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Mimics of L-Rhamnose: Anomeric Spirohydantoins and Diketopiperazines - Approaches to Novel N-Linked Glycopeptides of Rhamnofuranose

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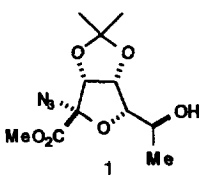
Abstract:: An α-azidocarboxylate of a tetrahydrofuran derived from L-rhamnose may be used as a divergent intermediate for a wide range of mimics of L-rhamnofuranose, which contain a constituent α-amino acid moiety at the anomeric position, and include anomeric spiroderivatives such as the rhamnose analogue of hydantocidin; such materials may be helpful in elucidating the biosynthesis of the cells walls of mycobacteria.

The preceding paper[1] describes the synthesis from L-rhamnose of the α-azidoester **1** as a potential divergent intermediate for the ready synthesis of a wide range of mimics of L-rhamnofuranose **2**. Both hydantoins[2] and diketopiperazines[3] are pharmacophores with a wide range of biological activities. Carbohydrates incorporating these structural features at the anomeric position have been shown to possess interesting biological properties; the natural product hydantocidin **3**[4] is a herbicide[5] and the spirodiketopiperazine of glucopyranose **4**[6] is a specific inhibitor of glycogen phosphorylase. Carbohydrate analogues possessing both an N-acyl group and a carbonyl function at the anomeric carbon are chemically quite stable in regard to both the anomeric configuration and the ring size of the sugar.[7]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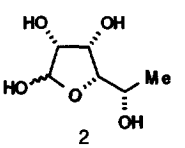
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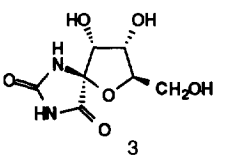
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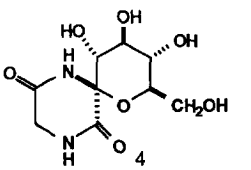
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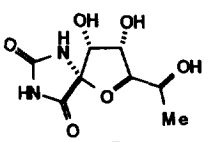
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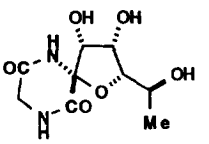
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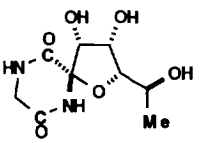
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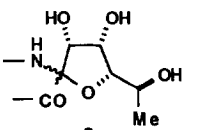
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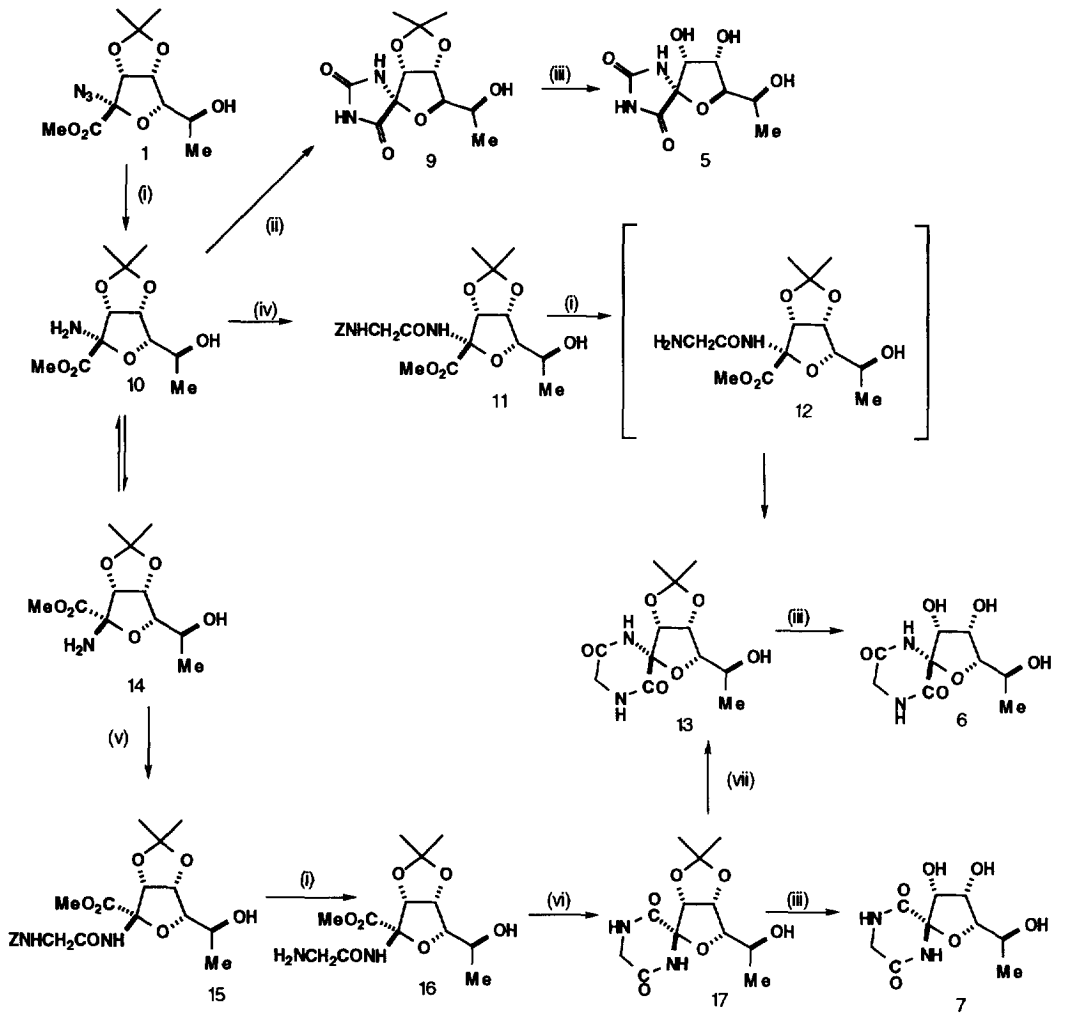
This paper reports the synthesis of the rhamnofuranose analogue of hydantocidin **5** and also highly stereoselective syntheses of the two anomeric diketopiperazines **6** and **7**. Differing acylation conditions with reactive and unreactive carbonyl electrophiles allow the stereochemistry of the anomeric position of such compounds to be controlled. This provides a strategy for the preparation of a wide range of analogues **8** in

