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COMMUNICATION

First synthesis of an ABCE ring substructure of daphnicyclidin A†

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The ABCE tetracyclic ring system of daphnicyclidin A was prepared using an intramolecular (4+3) cycloaddition of an oxidopyridinium ion as the key step. This route consists of a 10-step synthesis with an overall yield of 20.2%. This result offers support for the use of this strategy for total synthesis of daphnicyclidin A.

Daphnicyclidin A (**1**) is one of a family of *Daphniphyllum* alkaloids that consist of over 300 azapolycyclic natural products.[1] It was first isolated from the stems of *D. teijsmanni* and *humile*,[2] but is also found in other species (Fig. 1).[3] Its polycyclic structure as well as its biological activity have stimulated interest in the molecule. However, it has not been synthesized to date. Approaches to substructures of daphnicyclidin A involving the ABC,[4] the BCD,[5] and the ACE[6] rings have been made, with these efforts ranging from 7 to 19 steps with overall yields ranging from 2.5% to 11.4%.

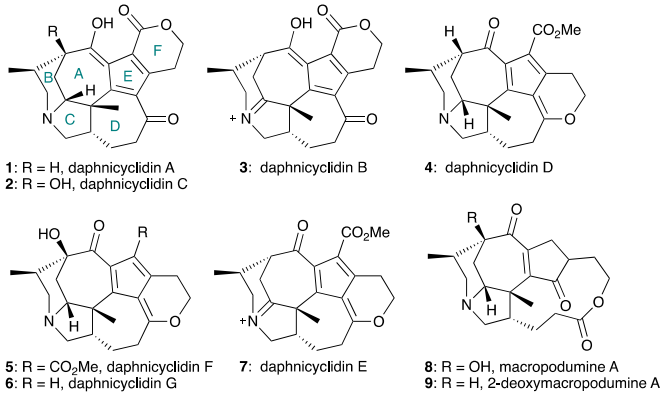
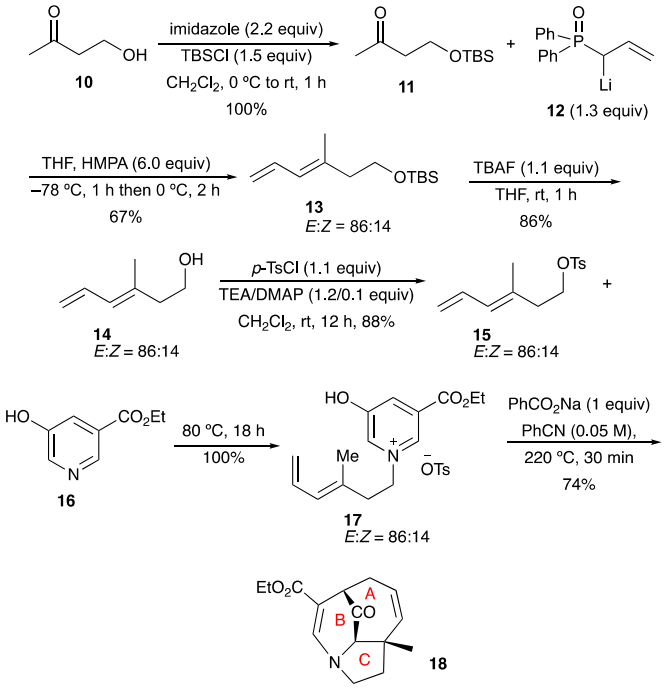


Fig. 1 Some alkaloids obtained from *Daphniphyllum*.

