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

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

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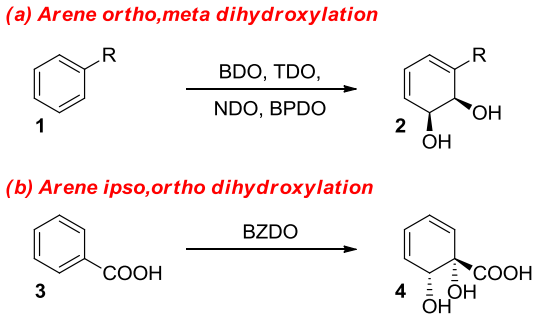
ABSTRACT

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.

1. Introduction

The dearomatisation–dihydroxylation of an arene by a microorganism was first reported by Gibson in 1968.[1] In the ensuing period, the arene *cis*-diol products of such biotransformations have been shown to be exceedingly versatile starting materials for synthesis.[2] For example, many natural products,[3] drug molecules,[4] polymers[5] and dyes[6] 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 stereochemical outcome of these biotransformations may be predicted by Boyd's model;[7] the sense of enantioinduction is conserved across organisms and substrates (Scheme 1a, *ortho,meta*-dihydroxylation). However, organisms expressing benzoate dioxygenase (BZDO)[8] 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.[9] 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[3a,j,9a,10] and others[3m,4,n,o,11] have reported uses of **4** in various synthetic contexts.



Scheme 1. Regio- and stereoselectivity of dioxygenases.

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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.[12] Various aminocyclitols are currently in clinical use;[13] most notably, voglibose **5**[14] and acarbose **6**[15] are α-glucosidase inhibitors used to treat type II diabetes, as is the structurally related iminosugar miglitol **7**[16] (Fig. 1). Voglibose is an *N*-alkylated derivative of a natural product, valiolamine **8**, which itself possesses α-glucosidase inhibitory activity.[17] Aminocyclitols are also being used or evaluated as therapies for other diseases of carbohydrate metabolism, such as *N*-octylvalienamine **9**,[18] amino derivatives **10**–**11** of *myo*-inositol,[19] bicyclic analogues **12**–**13**,[20] triazolylamino derivatives **14**[21] of *scyllo*-inositol and homologated calystegine **15**[22] for Gaucher disease and 4-*epi*-*N*-octylvalienamine **16**[13b,18,23] for G_{M1}-gangliosidosis. Aminocyclitols are core structural motifs of aminoglycoside antibiotics[12e,24] such as validamycin A **17** and antifungal activity of aminocyclitols such as salbostatin **18** has also been reported.[24e,25]

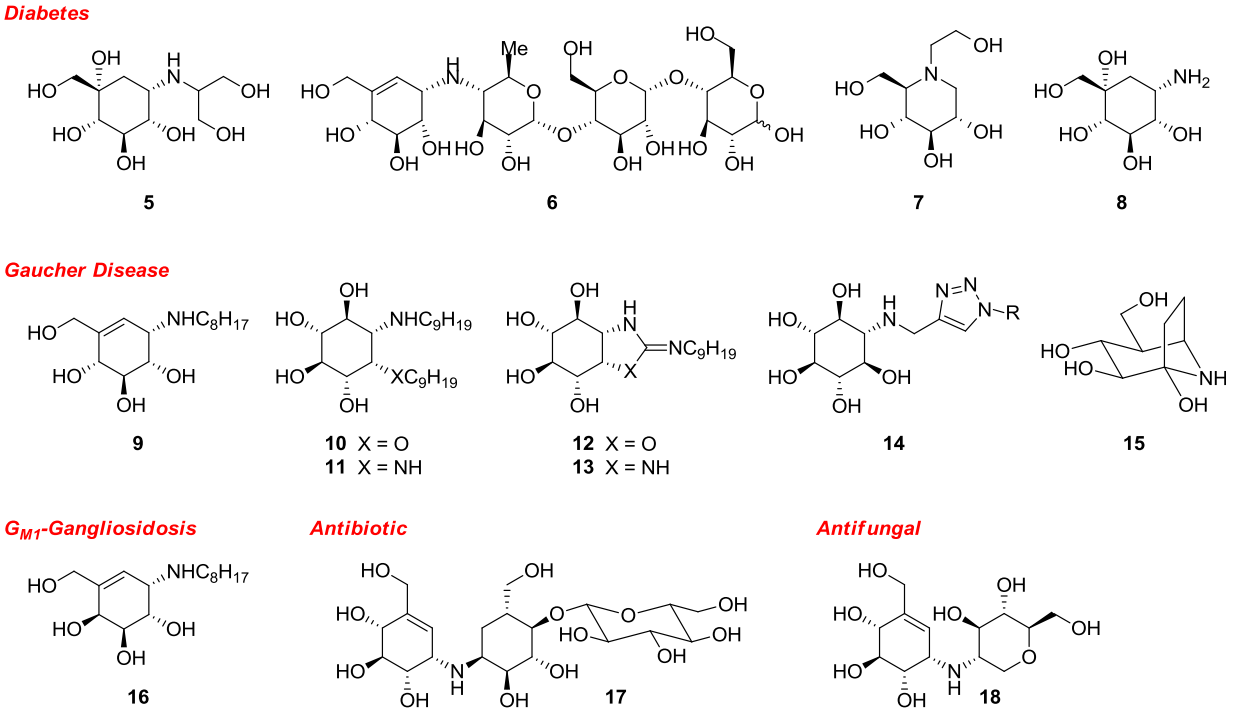


Fig. 1. Aminocyclitols of medicinal relevance.

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(η^5-cyclohexadienyl)iron complexes,[27] from inositols[28] and quercitols (deoxy-inositols),[29] from quinic acid[30] and by ring-closing metathesis.[30e,31] The impetus to discover new glycosidase inhibitors has led chemists to target not only naturally occurring aminocyclitols but also novel structural variants such as medium rings[31h,32] (e.g., **19**–**21**), polycyclics[30e,32d,33] (e.g., **22**–**25**) and fluorinated derivatives[33a,34] (e.g., **26**–**27**, Fig. 2).

Arene *cis*-diols are ideal starting materials for the synthesis of aminocyclitols[35]—the first two hydroxyl groups are introduced in the biotransformation and additional hydroxyls may be introduced by a variety of further oxidative transformations. The *ortho,meta* arene *cis*-diols of type **2** have been used extensively for this purpose. The first report[36a] dates from 1991, wherein Hudlický reported introducing the amino functionality by means of an acylnitroso cycloaddition (Scheme 2a). This approach has also been used on two subsequent occasions.[36b,c] Other reported methods for introduction of the nitrogen(s) are (i) alkene epoxidation and ring-opening with azide,[36b,37] phthalimide,[37d] ammonia[38] or other amines[36b,39] (Scheme 2b), (ii) alkene aziridination[37b,e,38b,40] (Scheme 2c), including aziridine opening with nitrogen nucleophiles to access vicinal diaminocyclitols,[38b,40b] (iii) displacement of a triflate by azide[34c] (Scheme 2d) and (iv) addition of trimethylsilylazide to an enone[41] (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 'inosaminoacids' (**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).

2. Results and discussion

Primary alcohol **46** is accessible from *ipso,ortho* arene *cis*-diol **4** by previously reported transformations:[11a,b,e] ketalisation, esterification and reduction (we have found $LiBH_4$ to be the most effective reductant[3a]). We intended to introduce nitrogen functionality by means of an acylnitroso Diels–Alder reaction whereby the dienophile is generated in situ under oxidative conditions (cf. Scheme 2a). Thus, protection of the free hydroxyl group was needed; introduction of a silyl ether proceeded to give **47** without any competing rearomatisation (a side reaction that can occur upon exposure of arene *cis*-diols to extremes of pH[43]). Fully protected diene **47** underwent cycloaddition to afford two isomeric products, **48** and **49** (Scheme 3).

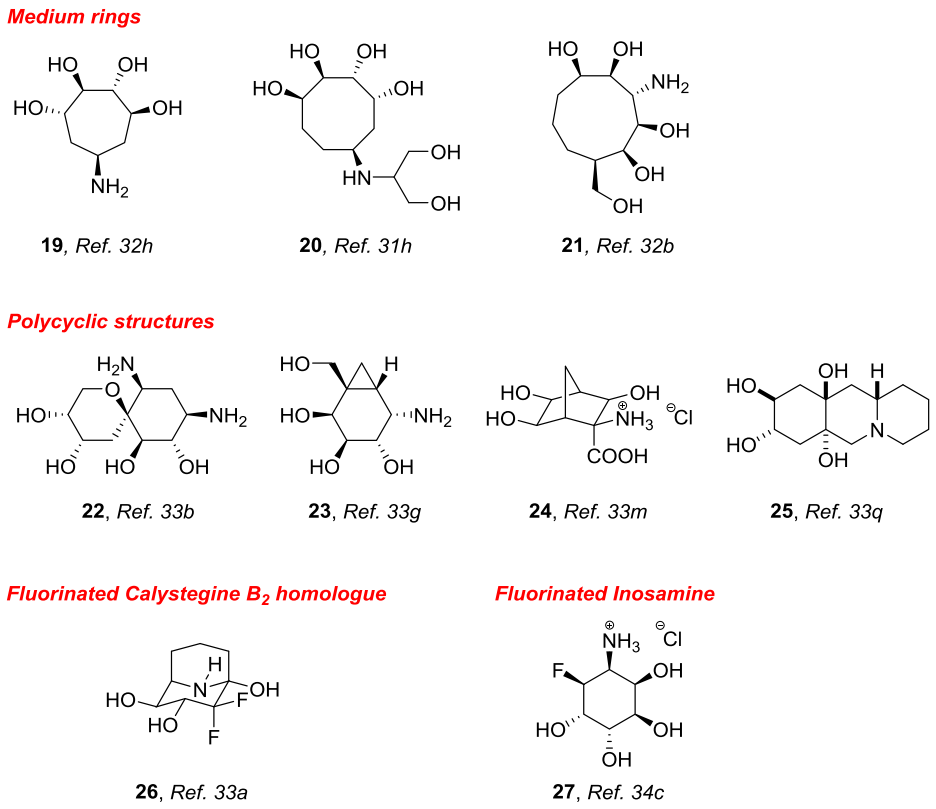


Fig. 2. Selected non-natural aminocyclitols.