which the anomeric carbon of rhamnofuranose is an α-amino acid constituent, including a set of novel N-linked glycopeptides.



Scheme: (i) H_2, Pd black, EtOH (ii) KCNO, MeCOOH (iii) 50% aq. CF_3COOH (iv) ZglyOH, ClCOOEt, Et_3N,THF; pyridine, MeCN (v) ZGlyOH, DCC, 1-hydroxybenzotriazole, DMF (vi) MeOH (vii) *tert*-BuOK, DMF

Hydrogenation of the azide **1** in ethanol in the presence of palladium black gives a single amine **10**[8] in 90% yield. Reaction of **10** with potassium cyanate in acetic acid afforded the isopropylidene spirohydantoin **9**[9] in 58% yield, the structure of which was firmly established by X-ray crystallographic analysis.[10] Further hydrolysis with aqueous acetic acid gave **5**,[11] in quantitative yield, as a rhamnofuranose analogue of hydantocidin.

The amine **10** was coupled with Z-glycine, activated as a mixed anhydride with ethyl chloroformate, to give the dipeptide **11**[12] [78% yield] in which the configuration at the anomeric centre has been retained; thus, the sterically hindered amine **10** readily attacks the reactive carbonyl group in the mixed anhydride. Removal of the Z-protecting group by hydrogenation in ethanol in the presence of palladium black gave the non-isolable amine **12** which rapidly and spontaneously cyclised to the diketopiperazine **13**[13] [85% yield], the structure of which was established by X-ray crystallographic analysis. Treatment of **13** with aqueous trifluoroacetic acid gave, in 95% yield, the unprotected rhamnofuranose derivative **6**.[14]

