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Mimics of L-Rhamnose: Synthesis of C-Glycosides of L-Rhamnofuranose and an α-Azidoester as Divergent Intermediates for Combinatorial Generation of Rhamnofuranose Libraries

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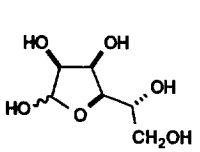
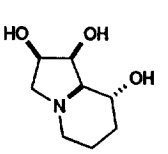
Abstract: The ring contraction of readily available δ-lactones provides a short route to the synthesis of both epimers of C-L-rhamnofuranosides, radical bromination of which give access to an α-azidocarboxylate as a divergent intermediate for applying combinatorial methodology for the preparation of a wide range of mimics of L-rhamnofuranose; such materials may provide an approach to the study of the biosynthesis of the cells walls of mycobacteria such as *Mycobacterium tuberculosis* and *M. leprae*.

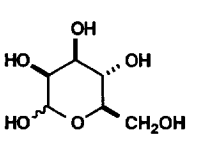
Tuberculosis, the causative agent of which is *Mycobacterium tuberculosis*, kills approximately 3 million people per year.[1] Recent studies on the structure of mycobacterial cell walls have identified a disaccharide linkage containing a L-rhamnopyranose unit which is apparently introduced into the cell wall *via* Tdp-rhamnose.[2,3] Rhamnose has no role in mammalian metabolism so that compounds which interfere specifically with rhamnose metabolism should not have any deleterious effect on humans. It is possible that a chemotherapeutic approach to the treatment of diseases induced by mycobacteria, such as tuberculosis and leprosy, would be to find compounds which inhibited either the biosynthesis of Tdp-rhamnose or its subsequent incorporation into the cell wall. There are at present no indications of the types of structures which might inhibit either of these two biochemical steps but it is reasonable to suggest that a molecule containing a rhamnose fragment might be an important antagonist of either process; thus the strategy outlined in this and the following two papers is that the enzymes involved in the biosynthesis and incorporation of Tdp-rhamnose will recognise a rhamnose epitope but that the other structural features for enzyme recognition are at present unknown; this is therefore an ideal project for generating libraries of compounds with diverse structures but all of which contain different potential rhamnose recognition elements.



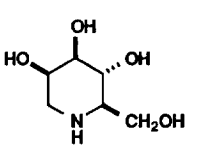
mannofuranose



swainsonine



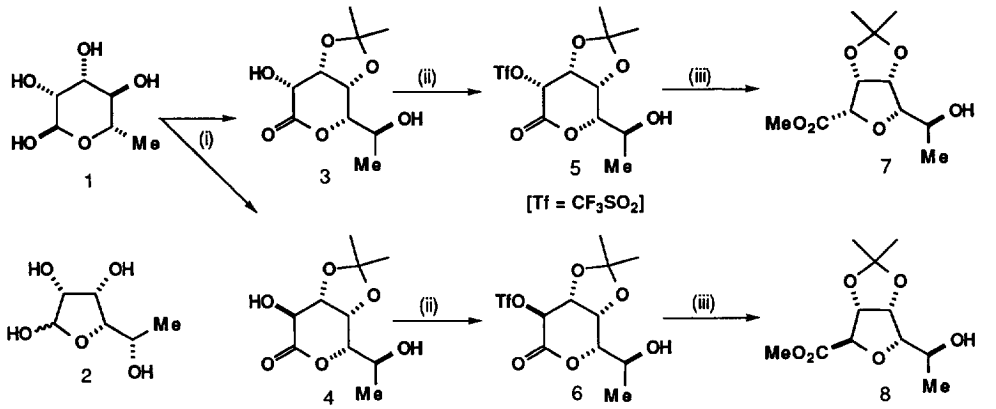
mannopyranose



deoxymannojirimycin

In general, the most powerful inhibitors of D-mannopyranosidases are mimics of D-mannofuranose, such as swainsonine, rather than mimics of D-mannopyranose, such as deoxymannojirimycin;[4,5] also, several furanose analogues of L-fucose are inhibitors of both fucosidases and

fucosyl transferases.[6] It may be that mimics of rhamnopyranose **1** and/or of rhamnofuranose **2** are suitable structures which may be recognised by enzymes involved in the biosynthesis of mycobacterial cell walls; screening of a wide range of structurally different mimics of L-rhamnose might provide new biochemical tools for the study of mycobacterial cell wall biosynthesis. This paper reports the synthesis of a series of seven carbon L-rhamnofuranose mimics, including readily accessible precursors to β- **8** and α-**7** C-glycosides, and an azidoester **10** which is a suitable precursor for a large number of rhamnofuranose analogues in which the anomeric position of L-rhamnofuranose comprises a constituent α-amino acid.



