Published in final edited form as:
Org Lett. 2010 November 19; 12(22): 5150–5153. doi:10.1021/ol102144g.

A De Novo Approach to the Synthesis of Glycosylated Methymycin Analogues with Structural and Stereochemical Diversity

Svetlana A. Borisova[§,1], **Sanjeeva R. Guppi**[†,1], **Hak Joong Kim**[§,1], **Bulan Wu**[†,1], **John H. Penn**[†], **Hung-wen Liu**[§], and **George A. O'Doherty**[‡]

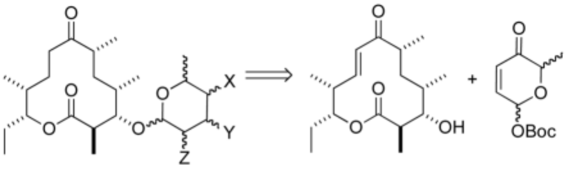
John H. Penn: john.penn@mail.wvu.edu; Hung-wen Liu: h.w.liu@mail.utexas.edu; George A. O'Doherty: g.odoherty@neu.edu

[†] Department of Chemistry, West Virginia University, Morgantown, WV 26506

[§] Department of Chemistry & Biochemistry, The University of Texas at Austin, 1 University Station A5300, Austin, TX 78712

[‡] Department of Chemistry & Chemical Biology, Northeastern University, Boston, MA 02115

Abstract



Methymycin L/D-Analogoues

A divergent and highly stereoselective route to eleven glycosylated methymycin analogues has been developed. The key to the success of this method was the iterative use of the Pd-catalyzed glycosylation reaction and post-glycosylation transformation. This unique application of Pd-catalyzed glycosylation demonstrates the breath of α/β-& D/L-glycosylation of macrolides that can be efficiently prepared using a de novo asymmetric approach to the carbohydrate portion.

Glycosylated macrolactones, known as macrolides, are an important class of polyketide antibiotics used to treat infections caused by Gram-positive bacteria.2 *Streptomyces venezuelae* ATCC 15439 produces several 12-membered ring macrolides, including methymycin **I** and neomethymycin **II** derived from 10-deoxymethynolide **III** (Figure 1).3 These macrolides consist of a lactone aglycon carrying a rare deoxyamino sugar, desosamine, which is important for their bioactivity. In fact, the biological activities of **I** and **II** are dramatically decreased when the sugar appendage is removed.

Since the deoxyaminosugar portion of macrolides is in general essential for their antimicrobial activities, 4 its modifications hold promise as a valuable approach towards preparing new macrolide antibiotics with improved and/or altered biological properties. 5 In this regard, several synthetic and biosynthetic approaches to novel glycosylated macrolides

---

Correspondence to: John H. Penn, `john.penn@mail.wvu.edu`; Hung-wen Liu, `h.w.liu@mail.utexas.edu`; George A. O'Doherty, `g.odoherty@neu.edu`.

[1] The order of these authors is alphabetical with the WVU group being responsible for the synthetic chemistry.

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

have been reported. 6 These approaches are limited in terms of the stereochemical diversity of structures that can be generated. In addition, the methods that use in vivo modified biosynthetic pathways and/or in vitro enzymatic reactions for the production of new glycosylated antibiotics7 are limited by the availability and the lability of the sugar nucleotide glycosyl donors. Similarly, these routes often suffer from the reduced catalytic efficiency of the glycosyltransferases involved when dealing with unnatural substrates.

To address these concerns we envisioned the development of a highly diastereoselective, yet stereo-divergent route that would allow for the mild installation of the sugar moieties onto complex antibiotic aglycons using simple achiral starting material. It is in this, as well as other, contexts that we developed a de novo asymmetric approach to carbohydrates, which we hoped would allow for the facile synthesis of various methymycin analogues for carbohydrate SAR-type studies (Figure 1). Herein, we report our successful efforts at the use of this approach for the synthesis of a stereochemically (L/D and α/β-) diverse glycosylated 8,9-dihydro-10-deoxymethymycin analogues.

