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Straightforward synthesis of derivatives of D- and L-galactonic acids as precursors of stereoregular polymers

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Abstract—High yielding routes for the synthesis of selectively protected derivatives of D- and L-galactonic acids, having free OH or NH_2 groups at the C-6 position, are reported. The successful direct per-*O*-methylation of galactonic acid derivatives from the corresponding galactono-1,4-lactones was developed as a key step of the sequence. For example, 6-azido-6-deoxy-L-galactono-1,4-lactone **16** was converted into the potassium salt and methylated (NaH, DMSO, MeI) to the methyl ester of the 2,3,4,5-tetra-*O*-methyl derivative **12**. Compound **16** was readily prepared by bromination at C-6 of L-galactonolactone **1** and isopropylidenation; followed by substitution of bromine by azide and removal of the protecting groups. Hydrolysis of the methyl ester of **12** and hydrogenation of the azide led to the tetra-*O*-methyl derivative of the 6-amino acid **18** with 52% overall yield from **1**. The same sequence applied to D-galactonolactone **19** led to the enantiomeric amino acid **25** with a 47% overall yield.

1. Introduction

Effective utilization of renewable natural resources as precursors of polymers and organic chemicals has recently become of interest since long-term access to fossil materials is expected to become increasingly difficult. In particular, carbohydrates have been employed as a source of optically active condensation polymers, which carry in their chains diverse functionalities.[1,2] Novel technological and biomedical applications have been found for such polymers that, in addition, are usually environmentally compatible.[3,4] Carbohydrate-based polyamides[5,6] have been prepared by polycondensation of amino acids derived from pentoses[7] and hexoses.[8] We have reported recently the preparation of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid as a precursor of a stereoregular polyamide.[9] The open-chain monomers of the galacto configuration are particularly interesting as they preferentially adopt a planar zigzag conformation in solution,[10] which is expected to favor the polycondensation reactions. Furthermore, it has been reported that the zigzag conformation of the galactaryl units of polygalactaramides induces an alignment of the chains in the solid state affording materials of improved mechanical properties.[11] Our already mentioned synthesis of the per-*O*-methyl-D-galactonic acid derivative,[9] from methyl 6-*O*-tosyl-α-D-galactopyranoside, involved seven steps (30% overall yield). A key intermediate of the sequence was methyl 6-azido-6-deoxy-2,3,4-tri-*O*-methyl-α-D-galactopyranoside, which was converted into a lactone by hydrolysis of the glycoside followed by oxidation of the anomeric center. While searching for a more direct route to D- and L-galactonic acid derivatives, alternative procedures were also explored starting from the respective aldonolactones. Herein we report the results of these investigations.

2. Results and discussion

For the synthesis of a selectively protected derivative of 6-amino-6-deoxy-L-galactonic acid we first selected the azide **5** as a key intermediate (Scheme 1). We successfully employed the enantiomer of **5** as a precursor of the target amino acid in the D-series.[9] The starting material 5,6-*O*-isopropylidene-L-galactono-1,4-lactone **2** was obtained from **1** following the procedure described for the acetonation of D-galactonolactone.[12] The next step of the sequence involved the opening of the lactone ring and the methylation of the alcohol functions. It is known that the alkylation of aldonolac-

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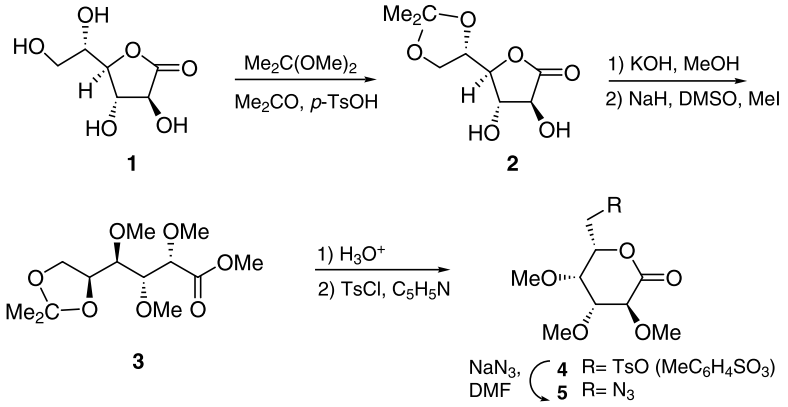


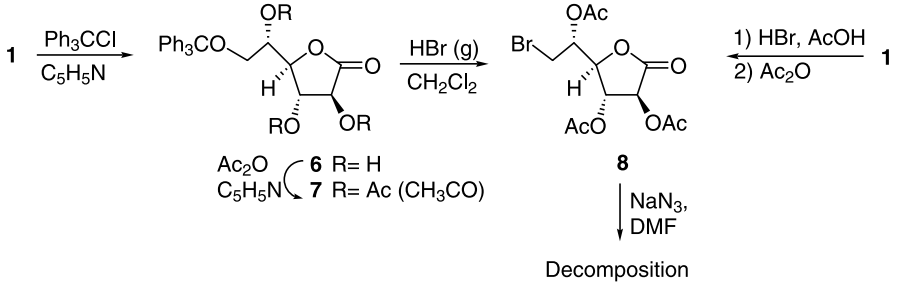
Scheme 1.

