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Efficient syntheses of chiral *myo*-inositol derivatives—key intermediates in glycosylphosphatidylinositol (GPI) syntheses

Fei Yu, Zhongwu Guo *

Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, MI 48202, USA

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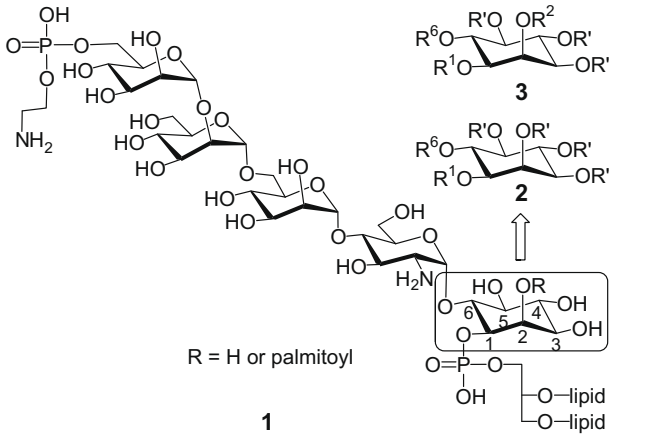
ABSTRACT

A facile and effective method was developed for large-scale syntheses of *myo*-inositol derivatives with the 1,2,6-O-positions differentiated from each other and from other positions as well. The syntheses started from methyl α-D-glucopyranoside, and the key steps are Ferrier rearrangement and a series of other regioselective and stereoselective reactions. The target compounds are key intermediates in the synthesis of GPIs.

GPI-anchoring of surface proteins to cell membranes is ubiquitous in the eukaryotic world, so GPIs and GPI-anchored proteins play an important role in various biological processes.[1,2] GPIs are complex glycolipids sharing a highly conserved core structure **1**, and the GPI-linked proteins are invariably attached to the phosphoethanolamine moiety at the non-reducing end of the GPI core glycan.[1,2] Due to the microheterogenic property of GPIs in nature, the access to homogeneous GPIs has to rely on chemical synthesis, which is currently a challenging topic. One of the challenges is access to appropriately protected optically pure *myo*-inositol derivatives—the key intermediates for GPI synthesis,[3–16] such as **2** and **3** that have the 1,6-O- and 1,2,6-O-positions differentiated from each other and from the remaining hydroxyl groups of inositol. This Letter describes a facile method to prepare these important synthetic intermediates.

In the past two decades, several methods have been established for the synthesis of optically pure inositol derivatives.[17,18] Some of the methods exploited naturally occurring optically active inositol and sugar derivatives,[19,20] while others were based on de novo syntheses, for example, via microbial oxidation of a derivatized arene[21,22] or via ring-closing metathesis of a chiral diene followed by stereoselective dihydroxylation.[23,24] The majority of the reported syntheses started with the readily available free achiral *myo*-inositol, and these methods needed to resolve the enantiomers of a chiral inositol derivative at certain synthetic stage.[17,18]



In our research to establish a truly practical method for the synthesis of 1,6-O-differentiated and 1,2,6-O-differentiated chiral *myo*-inositol derivatives, we became interested in a strategy[21,25–27] based on the stereospecific Ferrier rearrangement of sugar derivatives,[28] because the stereochemistries of reactions and intermediates involved in this synthesis were defined and the strategy could offer an easy and efficient access to a partially protected optically active inositol analog **6** starting from the readily available methyl α-D-glucopyranoside **4** (Scheme 1). However, a major challenge here is the design and implementation of a series of reactions for effective differentiation of the latent inositol 1,2,6-O-positions in **6**. Initially, we attempted to first protect the single free hydroxyl group of **6** to differentiate it from the other hydroxyl groups, but this strategy failed. Although a THP group could be introduced to

* Corresponding author. Tel.: +1 313 577 2557; fax: +1 313 577 8822.
E-mail address: zwguo@chem.wayne.edu (Z. Guo).

