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# Asymmetric Construction of Rings A–D of Daphnicyclidin Type Alkaloids

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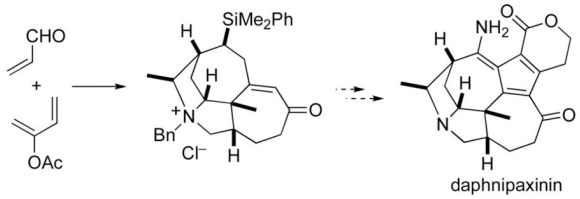
## Abstract




The aza-Cope–Mannich reaction and ring-closing metathesis are key steps in the assembly of intermediates containing rings A–D of *Daphniphyllum* alkaloids of the daphnicyclidin-type such as daphnipaxinin and oldhamine A.

Kobayashi reported in 2001 the first members of a structurally unprecedented group of fused hexa- or pentacyclic *Daphniphyllum* alkaloids, daphnicyclidins A (**1**)–H.[1] Daphnicyclidin-type alkaloids, which now number more than 15, have compact structures that are believed to derive via extensive structural modification of *Daphniphyllum* alkaloids generated from cyclization of squalene precursors.[2] Four representative examples are depicted in Figure 1. These compounds illustrate several of the remarkable structural features of these alkaloids, in particular ring E, which is found in all but two members as either a fulvene or a cyclopentadienyl anion unit. Structures for *Daphniphyllum* alkaloids of the daphnicyclidin-type have been secured on the basis of mass spectrometric, spectroscopic and X-ray data,[3] augmented by chemical correlations.[2] Daphnipaxinin (**3**) is notable as the first diamino *Daphniphyllum* alkaloid isolated.[4] Bioactivities of these alkaloids have been poorly studied, although several display moderate cytotoxicity,[1,2] and others were isolated from plants used in traditional medicine; for example, daphnipaxinin (**3**) is found in *D. paxianum*, an herb used in Chinese folk medicine for the treatment of inflammation.[4]

Stimulated by their unprecedented structures, their scarce natural supply,[5] and their largely unexplored pharmacological profiles, we initiated chemical synthesis studies towards *Daphniphyllum* alkaloids of the daphnicyclidin-type. Ring B is a piperidine in most members of this group, whereas it is a pyrrolidine in daphnipaxinin (**3**) and oldhamine A (**4**).

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**Supporting Information Available:** Experimental details and procedures, tabulated NMR data for compounds **27** and **31**, copies of $^{1}H$ and $^{13}C$ NMR spectra of new compounds, and an X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

We chose to pursue a potentially general strategy in which ring B would be constructed at an advanced stage of the synthesis by forming a bond to C18 from either N1 to form a pyrrolidine ring (as suggested in Scheme 1) or the conjugate base of a cyanomethyl derivative of this amine to construct a piperidine ring. We planned to assemble rings A and C and the five stereocenters of daphnicyclidin-type alkaloids early in the synthesis by aza-Cope–Mannich rearrangement (**8**→**7**) of a formaldiminium ion derived from an aminocyclohexanol precursor such as **8**.[6] We report herein enantioselective construction of the tetracyclic A–D fragment of daphnipaxinin (**3**) and oldhamine A (**4**) by this approach.[7]

The method we devised to access a 2-aminocyclohexanone intermediate incorporating the C2, C4 and C18 stereocenters of daphnicyclidin-type *Daphniphyllum* alkaloids is summarized in Scheme 2. The synthesis began with (*S*)-cyclohexenecarboxyaldehyde **11** (91% ee), which was prepared by the organocatalytic Diels–Alder method of MacMillan.[8] To effectively carry out the cycloaddition of 2-acetoxy-1,3-butadiene and acrolein, it was important to use the hydrotriflate salt of catalyst **10** (2.5 mol %) and water-saturated nitromethane as the reaction solvent.[9] The C18 stereocenter was incorporated by nickel-catalyzed methylation of the aldehyde using 2 mol % of the ($R_p$,*S*,*S*)-phosphoramidite catalyst **12**, following the general prescriptions of Woodward.[10,11] In three conventional steps, product **13** was converted to siloxycyclohexadiene **14**.[12] The amino substituent was then introduced by a two-step sequence that began with hetero Diels–Alder reaction of diene **14** with (nitrosocarbonyl)benzene to give a 6:1 mixture of major adducts **15** and **16**.[13,14] Although these products could be isolated in pure form and processed separately to intermediate **18**, it was more convenient to directly reduce the mixture of stereoisomeric cycloadducts with $Mo(CO)_6$ to form cyclohexenone **17** in good yield, as a ca 5:1 mixture of benzoylamino epimers.[15] The silyl substituent, which we envisioned as a precursor of a carbonyl group at C1, was introduced at this point by conjugate addition of a zincate reagent generated from phenyldimethylsilyllithium.[16] Base-catalyzed epimerization of this product then delivered benzoylaminocyclohexanone **18** in 41% overall yield from siloxycyclohexadiene **14**. In three additional steps, this intermediate was transformed to the *N*-benzyl,*N*-cyanomethyl congener **19** in high overall yield.

