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Total synthesis of a putative yuzurimine-type *Daphniphyllum* alkaloid C_{14}–*epi*-deoxycalyciphylline H

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ABSTRACT

One of the largest subfamilies within the famous *Daphniphyllum* alkaloid family is made up of the yuzurimine-type (or macrodaphniphyllamine-type) alkaloids. Their complex aza-polycyclic caged structures, several contiguous stereogenic centers, and vicinal all-carbon quaternary centers make these alkaloids formidable challenge for synthetic chemists. Recently, synthesis of these alkaloids has received extensive attention from our community. Herein, we wish to report the total synthesis of C_{14}–*epi*-deoxycalyciphylline H, a putative member of yuzurimine-type alkaloid subfamily. Key transformations employed in our approach include an intramolecular Prins reaction and a Pd-catalyzed enyne cycloisomerization. In addition, synthesis of a daphnezomine L-type alkaloid, paxdaphnidine A, was also studied.

In recent decades, the *Daphniphyllum* alkaloids have drawn a lot of interest from our community due to their intriguing biological activity and fascinating cage-like structures [1–9]. The groups of Heathcock [10–13], Carreira [14], Li [15–19], Smith [20,21], Hanessian [22], Fukuyama/Yokoshima [23], Dixon [24,25], Zhai [26,27], Qiu [28,29], Gao [30], Sarpong [31,32], Li [33], Lu [34] and Li [35] successively reported their impressive synthesis of more than thirty *Daphniphyllum* alkaloids. Also, our group accomplished the total synthesis of ten *Daphniphyllum* alkaloids from six different subfamilies, including himalensine A, 10-deoxydaphnipaxianine A, daphlongamine E and calyciphylline R (calyciphylline A-type), dapholdhamine B (daphnezomine A-type), caldaphnidine O (bukittinggine-type), caldaphnidine J (yuzurimine-type), daphnezomine L methyl ester and calyciphylline K (daphnezomine L-type) and caldaphnidine D (secodaphniphylline-type) [36–41].

Since Hirata's seminal discovery in 1966, nearly fifty yuzurimine-type (or macrodaphniphyllamine-type) alkaloids—or about one-sixth of all *Daphniphyllum* alkaloids now known—have been identified (Fig. 1). It is acknowledged that the individuals within this subfamily possess intricate and caged hexacyclic skeleton, thus presents significant synthetic challenge. In 2020, our group achieved the first total synthesis of a member within this subfamily, caldaphnidine J [39]. Later, Li reported their impressive total synthesis of five macrodaphniphyllamine-type alkaloids [19].

Based on the biosynthetic pathway of yuzurimine-type alkaloids [6,8], it is reasonable to assume that C_{14}–*epi*-deoxycalyciphylline H could be an actual member of the yuzurimine-type alkaloid subfamily, yet to be isolated. As our interests in natural product synthesis continues [42–44], we wish to describe here our endeavor towards the total synthesis of calyciphylline H [45] that led us to finally access one of its close derivatives, C_{14}–*epi*-deoxycalyciphylline H.

As depicted in Scheme 1, the retrosynthetic analysis of calyciphylline H indicated that it could be derived from C_{14}–*epi*-deoxycalyciphylline H *via* C-14 epimerization and a Polonovski reaction [19]. Next, we envisioned that an enyne cycloisomerization of compound **1** would allow facile access to the key tetrahydropyrrole motif as well as the C3-C4 alkene motif in our target molecules. Next, it was envisaged that compound **1** could be synthesized from compound **2** *via* homologation and propargylation. One of the critical five-membered rings in compound **2** could be fabricated *via* a Prins reaction from aldehyde **3**. This aldehyde compound was envisioned to be derived from the tetracyclic compound **4**, which can be produced from tricycle **5** through our previously reported procedures [37–39].

