Catalytic asymmetric synthesis of mycocerosic acid†

Bjorn ter Horst, Ben L. Feringa* and Adriaan J. Minnaard*

Received (in Cambridge, UK) 1st September 2006, Accepted 6th October 2006
First published as an Advance Article on the web 6th November 2006
DOI: 10.1039/b612593j

The first catalytic asymmetric total synthesis of mycocerosic acid was achieved *via* the application of iterative enantioselective 1,4-addition reactions and allows for the efficient construction of 1,3-polymethyl arrays with full stereocontrol; further exemplified by the synthesis of tetramethyl-decanoic acid, a component of the preen-gland wax of the graylag goose, *Anser anser*.

Mycobacterium tuberculosis, the perpetrator of tuberculosis, is still one of the predominant infectious agents. Irresponsible use of available antibiotics has resulted in the emergence of resistant strains. The bacterium has an unusually thick cell wall, which consists partly of long-chain lipids,[1] providing a very hydrophobic barrier to antibiotics and other molecules. These lipids are potential drug targets because they induce an immune response and play an important role in the build up and strength of the cell wall.[2] One of these lipids[1] is PDIM A (Fig. 1), a wax which contains two tetramethyl substituted saturated acids (mycocerosic acid). For physiological and, especially, immunological studies, access to pure cell wall lipidic compounds is of paramount importance. However, in addition to regulatory restrictions, culturing of *M. tuberculosis* is difficult and purification of components from the lipid fraction is complicated. An effective synthetic route to these lipids is therefore highly desirable but has not been reported until now.

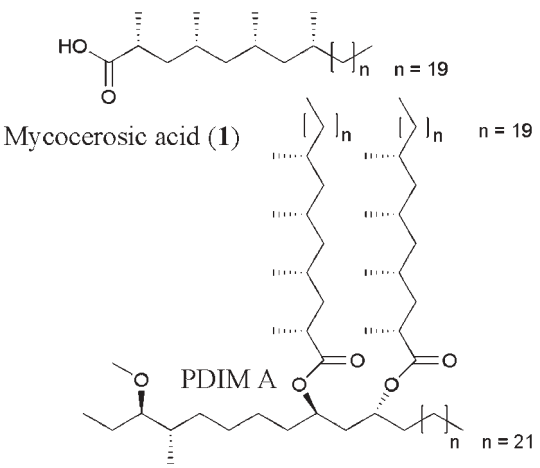


Fig. 1 PDIM A and mycocerosic acid.

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands. E-mail: B.L.Feringa@rug.nl; A.J.Minnaard@rug.nl

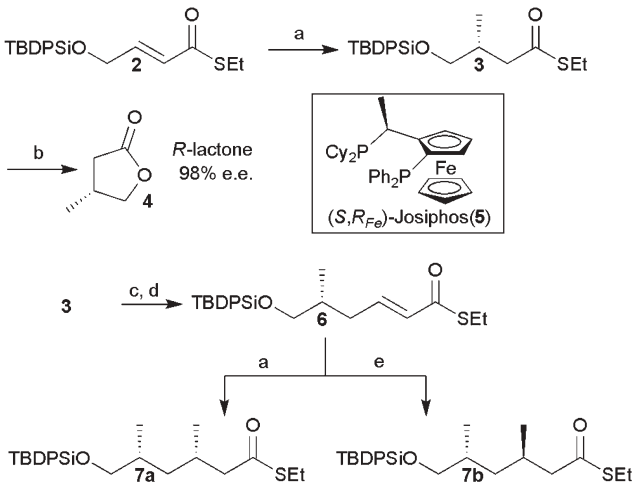
† Electronic supplementary information (ESI) available: Detailed experimental procedures, ^{1}H and ^{13}C NMR spectroscopic and analytical data of all compounds in Schemes 1, 2 and 3. See DOI: 10.1039/b612593j

Mycocerosic acid, one of the many methyl-branched fatty acids from *M. tuberculosis*, was first elaborated by Marks and Polgar[3] in the fifties. In 1963 Polgar and Smith[4] elucidated the absolute stereochemistry by degradation studies, which was confirmed subsequently by the synthesis of mycocerosic acid starting from chiral pool compounds or *via* a route involving kinetic resolution.[5,6] These studies confirmed that the natural product was laevorotatory and possessed an all-*R* configuration. Rainwater and Kolattukudy[7] studied the biosynthesis of mycocerosic acid and found that the enzyme responsible was specific for methylmalonyl-CoA and would not incorporate malonyl-CoA into fatty acids.

