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Synthetic Studies of Ambruticin: Preparation of the C1-C8 Tetrahydropyran and the C17-C24 Dihydropyran Segments

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Abstract: The C1-C8 tetrahydropyran and the C17-C24 dihdropyran segments of ambruticin were prepared from L-arabinose in 11 steps, 7.6% overall yield and from (*S*)-ethyl lactate in 8 steps, 22.2% overall yield respectively.

Keywords: Natural products; *C*-glucosides; Oxonium ion; Cyclocondensation.

Introduction

Ambruticin (**1**, Fig. 1) is a structurally unique carboxylic acid isolated from *Polyangium cellulosum var. fulvum* which exhibits potent oral antifungal activity against *Coccidioides immitis, Histoplasma capsulatum, and Blastomyces dermititidis* [1]. Extensive spectral analysis revealed that the structure of **1** consists of a tetrahydropyran ring, a dihydropyran ring, and a divinylcyclopropane ring. More recently the jerangolids A and D (**2a**, **b**), isolated from a strain of *Sorangium cellulosum* (So ce 307), were found to exhibit antifungal activity similar to **1** [2]. The structure of **2** from C6-C17 is identical with the C13-C24 segment of ambruticin, and the similar antibiotic spectrum of **1** and **2** suggests that these segments are responsible for their biological activity. More over, the first four genes encoding for the polyketide synthesase for **1** and **2** are >90% identical [3]. The complex array of diverse functionality present in both **1** and **2** has generated considerable synthetic interest[4], including total syntheses of **1** by the groups of Kende [5], Jacobsen [6], Martin[7], Lee [8], and Hanessian[9], and of **2b** by Marko[10] and **2a** by Hanessian [11].

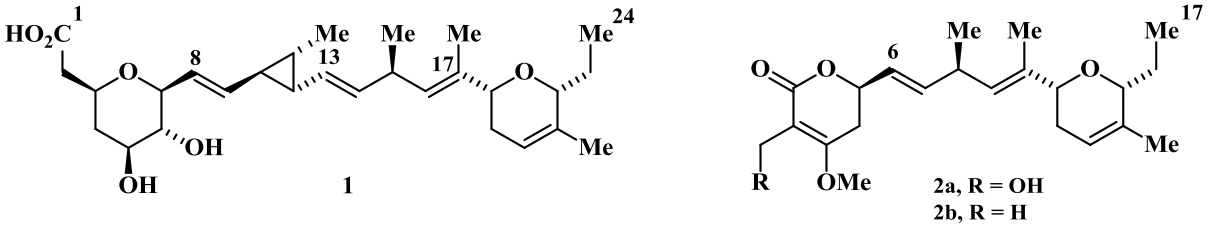

Figure 1. Structures of ambruticin (**1**) and the jerangolides (**2a/b**).

Our retrosynthetic analysis of **1** dissected the molecule at the C8-C9 and C16-C17 olefins into a *cis*-tetrahydropyran segment **3** and a *cis*-dihydropyran segment **4** (Fig. 2). Notably, Just and Potvin confirmed the absolute configuration of ambruticin by preparation of **3** in optically active form, which they could compare to a sample obtained by degradation of **1** [4a]. Addition syntheses of **3** are reported by the groups of Martin [7], Lee [8] and Michelet [4j]. Furthermore, Martin[7], Marko[10], and Hanessian [9,11] have prepared segment **4** as part of their syntheses of **1** and **2**. We have previously reported the preparation of segments **3** and **4** in communication form[12]. We herein report the full experimental details for these syntheses.

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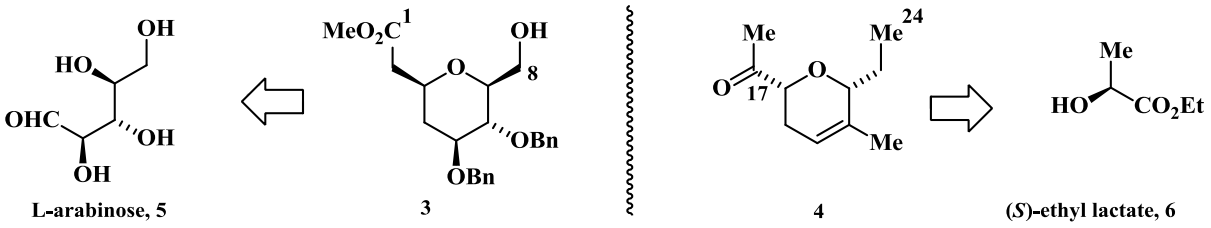


Figure 2. Retrosynthetic analysis of segments **3** and **4** into chiral pool precursors.

Results and Discussion

We envisioned segments **3** and **4** arising via C-glycosylation of an *in-situ* generated oxonium cation with an appropriate weak carbon nucleophile[13] (Fig. 3). These reactions are known to generally result in the formation of a *trans*-2,6-disubstituted tetrahydro- or dihydropyran due to the propensity for axial nucleophilic attack on the oxonium cation [14]. We rationalized that the *trans*-disubstituted products could subsequently be converted into the more thermodynamically stable *cis*-stereoisomers by epimerization.

