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The first total synthesis and structural determination of lagunamycin

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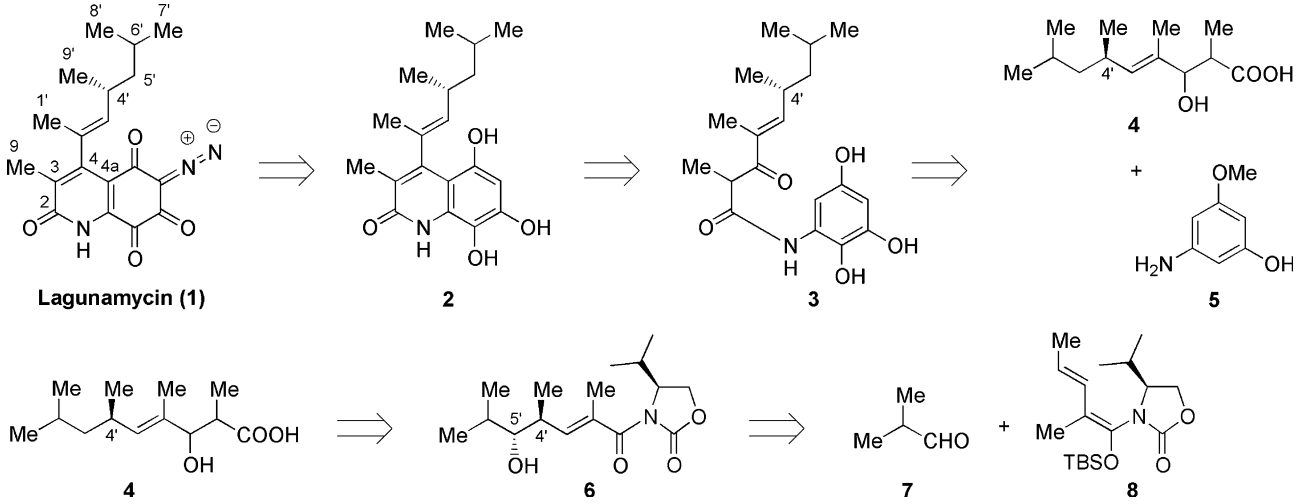
Abstract—Lagunamycin (**1**) has been synthesized by using our developed remote stereoinduction, Knorr condensation, periodinane oxidation, and diazonation. This enantioselective synthesis determined the absolute configuration of lagunamycin. Existence of rotational conformers was confirmed by NMR studies.

Lagunamycin (**1**), a metabolite isolated from the culture filtrate of *Streptomyces* sp. AA0310 showed inhibitory activity against 5-lipoxygenases and antibacterial activity against Gram-positive bacteria.[1a] The structure of lagunamycin (**1**) has been elucidated to possess the diazotetraoxoquinoline skeleton attaching the branched alkyl chain as shown in Figure 1 by a combination of NMR studies and chemical degradations.[1b] The complexity of NMR spectra of lagunamycin (**1**) has been believed to be the result from the rotational isomers caused by the bulky side chain against the 9-methyl group attaching on quinoline plane.[1b] Interested in the structure and bioactivities, we embarked on the synthetic studies on lagunamycin (**1**). Herein, we present the first total synthesis and structural determination of lagunamycin (**1**).

Our retrosynthetic analysis is shown in Scheme 1. The diazo group would be introduced in the final step and oxygenated quinoline moiety could be synthesized from



Scheme 1. Retrosynthetic analysis of lagunamycin.