Our basic retrosynthetic analysis for the preparation of the stereochemically diverse methymycin analogues is shown in Scheme 1. The plan was that various amino- and/or deoxy-sugar glycosylated macrolide analogues could be prepared from methynolides like **12** with the desired pyranone stereochemistry. The macrolides **12**, in turn, could be prepared by a stereospecific Pd-catalyzed coupling of macrolide **III** and **13a–d**.8,9 The required pyranone stereoisomers **13a–d** can be stereoselectively prepared from the achiral acetyl furan **14** via our de novo asymmetric synthesis approach.10

Accordingly, our synthetic effort began with the isolation of 10-deoxymethynolide **III**5 and preparation of the required D/L-, α/β-Boc-pyranones **13a–d** for coupling.9 As previously described, the Pd-glycosyl donors **13a–d** were synthesized from the achiral acetyl furan **14** by a very practical three-step sequence, employing an enantioselective Noyori reduction (**14** to **15**/*ent*-**15**), an Achmatowicz oxidation, and a stereodivergent *tert*-butyl carbonate formation (See Scheme 2).11

The double bond of 10-deoxymethynolide **III**5 was then selectively reduced by treatment with excess diimide (NBSH, Et_3N) 12 to give the desired 8,9-dihydro-10-deoxymethynolide **(16)** in 95% yield (Scheme 3). The resulting macrolactone **16** was subjected to the diastereoselective Pd-catalyzed glycosylation with α-L-Boc-pyranone **13a**, producing α-L-glycoside **12** as a single diastereomer in good yield (86%). A $NaBH_4$ reduction13 of enone **12** gave the equatorial allylic alcohol **17** in 82% yield. Diimide reduction of **17** with an excess triethylamine and *O*-nitrophenylsulfonyl hydrazide led to the dideoxy analogue **1** in excellent yield (90%). Preparation of the *rhamno*-sugar analogue **2** was accomplished by diastereoselective dihydroxylation of **17** under Upjohn conditions14 (OsO_4/NMO) in 85% yield.

We next investigated methods for the construction of various *C*-4-amino/azido sugar analogues (Scheme 4). Towards this goal, a methyl carbonate leaving group was installed on the allylic alcohol by reaction of **17** with methyl chloroformate to form the *C*-4-carbonate **18** in 70% yield. Exposing carbonate **18** to the Sinou conditions15 ($TMSN_3$, $(Pd(allyl)Cl)_2$/1,4-bis(diphenylphosphino)-butane) afforded a single regio- and stereoisomeric allylic azide **19** in 75% yield. However, when alcohol **17** was subjected to Mitsunobu conditions using TMS azide as the nucleophile, no desired *C*-4-azido compound **21** was formed. Therefore a two-step S_N2 reaction route was employed, in which the allylic alcohol **17** was converted into mesylate **20** (MsCl/Et_3N) in an excellent yield (88%), followed by treatment of **20** with NaN_3/THF to afford the inverted *C*-4-azido isomer **21** in 86% yield.

These azide intermediates can now be converted to different amino sugar analogues. As depicted in Scheme 4, hydrogenolysis (Pd/C, H_2, MeOH) of allylic azide **19** via a one-pot reduction of both azide and allylic double bond gave the dideoxy amino sugar analogue **3** in 82% yield. As before, diimide reduction of the allylic azide **19** gave 2,3-dideoxy analogue **4** in 90% yield. Alternatively, diastereoselective dihydroxylation (OsO_4/NMO) of **19**, followed by reduction of azide (Pd/C, H_2, MeOH) produced the aminomannose analogue **6** via a *rhamno*-azidosugar **5** intermediate.

