

Construction of the [6–7–5–5] tetracyclic core, all the carbocyclic framework of yuzurimine-type alkaloids†

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Yuzurimine-type alkaloids make up a sub-family of *Daphniphyllum* alkaloids structurally featuring a [6–7–5–5] tetracycyclic core framework. In this manuscript, we describe our construction of the [6–7–5–5] tetracycyclic core of yuzurimine-type alkaloids by using unique in situ intramolecular Wittig reaction and Sm-mediated cyclization as key steps.

Daphniphyllum alkaloids possess a complex polycyclic condensed ring-system, and various analogues have been reported so far.¹ Yuzurimine (1)-type alkaloids make up a sub-family of *Daphniphyllum* alkaloids isolated from *Daphniphyllum macropodum* by Hirata and co-workers (Fig. 1).² The structural feature of yuzurimine-type alkaloids is the [6–7–5–5] tetracycyclic core framework fused with an indolizidine unit. In addition, calyciphylline A (2)-type³ and daphmanidin A (3)-type⁴ alkaloids share a similar tetracycyclic core framework for the A–D ring portion of yuzurimine-type alkaloids, except for the condensed heterocyclic ring system. The unique structures of yuzurimine-type alkaloids have made them attractive targets for total synthesis. In 2011, Carreira and Weiss reported the total synthesis of (+)-daphmanidin E,⁵ which is C14–C15 dehydro daphmanidin A. This synthesis was the first total synthesis of *Daphniphyllum* alkaloids possessing a [6–7–5–5] tetracycyclic core framework. Recently, Smith and Shvartsbart achieved the total synthesis of related daphmanidin A-type alkaloids, (–)-calyciphylline N.⁶ Also, several groups have reported approaches to the synthesis of yuzurimine-type alkaloids.⁷ However, with the exception of the work of the above-mentioned groups of Carreira and Smith, synthetic approaches to the [6–7–5–5] tetracycyclic core of

yuzurimine-type alkaloids have never been reported. In this manuscript, we describe the construction of the [6–7–5–5] tetracycyclic core of yuzurimine-type alkaloids by using a unique in situ intramolecular Wittig reaction and Sm-mediated cyclization as key steps.

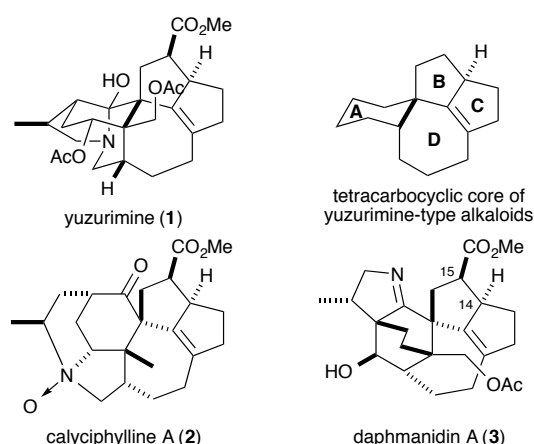


Fig. 1 Structures of the *Daphniphyllum* alkaloids

The retrosynthetic pathway of the tetracycyclic core of yuzurimine-type alkaloids is shown in Scheme 1. The A- and D-rings could be constructed by Sm-mediated domino cyclization⁸ of the α,β -unsaturated ester and aldehyde 5. The α,β -unsaturated ester and aldehyde 5 would be synthesized by using an aldol reaction between lactone 6 and aldehyde 7. Finally, lactone 6 could be generated from commercially available dicyclopentadiene (8).

