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Highly Substituted *cis*-β-Cyclopentane Amino Acids: an Approach to the Synthesis of Trehazolin Analogues

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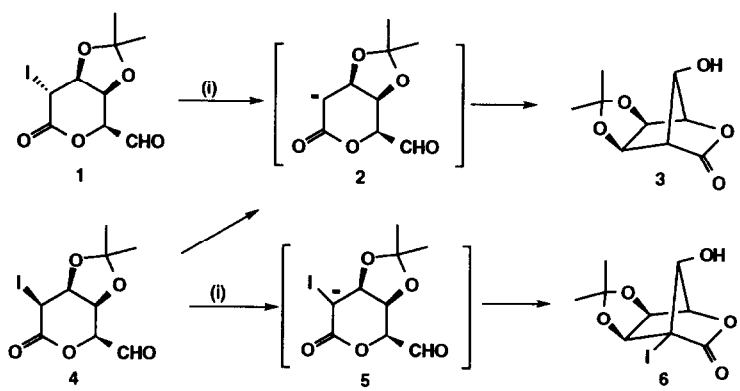
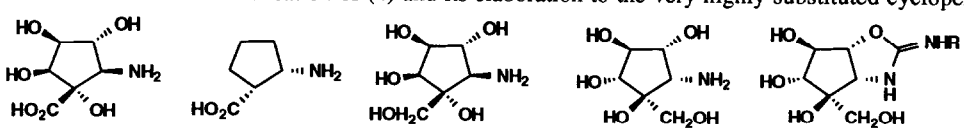
Abstract: An efficient aldol condensation of a 2-iodo-5-formyl-1,5-lactone provides a short route to precursors for both *cis*-β-cyclopentane amino acids and trehalostatin analogues with control of the stereochemistry at all 5 carbons of the cyclopentane ring.

We recently reported that treatment of the iodo-aldehyde (1) with lithium iodide in tetrahydrofuran at room temperature gave the bicyclic lactone (3),[1] in 55% yield, probably by iodide reacting by nucleophilic attack on iodine in (1) to give the anion (2) which then cyclises to give the least hindered alcohol at the new chiral centre [Scheme 1].



