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Carbonylation approaches to oxygen heterocyclic compounds

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Abstract

Reactions of 3-(3′,4′,6′-tri-*O*-benzyl-β-D-glucopyranosyl)propene with H_2/CO in the presence of rhodium catalysts can give high yields of a linear aldehyde which can be further modified to give fused 6,7-oxygen heterocyclic compounds. These are useful as intermediates in the synthesis of cyclic polyethers, e.g., the marine toxin, ciguatoxin CTX1. Almost complete regioselectivity for the linear aldehyde was obtained using the bulky bidentate diphosphite ligand, BIPHEPHOS.

Keywords: Carbonylation; Hydroformylation; Rhodium; Oxygen heterocycles; Carbohydrate; Ciguatoxin

1. Introduction

The ciguatoxins are members of a small, closely-related family of marine polyether toxins [1]. As in the cases of the brevetoxins [2] and maitotoxins [3] they consist of contiguous, *trans*-fused cyclic ethers, of varying ring sizes. We were interested in investigating the use of carbonylation reactions in the synthesis of fragments of these natural products.

Our strategy is outlined in Fig. 1 and involves regioselective carbonylation of D-glucose-derived (**3**) to give (**2**) (or a closely-related intermediate) followed by conversion of the lactone into (**1**).

In this paper, we disclose our results on the regioselective preparation of a 6,7-*trans*-fused bicyclic system (**2**) which should serve as a useful precursor to the A/B ring system (e.g., CTX1 A/B fragment (**1**), Fig. 1) of the ciguatoxins.

2. Experimental

2.1. General methods

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose was purchased from Sigma. The complexes HRh(CO)$(PPh_3)_3$ and Pd(II)$(OAc)_2$ were purchased from Aldrich and (−)-DIOP was purchased from

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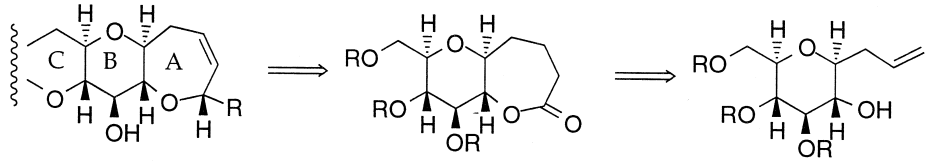


(1) (2) (3)

Fig. 1.

Strem. BIPHEPHOS was prepared according to the method of Cuny and Buchwald [4]. Rhodium acetate dimer was prepared according to the method of Legzdins et al. [5]. All reactions of rhodium complexes were carried out under an atmosphere of nitrogen using distilled and deoxygenated solvents. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX 400 or a Varian Mercury 300 spectrometer and referenced in the standard way. Assignments in some cases were confirmed by HETCOR and COSY spectra. Mass spectrometry (ESI) was performed using samples in MeOH on a Micromass Platform QMS spectrometer. Accurate mass determinations were recorded on a Bruker BioApex 47e FTMS fitted with an Analytica electrospray source using NaI for accurate mass calibration (accuracy $\pm$ 3 ppm). Optical rotations were recorded at 28°C with a Perkin-Elmer 141 polarimeter. Elemental microanalysis was carried out by the University of Otago, Chemistry Department, Dunedin, New Zealand. Silica gel used for flash chromatography was 40–63 μm (230–400 mesh) silica gel 60 (Merck No. 9385).

2.2. Preparation of substrates

Commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose was oxidised to the gluconolactone [6] which was then reacted with allylmagnesium chloride [7]. The Grignard product was reduced using triethylsilane/boron trifluoride etherate [7] to give 3-(tetra-*O*-benzyl-β-D-glucopyranosyl)propene (**4**) whose physical and spectroscopic data [8] were consistent with literature values, e.g., m.p. 89–89.5°C (lit., Ref. [7] 89–90°C). Conversion to 3-(3′,4′,6′-tri-*O*-benzyl-β-D-glucopyranosyl)propene (**6**) was achieved by iodination followed by reaction with zinc/acetic acid [9]. The hydroxyallyl compound (**6**) had m.p. 62–64°C (lit., Ref. [9] 63–65°C) and ^{1}H and ^{13}C NMR spectra were consistent with literature values [9].

2.3. Hydroformylation reactions

Reactions were carried out using H_2/CO (1:1), 400 psi (2.76 MPa) initial pressure in a Parr 100 ml stainless steel autoclave with a glass liner. The temperature was measured using a thermocouple inserted between the autoclave and the heating block. All reactions were carried out at 80°C in magnetically stirred ethyl acetate solutions. The substrate:ligand:catalyst ratio was ca. 100:4:1. The reactions were allowed to cool, the contents filtered through a pad of celite and the solvent removed under vacuum.

