



 Cite this: *RSC Adv.*, 2024, **14**, 21102

 Received 16th April 2024
 Accepted 18th June 2024

DOI: 10.1039/d4ra02821j

rsc.li/rsc-advances

A concise and stereoselective synthesis of the BCDF tetracyclic ring system of C₁₉-diterpenoid alkaloids†

 Fangzhou Yu and Liang Xu *

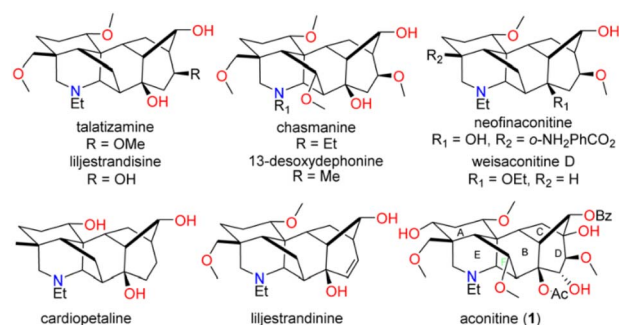
A new synthetic route for the BCDF tetracyclic ring system of C₁₉-diterpenoid alkaloids (C₁₉-DTAs) has been developed. The key step is a Pd-catalyzed transannular alkenylation that installs a functionalized bridged F ring. The overall strategy is concise and stereoselective, and it provides a valuable new tool for the synthesis of C₁₉-DTAs. The synthesis begins with a bridged [3.2.1] ring system, which is converted to a key intermediate through a series of highly regio- and stereoselective processes. The introduction of an allylic side chain with high precision is accomplished, culminating in a Pd-catalyzed transannular alkenylation that installs a functionalized bridged F ring to yield the BCDF tetracyclic analog of C₁₉-DTAs.

Introduction

Aconitine (**1**), first isolated by Manske in 1833 and its structure elucidated in 1959,^{1,2} is a prototypical C₁₉ diterpenoid alkaloid (C₁₉-DTAs). It is the major toxic component of over 250 species of *Aconitum* plants, commonly referred as monkshood or wolf's bane, which have long been used in traditional medicine.³ Aconitine's primary mode of action involves potent activation of sodium ion channels, preventing repolarization of muscles and neurons. As a result, it can induce ventricular arrhythmias, potentially leading to death.³ While aconitine's high toxicity has limited its clinical use, less toxic analogs and derivatives are emerging as promising candidates for the treatment of pain, inflammation, or arrhythmias.⁴ They share a common hexacyclic ring system (ABCDEF ring) and typically possess three to nine oxygen substituents such as hydroxy, methoxy, and acyloxy groups (Fig. 1). Their intricate structures and diverse biological activities have attracted considerable attention from synthetic chemists over the past five decades.⁵ As pioneers in the field, Wiesner *et al.* developed four generations of fundamental synthetic strategies for the practical synthesis of talatisamine, chasmanine, and 13-desoxydelphosphine in the 1970s.⁶ In the last decade, research groups led by Gin,⁷ Sarpong,⁸ Fukuyama,⁹ Inoue¹⁰ and Reisman¹¹ have made significant contributions, culminating in the elegant total syntheses of weisaconitine D, liljestrandinine, cardiopetaline, talatisamine and puberuline C.

Recently, Qin and co-workers reported an ingenious total synthesis of vilmoraconitine by using an efficient hydrodealkenylative fragmentation/Mannich strategy.¹² While other synthetic efforts exist,¹³ these remain the only eight natural C₁₉ (C₁₈) DTAs with successful total syntheses to date. Notably, all synthesized C₁₉-DTAs or C₁₈-DTAs possess only three to six oxygen functionalities. The total synthesis of C₁₉-DTAs with a more oxygenated ring system, such as aconitine (**1**) with its unprecedented nine oxygen functionalities, remains a significant challenge.