tones and aldonic acids in the presence of strong bases is difficult, as usual isomerizations and eliminations are produced.[13,14] As a result per-*O*-alkylated aldonolactones were prepared by the classical method of hydrolysis of alkylated glycosides followed by oxidation,[8,15] or by means of specific reagents[16] or procedures.[17] However, we could only succeed in the per-*O*-methylation of derivatives of aldonic acids by opening the lactone ring previous to the addition of the methylation reagent. Thus, treatment of **2** with a methanolic solution of KOH afforded the potassium salt of the aldonic acid. The opening of the lactone was evidenced by the ^{13}C NMR spectrum of the salt, which showed a strong upfield shifting of the C-4 resonance compared with the same signal in **2**. The dried potassium salt, dissolved in dimethylsulfoxide (DMSO) was methylated with methyl iodide in the presence of sodium hydride to give the methyl ester of the methylated aldonic acid derivative **3**. This reaction proved to be quite general as when applied to other aldonolactone derivatives (as discussed later) it gave, in all cases, good yields of the methylated product.

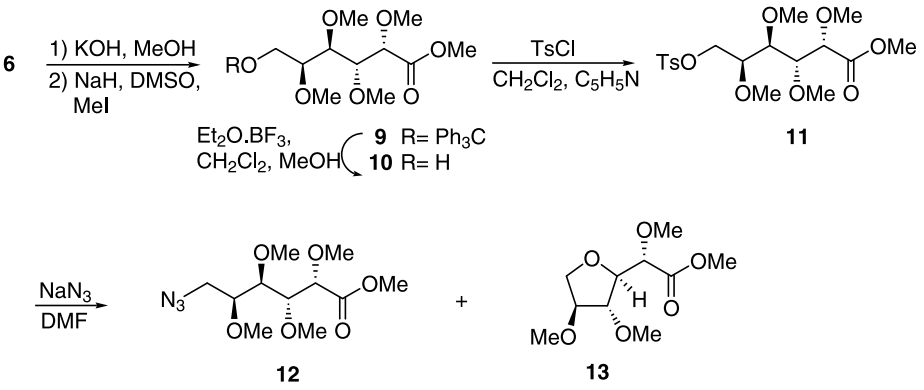
Compound **3** was subjected to acid hydrolysis for the removal of the isopropylidene group and to promote the 1,5-lactonization of the resulting 5-hydroxy acid. However, the NMR spectra of the product showed that only partial lactonization had taken place, even upon prolonged drying. The crude mixture of hydrolysis was tosylated to give a low yield of the expected monotosyl derivative of the 1,5-lactone **4**. The poor yield was consistent with the fact that **4** reverted partially to the 5-hydroxy acid during chromatographic purification.

Due to the difficulties in the preparation of **4**, we attempted an alternative strategy (Scheme 2) for the synthesis of the 6-amino-6-deoxyhexonolactone analogue of **5**. In this case, a good leaving group at C-6 of **1** was introduced in the first stages of the sequence. Thus, the 6-bromo derivative **8** was prepared via the 6-*O*-trityl lactone **6**, or directly from **1** by the procedure described by Pedersen et al.[18] Tritylation of **1** under standard conditions afforded **6** as a crystalline product (93% yield), which was quantitatively acetylated to **7**. This compound was also prepared (85% yield) by a one-pot tritylation and acetylation of **1**.[19] Treatment of **7** with hydrogen bromide in methylene chloride led to **8**. Alternatively, bromination of **1** with HBr–acetic acid and further acetylation rendered **8** (62% yield).[18] Unfortunately, the bromide substitution in **8** by azide was unsuccessful, as extensive decomposition of the starting material occurred under different reaction conditions.

As the 6-*O*-trityl derivative **6** could be readily prepared from **1**, it was selected as the starting material for the synthesis of **12** (Scheme 3), a direct precursor of the desired amino acid. Methylation of **6**, under the conditions described for **2**, led to **9** in 80% yield. Removal of the trityl group of **9** with boron trifluoride–ethyl etherate afforded **10**. Compound **10** itself can be seen as the monomer precursor of a stereoregular polyester, as successful polymerization of the lactones of substituted ε-hydroxyacids has recently been reported.[20] On the other hand, for the synthesis of **12**, the free hydroxyl group of **10** was tosylated to afford **11**. The ^1H NMR spectrum of **11** showed the signals of H-6 and H-6′ at



Scheme 2.