We next investigated the synthesis of the 2,6-dideoxy β-L-*allo*-sugar analogue **7** of methymycin (Scheme 5), which builds on our digitoxin work.16 Thus, macrolide **16** and β-L-pyranone **13b** were subjected to Pd-catalyzed glycosylation to give β-L-glycoside **22** as a single diastereomer in good yield (87%). A $NaBH_4$ reduction of ketone **22** provided a mixture of diastereomeric allylic alcohols **23** in 93% yield. Exposing the mixture of allylic alcohols **23** to the Myers' reductive rearrangement conditions17 (NBSH/PPh_3/DEAD, NMM, −30 °C to rt) provided olefin **24** in a moderate yield (60%). Finally, Upjohn dihydroxylation of olefin **24** (OsO_4/NMO) gave exclusively the 2,6-dideoxy *allo*-sugar analogue **7** in 87% yield.

In a similar fashion, aglycon **16** was subjected to a diastereoselective Pd-catalyzed glycosylation with α-D-Boc-pyranone **13c** producing α-D-glycoside **25** as a single diastereomer in good yield (85%) (Scheme 6). A $NaBH_4$ reduction of enone **25** afforded the equatorial allylic alcohol **26** in 83% yield. Diimide reduction of the allylic alcohol **26** (NBSH/Et_3N) as described above led to the dideoxy analogue **8** in an excellent yield (90%). The final conversion of **26** to the *rhamno*-sugar analogue **9** was achieved by diastereoselective dihydroxylation using the Upjohn conditions (OsO_4/NMO). The desired product was obtained in 85% yield.

Via a similar two-step S_N2 reaction route, allylic alcohol **26** was converted into the inverted *C*-4-azido compound **27** in 86% yield by mesylation (MsCl/Et_3N; 88%) followed by treatment with NaN_3/Acetone$_{(aq)}$. Reduction of the *C*-4-azido group and allylic double bond in compound **27** under hydrogenolysis conditions (Pd/C, H_2, MeOH) gave the *C*-4-deoxy-amino analogue of methymycin **10**. The desired compound was isolated in a modest yield (63%) through reverse phase chromatography.

The synthesis of the 2,6-dideoxy β-D-*allo*-sugar analogue **11** of methymycin was performed according to an analogous sequence as described above for the synthesis of **7** (Scheme 7). Namely, Pd-catalyzed glycosylation of macrolactone **16** using β-D-pyranone **13d** gave β-D-glycoside **28** as a single diastereomer in good yield (90%). A $NaBH_4$ reduction of ketone **28** afforded a mixture of diastereomeric allylic alcohols **29** that was converted to olefin **30** under the Myers' reductive rearrangement conditions (NBSH/PPh_3/DEAD, NMM, −30 °C to rt) in moderate yield (63%). Finally, Upjohn dihydroxylation of olefin **30** gave exclusively the 2,6-dideoxy *allose*-sugar analogue **11** in 90% yield.

In conclusion, a divergent yet highly stereoselective route to eleven variously substituted (amino/azido/dideoxy) methymycin analogues has been developed. The key to the success of this method is the iterative use of the Pd-catalyzed glycosylation reaction, ketone reduction/Myers' reductive rearrangement, diastereoselective dihydroxylation, and regioselective reductions. This unique application of the established Pd-catalyzed glycosylation strategy allows for efficient preparation of challenging and stereochemically diverse glycoside macrolide targets. While some post-glycosylation transformations were not compatible with the macrolide double bond, there was no need for ketone protection.18 The testing of these macrolide analogs will be reported in due course as well as the use of this methodology towards other biologically important aglycons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to NIH (GM054346 and GM035906 to H.-w.L., and GM088839 to G.A.O.) and NSF (CHE-0749451 to G.A.O.) for the support of our research.

References

2. (a) Rawlings BJ. Nat Prod Rep. 2001; 18:190–227. [PubMed: 11336289] (b) Rawlings BJ. Nat Prod Rep. 2001; 18:231–281. [PubMed: 11476481] (c) Staunton J, Weissman KJ. Nat Prod Rep. 2001; 18:380–416. [PubMed: 11548049] (d) Walsh, C. Antibiotics: Actions, Origins, Resistance. ASM Press; Washington, D.C: 2003. (e) Weissman KJ. Philos Trans R Soc London, Ser A. 2004; 362:2671–2690.