Due to our long-standing research interest in the chemistry of C₁₉-DTAs, we embarked on synthetic studies of aconitine and other bioactive C₁₉-DTAs. In previous synthetic efforts, we have constructed several important ring systems, such as the AEF, ABEF, ABF, BCD and BCDE rings of C₁₉-DTAs.¹⁴ In particular, we have previously utilized a cascade oxidative dearomatization/dimerization/retro-DA/IMDA reaction and the Wagner–Meerwein rearrangement as key steps to successfully construct the tricyclic [6.2.1.0] carbocyclic BCD ring analog, providing


 Fig. 1 Structures of C₁₈- or C₁₉-diterpenoid alkaloids.

Key Laboratory of Drug Targeting and Drug Delivery Systems of the Ministry of Education, West China School of Pharmacy, Sichuan University, Chengdu 610041, P. R. China. E-mail: liangxu@scu.edu.cn

† Electronic supplementary information (ESI) available: Copies of ¹H and ¹³C NMR spectra for all new compounds. CCDC 2362943. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ra02821j>



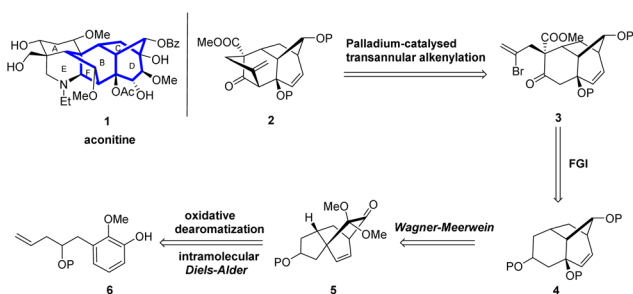
a potential approach for the construction of the bridged A, E, and F rings in aconitine.

However, the stereoselectivity for the preparation of the key rearrangement precursor was still undesirable and needed further improvement. Herein, we report further synthetic studies on the highly functionalized BCD ring analog **4** *via* an improved synthetic route that further introduced a functionalized bridged F ring *via* a Pd-catalyzed transannular alkenylation reaction to successfully afford the tetracyclic BCDF ring compound **2**, which is an important model substrate intermediate for the total synthesis of aconitine.

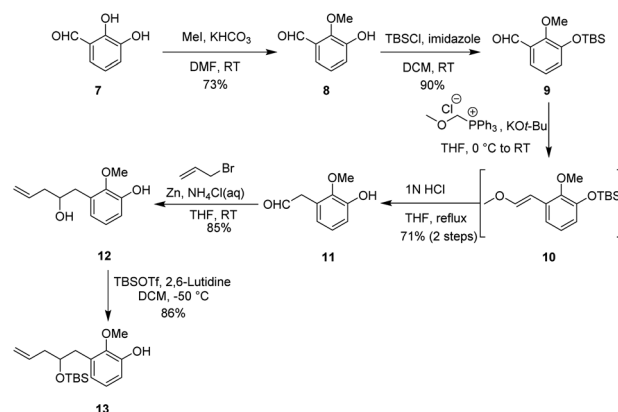
We envisioned the synthesis of the tetracyclic aconitine BCDF ring analog **2** (Scheme 1). Initially, compound **3**, featuring a [3.2.1] bridged ring structure, could be transformed from compound **2** through a transannular alkenylation reaction.¹⁵ Compound **2** could be obtained from ketone **4** *via* regioselective acylation and stereoselective alkylation reactions. Ketone **4**, in turn, could be derived from the 5/6/6 tricyclic ketone **5** *via* a Wagner–Meerwein rearrangement.¹⁶ Finally, compound **5** could be synthesized in a single step through an intramolecular oxidative dearomatization/IMDA cascade reaction of phenol **6** with a dienophile side chain. Although we have previously synthesized analogous tricyclic compounds to **4**, developing a rapid, highly stereoselective, and gram-scalable method for the synthesis of the BCD tricyclic compound **4** is still necessary to further expand our synthetic work.

