Tetrahedron Letters 53 (2012) 2253–2256

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

1,2;3,4-Di-*O*-isopropylidene-L-galactose synthesis from its D-enantiomer

Bogdan Doboszewski [†], Piet Herdewijn [*]

Rega Institute for Medical Research, Laboratory of Medicinal Chemistry, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 30 November 2011
Revised 14 February 2012
Accepted 20 February 2012
Available online 28 February 2012

Keywords:
L-Galactose
D-Galactose
Acetyl migration

ABSTRACT

Easy procedure was devised to obtain di-*O*-isopropylidene-L-galactose from di-*O*-isopropylidene-D-galactose.

D-Galactose is an easily available hexose whose alditol has a plane of symmetry. This implies an enantiotopic relation between both terminal hydroxymethyl groups in galactitol, and enables a transformation of D-galactose into L-galactose or vice versa as shown in the Scheme 1. The same applies to other sugars like erythrose, xylose, ribose, and allose.

Transformation of D-Gal into L-Gal based on this principle is known[1–4] and requires sodium amalgam as a critical reducer. Due to current environmental concerns, the use of large quantities of mercury is unacceptable. Consequently we searched for an alternative method of synthesis of L-Gal starting from D-Gal.

L-Galactose can be obtained from natural sources (flaxseed,[5] galactogen[6], or seaweeds[7]), from L-ascorbic acid,[8] from 1-deoxy-1-nitro-L-galactitol[9] (obtainable from L-xylose), from 1-L-(−)-2-*O*-methyl-chiroinositol (quebrachitol),[10] via total synthesis using either furfural[11] or allyl alcohol,[12] or via enzymatic processes which use either galactitol[13–15] or L-sorbose[16] as substrates. Dithioacetals of D-Gal were used to mask the carbonyl function during conversion into L-Gal,[17,18] and finally 6,7-dideoxy-1,2;3,4;-di-*O*-isopropylidene-α-D-galacto-hept-6-enose was used.[19] Total syntheses of carbohydrates in general have been reviewed.[20–22]

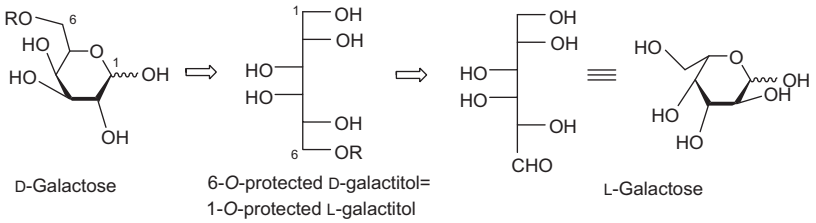
Our interest in L-galactose results from a possibility to use it as a source of the C3 chiral fragment **1**, as shown in the Figure 1. Since enantiomeric **2** can be obtained from D-galactose, the procedure would be stereospecific and would allow accessing both **1** and **2** via uniform procedures.

Our initial approach to get L-Gal from D-Gal is shown in the Scheme 2.

The known 6-*O*-*t*-butyldiphenylsilyl-D-galactopyranose **3**[23,24] was sequentially reduced with $NaBH_4$ (→**4**) and conventionally acetylated (→**5**). Apparently simple desilylation with Bu_4NF for 20 min at rt furnished 1,2,3,5,6-penta-*O*-acetyl-D-galactitol **7** as the only product. Evidently, under slightly basic conditions acetyl group migration took place in initially formed **6** presumably via a chair-like conformation **8** which approximates 6-OH group and the carbonyl group of the 4-OAc. The position of the acetates was established by heteronuclear multiple bond correlation (HMBC) spectrum, which shows no cross-peak joining the signal of the H4 and a carbonyl group via three bonds. It should be stressed that in the substrate **5**, there is no correlation between the signals of both $-C\mathbf{H_2}-OSi\mathit{t}BuPh_2$ hydrogen atoms and a carbonyl group which proves that no silicon migration took place during either a reduction (→**4**) or during acetylation (→**5**). As a point of interest: bulky $\mathit{t}BuPh_2Si-$ prefers primary versus secondary positions by *ca* 8–9 kJ/mol.[25] Migrations of the acetyl (acyl) groups are a known phenomenon which can take place in basic, acidic, or neutral medium,[26] occur in acyclic[27,28] or cyclic compounds,[29–35] and can be either intra- or intermolecular.[32] Such migrations are a frequent nuisance during desilylations using tetrabutylammonium fluoride (TBAF) due to the presence of water which makes it basic and promotes migrations via transient orthoesters.[27,28,31,32] Neutralization of TBAF with acetic acid is known to suppress this process[36–38] but due to variable quantities of water in commercial reagents, this is rather inconvenient. It should be firmly stressed that acetyl migrations are known even in neutral medium.[26] Anhydrous organic sources of the fluoride anion are known, for example, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF),[39] tetrabutylammonium tetra(*t*-butanol) fluoride[40] or genuinely

* Corresponding author. Tel.: +32 16 337387; fax: +32 16 337340.
E-mail address: piet.herdewijn@rega.kuleuven.be (P. Herdewijn).
† Permanent address: Departamento de Química, Universidade Federal Rural de Pernambuco, 52171-900 Recife, PE, Brazil.