2.4. Hydroformylation of 3-(tetra-O-benzyl-β-D-glucopyranosyl)propene (4)

A reaction of (**4**) (186 mg, 0.33 mmol), $[Rh(OAc)_2]_2$ (1.8 mg, 0.004 mmol) and BIPHEPHOS (12.2 mg, 0.016 mmol) in ethyl acetate (8 ml) for 6.5 h gave an oil whose ^{1}H NMR spectrum showed

a mixture of the linear aldehyde (**6**) and a trace of unreacted starting material. Chromatography on silica (ethyl acetate/light petroleum, 10:90) gave a pure sample of 4-(tetra-*O*-benzyl-β-D-gluco-pyranosyl)butanal (**6**) (108 mg, 55%) as a solid, m.p. 58–58.5°C, $[\alpha]_D$ −2.1° (*c*, 1.0 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42–1.89 (m, 4H, H3, H4), 2.42 (td, *J* 7.1, 1.6 Hz, 2H, H2), 3.18–3.30 (m, 2H, H1′, H2′), 3.38 (ddd, *J* 9.3, 3.9, 2.3 Hz, 1H, H5′), 3.61 (t, *J* 9.2 Hz, 1H, H3′ or H4′), 3.65–3.73 (m, 3H, H6′ and H3′ or H4′), 4.53 and 4.62 (ABq, *J* 12.4 Hz, 2H, CH_2Ph), 4.56 and 4.88 (ABq, *J* 10.7 Hz, 2H, CH_2Ph), 4.63 and 4.82 (ABq, *J* 10.9 Hz, 2H, CH_2Ph), 4.90, (bs, 2H, CH_2Ph), 7.14–7.35 (m, 20 H, 4 × Ph), 9.72 (t, *J* 1.7 Hz, 1H, H1). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.5 (C3), 31.1 (C4), 43.8 (C2), 69.1 (C6′), 73.5, 75.0, 75.3, 75.6 (*C*H_2Ph) 78.6, 78.8, 78.9 (C1′,C4′,C5′), 82.0 (C2′), 87.3 (C3′) 127.5, 127.5, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0, 128.3, 128.3, 128.4, 128.5 (ArCH), 138.0, 138.0, 138.1, 138.5 (ArC), 202.3 (C1). IR (Nujol) 1728 s cm^{-1}. HRMS (ESI) *m/z* found: 617.2876. Calc. for $(C_{38}H_{42}O_6Na)^+$: 617.2879.

A similar reaction of (**4**) (282 mg, 0.5 mmol), $[Rh(OAc)_2]_2$ (2.2 mg, 0.005 mmol) and PPh_3 (5.2 mg, 0.02 mmol) in ethyl acetate (10 ml) at 80°C for 20 h gave a brown oil shown by ^1H and ^{13}C NMR spectra to be a mixture of the linear (**6**) and the branched aldehydes (**7**) (1:1 ratio of diastereomers) in ratio 60:40. Chromatography (ethyl acetate/light petroleum, 10:90) did not lead to complete separation but fractions rich in each of the isomers were obtained. Spectral data for the linear isomer (**6**) were identical to those described above. Data for the branched aldehydes (**7**) are given for the 1:1 mixture of diastereoisomers. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.07 (d, *J* 7.2 Hz, Me), and 1.10 (d, *J* 7.2 Hz, Me), 1.60–1.89 (m, 1H) and 2.08–2.23 (m, 1H) (H3), 2.50–2.66 (m, 1H, H2), 3.20–3.45 (m, 3H, H1′, H2′, H5′), 3.56–3.78 (m, 4H, H3′, H4′, H6′), 4.46–4.70 (m, 4H) and 4.78–4.98 (m, 4H) (CH_2Ph), 7.10–7.42 (m, 20H, 4 × Ph), 9.59 (d, *J* 2.4 Hz, H1) and 9.61 (d, *J* 1.5 Hz, H1). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.6 and 13.9 (Me), 33.1 and 33.4 (C3), 43.0 and 43.9 (C2), 68.8 and 68.9 (C6′), 73.5, 74.9, 75.1, 75.5 (*C*H_2Ph), 76.5, 77.3, 78.3, 78.8 and 78.9 (C1′, C4′, C5′), 82.0 and 82.3 (C2′), 87.1 (C3′), 127.5, 127.6, 127.6, 127.7, 127.9, 127.9, 128.2, 128.3, 128.3, 128.3 (ArCH), 137.9, 137.9, 138.0, 138.4 (ArC), 204.3 and 204.6 (C1). IR (Nujol) 1728s cm^{-1}.

*2.5. Hydroformylation of 3-(3′,4′,6′-tri-O-benzyl-β-D-glucopyranosyl)propene (**5**)*

