

Cite this: *Chem. Sci.*, 2020, **11**, 7177

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

Received 18th May 2020
Accepted 17th June 2020

DOI: 10.1039/d0sc02829k

rsc.li/chemical-science

Total synthesis of crotophorbolone†‡

Tianzi Yu, Ying Sun, Canhui Tu, Ting Chen, Shaomin Fu[†] and Bo Liu^{‡*}

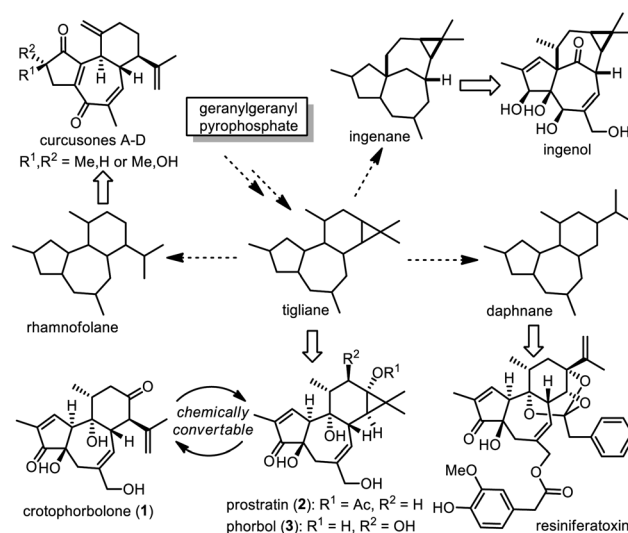
As a natural diterpenoid, crotophorbolone possesses a challenging *trans,trans*-5/7/6 framework decorated with six contiguous stereogenic centers and is structurally and biogenetically related to tigliane-type diterpenoids with intriguing bioactivities such as phorbol and prostratin. Based on the convergent strategy, we completed an eighteen-step total synthesis of crotophorbolone starting from (–)-carvone and (+)-dimethyl-2,3-*O*-isopropylidene-*L*-tartrate. The key elements of the synthesis involve expedient installation of the six-membered ring and the five-membered ring with multiple functional groups at an early stage, cyclization of the seven-membered ring through alkenylation of the ketone between the five-membered ring and the six-membered ring, functional group-sensitive ring-closing metathesis and final selective introduction of hydroxyls at C₂₀ and C₄.

Introduction

Diterpenoid natural products are structurally versatile and can be classified into different families, many of which are biogenetically correlated. Hecker proposed that among them, tigliane might be regarded as the biosynthetic precursor of ingenane, daphnane and rhamnofolane (Scheme 1),¹ and this hypothesis was partially supported by co-occurrence of these diterpenoids in the plant families Euphorbiaceae and Thymelaeaceae.² Tigliane could be biosynthetically achieved initially from abundant geranylgeranyl pyrophosphate (GGPP) *via* formation of casbene and lathyrane.³ Thus it is intriguing to manifest chemical interconversion among tigliane, ingenane, daphnane and rhamnofolane to probe insightful information on the biosynthetic mechanism. In fact, the Wender group was able to transform crotophorbolone (1) to prostratin (2),⁴ a tigliane-type diterpenoid used as a potential adjuvant in highly active anti-retroviral therapy (HAART) for HIV.⁵ Interestingly, acid treatment of phorbol (3),⁶ a typical tigliane-type diterpenoid, led to formation of crotophorbolone as a reaction product as early as in 1934,⁷ although the first isolation of 1 from natural sources had not been reported until 2010.⁸

Allured by their impressive structures and bioactivities, chemists have made numerous synthetic endeavors toward natural ingenane-type, tigliane-type and daphnane-type diterpenoids,⁹ leading to chemical syntheses of ingenol and its

natural derivatives,¹⁰ phorbol,¹¹ prostratin,^{5,12} and resiniferatoxin.¹³ All of these natural diterpenoids contain a similar tricyclic scaffold embedded with multiple stereogenic centers. Compared to tigliane-type and daphnane-type diterpenoids, rhamnofolane-type diterpenoids belong to a small family with about thirty members.^{2a,14} As illustrated, crotophorbolone (1) possesses a *trans,trans*-5/7/6 tricyclic ring system decorated with six contiguous stereogenic centers: two quaternary centers and four tertiary centers. Crotophorbolone (1) is often regarded as a tigliane-type diterpenoid due to its similar oxidation style to phorbol (3) and its biogenesis from phorbol, although it shares a similar carbon skeleton with rhamnofolane-type diterpenoids.



