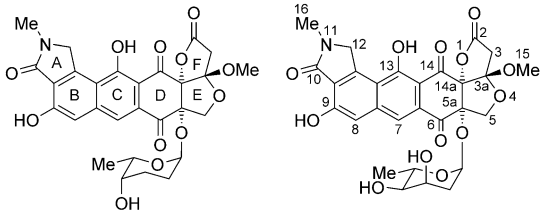
VIP Natural Product Synthesis

DOI: 10.1002/anie.201209205

Total Syntheses of Lactonamycin and Lactonamycin Z with Late-Stage A-Ring Formation and Glycosylation**

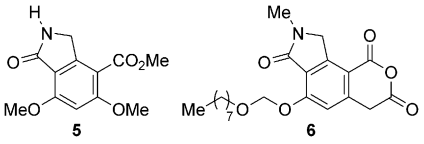
Satoshi Adachi, Kana Watanabe, Yusuke Iwata, Shunsuke Kameda, Yoshihito Miyaoka, Masao Onozuka, Ryo Mitsui, Yoko Saikawa, and Masaya Nakata**

Lactonamycin (**1**; Scheme 1) was isolated in 1996 by Matsumoto et al. from a culture broth of *Streptomyces rishiriensis* MJ773-88K4 collected at Yokohama, Japan.[1] Its potent antimicrobial activities against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), as well as its cytotoxicity against various tumor cell lines[1b] make it extremely attractive as a lead compound for drug discovery. Lactonamycin Z (**2**; Scheme 1),[2] which is less potent against Gram-positive bacteria, was later isolated and found to be a sugar analogue of **1** glycosylated by digitoxose instead of L-rhodinose. However, the absolute configuration and stereochemical relationship between the aglycon and sugar moieties have not been determined. The unique hexacyclic core structure incorporating a densely oxygenated hydrofuran hydrofuranone (EF) ring system has initiated many synthetic efforts[3] including the synthesis of racemic aglycon ((±)-lactonamycinone ((±)-**3**); Scheme 1) by the Danishefsky group.[4] We reported the synthesis of the model BCDEF aglycon (±)-**4** (Scheme 1); this synthesis featured an effective and original EF-ring formation.[5] Recently, Tatsuta et al. achieved the first total synthesis of lactonamycin (**1**) through the resolution of the racemic DEF quinonoid compound by glycosylation with the thiosugar derivative as well as a Michael–Dieckmann-type condensation between the resulting optically active glycoside and AB sulfone thioester.[6]



Scheme 1. Lactonamycin (**1**), lactonamycin Z (**2**), lactonamycinone (**3**), and model BCDEF aglycon (±)-**4**.

The sugar moiety of glycosylated biologically active polyketides is important for the activity,[7] as exemplified in the difference in potency between lactonamycin (**1**) and lactonamycin Z (**2**). Therefore, to efficiently synthesize lactonamycin sugar derivatives as candidates for pharmaceuticals, a final-stage glycosylation strategy would be appropriate. Another important factor is the timing of the A-ring formation. Isoindolinones typically undergo air oxidation readily to give phthalimides under basic conditions.[8] As an example relating to the lactonamycin synthesis, Barrett and co-workers encountered this problem in the N-methylation of the intermediate **5** (Scheme 2).[3e] Moreover, Danishefsky and co-workers encountered poor solubility of the isoindolinone in their lactonamycinone synthesis. To overcome this, they used octyloxymethyl ether **6** instead of the corresponding methyl ether.[4c,d] The intractable properties of the isoindolinone skeleton prompted us to adopt a synthetic route involving a late-stage A-ring formation.



Scheme 2. Intermediates **5** and **6** synthesized by other research groups.

