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The first total synthesis of lactonamycin, a hexacyclic antitumor antibiotic

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ABSTRACT

The total synthesis of lactonamycin has been achieved. The synthesis includes sequential intramolecular conjugate addition of alcohols to the acetylenic ester, stereoselective glycosylation of the tertiary alcohol, and Michael–Dieckmann type cyclization with the thioester, by which the highly convergent route has been established.

Lactonamycin (**1**, Fig. 1) was isolated from a culture broth of *Streptomyces rishiriensis* MJ773-88K4 by Matsumoto and colleagues in 1996. Lactonamycin (**1**) showed potent antimicrobial activities against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) as well as antitumor activities.[1] The unique structure of **1**, including the hexacyclic system and the glycosidic bond at the *t*-alcohol, was determined by X-ray crystallography and degradation studies.[1c] By the remarkable structure and activities, many groups have been attracted and challenged to synthesize this compound;[2,3] nevertheless, the total synthesis has been unprecedented. In this Letter, we disclose the first total synthesis of lactonamycin (**1**).

Our synthetic plan is shown in Scheme 1. Taking a highly convergent route, lactonamycin (**1**) was separated to three segments including ABC segment **2**, thioester **3**, and rhodinose derivative **4**. Therefore, ABC segment **2** would be glycosylated with **4** and then coupled with thioester **3** by Michael–Dieckmann type cyclization. The stereoselective glycosylation of the tertiary alcohol with the 2,3-deoxysugar is challenging, and rhodinose derivative **4** would be used as a resolving agent for racemic **2**.

Thioester **3** was synthesized from 4-bromo-3,5-dimethylphenol **5** (Scheme 2). O-Methylation of **5** and subsequent lithiation followed by methoxycarbonylation gave ester **6**.[4] After Friedel–Crafts

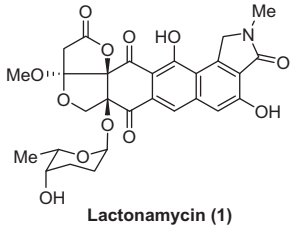
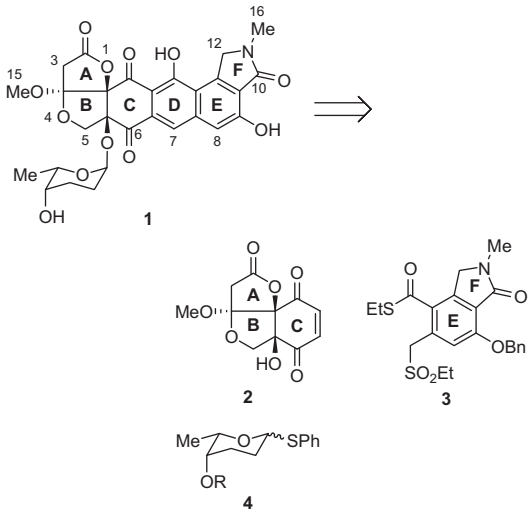


Figure 1. Structure of lactonamycin (**1**).



Scheme 1. Retrosynthetic analysis of lactonamycin.