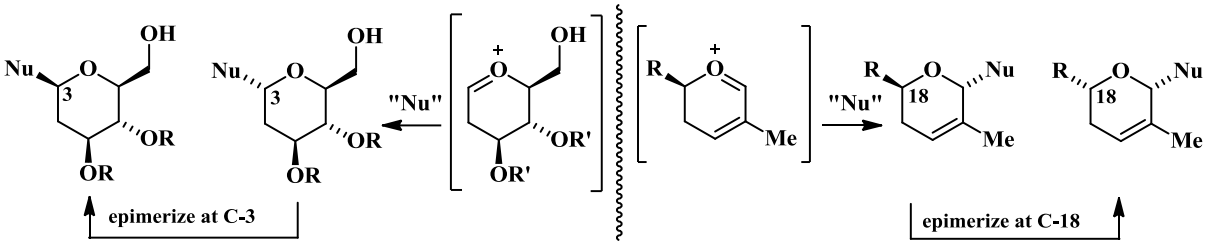
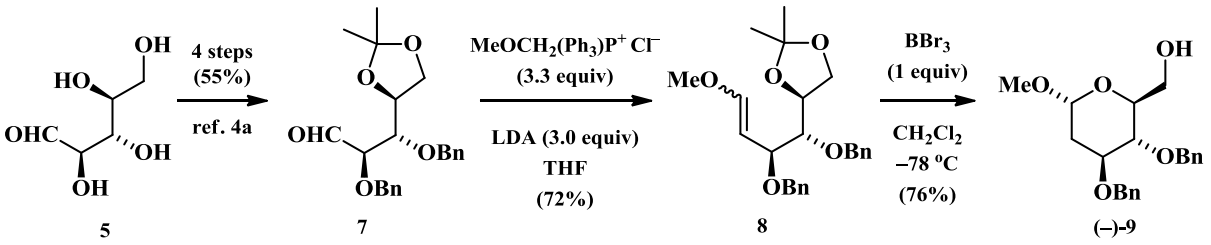


Figure 3. C-glycosylation and epimerization to *cis*-tetrahydro- and *cis*-dihydro-pyrans.

2,3-Di-*O*-benzyl-4,5-isopropylidene-l-arabinose **7** was prepared from L-arabinose **5** in 4 steps, 55% overall yield, via the literature procedure[4a]. Attempted Wittig olefination of **7** with (methoxymethyl)triphenylphosphonium chloride using NaH/DMSO was unsuccessful and resulted in products which appear to arise from elimination. Alternatively, olefination of **7** with the ylide prepared using lithium diisopropylamine (LDA) proceeded in good yield to give **8** as a nearly equimolar mixture of *E*- and *Z*-isomers (Scheme 1).



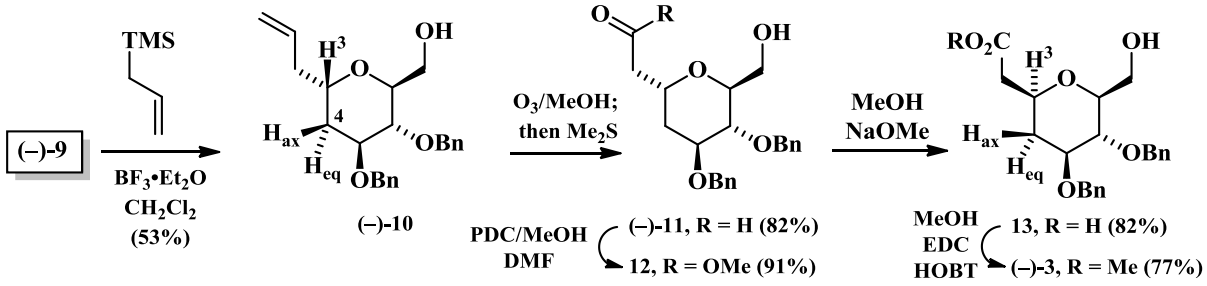
Scheme 1. Synthesis of the methyl 3,4-bis-*O*-benzyl-2-deoxy-L-glucose (-)-**9**.

Attempted hydrolysis of the enol ether **8** with aqueous acetic acid/p-TsOH gave an enal, due to elimination of a molecule of benzyl alcohol. Alternatively, cleavage of the 5,6-acetonide group of **8** with BBr_3 proceeded with cyclization to the methyl glucoside (-)-**9**.

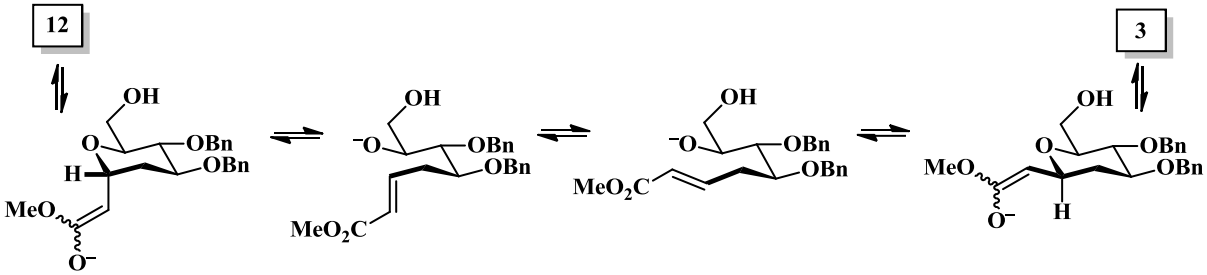
Ionization of the α-methoxy group with BF_3•Et_2O and subsequent nucleophilic attack with allyl trimethylsilane proceeded to give the tetrahydropyran (-)-**10** (Scheme 2).