We focused on a Bischler–Napieralski-type cyclization to achieve the late-stage A-ring formation. The Bischler–Napieralski reaction was originally reported in 1893 as a method for synthesizing 3,4-dihydroisoquinolines from *N*-acetyl phenethylamines in the presence of P_2O_5.[9] Three years later, Pictet and Hubert applied this reaction to the synthesis of phenanthridinone from 2-ethoxycarbonylaminobiphenyl

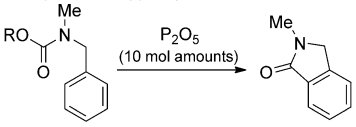
[*] S. Adachi, K. Watanabe, Y. Iwata, S. Kameda, Y. Miyaoka, M. Onozuka, R. Mitsui, Prof. Dr. Y. Saikawa, Prof. Dr. M. Nakata
Department of Applied Chemistry
Faculty of Science and Technology, Keio University
3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522 (Japan)
E-mail: saikawa@applc.keio.ac.jp
msynktxa@applc.keio.ac.jp

[**] We thank the Institute of Microbial Chemistry, Microbial Chemistry Research Foundation for providing us with natural lactonamycin. We are also grateful to Emeritus Professors Hans-Peter Fiedler (Universität Tübingen), for providing us natural lactonamycin Z, and Ronald Parry (Rice University), for the discussion about the absolute configuration of lactonamycin Z. This research was partially supported by a "MEXT-Supported Program for the Strategic Research Foundation at Private Universities 2012-2016".

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209205.

using zinc chloride.[10a] 100 years of continuous improvements has made this series of Friedel–Crafts-type cyclizations useful for the construction of dihydroisoquinolinones.[10b–h] In particular, this cyclization has the advantage of the direct formation of aromatic lactams from one substituent on an aryl substrate. The alternative standard lactamization requires initial introduction of both a ω-aminoalkyl group and a carboxy or alkoxycarbonyl group on adjacent positions of the aryl substrate. However, there is no report on the application of these reactions to the construction of the isoindolinone skeleton. Our first concern was to evaluate the applicability of Bischler–Napieralski-type cyclization to isoindolinone synthesis (Table 1).[11] Through the examination of several reagents ($POCl_3$,[10e] $POCl_3/P_2O_5$,[10b,g] PPA,[10d] Tf_2O[10f]) for the cyclization of model compound **7a** (R = Me), we found that P_2O_5 was suitable. Similar to the previous dihydroisoquinolinone synthesis,[10c] treatment of **7a** with P_2O_5 in toluene at 110 °C for 3 days afforded the desired isoindolinone **8** in 42% yield with recovery of 48% of **7a** (entry 1). CH_2Cl_2 was the solvent of choice as in this solvent the formation of **8** proceeded smoothly at a lower temperature with high yield (63%; entry 2). The most significant improvement was realized when the alkoxy moiety of the carbamate group was changed (entries 2–5). In the case of ethyl carbamate **7b**, **8** was obtained in 81% yield after 3 days (entry 3). Surprisingly, **8** was obtained in 72% yield even at room temperature after 1 day (entry 4). Finally, we found that isopropyl carbamate **7c** was converted smoothly into **8** in 85% yield at room temperature after only 1 h (entry 5). Encouraged with this success, we envisioned the detailed route to the total synthesis of lactonamycin (**1**) and lactonamycin Z (**2**; Scheme 3).

Table 1: Bischler–Napieralski-type cyclization of carbamates **7**.

