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Carbohydrate Research 343 (2008) 1743–1753
Carbohydrate RESEARCH

Synthesis of octahydropyrano[3,2-*b*]pyrrole-2-carboxylic acid derivatives from D-mannose

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Received 25 November 2007; received in revised form 6 March 2008; accepted 10 March 2008
Available online 15 March 2008

Abstract—Bicyclic amino acids are useful building blocks in synthesizing biologically active molecules and peptidomimetics. 2-Carboxy-6-hydroxyloctahydroindole (Choi) is a novel bicyclic amino acid found in the marine natural products aeruginosins. Many compounds in the aeruginosin family exhibit inhibition activities toward serine proteases including thrombin and trypsin. The unique Choi structure is the common feature of this family of oligopeptides and this motif is important for their observed biological activities. To better understand the influence of the stereochemistry of the Choi core structure on the inhibition activities, we have previously synthesized ring-oxygenated variants from glucose. The preparation of octahydro-pyrano[3,2-*b*]pyrrole 2-carboxylic acids from D-mannose is reported here. These novel bicyclic amino acids can be used in the preparation of aeruginosin analogs, as well as conformationally constrained peptidomimetics or other biologically active molecules.

Keywords: Aerguginosin; Octahydroindole 2-carboxylic acid; Rigid conformation; Thrombin inhibitor

1. Introduction

Structurally constrained bicyclic amino acids are useful building blocks for the preparation of peptidomimetics and other biologically important molecules.[1–3] Several examples of these types of compounds (**1**–**5**) are shown in Chart 1. The conformationally constrained synthetic bicyclic amino acids **1**–**3** has been used in the preparation of thrombin inhibitors such as **6**–**8** (Chart 2).[4–6] 2-Carboxy-6-hydroxyloctahydroindole (Choi) **4** is another conformationally rigid amino acid, which is the core structure present in the marine natural products called aeruginosins.[7–11] The dihydroxylated compound **5** is the core structure of similar natural products, dysinosins (Chart 3).[12,13]

A majority of the naturally occurring aeruginosins share the same stereochemistry and substitution pattern although some exceptions have been reported. Several structures of aeruginosins and related compounds (**9**–**12**) are shown in Chart 3.[11,12] Many aeruginosins are found to be inhibitors of serine proteases including blood coagulation factors, such as thrombin and factor VIIa. The unusual octahydroindole core structure is important for their observed biological activities. Direct inhibition of thrombin has demonstrated utility in treating thrombosis-related disorders;[13] however, more

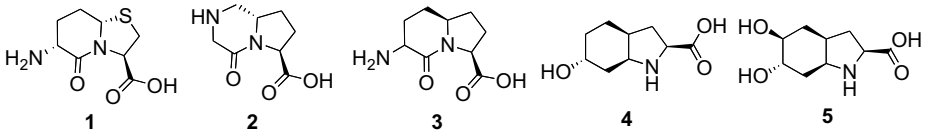

Chart 1. Structures of bicyclic amino acids that are useful building blocks.

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doi:10.1016/j.carres.2008.03.017

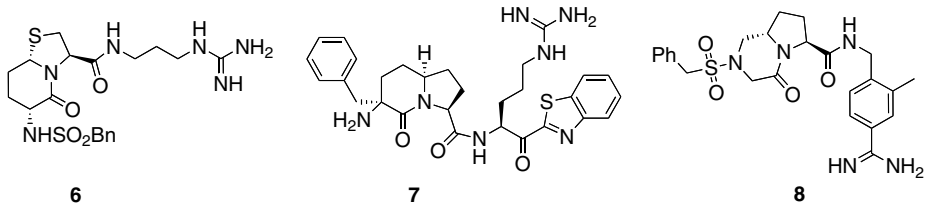


Chart 2. Structures of thrombin inhibitors containing fused amino acids.

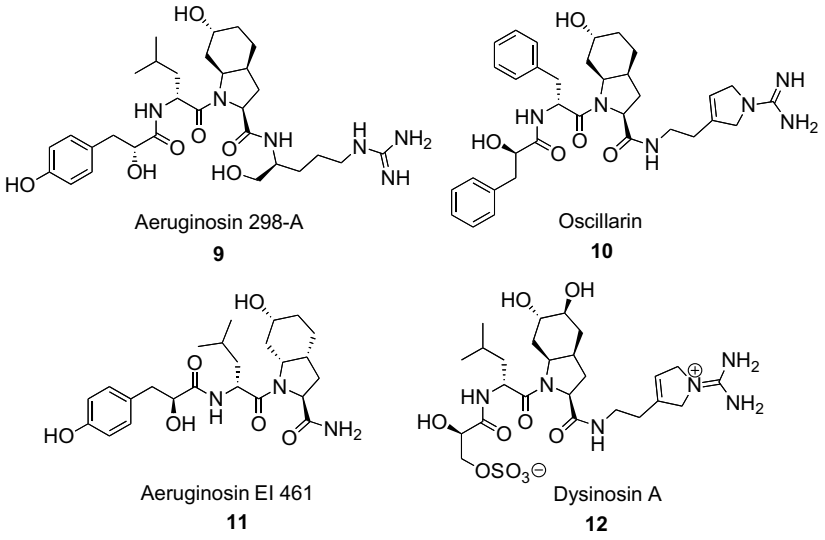


Chart 3. Structures of aeruginosins and related compounds.

efficient oral anticoagulants remain elusive. In this regard, aeruginosins are promising natural products that can be explored and optimized to obtain potent and selective thrombin inhibitors.

Because of the biological importance of this class of molecules, the total synthesis of Aeruginosin 298-A (Chart 3),[14–17] Aeruginosin EI461,[18] Oscillarin,[11] and Dysinosins[19,20] have been accomplished by a few research groups. Several syntheses of the Choi fragment and analogs have also been reported.[21–25] In addition, aeruginosin analogs have also been designed and synthesized in the search for improved thrombin inhibitors.[26–28] We were intrigued by this unusual amino acid and developed an efficient method to synthesize protected ring-oxygenated variants (**14**, **15**) from D-glucose **13** as shown in Figure 1.[25,29] Sugars are readily available renewable resources, and they contain abundant chiral centers that can be used as chiral pool starting materials for the synthesis of more complex molecules. We have also synthesized the bicyclic amino acid **16** using L-glucose as the starting material and tetrapeptides containing the Choi variant **16**.[29] We envisioned that by using a different monosaccharide such as D-mannose as the starting material, bicyclic amino acids **17** and **18** can be prepared using a similar method for the preparation of **14** and **15**. Similarly, if D-galactose is used as the starting material, the *trans O*-Choi analogs **19** can be synthesized. These ring-oxygenated variants of 2-carboxy-6-hydroxyoctahydroindole can be used as surrogates of Choi in the design and synthesis of

