



Determination of the absolute configuration of nodulisporacid A by the concise synthesis of four stereoisomers via three-component reaction and one-pot construction of the framework

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ABSTRACT

Four stereoisomers of nodulisporacid A (**1**) were synthesized by the concise approach which includes three-component reaction and subsequent one-pot construction of the whole framework. The ¹H NMR comparison of the derivatives (**10–12**) revealed the absolute configuration of natural **1** to be 4*R*,4'*R*,6'*R*.

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Nodulisporacid A (**1**) was isolated from a marine-derived fungus, *Nodulisporium* sp. CRIF1, by Kittakoop et al. in 2008 as an antiplasmodial agent (Fig. 1).¹ This compound was reported to exist as a 1:1 equilibration mixture of the (*E*)- and (*Z*)-isomers. Although the stereochemistry at the three asymmetric centers of nodulisporacid A (**1**) could not be clarified, the stereogenic centers were, based on the spectroscopic similarity, assumed to be the same as those of lowdenic acid (**2**),² whose relative stereochemistry has been elucidated by X-ray crystallographic analysis. Herein, we report a synthesis of four stereoisomers of **1** and determination of the absolute configuration of the natural product.

Our synthetic strategy is shown in Scheme 1. The framework of the target molecule would be constructed by the successive intramolecular Claisen condensation, enol etherification of the resulting acyltetramic acid derivative, and dehydration of **A**. Compound **A**, a β-ketoester of malate, was expected to be prepared readily by the three-component reaction reported by Mukaiyama.³

Two diastereomers of the aldehyde (**7**) were prepared as shown in Scheme 2. A protected glyceraldehyde (*R*)-**3**⁴ was reacted with a Grignard reagent prepared from commercially available **4** (purchased from Sigma–Aldrich) and the resulting alcohol was oxidized to ketone **5** by Dess–Martin periodinane. Methylation in the mode of α-chelation was performed in the presence of SnCl₄ and **6** was obtained in an excellent stereoselectivity (>20:1).⁵ After protecting

the tertiary alcohol as a TBS ether, treatment with periodic acid caused a hydrolysis of acetonide followed by an oxidative cleavage of the resulting glycol to afford (2*S*,4*S*)-**7**. Another isomer, (2*R*,4*S*)-**7**, was also prepared in a similar manner starting from the enantiomeric aldehyde [(*S*)-**3**].⁶

With two stereoisomers of **7** in hand, the three-component reaction was investigated (Scheme 3). According to the procedure reported by Mukaiyama, large excess amount of the simple alcohol (e.g., MeOH and EtOH) was added to the premixed aldehyde, diketene, and TiCl₄ in CH₂Cl₂.³ However, we were pleased to find that the amount of alcohol (dimethyl malate) could be minimized to

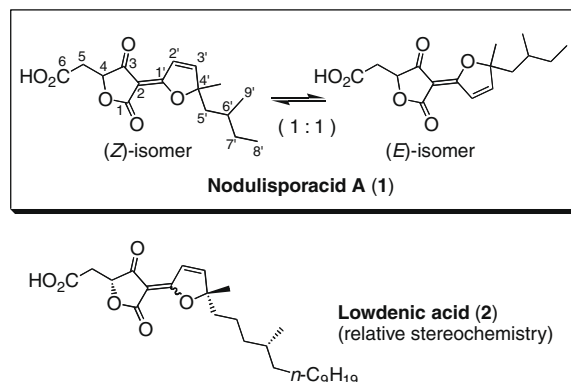
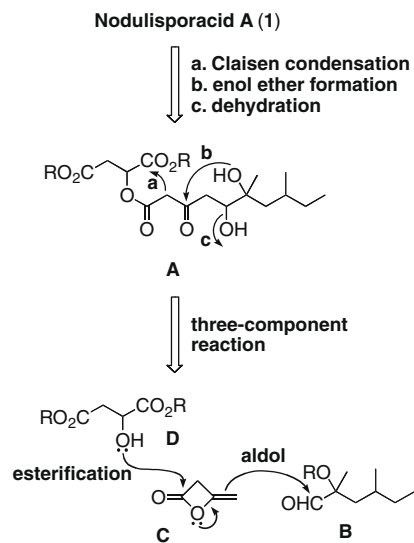


Figure 1. Structures of nodulisporacid A (**1**) and lowdenic acid (**2**).