Our study commenced from known tricyclic compound **5**, which was converted to vicinal diol **4** *via* a 7-step procedure involving ring-expansion and cyclopentane formation (Scheme 2) [37–39]. Then, under Ando's olefination conditions (*p*-TSA,

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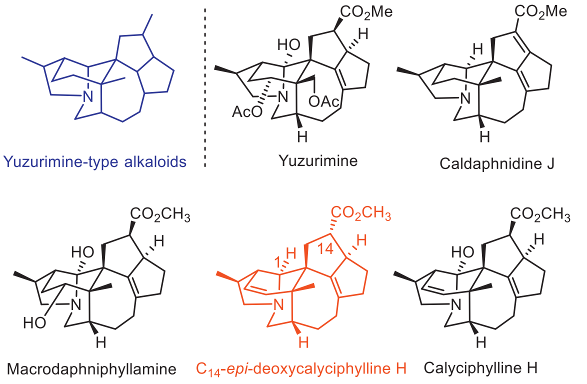
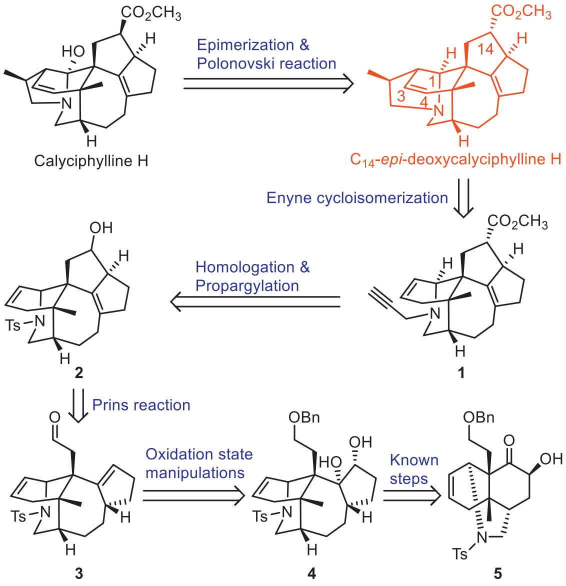
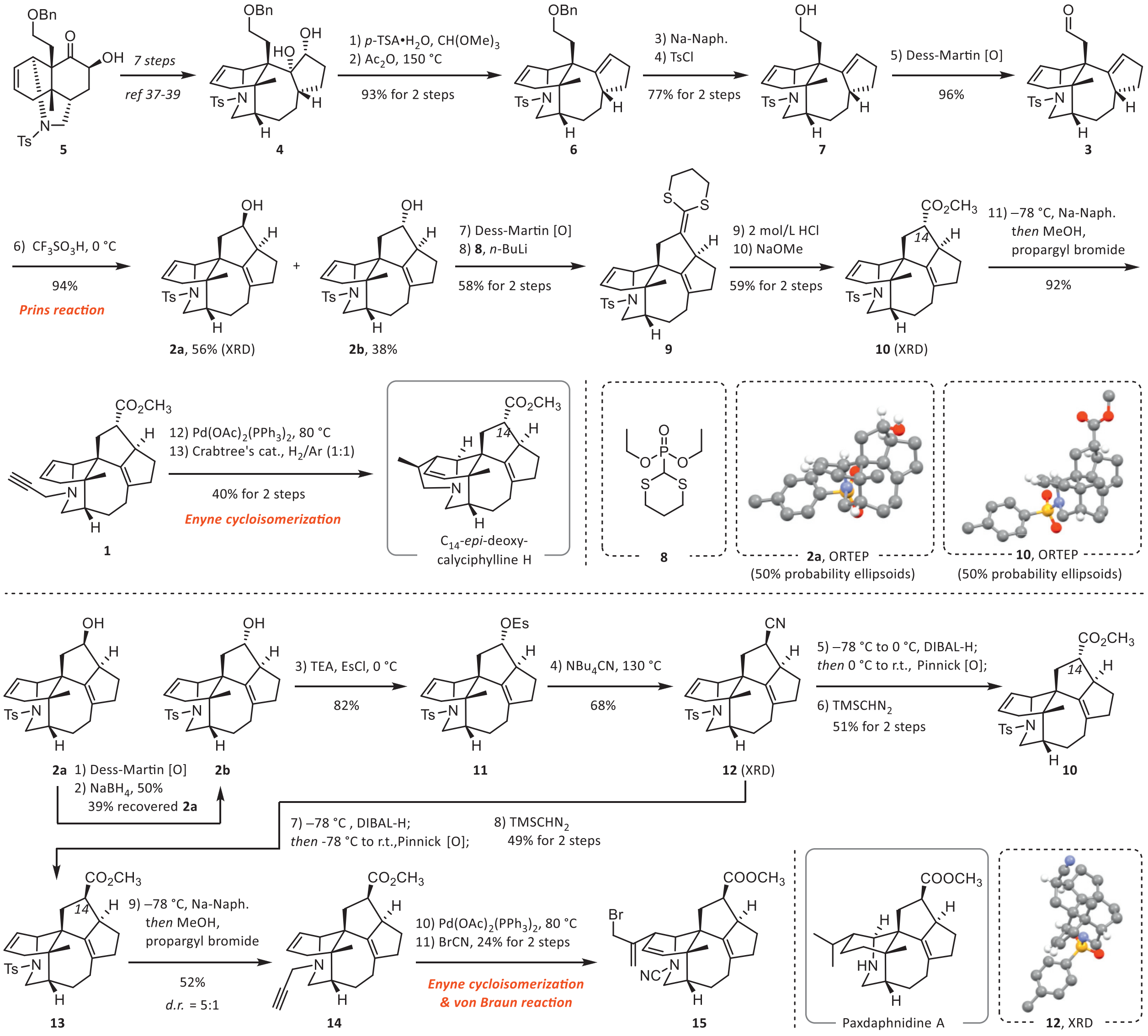