A solution of the hydroxyalkene (**5**) (1.00 g, 2.05 mmol), $[Rh(OAc)_2]_2$ (9.3 mg, 0.021 mmol) and BIPHEPHOS (65.8 mg, 0.084 mmol) in ethyl acetate (50 ml) was reacted at 80°C for 20 h. Filtration to remove catalyst and evaporation of the solvent under reduced pressure gave a solid which by ^1H NMR spectroscopy ($CDCl_3$) was shown to consist of the linear aldehyde (**8**) together with its cyclic hemiacetal isomer (**10**) (ca. 10%). Chromatography on silica (ethyl acetate/light petroleum, 30:70) gave 4-(3′,4′,6′-tri-*O*-benzyl-β-D-glucopyranosyl)butanal (**8**) (0.85 g, 82%), m.p. 89.5–90°C. ^1H NMR (300 MHz, $CDCl_3$]: δ (ppm) 1.38–1.91 (m, 4H, H3, H4), 2.06 (bs, 1H, OH), 2.47, (td, *J* 7.1, 1.6 Hz, 1H, H2), 3.15 (td, *J* 9.0, 2.2 Hz, 1H, H1′), 3.30 (apparent t, *J* ∼9 Hz, 1H, H2′), 3.39 (dt, *J* 9.6, 2.9 Hz, 1H, H5′), 3.45 (apparent t, *J* 8.9 Hz, 1H, H3′), 3.62 (apparent t, *J* 9.3 Hz, 1H, H4′), 3.65–3.75 (m, 2H, H6′), 4.55 and 4.63 (ABq, *J* 12.3 Hz, 2H, CH_2Ph), 4.59 and 4.80 (ABq, *J* 10.7 Hz, 2H, CH_2Ph), 4.71 and 4.97 (ABq, *J* 11.7 Hz, 2H, CH_2Ph), 7.1–7.4 (m, 15H, 3 × Ph), 9.74 (t, *J* 1.7 Hz, 1H, H1). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.2 (C3), 31.1 (C4), 43.9 (C2), 69.0 (C6′), 73.5 (*C*H_2Ph), 73.7 (C2′), 74.8, 75.2 (*C*H_2Ph), 78.4 (C4′), 79.0 (C5′), 79.1 (C1′), 86.8 (C3′), 127.5, 127.7, 127.8, 127.8, 127.9, 128.3, 128.3, 128.4, 128.6 (ArCH), 137.9, 138.0, 138.4 (ArC), 202.5 (C1). MS(ESI): *m/z* 527.3 $(M + Na)^+$, 543.2 $(M + K)^+$. HRMS (ESI) *m/z* found: 527.2424. Calc. for

$(C_{31}H_{36}O_6Na)^+$ 527.2410. The ^1H and ^{13}C NMR spectra of hemiacetal (**10**) ((2*R*,3*R*,4*S*,4a*S*,9a*S*)-3,4-dibenzyloxy-2-benzyloxymethyl-6-hydroxy-3,4,4a,6,7,8,9,9a-octahydro-2*H*-pyrano[3,2-*b*]oxepine) were recorded in a range of solvents and complete data is given for spectra in d_6-acetone. ^1H NMR (300 MHz, d_6-acetone): δ (ppm) 1.33–1.42 (m, 2H) and 1.46–1.67 (m, 2H) (H7, 2 × H8, H9), 1.96–2.18 (m, 2H, H7, H9), 3.20 (ddd, *J* 15.3, 9.7, 5.5 Hz, 1H, H9a), 3.37–3.42 (m, 1H, H2), 3.45, (dd, *J* 9.5, 8.2 Hz, 1H, H3), 3.49 (dd, *J* 9.2, 8.1 Hz, 1H, H4), 3.66 (dd, *J* 10.7, 4.1 Hz, 1H, H2′), 3.71 (dd, *J* 10.7, 2.0 Hz, 1H, H2′), 3.78 (dd, *J* 9.1, 8.7 Hz, 1H, H4a), 4.51 and 4.57 (ABq, *J* 12.1 Hz, 2H, C*H*$_2$Ph), 4.56 and 4.80 (ABq, *J 11.0 Hz*, *2H*, C*H*$_2$Ph), 4.71 and 5.16 (ABq, *J* 11.4 Hz, 2H, C*H*$_2$Ph), 5.02 (d, *J* 5.5 Hz, 1H, OH), 5.14 (dt, *J* 9.2, 5.5 Hz, 1H, H6), 7.17–7.41 (m, 15H, 3 × Ph); ^{13}C NMR (75 MHz, d_6-acetone): δ (ppm) 19.4 (C8), 36.5 (C7), 37.0 (C9), 70.4 (C2′), 74.7 (C4a), 73.6, 75.2, 75.5 (3 × *C*H$_2$Ph) 78.5 (C3), 79.0 (C2), 79.1 (C9a), 86.4 (C4), 95.8 (C6), 127.6, 127.9, 128.2, 128.3, 128.4, 128.6, 128.7, 128.8 (ArCH), 138.3, 139.7, 140.6 (ArC). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 95.3 (C6). HRMS (ESI) *m/z* found: 527.2424. Calc. for $(C_{31}H_{36}O_6Na)^+$: 527.2410.

This reaction was repeated 12 times and on all but two occasions gave results identical to that above. However, two reactions of (**4**) (1.13 g) under apparently identical conditions gave a product (1.12 g, 94%) which by ^1H NMR and ^{13}C NMR spectroscopy was shown to be a ca. 1:1 mixture of the linear aldehyde (**8**) and the hemiacetals (**11**) derived from the branched aldehyde (**9**). Chromatography with gradient elution (100% light petroleum to ethyl acetate/light petroleum 30:70) gave initially the mixture of stereoisomeric hemiacetals (**11**) (0.56 g, 47%), ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.9–1.0 (m, CH_3), 1.1–2.4 (m, 3H, CH_2, C*H*CH$_3$), 3.1–3.9 (m, 7H, C*H*OR, C*H*$_2$OR), 4.4–5.1 (m, 7H, C*H*$_2$Ph and anomeric CH). Proof of structure came from oxidation of this mixture to the lactones (**12**) (see below). Further elution gave the linear aldehyde (**8**) (0.56 g, 47%).

