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De Novo Synthesis of the Trisaccharide Subunit of Landomycins A and E

Maoquan Zhou and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

george.odoherty@mail.wvu.edu

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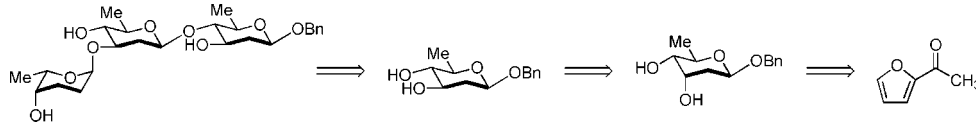
ABSTRACT



A highly enantio- and diastereoselective synthesis of α-L-rhodinose, β-D-olivose as well as the trisaccharide portion of landomycin A from achiral acetyl furan has been developed. The key transformations include the palladium-catalyzed glycosylation, Myers' reductive rearrangement, diastereoselective dihydroxylation, and regioselective Mitsunobu inversion. A Mitsunobu reaction on a six member ring *cis*-1,2-diol was found to chemoselectively discriminate between equatorial and axial alcohols and to stereoselectively convert *cis*-1,2-diol into *anti*-1,2-diol.

The landomycins, a unique class of angucycline-type antibiotics, display potent antitumor and antibacterial activity.[1] Landomycin A (**1**),[2] the most complex member of the family, was first discovered in 1990 as the principle product of *Streptomyces cyanogenus* S136 bearing a deoxysugar containing hexasaccharide made up of two repeating trisaccharides (α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose) (Figure 1). Of particular interest, landomycin A possesses significant antitumor activity against a range of 60 cancer cell lines.[3] The structure−activity relationship (SAR) studies suggested that the high cytotoxic activity of landomycin A depends on the length of the glycan chain, in which Landomycin B, J, E, D, I with shorter sugar side chain (Figure 1), showed diminished cytotoxic activities. Although it is known that landomycin A interacts with DNA, inhibits DNA synthesis, and halts G_1/S cell cycle progression,[4] the specific mechanism of action of landomycin A on cancer cells has not yet been determined. As part of a program aimed at the synthesis and biological study of carbohydrate containing natural products, we became interested in the synthesis

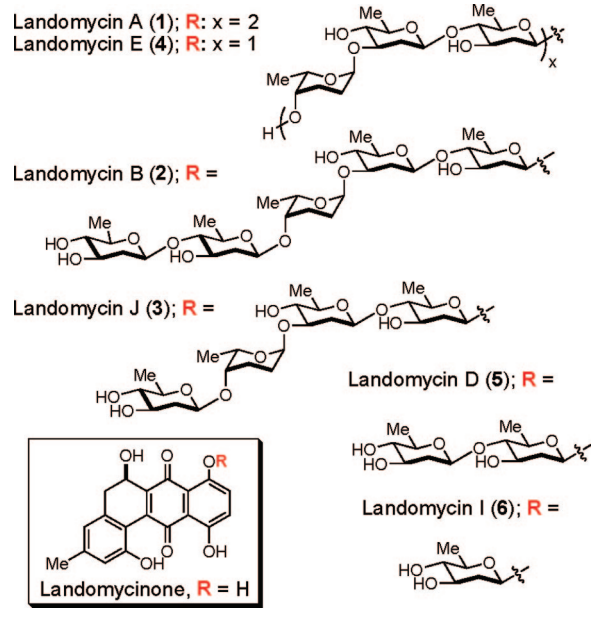


Figure 1. Structures of landomycins A, B, J, E, D, and I.

(1) (a) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103. (b) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127. (c) Andriy, L.; Andreas, V.; Andreas, B. *Mol. BioSyst.* **2005**, *1*, 117–126.

