

Cite this: *Chem. Sci.*, 2023, 14, 5699

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 2nd February 2023

Accepted 1st May 2023

DOI: 10.1039/d3sc00582h

rsc.li/chemical-science

Enantioselective total syntheses of six natural and two proposed meroterpenoids from *Psoralea corylifolia*†

Xiao-Wei Chen,^a Zi-Chao Hou,^a Chi Chen,^a Ling-Hui Zhang,^a Meng-En Chen^a and Fu-Min Zhang[†]^{*,ab}

The first enantioselective total syntheses of six natural and two proposed meroterpenoids isolated from *Psoralea corylifolia* have been achieved in 7–9 steps from 2-methylcyclohexanone. The current synthetic approaches feature a high level of synthetic flexibility, stereodivergent fashion and short synthetic route, thereby providing a potential platform for the preparation of numerous this-type meroterpenoids and their *pseudo*-natural products.

Synthetic strategies play a central role in the total syntheses of natural products; therefore, numerous synthetic strategies have been developed, such as diversity-oriented synthesis, function-oriented synthesis, two-phase synthesis, convergent synthesis, modular synthesis, C–H bond functionalization, and so on.¹ Although considerable advances in these regards have been made, the pursuit of “ideal synthesis”² has been attracting attention from synthetic chemists to continually explore new synthetic strategies, including the innovative applications of existing synthetic methodologies.

The carbonyl group is one of the most fundamental functionalities in organic chemistry,³ either as a crucial scaffold in countless organic molecules or as a universal and valuable reactive linchpin in synthetic chemistries. Due to its polarized C=O bond and the resultant acidic proton at the α -position of the carbonyl and/or the activation of the β -position through the formation of enolization-related reactive species, carbonyl-based chemical conversions have been an essential topic in organic synthesis, spawning numerous venerable organic reactions, particularly at the *ipso*-, α -, and β -positions of the carbonyl group.⁴ These excellent achievements of carbonyl conversions serve as a great reservoir for designing and developing novel transformations in the total syntheses of natural products.⁵ To add “a drop water” in “the ocean” of carbonyl-based conversion synthetic strategies, in the current work we

pursued the collective total syntheses of natural meroterpenes using such a strategy.

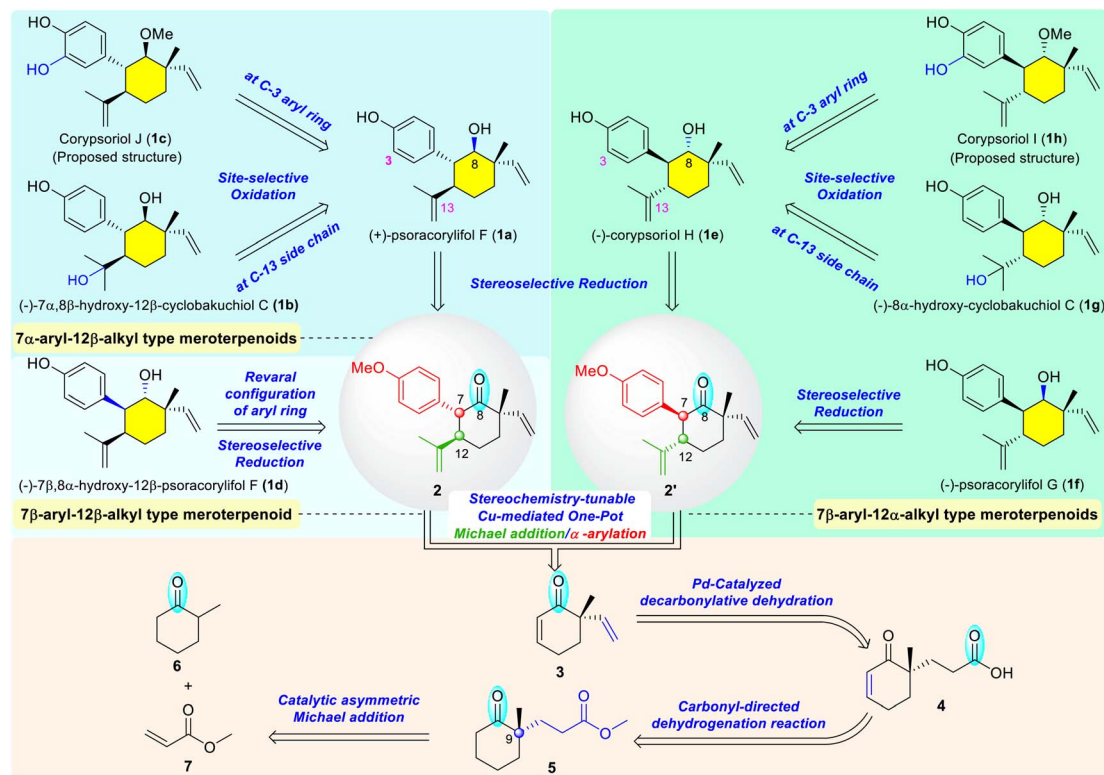
Meroterpenoids of the monoterpene phenol family were isolated from *Psoralea corylifolia*, a well-known medicinal plant that has been widely used for the treatment of various diseases in China, India, and other countries.⁶ Some representative natural meroterpenes are shown in Scheme 1, including (+)-psoracorylifol F (**1a**),^{7a} (–)-7 α ,8 β -hydroxy-12 β -cyclobakuchiol C (**1b**),^{7c} corypsoriol J (**1c**),^{7b} (–)-7 β ,8 α -hydroxy-12 β -psoracorylifol F (**1d**),^{7c} (–)-corypsoriol H (**1e**),^{7b} (–)-psoracorylifol G (**1f**),^{7f} (–)-8 α -hydroxy-cyclobakuchiol C (**1g**),^{7c} corypsoriol I (**1h**),^{7b} and other analogues.⁷ Structurally, these meroterpenes possess a densely functionalized cyclohexane containing four contiguous chiral centers, with one of which being all-carbon stereocenter. Besides the distinct stereochemistry of the substituents at C-7, C-8, and C-12 positions, they also feature a diversity of oxidation states for the sidechain at C-12 position as well as the aryl ring at C-7 position. Therefore, they may serve as an ideal arsenal to interpret the magic of the stereodivergent synthesis.^{1a} To the best of our knowledge, the total syntheses of these meroterpenes bearing four contiguous stereogenic centers have not been achieved to date.⁸ Inspired by the unique structural features of the abovementioned meroterpenes and our research interest in carbonyl-related synthetic chemistry,⁹ we designed a carbonyl-based conversion synthetic strategy and anticipated that these target molecules could be collectively synthesized through sequential transformations directed by the carbonyl group of synthetic intermediates in each crucial step (Scheme 1). Guided by this strategy, we speculated that the structural simplification of all target meroterpenes **1a–1h** to the key common intermediate **2** or its diastereomer **2'** would be feasible. For the 7 α -aryl-12 β -alkyl series, the hydroxy group at the C-13 position of 7 α ,8 β -hydroxy-12 β -cyclobakuchiol C (**1b**) or the C-3 position of corypsoriol J (**1c**) would be introduced *via*