A hydroformylation of the hydroxyalkene (**5**) (0.24 g, 0.5 mmol), $[Rh(OAc)_2]_2$ (2.2 mg) and BIPHEPHOS (15.6 mg) in methanol (10 ml) for 20 h at 80°C using H_2/CO, 1:9 gave 4-(3′,4′,6′-tri-*O*-benzyl-β-D-glucopyranosyl)-1,1-dimethoxybutane (**14**) (0.27 g, 97%). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.34–1.70 (m, 4H) and 1.71–1.98 (m, 2H) (H2, H3, H4), 3.15 (td, *J* 8.2, 2.5 Hz, 1H, H1′), 3.26–3.32 (m, 1H, H2′), 3.29 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.40 (apparent dt, *J* 9.8, 3.5 Hz, 1H, H5′), 3.45 (apparent t, *J* 8.8 Hz, 1H, H3′), 3.62 (apparent t, *J* ∼9.4 Hz, 1H, H4′), 3.66–3.76 (m, 2H, H6′), 4.35 (t, *J* 5.5 Hz, 1H, H1), 4.55 and 4.64 (ABq, *J* 12.3 Hz, 2H, C*H*$_2$Ph), 4.59 and 4.80 (ABq, *J* 10.8 Hz, 2H, C*H*$_2$Ph), 4.72 and 4.96 (ABq, *J* 11.6 Hz, 2H, C*H*$_2$Ph), 7.18–7.36 (m, 15H, 3 × Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.7 (C3), 31.6 (C4), 32.5 (C2), 52.6 (OMe), 52.7 (OMe), 69.0 (C6′), 73.5 (*C*H$_2$Ph), 73.9 (C2′) 74.8, 75.2 (*C*H$_2$Ph), 78.5 (C4′), 79.1 (C5′), 79.3 (C1′), 86.9 (C3′), 104.4 (C1), 127.5, 127.7, 127.7, 127.8, 128.2, 128.3, 128.6 (ArCH), 138.0, 138.1, 138.5 (ArC). HRMS (ESI) *m/z* found: 573.2828. Calc. for $(C_{33}H_{42}O_7Na)^+$: 573.2828.

A sample of this compound was prepared by stirring the linear aldehyde (**8**) (0.2 g) in methanol (50 ml) for 10 min at ambient temperature in the presence of *p*-toluenesulphonic acid (3 mg). Chromatography gave a quantitative yield of the dimethyl acetal (**14**).

A sample of the acetal (**14**) (0.2 g, 0.4 mmol) was heated in toluene (50 ml) with a small amount of *p*-toluenesulphonic acid (3 mg) in a Dean-Stark apparatus. The solution was cooled, washed ($NaHCO_3$, NaCl), dried and the solvent evaporated to give a solid which was recrystallised (hexane) to give (2*R*,3*R*,4*S*,4a*S*,9a*S*)-3,4-dibenzyloxy-2-benzyloxymethyl-6-methoxy-3,4,4a,6,7,8,9,9a-octahydro-2*H*-pyrano[3,2-*b*]oxepine (**15**) (0.1 g, 53%), m.p. 95.5–96°. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.38–1.47 (m, 2H, H8, H9), 1.53–1.67 (m, 2H, H7, H8), 2.05–2.10 (m, 1H, H7), 2.22–2.25 (m, 1H, H9), 3.22–3.29 (m, 1H, H9a), 3.25 (s, 3H, OMe), 3.43–3.47 (m, 1H, H2), 3.52–3.60 (m, 2H, H3, H4), 3.65 (dd, *J* 10.7, 4.7 Hz, 1H, H2′), 3.71 (dd, *J* 10.7, 1.9 Hz, 1H, H2′), 3.72 (apparent t,

$J \sim 9$ Hz, 1H, H4a), 4.51 and 4.72 (ABq, J 10.5 Hz, 2H, CH_2Ph), 4.55 and 4.61 (ABq, J 11.3 Hz, 2H, CH_2Ph), 4.91 and 4.97 (ABq, J 10.6 Hz, 2H, CH_2Ph), 7.05–7.36 (m, 15H, 3 × Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.3 (C8), 34.5 (C7), 36.2 (C9), 55.8 (OMe), 69.2 (C2′), 73.0 (C4a), 73.5, 75.0, 75.2 (*C*H$_2$Ph), 78.6, 78.6 (C2, C3), 78.9 (C9a), 85.4 (C4), 102.9 (C6), 126.9, 127.1, 127.5, 127.6, 127.7, 127.9, 128.0, 128.2, 128.4 (ArCH), 138.1, 138.2, 139.0 (ArC). MS (ESI): m/z 541.3 $(M + Na)^+$, 557.2 $(M + K)^+$. Elemental analysis (%) found: C 73.86, H, 7.53. Calc. for $C_{32}H_{38}O_6$: C 74.11, H, 7.39.

A similar reaction of the hydroxyalkene (**5**) (0.24 g, 0.5 mmol), $[Rh(OAc)_2]_2$ (2.2 mg, 0.005 mmol) and PPh_3 (5.2 mg, 0.02 mmol) in ethyl acetate (10 ml) for 20 h at 80°C gave a complex mixture (0.21 g, 82%) consisting of the hemiacetals (**10**) and (**11**) with a trace of the aldehydes (**8**) and (**9**). Integration of the CH_3 and aromatic signals suggested an approximate ratio of 70:30 for linear vs. branched products.