Our group recently also published a synthesis of ABC tricyclic ring system of daphnicyclidin A using an intramolecular (4+3) cycloaddition with an overall 36.5% yield over 6 steps (Scheme 1).[7] The challenge in applying this methodology to total synthesis is that there are still many features of the reaction that need to be explored. We were particularly interested in the synthesis of the ABCE portion of daphnicyclidin A, as we thought it a challenge for the methodology. Moreover, the ABCE tetracyclic ring is also a substructure of macropudumine A (**8**, Fig.1), another alkaloid found in *Daphniphyllum*.[8] In order to make the required oxidopyridinium ion, a 1,2-bis-alkylidenecyclopentane must be made, something we anticipated to be more sensitive than other dienes with which



Scheme 1 Intramolecular (4+3) cycloaddition approach to the ABC ring substructure of daphnicyclidin A.

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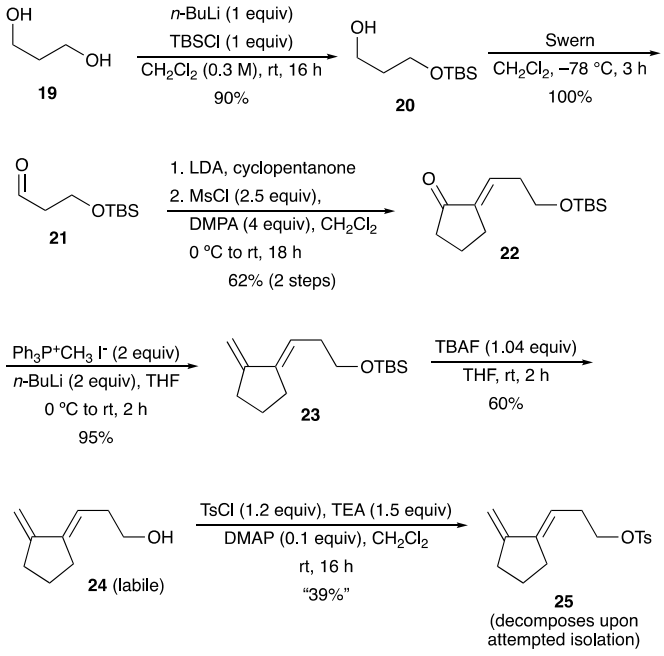
we have previously worked, due to the propensity of exocyclic alkenes to become endocyclic.[9] In the end, it was a challenge that could be met. Herein, we report a 10-step synthesis of the ABCE tetracyclic ring system of daphnicyclidin A using an intramolecular (4+3) cycloaddition of an oxidopyridinium ion as the key step.

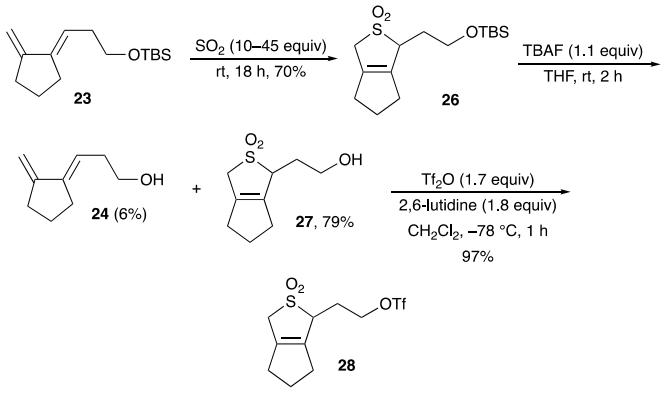
To achieve our goals, we required diene **24**, which was synthesized in 6 steps as shown in Scheme 2. Our synthesis began with the simple propane-1,3-diol **19**, which underwent a mono TBS protection to give alcohol **20** in 90% yield.[10] Alcohol **20** was then converted to its corresponding aldehyde **21** via a Swern oxidation in quantitative yield following literature procedures.[11] With **21** in hand, an aldol reaction with cyclopentanone followed by elimination afforded enone **22** in 62% yield over 2 steps. Wittig olefination gave diene **23** in 95%