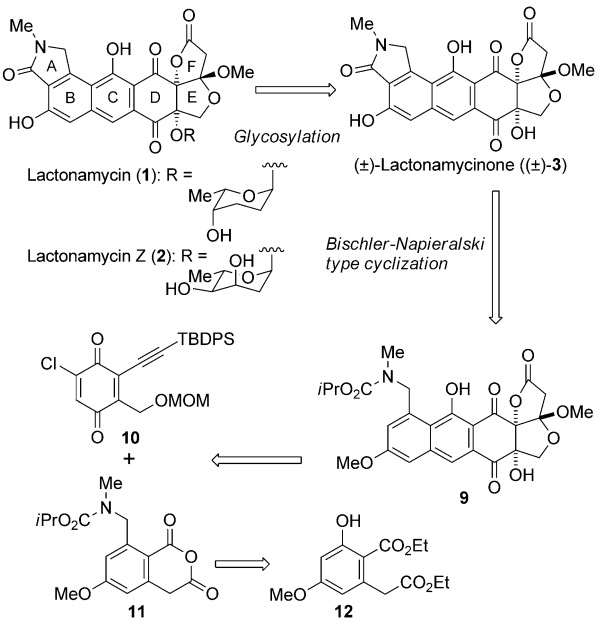


7 **8**

Entry	Substrate	Solvent 0.06 M for **7**	*T*	*t*	Yield [%][a]
1	**7a** (R = Me)	toluene	110 °C	3 days	42 (**8**) 48 (**7a**)
2	**7a** (R = Me)	CH_2Cl_2	40 °C	3 days	63 (**8**) 22 (**7a**)
3	**7b** (R = Et)	CH_2Cl_2	40 °C	3 days	81 (**8**) 7 (**7b**)
4	**7b** (R = Et)	CH_2Cl_2	RT	1 days	72 (**8**) 12 (**7b**)
5	**7c** (R = *i*Pr)	CH_2Cl_2	RT	1 h	85 (**8**)

[a] Yields are of the isolated products.

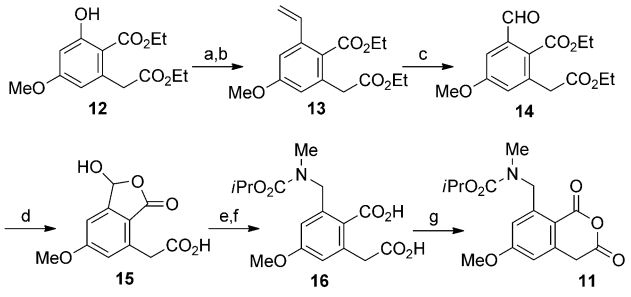
As mentioned above, we adopted the final-stage glycosylation step using lactonamycinone (**3**) as an acceptor (Scheme 3). Lactonamycinone (**3**) would be synthesized by a Bischler–Napieralski-type cyclization of isopropyl carbamate **9**, the EF ring system of which is expected to tolerate acidic conditions.[5] Isopropyl carbamate **9** would be obtained



Scheme 3. Retrosynthetic analysis of lactonamycin (**1**) and lactonamycin Z (**2**). TBDPS = *tert*-butyldiphenylsilyl, MOM = methoxymethyl.

from chloroethynylquinone **10** and the enolate derived from homophthalic anhydride **11** by regioselective cycloaddition, oxy-palladation, and a palladium-catalyzed methoxycarbonylation.[5] Chloroethynylquinone **10** could be synthesized according to a previously reported method.[5] Homophthalic anhydride **11** would be synthesized by the introduction of the *N*-methylaminomethyl functionality onto the known phenol **12**. The isopropyl carbamate plays important roles as not only the A-ring precursor, but also the amino protecting group.

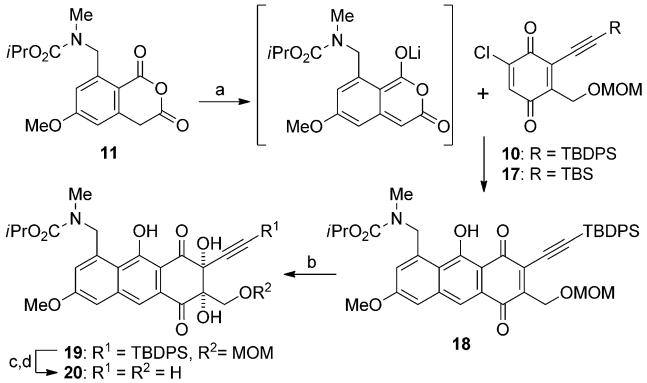
Synthesis of the homophthalic anhydride unit **11** began with the known phenol **12**, which was derived from silyl ketene acetal and tetramethoxymethane in one step (Scheme 4).[12] Phenol **12** was converted into a triflate (95%),[12] which was subjected to a Stille coupling with tetravinyltin to afford styrene **13** in 71% yield.[13] The resulting vinyl group was subjected to ozonolysis to give



