# Total Synthesis of (+)-Caldaphnidine J

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"What makes a natural product attractive to synthetic chemists?" asks Professor Jing Xu from SUSTech, Shenzhen (P. R. of China): "The answer is usually the biological activity, or the pharmaceutical potential, or the structural complexity that represents an intriguing synthetic challenge." It is Professor Xu's opinion that the daphniphyllum alkaloids – isolated from plants of the genus *Daphniphyllum* – clearly belong to this category of compounds, since there is no doubt that they have long attracted a lot of attention from the synthetic community. "Since the milestone synthetic achievements by Professor Clayton H. Heathcock three decades ago, the synthesis of various members of daphniphyllum alkaloids has bloomed in this decade, too," added Professor Xu, who went on to explain that there are more than 300 daphniphyllum alkaloids known to date, making up a structurally remarkably diversified and fascinating natural product family. As shown in Figure 1, daphniphyllum alkaloids from nine subfamilies have been synthetically accessed so far. "Our group has a research focus on the total synthesis of daphniphyllum alkaloids with highly diversified structures, including calyciphylline A-type (*Angew. Chem. Int. Ed.* **2019**, *58*, 7390–7394), daphnezomine A-type (*J. Am. Chem. Soc.* **2019**, *141*, 11713–11720), bukittinggine-type (*J. Am. Chem. Soc.* **2019**, *141*, 13043–13048), yuzurimine-type (*Nat. Commun.* **2020**, DOI: 10.1038/s41467-020-17350-x), daphniglaucin C-type (*Org. Lett.* **2019**, *21*, 4309–4312) and daphnilactone B-type alkaloids (*Chin. J. Org. Chem.* **2019**, *39*, 1079–1084)," said Professor Xu.

Since Hirata's isolation of yuzurimine in 1966, nearly 50 yuzurimine-type alkaloids have been isolated, which account for about one-sixth of all known daphniphyllum alkaloids. "Despite extensive synthetic studies, no total synthesis of any member from this largest subfamily of daphniphyllum alkaloids has been achieved. Caldaphnidine J was isolated by the Yue group in 2008. It possesses a hexacyclic ring system, six contiguous stereogenic centers, two quaternary centers, and an α,β,γ,δ-unsaturated carboxylic ester. This formidable synthetic challenge prompted us to initiate a research program toward its synthesis," explained Professor Xu. He continued: "It was a long, extremely difficult but finally successful journey. As depicted in Scheme 1, the highlights of our approach include 1) a facile six- → seven-membered ring expansion strategy; 2) Shi's Pd-catalyzed regioselective hydroformylation; 3) a Sm(II)-mediated pinacol coupling; 4) a novel, one-pot Swern oxidation/ketene dithioacetal Prins reaction; 5) a regioselective elimination; and 6) a regio- and diastereoselective hydrogenation." The group's work resulted in the first synthesis of a

