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Synthesis of the [7-5-5] Tricyclic Core of Daphniphyllum Alkaloids

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The [7-5-5] tricyclic core of the *Daphniphyllum* alkaloids was constructed, featuring a Claisen-Ireland rearrangement to install the two contiguous stereogenic centers, E1cB elimination to form the tetrasubstituted C-C double bond, and a 2,3-Wittig rearrangement to construct the quaternary carbon. Ring-closing metathesis and an intramolecular carbonyl ene reaction were employed for construction of the requisite ring system.

Alkaloids with a vast range of diversity have been isolated from plants of the genus *Daphniphyllum*.[1] According to their structure, these alkaloids can be classified into several groups, including yuzurimine-, yuzurine-, calyciphylline A-, calyciphylline C- and daphmanidin A-type (Fig. 1). Each group is composed of alkaloids that have the same carbon skeleton but different oxidation states and substituents. A common core structure is present across these groups, that is, a [7-5-5] tricyclic core **7** that features a quaternary carbon and two contiguous stereogenic centers, adjacent to which is a tetrasubstituted C-C double bond. Although a variety of syntheses of *Daphniphyllum* alkaloids have been reported to date,[2] the Smith's synthesis of calyciphylline N is the only example that has succeeded in constructing the above common core.[2k, 2l]
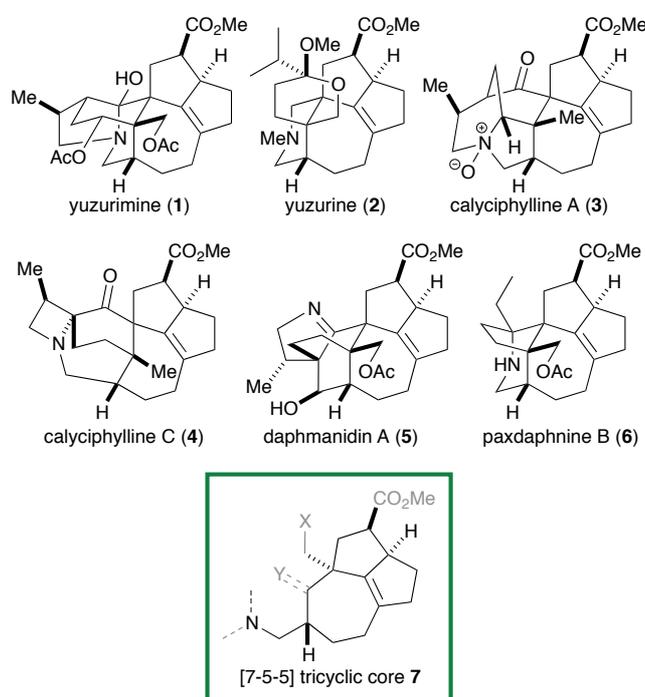
Fig. 1 Daphniphyllum alkaloids.

Among the structural features of the [7-5-5] tricyclic core **7**, the installation of the tetrasubstituted C-C double bond has been explored only to a limited extent. In the Smith's synthesis,[2k, 2l] this feature was realized by selective hydrogenation of a diene moiety in **8** using the BArF analog of the Crabtree catalyst (Scheme 1).[3] Dixon and coworkers reported isomerization of **10** into **11** under basic conditions,[4] which was employed by Zhai and coworkers in their synthesis of daphnilongeranin B.[2p] Very recently, Li and coworkers also reported the synthesis of daphnilongeranin B by employing the Dixon's strategy.[2r] In this case, the carbonyl group of the resulting enone, which fixes the position of the C-C double bond, is the constituent of the target alkaloid. Embedding a planar C-C double bond in a bowl-like [5-5] bicyclic system