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2012.02.091



Scheme 1. Transformation of D-galactose into L-galactose.

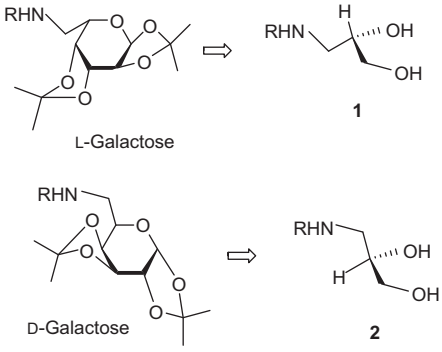


Figure 1. Application of L- and G-galactose derivatives as a source of chiral C3 fragments.

anhydrous tetrabutylammonium fluoride[41] prepared from hexafluorobenzene, and tetrabutylammonium cyanide (see Ref. 42 for the results of attempted drying of $Bu_4NF \times H_2O$). These reagents are rather inconvenient due to their hygroscopic nature, or a necessity to prepare them before use. Considering these factors the use of **4** as a starting material to obtain the target **17** was abandoned.

Compound **7** co-crystallized upon mixing with triphenylphosphine oxide[43,44] and was submitted to X-ray analysis.

Since pivaloyl groups are less prone to migrate,[26] we tried to obtain 6-*O*-*t*-butyl-diphenylsilyl-1,2,3,4,5-penta-*O*-pivaloyl-D-galactitol. Nevertheless, attempts to get this compound by reaction of **4** with pivaloyl chloride in pyridine and DMAP resulted in complex mixtures.

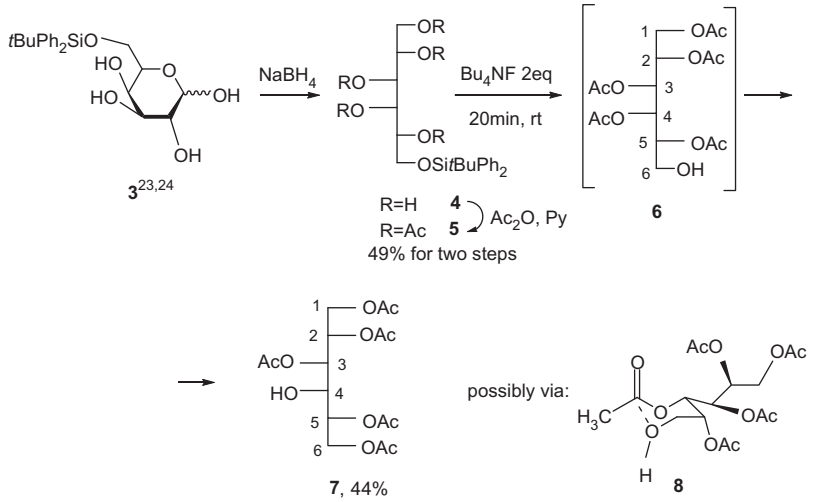
The disappointing result presented above prompted us to examine an alternative strategy as shown in the Scheme 3.

Isopropylidene groups in the known 6-*O*-benzyl-diisopropylidene-D-galactose **10**[45] were hydrolyzed by treatment with 80% trifluoroacetic acid, and without characterization the resulting **11** was reduced ($NaBH_4$) and conventionally acetylated to furnish 1,2,3,4,5-penta-*O*-acetyl-6-*O*-benzyl-D-galactitol **13**. This compound can be also named 2,3,4,5,6-penta-*O*-acetyl-1-*O*-benzyl-L-galactitol, but we prefer the former name to stress the origin of this compound from D-galactose. Hydrogenation over Adamś catalyst furnished the overreduced cyclohexylmethyl ether **14** together with the expected 1,2,3,4,5-penta-*O*-acetyl-D-galactitol **6**, which can be easily separated by flash chromatography. No acetyl migration in **6** took place during handling or chromatography as evidenced by the HBMC spectrum: the $-C\mathbf{H_2}OH$ protons do not correlate with any of the carbonyl groups present. A structure of **6** was submitted to X-ray analysis and will be published in due course. Subsequent Dess–Martin periodinane oxidation by analogy to a published procedure[46] (→**15**), followed by Zemplén deacetylation (→**16**) and final isopropylidenation furnished the target 1,2;3,4-di-*O*-isopropylidene-L-galactose **17**, whose properties (^1H, ^{13}C and optical rotation) match those of the compound obtained by direct acetonation of L-galactose.[47]