Scheme 1. (i) LiI, THF, 12 h, room temp

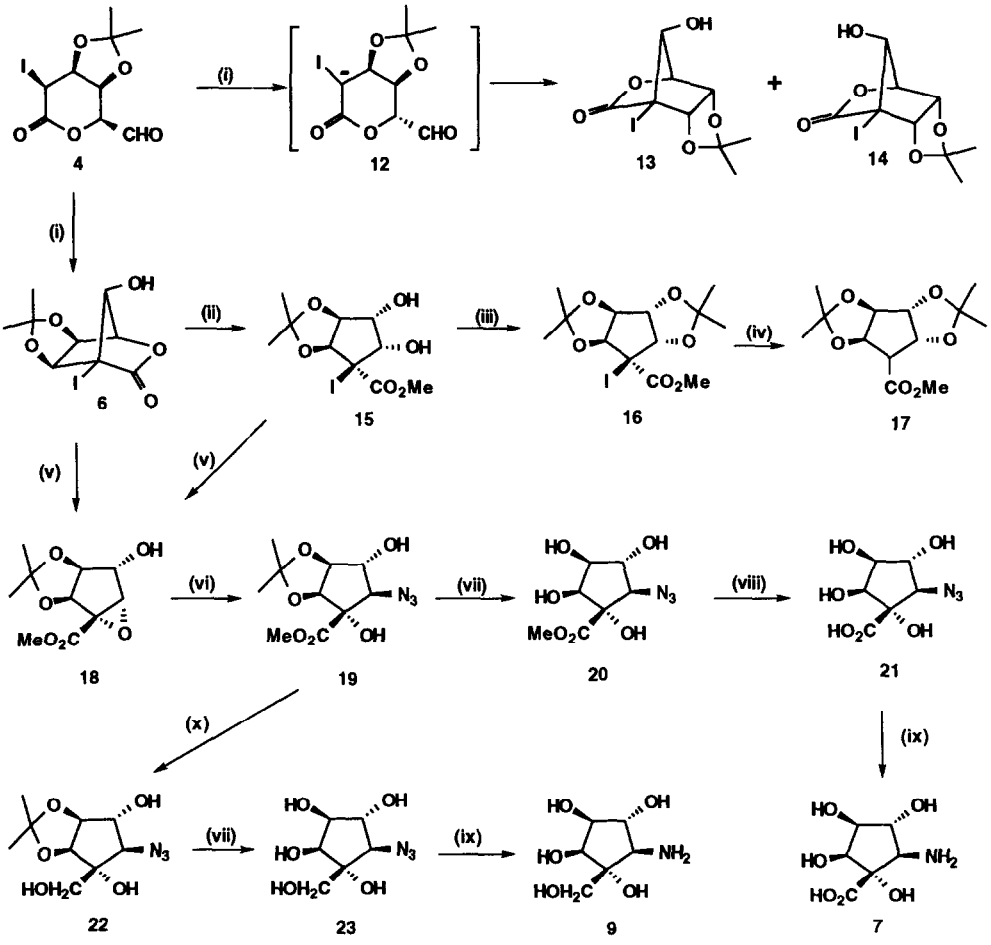
Thus, (3) is formed by an overall reductive aldol condensation. In contrast to the behaviour of (1), the epimeric iodide (4) gave a low yield of (3) [about 5-10%] together with the bridgehead iodolactone (6) in 27% yield as the major product; thus (4) undergoes a non-reductive aldol cyclisation under these conditions, the base presumably arising from a small amount of reduction of the iodoaldehyde. Bicyclic structures such as (6) should allow access to very highly substituted cyclopentanes. This paper reports suitable conditions for the intramolecular aldol condensation of (4) and its elaboration to the very highly substituted cyclopentane β-



7 8 9 10 11: R= α-glucopyranosyl

amino acid (7), an analogue of the antifungal antibiotic *cis*-pentacin (8)[2,3] effective against various models[4] of systemic mycoses in mice. The synthesis of the aminopentaol (9) is also described; (9) is a diastereomer of (10)[5,6] a constitutive part of the structure of the trehalase inhibitor trehazolin (11).[7]

Reaction of the iodoaldehyde (4) with potassium fluoride in acetonitrile in the presence of 18-crown-6, after workup by addition of ethyl acetate and brine, gave (6), identical in all respects with authentic material,[1] in 81% yield; also isolated from the reaction were two[8,9] other iodolactones (13),[10] in 14% yield, and (14)[11] in trace amounts [Scheme 2]. While the major product (6) is formed from intramolecular cyclisation of the carbanion (5), the minor bridgehead epimeric alcohols (13) and (14) are formed from the alternative closures of the epimeric enolate (12).



Scheme 2. (i) KF, 18-crown-6, MeCN, -6°C (ii) K_2CO_3, MeOH, -20°C (iii) Me_2CO, $Me_2C(OMe)_2$, CSA, (iv) H_2, Pd black, NaOAc, MeOH (v) K_2CO_3, MeOH, room temp. (vi) NaN_3, NH_4Cl, aq. MeOH (vii) 40% aq. CF_3COOH (viii) aq. NaOH, then ion exchange chromatography (ix) H_2, Pd black, H_2O (x) $LiBH_4$, THF, 0°C

The combined overall yield of over 95% of the bicyclic iodolactones is remarkable; aldol condensations of carbohydrates to give cyclopentanes are rare[12] and do not in general proceed in good yield.[13] The Ferrier cyclisation, which is widely used for the synthesis of 3-hydroxycyclohexanones, cannot be used for the synthesis of complex cyclopentanes.[14] The relative proportions of the lactones may be varied by adjusting the temperature of the reaction, the method of quenching and the length of time the reaction is left. The epimeric iodoaldehyde (1) gives negligible yields of any bicyclic lactones under similar conditions to the successful cyclisation of (4). This suggests that the proton at C-2 of (4) is kinetically more acidic than that of (1).

