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Synthesis of Cyclopentane Spirohydantoins by Aldol Cyclisations: an Approach to Highly Substituted α-Cyclopentane Amino Acids

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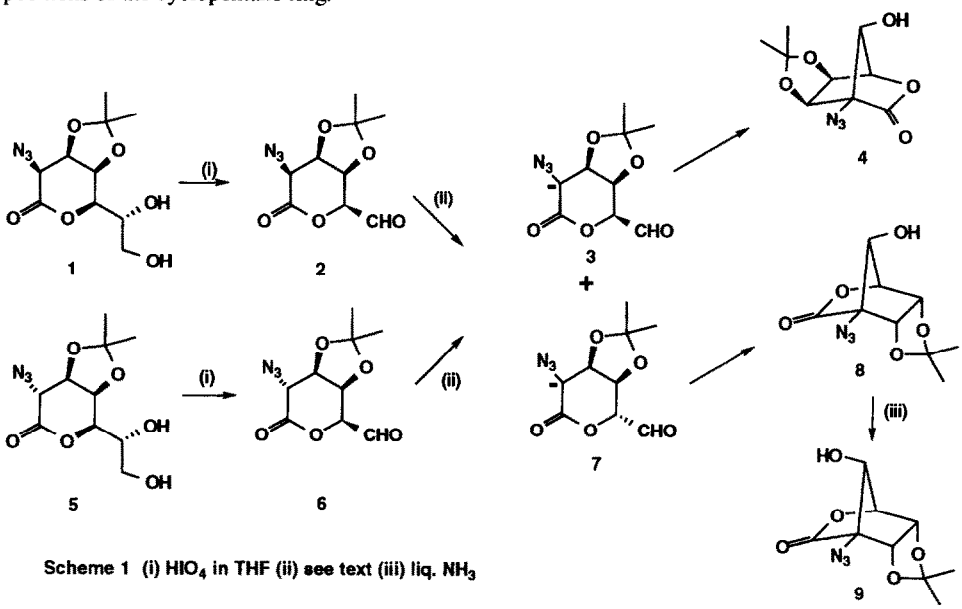
Abstract: Efficient but reversible aldol condensations of 2-azido-5-formyl-1,5-lactones provide short routes to precursors for α-cyclopentane amino acids, some aminopseudosugars and spirohydantoins of cyclopentanes with control of the stereochemistry at all 5 carbons bearing functional groups. The effects of some of the compounds on human liver glycosidases are described.

The preceding paper[1] describes the efficient aldol condensation of an iodoformyl lactone to give bicyclic iodolactones; this paper reports the analogous reactions of the epimeric azidoaldehydes (2) and (6) to give bicyclic azidolactones (4) (8) and (9), suitable precursors for the synthesis of highly substituted cyclopentanes; ring opening reactions of the azidolactones allow relatively short syntheses of homochiral cyclopentylamines with a nitrogen attached to a quaternary position and control of the stereochemistry at all five positions of the cyclopentane ring.