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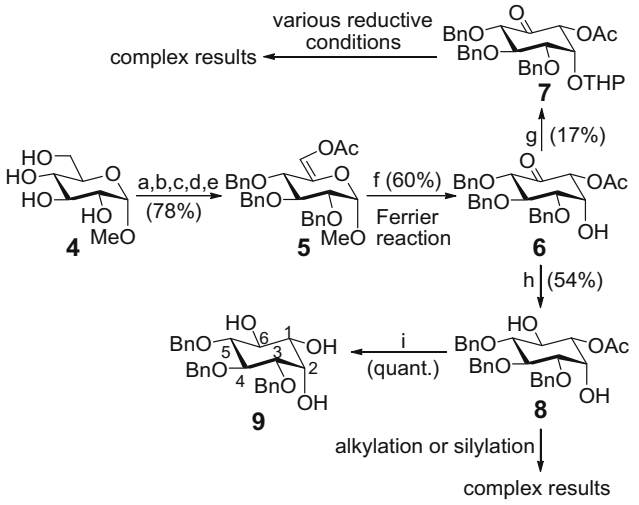
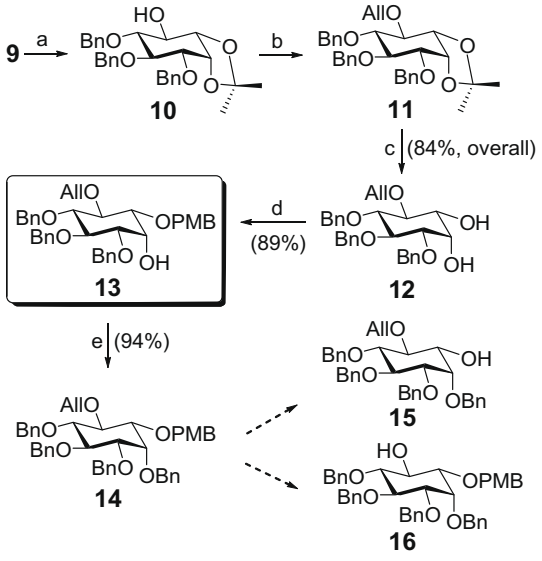


Scheme 1. Reagents and conditions: (a) TrCl, pyr., reflux; (b) BnBr, NaH, DMF, rt; (c) H_2SO_4, MeOH, rt; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; (e) Ac_2O, K_2CO_3, CH_3CN, 80 °C; (f) $Hg(OAc)_2$, CH_3COCH_3/H_2O, rt, then NaCl, rt; (g) DHP, PPTS, CH_2Cl_2, rt; (h) $NaBH(OAc)_3$, CH_3CN/AcOH, rt; (i) NaOH, MeOH, reflux.

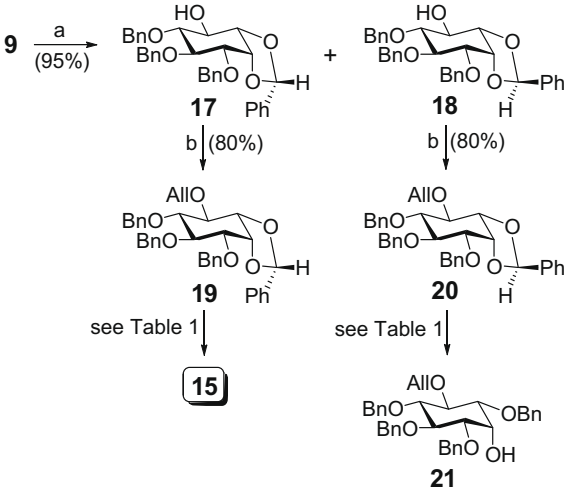
protect the free hydroxyl group of **6**, the attempts to reduce the carbonyl group of **7** under various conditions were unsuccessful. Therefore, the carbonyl group of **6** was reduced with $NaBH(OAc)_3$ to give **8** stereospecifically.[25] The stereochemistry of **8** was confirmed by the observed large coupling constants between H-6 and H-1/H-5 for its ^1H NMR spectrum. In this transformation, the free hydroxyl group of **6** might have assisted the stereoselectivity by, for example, coordinating with the reducing reagent. Next, we tried to selectively protect one of the two hydroxyl groups of **8** with an alkyl or silyl group, but under various conditions, including the use of mild bases and acids as catalysts, the reaction gave complex results, probably due to acetyl migration and/or due to the lack of regioselectivity. Consequently, **8** was deacetylated.