The selectivity of cycloadditions employing dienes derived from arene cis-diols has been studied previously;[44] precedent suggested that approach of the dienophile to the diene face opposite the acetonide would be favoured.[11e,36a,45] 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 $\nu_{(C=O)}$ absorbance at 1808 cm^{-1} and a ^{13}C NMR resonance at δ=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–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 δ=154.6 ppm, comparable with **52**.

Hydrogenolysis of diols **50** and **51**, as well as their less highly oxygenated precursors **48** and **49** proceeded smoothly over palladium on carbon, effecting multiple reductive transformations in one-pot (N–O bond scission, Cbz deprotection, alkene reduction; Scheme 5). The more functionalised products **58** and **59** were isolated in lower yield than **56** and **57**, which we ascribe to their unavoidable partial retention on Celite and/or silica.

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[46] against α-glucosidase (type I from *Saccharomyces cerevisiae*), β-glucosidase (almond), β-galactosidases (from *Aspergillus oryzae* and *Escherichia coli*) and β-glucuronidases (from bovine liver, *E. coli* and *Patella vulgata*); no inhibitory activity at 100 μM was observed.

3. Conclusion

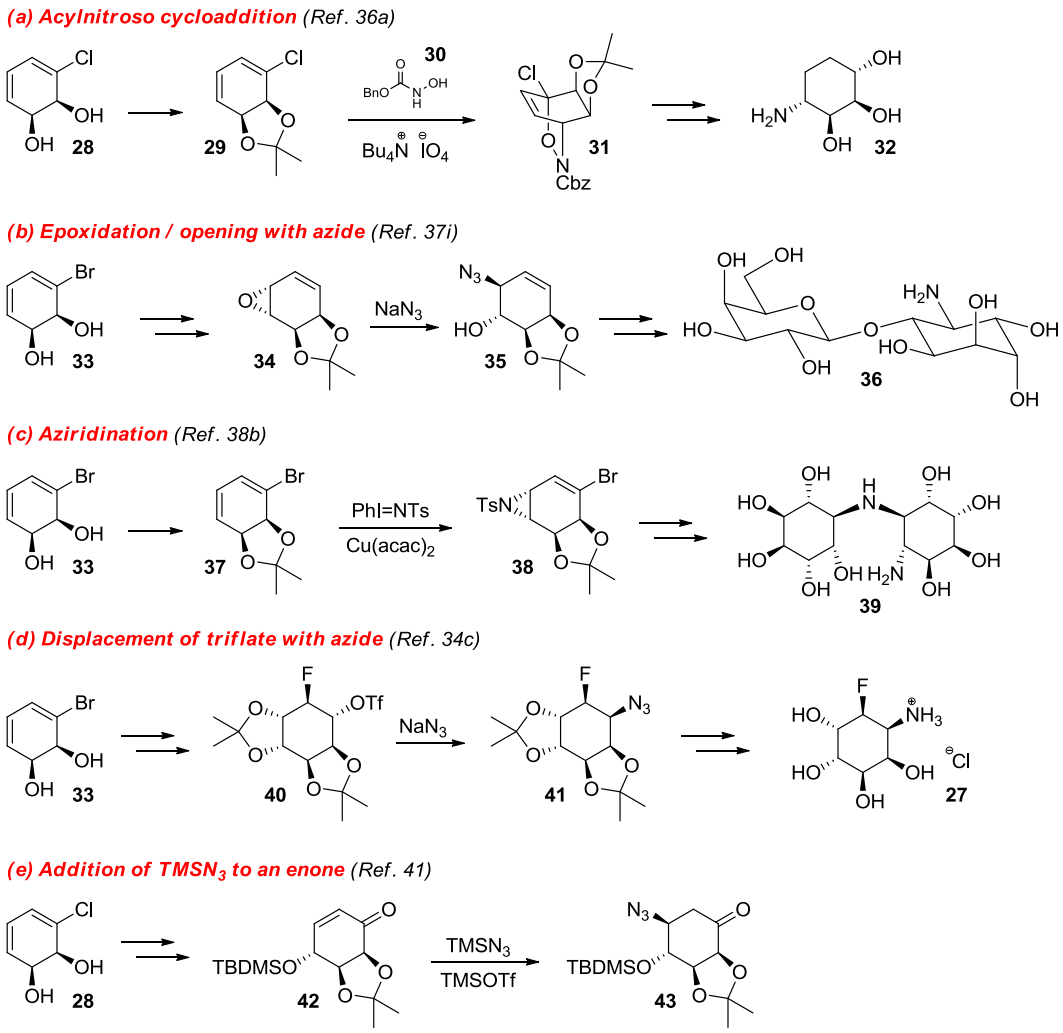
We have described herein the synthesis of novel, densely functionalised aminocyclitols from a simple aromatic precursor, using a biotransformation and a hetero-Diels–Alder reaction. The brevity of this route (nine steps from benzoic acid to products bearing six contiguous stereocentres, including a quaternary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



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

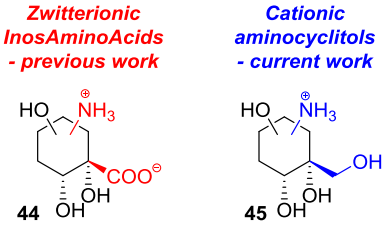
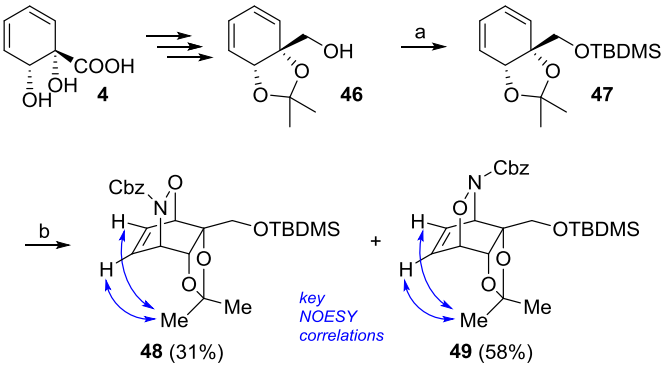


Fig. 3. Contrasting current and previous work.

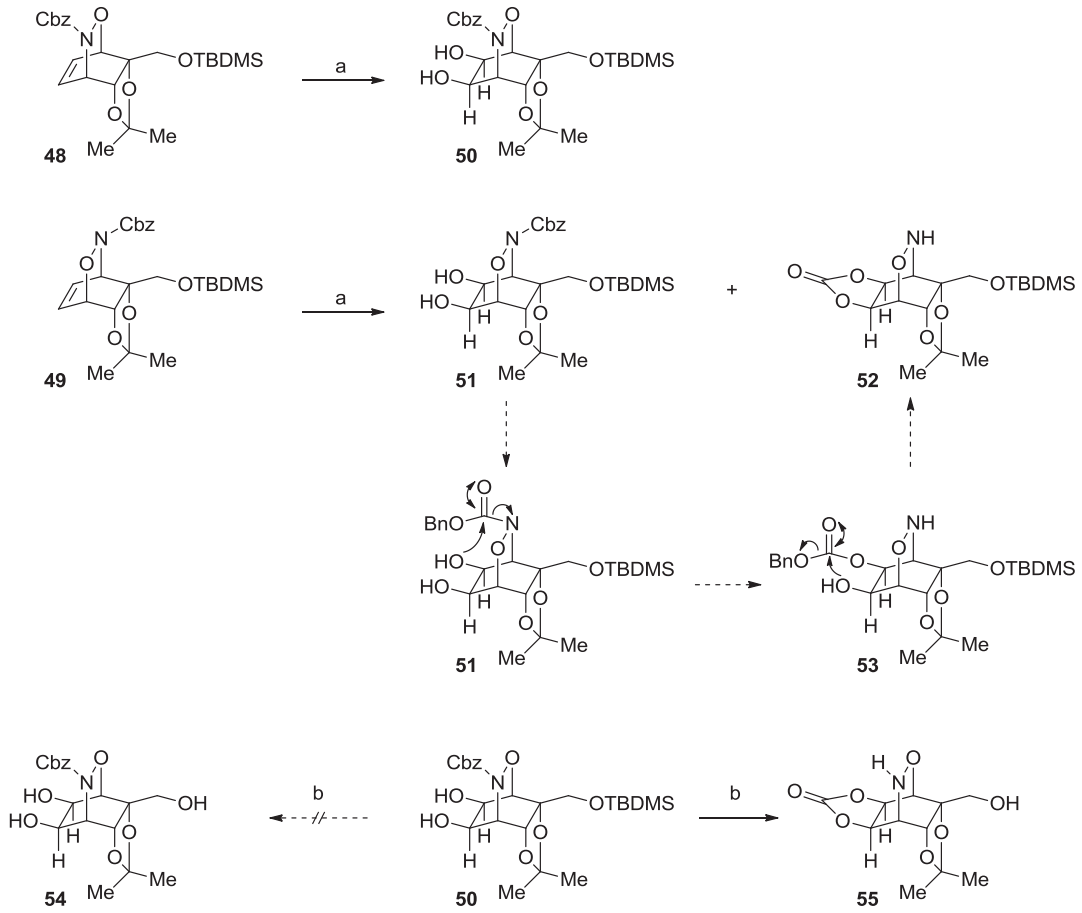
stirred at 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.829 mL, 3.61 mmol, 1.20 equiv) was added dropwise at 0 °C over 5 min. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was transferred to a separating funnel, saturated brine (10 mL) was added then extracted with ethyl acetate (3×10 mL). 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: R_f 0.56 (15% ethyl acetate–petrol); $[\alpha]_D^{25}$ −137.5 (*c* 9.4, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2987, 2954, 2930, 2898, 2857, 1472, 1463, 1414, 1378, 1368, 1251, 1214, 1172, 1151, 1130, 1093, 1076, 1038, 1006, 938, 915, 834, 775, 709, 664, 641; ^{1}H NMR (250 MHz, $CDCl_3$); δ 6.10–5.94 (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