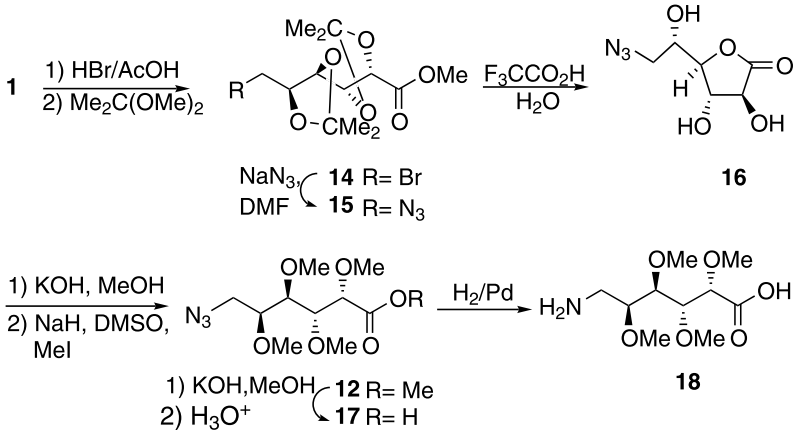


Scheme 3.

low field, due to the deshielding effect of the tosylate. The large value for $J_{3,4}$ and the smaller ones for $J_{2,3}$ and $J_{4,5}$ indicated, as expected for a derivative having galacto configuration,[10] a planar zigzag conformation for the backbone chain of **11**.

The nucleophilic substitution of the tosylate group of **11** by sodium azide, under different reaction conditions gave moderate yields (~50%) of the expected azide derivative **12**. In all instances, a by-product was isolated with its proportion in the reaction mixture increasing when the reactions were conducted at higher temperatures and for longer times. The ^{1}H NMR spectrum of this by-product showed only four methyl groups instead of the expected five; one of them was assigned to the methyl ester because of its characteristic chemical shift (δ 3.76 in $CDCl_3$). The spectral data suggested the formation of a 3,6-anhydro bridge and so the by-product was formulated as **13**. In accordance with the structure proposed, the NMR spectrum of the product showed the C-6 resonance at low field, as observed for 1,4-anhydrogalactitol, which possesses as **13** an 1,4-anhydro ring.[21] Also, both compounds exhibited the resonances for all of the other ring carbons at low field. The mass spectrum of the by-product supported the structural assignments. Similar to per-*O*-methylated 3,6-anhydro-D-galactitol,[22] the mass spectrum of **13** showed a diagnostic peak at m/z 131 (63%), characteristic of the 3,6-anhydro ring. The fragment of the lateral chain (m/z 103, 6%) was also observed. The structure of **13** was confirmed chemically by the simple heating of a toluene solution of the tosylate **11**, which led to the anhydro sugar **13**, in 92% yield. The rather unusual cyclization of **11**, suggested the attack of the methoxy group at C-3 to C-6, with nucleophilic displacement of the tosylate and subsequent *O*-demethylation.

The formation of the by-product **13** lowered the yield of the azide derivative **12**, a key intermediate to the target molecule and so another route (Scheme 4) for the synthesis of **12** starting from **1**, was attempted. Treatment of **1** with 32% HBr in acetic acid afforded the corresponding 6-bromo-6-deoxy derivative, which was employed crude for the next step. The traces of acids (HBr and AcOH) present in the crude product, catalyzed the acetonation with 2,2-dimethoxypropane, to give the di-*O*-isopropylidene derivative **14** in 99% yield from **1**. The methanol released during the reaction from the acetonation reagent produced the simultaneous formation of the methyl ester, as observed for analogous isopropylidenation of aldonolactones.[23,24] Substitution of the bromide of **14** by sodium azide readily took place to give the 6-azido-6-deoxy product **15** in 87% yield. Removal of the ketal protecting groups by acid hydrolysis led to **16** (93% yield).



Scheme 4.

Per-*O*-methylation of **16**, by the procedure described above for similar aldonolactone derivatives, afforded **12** in 77% yield. Hydrolysis of the ester function of **12** under alkaline conditions led to the acid derivative **17**. The last step of the sequence, the hydrogenation of **17**, afforded the target compound **18**, in crystalline form. The corresponding enantiomer **25** was also obtained from D-galactono-1,4-lactone **19** by using the same procedure (Scheme 5).

In summary, we have reported alternative procedures for the synthesis of derivatives of L-galactonic acid. A straightforward route has been developed to prepare, starting from the L- and the D-galactonolactones **1** and **19**, the respective ω-aminoacid derivatives **18** and **25**, in 52 and 47% overall yield. The key step of the synthesis was the successful direct methylation of the aldonolactones to afford the corresponding esters of per-*O*-methyl aldonic acids. These bifunctional compounds are useful monomers for the construction of optically active, stereoregular AB-type polyamides. Also, the intermediate **15** would render, upon hydrogenation, a precursor of a similar polyamide having protecting groups that could be readily removed by hydrolysis. Different properties (i.e. solubility) should be expected for the resulting polymer. Furthermore, the ω-hydroxy-acid derivative **10** constitutes a potentially useful precursor for the synthesis of a stereoregular polyester or co-polyester.