Scheme 1 Biogenetic correlation between tigliane, ingenane, daphnane and rhamnofolane.

Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, 29 Wangjiang Rd., Chengdu, Sichuan 610064, China. E-mail: chembliu@scu.edu.cn

† Dedicated to the 70th anniversary of the Shanghai Institute of Organic Chemistry and in memory of Prof. Wei-Shan Zhou.

‡ Electronic supplementary information (ESI) available: Experimental procedures and details of the electrochemical apparatus employed. CCDC 1989322 and 1989323. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc02829k

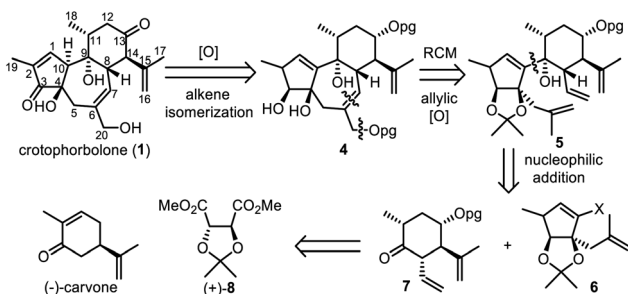
Accompanied by successful chemical syntheses of tigliane-type diterpenoids including prostratin and phorbol,^{5,11,12} the first total synthesis of crotophorbolone was achieved by the Inoue group.¹⁵ In their pioneering work, an impressive strategy was accomplished in thirty four linear steps, featuring smart construction of a unique oxabicyclo[2.2.2]octane intermediate, followed by diastereoselective radical Michael addition to close the middle cycloheptene, which was triggered by cleavage of a bridgehead C–Se bond. Recently, we became interested in developing a convergent synthetic strategy toward natural daphnane-type and rhamnofolane-type diterpenoids,¹⁶ based on our persistent research on total synthesis of terpenoids.¹⁷ Herein, we would like to present our efforts on convergent total synthesis of crotophorbolone.

Crotophorbolone could be retrosynthetically derived from compound **4** after oxidation of alcohols and alkene isomerization (Scheme 2). Cleavage of the allylic alcohol at C₂₀ and the C₆=C₇ double bond in **4** would lead to its precursor **5**, which could be obtained by coupling **6** and **7** through nucleophilic addition. Fragments **6** and **7** could be synthesized from commercially available (–)-carvone and (+)-dimethyl-2,3-O-isopropylidene-L-tartrate [(+)-**8**] respectively.

