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Synthesis of chiral *trans*-fused pyrano[3,2-*c*][2]benzoxocines from D-mannose by regioselective 8-*endo*-aryl radical cyclization

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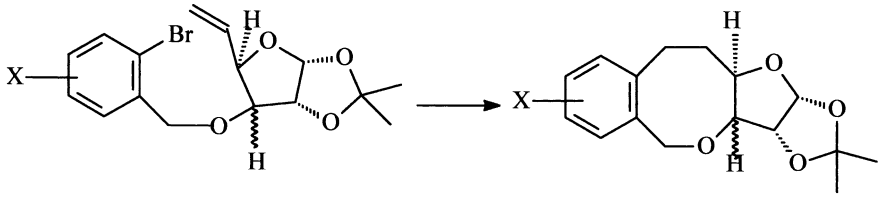
Abstract—A simple chiral synthesis of *trans*-pyrano[3,2-*c*][2]benzoxocines **8a–d** in good yields (60–75%) through regioselective 8-*endo*-*trig* aryl radical cyclization of the D-mannose derived enopyranosides **7a–d** with Bu_3SnH is described.

The synthesis of conformationally flexible medium ring ethers, the structural core of a large number of linearly condensed cyclic polyether marine neurotoxins,[1] has received considerable attention.[1,2] Interest in the use of easily accessible carbohydrates from the chiral pool, first recorded in the synthesis of 8- and 9-membered ring ethers from D-glucose involving regioselective radical cyclization[3] and Oxy–Cope rearrangement,[4] respectively, has been growing rapidly. In 1998, Nicolaou and his group[5] reported the total synthesis of brevetoxin-A, which includes condensed 8- and 9-membered cyclic ethers, from D-glucose and D-mannose using Yamaguchi lactonization and phosphate cross-coupling reactions.[6] Very recently, Hirama et al.[7] have achieved the total synthesis of the highly complex ciguatoxin CTX3C from a series of sugar derivatives by chemoselective ring closing metathesis.

These,[8a,b,9] as well as a few other reactions,[10] have also been extended for the construction of medium ring ethers from sugar derivatives. We have reported[11] a convenient synthesis of chiral *cis* and *trans*-furo[3,2-*c*][2]benzoxocines **II** through *endo*-*trig* aryl radical cyclization via a Bu_3SnH (TBTH) induced reaction of the respective olefins **Ia**,**b** easily derived from D-glucose (Eq. (1)).

In this communication, we record a simple and convenient conversion of D-mannose to the linearly benzannulated tricyclic analogues (Scheme 2) of the synthetically challenging *trans* 6,8-ring fused cyclic ethers, a common structural feature present in many bioactive marine neurotoxins,[1] by 8-*endo*-*trig* aryl radical cyclization.[12]

The key olefinic substrates **7a–d**, for radical reaction, were prepared from D-mannose. Thus, the *O*-methyl ether of mannopyranoside was transformed into diol **1**[13] and then into alcohol **2**, using conventional protection and deprotection protocols.[16] *O*-Arylation of **2**



(1)

I **II**

a; αH **b**; βH

X= H , OMe, etc

Keywords: pyranobenzoxocines; radical cyclization; Bu_3SnH; carbohydrate.