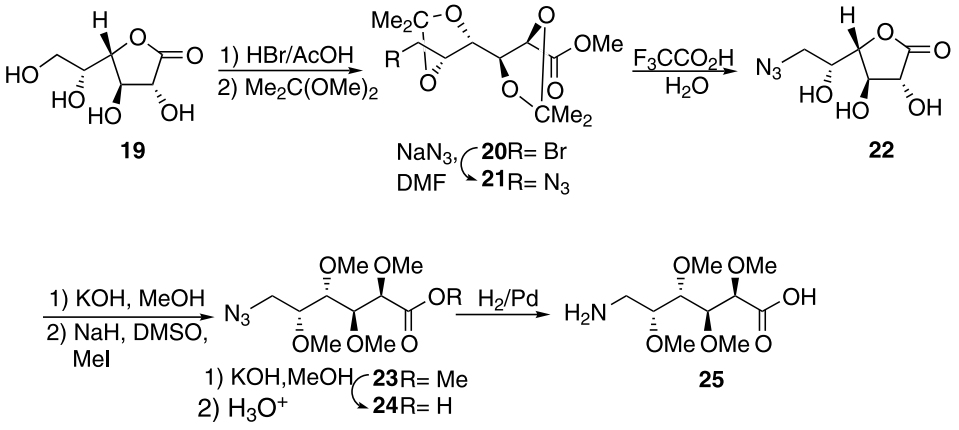
3. Experimental

3.1. General methods

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (E. Merck) aluminum-supported plates (layer thickness 0.2 mm). Visualization of the spots was effected by exposure to UV light or by charring with a solution of 5% (v/v) sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was carried out with Silica Gel 60 (230–400 mesh, E. Merck). Optical rotations were measured with a Perkin–Elmer 343 digital polarimeter at 25°C. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AC 200 or, when indicated, with a Bruker AMX 500 instrument, in $CDCl_3$ solutions (tetramethylsilane as internal standard) unless otherwise indicated. For those fully assigned ^1H NMR spectra, 2D COSY experiments were conducted. For the assignment of the ^{13}C NMR spectra, DEPT techniques were employed. Electron impact-mass spectra (EI-MS) were performed with a Shimadzu QP 5000 mass spectrometer, operating at 70 eV.

3.2. Methyl 5,6-*O*-isopropylidene-2,3,4-tri-*O*-methyl-L-galactonate 3

To a solution of **2**[12] (1.00 g, 4.59 mmol) in dry MeOH (10 mL) was added dropwise and with stirring a 30% solution of KOH in MeOH. When the solution became slightly alkaline (pH ~7.5) the solvent was evaporated under reduced pressure. The resulting solid potassium salt of the L-galactonic acid derivative was dried in vacuum and then dissolved in dimethylsulfoxide (DMSO, 7 mL). The solution was externally cooled (ice bath) after which it was added to a suspension of NaH (1.7 g) in DMSO (10 mL). After 30 min of stirring at room temperature, the mixture was cooled (ice bath) and methyl iodide (2.60 mL) was slowly added with vigorous stirring. When the addition was finished, the reaction mixture was stirred at room temperature for 2 h at which point TLC (5:1 hexane–EtOAc) showed a major product (R_f 0.70) with no starting material being detected. Upon addition of MeOH, the mixture was neutralized with acetic acid, diluted with water (30 mL) and extracted with CH_2Cl_2 (3×80 mL). The organic extract was dried over $MgSO_4$ and then concentrated. Column chromatography purification of the residue afforded **3** (0.72 g, 56%) as an oil, $[\alpha]_D = +10.2$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 4.22 (ddd, 1H, $J_{4,5} = 4.8$, $J_{5,6} = 6.2$, $J_{5,6'} = 8.0$ Hz, H-5), 4.03 (d, 1H, $J_{2,3} = 2.2$ Hz, H-2), 4.01 (dd, 1H, $J_{6,6'} = 8.0$ Hz, H-6), 3.81 (t, 1H, H-6′), 3.80 (s, 3H, CO_2CH_3), 3.65 (dd, 1H, $J_{3,4} = 9.1$ Hz, H-3), 3.48, 3.47, 3.33 (3s, 9H, 3 OCH_3), 3.34 (dd, 1H, H-4), 1.42, 1.37 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR δ 171.7, 108.5, 82.3, 79.2, 79.1, 76.8, 66.1, 60.7, 60.1, 58.6, 51.8, 26.3, 25.7. Anal. calcd for $C_{13}H_{24}O_7$: C, 53.40; H, 8.28. Found: C, 53.73; H, 8.42.



Scheme 5.