Some ring opening reactions of the major product (6) were investigated. Reaction of (6) with potassium carbonate in methanol at -20°C gave the iododiol (15), m.p. 127°C, $[\alpha]_D^{20}$ +36.1 (*c*, 1.0 in $CHCl_3$), in quantitative yield. Treatment of (15) with acetone and dimethoxypropane in the presence of camphor sulphonic acid gave the diacetonide (16), m.p. 71-73°, $[\alpha]_D^{20}$ +26.8 (*c*, 1.0 in $CHCl_3$), which on hydrogenation in the presence of palladium black and sodium acetate gave the ester (17) identical to authentic material[1] in 65% yield. If the iodolactone (6) was treated at room temperature with potassium carbonate in methanol, the epoxide (18), m.p. 122-123°C, $[\alpha]_D^{20}$ -36.1 (*c*, 1.0 in $CHCl_3$) was formed in quantitative yield; the same epoxide (18) was also obtained by reacting the iododiol (15) under the same conditions. Treatment of (18) with sodium azide in methanol in the presence of ammonium chloride gave the azidodiol (19)[15] in 83% yield.[16]

The β-azidoester (19) has potential as an intermediate for a range of highly functionalised targets. For example, removal of the isopropylidene protecting group by aqueous trifluoroacetic acid afforded the tetraol (20), m.p. 156-157°C; $[\alpha]_D^{20}$ +53.5 (*c*, 1.0 in CH_3OH), [96% yield] which on further reaction with aqueous sodium hydroxide and work-up with ion exchange chromatography gave the azidocarboxylic acid (21), hygroscopic foam, $[\alpha]_D^{20}$ +51.8 (*c*, 1.3 in H_2O), [quantitative yield]. Hydrogenation of (21) in water in the presence of palladium black produced the highly functionalised β-amino acid (7)[17] in 98% yield.

Reduction of (19) with lithium borohydride in tetrahydrofuran at 0°C gave the azidotriol (22) [94% yield] from which the ketal protecting group was removed by aqueous trifluoroacetic acid to give the pentahydroxyazide (23), oil, $[\alpha]_D^{20}$ -25.7 (*c*, 1.2 in CH_3OH), [80% yield]. Hydrogenation of (23) in water in the presence of palladium black formed the amine (9)[18] in quantitative yield.

Trehazolin (11) is a powerful inhibitor of trehalase[19] and it is not yet clear how much of the structure is necessary to get significant levels of enzyme inhibition;[6] some highly functionalised aminocyclopentanes have been shown to be strong mannosidase inhibitors.[20] It is difficult to predict the efficacy of 5 ring analogues of sugars as glycosidase inhibitors;[21] accordingly, the aminopentaol (9), which is an analogue of the trehazolin fragment (10), was tested for its ability to inhibit human liver glycosidases using synthetic enzyme substrates.[22] No strong inhibition of any glycosidases was found, although (9) was a weak inhibitor of α-L-fucosidase (44% at 1mM) and a weak activator of α-D-glucosidase (33% at 1mM); the presence of the amino group did not lead to significant inhibition of β-hexoseaminidase (only 20% at 1mM).