Fig. 1. Representative yuzurimine-type alkaloids.

CH(OMe)$_3$; then Ac$_2$O, 150 °C) [46], alkene **6** was effectively derivatized from diol **4** in excellent yield (93%). Removal of the benzyl group in compound **6** suffered partial *N*-detosylation under sodium naphthalene conditions, hence, re-tosylation was necessary to provide a satisfactory yield of compound **7**. A facile Dess-Martin



Scheme 1. Retrosynthetic analysis.



Scheme 2. Total synthesis of C$_{14}$–*epi*-deoxycalyciphylline H, a putative yuzurimine-type alkaloid and synthetic study towards the daphnezomine L-type alkaloid paxdaphnidine A.

oxidation of the primary hydroxyl group in compound **7** furnished aldehyde **3** in nearly quantitative yield. Next, under the acidic conditions (TfOH, 0 °C), a Prins reaction was triggered between the aldehyde motif and the alkene motif in compound **3**, fabricating alcohols **2a** (56%) and **2b** (38%). The absolute stereochemical configuration of **2a** was unambiguously assigned *via* a single-crystal X-Ray diffraction (CCDC: 2258010), while that of **2b** was assigned by its conversion to **2a** *via* oxidation and reduction. At this point, a homologation was required for introducing the C-14 carboxylic acid ester moiety. To this end, a Dess-Martin oxidation of the mixture of **2a** and **2b** yielded the corresponding ketone compound, which unfortunately failed to react under various homologation conditions (Wittig, Peterson, MeLi, MeMgBr, Nysted, Van Leusen). Gratifyingly, treating it with Horner-Wadsworth-Emmons conditions (**8**, *n*-BuLi) [37–39,41] successfully gave homologated product **9**. Following hydrolysis of the ketene dithioacetal moiety in compound **9** yielded compound **10** with an α-faced carboxylic acid ester at C-14. This outcome was attributed to its thermodynamically favored stereochemistry, which was assigned by a single-crystal XRD (CCDC: 2258012). Replacement of the *N*-tosyl group with the propargyl group afforded enyne compound **1** in 92% yield. Finally, a Pd-catalyzed enyne cycloisomerization [47] produced key tetrahydropyrrole motif as well as the C3-C4 alkene motif in the corresponding diene, which was further selectively hydrogenated (H_2, Crabtree's catalyst) to yield C_{14}–*epi*-deoxycalyciphylline H. In addition, transformation of this compound to natural calyciphylline H is currently under investigation.