When Z-glycine was activated by dicyclohexyl carbodiimide (DCC), the major product from coupling with the amine **10** was the dipeptide **15**[15] [62% yield], together with a small amount of **11** [8% yield]. In the case of DCC activation, the carbonyl group is less electrophilic than is the case in activation by ethyl chloroformate. Thus, **10** must equilibrate to a small amount of the less stable, but more reactive, amine **14** prior to acylation; the less stable, but less sterically hindered, amine **14** thus reacts preferentially with the less reactive electrophile generated as the acylating agent by DCC. Hydrogenation of **15** in the presence of palladium black gave the amine **16** [96% yield]. In contrast to **12**, **16** underwent a very much slower cyclisation in methanol over three days to **17**[16] [60% yield]; the ester carbonyl in **16** is much more sterically hindered than is the corresponding carbonyl group in **12**, accounting for the difference in rates of cyclisation of the two compounds. Removal of the acetonide in **17** by aqueous acid hydrolysis gave the deprotected epimeric spirodiketopiperazine **7**[17] [91% yield].

As is the case with spirodiketopiperazines of mannose[18] and spirohydantoins of the ribose,[19] the epimer **13** in which the nitrogen is *cis* to the diol unit is thermodynamically more stable than **17** in which the diol unit is *trans* to the nitrogen substituent. Thus **17** is transformed into **13** by treatment with potassium *tert*-butoxide in dimethyl formamide.

In summary, this paper demonstrates the potential of the azidoester **1** for the generation of a wide range of rhamnofuranose mimics. The following paper[20] describes the synthesis of rhamnose analogues that contain both a nitrogen and carbon substituent at the anomeric position of rhamnopyranose.[21]

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[8] Selected data for **10**: gum, $[\alpha]_D^{20}$: -18.9 (c, 0.7 in MeOH) δ_H (200 MHz, $CDCl_3$): 1.14 (d, $J_{6,7}$ 6.5 Hz, 3H, -CH_3), 1.25, 1.41 (2xs, 6H, 2x-CH_3), 3.37 (dd, 1H), 3.67 (s, 3H, -$COOCH_3$), 3.75-3.93 (m, 1H), 4.71-4.82 (m, 2H); δ_C (50.3 MHz, $CDCl_3$): 20.34, 24.29, 25.78 (3xq, 3x-CH_3), 52.41 (q, -$COO\underline{C}H_3$), 66.12, 80.76, 81.01, 81.88 (4xd, 4x-CH-), 92.47, 112.40 (2xs, 2x-C-), 168.84 (s, C=O).

[9] Selected data for **9**: m.p. 215-216 °C, $[\alpha]_D^{20}$ -50 (c, 0.25 in MeOH), δ_H (200 MHz, $CDCl_3$): 1.33 (d, J 6.0 Hz, 3H, -CH_3), 1.39 (s, 3H, -CH_3), 1.55 (s, 3H, -CH_3), 3.62-4.32 (m, 2H), 4.79 (d, 1H), 5.05 (dd, 1H), 6.47 (bs., 1H, -NH), 8.96 (bs., 1H, -NH); δ_C (50.3 MHz, $CDCl_3$): 19.61, 23.13, 24.63 (3xq, 3x-CH_3), 64.54, 79.77, 80.25, 82.16 (4xd, 4x-CH), 92.46, 113.23 (2xs, 2x-C-), 156.97, 174.27 (2xs, 2xC=O).

[10] The structures of **9** and **13** have been firmly established by X-ray crystallographic analysis; details will be provided in the full paper.

[11] Selected data for **5**: amorphous solid, δ_H (200 MHz, CD_3OD): 1.24 (d, J 6.3 Hz, 3H, -CH_3), 3.71 (dd, 1H), 3.92-4.02 (m, 1H), 4.29 (t, 1H), 4.36 (d, 1H). δ_C (50.3 MHz, CD_3OD): 20.41 (q, -CH_3), 66.46, 72.32, 75.48, 86.23 (4xd, 4x-CH), 93.53 (s, -C-), 158.28, 176.26 (2xs, 2xC=O).