2.6. Oxidation of hemiacetals

2.6.1. Oxidation of the six-ring hemiacetals (*11*)

Tetrapropylammonium perruthenate (TPAP) (20 mg, 0.06 mmol), *N*-methylmorpholine-*N*-oxide (194 mg, 1.66 mmol) and 4 Å molecular sieves (557 mg) were added to a solution of a diastereomeric mixture of the 6,6-hemiacetals (**11**) (557 mg, 1.1 mmol) in anhydrous acetonitrile (12 ml) under N_2. The reaction was stirred at ambient temperature overnight, the solvent evaporated, the residue diluted with dichloromethane (10 ml) and filtered through a pad of celite/silica which was rinsed with EtOAc. The solvent was removed to give a black oil which was treated with activated carbon in ether and filtered through a pad of celite/silica to give a clear oil (461 mg) containing a 4:1 mixture of (2*R*,3*R*,4*S*,4a*S*,8a*S*)-3,4-dibenzyloxy-2-benzyloxymethyl-7-methyl-2,3,4,4a,8,8a-hexahydropyrano-[3,2-*b*]pyran-6(7*H*)one (**12**) and starting hemiacetals (**11**). Preparative chromatography on silica (ethyl acetate/light petroleum 1:5) gave pure samples of the two diastereoisomers of (**12**). Higher R_f isomer (R_f 0.33): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.23 (d, J 6.6 Hz, 3H, Me), 1.87–1.98 (m, 1H, H8), 2.05–2.25 (m, 1H, H8), 2.76–2.87 (m, 1H, H7), 3.47–3.58 (m, 2H, H2, H8a), 3.61–3.73 (m, 3H, H2′, H3), 3.79 (apparent t, J 8.7 Hz, 1H, H4), 4.16 (apparent t, J 9.5 Hz, 1H, H4a), 4.48 and 4.85 (ABq, J 11.0 Hz, 2H, CH_2Ph), 4.52 and 4.61 (ABq, J 12.2 Hz, 2H, CH_2Ph), 4.78 and 5.01 (ABq, J 10.9 Hz, 2H, CH_2Ph), 7.10–7.42 (m, 15 H, 3 × Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 16.0 (Me), 31.9 (C8), 32.2 (C7), 68.7 (C2′), 72.1 (C2 or C8a), 73.6, 75.3, 75.4 (*C*H$_2$Ph), 77.3 (C3), 79.3 (C2 or C8a), 79.5 (C4a), 83.6 (C4), 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4 (ArCH), 137.7, 137.8, 138.0 (ArC), 174.5 (C6). HRMS (ESI) m/z found: 525.2261. Calc. for $(C_{31}H_{34}O_6Na)^+$: 525.2253.

Lower R_f isomer (R_f 0.27): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.38 (d, J 7.3 Hz, 3H, Me), 1.71 (apparent dt, J 12.7, 11.6 Hz, 1H, H8), 2.35 (ddd, J 12.7, 7.3, 4.3 Hz, 1H, H8), 2.70 (ddq, J 11.5, 7.2, 7.2 Hz, 1H, H7), 3.46–3.56 (m, 2H, H2, H8a), 3.70 (dd, J 9.8, 8.3 Hz, 1H, H3), 3.65 (dd, J 10.7, 4.3 Hz, 1H, H2′), 3.71 (dd, J 10.7, 2.1 Hz, 1H, H2′), 3.75 (dd, J 9.0, 8.4 Hz, 1H, H4), 4.08 (dd, J 9.7, 9.0 Hz, 1H, H4a), 4.47 and 4.84 (ABq, J 10.8 Hz, 2H, CH_2Ph), 4.52 and 4.60 (ABq, J 12.2 Hz, 2H, CH_2Ph), 4.77 and 5.06 (ABq, J 11.0 Hz, 2H, CH_2Ph), 7.10–7.42 (m, 15H, 3 × Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.4 (Me), 34.5 (C8), 34.8 (C7), 68.8 (C2′), 72.4 (C2 or C8a), 73.6, 75.4, 75.4 (*C*H$_2$Ph), 77.3 (C3), 79.4 (C2 or C8a), 82.9 (C4a), 83.9 (C4), 127.7, 1276.7, 127.8, 127.8, 127.9, 128.1, 128.2, 128.3, 128.3 (ArCH), 137.7, 137.8, 138.1 (ArC), 172.1 (C6). HRMS (ESI) m/z found: 525.2259. Calc. for $(C_{31}H_{34}O_6Na)^+$: 525.2253.

