
Link to official URL (if available):
http://dx.doi.org/10.1016/j.tet.2013.04.033

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New aminocyclitols with quaternary stereocentres via acylnitroso cycloaddition with an ipso,ortho arene dihydrodiol

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ARTICLE INFO

Article history:
Received 30 January 2013
Received in revised form 23 March 2013
Accepted 8 April 2013
Available online 18 April 2013

Dedicated to the memory of Professor J. Grant Buchanan (1926–2012)

Keywords:
Microbial arene oxidation
Biotransformation
Aminocyclitol
Acylnitroso
Cycloaddition

Abstract

Microbial ipso,ortho-dihydroxylation of benzoic acid by the B9 mutant strain of Ralstonia eutropha permits rapid construction of aminocyclitols containing a quaternary stereocentre. Installation of the amine functionality is achieved by use of an acylnitroso dienophile for a hetero-Diels–Alder reaction. Both aminotetrols and aminohexols are accessible as single enantiomers by this route. Both NOESY spectroscopic and X-ray crystallographic analyses were required to distinguish cycloadduct isomers. Notably, subsequent to the biooxidation step, all new stereocentres are installed under substrate control. Thus, all stereochemical information is ultimately of enzymatic origin.

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1. Introduction

The dearomatisation–dihydroxylation of an arene by a microorganism was first reported by Gibson in 1968. In the ensuing period, the arene cis-diol products of such biotransformations have been shown to be exceedingly versatile starting materials for synthesis. For example, many natural products, drug molecules, polymers and dyes have all been synthesised by routes, which take advantage of the diverse functionality in these building blocks. Such syntheses are often of single enantiomers, as the metabolism of substituted arenes gives rise to enantiopure diols in most instances. The microorganisms employed for the production of arene cis-diols are usually those expressing benzene dioxygenase (BDO), toluene dioxygenase (TDO), naphthalene dioxygenase (NDO) and biphenyl dioxygenase (BPDO) enzymes. The regio- and stereoselective outcome of these biotransformations may be predicted by Boyd’s model; the sense of enantioinduction is conserved across organisms and substrates (Scheme 1a, ortho,meta-dihydroxylation).

However, organisms expressing benzoate dioxygenase (BZDO) oxidise benzoic acids with both different regioselectivity and also the opposite absolute sense of enantioinduction (Scheme 1b, ipso,ortho-dihydroxylation). Certain substituted benzoic acids also undergo dearomatisation–dihydroxylation. The synthetic exploitation of ipso,ortho arene cis-diols such as 4 has been infrequent compared to ortho,meta arene cis-diols of type 2. Nevertheless, we and others have reported uses of 4 in various synthetic contexts.

(a) Arene ortho,meta dihydroxylation

(b) Arene ipso,ortho dihydroxylation

Scheme 1. Regio- and stereoselectivity of dioxygenases.


Aminocyclitols (or ‘azacarbasugars’) are a privileged class of structures for drug development as they can serve as effective mimics of natural carbohydrates. The amino functionality can impart modified biological activity with respect to the parent carbohydrate and the lack of an endocyclic oxygen leads to enhanced hydrolytic stability.24 Various aminocyclitols are currently in clinical use,13 most notably, voglibose36 are α-glucosidase inhibitors used to treat type II diabetes, as is the structurally related iminosugar,17 not only naturally occurring aminocyclitols 

but also novel structural variants such as medium rings31h,32 (e.g., octylvalienamine918 amino derivatives 10–11 of myo-inositol,19 bicyclic analogues12–13,20 triazolylamino derivatives1421 of scylla-inositol and homologated calystegine1512 for Gaucher disease and 4-epi-N-acetylvalienamine1613b,18,23 for GM1-gangliosidosis. Aminocyclitols are core structural motifs of aminoglycoside antibiotics12e,24 such as validamycin A12b and antifungal activity of aminocyclitols such as salbostatin18 has also been reported.24e,25