Scheme 3. Cycloaddition of diene derived from *ipso,ortho* arene *cis*-diol **4**. Reagents and conditions: (a) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, 72%; (b) BnOC(O)NHOH **30**, Bu_4NIO_4 CH_2Cl_2, −78 °C, 20 h.

(s, 3H), 1.36 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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; HRMS *m/z* (ES$^+$) [found (M+Na)$^+$ 319.1705, $C_{16}H_{28}NNaO_3Si$ requires M$^+$, 319.1688].

4.1.2. (3aR,4R,7S,7aR)-Benzyl 3a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,7,7a-tetrahydro-4,7-(epoxyimino)benzo[d]



Scheme 4. Dihydroxylation of cycloadducts. Reagents and conditions: (a) 2 mol % OsO_4, 1 equiv NMO, acetone/H_2O 4:1, rt, 48 h, 81% (**50**), 44% (**51**), 17% (**52**); (b) 1 equiv TBAF, THF, 0 °C, 12 h, 24%.

*[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 °C was added *N*-(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 °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–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–petrol); $[\alpha]_D^{25}$ +1.53 (*c* 0.66, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3515, 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, $CDCl_3$); 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, $CDCl_3$); δ 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 $(M+Na)^+$ 484.2140, $C_{24}H_{35}NaO_6Si$ requires M^+, 484.2131]. Compound **49**: R_f 0.28 (15% ethyl acetate–petrol); $[\alpha]_D^{25}$ +12.6 (*c* 0.87, CH_2Cl_2); ν_{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, $CDCl_3$) δ 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,

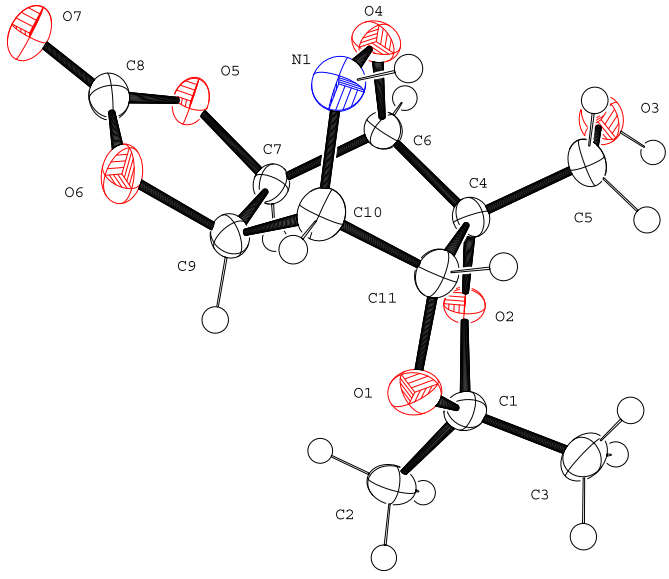
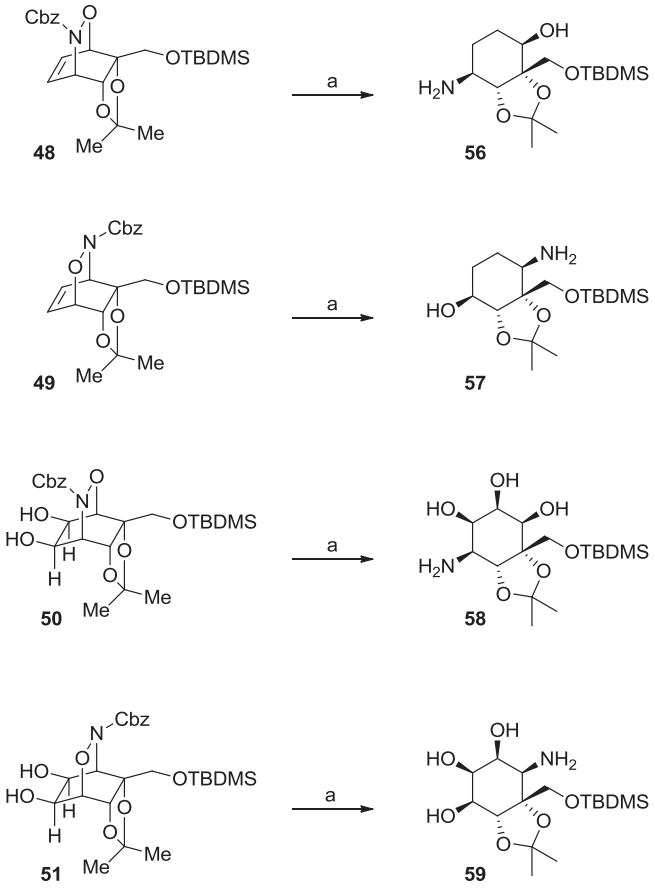


Fig. 4. ORTEP diagram of **55** showing ellipsoids at 50% probability. H atoms are shown as spheres of arbitrary radius.

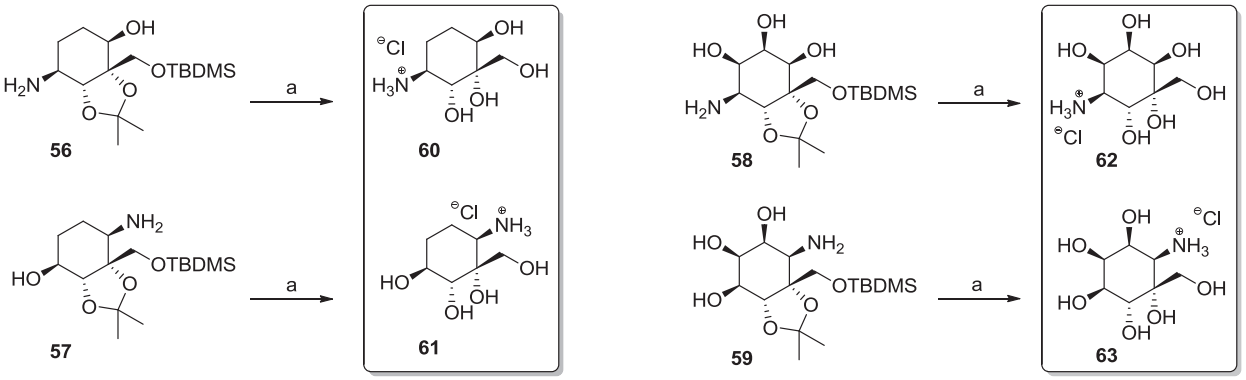


Scheme 5. Hydrogenolysis. Reagents and conditions: (a) H_2, Pd/C, EtOAc, rt, 24 h, 99% (**56**), 98% (**57**), 50% (**58**), 45% (**59**).

1H), 5.06 (ddd, *J*=5.0, 5.0, 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, $CDCl_3$); δ 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^+) [found $(M+Na)^+$ 484.2108, $C_{24}H_{35}NaO_6Si$ requires M^+, 484.2131].

*4.1.3. (3aR,4R,5S,6R,7S,7aR)-Benzyl 3a-(((tert-butyldimethylsilyl) oxy)methyl)-5,6-dihydroxy-2,2-dimethylhexahydro-4,7-(epoxyimino)benzo[d][1,3]dioxole-8-carboxylate (**50**).* To alkene **48** (195 mg, 0.422 mmol, 1.00 equiv) in acetone–water (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 μL, 8.4 μmol, 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, $CHCl_3$); ν_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 156.8, 135.4, 128.2, 128.1, 127.9, 111.1, 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^+) [found $(M+Na)^+$ 496.2400, $C_{24}H_{37}NNaO_8Si$ requires M^+, 496.2367].