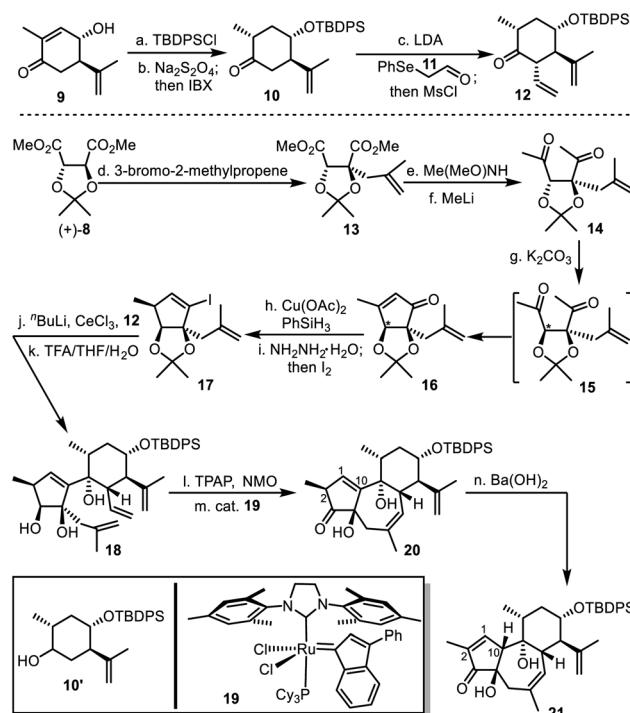
Results & discussion

Accordingly, we started synthesis of the fully functionalized six-membered ring **12** from compound **9** (Scheme 3), feasibly produced after treating (–)-carvone with a copper–aluminium mixed oxide.¹⁸ After silyl protection of the secondary alcohol, the intermediate underwent reduction with sodium dithionite to give a mixture of compounds **10** and **10'**,¹⁹ which was treated with IBX to afford the pure **10**. Coupling compound **10** and 2-(phenylselenenyl)-acetaldehyde (**11**)²⁰ resulted in an aldol intermediate, and mesylation of the resultant secondary alcohol led to elimination to produce compound **12**,²¹ as the equivalent of the fully functionalized six-membered fragment **7**.

Then synthesis of the five-membered fragment **17** began with methallylation of compound (+)-**8** with high yield and diastereoselectivity.²² Sequential Weinreb amidation and nucleophilic addition with methyl lithium led to compound **14**. The following treatment with potassium carbonate resulted in the functionalized cyclopentenone **16**.²³ This process involved inversion of the tertiary stereogenic center and intramolecular aldol condensation to generate the thermodynamically more



Scheme 2 Retrosynthetic analysis.

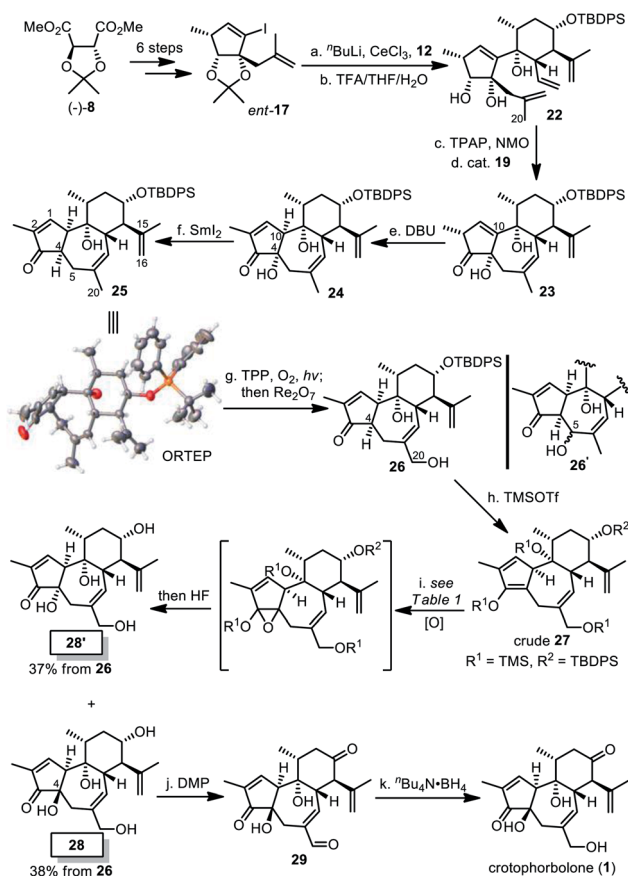


Scheme 3 Synthesis of 5/7/6 tricyclic intermediate **21**. Reagents and conditions: (a) TBDPSCl, imidazole, DCM, rt, 3 h, 78%; (b) Na₂S₂O₄, Adogen® 464, PhMe/H₂O (1/1), reflux, 1.5 h; and then IBX, EtOAc, 80 °C, 12 h, 77%, dr 3.3 : 1; (c) LDA, PhSeCH₂CHO, THF, –78 °C to –55 °C, 2 h; and then MsCl, Et₃N, DCM, 0 °C, 2 h, 59%; (d) LiHMDS, 3-bromo-2-methylpropene, HMPA, THF, –78 °C, 4 h, quant., dr > 20 : 1; (e) Me(MeO)NH·HCl, ^tBuLi, THF, –55 °C, 1 h; (f) MeLi, THF, –78 to rt, 1.5 h, 72% over two steps; (g) K₂CO₃, MeOH/EtOH (2/1), rt, 13 h, 72%; (h) Cu(OAc)₂, PPh₃, PhSiH₃, PhMe, rt, 5 h, 69%; (i) NH₂NH₂·H₂O, Et₃N, EtOH, 80 °C, 20 h; and then I₂, Et₃N, THF, 0 °C, 0.5 h, 85%; (j) ^tBuLi, CeCl₃, **12**, THF, –78 °C, 1 h; (k) TFA/THF/H₂O (3/4/4), rt, 3 h, 65% over two steps; (l) TPAP, NMO, DCM, 0 °C, 3 h, 72%; (m) cat. **19**, C₆F₆, reflux, 2 h, 88%; and (n) Ba(OH)₂, MeOH/toluene (2/1), 55 °C, 10 min, 44%. TBDPSCl = *tert*-butyldiphenylsilyl chloride, Adogen® 464 = methyltrialkyl(C₈–C₁₀)ammonium chloride, IBX = 2-iodoxybenzoic acid, MsCl = methanesulfonyl chloride, LiHMDS = lithium bis(trimethylsilyl)amide, TFA = trifluoroacetic acid, TPAP = tetrapropylammonium perruthenate, and NMO = *N*-methylmorpholine *N*-oxide.