(2) (a) Henkel, T.; Rohr, J.; Beale, J. M.; Schwenen, L. *J. Antibiot.* **1990**, *43*, 492. (b) Weber, S.; Zolke, C.; Rohr, J.; Beale, J. M. *J. Org. Chem.* **1994**, *59*, 4211. The structure of the Landomycin A aglycon is still under debate, see: (c) Roush, W. R.; Neitz, R. J. *J. Org. Chem.* **2004**, *69*, 4906. (d) Zhu, L. I.; Luzhetskyy, A.; Luzhetska, M.; Mattingly, C.; Adams, V.; Bechthold, A.; Rohr, J. *ChemBioChem* **2007**, *8*, 83–88.

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(4) Crow, R. T.; Rosenbaum, B.; Smith, R., III; Guo, Y.; Ramos, K. S.; Sulikowski, G. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1663–1666.

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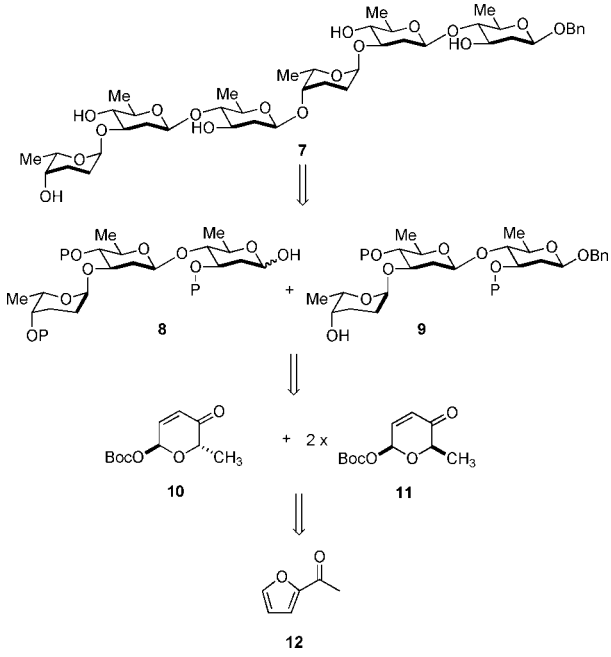
of the trisaccharide portion of Landomycin E, which is the repeat unit of the hexasaccharide portion of Landomycin A. Ultimately, we hope to use this trisaccharide to study its properties in cellular transportation and DNA binding ability (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Landomycin A Hexasaccharide

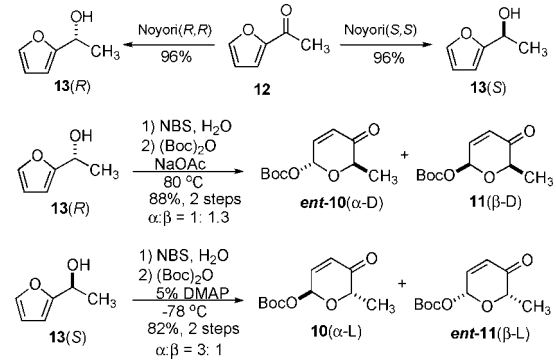


While there are no reports of the total synthesis of landomycin A,[2c,5] the synthesis of the hexasaccharide fragment has been completed by three groups (Sulikowski, Yu, and Roush).[6] In contrast to the previous syntheses of the landomycin A hexasaccharide, which derived their asymmetry from carbohydrate starting material, we were interested in a de novo asymmetric approach that would use asymmetric catalysis to install the 22 stereocenters of the landomycin A hexasaccharide from achiral starting materials. While we previously have had some success using our Pd-catalyzed glycosylation and postglycosylation reactions for the synthesis of several naturally occurring structural motifs, the landomycins offered the opportunity to apply this methodology for the synthesis of new carbohydrate subunits (e.g., α-L-rhodinose and β-D-olivose).[7,8] For example, the β-D-olivose required the development of new postglycosylation transformations. In particular, we anticipated a need for a new transformation that allowed for the net 1,2-trans-diequatorial addition of two hydroxyl groups across a six-membered ring alkene.