^aState Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China. E-mail: zhangfm@lzu.edu.cn

^bShanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China

† Electronic supplementary information (ESI) available. CCDC 2226749, 2226751, 2226753, 2226754, 2226756, 2226759 and 2226760. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc00582h>



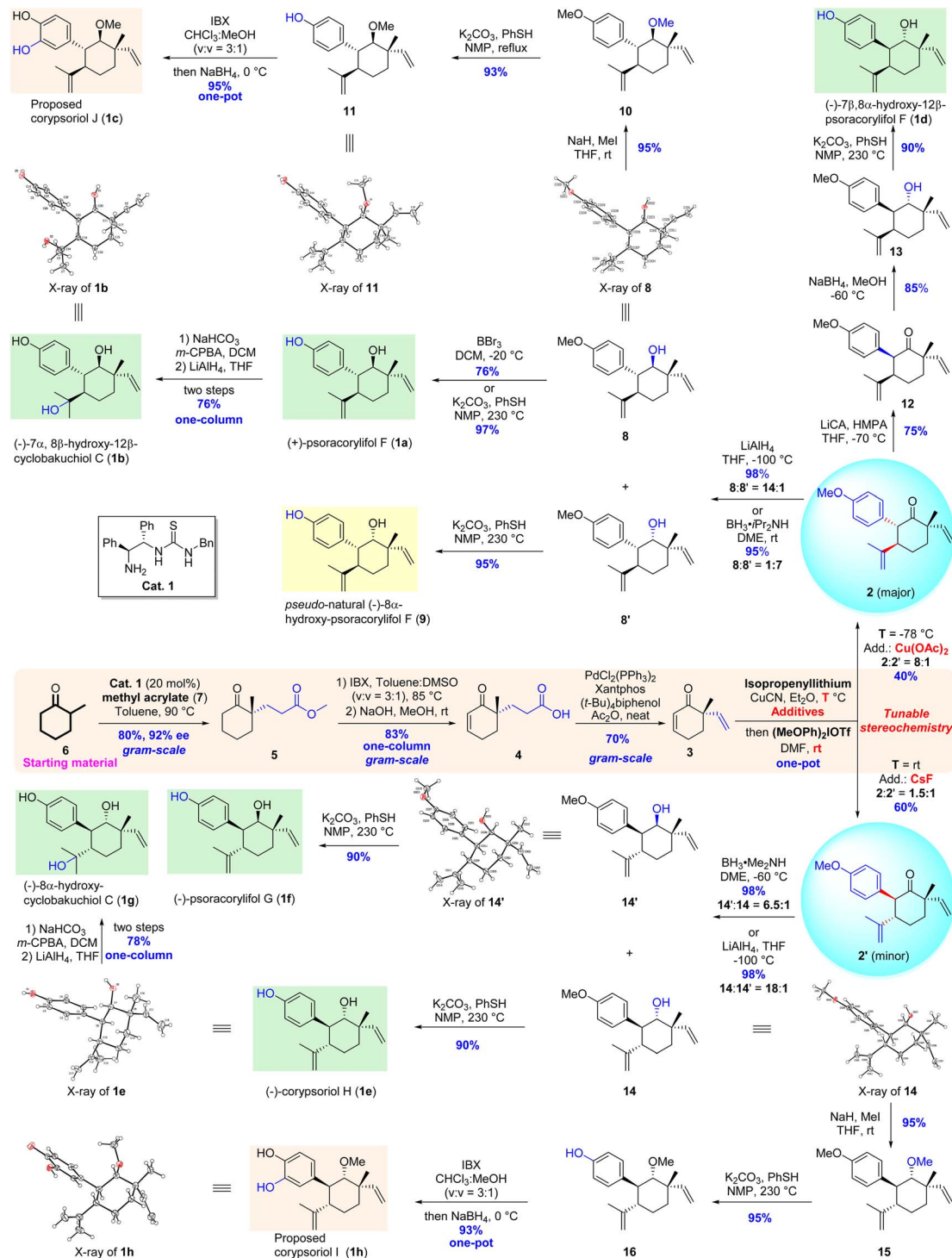


Scheme 1 The retrosynthetic analysis of meroterpenes using carbonyl-based conversions.

site-selective oxidation from psoracyrilifol F (**1a**) or its C-8 methylether (not shown), respectively. Psoracyrilifol F (**1a**), in turn, might be obtained *via* stereoselective reduction from the intermediate **2**. For 7 β -aryl-12 β -alkyl meroterpenes, such as 7 β ,8 α -hydroxy-12 β -psoracyrilifol F (**1d**), the stereochemistry of the aryl ring could be reversed through an *in situ* carbonyl-mediated enolization/protonation process from the intermediate **2**; the β -hydroxyl group at the C-8 position would be acquired by the subsequent stereoselective reduction of the carbonyl group. Comparably, the 7 β -aryl-12 α -alkyl series, such as corypsoriol H (**1e**), psoracyrilifol G (**1f**), 8 α -hydroxycyclobakuchiol C (**1g**), and corypsoriol I (**1h**), could be achieved as well *via* similar transformations employing compound **2**, a diastereomer of intermediate **2**, as the key precursor. The aryl ring at the C-7 position and transformable isopropenyl substituent at the C-12 position of the desired intermediates **2** and **2'** would be simultaneously assembled, in a stereochemistry-tunable fashion, using our developed Cu-mediated one-pot Michael addition/ α -arylation reaction from enone **3**.^{9a} Inspired by the excellent work of Stoltz,¹⁰ the vinyl group of enone **3** would be generated through the Pd-catalyzed decarbonylative dehydration of acid **4**. The conjugated double bond in the acid **4** would be introduced by the carbonyl-based regioselective dehydrogenation of the δ -keto ester **5**. The all-carbon quaternary center at the C-9 position of δ -keto ester **5** would be constructed by the catalytic asymmetric Michael addition of the enolate of 2-methylcyclohexanone **6** to methyl acrylate **7**.