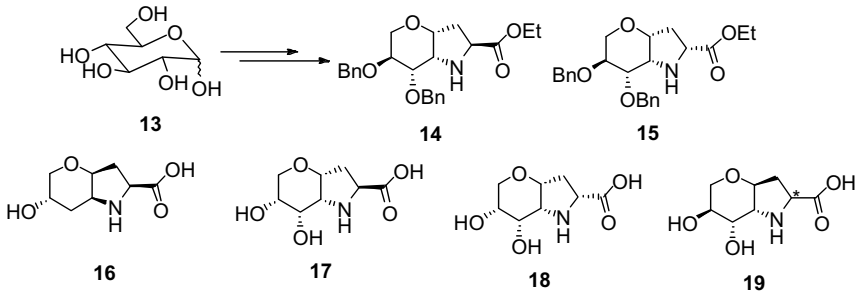


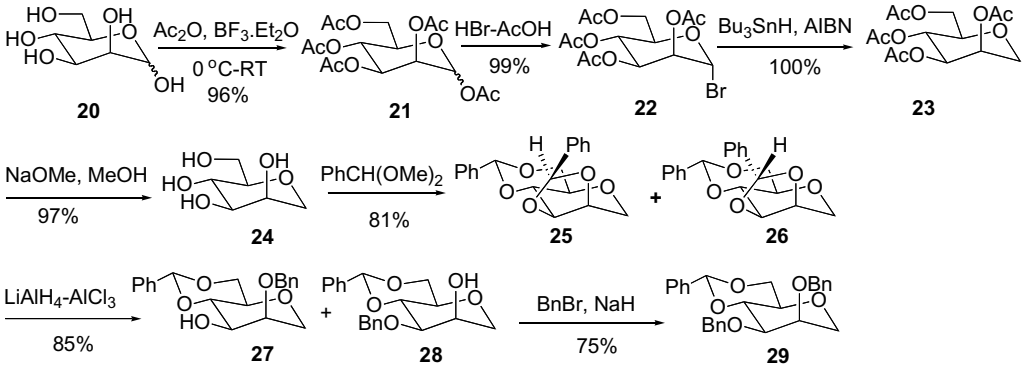
Figure 1. *O*-Choi analogs that can be synthesized from monosaccharides.

aeruginosin-based thrombin inhibitors. These compounds can also be used in synthesizing peptidomimetics with particular conformational features. We report here the progress on the preparation of Choi analogs using D-mannose and D-galactose as the starting materials.

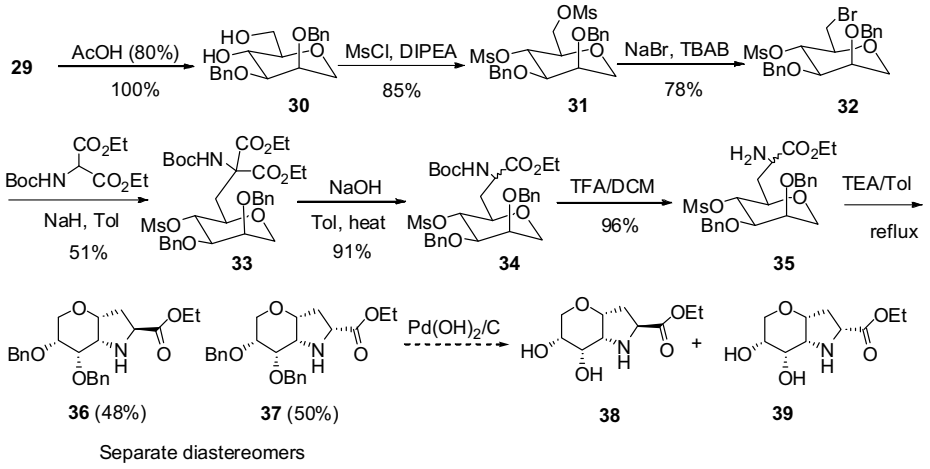
2. Results and discussion

To synthesize the *O*-Choi analogs from D-mannose, a modified route of our previous approach using D-glucose as the starting material was used.[25] As shown in Schemes 1 and 2, D-mannose (**20**) was smoothly converted to 1,5-anhydro-mannitol **24** in four steps using our previous procedure.[25] Because the hydroxyl groups at C-2 and C-3 in compound **24** are cis, selective protection of the C-4 and C-6 hydroxyl groups as an acetal proved to be difficult, so the corresponding diacetals were synthesized instead (Scheme 1). The diastereomeric acetals **25** and **26** were obtained in approximately a 1:1 ratio. Selective reduction of this diacetal mixture under carefully monitored conditions afforded the ring opening products **27** and **28**, in which only the five membered rings were reductively opened. The mixture of these two intermediates was then benzylated to give the only dibenzylated product, **29**.

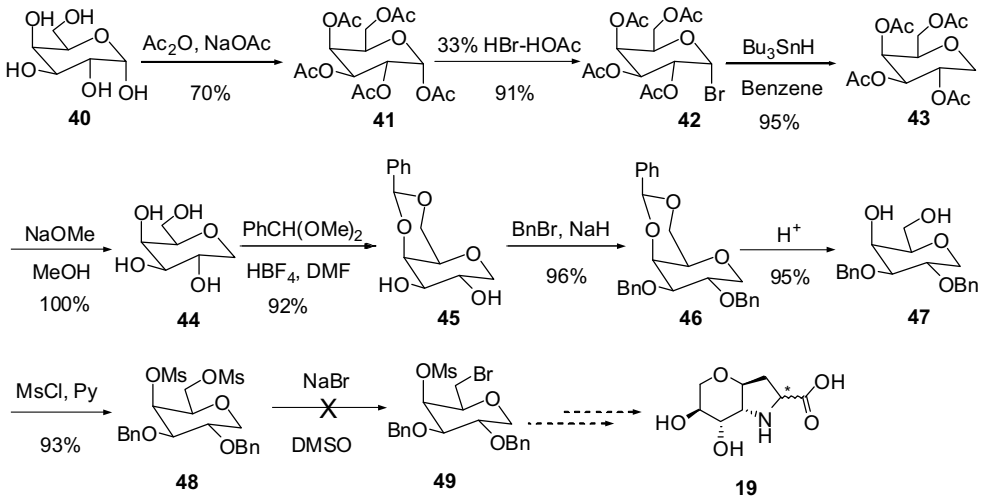
The dibenzylated compound **29** was then successfully converted to the protected *O*-Choi analogs **36** and **37** as shown in Scheme 2. The benzylidene acetal in intermediate **29** was quantitatively hydrolyzed using concentrated acetic acid to afford diol **30**. Dimesylation of both hydroxyl groups was achieved in good yield by reacting **30** with methanesulfonyl chloride in dichloromethane. Selectively substituting the primary mesylate in **31** with bromide using sodium bromide and a catalytic amount of tetrabutylammonium bromide afforded compound **32**. Displacement of the 6-bromide with *N*-Boc protected diethylaminomalonate under basic conditions gave compound **33**, which was decarboxylated in very good yield to give intermediate **34** as a 1:1 ratio of diastereomers. *N*-Boc deprotection of **34** afforded **35** and subsequent intramolecular cyclization led to the protected ring-oxygenated Choi analogs **36** and **37** in good yield. These two compounds can be separated via chromatography and can be deprotected or used



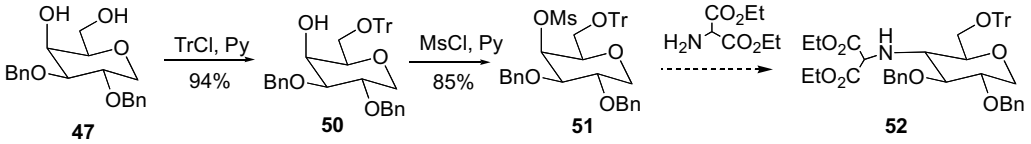
Scheme 1. Preparation of the protected 1,5-anhydro-D-mannitol intermediate **29**.



Scheme 2. Synthesis of dihydroxyl *O*-Choi variants from D-mannose.



Scheme 3. Synthesis of intermediate **48** from D-galactose.



Scheme 4. An alternative route for converting D-galactose derivatives to Choi analogs.

directly in coupling reactions with other compounds. In the decarboxylation, there is no diastereoselectivity for the stereocenter generated, and a 1:1 ratio of diastereomers of **34** was obtained. If the decarboxylation reaction is executed after the cyclization, there will be a facial selectivity favoring one isomer over the other. However, it is also possible to epimerize this position if needed.