Strategically, the two trisaccharide derivatives **8** and **9** can be coupled together to build the final hexasaccharide in a fashion akin to the approach by Sulikowski and co-workers (P = Ac).[6b] The trisaccharide **8** could easily be prepared from **9**, which allows us to maximize the convergency. By means of a sequence of palladium catalyzed glycosylations and subsequent postglycosylation modifications[9] we foresaw the trisaccharide **9** as being derived from one unit of the α-L-pyranone **10** and two units of β-D-pyranone **11**. Finally, the α-L-rhodinose precursor pyranone **10** and β-D-olivose precursor pyranone **11** could be easily prepared from achiral acylfuran **12**.

Previously, we have shown that the α- and β-stereoisomers of either enantiomer of pyranones **10** and **11** can be prepared from acyl furan **12** by employing an enantioselectively Noyori reduction (**12** to **13**/*ent*-**13**),[10,11] an Achmatowicz oxidation, and diastereoselective *tert*-butyl carbonate formation (Scheme 2).[12] The β-pyranone **11** and *ent*-**11** can be isolated in ~50% yield when the Boc-protection was preformed at elevated temperature ((Boc)$_2$O/NaOAc in benzene at 80 °C). Alternatively, α-pyranones **10** and *ent*-**10** can be selectively prepared (α:β = 3:1) at low temperatures (−78 °C).

Scheme 2. Synthesis of D/L-α/β-Boc-pyranones

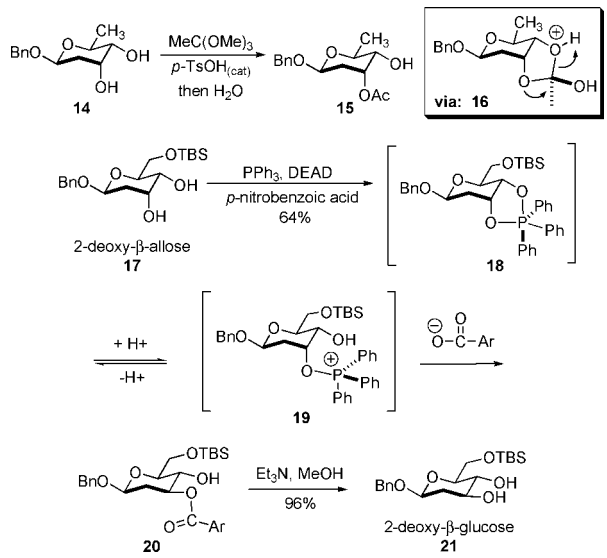


Our planned synthesis of landomycin A hexasaccharide was built up from the previous successful approach to 2-deoxy-β-glycoside associated with digitoxin.[13] To do this would require the selective conversion of the *allo*-stereochemistry of digitoxose into the *gluco*-stereochemistry of olivose. That is to say, invert the C-3 axial alcohol to a C-3 equatorial alcohol, which we hoped to achieve without any unnecessary protection/deprotection steps.

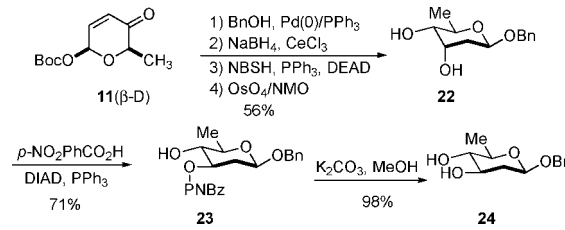
As part of our approach to the digitoxin trisaccharides, we have shown the axial alcohol of the C-3/C-4 *cis*-diol in *allo*-sugars could be regioselectively acylated via the known stereoelectronically controlled ortho-ester hydrolysis (i.e., **14** to **15** via **16**, Scheme 3).[13,14] We postulated that a similar stereoelectronic control could govern the protonation and subsequent Mitsunobu-type opening of a dioxyphosphorane fused to a six membered ring, as in **18** the one formed from the reaction of **17** with PPh_3 and DIAD.[15] Thus, selective protonation of the initially formed pentacoordinated dioxyphosphorane **18**[16,17] should preferentially form the oxyphosphonium betaine **19**, which after subsequent S_N2 displacement of Ph_3PO by *p*-nitrobenzoate ion should afford the *C*-3-OPNBz regioisomer **20**.

