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Catalytic Asymmetric Synthesis of Phthioceranic Acid, a Heptamethyl-Branched Acid from *Mycobacterium tuberculosis*

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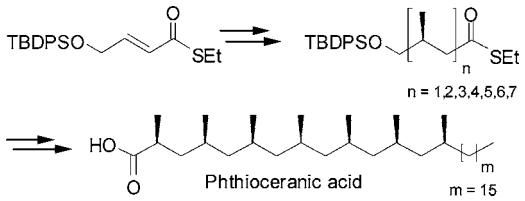
ABSTRACT



The first total synthesis of phthioceranic acid (1) has been achieved by an iterative catalytic asymmetric 1,4-addition protocol. This method provides a robust and high-yielding route for the preparation of 1,3-oligomethyl (deoxypropionate) arrays. After the desired number of methyl groups has been introduced, these arrays can be further functionalized at both ends to polymethyl-substituted lipids such as phthioceranic acid, a heptamethyl-branched fatty acid from the virulence factor Sulfolipid-I (2), found in *Mycobacterium tuberculosis*.

Mycobacterium tuberculosis is still one of the most lethal infectious diseases in the world, with approximately three million casualties annually.[1] The rising number of human immunodeficiency virus (HIV) infected people is a major risk factor for the development of tuberculosis. Although efforts are made to control tuberculosis, mutations within the bacterium and irresponsible use of antibiotics are blocking a final stop to the disease.[1,2] New drugs are currently under investigation.[1,2]

One of the reasons that *M. tuberculosis* is so hard to destroy is the unusual thick cell wall of the bacteria.[3] The cell wall of *M. tuberculosis* consists partly of long chain lipids which create a hydrophobic barrier for antibiotics and other molecules. Components of that cell wall however are known to induce an immune response in the human body and are therefore potential candidates for vaccines or adjuvants.[4] A compound class that is found in the cell wall of the bacterium comprises the Sulfolipids.[4,5] Sulfolipids are acyl-substituted trehaloses containing a sulfate functionality. Sulfolipid-I (SL-I) (**2**, Figure 1) is of particular interest because it is known to induce an immune response.[5,6] SL-I (2,3,6,6′-tetraacyltrehalose 2′-sulfate, **2**) and its acyl groups were characterized by Goren decades ago[7,8] and shown to

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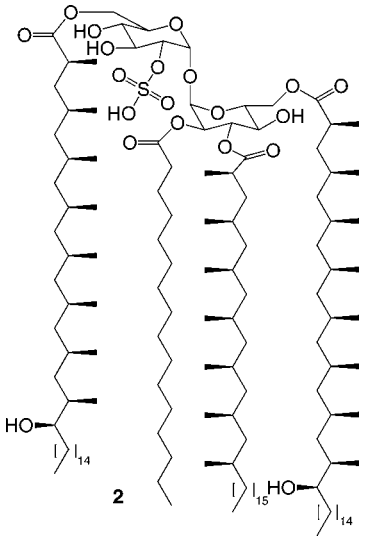

Figure 1. Sulfolipid-I (SL-I).

contain one palmitic acid, one phthioceranic acid, and two hydroxyphthioceranic acid residues.

Phthioceranic (**1**) and hydroxyphthioceranic acid are hepta- and octamethyl-branched dextrorotatory deoxypropionates, respectively, containing a palmitoyl chain and a hydroxy functionality at C17 for the latter. There is strong evidence that the stereochemistry at the methyl branches is all-*L*,[4a,7] e.g., all-*S* for phthioceranic acid and 2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,-14*R*,16*R* for hydroxyphthioceranic acid. The absolute stereochemistry of tetramethyl-substituted laevorotatory mycocerosic acid has been determined as all-*D* (*R*) by degradation studies.[4a] Phthioceranic acids were compared to mycocerosic acid and all-*S* dextrorotatory mycolipenic acids (2,4,6-trimethyl-tetracos-2-enoic acid).[4a] More recent studies showed that mycocerosic acid is produced by the enzyme mycocerosic acid synthase (MAS), whereas phthioceranic and hydroxyphthioceranic acid are produced by polyketide synthase, Pks2.[3,6g] This accounts for the opposite stereochemistry observed. The biosynthesis of the mycolipenic acids is genetically closely related to that of the phthioceranic acids.[6d,g] The hydroxy group in hydroxyphthioceranic acid is assumed to be *D* (*R*), but no direct evidence exists to this date.

There is a broad interest in the synthesis of 1,3-polymethyl arrays because of their presence in many natural products such as fatty acids and lipids, antibiotics, and marine natural products.[9−11] Most of the current synthetic approaches are based on iterative chiral auxiliary strategies. For compounds containing multiple methyl groups, such as **1**, these approaches are however laborious and less practical. An efficient catalytic asymmetric approach is therefore highly warranted.

Recently, we showed that the asymmetric conjugate addition of MeMgBr catalyzed by a [**4**·CuBr] complex comprises a very powerful iterative method for the preparation of deoxypropionates.[14,16,17] On the basis of this method, we prepared mycoceranic acid, a compound related to **1** but of opposite stereochemistry and containing an array of four methyl groups.[14,15]

An alternative method based on an asymmetric zirconium-catalyzed carboalumination, palladium-catalyzed cross-coupling has been reported by Negishi and co-workers. This method was used in the synthesis of a four-methyl-branched fatty acid from the graylag goose.[12] Very recenty, Burgess and co-workers reported an asymmetric hydrogenation approach to deoxypropionates starting with building blocks based on the Roche ester.[13]

To put the robustness and efficiency of our iterative catalytic conjugate addition methodology to the test, and as a prelude to the enantioselective total synthesis of Sulfolipid-I, we decided to embark on the first synthesis of phthioceranic acid, a heptamethyl-substituted fatty acid from *M. tuberculosis*.