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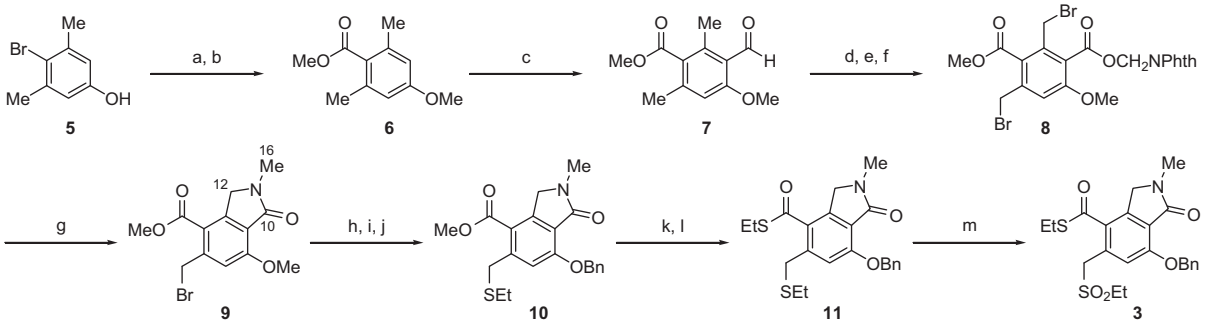
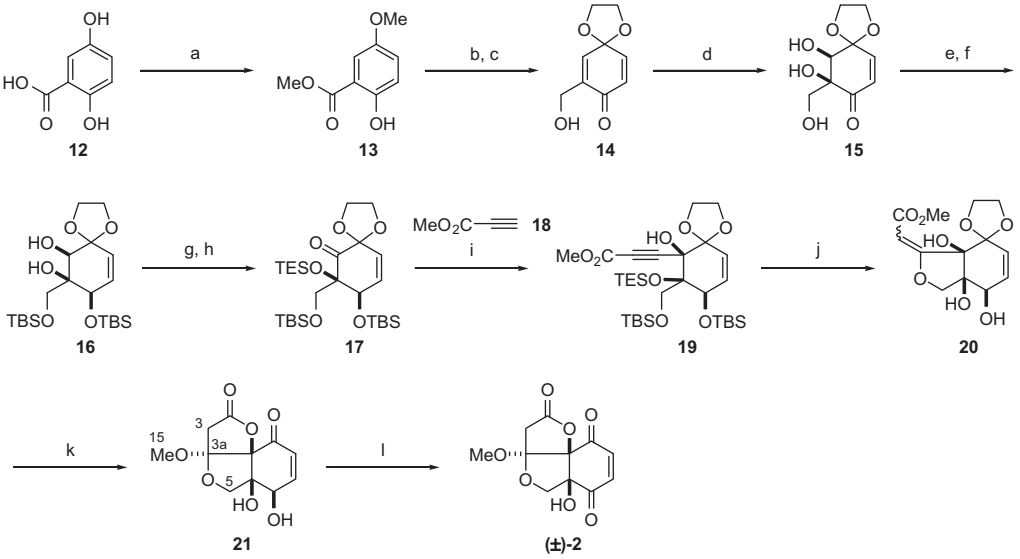


Scheme 2. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, 40 °C, 17 h, 99%; (b) *n*-BuLi, $ClCO_2Me$, THF, −78 °C, 0.5 h, 88%; (c) Cl_2CHOMe, $SnCl_4$, CH_2Cl_2, 0 °C, 3 h, 95%; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq *t*-BuOH, rt, 8 h; (e) $PhthNCH_2Br$, K_2CO_3, acetone, 40 °C, 9 h; (f) NBS, AIBN, CCl_4, 80 °C, 2 h, 40% in three steps; (g) $MeNH_2$, THF, rt, 2 h, 42%; (h) BCl_3, CH_2Cl_2, 0 °C to rt, 1.5 h, 78%; (i) BnBr, Ag_2O, MeCN, rt, 23 h, 78%; (j) EtSH, DBU, PhMe, 60 °C, 3.5 h, 89%; (k) LiOH·H_2O, aq THF, 70 °C, 7 h; (l) EtSH, WSCI·HCl, DMAP, CH_2Cl_2, rt, 3 h, 87% in two steps; (m) *m*CPBA, CH_2Cl_2, rt, 0.5 h, 73%.



Scheme 3. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, 50 °C, 30 h, 94%; (b) $LiBH_4$, THF, 50 °C, 10 h; (c) ethylene glycol, PIFA, CH_2Cl_2, 0 °C, 1 h, 84% in two steps; (d) OsO_4, NMO·H_2O, acetone, rt, 4.5 h, 48%; (e) $NaBH_4$, MeOH, 0 °C, 1 h, ds 13:1; (f) TBSCl, imidazole, DMF, 0 °C to rt, 20 h, 67% in two steps; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h, 71%; (h) TESOTf, pyridine, rt, 14 h, 93%; (i) NaHMDS, THF, −100 °C, 2 h, 93%; (j) TBAF (0.5 equiv), THF, rt, 1.5 h; (k) AcCl, MeOH, 0 °C to rt, 12 h, then addition of PhMe and concentration, 55% in two steps; (l) IBX, $(CH_2Cl)_2$, 70 °C, 15 h, 94%.

type formylation[5] of **6**, the resulting aldehyde **7** was oxidized to carboxylic acid, which was converted into phthalimidylmethyl ester, and the successive bromination provided dibromide **8**. Treatment of **8** with methylamine promoted the substitution of bromide to amine and the sequential lactamization to give bicyclic **9**. After exchange of *O*-Me to *O*-Bn, the resulting bromide was converted into thioether to yield **10**. Hydrolysis of methyl ester followed by condensation with ethanethiol afforded thioester **11**. The thioether was oxidized with *meta*-chloroperbenzoic acid to give sulfone **3**.