3.3. 2,3,4-Tri-*O*-methyl-6-*O*-tosyl-L-galactono-1,5-lactone 4

A solution of **3** (0.14 g, 0.48 mmol) in 5% aqueous HCl was heated at 50°C for about 1 h, while the solvent was slowly evaporated by adjusting the pressure in the rotatory evaporator. The residue obtained upon addition of water and further concentration revealed by TLC the consumption of the starting material. The resulting syrup was dried and dissolved in pyridine (0.7 mL) after which tosyl chloride (0.15 g, 0.78 mmol) was added to the solution. The mixture was stirred at room temperature for 3 h, diluted with water (20 mL) and extracted with CH_2Cl_2 (3×30 mL). The extract was dried and concentrated and the resulting syrup purified by column chromatography with mixtures of hexane–EtOAc of increasing polarity (from 5:1 to 1:1). From the column, was isolated the oil **4** (0.036 g, 20%); $[\alpha]_D=-32.7$ (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.79, 7.36 (2d, 4H, $J=8.4$ Hz, H-aromatic), 4.40 (ddd, 1H, $J_{4,5}=1.8$, $J_{5,6}=7.5$, $J_{5,6'}=5.9$ Hz, H-5), 4.22 (dd, 1H $J_{6,6'}=9.9$ Hz, H-6), 4.08 (dd, 1H, H-6‘), 3.98 (d, 1H, $J_{2,3}=9.5$ Hz, H-2), 3.92 (t, 1H, $J_{3,4}=2.2$ Hz, H-4), 3.54 (dd, 1H, H-3), 3.66, 3.52, 3.51, (3s, 9H, OCH_3), 2.45 (s, 3H, $ArCH_3$); ^{13}C NMR δ 168.9, 145.5, 132.1, 130.0, 128.0, 81.6, 78.8, 75.7, 73.1, 66.3, 61.1, 61.0, 58.5, 21.7. Anal. calcd for $C_{16}H_{22}O_8S.0.5H_2O$: C, 50.12; H, 6.06; S, 8.35. Found: C, 50.49; H, 5.95; S, 8.17.

3.4. 6-*O*-Trityl-L-galactono-1,4-lactone 6

To a suspension of **1** (1.0 g, 5.61 mmol) in anhydrous pyridine (8.4 mL) was added triphenylmethyl chloride (trityl chloride, 1.87 g, 6.72 mmol). The mixture was maintained in the dark with occasional stirring, at room temperature for 48 h. The solvent was evaporated and the residue purified by column chromatography with EtOAc–hexane (from 1:1 to 3:1) to afford crystalline **6** (2.20 g, 93%), mp 77–78°C, $[\alpha]_D=-22.4$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 7.26–7.42 (m, 15H, H-aromatic), 6.08 (d, 1H, $J=6.6$ Hz, disappeared on deuteration, OH), 5.48 (d, 1H, $J=5.3$ Hz, OH), 5.28 (d, 1H, $J=6.6$ Hz, OH), 4.34–4.08 (m, 3H), 3.81 (bq, 1H), 3.10 (dd, 1H, $J=6.3$, $J=8.6$ Hz), 2.93 (bt, 1H, $J=8.4$ Hz); ^{13}C NMR (DMSO-d_6) δ 174.5, 143.6, 128.2, 127.8, 127.0, 86.0, 79.4, 73.8, 72.1, 65.8, 63.9. Anal. calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.48; H, 5.86.

3.5. 2,3,5-Tri-O-acetyl-6-*O*-trityl-L-galactono-1,4-lactone 7

Compound **1** (1.00 g, 2.38 mmol) was tritylated as described previously and to the crude mixture acetic anhydride was added dropwise, while stirring. After 5 h of stirring at room temperature, the mixture was concentrated to a solid residue, which crystallized from a 5:1 hexane–EtOAc to give **7** (2.61 g, 85%); mp 75–77°C; $[\alpha]_D=+35.0$ (*c* 0.9, $CHCl_3$); lit.[19] $[\alpha]_D=-38.7$ for the enantiomer. The ^{1}H and ^{13}C NMR spectra of **7** were identical to those reported for the enantiomer.[19]

3.6. 6-Bromo-6-deoxy-2,3,5-tri-*O*-acetyl-L-galactono-1,4-lactone 8

Hydrogen bromide was bubbled through an externally cooled (ice bath) solution of **7** (0.50 g, 0.92 mmol) in dry CH_2Cl_2 (12.5 mL). The reaction was monitored by TLC (1:1 hexane–EtOAc) and showed a gradual conversion of **7** (R_f 0.66) into a more polar product (R_f 0.57). When the conversion was complete, the solution was concentrated and the residue purified by column chromatography using hexane–EtOAc (from 5:1 to 4:1) to give **8** (0.17 g, 51%); mp 100°C; $[\alpha]_D=+9.2$ (*c* 0.8, $CHCl_3$). Lit.[18] mp 100–101°C; $[\alpha]_D=-10.1$, for the enantiomer.

Alternatively, the bromide **8** was prepared by bromination and acetylation of **1**, following the procedure described by Pedersen[18] for the enantiomer of **1**.