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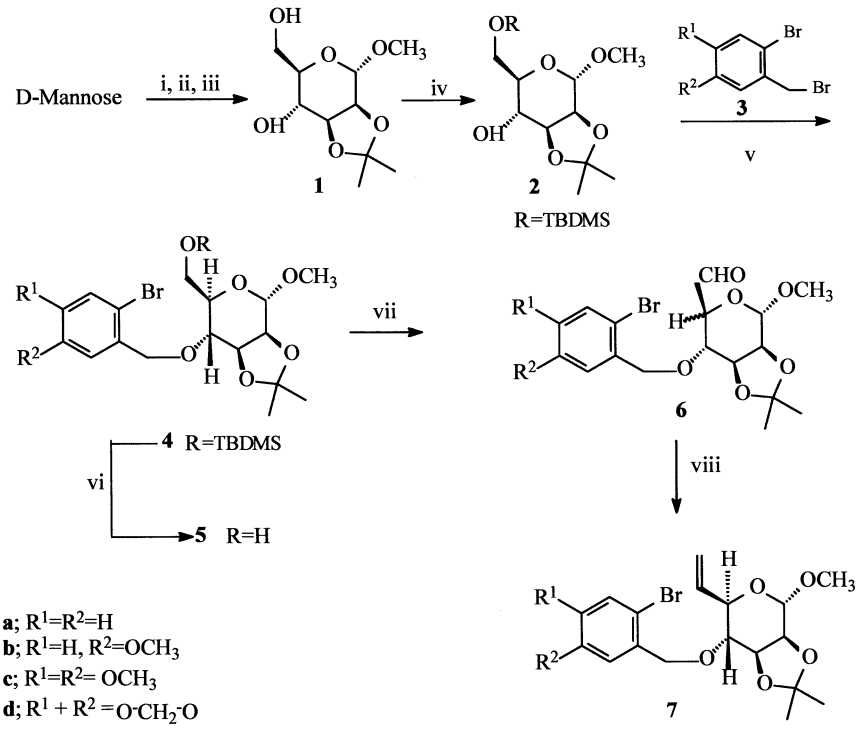
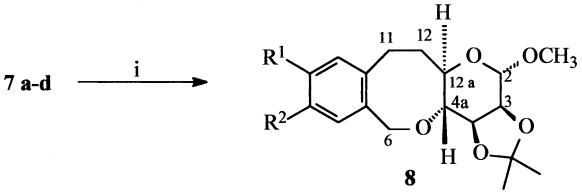


Scheme 1. (i) MeOH, H^+ resin, reflux, 2 h, 70%; (ii) DMP, DMF, PTSA, rt,12 h, 70%; (iii) AcOH/H_2O (1:3), 6 h, rt, stirring, 56%; (iv) TBDMSCl, imidazole, CH_2Cl_2, 0°C, 1 h, stirring, 78%; (v) TBAB, 50% NaOH, CH_2Cl_2, 25°C, 8 h, 75–80%; (vi) TBAF, THF, reflux, 4 h, 67–73%; (vii) DMSO, $(COCl)_2$, CH_2Cl_2, −40°C, 1 h and then Et_3N, −40°C to rt; (viii) $Ph_3P{=}CH_2$, THF, −78°C to rt, overall yield 50–60% two steps from **5**.

with each of the bromides **3a–d** using TBAB/aq. NaOH under phase transfer conditions afforded the respective *O*-2-bromobenzylated mannopyranosides **4a–d**. Deprotection of silyl ethers **4a–d** to **5a–d** was realized smoothly in the presence of TBAF/THF. Swern oxidation of **5a–d**, according to the procedure described by Sinaÿ,[17] afforded the corresponding hydrates of aldehydes **6a–d**. After azeotropic removal of the water of hydration, each of these crude intermediates **6a–d** was submitted to Wittig olefination[18] to afford a single epimer of enopyranosides **7a–d** in good yields (50–60%) in each case (Scheme 1). The assigned stereochemistry is based upon the comparison of the reported *J* values for comparable products by Aurrecoechea et al.[18] Unlike the low yields (15–20%) of the *trans*-furobenzoxocines (**IIb**)[11] due to the unfavorable steric disposition from the parent enofuranosides (**Ib**) compared to those in *cis*-olefins (**Ia**) (Eq. (1)), radical cyclization of each of the enopyranosides **7a–d** with TBTH and a catalytic amount of AIBN in refluxing benzene furnished the respective crystalline tricyclic ethers **8a–d** (Scheme 2) in good yields (60–75%) as the only isolable product after separation of tin compounds[19] followed by chromatography. The assigned structures† of the products **8a–b** resulting from 8-*endo*-aryl radical cyclization‡ were based upon spectroscopic data.[22]



Scheme 2. (i) TBTH (3 equiv.), AIBN, benzene, reflux (300 W lamp), 4 h, 60–75%.