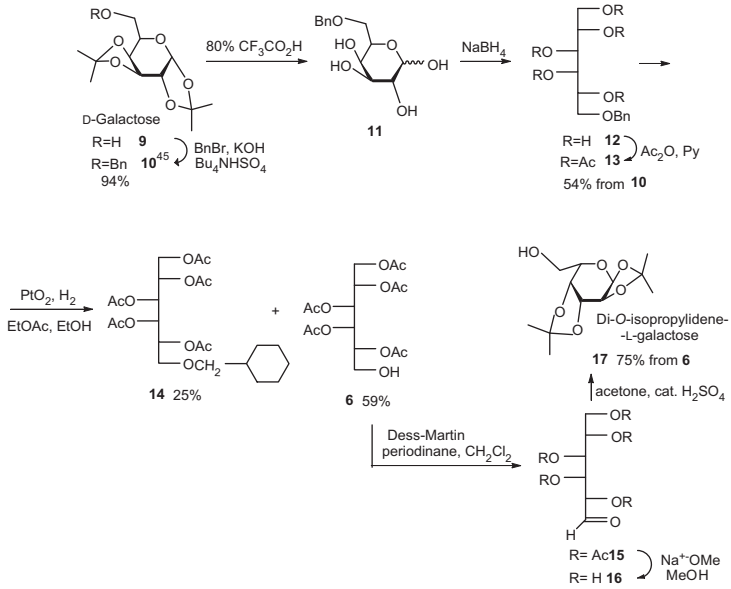
In conclusion, easy conversion[48] of commercial diisopropylidene-D-galactose into diisopropylidene-L-galactose was devised, which complements the existing methods described in the Refs. 17–19, and which avoids toxic mercury[1–4] or badly smelling sulfur compounds.[17,18]

Acknowledgments

Professor Eveline Lescrinier and Professor Jef Rozenski, Laboratory of Medicinal Chemistry, Rega Institute, are thanked for 500 MHz and exact mass measurements, respectively, Professor



Scheme 2. Formation of 1,2,3,5,6-penta-*O*-acetyl-D-galactitol (1,2,4,5,6-penta-*O*-acetyl-L-galactitol) **7** during desilylation of **5**.



Scheme 3. Synthesis of di-*O*-isopropylidene-L-galactose **17** from its enantiomer **9**.

Wim De Borggraeve, Department of Chemistry, Katholieke Universiteit Leuven for access to the medium pressure Parr hydrogenation facilities, and Chantal Biernaux and Christiane Callebaut for editorial work.