Following our retrosynthetic considerations, we commenced our total synthesis with the installation of the quaternary stereogenic centers of the target molecules. Using a modification of the method described by Cheong and Carter,¹¹ an intermolecular Michael addition between commercially available 2-methylcyclohexanone (**6**) and methyl acrylate (**7**) catalyzed by a chiral thiourea catalyst (Cat. **1**) afforded the expected adduct **5** with excellent enantiomeric excess (92% ee) and yield (80%) (Scheme 2). The conjugated double bond was introduced *via* carbonyl-directed dehydrogenation.¹² Although the classical enolization and subsequent oxidation developed by Saegusa¹³ led to the desired desaturated enone **5'** (not shown, 65% yield),¹⁴ 1.0 equivalent amount of Pd(OAc)₂ was necessary to achieve the complete conversion of the starting material **5**. Hence, a one-step approach using a stoichiometric amount of 2-iodoxybenzoic acid (IBX) as an oxidant¹⁵ was examined. To our delight, δ -keto ester **5** was smoothly converted to the corresponding conjugated enone **5'** (86% yield), which was then hydrolyzed to release the acid **4** in 97% yield.¹⁴ To further improve the synthetic efficiency, a two-step/one-column protocol was applied, affording the acid **4** in 83% yield. Subsequently, the Pd-catalyzed decarbonylative dehydration conditions developed by Stoltz¹⁰ were employed to introduce a vinyl group at the C-9 position, and the expected enone **3** was smoothly obtained in 70% yield. After the introduction of a vinyl group at the quaternary carbon center on the cyclohexenone skeleton, we turned our attention to the assembly of vicinal difunctionalities of the precursors **2** and **2'** from enone **3**. Our





Scheme 2 Collective total syntheses of meroterpenes from *Psoralea corylifolia*.

developed Cu-mediated one-pot Michael addition/ α -arylation sequence was extensively investigated by varying the reaction temperature, the amount of the diaryliodonium salt, copper salts, additives, and reaction solvent.¹⁴ Under the optimal reaction conditions, the expected product **2** along with its isomer **2'** was isolated in good stereoselectivity (8:1 dr) with moderate yield (40%, two-steps in one-pot). At this stage, the expected functionalities, including three chiral centers and one

transformable carbonyl group, were efficiently assembled in the cyclohexane skeleton through five-step asymmetric transformations from two chemical feedstocks. With the key intermediate **2** in hand, we continued our efforts to achieve the collective total syntheses of representative target meroterpenes.