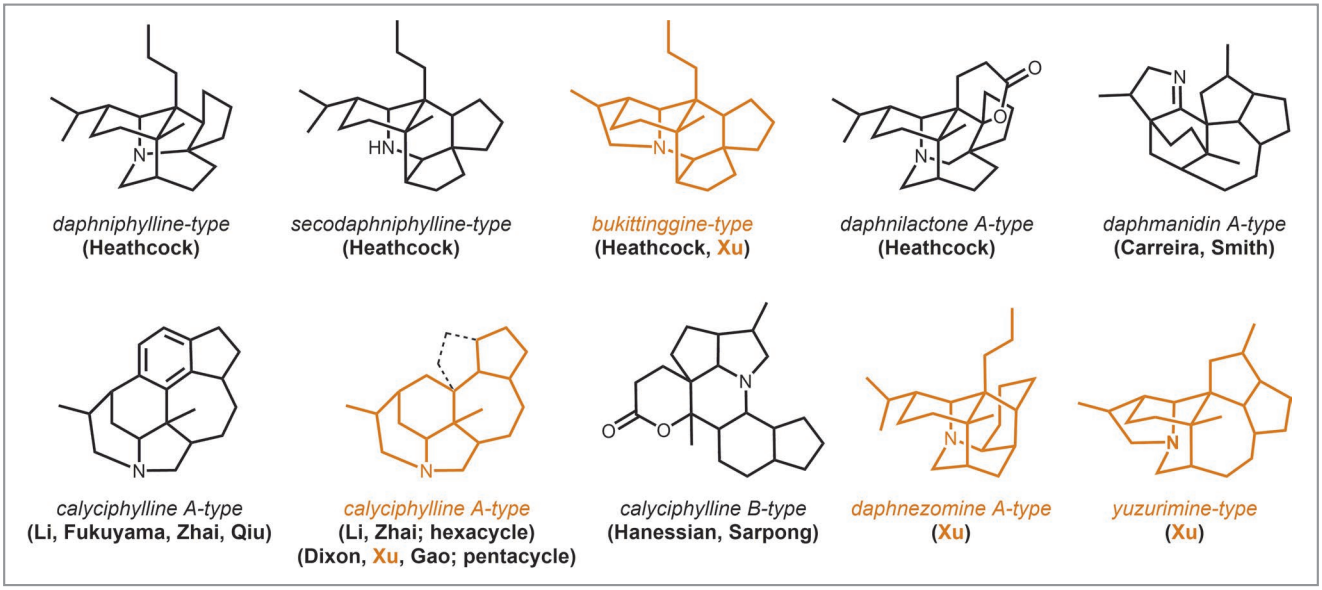
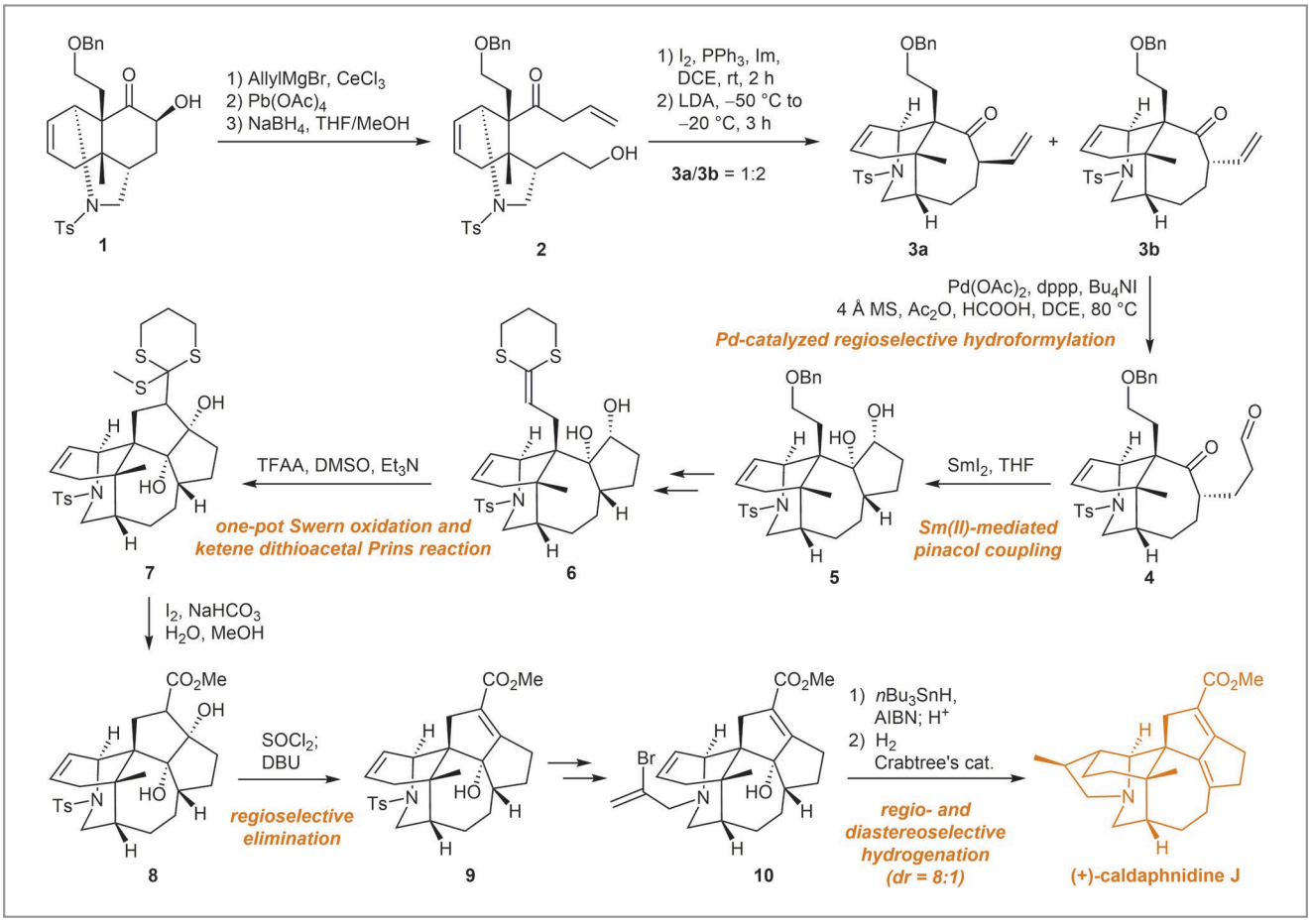