3. (a) Donin MN, Pagano J, Dutcher JD, McKee CM. Antibiotics Annu. 1953–1954; 1:179–185. (b) Djerassi C, Zderic JA. J Am Chem Soc. 1956; 78:6390–6395. (c) Xue Y, Zhao L, Liu H-w, Sherman DH. Proc Natl Acad Sci USA. 1998; 95:12111–12116. [PubMed: 9770448]

4. (a) Weymouth-Wilson AC. Nat Prod Rep. 1997; 14:99–110. [PubMed: 9149408] (b) Thorson JS, Hosted J, Jiang J, Biggins JB, Ahlert J. Curr Org Chem. 2001; 5:139–167. (c) Kren V, Martinkova L. Curr Med Chem. 2001; 8:1303–1328. [PubMed: 11562268]

5. (a) He XM, Liu H-w. Annu ReV Biochem. 2002; 71:701–754. [PubMed: 12045109] (b) Thibodeaux CJ, Melancon CE III, Liu H-w. Nature. 2007; 446:1008–1016. [PubMed: 17460661] (c) Thibodeaux CJ, Melancon CE III, Liu H-w. Angew Chem Int Ed. 2008; 47:9814–9859. (d) Borisova SA, Zhao L, Sherman DH, Liu H-w. Org Lett. 1999; 1:133–136. [PubMed: 10822548]

6. (a) Velvadapu V, Andrade RB. Carb Res. 2008; 343:145–150. (b) Packard GK, Scott D, Rychnovsky SD. Org Lett. 2001; 3:3393–3396. [PubMed: 11594842]

7. (a) Mendez C, Salas JA. Trends Biotechnol. 2001; 19:449–456. [PubMed: 11602309] (b) Griffith BR, Langenhan JM, Thorson JS. Curr Opin Biotechnol. 2005; 16:622–630. [PubMed: 16226456] (c) Melançon CE, Thibodeaux C, Liu H-w. ACS Chem Biol. 2006; 1:499–504. [PubMed: 17168536] (d) Mendez C, Luzhetskyy A, Bechthold A, Salas JA. Curr Top Med Chem. 2008; 8:710–724. [PubMed: 18473893] (e) Williams GJ, Gantt RW, Thorson JS. Curr Opin Chem Biol. 2008; 12:556–564. [PubMed: 18678278]

8. (a) Babu RS, O'Doherty GA. J Am Chem Soc. 2003; 125:12406–12407. [PubMed: 14531673] (b) Comely AC, Eelkema R, Minnaard AJ, Feringa BL. J Am Chem Soc. 2003; 125:8714–8715. [PubMed: 12862452] (c) Kim H, Men H, Lee C. J Am Chem Soc. 2004; 126:1336–1337. [PubMed: 14759180] (d) Babu RS, Zhou M, O'Doherty GA. J Am Chem Soc. 2004; 126:3428–3429. [PubMed: 15025462]

9. (a) Harris JM, Keranen MD, O'Doherty GA. J Org Chem. 1999; 64:2982–2983. [PubMed: 11674384] (b) Harris JM, Keranen MD, Nguyen H, Young VG, O'Doherty GA. Carbohydr Res. 2000; 328:17–36. [PubMed: 11005573] For its use in oligosaccharide synthesis see: (c) Guo H, O'Doherty GA. Angew Chem Int Ed. 2007; 46:5206–5208. (d) Zhou M, O'Doherty GA. Org Lett. 2008; 10:2283–2286. [PubMed: 18461951]

10. (a) Fujii A, Hashiguchi S, Uematsu N, Ikariya T, Noyori R. J Am Chem Soc. 1996; 118:2521–2522. (b) Li M, Scott JG, O'Doherty GA. Tetrahedron Lett. 2004; 45:1005–1009. (c) Li M, O'Doherty GA. Tetrahedron Lett. 2004; 45:6407–6411.