The oxidation state at the C-8 position of precursor **2** was adjusted by reduction with LiAlH_4 in tetrahydrofuran (THF) at -100°C to produce the major β -OH alcohol **8** and its minor



isomer **8'** with excellent levels of selectivity (14 : 1 dr) and yield (98%), while the selectivity was reversed (1 : 7 dr with 95% yield) using $\text{BH}_3 \cdot \text{iPr}_2\text{NH}$ as a reductant in 1,2-dimethoxyethane (DME) at room temperature. The structure of alcohol **8** was further confirmed by X-ray crystallographic analysis, in which the absolute configurations of the four stereogenic centers were unambiguously verified. Subsequently, the treatment of alcohol **8** with BBr_3 in CH_2Cl_2 removed the methyl ether at the aryl ring to afford (+)-psoracorylifol F (**1a**) in 76% yield, and an improved yield (97%) was observed when a combination of PhSH and K_2CO_3 in *N*-methylpyrrolidone (NMP) at 230 °C was applied.¹⁶ Pleasingly, the spectral data of **1a** were consistent with the reported literature.^{7a} Hence, the first total synthesis of (+)-psoracorylifols F was achieved in just 7 steps (Scheme 2). A similar deprotection of the methylether of the product **8'** yielded *pseudo*-natural (–)-8 α -hydroxy-psoracorylifol F (**9**).

The site-selective epoxidation of the disubstituted double bond of (+)-psoracorylifol F with *m*-chloroperoxybenzoic acid (*m*-CPBA) and the subsequent reduction of the resulting epoxide with LiAlH_4 produced natural (–)-7 α ,8 β -hydroxy-12 β -cyclobakuchiol C (**1b**) in 76% yield (two steps), and its structure was also confirmed by X-ray crystallographic analysis (Scheme 2).

To achieve the total synthesis of corypsoriol J (**1c**), alcohol **8** was treated with MeI to produce methylether **10** in 95% yield. The selective removal of methyl phenol ether was then examined, and the expected phenol **11** was obtained in excellent yield (93%) using the $\text{PhSH}/\text{K}_2\text{CO}_3/\text{NMP}$ reaction system.¹⁶ To install an OH group at the C-3 position of the aryl ring, a two-step one-pot transformation¹⁷ involving IBX-mediated oxidation and subsequent reduction of the resultant *ortho* diketone with NaBH_4 yielded the proposed corypsoriol J (**1c**) (95% yield) (Scheme 2). Unfortunately, the spectral data of synthetic corypsoriol J were not consistent with the reported ones of the natural product.^{7b} Efforts to obtain the X-ray crystallographic structures of the synthetic corypsoriol J and its three derivatives were not successful.¹⁴ However, subsequent synthetic endeavors further confirmed that the structure of the proposed corypsoriol J needs to be revised.

Due to 7 β ,8 α -hydroxy-12 β -psoracorylifol F (**1d**) featuring a *cis*-configuration of the aryl ring at the C-7 position and an alkyl substituent at the C-12 position, a one-pot protocol involving the enolization/protonation of the key precursor **2** was carried out to reverse the configuration of the aryl ring. The desired product **12** was obtained in 75% yield using lithium isopropylcyclohexylamide (LiCA) as a base in THF at –70 °C, along with a recovery of the precursor **2** (10% yield). The subsequent stereoselective reduction of the carbonyl group of compound **12** generated alcohol **13** as a single isomer (85% yield), without the isolation of another diastereoisomer. The demethylation of **13** completed the total synthesis of (–)-7 β ,8 α -hydroxy-12 β -psoracorylifol F (**1d**) in 90% yield, and its spectral data were consistent with those of the corresponding natural product^{7c} (Scheme 2).