Results and discussion

Our synthetic studies began with the preparation of vinyl arene **13** as shown in Scheme 2. First, commercially available 2,3-dihydroxybenzaldehyde **7** was converted on a 10 gram scale to 3-hydroxy-2-methoxybenzaldehyde **8** *via* a known regioselective phenolic hydroxyl–methylation reaction.¹⁷ Compound **8** was then converted to the TBS phenol ether **9** under standard conditions. Next, the Wittig reaction of compound **9** with a phosphonium salt generated the enol ether intermediate **10**, which was subsequently subjected to *in situ* acid-promoted hydrolysis, affording the one-carbon homologated aldehyde **11** with an overall yield of 71% across two steps.¹⁸ Finally, aldehyde **11** was subjected to a Barbier allylation reaction¹⁹ with allyl bromide in the presence of Zn/NH₄Cl to introduce the terminal olefin side chain, yielding highly functionalized phenol **12**.



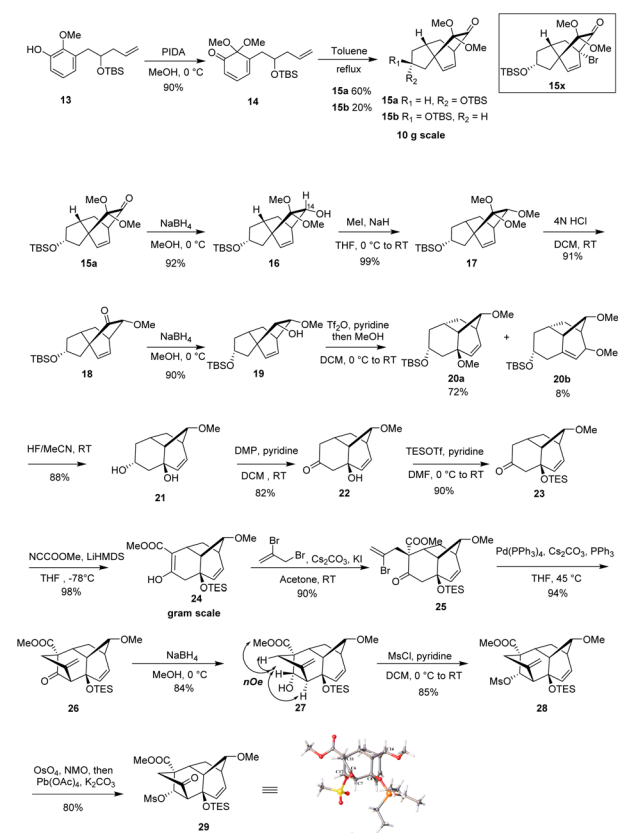
Scheme 1 Synthetic plan for the BCDF ring system 2.



Scheme 2 Synthesis of vinyl arene **13**.

Selective protection of the resulting homoallylic alcohol with TBS then afforded phenol **13**.

After successfully obtaining vinyl phenol **13**, we proceeded with the oxidative dearomatization/intramolecular Diels–Alder reaction (IMDA) and the subsequent planned Wagner–Meerwein rearrangement (Scheme 3). Fortunately, phenol **13** with bis(acetoxy)iodobenzene (PIDA) under standard oxidative conditions, uniquely produced the relatively stable *o*-quinone monoacetal **14** at 0 °C in methanol and, notably, the typically observed *o*-quinone monoacetal dimerization at room



Scheme 3 Synthesis of BCDF analogue **29**.