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induces a sizable strain; therefore, the double bond tends to move away from the ring juncture. In fact, Sakai and coworkers reported that an intramolecular aldol reaction of **14** under thermal and acidic conditions produced β,γ-unsaturated ketone **16** as the major product.[5] Hayakawa and coworkers also reported that calculations predicted the same stability profile in a trisubstituted olefin and a tetrasubstituted olefin.[6] Herein, we disclose our efforts on constructing the [7-5-5] tricyclic core of the *Daphniphyllum* alkaloids.
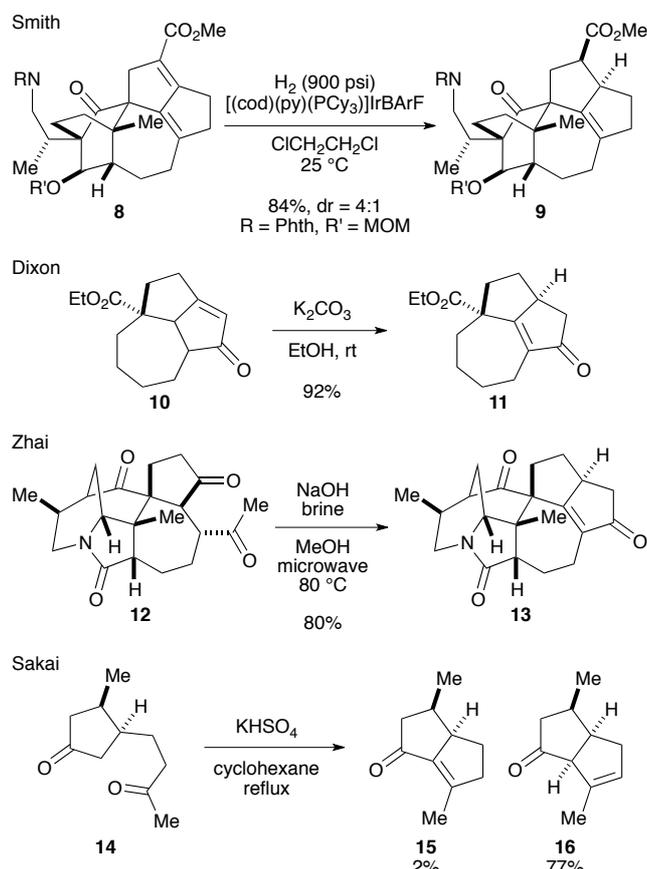
Scheme 1 Installation of tetrasubstituted C-C double bond.

Our synthesis commenced with the construction of two contiguous stereogenic centers via a Claisen-Ireland rearrangement. Protection of 4-pentyn-1-ol (**17**) with a TBS group, followed by hydroxymethylation of the terminal alkyne, afforded alcohol **18**. After partial reduction of the alkyne moiety, the resulting *cis*-allyl alcohol was condensed with carboxylic acid **A** to furnish ester **19**.[7] Upon treatment with LHMDS and TMSCl, **19** underwent a smooth Claisen-Ireland rearrangement,[8] giving carboxylic acid **20** in 73% yield with a diastereomeric ratio of 6.3:1. Sodium borohydride reduction of the mixed anhydride derived from the carboxylic acid afforded an alcohol, which was then protected as its benzyl ether. Ring closing metathesis of **21** was performed with the Zhan catalyst-1B (**B**) to give trisubstituted olefin **22**. After a 2-step conversion of the silyl ether moiety in **22** to aldehyde **23**, a carbonyl ene reaction was conducted by treatment with boron trifluoride to give bicyclic compound **24** in 93% yield.[9]
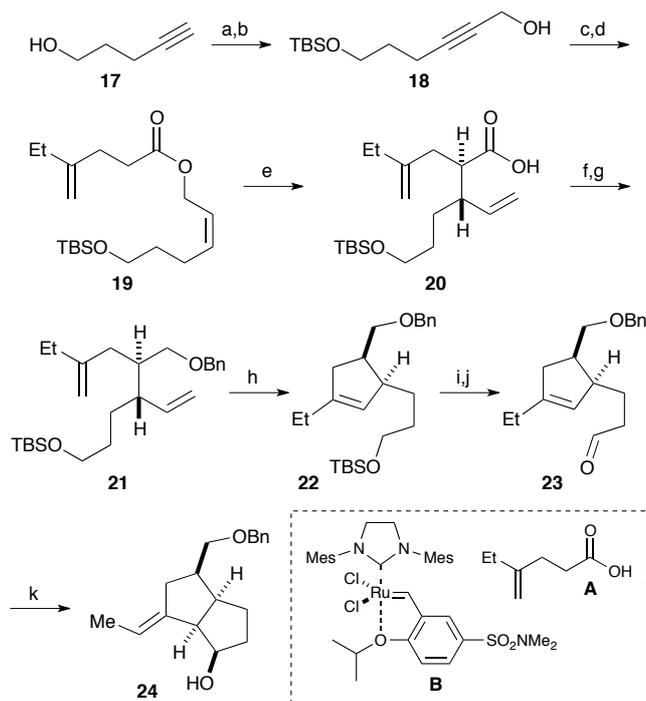
Scheme 2 Stereoselective construction of the bicyclo[3.3.0]octane system. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, rt, 99%; (b) *n*-BuLi, THF, −78 °C; (HCHO)$_n$, −78 °C, 70%; (c) H_2, Lindlar catalyst, quinoline, EtOAc, rt, quant; (d) **A**, EDCI, DMAP, CH_2Cl_2, rt, 89%; (e) LHMDS, TMSCl, Et_2O, −78 to 40 °C, 73%, dr = 6.3:1; (f) Boc_2O, pyridine, THF, rt; $NaBH_4$, H_2O, 0 °C, 98%; (g) BnBr, NaH, THF, 0 °C to rt, 83%; (h) **B**, toluene, 50 °C, 95%; (i) TBAF, THF, rt, 90%; (j) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 90%; (k) $BF_3·OEt_2$, CH_2Cl_2, −78 °C, 93%.