The synthesis of ABC segment **2** started from 2,5-dihydroxybenzoic acid **12** (Scheme 3). Selective O-methylation of **12** afforded methyl 2-hydroxy-5-methoxybenzoate **13**. Reduction of methyl ester and the successive oxidation of the aromatic ring in the presence of ethylene glycol gave quinone mono-acetal **14**.[6] Dihydroxy-

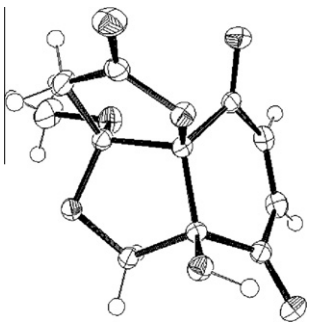
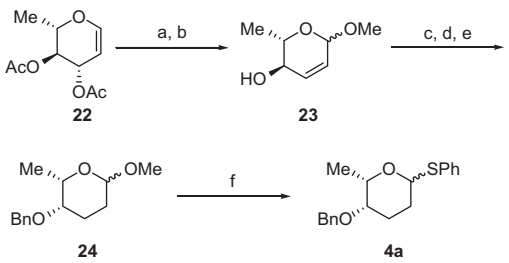
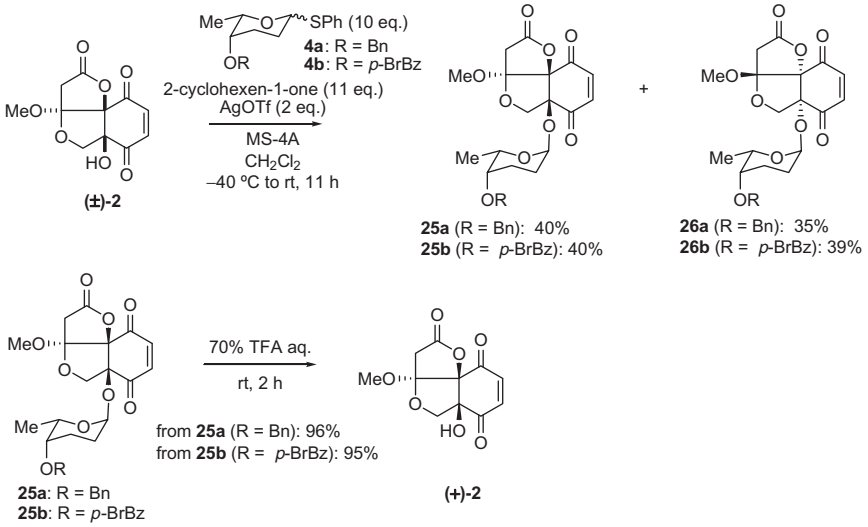


Figure 2. ORTEP drawing of crystal (±)-**2**.



Scheme 4. Reagents and conditions: (a) MeOH, BF_3·OEt_2, CH_2Cl_2, rt, 4 h, 73%; (b) NaOMe, MeOH, rt, 12 h; (c) HCO_2H, PPh_3, DEAD, THF, rt, 12 h, 84% in two steps; (d) NaOMe, MeOH, rt, 6 h, then CG 50, H_2, Pd–C, MeOH, rt, 30 min; (e) BnBr, NaH, THF, 60 °C, 12 h, 64% from **23**; (f) PhSH, CSA, CH_2Cl_2, rt, 10 h, 93%.



Scheme 5. Glycosylation and separation to obtain **25a** and **25b**.

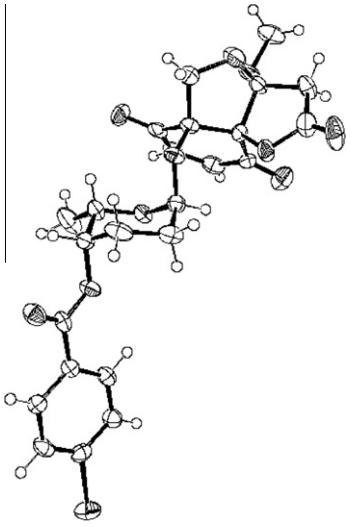


Figure 3. ORTEP drawing of crystal **25b**.

