JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
COMMUNICATION
pubs.acs.org/JACS

Total Synthesis of Landomycin A, a Potent Antitumor Angucycline Antibiotic

Xiaoyu Yang, Boqiao Fu, and Biao Yu*

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

S Supporting Information

ABSTRACT: The first total synthesis of landomycin A, the longest and most potent antitumor angucycline antibiotic, has been achieved in 63 steps and 0.34% overall yield starting from 2,5-dihydroxybenzoic acid, 3,5-dimethylphenol, triacetyl D-glucal, and D-xylose, with a convergent linear sequence of 21 steps.

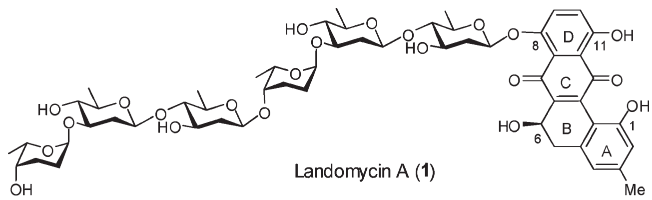


Figure 1

The landomycins constitute a unique group of angucycline antibiotics featuring a benz[*a*]anthraquinone aglycone (i.e., a landomycinone) with a dearomatized B ring and deoxyoligosaccharide chains of various lengths attached at the C8 OH.[1,2] These compounds show potent antitumor activities; the potency varies with variation of the sugar residues and is also relevant to the cell types.[3,4] The mechanism of the antitumor action remains uncertain, and it also seems to be dependent on the sugar residues.[3b,c] The biosynthetic pathway toward these tetracyclic decaketide glycoconjugates is intriguing, especially in the introduction of the four oxygens (out of six) from air and in the iterative introduction of the monosaccharide residues.[4] The chemical synthesis of the landomycins has challenged chemists for many years. The major synthetic difficulties include the following: (1) the construction of landomycinone demands avoidance of the extremely easy process of dehydrative aromatization of the B ring; (2) assembly of the deoxyoligosaccharides requires special devices to control the stereochemistry as well as to avoid the cleavage/anomerization of the extremely acid-labile di- and trideoxyglycosidic linkages; and moreover, (3) attachment of the sugars to the poorly nucleophilic hydrogen-bonded C8 phenol of landomycinone is difficult. In fact, the synthesis of landomycinone has to date been achieved only by the Roush group;[5] the synthesis of the longest hexasaccharide residue of landomycin A has been accomplished by the Sulikowski, Roush, Yu, and Takahashi groups, the trisaccharide fragment by the Kirschning and O'Doherty groups, and the disaccharide fragment by the McDonald group.[6] However, attachment of the sugar residues to landomycinone to accomplish the total synthesis of landomycins has remained an elusive task. Here we report the total synthesis of landomycin A (Figure 1), the longest and most potent antitumor congener of the landomycins.