We next focused on introducing the tetrasubstituted C-C double bond. TPAP oxidation of the secondary alcohol moiety in **24**,[10] followed by the addition of three-carbon unit **26** in the presence of cerium chloride,[11] afforded **27**. Ozonolysis of the C-C double bond and protection of the tertiary alcohol moiety with a TMS group produced **28**. We next conducted the E1cB-elimination of **28** to furnish α,β-unsaturated ketone **29**.[12] During the course of the investigations, we realized that the order of mixing the reagent was important. While addition of potassium *tert*-butoxide to a solution of the substrate induced isomerization of the α,β-unsaturated ketone to the corresponding β,γ-unsaturated ketone, addition of a solution of **28** in THF to a solution containing an excess amount of potassium *tert*-butoxide (10 equiv) at 0 °C gave **29** in 78% yield. To the carbonyl group in enone **29** was added an ethoxyacetylene moiety, and the resulting product **30** was subjected to the Meyer-Schuster rearrangement by treatment with Sc(OTf)$_3$.[13,14] The reaction occurred via protonation from the less hindered side of the allenyl intermediate **31**, giving unsaturated ester **32**, which was reduced with DIBAL to afford alcohol **33**.
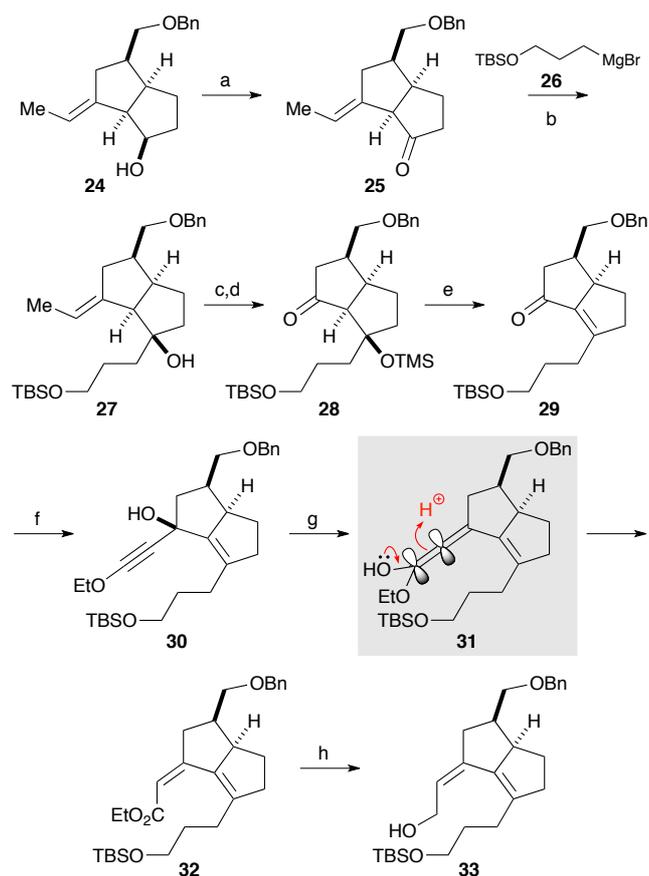
Scheme 3 Formation of the tetrasubstituted olefin moiety. Reagents and conditions: (a) TPAP, NMO, MS4A, CH₂Cl₂, 0 °C, 84%; (b) TBSO(CH₂)₃MgBr (**26**), CeCl₃, THF, 0 °C, 81%; (c) O₃, CH₂Cl₂-MeOH, −78 °C; Ph₃P, −78 °C to rt, 75%; (d) TMSCl, imidazole, DMF, rt, 92%; (e) KOt-Bu, THF, 0 °C, 78%; (f) EtMgBr, ethoxyacetylene, Et₂O, 0 °C, 78%; (g) Sc(OTf)₃, EtOH, CH₂Cl₂, 0 °C, 93%; (h) DIBAL, CH₂Cl₂, −78 to 0 °C, 77%.