stable *cis*-fused 5/5 bicyclic ring system. Copper-catalyzed 1,4-reduction delivered an intermediate, which was transformed to compound **17** as a surrogate of fragment **6** after formation of hydrazone and subsequent iodination.

Inspired by preceding synthetic studies,²⁴ we attempted connection between the six-membered ring **12** and the five-membered ring **17**. In the presence of CeCl₃, the alkenyl lithium generated from **17** and butyl lithium were added to the ketone **12** to afford a diastereoselective adduct, the acetonide of which was removed to yield compound **18**. It was then converted into compound **20** with the desired 5/7/6 tricyclic skeleton, after oxidation of the secondary alcohol and ring-closing metathesis (RCM) in C₆F₆ (ref. 25) using Nolan's ruthenium catalyst **19** to achieve high yield.²⁶ With compound **20** in hand, we had expected that the desired *trans*-5,7-fused ring system with α-H at C₁₀ would be constructed after alkene isomerization from C₁=C₁₀ to C₁=C₂,^{15a,27} at least co-existing with the *cis*-5,7-fused ring





Scheme 4 Total synthesis of crotophorbolone. Reagents and conditions: (a) n BuLi, $CeCl_3$, **12**, THF, $-78\text{ }^\circ\text{C}$, 1 h; (b) TFA/THF/ H_2O (3/4/4), rt, 4 h, 86% over two steps; (c) TPAP, NMO, DCM, $0\text{ }^\circ\text{C}$, 2.5 h, 78%; (d) cat. **19**, C_6F_6 , reflux, 3 h, 96%; (e) DBU, MeOH, $0\text{ }^\circ\text{C}$ to rt, 1.5 h, 94%; (f) Sml_2 , THF, $0\text{ }^\circ\text{C}$, 20 min, 63% (brsm 90%); (g) TPP, O_2 , $h\nu$, DCE, 12 h, PPh₃; and then Re_2O_7 , 15 min, 32% (brsm 45%) after two cycles; (h) TMSOTf, Et_3N , DCM, $0\text{ }^\circ\text{C}$, 3 h, 72%; (i) see Table 1, then 40% HF/MeCN (1/4), $60\text{ }^\circ\text{C}$, 4 h, **28/28'** = 38%/37%; (j) Dess–Martin periodinane, $NaHCO_3$, DCM, rt, 3 h, quant.; and (k) n Bu₄N·BH₄, MeOH, $-40\text{ }^\circ\text{C}$, 10 min, 92%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TPP = 5,10,15,20-tetraphenylporphyrin, DCE = 1,2-dichloroethane, and brsm = based on the recovery of the starting material.

system (**21**). Unfortunately, we failed to gain the desired compound after numerous trials. Treating **20** with $Ba(OH)_2$ in hot methanol only led to compound **21** in 44% yield, while

recovery or decomposition of compound **20** was observed in other cases.

