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Stereospecific synthesis of a new class of aminocyclitol with the conduramine D-2 configuration

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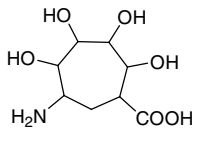
Abstract—A new aminocyclitol derived from bicyclo[4.2.0^{1,6}]octane was synthesized starting from cyclooctatetraene. Photooxygenation of *trans*-7,8-diacetoxy-bicyclo[4.2.0]octa-2,4-diene afforded a bicyclic endoperoxide. Reduction of the endoperoxide with thiourea followed by a palladium-catalyzed ionization/cyclization reaction gave an oxazolidinone derivative. Oxidation of the double bond in the oxazolidinone with $KMnO_4$ followed by acetylation gave the oxazolidinone-tetraacetate whose exact configuration was determined by X-ray diffraction analysis. Hydrolysis of the oxazolidinone ring and removal of the acetate groups furnished the desired aminocyclitol.

Carbohydrates are important biomolecules, the biological importance of which was first recognized from their role in metabolism and energy storage. As constituents of glycoproteins and glycolipids, they are key elements in a variety of processes such as signalling, cell–cell communication and cell growth.[1] Aminocyclitols are cyclitols in which one of the hydroxyl groups is exchanged with an amino functional group. In turn, they constitute a wide group of natural products with interesting biological properties and are widely distributed throughout Nature.[2] They show interesting inhibitor activity for some glycosidases.[3]

In recent years, there has been considerable interest in the design of carbohydrate mimetics,[4] which are compounds that have multiple hydroxy groups and therefore, look somewhat like a sugar or saccharide (**1**–**3**). More recently, attention has been directed towards the synthesis of seven-[5] and eight-membered rings[6] and bicyclooctane,[7] bicyclononane and decane derivatives[8] containing polyhydroxy and amino groups.



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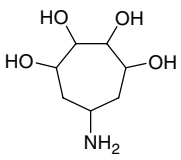

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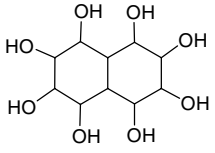

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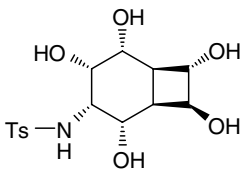
In particular, antibiotics containing an aminocyclitol unit have stimulated the development of synthetic methodologies[9,10] in the search for analogues with enhanced pharmacological profiles.[11]

As a part of our programme directed towards the synthesis of potential glycosidase inhibitors we used a bicyclo[4.2.0]octane as the framework for OH and NH_2 groups as an intriguing carbohydrate alternative. Herein, we report the synthesis and characterization of a new aminocyclitol analogue **4** synthesized from cyclooctatetraene.



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Keywords: Cyclitols; Aminocyclitol; Endoperoxide; Bicyclic aliphatic compounds; Oxidation; X-ray analysis.
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† Author to whom inquiries concerning the X-ray structure should be directed.

