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Biomimetic syntheses of kadcoccitane H and kadcotrione C methyl ester†‡

Dattatraya H. Dethe,^{ID}* Salman A. Siddiqui^{ID} and Chirantan Singha^{ID}

Kadcotrones and kadcoccitane, renowned for their intricate 6/6/5-tricyclic and 6/6/5/6-tetracyclic ring systems, respectively, exhibit promising biological activities. This work proposes a biosynthetic pathway that elucidates how nature synthesizes these triterpenoids from lanosterol. Inspired by this pathway, we present the first biomimetic syntheses of kadcoccitane H and kadcotrione C methyl ester. These syntheses showcase key transformations including olefin transposition, a biomimetic ring contraction/expansion, SeO₂ mediated one-pot allylic oxidation/isomerization–elimination/allylic oxidation cascade, regioselective dihydroxylation of sterically hindered double bond, unusual POCl₃ mediated cleavage of diol and Still–Gennari olefination.

Plants of the family Schisandraceae, consisting of the genera *Schisandra* and *Kadsura*, are a rich source of triterpenoids with novel complex polycyclic structures and diverse biological activities.¹ *Kadsura coccinea*, an evergreen climbing shrub widely distributed in the southwestern provinces of China, is one of the few intensively studied *Kadsura* species. This is partly because it has long been used as traditional Chinese medicine for its beneficial pharmacological effects, such as gastropathy, rheumatic arthritis, anticancer, antihepatitis, and anti-HIV-1 activities. Furthermore, it has been proven to be a rich source of novel kadcotrones and kadcoccitane which are 14(13 → 12)-*abeo*-12,13-*seco*-lanostane and 14(13 → 12)-*abeo*-lanostane triterpenoids, respectively, possessing rearranged lanostane frameworks with interesting structural features of daedal oxygenation and cleavage patterns.

In 2013, Sun and co-workers isolated kadcotrones A–C (1–3, Fig. 1)² and subsequently in 2015 the same group reported the isolation of kadcoccinic acids A–J.³ Later in 2019, Puno and co-workers isolated kadcoccitane A–D⁴ and recently in 2023, they reported the isolation of kadcoccitane E–H (4–6, Fig. 1)⁵ from the stem of *Kadsura coccinea*. Kadcotrones possess 6/6/6-fused tricyclic (for kadcotrione A) and 6/6/5-fused tricyclic (for kadcotrones B–C) ring skeletons with a unique keto–acid side chain. In addition to that, kadcoccitane E–H have a unique 6/6/5/6-fused tetracyclic ring skeleton featuring $\alpha,\beta,\gamma,\delta$ -unsaturated aldehyde or $\alpha,\beta,\gamma,\delta,\epsilon,\zeta$ -unsaturated aldehyde/ketone and an α,β -unsaturated acid side chain with *Z*-olefin geometry.

Kadcoccitane and kadcotrones contain three quaternary carbons and four to six stereocenters.

Herein, we report expeditious syntheses of kadcoccitane H and kadcotrione C methyl ester starting from commercially available lanosterol and making use of biomimetic and diastereoselective transformations. Prior to our synthesis, Trost's group⁶ reported an elegant synthesis of the trimethyl ester of kadcoccinic acid A (7) in 23 LLS, starting from 2-methyl-1,3-cyclohexadione. Our synthesis, which entails an oxidative olefin transposition, Wagner–Meerwein type rearrangement, dihydroxylation/diol cleavage, and finally a Still–Gennari olefination reaction, enables the rapid construction of these

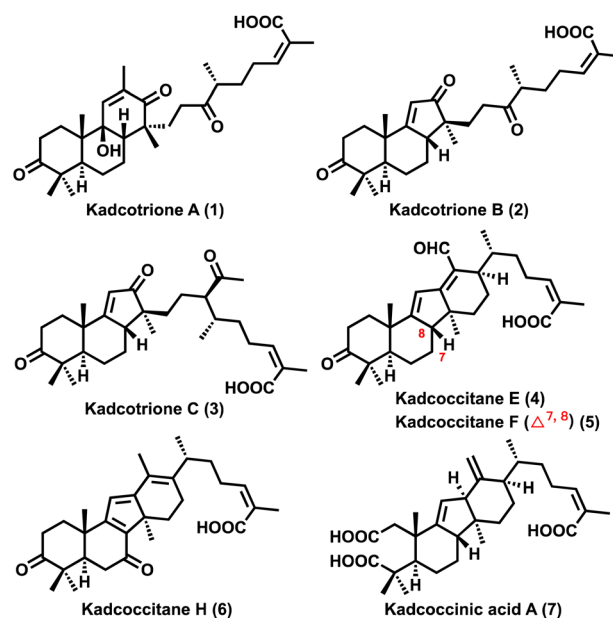


Fig. 1 Kadcotrones A–C and kadcoccitane E–H.

