

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

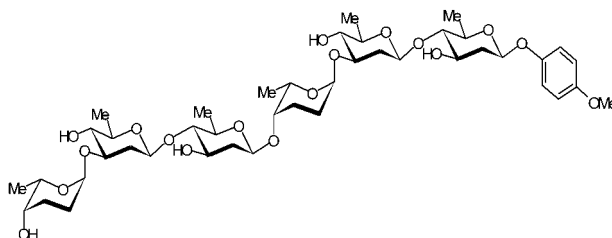
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ABSTRACT



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 G₁/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 deoxyligosaccharides, 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 \rightarrow 3)- β -D-olivose-(1 \rightarrow 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.

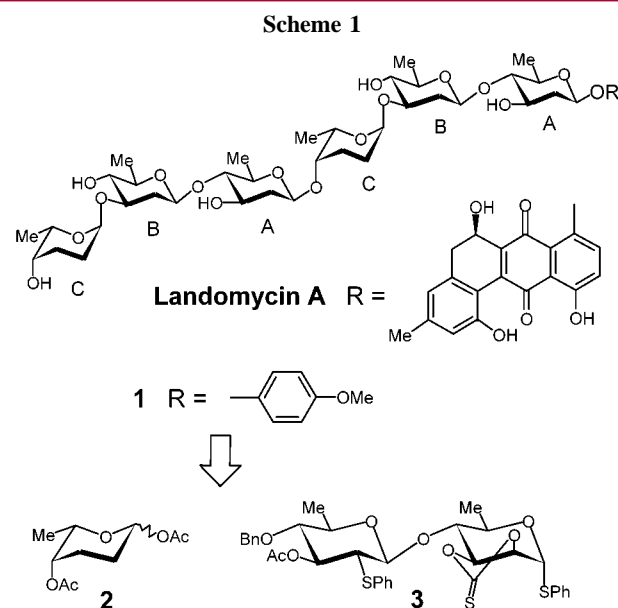
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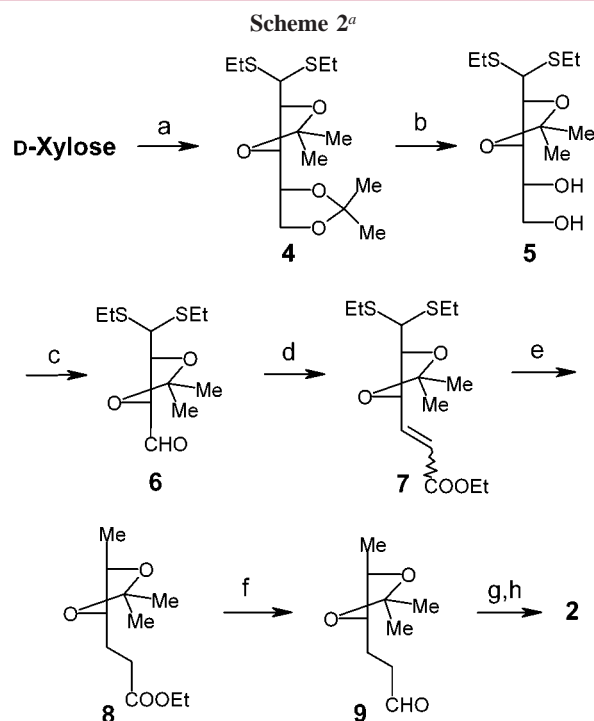
was synthesized in a total of 33 steps and an overall yield of <0.01% starting from L- and D-rhamnal, whereupon L-rhodinosyl tetrazoles⁷ and D-oliviosyl phosphites⁸ were used as donors to build the corresponding α -L-rhodinoside and β -D-olivioside linkages, respectively. The stereoselectivities for 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-olivioside 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,



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 formylmethylene-triphenylphosphorane with ethyl (triphenylphosphoranylidene)acetate in the Wittig reaction with tartraldehyde **6**; we



^a Reaction conditions: (a) EtSH (3.0 equiv), HCl (concd), 0 °C; then (MeO)₂CMe₂, 69%. (b) 80% HOAc, 40 °C, 82%. (c) Pb(OAc)₄ (1.1 equiv), PhMe, 0 °C, 100%. (d) Ph₃P=CHCO₂Et, CH₂Cl₂, 30 °C, 78%. (e) Raney Ni, H₂, EtOH, 60 °C, 59%. (f) DIBAL-H (1.2 equiv), CH₂Cl₂, –78 °C, 78%. (g) 67% HOAc, 50 °C, 98%. (h) Ac₂O, pyridine, rt, 98%.