References and notes

1. Glatthaar, C.; Reichstein, T. *Helv. Chim. Acta* **1937**, *20*, 1537–1541.
2. Frush, H. L.; Isbell, H. S. *Methods Carbohydr. Chem.* **1962**, *1*, 127–131. Whistler.
3. Pizzarello, R. A.; Freudenberg, W. *J. Am. Chem. Soc.* **1939**, *61*, 611–613.
4. Binch, H.; Stangier, K.; Thiem, J. *Carbohydr. Res.* **1998**, *306*, 409–419.
5. Anderson, E. *J. Biol. Chem.* **1933**, *100*, 249–253.
6. May, F.; Wieland, H. *Hoppe Seylers Z. Physiol. Chem.* **1954**, *296*, 154–166.
7. Nunn, J. R.; von Holdt, H. H. *J. Chem. Soc.* **1957**, 1094–1097.
8. Kim, K. S.; Cho, B. H.; Shin, I. *Bull. Korean Chem. Soc.* **2002**, *23*, 1193–1194.
9. Kubala, J.; Caplovic, J.; Svec, J. Czechoslovak Patent CS 227527 (B1), **1985**; *Chem. Abstr.* **1985**, *106*, 176796.
10. Chida, N.; Suzuki, M.; Suwama, M.; Ogawa, S. *J. Carbohydr. Chem.* **1989**, *8*, 319–332.
11. Takeuchi, T.; Taniguchi, T.; Ogasawara, K. *Synthesis* **1999**, 341–354.
12. Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245–264.
13. Yadav, K. K.; Vernwal, S. K.; Afaq, Z.; Yadav, K. D. S. *Indian J. Chem. Techn.* **2002**, *9*, 218–222.
14. Yadav, K. K.; Vernwal, S. K.; Afaq, Z.; Yadav, K. D. S. *J. Sci. Ind. Res. India* **2002**, *61*, 361–365.
15. Woodyer, R. D.; Christ, T. N.; Deweese, K. A. *Carbohydr. Res.* **2010**, *345*, 363–368.
16. Leang, K.; Maekawa, K.; Menavuvu, B. T.; Morimoto, K.; Granström, T. B.; Takada, G.; Izumori, K. *J. Biosci. Bioeng.* **2004**, *97*, 383–388.
17. González, F. S.; Baer, H. H. *Carbohydr. Res.* **1990**, *202*, 33–47.
18. Brackhagen, M.; Boye, H.; Vogel, C. *J. Carbohydr. Chem.* **2001**, *20*, 31–43.
19. Lay, H.; Lehmann, J.; Ziser, L.; Reutter, W. *Carbohydr. Res.* **1989**, *195*, 145–149.
20. ÓAllonzo, D.; Guaragna, G.; Palumbo, G. *Curr. Org. Chem.* **2009**, *13*, 71–98.
21. Vogel, P.; Robina, I. Synthesis of Monosaccharides and Analogs In *Comprehensive Glycoscience*; Camerling, J. P., Ed.; Elsevier, 2007; Vol. 1, pp 489–582. chapter 1.13.
22. Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1–129.
23. Fylaktakidou, K. C.; Duarte, C. D.; Koumbis, A. E.; Nicolau, C.; Lehn, J.-M. *ChemMedChem* **2011**, *6*, 153–168.
24. Boto, A.; Hernández, D.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2006**, *71*, 1938–1948.
25. Muzler, J.; Schöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431–432.
26. Tomić, S.; Petrović, V.; Matanović, M. *Carbohydr. Res.* **2003**, *338*, 491–494.
27. Stamatov, S. D.; Stawiński, J. *Org. Biomol. Chem.* **2010**, *8*, 463–477.
28. Stamatov, S. D.; Stawiński, J. *Org. Biomol. Chem.* **2007**, *5*, 3787–3800.
29. Angyal, S. J.; Melrose, G. J. H. *J. Chem. Soc.* **1965**, 6494–6500.
30. Nkambule, C. M.; Kwezi, N. W.; Kinfe, H. H.; Nokwequ, M. G.; Gammon, D. W.; Oscarson, S.; Karlsson, E. *Tetrahedron* **2011**, *67*, 618–623.
31. Hamdouchi, C.; Jaramillo, C.; Lopez-Prados, J.; Rubio, A. *Tetrahedron Lett.* **2002**, *43*, 3875–3879.
32. Chevallier, O. P.; Migaud, M. E. *Beilstein. Org. Chem.* **2006**, *2*.
33. Roslund, M. U.; Aitio, O.; Wärnå, J.; Maaheimo, H.; Murzin, D. Y.; Leino, R. *J. Am. Chem. Soc.* **2008**, *130*, 8769–8772.
34. Yoshimoto, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1983**, *31*, 4324–4334.
35. Kovač, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1985**, *140*, 313–318.
36. DiLauro, A. M.; Seo, W.; Philips, S. T. *J. Org. Chem.* **2011**, *76*, 7352–7358.
37. Wu, X.; Zhou, J.; Snider, B. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1283–1286.