3.7. Methyl 2,3,4,5-tetra-*O*-methyl-6-*O*-trityl-L-galactonate 9

To a solution of **6** (1.00 g, 2.38 mmol) was slowly added 30% KOH in MeOH with stirring. When the alkalinity of the solution (pH ~7.5) persisted for about 30 min, the solvent was evaporated to afford the solid potassium salt (^{13}C NMR (DMSO-d_6) δ 175.6, 144.3, 128.8, 128.4, 127.6, 126.9, 126.7, 85.7, 72.1, 71.8, 70.4, 68.9, 65.7). The dried solid was then dissolved in anhydrous DMSO (6.5 mL), and to this cooled solution (ice bath) was added a suspension of NaH (1.15 g) in DMSO (10 mL). The mixture was stirred at room temperature for 30 min, cooled to 0°C and methyl iodide (1.75 mL) added. After 2 h of vigorous stirring at room temperature, MeOH was added carefully to the suspension, which was then neutralized with acetic acid, diluted with water and extracted with CH_2Cl_2 (3×80 mL). The extract was dried over $MgSO_4$ and concentrated to afford a syrup that was subjected to column chromatography with 5:1 hexane–EtOAc. Compound **9** was isolated as a colorless oil (0.96 g, 80%); $[\alpha]_D=-5.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.49–7.20 (m, 15H), 4.00 (d, 1H, $J=2.0$ Hz, H-2), 3.81 (s, 3H), 3.79 (dd, 1H, $J=2.0$, $J=9.3$ Hz), 3.61–3.45 (m, 3H), 3.47 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H), 3.22 (dd, 1H), 3.21 (s, 3H); ^{13}C NMR δ 172.1, 143.9, 128.8, 128.6, 128.5, 127.8, 127.1, 127.0, 87.2, 80.6, 79.3, 78.8, 78.5, 62.0, 60.6, 59.8, 58.5, 58.3, 51.8. Anal. calcd for $C_{30}H_{36}O_7.H_2O$: C, 68.39; H, 7.29. Found: C, 68.61; H, 7.28.

3.8. Methyl 2,3,4,5-tetra-*O*-methyl-L-galactonate 10

Boron trifluoride–ethyl etherate (0.2 mL) and MeOH (0.6 mL) were added to a solution of **9** (0.75 g, 1.48 mmol) in CH_2Cl_2 (40 mL). The solution was stirred at room temperature for 1 h, when TLC revealed complete consumption of starting **9**. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over $MgSO_4$ and concentrated. The resulting syrup was purified by column chromatography (9:1 EtOAc–hexane) to give oily **10** (0.27 g, 70%); $[\alpha]_D=-10.5$ (*c* 0.9, $CHCl_3$); ^{1}H NMR δ 4.01 (d, 1H, $J=2.0$ Hz), 3.87–3.79 (m, 3H),

3.81 (s, 3H), 3.51–3.42 (m, 2H), 3.49, 3.48, 3.47, 3.35 (4s, 12H); ^{13}C NMR δ 172.0, 81.0, 80.0, 79.4, 79.1, 61.4, 60.5, 59.7, 58.5, 58.0, 51.8. Anal. calcd for $C_{11}H_{22}O_7$: C, 49.61; H, 8.30. Found: C, 50.03; H, 7.97.

3.9. Methyl 2,3,4,5-tetra-*O*-methyl-6-*O*-tosyl-L-galactonate 11

To a solution of **10** (0.10 g, 0.38 mmol) in CH_2Cl_2 (1 mL) and pyridine (0.1 mL) was added tosyl chloride (0.11 g, 0.57 mmol). The mixture was stirred at room temperature for 6 h, when TLC (EtOAc) revealed the complete consumption of the starting material (R_f 0.66). Water (30 mL) was added to the reaction mixture followed by extraction with CH_2Cl_2 (3×50 mL). The organic extract was dried over $MgSO_4$ and concentrated. Chromatographic purification of the residue using 2:1 hexane–EtOAc as solvent gave **11** (0.134 g, 85%); $[\alpha]_D = -14.3$ (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.81, 7.36 (2d, 4H, $J = 8.2$ Hz, H-aromatic), 4.26 (dd, 1H, $J_{5,6} = 6.1$, $J_{5,6'} = 10.1$ Hz, H-2), 3.80 (s, 3H, CO_2CH_3), 3.77 (dd, 1H, $J_{3,4} = 9.3$ Hz, H-3), 3.61 (dt, 1H, $J_{4,5} = 2.0$ Hz, H-5), 3.46, 3.40, 3.35, 3.29 (4s, 12H, 4 OCH_3), 3.42 (dd, 1H, H-4), 2.45 (s, 3H, $ArCH_3$); ^{13}C NMR δ 171.8, 145.0, 132.6, 129.9, 127.9, 85.1, 80.4, 78.9, 78.4, 77.3, 68.0, 60.7, 69.6, 68.8, 68.4, 51.9, 21.6. Anal. calcd for $C_{18}H_{28}O_9S$: C, 51.42; H, 6.71. Found: C, 51.21; H, 6.71.

3.10. Methyl 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonate 12 and methyl 3,6-anhydro-2,4,5-tri-*O*-methyl-L-galactonate 13