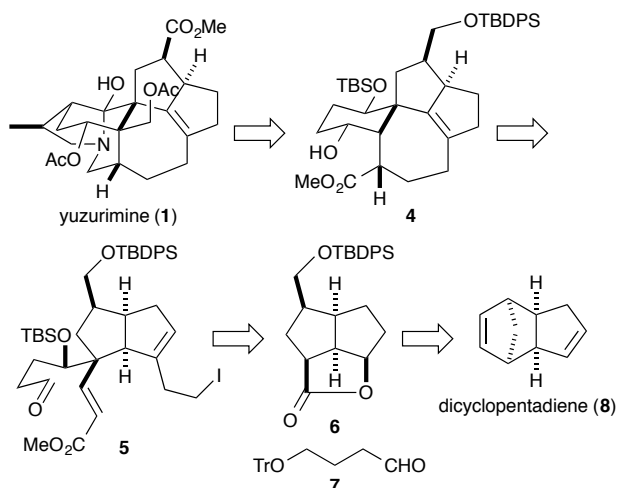
The known racemic alcohol 9 was synthesized from commercially available dicyclopentadiene (8, Scheme 2).⁹ Ozonolysis of alcohol 9 gave hemiacetal 11, which was converted into carboxylic acid 12 by using AZADO[®].¹⁰ Selective reduction of carboxy group in 12 and silylation of the resulting primary hydroxy group afforded lactone 6. Next, we attempted stereoselective construction of the quaternary carbon at C8 by utilizing the bowl shape of lactone 6. Thus, treatment of lactone 6 with LDA generated an ester enolate, which reacted with aldehyde 7¹¹ to produce aldol adducts 13a and 13b

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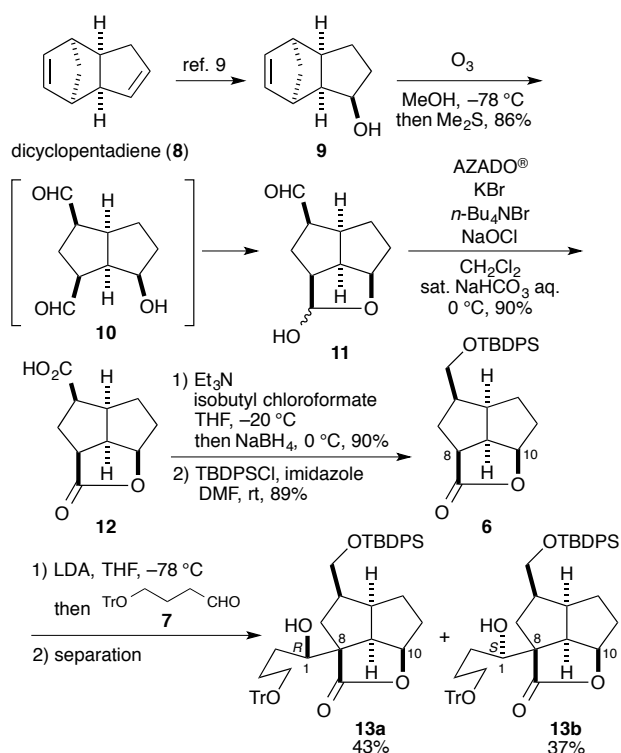
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as mixtures of diastereomers at C1. Aldol products **13a** and **13b** both arose from a highly stereoselective addition to the convex face of the enolate anion (obtained upon deprotonation of **6**) and differed only in their relative stereochemistry at C1. The stereochemistry of C1 was of little consequence as it was envisaged that it would be oxidized to the ketone at a later stage in the synthesis. The two aldol products could be separated by silica gel chromatography. The relative stereochemistries of C1 and C8 in **13a** and **13b** were determined at a later stage (Scheme 5).