38. Siegel, D. S.; Piizi, G.; Piersanti, G.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 9292–9304.
39. Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436–6437.
40. Kim, D. W.; Jeong, H.-J.; Lim, S. T.; Sohn, M. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 8404–8406.
41. Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051.
42. Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112–2114.
43. Etter, M. C.; Baures, P. W. *J. Am. Chem. Soc.* **1988**, *110*, 639–640.
44. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126.
45. Ballou, C. E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1954**, *76*, 3188–3193.
46. Hajkó, J.; Liptak, A.; Pozsgay, V. *Carbohydr. Res.* **1999**, *321*, 116–120.
47. Pedatella, S.; Guaragna, A.; ÓAlonzo, D.; De Nisco, M.; Palumbo, G. *Synthesis* **2006**, 305–308.
48. 6-*O*-*t*Butyldiphenylsilyl-D-galactopyranose **3**: D-galactose (18.0 g; 100 mmol) was silylated in dry DMF (1800 mL) using *t*BuPh$_2$SiCl, (27.2 mL; 28.9 g; 105 mmol) and Et$_3$N (19.4 mL; 14.1 g; 140 mmol) under argon during 20 h. Extraction (EtOAc-brine), drying, evaporation, and chromatography (gradient CH_2Cl_2–MeOH 100:11→100:14 furnished a colorless foam (32.6 g; 78%; R_f 0.26 CH_2Cl_2–MeOH); α_D +15.6° (c 5.1; MeOH; not reported in Refs. 23,24). ^{1}H(300 MHz, DMSO-d_6 after exchange with D_2O): 7.68–7.40(two groups of signals), 4.25 (d, J = 7.2 Hz), 3.96(t, J = 6.5 Hz), 3.87–3.72(unresolved signal superimposed on HOD), 3.64–3.46(m), 3.30 (dd, J = 3.1 Hz, 9.6 Hz), 3.24(dd, J = 7.1 Hz, 9.5 Hz), 0.96(s, 9H). ^{13}C (75 MHz, DMSO-d_6): 135.07, 135.02, 133.12, 133.07, 133.04, 129.78,127.84, 97.49, 92.69, 74.51, 73.43, 71.99, 70.14, 69.38, 3876, 68.67, 68.09, 63.00, 62.95, 26.64, 18.79.
1,2,3,4,5-Penta-*O*-acetyl-6-*O*-*t*butyldiphenylsiyl-D-galactitol **5**: Compound **3** (8.14 g; 19.5 mmol) in techn. EtOH (60 mL) was cooled in ice-water bath and $NaBH_4$, 0.89 g, 23.5 mmol was added with magnetic stirring. After 1 h, more $NaBH_4$ was added (0.83 g) and water bath was removed. After a total of 6 h the mixture was partitioned between EtOAc, brine, and aq. $(NH_4)_2SO_4$. Aqueous phase was extracted second time with EtOAc. Combined organic phases were washed with H_2O, dried, evaporated, and co-evaporated with MeOH (500 mL) twice. Final drying furnished **5** as a foam, 8.39 g evidently contaminated (theoretical yield is 8.18 g). Exact mass (electrospray): calc. for $C_{22}H_{32}O_6Si+Na^+$ = 443.1866, found: 443.1852. This material was acetylated overnight using pyridine (150 mL), Ac_2O (70 mL), and DMAP (0.5 g). Conventional extractive work-up and co-evaporation with xylenes followed by chromatography in hexane-EtOAc 3:1 furnished **5** (6.0 g; 49% for two steps) which spontaneously crystallized. Mp. 105–120°, R_f 0.41 (hexane–EtOAc 3:1), α_D −18.2° (c 2.7; $CHCl_3$), exact mass (electrospray): calc. for $C_{32}H_{42}O_{11}Si+Na^+$ = 653.2394, found: 653.2393. ^{1}H (500 MHz, $CDCl_3$, connectivity established by COSY): 7.615–7.365 (H aromatic), 5.450 (dd, J = 1.8 Hz, 9.9 Hz, 1H, H4), 5.314 (dd, J = 1.9 Hz, 9.9 Hz, 1H, H3), 5.24–5.20 (unresolved, 2H, H2,5), 4.275 (dd, J = 4.9 Hz, 11.7 Hz, 1H, H1a), 3.851 (dd, J = 11.7 Hz, 11.7 Hz, 1H, H1b), 3.595 (d, J = 10.8 Hz, 1H), 3.559 (d, J = 11.0 Hz, 1H), 2.113, 2.080, 2.026, 2.015, 1.951(five s, total 15H). ^{13}C (75 MHz, $CDCl_3$): 170.60, 170.43, 170.31, 169.99, 169.59, 135.80, 135.69, 133.12, 133.04, 129.99,