We developed three synthetic methods for differentiating the free hydroxyl groups of **9**. The first method (Scheme 2) was based on the protection of the 1,2-*cis*-diol of **9** with an isopropylidene group followed by 6-O-alkylation and then regioselective reactions to distinguish 1,2-O-positions. The reaction of **9** and $Me_2C(OMe)_2$ was regiospecific, and the location of the ketal functionality in **10** was confirmed via acetylating the remaining free hydroxyl group, which resulted in a significant downfield shift of the H-6 NMR signal. Allylation of **10** was straightforward to give **11**, which was subjected to acidic hydrolysis to form **12**. For the large scale preparation, reaction intermediates **10** and **11** were not purified, and the desired product **12** was obtained in an excellent overall yield (84%) after three steps of transformation. As previously reported,[15] regioselective p-methoxybenzylation of the C-1-hydroxyl group of **12** was achieved via a tin-complex to afford **13**, which has differentiated 1,2,6-O-positions. Compound **13** was the key intermediate in our synthesis of CD52 GPI containing a 2-O-acylated inositol residue.[16] Meanwhile, the free hydroxyl group of **13** was readily benzylated to form **14**, which has differently protected 1,6-O-positions and should be useful for the synthesis of other GPIs. For example, the allyl (All) and *p*-methoxybenzyl (PMB) groups of **14** can be easily and selectively removed to produce **15** and **16**, respectively, which are ready for 1-O-phospholipidation and 6-O-glycosylation which are necessary steps in GPI synthesis.

The other synthetic method developed for differentiating the free hydroxyl groups of **9** combined regioselective protection of the 1,2-*cis*-diol with a benzylidene group and subsequent regioselective ring opening of the resulting acetal (Scheme 3). The reaction between **9** and $PhCH(OMe)_2$ was highly regioselective for the 1,2-*cis*-diol to afford a 1:1 mixture of the *endo* and *exo* acetals, **17** and **18**, in an excellent yield (95%). The regiochemistry of **17** and **18** was confirmed via acetylating the remaining free hydroxyl groups, which resulted in major downfield shifts of the H-6 NMR signals. The stereochemistry of **17** and **18** was determined by NMR NOE experiments, where strong NOEs were observed between the acetal H and H-2,3 for **17** and strong NOEs were observed between the acetal H and H-6 for **18**. Allylation of **17** and **18** was simple, which gave **19** and **20**, respectively. The reductive ring opening reactions of **19** and **20** proved to be regiospecific, and each reaction gave only one product (Table 1, entries 1–6). However, it is interesting to notice that the *endo* epimer **19** only gave **15** while the *exo* epimer **20** only gave **21**, no matter which reducing reagent and acid catalyst, including both HCl and sterically hindered Lewis acids, were utilized. Again, the regiochemistry of **15** and **21** was confirmed by acetylation experiments. These results were in contrast to literature results observed with cyclic acetals of carbohydrates.[29,30] A



Scheme 2. Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH, DMF, rt; (b) AllBr, NaH, DMF, rt; (c) HCl, MeOH, rt; (d) Bu_2SnO, TBAI, toluene, reflux, then PMBCl, CsF, reflux; (e) BnBr, NaH, DMF, rt.



Scheme 3. Reagents and conditions: (a) $PhCH(OMe)_2$, *p*-TsOH, CH_3CN, rt; (b) AllBr, NaH, DMF, rt.

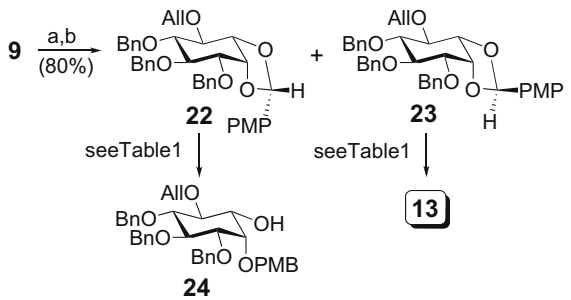
Table 1
Results of the reductive ring opening of acetals **19**, **20**, **22** and **23** under various conditions