Next, our attention turned to a complex member of daphnezomine L-type alkaloids, paxdaphnidine A. It was envisioned that a S_N2-substitution reaction using a cyanide anion may set the desired stereogenic configuration at C-14. Bearing this in mind, alcohol **2a** was converted to its epimer, **2b**, which was then sulfonylated to give compound **11**. Heating this compound with NBu_4CN in DMF produced nitrile **12** with the desired stereogenic outcome, which was also unambiguously confirmed by a single-crystal XRD (CCDC: 2258013). It should be noted that other attempts of this type of transformation gave lower yields (-OMs, NaCN, DMSO, 120 °C, 41%; -OEs, NaCN, DMF or DMSO, 130 °C, <10%; -OTs, NaCN, DMF, 130 °C, 43%; -OTs, NaCN, DMSO, 130 °C, 26%). More experimental evidence further indicated the thermodynamical bias at C-14. When subjecting nitrile **12** to DIBAL-H (−78 °C to 0 °C) followed by a Pinnick oxidation (0 °C to room temperature) and methylation, compound **10** with the undesired C-14 stereogenic center was produced as the main product. However, when the DIBAL-H reduction as well as the Pinnick oxidation was carefully performed at −78 °C, compound **13** was successfully produced with the desired C-14 stereochemistry. Afterwards, detosylation and propargylation of compound **13** produced tertiary amine **14**. Next, a Pd-catalyzed enyne cycloisomerization forged the tetrahydropyrrole ring. The so-afforded hexacyclic diene was then subjected to the von Braun reaction conditions (BrCN, K_2CO_3) [41,48,49] to cleave the C–N bond in a regioselective manner to give compound **15**. This regioselectivity was likely dominated by the drastically different steric hindrances between three C–N bonds. The final-stage transformation of compound **15** to paxdaphnidine A, is still under investigation in our laboratory.

In summary, the total synthesis of C_{14}–*epi*-deoxycalyciphylline H, a possible yuzurimine-type alkaloid family member and a close derivative of its natural congener calyciphylline H, was accomplished. Key cyclization methods, such as Prins reaction and enyne cycloisomerization paved the road to the target molecule. Synthesis towards a daphnezomine L-type alkaloid, paxdaphnidine A, was also studied, featuring a late-stage von Braun reaction. Our findings may benefit the research in this active field—*Daphniphyllum* alkaloid synthesis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108733.

References

[1] L.D. Guo, Y.Y. Chen, J. Xu, Acc. Chem. Res. 53 (2020) 2726–2737.
[2] Z.Y. Li, Y.W. Guo, Chin. J. Org. Chem. 27 (2007) 565–575.
[3] X. Liang, X.Z. Yang, L. Chen, et al., Med. Chem. Res. 30 (2021) 1–14.
[4] H.F. Wu, X.P. Zhang, L.S. Ding, et al., Plant. Med. 79 (2013) 1589–1598.
[5] J.B. Xu, H. Zhang, L.S. Gan, et al., J. Am. Chem. Soc. 136 (2014) 7631–7633.
[6] J. Kobayashi, T. Kubota, Nat. Prod. Rep. 26 (2009) 936–962.
[7] A.K. Chattopadhyay, S. Hanessian, Chem. Rev. 117 (2017) 4104–4146.
[8] J. Zhong, H. Wang, Q. Zhang, S.H. Gao, Alkal. Chem. Biol. 85 (2021) 113–176.
[9] J.X. Zhao, J.M. Yue, Sci. China Chem. 66 (2023) 928–942.
[10] C.H. Heathcock, S.K. Davidsen, S. Mills, M.A. Sanner, J. Am. Chem. Soc. 108 (1986) 5650–5651.
[11] R.B. Ruggeri, M.M. Hansen, C.H. Heathcock, J. Am. Chem. Soc. 110 (1988) 8734–8736.
[12] S. Piettre, C.H. Heathcock, Science 248 (1990) 1532–1534.
[13] R.B. Ruggeri, K.F. McClure, C.H. Heathcock, J. Am. Chem. Soc. 111 (1989) 1530–1531.
[14] M.E. Weiss, E.M. Carreira, Angew. Chem. Int. Ed. 50 (2011) 11501–11505.
[15] Z.Y. Lu, Y. Li, J. Deng, A. Li, Nat. Chem. 5 (2013) 679–684.
[16] J. Li, W.H. Zhang, F. Zhang, Y. Chen, A. Li, J. Am. Chem. Soc. 139 (2017) 14893–14896.
[17] Y. Chen, W.H. Zhang, L. Ren, J. Li, A. Li, Angew. Chem. Int. Ed. 57 (2018) 952–956.
[18] W.H. Zhang, M. Ding, J. Li, et al., J. Am. Chem. Soc. 140 (2018) 4227–4231.
[19] W.H. Zhang, M. Lu, L. Ren, et al., Org. Chem. (2022). doi:10.26434/chemrxiv-2022-j8fzb (accessed 2022-08-16).
[20] A. Shvartsbart, A.B. Smith III, J. Am. Chem. Soc. 136 (2014) 870–873.
[21] A. Shvartsbart, A.B. Smith III, J. Am. Chem. Soc. 137 (2015) 3510–3519.
[22] A.K. Chattopadhyay, V.L. Ly, S. Jakkepally, G. Berger, S. Hanessian, Angew. Chem. Int. Ed. 55 (2016) 2577–2581.
[23] R. Yamada, Y. Adachi, S. Yokoshima, T. Fukuyama, Angew. Chem. Int. Ed. 55 (2016) 6067–6070.
[24] H.Y. Shi, I.N. Michaelides, B. Darses, et al., J. Am. Chem. Soc. 139 (2017) 17755–17758.
[25] R. Kučera, S.R. Ellis, K. Yamazaki, et al., J. Am. Chem. Soc. 145 (2023) 5422–5430.
[26] X.M. Chen, H.J. Zhang, X.K. Yang, et al., Angew. Chem. Int. Ed. 57 (2018) 947–951.
[27] S.B. Su, C.C. Lin, H.B. Zhai, Angew. Chem. Int. Ed. 62 (2023) e202303402.
[28] B. Xu, B.Y. Wang, W. Xun, F.Y.G. Qiu, Angew. Chem. Int. Ed. 58 (2019) 5754–5757.
[29] B.Y. Wang, B. Xu, W. Xun, et al., Angew. Chem. Int. Ed. 60 (2021) 9439–9443.
[30] J.X. Zhong, K.W. Chen, Y.Y. Qiu, H.B. He, S.H. Gao, Org. Lett. 21 (2019) 3741–3745.
[31] C.L. Hugelshofer, V. Palani, R. Sarpong, J. Am. Chem. Soc. 141 (2019) 8431–8435.
[32] C.L. Hugelshofer, V. Palani, R. Sarpong, J. Org. Chem. 84 (2019) 14069–14091.
[33] G.P. Xu, J.B. Wu, L.Y. Li, Y.N. Lu, C. Li, J. Am. Chem. Soc. 142 (2020) 15240–15245.