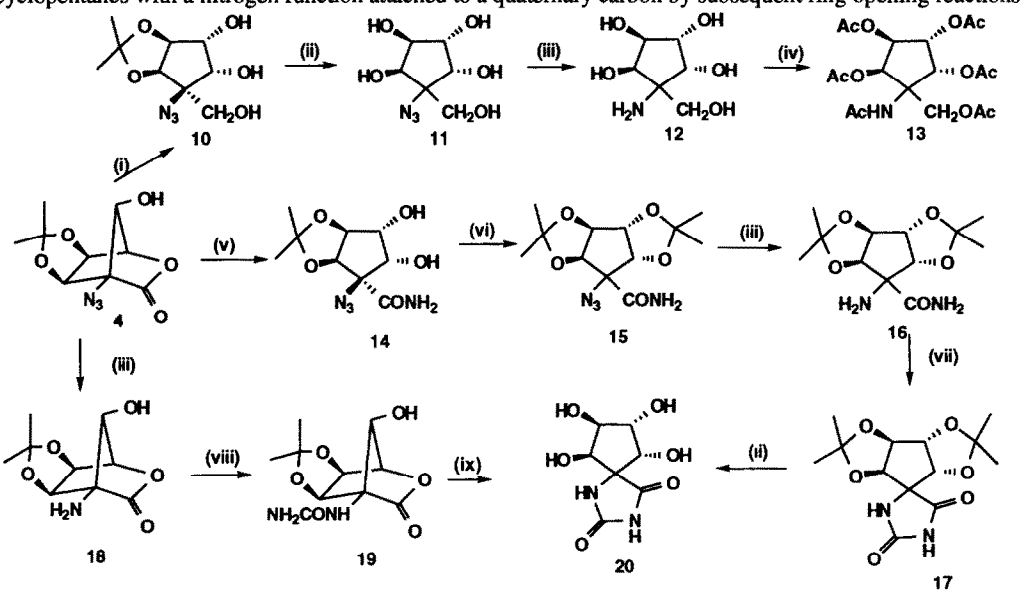


Scheme 1 (i) HIO_4 in THF (ii) see text (iii) liq. NH_3

Treatment of the readily available azidodiol (1)[2] with periodic acid in tetrahydrofuran at room temperature gave the aldehyde (2) in quantitative yield. The reaction of (2) with potassium fluoride in acetonitrile at -6°C in the presence of 18-crown-6 gave, after quenching with brine, as the major product the crystalline azidolactone (4), m.p. 72°C, $[\alpha]_D^{20}$ +29.6 (*c*, 1.0 in $CHCl_3$), in 58% yield together with a small amount (15%) of the isomeric bicycle (8), m.p. 116-117°C, $[\alpha]_D^{20}$ +167.8 (*c*, 1.0 in $CHCl_3$). Under these conditions the major product (4) is formed by an intramolecular closure of the anion (3), whereas the minor

product (8) is formed from the closure of the anion (7) which requires a prior epimerisation of the carbon bearing the aldehyde function. When the aldol closure was catalysed by sodium azide as the base in acetonitrile in the presence of 18-crown-6 a much slower cyclisation occurred to give (8) as the major product in 66% yield together with azidolactone (4) in 22% yield. Thus sodium azide results in significantly more epimerisation of the aldehyde bearing carbon of the lactone (2) before aldol cyclisation than is the case using potassium fluoride. It is also possible that a small amount of a third azidolactone (9), which is more polar, is also formed but (9) is not easily separable from the starting aldehyde (2). When the lactone (8) is treated with liquid ammonia, the isomeric lactone (9)[3], m.p. 127-128°C, $[\alpha]_D^{20}$ +44.8 (*c*, 0.92 in EtOH), is formed in 63% yield, 82% based on unrecovered starting material; the principal pathway under these conditions is an aldol equilibration rather than opening of either of the two lactones by the nitrogen nucleophile. On the basis of these observations it appears that the closure of the anion (7) occurs kinetically to give (8) but that (9) is thermodynamically more stable.

Because of the different behaviour in aldol closures of the epimeric iodoaldedehydes corresponding to (2) and (6), the base catalysed cyclisations of (6) were also studied. The azidodiol (5), m.p. 81-82°C, $[\alpha]_D^{20}$ +184.0 (*c*, 1.05 in $CHCl_3$) - prepared by aqueous acetic acid hydrolysis of the corresponding acetonide[4] - reacted with periodic acid in tetrahydrofuran to give the aldehyde (6) in 84% yield. Treatment of (6) with potassium fluoride gave only low yields of (4) [5%] and (8) [17%] and this behaviour parallels the low yield of aldol cyclisation of the iodoaldehyde analogue of (6). However, sodium azide induced an efficient cyclisation of (6) to give (8) as the major product [60%], together with a small amount of (4) [17%]; thus very similar behaviour is observed in the sodium azide catalysed cyclisations of both (2) and (6). A detailed study of the equilibration of the bicyclic azidolactones will be published in due course, but these procedures give access to the bicyclic lactones (4) and (8) in oligogram amounts and allow the synthesis of highly substituted cyclopentanes with a nitrogen function attached to a quaternary carbon by subsequent ring opening reactions.