The *trans*-stereochemical assignment for **10** was based on its ^{1}H NMR spectral data. In particular, the signals H-4ax and H-4eq appear at δ 1.74 and 2.01 ppm with a geminal coupling of 14.0 Hz. However, the absence of a large coupling between H-4ax and H-3 indicates that H-3 occupies an equatorial position. Ozonolysis of **10** in methanol, followed by reductive workup with dimethyl sulfide gave the corresponding aldehyde (-)-**11**. Notably, use of CH_2Cl_2 for solvent in this ozonolysis proceeded in poor yields. Aldehyde **11** underwent oxidation to the carboxylic acid slowly under a stream of air; this oxidation was more rapid in diethyl ether/methanol containing a catalytic amount of sodium methoxide. Due to difficulties in purification of the corresponding carboxylic acid, an alternative route utilized pyridinium dichromate in DMF containing 2.5% methanol to afford the ester **12** in high yield,

presumably via the hemiacetal. Treatment of **12** with sodium methoxide in methanol/water/toluene proceeded to afford the *cis*-tetrahydropyran carboxylic acid **13**. This product arises via an elimination/addition reaction to equilibrate the less stable **12** to the more stable **3**, followed by saponification (Scheme 3). Diimide mediated coupling of **13** with methanol gave the C1-C8 tetrahydropyran segment (-)-**3**. The *cis*-stereochemical assignment for **3** was based on its ^{1}H NMR spectral data. In particular, the signals H-4ax appears as a quartet (J = 12.5 Hz) at δ 1.42 ppm. The large magnitude of these couplings are attributed to geminal coupling to H-4eq, as well as *trans*-diaxial couplings to H-3 and H-5. By this route, the C1-C8 segment (-)-**3** was prepared from L-arabinose in 11 steps and 7.6% overall yield.

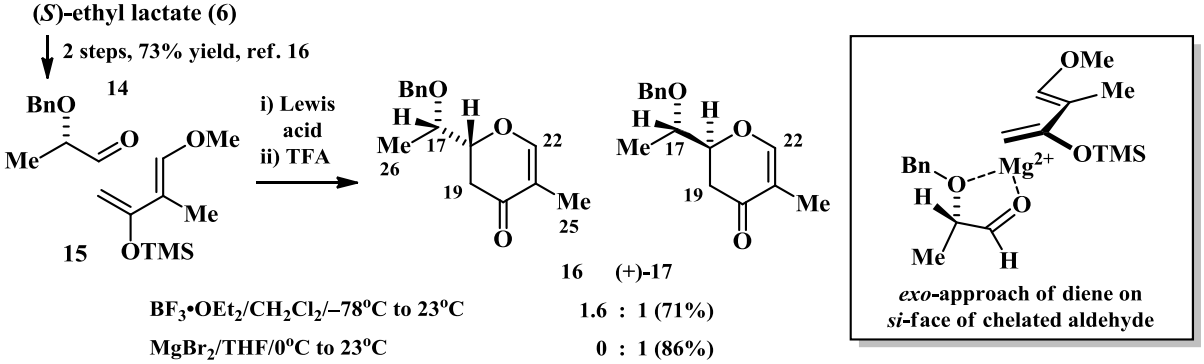


Scheme 2. Synthesis of the C1-C8 segment (-)-**3**.

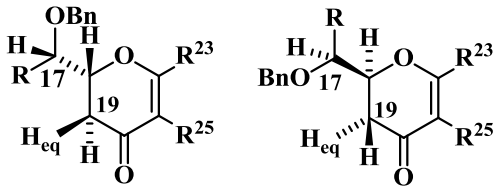


Scheme 3. Epimerization of *trans*-**12** to *cis*-**3**.

Construction of dihydropyran **4** was envisioned by means of a Lewis acid catalyzed diene-aldehyde cyclocondensation reaction [15]. To this end, 2(*S*)-benzyloxypropanal (**14**) was prepared from (S)-ethyl lactate (**6**) in two steps, 73% overall yield, by the literature procedure [16]. Reaction of **14** with 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-butadiene (**15**) [17] in the presence of BF_3•Et_2O, followed by work-up with trifluoroacetic acid gave an inseparable mixture of diastereomeric dihydropyrones **16** and **17** in a 1.6:1 ratio (Scheme 4). The structural assignments of **16** and **17** were based on comparison of their ^{1}H NMR spectral data. In particular, the signals for H-17 and H-19eq (ambruticin numbering) of **17** (δ 3.69 and 2.36 ppm respectively) appear upfield of the corresponding signals for **16** (δ 3.81 and 2.56 ppm respectively). These relative chemical shifts are quite characteristic of diastereomeric dihydropyrones with an α-benzyloxy group (Figure 4) [18]. Use of $MgBr_2$ as Lewis acid (instead of BF_3•Et_2O) in the cyclocondensation reaction gave only **17** after acidic workup. The exclusive formation of **17** under $MgBr_2$ mediated conditions is the result of approach of the diene in an *exo* sense on the less hindered face of a Mg^{2+} chelated form of aldehyde **14** (see insert, Scheme 3).



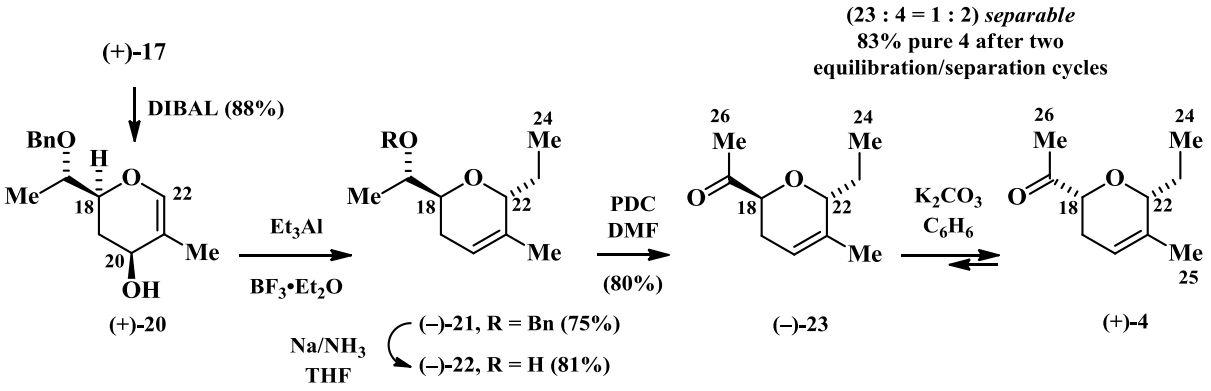
Scheme 4. Aldehyde-silyloxy diene cyclocondensation.