*4.1.4. (3aR,4S,5S,6R,7R,7aR)-Benzyl 7a-(((tert-butyldimethylsilyl) oxy)methyl)-5,6-dihydroxy-2,2-dimethylhexahydro-4,7-(epoxyimino)benzo[d][1,3]dioxole-8-carboxylate (**51**) and (3aS,4S,4aR,7aR,8R,8aR)-7a-(((tert-butyldimethylsilyl)oxy)methyl)-6,6-dimethylhexahydro-4,8-(epoxyimino)benzo[1,2-d:4,5-d′]bis([1,3]dioxole)-2-one (**52**).* To alkene **49** (489 mg, 1.06 mmol, 1.00 equiv) in acetone–water (4/1, 20 mL) was added *N*-methylmorpholine *N*-oxide (124 mg, 1.06 mmol, 1.00 equiv) as a solid. Osmium tetroxide (2.5% in *tert*-butanol, 160 μL, 0.011 mmol, 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 and the reaction mixture was transferred to a separating funnel, diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium thiosulfate (5 mL) then 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 **51** (230 mg, 44%) and **52** (70 mg, 17%) both as colourless oils. Also isolated was recovered **49** (97 mg, 19%). Compound **51**: R_f 0.36 (50% ethyl acetate–petrol); $[\alpha]_D^{25}$ +17 (*c* 11.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3428, 2929, 2856, 1710, 1498, 1454, 1383, 1256, 1102, 1064, 835, 777; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5H), 5.20 (s, 2H), 4.67 (br s, 1H), 4.39 (br s, 1H), 4.25–4.21 (m, 3H), 3.84 (d, *J*=10.0 Hz, 1H), 3.78 (d, *J*=10.0 Hz, 1H) 3.54 (br s, 1H), 3.32 (d, *J*=5.0 Hz, 1H) 1.44 (s, 3H), 1.42 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 135.5, 128.5, 128.3, 128.3, 111.7, 83.1, 76.2, 73.2, 68.3, 66.0, 62.5, 61.4, 58.9, 26.7, 26.6, 25.9, 18.4, −5.5, −5.6; HRMS *m*/*z* (ES^+) [found $(M+Na)^+$ 518.2210, $C_{24}H_{37}NNaO_8Si$ requires M^+, 518.2186].



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**: R_f 0.57 (50% ethyl acetate–petrol); $[\alpha]_D^{25}$ −6.5 (*c* 3.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3270, 2955, 2930, 2857, 1808, 1463, 1361, 1254, 1166, 1077, 836, 779; ^1H NMR (300 MHz, $CDCl_3$) 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 (br s, 1H) 1.45 (s, 3H), 1.44 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 110.9, 81.8, 73.7, 71.7, 69.9, 68.3, 66.2, 53.4, 26.9, 26.6, 25.8, 18.3, −5.4, −5.5; HRMS *m*/*z* (ES^+) [found $(M+Na)^+$ 410.1664, $C_{17}H_{29}NNaO_7Si$ requires M^+, 410.1611].

*4.1.5. (3aS,4R,4aR,7aR,8S,8aR)-4a-(Hydroxymethyl)-6,6-dimethylhexahydro-4,8-(epoxyimino)benzo[1,2-d:4,5-d′]bis([1,3]dioxole)-2-one (**55**).* To silyl ether **50** (165 mg, 0.333 mmol, 1.00 equiv) in THF (20 mL) at 0 °C was added tetrabutylammonium fluoride (0.33 mL, 1.0 M in THF, 1.00 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. R_f 0.20 (50% ethyl acetate–petrol); $[\alpha]_D^{25}$ −1.5 (*c* 1.7, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3268, 2992, 2923, 1800, 1780, 1454, 1369, 1165, 1067, 770; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 6.88 (br s, 1H), 5.16 (dd, *J*=8.0, 4.0 Hz, 1H), 5.09 (d, *J*=8.0 Hz, 1H), 4.42 (d, *J*=4.0 Hz, 1H), 4.27 (t, *J*=4.0 Hz, 1H), 4.19 (br s, 1H), 3.97–3.84 (m, 3H), 1.50 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 154.5, 110.1, 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, $C_{11}H_{16}NNaO_7Si$ requires M^+, 296.0746].

*4.1.6. (3aS,4R,7S,7aR)-7-Amino-3a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxol-4-ol (**56**).* To alkene **48** (61 mg, 0.13 mmol, 1.0 equiv) in ethyl acetate (20 mL) was added palladium on carbon (6.0 mg, 10 mass %). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h, then filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (50% ethyl acetate–petrol) to give **56** as a colourless oil (43 mg, 99%). R_f 0.85 (50% ethyl acetate–petrol); $[\alpha]_D^{25}$ −15 (*c* 0.55, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2961, 2927, 2854, 1590, 1519, 1463, 1392, 1300, 1251, 1215, 1151, 1033, 747; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (d, *J*=3.0 Hz, 1H), 3.97 (d, *J*=12.0 Hz, 1H), 3.83 (d, *J*=12.0 Hz, 1H), 3.80 (app q, *J*=3.0 Hz, 1H), 3.46–3.42 (m, 1H), 2.76 (br s, 3H), 2.02–1.87 (m, 1H), 1.83–1.72 (m, 2H), 1.61–1.51 (m, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.1, 83.6, 80.1, 73.2, 65.1, 47.4, 28.1, 26.7, 25.9, 25.4, 24.5, 18.3, −5.5, −5.6; HRMS *m*/*z* (ES^+) [found $(M+Na)^+$ 354.2054, $C_{16}H_{33}NNaO_4Si$ requires M^+, 354.2076].

*4.1.7. (3aR,4S,7R,7aR)-7-Amino-7a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxol-4-ol (**57**).* To alkene **49** (253 mg, 0.548 mmol, 1.00 equiv) in ethyl acetate (20 mL) was added palladium on carbon (26 mg, 10 mass %). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h, then filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (20% methanol–79% ethyl acetate–1% triethylamine) to give **57** as a colourless oil (179 mg, 98%). R_f 0.43 (20% methanol–79% ethyl acetate–1% triethylamine); $[\alpha]_D^{25}$ −37 (*c* 3.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3282, 2998, 2930, 2856, 1472, 1378, 1250, 1216, 1087, 963, 835; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (br s, 1H), 3.96–3.93 (m, 2H), 3.70 (d, *J*=11.0 Hz, 1H), 3.36 (br s, 3H), 3.12 (br s, 1H), 2.00–1.88 (m, 1H), 1.82–1.72 (m, 2H), 1.62–1.58 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), −0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.4, 83.1, 79.8, 67.3, 65.8, 52.3, 27.5, 26.3, 26.0, 25.9, 23.7, 18.3, −5.3, −5.5; HRMS *m*/*z* (ES^+) [found $(M+Na)^+$ 354.2076, $C_{16}H_{33}NNaO_4Si$ requires M^+, 354.2076].

*4.1.8. (3aS,4R,5R,6R,7S,7aR)-7-Amino-3a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-4,5,6-triol (**58**).* To diol **50** (28 mg, 0.056 mmol, 1.0 equiv) in ethyl acetate (20 mL) was added palladium on carbon (5.0 mg, 20 mass %). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h, then filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% methanol–89% chloroform–1% triethylamine) to give **58** as a colourless oil (11 mg, 50%). R_f 0.25 (15% methanol–84% ethyl acetate–1% triethylamine); $[\alpha]_D^{25}$ +43 (*c* 0.6, H_2O); ν_{max} (neat)/cm^{-1} 3324, 3256, 2965, 2813, 2787, 1432, 1376, 1244, 1156, 1020, 978, 836, 774; ^1H NMR (300 MHz, $CDCl_3$) δ 4.46–3.93 (m, 10H), 1.45 (s, 3H), 1.39 (s, 3H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 83.8, 74.3, 70.6, 67.6, 65.3, 64.7, 51.9, 29.6, 27.9, 26.6, 26.0, 25.9, 18.4, −5.3, −5.4; HRMS *m*/*z* (ES^+) [found $(M+Na)^+$ 386.1968, $C_{16}H_{33}NNaO_6Si$ requires M^+, 386.1907].

*4.1.9. (3aR,4S,5S,6S,7R,7aR)-7-Amino-7a-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydrobenzo[d][1,3]dioxole-4,5,6-triol (**59**).* To diol **51** (120 mg, 0.242 mmol, 1.00 equiv) in ethyl acetate (20 mL) was added palladium on carbon (12 mg, 10 mass %). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 24 h, then filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (50% ethyl acetate–petrol) to give **59** as a colourless oil (39 mg, 45%). R_f 0.35 (50% ethyl acetate–petrol); $[\alpha]_D^{25}$ +33 (*c* 0.39, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3404, 2958, 2930, 2857, 1463, 1382, 1255, 1210, 1101, 1060, 863, 779; ^1H NMR (500 MHz, $CDCl_3$) δ 4.25–4.20 (m, 2H), 4.18–4.15 (m, 2H), 4.03 (d, *J*=15.0 Hz, 1H), 3.91 (d, *J*=15.0 Hz, 1H), 3.30 (s, 1H), 1.46 (br s, 3H), 1.43 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.3, 81.9, 73.8, 72.9, 66.7, 62.7, 60.2, 58.3, 26.8, 26.8, 25.9, 18.4, −5.3, −5.4; HRMS *m*/*z* (ES^+) [found $(M+H)^+$ 364.2093, $C_{16}H_{33}NO_6Si$ requires M^+, 364.2155].

