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Efficient Synthesis of the Hexasaccharide Fragment of Landomycin A: Using Phenyl 2,3-*O*-Thionocarbonyl-1-thioglycosides as 2-Deoxy-β-glycoside Precursors

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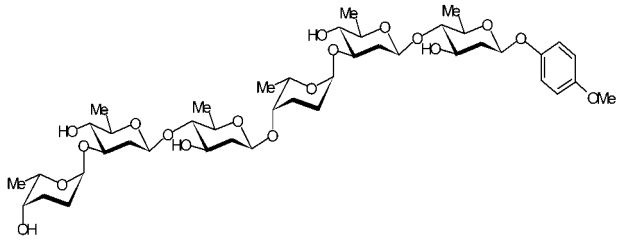
ABSTRACT



The β-*p*-methoxyphenol hexadeoxysaccharide fragment of landomycin A was synthesized in a total of 33 steps and 0.5% overall yield starting from D-mannose and D-xylose, featuring the use of phenyl 2,3-*O*-thionocarbonyl-1-thioglycosides as 2-deoxy-β-glycoside precursors.

Landomycin A,[1] the principal metabolite of *Streptomyces cyanogenus*, is a member of the angucycline antibiotic family with the longest glycan so far disclosed.[2] The potent antitumor activities of landomycin A, associated with its inhibition of DNA synthesis and G_1/S cell cycle progression, is dependent on its glycan.[3] Thus, landomycins B, D, and E, with shorter glycans, show diminished activities. The interaction of several deoxyoligosaccharides, e.g., those of calicheamicins, with DNA has been well documented,[4] yet not for the landomycin glycans. Synthesis of the hexasaccharide of landomycin A and its congeners thereafter would facilitate detailed studies on this interesting topic. The hexasaccharide itself, comprising two repeating trisaccharides of the sequence α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose, is a challenging target for synthetic chemists. Not only is the stereocontrolled construction of the 2-deoxy-β-D-glycoside linkages a formidable task, but the preservation of such acid labile linkages, especially the trideoxy rhodinose linkages, is also difficult in the subsequent manipulation.[5] Sulikowski and Guo have pioneered the synthesis of the acetylated landomycin A hexasaccharide.[6] Thus, the corresponding fully acetylated β-*p*-methoxyphenol hexasaccharide

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(4) See ref 5a, pp 47−50 and relevant citations.

(5) See reviews: (a) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1. (b) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285.

(6) Guo, Y.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 1392.

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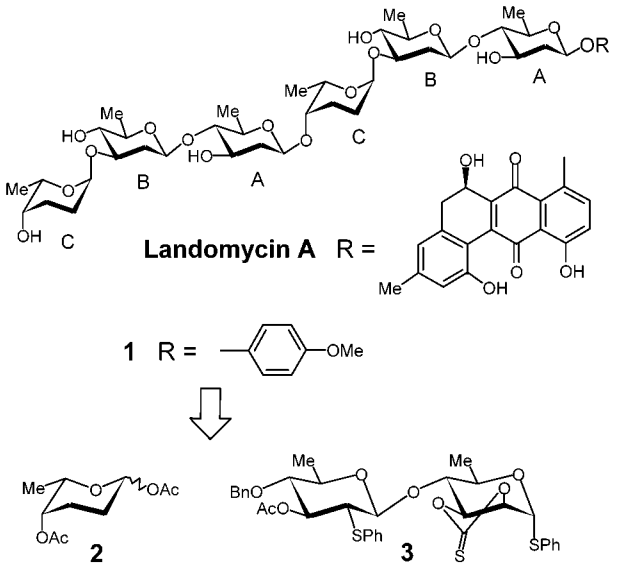
was synthesized in a total of 33 steps and an overall yield of <0.01% starting from L- and D-rhamnal, whereupon L-rhodinosyl tetrazoles[7] and D-olivosyl phosphites[8] were used as donors to build the corresponding α-L-rhodinoside and β-D-olivoside linkages, respectively. The stereoselectivities for the synthesis of the later linkages were only moderate. Roush and Bennett achieved the synthesis of the hexasaccharide glycal in a highly stereoselective manner,[9] taking full advantage of the use of their well-advanced 2-deoxy-2-iodo-glucopyranosyl trichloroacetimidate donors for the construction of the required 2-deoxy-β-glycoside linkages.[10] In addition, L-rhodinosyl acetates were successfully employed for the synthesis of the α-L-rhodinoside linkages.[11] Statistically, the whole synthetic route consists of 35 steps and was achieved in 0.6% overall yield starting from (*S*)-lactate and triacetyl D-glucal. In a previous report on the synthesis of an A−B−C trisaccharide derivative by Kirschning,[12] 2,6-dideoxy-2-iodo-glucopyranosyl acetates were employed as donors for the stereoselective synthesis of the β-D-olivoside linkages, albeit in lower yields. Here we report a novel and efficient synthesis of the hexadeoxysaccharide fragment of landomycin A (**1**) utilizing our newly developed method of using phenyl 2,3-*O*-thionocarbonyl-1-thioglycosides as 2-deoxy-β-glycoside precursors.[13]