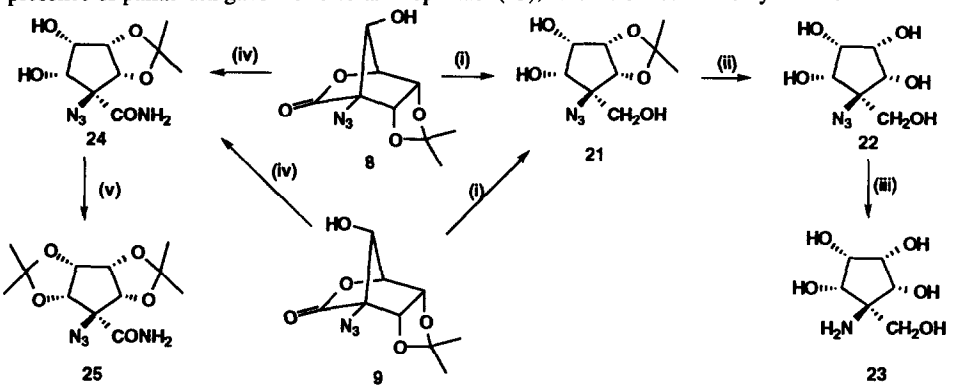


Scheme 2. (i) $NaBH_4$, EtOH (ii) aq. CF_3COOH (iii) H_2, Pd black (iv) Ac_2O, DMAP, pyridine (v) NH_3, aq. MeOH (vi) Me_2CO, $Me_2C(OMe)_2$, CSA (vii) Im_2CO, toluene (viii) KNCO, AcOH (ix) HCl, MeOH

The azidolactone (4) [Scheme 2] reacted with sodium borohydride in ethanol to undergo reductive ring opening of the lactone to the azidotriol (10) [84% yield] from which the isopropylidene protecting group was removed by 40% aqueous trifluoroacetic acid to give the azidopentaol (11),[5] oil $[\alpha]_D^{20}$ +41.6 (*c*, 0.9 in MeOH), in 90% yield. Hydrogenation of the azide (11) in water in the presence of palladium black afforded

the hygroscopic aminopentaol (12)[6] [99% yield], which was characterised as the peracetate (13), oil $[\alpha]_D^{20}$ +14.1 (*c*, 0.8 in MeOH). Clean ring opening was also observed when the azidolactone (4) was treated with ammonia in aqueous methanol, to afford the azidoamide (14), m.p. 147-150°C, $[\alpha]_D^{20}$ +30.7 (*c*, 1.0 in MeCN), in 78% yield; reaction of (14) with dimethoxypropane in acetone in the presence of camphor sulphonic acid resulted in the efficient formation of the diacetonide (15) [93% yield], confirming that the diol unit in (14) was *cis*. Reduction of the azide (15) by hydrogenation in the presence of palladium black afforded aminoamide (16), m.p. 179-182°C, $[\alpha]_D^{20}$ +46.1 (*c*, 1.0 in EtOH), 100% yield, which with carbonyl diimidazole gave the protected hydantoin (17), m.p. 203-205°C, in 80% yield. Removal of the isopropylidene protecting groups from (17) gave the spirohydantoin (20)[7] in 50% yield. The lactone (4) could be converted into (20) by a much shorter sequence; hydrogenation of (4) in the presence of palladium black gave the amino lactone (18), m.p. 193-196°C, $[\alpha]_D^{20}$ -15.3 (*c*, 0.3 in MeOH), [83% yield], which with potassium cyanate in acetic acid led to the urea (19), m.p. 210-215°C, $[\alpha]_D^{20}$ -17.6 (*c*, 0.25 in MeOH), in 90% yield. Subsequent treatment of (19) with methanolic hydrogen chloride gave the hydantoin (20), identical to the material produced in the longer sequence. Thus, in all the ring opening reactions of (4) reported above, there is no significant amount of change in the stereochemistry of the carbon bearing the free hydroxyl group resulting from reverse aldol condensation of either the bicyclic lactone or of the open chain products.