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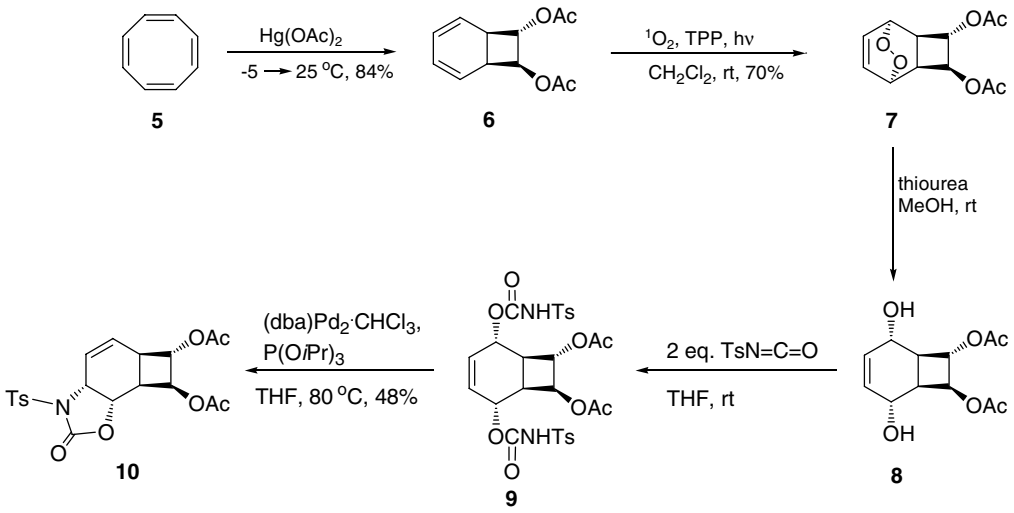
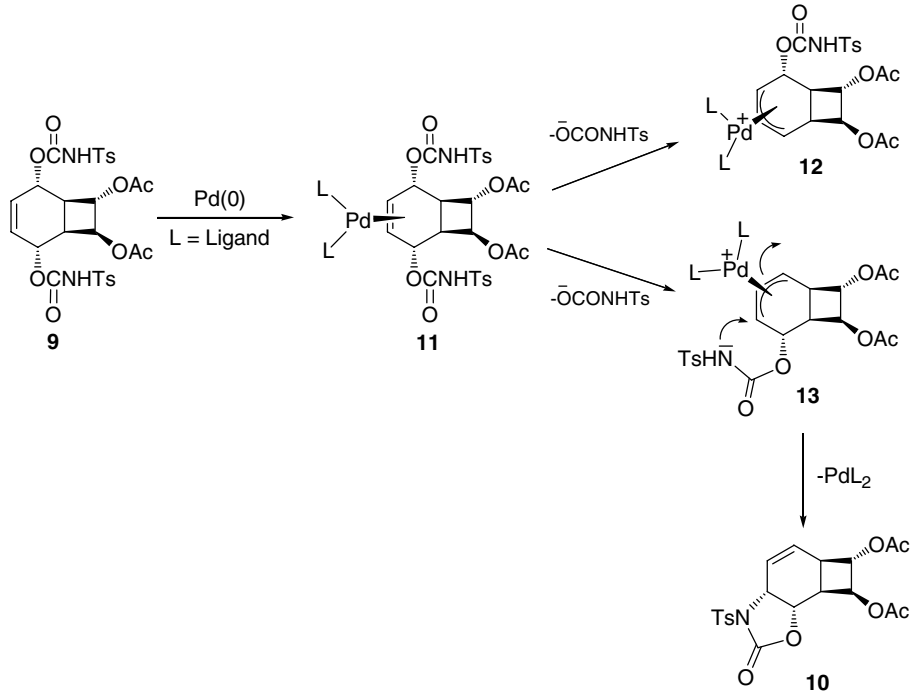
The starting material, diacetoxydiene **6**, for the construction of the bicyclo[4.2.0]octane skeleton was synthesized from cyclooctatetraene **5** by the addition of mercury(II) acetate in 84% yield.[12] We have previously reported a photooxygenation reaction for the introduction of two oxygen functionalities at the C-1 and C-4 positions of dienes.[13] Tetraphenylporphyrin (TPP) sensitized photooxygenation of diacetoxydiene **6** in methylene chloride at room temperature afforded endoperoxide **7**[8c] (Scheme 1).