Strategically, coupling of two A−B−C trisaccharide derivatives to build the final hexasaccharide is a convergent, and therefore very efficient, synthetic route. And such a tactic was successfully employed in both Sulikowski's and Roush's syntheses.[6,9] Alternatively, stepwise elongation is amenable to the synthesis of shorter or longer congeners. The finding that landomycins D, E, and B, having glycans of A−B, A−B−C, and A−B−C−A−B, respectively, are the biosynthetic intermediates of landomycin A implies a biosynthetic route that is between completely convergent and stepwise glycosylation.[14] We thus planned our synthesis in a similar fashion, i.e., elongation from A−B to A−B−C and then to A−B−C−A−B and finally to the target hexasaccharide. Accordingly, phenyl 3′-*O*-acetyl-2,3-*O*-thionocarbonyl-2′-*S*-phenyl-1-thiodisacchride **3** and L-rhodinosyl acetate **2** would be the key intermediates (Scheme 1).

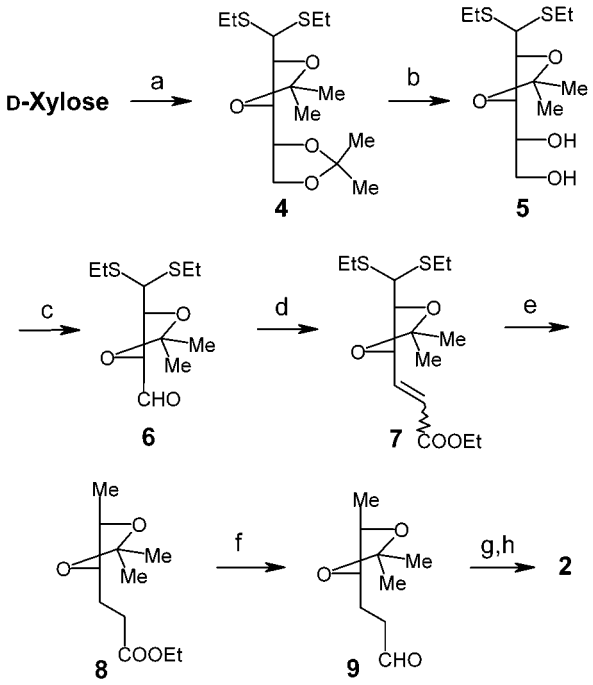
L-Rhodinose, a constituent of several classes of natural products, has been synthesized by over a dozen approaches.[15] We adopted modifications of Herczegh's route for preparation of **2**[16] (Scheme 2). Instead of starting from L-arabinose, we began the synthesis with the much cheaper D-xylose,

Scheme 1



which differs from the former only at the configuration of C-4, which will finally be reduced into a methylene. Another major modification is the replacement of formylmethylenetriphenylphosphorane with ethyl (triphenylphosphoranylidene)acetate in the Wittig reaction with tartraldehyde **6**; we

Scheme 2[a]



[a] Reaction conditions: (a) EtSH (3.0 equiv), HCl (concd), 0 °C; then $(MeO)_2CMe_2$, 69%. (b) 80% HOAc, 40 °C, 82%. (c) $Pb(OAc)_4$ (1.1 equiv), PhMe, 0 °C, 100%. (d) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 30 °C, 78%. (e) Raney Ni, H_2, EtOH, 60 °C, 59%. (f) DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, 78%. (g) 67% HOAc, 50 °C, 98%. (h) Ac_2O, pyridine, rt, 98%.

(7) (a) Falahatpisheh, N.; Sulikowski, G. A. *Synlett* **1994**, 672. (b) Sobti, K.; Kim, K.; Sulikowski, G. A. *J. Org. Chem.* **1996**, *61*, 6.

(8) Recently, Sulikowski described a one-pot method using glycosyl phosphites for the synthesis of 2-deoxy-β-oligosaccharides; see: Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 3523.

(9) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124.

(10) (a) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. (b) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891.

(11) Roush, W. R.; Bennett, C. E.; Roberts, S. E. *J. Org. Chem.* **2001**, *66*, 6389.

(12) Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267.

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

(14) See ref 5a, pp 25−27.

(15) See relevant citations in ref 11.