3.10.1. Starting from 11. To a solution of **11** (0.12 g, 0.29 mmol) in dry DMF (1.7 mL) was added sodium azide (0.057 g, 0.87 mmol) with the resulting mixture heated to 80°C. After 4 h TLC (10:1 hexane–EtOAc) showed complete conversion of **10** into two main products having R_f 0.76 and 0.62. The mixture was filtered and the filtrate concentrated. The resulting residue was purified by column chromatography (5:1 hexane–EtOAc) to afford compound **12** (0.04 g, 47%); $[\alpha]_D = +4.3$ (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 4.00 (d, 1H, $J_{2,3} = 2.0$ Hz, H-2), 3.81 (s, 3H, CO_2CH_3), 3.80 (dd, 1H, $J_{3,4} = 9.3$ Hz, H-3), 3.62 (dd, 1H, $J_{5,6} = 6.4$, $J_{6,6'} = 12.1$ Hz, H-6), 3.55 (ddd, 1H, $J_{4,5} = 2.2$, $J_{5,6'} = 6.5$ Hz, H-5), 3.50, 3.49, 3.46 (3s, 9H, 3OCH_3), 3.45 (dd, 1H, H-4), 3.42 (dd, 1H, H-6‘), 3.35 (s, 3H, OCH_3); ^{13}C NMR δ 171.9, 80.7, 78.9, 78.8, 78.5, 60.8, 59.6, 58.5, 58.4, 51.9, 50.6 (C-6). Anal. calcd for $C_{11}H_{21}O_6N_3$: C, 45.35; H, 7.27; N, 14.43. Found: C, 45.70; H, 7.26; N, 14.09.

From the next fractions of the column was isolated the more polar product (R_f 0.62), which was identified as the 3,6-anhydro derivative **13** (0.02 g, 24%); $[\alpha]_D = -50.8$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 3.91 (d, 1H, $J_{2,3} = 5.5$ Hz, H-2), 3.81 (ddd, 1H, $J_{4,5} = 2.0$, $J_{5,6} = 2.5$, $J_{5,6'} = 4.6$ Hz, H-5), 3.78 (ddd, 1H, $J_{4,6} = 0.7$, $J_{6,6'} = 10.1$ Hz, H-6), 3.76 (dd, 1H, $J_{3,4} = 4.6$ Hz, H-3), 3.72 (dd, 1H, H-6‘), 3.69 (ddd, 1H, H-4), 3.67, 3.31, 3.28, 3.24 (4s, 12H, CH_3O); ^{13}C NMR ($CDCl_3$) δ 170.5, 85.1, 84.7, 83.4, 80.9, 71.4 (C-6), 58.7, 57.5, 56.8, 52.0; EI-MS: 202 (1%), 175 (6), 143 (5), 131 (63), 104 (12), 101 (45), 99 (58), 75, (22), 73, (44), 71 (57), 59 (20), 58 (25), 45 (100). Anal. calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.03; H, 7.40.

Compound **13** was also prepared starting from **11** (78 mg, 0.18 mmol). A solution of **11** in toluene (1 mL) was heated at 80°C for 16 h, when TLC (EtOAc) showed complete conversion of the starting material (R_f 0.77) into **13** (R_f 0.62). The mixture was concentrated and the residue purified by column chromatography (2:1 hexane–EtOAc) to afford the oil **13** (40 mg, 92%), which showed the same spectral and physical properties as those described previously.

3.10.2. Synthesis of 12 starting from 6-azido-6-deoxy-L-galactono-1,4-lactone 16. Compound **16** (0.69 g, 3.39 mmol) was treated with 30% solution of KOH in MeOH, as described for the preparation of **3** and **9**. The resulting salt was dried, dissolved in DMSO (6 mL), slowly added to a suspension of NaOH (1.20 g) in DMSO (8.6 mL) and then cooled to 0°C (ice-bath). The mixture was vigorously stirred for 20 min, and upon the dropwise addition of methyl iodide (2.3 mL), was stirred at room temperature for 2.5 h. The usual work-up of the reaction mixture, followed by chromatographic purification (5:1 hexane–EtAcO), led to **12** (0.76 g, 77%). Compound **12** gave the same physical and spectral properties as the product described in Section 3.10.1.

3.11. Methyl 6-bromo-6-deoxy-2,3:4,5-di-*O*-isopropylidene-L-galactonate 14

Compound **1** (1.00 g, 5.62 mmol) was dissolved in 32% HBr in acetic acid (7.5 mL). The solution was stirred at room temperature for 2 h, when TLC (10:1 EtOAc–MeOH) showed just a main spot (R_f 0.43) and none of the starting material **1** (R_f 0.13). MeOH was added slowly and the solution concentrated. This procedure was repeated twice in order to remove the acids. The crude product was dissolved in 2,2-dimethoxypropane (26 mL) and acetone (2 mL) and the solution stirred for 16 h at room temperature. Monitoring of the mixture by TLC (5:1 hexane–EtOAc) showed a single spot having an R_f value of 0.43. The solution was neutralized with concentrated aqueous ammonia and the solvent evaporated. The resulting residue was purified by column chromatography (10:1 hexane–EtOAc) to give crystalline **14** (1.97 g, 99%); mp 52°C; $[\alpha]_D = +7.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 4.57 (d, 1H, $J_{2,3} = 5.2$ Hz, H-2), 4.39 (dd, 1H, $J_{3,4} = 7.2$ Hz, H-3), 4.23 (ddd, 1H, $J_{4,5} = 6.8$, $J_{5,6} = 4.3$, $J_{5,6'} = 5.2$ Hz, H-5), 3.96 (t, 1H, H-4), 3.80 (s, 3H, CO_2CH_3), 3.64 (dd, 1H, $J_{6,6'} = 10.9$ Hz, H-6), 3.50 (dd, 1H, H-6‘), 1.47, 1.45, 1.41 (3s, 12 H, 2 $(CH_3)_2C$); ^{13}C NMR δ 171.2, 112.4, 110.1, 79.8, 79.7, 78.6, 77.3, 52.5, 32.8, 27.3, 27.1, 26.0. Anal. calcd for $C_{13}H_{21}O_6Br$: C, 44.21; H, 5.99; Br, 22.62. Found: C, 44.49; H, 6.02; Br, 22.44.