Entry	Reaction conditions	Reactant	Product yield (%)
1	$NaBH_3CN$, $AlCl_3$, THF, 0 °C	**19**	**15** (81)
2	$NaBH_3CN$, HCl, Et_2O, THF, 0 °C	**19**	**15** (67)
3	$NaBH_3CN$, $AlCl_3$, THF, 0 °C	**20**	**21** (82)
4	$NaBH_3CN$, HCl, Et_2O, THF, 0 °C	**20**	**21** (83)
5	Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C	**20**	**21** (58)
6	$LiAlH_4$, $AlCl_3$, CH_2Cl_2, Et_2O, refl.	**20**	**21** (71)
7	$NaBH_3CN$, $AlCl_3$, THF, 0 °C	**22**	**24** (62)
8	$NaBH_3CN$, HCl, Et_2O, THF, 0 °C	**22**	**24** (72)
9	$LiAlH_4$, $AlCl_3$, CH_2Cl_2, Et_2O, refl.	**22**	**24** (56)
10	$NaBH_3CN$, $AlCl_3$, THF, 0 °C	**23**	**13** (67)
11	$NaBH_3CN$, HCl, Et_2O, THF, 0 °C	**23**	**13** (72)
12	$LiAlH_4$, $AlCl_3$, CH_2Cl_2, Et_2O, refl.	**23**	**13** (54)

potential explanation for these observations is that the O-1 position of **19** is less sterically hindered than the O-2 position, thus, the acid catalyst would preferably attack O-1 to afford **15** as the ring opening product, but for **20** the O-2 position may be more accessible for the acid catalyst. We have also examined the ring opening reaction using other reagents and catalysts, such as BH_3•THF/TMSOTf, BH_3•THF/$CoCl_2$, BH_3•THF/Cu(OTf)$_2$, and DIBAL-H, but we observed that under these conditions the reaction was either very complex or did not proceed at all.

Finally, the 1,2-*cis*-diol of **9** was also protected with a *p*-methoxybenzylidene group, which was followed by allylation to give isomers **22** and **23** in a combined over yield of 80% (Scheme 4). The configurations of **22** and **23** were determined by NOE experiments and by comparing their ^{1}H NMR spectra with that of **19** and **20**.[22] Similar to **19** and **20**, the reductive ring opening of the acetal group of **22** and **23** was regiospecific to afford only **24** and **13**, respectively, under several reductive conditions (Table 1, entries 7–12). Since compound **24** has 1,2,6-O-positions differentiated as well, it should be also useful for GPI syntheses.

In summary, three efficient and practical synthetic methods have been developed for large-scale preparations of chiral *myo*-inositol derivatives that have distinctive protections at 1,2,6-O-positions. Compound **13**[32] was prepared in 11–12 steps starting from methyl α-D-glucopyranoside (Schemes 1, 2 and 4) to obtain 15–19% overall yields. Compounds **15**, **21** and **24**[32] were prepared in 10–11 steps (Schemes 1, 3 and 4) with 13–17% overall yields. All these compounds are useful intermediates in GPI synthesis, depending on the specific design for a GPI synthesis and the intermediates involved; therefore, all three synthetic methods are useful. However, the method described in Scheme 2 is recommended for most applications, because of its higher overall yield and flexibility to introduce different protecting groups at 1,2,6-O-positions in the synthesis.



Scheme 4. Reagents and conditions: (a) *p*-MeOPhCH(OMe)$_2$, *p*-TsOH, CH_3CN, rt; (b) AllBr, NaH, DMF, rt.