The quaternary carbon was next constructed using the allyl alcohol moiety in **33**. After extensive investigations involving reactions related to Claisen rearrangement[15] or Lewis acid-mediated rearrangement of epoxyalcohol derivatives,[16] we found that 2,3-Wittig rearrangement was effective for achieving this transformation.[17] Alkylation of the hydroxy group in **33** with *n*-Bu₃SnCH₂I in the presence of potassium hydride furnished **34**, which was treated with methyllithium in diethyl ether.[18] The requisite 2,3-Wittig rearrangement stereoselectively occurred on the less hindered, convex face of the bicyclic system to produce alcohol **36** having a vinyl group[19] that was to be used for construction of the 7-membered ring. After protecting the hydroxy group with a MOM group, the three-carbon chain was elongated in a 3-step sequence comprising cleavage of the TBS ether, oxidation to aldehyde, and a Wittig reaction. The resulting diene **38** was subjected to ring-closing metathesis with the second-generation Grubbs catalyst to form a seven-membered ring in a quantitative yield.[20] Thus, the [7-5-5] tricyclic core containing the quaternary carbon, two contiguous stereogenic centers, and the tetrasubstituted C-C double bond was successfully constructed. A preliminary investigation involving 1,3-dipolar cycloaddition of a nitrile oxide, generated from **40**, to **39**

afforded isoxazoline **41** in a 1.1:1 diastereomer ratio.[21] Reduction of the isoxazoline ring with nickel boride, followed by protection of the resulting amine with a Cbz group, gave **42**.
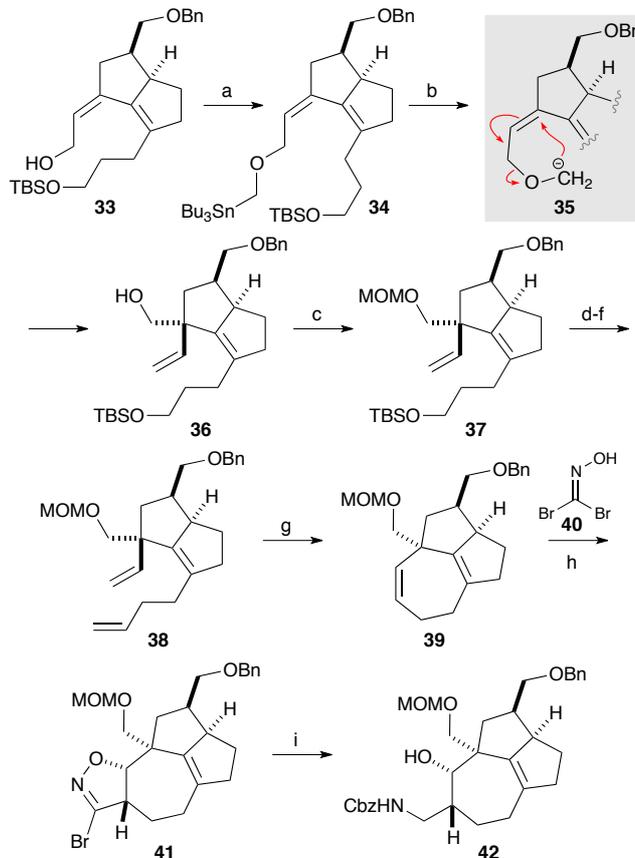
Scheme 4 Construction of the [7-5-5] tricyclic core. Reagents and conditions: (a) KH, Bu₃SnCH₂I, THF, rt; (b) MeLi, Et₂O, 0 °C; (c) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, rt, 64% (3 steps); (d) TBAF, THF, rt, 92%; (e) TPAP, NMO, MS4A, CH₂Cl₂, 0 °C; (f) Ph₃PCH₃Br, *n*-BuLi, THF, 0 °C, 53% (2 steps); (g) Grubbs II, ClCH₂CH₂Cl, 50 °C, quant; (h) **40**, NaHCO₃, CH₂Cl₂, rt, 70%, dr = 1.1:1; (i) NiCl₂, NaBH₄, MeOH, −78 °C; CbzCl, aq NaHCO₃, CH₂Cl₂, 0 °C, 39%.

In conclusion, we have constructed the [7-5-5] tricyclic core of the *Daphniphyllum* alkaloids. The present synthesis features a Claisen-Ireland rearrangement to install the two contiguous stereogenic centers, E1cB elimination to form the tetrasubstituted C-C double bond, and a 2,3-Wittig rearrangement to construct the quaternary carbon. Ring-closing metathesis and an intramolecular carbonyl ene reaction formed the ring system. These findings provide a basis for the total synthesis of the *Daphniphyllum* alkaloids that have the [7-5-5] tricyclic core.

Conflicts of interest

There are no conflicts to declare.

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