**Figure 1** Daphniphyllum alkaloids from nine subfamilies have been synthetically accessed




**Scheme 1** Total synthesis of (+)-caldaphnidine J

member of the largest subfamily of daphniphyllum alkaloids. Professor Xu remarked: "We believe that the strategies and methods applied in our work should inspire further advances in the synthesis of daphniphyllum alkaloids and much more."

Professor Xu commented that one of the most interesting findings in the group's approach to the title compound was probably the one-pot Swern oxidation/ketene dithioacetal Prins reaction. "As we mentioned in our manuscript, the oxidation of the secondary hydroxyl group in compound **6** gave decomposition or messy results under various conditions," he explained, continuing: "However, the TFAA/DMSO conditions gave a relatively 'clean' reaction that produced a major, yet unknown, product." He concluded: "To our great pleasure, thorough characterizations of this unknown compound finally disclosed a novel one-pot Swern oxidation/ketene dithioacetal Prins reaction."

## About the authors

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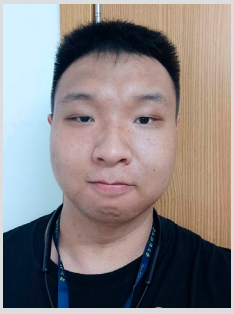
**Lian-Dong Guo** obtained his PhD in 2016 from Xiamen University (P. R. of China) under the direction of Professor Pei-Qiang Huang. He joined Professor Jing Xu's group at SUSTech as a postdoctoral researcher from 2016–2020. His research focuses on the total synthesis of natural products, in particular, the synthesis of alkaloids.



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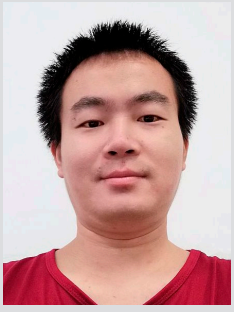

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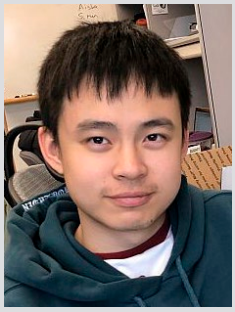

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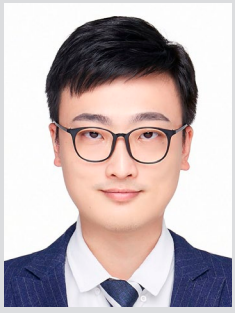

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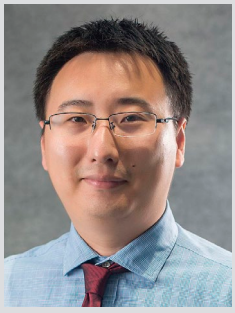

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