Scheme 4. Synthesis of diene precursor **11**. a) Tf_2O, Et_3N, CH_2Cl_2, 0 °C, 95%; b) tetravinyltin, $[PdCl_2(PPh_3)_2]$, LiCl, 4-*t*Bu-catechol, PPh_3, DMF, 100 °C, 71%; c) O_3/O_2, CH_2Cl_2, −78 °C, then PPh_3, 83%; d) aq KOH, dioxane, RT, 91%; e) $MeNH_2$, MeOH, RT, then $NaBH_4$; f) $ClCO_2iPr$, THF/acetone/H_2O (1:1:1 v/v), RT; g) AcCl, CH_2Cl_2, 40 °C. DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

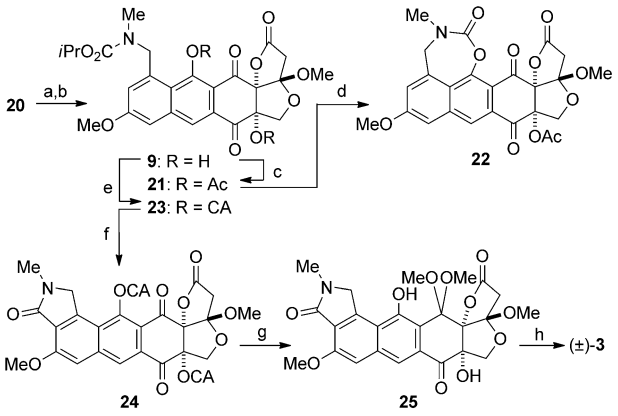
aldehyde **14** in 83% yield. Reductive amination of **14** with methylamine and sodium borohydride resulted in γ-lactam formation. To avoid this undesired cyclization,[14] hydrolysis of the ethyl ester was performed prior to reductive amination to afford lactol **15** in 91% yield. Reductive amination of **15** followed by isopropylcarbamate formation gave dicarboxylic acid **16**. Anhydride formation of **16** with acetyl chloride provided the desired diene precursor **11**.

We next conducted the reliable cycloaddition[5,15] of the diene derived from homophthalic anhydride **11** and chloroethynylquinone **10**, which is a slightly modified dienophile from the previously reported dienophile **17** (Scheme 5).[5] This crucial coupling was realized by treating **11** with LDA to form the enolate and subsequent addition of **10**, thus regioselectively giving anthraquinone **18** in 45% yield from lactol **15**. In the case of the model system, the $RuCl_3/NaIO_4$ dihydroxylation[16] of the anthraquinone having a TBS-protected alkyne group proceeded in low (33%) yield.[5] However, the dihydroxylation of **18** gave a good yield as expected (71% yield of the desired diol **19**), probably owing to the more effective shielding of the labile alkyne functionality by the TBDPS group than the TBS group. Next, an unprecedented deprotection of the ethynyl TBDPS group via silver acetylide was realized by using AgF[17] in 85% yield, whereas a standard TBAF desilylation resulted in decomposition of the base-sensitive substrate. Deprotection of the MOM ether was realized by using aqueous HCl to give **20** (99% yield).



Scheme 5. Construction of the BCD ring system. a) **11**, LDA, THF, 0°C, 3 min, then **10** in THF, 0°C, 4 min, 45% from **15**; b) $RuCl_3$, $NaIO_4$, MeCN/ethyl acetate/H_2O (20:20:1 v/v), 0°C, 71%; c) AgF, MeCN, then *p*-toluenesulfonic acid monohydrate, RT, 85%; d) aq HCl, THF, RT, 99%. LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl.

