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Mimics of L-Rhamnose: Analogues of Rhamnopyranose Containing a Constituent α-Amino Acid at the Anomeric Position. A Rhamnopyranose Analogue of Hydantocidin

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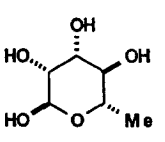
Abstract: Ionic brominative oxidation of 2-amino derivatives of protected heptonolactones derived from L-rhamnose provides a key bicyclic intermediate for the synthesis of analogues of L-rhamnopyranose with spirohydantoins and spirodiketopiperazines at the anomeric position; the same intermediate can be used for the synthesis of novel glycopeptides containing a constituent rhamnopyranose amino acid. Such materials may allow an approach to new studies of diseases induced by mycobacteria, such as tuberculosis and leprosy.

As part of a project with the aim of discovering inhibitors of cell wall biosynthesis of mycobacteria,[1] the preceding paper[2] described a number of seven carbon mimics of L-rhamnofuranose **1** in which a key step was the radical bromination of tetrahydrofuran carboxylates. Recently, both a spirohydantoin[3] and a spirodiketopiperazine[4] of glucopyranose have been shown to be specific inhibitors of glycogen phosphorylase, a glucosyl transferase, and these rhamnose analogues may interact with the active site of some rhamnose processing enzymes.



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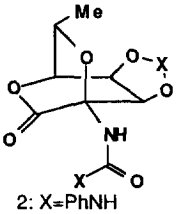
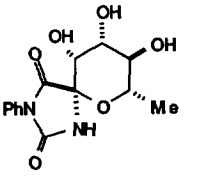


2: X=PhNH
3: X=ZNHCH$_2$



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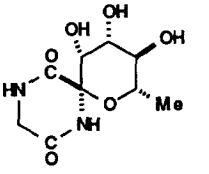

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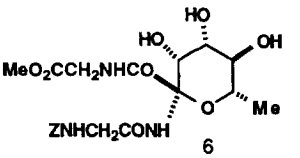
This paper reports the synthesis of analogues of L-rhamnopyranose **1** in which an ionic brominative oxidation gives access to stable bicyclic intermediates **2** and **3** with both a nitrogen and a carbonyl function at the anomeric position of rhamnopyranose: the configuration at the anomeric position is defined by the structural requirements of the lactones **2** and **3**, so that stereospecifically defined anomers of the spirohydantoin **4**, the spirodiketopiperazine **5** and the glycopeptide **6** are easily accessible.