11. (a) Babu RS, O'Doherty GA. J Carbohydr Chem. 2005; 24:169–177. (b) Li M, Scott JG, O'Doherty GA. Tetrahedron Lett. 2004; 45:1005–1009.

12. Haukaas MH, O'Doherty GA. Org Lett. 2002; 4:1771–1774. [PubMed: 12000295]

13. (a) Luche JL. J Am Chem Soc. 1978; 100:2226–2227. (b) Haukaas MH, O'Doherty GA. Org Lett. 2001; 3:401–404. [PubMed: 11428024]

14. VanRheenen V, Kelly RC, Cha DY. Tetrahedron Lett. 1976; 17:1973–1976.

15. de Oliveira RN, Cottier L, Sinou D, Srivastava RM. Tetrahedron. 2005; 61:8271–8281.

16. Zhou M, O'Doherty GA. Org Lett. 2006; 8:4339–4342. [PubMed: 16956221]

17. (a) Myers AG, Zheng B. J Am Chem Soc. 1996; 118:4492–4493. (b) Myers AG, Zheng B. Tetrahedron Lett. 1996; 37:4841–4844. (c) Myers AG, Zheng B, Movassaghi M. J Org Chem. 1997; 62:7507. [PubMed: 11671877] (d) Haukaas MH, O'Doherty GA. Org Lett. 2002; 4:1771–1774. [PubMed: 12000295]
18. This compatibility with the macrocyclic ketone functionality is important as there are many ketone conatining macrolide aglycons which can be used with this methodology, see: Ma Z, Nemoto PA. Curr Med Chem Anti-Infective Agents. 2002; 1:15–34.

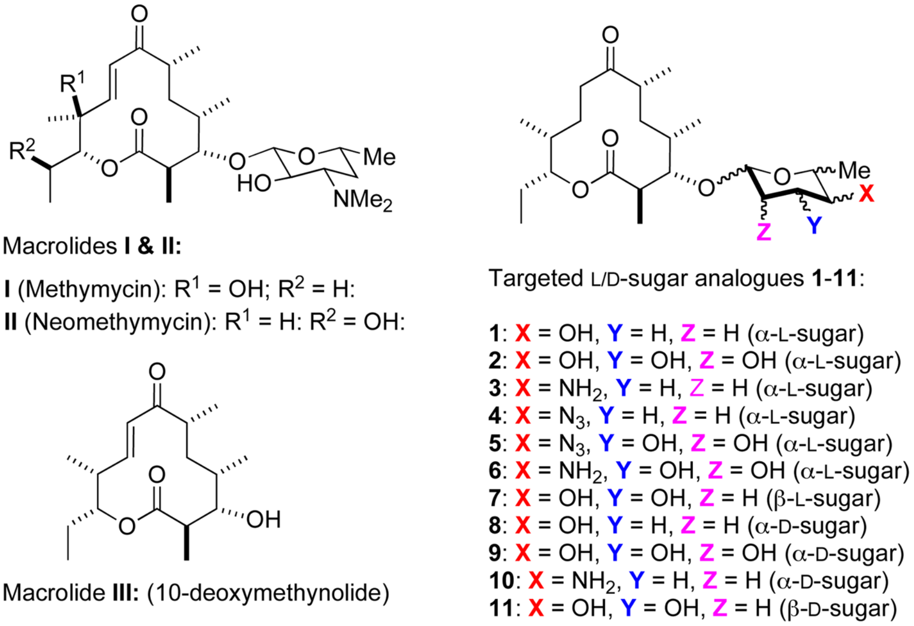
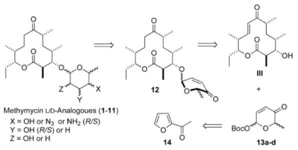


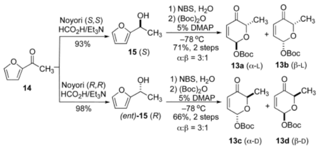
Figure 1.