(5) For the biosynthesis of the landomycin, see: (a) Von Mulert, U.; Luzhetskyy, A.; Hofmann, C.; Mayer, A.; Bechthold, A. *FEMS Microbiol. Lett.* **2004**, *230*, 91–97. (b) Baig, I.; Kharel, M.; Kobylyanskyy, A.; Zhu, L.; Rebets, Y.; Ostash, B.; Luzhetskyy, A.; Bechthold, A.; Fedorenko, V. A.; Rohr, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7842–7846.

Scheme 3. Synthesis of 2-Deoxy-β-glucose from 2-Deoxy-β-allose



Scheme 4. Synthesis of Monosaccharide β-D-Olivose



To our delight, the direct Mitsunobu reaction[18] on the diol **17** gave only the C-3 equatorial nitro-benzoate product **20** in 64% yield along with 30% recovered **17** (Scheme 3). Upon basic hydrolysis, ester **20** was converted to the 2-deoxy-β-glucose **21**, which has the desired β-olivose stereochemistry (2,6-dideoxy-β-glucose). The stereochemistry was confirmed by ^{1}H NMR coupling constant analysis. The coupling constant $^3J_{H3-H4}$ in diol **17** is 3.0 ppm, which is the typical axial−equatorial proton coupling constant; while in diol **21**, the axial−axial $^3J_{H3-H4}$ equal to 8.4 ppm.[19]

With this highly chemoselective discrimination and stereoselective inversion of the 1,2-diol established, we then applied this transformation to the synthesis of landomycin A monosaccharide β-D-olivose (Scheme 4). As the starting point, both the enantiopure pyranones α-L-**10** and β-D-**11** were diastereoselectively prepared as the major products (Scheme 2).[9a,13] Subjecting pyranone **11** to the following 4-step sequence: palladium catalyzed glycosylation with BnOH, Luche reduction[20] of the keto group, Myers' reductive 1,3-allylic transposition[21] and dihydroxylation,[22] gave exclusively the diol **22** in 56% overall yield.[13] Under Mitsunobu reaction conditions, the digitoxose **22** was cleanly converted to protected β-D-olivose **23** in 71% yield while the benzoate group also served as a temporary protecting group. A simple hydrolysis of benzoate group with K_2CO_3 fashioned the monosaccharide β-D-olivose **24** in 98% yield.

With a viable route to the β-D-*olivo*-sugar **24** in hand, our efforts turned to the construction of the di- and trisaccharide (Schemes 5 and 6). Thus, the *olivo*-sugar **23** and β-D-pyranone **11** were subjected to the typical palladium-catalyzed glycosylation conditions, which afforded the C-4 glycosylated disaccharide **25** in 85% yield with complete

(6) For chemical synthesis of the trisaccharide, see: (a) Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267. For chemical synthesis of hexasaccharide, see: (b) Guo, Y.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 1392. (c) Yu, B.; Wang, P. *Org. Lett.* **2002**, *4*, 1919. (d) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124. For chemical synthesis of the aglycon, see ref 2c.

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(8) For a review of deoxysugar syntheses, see: Kirschning, A.; Jesberger, M.; Schöning, K.-U. *Synthesis* **2001**, 507–540.

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(11) (a) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005–1009. (b) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407–6411.

(12) For the preparation of Boc-protected pyranones, see: (a) Babu, R. S.; O'Doherty, G. A. *J. Carb. Chem.* **2005**, *24*, 169–177. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921–3924.

(13) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485–2493.

(14) (a) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754–1769. (b) Lowary, T. L.; Hindsgaul, O. *Carbohydr. Res.* **1994**, *251*, 33–67.

(15) (a) Garcia-Delgado, N.; Riera, A.; Verdaguer, X. *Org. Lett.* **2007**, *9*, 635–638. (b) Mathieu-Pelta, I.; Evans, S. A., Jr. *J. Org. Chem.* **1992**, *57*, 3409–3413.