129.95, 127.88, 70.18, 67.98, 67.85, 67.37, 62.39, 61.74, 26.84, 20.97, 20.84, 20.80, 20.59, 19.24.

1,2,3,5,6-Penta-*O*-acetyl-D-galactitol (1,2,4,5,6-penta-*O*-acetyl-L-galactitol) **7**: Desilylation of **5** (0.22 g; 0.35 mmol) in THF (12 mL) and 1 M Bu_4NF (0.7 mL) during 20 min at rt, followed by extractive work-up (CH_2Cl_2–water) and flash chromatography in hexane–EtOAc 9:11 furnished **7** (0.060 g; 44%) as a syrup which chars very weakly with 2% CrO_3 in 10% aq H_2SO_4 system. α_D +1.3° (c 2.1; $CHCl_3$), R_f 0.37 (hexane–EtOAc 3:1, exact mass (electrospray): calc. for $C_{16}H_{24}O_{11}$+Na^+ = 415.1211, found: 415.1224. ^1H (500 MHz, $CDCl_3$, connectivity established by COSY): 5.479 (ddd, *J* = 1.7 Hz, 4.5 Hz, 7.5 Hz, 1H, H2), 5.175 (ddd, *J* = 1.7 Hz, 4.7 Hz, 7.7 Hz, 1H, H5), 5.100 (dd, *J* = 1.7 Hz, 9.9 Hz, 1H, H3), 4.413 (dd, *J* = 4.7 Hz, 11.7 Hz, 1H, H6a), 4.247 (dd, *J* = 4.5 Hz, 11.9 Hz, H1a), 4.154 (dd, *J* = 7.8 Hz, 11.7 Hz, H6b), 4.20 (dd, *J* = 7.9 Hz, 11.9 Hz, H1b), 3.755 (ddd, *J* = 1.5 Hz, 6.9 Hz, 8.7 Hz, H4), 3.479 (d, *J* = 7.0 Hz, –OH, exchangeable), 2.168, 2.083, 2.076, 2.047, 2.046 (–OAc, total 15H). ^{13}C (75 MHz, $CDCl_3$):172.03, 171.07, 170.61, 170.04, 70.02, 69.45, 68.71, 67.82, 63.36, 62.86, 20.93, 20.77.6.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-benzyl-D-galactose **10**: To a solution of commercial 1,2;3,4-di-*O*-isopropylidene-D-galactose (Acros, α_D-56.8° c 5.9 $CHCl_3$) (20.8 g; 80 mmol) in toluene (100 mL) was added KOH (30 g; crushed in a mortar under protective layer of hexane), benzyl bromide (16.6 mL; 24 g; 140 mmol), and Bu_4NHSO_4 (0.5 g). This mixture was magnetically stirred on an oil bath at ca 100°. After ca 30 min most of KOH formed lumps. Water (30 mL) was added to solubilize KOH and to change a mode of catalysis from solid-liquid to liquid–liquid. After a total time of 3 h, TLC showed that all substrate R_f 0.21 formed the product R_f 0.64 (hexane–EtOAc 3:1). Organic phase was separated and washed with dil. HCl, and twice with water. Evaporation and chromatography (gradient hexane–EtOAc 20:1→20:2→20:3) furnished **10** as an oil, (26.3 g; 94%) α_D −68° (c 6.7; $CHCl_3$), α_D was not mentioned in Ref. 45. ^1H(300 MHz, $CDCl_3$): 7.36–7.25(H aromatic), 5.54 (d, *J* = 5.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.60(dd, *J* = 2.4 Hz, 7.8 Hz, 1H), 4.55(d, *J* = 12.1 Hz, 1H), 4.31(dd, *J* = 2.3 Hz, 5.0 Hz, 1H), 4.27(dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 4.01(dt, *J* = 1.7 Hz, 6.1 Hz, 6.1 Hz, 1H), 3.70(dd, *J* = 5.9 Hz, 10.0 Hz, 1H), 3.61 (dd, *J* = 6.7 Hz, 10.0 Hz, 1H), 1.54, 1.44, 1.34, 1.33(four s, 12H total). ^{13}C (75 MHz, $CDCl_3$): 138.56, 128.51, 127.91, 127.74, 109.43, 108.74, 96.59, 73.52, 71.40, 70.88, 70.83, 69.10, 67.11, 26.31, 26.20, 25.15, 24.66.