Aminoketone **19** can serve as a precursor for fashioning various cycloheptapyrrolidine intermediates by the aza-Cope–Mannich transformation. Considerable effort was invested to find useful conditions for the addition of vinyl organometallic nucleophiles to this hindered ketone. Premixing ketone **19** with $CeCl_3 \cdot 2LiCl$[17] at room temperature, addition of vinyl iodide **20a**, and subsequent dropwise addition of *t*-BuLi at −78 °C provided tertiary alcohol **21a** in 73% yield. Exposing this product to 1.2 equiv of $AgNO_3$ in ethanol at room temperature delivered cycloheptapyrrolidine **22a**[18] as a single stereoisomer in 89% yield. In related fashion, ketone **19** and vinyl iodide **20b** were converted in two steps to cycloheptapyrrolidine **22b** (64% overall yield). The aza-Cope–Mannich transformation to form **22a** and **22b** generated the A and C rings and C5 and C6 stereocenters of the daphnicyclidin-type alkloids in high yield and with complete stereocontrol.

Several approaches for forming the B and D rings were investigated. In one approach, the B ring was formed first by sequential treatment of cycloheptapyrrolidine **22b** with aqueous HF to cleave the TBDPS group, and methanesulfonyl chloride to activate the alcohol for intramolecular alkylation by the tertiary amine. Hydrogenolysis of the resulting quaternary ammonium salt cleaved both benzyl groups to deliver tricyclic aminoketone **23** in 70% overall yield. Although this product could be elaborated to a β-ketophosphonate derivative, all attempts to form the seven-membered D ring by intramolecular Horner–Wadsworth–Emmons reaction failed.[19] Alternatively, **23** could be converted to (*Z*)-vinyl iodide **24**, but attempted ring closure by lithium halogen exchange or under Nozaki–Hiyama–Kishi conditions[20] resulted in protodeiodination of the starting material. Our first success in

fashioning this ring was achieved by first transforming amino ketone **23** to diene **25** by a sequence of three standard reactions. Ring-closing metathesis of amino diene **25** proceeded in good yield using the Grubbs second-generation catalyst **26**[21] to form tetracyclic amine **27** in 81% yield.

Alternatively, the seven-membered D ring could be fashioned prior to forming ring B (Scheme 5). Exposure of cycloheptapyrrolidine **22a** to an excess of vinylmagnesium bromide and $CeCl_3 \cdot 2LiCl$ in THF at −78 °C provided a single allylic alcohol product **28** in 72% yield. Cyclization of this diene in refluxing $CH_2Cl_2$ in the presence of catalyst **26** provided tricyclic amine **29** in nearly quantitative yield. Although one-step procedures for converting tertiary allylic alcohol **29** to enone **30** failed, this transformation could be realized in a step-wise fashion. Thus, exposing allylic alcohol **29** to thionyl chloride and pyridine, followed by hydrolysis of the resulting transposed allylic chloride upon adding alumina and water and subsequent Dess–Martin oxidation[22] provided enone **30** in 45% yield. The B ring could then be constructed in good yield by the previously described two-step sequence.