Macrolides (I–III) and targeted methymycin analogues **1**–**11**



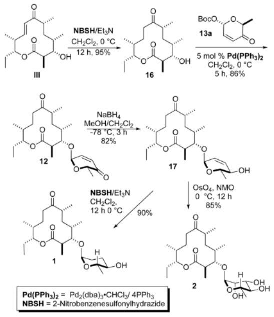
Scheme 1.

Retrosynthetic analysis of methymycin analogues



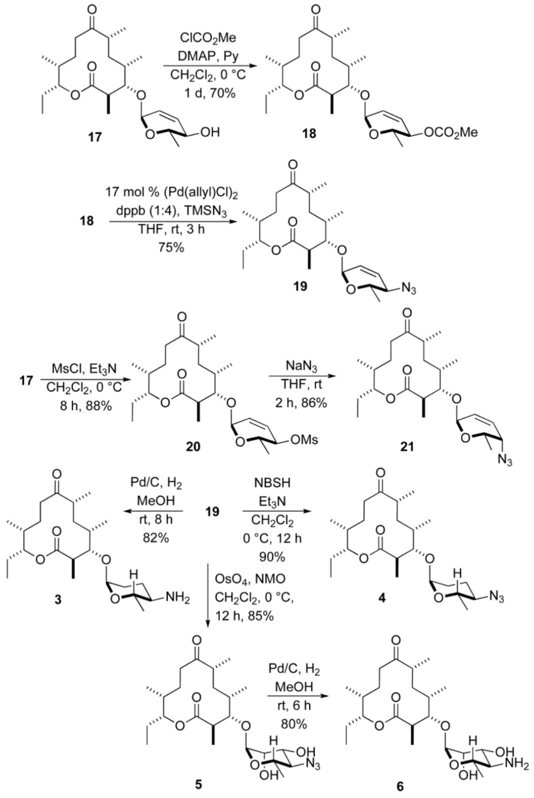
Scheme 2.

Synthesis of D/L-, α/β-Boc-pyranones **13a–d**



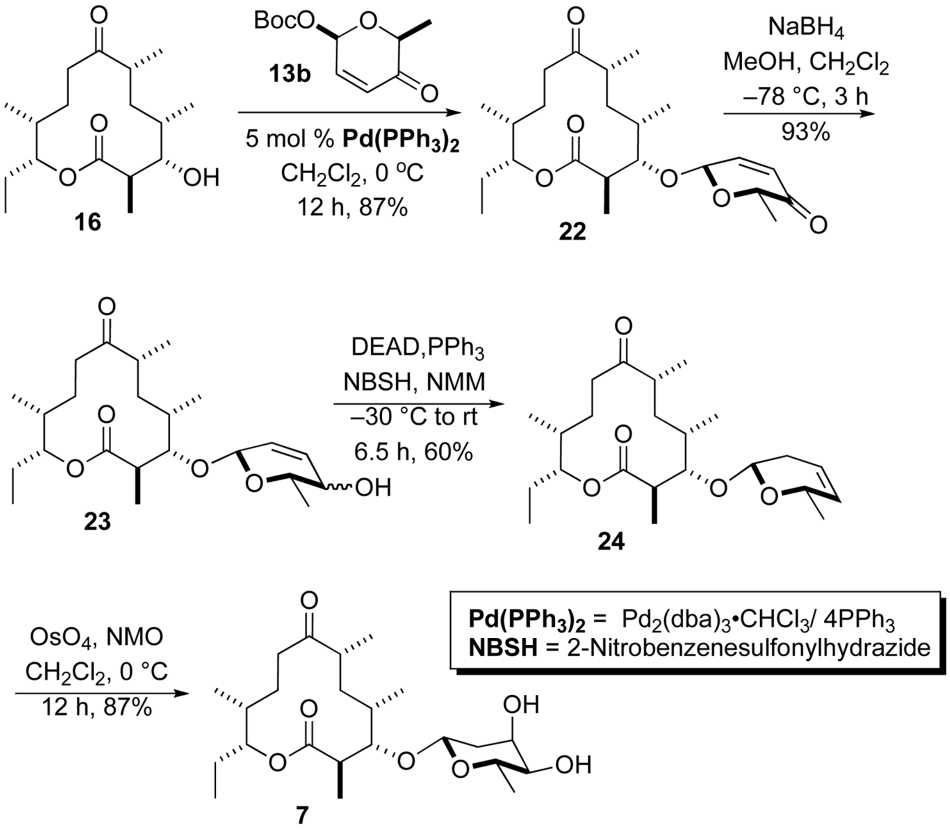
Scheme 3.