To introduce proper stereochemistry at C₁₀, we decided to invert the absolute configuration of the five-membered fragment by starting the synthesis from (–)-**8** (Scheme 4). Thus compound *ent*-**17**, prepared by the same synthetic procedure as compound **17**, was coupled with compound **12**. The resultant intermediate was converted into compound **22** after acidic removal of the acetonide. Then TPAP oxidation and RCM cyclization smoothly afforded compound **23**. In contrast to low conversion of **20** into **21** by using $Ba(OH)_2$, treating **23** with DBU promoted alkene isomerization to deliver compound **24** in 94% yield, as a *cis*-5/7 ring system with identical stereochemistry at C₁₀ to **1**. At this stage, directly inverting the stereochemistry of the quaternary stereogenic center at C₄ was unfeasible. So the α -OH at C₄ in **24** was cleaved with samarium(II) iodide to afford compound **25**, whose relative stereochemistry was unambiguously established by single crystal X-ray diffraction. Subsequently, we proposed that a primary allylic alcohol at C₂₀ be selectively introduced to generate compound **26** in the presence of the other two alkenes. However, oxidation with stoichiometric selenium dioxide in THF at $50\text{ }^\circ\text{C}$ resulted in **26'** instead, while its application in other solvents and the combination of catalytic SeO_2 and t BuOOH led to decomposition of **25**. Then White's protocol with $Pd(OAc)_2$ -sulfoxide catalysis was attempted,²⁸ but no reaction was observed. Finally, **26** was obtained by means of the Schenck ene reaction with singlet oxygen,²⁹ followed by Re_2O_7 -mediated rearrangement.³⁰ Notably, allylic positions adjacent to C₁=C₂ and C₁₅=C₁₆ were inert, probably due to the electron-deficient properties of C₁=C₂ and the shielding effect of neighbouring TBDPS ether near C₁₅=C₁₆ respectively.

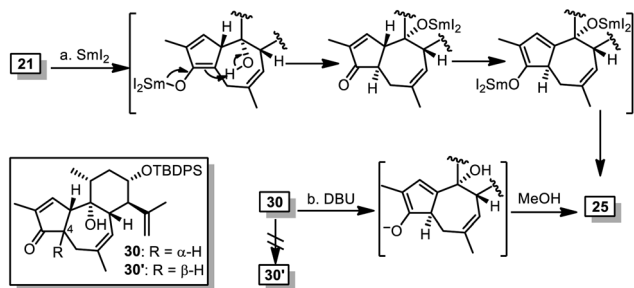
To introduce a hydroxyl group at C₄, we decided to examine the feasibility of a three-step sequence involving silyl enolation, diastereoselective epoxidation and global deprotection to afford the desired compound **28**. Crude **27** was first obtained *in situ* by silylation of compound **26**. As summarized in Table 1, in the presence of oxone or $MeReO_3/H_2O_2$, epoxidation of crude **27** only resulted in the undesired *cis*-product **28'** after desilylation (entries 1 and 2). Although application of *meta*-chloroperbenzoic acid (*m*CPBA) at $-78\text{ }^\circ\text{C}$ afforded no reaction (entry 3), and epoxidation with it at higher temperature did take place, which was followed by global desilylation to afford a mixture of diastereomers **28** and **28'** in almost a 1 : 1 ratio (entries 4 and 5).

Table 1 Screening for sequential transformation from **26** to **28/28'**

Entry	Conditions in the epoxidation step	Result ^a
1	Oxone (1.5 equiv.), $NaHCO_3$ (3.0 equiv.) acetone, $0\text{ }^\circ\text{C}$	28' (67%)
2	$MeReO_3$ (0.25 equiv.), pyridine (2.5 equiv.), H_2O_2 (2.5 equiv.), MeCN/AcOH (19/1), $0\text{ }^\circ\text{C}$	28' (57%)
3	$NaHCO_3$ (2 equiv.), DCM, dropwise addition of <i>m</i> CPBA (1.05 equiv.) in DCM, $-78\text{ }^\circ\text{C}$	N. R. ^b
4	$NaHCO_3$ (2 equiv.), DCM, dropwise addition of <i>m</i> CPBA (1.05 equiv.) in DCM, $-40\text{ }^\circ\text{C}$	28/28' (1/1.4) 67%
5	$NaHCO_3$ (2 equiv.), DCM, dropwise addition of <i>m</i> CPBA (1.05 equiv.) in DCM, $0\text{ }^\circ\text{C}$	28/28' (1.4/1) 59%
6	$NaHCO_3$ (2 equiv.), DCM, one-batch addition of <i>m</i> CPBA (1.05 equiv.), $0\text{ }^\circ\text{C}$	28 (38%) ^c 28' (37%) ^c

^a Overall isolated yield from **27**. ^b N. R. = no reaction. ^c Overall isolated yield from **26**. *m*CPBA = *meta*-chloroperbenzoic acid.