The work described above and our previous studies have shown that we can successfully prepare Choi analogs from D-glucose and D-mannose. However, we have encountered problems when using D-galactose (**40**) to prepare Choi analogs with trans ring junctures. Initially, we had hoped that the synthesis could be accomplished by a method similar to the one starting from D-mannose. To this end, as shown in Scheme 3, we could successfully prepare dimesylate **48**. However, the 6-mesylate group in **48** could not be converted to the corresponding bromide due to steric hindrance posed by the axial group at 4-position.

Therefore, a modified route was explored in which the alkylation sequence was switched. As shown in Scheme 4, this approach involves the protection of the 6-hydroxyl group in **47** with a protecting group such as trityl and displacement of the 4-mesylate group to give the key intermediate **52**. Compound **51** can be prepared smoothly; however, several attempts to displace the 4-mesylate group in **51** with diethylaminomalonate proved problematic. The use of a smaller or electron withdrawing protecting group on O-6, instead of trityl, may give positive results and we are currently exploring alternative routes to synthesize trans-fused Choi analogs.

In conclusion, we have efficiently synthesized octahydro-pyrano[3,2-*b*]pyrrole-2-carboxylic acid derivatives starting from D-mannose. The synthesis of trans-fused bicyclic amino acids from D-galactose cannot be achieved using a similar method due to steric hindrance at the 4-position, which prevents a key substitution reaction. Therefore, alternative approaches are necessary to complete the synthesis of these bicyclic amino acids from D-galactose. The readily available monosaccharides including D-glucose, D-mannose, and D-galactose are useful chiral pool materials and they are stereoisomers in which the configuration of one hydroxyl group differs from each other. From the data presented above, this difference significantly affects the reaction outcome. The conformationally rigid bicyclic amino acids synthesized here can be used in the synthesis of aeruginosin analogs or peptidomimetics with special structural requirement.

3. Experimental

3.1. General methods

All reagents, solvents, and starting materials were purchased from Aldrich or Lancaster unless otherwise specified. Anhydrous solvents were purchased from

Aldrich in sure-seal bottles and used directly without further treatment. ^{1}H and ^{13}C NMR spectra were acquired on Varian 400 MHz NMR spectrometer. Melting points were measured using a Fisher–Jones melting point apparatus. Typically thin layer chromatography (60 Å pore, UV254, phosphomolybdic acid as the staining agent) was used to monitor reactions. Silica Gel (230–400 meshes) was used for flash chromatography. Solvents were generally removed under reduced pressure using a rotary evaporator (Buchi rotavapor R200).

3.2. 1,2,3,4,6-Penta-*O*-acetyl-α-D-mannopyranose (21)

D-Mannose **20** (19.0 g, 106 mmol) was dissolved in Ac_2O (55.0 mL, 582 mmol) and the mixture was cooled to 0 °C. Boron trifluoride diethyletherate (8.00 mL, 64.0 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature for 1.5 h. The mixture was poured into a beaker containing 200 mL of ice and stirred for 1 h. The product was extracted three times using CH_2Cl_2, the organic phase was washed with saturated $NaHCO_3$ and water and then dried over Na_2SO_4. After filtration, concentration, and drying under vacuum, the product was obtained as a brown oil in 96% yield (39.9 g, 102 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 5.86 (d, 1H, $J = 1.0$ Hz), 5.49 (dd, 1H, $J = 3.2$, 0.9 Hz), 5.29 (t, 1H, $J = 9.9$ Hz), 5.13 (dd, 1H, $J = 9.9$, 3.3 Hz), 4.31 (dd, 1H, $J = 12.4$, 5.4 Hz), 4.14 (dd, 1H, $J = 12.4$, 2.3 Hz), 3.80 (m, 1H), 2.22 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 170.2, 169.8, 169.4, 169.3, 168.0, 90.1, 72.8, 70.3, 67.9, 65.2, 61.8, 20.4. HRMS calcd for $C_{16}H_{22}O_{11}Na$ $[M+Na]^+$ 413.1060, found 413.1055.

3.3. 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl bromide (22)[30]

Compound **21** (19.8 g, 51.0 mmol) was mixed with Ac_2O (14.4 mL, 152 mmol) and the mixture was cooled to 0 °C. HBr (33% in acetic acid, 45.0 mL, 2.57 mmol) was added to the solution, which was stirred at room temperature for 4.5 h. The mixture was then poured into a beaker containing about 200 mL of ice, stirred for 10 min, and extracted with dichloromethane. The organic phase was washed with saturated $NaHCO_3$ and water and then dried over Na_2SO_4. After filtration and concentration, the crude mixture was dried under high vacuum and the product was obtained as a light yellow oil in 99% yield (20.9 g, 50.8 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 6.29 (br s, 1H), 5.71 (dd, 1H, $J = 10.2$, 3.4 Hz), 5.44 (dd, 1H, $J = 3.4$, 1.6 Hz), 5.36 (t, 1H, $J = 10.2$ Hz), 4.32 (dd, 1H, $J = 12.5$, 4.9 Hz), 4.21 (m, 1H), 4.13 (dd, 1H, $J = 12.4$, 2.1 Hz), 2.17 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 170.5, 169.7, 169.6, 169.7, 83.0, 72.8, 72.1, 67.9, 65.3, 61.4, 20.8, 20.7, 20.6, 20.5.

3.4. 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-mannitol (23)

Compound **22** (16.8 g, 40.9 mmol) was dissolved in anhydrous benzene (20.0 mL). Tributyltin hydride (11.0 mL, 41.5 mmol) and AIBN (a few mg) were added to the solution and the mixture was refluxed for 1.5 h. The mixture was then cooled to room temperature and diluted with diethyl ether (100 mL). Potassium fluoride (7.20 g, 124 mmol in 30 mL of water) was added to the mixture and stirred for 2 h. The precipitated Bu_3SnF was filtered out and the water phase separated from the ether. The organic phase was washed with water and dried over Na_2SO_4. After filtration, concentration, and drying under high vacuum, the product was obtained as a light yellow oil in quantitative yield (13.6 g, 40.9 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 5.27 (br s, 1H), 5.24 (t, 1H, $J = 10.2$ Hz), 5.01 (dd, 1H, $J = 10.0$, 3.5 Hz), 4.19 (dd, 1H, $J = 12.3$, 5.6 Hz), 4.08 (dd, 1H, $J = 12.2$, 2.0 Hz), 4.01 (dd, 1H, $J = 13.2$, 1.8 Hz), 3.64 (d, 1H, $J = 13.2$ Hz), 3.55 (m, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 170.6, 170.3, 170.0, 169.5, 76.6, 71.5, 68.5, 68.0, 66.0, 62.6, 20.8, 20.7, 20.6, 20.5. HRMS calcd for $C_{14}H_{20}O_9Na$ $[M+Na]^+$ 355.1005, found 355.1015.

