interestingly, our procedure seemed also convenient for the synthesis of N-homophytoceramide (5), which can serve as key intermediate for the synthesis of α-galactosyl-N-homoceramide. This latter compound represents a homologue of α-galactosylceramide, a potentially useful agent for the treatment of autoimmune diseases.

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7 Salbutamol is the representative treatment for asthma and chronic obstructive pulmonary disease (COPD) in the WHO Essential Medicines Library (EMLib); Web site: http://www.who.int/medicines/EMLib.
Epoxide synthon 6 (Scheme 1), prepared from D-isoascorbic acid as previously described, provided the stereochemical and structural features required for our synthetic approach. Since epoxide opening is often hampered by regioselectivity issues involving the use of hazardous cyanide or additional synthetic steps implicated in allylic transformations, we opted to use 1,3-dithiane to introduce branching.

Scheme 1. Synthesis of key intermediate 8.

Assignment of the *erythro* configuration was achieved by converting intermediate 10 to the 3,4-isopropylidene protected triol 11 in a two steps sequence entailing silyl deprotection and dioxolane formation (Scheme 3; 51%) and subsequent comparison of ¹H NMR data with similarly protected natural D-ribo-azidophytosphingosine 12.


Hence, tritylation followed by reduction of the ester and subsequent epoxide opening with 2-lithio-1,3-dithiane produced intermediate 1,3-diol 7 with complete regioselectivity (47% yield in six steps from D-isoascorbic acid). Protection of 1,3-diol 7 with di-tert-butyldisilyl ditriflate followed by dithiane deprotection with MeI under alkaline conditions and final reduction of the unmasked aldehyde with NaBH₄ gave access to 8 (75% from 7, 36% from D-isoascorbic acid in 9 steps), which represents a unique intermediate from which each of the primary alcohols can selectively be addressed for further modification.

Access to D-ribo-N-homophytoceramide 5 is outlined in Schemes 2 and 3. Mesylation of intermediate 8 followed by azide introduction and trityl removal yielded alcohol 9 in good yield (83%). Subsequent periodinane oxidation and addition of tetradecylmagnesium chloride to the thus formed aldehyde furnished protected azido-N-homophytosphingosine 10 (40%) as a single diastereomeric form.


14 (a) Compound 12 has been prepared according to literature procedures starting from commercially available D-ribo-phytosphingosine (ref. 15) (b) Both 11 (¹J₃,₄ = 5.57 Hz) and 12 (¹J₃,₄ = 5.38 Hz) exhibit a comparable vicinal coupling constant thereby indicating a cis-relationship of the ring substituents (standard sphingolipid numbering is used for clarity reasons).
Azide reduction under Staudinger conditions following TBDS protection of the secondary alcohol in 10 and subsequent acylation of the primary amine with palmitoyl chloride afforded silyl protected intermediate 13 (39%). Final desilylation with TBAF furnished D-ribo-N-homophytoceramide 5 (62%).

Subsequent oxidation of the primary alcohol with Dess-Martin periodinane yielded the intermediate aldehyde. Although reaction conditions specifically addressed the E-isomer, Schlosser-Wittig olefination surprisingly only produced Z-isomer 15. Hydrazine mediated phthalimide deprotection followed by acylation with palmitoyl chloride and silyl deprotection with TBAF furnished Z-N-homoceramide 2 (Scheme 5; 59%). Photoinduced double bond isomerisation in the presence of diphenyl disulfide as sensitizer produced, after two recrystallisations, isomerically pure E-N-homoceramide 3 (38%). Finally, hydrogenation of the Z-double bond in 2 gave access to dihydro-N-homoceramide 4 (84%).

In summary, we have reported an expedient route towards a versatile (S)-3-(hydroxymethyl)butane-1,2,4-triol scaffold starting from D-ascorbic acid, a common food preservative. The key transformation in this approach was the introduction of branching through a high yield and fully regioselective 2-lithio-1,3-dithiane epoxide opening. Based on this flexible synthon, we report the first synthesis of (dihydro)-N-homoceramides 2-4. In addition, a fully stereoselective Grignard reaction gave access to D-ribo-N-homophytoceramide 5, which will be utilised in a further study towards the elaboration of its α-galacosyl derivative.

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Supporting Information Available. Full experimental details and copies of 1H and 13C spectra are available free of charge via the Internet at http://pubs.acs.org

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Scheme 5. Access to (dihydro)-N-homoceramides 2-4.

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