H[17]	H[19eq]		R	R[25]	R[23]		H[17]	H[19eq]	ref.
δ 3.48	δ 2.27	**18a**	Me	H	Et	**19a**	δ 3.68	δ 2.44	18
δ 3.72	δ 2.40	**18b**	H	H	Me	**19b**	δ 3.82	δ 2.53	18
δ 3.69	δ 2.36	**16**	H	Me	Me	**17**	δ 3.81	δ 2.56	this work

Figure 4. Characteristic proton chemical shifts of diastereomeric dihydropyrones.

Pyranone **17** underwent reduction with DIBAL via axial addition of hydride to give the pseudoglycal (+)-**20** as a single diastereomer (Scheme 5). Reaction of pseudoglycal **20** with the weak nucleophile triethylaluminum, in the presence of BF_3•Et_2O, gave a mixture of *trans*- and *cis*-dihydropyrans (8:1 ratio). The major diastereomer (-)-**21**, was obtained in good yield after column chromatography, and its structure was tentatively based on previous results from our laboratory as well as others on *C*-glycosidation reactions with trialkylaluminum [19]. Eventual transformation of **21** into known (+)-**4** corroborated this tentative assignment. Removal of the benzyl protecting group under dissolving metal conditions, followed by oxidation gave (-)-**23**. Base-catalyzed epimerization of the *trans*-ketone, in benzene, gave a separable mixture of **23** and **4** (1:2 ratio). Two equilibration/separation cycles gave pure (+)-**4** in 83% combined yield. By this route, the C17-C24 segment (+)-**4** was prepared from (*S*)-ethyl lactate in 8 steps and 22.2% overall yield.



Scheme 5. Synthesis of dihydropyran segment **4**.

Conclusion

The synthesis of the tetrahydropyran and dihydropyran segments of ambruticin were prepared from chiral pool precursors. The C1-C8 segment, (-)-**3**, was prepared from L-arabinose in 11 steps, 7.6% overall yield and the C17-C24 segment, (+)-**4**, was prepared from (*S*)-ethyl lactate in 8 steps, 22.2% overall yield. In both cases, the synthetic strategy relied on *C*-glycosylation followed by epimerization to the more stable *cis*-stereoisomers.

Acknowledgements

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Experimental Section

H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively unless otherwise indicated. High-resolution mass spectra were obtained from the Washington University Resource for Biomedical and Bioorganic mass spectrometry. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Anhydrous CH_2Cl_2 and anhydrous DMF were purchased from Aldrich Chemical Company. Reactions were performed in flame-dried glassware under an atmosphere of N_2 unless otherwise noted. Compounds **7**[4a], **14**[16], and **15**[17] were prepared by literature procedures.

2-Deoxy-1-*O*-methyl-5,6-*O*-(1-methylethylidene)-3,4-bis-*O*-(phenylmethyl)-L-*arabino*-hex-1-enitol (8).

To a solution of (methoxymethyl)triphenylphosphonium chloride (1.45 g, 4.24 mmol) in anhydrous THF (10 mL) under nitrogen at -78 °C was added a solution of

lithium diisopropylamine (1.5 mL, 2.0 M in benzene/THF, 3.0 mmol). The mixture was stirred for 30 min. A solution of **7** (0.477 g, 1.29 mmol) in anhydrous THF (5 mL), pre-cooled to -78 ºC, was added over a period of 10 min. After completion of the addition, the reaction mixture was warmed to room temperature and stirred for 20 min. The reaction mixture was diluted with ice-water, extracted several times with diethyl ether, and the combined extracts were washed with water, followed by brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-ethyl acetate = 9:1), to give a mixture of *E*/Z-isomers **8** (0.37 g, 72%) as a light yellow oil; $[\alpha]_D^{23}$ -21 (c = 0.91, $CHCl_3$). IR (neat): 2979, 2958, 2916, 2870, 1609, 1598, 1465, 1443, 1330, 1259, 1098, 967 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.27-7.39 (m, 10H), 6.47 (d, *J* = 13.0 Hz, 0.58H, C=C*H*(OMe)), 6.10 (d, *J* = 6.0 Hz, 0.42H, C=C*H*(OMe)), 3.73-4.84 (m, 9H), 3.62 (s, 1.3H, OMe), 3.53 (s, 1.7H, OMe), 1.42 (s, 3H), 1.34 (s, 3H). MS (FAB/KI) *m/z* 437 (calcd for $C_{24}H_{30}O_5K$ [M+K^+] *m/z* 437).

Methyl 2-deoxy-3,4-bis-*O*-(phenylmethyl)-α-L-*arabino*-hexopyranoside ((-)-9).

