“InosAminoAcids”: Novel Inositol–Amino Acid Hybrid Structures Accessed by Microbial Arene Oxidation

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Microbial 1,2-dihydroxylation of sodium benzoate permits rapid construction of novel inositol-amino acid hybrid structures. Both β- and γ-amino acids are accessible by means of an acylnitroso Diels–Alder cycloaddition.

Azacarbasugars are a privileged class of structures for drug development as the amino functionality can modulate biological activity with respect to the parent carbohydrate and replacement of the endocyclic oxygen with carbon confers hydrolytic stability. Azacarbasugar motifs are present in many compounds of medicinal interest. Acarbose 1 and voglibose 2 are α-glucosidase inhibitors used clinically to treat type II diabetes. Antibiotic 3 and antifungal 4,5 properties of azacarbasugars have been reported. The use of N-octylvalienamine 3 and its 4-epimer as therapies for Gaucher disease and G$\alpha$S-gangliosidosis is under investigation. In addition, the anti-influenza drug oseltamivir 4 may also be considered to be an azacarbasugar (Figure 1).

![Fig. 1](representative-azacarbasugars-and-cyclic-amino-acids)

In the field of peptide engineering, incorporation of non-natural β- and γ- amino acids has been employed to furnish peptides with designed properties. Constrained cyclic amino acids are effective for imparting secondary structure to peptides and the cyclohexane γ-amino acid 5 has been employed for the construction of peptide nanotubes with hydrophobic cavities. Polyhydroxylated analogues of 5 would permit control of the hydrophobicity of such cavities and allow for modified secondary structures based on additional hydrogen bonding interactions.

Enzymatic dihydroxylation of arenes to produce enantiopure building blocks for synthesis is well established methodology. For dihydroxylation of monosubstituted arenes, the most common regiochemical outcome is installation of the diol ortho,meta to the pre-existing substituent (7, Scheme 1a). However, R. eutrophus B911,11 and certain other organisms12 are able to metabolise benzoates such that the diol is introduced ipso,ortho to the carboxy functionality (Scheme 1b). The chiron 9 derived from the oxidation of benzoate has found diverse synthetic applications13 and we have recently demonstrated access to new reaction manifolds by means of tricarbonyliron complexes of 9.14 Arene diols are ideal starting materials for azacarbasugar synthesis; ortho,meta diols of type 7 have been utilised in this context.15 In contrast, ipso,ortho diols of type 9 have remained unexploited to date. We targeted efficient access to C-substituted azacarbasugar structures from 9, made possible by the pre-existing quaternary centre. Specifically, we sought to access C-carboxy inosamines (“InosAminoAcids”), a hitherto unknown class of compound.

![Scheme 1](regio- and stereoselectivity-of-dioxygenases)

Formation of the known13a-g acetonide of 9, followed by carboxylate benzylation afforded protected diene 10, which was employed in an acylnitroso cycloaddition. The dienophile was generated in situ by the action of tetrabutylammonium periodate on N-(benzoyloxy)carbonylhydroxylamine 11.15b,16 Selectivity in cycloadditions employing arene diol-derived dienes has been extensively studied17 and precedent suggested that approach of the dienophile to the diene face opposite the acetone would be favoured.13a,15b,16c,18 In the event, only two of four possible regiosomers were isolated (12 and 13, Scheme 2).

![Scheme 2](acylnitroso-cycloaddition)
The major product of the cycloaddition (12) was that in which the
Cbz group was introduced distal to the benzyl ester, which we
attribute to decreased steric hindrance with respect to formation
of 13. Major adduct 12 was treated with molybdenum
hexacarbonyl to effect selective N–O bond scission, followed by
formation of crystalline p-nitrobenzoate derivative 15. The
absolute structure of 15 was confirmed by X-ray crystallography,
from which the structure of 12 was inferred. The same sequence
of transformations did not furnish a crystalline derivative when
applied to minor adduct 13. Thus, the structure of 13 was
elucidated by means of NOESY correlations. Specifically, an
interaction between the olefinic protons and the acetonide
interaction would not be expected for cycloadducts arising from
dienophile approach to the diene face bearing the acetone.

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\begin{align*}
\text{Scheme 3} & \quad \text{Structural elucidation of 12 and 13. NOESY correlations are shown with double-headed arrows. ORTEP Diagram of 15 shows ellipsoids at 50% probability. Solvent and disorder in the Cbz phenyl ring are omitted for clarity. H atoms are shown as spheres of arbitrary radius.} \\
\text{Scheme 4} & \quad \text{(a) NMO, cat. OsO}_4, \text{acetone/H}_2\text{O 4:1, 24 h, rt. NOESY correlations are shown with double-headed arrows.} \\
\end{align*}
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Cycloadducts 12 and 13 were subjected to Upjohn
odihydroxylation conditions, affording in each instance the diol
corresponding to approach of the oxidant to the less hindered face
of the olefin. Stereochemistry of addition was again elucidated by
NOESY correlation (Scheme 4). For both diols 16 and 18,
interaction of the acetonide endo methyl protons with the
hydroxyl group methines was observed, indicative of the axial
orientation of the methines and, by inference, the equatorial
orientation of the hydroxyl groups. In the dihydroxylation of 12,
unexpected cyclic carbamate 17 was also formed. Hydrogenolysis
of diols 16 and 18 effected multiple reductive operations cleanly,
allowing access to the target inosaminoacids 20 and 22 (Scheme
5) simply by acetonide removal in aqueous hydrochloric acid.

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\begin{align*}
\text{Scheme 5} & \quad \text{(a) H}_2, \text{Pd/C, MeOH, 24 h, rt. (b) 1 M HCl}(aq) \text{ 24 h, rt. (c) C}_18 \text{ reversed-phase chromatography. (d) Trituration with EtOH} \\
\text{Scheme 6} & \quad \text{(a) H}_2, \text{Pd/C, MeOH, 24 h, rt. (b) 1 M HCl}(aq) \text{ 24 h, rt. (c) C}_18 \text{ reversed-phase chromatography.} \\
\end{align*}
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Conduramine derivative 24 was highly crystalline and submitted
to X-ray crystallography (Figure 2), providing further
confirmation for the assignment of 12 and 13. It is noteworthy
that in the solid state 24 adopts a near-perfect chair conformation.

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\begin{align*}
\text{Fig. 2} & \quad \text{ORTEP Diagram of 24 shows ellipsoids at 50% probability. H atoms are shown as spheres of arbitrary radius.} \\
\text{Inosaminoacids 20 and 22 and conduramine derivative 24 were} & \quad \text{evaluated for inhibition of glycosidase activity against α-glucosidase (type I from Baker’s yeast), β-D-glucosidase} \\
& \text{and β-D-galactosidase (from almond), β-galactosidase (from A. oryzae and E. coli) and β-D-glucuronidases (from bovine} \\
& \text{liver, E. coli and P. vulgata); no inhibitory activity was observed.} \\
\text{In summary, we have described a very concise synthetic route} & \quad \text{of diols 16 and 18, interaction of the acetonide endo methyl protons with the} \\
\end{align*}
\]
to a novel class of azacarbamates. Isoaminooacids 20 and 22 contain six contiguous stereocentres (including a quaternary centre), yet are accessed in just seven steps from sodium benzoate. Current work in our laboratory concerns accessing isoaminooacids having alternative stereochemistries and their incorporation into oligopeptides.

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Notes and references