In summary, an enantioselective synthesis of an advanced tetracyclic intermediate containing all of the stereocenters found in daphnipaxinin and oldhamine A has been developed. A high-yielding aza-Cope–Mannich reaction was utilized to generate the A and C ring cycloheptapyrrolidine core and install both the C5 quaternary carbon stereocenter as well as the adjacent C6 stereocenter. An intramolecular amino alkylation/RCM sequence was then used to form the B and D rings, respectively. Efforts toward construction of the remaining E and F rings to complete an enantioselective synthesis of daphnipaxinin are currently underway.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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18. Aza-Cope–Mannich product **22a** was elaborated to a tricyclic pyrrolidinium salt by cleavage of TBDPS group and intramolecular quaternization by the sequence illustrated in Schemes 4 and 5; see Supporting Information for details. Single crystal X-ray analysis of this derivative confirmed the relative and absolute configuration of **22a**. Crystallographic data for this compound were deposited with the Cambridge Crystallographic Data Centre: CCDC 751136.
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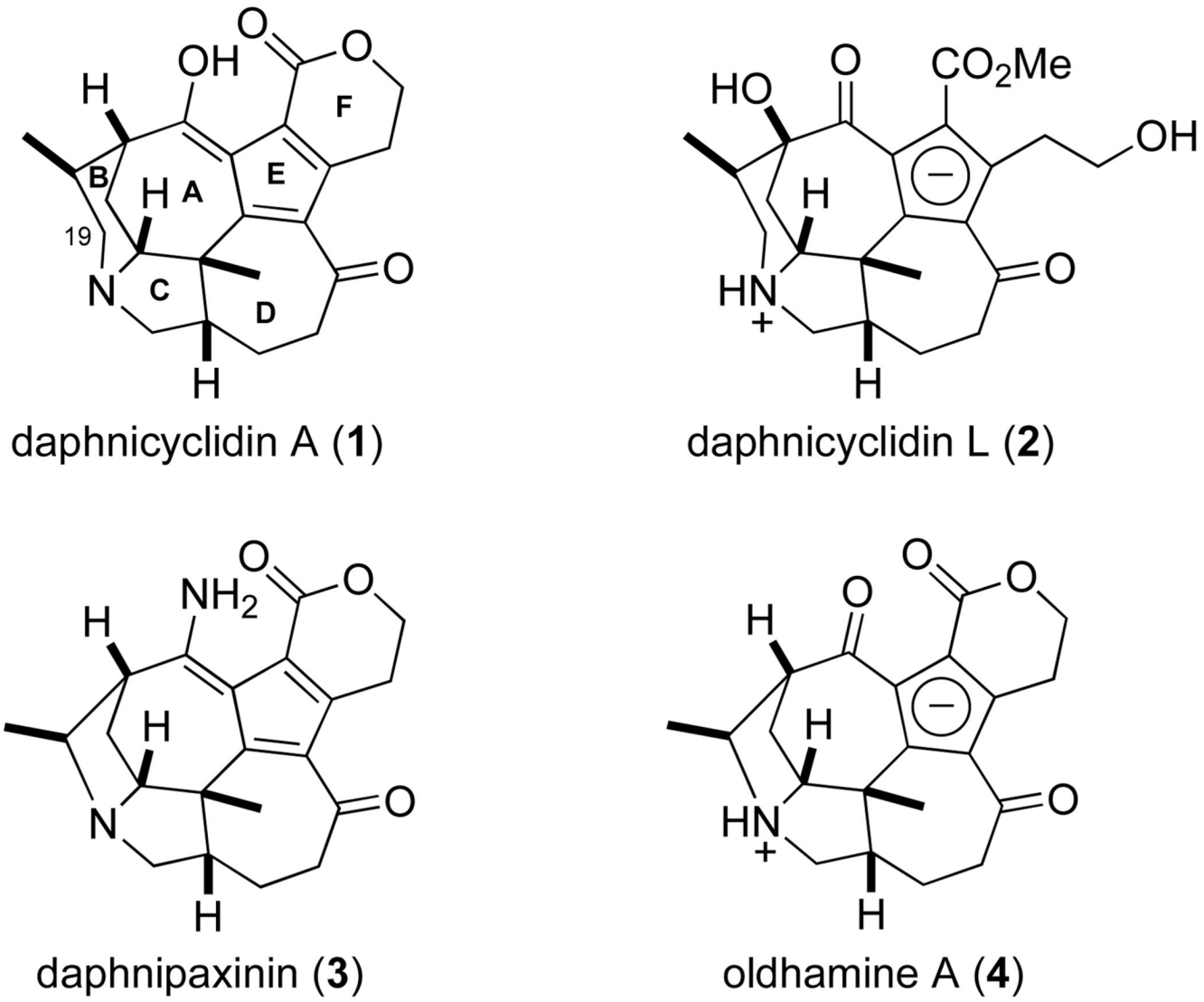
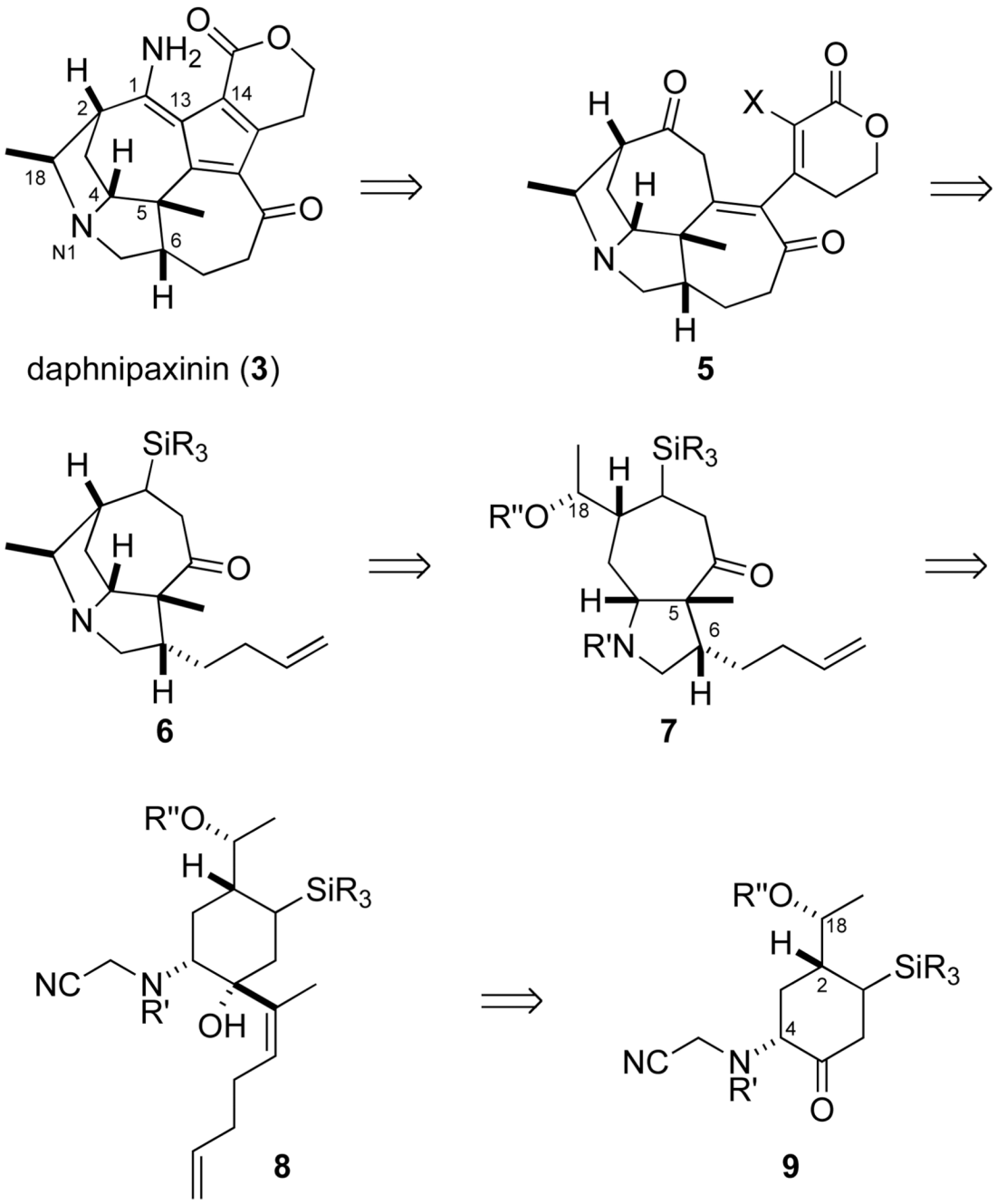
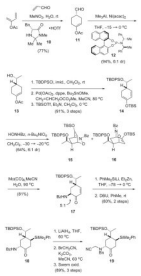