(16) (c) Robinson, P. L.; Barry, C. N.; Kelley, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 5210–5219. (d) Robinson, P. L.; Barry, C. N.; Bass, S. W.; Jarvis, S. E.; Evans, S. A., Jr. *J. Org. Chem.* **1983**, *48*, 5396–5398. Luckenbach, R. *Dynamic Stereochemistry of Pentacoordinated Phosphorus and Related Elements*; George Thieme: Stuttgart, FRG, 1973.

(17) A pentacoordinated dioxyphosphorane like **18** was suggested to have a trigonal-bipyramidal configuration with a the two P−O bonds to occupying an equatorial−axial position on the phosphorous, see: (a) Holmes, R. R. *J. Am. Chem. Soc.* **1978**, *100*, 433. (b) Holmes, R. R. *Pentaroordinated Phosphorus*; American Chemical Society: Washington, DC, 1980; Vols. I, 11; ACS Monograph No. 175, p 176.

(18) For reviews on Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* 1981128. (b) Hughes, D. L. *Org. Prep.* **1996**, *28*, 127–164. For examples of the Mitsunobu reaction on acyclic 1,2-diols, see: (c) He, L.; Wanunu, M.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1999**, *64*, 6049–6055. (d) Ko, S. Y. *J. Org. Chem.* **2002**, *67*, 2689–2691. (e) Pautard-Cooper, A.; Evans, S. A., Jr. *J. Org. Chem.* **1989**, *54*, 2485–2488, 4974.

(19) To the best of our knowledge, this is the first example of this type of 1,2-*cis*-diol Mitsunobu in a six-membered ring system, which when used in conjunction with a highly diastereoselective dihydroxylation reaction constitutes a nice solution to the problem associated with the net 1,2-diequatorial addition to a cyclohexene.

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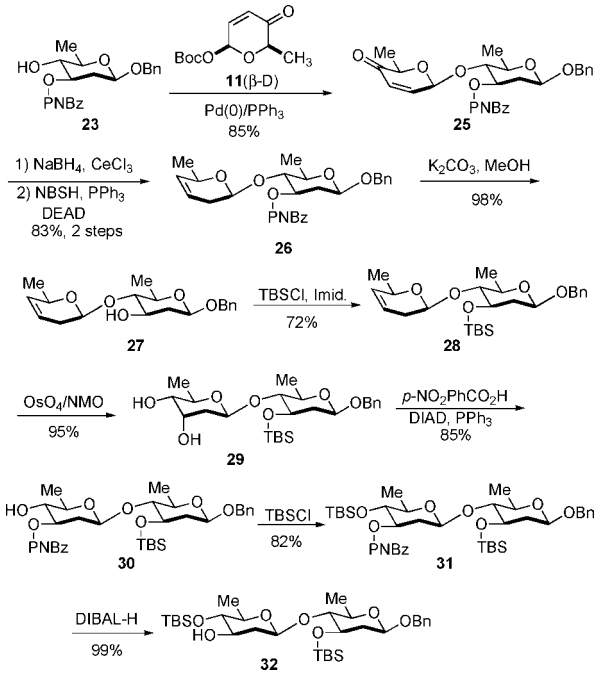
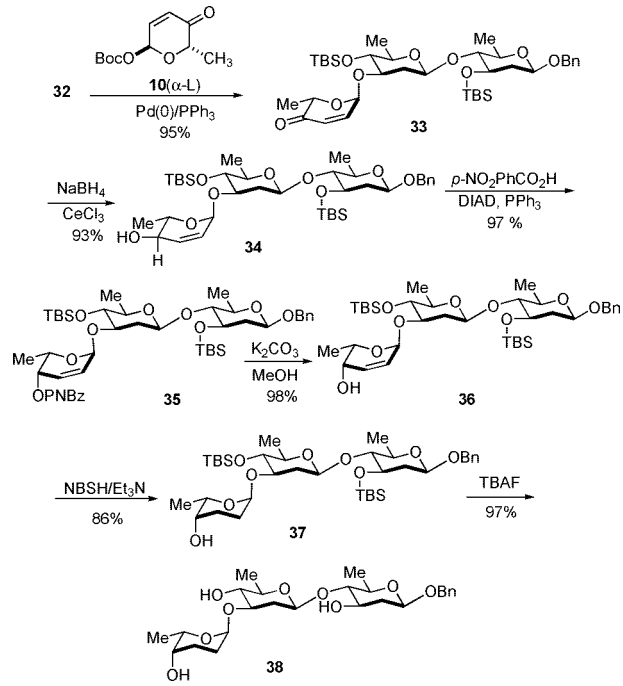
(21) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492–4493. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771–1774.