This paper further demonstrates the value of sugar δ-lactones in the synthesis of highly functionalised targets.[23,24] In summary, the iodoaldehyde (4) gives an unexpectedly high yield of iodobicyclic lactones by an intramolecular aldol condensation which can be used for the synthesis of β-aminoacids and aminopseudosugars; the following paper[25] further demonstrates the potential of such aldol reactions in synthesis in the preparation of highly functionalised cyclopentanes derived from an azidolactone.[26]

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8. Spectrocopic and/or microanalytical data consistent with the proposed structures have been obtained for all new compounds reported in this paper.
9. The assignments of the stereochemistries of the bicyclic iodolactones (13) and (14) are given on the basis of equilibrium n.O.e. experiments.
10. Selected data for (13): m.p. 116-117°C, $[\alpha]_D^{20}$ +167.8 (*c*, 1.0 in $CHCl_3$), δ_H ($CDCl_3$): 1.39, 1.51 (6H, 2s, $C(CH_3)_2$); 3.62 (1H, br s ex in D_2O, OH); 4.62 (1H, d, *J* 2.5 Hz); 4.70 (1H, d, *J* 1.3 Hz); 5.07 (1H, dd, *J* 1.3 Hz, $J_{5,6}$ 7.4 Hz); 5.14 (1H, dd, *J* 2.5 Hz); δ_C ($CDCl_3$): 25.1, 25.5 (2q, $C(CH_3)_2$); 75.2 (s, C-1); 76.6, 79.4, 80.1, 82.2 (4d, C-4, C-5, C-6, C-7); 117.9 (s, $C(CH_3)_2$); 169.0 (s, C-2)
11. Selected data for (14): δ_H (d_6 acetone:$CDCl_3$, 5:1, 400 MHz): 1.32. 1.40 (6H, 2s, $C(CH_3)_2$); 4.48 (1H, d, $J_{7,OH}$ 4.1 Hz, H-7); 4.76 (1H, m, H-4); 4.89 (1H, dd, $J_{5,6}$ 7.3 Hz, *J* 2.2 Hz, H-5); 4.99 (1H, dd, *J* 1.0 Hz, H-6); 5.77 (1H, d ex in D_2O, OH). δ_C (d_6 acetone): 24.6, 25.1 (2q, $C(CH_3)_2$); 46.8 (s, C-1); 77.5, 80.9, 81.0, 83.5 (4d, C-4, C-5, C-6, C-7); 113.8 (s, $C(CH_3)_2$); 170.1 (s, C-2).
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15. Selected data for (19): m.p. 91-92°C, $[\alpha]_D^{20}$ +100.8 (*c*, 1.0 in $CHCl_3$), δ_H (d_6 benzene, 500 MHz): 0.96, 1.27 (6H, 2s, $C(CH_3)_2$); 1.81 (1H, br s ex in D_2O, OH); 3.38 (3H, s , CO_2CH_3); 3.67 (1H, d, *J* 10.0 Hz); 3.95 (1H, s ex in D_2O, OH); 4.10 (1H, dd, *J* 4.3 Hz, *J* 8.5 Hz); 4.26 (1H, d, *J* 4.3 Hz, *J* 8.5 Hz); 4.26 (1H, d, *J* 8.5 Hz); 4.40 (1H, dd, *J* 10.0 Hz); δ_C ($CDCl_3$): 24.0, 25.4 (2q, $C(CH_3)_2$); 53.1 (q, CO_2CH_3); 72.4, 78.2, 82 6, 84.4 (4d, C-2, C-3, C-4, C-5); 84.1 (s, C-1); 114.4 (s, $C(CH_3)_2$); 170.9 (s, CO_2CH_3).
16. The structure of the azide (19) was firmly established by single crystal X-ray crystallographic analysis.
17. Selected data for (7): δ_H (D_2O, 500MHz): 3.33 (1H, d, *J* 7.7 Hz), 4.04-4.08 (2H, m), 4.30 (1H, dd, *J* 7.7 Hz, *J* 4.9Hz); δ_C (D_2O, 125MHz): 62.4 (d, C-5), 76.1, 77.0, 79.8, 83.4 (3 x d, C-2, C-3, C-4), 83.1 (s, C-1), 175.6 (s, COOH).
18. Selected data for (9): δ_C (D_2O, 125MHz): 62.9 (t, C-6), 64.9, 76.4, 77.2, 83.4 (4 x d, C-2, C-3, C-4, C-5), 80.9 (s, C-1)
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