1.2.3.4.5-Penta-*O*-acetyl-6-*O*-benzyl-D-galactitol **13**: Compound **10** (24.2 g; 69.1 mmol) was mixed with 80% aq CF_3CO_2H. After 15 min TLC showed that all the substrates reacted to form a new spot R_f 0.45 (CH_2Cl_2–MeOH 4:1). The volatiles were removed by evaporation and the residue was briefly dried on an oil pump. Water 200 mL was added to a residual oil followed by Amberlite IRA 400 $^-$OH until neutrality. The resin was filtered and washed with water 1 L. Combined filtrates were evaporated and thoroughly dried on an oil pump to furnish **11** (13.8 g); exact mass: calc. for $C_{13}H_{18}O_6$+Na^+ = 293.0996, found: 293.1021. Alternatively 1 M HCl can be used to hydrolyze the acetonides.[49] The crude **11** was solubilized in techn. EtOH (50 mL) and water (180 mL) and after chilling in ice-bath, $NaBH_4$ (2.8 g; 75 mmol) was added portionwise during *ca* 10 min while maintaining magnetic stirring. The cooling bath was removed. After 2 h, more $NaBH_4$ (1.3 g) was added. After a total reduction time of 3 h, dil. AcOH was added and the opaque solution was passed successively through a bed of Amberlite IRA 400 $^-$OH followed by Amberlite IRC 50 H^+. The resins were washed with MeOH–H_2O 9:1 mixture. Combined filtrates were evaporated, and co-evaporated four times with MeOH (400 mL) to remove any boron compounds potentially present. After final drying on an oil pump, the residue was acetylated in pyridine (180 mL), Ac_2O (120 mL), and DMAP (1 g). After overnight reaction TLC showed a spot R_f 0.31 (hexane–EtOAc 7:3), together with minor impurities. Extractive work-up and chromatography in hexane-EtOAc 2:1 yielded **13** (13.3 g; 54%) for three steps of oil which spontaneously crystallized. Mp 112–115°, α_D −18.2° (c 1.6; $CHCl_3$). Data for enantiomeric product prepared via dithioacetal of D-galactose[50]: mp 107–109°, α_D (+20.3°; c 3.7; $CHCl_3$). Exact mass: calcd for $C_{23}H_{30}O_{11}$+Na^+ = 505.1680, found: 505.1674. ^1H (300 MHz, $CDCl_3$): 7.35-7.27 (H aromatic), 5.42 (dd, J = 1.8 Hz, 9.9 Hz, 1H), 5.34 (dd, *J* = 1.9 Hz, 9.9 Hz, 1H), 5.31–5.23 (m, 2H),4.49 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.27 (dd, *J* = 4.8 Hz, 11.7 Hz, 1H), 3.85(dd, *J* = 7.5 Hz, 11.6 Hz, 1H),3.45(d, *J* = 6.1 Hz, 2H), 2.09, 2.08, 2.07, 2.03, 2.01five s, 15H; ^{13}C (75 MHz, $CDCl_3$): 170.53, 170.41, 169.92, 127.91, 137.69, 128.51, 127.94, 127.92, 73.52, 68.44, 67.91, 67.85, 67.78, 62.40, 20.97, 20.86, 20.73.

1,2,3,4,5-Penta-*O*-acetyl-6-*O*-cyclohexylmethyl-D-galactitol **14** and 1,2,3,4,5-penta-*O*-acetyl-D-galactitol **6**: Compound **13** (1.74 g; 3.6 mmol) was solubilized in EtOAc (20 mL) and abs. EtOH was added (20 mL) followed by PtO_2 (0.149 g) in a medium pressure vessel and hydrogenation was performed on a Parr apparatus during 3 h at initial pressure of 45 psi. Tlc sprayed with Hanessiańs stain showed strongly charring spot of **14** R_f 0.81 (hexane–EtOAc 9:1) and very weakly charring spot of **6** R_f 0.45; substratés R_f is 0.74. Filtration through a sintered glass (attention: Pt must not be let dry to avoid potential self-ignition), evaporation and flash chromatography using a gradient hexane–EtOAc.

2:1→9:12, gave **14** (0.45 g; 25%) and **6** (0.84 g; 59%). Data of **14**: mp 95–97° (hexane–EtOAc), α_D −7.1° (c 2.6; $CHCl_3$), exact mass: calc. for $C_{23}H_{36}O_{11}$+H^+ = 489.2330, found: 489.2333. ^1H(300 MHz, $CDCl_3$): 5.38–5.21 (m, 4H), 4.28 (dd, *J* = 4.8 Hz, 11.7 Hz, 1H), 3.85 (dd, *J* = 7.5 Hz, 1107 Hz, 1H), 3.37 (apparent d, *J* = 6.1 Hz, 2H), 3.21 (dd, *J* = 6.6 Hz, 9.0 Hz, 1H), 3.11 (dd, *J* = 6.4 Hz, 9.0 Hz, 1H), 2.11, 2.09, 2.08, 2.07, 2.02 five s, total 12H, 1.71–1.51, 1.28–1.11 and 0.93–0.86 three groups of multiplets, total 11H. ^{13}C (75 MHz, $CDCl_3$): 170.53, 170.39, 170.36, 169.94, 169.79, 77.47, 69.31, 68.47, 67.94, 67.88, 67.77, 62.42, 37.99, 29.94, 26.68, 25.94, 20.94, 20.82, 20.74. Data of **6**: mp. 145–147° (hexane–EtOAc), α_D −19.9° (c 4; $CHCl_3$), exact mass: cacl. for $C_{16}H_{24}O_{11}$+Na^+ = 415.1211, found: 415.1215. ^1H (500 MHz, $CDCl_3$; connectivity established by COSY): 5.257 (dd, J_{32} = 2.0 Hz, J_{34} = 10.0 Hz, H3), 5.235 (ddd, J_{23} = 2.0 Hz, J_{21a} = 4.7 Hz, J_{21b} = 7.6 Hz, H2), 5.176 (dd, J_{45} = 1.8 Hz, J_{43} = 10.0 Hz, H4), 4.924 (ddd, J_{54} = 1.7 Hz, J_{56} = 6.3 Hz, J_{56} = 7.3 Hz, H5), 4.158 (dd, J_{1a2} = 4.7 Hz, J_{11} = 11.7 Hz, H1a), 3.742 (dd, J_{1b2} = 7.6 Hz, J_{11} = 11.7 Hz, H1b) 3.454–3.407 (m, H6a), [after D_2O exchange: dd, J_{65} = 6.2 Hz, J_{66} = 11.8 Hz], 3.338–3.301(m, H6b), [after D_2O exchange: dd, J_{65} = 7.7 Hz, J_{66} = 11.7 Hz], 2.826 (t, *J* = 5.8 Hz, exchangeable, –OH), 2.018, 1.992, 1.961, 1.903. ^{13}C (125 MHz, $CDCl_3$):171.17, 170.45, 170.41, 170.25, 169.73, 70.01, 67.76, 67.61, 67.35, 62.24, 59.91, 20.69, 20.57, 20.53, 20.45.

