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Total Synthesis of Enantiopure $\beta$-$\alpha$-Mannosyl Phosphomycoketides from Mycobacterium tuberculosis

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$\beta$-Mannosyl phosphomycoketides (MPMs) 1 and 2 are potent mycobacterial antigens for T cells that were isolated in 2000 from Mycobacterium tuberculosis and Mycobacterium avium, respectively (Figure 1).1 Initial structural characterization did not include assignment of the stereochemistry of the highly unusual saturated oligoisoprenoid chain. However, the recent elucidation of the biosynthetic pathway of the side chain shows that all methyl-substituted stereogenic centers are introduced via the same mechanism through the iterative action of a polyketide synthase.2

In 2002, a synthesis of 2 was reported, confirming the overall molecular structure.3 However, as a stereorandom alkyl chain was used, the stereochemistry of the lipid part remained unsolved. Since the side chain is the only structural feature that distinguishes foreign antigens 1 and 2 from endogenous $\beta$-mannosyl phosphodolichols, its fine structure must be the basis on which the immune system discriminates. Further insight into the relationship between structure and activity requires a general synthetic protocol to synthesize MPMs with lipid chains of any desired length and stereochemistry.

Our efforts toward a stereoselective total synthesis of 1 were inspired by the notion that it would be an ideal target to test our recently reported conjugate addition (CA) protocols. As outlined in the retrosynthetic scheme (Figure 1), we envisaged that 1 could be assembled by connection of four chiral building blocks (3−6).

The construction of building block 3 started with a Wittig reaction of the readily accessible aldehyde 9 with PPh3CHO-SEt, to afford $\alpha,\beta$-unsaturated thioester 10 (Scheme 1).7 CA of MeMgBr to trans-10 in the presence of CuBr-SMe2 and chiral ligand L* resulted in the formation of (3R)-7 with excellent selectivity (93% ee).5 LiAIH4 reduction of the thioester proceeded readily to provide the corresponding primary alcohol 11. Finally, 11 was converted into sulfone (3R)-3 via Mitsunobu reaction with 1-tert-butyltetrazole-5-thiol, followed by oxidation with mCPBA.8

To prepare fragments 4 and 5 (Scheme 2), the hydroxyl moiety of (3R,7S)-8 was protected as a silyl ether, after which the methyl ester was reduced to afford the common precursor 12. Sulfone (3R,7S)-4 was subsequently obtained from 12 analogously to the synthesis of 3 from 11. For the assembly of 5, 12 was converted into the corresponding tosylate and then subjected to a Cu-catalyzed chain elongation reaction with n-pentylmagnesium bromide to give 13. Finally, treatment of 13 with TBAF furnished the primary alcohol, which was oxidized with TPAP/NMO to give aldehyde (2S,6S)-5.9

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Coupling of 4 with a small excess of 5 (1.15 equiv) in the presence of LiHMDS (1.05 equiv) yielded disoprenoid 14 (predominantly trans) in a rewarding 74%. The highest yields were obtained when 4 and 5 were mixed prior to addition of the base. Similar procedures using Wittig or Horner–Wadsworth–Emmons analogues of 4 consistently gave inferior results. Direct formation of a C–C single bond by Cu-catalyzed cross-coupling of the corresponding alkyl halides either under Grignard conditions or in presence of SmI₂ was highly unreliable and invariably gave low yields in our hands. To make 14 suitable for coupling to fragment 3, the primary alcohol was deprotected and oxidized to give aldehyde 15 (cf. conversion of 13 into 5).

Julia–Kocienski coupling of 3 (1.2 equiv) to 15 using LiHMDS (1.1 equiv) as the base yielded 16 (predominantly trans) in a satisfying 80% yield. Exposure to hydrogen over Pd/C simultaneously deprotected the primary alcohol and hydrogenated the double bonds to give saturated isoprenoid (all-S)-17. Assembly of fragment 6 (Scheme 3) started with the reaction of hemiacetal 18 with limiting diphenyl chlorophosphate in the presence of DMAP to give diphenyl [β-mannosyl] phosphate 19. We were pleased to find that coupling of a 2-fold excess of readily available 6 to (all-S)-17 (1.0 equiv) in the presence of 2,4,6-trisopropylbenzenesulfonyl chloride (3.0 equiv) proceeded well to give 20 in a gratifying 79% yield. Finally, deacetylation using NaOMe gave the target molecule (all-S)-1 in quantitative yield.

Biological evaluation of (all-S)-1 revealed that its antigenic potency for T cells is identical to that of the natural product within the margin of error, while stereorandom 2 is significantly less potent. The latter result implies that the stereochemistry of the lipid part has an unexpectedly strong influence on T-cell response.

In summary, we disclose the first (general) procedure for the total synthesis of enantiopure MPMs. To this end, a fully catalytic method to synthesize saturated oligoisoprenoids was developed. In addition, an alternative approach for the formation of the β-mannosyl phosphate linkage was shown to be successful. The synthetic viability of this new protocol is demonstrated by the concise total synthesis of (all-S)-1 with an overall yield of 6.7% and a longest linear sequence of 18 steps.

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Supporting Information Available: Detailed experimental procedures and spectroscopic (1H and 13C NMR) and analytical data of all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

References


2. Matsunaga, I.; Bhatt, A.; Young, D. C.; Cheng, T.-Y.; Eyles, S. J.; Besra, G. S.; Birken, V.; Porcelli, S. A.; Costello, C. E.; Jacobs, W. R., Jr.; Moody, D. B.; J. Exp. Med. 2004, 200, 1559–1569. On the basis of the biosynthetic pathway of mycoketidins and the prediction by the authors that the absolute stereochemistry of the alkyl chain is most likely all-S, we chose to prepare the molecule with that configuration.


10. Under these conditions, no epimerization at the α position of the aldehyde was observed.


12. GC analysis (see Supporting Information) showed a single isomer of 17, although it is likely that a trace of the diastereomer originating from incorporation of (S)-3 is still present.


15. The anomeric configuration of (all-S)-1 was unequivocally determined by NOE correlation between the anomeric hydrogen and H's 3 and 5 of the sugar moiety and by a cross-ring fragmentation (m/z 587.5) and a dehydration (m/z 689.5) in the low-energy ESI CID spectrum. Additional support was given by comparison of the chemical shift of the anomeric proton of 1 with that of the anomeric proton of the independently synthesized (all-S)-α-1 analogue as well as by comparison of the 1H NMR coupling of both anomers (α = 169 Hz, β = 159 Hz).

16. Bioassays were conducted at the Brigham and Women's Hospital, Harvard Medical School. Details will be reported in due course.