In view of the many current and potential therapeutic applications of aminocyclitols, they have attracted a great degree of attention from the synthetic community. For example, syntheses of natural and non-natural aminocyclitols have been reported starting from carbohydrates by the Ferrier reaction,26 from tricarbonyl(η2-cyclohexadienyl)iron complexes,27 from inositols28 and quercitols19 from carbohydrates by the Ferrier reaction,26 from tricarbonyl(η2-cyclohexadienyl)iron complexes,27 from inositols28 and quercitols19 and antifungal activity of aminocyclitols such as salbostatin18 has also been reported.24e,25

Diabetes

Gaucher Disease

Fig. 1. Aminocyclitols of medicinal relevance.

2. Results and discussion

Primary alcohol46 is accessible from ipso,ortho arene cis-diols 4 by previously reported transformations:11a,b,h,k ketosilation, esterification and reduction (we have found LiBH4 to be the most effective reductant). We intended to introduce nitrogen functionality by means of an acylaziridino cycloaddition (Scheme 2a). This approach has also been used on two subsequent occasions.36e Other reported methods for introduction of the nitrogen(s) are (i) alkene epoxidation and ring-opening with azide,36b,37 phthalimide,38 or other amines36b,39 (Scheme 2b), (ii) alkene aziridination37d,38 (Scheme 2c), including aziridine opening with nitrogen nucleophiles to access vicinal diamino cyclitols,36b,40b (iii) displacement of a triflate by azide44 (Scheme 2d) and (iv) addition of trimethylsilylazide to an enone41 (Scheme 2e).

In contrast to ortho,meta arene cis-diols of type 2, the ipso,ortho arene cis-diols had not been used for aminocyclitol synthesis until our report in 2011 on the preparation from 4 of ‘inosaminocids’ (44), zwitterionic aminocyclitols bearing a C-carboxy substituent.42 In the present paper we describe the synthesis from 4 of aminocyclitols in which the side chain is in a lower oxidation state (45); these aminocyclitols were anticipated to have markedly different solubilities (due to their non-zwitterionic nature) and glycosidase inhibitory activities to those we have previously reported (Fig. 3).

Scheme 2a). Thus, protection of the free hydroxyl group was achieved by azide14 (Scheme 2c), including aziridine opening with nitrogen nucleophiles to access vicinal diamino cyclitols,36b,40b (iii) displacement of a triflate by azide44 (Scheme 2d) and (iv) addition of trimethylsilylazide to an enone41 (Scheme 2e).

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The selectivity of cycloadditions employing dienes derived from arene cis-diols has been studied previously; precedent suggested that approach of the dienophile to the diene face opposite the acetonide would be favoured. NOESY spectra for both adducts showed correlations between the olefinic protons and the acetonide endo methyl protons, confirming the approach of the dienophile to the upper face. Distinguishing the two structures in which the Cbz group is distal (48) or proximal (49) to the silyl ether was not possible by NMR methods and required crystallographic analysis of a derivative (see below).

The residual alkenes in 48 and 49 were dihydroxylated under Upjohn conditions; cycloadduct 48 afforded a single cis-diol 50 in good yield, but surprisingly the corresponding transformation of 49 to cis-diol 51 was lower yielding and hampered by the formation of tetracyclic carbonate side-product 52. The structure of 52 was assigned on the basis of its molecular mass, a characteristic n(C=O) absorbance at 1808 cm\(^{-1}\) and a \(^{13}\)C NMR resonance at \(\delta=154.4\) ppm. We propose that 52 is formed from 51 by attack of a newly introduced hydroxyl group on the carbamate carbonyl and C\(_{e}\)N bond cleavage, followed by attack of the other hydroxyl group and extrusion of benzyl alcohol (Scheme 4). Also in support of the structure of 52, treatment of cis-diol 50 with TBAF did not give the expected desilylated structure 54, but instead gave cyclic carbonate 55, the structure of which was secured by X-ray crystallographic analysis (Fig. 4). Cyclic carbonate 55 has \(\nu(C=O)=1800\) cm\(^{-1}\) and a \(^{13}\)C NMR resonance at \(\delta=154.6\) ppm, comparable with 52.