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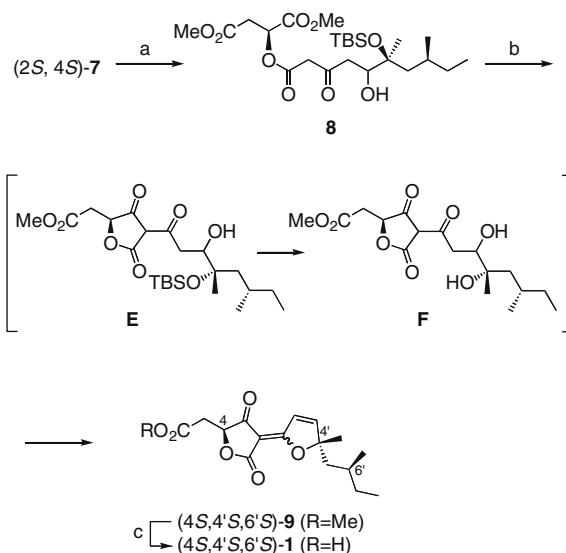
E-mail address: ashuten@mail.ecc.u-tokyo.ac.jp (H. Watanabe).



Scheme 1. Retrosynthetic analysis.

2 equiv which enabled the easier isolation of the product, and **8** was obtained in 62% yield as a single isomer (stereochemistry not determined). The next step, one-pot reaction for the construction of the whole framework, could be carried out successfully by the successive treatment with TBAF⁷ and HCl in 51% yield. During the reaction, stepwise generation of intermediates (**E** and **F**) could be monitored on TLC, and after the complete deprotection, the reaction mixture was acidified by the addition of HCl to cause the enol ether formation. It should be noted that when the TBAF treatment was carried out at higher temperature (80 °C), partial epimerization at C-4 has taken place. The methyl ester of (4*S*,4'*S*,6'*S*)-**9** was then hydrolyzed to afford (4*S*,4'*S*,6'*S*)-**1** as a 1:1 mixture of (*E*)- and (*Z*)-isomers.

Similarly, by changing the combination of stereoisomers of **7** and dimethyl malate, four diastereomeric methyl esters (**9**) were synthesized and their ¹H NMR spectral data were compared with those reported for the methyl ester of natural nodulisporacid A.¹ Among the four isomers, only (4*S*,4'*S*,6'*S*)-**9** showed complete accordance with the natural product derivative while other is-



Scheme 3. Synthesis of (4*S*,4'*S*,6'*S*)-**1**. Reagents and conditions: (a) diketene (2 equiv), TiCl₄ (1.2 equiv), CH₂Cl₂, −78 °C, 15 min then dimethyl (*S*)-malate (2 equiv), −78 to 0 °C, over 3 h, 62%; (b) TBAF (1 equiv), THF, 0 °C to rt, 1 h, then TBAF (2 equiv), rt, 20 h, then concd HCl, rt, 5 h, 51%; (c) 6 N HCl, 1,4-dioxane, rt, 97%.

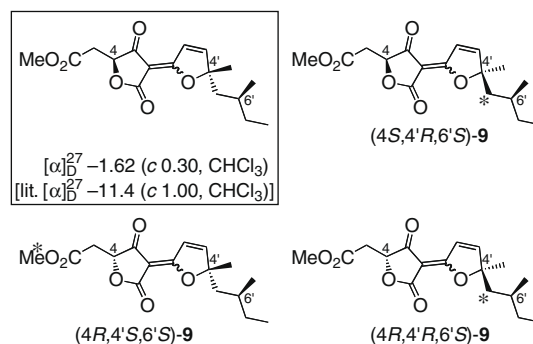
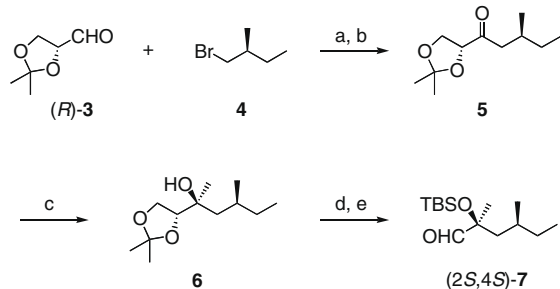
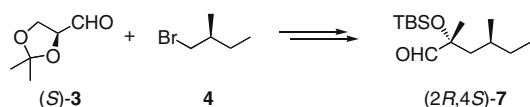


Figure 2. Synthesized stereoisomers of nodulisporacid A methyl ester.