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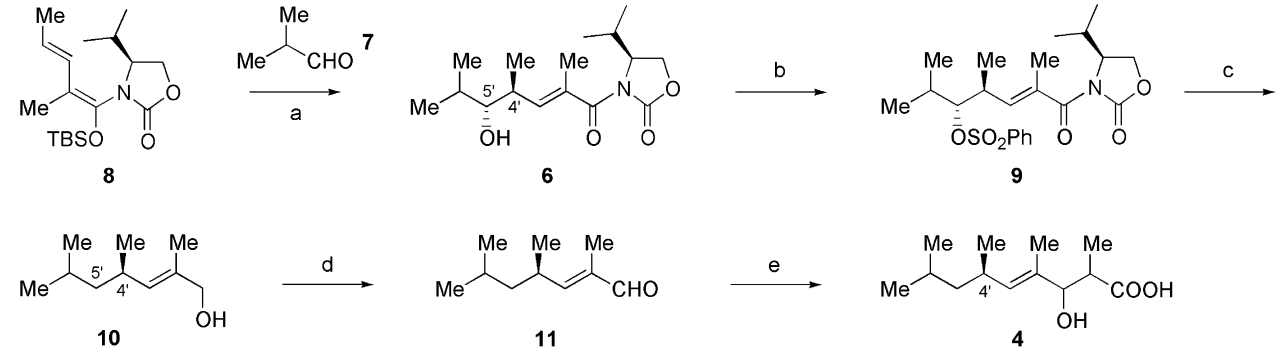
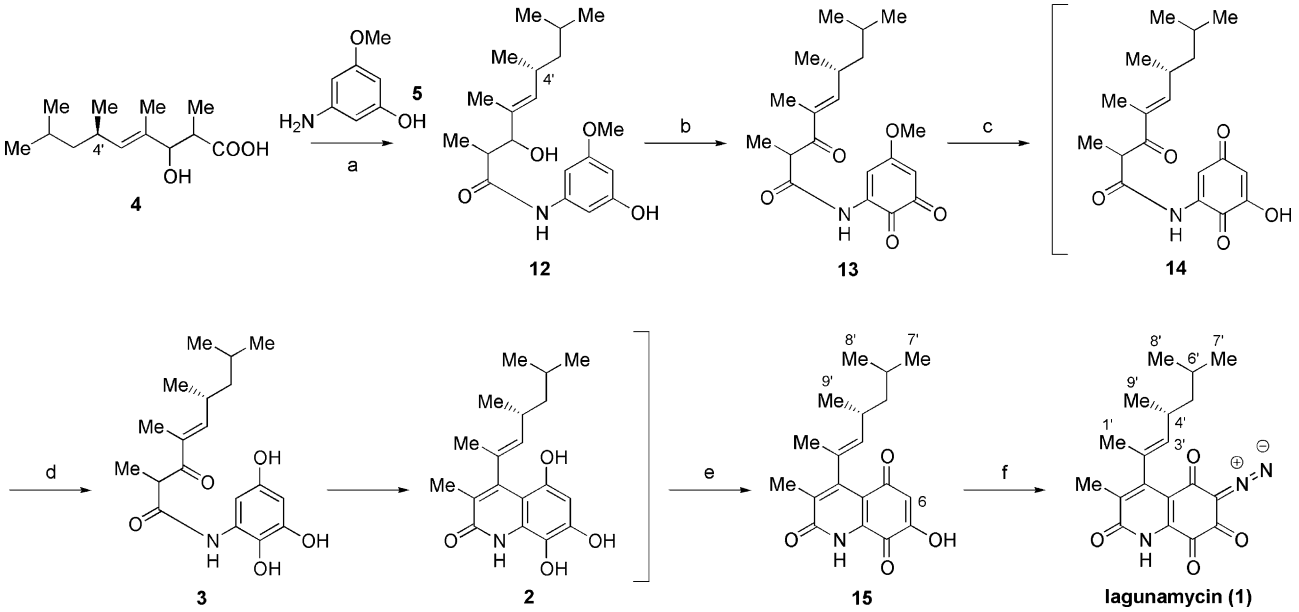
2. To avoid the difficulty from steric interaction between the side chain and the quinolone moiety, we planned to construct the quinolone **2** by Knorr condensation with the β-ketoamide **3**,[2] which would be obtained by coupling of the β-hydroxycarboxyacid **4** and the aniline **5**. The β-hydroxycarboxyacid **4** might be derived from the α,β-unsaturated imide **6**,[3c] which had already been obtained by our developed remote stereoinduction reaction with the *N*,*O*-ketene acetal **8**.[3]

The actual synthesis of lagunamycin (**1**) was started from construction of the side chain moiety **4** (Scheme 2). Our remote stereoinduction reaction with the ketene *N*,*O*-acetal **8** and isobutyraldehyde (**7**) gave the adduct **6** in excellent yield and stereoselectivity in multi-gram scale as expected from our previous report.[3c] De-oxygenation at C5′ position was realized by hydride reduction with the sulfonate **9**. Treatment of phenylsulfonate **9** with super hydride ($LiBEt_3H$) made rapid progress of the reductive removal of oxazolidine ring at −78 °C and promoted de-sulfonation at room temperature to give the primary alcohol **10**. The allylic alcohol **10** was oxidized to the aldehyde **11**,[4] which was submitted to aldol reaction with the dianion derived from propionic acid. The resulting β-hydroxycarboxylic acid **4** was used for the further transformation as a diastereomeric mixture.