3.5. 1,5-Anhydro-D-mannitol (24)

Compound **23** (15.5 g, 46.7 mmol) was dissolved in anhydrous MeOH (20.0 mL). Sodium methoxide (0.252 g, 4.67 mmol) was added to the solution and the mixture was stirred for 16 h at room temperature. The MeOH was evaporated under vacuum and the crude mixture was co-distilled with anhydrous toluene. After drying under high vacuum, the product was obtained without purification as a viscous yellow oil in 97% yield (7.40 g, 45.1 mmol). ^{1}H NMR (D_2O, 400 MHz); δ 3.83 (m, 1H), 3.77 (t, 2H, $J = 12.9$ Hz), 3.54 (dd, 1H, $J = 12.2$, 6.5 Hz), 3.51 (m, 1H), 3.48 (dd, 1H, $J = 7.5$, 3.2 Hz), 3.43 (pseudo d, 1H, $J = 9.5$ Hz), 3.15 (pseudo t, 1H, $J = 7.0$ Hz). ^{13}C NMR (D_2O, 100 MHz); δ 81.9, 74.9, 71.2, 70.5, 68.7, 62.7. HRMS calcd for $C_6H_{12}O_5Na$ $[M+Na]^+$ 187.0582, found 187.0584.

3.6. 1,5-Anhydro-(2*S*)-2,3:4,6-di-*O*-benzylidene-D-mannitol (25) and 1,5-anhydro-(2*R*)-2,3:4,6-di-*O*-benzylidene-D-mannitol (26)

Compound **24** (0.157 g, 0.958 mmol) was dissolved in anhydrous DMF (2.00 mL). *p*-Toluenesulfonic acid (0.055 g, 0.289 mmol) and benzaldehyde dimethyl acetal (0.580 mL, 3.86 mmol) were added to the solution and the mixture was stirred at 60 °C for 24 h. The solution was cooled to room temperature, diluted with dichloromethane, and then cooled to 0 °C. The reaction was quenched by the addition of saturated $NaHCO_3$. The

organic phase was separated from the water layer and washed three times with 60 mL of H_2O. After drying on sodium sulfate, the CH_2Cl_2 was evaporated and the product was dried under high vacuum without further purification to afford a light yellow solid containing both *endo*- and *exo*-isomers (0.264 g, 0.776 mmol) in 81% overall yield. Compounds **25** and **26** can be separated by recrystallization in ethanol or by flash chromatography if necessary. Compounds **25** (*exo* isomer): ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.58–7.33 (m, 10H), 6.00 (s, 1H), 5.54 (s, 1H), 4.51 (m, 1H), 4.37 (m, 2H), 4.20 (dd, 1H, $J = 5.3$, 2.2 Hz), 3.93 (m, 1H), 3.78 (m, 2H), 3.32 (dt, 1H, $J = 9.9$, 5.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.9, 137.1, 129.3, 128.9, 128.4, 128.1, 126.5, 126.1, 104.2, 101.6, 81.3, 76.4, 74.7, 69.1, 68.6, 66.8. HRMS calcd for $C_{20}H_{21}O_5$ $[M+H]^+$ 341.1389, found 341.1378. Compound **26** (*endo* isomer): ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.58–7.33 (m, 10H), 6.35 (s, 1H), 5.65 (s, 1H), 4.51 (m, 1H), 4.37 (m, 2H), 4.20 (dd, 1H, $J = 5.3$, 2.2 Hz), 3.93 (m, 1H), 3.78 (m, 2H), 3.32 (td, 1H, $J = 9.9$, 5.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.9, 137.2, 129.3, 129.0, 128.3, 128.2, 126.2, 125.9, 103.0, 101.8, 78.2, 76.0, 73.5, 69.2, 68.6, 67.1. HRMS calcd for $C_{20}H_{21}O_5$ $[M+H]^+$ 341.1389, found 341.1378.

3.7. 1,5-Anhydro-2-*O*-benzyl-4,6-*O*-benzylidene-D-mannitol (27) and 1,5-anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-D-mannitol (28)

A 1:1 mixture of diacetals **25** and **26** (0.207 g, 0.608 mmol) was dissolved in a 1:1 mixture of anhydrous CH_2Cl_2 and ether (2.00 mL). The solution was cooled to 0 °C and carefully protected from moisture in the air, aluminum chloride (0.081 mg, 0.607 mmol) and lithium aluminum hydride (0.023 g, 0.606 mmol) were added to the reaction mixture. After stirring at room temperature for 30 min, the solution was cooled to 0 °C and the reaction was quenched by ice. The solution was diluted with CH_2Cl_2 and the two phases were separated. The organic phase was washed with a solution of saturated $NaHCO_3$ and with H_2O. After drying on Na_2SO_4, the organic phase was evaporated and the product was obtained as a colorless oil in 85% yield (0.176 g, 0.514 mmol). The product is composed of a mixture of the 2-OBn and 3-OBn isomers. A portion of the mixture was purified on silica gel with a gradient of solvent system using hexane to hexane/EtOAc 3:1 to give the isolated compounds **27** and **28**. Compound **27**: ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.52–7.29 (m, 10H), 5.58 (s, 1H), 4.79 (d, 1H, $J = 12.1$ Hz), 4.62 (d, 1H, $J = 12.1$ Hz), 4.29 (dd, 1H, $J = 10.4$, 4.9 Hz), 4.16 (dd, 1H, $J = 12.9$, 1.6 Hz), 3.85 (m, 4H), 3.51 (dd, 1H, $J = 12.9$, 0.7 Hz), 3.35 (td, 1H, $J = 10.4$, 4.9 Hz), 2.29 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.6, 137.3, 129.1, 128.6, 128.2, 128.0, 127.9, 126.3, 102.0, 79.7, 76.7, 72.1, 71.8, 71.4, 68.5, 67.8. HRMS calcd for $C_{20}H_{22}O_5Na$ $[M+Na]^+$ 365.1365, found 365.1365. Compound **28**: ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.56–7.32 (m, 10H), 5.64 (s, 1H), 4.89 (d, 1H, $J = 12.0$ Hz), 4.77 (d, 1H, $J = 12.0$ Hz), 4.33 (dd, 1H, $J = 10.4$, 4.9 Hz), 4.13 (t, 1H, $J = 9.4$ Hz), 4.10 (dd, 1H, $J = 12.7$, 1.6 Hz), 4.00 (m,1H), 3.84 (t, 1H, $J = 10.3$ Hz), 3.69 (dd, 1H, $J = 9.4$, 3.5 Hz), 3.56 (dd, 1H, $J = 12.7$, 1.5 Hz), 3.35 (dt, 1H, $J = 9.8$, 4.9 Hz), 2.79 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.8, 137.5, 128.8, 128.3, 128.1, 127.8, 127.7, 125.9, 101.3, 78.9, 77.4, 72.5, 71.6, 70.1, 68.4, 68.2. HRMS calcd for $C_{20}H_{22}O_5Na$ $[M+Na]^+$ 365.1365, found 365.1365.

3.8. 1,5-Anhydro-2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-mannitol (29)

A 1:1 mixture of compounds **27** and **28** (155 mg, 0.453 mmol) was dissolved in anhydrous DMF (2.50 mL). The solution was cooled to 0 °C and sodium hydride (54.4 mg, 2.27 mmol) was added to the reaction flask under anhydrous conditions. The mixture was left stirring at room temperature for 30–35 min, after which benzyl bromide (0.220 mL, 1.85 mmol) was added to the mixture and the reaction was left stirring for another 12 h. The solution was cooled to 0 °C and diluted with CH_2Cl_2, then quenched with ice. After stirring for another 15 min the organic phase was separated from the water layer and washed with saturated NH_4Cl and then with H_2O three times. After drying over Na_2SO_4, the CH_2Cl_2 was evaporated and the crude mixture was purified on SiO_2 gel with a gradient of solvent system, hexane to hexane/CH_2Cl_2/THF 15:1:1. The pure product was obtained as a white solid with a 75% yield (146 mg, 0.338 mmol). Mp: 84–85 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.55–7.24 (m, 15H), 5.67 (s, 1H), 4.81 (m,3H), 4.77 (d, 2H, $J = 12.4$ Hz), 4.29 (m, 2H), 4.08 (dd, 1H, $J = 12.6$, 1.9 Hz), 3.87 (t, 1H, $J = 10.3$ Hz), 3.81 (m, 1H), 3.69 (dd, 1H, J = 9.8, 3.3 Hz), 3.45 (d, 1H, $J = 12.6$ Hz), 3.36 (dt, 2H, $J = 9.9$, 4.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.5, 138.2, 137.7, 128.8, 128.4, 128.3, 128.2, 128.0, 127.7, 127.5, 125.9, 101.3, 79.2, 78.5, 74.3, 72.6, 72.4, 72.2, 68.9, 68,6. HRMS calcd for $C_{27}H_{28}O_5Na$ $[M+Na]^+$ 455.1834, found 455.1827.