To a solution of **8** (2.52 g, 6.33 mmol) in CH_2Cl_2 (50 mL) at -78 °C was slowly added a solution of BBr_3 (0.65 mL, 1.0 M in CH_2Cl_2, 0.65 mmol). The color of the reaction solution immediately changed from light yellow to darkness and heat was released when the BBr_3 was added. After completion of addition, the reaction solution was gradually warmed to room temperature and stirred for 30 min. The reaction mixture was diluted with diethyl ether and washed with saturated aqueous $NaHCO_3$, followed by water, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-acetone = 9:1) to give (-)-**9** (1.72 g, 76%) as a pale oil; $[\alpha]_D^{23}$ -54.0 (c = 0.78, $CHCl_3$) [for D-enantiomer lit.[20] $[\alpha]_D^{30}$ = +69 (c 0.43, $CHCl_3$)]. IR (neat): 3600-3200, 3085, 3060, 3035, 2983, 2910, 1720, 1454, 1365, 1207, 1127, 1098, 1050, 1028, 987 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.39-7.27 (m, 10H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 3.0 Hz, 1H), 4.71-4.62 (m, 3H), 4.04-3.94 (m, 1H), 3.83-3.71 (m, 2H), 3.64 (dt, *J* = 10.0, 4.0 Hz, 1H), 3.50 (t, *J* = 12.0 Hz, 1H), 3.31 (s, 3H), 2.30 (ddd, *J* = 12.0, 4.5, 1.5 Hz, 1H), 1.78 (dd, *J* = 7.5, 6.0 Hz, 1H), 1.65 (ddd, *J* = 12.0, 10.0, 4.0 Hz, 1H). ^1H NMR spectral data for this compound was consistent with the literature values for the D-enantiomer[20]. MS (DCI/NH_3) *m/z* 376 (calcd for $C_{21}H_{26}O_5$•NH_4, [M+NH_4^+] *m/z* 376).

4,8-Anhydro-1,2,3,5-tetradeoxy-6,7-bis-*O*-(phenylmethyl)-L-*manno*-non-1-enitol ((-)-10).

A solution of **9** (1.01 g, 2.82 mmol) and allyl trimethylsilane (1.00 g, 8.76 mmol) in CH_2Cl_2 (30 mL) at 0 °C was treated with BF_3•Et_2O (0.85 mL, 0.98 g, 6.96 mmol).

The color of the reaction mixture changed from light yellow to darkness immediately after adding the Lewis acid. The reaction solution was stirred at 0 °C for 30 min under nitrogen. The mixture was diluted with diethyl ether, followed by slow addition of saturated aqueous $NaHCO_3$. The organic layer was separated and washed with saturated aqueous $NaHCO_3$, followed by water, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-acetone = 9:1) to give (-)-**10** as an oil (0.552 g, 53%); $[\alpha]_D^{23}$ -36.4 (c = 0.87, $CHCl_3$). IR (neat): 3600-3200, 3065, 3030, 2926, 2874, 1454, 1365, 1209, 1099, 1048, 1028, 999 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.27-7.39 (m, 10H), 5.82-5.67 (m, 1H), 5.18-5.01 (m, 2H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.65-4.41 (m, 3H), 3.59-3.86 (m, 4H), 4.08-3.99 (m, 1H), 3.43 (t, *J* = 7.0 Hz, 1H), 2.46 (pent of d, *J* = 7.0, 1.0 Hz, 1H), 2.11 (pent, *J* = 7.0 Hz, 1H), 2.01 (dt, *J* = 14.0, 4.5 Hz, 1H), 1.92 (t, *J* = 7.0 Hz, 1H), 1.80-1.69 (m, 1H). ^{13}C NMR ($CDCl_3$): δ = 138.3, 138.2, 134.4, 128.4, 128.0, 127.8, 127.7, 117.3, 77.6, 76.5, 74.3, 73.2, 71.4, 70.7, 62.3, 36.6, 32.7. FAB-HRMS *m/z* 369.2065 (calcd for $C_{23}H_{29}O_4$ [M+H^+] *m/z* 369.2066).

3,7-Anhydro-2,4-dideoxy-5,6-bis-*O*-(phenylmethyl)-L-*manno*-octose (-)-11.

A solution of **10** (0.552 g, 1.50 mmol) in methanol (10 mL) was cooled to -78 °C in a dry ice/acetone bath. The system was purged with carrier gas (compressed air) for 20 min and then ozone (generated from compressed air with a Welsbach apparatus) was bubbled through the solution until a blue color persisted. The system was purged with carrier gas until the blue color disappeared. Dimethyl sulfide (0.5 mL) and water (0.2 mL) were added to the reaction mixture and this was stirred for 3 h. After concentration in vacuo, the reaction mixture was diluted with diethyl ether and water. The organic layer was separated and washed with water, followed by brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexane-acetone = 13:7), to give (-)-**11** (0.455 g, 82%) as an oil; $[\alpha]_D^{23}$ -10.5 (c = 1.27, $CHCl_3$). IR (neat): 3600-3200, 3085, 3060, 3035, 2926, 2876, 1723, 1497, 1454, 1365, 1314, 1270, 1208, 1097, 1028 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 9.76 (t, *J* = 1.0 Hz, 1H, CHO), 7.39-7.26 (m, 10H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.66-4.53 (m, 3H), 4.04 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.81-3.73 (m, 2H), 3.59 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.39 (t, *J* = 6.0 Hz, 1H), 2.84 (ddd, *J* = 17.0, 9.0, 2.0 Hz, 1H), 2.52 (ddd, *J* = 17.0, 4.5, 1.0 Hz, 1H), 2.00-1.91 (m, 1H), 1.83-1.73 (m, 1H); signal for OH not observed. ^{13}C NMR ($CDCl_3$): δ = 200.0, 138.0, 128.5, 127.9, 127.8, 127.6, 74.90, 74.85, 73.3, 71.5, 63.5, 61.0, 47.2, 32.4. MS (DCI/NH_3) *m/z* 388 (calcd for $C_{22}H_{26}O_5$•NH_4 [M+NH_4^+] *m/z* 388).

Methyl 3,7-anhydro-2,4-dideoxy-5,6-bis-*O*-(phenylmethyl)-L-*manno*-octanoate (12).