Construction of the quinolone moiety and completion of total synthesis of lagunamycin is described in Scheme 3. Condensation of the β-hydroxycarboxylic acid **4** and the aniline **5**[5] with WSCI afforded the anilide **12** in excellent yield. Treatment of anilide **12** with *o*-iodoxybenzoic acid (IBX) to promote Nicolaou oxidation[6] smoothly (30 min) at room temperature gave the quinone moiety and oxidation of allylic alcohol slowly (overnight) at 40 °C gave the β-ketoamide **13**. The structure of **13**[4] was determined as *o*-quinone as shown in Figure 1. The NOE between the methoxy proton and both protons on the quinone ring was observed. Additionally, the HMBC spectrum shows the cross peaks between the methoxy proton and both C3 and C5 carbons. These results support the *o*-quinone structure of **13**. The



Scheme 2. Reagents and conditions: (a) Ref. 3c; (b) LHMDS, $PhSO_2Cl$, THF, −78 to −40°C, 94%; (c) $LiBEt_3H$, THF, −78 °C to rt, 12 h, 65%; (d) MnO_2, hexane, 40°C, 12 h, 92%; (e) LDA, $CH_3CH_2CO_2H$, THF, −78 °C, 30 min, 70%.



Scheme 3. Reagents and conditions: (a) WSCI·HCl, CH_2Cl_2, rt, 2 h, 96%; (b) IBX, PhMe–DMSO, rt, 30 min, then 40 °C, 12 h, 83%; (c) 10% H_2SO_4 aq, CH_3CN, rt, 15 min; (d) $Na_2S_2O_4$, 40 °C, 12 h; (e) OXONE®, rt, 15 min, 87% from **13**; (f) *p*-acetamidobenzenesulfonyl azide, DBU, THF, rt, 4 h, 52%.

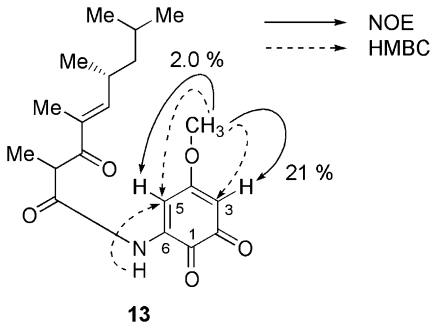


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Figure 1. Structure of *o*-quinone **13**.

o-quinone **13** was transformed to the quinolone **15** by the one-pot procedure. Subsequent manipulation of quinone **13** (red solution) including (i) hydrolysis of methyl ether to convert to the unstable quinone **14** (yellow solution), (ii) selective reduction of the quinone moiety with $Na_2S_2O_4$ to provide the very labile trihydroxyanilide **3** (colorless solution), (iii) Knorr condensation under the acidic conditions[2] to give quinolone **2** (pale yellow solution), and (iv) oxidation of hydroquinone with Oxone, delivered the quinone **15**[4] (orange solution) in high yield.[7] Finally, treatment of **15** with *p*-acetamidobenzenesulfonyl azide[8] in the presence of DBU gave lagunamycin (**1**),[9] whose analytical data were consistent with those reported previously.[1] Thus, total synthesis of lagunamycin was accomplished and the absolute structure of **1** was determined as 4′*R* configuration.