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur – 208016, India. E-mail: ddethe@iitk.ac.in

† This work is dedicated to Prof. Vinod K. Singh, IIT Kanpur, on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available. CCDC 2404778. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5sc00669d>

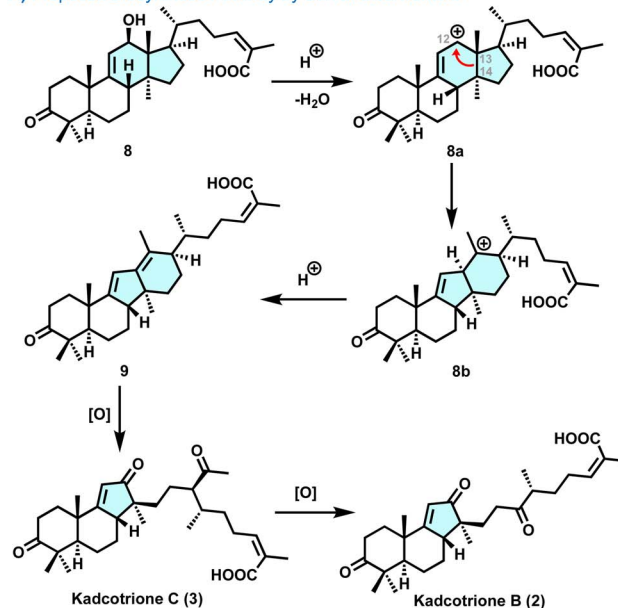
unusual natural products. This strategy also provides access to various kadcoccitane analogues that do not exist in nature which might be useful in investigating the biological activities of these unique natural products. In recent years, rearranged steroids have garnered significant attention from synthetic chemists, driven by their diverse structural motifs and intriguing biological activities. A significant subgroup of rearranged steroids, known as *abeo*-steroids, are often produced naturally from classical steroids.^{7a-d}

Our synthetic strategy for kadcotrine C (**3**) was primarily guided by a biosynthetic pathway proposed by Sun and co-workers (Scheme 1A).² They suggested that diene intermediate **9** might be derived from 12 β -hydroxycoccinic acid **8** by means of a carbocation intermediate followed by oxidation of **9** which would afford kadcotrine B & C. This proposed biosynthetic pathway motivated us to design a practical and efficient route to synthesize these rearranged lanostane frameworks since the carbocation intermediate **8a** is likely to undergo a C13–C14 bond migration from the C13 to C12 position to afford **8b** (Scheme 1A).^{7ef} Further, we have proposed and experimentally validated a combined biosynthetic analysis (Scheme 1B) for kadcotrine C and kadcoccitane H, highlighting a 6/6/5/6-fused tetracyclic ring system, likely originating from lanosterol (**10**). It was envisioned that regioselective olefin transposition would occur from C8–C9 to C9–C11 positions, followed by enzymatic oxidation to form 12 β -hydroxycoccinic acid **8**. The alcohol group in **8** could facilitate a Wagner–Meerwein type rearrangement, leading to the formation of diene **9** via carbocation intermediate **8b**. Thereafter, further oxidation of **9** could yield kadcoccitane H (**6**). On the other hand, chemoselective oxidative cleavage of the C12–C13 double bond in **10** would generate kadcotrine C (**3**).