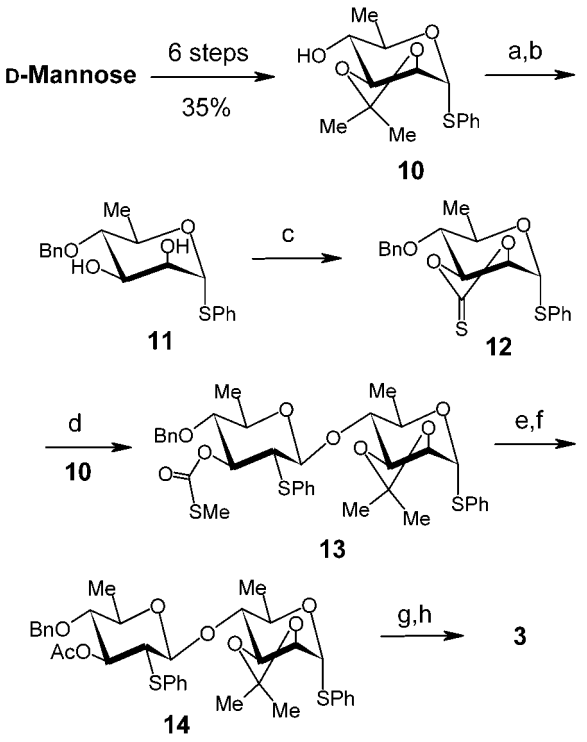
(16) (a) Herczegh, P.; Zsély, M.; Kovács, I.; Batta, Gy.; Sztaricskai, F. J. *Tetrahedron Lett.* **1990**, *31*, 1195. (b) Herczegh, P.; Kovács, I.; László, A.; Dinya, Z.; Sztaricskai, J. *Liebigs Ann. Chem.* **1991**, 599.

found the later conversion much easier to handle and more reproducible. Conveniently, 1,4-di-*O*-Ac-L-rhodinose was prepared from cheap D-xylose in a total of eight steps and in 20% overall yield.

Phenyl 1-thioglycoside **10** was readily prepared from D-mannose in six steps and in 35% overall yield following routine transformations.[17] Compound **10** was then converted into the key monosaccharide donor **12** in three easy transformations with 81% yield, i.e., protection of the 4-OH with a benzyl group, removal of the 2,3-*O*-isopropylidene, and then installation of the 2,3-*O*-thionocarbonyl function (Scheme 3).[13] Coupling of phenyl thioglycosides **10** (1.0 equiv) and **12** (1.2 equiv), under the promotion of MeOTf (1.4 equiv) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv) at room temperature, led expectedly to the β-(1→4)-linked disaccharide **13** in good yield (88%), with the anomeric phenylthio group of **12** stereospecifically migrating to the neighboring C-2 and that of **10** remaining intact.[13] The 3′-*O*-(methylthio)carbonyl group in **13** was found to be rather robust and thus was removed at 60 °C in 3 days in the presence of 3.0 equiv of NaOMe in a mixture of MeOH and CH_2Cl_2 (v/v 4:1) in 80% yield. Acetylation of the resulting alcohol gave **14**. Transformation of 2,3-*O*-isopropylidene **14** into 2,3-*O*-thionocarbonyl **3** employed operations similar to those used in the conversion **10**→**12**. Compound **3** was thus obtained in 97% yield, which was expected to be the crucial precursor for β-D-olivose-(1→4)-β-D-olivoside units.

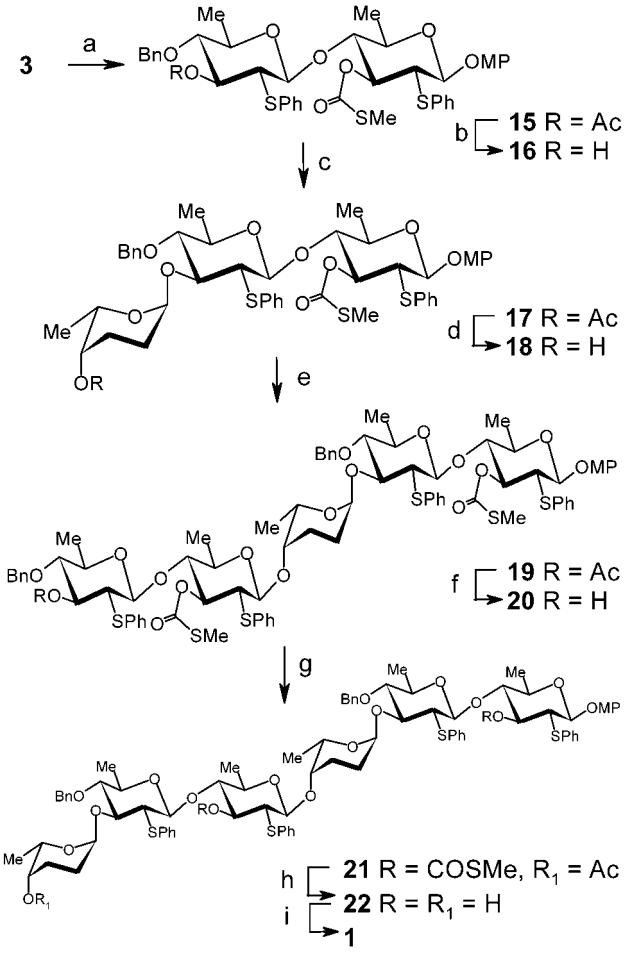
With easily prepared **2** and **3** abundantly available, the remaining route to the final target hexasaccharide **1** would be very straightforward and has been delightfully witnessed as shown in Scheme 4. Going from **3** to **1** required a total of nine steps (12% overall yield), whereupon only four types of familiar operations were executed. (1) Glycosylation using **3** as donor (MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, rt)