The final removal of acid-labile protecting groups could be executed in a succinct manner simply by exposing 56–59 to aqueous hydrochloric acid, followed by an organic extraction to remove the lipophilic silanol byproduct. Concentration of the aqueous phase gave pure novel aminocyclitols 60–63 (Scheme 6). Aminotetrols 61 and 62 and aminohexols 63 and 64 were evaluated for the inhibition of glycosidase activity against \(\alpha\)-glucosidase (type I from \(\text{Saccharomyces cerevisiae}\)), \(\beta\)-glucosidase (almond), \(\beta\)-galactosidases (from \(\text{Aspergillus oryzae}\) and \(\text{Escherichia coli}\)) and \(\beta\)-glucuronidases (from bovine liver, \(E.\) coli and \(\text{Patella vulgaris}\)); no inhibitory activity at 100 \(\mu\)M was observed.

3. Conclusion

We have described herein the synthesis of novel, densely functionalised aminocyclitols from a simple aromatic precursor, using a biotransformation and a hetero-Diels–Alder reaction. The brevity of this route (nine steps from benzoic acid to products bearing six contiguous stereocentres, including a quaternary stereocentre) underscores the utility of microbial arene oxidation for the rapid introduction of complexity.

4. Experimental section

4.1. General

For general experimental methods, please see the Supplementary data.

4.1.1. tert-Butyl(((3aR,7aR)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxol-3a-yl)methoxy)dimethylsilane (47). To alcohol 46 (548 mg, 3.01 mmol, 1.00 equiv) dissolved in dichloromethane (30 mL), triethylamine (1.06 mL, 7.52 mmol, 2.50 equiv) was added and
stirred at 0 °C. tert-Butyldimethylsilyl trifluoromethanesulfonate (0.829 mL, 3.61 mmol, 1.20 equiv) was added dropwise at 0 °C over 5 min. The resulting mixture was stirred at 0 °C for 1 h. The organic phase was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and purified via column chromatography (15% ethyl acetate–petrol) to give 47 (636 mg, 72%) as a colourless oil:

\[
\text{Rf} = 0.56 \text{ (15% ethyl acetate–petrol); } \]
\[
\left[ \alpha \right]_D^{25} = 137.5 (c 9.4, \text{CH}_2\text{Cl}_2); \]
\[
\text{n}_\text{max} (\text{neat})/\text{cm}^{-1} = 2987, 2954, 2898, 2857, 1742, 1463, 1414, 1378, 1368, 1251, 1214, 1172, 1151, 1130, 1093, 1076, 1038, 1006, 938, 915, 834, 775, 709, 664, 641; \]
\[
\text{1H NMR (250 MHz, CDCl}_3) \delta = 6.20–5.94 (m, 3H), 5.67 (d, J = 10.0 Hz, 1H), 4.52 (d, J = 5.0 Hz, 1H), 3.55 (d, J = 12.0 Hz, 1H), 3.44 (d, J = 12.0 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); \]
\[
\text{13C NMR (75 MHz, CDCl}_3) \delta = 129.6, 125.1, 124.5, 122.6, 105.7, 80.1, 71.2, 65.8, 27.1, 26.5, 25.7, 18.2, -5.3, -5.5; \]
\[
\text{HRMS m/z (ES\textsuperscript{+}) [found (M+Na\textsuperscript{+})]} = 319.1705, \text{C}_{16}\text{H}_{28}\text{NNaO}_3\text{Si requires M}\textsuperscript{+}, 319.1688. \]

Scheme 2. Representative examples of reported strategies for introduction of nitrogen in the synthesis of aminocyclitols from ortho,meta arene cis-diols.