*4.1.10. (1S,2R,3S,4R)-2,3,4-Trihydroxy-3-(hydroxymethyl)cyclohexylammonium chloride (**60**).* Hydroxyamine **56** (43 mg, 0.13 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with ethyl acetate (2×10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **60** as a colourless oil (26 mg, 94%). $[\alpha]_D^{25}$ +22 (*c* 1.3, H_2O); ν_{max} (neat)/cm^{-1} 3336, 2981, 2482, 1602, 1383, 1233, 1156, 1069, 1021, 956, 797; ^1H NMR (300 MHz, D_2O) δ 3.85 (s, 1H), 3.64 (d, *J*=12.0 Hz, 1H), 3.57 (d, *J*=12.0 Hz, 1H), 3.55 (d, *J*=9.0 Hz, 1H), 3.37–3.18 (m, 1H), 1.80–1.55 (m, 4H); ^{13}C NMR (75 MHz, D_2O) δ 76.0, 69.9, 68.6, 63.5, 52.1, 25.8, 22.7; HRMS *m*/*z* (ES^+) [found $(M+Na)^+$ 200.0906, $C_7H_{15}NNaO_4$ requires M^+, 200.0898].

*4.1.11. (1R,2R,3R,4S)-2,3,4-Trihydroxy-2-(hydroxymethyl)cyclohexylammonium chloride (**61**).* Hydroxyamine **57** (30 mg, 0.090 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with ethyl acetate (2×10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **61** as a pale yellow oil (17 mg, 88% yield). $[\alpha]_D^{25}$ +35 (*c* 0.85, H_2O); ν_{max} (film)/cm^{-1} 3317, 2940, 2508, 1400, 1071, 1027, 972, 799; ^1H NMR (300 MHz, D_2O) δ 3.86 (d, *J*=12.0 Hz, 1H), 3.81 (td, *J*=7.5, 4.0 Hz, 1H), 3.55 (d, *J*=12.0 Hz, 1H), 3.49 (d, *J*=6.0 Hz, 1H), 3.38–3.34 (m, 1H), 1.92–1.63 (m, 3H), 1.52–1.40 (m, 1H); ^{13}C NMR

(75 MHz, D_2O) δ 74.1, 72.3, 69.8, 63.4, 54.0, 26.0, 22.8; HRMS *m*/*z* (ES^+) [found $(M+H)^+$ 179.1129, $C_7H_{16}NO_4$ requires M^+ 179.1157].

*4.1.12. (1S,2R,3R,4R,5R,6R)-2,3,4,5,6-Pentahydroxy-3-(hydroxymethyl)cyclohexylammonium chloride (**62**).* Aminotriol **58** (11 mg, 0.030 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with ethyl acetate (2×10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **62** as a colourless oil (8 mg, 99%). $[\alpha]_D^{25}$ −47 (*c* 0.4, H_2O); ν_{max} (neat)/cm^{-1} 3302, 2958, 2511, 1629, 1508, 1077, 1028, 808, 723; ^1H NMR (300 MHz, D_2O) δ 4.24 (q, *J*=3.0 Hz, 1H), 4.04–3.99 (m, 3H), 3.89 (d, *J*=12.0 Hz, 1H), 3.75 (d, *J*=12.0 Hz, 1H), 3.57 (dd, *J*=10.5, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 75.5, 72.6, 70.4, 65.6, 65.1, 62.8, 53.3; HRMS *m*/*z* (ES^+) [found $(M+Na)^+$ 232.0783, $C_7H_{15}NNaO_6$ requires M^+ 232.0797].

*4.1.13. (1R,2R,3R,4S,5S,6S)-2,3,4,5,6-Pentahydroxy-2-(hydroxymethyl)cyclohexylammonium chloride (**63**).* Triol **59** (35 mg, 0.096 mmol) was stirred in aqueous hydrochloric acid (1.0 M, 20 mL) at room temperature for 24 h. The aqueous phase was washed with ethyl acetate (2×10 mL) to remove the silanol byproduct. The aqueous phase was concentrated under reduced pressure to give **63** as a pale yellow oil (21 mg, 80%). $[\alpha]_D^{25}$ +32 (*c* 0.5, H_2O); ν_{max} (neat)/cm^{-1} 3272, 2943, 2507, 1622, 1496, 1398, 1184, 1155, 1074, 1025, 928, 892, 814, 712; ^1H NMR (250 MHz, D_2O) δ 4.16–4.14 (m, 2H), 3.91 (d, *J*=12.0 Hz, 1H), 3.83–3.70 (m, 3H), 3.59–3.56 (br t, *J*=2.5 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 75.9, 75.6, 72.4, 69.3, 66.3, 66.1, 59.9; HRMS *m*/*z* (ES^+) [found $(M+H)^+$ 210.0965, $C_7H_{16}NO_6$ requires M^+, 210.0978].