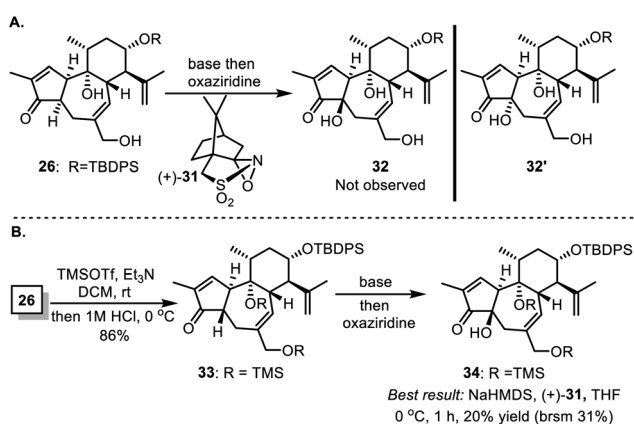


Scheme 5 Thermodynamic stability of 25 over 30'. Reagents and conditions: (a) SmI_2 , THF, 0 °C, 20 min, 74%; and (b) DBU, MeOH, rt–40 °C, 16 h, 63%.

To our delight, we found that direct addition of *m*CPBA in one batch into the DCM solution of crude 27 at 0 °C provided the optimal result, eventually producing 28 in 38% yield and 28' in 37% yield from 26 (entry 6). Finally, oxidation with Dess–Martin periodinane gave compound 29, and selective reduction of the aldehyde accomplished the total synthesis of crotophorbolone (1).

Surprisingly, similar to that of 24, treatment of 21 with SmI_2 in THF led to 25 as the sole isolable product. This indicated the unexpected thermodynamic stability of 25 over 30' although both compounds contain *cis*-fused 5/7 ring systems, which was further evidenced by base-mediated conversion of 30 into 25 without 30' being detected (Scheme 5).

Actually, to properly install the hydroxyl group at C_4 , we first attempted deprotonation of compound 26 and coupled the resulting enolate with different oxaziridines including the Davis' reagent (+)-31 (Scheme 6A). Unfortunately, under these conditions, either no reaction was observed, or only a trace amount of 32' with the *cis*-5/7 ring system was generated instead of the desired 32. By supposing that protection of free alcohols and enhancement of opposite steric hindrance might induce favored diastereoselective hydroxylation, we transformed 26 to 33 to test the practicability (Scheme 6B). In most cases, enolation of 33 with strong bases, followed by treatment with oxaziridine, led to either no reaction or decomposition of the reactant. The best 20% (brsm 31%) yield of the desired



Scheme 6 Attempts to install β -OH at C_4 .

compound 34 was achieved when 33 was treated with sodium hexamethyldisilazide (NaHMDS) and (+)-31 in THF at 0 °C. Fortunately, a three-step manipulation was developed to successfully transform 26 to 28 as illustrated in Scheme 4.

Conclusions

In general, we have completed a convergent total synthesis of crotophorbolone in eighteen longest linear steps. The synthesis features expedient construction of the fully functionalized substructures, *i.e.* the six-membered fragment 12 through diastereoselective hydroxylation and vinylation, the five-membered fragment 17 through selective methallylation and aldol condensation, and the 5/7/6 tricyclic framework through nucleophilic coupling and RCM cyclization. Selective installation of alcohols at C_{20} and C_4 proved challenging but accessible. Undoubtedly, our discovery on stability of 25 over 30' would benefit the design of concise routes in the future total synthesis of crotophorbolone and other structurally and biosynthetically related diterpenoids.

Conflicts of interest

The authors declare no competing interests.

Acknowledgements

We acknowledge financial support from the NSFC (21925106, 21672153, 21921002) and Fundamental Research Funds for the Central Universities. We thank the Analytical & Testing Center of Sichuan University for NMR recording and X-ray diffraction work. We are grateful to Dr Daibing Luo at Sichuan University for his help in single crystal analysis.