Zwitterionic inosAminoAcids
- previous work

![Image](44.png)

Cationic aminocyclitols
- current work

![Image](45.png)

Fig. 3. Contrasting current and previous work.

4.1.2. (3aR,4R,7S,7aR)-Benzyl 3a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,7a-tetrahydro-4,7-(epoxyimino)benzo[d]
[1,3]dioxole-8-carboxylate (48) and (3aR,4S,7R,7aR)-benzyl 7a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-(epoxyimino)benzo[d][1,3]dioxole-8-carboxylate (49). To a solution of diene 47 (446 mg, 1.50 mmol, 1.00 equiv) and tetrabutylammonium periodate (1.30 g, 3.01 mmol, 2.00 equiv) in dichloromethane (30 mL) at \(78^\circ C\) was added 2-(benzyloxycarbonyl)hydroxylamine (503 mg, 3.01 mmol, 2.00 equiv) in dichloromethane (10 mL) dropwise via cannula over 5 min. The reaction mixture was stirred at \(78^\circ C\) under N\(_2\) for 20 h, then diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium thiosulfate solution (5 mL) and then brine (5 mL). The organic layer was separated and dried over magnesium sulfate, then concentrated under reduced pressure and purified by column chromatography (5% ethyl acetate in petrol) to give 48 (217 mg, 31%) as a colourless oil and 49 (403 mg, 58%) as a colourless oil. Compound 48: \(R_f 0.19\) (15% ethyl acetate in petrol); \([\alpha]_D^{25} +1.53\) (c 0.66, CH\(_2\)Cl\(_2\)); \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 13515, 2929, 2857, 1747, 1713, 1497, 1455, 1379, 1312, 1284, 1248, 1211, 1184, 1151, 1097, 1061, 1024, 984, 929, 910, 776, 751, 731, 696, 616; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.25\) (s, 5H), \(6.46\) (br t, \(J = 5.0\) Hz, 1H), \(6.28\) (ddd, \(J = 7.5, 2.5, 1.5\) Hz, 1H), \(5.10\) (d, \(J = 10.0\) Hz, 1H), \(5.06\) (dd, \(J = 6.0, 3.0\) Hz, 1H), \(5.02\) (d, \(J = 10.0\) Hz, 1H), \(4.82\) (ddd, \(J = 6.0, 3.0, 1.5\) Hz, 1H), \(4.07\) (d, \(J = 3.0\) Hz, 1H), \(3.80\) (d, \(J = 12.0\) Hz, 1H), \(3.76\) (d, \(J = 12.0\) Hz, 1H), \(1.30\) (s, 3H), \(1.21\) (s, 3H), \(0.08\) (s, 9H), \(0.01\) (s, 3H), \(0.01\) (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 158.2, 135.5, 132.4, 129.0, 128.4, 128.2, 128.0, 112.3, 84.0, 75.7, 72.2, 68.0, 66.2, 53.6, 28.0, 27.0, 25.9, 18.4, −5.5, −5.6; HRMS m/z (ES\(^+\)) [found (M+Na\(^+\))] 594.2140, C\(_{24}\)H\(_{35}\)NaO\(_6\)Si requires M\(^+\), 594.2131. Compound 49: \(R_f 0.19\) (15% ethyl acetate-petrol); \([\alpha]_D^{25} +12.6\) (c 0.87, CH\(_2\)Cl\(_2\)); \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2930, 2857, 1748, 1709, 1498, 1462, 1380, 1370, 1327, 1295, 1248, 1214, 1170, 1150, 1096, 1080, 1065, 1026, 1005, 934, 904, 836, 776, 736, 696, 683, 670; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.34\) (s, 5H), 6.53 (ddd, \(J = 7.5, 2.5, 1.5\) Hz, 1H), 6.42 (br t, \(J = 5.0\) Hz, 1H), 5.22 (d, \(J = 12.0\) Hz, 1H), 5.19 (d, \(J = 12.0\) Hz, 0°C, 12 h, 24%).