In the ^1H spectra of **8a–d**,[22,23] the furthest downfield signal due to a sugar proton could be assigned to H-2; it appears around δ 4.7 as a singlet, indicating that the dihedral angle between H-2 and H-3 is ca. 90°. The signal due to H-3 exhibits a doublet around δ 4.0 ($J = 5.7$–6 Hz), being coupled to both H-3 and H-4a and the signal due to H-4 appears as a triplet at δ 4.2 ($J = 6$ Hz). The H-4a signal exhibits a double doublet pattern around δ 3.4–3.5 ($J_{4,4a} = 6.3$–6.6, $J_{4a,12a} = 9.6$–9.9 Hz). A double triplet could be assigned to H-12a near δ 3.5–3.7 ($J^b_{12a,12H} = 9.6$–9.9, $J_{4a,12a} = 9.6$–9.9, $J^a_{12a,12H} = 6.3$ Hz) being split by H-4a, H^b of H_2-12 and H^a of H_2-12.

In conclusion we have demonstrated the usefulness of the present methodology for the convergent syntheses of benzannulated analogues of the *trans*-6,8-fused ring ether systems common to marine neurotoxins, starting from sugar derivatives.

† Assignment of the *trans* geometry of the pyranoxocine ring in **8a–d** is supported by ^1H–^1H COSY results and decoupling studies ($J_{4a,12a}$ 9.9 Hz suggesting a *trans* assignment).

‡ As predicted by MO calculations and experimentally corroborated by Beckwith (Ref. 20) and others (Refs. 8a,12,21), 8-*endo* cyclization is preferred over the 7-*exo* process.

Acknowledgements

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22. Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds. Selected data for **8a**: mp: 94–95°C; $[\alpha]_D^{29}$ +52.7 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.33$ (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.60–1.71 (1H, m, H^a of H_2-12), 2.29–2.38 (1H, m, H^b of H_2-12), 2.73–2.80 (1H, brt, H^a of H_2-11), 3.22–3.34 (1H, t-like, overlapped by OCH_3 signal, H^b of H_2-11), 3.34 (3H s, OCH_3), 3.47–3.52 (1H, dd, $J_{4,4a}=6.6$, $J_{4a,12a}=9.9$ Hz, H-4a), 3.59–3.68 (1H, dt, $J^b_{12a,12H}=9.9$, $J_{4a,12a}=9.9$, $J^a_{12a,12H}=6.3$ Hz, H-12a), 4.06 (1H, d, $J=5.7$ Hz, H-3), 4.21–4.25 (1H, t, $J=6$ Hz, H-4), 4.73 (1H, s, H-2), 4.87 (1H, d, $J=14$ Hz, H^a of $ArCH_2$), 5.14 (1H, d, $J=14$ Hz, H^b of $ArCH_2$), 7.01–7.26 (4H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.60 (CH_3), 28.12 (CH_3), 29.66 (CH_2), 35.20 (CH_2), 55.34 (OCH_3), 67.50 (CH), 73.81 (CH_2), 75.83 (CH), 77.69 (CH), 78.47 (CH), 98.19 (CH), 109.60(C), 126.79 (CH), 128.34 (CH), 128.55 (CH), 131.74 (CH), 136.23 (C), 142.35 (C). MS (EI) *m*/*z* 320 (M^+, 10%); **8b**: mp: 90–91°C; $[\alpha]_D^{29}$ +22.9 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.33$ (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.60–1.67 (1H, m, H^a of H_2-12), 2.28–2.32 (1H, m, H^b of H_2-12), 2.71–2.75 (1H, brt, H^a of H_2-11), 3.14–3.21 (1H, t, $J=12$ Hz, H^b of H_2-11), 3.34 (3H, s, OCH_3), 3.46–3.52 (1H, dd, $J_{4,4a}=6.6$, $J_{4a,12a}=9.9$ Hz, H-4a), 3.56–3.67 (1H, dt, $J^b_{12a,12H}=9.9$, $J_{4a,12a}=9.9$, $J^a_{12a,12H}=6.3$ Hz, H-12a), 3.77 (3H, s, OCH_3), 4.06 (1H, d, $J=5.7$ Hz, H-3), 4.21–4.25 (1H, t, $J=6$ Hz, H-4), 4.73 (1H, s, H-2), 4.81 (1H, d, $J=14.5$ Hz, H^a of Ar-CH_2), 5.10 (1H, d, $J=14.5$ Hz, H^b of Ar-CH_2), 6.56 (1H, s, Ar-H), 6.77 (1H, dd, $J=8.4$, 2.4 Hz Ar-H), 7.05 (1H, d, $J=8.3$ Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.57 (CH_3), 28.16 (CH_3), 28.86 (CH_2), 35.51 (CH_2), 55.34 (OCH_3), 55.66 (OCH_3), 67.51 (CH), 73.79 (CH_2), 75.84 (CH), 77.95 (CH), 78.45 (CH), 98.21 (CH), 109.60 (C), 113.61 (CH), 113.68 (CH), 132.81 (CH), 134.36 (C), 137.49 (C), 158.45 (C) ppm. MS (EI) *m*/*z* 350 (M^+, 73%); **8c**: mp: 56–58°C; $[\alpha]_D^{29}$ +15.2 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$), $\delta=1.33$ (3H, s, CH_3), 1.39 (3H, s,