Having accomplished the total syntheses of two natural 7 α -aryl-12 β -alkyl meroterpenoids, a proposed one, a *pseudo*-natural product, along with a 7 β -aryl-12 β -alkyl meroterpenoid, we focused on a third set of meroterpenoids, namely, 7 β -aryl-12 α -

alkyl substituted natural products **1e–1h** (Scheme 2), whose C-7 and C-12 stereocenters are reversal compared with the synthetic compounds **1a–1c**. Fortunately, these natural meroterpenoids possess the same configuration of the minor product **2'** obtained from the previous key one-pot Michael addition/ α -arylation reaction. Therefore, the tuning of the selectivity of the one-pot reaction is important. Various reaction conditions were again investigated to optimize the selectivity; the best results were obtained with an acceptable amount of product **2'** and its isomer **2** (ratio = 1 : 1.5, 60% combined yield for two steps).¹⁴ With the desired precursor **2'** in hand, chemical transformations similar to those for the syntheses of target molecules **1a–1c** were performed to complete the total syntheses of four 7 β -aryl-12 α -alkyl substituted meroterpenoids. The stereoselective reduction of the carbonyl group at the C-8 position with LiAlH_4 in THF at –100 °C provided two isomers **14** and **14'** with an excellent level (18 : 1 dr); in contrast, the treatment of **2'** with $\text{BH}_3 \cdot \text{Me}_2\text{NH}$ in DME at –60 °C resulted in reverse selectivity, affording isomers **14'** and **14** (6.5 : 1 dr). The demethylation of compounds **14** and **14'** yielded (–)-corypsoriol H (**1e**) and (–)-psoracorylifol G (**1f**), respectively. The site-selective epoxidation of (–)-corypsoriol H and subsequent reductive ring-opening of the resultant epoxide completed the total synthesis of (–)-8 α -hydroxy-cyclobakuchiol C (**1g**) in 78% yield (two steps). The spectroscopic data of these three synthesized natural products were fully consistent with those reported in the literature, respectively.^{7b,cf} Finally, using an approach similar to that for the proposed corypsoriol J, corypsoriol I (**1h**) was also synthesized in 4 steps with 66% overall yield from the precursor **2'**. Its chemical structure was unambiguously confirmed by X-ray crystallographic analysis. Unfortunately, the spectral data of synthetic corypsoriol I were also not consistent with the reported literature^{7b} (Scheme 2). Therefore, the chemical structures of natural corypsoriols I and J need to be reassigned.

In summary, the first enantioselective total syntheses of six meroterpenoids, *i.e.* (+)-psoracorylifol F, (–)-7 α , 8 β -hydroxy-12 β -cyclobakuchiol C, (–)-7 β , 8 α -hydroxy-12 β -psoracorylifol F, (–)-corypsoriol H, (–)-psoracorylifol G, and (–)-8 α -hydroxy-cyclobakuchiol C, and two proposed corypsoriols I and J, along with *pseudo*-natural (–)-8 α -hydroxy-psoracorylifol F, have been accomplished using a carbonyl-based conversion synthetic strategy to install all stereogenic centers and the corresponding functionalities. The key transformations include organocatalytic Michael addition to construct a quaternary carbon center, Nicolaou oxidation to yield an enone, Pd-catalyzed decarbonylative dehydration to introduce a vinyl group, one-pot Michael addition/ α -arylation to assemble two vicinal stereocenters, epimerization to reverse the configuration of the aryl group, and stereoselective reduction of ketone to acquire hydroxyl groups with different C-8 configurations. We envision that our stereodivergent synthetic route for the meroterpenoids reported here will facilitate further investigation of the biological activities of natural products, *pseudo*-natural ones, and their non-natural analogues. Further extension of this carbonyl-based conversion synthetic strategy for the total



syntheses of natural products is being carried out in our laboratory.

Data availability

The datasets and spectra supporting this article have been uploaded as part of the ESI material.† Crystallographic data for compounds **1b**, **1e**, **1h**, **8**, **11**, **14** and **14'** have been deposited in the Cambridge Crystallographic Data Center under accession numbers CCDC 2226760 (**1b**), CCDC 2226749 (**1e**), CCDC 2226751 (**1h**), CCDC 2226753 (**8**), CCDC 2226754 (**11**), CCDC 2226756 (**14**), and CCDC 2226759 (**14'**).†

Author contributions

F.-M. Z. designed the project and wrote the manuscript. X.-W. C., Z.-C. H., C. C., and L.-H. Z. performed all the experiments. X.-W. C. prepared the ESI.† L.-H. Z. and M.-E. C. prepared some starting material and part of the ESI.† All of the authors discussed the results.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the NSFC (No. 22278200, 21971095 and 91956203) for financially supporting this work.