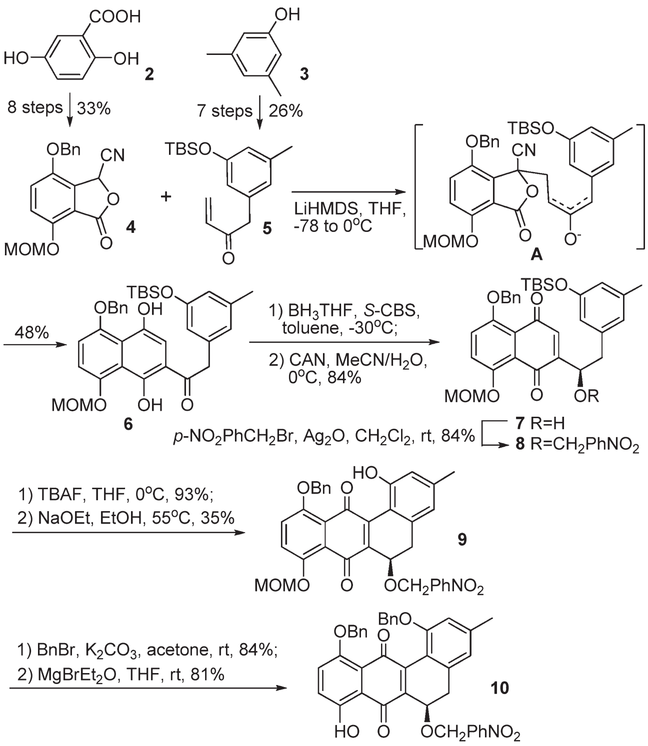
To realize the total synthesis of a landomycin, any of the preceding synthetic approaches toward landomycinone and the deoxyoligosaccharides must be adjusted to enable selective removal of protecting groups and the subsequent coupling of the aglycone and sugars. Thus, landomycinone derivative **10** having the OH groups at the 1, 6, and 11 positions protected with benzyl or *p*-nitrobenzyl groups was desired for the subsequent sugar assembly. The synthesis of **10** was accomplished in a convergent manner, employing Hauser annulation[7] to form the C ring and Roush's intramolecular Michael addition[5] to form the B ring (Scheme 1). Cyanophthalide **4** and enone **5** were prepared from 2,5-dihydroxybenzoic acid (**2**) and 3,5-dimethylphenol (**3**) in eight and seven steps, respectively, not without complications.[8] Treatment of **4** with LiHMDS in THF at −78 °C followed by addition of **5** at 0 °C led to the desired naphthalene **6** in 48% yield. The corresponding 1,4-adduct could transform rapidly into the thermodynamically favored enolate having extended conjugation with the benzene ring to escape the annulation.[9] Asymmetric reduction of ketone **6** with $BH_3 \cdot THF$/(*S*)-CBS[10] led to the naphthodihydroquinone C6-ol derivative, which was vulnerable to air and thus was completely converted with ceric ammonium nitrate (CAN) at 0 °C into quinone **7** in 84% yield with 93% ee. Protection of the C6 OH in **7** with a *p*-nitrobenzyl group provided **8**; the benzyl-protected counterpart was surprisingly unstable. Removal of the 1-*O*-TBS protection in **8** gave the phenol, which was unstable and thus was immediately subjected to the intramolecular Michael addition. Thanks to the careful studies on a similar substrate by Roush and Neitz,[5] we were able to furnish the desired landomycinone derivative **9** in 35% yield under slightly modified conditions [NaOEt, EtOH, 4 Å molecular sieves (MS), air, 55 °C], with isolation of the 1-methyl-3-hydroxy regioisomer in 8% yield and recovery of the starting phenol in 27% yield. This transformation was reproducible in a gram-scale synthesis. Protection of the C1 phenol with a benzyl group (84%) and removal of the 8-*O*-MOM group [$MgBr_2 \cdot Et_2O$, THF, room temperature (rt), 81%][5] provided the desired landomycinone **10**.

The phenolic C8 OH in landomycinone **10** is situated on an electron-deficient naphthoquinone skeleton and hydrogen-bonded, which makes its glycosidation extremely challenging. In addition, the vulnerability of the substrate toward aromatization

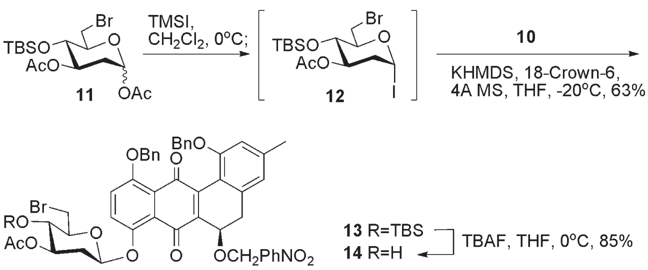
Received: June 9, 2011
Published: July 25, 2011