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Supplementary data

^1H and ^{13}C 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

1. Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R. E. *Biochemistry-US* **1968**, *7*, 3795.
2. For reviews, see: (a) Bon, D. J.-Y.; Lee, B.; Banwell, M. G.; Cade, I. A. *Chim. Oggi* **2012**, *30*, 22; (b) Hudlický, T.; Reed, J. W. *Synlett* **2009**, 685; (c) Austin, K. A. B.; Matveenko, M.; Reekie, T. A.; Banwell, M. G. *Chem. Aust.* **2008**, *75*, 3; (d) Boyd, D. R.; Bugg, T. D. H. *Org. Biomol. Chem.* **2006**, *4*, 181; (e) Johnson, R. A. *Org. React.* **2004**, *63*, 117; (f) Hudlický, T.; Gonzales, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, *32*, 35; (g) Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Janssen Chim. Acta* **1990**, *8*, 3.
3. For very recent (2011 onwards) examples, see: (a) Varghese, V.; Hudlický, T. *Synlett* **2013**, 369; (b) Bon, D. J.-Y. D.; Banwell, M. G.; Ward, J. S.; Willis, A. C. *Tetrahedron* **2013**, *69*, 1363; (c) Palframan, M. J.; Kociok-Köhn, G.; Lewis, S. E. *Chem.—Eur. J.* **2012**, *18*, 4766; (d) Boyd, D. R.; Sharma, N. D.; Kaik, M.; McIntyre, P. B. A.; Stevenson, P. J.; Allen, C. C. R. *Org. Biomol. Chem.* **2012**, *10*, 2774; (e) Sharma, M. K.; Banwell, M. G.; Willis, A. C.; Rae, A. D. *Chem. Asian J.* **2012**, *7*, 676; (f) Banwell, M. G.; Gao, N. Y.; Schwartz, B. D.; White, L. V. *Top. Curr. Chem.* **2012**, *309*, 163; (g) Banwell, M. G.; Gao, N. Y.; Ma, X.; Petit, L.; White, L. V.; Schwartz, B. D.; Willis, A. C.; Cade, I. A. *Pure Appl. Chem.* **2012**, *84*, 1329; (h) Bon, D. J.-Y. D.; Banwell, M. G.; Cade, I. A.; Willis, A. C. *Tetrahedron* **2011**, *67*, 8348; (i) Endoma-Arias, M. A. A.; Hudlický, T. *Tetrahedron Lett.* **2011**, *52*, 6632; (j) Schwartz, B. D.; Banwell, M. G.; Cade, I. A. *Tetrahedron Lett.* **2011**, *52*, 4526; (k) White, L. V.; Schwartz, B. D.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2011**, *76*, 6250; (l) Palframan, M. J.; Kociok-Köhn, G.; Lewis, S. E. *Org. Lett.* **2011**, *13*, 3150; (m) Duchek, J.; Piercy, T. G.; Gilmet, J.; Hudlický, T. *Can. J. Chem.* **2011**, *89*, 709; (n) Banwell, M. G.; Lehmann, A. L.; Menon, R. S.; Willis, A. C. *Pure Appl. Chem.* **2011**, *83*, 411; (o) Adams, D. R.; Aichinger, C.; Collins, J.; Rinner, U.; Hudlický, T. *Synlett* **2011**, 725; (p) Labora, M.; Schapiro, V.; Pandolfi, E. *Tetrahedron: Asymmetry* **2011**, *22*, 1705.
4. For selected examples, see: (a) Vshyvenko, S.; Scattolon, J.; Hudlický, T.; Romero, A. E.; Kornienko, A.; Ma, D.; Tuffley, I.; Pandey, S. *Can. J. Chem.* **2012**, *90*, 932; (b) Ma, D.; Tremblay, P.; Mahngar, K.; Akbari-Asl, P.; Collins, J.; Hudlický, T.; McNulty, J.; Pandey, S. *Invest. New Drug.* **2012**, *30*, 1012; (c) Ma, D.; Tremblay, P.; Mahngar, K.; Collins, J.; Hudlický, T.; Pandey, S. *PLoS One* **2011**, *6*, e28780; (d) Ma, D.; Tremblay, P.; Mahngar, K.; Akbari-Asl, P.; Collins, J.; Hudlický, T.; Pandey, S. *Am. J. Biomed. Sci.* **2011**, *3*, 278; (e) Werner, L.; Machara, A.; Sullivan, B.; Carrera, I.; Moser, M.; Adams, D. R.; Hudlický, T. *J. Org. Chem.* **2011**, *76*, 10050; (f) Vshyvenko, S.; Scattolon, J.; Hudlický, T.; Romero, A. E.; Kornienko, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4750; (g) Collins, J.; Rinner, U.; Moser, M.; Hudlický, T.; Ghiviriga, I.; Romero, A. E.; Kornienko, A.; Ma, D.; Griffin, C.; Pandey, S. *J. Org. Chem.* **2010**, *75*, 3069; (h) Werner, L.; Machara, A.; Hudlický, T. *Adv. Synth. Catal.* **2010**, *352*, 195; (i) Fabris, F.; Collins, J.; Sullivan, B.; Leisch, H.; Hudlický, T. *Org. Biomol. Chem.* **2009**, *7*, 2619; (j) Sullivan, B.; Carrera, I.; Drouin, M.; Hudlický, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 4229; (k) Matveenko, M.; Willis, A. C.; Banwell, M. G. *Tetrahedron Lett.* **2008**, *49*, 7018 **2009**, *50*, 2982; (l) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5788; (m) Omori, A. T.; Finn, K. J.; Leisch, H.; Carroll, R. J.; Hudlický, T. *Synlett* **2007**, 2859; (n) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science* **2005**, *308*, 395; (o) Charest, M. G.; Siegel, D. R.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 8292.
5. (a) Bui, V. P.; Hudlický, T. *Tetrahedron* **2004**, *60*, 641; (b) Williams, M. G.; Olson, P. E.; Tautvydas, K. J.; Bitner, R. M.; Mader, R. A.; Wackett, L. P. *Appl. Microbiol. Biotechnol.* **1990**, *34*, 316; (c) Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S. C. *Macromolecules* **1988**, *21*, 294; (d) Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.* **1983**, 954.
6. (a) Royo, J. L.; Moreno-Ruiz, E.; Cebolla, A.; Santero, E. *J. Biotechnol.* **2005**, *116*, 113; (b) Kim, J. Y.; Lee, K.; Kim, Y.; Kim, C.-K.; Lee, K. *Lett. Appl. Microbiol.* **2003**, *36*, 343; (c) Berry, A.; Dodge, T. C.; Pepsin, M.; Weyler, W. *J. Ind. Microbiol. Biotechnol.* **2002**, *28*, 127; (d) Ensley, B. D.; Ratzkin, B. J.; Osslund, T. D.; Simon, M. J.; Wackett, L. P.; Gibson, D. T. *Science* **1983**, *222*, 167.
7. Boyd, D. R.; Sharma, N. D.; Hand, M. V.; Groocock, M. R.; Kerley, N. A.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1993**, 974.
8. (a) Sun, S.-Y.; Zhang, X.; Zhou, Q.; Chen, J.-C.; Chen, G.-Q. *Appl. Microbiol. Biotechnol.* **2008**, *80*, 977; (b) Cass, A. E. G.; Ribbons, D. W.; Rossiter, J. T.; Williams, S. R. *Biochem. Soc. Trans.* **1986**, *14*, 1268; (c) Reiner, A. M.; Hegeman, G. D. *Biochemistry* **1971**, *10*, 2530; (d) Johnson, B. F.; Stanier, R. Y. *J. Bacteriol.* **1971**, *107*, 476.
9. (a) Griffen, J. A.; le Coz, A. M.; Kociok-Köhn, G.; Ali Khan, M.; Stewart, A. J. W.; Lewis, S. E. *Org. Biomol. Chem.* **2011**, *9*, 3920; (b) Engesser, K.-H.; Schmidt, E.; Knackmuss, H.-J. *Appl. Environ. Microbiol.* **1980**, *39*, 68; (c) Reineke, W.; Otting, W.; Knackmuss, H.-J. *Tetrahedron* **1978**, *34*, 1707; (d) Reineke, W.; Knackmuss, H.-J. *Biochim. Biophys. Acta* **1978**, *542*, 412; (e) Knackmuss, H.-J.; Reineke, W. *Chemosphere* **1973**, *2*, 225.
10. (a) Ali Khan, M.; Mahon, M. F.; Lowe, J. P.; Stewart, A. J. W.; Lewis, S. E. *Chem.—Eur. J.* **2012**, *18*, 13480; (b) van der Waals, D.; Pugh, T.; Ali Khan, M.; Stewart, A. J. W.; Johnson, A. L.; Lewis, S. E. *Chem. Cent. J.* **2011**, *5*, 80; (c) Ali Khan, M.; Lowe, J. P.; Johnson, A. L.; Stewart, A. J. W.; Lewis, S. E. *Chem. Commun.* **2011**, 215; (d) Ali Khan, M.; Mahon, M. F.; Stewart, A. J. W.; Lewis, S. E. *Organometallics* **2010**, *29*, 199.
11. (a) Fischer, T. C. M.; Leisch, H. G.; Mihovilovic, M. D. *Monatsh. Chem.* **2010**, *141*, 699; (b) Mihovilovic, M. D.; Leisch, H. G.; Mereiter, K. *Tetrahedron Lett.* **2004**, *45*, 7087; (c) Parker, M. H.; Maryanoff, B. E.; Reitz, A. B. *Synlett* **2004**, 2095; (d) Myers, A. G.; Siegel, D. R.; Buzard, D. J.; Charest, M. G. *Org. Lett.* **2001**, *3*, 2923; (e) Jenkins, G. N.; Ribbons, D. W.; Widdowson, D. A.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2647.
12. For reviews, see: (a) Diaz, L.; Delgado, A. *Curr. Med. Chem.* **2010**, *17*, 2393; (b) Delgado, A. *Eur. J. Org. Chem.* **2008**, 3893; (c) Arjona, O.; Gómez, A. M.; López, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919; (d) Chen, X.; Fan, Y.; Zheng, Y.; Shen, Y. *Chem. Rev.* **2003**, *103*, 1955; (e) Mahmud, T. *Nat. Prod. Rep.* **2003**, *20*, 137; (f) Asano, N. *Glycobiology* **2003**, *13*, 93R; (g) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.
13. For reviews, see: (a) *Iminosugars from Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; John Wiley & Sons: Chichester, UK, 2007; (b) Ogawa, S.; Kanto, M.; Suzuki, Y. *Mini Rev. Med. Chem.* **2007**, *7*, 679.
14. (a) Chen, X.; Zheng, Y.; Shen, Y. *Curr. Med. Chem.* **2006**, *13*, 109; (b) Zhou, H.-P.; Chen, X.-Y. *Zhongguo Yiyao Gongye Zazhi* **2006**, *37*, 574; (c) Horii, S.; Takeda, J. *Res. Lab.* **1993**, *52*, 1; (d) Fukase, H.; Horii, S. *J. Org. Chem.* **1992**, *57*, 3651; (e) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038.
15. Schmidt, D. D.; Frommer, W.; Junge, B.; Mueller, L.; Wingender, W.; Truscheit, E.; Schaefer, D. *Naturwissenschaften* **1977**, *64*, 535.
16. Lembcke, B.; Foelsch, U. R.; Creutzfeldt, W. *Digestion* **1985**, *31*, 120.
17. Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. *J. Antibiot.* **1984**, *37*, 1301.
18. (a) Kuno, S.; Takahashi, A.; Ogawa, S. *Carbohydr. Res.* **2013**, *368*, 8; (b) Suzuki, Y.; Ogawa, S.; Sakakibara, Y. *Perspect. Med. Chem.* **2009**, *3*, 7.
19. (a) Trapero, A.; Gonzalez-Bulnes, P.; Butters, T. D.; Llebaria, A. *J. Med. Chem.* **2012**, *55*, 4479; (b) Trapero, A.; Llebaria, A. *ACS Med. Chem. Lett.* **2011**, *2*, 614.
20. Trapero, A.; Alfonso, I.; Butters, T. D.; Llebaria, A. *J. Am. Chem. Soc.* **2011**, *133*, 5474.
21. Diaz, L.; Casas, J.; Bujons, J.; Llebaria, A.; Delgado, A. *J. Med. Chem.* **2011**, *54*, 2069.