[12] Selected data for **11**: white amorphous solid, $[\alpha]_D^{20}$ + 10.1 (c, 1 in $CHCl_3$), δ_H (200 MHz, $CDCl_3$): 1.29-1.32 (m, 6H, 2x-CH_3), 1.45 (s, 3H, -CH_3), 2.83-4.10 (m, 7H), 4.76-4.87 (m, 2H), 5.09 (s, 2H), 5.87 (bs, 1H, -NH), 7.24-7.31 (m, 5H, 5xAr-H), 7.45 (bs, 1H, -NH); δ_C (50.3 MHz, $CDCl_3$): 20.39, 24.60, 25.54 (3xq, 3x-CH_3), 44.29, 67.08 (2xt, 2x-CH_2-), 53.09 (q, -$COO\underline{C}H_3$), 66.03, 80.21, 82.61, 83.06 (4xd, 4x-CH-), 128.24, 128.39, 128.71 (3xd, 5xAr-H), 88.69, 114.13, 136.35 (3xs, 3x-C-), 156.87, 169.28, 169.55 (3xs, 3xC=O)

[13] Selected data for **13**: m.p. 247-248 °C, $[\alpha]_D^{20}$:-92.8 (c, 0.25 in MeOH), δ_H (500 MHz, CD_3CN): 1.19 (d, J 7.3 Hz, 3H, -CH_3), 1.38, 1.52 (2xs, 6H, 2x-CH_3), 2.81 (d, J 5.9 Hz, 1H, -OH), 3.65 (dd, 1H), 3.78 (dd, 1H), 3.87-3.91 (m, 1H), 4.01-4.09 (m, 1H), 4.92-4.95 (m, 2H), 6.55 (bs, 1H, -NH), 6.70 (bs, 1H, -NH); δ_C (50.3 MHz, CD_3CN): 21.77, 25.29, 26.83 (3xq, 3x-CH_3), 45.80 (t, -CH_2-), 66.54, 81.80, 82.40, 84.51 (4xd, 4x-CH-), 88.52, 114.46 (2xs, 2x-C-), 166.02, 167.92 (2xs, 2xC=O).

[14] Selected data for **6**: δ_H (200 MHz, CD_3OD): 1.22 (d, J 6.4 Hz, 3H, -CH_3), 3.69 (dd, 1H), 3.74,-4.08 (m, 3H), 4.32 (t, 1H), 4.71 (d, 1H); δ_C (50.3 MHz, CD_3OD): 20.42 (q, -CH_3), 45.36 (t, -CH_2-), 66.52, 72.69, 75.31, 86.29 (4xd, 4x-CH-), 89.50 (s, -C-), 167.87, 169.25 (2xs, 2xC=O).

[15] Selected data for **15**: δ_H (200 MHz, $CDCl_3$): 1.36-1.38 (m, 6H, 2x-CH_3), 1.53 (s, 3H, -CH_3), 3.79-4.14 (m, 7H), 4.80-4.93 (m, 2H), 5.15 (s, 2H), 5.38 (bs, 1H, -NH), 7.20 (bs, 1H, -NH), 7.37 (m, 5H, 5xAr-H); δ_C (50.3 MHz, CD_3OD): 21.20, 25.10, 25.96 (3xq, 3x-CH_3), 44.54, 67.83 (2xt, 2x-CH_2-), 53.01 (q, -$COO\underline{C}H_3$), 65.72, 81.34, 85.60, 87.40 (4xd, 4x-CH-), 93.13, 114.66, 138.10 (3xs, 3x-C-), 128.91, 129.04, 129.49 (3xd, 5xAr-H), 158.98, 168.78, 172.01 (3xs, 3xC=O).

[16] Selected data for **17**: δ_H (200 MHz, CD_3CN): 1.25-1.30 (m, 6H, 2x-CH_3), 1.41 (s, 3H, -CH_3), 3.63-4.11 (m, 4H), 4.82-4.96 (m, 2H), 6.57 (bs, 1H, -NH), 7.13 (bs, 1H, -NH), ; δ_C (50.3 MHz, CD_3CN): 21.13, 25.20, 25.76 (3xq, 3x-CH_3), 45.89 (t, -CH_2-), 65.68, 81.26, 85.66, 89.40 (4xd, 4x-CH-), 92.40, 114.80 (2xs, 2x-C-), 165.21, 167.57 (2xs, 2xC=O).

[17] Selected data for **7**: δ_H (200 MHz, CD_3OD): 1.22 (d, J 6.1 Hz, 3H, -CH_3), 3.56-4.16 (m, 4H), 4.19 (t, 1H), 4.37 (d, 1H).

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