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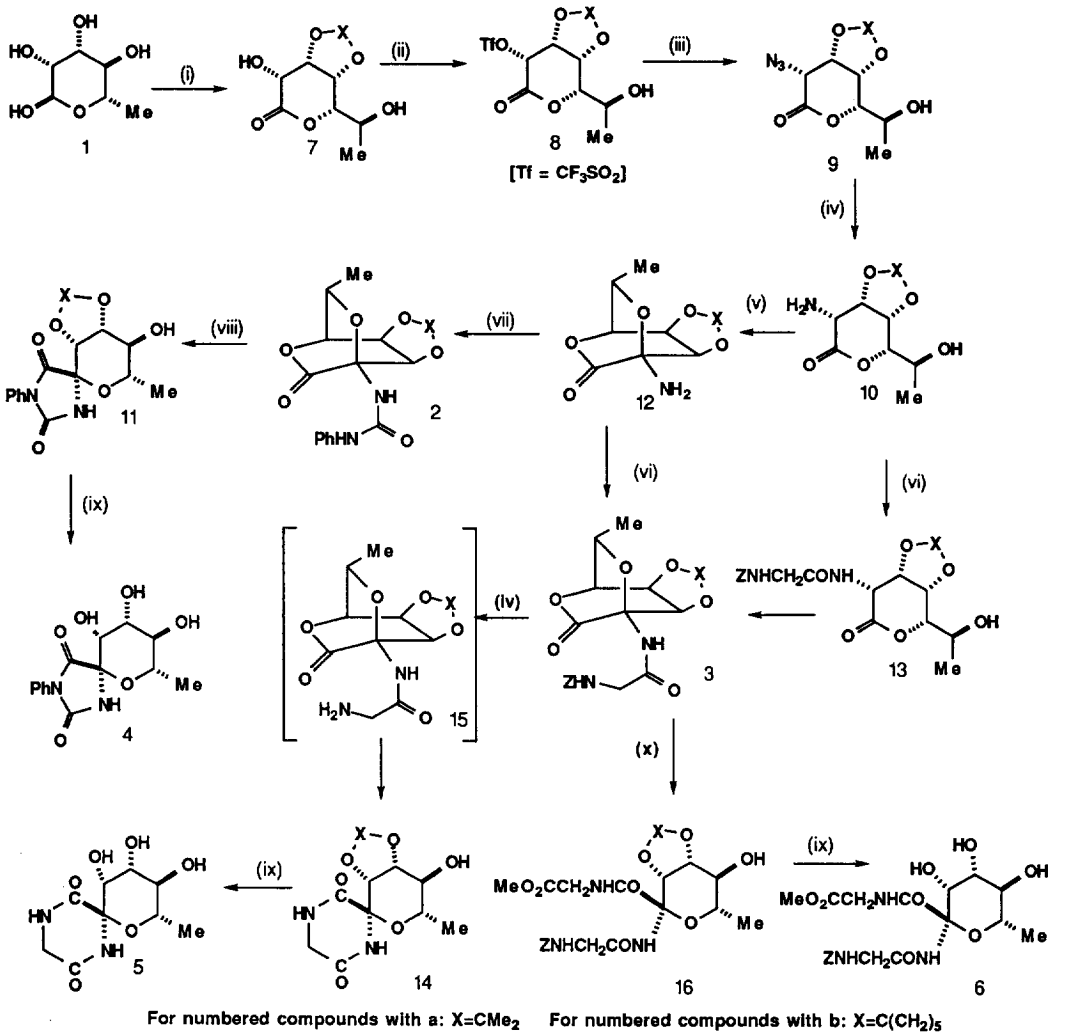
The Kiliani reaction on ketals of rhamnose allows ready access to the isopropylidene **7a** and cyclohexylidene **7b** lactones;[5] the following sequences of transformations [Scheme] were conducted on both lactones to see if there was any advantage - for example in different solubilities or stabilities of intermediates - in any of the steps for one protecting group rather than the other. It was found however that the sole advantage in the use of cyclohexylidene over the isopropylidene ketals is the ease of crystallisation of the bicyclic lactone **3b** in comparison with the isopropylidene analogue **3a**. A highly selective esterification of the hydroxyl group adjacent to the carbonyl function of the acetonide **7a** resulted on treatment with trifluoromethanesulfonic (triflic) anhydride to form the triflate **8a** which, on treatment with sodium azide in DMF, gave the azidolactone **9a**, m.p. 107-108°C, $[\alpha]_D^{21}$ -113.2 (*c*, 1.0 in $CHCl_3$), in 83% overall yield with clean overall retention of configuration [Scheme]. Similar treatment of the cyclohexylidene derivative **7b** afforded the corresponding cyclohexylidene azidolactone **9b**, m.p. 133-134°C, $[\alpha]_D^{25}$ -101.6 (*c* , 0.95 in $CHCl_3$) .[6]

Hydrogenation of the isopropylidene protected azide **9a** in ethanol in the presence of palladium black gave the amine **10a**, m.p. 185-186°C, $[\alpha]_D^{20}$ -93.9 (*c*, 1.0 in MeOH) in 90% yield. Anionic bromine oxidation of aminolactone **10a**, with *N*-bromosuccinimide and sodium acetate in acetonitrile, gave the bicyclic amine **12a**,[7] which has a characteristic ^{13}C singlet for bridgehead C-2 at δ 82.4; the yield of the amine, which decomposes partially during flash column purification, is variable but may be as high as 79% if it is rapidly purified on a short column. The stability of the bicyclic amine **12a** is thus intermediate between the stability of the corresponding ribose analogue[8] [which is a stable crystalline compound] and that of the mannose analogue[9] [which cannot readily be isolated].