Both the azido lactones (8) and (9) reacted with sodium borohydride in ethanol to undergo reductive ring opening of the lactone to the *same* azidotriol (21), oil $[\alpha]_D^{20}$ -7.0 (*c*, 0.63 in $CHCl_3$), in 83% and 89% yields, respectively [Scheme 3]. It is thus clear that the kinetically formed (8) is isomerised to the more stable (9) under the basic conditions of the borohydride reduction ; also, the bicyclic lactone (9) with the free hydroxyl group *syn* to the lactone ring undergoes nucleophilic attack by hydride more rapidly than such attack on the *anti* epimer (8). The stereochemistry in (21) was confirmed by removal of the ketal by reaction with aqueous trifluoroacetic acid to give the optically inactive azide (22) in 84% yield which, on hydrogenation in the presence of palladium gave the *meso* aminopentaol (23),[8] characterised as the hydrochloride.

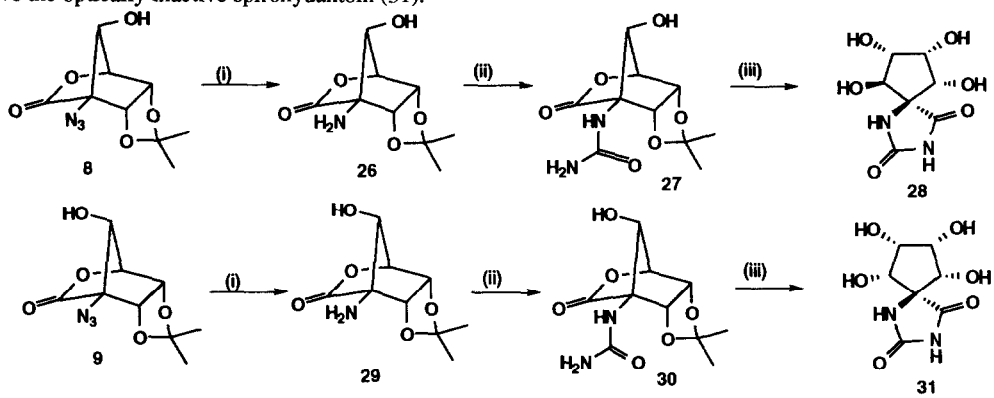


Scheme 3. (i) $NaBH_4$, EtOH (ii) 40% aq. CF_3COOH (iii) H_2, Pd black, MeOH (iv) NH_3, MeOH (v) Me_2CO, $Me_2C(OMe)_2$, CSA

Reaction of both lactones (8) and (9) with ammonia in methanol again gave the *same* aminoamide (24), m.p. 147-148°C, $[\alpha]_D^{20}$ +0.4 (*c*, 1.02 in MeOH), in 31% and 48% yields, respectively, indicating that as in the case with borohydride reduction, the equilibration of (8) to (9) precedes nucleophilic ring opening of the lactone, and that again (9) is the more susceptible to attack by the nitrogen nucleophile. The stereochemistry in (24) was established by conversion to the optically inactive diacetonide (25), m.p. 218-220°C, $[\alpha]_D^{20}$ 0.0 (*c*, 0.93 in $CHCl_3$), in 80% yield.