 © 2011 American Chemical Society

Scheme 1

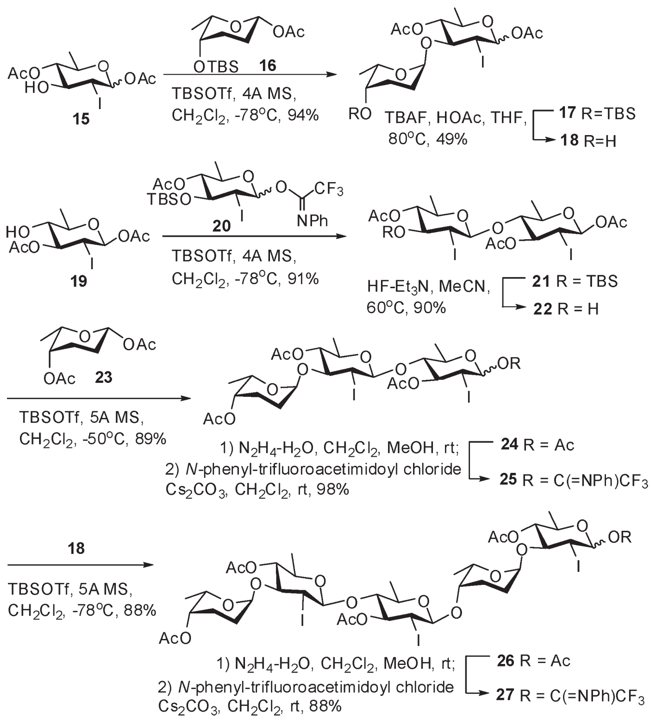


Scheme 2



of the B ring would rule out the applicability of most of the powerful glycosylation conditions. From the viewpoint of the sugar part, formation of the β-D-olivopyranoside linkage is also a difficult task that requires special devices.[6] Thus, not surprisingly, numerous attempts at glycosylation of **10** failed, including adoption of the previously well-established methods with 2-deoxy-2-iodoglycosyl trichloroacetimidates,[11] 2-deoxy-2-selenophenyl-α-D-glucopyranoses (under Mitsunobu conditions),[12] and 2,3-*O*-thionocarbonyl-1-thioglycosides as donors.[6c,13] Finally came a fortuitous try with glycosyl iodide under anionic conditions, a protocol developed by the Gervay-Hague group.[14] Thus, treatment of 3-*O*-acetyl-6-bromo-4-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-glucopyranosyl acetate (**11**, six steps from triacetyl D-glucal)[8] with TMSI (CH_2Cl_2, 0 °C) led to the clean formation of α-iodide **12**. S_N2-type substitution of iodide **12** using the naphthoate anion derived from landomycinone **10** (KHMDS, 18-crown-6, 4 Å MS, THF) at −20 °C furnished β-glycoside **13** in a satisfactory 63% yield, along with a 14% yield of the undesired product formed by elimination to provide the corresponding $\Delta^{5,6}$ derivative (Scheme 2). It is worth noting that the 6-bromo substituent in

Scheme 3

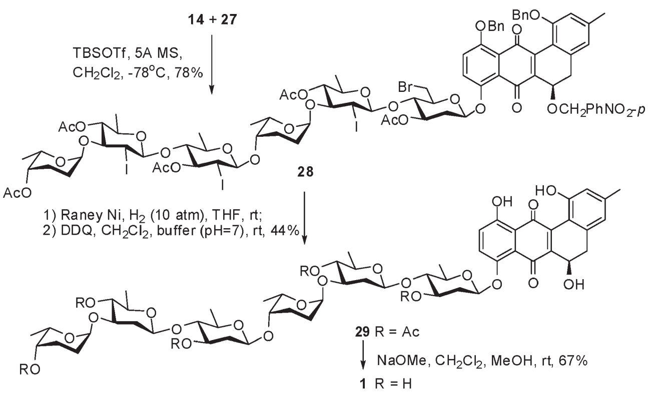


11 is crucial to the reaction; the similar reaction with the 6-deoxy counterpart led only to the corresponding glycal. Selective removal of the 4′-*O*-TBS group on **13** provided **14** (85%), which was ready for subsequent sugar elongation.