**Figure 1.**
Representative *Daphniphyllum* alkaloids of the daphnicyclidin-type.




**Scheme 1.**



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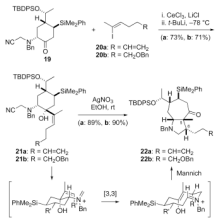
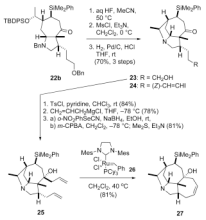


**Scheme 3.**



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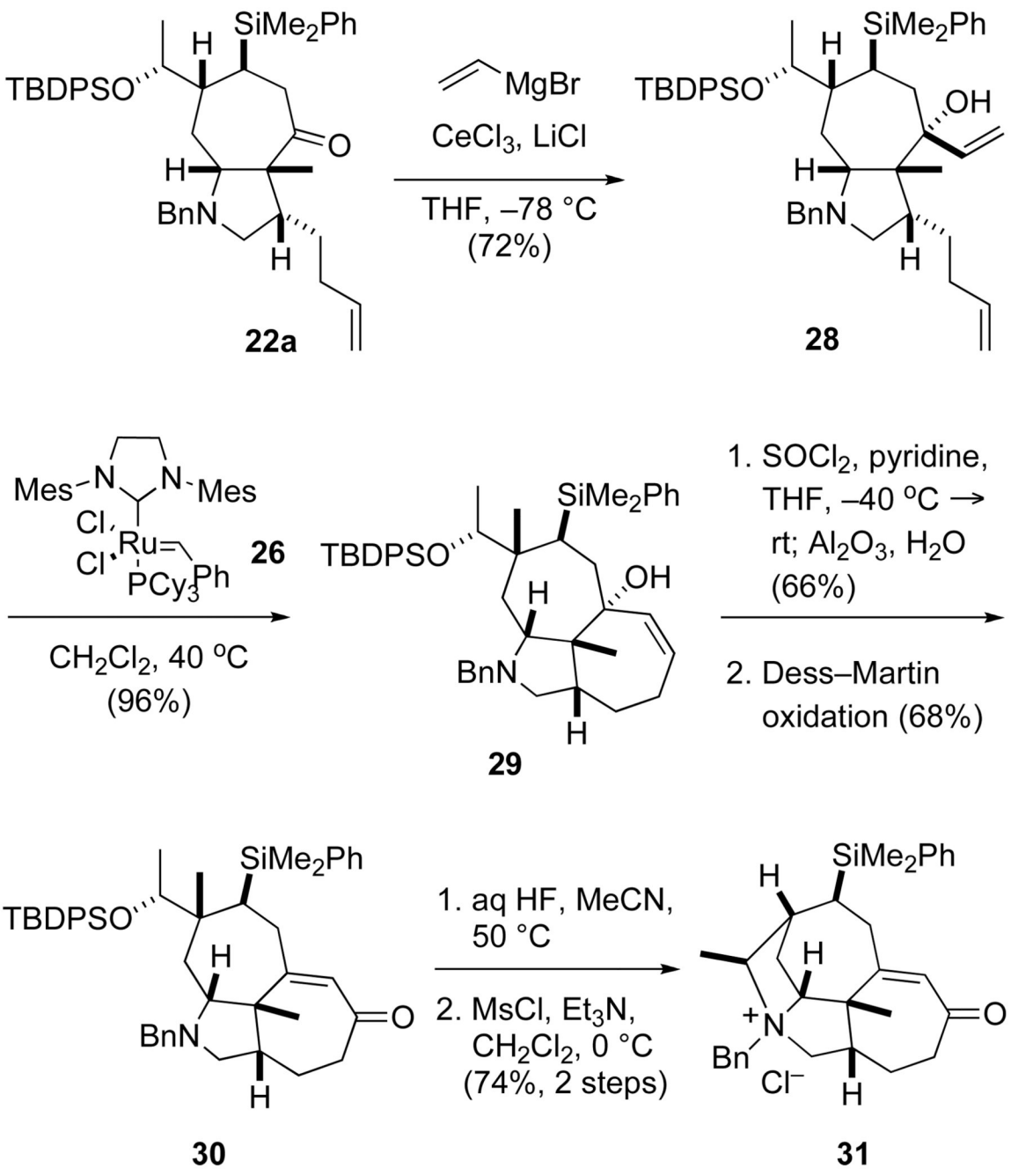


**Scheme 5.**