Scheme 2 Synthesis of the dienyl alcohol.‡

yield.[12] However, deprotection of **23** gave **24** in only moderate yield. Alcohol **24** is labile and decomposed slowly after isolation. Moreover, converting alcohol **24** to its corresponding tosylate **25** proceeded in low yield. Tosylate **25** was only observed on TLC, and the combined fractions after flash chromatography decomposed and no meaningful NMR or other analytical data could be collected.‡ Since quaternization of **16** using **25** or an analogue would be required in subsequent steps of our process, this was a major problem. We ascribed the instability of **25** to neighbouring-group participation, the diene being sufficiently electron-rich to assist in the departure of the tosylate group, leading to side reactions.[13]

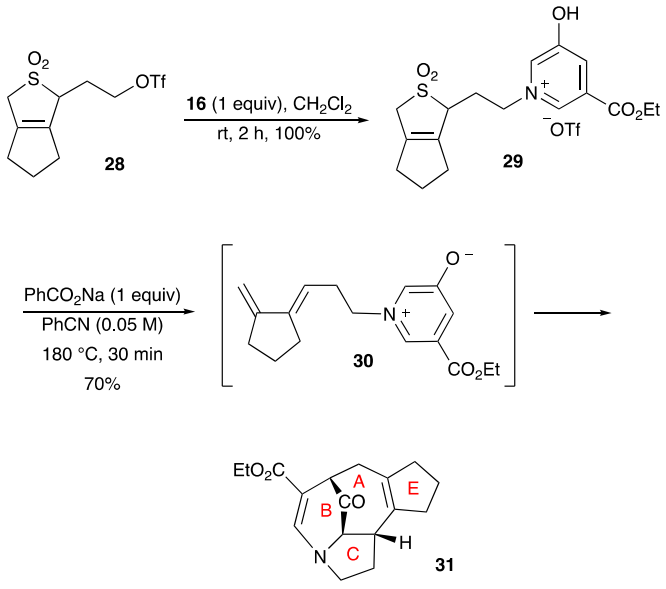
To solve this problem, we decided to protect the diene in such a way that it could be revealed thermally under conditions used for the (4+3) cycloaddition. Sulfur dioxide (SO_2) was the ideal choice to protect as it is well known that diene adducts of SO_2 undergo thermal retro-cheletropic addition upon simply heating.[14]



Scheme 3 Diene protection and triflate formation.

Protection was performed by treating **23** with liquid SO_2 (neat) to give sulfone **26** in 70% yield (Scheme 3). The TBS protecting group of **26** was then removed to give alcohol **27** in 79% yield. Interestingly, a small amount of **24** formed as a side product during this process, though it is not clear whether fluoride had a role in its formation. In considering how to functionalize **27**, we hoped that the protection of the diene would allow us to prepare the corresponding triflate to use in the pyridine quaternization step. This was indeed the case, with triflate **28** being formed in 97% yield.

Triflate **28** was then reacted with ethyl 5-hydroxynicotinate (**16**) without applying any external heat, resulting in the formation of pyridinium salt **29** in quantitative yield (Scheme 4). Finally, salt **29** underwent a one-step sulfone deprotection/ intramolecular (4+3) cycloaddition to give cycloadduct **31**, which possesses the ABCE tetracyclic ring system of daphnicyclidin A, in 70% yield.



Scheme 4 Preparation of the ABCE carbocyclic ring structure of daphnicyclidin A.

Conclusions

In summary, we have developed an extremely simple, step-economical approach to the ABCE ring system of daphnicyclidin A via an intramolecular (4+3) cycloaddition of an oxidopyridinium ion. More generally, the methodology should be useful in the synthesis of rigid, nitrogenous molecular scaffolds of many types. Further studies of the reaction, including streamlining diene synthesis, and attempts to refine the chemistry for the synthesis of daphnicyclidin A or macropudumine A and their congeners are underway. Results will be reported in due course.

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Author Contributions

The manuscript was written through contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ The yield for **25** shown in Scheme 2 was calculated based on the mass of the material obtained after flash chromatographic purification. As solvent was removed, this material turned dark brown, and exhibited a complex ^{1}H NMR and TLC chromatogram.

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