temperature²⁰ did not occur. Rapid column chromatographic purification of compound **14**, followed by reflux in toluene, easily afforded a separable mixture of *endo* diastereoisomers **15a** and **15b**, with a small amount of the undesired *exo* addition product (15%),²¹ achieving the expected *endo* stereoselectivity with a combined yield of 72% for the two steps. The α -stereochemistry of the OTBS substituent was determined in **15a** by observing the NOE correlation between the vinyl proton signal ($\delta = 6.24$, m) and the *tert*-butyl proton signal ($\delta = 0.88$, s) of the OTBS substituent. Notably, **15a** or **15b** showed a resemblance in the position of the carbonyl and acetal substituents adjacent to the [2.2.2] bicyclooctane bridge portion with our previously synthesized tricyclic analog **15x**,¹⁴ which could potentially enhance the stereoselectivity of the key Wagner–Meerwein rearrangement precursor. It was encouraging to find that the ketone carbonyl reduction of **15a** proceeded exclusively from the more hindered β -face. This selectivity may have been influenced by the potential torsional steering effect of the neighboring *gem*-dimethoxy group.⁸ By using sodium borohydride (NaBH₄) for the attack from the more crowded β -face, we were able to synthesize compound **16** with high stereoselectivity. Subsequent treatment with sodium hydride (NaH) and iodomethane (MeI) converted the newly formed methylene hydroxy group into the methoxy ether compound **17**, achieving a 99% yield. After removal of the dimethyl ketal functional group under acidic conditions to give the ketone **18**, a stereoselective reduction with NaBH₄ occurred from the β -side again (due to the steric hindrance of the α -side OMe substituent), leading to the formation of alcohol **19** with the hydroxy group oriented to the α -position in a combined yield of 82% in two steps. Subsequently, by activating **19** with trifluoromethanesulfonic anhydride (Tf₂O) in DCM and using methanol as nucleophile, the key Wagner–Meerwein rearrangement was performed in a one-pot manner without the need to isolate the potential intermediate triflate, directly yielded the allyl methyl ether isomers **20a** and **20b** in yields of 72% and 8%, respectively.²² We attribute the predominance of **20a** as the major product to the absence of a strained bridgehead double bond. In contrast, **20b** has a strained bridgehead olefin, making its formation less favored. When water is used instead of methanol to trap the allyl carbocation, the C8-hydroxy substituted rearranged product is generated, along with a small amount of the allyl isomer, although in lower yield.

After successfully synthesizing bicyclo [3.2.1] octane vinyl ether isomers **20a** and **20b**, we investigated their further transformation into the BCDF tetracyclic target molecule. Treatment of a mixture of **20a** and **20b** with 40% aqueous HF resulted in both TBS deprotection and removal of the allylic methyl ether, forming the diol **21**. This demonstrates that the vinyl isomer **20b** can also generate the same allylic alcohol under acidic conditions, probably due to the formation of a more stable allylic tertiary carbocation. The addition of the hydroxy group is controlled by the relative stability of the olefin isomers. Subsequent oxidation of the C-17 secondary alcohol in **21** with Dess–Martin periodinane (DMP) afforded the alcohol–ketone **22**. After TES protection of the exposed C-8 tertiary alcohol, deprotonation of ketone **23** with lithium hexamethyldisilazane

(LiHMDS) and subsequent introduction of a methoxycarbonyl group using Mander's reagent²³ (methyl cyanofornate) afforded enol ester **24** in high regioselectivity (98% yield) due to the steric hindrance caused by the OTES group at the adjacent C-7 position. C-Alkylation of enol ester **24** at C-11 with 2,3-dibromopropene to introduce the F ring side chain initially yielded significant O-alkylation by-products. However, the addition of KI as an additive²⁴ facilitated the regioselective formation of the C-alkylated product **25** in 90% yield. Based on HSAB²⁵ theory, this improved regioselectivity is attributed to the *in situ* replacement of the allyl bromide atom with a more nucleophilic iodide ion, forming a softer allyl iodine intermediate that preferentially reacts with the carbon nucleophile. Although the stereochemistry of the newly installed allylic side chain was initially unclear, subsequent experiments revealed an 11 β configuration, likely due to the greater accessibility of the *exo* face of the ester enolate intermediate. Transannular alkenylation²⁶ with Pd(PPh₃)₄ efficiently completed the F ring construction, affording the BCDF tetracyclic product **26**. Initially, low yields were observed, we speculated this may be attributed to the degradation of catalyst Pd(PPh₃)₄ during the reaction. Adding PPh₃ ligand to the reaction inhibited ligand dissociation from the Pd(0) center, ultimately leading to a successful 94% yield under milder conditions. Finally, reduction of the C-17 ketone in **26** with NaBH₄ provided the β -hydroxy compound **27** in a highly stereoselective manner. NOE experiments on **27** confirmed the 11 β configuration of the allyl side chain, as evidenced by the spatial correlations between the C-17 hydroxy methine protons and both the C-5 methylene and ester methoxy methylene protons. The whole stereochemical structure of **27** was further unambiguously established on the basis of the X-ray crystallography analysis of its ketone derivative **29**, which was prepared by sequential sulfonylation of hydroxyl group to give **28** and oxidative cleavage of the exocyclic olefin by treatment with osmium tetroxide/NMO followed by lead tetraacetate.