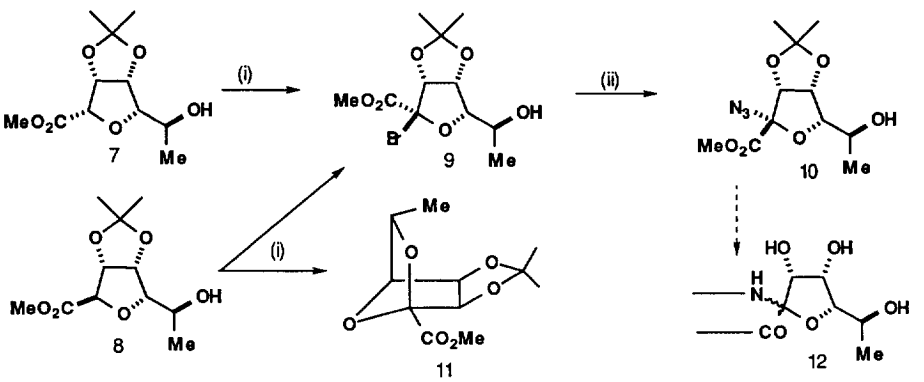
Scheme 1: (i) ref 7 (ii) Tf_2O, pyridine, CH_2Cl_2, -50°C to -20°C (iii) K_2CO_3, MeOH

The Kiliani chain extension of isopropylidene rhamnose[7] gives the epimeric δ-lactones **3** and **4**. Esterification of the major isomer **3** with trifluoromethanesulfonic (triflic) anhydride and pyridine in dichloromethane [Scheme 1] gave the corresponding triflate **5** which, with potassium carbonate in methanol, gave the tetrahydrofuran **7**[8] in 41% overall yield [Scheme 1]. Similar treatment of **4**, the minor lactone from the chain extension, gave the triflate **6** which afforded the epimeric α-carboxylate **8**[9] in 36% yield. The configurations at the carboxylate-substituted carbon were determined by equilibrium n.O.e. experiments and are consistent with the stereochemical outcome of other ring contraction reactions of γ-lactones.[10,11] The epimeric esters **7** and **8** are ideal intermediates for the generation of β- and α-C-glycosides of L-rhamnofuranose.

Radical bromination[12,13] [Scheme 2] of the more accessible ester **7** by treatment with N-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide produced a single, relatively unstable, bromide **9**[14] which reacted with sodium azide in dimethyl formamide to give the azide **10**[15] in an overall yield of 60%. When the epimeric ester **8** was subjected to the same bromination conditions, a mixture of the bromide **9** was formed, together with the bicyclic ester **11**[16] in 36% yield.

The difficulty in the separation of **11** from either the bromide **9** or the azide **10** means that it is much more convenient to prepare the azide **10** from **7** rather than the epimer **8**; in any case, it is also easier to make larger quantities of **7** rather than **8**. The difference in behaviour of the two epimers under radical bromination conditions could be that the radical at the anomeric position is relatively short lived; thus the radical generated

from **7** gives bromide **9** with retention of configuration. In contrast, **8** forms **9** in a sequence which requires inversion of the initially formed radical before capture; the bromide formed from **8** with retention of configuration is apparently unstable and spontaneous closes, presumably *via* an ionic S_N1-like process, to give the bicyclic ester **11**.



Scheme 2: (i) N-bromosuccinimide, $(PhCO_2)_2$, CCl_4 (ii) NaN_3, DMF

The azidoester **10**, which has the components of an α-amino acid at the anomeric position, is a potential intermediate for the generation of a wide range of compounds **12**. This is an ideal situation for applying combinatorial methodology as the materials would contain the rhamnofuranose epitope but would otherwise allow the formation of a broad library of compounds. The potential of this approach is exemplified in the following paper[17] by the preparation from **10** of spirohydantoins and spirodiketopiperazines of L-rhamnofuranose. In summary, this paper reports intermediates from which a wide range rhamnofuranose mimics could be generated.[18]

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[8] Selected data for **7**: m.p. 72-74 °C, $[\alpha]_D^{20}$ - 28 (c, 0.5 in $CHCl_3$), δ_H (500 MHz, $CDCl_3$): 1.34, 1.48 (2xs, 6H, 2x-CH_3), 1.38 (d, $J_{6,7}$ 6.4 Hz, 3H, -CH_3), 3.39 (dd, $J_{5,6}$ 7.9 Hz, $J_{4,5}$ 3.7 Hz, 1H, H_5), 3.81 (s, 3H, -$COOCH_3$), 4.19-4.24 (m, 1H, H_6), 4.26 (d, $J_{2,3}$ 4.3 Hz, 1H, H_2), 4.85 (dd, $J_{3,4}$ 6 Hz, 1H, H_4), 4.98 (dd, 1H, H_3); δ_C (50.3 MHz, $CDCl_3$): 20.57, 24.91, 25.63 (3xq, 3x-CH_3), 52.10 (q, -$COO\underline{CH_3}$), 65.85, 80.29, 80.91, 81.65, 85.61 (5xd, 5x-CH-), 113.53 (s, -C-), 167.95 (s, C=O].