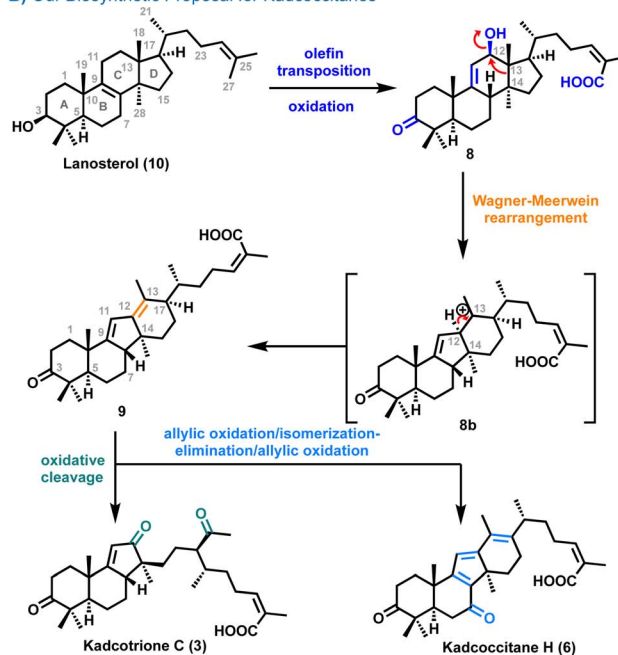
Although the total synthesis of the kadcoccinic acid A trimethyl ester was reported by Trost's group from the (+)-Wieland–Miescher ketone derivative, we chose a semisynthetic route to this *C-nor-D-homo* steroid substructure for the sake of brevity and efficiency. We presumed that the cationic rearrangement of 12 β -hydroxy steroids into their *C-nor-D-homo* counterparts⁸ was a much easier approach. Since 12 β -hydroxy steroids are rare and properly functionalized, one resembling the kadcoccitane ABCD skeleton was not available, so we envisioned the hydroxylation of commercially available steroids (e.g. lanosterol) at the C12 position by olefin transposition followed by allylic oxidation.

To experimentally validate the biosynthetic proposal, our synthesis commenced with the known acid⁹ **11** that was prepared from technical grade lanosterol (**8**) (ca. 50% pure) in two steps and 47% overall yield (Scheme 2). Acid **11** was converted to the corresponding methyl ester using K₂CO₃/MeI. Next, we focused on installing an olefin at the C9–C11 position by transposing the C8–C9 olefin, which could be used as a handle for the allylic oxidation to obtain kadcoccitane H. To our delight, exposure of the methyl ester to conditions described by Staliński and Paryzek¹⁰ (CrO₂Cl₂, CH₂Cl₂, –30 °C) led to $\Delta^{9(11)}$ -7-oxo **12** as the major product (60%, 95% brsm), with the desired configuration at C8. The high regio- and stereoselectivity of this transformation could be attributed to the specific scaffold of the $\Delta^{8(9)}$ -lanostane substrate. Direct

A) Proposed Biosynthetic Pathway by Sun and co-workers



B) Our Biosynthetic Proposal for Kadcoccitane

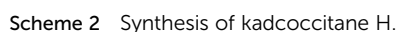


Scheme 1

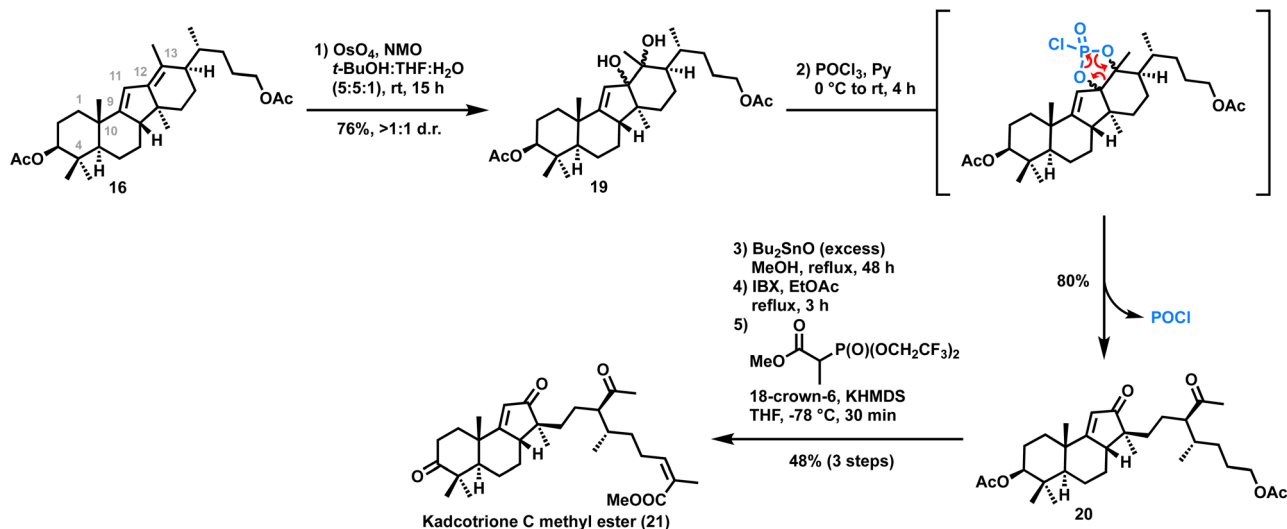
deoxygenation at C7 in **12** was unsuccessful; therefore, the 7-oxo derivative **12** was transformed into the corresponding xanthate through reduction with NaBH₄, followed by treatment of the resultant alcohol with CS₂ and MeI in the presence of DBU. Subsequent Barton–McCombie deoxygenation (AIBN/^tBu₃SnH) provided **13** (overall 75% in three steps).