Conclusions

In summary, we have developed an efficient synthetic route that, for the first time, assembles the tetracyclic BCDF ring analog of C₁₉-DTAs in 14 steps with an overall yield of 10.8%. This synthetic route is based on the preparation of the gram-scale tricyclic BCD compound **24**, with key steps including the highly stereoselective reduction of the ketone intermediate **15a**, followed by a Wagner–Meerwein rearrangement, then introduce an allylic side chain with high regioselectivity and stereoselectivity. Finally, a Pd-catalyzed transannular alkenylation was used to further introduce a functionalized bridged F-ring, efficiently providing the BCDF tetracyclic analog of C₁₉-DTAs. Further experiments are in progress.

Data availability

The data supporting this article have been included as part of the ESI. Crystallographic data for compound **29** has been

deposited at the CCDC under [accession number 2362943] and can be obtained from <https://deposit.ccdc.cam.ac.uk/>.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support for this work was provided by the National Natural Science Foundation of China (Grant Numbers 21472129 and 21272163).

Notes and references

- 1 M. Przybylska and L. Marion, *Can. J. Chem.*, 1959, **37**, 1116; K. Wiesner, D. L. Simmons and L. R. Fowler, *Tetrahedron Lett.*, 1959, **18**, 1.
- 2 F. P. Wang and Q. H. Chen, *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, 2010, p. 1.
- 3 Y. Fujita, K. Terui, M. Fujita, A. Kakizaki, N. Sato, K. Oikawa, H. Aoki, K. Takahashi and S. Endo, *J. Anal. Toxicol.*, 2007, **31**, 132.
- 4 A. Ameri, *Prog. Neurobiol.*, 1998, **56**, 211; M. Stevens, S. Peigneur and J. Tytgat, *Front. Pharmacol.*, 2011, **2**, 71; B. Borcsa, L. Fodor, D. Csupor, P. Forgo, A. t. Molnar and J. Hohmann, *Planta Med.*, 2014, **80**, 231.
- 5 M. Brimble, K. Goodall and D. Barker, *Synlett*, 2005, **2005**, 1809; A. M. Hamlin, J. K. Kisunzu and R. Sarpong, *Org. Biomol. Chem.*, 2014, **12**, 1846; B. Liu, G. Zhu and R. Liu, *Synthesis*, 2015, **47**, 2691; X. Y. Liu and Y. Qin, *Synlett*, 2015, **4**, 1010.
- 6 K. Wiesner, T. Tsai, K. Huber, S. Bolton and R. Vlahov, *J. Am. Chem. Soc.*, 1974, **96**, 4990; K. Wiesner, *Pure Appl. Chem.*, 1975, **41**, 93; S.-F. Lee, G. M. Sathe, W. W. Sy, P.-T. Ho and K. Wiesner, *Can. J. Chem.*, 1976, **54**, 1039; K. Wiesner, T. Y. Tsai and K. P. Nambiar, *Can. J. Chem.*, 1978, **56**, 1451; K. Wiesner, *Pure Appl. Chem.*, 1979, **51**, 689.
- 7 Y. Shi, J. T. Wilmot, L. U. Nordstrom, D. S. Tan and D. Y. Gin, *J. Am. Chem. Soc.*, 2013, **135**, 14313.
- 8 C. J. Marth, G. M. Gallego, J. C. Lee, T. P. Lebold, S. Kulyk, K. G. Kou, J. Qin, R. Lilien and R. Sarpong, *Nature*, 2015, **528**, 493; K. G. M. Kou, S. Kulyk, C. J. Marth, J. C. Lee, N. A. Doering, B. X. Li, G. M. Gallego, T. P. Lebold and R. Sarpong, *J. Am. Chem. Soc.*, 2017, **139**, 13882.
- 9 Y. Nishiyama, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2016, **18**, 2359; Y. Nishiyama, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2017, **19**, 5833.
- 10 K. Hagiwara, T. Tabuchi, D. Urabe and M. Inoue, *Chem. Sci.*, 2016, **7**, 4372; D. Kamakura, H. Todoroki, D. Urabe, K. Hagiwara and M. Inoue, *Angew. Chem., Int. Ed.*, 2020, **59**, 479; T. Shimakawa, S. Nakamura, H. Asai, K. Hagiwara and M. Inoue, *J. Am. Chem. Soc.*, 2023, **145**(1), 600–609.