Notes and references

- For recently selected books, reviews, and examples, see: (a) P.-Q. Huang, Z.-J. Yao and R. P. Hsung, *Efficiency in natural product total synthesis*, Wiley, Hoboken, 2018; (b) K. C. Nicolaou, S. Rigol and R. Yu, *CCS Chem.*, 2019, **1**, 3–37; (c) B. Mikulak-Klucznik, P. Gołębiewska, A. A. Bayly, O. Popik, T. Klucznik, S. Szymkuć, E. P. Gajewska, P. Dittwald, O. Staszewska-Krajewska, W. Beker, T. Badowski, K. A. Scheidt, K. Molga, J. Mlynarski, M. Mrksich and B. A. Grzybowski, *Nature*, 2020, **588**, 83–88; (d) P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Res.*, 2008, **41**, 40–49; (e) C. J. Gerry and S. L. Schreiber, *Curr. Opin. Chem. Biol.*, 2020, **56**, 1–9; (f) E. Lenci and A. Trabocchi, *Eur. J. Org. Chem.*, 2022, **2022**, e202200575; (g) R. Chen, Y. Shen, S. Yang and Y. Zhang, *Angew. Chem., Int. Ed.*, 2020, **59**, 14198–14210; (h) Y. Kanda, Y. Ishihara, N. C. Wilde and P. S. Baran, *J. Org. Chem.*, 2020, **85**, 10293–10320; (i) C. K. G. Gerlinger and T. Gaich, *Chem.–Eur. J.*, 2019, **25**, 10782–10791; (j) M. Elkin and T. R. Newhouse, *Chem. Soc. Rev.*, 2018, **47**, 7830–7844; (k) C. W. Coley, D. A. Thomas, J. A. M. Lummiss, J. N. Jaworski, C. P. Breen, V. Schultz, T. Hart, J. S. Fishman, L. Rogers, H. Gao, R. W. Hicklin, P. P. Plehiers, J. Byington, J. S. Piotti, W. H. Green, A. J. Hart, T. F. Jamison and K. F. Jensen, *Science*, 2019, **365**, eaax1566; (l) M. Sc. L. Koser, M. Sc. V. M. Lechner and T. Bach, *Angew. Chem., Int. Ed.*, 2021, **60**, 20269–20273; (m) F. Schneider, K. Samarin, S. Zanella and T. Gaich, *Science*, 2020, **367**, 676–681; (n) L. Li, Z. Chen, X. Zhang and Y. Jia, *Chem. Rev.*, 2018, **118**, 3752–3832; (o) R. Roddan, E. M. Carter, B. Thair and H. C. Hailes, *Nat. Prod. Rep.*, 2022, **39**, 1375–1382; (p) M. Munda, S. Niyogi, K. Shaw, S. Kundu, R. Nandia and A. Bisai, *Org. Biomol. Chem.*, 2022, **20**, 727–748; (q) S. P. Pitre and L. E. Overman, *Chem. Rev.*, 2022, **122**, 1717–1751; (r) O. Baudoin, *Angew. Chem., Int. Ed.*, 2020, **59**, 17798–17809; (s) H. Yan and F.-E. Chen, *Adv. Synth. Catal.*, 2022, **364**, 1934–1961; (t) L. Cai, I. B. Seiple and Q. Li, *Acc. Chem. Res.*, 2021, **54**, 1891–1908; (u) Y. Jiao and T. Luo, *Nat. Sci. Rev.*, 2022, nwac029; (v) Y. Zhang, A. A. Vinogradov, J. S. Chang, Y. Goto and H. Suga, *Org. Lett.*, 2022, **24**, 7894–7899; (w) J. Li, F. Chen and H. Renata, *J. Am. Chem. Soc.*, 2022, **144**, 19238–19242.
- For recently selected references, see: (a) R. Noyori, *Nat. Chem.*, 2009, **1**, 5–6; (b) P. A. Wender, *et al.*, *Organic synthesis: Theory and applications*, ed. T. Hudlicky, JAI Press, Greenwich, 1993, vol. 2, pp. 27–66; (c) J. B. Hendrickson, *J. Am. Chem. Soc.*, 1975, **97**, 5784–5800; (d) B. M. Trost, *Science*, 1991, **254**, 1471–1477; (e) N. Z. Burns, P. S. Baran and R. W. Hoffmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 2854–2867.
- For the selected book and reviews, see: (a) *Modern carbonyl chemistry*, ed. J. Otera, Wiley-VCH, Weinheim, 2000; (b) Y. Xue and G. Dong, *Acc. Chem. Res.*, 2022, **55**, 2341–2354; (c) D. J. Foley and H. Waldmann, *Chem. Soc. Rev.*, 2022, **51**, 4094–4120; (d) H.-M. Huang, P. Bellotti and F. Glorius, *Acc. Chem. Res.*, 2022, **55**, 1135–1147; (e) X.-J. Dai, C.-C. Li and C.-J. Li, *Chem. Soc. Rev.*, 2021, **50**, 10733–10742; (f) H. Albright, A. J. Davis, J. L. Gomez-Lopez, H. L. Vonesh, P. K. Quach, T. H. Lambert and C. S. Schindler, *Chem. Rev.*, 2021, **121**, 9359–9406; (g) Á. Péter, S. Agasti, O. Knowles, E. Pye and D. J. Procter, *Chem. Soc. Rev.*, 2021, **50**, 5349–5365; (h) S. Wang and B. König, *Angew. Chem., Int. Ed.*, 2021, **60**, 21624–21634; (i) Z. Yang, *Acc. Chem. Res.*, 2021, **54**, 556–568; (j) B. Delayre, Q. Wang and J. Zhu, *ACS Cent. Sci.*, 2021, **7**, 559–569.
- (a) P.-Q. Huang, *Organic named reactions, reagents and rules*, Chemical Industry Press, 2nd edn, Beijing, 2019; (b) L. L. Jack, *Named reactions*, Springer-Verlag Berlin Heidelberg, 2009; (c) L. Kürti and B. Czako, *Strategic applications of named reactions in organic synthesis: background and detailed mechanisms*, Elsevier Academic Press, San Diego, CA, 2005.
- For recently selected examples, see: (a) Z. Wu, X. Xu, J. Wang and G. Dong, *Science*, 2021, **374**, 734–740; (b) J. Xie, X. Liu, N. Zhang, S. Choi and G. Dong, *J. Am. Chem. Soc.*, 2021, **143**, 19311–19316; (c) Z. Wu and G. Dong, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201239; (d) S. Jin, X. Zhao and D. Ma, *J. Am. Chem. Soc.*, 2022, **144**, 15355–15362; (e) G. Sennari, K. E. Gardner, S. Wiesler, M. Haider, A. Eggert and R. Sarpong, *J. Am. Chem. Soc.*, 2022, **144**, 19173–19185; (f) W. M. Amberg and E. M. Carreira, *J. Am. Chem. Soc.*, 2022, **144**, 15475–15479; (g) T. Ma, H. Cheng, M. Pitchakuntla, W. Ma and Y. Jia, *J. Am. Chem. Soc.*, 2022,