*2.6.2. Oxidation of the seven-ring hemiacetals (**10**)*

A similar oxidation of the 6,7 hemiacetals (**10**) (557 mg, 1.1 mmol) in anhydrous acetonitrile (12 ml) using 4 Å molecular sieves (557 mg), *N*-methylmorpholine-*N*-oxide (194 mg) and TPAP (20 mg) gave a product which was chromatographed on silica (100% dichloromethane to give (2*R*,3*R*, 4*S*,4a*S*,9a*S*)-3,4-dibenzyloxy-2-benzyloxymethyl-3,4,4a,8,9,9a-hexahydro-2*H*-pyrano[3,2-*b*]oxepin-6(7*H*)one (13). R_f (EtOAc/light petroleum 1:5) 0.12. $[\alpha]_D$ +37.8° (*c*, 0.87 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.63–1.69 (m, 2H, H8, H9), 1.92–1.96 (m, 1H, H8), 2.28–2.33 (m, 1H, H9), 2.51–2.58 (m, 1H, H7), 2.69 (dd, *J* 14.5, 7.1 Hz, 1H, H7), 3.39–3.46 (m, 2H, H2, H9a), 3.58 (dd, *J* 9.8, 9.2 Hz, 1H, H3), 3.64 (dd, *J* 10.8, 4.6 Hz, 1H, H2′), 3.71 (dd, *J* 10.8, 2.0 Hz, 1H, H2′), 3.79 (dd, *J* 9.0, 8.4 Hz, 1H, H4), 4.14 (dd, *J* 9.2, 8.5 Hz, 1H, H4a), 4.53 and 4.58 (ABq, *J* 12.2 Hz, 2H, CH_2Ph), 4.55 and 4.83 (ABq, *J* 10.8 Hz, 2H, CH_2Ph), 4.81 and 4.99 (ABq, *J* 10.8 Hz, 2H, *CH*$_2$Ph), 7.14–7.37 (m, 15H, 3 × Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.0 (C8), 34.5 (C7), 35.3 (C9), 68.9 (C2′), 73.5, 75.0, 76.0 (*C*H$_2$Ph), 76.2 (C2 or C9a), 77.3 (C3), 78.0 (C2 or C9a), 82.5 (C4a), 84.6 (C4), 127.7, 127.7, 127.8, 127.8, 127.9, 128.2, 128.4, 128.4 (ArCH), 138.0, 138.0, 138.2 (ArC), 174.1 (C6). IR (neat) 1738 s cm^{-1}. HRMS (ESI) *m/z* found: 525.2242. Calc. for $(C_{31}H_{34}O_6Na)^+$: 525.2253.

*2.7. Attempted carbonylations of the hydroxyalkene (**5**)*

Reactions of (**5**) (0.24 g), $[Rh(OAc)_2]_2$ (2.2 mg) and BIPHEPHOS (5.6 mg) in ethyl acetate (10 ml) with H_2/CO, 1:9 at 80° for 20 h gave a product (0.25 g) which by ^{1}H NMR spectroscopy was identical to that of the linear aldehyde (**8**). Attempted carbonylations of (**5**) (0.24 g) with $HRh(CO)(PPh_3)_3$ (9.2 mg) and CO (400 psi) at 80° for 20 h gave recovered hydroxyalkene (**5**) (0.24 g). Similarly, starting material was recovered quantitatively from an attempted reaction of (**5**) (0.24 g) with H_2/CO, 1:5 (600 psi) using $Pd(OAc)_2$ (1.2 mg) and DIOP (0.5 mg) in dichloromethane (10 ml) at 100°C for 48 h.

3. Results and discussion

3.1. Hydroformylation and carbonylation of amino- and hydroxyalkenes

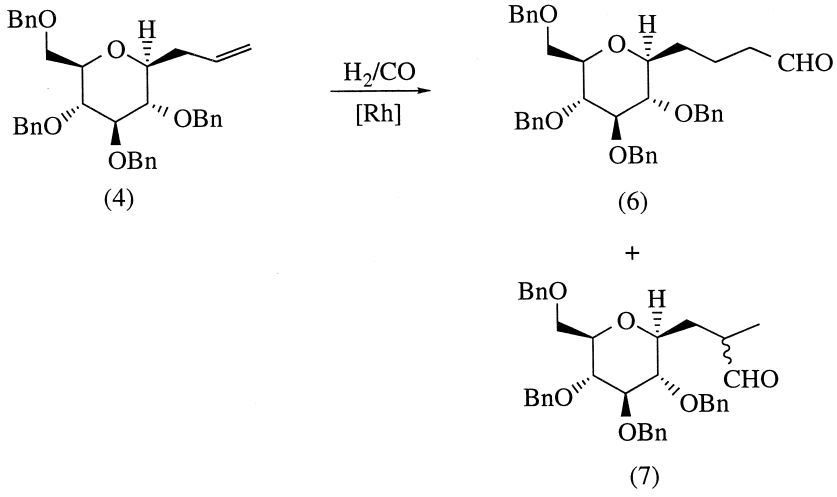
Metal catalysed hydroformylation (addition of H_2 and CO) and carbonylation (addition of CO) reactions of unsaturated amines and alcohols have been explored previously as routes to heterocyclic compounds [10]. Many examples of the preparation of nitrogen heterocycles by hydroformylation of unsaturated amines [11,12] and the formation of lactams by carbonylation of some β- and γ-aminoalkenes have been reported [11,13]. The formation of oxygen heterocycles by hydroformylation of hydroxyalkenes is less frequently encountered, probably because the resulting hemiacetals are in equilibrium with the open chain hydroxyaldehyde isomers [10]. Carbonylation of hydroxyalkenes leading to lactone formation has been successfully applied to the preparation of five- and six-membered ring lactones [13].