Acknowledgments

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References and notes

1. Ferguson, M. A. J.; Williams, A. F. *Ann. Rev. Biochem.* **1988**, *57*, 285.
2. Thomas, J. R.; Dwek, R. A.; Rademacher, T. W. *Biochemistry* **1990**, *29*, 5413.
3. Udodong, U. E.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 7886.
4. Campbell, A. S.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 10387.
5. Baeschlin, D. K.; Chaperon, A. R.; Charbonneau, V.; Green, L. G.; Ley, S. V.; Lucking, U.; Walther, E. *Angew. Chem., Int. Ed.* **1998**, *37*, 3423.
6. Baeschlin, D. K.; Chaperon, A. R.; Green, L. G.; Hahn, M. G.; Ince, S. J.; Ley, S. V. *Chem. Eur. J.* **2000**, *6*, 172.
7. Martin-Lomas, M.; Khiar, N.; Garcia, S.; Koessler, J.-L.; Nieto, P. M.; Rademache, T. W. *Chem. Eur. J.* **2000**, *6*, 3608.
8. Dietrich, H.; Espinosa, J. F.; Chiara, J. L.; Jimenez-Barbero, J.; Leon, Y.; Varela-Nieto, I.; Mato, J.-M.; Cano, F. H.; Foces-Foces, C.; Martin-Lomas, M. *Chem. Eur. J.* **1999**, *5*, 320.
9. Murakata, C.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 2439.
10. Murakata, C.; Ogawa, T. *Carbohydr. Res.* **1992**, *235*, 95.
11. Murakata, C.; Ogawa, T. *Tetrahedron Lett.* **1991**, *32*, 671.
12. Mayer, T. G.; Kratzer, B.; Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2177.
13. Mayer, T. G.; Weingart, R.; Münstermann, F.; Kawada, T.; Kurzchalia, T.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, 2563.
14. Kratzer, B.; Mayer, T. G.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 291.
15. Xue, J.; Guo, Z. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2015.
16. Xue, J.; Guo, Z. *J. Am. Chem. Soc.* **2003**, *125*, 16334.
17. Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003**, *103*, 4477.
18. Guo, Z.; Bishop, L. *Eur. J. Org. Chem.* **2004**, 3585.
19. Luchetti, G.; Ding, K.; Kornienko, A.; d'Alarcao, M. *Synthesis* **2008**, 3148.
20. Kornienko, A.; Turner, D. I.; Jaworek, C. H.; d'Alarcao, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2783.
21. Jia, Z. J.; Olsson, L.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 631.
22. Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553.
23. Conrad, R. M.; Grogan, M. J.; Bertozzi, C. R. *Org. Lett.* **2002**, *4*, 1359.
24. Luchetti, G.; Ding, K.; d'Alarcao, M.; Kornienko, A. *Synthesis* **2008**, 3142.
25. Bender, S. L.; Budhu, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 9883.
26. Estevez, V. A.; Prestwich, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 9885.
27. Lu, J.; Jayaprakash, K. N.; Fraser-Reid, B. *Tetrahedron Lett.* **2004**, *45*, 879.
28. Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.
29. Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201.
30. Johnsson, R.; Olsson, D. U. E. *J. Org. Chem.* **2008**, *73*, 5226.
31. Crossman, A., Jr.; Paterson, M. J.; Ferguson, M. A. J.; Smith, T. K.; Brimacombea, J. S. *Carbohydr. Res.* **2002**, *337*, 2049.