- 144, 20196–20200; (h) B. Yang, J. Dai, Y. Luo, K. K. Lau, Y. Lan, Z. Shao and Y. Zhao, *J. Am. Chem. Soc.*, 2021, **143**, 4179–4186; (i) Z. Xin, H. Wang, H. He, X. Zhao and S. Gao, *Angew. Chem., Int. Ed.*, 2021, **60**, 12807–12812; (j) P. Yang, Y.-Y. Li, H. Tian, G.-L. Qian, Y. Wang, X. Hong and J. Gui, *J. Am. Chem. Soc.*, 2022, **144**, 17769–17775; (k) Y. Zhao, J. Hu, R. Chen, F. Xiong, H. Xie and H. Ding, *J. Am. Chem. Soc.*, 2022, **144**, 2495–2500; (l) Y.-J. Hu, C.-C. Gu, X.-F. Wang, L. Min and C.-C. Li, *J. Am. Chem. Soc.*, 2021, **143**, 17862–17870; (m) R. Andres, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201788.
- 6 For the recently selected reviews, see: (a) B. Z. Amirzakariya and A. Shakeri, *Phytochemistry*, 2022, **197**, 113130–113166; (b) N. Mahajan, B. Koul, P. Gupta, B. A. Shahd and J. Singh, *S. Afr. J. Bot.*, 2022, **149**, 963–993; (c) F. Alam, G. N. Khan and M. H. H. B. Asad, *Phytother. Res.*, 2018, **32**, 597–615; (d) X. Zhang, W. Zhao, Y. Wang, J. Lu and X. Chen, *Am. J. Chin. Med.*, 2016, **44**, 35–60; (e) L. Chen, S. Chen, P. Sun, X. Liu, Z. Zhan and J. Wang, *Chin. Med.*, 2023, **18**, 4; (f) A. R. Kangane, N. V. Gawali and S. D. Lokhande, *World J. Pharm. Sci.*, 2023, **12**, 1486–1498.
- 7 (a) G. Xiao, X. Li, T. Wu, Z. Cheng, Q. Tang and T. Zhang, *Fitoterapia*, 2012, **83**, 1553–1557; (b) Q.-X. Xu, W. Xu and X.-W. Yang, *Tetrahedron*, 2020, **76**, 131343–131348; (c) M. X. Xiu, Y. M. Zhao, Y. Zhang, D. X. Xiong, D. Wang, H. S. Lee and L. Cui, *Fitoterapia*, 2021, **151**, 104881–104885; (d) H.-T.-Y. Gao, G.-Z. Lang, Y.-D. Zang, J. Ma, J.-Z. Yang, F. Ye, J.-Y. Tian, P.-P. Gao, C.-J. Li and D.-M. Zhang, *Bioorg. Chem.*, 2021, **112**, 104924–104936; (e) Q. Xu, Q. Lv, L. Liu, Y. Zhang and X. Yang, *Chin. Med.*, 2021, **16**, 98–112; (f) X.-W. Yang, Q. Lü, Q.-X. Xu, W. Xu and Y.-T. Zhang, *Chin. Tradit. Herb. Drugs*, 2022, **53**, 3269–3277.
- 8 Two relative skeleton rearrangement natural products have been synthesized by Tong and coworkers, see: (a) J. Ren, Y. Liu, L. Song and R. Tong, *Org. Lett.*, 2014, **16**, 2986–2989; for the total syntheses of three relative natural products bearing three stereocentres, see: (b) H. Kawashima, Y. Kaneko, M. Sakai and Y. Kobayashi, *Chem.–Eur. J.*, 2014, **20**, 272–278; (c) H. Kawashima, M. Sakai, Y. Kaneko and Y. Kobayashi, *Tetrahedron*, 2015, **71**, 2387–2392; (d) V. Maurya and C. Appayee, *Org. Lett.*, 2018, **20**, 4111–4115; (e) M. Shoji, T. Esumi, N. Tanaka, M. Takeuchi, S. Yamaji, M. Watanabe, E. Takahashi, H. Kido, M. Yamamoto and T. Kuzuhara, *PLoS One*, 2021, **16**, e0248960.
