Construction of the [6-7-5-5] tetracyclic core of all the carbocyclic frameworks of yuzurimine-type alkaloids

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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] tetracarbocyclic core framework. In this manuscript, we describe our construction of the [6–7–5–5] tetracarbocyclic 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] tetracarbocyclic core framework fused with an indolizidine unit. In addition, calyciphylline A (**2**)-type[3] and daphmanidin A (**3**)-type[4] alkaloids share a similar tetracarbocyclic 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] tetracarbocyclic 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] tetracarbocyclic core of yuzurimine-type alkaloids have never been reported. In this manuscript, we describe the construction of the [6–7–5–5] tetracarbocyclic core of yuzurimine-type alkaloids by using a unique in situ intramolecular Wittig reaction and Sm-mediated cyclization as key steps.

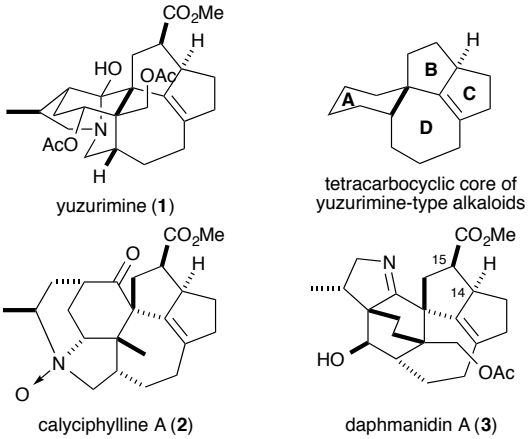

Fig. 1 Structures of the *Daphniphyllum* alkaloids

The retrosynthetic pathway of the tetracarbocyclic core of yuzurimine-type alkaloids is shown in Scheme 1. The A- and D-rings could be constructed by Sm-mediated domino cyclization[8] 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 **7**[11] to produce aldol adducts **13a** and **13b**

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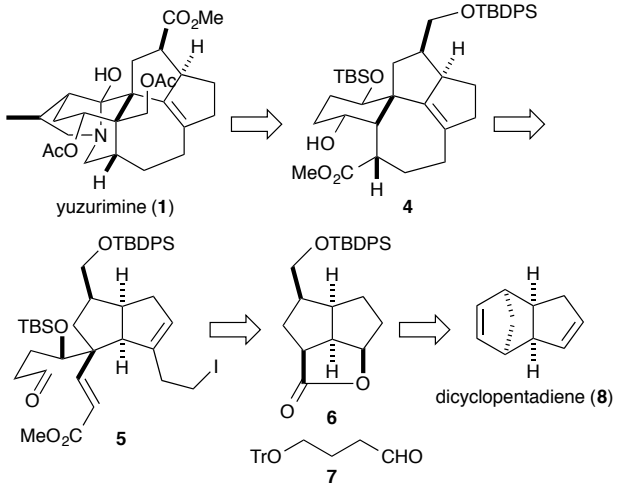
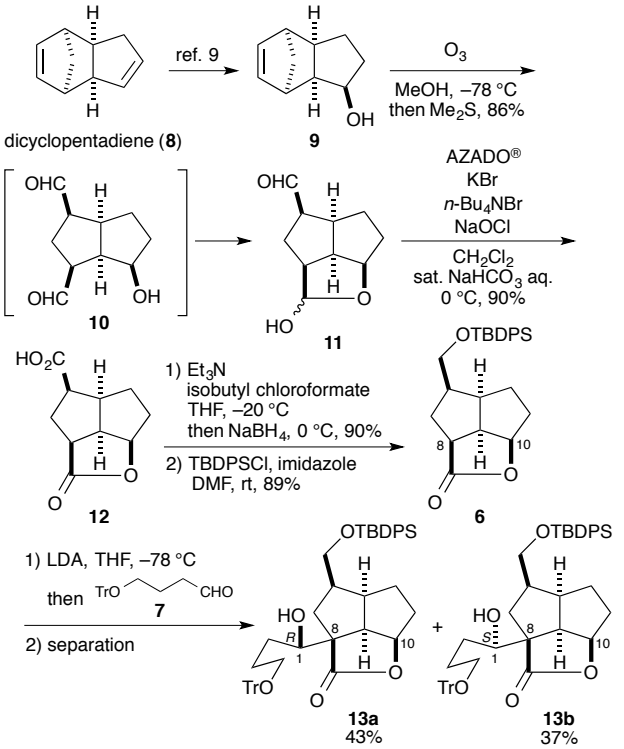
as mixtures of diastereomers at C1. Aldol products **13a** and **13b** both arose from a highly stereoselective addition to the convex face of the enolate anion (obtained upon deprotonation of **6**) and differed only in their relative stereochemistry at C1. The stereochemistry of C1 was of little consequence 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).