3.9. 1,5-Anhydro-2,3-di-*O*-benzyl-D-mannitol (30)

Compound **29** (1.71 g, 3.95 mmol) was dissolved in acetic acid (80% in H_2O, 20.0 mL). The solution was stirred at 45–50 °C for 12 h and cooled to 0 °C. The reaction mixture was neutralized with satd aq $NaHCO_3$ solution and water was then removed under reduced pressure. The crude mixture was taken up in EtOAc and the organic phase was washed with H_2O and dried over Na_2SO_4. After filtration and drying under high vacuum,

product **30** was obtained without further purification as a white solid in quantitative yield (1.36 g, 3.95 mmol). Mp: 82–83 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.41–7.25 (m, 10H), 4.73 (d, 1H, $J = 12.4$ Hz), 4.61 (t, 2H, $J = 11.8$ Hz), 4.46 (d, 1H, $J = 11.8$ Hz), 4.11 (dd, 1H, $J = 12.8$, 2.0 Hz), 4.00 (t, 1H, $J = 9.5$ Hz), 3.89 (dd, 1H, $J = 11.8$, 3.3 Hz), 3.79 (d, 1H, $J = 5.6$ Hz), 3.76 (m, 1H), 3.39 (dd, 1H, $J = 9.4$, 3.2 Hz), 3.35 (d, 1H, $J = 12.7$ Hz), 3.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 138.0, 137.8, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 82.2, 80.1, 71.9, 71.3, 71.1, 67.5, 67.1, 62.9. HRMS calcd for $C_{20}H_{24}O_5Na$ $[M+Na]^+$ 367.1521, found 367.1517.

3.10. 1,5-Anhydro-2,3-di-*O*-benzyl-4,6-di-*O*-methanesulfonyl-D-mannitol (31)

A solution of compound **30** (1.08 g, 3.14 mmol) in dichloromethane (15.0 mL) was cooled to 0 °C. Methanesulfonyl chloride (0.980 mL, 12.6 mmol) and Et_3N (3.00 mL, 21.5 mmol) were added to the reaction mixture. This solution was left stirring at 0 °C for 30 min and then at room temperature 14 h. The solution was then diluted with CH_2Cl_2 and the reaction was quenched with ice. After separating the phases, the organic phase was washed with water and dried on Na_2SO_4. The solvent was evaporated and the crude mixture was purified on SiO_2 gel using a gradient of hexane to hexane/EtOAc 2:1. The pure product was obtained as a light brown semi-solid in 85% yield (1.34 g, 2.68 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.38–7.24 (m, 10H), 4.84 (t, 1H, $J = 9.6$ Hz), 4.69 (d, 1H, $J = 12.2$ Hz), 4.59 (m, 2H), 4.44 (d, 1H, $J = 11.3$ Hz), 4.36 (dd, 1H, J = 11.5, 5.7 Hz), 4.14 (d, 1H, $J = 12.9$ Hz), 3.88 (br s, 1H), 3.68 (dd, 1H, $J = 9.4$, 2.8 Hz), 3.62 (m, 1H), 3.37 (d, 1H, $J = 12.9$ Hz), 3.01 (s, 3H), 2.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.5, 136.7, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 79.1, 76.2, 71.7, 71.0, 70.9, 68.4, 66.3, 38.4, 37.3. HRMS calcd for $C_{22}H_{28}O_9S_2Na$ $[M+Na]^+$ 523.1072, found 523.1087.

3.11. 1,5-Anhydro-2,3-di-*O*-benzyl-6-bromo-6-deoxy-4-*O*-methanesulfonyl-D-mannitol (32)

Compound **31** (0.920 g, 1.84 mmol) was dissolved in anhydrous DMSO (10.0 mL). Sodium bromide (1.14 g, 11.1 mmol) and tetrabutylammonium bromide (0.178 g, 0.552 mmol) were added to the solution and the mixture was stirred at 60 °C for 36 h. The reaction mixture was stirred under nitrogen atmosphere for 1–2 h, some DMSO was evaporated during this process, and the crude residue was taken up in CH_2Cl_2. The organic phase was washed three times with H_2O, dried over Na_2SO_4. The solvent was then removed under reduced pressure. The crude product was purified on SiO_2 gel using a gradient of hexane to hexane/EtOAc 6:1. The pure product was obtained as a light yellow solid in 78% yield (0.691 g, 1.42 mmol). Mp: 74–75 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.39–7.27 (m, 10H), 4.77 (m, 1H), 4.74 (m, 2H), 4.59 (t, 1H, $J = 12.5$ Hz), 4.39 (d, 1H, $J = 11.3$ Hz), 4.22 (dd, 1H, $J = 12.9$, 2.3 Hz), 3.86 (m, 1H), 3.81 (dd, 1H, $J = 10.9$, 1.8 Hz), 3.63 (dd, 1H, $J = 9.4$, 3.2 Hz), 3.52 (m, 2H), 3.36 (d, 1H, $J = 12.9$ Hz), 2.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 137.5, 136.8, 128.6, 128.5, 128.3, 127.9, 79.3, 79.0, 78.5, 71.7, 71.1, 71.0, 66.4, 38.6, 31.7. HRMS calcd for $C_{21}H_{25}BrO_6SNa$ $[M+Na]^+$ 507.0453, found 507.0471.

3.12. Diethyl 2-(((2*R*,3*R*,4*R*,5*R*)-4,5-bis(benzyloxy)-3-(methylsulfonyloxy)tetrahydro-2*H*-pyran-2-yl)methyl)-2-(*tert*-butoxycarbonylamino)malonate (33)

N-Boc-diethylaminomalonate (0.426 g, 1.55 mmol) was dissolved in anhydrous toluene (1 mL). After cooling to 0 °C, sodium hydride (57–63% in mineral oil, 65.3 mg, 1.55 mmol) was added and the solution was stirred for 45 min. Compound **32** (0.146 g, 0.301 mmol) in 1.00 mL of anhydrous toluene and TBAI (34.4 mg, 0.093 mmol) were added to the mixture and the solution was stirred under reflux for 14 h. The solution was cooled to room temperature, diluted with CH_2Cl_2, and quenched with ice. After separating the phases, the organic phase was washed twice with water and dried over Na_2SO_4. After filtration and concentration, the crude mixture was purified on SiO_2 gel using a gradient of solvent of hexane to hexane/EtOAc 6:1. The pure product was obtained as a white solid in 51% yield (104 mg, 0.153 mmol). Mp: 41–42 °C ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.37–7.25 (m, 10H), 6.03 (br s, 1H), 4.79–4.50 (m, 5H), 4.17 (m, 5H), 3.80 (m, 2H), 3.55 (d, 1H, $J = 8.3$ Hz), 3.39 (t, 1H, $J = 9.9$ Hz), 3.15 (d, 1H, $J = 12.8$ Hz), 2.93 (m, 3H), 2.54 (dd, 1H, $J = 14.9$, 10.8 Hz), 1.42 (s, 9H), 1.22 (t, 6H, $J = 6.7$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (major rotomer) 168.4, 153.9, 137.8, 128.4, 128.3, 127.9, 127.6, 81.6, 79.5, 74.7, 72.5, 71.2, 71.1, 66.3, 64.2, 62.5, 38.9, 35.0, 28.1, 13.7. (Minor rotomer) 167.8, 153.5, 137.3, 128.4, 128.3, 127.9, 127.6, 81.6, 79.3, 74.7, 72.4, 71.4, 70.9, 66.1, 64.2, 62.0, 38.6, 35.1, 27.8, 13.8. HRMS calcd for $C_{33}H_{45}NO_{12}SNa$ $[M+Na]^+$ 702.2560, found 702.2571.