To prove the existence of rotational isomers, the following NMR experiments were carried out. ^{1}H NMR spectra of lagunamycin (**1**) in dimethyl sulfoxide-d_6 were observed at different temperatures including 24 °C, 40 °C, 60 °C, 80 °C, and 110 °C (Fig. 2). The ^{1}H NMR spectrum of **1** at 24 °C showed two kinds of compounds. At 80 °C, the peaks assigned as H3′ and H4′ got simple, and a broad peak of H1′ became doublet showing allylic coupling with H3′ ($J_{1',3'} = 1.2$ Hz). The peaks around 0.9 ppm became simpler, however, nine peaks were observed yet. After cooling from 80 °C to room temperature, the resulting sample gave the same spectrum as the original one obtained at 24 °C. At 90 °C (not included in Fig. 2), eight peaks were observed around 0.9 ppm and the sample began to decompose slowly. At 110 °C, three methyl groups of lagunamycin including H7′, H8′, and H9′ appeared as three doublets, which imposed on the peaks of the unidentified degradation products (three doublets at 0.89, 0.92, and 1.00 ppm). Therefore, additional NMR experiments on rotation of the side chain were practiced with the more stable quinone **15** (Fig. 3). The ^{1}H NMR spectrum of **15** showed two isomers at 26 °C and its behavior at different temperatures was the same as that of lagunamycin (**1**) without remarkable decomposition. The peaks around 0.9 ppm became simpler at 100 °C, and finally, they fixed to three doublets at 110 °C. The spectrum at 110 °C became the simple one as expected from the planar structure of **15**. After cooling to room temperature, the resulting sample gave the same spectrum as the original one obtained at 26 °C. The feature of temperature-dependence of the quinone **15** was as same as that of lagunamycin (**1**). Thus, the origin of complexity of NMR spectra was confirmed due to the existence of a rotational isomer.

Additionally, the NOE experiments made clear the ratio of rotational isomers at room temperature (Fig. 4). The relations between H9 and H9′, H1′ and H4′, and between H9 and H6′ were observed. The 600 Hz ^{1}H NMR spectrum made it possible to distinguish the three methyl groups of rotational isomers (the major isomer:the minor isomer = 1.2:1).[9] The NOESY spectrum of **1** (in $CDCl_3$, 27 °C) determined the stereochemistry of these isomers. The relations between H9 and H6′ of the major isomer, H9 and H7′ of the major isomer,

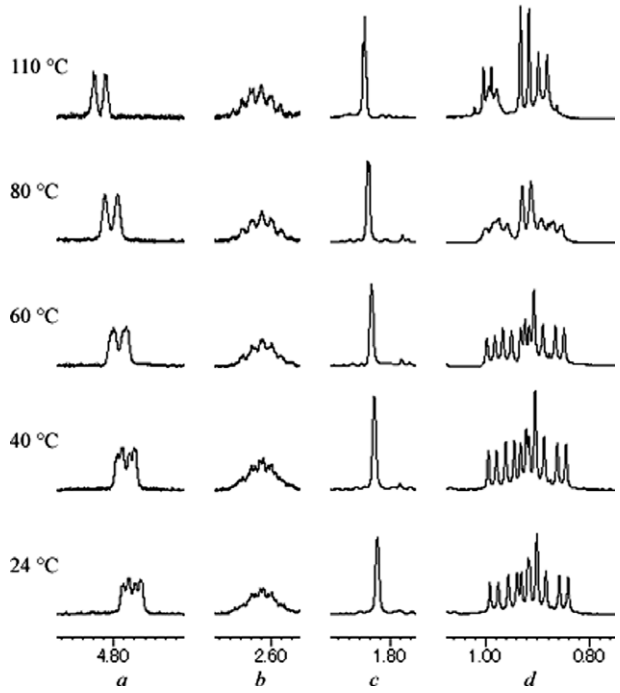

Figure 2. ^{1}H NMR spectrum of lagunamycin (**1**) in DMSO-d_6 at the various temperatures: (a) H3′; (b) H4′; (c) H1′; (d) H7′, 8′, and 9′.

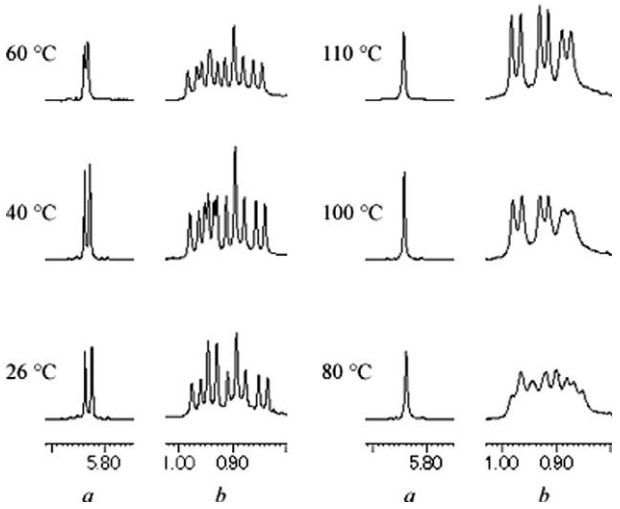

Figure 3. ^{1}H NMR spectrum of the quinone (**15**) in DMSO-d_6 at various temperatures: (a) H6; (b) H7′, 8′, and 9′.