With the well-defined tetracyclic core **13** in hand, we turned our attention to the key Wagner–Meerwein rearrangement. We initially attempted to introduce a hydroxyl group at the C12 position by allylic oxidation of **13** followed by ketone reduction





With the key tetracyclic diene **16** in hand, we embarked on the completion of the targets kadcoccitane E/H and kadcotriene C methyl ester. It was envisioned that selective allylic oxidation of the C13 methyl group would generate the fully functionalized core of kadcoccitane E; on the other hand, allylic oxidation of diene at the tertiary position (C8) would generate an allylic *tert*-alcohol which could be transformed to kadcoccitane H on



Scheme 3 Synthesis of kadcotrine C methyl ester.

further functional group manipulation. To our surprise, treatment of diene **16** with SeO_2/TBHP (for detailed screening of conditions, see the ESI †) directly generated $\alpha,\beta,\gamma,\delta,\epsilon,\zeta$ -unsaturated ketone **17** in 68% yield by a one-pot allylic oxidation/isomerization–elimination/allylic oxidation cascade (Scheme 2).¹² Next, to install the *Z*-olefinic acid side chain,¹³ diacetate in **17** was first hydrolyzed using $\text{K}_2\text{CO}_3/\text{MeOH}$ to the corresponding diol. IBX mediated oxidation of the diol followed by Still–Gennari olefination of the resultant keto–aldehyde yielded the desired *Z*-olefinic methyl ester **18** in 67% yield over three steps. Gratifyingly, hydrolysis of the methyl ester of **18** using lithium hydroxide afforded kadcoccitane **H** (**6**) in 81% yield. All analytical data (^1H NMR, ^{13}C NMR, HRMS, IR, and $[\alpha]_D^{20}$) of the synthesized **6** matched with the isolation report of the natural product.

On the other hand, synthesis of kadcotrine C methyl ester **22** was achieved by selective cleavage of the C12–C13 double bond of diene **16**. Thus, regioselective dihydroxylation of C12–C13 olefin **19** using NaIO_4 or $\text{Pb}(\text{OAc})_4$ was unsuccessful. Interestingly, while trying dehydration of one of the hydroxy groups in diol **19** using $\text{POCl}_3/\text{pyridine}$, we observed diol cleavage to afford the enone **20** in 80% yield which might be occurring *via* a 5-membered phosphorus(v) intermediate¹⁴ which eventually got cleaved, providing the tricyclic core skeleton of kadcotrine C. Although the reaction of a diol with POCl_3 to generate a 5-membered phosphorus(v) intermediate is reported in the literature,¹⁴ its cleavage to form a diketone has been observed for the first time. Next, the acetate groups of **20** were hydrolyzed. Thus, the treatment of **20** with $\text{K}_2\text{CO}_3/\text{MeOH}$ resulted in a 1:1 diastereomeric mixture, presumably due to epimerization of the acetyl group on the side chain of **20**. To address this issue, we employed dibutyltin oxide in MeOH, a mild *trans*-esterification reagent. Treatment of **20** with excess dibutyltin oxide followed by IBX mediated oxidation of the resultant diol provided the aldehyde. Still–Gennari olefination of the aldehyde afforded the desired *Z*-olefinic methyl ester of kadcotrine C **21** in 48% yield in three steps (Scheme 3).

Conclusion

In conclusion, we have developed a concise and efficient strategy for the syntheses of kadcoccitane **H** (17 steps, 6.8% overall yield) and kadcotrine C methyl ester (15 steps, 5.4% overall yield). These syntheses feature a regioselective olefin transposition, a biomimetic ring contraction/expansion, SeO_2 mediated one-pot allylic oxidation/isomerization–elimination/allylic oxidation cascade, chemoselective dihydroxylation of sterically hindered double bond, unusual POCl_3 mediated cleavage of diol and Still–Gennari olefination reaction. Our biomimetic approach highlights the power of steroidal skeletal rearrangements in efficiently synthesizing complex and biologically active natural products. Furthermore, additional manipulations of tetracyclic diene **16** could enable the synthesis of a broad range of natural and unnatural derivatives of kadcoccitanes. Work in this area is currently underway and will be reported in due course.