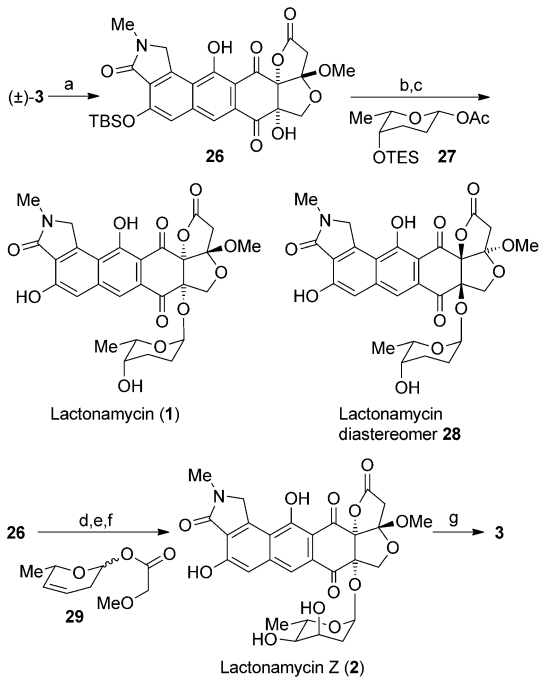
The previously established sequence,[5] that is, Pd-catalyzed E-ring formation and methoxycarbonylation,[18] and subsequent acid-catalyzed F-ring formation, could be applied to **20** to afford the BCDEF intermediate **9** in good yield without any side reactions arising from the A-ring precursor (Scheme 6). The first attempt of the challenging Bischler–Napieralski-type cyclization of **9** with P_2O_5 resulted in decomposition. In contrast, treatment of **21**, derived from **9** by diacetylation, with P_2O_5 gave cyclic carbamate **22** (71% yield), which could be formed through attack of the acylated



Scheme 6. Synthesis of (±)-lactonamycinone ((±)-**3**) through a Bischler–Napieralski-type cyclization. a) $PdCl_2$, 1,4-benzoquinone, CO, MeOH, RT, 69%; b) CSA, MeOH, 80°C, then evaporation, benzene, 80°C, 100%; c) AcCl, pyridine, CH_2Cl_2, RT, 95%; d) P_2O_5, CH_2Cl_2, RT, 71%; e) $ClCH_2COCl$, pyridine, CH_2Cl_2, RT, 99%; f) P_2O_5, CH_2Cl_2, RT, 75%; g) Et_3N, MeOH/CH_2Cl_2 (1:3 v/v), 40°C; h) $MgI_2{\cdot}OEt_2$, benzene, 80°C, 2 steps 56%. CSA = camphorsulfonic acid, CA = chloroacetyl.

The previously established sequence,[5] that is, Pd-catalyzed E-ring formation and methoxycarbonylation,[18] and subsequent acid-catalyzed F-ring formation, could be applied to **20** to afford the BCDEF intermediate **9** in good yield without any side reactions arising from the A-ring precursor (Scheme 6). The first attempt of the challenging Bischler–Napieralski-type cyclization of **9** with P_2O_5 resulted in decomposition. In contrast, treatment of **21**, derived from **9** by diacetylation, with P_2O_5 gave cyclic carbamate **22** (71% yield), which could be formed through attack of the acylated phenolic oxygen on the P_2O_5-activated carbonyl carbon. Therefore, in our next attempt we chose the chloroacetyl (CA) group, a more electron-withdrawing acyl group, for the protection of the two hydroxy groups. A-ring formation of the CA-protected carbamate **23** with P_2O_5 in CH_2Cl_2 at RT for 1 h afforded the protected lactonamycinone **24** in 75% yield, as expected. To achieve the synthesis of (±)-lactonamycinone ((±)-**3**), our first target in the total synthesis journey of lactonamycin (**1**), the remaining steps include the removal of the CA group and cleavage of the phenolic methyl ether. Methanolysis of the CA group of **24** under weakly-basic conditions[19] led to the formation of the unexpected dimethyl ketal **25**. Although the corresponding 1,4-diketone, obtained after the acidic work-up subsequent to the methanolysis of **24**, had poor solubility probably owing to the presence of A ring, the resulting ketal **25** was readily dissolved in benzene, a suitable solvent for the next deprotection, and was smoothly converted into (±)-lactonamycinone ((±)-**3**)[20] in 56% yield from **24**, by treatment with freshly prepared $MgI_2{\cdot}OEt_2$.[21]