To a solution of **11** (0.386 g, 1.04 mmol) in DMF (4 mL) containing methanol (0.1 mL) was added pyridinium dichromate (0.453 g, 1.20 mmol). The mixture was stirred at room temperature for 2 h, and then heated at 50 °C overnight. After cooling, the mixture was diluted with diethyl ether and water. The organic layer was separated and washed with 1 N aqueous HCl, followed by saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-acetone = 13:7), to give **12** (0.381 g, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 7.39-7.27 (m, 10H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.55-4.39 (m, 3H), 4.08 (ddd, *J* = 12.0, 7.5, 4.0 Hz, 1H), 3.88-3.74 (m, 2H), 3.69 (s, 3H), 3.53 (ddd, *J* = 12.0, 9.0, 3.0 Hz, 1H), 3.34 (t, *J* = 5.0 Hz, 1H), 2.68 (dd, *J* = 16.5, 10.0 Hz, 1H), 2.43 (dd, *J* = 16.5, 7.5 Hz, 1H), 2.01-1.91 (m, 1H), 1.81-1.72 (m, 1H) ; signal for OH not observed. ^{13}C NMR ($CDCl_3$): δ = 193.5, 138.0, 128.6, 127.9, 127.8, 127.6, 75.1, 74.9, 73.1, 71.5, 65.1, 60.8, 52.0, 38.3, 32.2. FAB-HRMS *m/z* 401.1963 (calcd for $C_{23}H_{29}O_5$ [M+H$^+$] *m/z* 401.1964).

Methyl 3,7-anhydro-2,4-dideoxy-5,6-bis-*O*-(phenylmethyl)-L-*gluco*-octanoate ((-)-3).

To a solution of **12** (0.381 g, 0.0953 mmol) in toluene (2 mL) was added 25% methanolic NaOMe (0.2 mL). The color of the reaction mixture changed from colorless to yellow immediately upon addition. The reaction mixture was stirred at 60 °C for 6 h in an open flask. Half of the solvent was evaporated during the reaction and some white precipitate was observed. The reaction mixture was partitioned between ethyl acetate and 1N HCl. The organic layer was separated, and the aqueous layer was extracted several times with ethyl acetate. The combined organic layers were washed with 1N HCl, then water, followed by brine, dried ($MgSO_4$) and concentrated to give **13** as an oil (0.301 g, 82%). This compound was used in the next step without further characterization. To a solution of **13** (0.155 g, 0.040 mmol) in CH_2Cl_2 (1 mL) at room temperature was added methanol (0.2 mL), ethyl dimethylaminopropyl carbodiimide hydrochloride (0.211 g, 0.11 mmol) and 1-hydroxy-benzotriazole hydrate (0.058 g, 0.043 mmol) and the mixture was stirred overnight. The reaction mixture was diluted with diethyl ether and water, the layers were separated and the aqueous layer was extracted several times with diethyl ether. The combined organic layers were washed with water, followed by brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-acetone = 9:1), to give (-)-**3** (0.124 g, 77%) as an oil. $[\alpha]_D^{23}$ -9.6 (c = 0.73, $CHCl_3$); +3.27 (c = 0.98, 95% ethanol); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39-7.28 (m, 10H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 3.93-3.85 (m, 1H), 3.83 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.70 (s, 3H), 3.75-3.65 (m, 2H), 3.44 (t, *J* = 10.0 Hz, 1H), 3.36-3.31 (m, 1H), 2.62 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.46 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.24 (ddd, *J* = 12.5, 6.0, 3.0 Hz, 1H), 1.42 (q, *J* = 12.5 Hz, 1H) ; signal for OH not observed. ^{13}C NMR ($CDCl_3$) δ 171.1, 138.4, 138.3, 128.4, 128.0, 127.7, 127.6, 80.5, 79.0, 78.2, 75.0, 71.8, 71.5, 62.4, 51.7, 40.4, 36.6. FAB-HRMS *m/z* 401.1963 (calcd for $C_{23}H_{29}O_5$ [M+H$^+$] *m/z* 401.1964).

(2*S*)-2,3-Dihydro-5-methyl-2-[(1*S*)-1-(phenylmethoxy)ethyl]-4*H*-pyran-4-one ((+)-17).

To a solution of **14** (1.27 g, 7.74 mmol) in dry THF (30 mL) at 0 °C was added a freshly prepared ethereal solution of $MgBr_2$ (4.0 mL, 2.2 M, prepared from 1,2-dibromoethane and magnesium turnings). This solution was stirred at 0 °C for 10 min and then a solution of **15** (3.04 g, 15.3 mmol) in dry THF (30 mL) was added. The reaction mixture was slowly warmed to room temperature. After 14 h the reaction mixture was washed with saturated aqueous $NaHCO_3$ and the combined aqueous layers were extracted several times with ether. The combined extracts were dried ($MgSO_4$) and concentrated. The black residue was dissolved in CH_2Cl_2 (75 mL) and treated with trifluoroacetic acid (4 mL). The reaction mixture was stirred at room temperature in air for 3 h and was then washed with saturated aqueous $NaHCO_3$ and the combined aqueous layers were extracted several times with CH_2Cl_2. The organic layers were dried ($MgSO_4$), concentrated, and the residue was purified by column chromatography (SiO_2, hexanes-ethyl acetate = 5:1) to give (+)-**17** (1.64 g, 86%) as a yellow oil: $[\alpha]_D^{23}$ +120 (c 0.330, $CHCl_3$). IR (neat): 2976, 2928, 2893, 1668, 1621, 1455, 1379, 1299, 1165, 1104 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.39-7.28 (m, 6H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.34 (ddd, *J* = 14.7, 3.8, 3.6 Hz, 1H), 3.69 (qd, *J* = 6.5, 4.7 Hz, 1H), 2.79 (dd, *J* = 16.4, 14.7 Hz, 1H), 2.36 (dd, *J* = 16.7, 3.2 Hz, 1H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (d_6-acetone): δ = 193.1, 160.3, 140.3, 129.6, 129.0, 128.8, 114.6, 82.8, 76.3, 72.5, 38.9, 16.1, 11.3; FAB-HRMS *m/z* 253.1428 (calcd for $C_{15}H_{18}O_3Li$ [M+Li$^+$] *m/z* 253.1416).