Scheme 4. Recrystallization and isomerization of **1**.

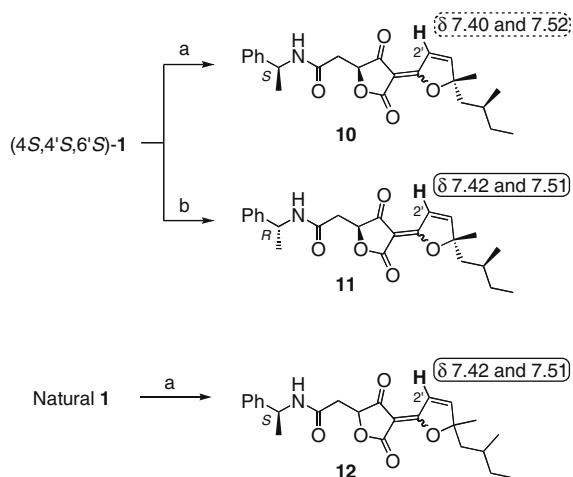
Similarly:



Scheme 2. Preparation of aldehyde **7**. Reagents and conditions: (a) Mg, THF, 0 °C to rt, 30%; (b) Dess–Martin periodinane, CH₂Cl₂, rt, 89%; (c) SnCl₄ (1 equiv), MeI (4 equiv), CH₂Cl₂, −78 °C, 60% (75% brsm); (d) TBSOTf, 2,6-lutidine, CH₂Cl₂, rt, 97%; (e) HIO₄·2H₂O, EtOAc, rt, 99%.

mers showed different chemical shifts of protons on the asterisked carbons (Fig. 2). However, the specific rotation of our synthetic (4*S*,4'*S*,6'*S*)-**9** ([α]_D²⁷ −1.62) was much smaller than the reported data ([α]_D²⁷ −11.4)¹ and the absolute configuration of the natural product could not be established.

In addition to that, the specific rotations of synthetic (4*S*,4'*S*,6'*S*)-**1** and natural nodulisporacid A were also different ([α]_D²⁸ −0.96 and [α]_D²⁷ −20.6,¹ respectively). Although the natural **1** was reported to be an amorphous solid, synthetic (4*S*,4'*S*,6'*S*)-**1** could be recrystallized from *i*-Pr₂O–CHCl₃–CCl₄ as a single (*Z*)-isomer (mp 124–125 °C) whose [α]_D value was +9.03 immediately after dissolution in methanol and gradually decreased to −0.96 in 3 h at rt by the isomerization (Scheme 4). From these values, the specific rotation of (*E*)-isomer was estimated to be −11.0. It



Scheme 5. Determination of the absolute configuration of nodulisporacid A (**1**) by ¹H NMR data comparison of (S)- or (R)-1-phenylethylamine derivative. Reagents and conditions: (a) (S)-1-phenylethylamine, EDCI, Et₃N, CH₂Cl₂; (b) (R)-1-phenylethylamine, EDCI, Et₃N, CH₂Cl₂.

was therefore difficult to determine the absolute configuration by the sign of rotation.

To determine the absolute configuration of the natural product unambiguously, amides (**10–12**) with (S)- or (R)-1-phenylethylamines were prepared from synthetic (4*S*,4'*S*,6'*S*)-**1** and their ¹H NMR spectra were compared (Scheme 5). As shown in Scheme 5, olefinic protons at C-2' of **10** and **11** appeared at the different chemical shifts and the optical purity of synthetic (4*S*,4'*S*,6'*S*)-**1** was found to be pure. On the other hand, **12** showed good accordance with **11**. From these results, we concluded that (4*S*,4'*S*,6'*S*)-**1** was an enantiomer of nodulisporacid A and the abso-

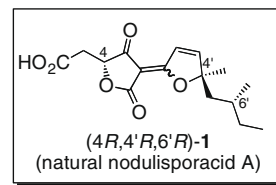


Figure 3. Absolute stereochemistry of nodulisporacid A.

lute configuration of the natural compound is 4*R*,4'*R*,6'*R* as depicted in Figure 3.

In summary, four stereoisomers of nodulisporacid A (**1**) were synthesized efficiently by the three-component reaction and one-pot construction of the whole framework. The NMR comparison of the methyl esters (**9**) enabled the determination of the relative stereochemistry and the absolute configuration was then established to be 4*R*,4'*R*,6'*R* by the derivatization to amides (**10–12**).

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