CH_3), 1.62–1.72 (1H, m, H^a of H_2-12), 2.24–2.31 (1H, m, H^b of H_2-12), 2.66–2.74 (1H, brt, H^a of H_2-11), 3.12–3.20 (1H, t, $J=12$ Hz, H^b of H_2-11), 3.34 (3H, s, OCH_3), 3.48–3.53 (1H, dd, $J_{4,4a}=6.3$, $J_{4a,12a}=9.6$ Hz, H-4a), 3.51–3.67 (1H, dt, $J^b_{12a,12H}=9.6$, $J_{4a,12a}=9.6$, $J^a_{12a,12H}=6.3$ Hz, H-12a), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.06 (1H, d, $J=6$ Hz, H-3), 4.21–4.26 (1H, t, $J=6$ Hz, H-4), 4.72 (1H, s, H-2), 4.76 (1H, d, $J=14$ Hz, H^a of $ArCH_2$), 5.06 (1H, d, $J=14$ Hz, H^b of $ArCH_2$), 6.55 (1H, s, ArH), 6.65 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$), δ 26.10 (CH_3), 27.67 (CH_3), 28.80 (CH_2), 34.82 (CH_2), 55.00 (OCH_3), 55.95 (OCH_3), 56.02 (OCH_3), 67.50 (CH), 72.74 (CH_2), 75.29 (CH), 76.81 (CH), 77.98 (CH), 98.00 (CH), 109.13 (C), 111.47 (CH), 114.26 (CH), 127.52 (C), 134.18 (C), 147.28 (C). 148.57 (C), MS (EI) m/z 380 M^+, 95%); **8d**: mp: 77°C; $[\alpha]_D^{29}$ +30.8 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), $\delta=1.33$ (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.58–1.67 (1H, m, H^a of H_2-12), 2.23–2.32 (1H, m, H^b of H_2-12), 2.62–2.70 (1H, brt, H_a of H_2-11), 3.11–3.19 (1H, brt, H_b of H_2-11), 3.34 (3H, s, OCH_3), 3.48–3.53 (1H, dd, $J_{4,4a}=6.6$, $J_{4a,12a}=9.9$ Hz, H-4a), 3.57–3.66 (1H, dt, $J^b_{12a,12H}=9.9$, $J_{4a,12a}=9.9$, $J^a_{12a,12H}=6.3$ Hz, H-12a), 4.05 (1H, d, $J=6$ Hz, H-3), 4.19–4.23 (1H, t, $J=6$ Hz, H-4), 4.71 (1H, s, H-2), 4.72 (1H, d, $J=14$ Hz, H^a of $ArCH_2$), 5.00 (1H, d, $J=14$ Hz, H^b of $ArCH_2$), 5.92 (2H, s, O-CH_2-O), 6.53 (1H, s, Ar-H), 6.63 (1H, s, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 26.47 (CH_3), 28.12 (CH_3), 29.38 (CH_2), 35.15 (CH_2), 55.40 (OCH_3), 67.82 (CH), 73.15 (CH_2), 75.72 (CH), 77.12 (CH), 78.37 (CH), 98.44 (CH), 101.37 (O-CH_2-O), 108.73 (CH), 109.54 (C), 111.40 (CH), 129.06 (C), 135.98 (C), 146.43 (C), 147.77 (C); MS (EI) m/z 364 (M^+, 75%).

23. The ^{1}H NMR assignments are based on ^{1}H–^{1}H COSY results.