[34] M.Y. Cao, B.J. Ma, Q.X. Gu, B. Fu, H.H. Lu, J. Am. Chem. Soc. 144 (2022) 5750–5755.
[35] L.X. Li, L. Min, T.B. Yao, et al., J. Am. Chem. Soc. 144 (2022) 18823–18828.
[36] Y.Y. Chen, J.P. Hu, L.D. Guo, et al., Angew. Chem. Int. Ed. 58 (2019) 7390–7394.
[37] L.D. Guo, J.P. Hou, W.T. Tu, et al., J. Am. Chem. Soc. 141 (2019) 11713–11720.
[38] L.D. Guo, J.P. Hu, Y. Zhang, et al., J. Am. Chem. Soc. 141 (2019) 13043–13048.
[39] L.D. Guo, Y. Zhang, J.P. Hu, et al., Nat. Commun. 11 (2020) 3538.
[40] Y. Zhang, Y.Y. Chen, M.R. Song, et al., J. Am. Chem. Soc. 144 (2022) 16042–16051.
[41] J.P. Hu, L.D. Guo, W.Q. Chen, et al., Org. Lett. 24 (2022) 7416–7420.
[42] S.L. Xie, C.Q. Ning, Q.Z. Yu, J.P. Hou, J. Xu, Chin. J. Chem. 39 (2021) 137–142.
[43] S.L. Xie, G. Chen, H. Yan, et al., J. Am. Chem. Soc. 141 (2019) 3435–3439.
[44] N. Zhao, S.Q. Yin, S.L. Xie, et al., Angew. Chem. Int. Ed. 57 (2018) 3386–3390.
[45] S. Saito, H. Yahata, T. Kubota, et al., Tetrahedron 64 (2008) 1901–1908.
[46] M. Ando, H. Ohhara, K. Takase, Chem. Lett. 15 (1986) 879–882.
[47] B.M. Trost, Acc. Chem. Res. 23 (1990) 34–42.
[48] J. von Braun, Ber. deut. Chem. Ges. 37 (1904) 3210.
[49] A.R. Surrey, Name Reactions in Organic Chemistry, 2nd ed, Academic Press, 1961, pp. 31–32.