The last significant step in the total synthesis is glycosylation of the aglycon with a 2-deoxysugar, L-rhodinose (Scheme 7). We chose an $Yb(OTf)_3$-catalyzed mild glycosylation method[22] using the known TES-protected L-rhodinosyl 1-acetate **27**.[23] First, (±)-lactonamycinone ((±)-**3**) was directly subjected to this glycosylation to give a highly polar product, which was probably formed by metal chelation between the amide carbonyl and the phenol functions. Therefore, the phenolic group of the B ring was converted into the TBS ether, and the resulting diol **26** was subjected to glycosylation. Treatment of **26** with excess rhodinosyl acetate **27** and $Yb(OTf)_3$ afforded a diastereomeric mixture of α-glycosides in 60% combined yield in a very short time. After separation of the two diastereomers by column chromatography, desilylation of each glycoside with TASF,[24] as the final step, gave natural lactonamycin (**1**) and its diastereomer **28** in 84% and 63% yields, respectively. The spectral data of the



Scheme 7. Completion of the total syntheses of lactonamycin (**1**) and lactonamycin Z (**2**). a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98 %; b) Yb(OTf)$_3$, **27**, molecular sieves (5 Å), CH_2Cl_2, 0 °C, 3 min, 60 % (d.r. = 1:1), then separation; c) TASF, DMF, RT, 84 % of **1**, 63 % of **28**, d) Yb(OTf)$_3$, **29**, molecular sieves (5 Å), CH_2Cl_2, 0 °C, 2 min, (−)-α-glycoside (12 %), (+)-β-glycoside (12 %), (−)-β-glycoside (5 %), (+)-α-glycoside (12 %); e) OsO_4, NMO, CH_2Cl_2, H_2O, RT, 5 h; f) TASF, DMF, RT, 15 min, 85 % (2 steps from (+)-α-glycoside, 1.4:1 mixture); g) 1 M aq HCl, RT, 4 h. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

synthetic lactonamycin (**1**) were identical with those of the natural product.

Encouraged by this success, we next applied the Yb(OTf)$_3$-catalyzed glycosylation in the first total synthesis of lactonamycin Z. However, some L-digitoxose derivatives, activated by Yb(OTf)$_3$, did not react with **26**. Then, we introduced a 3,4-unsaturated sugar onto **26**[25] followed by dihydroxylation. The donor **29**[26] reacted with **26** under catalysis by Yb(OTf)$_3$ to give a mixture of four glycosides arising from racemic aglycon and α,β-selectivity ((−)-α, (+)-β, (−)-β, and (+)-α-glycosides in 12 %, 12 %, 5 %, and 12 % yields, respectively) along with recovered **26** (54 %). The two α-glycosides were subjected to dihydroxylation followed by cleavage of the TBS ether to afford a mixture of two diastereomers in 85 % (from (+)-α-glycoside, ca 1.4:1) and 90 % (from (−)-α-glycoside, ca 1:1) yields. The spectral data of the major isomer[27] derived from (+)-α-glycoside were identical with those of natural lactonamycin Z. To determine the absolute configuration of lactonamycin Z, acidic hydrolysis of both natural lactonamycin Z and the synthesized product was conducted. The resulting aglycons showed the same retention time on a chiral HPLC as that of natural lactonamycinone (**3**) obatined from lactonamycin (**1**) itself, thus indicating that the absolute configuration of lactonamycin Z is as depicted in Scheme 7 (**2**).

In summary, we accomplished the total synthesis of lactonamycin (**1**) through cycloaddition, E- and F-ring formation, the late-stage A-ring construction by using the modified Bischler–Napieralski-type cyclization, and a final-stage glycosylation. Furthermore, the first total synthesis of lactonamycin Z (**2**) was realized and its absolute configuration was determined. The applicability of the established route to the divergent syntheses of lactonamycin sugar analogues is currently being investigated.

Received: November 16, 2012
Published online: January 9, 2013

Keywords: Bischler–Napieralski cyclization · glycosylation · natural products · polyketides · total synthesis

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[26] For the synthesis of the donor **29**, see the Supporting Information.
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