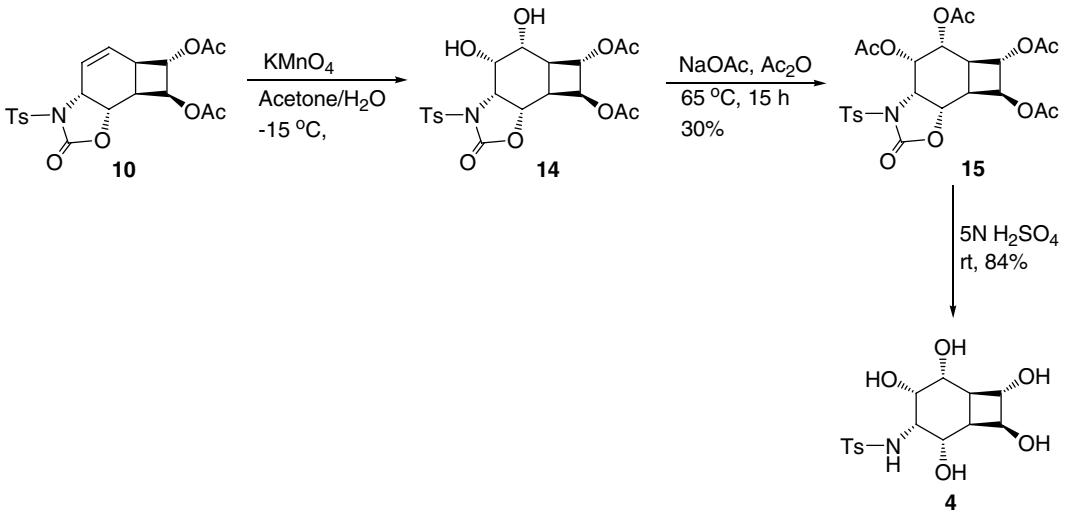
Since diacetoxydiene **6** has no plane of symmetry, singlet oxygen approaches the diene unit from the less hindered side. The exact configuration of the endoperoxide **7** was later proved by X-ray analysis of tetraacetate **12**. Reduction of the endoperoxide was performed with thiourea under mild conditions to give diol **8** in 99% yield. Since only the oxygen–oxygen bond in **7** was cleaved in this reaction, the configurations of the carbon atoms were preserved. For the introduction of the amino alcohol functionality, a regio- and stereoselective Pd(0) catalyzed reaction[10] of diol **8** in the presence of TsNCO was employed. Oxazolidinone **10** was prepared via in situ formation of bis-carbamate **9**. The ene-diol **8** was first treated with 2 equiv of toluenesulfonyl isocyanate to give the corresponding bis-carbamate **9**. The bis-carbamate solution was subsequently added to a solution of 5 mol % of catalyst prepared from tris(dibenz-



Scheme 1.



Scheme 2.



Scheme 3.

ylideneacetone)-dipalladium chloroform complex and triisopropylphosphine. The mixture was purified by chromatography on a silica gel column with hexane/ethyl acetate (65:35) as eluant to give oxazolidinone **10** in 48% yield (Scheme 1). The structure of **10**[14] was assigned from ^{1}H and ^{13}C NMR spectra and later from the X-ray analysis of product **15**.

The observed regio- and stereoselectivity for this reaction was remarkable since the leaving groups are diastereotopic. The basic catalytic cycle consists of metal–olefin complexation, ionization, substitution and decomplexation. Metal–olefin complexation is a potential source of stereoselection. Since only palladium–olefin complexation *anti* to the leaving group will lead to the product **10**,[15] the metal will approach the double bond in **9** from the side of the four-membered ring to form the complex **11** (Scheme 2). Since the double bond is not symmetrically disubstituted, palladium can theoretically form two different complexes **12** and **13** after ionization. We assume that the formation of complex **12** is hindered due to the presence of the acetate group in the *endo* position. The exclusive formation of the complex **13** is then accounted for the observed regioselectivity of this reaction.

cis-Dihydroxylation of **10** with $KMnO_4$ at -10 °C gave the corresponding diol **14**, which was converted into the tetraacetate **15**[15] by treatment with acetic anhydride/CH_3COONa (Scheme 3). Careful examination of the reaction mixture did not reveal the formation of any other isomer. The stereochemical course of the hydroxylation may be *syn* or *anti* with respect to the cyclobutane and oxazolidinone rings, however, NMR spectroscopic studies did not allow the assignment of the exact configuration of the hydroxyl groups. X-ray analysis[16] of **15** (Fig. 1) confirmed the structural assignment, and in particular the configurations of the endoperoxide **7**, oxazolidinone **10**, and cis-hydroxylation product **14**.