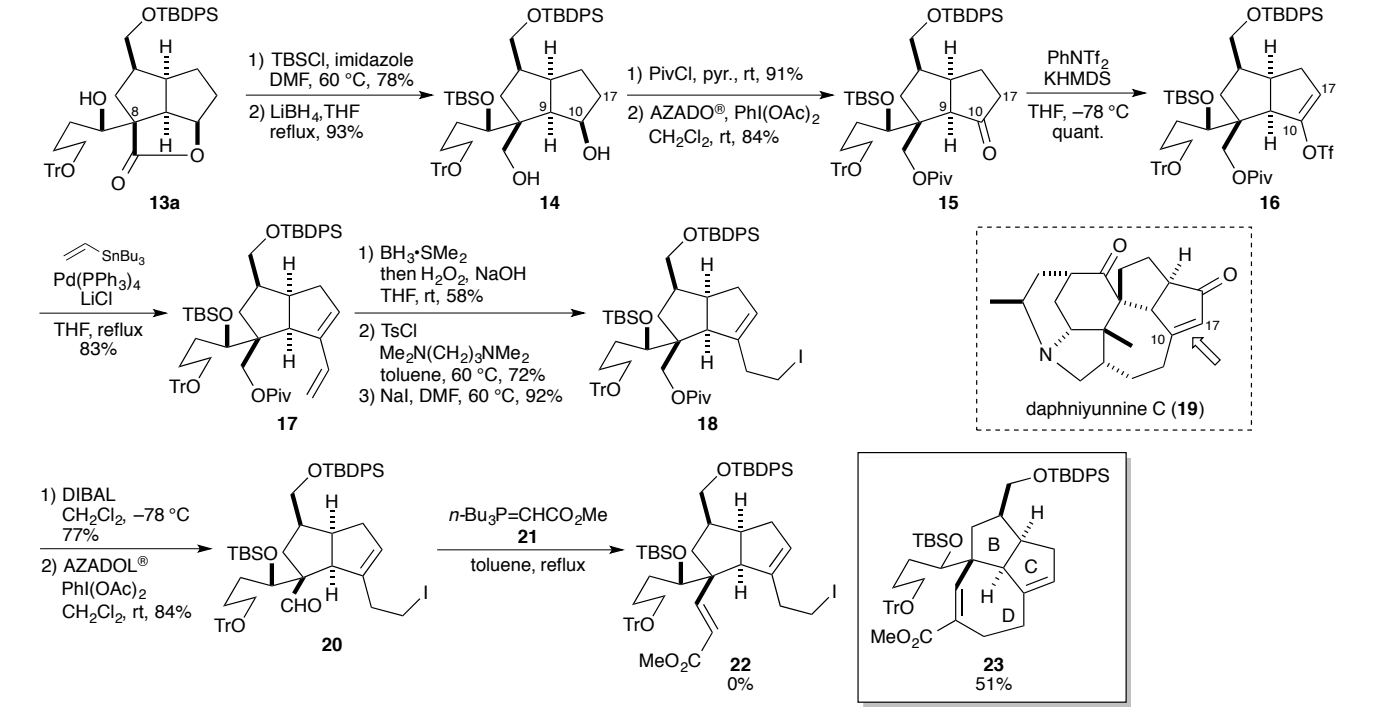
Scheme 1 Retrosynthetic pathway of the tetracarbocyclic core of yuzurimine-type alkaloids