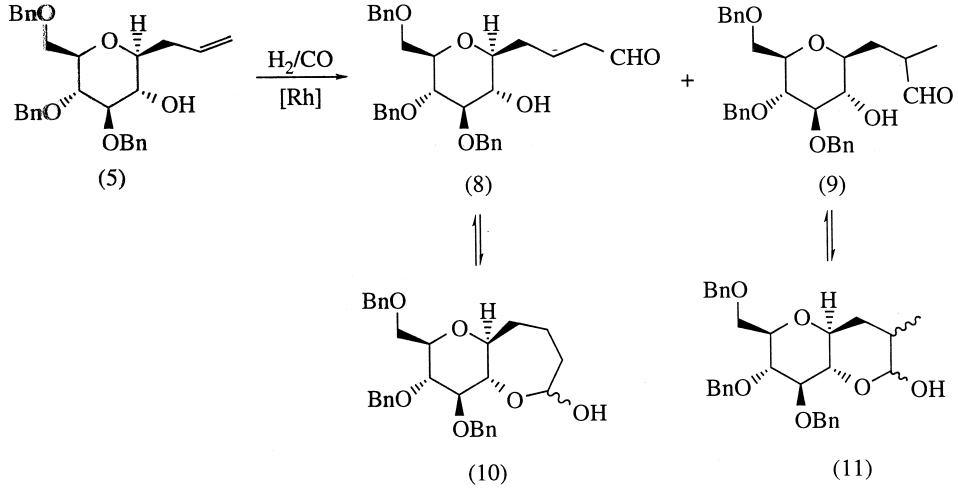
3.2. Reactions of unsaturated carbohydrates with H_2 and / or CO

The reaction of appropriately unsaturated carbohydrate derivatives (e.g., **3**) with H_2/CO represents a potential route to key intermediates (e.g., **2**) for the synthesis of the A/B ring system of marine

toxins (**1**) as outlined in Section 1 (Fig. 1). Rhodium-catalysed reactions of carbohydrate derivatives with H_2/CO have been described previously establishing that such reactions are tolerant to the presence of several oxygen-containing functional groups in the molecule [14].

The tetra-*O*-benzyl allylglucopyranose derivative (**4**) was prepared by a literature procedure [6–8] and reacted with H_2/CO in the presence of rhodium catalysts to establish the general sensitivity of the catalyst system to this heavily oxygenated substrate. A reaction using the BIPHEPHOS ligand led to regiospecific formation of the linear aldehyde (**6**) as was anticipated on the basis of previous highly regioselective hydroformylations which have been reported using this ligand [4,15,16]. A reaction using triphenylphosphine as ligand gave a mixture of linear (**6**) and branched chain (**7**) aldehydes in ratio ca. 60:40 in agreement with many reported product ratios.

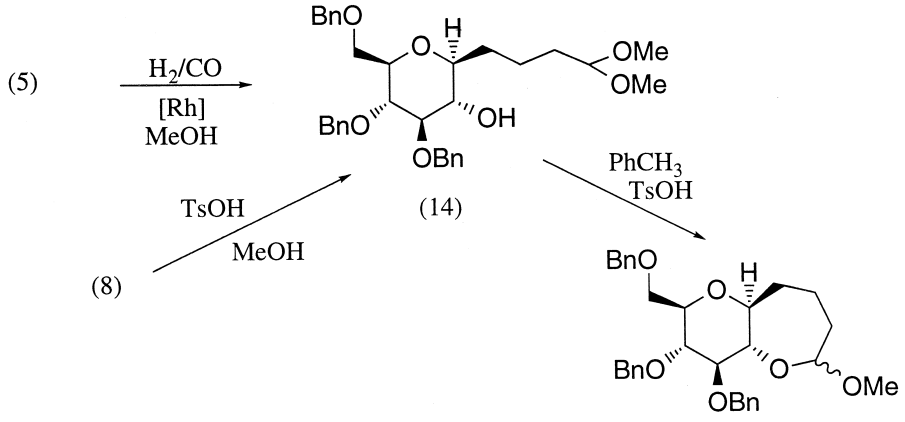




Reaction of the tri-*O*-benzyl-hydroxyallyl compound (**5**) [9] was again regiospecific leading to the linear aldehyde (**8**) and derived hemiacetals (**10**) when BIPHEPHOS was used as a ligand. The lack of branched chain products demonstrates that the bulk of the BIPHEPHOS ligand overcomes any

potential chelation effects of the hydroxy group either by oxygen chelation or hydrogen bonding to the rhodium catalyst as these would be expected to lead to branched chain products [17]. In solution, the aldehyde (**8**) was in equilibrium with the cyclic hemiacetals (**10**) as shown by ^{1}H NMR spectroscopy. The position of equilibrium was shown to be highly solvent dependent (see below). The hydroformylation reaction using BIPHEPHOS was repeated 12 times with varying quantities (0.2–1.1 g) of substrate giving (**8**) regiospecifically on all but two occasions. Surprisingly, two reactions of (**5**) gave almost equal amounts of branched and linear products. No explanation for these two results is available.

A reaction in methanol using BIPHEPHOS gave the linear dimethyl acetal (**14**) as the major product. Its structure was confirmed by cyclisation to the acetal (**15**) and by preparation of a sample from the aldehyde (**8**).