[9] Selected data for **8**: gum, $[\alpha]_D^{20}$ - 33.2 (c, 0.5 in $CHCl_3$), δ_H (500 MHz, $CDCl_3$): 1.26 (d, $J_{6,7}$ 6.6 Hz, 3H, -CH_3), 1.35, 1.47 (2xs, 6H, 2x-CH_3), 3.80 (s, 3H, -$COOCH_3$), 3.82-4.05 (m, 1H, H_6), 4.15 (dd, 1H, H_5), 4.79 (d, $J_{2,3}$ 6.4, 1H, H_2), 4.89 (dd, 1H, H_4), 5.01-5.03 (m, 1H, H_3); δ_C (50.3 MHz, $CDCl_3$): 19.51, 25.01, 26.23 (3xq, 3x-CH_3), 52.01 (q, -$COO\underline{CH_3}$), 68.19, 80.21, 81.25, 82.03, 88.62 (5xd, 5x-CH-), 113.78 (s, -C-), 169.33 (s, C=O].

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[14] Selected data for **9**: oil, δ_H (500 MHz, $CDCl_3$): 1.33, 1.42 (2xs, 6H, 2x-CH_3), 1.37 (d, $J_{6,7}$ 6.2 Hz, 3H, -CH_3), 3.90 (s, 3H, -$COOCH_3$), 4,01 (dd, $J_{5,6}$ 8.2 Hz, $J_{4,5}$ 4 .0 Hz, 1H, H_5), 4.08-4.28 (m, 1H, H_6), 5.01 (dd, $J_{3,4}$ 5.7 Hz, 1H, H_4), 5.30 (d, 1H, H_3); δ_C (50.3 MHz, $CDCl_3$): 20.33, 24.91, 25.69 (3xq, 3x-CH_3), 53.39 (q, -$COO\underline{CH_3}$), 64.98, 78.55, 86.96, 89.86 (4xd, 4x-CH-), 98.55, 113.78 (2xs, 2x-C-), 164.52 (s, C=O).

[15] Selected data for **10**: a gum, $[\alpha]_D^{20}$ -20 (c, 0.5 in $CHCl_3$), δ_H (500 MHz, $CDCl_3$): 1.36 (d, $J_{6,7}$ 6.4 Hz, 3H, -CH_3), 1.40, 1.62 (2xs, 6H, 2x-CH_3), 2.35 (d, 1H, -OH), 3.81 (dd, 1H), 3.84 (s, 3H, -$COOCH_3$), 4.10-4.17 (m, 1H), 4.81-5.02 (m, 2H); δ_C (50.3 MHz, $CDCl_3$): 20.16, 24.31, 25.08 (3xq, 3x-CH_3), 53.34 (q, -$COO\underline{CH_3}$), 66.23, 80.37, 83.47, 83.71 (4xd, 4x-CH-), 94.86, 114.39 (2xs, 2x-C-), 167.87 (s, C=O].

[16] Selected data for **11**: m.p.: 110-112 °C, $[\alpha]_D^{20}$: -88.2 (c, 0.5 in MeOH); δ_H (500 MHz, $CDCl_3$): 1.27 (d, $J_{6,7}$ 6.7 Hz, 3H, -CH_3), 1.32, 1.48 (2xs, 6H, 2x-CH_3), 3.91 (s, 3H, -$COOCH_3$), 4.03-4.07 (m, 1H, H_6), 4.55 (d, $J_{3,4}$ 5.4 Hz, 1H, H_4), 4.59 (d, $J_{4,5}$ 3.3 Hz, 1H, H_5), ; 4.72 (d, 1H, H_3); δ_C (50.3 MHz, $CDCl_3$): 14.66, 25.53, 25.95 (3xq, 3x-CH_3), 53.02 (q, -$COO\underline{CH_3}$), 72.66, 76.83, 81.12, 82.25 (4xd, 4x-CH-), 104.56, 112,89 (2xs, 2x-C-), 164.32 (s, C=O).

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