32. *Spectroscopic data of some synthetic targets* **13**:[15] $[\alpha]_D^{22} = -7.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.23 (m, 17 H, Ph), 6.90 (d, *J* = 8.8 Hz, 2H, Ph), 6.04–5.94 (m, 1H, —CH=), 5.30 (dd, *J* = 1.6, 18.0 Hz, 1H,=CH_2), 5.18 (dd, *J* = 1.6, 8.8 Hz, 1H,=CH_2), 4.94–4.81 (m, 4H, Bn), 4.72–4.61 (m, 4H, Bn), 4.40 (dd, *J* = 5.6, 12.0, Hz, 1H, CH_2—C=), 4.34 (dd, *J* = 5.6, 12.0 Hz, 1H, CH_2—C=), 4.17 (t, *J* = 2.4 Hz, 2-H), 3.99–3.91 (m, 1H, 4-H), 3.88–3.74 (m, 1H, 6-H), 3.82 (s, 3 H, OMe), 3.40 (t, *J* = 9.6 Hz, 1H, 5-H), 3.37 (dd, *J* = 2.4 Hz, 1H, 1-H), 3.31 (dd, *J* = 2.4, 8.8 Hz, 1H, 3-H), 2.46 (s, 3 H, OH). ^{13}C NMR ($CDCl_3$, 100.0 MHz): δ 159.3, 138.73, 138.65, 137.9, 135.3, 130.1, 129.8, 129.4, 128.4, 128.3, 128.0, 127.82, 127.79, 127.6, 127.5, 116.6, 83.1, 81.1, 80.8, 79.7, 79.2, 75.95, 75.89, 74.5, 72.6, 72.4, 67.6. MS (ESI) *m/z*: calcd for $C_{38}H_{42}O_7$ [M^+], 610.3. Found: 649.1 ($M+K^+$), 633.1 ($M+Na^+$).
Compound **15**:[31] $[\alpha]_D^{22} = -8.3$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.24 (m, 20H), 6.02–5.88 (m, 1H, —CH=), 5.26 (dd, *J* = 2.4, 17.1 Hz, 1H, =CH_2), 5.15 (d, *J* = 10.0 Hz, = CH_2), 5.04–4.66 (m, 8 H, Bn), 4.36 (dd, *J* = 7.6, 16.0 Hz, 1 H, CH_2—C=), 4.28 (dd, *J* = 7.6, 16.0 Hz, 1H, CH_2—C=), 4.06–4.00 (m, 2H, 2,4-H), 3.67 (t, *J* = 12.0, Hz, 1H, 5-H), 3.50–3.40 (m, 3H, 1,3,6-H). ^{13}C NMR ($CDCl_3$, 100.0 MHz): δ 138.7, 135.1, 128.4, 128.3, 128.0, 127.9, 127.75, 127.68, 127.6, 127.5, 117.1, 83.5, 81.9, 81.8, 81.1, 77.1, 75.9, 75.8, 74.7, 74.3, 73.0, 72.3. MS (ESI) *m/z*: calcd for $C_{37}H_{40}O_6$ [M^+], 580.0. Found: 619.1 ($M+K^+$), 603.1 ($M+Na^+$).
Compound **21**: $[\alpha]_D^{22} = -6.0$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.22 (m, 20H, Ph), 6.02–5.90 (m, 1H, —CH=), 5.27 (d, *J* = 16.8 Hz, 1H,=CH_2), 5.16 (d, *J* = 10.8 Hz, 1H,=CH_2), 4.90–4.64 (m, 8H, Bn), 4.38 (dd, *J* = 5.6, 12.0 Hz, 1H, CH_2—C=), 4.33 (dd, *J* = 5.6, 12.0 Hz, CH_2—C=), 4.19 (t, *J* = 2.1 Hz, 1H, 2-H), 3.98–3.91 (m, 1H, 4-H), 3.84 (t, *J* = 9.6 Hz, 1H, 5-H), 3.42–3.28 (m, 3H, 1,3,6-H). ^{13}C NMR ($CDCl_3$, 100.0 MHz): δ 138.7, 138.6, 137.9, 135.2, 128.4, 128.3, 128.0, 127.84, 127.81, 127.59, 127.56, 116.7, 83.1, 81.1, 80.8, 79.7, 79.6, 76.0, 75.9, 74.6, 72.8, 72.7, 67.6. HRMS (ESI): calcd for $C_{37}H_{40}O_6Na$ [$M+Na^+$]: 603.2723. Found: 603.2701.
Compound **24**: $[\alpha]_D^{22} = -5.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 17H, Ph), 6.86 (d, *J* = 8.0 Hz, 2H, Ph), 6.00–5.88 (m, 1H, —CH=), 5.25 (d,

J = 16.8 Hz, 1H,=CH_2), 5.15 (d, J = 9.2 Hz,=CH_2), 4.96–4.78 (m, 5H, Bn), 4.71–4.62 (m, 3H, Bn), 4.34 (dd, J = 5.2, 12.0 Hz, 1H, CH_2—C=), 4.25 (dd, J = 5.2, 12.0 Hz, 1H, CH_2—C=), 4.04–3.96 (m, 2H, 2,4-H), 3.80 (s, 3H, OMe), 3.64 (t, J = 9.6, Hz, 1H, 5-H), 3.46–3.36 (m, 3H, 1,3,6-H), 2.75 (d, J = 6.8 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 100.0 MHz): δ 135.1, 129.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.5, 117.0, 113.7, 83.5, 82.0, 81.7, 81.1, 76.4, 75.9, 75.7, 74.3, 72.0, 72.3, 55.3; HRMS (ESI): calcd for $C_{38}H_{42}O_7Na$ [M+Na$^+$]: 633.2828. Found: 633.2830.