Data availability

The data supporting this article have been included as part of the ESI † . Crystallographic data for compound **16** have been deposited at the CCDC under 2404778 and can be obtained from https://www.ccdc.cam.ac.uk/data_request/cif.

Author contributions

D. H. D. directed the project and wrote the manuscript. S. A. S. and C. S. prepared the ESI † and wrote the manuscript.

Conflicts of interest

The authors declare no competing financial interest.



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Notes and references

- 1 Y. Yang, N. Hussain, L. Zhang, Y. Jia, Y. Jian, B. Li, M. Iqbal Choudhary, A. Rahman and W. Wang, *Chin. Herb. Med.*, 2020, **12**, 214–223.
- 2 C.-Q. Liang, Y.-M. Shi, X.-Y. Li, R.-H. Luo, Y. Li, Y.-T. Zheng, H.-B. Zhang, W.-L. Xiao and H.-D. Sun, *J. Nat. Prod.*, 2013, **76**, 2350–2354.
- 3 C.-Q. Liang, Y.-M. Shi, W.-G. Wang, Z.-X. Hu, Y. Li, Y.-T. Zheng, X.-N. Li, X. Du, J.-X. Pu, W.-L. Xiao, H.-B. Zhang and H.-D. Sun, *J. Nat. Prod.*, 2015, **78**, 2067–2073.
- 4 H.-C. Xu, K. Hu, H.-D. Sun and P.-T. Puno, *Nat. Prod. Bioprospect.*, 2019, **9**, 165–173.
- 5 Q.-Q. Zhang, K. Hu, H.-D. Sun and P.-T. Puno, *Nat. Prod. Bioprospect.*, 2023, **13**, 12.
- 6 B. M. Trost, G. Zhang, H. Gholami and D. Zell, *J. Am. Chem. Soc.*, 2021, **143**, 12286–12293.
- 7 (a) F. Noack, R. C. Heinze and P. Heretsch, *Syntheses*, 2019, **51**, 2039–2057; (b) L. Min, L. P. Zhong and C. C. Li, *Acc. Chem. Res.*, 2023, **56**, 2378–2390; (c) M. Alekseychuk and P. Heretsch, *Chem. Commun.*, 2023, **59**, 6811–6826; (d) Y. Wang and J. Gui, *Acc. Chem. Res.*, 2024, **57**, 568–579; For rearranged lanostane frameworks forming through a carbocation intermediate: (e) H. Mitsunashi, K. Shibata, T. Sato and Y. Shimizu, *Chem. Pharm. Bull.*, 1964, **12**, 1–5; (f) P. Heretsch, S. Rabe and A. Giannis, *J. Am. Chem. Soc.*, 2010, **132**, 9968–9969.
- 8 R. Hirschmann, C. S. Snoddy and N. L. Wendler, *J. Am. Chem. Soc.*, 1952, **74**, 2693–2694.
- 9 X. Chen, X. Shao, W. Li, X. Zhang and B. Yu, *Angew. Chem. Int. Ed.*, 2017, **56**, 7648–7652.
- 10 K. Staliński and Z. Paryzek, *Org. Prep. Proced. Int.*, 1994, **26**, 593–595.
- 11 (a) A. Srikrishna and D. H. Dethe, *Org. Lett.*, 2003, **5**, 2295–2298; (b) W. Liu, Z. Yu and N. Winssinger, *Org. Lett.*, 2021, **23**, 969–973.
- 12 (a) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, 1972, **94**, 7154–7155; (b) D. Arigoni, A. Vasella, K. B. Sharpless and H. P. Jensen, *J. Am. Chem. Soc.*, 1973, **95**, 7917–7919; (c) J. Młochowski and H. Wójtowicz-Młochowska, *Molecules*, 2015, **20**, 10205–10243; (d) S. E. Dibrell, M. R. Maser and S. E. Reisman, *J. Am. Chem. Soc.*, 2020, **142**, 6483–6487.
- 13 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405–4408.
- 14 (a) P. M. Cullis, M. J. P. Harger and M. Lee, *Angew. Chem.*, 2000, **112**, 4415–4417; (b) F. Wang, S. Pan, P. Zhang, H. Fan, Y. Chen and J. Yan, *Fibers Polym.*, 2018, **19**, 1057–1063; (c) F. Nasuhipur, Z. Ghasemi, M. Poupon and M. Dušek, *RSC Adv.*, 2023, **13**, 17812–17816.