The 1,3,5,… *n*-polymethyl alkyl chains (where n = 7, 9, 11,…) ("deoxypropionate oligomers")[8] occur widely in many natural products including fatty acids and lipids,[1] marine natural products[9] and antibiotics.[10] Most of the synthetic procedures reported for 1,3-polymethyl arrays are based on laborious iterative chiral auxiliary strategies (*i.e.*, enolate alkylations, conjugate additions, and allylic alkylations).[11–13] Very recently, an attractive iterative catalytic asymmetric procedure for 1,3-dimethyl arrays was reported by Negishi and co-workers.[10,14]

Earlier work of our group demonstrated that iterative catalytic asymmetric conjugate additions of organometallic reagents lead to excellent stereochemical control in the synthesis of 1,3-methyl arrays.[15] Using a related approach, we reported recently an efficient strategy for the stereocontrolled synthesis of 1,5,9,*n*-polymethyl alkyl chains ("saturated polyisoprenoids"), applied in the synthesis of *beta*-D-mannosyl phosphomycoketides from *M. tuberculosis*.[16]

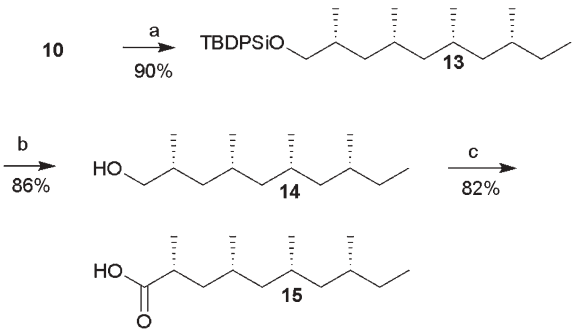
We anticipated that the Cu/Josiphos catalyzed iterative conjugate addition of MeMgBr to unsaturated thioesters[17] would be an excellent strategy for the total synthesis of enantiopure **1** (Scheme 1). The starting material should have a functionality at the terminus of the unsaturated thioester that is robust under the iterative reaction conditions (conjugate addition, Pd catalysed reduction, and Wittig reaction). For this reason we selected **2**, an unsaturated thioester with a protected hydroxyl group, prepared from glycol in 3 steps. Substrate **2** gave excellent enantioselectivity (98% ee) and complete regioselectivity in the copper catalysed 1,4-addition with MeMgBr and 1 mol% of CuBr/**5** (Scheme 1). Upon deprotection, the known lactone **4** was formed, which allowed confirmation of the absolute stereochemistry.[18] The pseudosymmetric bifunctional building block **3** was reduced to the corresponding aldehyde followed by a Wittig reaction[17] to give thioester **6**. The *syn*-selectivity of the second conjugate addition, leading to dimethyl thioester **7a**, could be established by ^{1}H-NMR spectroscopy in comparison with *anti* dimethyl thioester **7b**, prepared using *ent*-**5** (Scheme 1). The ratio *syn* : *anti* was higher than 96 : 4; for details see electronic supplementary information.†



Scheme 1 Conditions: (a) MeMgBr (1.2 equiv.), **5**·CuBr (1 mol%), *t*-BuOMe, −75 °C, overnight; (b) TBAF (2 equiv.), THF, 5 h; (c) 10% Pd/C (5 mol%), Et_3SiH (3 equiv.), CH_2Cl_2, rt, 20 min; (d) $Ph_3PCHCOSEt$, CH_2Cl_2, reflux 24 h; (e) MeMgBr (1.2 equiv.), *ent*-**5**.CuBr (1 mol%), *t*-BuOMe, −75 °C, overnight.

The reaction protocol shown in Scheme 1 was applied four times in an iterative procedure to arrive at the tetramethyl substituted compound **8** in ten steps with excellent selectivity[19,20] and an overall yield of 21% from **2** (Scheme 2). Twofold reduction of thioester **8** with DIBALH resulted in alcohol **9**, which was converted subsequently into **10** after treatment with TsCl. The introduction of the long alkyl chain was achieved by treatment of **10** with $C_{18}H_{37}MgBr$ and 20 mol% of CuBr·SMe_2 to give **11**, which was deprotected with TBAF to yield the tetramethyl substituted alcohol **12**. Oxidation of **12** gave mycocerosic acid (**1**) in 15 steps with an overall yield of 12% (86% average yield per step). Optical rotation (−6.4, c = 0.94, $CHCl_3$) and spectroscopic data are in agreement with the literature value[4] for the isolated product (−5.62, c = 8.9, $CHCl_3$).