22. Rasmussen, T. S.; Allman, S.; Twigg, G.; Butters, T. D.; Jensen, H. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1519.
23. (a) Suzuki, Y. *Cell. Mol. Life Sci.* **2008**, *65*, 351; (b) Suzuki, Y. *J. Inherit. Metab. Dis.* **2006**, *29*, 471; (c) Matsuda, J.; Suzuki, O.; Oshima, A.; Yamamoto, Y.; Noguchi, A.; Takimoto, K.; Itoh, M.; Matsuzaki, Y.; Yasuda, Y.; Ogawa, S.; Sakata, Y.; Nanba, E.; Higaki, K.; Ogawa, Y.; Tominaga, L.; Ohno, K.; Iwasaki, H.; Watanabe, H.; Brady, R. O.; Suzuki, Y. P. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 15912.
24. (a) Busscher, G. F.; Rutjes, F. P. J. T.; Van Delft, F. L. *Chem. Rev.* **2005**, *105*, 775; (b) Mingeot-Leclercq, M. P.; Glupczynski, Y.; Tulkens, P. M. *Antimicrob. Agents Chemother.* **1999**, *43*, 727; (c) Begg, E. J.; Barclay, M. L. *Br. J. Clin. Pharmacol.* **1995**, *39*, 597; (d) Iwasa, T.; Takeda, J. *Res. Lab.* **1978**, *37*, 307; (e) Iwasa, T.; Yamamoto, H.; Shibata, M. *J. Antibiot.* **1970**, *23*, 595.
25. (a) Vértsey, L.; Fehlhaber, H.-W.; Schulz, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1844; (b) Trinci, A. P. J. *Br. Mycol. Sy.* **1983**, *9*, 113.
26. For examples, see: (a) Pang, L.-J.; Wang, D.; Zhou, J.; Zhang, L.-H.; Ye, X.-S. *Org. Biomol. Chem.* **2009**, *7*, 4252; (b) Bauder, C. *Org. Biomol. Chem.* **2008**, *6*, 2952; (c) Pelyvas, I. F.; Madi-Puskas, M.; Toth, Z. G.; Varga, Z.; Hornyak, M.; Batta, G.; Sztaricskai, F. *J. Antibiot.* **1995**, *48*, 683; (d) Pelyvas, I. F.; Madi-Puskas, M.; Toth, Z. G.; Varga, Z.; Batta, G.; Saztaricskai, F. *Carbohydr. Res.* **1995**, *272*, C5; (e) Corbett, D. F.; Dean, D. K.; Robinson, S. R. *Tetrahedron Lett.* **1993**, *34*, 1525; (f) Saito, H.; Nishimura, Y.; Kondo, S.; Takeuchi, T. *Chem. Lett.* **1988**, *7*, 1235; (g) Sakairi, N.; Hayashida, M.; Kuzuhara, H. *Tetrahedron Lett.* **1987**, *28*, 2871; (h) Vass, G.; Krausz, P.; Quiclet-Sire, B.; Delaumeny, J. M.; Cleophax, J.; Gero, S. D. *C. R. Acad. Sci. II* **1985**, *301*, 1345.
27. (a) Sar, A.; Lindeman, S.; Donaldson, W. A. *Synthesis* **2011**, 924; (b) Sar, A.; Lindeman, S.; Donaldson, W. A. *Org. Biomol. Chem.* **2010**, *8*, 3908.
28. For examples, see: (a) Gurale, B. P.; Shashidhar, M. S.; Gonnade, R. G. *J. Org. Chem.* **2012**, *77*, 5801; (b) Murali, C.; Gurale, B. P.; Shashidhar, M. S. *Eur. J. Org. Chem.* **2010**, 755; (c) Schoffers, E.; Gurung, S. R.; Kohler, P. R. A.; Rossbach, S. *Bioorg. Med. Chem.* **2008**, *16*, 7838; (d) Krief, A.; Dumont, W.; Billen, D.; Letesson, J.-J.; Lestrate, P.; Murphy, P. J.; Lacroix, D. *Tetrahedron Lett.* **2004**, *45*, 1461; (e) Kim, S.-C.; Lee, S.-C.; Cheong, C.-S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1578; (f) Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4219; (g) Chida, N.; Nakazawa, K.; Ohtsuka, M.; Suzuki, M.; Ogawa, S. *Chem. Lett.* **1990**, *3*, 423.
29. (a) Worawalai, W.; Wacharasindhu, S.; Phuwapraisirisan, P. *MedChemComm* **2012**, *3*, 1466; (b) Wacharasindhu, S.; Worawalai, W.; Rungprom, W.; Phuwapraisirisan, P. *Tetrahedron Lett.* **2009**, *50*, 2189; (c) Ogawa, S.; Kanto, M. *J. Nat. Prod.* **2007**, *70*, 493; (d) Ogawa, S.; Asada, M.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. *Bioorg. Med. Chem.* **2005**, *13*, 4306; (e) Ogawa, S.; Ohishi, Y.; Asada, M.; Tomoda, A.; Takahashi, A.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. *Org. Biomol. Chem.* **2004**, *2*, 884; (f) Ogawa, S.; Aoyama, H.; Tezuka, Y. *J. Carbohydr. Chem.* **2001**, *20*, 703; (g) Suami, T.; Ogawa, S.; Yabe, K.; Uchida, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2804; (h) Suami, T.; Yabe, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1931.
30. (a) Shih, T.-L.; Yang, S.-Y. *Molecules* **2012**, *17*, 4498; (b) Schwardt, O.; Koliwer-Brandl, H.; Zimmerli, R.; Mesch, S.; Rossato, G.; Spreafico, M.; Vedani, A.; Kelm, S.; Ernst, B. *Bioorg. Med. Chem.* **2010**, *18*, 7239; (c) Shih, T.-L.; Li, H.-Y.; Ke, M.-S.; Kuo, W.-S. *Synth. Commun.* **2008**, *38*, 4139; (d) Prazeres, V. F. V.; Castedo, L.; González-Bello, C. *Eur. J. Org. Chem.* **2008**, 3991; (e) González-Bello, C.; Castedo, L.; Cañada, F. J. *Eur. J. Org. Chem.* **2006**, 1002; (f) Shing, T. K. M.; Wan, L. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1643.
31. For examples, see: (a) Bandyopadhyay, A.; Mitra, P.; Chattopadhyay, S. K. *Synthesis* **2013**, *45*, 536; (b) Ghosal, P.; Shaw, A. K. *J. Org. Chem.* **2012**, *77*, 7627; (c) Harrak, Y.; Barra, C. M.; Delgado, A.; Castano, A. R.; Llebaria, A. *J. Am. Chem. Soc.* **2011**, *133*, 12079; (d) Lahiri, R.; Kokatla, H. P.; Vankar, Y. D. *Tetrahedron Lett.* **2011**, *52*, 781; (e) Gupta, P.; Pal, A. P. J.; Reddy, Y. S.; Vankar, Y. D. *Eur. J. Org. Chem.* **2011**, 1166; (f) Doddi, V. R.; Kumar, A.; Vankar, Y. D. *Tetrahedron* **2008**, *64*, 9117; (g) Alegret, C.; Benet-Buchholz, J.; Riera, A. *Org. Lett.* **2006**, *8*, 3069; (h) Andriuzzi, O.; Gravier-Pelletier, C.; Vogel, P.; Le Merrer, Y. *Tetrahedron* **2005**, *61*, 7094; (i) Xin, C.; Liao, Q.-J.; Yao, Z.-J. *J. Org. Chem.* **2004**, *69*, 5314; (j) Crimmins, M. T.; Tabet, E. A. *J. Org. Chem.* **2001**, *66*, 4012; (k) Sellier, O.; Van de Weghe, P.; Le Nouen, D.; Strehler, C.; Eustache, J. *Tetrahedron Lett.* **1999**, *40*, 853.
32. For examples, see: (a) El-Mansy, M. F.; Sar, A.; Lindeman, S.; Donaldson, W. A. *Chem.—Eur. J.* **2013**, *19*, 2330; (b) Mehta, G.; Mohanrao, R.; Katukojvala, S.; Landais, Y.; Sen, S. *Tetrahedron Lett.* **2011**, *52*, 2893; (c) Girard, E.; Desvergnes, V.; Tarnus, C.; Landais, Y. *Org. Biomol. Chem.* **2010**, *8*, 5628; (d) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Org. Lett.* **2007**, *9*, 207; (e) Curti, C.; Zanardi, F.; Battistini, L.; Sartori, A.; Rassu, G.; Auzzas, L.; Roggio, A.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2006**, *71*, 225; (f) Andriuzzi, O.; Gravier-Pelletier, C.; Bertho, G.; Prangé, T.; Le Merrer, Y. *Beilstein J. Org. Chem.* **2005**, *1*, 12; (g) Andriuzzi, O.; Gravier-Pelletier, C.; Le Merrer, Y. *Tetrahedron Lett.* **2004**, *45*, 8043; (h) Gravier-Pelletier, C.; Maton, W.; Dintinger, T.; Tellier, C.; Le Merrer, Y. *Tetrahedron* **2003**, *59*, 8705; (i) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881; (j) Gravier-Pelletier, C.; Maton, W.; Lecourt, T.; Le Merrer, Y. *Tetrahedron Lett.* **2001**, *42*, 4475; (k) van Hooft, P. A. V.; Litjens, E. J. N.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Org. Lett.* **2001**, *3*, 731; (l) Grabowski, S.; Armbruster, J.; Prinzbach, H. *Tetrahedron Lett.* **1997**, *38*, 5485; (m) Dyong, I.; Bonn, R. *Chem. Ber.* **1973**, *106*, 944.