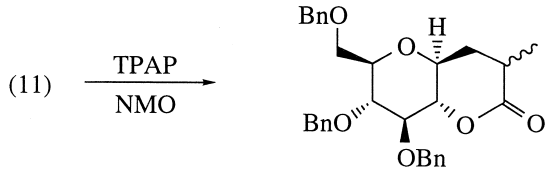
(15)

Hydroformylation of the hydroxyalkene (**5**) using triphenylphosphine as ligand gave a complex mixture of hemiacetals (**10**, **11**). The ratio of linear to branched products was estimated to be roughly 70:30, again showing no evidence for participation of the hydroxy group in regioselection.

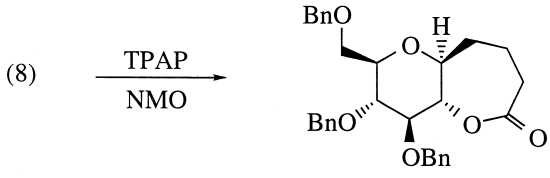
Direct formation of the lactones (**12**) and (**13**) was attempted under several conditions. Rhodium-catalysed reaction of (**5**) but with a 1:9 ratio of H_2 to CO still gave the linear aldehyde (**8**) as the sole product when BIPHEPHOS was used as ligand. The presence of some hydrogen is necessary to activate the above catalyst system and thus an attempted carbonylation of (**5**) was carried out using preformed $HRh(CO)(PPh_3)_3$ with CO alone. Only starting material was recovered as was also the case when a palladium-catalysed carbonylation was attempted [18].

*3.3. Oxidation of hydroxy aldehyde (**8**) and cyclic hemiacetals (**11**). Production of 6,6- and 6,7-bicyclic lactones (**12**) and (**13**)*

The cyclic hemiacetals (**11**) and the hydroxy aldehyde (**8**) were each oxidised to the corresponding lactones (**12**) and (**13**), respectively. In general, PDC gave relatively poor conversion, however Ley's oxidant, TPAP [6] proved to be significantly superior.



(12)



(13)

A study on the effect of solvent on the position of equilibrium between the open hydroxy aldehyde and the cyclic hemiacetals in the case of (**8**) was carried out. This involved dissolving samples of (**8**) in a series of different deuterated solvents (CD_2Cl_2, $CDCl_3$, d_6-acetone, CD_3CN, CD_3OD, C_6D_6, d_5-pyridine) and observing their ^1H NMR spectra. For all cases, except $CDCl_3$, (**8**) existed predominantly in its cyclic hemiacetal form. Hence it may be assumed that oxidation of this species, the hemiacetal (**10**), is more likely occurring rather than oxidation of the hydroxy aldehyde (**8**). In any event pure samples of the 6,6- and 6,7-bicyclic lactones were obtained thus establishing this chemistry as a viable route to carbohydrate-derived bicyclic lactones.

4. Note added in proof

NOE experiments showed the higher R_f isomer of the lactone (**12**) to be (7*S*) and the lower R_f isomer to be (7*R*).

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References

[1] T. Oka, K. Fujiwara, A. Murai, Tetrahedron Lett. 38 (1997) 8053.
[2] K.C. Nicolaou, Angew. Chem., Int. Ed. Engl. 35 (1996) 589.
[3] W. Zheng, J.A. De Mattei, J.-P. Wu, J.J.-W. Duan, L.R. Cook, H. Oinuma, Y. Kishi, J. Am. Chem. Soc. 118 (1996) 7946.
[4] G.D. Cuny, S.L. Buchwald, J. Am. Chem. Soc. 115 (1993) 2066.
[5] P. Legzdins, R.W. Mitchell, G.L. Rempel, J.D. Ruddick, G. Wilkinson, J. Chem. Soc. A (1970) 3322.
[6] W.P. Griffith, S.V. Ley, Aldrichimica Acta 23 (1990) 13.
[7] W.H. Best, V. Ferro, J. Harle, R.V. Stick, D.M.G. Tilbrook, Aust. J. Chem. 50 (1997) 463.
[8] M.D. Lewis, J.K. Cha, Y. Kishi, J. Am. Chem. Soc. 104 (1982) 4976.
[9] L. Cipolla, L. Lay, F. Nicotra, J. Org. Chem. 62 (1997) 6678.
[10] C. Botteghi, R. Ganzerla, M. Lenarda, G. Moretti, J. Mol. Catal. 40 (1987) 129.

[11] J.-Q. Zhou, H. Alper, J. Org. Chem. 57 (1992) 3328.
[12] Z. Zhang, I. Ojima, J. Organomet. Chem. 454 (1993) 281.
[13] A. Mullen, in: J. Falbe (Ed.), New Syntheses with Carbon Monoxide, Chap. 6, Springer-Verlag, New York, 1980, pp. 414–439.
[14] A. Polo, E. Fernandez, C. Claver, S. Castillon, J. Chem. Soc., Chem. Commun. (1992) 639.
[15] D.J. Bergmann, E.M. Campi, W.R. Jackson, Q.J. McCubbin, A.F. Patti, Tetrahedron 53 (1997) 17449.
[16] I. Ojima, M. Tzamarioudaki, M. Eguchi, J. Org. Chem. 60 (1995) 7078.
[17] K.J. Coutinho, R.S. Dickson, G.D. Fallon, W.R. Jackson, T. De Simone, B.W. Skelton, A.H. White, J. Chem. Soc., Dalton Trans. (1997) 3193.
[18] K. Okuro, H. Kai, H. Alper, Tetrahedron Asymmetry 8 (1997) 2307.