To assemble landomycin A in a convergent manner, pentasaccharide trifluoroacetimidate **27** was prepared (Scheme 3).[15] Glycosylation of **15**[11b] with L-rhodinosyl acetate **16**[8] under the catalysis of TBSOTf (0.2 equiv) at −78 °C afforded the thermodynamically favored α-disaccharide **17** (94%). Selective removal of the 4′-*O*-TBS group in **17** was surprisingly problematic; with TBAF/HOAc at 80 °C, the desired **18** was obtained in moderate yield (49%) with 28% recovery of **17**. Coupling of **19**[11b] with 2,6-dideoxy-2-iodoglucopyranosyl trifluoroacetimidate **20**[8] under the action of TBSOTf (0.2 equiv) at −78 °C afforded β-disaccharide **21** in excellent yield (91%) along with the corresponding α-disaccharide in ~5% yield. Removal of the 3-*O*′-TBS group in **21** was effected nicely with $HF\cdot Et_3N$ (MeCN, 60 °C), affording **22** in 90% yield. Glycosylation of **22** with L-rhodinosyl acetate **23**[8] promoted by TBSOTf (0.2 equiv) at a higher temperature (−50 °C) gave the desired trisaccharide **24** (89%). Selective cleavage of the anomeric acetate in **24** ($N_2H_4\cdot H_2O$, CH_2Cl_2, MeOH, rt)[11] followed by trifluoroacetimidate formation[16] afforded trisaccharide imidate **25** nearly quantitatively. Coupling disaccharide acceptor **18** with trisaccharide imidate **25** under the catalysis of TBSOTf (0.05 equiv) in the presence of 5 Å MS at −78 °C in CH_2Cl_2 afforded the desired pentasaccharide **26** in a satisfactory 88% yield. Pentasaccharide acetate **26** was then transformed to trifluoroacetimidate **27** in a manner similar to the **24** → **25** transformation in an excellent yield of 88%.

Coupling of landomycinone monoglycoside **14** with pentasaccharide trifluoroacetimidate **27** was achieved under the catalysis of TBSOTf (0.03 equiv) in the presence of 5 Å MS in CH_2Cl_2 at −78 °C, affording the desired hexasaccharide **28** in a

Scheme 4



good 78% yield (Scheme 4). Stronger conditions (e.g., a bit more TBSOTf or higher temperature) led to cleavage of the 2,3,6-trideoxy-α-glycosidic linkages and the C8−*O*-2′-deoxy-*β*-glycosidic linkage. Removal of the bromide and iodide and the benzylic protecting groups on the fragile landomycin A precursor **28** proved to be a big challenge. We first screened conditions on a landomycinone disaccharide[15] and then applied the optimized conditions to hexasaccharide **28**. Thus, hydrogenation (10 atm) of **28** with Raney Ni followed by oxidation of the resulting hydroquinone with DDQ afforded the desired deoxyhexasaccharide **29** in 44% yield, with the bromide, three iodide, and three benzylic groups being cleaved. Finally, the five acetyl groups remaining on the sugar residue were removed with NaOMe, providing landomycin A (**1**) in 67% yield. The analytical data of **1** were in good agreement with those reported for the natural product.[2a,c,8]

In conclusion, the first total synthesis of landomycin A (**1**), the longest and most potent antitumor congener of the angucycline antibiotics, has been achieved in 63 steps and 0.34% overall yield starting from 2,5-dihydroxybenzoic acid, 3,5-dimethylphenol, triacetyl D-glucal, and D-xylose, with a convergent linear sequence of 21 steps. The synthesis of other landomycin members and their derivatives has become a feasible task that would facilitate in-depth studies of their unusual spectrum of antitumor activities.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
byu@mail.sioc.ac.cn

■ ACKNOWLEDGMENT

This work was supported by the NSFC (20932009 and 20921091) and the MOST of China (2010CB529706).

■ REFERENCES

(1) (a) Rohr, J.; Thiericke, R. *Nat. Prod. Rep* **1992**, *9*, 103. (b) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127.

(2) (a) Henkel, T.; Rohr, J.; Beale, J. M.; Schwene, L. *J. Antibiot.* **1990**, *43*, 492. (b) Weber, S.; Zolke, C.; Rohr, J.; Beale, J. M. *J. Org. Chem.* **1994**, *59*, 4211. (c) Zhu, L.; Ostash, B.; Rix, U.; Nur-e-Alam, M.; Mayers, A.; Luzhetskyy, A.; Mendez, C.; Salas, J. A.; Bechthold, A.; Fedorenko, V.; Rohr, J. *J. Org. Chem.* **2005**, *70*, 631.