To demonstrate the versatility of this iterative synthetic approach further we decided to synthesize the related tetramethyl-substituted fatty acid **15**, found in the preen-gland wax of the graylag goose *Anser anser* (Scheme 3). An asymmetric total synthesis of **15** was recently reported by Negishi and co-workers.[21]



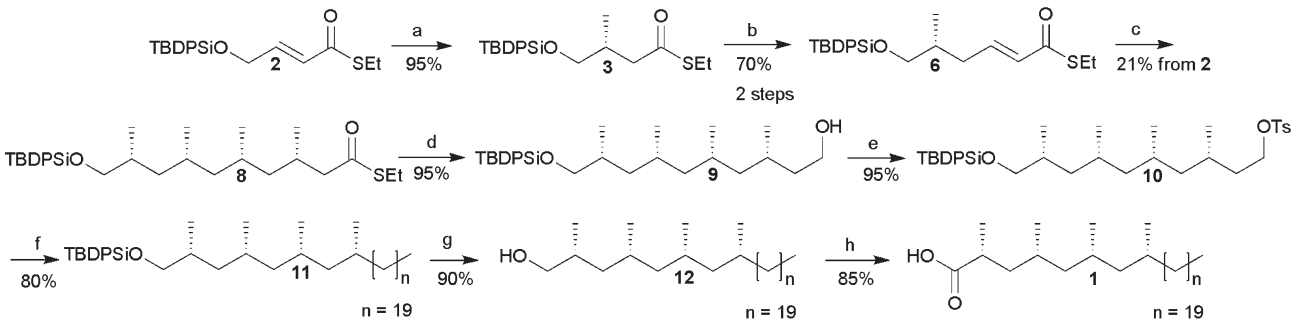
Scheme 3 Conditions: (a) $LiAlH_4$ (10 equiv.), THF, overnight; (b) TBAF (2 equiv.), THF, 5 h; (c) $RuCl_3·(H_2O)_x$ (1 mol%), $NaIO_4$ (4.2 equiv.) in a mixture of CCl_4, CH_3CN and H_2O, 3 h.

Treatment of tosylate **10** with an excess of $LiAlH_4$ gave silyl-protected alcohol **13** in high yield. Deprotection and oxidation as described for mycocerosic acid gave 2,4,6,8-tetramethyl-decanoic acid (**15**) in 15 steps starting from **2** with an overall yield of 13%.

Optical rotation (−27.8, c = 0.69, $CHCl_3$) and spectroscopic data are in agreement with literature values (−25.1, c = 0.2, $CHCl_3$).[21]

In summary, a highly efficient strategy for the preparation of deoxypropionates has been developed. It gives access to all possible stereoisomers since both *syn* and *anti* 1,3-polymethyl arrays are accessible. The methodology is illustrated by the preparation of two naturally occurring fatty acids, mycocerosic acid (**1**) and 2,4,6,8-tetramethyldecanoic acid (**15**). The overall yield of these syntheses (12% and 13%, respectively) is such that these and related compounds can be prepared readily for biological studies. Further applications using this strategy are in development currently in our laboratory.

We thank T. D. Tiemersma-Wegman (GC) and A. Kiewiet (MS) for technical support. Financial support from the Netherlands Organization for Scientific Research (NWO/CW) and a generous gift of Josiphos ligand from Solvias, Basel, are gratefully acknowledged.



Scheme 2 Conditions: (a) MeMgBr (1.2 equiv.), **5**.CuBr (1 mol%), *t*-BuOMe, −75 °C, overnight; (b) 10% Pd/C (5 mol%), Et_3SiH (3 equiv.), CH_2Cl_2, rt, 20 min, work up; $Ph_3PCHCOSEt$, CH_2Cl_2, reflux 24 h; (c) steps a, b were repeated two times followed by step a; (d) DIBALH (2 equiv.), CH_2Cl_2, −20 °C, 3–4 h, two times; (e) TsCl (2 equiv.), pyridine (2 equiv.), CH_2Cl_2, overnight; (f) $C_{18}H_{37}MgBr$ (3 equiv.) and CuBr·SMe_2 (20 mol%), THF, overnight; (g) TBAF (2 equiv.), THF, 5 h; (h) $RuCl_3·(H_2O)_x$ (1 mol%), $NaIO_4$ (4.2 equiv.) in a mixture of CCl_4, CH_3CN and H_2O, 3 h.

Notes and references

1 (*a*) D. E. Minnikin, L. Kremer, L. G. Dover and G. S. Besra, *Chem. Biol.*, 2002, **9**, 545; (*b*) J. S. Cox, B. Chen, M. McNeil and W. R. Jacobs, Jr., *Nature*, 1999, **402**, 79.