3.13. Ethyl 3-((2*R*,3*R*,4*R*,5*R*)-4,5-bis(benzyloxy)-3-(methylsulfonyloxy)tetrahydro-2*H*-pyran-2-yl)-2-(*tert*-butoxycarbonylamino)-propanoate (34)

A solution of compound **33** (220 mg, 0.324 mmol) in 5.00 mL of ethanol was treated with 1 N NaOH (5 mL), the reaction mixture was stirred at 40–50 °C for about 10 h. The solution was washed with ether several times, then the combined ether phases were extracted with water twice. The aqueous solution was

combined and acidified with 1 N HCl to pH 2–3, then extracted with chloroform several times, the combined chloroform solution was dried over Na_2SO_4, and concentrated. The residue was then subjected to decarboxylation reaction in refluxing toluene overnight. The reaction mixture was evaporated under reduced pressure to remove toluene, the residue was purified by flash chromatography on silica gel using hexane/ethyl acetate from 9:1 to 5:1 ratio. Product **34** was obtained as a colorless semi-solid in 91% yield (180 mg, 0.296 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.39–7.25 (m, 10H), 5.33 (m, 1H), 4.80–4.46 (m, 5H), 4.38 (m, 2H), 4.16 (m, 3H), 3.83 (d, 1H, $J = 15.8$ Hz), 3.58 (m, 1H), 3.46–3.29 (m, 1H), 3.27 (m, 1H), 2.91–2.85 (m, 3H), 2.11 (m, 1H), 1.44 (s, 9H), 1.28–1.23 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ (major isomer): 172.3, 155.6, 137.5, 136.7, 128.4, 128.3, 127.8, 79.8, 79.5, 75.7, 72.1, 71.9, 71.1, 70.8, 66.6, 61.1, 50.6, 38.5, 33.9, 28.1, 13.9. (Minor isomer): 172.1, 155.0, 137.6, 136.8, 128.4, 128.2, 127.8, 79.8, 79.3, 75.6, 72.1, 71.9, 71.1, 70.9, 66.3, 61.1, 50.9, 38.5, 33.9, 28.1, 13.8. Yield: 91%. HRMS calcd for $C_{30}H_{41}NO_{10}SNa$ $[M+Na]^+$ 630.2349, found 630.2346.

3.14. Ethyl 2-amino-3-((2*R*,3*R*,4*R*,5*R*)-4,5-bis(benzyloxy)-3-(methylsulfonyloxy) tetrahydro-2*H*-pyran-2-yl)propanoate (35)

Compound **34** (80 mg, 0.132 mmol) was treated with 1.00 mL TFA and 4.00 mL CH_2Cl_2 at 0 °C for 4–5 h. The solvent was evaporated under reduced pressure, and saturated $NaHCO_3$ (15.0 mL) and EtOAc (25.0 mL) were added to the residue. The aqueous layer was extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4. Solvent was removed using a rotovap and intermediate **35** was obtained as a yellow oil without further purification in a 96% yield (64.0 mg, 0.126 mmol). Compound **35** was used directly for the next cyclization step. ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.43–7.22 (m, 10H), 4.70 (m, 2H), 4.57 (m, 2H), 4.39 (d, 1H, $J = 11.1$ Hz), 4.19 (m, 4H), 3.86 (s, 1H), 3.65 (m, 2H), 3.41 (m, 1H), 2.89 (s, 3H), 2.38 (m, 2H), 1.26 (m, 3H).

3.15. (2*S*,3a*R*,6*R*,7*S*,7a*S*)-ethyl 6,7-bis(benzyloxy)octahydropyrano[3,2-*b*]pyrrole-2-carboxylate (36) and (2*R*,3a*R*,6*R*,7*S*,7a*S*)-ethyl 6,7-bis(benzyloxy)-octahydropyrano[3,2-*b*]pyrrole-2-carboxylate (37)

The crude product **35** (64 mg, 0.126 mmol) was dissolved in 5.00 mL of toluene, and 1.5 equiv of DIEA (0.236 mmol) was added to the reaction flask. The mixture was brought to refluxing for 2–3 h to give the cyclized products. The solvent was removed under reduced pressure and the crude products were purified by flash chromatography using a gradient of solvent systems of hexane/EtOAc from 3:1 to 1:1, then to 2% MeOH in EtOAc to give pure diastereomers **36** and **37** as a colorless oil. Compound **36** was obtained in a 48% yield (25.0 mg, 0.061 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.41–7.27 (m, 10H), 4.77 (d, 1H, $J = 12.5$ Hz), 4.76 (m, 2H), 4.65 (d, 1H, $J = 12.2$ Hz), 4.17 (q, 2H, $J = 7.0$ Hz), 4.14 (d, 1H, $J = 8.1$ Hz), 4.03 (d, 1H, $J = 12.6$ Hz), 3.94 (m, 1H), 3.69 (m, 2H), 3.52 (m, 1H), 3.27 (d, 1H, $J = 12.7$ Hz), 2.26 (dd, 1H, $J = 13.9$, 8.7 Hz), 2.09 (m, 1H), 1.29 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 175.3, 138.2, 138.1, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 79.6, 73.6, 72.7, 72.3, 69.1, 67.1, 60.7, 60.6, 58.5, 37.4, 14.1. HRMS calcd for $C_{24}H_{30}NO_5$ $[M+H]^+$ 412.2124, found 412.2133. Compound **37** was obtained in a 50% yield (26.0 mg, 0.063 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz); δ 7.49–7.26 (m, 10H), 4.81 (d, 1H, $J = 12.5$ Hz), 4.75 (d, 1H, $J = 12.5$ Hz), 4.69 (d, 1H, $J = 12.5$ Hz), 4.63 (d, 1H, $J = 12.5$ Hz), 3.82 (m, 2H), 3.72 (m, 2H), 3.23 (d, 2H, $J = 12.7$ Hz), 2.27 (m, 1H), 2.08 (dd, 1H, $J = 14.3$, 4.5 Hz), 1.19 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz); δ 173.3, 138.3, 138.1, 128.3, 128.2, 127.8, 127.6, 127.5, 127.4, 78.8, 73.8, 72.2, 71.9, 69.3, 66.9, 61.7, 60.9, 59.3, 38.1, 14.0. HRMS calcd for $C_{24}H_{30}NO_5$ $[M+H]^+$ 412.2124, found 412.2112.