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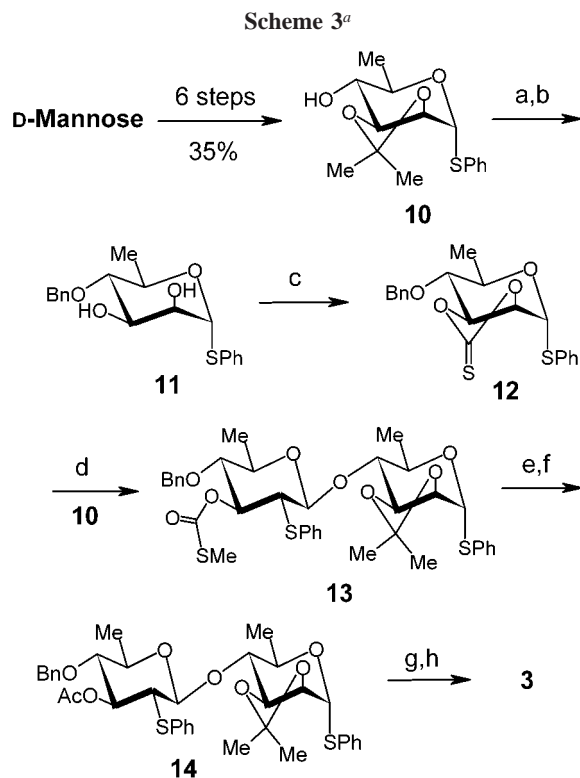
(16) (a) Herczegh, P.; Zsély, M.; Kovács, I.; Batta, Gy.; Sztaricskai, F. *J. Tetrahedron Lett.* **1990**, 31, 1195. (b) Herczegh, P.; Kovács, I.; László, A.; Dinya, Z.; Sztaricskai, J. *Liebigs Ann. Chem.* **1991**, 599.

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

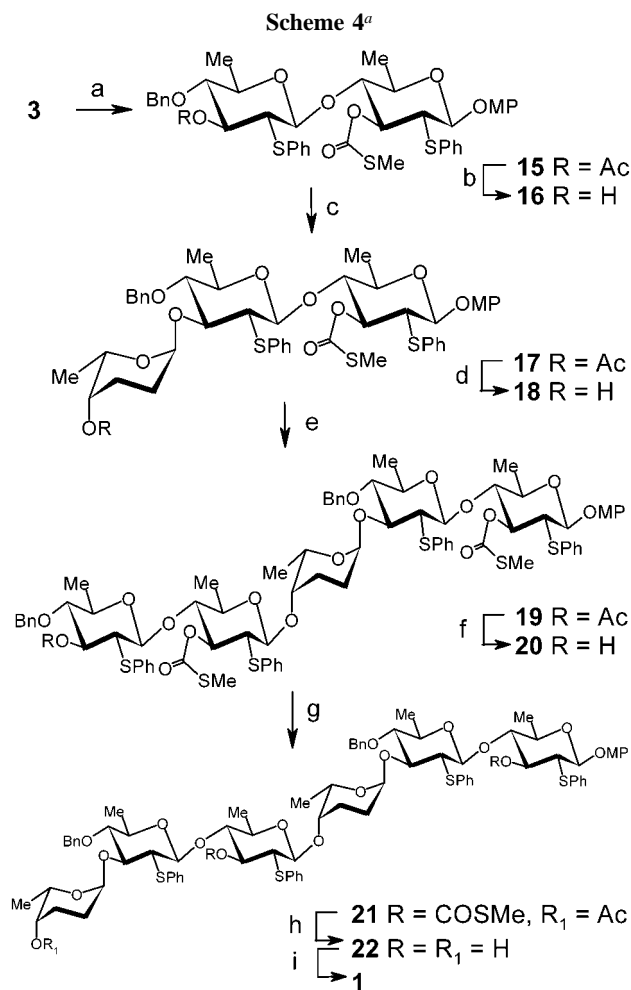
of MeOH and CH₂Cl₂ (v/v 4:1) in 80% yield. Acetylation of the resulting alcohol gave **14**. Transformation of 2,3-*O*-isopropylidene **14** into 2,3-*O*-thionocarbonyl **3** employed operations similar to those used in the conversion **10**→**12**. Compound **3** was thus obtained in 97% yield, which 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



^a Reaction conditions: (a) BnBr, NaH, Bu₄N⁺I⁻, DMF, rt. (b) 80% HOAc, 70 °C, 91%. (c) Im₂CS (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), CH₂Cl₂, 4 Å MS, rt, 88%. (e) NaOMe (3.0 equiv), MeOH/CH₂Cl₂ (v/v, 4:1), 60 °C, 3 days, 80%. (f) Ac₂O, pyridine, rt, 100%. (g) 80% HOAc, 70 °C. (h) Im₂CS (1.2 equiv), DMF, DMAP, 60 °C, 97%.

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



^a Reaction conditions: (a) **3**, *p*-methoxyphenol (1.4 equiv), MeOTf (1.4 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), CH₂Cl₂, 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), CH₂Cl₂, 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), CH₂Cl₂, 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%.

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)

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to build the later β -A \rightarrow OMP and β -A \rightarrow C linkages (**3** \rightarrow **15** and **18** \rightarrow **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, $-78\text{ }^{\circ}\text{C}$) to build the later α -C \rightarrow B linkages (**16** \rightarrow **17** and **20** \rightarrow **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, $40\text{ }^{\circ}\text{C}$) 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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