Scheme 3[a]



[a] Reaction conditions: (a) BnBr, NaH, $Bu_4N^+I^-$, DMF, rt. (b) 80% HOAc, 70 °C, 91%. (c) Im_2CS (1.2 equiv), THF, reflux, 92%. (d) **10** (1.0 equiv), **12** (1.2 equiv), MeOTf (1.4 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), CH_2Cl_2, 4 Å MS, rt, 88%. (e) NaOMe (3.0 equiv), MeOH/CH_2Cl_2 (v/v, 4:1), 60 °C, 3 days, 80%. (f) Ac_2O, pyridine, rt, 100%. (g) 80% HOAc, 70 °C. (h) Im_2CS (1.2 equiv), DMF, DMAP, 60 °C, 97%.

Scheme 4[a]



[a] Reaction conditions: (a) **3**, *p*-methoxyphenol (1.4 equiv), MeOTf (1.4 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), CH_2Cl_2, 4 Å MS, 25 °C. (b) MeONa/MeOH (0.1 N), 40 °C, 87% (two steps). (c) **2** (3.0 equiv), TBSOTf (0.08 equiv), CH_2Cl_2, 4 Å MS, −78 °C. (d) MeONa/MeOH (0.1 N), rt, 77% (for **18**), 15% (for β-anomer). (e) **3** (1.5 equiv), MeOTf (1.4 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), CH_2Cl_2, 4 Å MS, 25 °C, 45% (for **20**, after removal of the acetate in **19**), 15% (for **16**), 20% (for **18**). (f) Same as conditions b. (g) Same as conditions c. (h) MeONa (3.0 equiv), MeOH, 60 °C, 3 days, 72% (two steps). (i) Raney Ni, EtOH/THF (v/v, 4:1), 40 °C, 57%.

(17) Kerékgyártó, J.; Szurmai, Z.; Lipták, A. *Carbohydr. Res.* **1993**, *245*, 65.

to build the later β-A→OMP and β-A→C linkages (**3**→**15** and **18**→**19**).[13] When *p*-methoxyphenol was used as the acceptor alcohol, after an additional step for removal of the 3′-OAc group, the desired **16** was obtained in 87% yield. However, glycosylation of the trisaccharide monoalcohol **18** under similar conditions led to the expected pentasaccharide **19** and then to **20** (after cleavage of the acetate) in 45% yield. Besides, 20% of the starting **18** was recovered, and disaccharide **16**, resulting from the cleavage of the terminal L-rhodinosyl moiety of **18**, was isolated in 15% yield. These results evidenced the acid sensitivity of the trideoxyglycoside linkage. (2) Glycosylation using **2** as donor (0.08 equiv of TBSOTf, −78 °C) to build the later α-C→B linkages (**16**→**17** and **20**→**21**).[11] Both steps gave the desired α-glycosides (**17** and **21**) in more than 70% yields. (3) Cleavage of the only acetate protection (and also two (methylthio)-carbonyl groups for **21**) (NaOMe, MeOH) to give the corresponding monols (**16**, **18**, **20**) and **22**. (4) Final removal of the four 2-*S*-phenyl and two 4-*O*-benzyl groups (Raney nickel, EtOH, THF, 40 °C) to generate the target hexadeoxysaccharide **1**.

In conclusion, the β-*p*-methoxyphenol hexadeoxysaccharide of landomycin A (**1**) was efficiently synthesized in a total of 33 steps and 0.5% overall yield starting from cheap D-mannose and D-xylose, whereupon eight and nine steps, respectively, were required for the preparation of L-rhodinosyl acetate **2** (20% yield) and 6-deoxy-1-thio-D-mannoside **12** (29% yield). The present synthetic approach features the use of phenyl 2,3-*O*-thionocarbonyl-1-thioglycosides as 2-deoxy-β-glycoside precursors and a biomimetic A−B + C + A−B + C glycosylation sequence.

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Supporting Information Available: Experimental procedures and spectroscopic data for all numbered compounds (**1**−**22**). This material is available free of charge via the Internet at http://pubs.acs.org.

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