1,2;3,4-Di-*O*-isopropylidene-L-galactose **17**. To a magnetically stirred solution of **6** (1.34 g; 3.4 mmol) in dry CH_2Cl_2 (24 mL) was added a solution of Dess–Martin periodinane (Acros, 15 wt %, 0.35 mmol/mL) (14.6 mL; 5.1 mmol). The solution became turbid in a few min. After 1 h 20 min aq. sat.$NaHCO_3$ and aq. $Na_2S_2O_3$ were added and stirring was continued for 10 min. Extractive work-up (CH_2Cl_2-brine) and evaporation of volatiles furnished colorless oil of the 2,3,4,5,6-penta-*O*-acetyl-aldehydo-L-galactose **15** (exact mass: calc. for $C_{16}H_{22}O_{11}$+Na^+ = 413.1054, found: 413.1056), which chars intensely with Hanessiańs stain and has R_f practically the same as that of the substrate **6**. Abs. MeOH (30 mL) was added followed by a piece of Na. The resulting yellowish oil was kept in a refrigerator overnight. All **15** have disappeared to form L-galactose **16** (exact mass: calc. for $C_6H_{12}O_6$+Na^+ = 203.0526, found: 203.0536). Amberlite IRC 50H^+ was added, filtered out, and washed with MeOH–water. After evaporation of volatiles and drying on an oil pump, the yellow glassy residue was treated with dry acetone (prepared by shaking of techn. acetone with P_2O_5, filtration and distillation) (40 mL) and conc. H_2SO_4 (1 mL). After stirring for 4 h, TLC showed a spot of **17** R_f 0.36 (hexane-EtOAc 3:2) indistinguishable from commercial D form. Conc. NH_4OH was added to neutralize the mixture. Solid material was filtered out. The residual oil obtained after evaporation of acetone was purified by chromatography (hexane-EtOAc 6:5) to yield **17** (0.67 g; 75% for three steps). α_D +53°(c 4.4; $CHCl_3$), lit.[47] α_D +57° (c 0.9; $CHCl_3$); for D form: α_D −54.5° (c not mentioned)[51] and α_D −55° (c 3.5; $CHCl_3$).[52] Exact mass: calc. for $C_{12}H_{20}O_6$+Na^+ = 283.1152, found: 283.1152. ^1H (300 MHz, $CDCl_3$): 5.56 (d, J = 5.0 Hz, 1H), 4.61(dd, *J* = 2.3 Hz, 7.9 Hz, 1H), 4.33 (dd, *J* = 2.4 Hz, 5.0 Hz, 1H), 4.27 (dd, *J* = 1.5 Hz, 7.9 Hz, 1H), 3.90–3.70 (unresolved, 3H) [after D_2O exchange: 3.98–3.79, unresolved, 2H), 3.71 (dd, *J* = 4.1 Hz, 11.0 Hz, 1H)], 1.54, 1.45 two s, 3H each, 1.34(s 6H). ^{13}C (75 MHz, $CDCl_3$): 109.55, 108.80, 96.40, 71.58, 70.85, 70.69, 68.39, 62.22, 26.12, 26.04, 25.05, 24.44.

49. Anet, E. F. L. J. *Carbohydr. Res.* **1968**, *7*, 84–85.
50. Zinner, H.; Kleeschätzky, R.; Neels, P. *Chem. Ber.* **1965**, *98*, 1492–1497.
51. Martins Alho, M. A.; ĎAccorso, N. B.; Thiel, I. M. E. *J. Heterocycl. Chem.* **1996**, *33*, 1339–1343.
52. Schmidt, O. T. *Methods Carbohydr. Chem.* **1962**, *1*, 318–325.