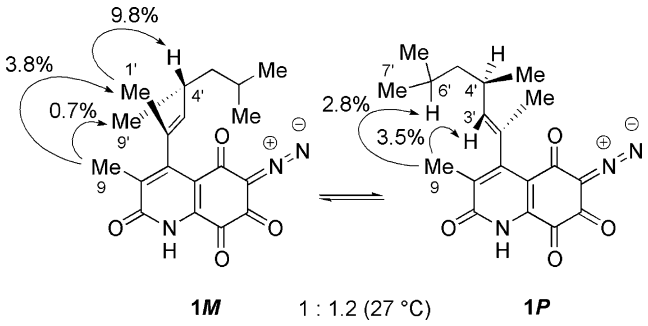

Figure 4. The NOE relation of rotational isomers in $CDCl_3$.

and between H9 and H9′ of the minor isomer were observed. These results revealed the ratio of two isomers at room temperature to be **1*M***:**1*P*** = 1:1.2.

In conclusion, we achieved the first total synthesis of lagunamycin to determine the absolute structure and confirmed the existence of rotational isomers.

Acknowledgments

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Supplementary data

The spectrum data of compounds **11**, **13**, and **15**, ^1H NMR spectra of synthetic lagunamycin (400 MHz and 600 MHz in $CDCl_3$), ^{13}C NMR spectrum of synthetic lagunamycin (100 MHz in $CDCl_3$) and NMR spectra of natural lagunamycin reprinted from Ref. 1a are provided as supplementary data, which can be found in the online version, at doi:10.1016/j.tetlet.2006.06.158.

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4. See Supplementary data.
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7. One-pot transformation of *o*-quinone **13** to *p*-quinone **15**: Quinone **13** (13.4 mg, 37.0 μmol) was dissolved into a mixture of acetonitril and 10% H_2SO_4 aq and the mixture was stirred at room temperature for 15 min. $Na_2S_2O_4$ (25.8 mg, 148 μmol) was then added and the resulting mixture was heated to 40 °C for 12 h. After cooling to room temperature, Oxone (182 mg, 297 μmol) was added to the mixture, which was stirred at room temperature for 15 min. The reaction mixture was extracted with ethyl acetate. Evaporation and purification by silica gel column chromatography (hexane:ethyl acetate = 2:1, containing 1% trifluoroacetic acid) gave orange solid **15** (10.6 mg, 87%).
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9. Lagunamycin (**1**) (the value in bracket is data of the isomer): (synthetic): $[\alpha]_D^{26}$ −33.0 (*c* 0.20, MeOH) {natural $[\alpha]_D^{26}$ −33 (*c* 0.20, MeOH)}; ^1H NMR (600 MHz, $CDCl_3$, 27 °C) δ 0.92 [0.89] (3H, d, J = 6.7 Hz), 0.93 [0.96] (3H, d, J = 6.7 Hz), 1.01 [1.02] (3H, d, J = 6.8 Hz), 1.11–1.27 (2H, m), 1.56–1.67 (1H, m), 1.903 [1.898] (1H, d, J = 1.3 Hz), 2.190 [2.186] (3H, s), 2.63–2.73 (1H, m), 4.87 [4.85] (1H, dd, J = 9.4, 1.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, 27 °C) δ 14.1 [14.0], 16.83 [16.80], 20.1 [20.6], 22.2 [22.5], 23.3 [23.2], 26.0 [25.6], 30.4 [30.3], 46.7 [46.5], 87.6 [87.7], 116.4 [116.3], 129.9 [129.8], 134.8 [135.3], 137.2 [137.1], 138.5 [138.7], 151.6 [151.5], 161.30 [161.35], 168.6 [168.7], 172.53 [172.4], 172.54 [172.6]; MS (FAB^+) *m*/*z* 356 $[M+H]^+$, 328 $[M+H-N_2]^+$; HRMS (FAB^+) calcd for $C_{19}H_{21}N_3O_4$ $[M+H]^+$ 356.1610, found 356.1589; IR (KBr) 3437 (br), 2954, 2926, 2870, 2146, 1716, 1682, 1651, 1632, 1387, 1369, 1321, 1286, 1178.