Acylation of the bridgehead amine **12** leads to a stable series of N-acylated compounds. Thus, reaction of **12a** with phenyl isocyanate and pyridine in tetrahydrofuran afforded the phenyl urea **2a** as an amorphous solid, $[\alpha]_D^{20}$ +13.2 (*c*, 0.5 in $CHCl_3$), in 85% yield. The urea **2a** spontaneously cyclised on refluxing in methanol to afford the protected hydantoin **11a**, m.p. 151-152°C, $[\alpha]_D^{20}$ -15.0 (*c*, 0.5 in $CHCl_3$). Treatment of **11a** with trifluoroacetic acid and water gave the fully deprotected pyranose *N*-phenylhydantoin **4**,[10] in 76% yield as a rhamnopyranose analogue of hydantocidin.

Reaction of **12a** with the mixed anhydride formed between with Z-glycine and ethyl chloroformate gave the dipeptide **3a** in 40% yield. The low yield in this reaction was probably due to both the instability and the low reactivity of the sterically hindered bicyclic amine **12a**. Accordingly, the amine **10a** was acylated prior to the brominative oxidation. Treatment of **10a** with Z-glycine and ethyl chloroformate gave **13a**, m.p. 211-212°C, $[\alpha]_D^{20}$ -109.0 (*c*, 0.5 in MeOH), in 85% yield. A solution of the dipeptide **13a** in acetonitrile with *N*-bromosuccinimide and sodium acetate gave the bicyclic dipeptide **3a** as a gum in 36% yield (67% yield based on unrecovered starting material). Hydrogenation of **3a** in ethanol in the presence of palladium black formed the pyranose diketopiperazine **14a**, m.p. 216-217°C, $[\alpha]_D^{20}$ -33.2 (*c*, 0.25 in MeOH), in quantitative yield; initial hydrogenolytic removal of the Z-protecting group in **3a** gave to **15a** as an unstable intermediate which underwent a rapid intramolecular nucleophilic attack by the free amine onto the carbonyl group of the lactone. Removal of the isopropylidene protecting group in **14a** by aqueous trifluoroacetic acid gave the spirodiketopiperazine of rhamnopyranose **5**[11] in 86% yield.



Scheme: (i) ref 5 (ii) Tf_2O, pyridine, CH_2Cl_2, -50°C to -20°C (iii) NaN_3, DMF (iv) H_2, Pd, EtOH (v) *N*-bromosuccinimide, NaOAc, MeCN (vi) ZglyOH, ClCOOEt, Et_3N, THF; pyridine, MeCN (vii) PhNCO, pyridine, THF (viii) MeOH, heat (ix) 50% aq. CF_3COOH (x) $MeO_2C.CH_2$. NH_3^+ Cl^-, NaOAc, DMF

A similar sequence of reactions was performed on the cyclohexylidene protected azide **9b**. Thus catalytic reduction of **9b** gave the amine **10b**, 90% yield, m.p. 149-150°C, $[\alpha]_D^{25}$ -83.2 (*c*, 0.5 in MeOH), which was coupled with Z-glycine to give the dipeptide **13b**, 90% yield, m.p. 145-146°C, $[\alpha]_D^{25}$ -109.3 (*c*, 1.0 in MeOH). Oxidation of **13b** with *N*-bromosuccinimide gave the bicyclic lactone **3b**, m.p. 77°C, $[\alpha]_D^{25}$ -4 (*c*, 0.2 in MeOH) in 68% yield based on unrecovered starting material; the ease of crystallisation of **3b** in comparison to that of **3a** may make **3b** a more attractive divergent intermediate. Hydrogenation of the cyclohexylidene protected lactone **3b** afforded **14b**, m.p. 223-224°C, $[\alpha]_D^{25}$ -16.6 (*c*, 0.35 in MeOH), in 97% yield from which the ketal protecting group was removed by aqueous acid to give **5** in 60% yield.

The bicyclic intermediate **3b** can also be used prepare oligopeptides in which one of the constituent amino acids contains an anomeric rhamnopyranose fragment. Thus reaction of methyl glycinate hydrochloride in DMF in the presence of sodium acetate give the protected tripeptide **16b**, m.p. 82°C, $[\alpha]_D^{25}$ -42.8 (*c*, 0.25 in MeOH), in 67% yield. The ketal protecting group can be removed from **16** by methanolic hydrogen chloride to give unprotected rhamnose derivatives **6**.