2 J. D. Mougous, R. H. Senaratne, C. J. Petzold, M. Jain, D. H. Lee, M. W. Schelle, M. D. Leavell, J. S. Cox, J. A. Leary, L. W. Riley and C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 4258.

3 G. S. Marks and N. J. Polgar, *J. Chem. Soc.*, 1955, 3851.

4 N. Polgar and W. Smith, *J. Chem. Soc.*, 1963, 3081.

5 (*a*) N. Polgar and W. Smith, *J. Chem. Soc.*, 1963, 3085; (*b*) N. Polgar and W. Smith, *Chem. Ind.*, 1961, 1958.

6 G. Odham, E. Stenhagen and K. Waern, *Ark. Kemi*, 1969, **31**, 533.

7 D. L. Rainwater and P. E. Kolattukudy, *J. Biol. Chem.*, 1985, **260**, 616.

8 For an excellent recent review on deoxypropionate units see S. Hanessian, S. Giroux and V. Mascitti, *Synthesis*, 2006, **7**, 1057.

9 (*a*) D. R. Williams, A. L. Nold and R. J. Mullins, *J. Org. Chem.*, 2004, **69**, 5374; (*b*) M. Magnin-Lachaux, Z. Tan, B. Liang and E.-I. Negishi, *Org. Lett.*, 2004, **6**, 1425.

10 T. Novak, Z. Tan, B. Liang and E.-I. Negishi, *J. Am. Chem. Soc.*, 2005, **127**, 2838.

11 (*a*) D. A. Evans, R. L. Dow, T. L. Shih, J. M. Takacs and R. Zahler, *J. Am. Chem. Soc.*, 1990, **112**, 5290; (*b*) A. G. Myers, B. H. Yang, H. Chen and D. J. Kopecky, *Synlett*, 1997, 457 and references therein; (*c*) B. Breit and C. Herber, *Angew. Chem., Int. Ed.*, 2004, **43**, 3790 and references therein.

12 J. P. Cooksey, P. J. Kocienski, Y.-F. Li, S. Schunk and T. N. Snaddon, *Org. Biomol. Chem.*, 2006, **4**, 3325.

13 M. Kaino, Y. Naruse, K. Ishihara and H. Yamamoto, *J. Org. Chem.*, 1990, **55**, 5814.

14 E.-I. Negishi, Z. Tan, B. Liang and T. Novak, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5782.

15 J. Schuppan, A. J. Minnaard and B. L. Feringa, *Chem. Commun.*, 2004, 792.

16 (*a*) R. P. van Summeren, D. B. Moody, B. L. Feringa and A. J. Minnaard, *J. Am. Chem. Soc.*, 2006, **128**, 4546; (*b*) R. P. van Summeren, S. J. W. Reijmer, B. L. Feringa and A. J. Minnaard, *Chem. Commun.*, 2005, 1387.

17 R. Des Mazery, M. Pullez, F. López, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2005, **127**, 9966.

18 (*a*) H. G. W. Leuenberg, W. Boguth, R. Barner, M. Schmid and R. Zell, *Helv. Chim. Acta*, 1979, **62**, 455; (*b*) T. Mukayama, K. Fujimoto, T. Hirose and T. Takeda, *Chem. Lett.*, 1980, 635; (*c*) K. Mori, *Tetrahedron*, 1983, **39**, 3107.

19 Second addition d.r.; (3*S*,5*R*) : (3*R*,5*R*) : (3*S*,5*S*) : (3*R*,5*S*) = 97 : 2 : 1 : 0, third addition d.r.; (3*S*,5*R*,7*R*) : (3*R*,5*R*,7*R*) : (3*S*,5*S*,7*R*) : (3*S*,5*R*,7*S*) = 95 : 2 : 2 : 1, fourth addition d.r.; (3*S*,5*S*,7*R*,9*R*) : (3*R*,5*S*,7*R*,9*R*) : (3*S*,5*R*,7*R*,9*R*) : (3*S*,5*S*,7*S*,9*R*) : (3*S*,5*S*,7*R*,9*S*) = 94 : 1 : 2 : 2 : 1. Diastereoisomers less than 0.04% were neglected. Ratios were calculated from *syn*/*anti* ratios (^{1}H-NMR spectroscopy). The final product did not contain any minor diastereoisomers most probably as a result of the chromatography steps. See electronic supporting information (ESI)† for details.

20 S. Hanessian, N. Chahal and S. Giroux, Iterative Synthesis of Deoxypropionate Units: The Inductor Effect in Acyclic Conformation Design, *J. Org. Chem.*, 2006, **71**, 7403.

21 B. Liang, T. Novak, Z. Tan and E.-I. Negishi, *J. Am. Chem. Soc.*, 2006, **128**, 2770.