The all cis stereochemistry of the four acetates and amino groups attached to the six-membered ring resembles

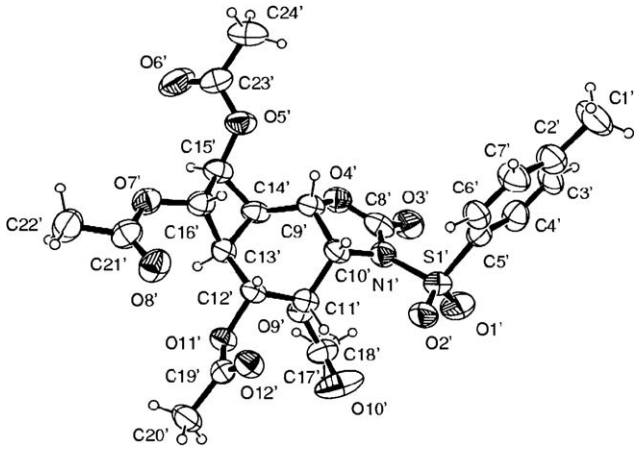


Figure 1. The thermal ellipsoid plot of the single crystal X-ray crystallographic structure of **15**.

the configuration of conduramine D-2.[17] Conduramines[11a] are aminocyclohexenetriols, which are structural elements of many naturally occurring biological compounds, formally derived from conduritols,[18] in which one of the OH groups is exchanged for an amino moiety. The least accessible of the conduritol isomers is conduritol-D having the all cis stereochemistry.

Removal of the acetate functionalities with H_2SO_4 proceeded smoothly to deliver aminocyclitol **4** in 84% yield. Compound **15** represents the first member of a new class of aminocyclitols, which is now available for various biological studies. Further research directed towards the synthesis of other aminocyclitols with bicyclo-[4.2.0^{1,6}]octane frameworks is currently in progress.