3.16. 1,2,3,5,6-Penta-*O*-acetyl-α-D-galactopyranose (41)

Sodium acetate (9.15 g, 112 mmol) was dissolved in Ac_2O (105 mL, 1.11 mol). The solution was heated to reflux temperature and D-galactose (**40**, 20.0 g, 111 mmol) was added in portions. The solution was stirred at 145 °C for 3 h, cooled to room temperature, and poured into a beaker containing 200 mL of ice H_2O. After stirring in water for 2 h, the product crystallized out and was filtered through a Buchner funnel. The solid product was washed thoroughly with cold water and recrystallized in EtOH to afford a white crystalline solid in 70% yield (30.3 g, 77.6 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.69 (d, 1H, $J = 8.3$ Hz), 5.42 (d, 1H, $J = 3.0$ Hz), 5.33 (dd, 1H, $J = 10.4$, 8.3 Hz), 5.07 (dd, 1H, $J = 10.4$, 3.4 Hz), 4.14 (m, 2H), 4.05 (t, 1 H, $J = 6.6$ Hz), 2.16 (s, 3H), 2.12 (s, 3H), 2.04 (br s, 6H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 169.8, 169.5, 168.9, 168.6, 91.7, 71.3, 70.4, 67.6, 66.6, 60.8, 20.2.

3.17. 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (42)[31]

A mixture of compound **41** (18.9 g, 48.3 mmol) and Ac_2O (14.0 mL, 148 mmol) was cooled to 0 °C and hydrobromic acid (33% in acetic acid, 42.4 mL, 242 mmol) was added to the reaction mixture. After stirring at room temperature for 90 min, the solution was poured into 200 mL of ice-water and stirred for 15 min. The product was extracted from the aqueous

phase using EtOAc. The organic phase was then washed two to three times with saturated $NaHCO_3$ and three times with H_2O. After drying with Na_2SO_4 overnight, the solvent was evaporated on a rotovap and the crude residue was dried under high vacuum to afford a light yellow powder in 91% yield (18.1 g, 44.0 mmol). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.69 (d, 1H, $J = 3.9$ Hz), 5.51 (m, 1H), 5.39 (dd, 1H, $J = 10.6$, 3.3 Hz), 5.04 (dd, 1H, $J = 10.6$, 3.9 Hz), 4.48 (t, 1H, $J = 6.5$ Hz), 4.18 (dd, 1H, $J = 11.4$, 6.4 Hz), 4.09 (dd, 1H, $J = 11.4$, 6.7 Hz), 2.14 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 170.1, 169.9, 169.8, 88.1, 71.0, 67.9, 67.7, 66.9, 60.8, 20.7, 20.6, 20.5, 20.4.

3.18. 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol (43)

Compound **42** (9.23 g, 22.4 mmol) was dissolved in anhydrous benzene (20.0 mL). Tributyltin hydride (5.95 mL, 22.4 mmol) and AIBN (a few mg) were added to the solution and the reaction was refluxed at 90 °C for 75 min. The solution was cooled to room temperature and diluted with Et_2O. Potassium fluoride (4.00 g, 68.8 mmol) dissolved in 30.0 mL of H_2O was added and the mixture was stirred at room temperature overnight and a white precipitate of Bu_3SnF was formed. The solid residue was filtered out and the organic phase was separated from the aqueous phase and dried over Na_2SO_4. The ether was evaporated using a rotavap and the product was dried under high vacuum to afford a white solid in 95% yield (7.09 g, 21.3 mmol). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.44 (d, 1H, $J = 3.3$ Hz), 5.22 (td, 1H, $J = 10.3$, 5.5 Hz), 5.04 (dd, 1H, $J = 10.2$, 3.4 Hz), 4.19 (dd, 1H, $J = 11.2$, 5.5 Hz), 4.06 (d, 2H, $J = 6.4$ Hz), 3.81 (t, 1H, $J = 6.4$ Hz), 3.28 (t, 1H, $J = 10.9$ Hz), 2.14 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 170.0, 169.9, 169.8, 74.7, 71.3, 67.6, 66.9, 66.2, 61.8, 20.6, 20.5, 20.4, 20.3. HRMS calcd for $C_{14}H_{21}O_9$ $[M+H]^+$ 333.1186, found 333.1174.

3.19. 1,5-Anhydro-D-galactitol (44)

Compound **43** (7.78 g, 23.4 mmol) was dissolved in anhydrous MeOH (30.0 mL). Sodium methoxide (127 mg, 2.35 mmol) was added to the solution and the reaction was stirred at room temperature for 16 h. The MeOH was evaporated under vacuum and the crude mixture was taken up in H_2O and neutralized to pH 5–6 with diluted HCl. The aqueous phase was washed two to three times with hexane and then concentrated on a rotovap, with co-distillation with toluene. The product was then dried under high vacuum to afford a yellow semi-solid in 94% yield (3.62 g, 22.1 mmol). ^1H NMR (D_2O, 400 MHz) δ 3.84 (dd, 1H, $J = 11.1$, 5.6 Hz), 3.79 (m, 1H), 3.67 (td, 1H, $J = 10.3$, 5.5 Hz), 3.55 (m, 2H), 3.41 (m, 2H), 3.03 (t, 1H, $J = 10.8$ Hz). ^{13}C NMR (D_2O, 100 MHz) δ 80.4, 75.1, 70.2, 70.1, 67.7, 62.4.

3.20. 1,5-Anhydro-4,6-*O*-benzylidene-D-galactitol (45)

Compound **44** (2.34 g, 14.3 mmol) was dissolved in anhydrous DMF (10.0 mL) and the solution was cooled to 0 °C. Benzaldehyde dimethyl acetal (3.22 mL, 21.5 mmol) and tetrafluoroboric acid (50% w/v in Et_2O, 0.750 mL, 17.1 mmol) were added and the solution was stirred at 0 °C for 15 min and at room temperature for 12–15 h. Et_3N (1.20 mL, 8.60 mmol) was added to the mixture and the solution was stirred at room temperature for 15 min. DMF was evaporated and the crude product was recrystallized in EtOAc to give the pure product as a white solid in 92% yield (3.32 g, 13.9 mmol). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (m, 2H), 7.38 (m, 3H), 5.56 (s, 1H), 4.31 (dd, 1H, $J = 12.6$, 1.4 Hz), 4.26 (m, 1H), 4.15 (dd, 1H, $J = 11.2$, 5.2 Hz), 4.05 (dd, 1H, $J = 12.6$, 1.8 Hz), 3.98 (td, 1H, $J = 10.2$, 5.2 Hz), 3.55 (m, 1H), 3.43 (m, 1H), 3.25 (t, 1H, $J = 11.0$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.4, 129.3, 128.3, 126.3, 101.5, 75.8, 74.8, 70.4, 69.7, 69.2, 68.2. HRMS calcd for $C_{13}H_{16}O_5$ $[M]^+$ 252.0999, found 252.0998.

3.21. 1,5-Anhydro-2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactitol (46)

Sodium hydride (1.60 mmol, 65.0 mg of 60% dispersed in mineral oil) was added to a magnetically stirring solution of compound **45** (0.100 g, 0.396 mmol) in 2.00 mL DMF and 1.00 mL toluene at 0 °C. The mixture was left stirring at room temperature for 1 h after which benzyl bromide (0.200 mL, 1.64 mmol) was added dropwise and the reaction was left stirring overnight under anhydrous conditions. The reaction mixture was then poured into ice water, extracted 4–5 times with ethyl acetate. The combined organic phase was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash chromatography to give the pure product **46** as white plate-like crystals in 96% yield (0.165 g, 0.381 mmol). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56–7.26 (m, 15H), 5.50 (s, 1H), 4.86 (d, 1H, $J = 11.5$ Hz), 4.80 (m, 2H), 4.67 (d, 1H, $J = 11.5$ Hz), 4.26 (dd, 1H, $J = 12.4$, 1.3 Hz), 4.21 (d, 1H, $J = 3.5$ Hz), 4.18–4.05 (m, 2H), 3.98 (dd, 1H, $J = 12.4$, 1.6 Hz), 3.58 (dd, 1H, $J = 9.1$, 3.6 Hz), 3.27 (m, 1H), 3.24 (t, 1H, $J = 10.6$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 138.5, 137.7, 128.9, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 126.3, 101.3, 80.9, 74.4, 74.0, 73.8, 71.5, 70.3, 69.7, 68.4. HRMS calcd for $C_{27}H_{28}O_5$ $[M]^+$ 433.2015, found 433.2000.