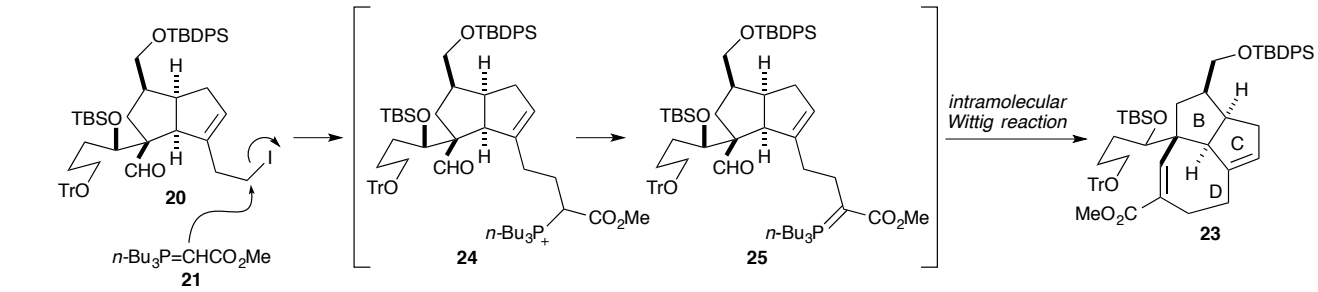
Scheme 2 Stereoselective construction of a quaternary carbon at C8

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 afforded 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 ocurring.



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 SmI_2, LiCl, and *t*-BuOH[18] 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] tetracarbocyclic 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] tetracarbocyclic 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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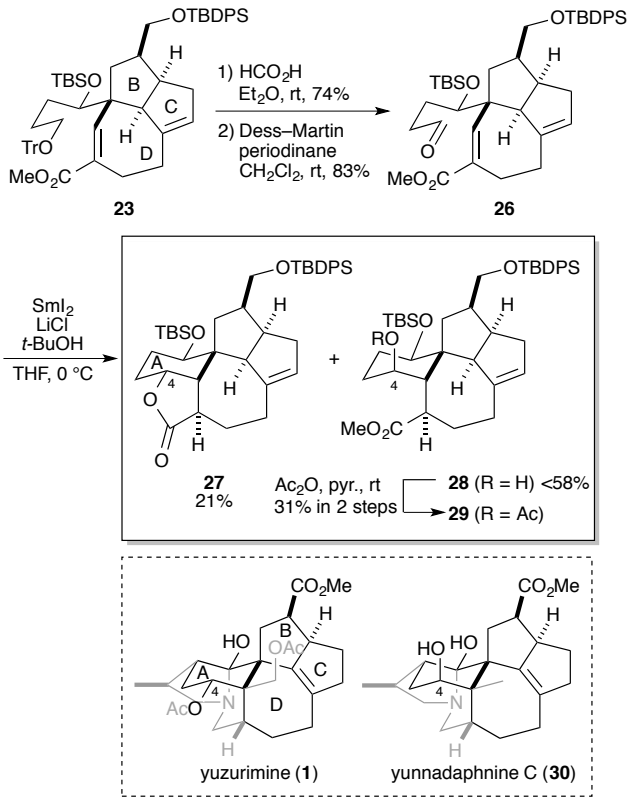

Scheme 5 Synthesis of the [6–7–5–5] tetracarbocyclic core of yuzurimine-type alkaloids

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19 Tetracyclic compound **28** contains a small amount of impurities. The yield of **29** was calculated from **26**.

20 The structures of lactone **27** and tetracyclic compound **28** were determined by analysis of 2D NMR spectra. The stereochemistry of tetracyclic compound **28** was established by NOESY correlations of acetate **29** (see the Supporting Information).

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