Notes and references

- (a) E. Hecker, *Pure Appl. Chem.*, 1977, **49**, 1423–1431; (b) W. Adolf and E. Hecker, *Isr. J. Chem.*, 1977, **16**, 75–83.
- (a) H. B. Wang, X. Y. Wang, L. P. Liu, G. W. Qin and T. G. Kang, *Chem. Rev.*, 2015, **115**, 2975–3011; (b) G. Appendino, *Prog. Chem. Org. Nat. Prod.*, 2016, **102**, 1–90; (c) Y. X. Jin, L. L. Shi, D. P. Zhang, H. Y. Wei, Y. Si, G. X. Ma and J. Zhang, *Molecules*, 2019, **24**, 1842; (d) S. G. Liao, H. D. Chen and J. M. Yue, *Chem. Rev.*, 2009, **109**, 1092–1140; (e) H. A. Abdelgadir and J. Van Staden, *S. Afr. J. Bot.*, 2013, **88**, 204–218; (f) R. K. Devappa, H. P. S. Makkar and K. Becker, *J. Am. Oil Chem. Soc.*, 2011, **88**, 301–322; (g) F. J. Evans and C. J. Soper, *Lloydia*, 1978, **41**, 193–233.
- R. J. Schmidt, *Bot. J. Linn. Soc.*, 1987, **94**, 221–230.
- G. A. Miana, M. Riaz, S. Shahzad-ul-Hussan, R. Z. Paracha and U. Z. Paracha, *Mini-Rev. Med. Chem.*, 2015, **15**, 1122–1130.
- P. A. Wender, J. M. Kee and J. M. Warrington, *Science*, 2008, **320**, 649–652.
- G. Goel, H. P. S. Makkar, G. Francis and K. Becker, *Int. J. Toxicol.*, 2007, **26**, 279–288.