Acknowledgements

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14. Physical data for selected compounds: **10**: (0.82 g, 48%). White crystals, mp 144–146 °C (from hexane/ethyl acetate). Found: C, 55.36; H, 5.01; N, 3.09; S, 7.19; $C_{20}H_{21}NO_8S$ requires C, 55.16; H, 4.86; N, 3.22; S, 7.36; ν_{max} (KBr) 2978, 2953, 1804, 1753, 1395, 1268, 1242, 1165, 1063, 680, 604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 7.94 (br d, A part of AA′BB′ system, $J = 8.3$ Hz, 2H, aromatic), 7.34 (d, B part of AA′BB′ system, $J = 8.3$ Hz, 2H, aromatic), 6.24 (ddd, A part of AB system, $J_{4,5} = 10.3$, $J_{5,5a} = 4.5$, and $J_{5,3a} = 1.1$ Hz, 1H, H-5), 6.01 (br d, B part of AB system, $J_{4,5} = 10.3$ Hz, 1H, H-4), 5.24 (ddd, 1H, $J_{7b,3a} = 9.2$, $J_{7b,7a} = 4.7$, $J_{7b,5a} = 1.3$ Hz, 1H, H-7b), 4.75–4.80 (m, 2H, H-3a and H-7), 4.42 (dt, $J_{6,5a} = J_{6,7} = 5.6$, and $J_{6,7a} = 1.1$ Hz, 1H, H-6), 3.14 (br t, $J_{7a,7} = J_{7a,5a} = 9.2$ Hz, 1H, H-7a), 2.70 (br dt, $J_{5a,7a} = 9.2$ Hz, and $J_{5a,5} = J_{5a,6} = 5.5$ Hz, 1H, H-5a), 2.45 (s, 3H, arom-CH_3), 2.09 (s, 3H, OC–CH_3), 2.07 (s, 3H, OC–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 171.2 (s), 170.8 (s), 152.5 (s), 147.2 (s), 137.4 (s), 131.7 d (2×), 130.6 (d), 124.7 (d), 80.6 (d), 72.0 (d), 71.3 (d), 55.9 (d), 35.9 (d), 33.5 (d), 23.7 (q), 22.5 (q, 2×).
Compound **15**: White crystals (30%), mp 105–107 °C from CH_3OH. Found: C, 51.68; H, 4.91; N, 2.69; S, 5.69; $C_{24}H_{27}NO_{12}S$ requires C, 52.08; H, 4.92; N, 2.53; S, 5.79; ν_{max} (KBr) 3004, 2927, 1753, 1651, 1525, 1523, 1446, 1395, 1242, 1191, 1114, 1089, 936 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (d, A part of AA′BB′ system, $J_{AB} = 8.3$ Hz, 2H, aromatic), 7.27 (d, B part of AA′BB′ system, $J_{AB} = 8.3$ Hz, 2H, aromatic), 5.70 (dd, $J = 3.4$ and 1.8 Hz, 1H, O–CH), 5.20 (dd, $J = 7.7$ and 6.2 Hz, 1H), 5.05 (dd, $J = 6.5$ and 1.6 Hz, 1H), 4.94 (dd, $J = 9.0$ and 6.0 Hz, 1H), 4.83 (br t, $J = 6.4$ Hz, 1H), 4.75 (dd, $J = 9.2$ and 3.4 Hz, 1H), 3.13 (m, 1H, H_{5a} or H_{7a}), 2.39 (s, 3H, arom-CH_3), 2.30 (m, 1H, H_{5a} or H_{7a}), 2.04 (s, 3H, OC–CH_3) 2.00 (s, 3H, OC–CH_3), 1.97 (s, 3H, OC–CH_3) 1.79 (s, 3H, OC–CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 171.9 (s), 171.7 (s), 171.1 (s), 171.0 (s), 153.3 (s), 147.8 (s), 136.4 (s), 131.7 (d), 130.6 (d), 77.9 (d), 72.7 (d), 71.3 (d), 71.2 (d), 69.7 (d), 59.1 (d), 39.0 (d), 38.2 (d), 23.6 (q), 22.6 (q), 22.5 (q) (2C), 22.4 (q).
Compound **4**: (84%). ν_{max} (KBr) 3401, 2931, 1735, 1450, 1234, 1157, 1103, 1049, 1010, 856, 817, 748, 671, 578, 555 cm^{-1}; Found: C, 49.98; H, 5.71; N, 3.79; S, 30.81. $C_{15}H_{21}NO_7S$ requires C, 50.13; H, 5.89; N, 3.90; S, 31.16; ^1H NMR (200 MHz, CD_3OD) 7.79 (d, A part of AA′BB′ system, $J = 8.3$ Hz, 2H, aromatic), 7.33 (d, B part of AA′BB′ system, $J_{AB} = 8.3$ Hz, 2H, aromatic), 4.91 (br s,

6H, –OH and –NH), 4.00–3.54 (m, 6H, O–CH and N–CH), 2.41 (s, 3H, arom-CH_3), 2.31 (m, 1H, C–CH), 2.04 (m, 1H, C–CH); ^{13}C NMR (50 MHz, CD_3OD) 146.3 (s), 141.5 (s), 132.2 (d), 130.3 (d), 77.8 (d), 75.3 (d), 71.7 (d), 70.9 (d), 70.2 (d), 62.8 (d), 45.0 (d), 38.5 (d), 23.2 (q).

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16. Supplementary data in the form of CIFs have been deposited with the Cambridge Crystallographic Data Centre (CCDC 299509). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Selected X-ray crystallographic data for **5** ($C_{25}H_{23}N_5O_4$); Space group: Orthorhombic, *Pbn*21; $a = 11.6906(4)$ Å, $b = 20.8899(10)$ Å, $c = 22.1919(9)$ Å, $V = 5419$ Å^3, $Z = 8$, $F(000) = 2320$, $D_{calc} = 1.36$ g cm^{-3}, Mo K_α radiation $\lambda = 0.71073$ Å, independent reflections 7705 ($R_{int} = 0.0421$), observed reflections 7093 ($I > 2\sigma I$), refinement method; full-matrix least-squares on F^2, data/restraints/parameters 7093/1/695, $R_1 = 0.0557$, $R_w = 0.1186$, goodness-of-fit on $F^2 = 1.21$.
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