Although ring opening of the lactones (8) and (9) under basic conditions appears usually to be accompanied by prior aldol equilibration, the spirohydantoins (28) and (31) could be prepared under acidic ring opening conditions which maintain the stereointegrity of the carbon bearing the free hydroxyl group. Thus hydrogenation of the azide (8) with palladium black in aqueous ethanol gave the amine (26), m.p. 185-

186°C, $[\alpha]_D^{20}$ +113.5 (*c*, 0.55 in MeOH), [97% yield] which with potassium cyanate in acetic acid gave the urea (27), m.p. 208-212°C, $[\alpha]_D^{20}$ +100.3 (*c*, 0.39 in MeOH), in 72% yield [Scheme 4]. Treatment of (27) with methanolic hydrogen chloride under reflux for 32 h gave the spirohydantoin (28),[9] in which the configuration of the carbon attached to the free alcohol has been retained, in 90% yield. Similarly, hydrogenation of the azide (9) gave the amine (29), m.p. 188-190°C, $[\alpha]_D^{20}$ +82.7 (*c*, 0.66 in MeOH), in 76% yield which was converted to the urea (30), m.p. >230°C, $[\alpha]_D^{20}$ +69.1 (*c*, 0.47 in DMSO), in 78% yield by treatment with potassium cyanate in acetic acid. Reaction of (30) with methanolic hydrogen chloride gave the optically inactive spirohydantoin (31).[10]



Scheme 4. (i) H_2, Pd black, aq. EtOH (ii) KCNO, AcOH (iii) HCl, MeOH

Both highly substituted aminocyclopentanes[11] and sugar-derived spirohydantoins[12] may have interesting interactions with carbohydrate metabolising enzymes: accordingly, the aminopentaols (12) and (22) and the spirohydantoin (20) were tested for their ability to inhibit human liver glycosidases using synthetic enzyme substrates.[13] Cyclopentylamine (12), which has structural features in common with a carbocyclic analogue of α-D-mannofuranosylamine or of α-L-fucofuranosylamine, shows moderate inhibition of both α-D-mannosidase [I_{50} 0.2 mM] and of α-L-fucosidase [I_{50} 0.25 mM]; in contrast, the spirohydantoin (20) only inhibited α-L-fucosidase [I_{50} 0.6 mM]. These results will be discussed elsewhere.

This paper extends the versatility of azidolactones such as (2) in short syntheses of highly functionalised targets.[14] It is clear that the bicyclic azidolactones (4), (8) and (9) should also be good precursors for α-cyclopentane amino acids, however, the ring opening reactions to produce aminoacids are fraught with reversible aldol reactions and are under current investigation.[15]

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3. The structure of (9) has been firmly established by single crystal X-ray crystallographic analysis
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5. The quaternary carbons in (11) (12) (13) (15) (16) (17) and (20) are non-stereogenic
6. Data for (12):$[\alpha]_D^{20}$ +11.9 (*c*, 1.0 in H_2O), δ_C (D_2O): 62.7 (s) 63.9 (t) 71.1, 75.2, 75.3, 76.7 (4 d).
7. Data for (20). $[\alpha]_D^{20}$ +60.3 (*c*, 0.7 in H_2O),δ_C (D_2O). 73.7, 74.2, 76.6, 76.9 (4 d), 74.4, 159.6, 176.7 (3 s)
8. Data for (23) as base: δ_C (D_2O) 62.7 (t), 63.5 (s), 71.3, 77.7 (2 d): as HCl salt: δ_C (D_2O): 59.4 (t,), 66.7 (s), 70.7, 74.3 (2 d)
9. Data for (28): $[\alpha]_D^{20}$ +33.0 (*c*; 0.93 in MeOH), δ_C (D_2O) 73.0 (s), 70.9, 75.8, 76.0, 77.5 (4 d), 159.9 (s), 177.7 (s)
10. Data for (31): $[\alpha]_D^{20}$ +0.0 (*c*; 0.54 in H_2O), δ_C (D_2O) 70.9, 74.3 (2 d), 78.0, 160.1, 176.6 (3 s).
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