(2*R*)-2,3-Dihydro-5-methyl-2-[(1*S*)-1-(phenylmethoxy)ethyl]-4*H*-pyran-4-one (16) and (2*S*)-2,3-Dihydro-5-methyl-2-[(1*S*)-1-(phenylmethoxy)ethyl]-4*H*-pyran-4-one ((+)-17).

To a solution of **14** (0.932 g, 5.67 mmol) in anhydrous CH_2Cl_2 (10 mL) at -78 °C was added a solution of BF_3•Et_2O (1.10 mL, 9.07 mmol) in anhydrous CH_2Cl_2 (60 mL) was added. After 10 min, a solution of **15** (1.631 g, 8.505 mmol) in anhydrous CH_2Cl_2 (10 mL) was added. The reaction mixture was slowly allowed to warm to room temperature over 18 h and then worked up with TFA

in a fashion similar to the preparation of **17**. The residue was purified by column chromatography (SiO_2, hexanes-ethyl acetate = 3:1), to afford an inseparable mixture of **16** and **17** (1.6:1) as determined by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$) (in addition to the signals reported above for **17**, the following signals were assigned to **16**) δ 7.39-7.27 (m, 6H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.33 (ddd, *J* = 14.4, 3.8, 3.8 Hz, 1H), 3.81 (qd, *J* = 6.5, 4.1 Hz, 1H), 2.68 (dd, *J* = 16.7, 14.4 Hz, 1H), 2.56 (dd, *J* = 16.7, 3.5 Hz, 1H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 192.3, 158.7, 137.7, 128.1, 127.5, 127.3, 113.7, 82.1, 75.2, 71.7, 37.6, 16.4, 11.3.

3,7-Anhydro-1,4,6-trideoxy-6-methyl-2-*O*-(phenylmethyl)-D-xylo-hept-6-enitol ((+)-**20).**

To a solution of **17** (6.190 g, 25.16 mmol) in benzene (370 mL) cooled to 0 °C was added a solution of DIBAL (50.0 mL, 1.0 M in hexanes, 50 mmol). The reaction mixture was stirred for 3 h at 0 °C and then was quenched by the dropwise addition of saturated aqueous $NaHCO_3$ solution (200 mL). The layers were separated and the aqueous layers were extracted several times with ethyl acetate. The organic layers were dried ($MgSO_4$), filtered through celite in a sintered glass funnel, and concentrated. The residue was purified by chromatography (SiO_2, hexanes-ethyl acetate = 4:1) to give (+)-**20** (5.48 g, 88%) as a colorless solid: mp 48-50 °C; $[\alpha]_D^{23}$ +18 (c 0.214 $CHCl_3$). IR (KBr): 3231, 2955, 2880, 1667, 1497, 1454, 1372, 1350, 1057, 981 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.36-7.27 (m, 5H), 6.19 (s, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.27 (dd, *J* = 13.2, 7.6 Hz, 1H), 3.94 (ddd, *J* = 11.1, 4.7, 2.4 Hz, 1H), 3.64 (qd, *J* = 6.3, 4.7 Hz, 1H), 2.19 (ddd, *J* = 13.2, 6.5, 2.4 Hz, 1H), 1.82 (ddd, *J* = 13.2, 11.0, 8.9 Hz, 1H), 1.61 (s, 3H), 1.52 (d, *J* = 7.3 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ□= 140.3, 138.5, 128.5, 127.9, 127.7, 111.6, 77.2, 75.5, 71.5, 66.0, 33.9, 15.6, 14.1. Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.29; H, 7.87%.

(2*R*,6*S*)-2-Ethyl-5,6-dihydro-3-methyl-6-[(1*S*)-1-phenylmethoxy)ethyl]-2H-pyran ((-)-**21)**

To a solution of **20** (2.691g, 10.85 mmol) in anhydrous CH_2Cl_2 (210 mL), cooled to -40 °C, was added a solution of triethylaluminum (2.2 mL, 1.0 M in hexanes, 0.037 mol,), followed by BF_3•Et_2O (1.4 mL, 0.011 mol). The reaction mixture was stirred at -40 ºC for 3 h and at 0 °C for 1.5 h and then was quenched with saturated aqueous sodium potassium tartrate solution (100 mL). The biphasic reaction mixture was allowed to warm to room temperature, the layers were separated, and the aqueous layer was extracted several times with CH_2Cl_2. The organic layers were dried ($MgSO_4$) and concentrated giving the crude material as a 1:8 ratio of *cis* and *trans* isomers. Separation of this crude mixture by column chromatography (SiO_2, hexanes-ethyl acetate = 75:1) afforded pure (-)-**21** (2.121 g, 75%) as a colorless oil; $[\alpha]_D^{23}$ -70 (c = 0.26, $CHCl_3$). IR (neat): 2973, 2875, 1741, 1497, 1454, 1374, 1207, 1101, 1050, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.40-7.22 (m, 5H), 5.46 (ddd, *J* = 3.5, 1.8, 1.8 Hz, 1H), 4.67 (s, 2H), 3.89 (dd, *J* = 6.7, 6.7 Hz, 1H), 3.62 (qd, *J* = 5.6, 3.5 Hz, 1H), 3.53 (ddd, *J* = 12.0, 6.4, 6.4 Hz, 1H), 2.12 (dddd, *J* = 17.0, 10.6, 4.7, 2.3 Hz, 1H), 1.86-1.74 (m, 1H), 1.66-1.54 (m, 5H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 139.3, 136.5, 128.5, 128.1, 127.6, 119.0, 78.5, 77.9, 72.3, 70.6, 27.5, 24.8, 20.5, 16.5, 11.4; FAB-HRMS *m/z* 267.1941 (calcd for $C_{17}H_{24}O_2Li$ [M+Li$^+$] *m/z* 267.1936).

