Construction of the [6-7-5-5] tetracyclic core of all the carbocyclic frameworks 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)-type3 and daphmanidin A (3)-type4 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.

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 cyclization6 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.
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 significance and differed only in their relative stereochemistry at C1. The face of the enolate anion (obtained upon deprotonation of 1) arose from reaction to afford seven unexpected seven-membered enones 13a and 13b were determined at a later stage.

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 aldehyde 13a with a TBS group and reduction of the lactone gave diol 14, which was transformed into ketone 15 by the protecting of the resulting primary hydroxy group as a pivaloyl ester and oxidation of a secondary hydroxy group by using AZADO®. Ketone 15 was converted into enol triflate 16, which was transformed into diene 17 by Stille coupling. 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. The enol triflate 16 can be used for construction of the C10–C17 double bond of daphniyunnine C (19). Hydroboration and oxidation of the terminal olefin in diene 17 gave an alcohol, which was converted into iodide 18 in 2 steps. 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) was examined. However, we could not obtain the desired α,β-unsaturated ester 22; only the unexpected seven-membered enone 23 was formed.

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.
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-BuOH afforded lactone 27 (21%) and tetracyclic compound 28 (<58%), which are diastereomeric at C4. These compounds 27 and 28 contain the [6–7–5–5] tetracarbocyclic cores of yuzurimine-type alkaloids. The tetracyclic compound 28 was transformed into acetate 29 for purification and determination of the stereochemistry at C4 (31% in 2 steps). The axial configuration at the C4 hydroxy group in 28 was the same as that of yunnadaphnaine C (30).

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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Notes and references

13. We could not get the fully substituted enol triflate even under thermodynamic conditions. Preliminary calculation of simpler model bicyclic enol triflate suggested that the less-substituted enol triflate in 16 is more stable than the fully substituted one. In the tricyclic [7–5–5] system, the trisubstituted olefin in 4 is suggested to be less stable than the trisubstituted olefin. However, the energy difference is smaller than in the bicyclic system. We would have a chance of isomerization into the desired isomer after construction of [7–5–5] or [6–7–5–5] carbocyclic skeleton. Currently, we are examining the isomerization of the double bond from the C10–C17 to the C9–C10 for the synthesis of yuzurimine-type alkaloids.
16. In our unpublished result, elongation reaction of a similar aldehyde to an α,β-unsaturated ester was only proceeded by using phosphorane 21; C. Hareken and S. F. Martin, *Org. Lett.*, 2001, 3, 3591.
17. The structure of seven-membered enone 23 was determined by analysis of 2D NMR spectra (see the Supporting Information).
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).