Fig. 4. ORTEP diagram of 55 showing ellipsoids at 50% probability. H atoms are shown as spheres of arbitrary radius.
1H), 5.06 (ddd, J = 5.0, 0.5, 1.5 Hz, 1H), 4.89 (dd, J = 5.0, 2.5 Hz, 1H), 4.18 (d, J = 2.5 Hz, 1H), 3.90 (s, 2H), 1.39 (s, 3H), 1.28 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); \( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 157.5, 135.5, 131.1, 129.8, 128.4, 128.3, 128.1, 112.5, 84.1, 75.1, 71.5, 68.1, 65.6, 53.6, 28.3, 27.1, 26.0, 18.5, -5.3, -5.4; HRMS \( m/z \) (ES\( ^{+} \)) \[\text{found (M+Na)}^{+} \] 484.2108, C\(_{24}\)H\(_{32}\)NaO\(_{8}\)Si requires \( M^{+} \), 484.2131.

4.1.3. (3aR,4R,5S,6R,7S,7aR)-Benzy1 7a-(((tert-butyldimethylsilyl) oxy)methyl)-5,6-dihydroxy-2,2-dimethylhexahydro-4,7-(epoxyiminobenzod[1,3]dioxole-8-carboxylate (50). To alkene 48 (195 mg, 0.422 mmol, 1.00 equiv) in acetonewater (4/1, 20 mL) was added N-methylmorpholine N-oxide (49 mg, 0.422 mmol, 1.00 equiv) as a solid. Osmium tetroxide (2.5% in tert-butanol, 80 \( \mu \)L, 8.4 \( \mu \)mol, 2.0 mol %) was added via syringe and the reaction mixture was stirred at room temperature for 48 h. A colour change from colourless to pale yellow was observed. The reaction mixture was transferred to a separating funnel, diluted with ethyl acetate (15 mL) and washed with saturated aqueous sodium thiosulfate (5 mL) and brine (5 mL). The organic phase was separated and dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography (50% ethyl acetate–petrol) to give 50 (172 mg, 81%), as a colourless oil. \( R_{f} \) 0.38 (40% ethyl acetate–petrol); [\( \alpha \)]\(_D\)\(^{25} \) +27 (c 8.2, CHCl\(_3\)) \( \rho_{\text{max}} \) (neat/cm\(^{-1} \)) \( 3419, 2959, 2929, 2886, 2857, 1708, 1553, 1498, 1460, 1408, 1384, 1258, 1212, 1071, 836, 779; \( ^{1} \)H NMR (250 MHz, CDCl\(_3\)) \( \delta \) 7.36–7.30 (m, 5H), 5.18 (s, 2H), 4.66 (br s, 1H), 4.38 (br s, 1H), 4.24–4.17 (m, 3H), 3.82 (d, \( J \) = 12.5 Hz, 1H), 3.75 (d, \( J \) = 12.5 Hz, 1H) 3.75–3.63 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H); \( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 156.8, 135.4, 128.2, 128.1, 111.7, 82.0, 78.0, 76.4, 72.3, 67.9, 64.9, 61.8, 61.2, 26.5, 26.4, 25.7, 18.2, -5.6, -5.7; HRMS \( m/z \) (ES\( ^{+} \)) \[\text{found (M+Na)}^{+} \] 496.2400, C\(_{24}\)H\(_{37}\)NaO\(_{8}\)Si requires \( M^{+} \), 496.2367.

Scheme 5. Hydrogenolysis. Reagents and conditions: (a) \( H_2 \), Pd/C, EtOAc, rt, 24 h, 99% (56), 98% (57), 50% (58), 43% (59).