The synthesis of **1** starts with **3**[14] that was submitted to an enantioselective 1,4-addition with MeMgBr, catalyzed by 1 mol % of **4**·CuBr in *t*-BuOMe at −78 °C (Scheme 1). The corresponding thioester **5** was isolated in an excellent

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(10) For a recent review on deoxypropionate units, see: Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, *7*, 1057−1076.

(11) Review: Modern aldol methods for the total synthesis of polyketides. Schetter, B.; Mahrwald, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 7506−7525.

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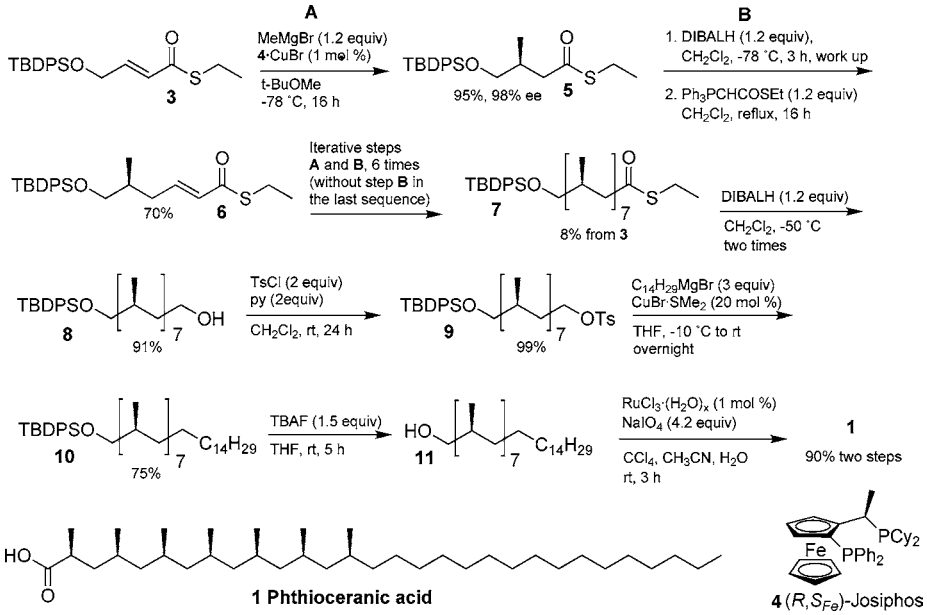
Scheme 1



95% yield and 98% ee. This conjugate addition reaction was followed by a two-step transformation of **5** into **6** via reduction of the thioester to its corresponding aldehyde and subsequent Wittig reaction with $Ph_3PCHCOSEt$ (E/Z > 95:5). By repeating this sequence of 1,4-addition, reduction, and Wittig olefination, we introduced all seven methyl groups in a 1,3-*syn* fashion with excellent stereoselectivity and very high yield. Thus, heptamethyl-substituted thioester **7** was synthesized in 19 steps with 8% overall yield starting from **3**. The diastereoselectivity of all iterative conjugate addition reactions was >96%, as calculated from the clearly observed *syn*/*anti* isomers by ^{1}H NMR.[18]

Thioester **7** was reduced with DIBALH[19] to alcohol **8**, which was subsequently converted into tosylate **9** with 2 equiv of TsCl and pyridine. The long aliphatic chain was introduced via a copper-catalyzed coupling reaction with $C_{14}H_{29}MgBr$ (3 equiv) and 20 mol % of $CuBr{\cdot}SMe_2$. The resulting silylether **10** was deprotected with TBAF to give alcohol **11**, which was finally oxidized to title compound **1** with catalytic $RuCl_3{\cdot}(H_2O)_x$ and $NaIO_4$ in 90% over two steps. The overall yield of the synthesis is 4% over 24 steps. No minor diastereomers of **1** could be observed by ^{1}H or ^{13}C NMR, most probably as a result of the chromatography steps which remove traces of minor diastereoisomers. The optical rotation of synthetic **1** was +4.60 ($[\alpha]_D$, c = 1.12, $CHCl_3$). To compare our material with the available literature data for the natural product, a sample of **1** was converted into the corresponding methyl ester. Its optical rotation, $[\alpha]_D$ = +6.2 (c = 0.55, $CHCl_3$), is in agreement with the value reported for the isolated compound, which consists of a mixture of phthioceranic acid homologues ($[\alpha]_D$ = +7.9 (c = 2.03, $CHCl_3$)).[7c] The mass spectra of the methyl esters of both synthetic **1** and the natural product were compared and are in agreement (M = 564) (see Supporting Information for details).

In summary, we have completed the first synthesis of phthioceranic acid as a prelude to the synthesis of SL-I. By applying the iterative 1,4-addition protocol, we were able to introduce an unprecedented array of seven methyl groups in a 1,3-*syn* fashion. Overall, **1** was prepared in 24 steps with excellent stereoselectivity. With this synthesis, the structure and stereochemistry of phthioceranic acid has been confirmed and **1** is available in sufficient quantities for the synthesis of **2**. Currently, the iterative protocol is being explored in our labs for the synthesis of hydroxyphthioceranic acid.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For full details, see Supporting Information.
(19) The thioester was reduced with DIBALH in two steps via the aldehyde.