(α*S*,2*S*,6*R*)-6-Ethyl-3,6-dihydro-α,5-dimethyl-2*H*-pyran-2-methanol ((-)-**22).**

In a two necked flask cooled to -78 °C was condensed ammonia (30 mL). A solution of **21** (1.003 g, 3.858 mmol) in THF (15 mL) was added, followed by the careful slow addition of small pieces of sodium metal until the reaction became and remained blue in color (1.495 g, 6.173 mmol). The reaction mixture was stirred under N_2 for 2.5 h. Solid NH_4Cl (4.186 g, 78.26 mmol) was then added portion-wise until the reaction mixture became colorless. The cooling bath was removed and the ammonia was slowly allowed to evaporate under N_2. After the ammonia has completely evaporated, THF (20 mL) was added followed by the drop-wise addition of isopropanol (5 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted several times with ethyl acetate. The organic layers were dried ($MgSO_4$), concentrated, and the crude oil was purified by chromatography (SiO_2, ethyl acetate-hexanes = 0 → 20% gradient) affording (-)-**22** (0.528 g, 81%) as a colorless oil; $[\alpha]_D^{23}$ -78.4 (c 0.340, $CHCl_3$). IR (neat): 3465, 2972, 2932, 2875, 1453, 1367, 1261, 1107, 1042, 926, 891 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 5.46 (ddd, *J* = 6.2, 2.9, 1.5 Hz, 1H), 3.87 (dd, *J* = 7.0, 6.5 Hz, 1H), 3.62 (qd, *J* = 7.2, 6.5 Hz, 1H), 3.36 (ddd, *J* = 9.1, 7.6, 5.3 Hz, 1H), 1.96-1.88 (m, 2H), 1.67-1.55 (m, 5H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H) ; signal for OH not observed. ^{13}C NMR ($CDCl_3$): δ□= 136.2, 118.3, 78.2, 71.5, 70.7, 27.5, 24.5, 20.2, 18.3, 11.3. EI-HRMS *m/z* 170.1311 (calcd for $C_{10}H_{18}O_2$ *m/z* 170.1307).

1-((2*S*,6*R*)-6-Ethyl-3,6-dihydro-5-methyl-2*H*-pyran-2-yl)ethanone ((-)-**23)**

To a solution of **22** (1.222 g, 7.188 mmol) in anhydrous DMF (80 mL) was added pyridinium dichromate (13.491 g, 35.880 mmol). The reaction mixture was stirred at room temperature for 18 h and was then partitioned between ether and water. The layers were separated, the aqueous layer was extracted several times with ether, and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude oil was adsorbed onto silica and purified

by chromatography (SiO_2, hexanes-ethyl acetate = 8:1) to give (-)-**23** (0.971 g, 80%) as a colorless oil; $[\alpha]_D^{23}$ -129.2 (c 0.3320, $CHCl_3$). IR (neat): 2967, 2934, 2876, 1717, 1453, 1355, 1120, 1053, 924 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 5.49 (ddd, *J* = 6.2, 3.5, 1.8 Hz, 1H), 4.06 (dd, *J* = 7.9, 5.9 Hz, 1H), 4.00 (br d, *J* = 9.7 Hz, 1H), 2.24 (s, 3H), 2.22-2.14 (m, 2H), 1.70 (s, 3H), 1.74-1.49 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 209.6, 136.0, 118.1, 78.1, 73.3, 26.8, 26.2, 24.7, 20.1, 10.7; EI-HRMS *m/z* 168.1150 (calcd for $C_{10}H_{16}O_2$ *m/z* 168.1136).

1-((2*R*, 6R)-6-Ethyl-3, 6-dihydro-5-methyl-2*H*-pyran-2-yl)ethanone ((+)-4)

To a solution of **23** (0.911 g, 5.35 mmol) in benzene (50 mL) was added methanolic potassium carbonate (5 mL). The reaction mixture became bright yellow in color and was stirred at room temperature for 63 h. The reaction mixture was then washed with 1.0 M HCl (2 x 100 mL) and extracted several times with ether. The organic layers were dried ($MgSO_4$) and concentrated affording a mixture of diastereomers **4** and **23** (2:1 by ^1H NMR integration). Separation of the mixture by column chromatography (SiO_2, hexanes-ethyl acetate = 75:1) gave **4** (0.562 g, 62%) followed by **23** (0.330 g, 36%). The recovered **23** isomer was resubjected to the above epimerization-separation procedure. (+)-**4**: $[\alpha]_D^{23}$ +172 (c 0.248, $CHCl_3$) [lit.[9] $[\alpha]_D$ +191.7 (c 1.57, $CHCl_3$); lit.[10] $[\alpha]_D^{20}$ +181 (c 0.257, $CDCl_3$),]; IR (neat): 2966, 2936, 2879, 1721, 1435, 1352, 1229, 1116, 1058, 927 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.60-5.33 (m, 1H), 4.13-4.05 (m, 1H), 3.92 (dd, *J* = 10.4, 4.4 Hz, 1H), 2.25 (s, 3H), 2.21-2.00 (m, 2H), 1.81 (ddq, *J* = 14.9, 10.9, 3.5 Hz, 1H), 1.60 (ddd, *J* = 2.4, 2.4, 1.4 Hz, 3H), 1.54 (ddq, *J* = 14.1, 7.0, 7.0 Hz, 1H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 210.0, 135.7, 119.7, 79.0, 78.5, 27.6, 26.1, 25.9, 19.2, 9.0.

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