33. For examples, see: (a) Kyne, S. H.; Miles, J. A. L.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2012**, *77*, 991; (b) Cottin, T.; Pyrkotis, C.; Stathakis, C. I.; Mavridis, I.; Katsoulis, I. A.; Anastasopoulou, P.; Kythreoti, G.; Zografos, A. L.; Nahmias, V. R.; Papakyriakou, A.; Vourloumis, D. *ChemBioChem* **2011**, *12*, 71; (c) Rasmussen, T. S.; Koldsø, H.; Nakagawa, S.; Kato, A.; Schiøtt, B.; Jensen, H. H. *Org. Biomol. Chem.* **2011**, *9*, 7807; (d) Rasmussen, T. S.; Jensen, H. H. *Org. Biomol. Chem.* **2010**, *8*, 433; (e) Katsoulis, I. A.; Pyrkotis, C.; Papakyriakou, A.; Kythreoti, G.; Zografos, A. L.; Mavridis, I.; Nahmias, V. R.; Anastasopoulou, P.; Vourloumis, D. *ChemBioChem* **2009**, *10*, 1969; (f) Kaliappan, K. P.; Das, P.; Chavan, S. T.; Sabharwal, S. G. *J. Org. Chem.* **2009**, *74*, 6266; (g) Wang, Y.; Bennet, A. J. *Org. Biomol. Chem.* **2007**, *5*, 1731; (h) Groetzl, B.; Handa, S.; Malpass, J. R. *Tetrahedron Lett.* **2006**, *47*, 9147; (i) Buser, S.; Vasella, A. *Helv. Chim. Acta* **2006**, *89*, 614; (j) Skaanderup, P. R.; Madsen, R. *J. Org. Chem.* **2003**, *68*, 2115; (k) Remen, L.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 1118; (l) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705; (m) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **2001**, *66*, 4941; (n) Lalk, M.; Reinke, H.; Peseke, K. *Eur. J. Org. Chem.* **2001**, 759; (o) Cachet, X.; Deguin, B.; Tillequin, F.; Rolland, Y.; Koch, M. *Helv. Chim. Acta* **2000**, *83*, 2812; (p) Smith, C. A.; Harper, A. E.; Coombs, M. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2745; (q) Kupchan, S. M.; Block, J. H.; Isenberg, A. C. *J. Am. Chem. Soc.* **1967**, *89*, 1189; (r) Kupchan, S. M.; Flouret, G. R.; Matuszak, C. A. *J. Org. Chem.* **1966**, *31*, 1707.
34. (a) Csuk, R.; Prell, E.; Reissmann, S.; Korb, C. *Z. Naturforsch., B: Chem. Sci.* **2010**, *65*, 445; (b) De Almeida, M. V.; Da Silva, E. T.; Le Hyaric, M.; Machado, A. S.; De Souza, M. V. N.; Santiago, R. M. *J. Carbohydr. Chem.* **2003**, *22*, 733; (c) Oppong, K. A.; Hudlický, T.; Yan, F.; York, C.; Nguyen, B. V. *Tetrahedron* **1999**, *55*, 2875; (d) Kuwahara, R.; Tsuchiya, T. *Carbohydr. Res.* **1997**, *299*, 271; (e) Kobayashi, Y.; Tsuchiya, T. *Carbohydr. Res.* **1997**, *298*, 261; (f) Shitara, T.; Umemura, E.; Tsuchiya, T.; Matsuno, T. *Carbohydr. Res.* **1995**, *276*, 75; (g) Faug, A. H. U.S. Patent 4,937,390, 1990.
35. For a review, see: Duchek, J.; Adams, D. R.; Hudlický, T. *Chem. Rev.* **2011**, *111*, 4223.
36. (a) Hudlický, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077; (b) Hudlický, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907 corrigendum **1993**, 535; (c) Akgün, H.; Hudlický, T. *Tetrahedron Lett.* **1999**, *40*, 3081.
37. (a) Carless, H. A. J.; Malik, S. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1135; (b) Hudlický, T.; Abboud, K. A.; Entwistle, D. A.; Fan, R.; Maurya, R.; Thorpe, A. J.; Bolonick, J.; Myers, B. *Synthesis* **1996**, 897; (c) Lallemand, M.-C.; Desjardins, M.; Freeman, S.; Hudlický, T. *Tetrahedron Lett.* **1997**, *38*, 7693; (d) Banwell, M. G.; Haddad, N.; Hudlický, T.; Nugent, T. C.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1779; (e) Desjardins, M.; Lallemand, M.-C.; Freeman, S.; Hudlický, T.; Abboud, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 621; (f) Orsini, F.; Sello, G.; Bernasconi, S.; Fallacara, G. *Tetrahedron Lett.* **2004**, *45*, 9253; (g) Fonseca, G.; Seoane, G. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1393; (h) Bellomo, A.; Giacomini, C.; Brena, B.; Seoane, G.; Gonzalez, D. *Synth. Commun.* **2007**, *37*, 3509; (i) Bellomo, A.; Bonilla, J. B.; López-Prados, J.; Martín-Lomas, M.; Gonzalez, D. *Tetrahedron: Asymmetry* **2009**, *20*, 2061; (j) de la Sovera, V.; Bellomo, A.; Gonzalez, D. *Tetrahedron* **2011**, *52*, 430; (k) de la Sovera, V.; Bellomo, A.; Pena, J. M.; Gonzalez, D.; Stefani, H. A. *Mol. Diversity* **2011**, *15*, 163.
38. (a) Hudlický, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553; (b) Paul, B. J.; Willis, J.; Martinot, T. A.; Ghiviriga, I.; Abboud, K. A.; Hudlický, T. *J. Am. Chem. Soc.* **2002**, *124*, 10416.
39. Freeman, C.; Liu, L.; Banwell, M. G.; Brown, K. J.; Bezos, A.; Ferro, V.; Parish, C. R. *J. Biol. Chem.* **2005**, *280*, 8842.
40. (a) Hudlický, T.; Abboud, K. A.; Bolonick, J.; Maurya, R.; Stanton, M. L.; Thorpe, A. J. *Chem. Commun.* **1996**, 1717; (b) Paul, B. J.; Hobbs, E.; Buccino, P.; Hudlický, T. *Tetrahedron Lett.* **2001**, *42*, 6433; (c) Schilling, S.; Rinner, U.; Chan, C.; Ghiviriga, I.; Hudlický, T. *Can. J. Chem.* **2001**, *79*, 1659; (d) Paul, B. J.; Martinot, T. A.; Willis, J.; Hudlický, T. *Synthesis* **2001**, 952.
41. Hudlický, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.* **1994**, *116*, 5099.
42. Pilgrim, S.; Kociok-Köhn, G.; Lloyd, M. D.; Lewis, S. E. *Chem. Commun.* **2011**, 4799.
43. (a) Boyd, D. R.; Blacker, J.; Byrne, B.; Dalton, H.; Hand, M. V.; Kelly, S. C.; More O'Ferrall, R. A.; Rao, S. N.; Sharma, N. D.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1994**, 313; (b) Kudavalli, J. S.; Boyd, D. R.; Coyne, D.; Keeffe, J. R.; Lawlor, D. A.; MacCormac, A. C.; More O'Ferrall, R. A.; Rao, S. N.; Sharma, N. D. *Org. Lett.* **2010**, *12*, 5550; (c) Lawlor, D. A.; Kudavalli, J. S.; MacCormac, A. C.; Coyne, D. A.; Boyd, D. R.; More O'Ferrall, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 19718; (d) Lawlor, D. A.; Bean, D. E.; Fowler, P. W.; Keeffe, J. R.; Kudavalli, J. S.; More O'Ferrall, R. A.; Rao, S. N. *J. Am. Chem. Soc.* **2011**, *133*, 19729; (e) Kudavalli, J. S.; Coyne, D.; More O'Ferrall, R. A. *J. Org. Chem.* **2012**, *77*, 563; (f) Kudavalli, J. S.; Rao, S. N.; Bean, D. E.; Sharma, N. D.; Boyd, D. R.; Fowler, P. W.; Gronert, S.; Kamerlin, S. C. L.; Keeffe, J. R.; More O'Ferrall, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 14056.
44. (a) Pye, C. C.; Poirier, R. A.; Burnell, D. J.; Klapstein, D. *J. Mol. Struct. Theochem.* **2009**, *909*, 66; (b) Ogbomo, S. M.; Burnell, D. J. *Org. Biomol. Chem.* **2006**, *4*, 3838; (c) Gillard, J. R.; Burnell, D. J. *Can. J. Chem.* **1992**, *70*, 1296; (d) Gillard, J. R.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1439.
45. (a) Jana, C. K.; Grimme, S.; Studer, A. *Chem.—Eur. J.* **2009**, *15*, 9078; (b) Lin, K.-W.; Wang, Y.-C.; Yan, T.-H. *J. Chin. Chem. Soc.-Taip.* **2008**, *55*, 418; (c) Gamenara, D.; Seoane, G.; Heinzen, H.; Moyna, P. *Lat. Am. J. Pharm.* **2008**, *27*, 34; (d) Yamamoto, Y.; Yamamoto, H. Patent WO2005/068457. (e) Elango, S.; Yan, T.-H. *J. Org. Chem.* **2002**, *67*, 6954; (f) Elango, S.; Wang, Y.-C.; Cheng, C.-L.; Yan, T.-H. *Tetrahedron Lett.* **2002**, *43*, 3757; (g) Noguchi, H.; Aoyama, T.; Shioiri, T. *Heterocycles* **2002**, *58*, 471; (h) Noguchi, H.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1997**, *38*, 2883; (i) Hudlický, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108; (j) Hudlický, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694; (k) Schürrle, K.; Beier, B.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2407; (l) Mahon, M. F.; Molloy, K.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O.; Winders, J. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1255; (m) Geary, P. J.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Winders, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 204; (n) Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1160; (o) Cotterill, I. C.; Roberts, S. M.; Williams, J. O. *J. Chem. Soc., Chem. Commun.* **1988**, 1628.
46. Ball, A. L.; Chambers, K. A.; Hewinson, M.; Navaratanarajah, S.; Samrin, L.; Thomas, N.; Tyler, A. H.; Wall, A. J.; Lloyd, M. D. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 131.