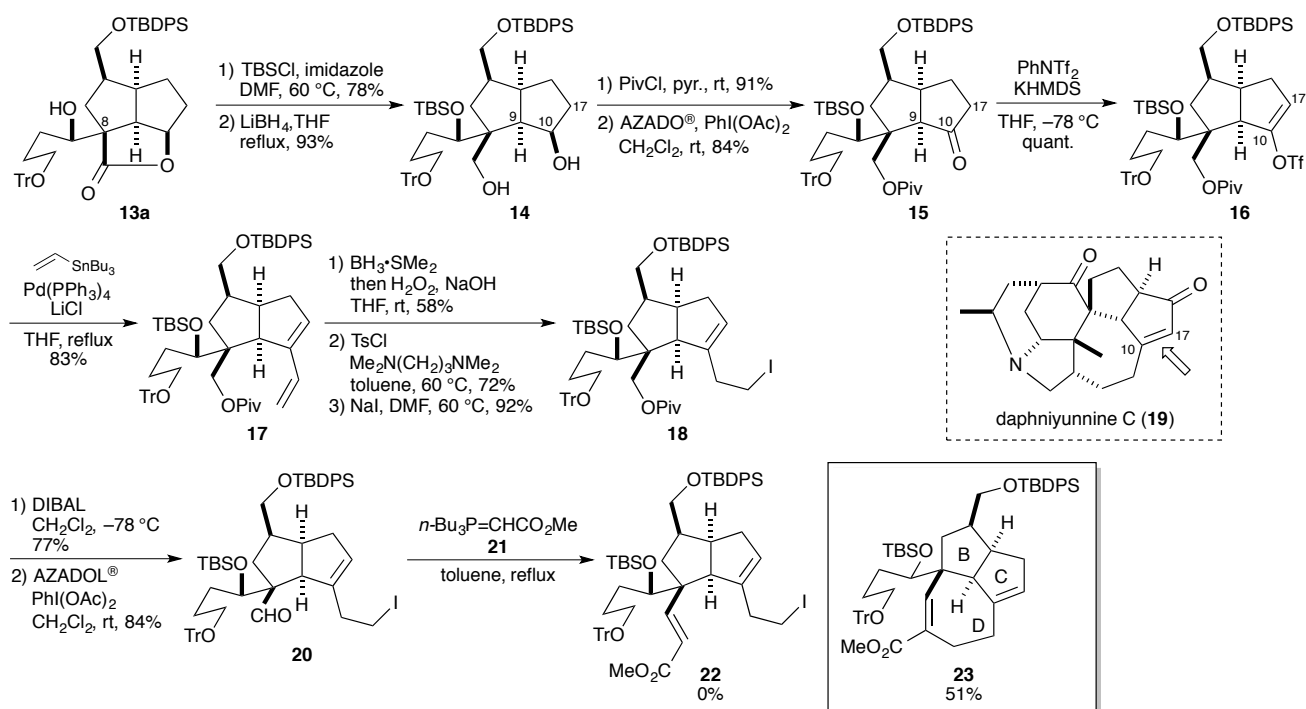
Scheme 1 Retrosynthetic pathway of the tetracyclic core of yuzurimine-type alkaloids



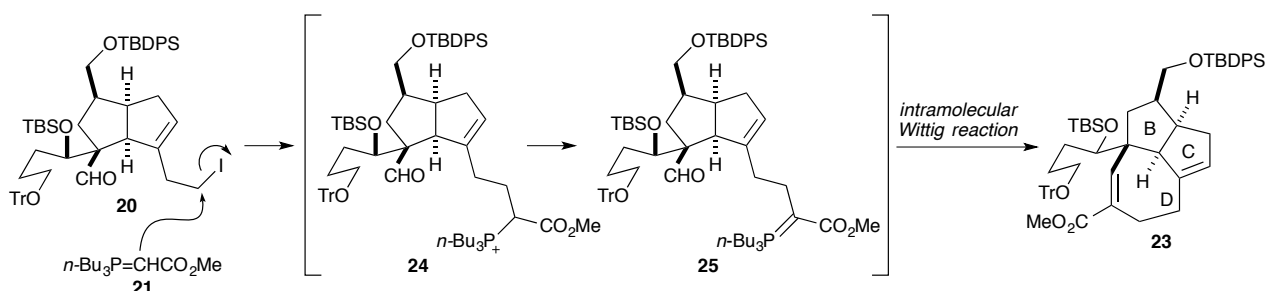
Scheme 2 Stereoselective construction of a quaternary carbon at C8

We next attempted the synthesis of a precursor for Sm-mediated cyclization as follows (Scheme 3). Protection of the secondary hydroxy group of aldol product **13a** with a TBS group and reduction of the lactone gave diol **14**, which was transformed into ketone **15** by the protection of the resulting primary hydroxy group as a pivaloyl ester and oxidation of a secondary hydroxy group by using AZADO[®].¹⁰ Ketone **15** was converted into enol triflate **16**, which was transformed into diene **17** by Stille coupling.¹² For this step, although we examined various conditions for preparing the fully-substituted enol triflate (C9–C10 double bond of yuzurimine-type alkaloids), we were unable to obtain it. The less-substituted olefin would be isomerized into the more-substituted olefin at a later stage.¹³ The enol triflate **16** can be used for construction of the C10–C17 double bond of daphniyunnine C (**19**).¹⁴ Hydroboration and oxidation of the terminal olefin in diene **17** gave an alcohol, which was converted into iodide **18** in 2 steps.¹⁵ Removal of the pivaloyl group in **18** and oxidation of the resulting primary hydroxy group afforded aldehyde **20**. We next attempted to convert aldehyde **20** into α,β -unsaturated ester **22**. For this purpose, Wittig reaction of aldehyde **20** with (methoxycarbonylmethylene)tributylphosphorane (**21**)¹⁶ was examined. However, we could not obtain the desired α,β -unsaturated ester **22**; only the unexpected seven-membered enone **23** was formed.¹⁷