3.22. 1,5-Anhydro-2,3-di-*O*-benzyl-D-galactitol (47)

Compound **46** (0.165 g, 0.381 mmol) was dissolved in 50% acetic acid (10.0 mL). Sulfuric acid (10%, 3.00 mL) was added and the reaction was stirred at 55 °C for 12 h. The solution was neutralized with saturated $NaHCO_3$ and the solvent was evaporated. The crude residue was taken up in EtOAc and the solid salts were filtered out. After concentration of the organic phase, the crude mixture was purified on SiO_2 gel using a gradient of hexane/EtOAc 4:1 to 1:1. The pure product was obtained as a colorless oil in 95% yield (0.125 g, 0.363 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.28 (m, 10H), 4.76 (m, 3H), 4.64 (d, 1H, $J = 11.6$ Hz), 4.08 (dd, 1H, $J = 11.2$, 5.5 Hz), 4.05 (d, 1H, $J = 3.3$ Hz), 3.91 (td, 1H, $J = 10.2$, 5.5 Hz), 3.90 (dd, 1H, $J = 11.7$, 6.4 Hz), 3.74 (dd, 1H, $J = 11.6$, 4.6 Hz), 3.50 (dd, 1H, $J = 9.1$, 3.3 Hz), 3.35 (t, 1H, $J = 5.5$ Hz), 3.18 (t, 1H, $J = 11.0$ Hz), 2.98 (br s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 137.8, 128.4, 128.3, 127.8, 127.7, 127.6, 81.6, 78.3, 74.3, 73.3, 71.9, 68.1, 67.6, 62.5. HRMS calcd for $C_{20}H_{25}O_5$ $[M+H]^+$ 345.1702, found 345.1686.

3.23. 1,5-Anhydro-2,3-di-*O*-benzyl-4,6-di-*O*-methanesulfonyl-D-galactitol (48)

Compound **47** (0.125 g, 0.363 mmol) was dissolved in anhydrous dichloromethane (2.00 mL). Methanesulfonyl chloride (0.110 mL, 1.42 mmol) and pyridine (2.00 mL, 24.7 mmol) were added to the solution and the reaction was stirred at room temperature for 14 h. The solution was diluted with CH_2Cl_2 and washed 3–4 times with H_2O. After drying on Na_2SO_4, the organic phase was concentrated and the crude mixture was purified on SiO_2 gel using a gradient of hexane/EtOAc 4:1 to 3:1. The pure product was obtained as a light yellow oil in 93% yield (0.168 g, 0.336 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.27 (m, 10H), 5.21 (m, 1H), 4.82 (d, 1H, $J = 10.9$ Hz), 4.77 (d, 1H, $J = 11.7$ Hz), 4.73 (d, 1H, $J = 10.9$ Hz), 4.66 (d, 1H, $J = 11.7$ Hz), 4.37 (dd, 1H, $J = 10.5$, 6.6 Hz), 4.23 (dd, 1H, $J = 10.5$, 6.2 Hz), 4.09 (dd, 1H, $J = 11.5$, 5.4 Hz), 3.81 (m, 2H), 3.63 (dd, 1H, $J = 9.4$, 3.0 Hz), 3.24 (t, 1H, $J = 11.3$ Hz), 3.07 (s, 3H), 3.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.8, 137.0, 128.6, 128.5, 128.3, 128.2, 127.9, 127.8, 79.9, 76.6, 74.8, 73.7, 73.5, 73.2, 68.4, 67.1, 39.0, 37.5. HRMS calcd for $C_{22}H_{28}O_9S_2Na$ $[M+Na]^+$ 523.1072, found 523.1046.

3.24. 1,5-Anhydro-2,3-di-*O*-benzyl-6-*O*-trityl-D-galactitol (50)

Compound **47** (0.530 g, 1.54 mmol) was dissolved in anhydrous CH_2Cl_2 (5.00 mL). Trityl chloride (0.495 g, 3.41 mmol) and pyridine (0.240 mL, 2.97 mmol) were added to the solution and the reaction was stirred for 12 h. The solution was diluted with CH_2Cl_2 and quenched with ice water. The organic phase was washed 2–3 times with water and dried over Na_2SO_4. After filtration and concentration, the crude product was purified on SiO_2 gel using a solvent system of hexane/EtOAc 10:1. The pure product was obtained as a white solid in 94% yield (0.842 g, 1.44 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.21 (m, 25H), 4.78 (m, 3H), 4.65 (d, 1H, $J = 11.6$ Hz), 4.08 (m, 1H), 4.05 (dd, 1H, $J = 11.2$, 5.5 Hz), 3.89 (td, 1H, $J = 10.0$, 5.5 Hz), 3.49 (dd, 1H, $J = 9.1$, 3.2 Hz), 3.37 (m, 3H), 3.15 (t, 1H, $J = 10.9$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.8, 138.4, 138.1, 128.7, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 127.5, 127.0, 86.9, 81.9, 77.6, 74.5, 73.5, 72.1, 68.4, 67.5, 63.0.

3.25. 1,5-Anhydro-2,3-di-*O*-benzyl-4-*O*-methanesulfonyl-6-*O*-trityl-D-galactitol (51)

Compound **50** (0.480 g, 0.818 mmol) was dissolved in anhydrous CH_2Cl_2 (3.00 mL). Methanesulfonyl chloride (0.130 mL, 1.67 mmol) and pyridine (0.133 mL, 1.64 mmol) were added to the solution and the reaction was stirred at room temperature for 18 h. The solution was diluted with CH_2Cl_2 and quenched with ice H_2O. The organic phase was washed with saturated $NaHCO_3$ and with H_2O 2–3 times. After drying with Na_2SO_4, filtration and concentration, the crude mixture was purified on SiO_2 gel with a gradient of solvent system of hexane/EtOAc 10:1 to 7:1. The pure product was obtained as a light yellow solid in 85% yield (0.460 g, 0.692 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.21 (m, 25H), 5.25 (m, 1H), 4.88 (d, 1H, $J = 11.2$ Hz), 4.75 (d, 1H, $J = 11.6$ Hz), 4.69 (d, 1H, $J = 11.2$ Hz), 4.63 (d, 1H, $J = 11.6$ Hz), 4.00 (dd, 1H, $J = 11.3$, 5.5 Hz), 3.76 (td, 1H, $J = 10.1$, 5.5 Hz), 3.47 (m, 2H), 3.27 (m, 2H), 3.11 (t, 1H, $J = 11.1$ Hz), 2.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6, 138.1, 137.5, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.2, 87.4, 80.5, 77.4, 76.5, 73.9, 73.6, 72.7, 68.5, 62.4, 38.9.

Acknowledgments

We are grateful to the financial support from the American Heart Association (Grant # 043285N). We would also like to thank Branden Hopkinson and Jiang Qian for their help in synthesizing several intermediates.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.03.017.

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