(22) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

Scheme 5. Synthesis of Disaccharide Benzyl β-D-Olivose-(1→4)-β-D-olivose



Scheme 6. Synthesis of Landomycin A and E Trisaccharide



stereocontrol at the anomeric center (Scheme 5). Luche reduction of the keto-group in pyranone **25** provided a mixture of allylic alcohols, which when exposed to the Myers' reductive 1,3-allylic transposition conditions provided olefin **26** in 83% yield for two steps. At this stage, the replacement of *p*-nitrobenzoyl group (PNBz) is necessary because another Mitsunobu reaction will take place and these two hydroxyl groups will need to be differentiated. Thus, the *p*-nitrobenzoate group was easily hydrolyzed with K_2CO_3 and MeOH to give alcohol **27** in 98% yield. Protection of the alcohol with TBSCl provided the olefin **28** in 72% yield. The dihydroxylation of **28** gave exclusively the diol **29** in 95% yield.

When applying the regioselective Mitsunobu reaction to diol **29**, the benzoate **30** was afforded in 85% yield. Because the C-3 free hydroxy group will be the glycosyl acceptor for next glycosylation, the protection of the C-4 alcohol and deprotection of C-3 benzoate are needed. Thus, treating the alcohol **30** with TBSCl provided the silyl ether **31** in 82% yield. The initial effort toward the hydrolysis of benzoate in **31** with K_2CO_3 and MeOH proved to be troublesome, giving the desired product **32** along with the C-3-OTBS product in a ratio of 1:1.4. Presumably the C-3-OTBS product is formed by a base promoted TBS group migration from C-4 hydroxy group to C-3 hydroxy group. A much cleaner reaction resulted from the reduction of the benzoate **31** with DIBAL-H, which gave alcohol **32** in 99% yield.

The last sugar of the trisaccharide was α-L-rhodinose, which was derived from the α-L-pyranone **10** (Scheme 6). The glycosylation of alcohol **32** and α-L-**10** provided the trisaccharide pyranone **33** in 95% yield, which underwent Luche reduction to give exclusively the allylic alcohol **34** in 93% yield. Because the stereochemistry of the C-4 hydroxy group was not identical to the target compounds, it had to be reversed. Gratifyingly, this was achieved by Mitsunobu reaction, which gave the desired product **35** in 97% yield. Upon hydrolysis, the benzoate in **35** was removed to give the alcohol **36** in 98% yield. The diimide reduction of the olefin in **36** provided the trisaccharide **37**. Finally, the landomycin A and E trisaccharide **38** was achieved by removing the two TBS groups with TBAF (97%). Overall, the trisaccharide **38** was prepared from the achiral acylfuran **12** in 22 steps and 4.5% overall yield.

In conclusion, a highly enantioselective route to landomycin E trisaccharide **38** has been developed. The key transformations include: the palladium catalyzed glycosylation reaction, Myers' reductive rearrangement, diastereoselective dihydroxylation, and the regioselective Mitsunobu reaction. This is the first example of the chemoselective discrimination and stereoselective inversion of the 1,2-diol on a sugar system using a direct Mitsunobu reaction on diol. The preparation of other analogues as well as landomycin A and E are ongoing.

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

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