3.12. Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-L-galactonate 15

A solution of **14** (1.58 g, 4.36 mmol) and sodium azide (0.55 g, 8.72 mmol) was stirred at 85°C for 16 h. TLC

(5:1 hexane–EtOAc) revealed a single spot (R_f 0.40) having similar mobility of the starting material (R_f 0.42). However, the color of the spot with the *p*-anisaldehyde–H_2SO_4 reagent was brown for the azide and black for **13**. The mixture was cooled, filtered, and concentrated to a syrup, which was subjected to chromatographic purification (3:1 hexane–EtOAc). Compound **15** (1.20 g, 87%) was isolated as a colorless oil, $[\alpha]_D = -30.0$ (*c* 0.8, $CHCl_3$). (Lit.[23] $[\alpha]_D = +30.9$ for the enantiomer). The ^1H and ^{13}C NMR spectra were identical to those reported for the enantiomer.[23]

3.13. 6-Azido-6-deoxy-L-galactono-1,4-lactone 16

A solution of **15** (1.00 g, 13.17 mmol) in trifluoroacetic acid-water (4:1 14 mL) was stirred at room temperature. After 2.5 h, TLC (EtOAc) showed complete conversion of **15** into a more polar product (R_f 0.53). The solution was concentrated and the syrup was chromatographically purified (3:1 EtOAc–hexane) to afford **16** (0.60 g, 93%); $[\alpha]_D = +65.1$ (*c* 0.8, EtOAc). (Lit.[23] $[\alpha]_D = -70.3$ for the enantiomer). The spectral data of **16** were identical to those reported for the enantiomer.[23]

3.14. 6-Azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid 17

To a solution of **12** (0.41 g, 1.41 mmol) in MeOH-water (3:1 4 mL) was added KOH (0.10 g) dissolved in MeOH (0.3 mL). The mixture was stirred at room temperature for 3 h, when TLC (1:1 hexane–EtOAc) showed no starting material **17** (R_f 0.70) remaining. The solution was diluted with 5% aqueous KOH (30 mL) and extracted with CH_2Cl_2 (2×30 mL). The aqueous phase was acidified (pH 2–3) with 10% aqueous HCl and extracted with CH_2Cl_2 (3×50 mL). The organic extract was dried over $MgSO_4$ and concentrated to syrupy **17** (0.35 g, 90%). This crude product was pure enough for the following step. A portion was chromatographed (4:1 hexane–EtOAc) to give analytically pure **17**; $[\alpha]_D = +7.6$ (*c* 0.7, MeOH); lit.[9] $[\alpha]_D = -11$ for the enantiomer. The ^1H and ^{13}C NMR spectra of **17** were identical to those of the enantiomer.[9]

3.15. 6-Amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid 18

Hydrogenation of crude **17** (0.26 g, 0.94 mmol) under the conditions already described,[9] followed by ion exchange chromatography afforded **18** (0.22 g, 93%); mp 172°C (decomposition); $[\alpha]_D = -20.6$ (*c* 0.8, H_2O). Lit.[9] mp 161°C, $[\alpha]_D = +13$ for the enantiomer, and identical NMR data.

3.16. Synthesis of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid 25

The synthesis of **25** from D-galactono-1,4-lactone **19** was performed following the sequence depicted in Scheme 5. All the steps were conducted as described for the preparation of the analogous intermediates of the L-series (Scheme 4). The yield of the product and its optical rotation is reported for each individual case. The ^1H and ^{13}C spectra of **20**–**25** were identical to those of the respective analogue in the L-series **13**–**18**.

3.16.1. Methyl 6-bromo-6-deoxy-2,3:4,5-di-*O*-isopropylidene-L-galactonate 20. Yield 93%; $[\alpha]_D = -7.6$ (*c* 1.3, $CHCl_3$).

3.16.2. Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-L-galactonate 21. Yield 85%; $[\alpha]_D = +29.4$ (*c* 1.1, $CHCl_3$).

3.16.3. 6-Azido-6-deoxy-L-galactono-1,4-lactone 22. Yield 93%; $[\alpha]_D = -75.8$ (*c* 0.8, $CHCl_3$).

3.16.4. Methyl 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonate 23. Yield 74%; $[\alpha]_D = -2.7$ (*c* 1.4, $CHCl_3$).

3.16.5. 6-Azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid 24. $[\alpha]_D = -8.2$ (*c* 1.0, $CHCl_3$).

3.16.6. 6-Amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid 25. Yield 86% (from **23**); $[\alpha]_D = +20.0$ (*c* 0.9, H_2O).

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