A plausible reaction pathway for the formation of the unexpected seven-membered enone **23** is shown in Scheme 4. Alkylation of iodide **20** with phosphorane **21** followed by deprotonation with an excess of phosphorane **21** might afford ylide **25**. Ylide **25** was then cyclized by intramolecular Wittig reaction to afford seven-membered enone **23**. In this hypothesis, the intermolecular alkylation of the phosphorane occurs faster than an intermolecular Wittig reaction, possibly because of steric hindrance around the aldehyde that prevents the latter from occurring.



Scheme 3 Construction of the BCD ring portion of yuzurimine-type alkaloids

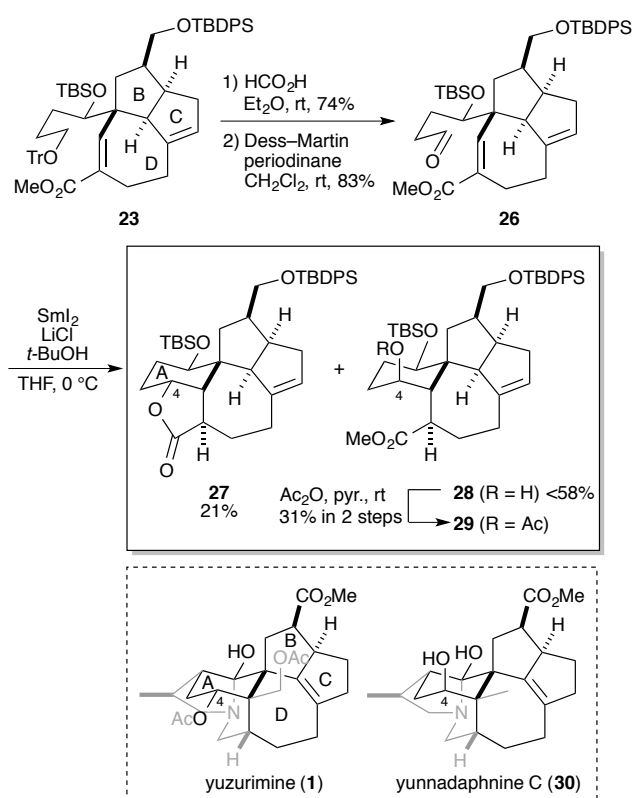


Scheme 4 Plausible reaction pathway of the construction of seven-membered enone **23**

With the BCD ring of the yuzurimine-type alkaloid **23** in hand, we next examined construction of the A-ring portion (Scheme 5). Removal of the trityl group in **23** and oxidation of the resulting hydroxy group gave aldehyde **26** as a precursor of Sm-mediated cyclization. Treatment of aldehyde **26** with SmI₂, LiCl, and *t*-BuOH¹⁸ afforded lactone **27** (21%) and tetracyclic compound **28** (<58%),¹⁹ which are diastereomeric at C4. These compounds **27** and **28** contain the [6–7–5–5] tetracyclic cores of yuzurimine-type alkaloids.²⁰ The tetracyclic compound **28** was transformed into acetate **29** for purification and determination of the stereochemistry at C4 (31% in 2 steps).²⁰ The axial configuration at the C4 hydroxy group in **28** was the same as that of yunnadaphnine C (**30**).²¹

In conclusion, we have established a method for the construction of the [6–7–5–5] tetracyclic core of yuzurimine-type alkaloids by using a unique in situ intramolecular Wittig reaction and Sm-mediated cyclization as key steps. Construction of the heterocyclic portion of yuzurimine-type alkaloids toward the total synthesis is currently underway in our group.

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Scheme 5 Synthesis of the [6-7-5-5] tetracycyclic core of yuzurimine-type alkaloids

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