Scheme 6. One-pot deprotection. Reagents and conditions: (a) 1 M HCl(aq), rt, 24 h; EtOAc extraction, 80% (62), 94% (63), 88% (64), 99% (65).
Compound 52: Rf 0.57 (50% ethyl acetate–petrol); [α]D23 +6.5° (c 3.5, CHCl3); 1H NMR (300 MHz, CDC13) δ 6.06 (br s, 1H), 5.03–5.02 (m, 2H), 4.33 (d, J = 6.0 Hz, 1H), 4.21 (d, J = 6.0 Hz, 1H), 4.08 (d, J = 12.0 Hz, 1H), 3.90 (d, J = 12.0 Hz, 1H), 3.67 (brs, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 0.90 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); 13C NMR (75 MHz, CDC13) δ 154.0, 110.4, 81.8, 73.7, 71.7, 69.9, 63.3, 66.2, 53.4, 26.9, 26.6, 25.8, 18.3, −5.4, −5.5; HRMS m/z (ES+) [found (M+Na)+ 354.2076] C16H23NaNO4S requires M+, 354.2076.

1.4.1. (3aS,4R,4aR,7aR,8S,8aR)-4-((Hydroxymethyl)-6,6-dimethylhexahydro-4,8-(epoxyimino)benzo[d]1,2-d:4,5-d’bis[1,3]dioxole-2-one (55). To silyl ether 50 (165 mg, 0.33 mmol, 1.0 equiv) in THF (20 mL) at 0 °C was added tetrabutylammonium fluoride (0.33 mL, 1.0 M in THF, 1.0 equiv) dropwise over 5 min. The reaction mixture was stirred at 0 °C for 12 h, then transferred to a separating funnel and diluted with ethyl acetate (20 mL) and washed with water (2×10 mL). The organic phase was then washed further with brine (5 mL), dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography (50% ethyl acetate–petrol) to give 55 (34 mg, 24%). As a colourless oil. Rf 0.20 (50% ethyl acetate–petrol); [α]D23 +1.5° (c 0.5, CHCl3); 1H NMR (300 MHz, CDCl3) δ 1.57 (6H, s), 1.56 (6H, s), 1.06 (7H, m), 0.77 (3H, d, J = 6.8 Hz); 13C NMR (75 MHz, CDCl3) δ 54.4, 81.9, 81.7, 73.7, 72.0, 70.6, 69.4, 64.5, 51.6, 25.8, 25.6; HRMS m/z (ES+) [found (M+Na)+ 296.0787] C16H23NaNO4S requires M+, 296.0746.

1.4.2. 1H NMR (300 MHz, CDCl3) δ 4.88 (br s, 1H), 3.92 (d, J = 6.0 Hz, 1H), 1.73 (m, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 0.91 (s, 3H), 0.10 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 108.1, 83.6, 80.1, 73.2, 65.1, 47.4, 28.1, 26.7, 25.9, 24.5, 18.3, −5.5, −5.6; HRMS m/z (ES+) [found (M+Na)+ 354.2054] C16H23NaNO4S requires M+, 354.2076.

1.4.3. 1H NMR (300 MHz, CDCl3) δ 4.19 (d, J = 6.0 Hz, 1H), 4.03 (d, J = 5.6 Hz, 1H), 3.92 (d, J = 6.0 Hz, 1H), 2.85 (dd, J = 12.0 Hz, 1H), 1.29 (m, 1H), 1.18 (s, 3H), 1.06 (s, 3H), 0.92 (s, 3H), 0.11 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 108.0, 82.9, 81.9, 73.8, 72.9, 66.7, 62.7, 60.2, 58.3, 26.8, 25.9, 18.4, −5.3, −5.4; HRMS m/z (ES+) [found (M+Na)+ 364.2093] C16H23NaNO4S requires M+, 364.2155.
Supplementary data

1H and 13C NMR spectra for all novel compounds, as well as selected 2D NMR spectra. X-ray crystallographic data for 55 (CCDC: #908420). Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.033.

References and notes