- 9 (a) J.-L. Pan, T. Chen, Z.-Q. Zhang, Y.-F. Li, X.-M. Zhang and F.-M. Zhang, *Chem. Commun.*, 2016, **52**, 2382–2385; (b) T. Chen, Y.-F. Li and F.-M. Zhang, *Org. Lett.*, 2016, **18**, 4754–4757; (c) T. Chen, R. Peng, W. Hu and F.-M. Zhang, *Org. Biomol. Chem.*, 2016, **14**, 9859–9867; (d) Z.-Q. Zhang, T. Chen and F.-M. Zhang, *Org. Lett.*, 2017, **19**, 1124–1127; (e) S.-Z. Tang, W. Zhao, T. Chen, Y. Liu, X.-M. Zhang and F.-M. Zhang, *Adv. Synth. Catal.*, 2017, **359**, 4177–4183; (f) S.-Z. Tang, H.-L. Bian, Z.-S. Zhan, M.-E. Chen, J.-W. Lv, S. Xie and F.-M. Zhang, *Chem. Commun.*, 2018, **54**, 12377–12380; (g) Y. An, X.-M. Zhang, Z.-Y. Li, W.-H. Xiong, R.-D. Yu and F.-M. Zhang, *Chem. Commun.*, 2019, **55**, 119–122; (h) Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *Nat. Commun.*, 2019, **10**, 2507–2514; (i) Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *J. Org. Chem.*, 2019, **84**, 12664–12671; (j) H.-L. Bian, S.-Z. Tang, M.-E. Chen, X.-M. Zhang, J.-W. Lv, X.-W. Chen, F.-M. Qi, S.-W. Chen and F.-M. Zhang, *Org. Lett.*, 2020, **22**, 5314–5317; (k) S. Xie, Z.-J. He, L.-H. Zhang, B.-L. Huang, X.-W. Chen, Z.-S. Zhan and F.-M. Zhang, *Chem. Commun.*, 2021, **57**, 2069–2072; (l) X. Han, L.-X. Shan, J.-X. Zhu, C.-S. Zhang, X.-M. Zhang, F.-M. Zhang, H. Wang, Y.-Q. Tu, M. Yang and W.-S. Zhang, *Angew. Chem., Int. Ed.*, 2021, **60**, 22688–22692; (m) J.-S. Yang, K. Lu, C.-X. Li, Z.-H. Zhao, X.-M. Zhang, F.-M. Zhang and Y.-Q. Tu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202114129; (n) M.-E. Chen, S.-Z. Tang, Y.-H. Hu, Q.-T. Li, Z.-Y. Gan, J.-W. Lv and F.-M. Zhang, *CCS Chem.*, 2022, **4**, 3378–3390; (o) M.-E. Chen, Z.-Y. Gan, Y.-H. Hu and F.-M. Zhang, *J. Org. Chem.*, 2023, **88**, 3954–3964.
- 10 Y. Liu, S. C. Virgil, R. H. Grubbs and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2015, **54**, 11800–11803.
- 11 (a) J. Y. Kang and R. G. Carter, *Org. Lett.*, 2012, **14**, 3178–3181; (b) J. Y. Kang, R. C. Johnston, K. M. Snyder, P. H.-Y. Cheong and R. G. Carter, *J. Org. Chem.*, 2016, **81**, 3629–3637.
- 12 For the recently selected reviews, see: (a) S. Gnaim, J. C. Vantourout, F. Serpier, P.-G. Echeverria and P. S. Baran, *ACS Catal.*, 2021, **11**, 883–892; (b) T. Hirao, *J. Org. Chem.*, 2019, **84**, 1687–1692.
- 13 Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011–1013.
- 14 For the details, please see the ESI.†
- 15 (a) K. C. Nicolaou, Y. L. Zhong and P. S. Baran, *J. Am. Chem. Soc.*, 2000, **122**, 7596–7597; (b) K. C. Nicolaou, T. Montagnon, P. S. Baran and Y.-L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2245–2258.
- 16 L. Sharma, M. K. Nayak and A. K. Chakraborti, *Tetrahedron*, 1999, **55**, 9595–9600.
- 17 (a) A. Pezzella, L. Lista, A. Napolitano and M. ĩschia, *Tetrahedron Lett.*, 2005, **46**, 3541–3544; (b) M. L. N3voa, F. J. Salazara, C. G3mez, A. Y. Angarita, E. Tropper, N. Canudas and J. E. Villamizar, *Nat. Prod. Commun.*, 2014, **9**, 355–358.