- 11 A. R. Wong, N. J. Fastuca, V. W. Mak, J. K. Kerkovius, S. M. Stevenson and S. E. Reisman, *ACS Cent. Sci.*, 2021, **7**, 1311.
- 12 J. Ji, J. Chen, S. Qin, W. Li, J. Zhao, G. Li, H. Song, X. Y. Liu and Y. Qin, *J. Am. Chem. Soc.*, 2023, **145**, 3903.
- 13 R. M. Conrad and J. D. B. RM Conrad, *Org. Lett.*, 2007, **9**, 5465; Z.-K. Yang, Q.-H. Chen and F.-P. Wang, *Tetrahedron Lett.*, 2011, **67**, 4192; K. J. Goodall, M. A. Brimble and D. Barker, *Tetrahedron Lett.*, 2012, **68**, 5759; T. Tabuchi, D. Urabe and M. Inoue, *J. Org. Chem.*, 2016, **81**, 10204; X.-H. Zhou, Y. Liu, R.-J. Zhou, H. Song, X.-Y. Liu and Y. Qin, *Chem. Commun.*, 2018, **54**, 12258; R.-J. Zhou, G.-Y. Dai, X.-H. Zhou, M.-J. Zhang, P.-Z. Wu, D. Zhang, H. Song, X.-Y. Liu and Y. Qin, *Org. Chem. Front.*, 2019, **6**, 377; Z. Meng, F. Mi, F. Lu, W. Tan, X.-Y. Liu and Y. Qin, *Chin. Chem. Lett.*, 2020, **31**, 1903.
- 14 H. Cheng, F.-H. Zeng, D. Ma, M.-L. Jiang, L. Xu and F.-P. Wang, *Org. Lett.*, 2014, **16**, 2299; X. Yang, B. Cheng, H. Cheng, L. Xu and J.-L. Wang, *Chin. Chem. Lett.*, 2017, **28**, 1788; M. Liu, C. Cheng, W. Xiong, H. Cheng, J.-L. Wang and L. Xu, *Org. Chem. Front.*, 2018, **5**, 1502; Z. Lv, L. Gao, C. Cheng, W. Niu, J. L. Wang and L. Xu, *Chem.-Asian J.*, 2018, **13**, 955; S.-Y. Cao, H.-J. Yue, M.-Q. Zhu and L. Xu, *Org. Chem. Front.*, 2020, **7**, 933; T. Guo, F. Peng, X. Song, J. Lei, F. Yu, H. Chu, K. Yang and L. Xu, *Org. Chem. Front.*, 2023, **10**, 675.
- 15 D. Bankston, F. Fang, E. Huie and S. Xie, *J. Org. Chem.*, 1999, **64**, 3461; M. Oestreich, P. R. Dennison, J. J. Kodanko and L. E. Overman, *Angew. Chem., Int. Ed.*, 2001, **40**, 1439; A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945; L. A. Arnold, W. Luo and R. K. Guy, *Org. Lett.*, 2004, **6**, 3005.
- 16 For examples of the transformation of the bicyclo[2.2.2] to [3.2.1] skeleton through the Wagner–Meerwein rearrangement, see: S. P. Sethi, K. S. Atwal, R. M. Marini-Bettolo, T. Y. R. Tsai and K. Wiesner, *Can. J. Chem.*, 1980, **58**, 1889–1891; M. Asaoka and H. Takei, *Tetrahedron Lett.*, 1987, **28**, 6343–6346; W. G. Earley, J. E. Jacobsen, A. Madin, G. P. Meier, C. J. O'donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *J. Am. Chem. Soc.*, 2005, **127**, 18046–18053; F. Leonelli, F. Blesi, P. Dirito, A. Trombetta, F. Ceccacci, A. L. Bella, L. M. Migneco and R. M. Bettolo, *J. Org. Chem.*, 2011, **76**, 6871–6876; L. Q. Song, G. L. Zhu, Y. J. Liu, B. Liu and S. Qin, *J. Am. Chem. Soc.*, 2015, **137**, 13706–13714; C. J. Marth, G. M. Gallego, J. C. Lee, T. P. Lebold, S. Kulyk, K. G. Kou, J. Qin, R. Lilien and R. Sarpong, *Nature*, 2015, **528**, 493; X. Y. Liu, F. P. Wang and Y. Qin, *Acc. Chem. Res.*, 2021, **54**, 22–34.
- 17 D. L. Boger, J. Hong, M. Hikota and M. Ishida, *J. Am. Chem. Soc.*, 1999, **121**, 2471; A. N. Lowell, P. D. Wall, S. P. Waters and M. C. Kozlowski, *Tetrahedron*, 2010, **66**, 5573.
- 18 L. Fitjer and U. Quabeck, *Synth. Commun.*, 1985, **15**, 855.
- 19 C. Petrier and J. L. Luche, *J. Org. Chem.*, 1985, **50**, 910.
- 20 Y.-K. Chen, R. K. Peddinti and C.-C. Liao, *Chem. Commun.*, 2001, **15**, 1340; S. K. Chittimalla, S. K. Chittimalla, H.-Y. Shiao, H.-Y. Shiao, C.-C. Liao and C.-C. Liao, *Org. Biomol. Chem.*, 2006, **4**, 2267; H. Cheng, F. H. Zeng, X. Yang, Y. J. Meng, L. Xu and F. P. Wang, *Angew. Chem., Int. Ed.*, 2015, **128**, 400.