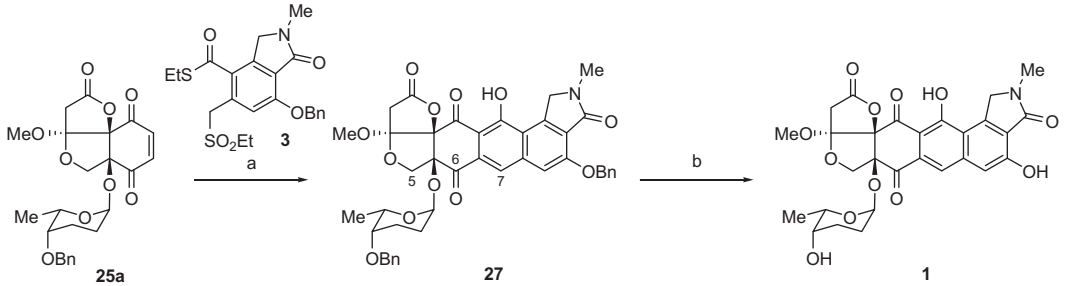
lation of the tri-substituted olefin of **14** provided triol **15**, which was subjected to stereoselective reduction and protection to obtain diol **16**. After oxidation of the secondary alcohol of **16**, the tertiary alcohol was protected as triethylsilyl ether to yield **17**. Methyl propiolate **18** was introduced in the stereospecific manner under the basic conditions to give the *cis*-tertiary diol **19**. De-silylation and conjugate addition of the resulting primary alcohol proceeded to afford **20** with 0.5 equiv of TBAF. Treatment of ester **20** in methanol under the acidic conditions gave tricyclic **21**, which was oxidized to 1,4-diketone, the ABC segment **2**. The structure of **2** was confirmed by X-ray crystallography as shown in Figure 2.[7]

Rhodinose derivative **4a** was synthesized from L-rhamnal **22** (Scheme 4). Ferrier reaction in MeOH and the successive deacetylation gave allyl alcohol **23**. Inversion of the stereochemistry of the secondary alcohol by Mitsunobu reaction was followed by hydrogenation with a concomitant solvolysis of formyl ester, and the resulting alcohol was protected as benzyl ether **24**.[8] The C1 position of the saccharide was activated as thioether **4a**.

The racemic **2** was subjected to glycosylation with **4a** and **4b** in the presence of silver triflate,[9] which gave a diastereomeric mixture of α-glycosides **25a** and **26a** and a mixture of **25b** and **26b**, respectively (Scheme 5). The reaction proceeded stereospecifically for the glycoside donor, and the resulting α-glycosides were separated by silica gel column chromatography. Crystals of *p*-bromobenzoate **25b** were submitted to X-ray crystallography (Fig. 3).[7] The stereochemistry of **25a** was determined by hydrolysis to give (**+**)-**2**, which was also obtained by hydrolysis of *p*-bromobenzoate **25b**.

The total synthesis of lactonamycin was accomplished in two steps from **25a** (Scheme 6). Michael–Dieckmann type condensation[10] with enone **25a** and thioester **3** gave the protected lactonamycin **27**. Hydrogenolysis of **27** afforded lactonamycin (**1**). The physico-chemical data of the synthetic **1** were identical to those of the natural product,[11] completing the total synthesis of lactonamycin (**1**).

In conclusion, the first total synthesis of lactonamycin (**1**) has been achieved. The synthesis features the highly convergent strat-



Scheme 6. Reagents and conditions: (a) **3** (1 equiv), KHMDS (1.1 equiv), then **25a**, THF, −78 °C then reflux, 7 h, 37%; (b) H_2, Pd-black, THF, rt, 10 min, 40%.

egy, stereoselective synthesis of highly functionalized ABC ring system, stereoselective glycosylation of a tertiary alcohol with a 2,3-deoxy-sugar, and Michael–Dieckmann type condensation with thioester. These strategies and methodologies realized the straightforward synthesis of lactonamycin (**1**).

Acknowledgments

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Supplementary data

Supplementary data (the spectrum data of compounds (±)-**2**, **3**, **4a**, **8**, **9**, **10**, **15**, **16**, **19**, **20**, **21**, **25a**, **27** and synthetic lactonamycin (**1**), and ^{1}H NMR spectrum (600 MHz in $CDCl_3$) and ^{13}C NMR spectrum (150 MHz in $CDCl_3$) of synthetic lactonamycin (**1**)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.035.

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7. Crystallographic data (excluding structure factors) for the structures of (±)-**2** and **25b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 770402 for (±)-**2** and 770403 for **25b**.
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11. The authentic sample of the natural product was provided by Dr. Yoshikazu Takahashi in Microbial Chemistry Research Center and purified by our procedures: $[\alpha]_D^{26} + 45^\circ$ (*c* 0.22, MeCN), mp 103–107 °C (decomp.). The decomposition was observed by using a polarization microscope.