Thus, in summary, this paper reports the preparation of a number of mimics of L-rhamnopyranose *via* [2.2.2]bicyclic lactones which control the stereochemistry of the substituent at the anomeric position and with the two preceding papers provides a strategy for the synthesis of a wide range of rhamnose derivatives; biological assays of these and other rhamnose mimics will be reported in due course.[12]

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[7] Selected data for **12a**: ν_{max} (KBr/cm^{-1}): 1762 (C=O); δ_H (500 MHz, $CDCl_3$): 1.38, 1.65 (6H, 2 s, $C(\underline{CH_3})_2$), 1.55 (3H, d, $J_{3',3}$ 6.9 Hz, CH_3, H-3'), 2.31 (2H, br s, NH_2), 4.31 (1H, d, $J_{7,8}$ 8.4 Hz, H-7), 4.32 (1H, m, H-3), 4.57 (1H, dd, $J_{4,3}$ 1.6, $J_{4,8}$ 4.5 Hz, H-4), 4.68 (1H, ddd, $J_{8,3}$ 1.6, $J_{8,4}$ 4.5, $J_{8,7}$ 8.4 Hz, H-8); δ_C (50.3 MHz, $CDCl_3$): 17.0, 24.1, 24.8 (3 q, C-3', $C(\underline{C}H_3)_2$), 72.5, 74.3, 75.9, 76.4 (4 d, C-3, C-4, C-7, C-8), 82.4, 114.9 (2 s, C-1, $\underline{C}(CH_3)_2$), 169.4 (s, C=O).
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[9] J. C. Estevez, D. D. Long, M. R. Wormald, R. A. Dwek and G. W. J. Fleet, *Tetrahedron Lett.*, 1995, **36**, 8287.
[10] Selected data for **4**: m.p. 202-203°C; $[\alpha]_D^{20}$ -42.0 (*c*, 0.25 in MeOH); δ_H (500 MHz, CD_3OD): 1.29 (3H, d, $J_{2',2}$ 6.2 Hz, H-2'), 3.47 (1H, t, J 9.2 Hz, H-3), 4.05 (1H, d, $J_{5,4}$ 3.4 Hz, H-5), 4.12 (1H, dq, $J_{2,2'}$ 6.2, $J_{2,3}$ 9.3 Hz, H-2), 4.17 (1H, dd, $J_{4,5}$ 3.4, $J_{4,3}$ 9.2 Hz, H-4), 7.35-7.41 (3H, m, 3 Ar-H), 7.45-7.49 (2H, m, 2 Ar-H); δ_C (125MHz, CD_3OD): 18.6 (q, C-2'), 71.7, 72.4, 73.0, 73.1 (4 d, C-2, C-3, C-4, C-5), 127.7, 129.4, 130.0 (3 d, 5 Ar-H), 87.8, 132.7 (2 s, C-6, NPh), 156.5, 171.2 (2 s, 2 C=O).
[11] Selected data for **5**: m.p. 146°C; $[\alpha]_D^{25}$ -63.0 (*c*, 1.0 in MeOH); δ_H (500MHz, CD_3OD): 1.25 (3H, d, $J_{2,2'}$ 6.1 Hz, H-2'), 3.34 (1H, dd, $J_{3,2}$ 9.4, J 11.1 Hz, H-3), 3.49 (1H, dq, $J_{2,2'}$ 6.1, $J_{2,3}$ 9.4 Hz, H-2), 3.75 (1H, d, $J_{9',9}$ 17.9 Hz, H-9'), 3.99 (1H, d, $J_{5,4}$ 3.8 Hz, H-5), 4.10 (1H, d, $J_{9,9'}$ 17.9 Hz, H-9), 4.36 (1H, dd, $J_{4,5}$ 3.7, J 9.3 Hz, H-4); δ_C (125.7 MHz, CD_3OD): 18.3 (q, C-2'), 45.8 (t, C-9), 70.9, 73.2, 73.4, 73.5 (4 d, C-2, C-3, C-4, C-5), 84.1 (s, C-6), 167.5, 171.4 (2 s, 2 C=O).
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