- 21 A small amount of the undesired *exo* addition product **15c** (ca. 15%, see the ESI†) was isolated in the reaction mixture, and the two desired OTBS substituted diastereomers **15a** and **15b** could be used as a mixture to transform into the ketone intermediates **22**. For clarity of the NMR spectra, the single major isomer **15a** was separated from **15b** to perform subsequent transformation.
- 22 I. Fernández, F. P. Cossío and M. A. Sierra, *Chem. Rev.*, 2009, **109**, 6687; O. Gutierrez and D. J. Tantillo, *J. Org. Chem.*, 2012, **77**, 8845; C. L. Hugelshofer and T. Magauer, *Nat. Prod. Rep.*, 2017, **34**, 228.
- 23 L. N. Mander and S. P. Sethi, *Tetrahedron Lett.*, 1983, **24**, 5425.
- 24 B. Hegedüs and A. F. Krassó, *Helv. Chim. Acta*, 2004, **53**, 959; K. C. Nicolaou, P. K. Sasmal and H. Xu, *J. Am. Chem. Soc.*, 2004, **126**, 5493.
- 25 N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Am. Chem. Soc.*, 1955, **77**, 6269; R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, 1967, **89**, 1827.
- 26 J. M. Smith, J. Moreno, B. W. Boal and N. K. Garg, *Angew. Chem., Int. Ed.*, 2015, **54**, 400; S. Z. Jiang, X. Y. Zeng, X. Liang, T. Lei, K. Wei and Y. R. Yang, *Angew. Chem., Int. Ed.*, 2016, **55**, 4044; G. Li, X. Xie and L. Zu, *Angew. Chem., Int. Ed.*, 2016, **55**, 10483; W. Ren, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 3500; M. Jarret, A. Tap, C. Kouklovsky, E. Poupon, L. Evanno and G. Vincent, *Angew. Chem., Int. Ed.*, 2018, **57**, 12294; S. Pan, S. Chen and G. Dong, *Angew. Chem., Int. Ed.*, 2018, **57**, 6333; X. Zhang, B. N. Kakde, R. Guo, S. Yadav, Y. Gu and A. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 6053; A. Turlik, Y. Chen, A. C. Scrusse and T. R. Newhouse, *J. Am. Chem. Soc.*, 2019, **141**, 8088–8092.