(3) (a) Depenbrock, H.; Bornschlegl, S.; Peter, R.; Rohr, J.; Schmid, P.; Schweighart, P.; Block, T.; Rastetter, J.; Kanauske, A. R. *Ann. Hematol.* **1996**, 73, A80/316. (b) Crow, R. T.; Rosenbaum, B.; Smith, R., III; Guo, Y.; Ramos, K. S.; Sulikowski, G. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1663. (c) Korynevska, A.; Heffeter, P.; Matselyukh, B.; Elbling, L.; Micksche, M.; Stoika, R.; Berger, W. *Biochem. Pharmacol.* **2007**, *74*, 1713. (d) Shaaban, K. A.; Srinivasan, S.; Kumar, R.; Damodaran, C.; Rohr, J. *J. Nat. Prod.* **2011**, *74*, 2.

(4) (a) Ostash, B.; Rix, U.; Rix, L. L. R.; Liu, T.; Lombo, F.; Luzhetskyy, A.; Gromyko, O.; Wang, C.; Braña, A. F.; Méndez, C.; Salas, J. A.; Fedorenko, V.; Rohr, J. *Chem. Biol.* **2004**, *11*, 547. (b) Luzhetskyy, A.; Zhu, L.; Gibson, M.; Fedoryshyn, M.; Dürr, C.; Hofmann, C.; Hoffmeister, D.; Ostash, B.; Mattingly, C.; Adams, V.; Fedorenko, V.; Rohr, J.; Bechthold, A. *ChemBioChem* **2005**, *6*, 675. (c) Zhu, L.; Luzhetskyy, A.; Luzhetska, M.; Mattingly, C.; Adams, V.; Bechthold, A.; Rohr, J. *ChemBioChem* **2007**, *8*, 83.

(5) Roush, W. R.; Neitz, R. J. *J. Org. Chem.* **2004**, *69*, 4906. In this paper, Roush and Neitz described the synthesis of the structure originally assigned to the aglycone of landomycin A (i.e., landomycinone) and confirmed the structure of the synthetic sample by X-ray analysis. However, comparison of spectroscopic data for synthetic landomycinone with published data for the natural aglycone as well as with copies of ^{1}H NMR spectra provided by Prof. Rohr to Prof. Roush led these authors to conclude that their synthetic material was not identical to naturally occurring landomycinone. However, a paper subsequently appeared from Rohr's laboratory that provided a new set of ^{1}H NMR data for natural landomycinone that exactly matched the data obtained by Roush and Neitz for their synthetic landomycinone (ref 2c). The latter information, together with our successful total synthesis of landomycinone A described here, leaves no doubt that Roush and Neitz indeed synthesized landomycinone.

(6) (a) Guo, Y.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 1392. (b) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124. (c) Yu, B.; Wang, P. *Org. Lett.* **2002**, *4*, 1919. (d) Tanaka, H.; Yamaguchi, S.; Yoshizawa, A.; Takagi, M.; Shin-ya, K.; Takahashi, T. *Chem.—Asian J.* **2010**, *5*, 1407. (e) Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267. (f) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 2283. (g) McDonald, F. E.; Reddy, K. S. *J. Organomet. Chem.* **2001**, *617*−*618*, 444.

(7) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892.

(8) See the Supporting Information for details.

(9) Couladouros, E. A.; Strongilos, A. T.; Papageorgiou, V. P.; Plyta, Z. F. *Chem.—Eur. J.* **2002**, *8*, 1795.

(10) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(11) (a) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891. (b) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1875.

(12) Roush, W. R.; Lin, X. F. *J. Am. Chem. Soc.* **1995**, *117*, 2236.

(13) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377.

(14) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2003**, *5*, 4219.

(15) We had examined the glycosylation of landomycinone monoglycoside **14** with a relevant monosaccharide donor and found 3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-D-glucopyranosyl trifluoroacetimidate to be superior to afford the corresponding *β*-disaccharide in good yield (data not shown).

(16) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405. (b) Yu, B.; Sun, J. *Chem. Commun.* **2010**, *46*, 4668.