Synthesis of α-L-sugar analogues **1** and **2**



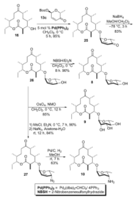
Scheme 4.

Syntheses of α-L-amino sugar analogues **3–6**



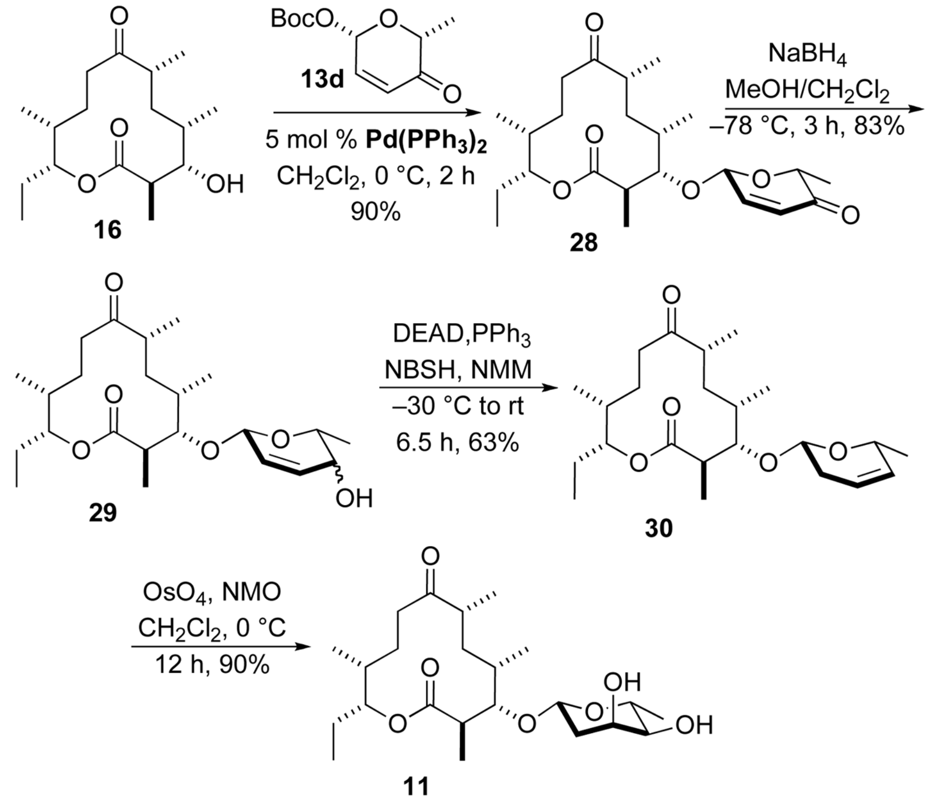
Scheme 5.

Synthesis of β-L-sugar analogue **7**



Scheme 6.

Syntheses of α-D-sugar analogues **8–10**



Scheme 7.

Synthesis of β-D-sugar analogue **11**