- 7 (a) B. Flaschentrager and F. F. Falkenhausen, *Justus Liebigs Ann. Chem.*, 1934, **514**, 252–260; (b) H. W. Thielmann and E. Hecker, *Justus Liebigs Ann. Chem.*, 1969, **728**, 158–183.
- 8 H. B. Wang, W. J. Chu, Y. Wang, P. Ji, Y. B. Wang, Q. Yu and G. W. Qin, *J. Asian Nat. Prod. Res.*, 2010, **12**, 1038–1043.
- 9 (a) R. Liu, J. Feng and B. Liu, *Acta Chim. Sin.*, 2016, **74**, 24–43; (b) Y. Li, M. Wei and M. Dai, *Tetrahedron*, 2017, **73**, 4172–4177; (c) L. V. Nguyen and A. B. Beeler, *Org. Lett.*, 2018, **20**, 5177–5180; (d) Z. G. Brill, Y.-M. Zhao, V. H. Vasilev and T. J. Maimone, *Tetrahedron*, 2019, **75**, 4212–4221; (e) K. Watanabe, Y. Suzuki, K. Aoki, A. Sakakura, K. Suenaga and H. Kigoshi, *J. Org. Chem.*, 2004, **69**, 7802–7808; (f) X. Liu, J. Liu, J. Zhao, S. Li and C. C. Li, *Org. Lett.*, 2017, **19**, 2742–2745; (g) K. Murai, S.-i. Katoh, D. Urabe and M. Inoue, *Chem. Sci.*, 2013, **4**, 2364–2368; (h) J. K. Cha and O. L. Epstein, *Tetrahedron*, 2006, **62**, 1329–1343; (i) S. Chow, T. Krainz, P. V. Bernhardt and C. M. Williams, *Org. Lett.*, 2019, **21**, 8761–8764; (j) A. Pascual-Escudero, M. González-Esguevillas, S. Padilla, J. Adrio and J. C. Carretero, *Org. Lett.*, 2014, **16**, 2228–2231; (k) A. J. Catino, A. Sherlock, P. Shieh, J. S. Wzorek and D. A. Evans, *Org. Lett.*, 2013, **15**, 3330–3333; (l) C. Stewart, R. McDonald and F. G. West, *Org. Lett.*, 2011, **13**, 720–723; (m) G. L. Carroll and R. D. Little, *Org. Lett.*, 2000, **2**, 2873–2876.
- 10 (a) J. D. Winkler, M. B. Rouse, M. F. Greaney, S. J. Harrison and Y. T. Jeon, *J. Am. Chem. Soc.*, 2002, **124**, 9726–9728; (b) K. Tanino, K. Onuki, K. Asano, M. Miyashita, T. Nakamura, Y. Takahashi and I. Kuwajima, *J. Am. Chem. Soc.*, 2003, **125**, 1498–1500; (c) A. Nickel, T. Maruyama, H. Tang, P. D. Murphy, B. Greene, N. Yusuff and J. L. Wood, *J. Am. Chem. Soc.*, 2004, **126**, 16300–16301; (d) I. Kuwajima and K. Tanino, *Chem. Rev.*, 2005, **105**, 4661–4670; (e) T. Ohyoshi, S. Funakubo, Y. Miyazawa, K. Niida, I. Hayakawa and H. Kigoshi, *Angew. Chem., Int. Ed.*, 2012, **51**, 4972–4975; (f) L. Jorgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding and P. S. Baran, *Science*, 2013, **341**, 878–882; (g) S. J. McKerrall, L. Jorgensen, C. A. Kuttruff, F. Ungeheuer and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5799–5810; (h) Y. Jin, C. H. Yeh, C. A. Kuttruff, L. Jorgensen, G. Dunstl, J. Felding, S. R. Natarajan and P. S. Baran, *Angew. Chem., Int. Ed.*, 2015, **54**, 14044–14048.
- 11 (a) P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger, R. S. Wilhelm and P. D. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 8957–8958; (b) P. A. Wender and F. E. McDonald, *J. Am. Chem. Soc.*, 1990, **112**, 4956–4958; (c) P. A. Wender, K. D. Rice and M. E. Schnute, *J. Am. Chem. Soc.*, 1997, **119**, 7897–7898; (d) K. Lee and J. K. Cha, *J. Am. Chem. Soc.*, 2001, **123**, 5590–5591; (e) S. Kawamura, H. Chu, J. Felding and P. S. Baran, *Nature*, 2016, **532**, 90–93.
- 12 (a) G. Tong, Z. Liu and P. Li, *Chem*, 2018, **4**, 2944–2954; (b) G. Tong, Z. Ding, Z. Liu, Y. Ding, L. Xu, H. Zhang and P. Li, *J. Org. Chem.*, 2020, **85**, 4813–4837.
- 13 (a) P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe and Y. Ueno, *J. Am. Chem. Soc.*, 1997, **119**, 12976–12977; (b) P. A. Wender, N. Buschmann, N. B. Cardin, L. R. Jones, C. Kan, J. M. Kee, J. A. Kowalski and K. E. Longcore, *Nat. Chem.*, 2011, **3**, 615–619; (c) S. Hashimoto, S.-i. Katoh, T. Kato, D. Urabe and M. Inoue, *J. Am. Chem. Soc.*, 2017, **139**, 16420–16429.
- 14 A. Vasas and J. Hohmann, *Chem. Rev.*, 2014, **114**, 8579–8612.
- 15 (a) T. Asaba, Y. Katoh, D. Urabe and M. Inoue, *Angew. Chem., Int. Ed.*, 2015, **54**, 14457–14461; (b) D. Urabe, T. Asaba and M. Inoue, *Bull. Chem. Soc. Jpn.*, 2016, **89**, 1137–1144.
- 16 (a) J. Feng, H. Yin, Y. Man, S. Fu and B. Liu, *Chin. J. Chem.*, 2018, **36**, 831–836; (b) J. Feng, T. Yu, Z. Zhang, J. Li, S. Fu, J. Chen and B. Liu, *Chem. Commun.*, 2018, **54**, 7665–7668.
- 17 (a) C. Yuan, B. Du, L. Yang and B. Liu, *J. Am. Chem. Soc.*, 2013, **135**, 9291–9294; (b) L. Song, G. Zhu, Y. Liu, B. Liu and S. Qin, *J. Am. Chem. Soc.*, 2015, **137**, 13706–13714; (c) H. Deng, W. Cao, R. Liu, Y. Zhang and B. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 5849–5852; (d) C. Yuan, B. Du, H. Deng, Y. Man and B. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 637–640; (e) B. Du, Z. Huang, X. Wang, T. Chen, G. Shen, S. Fu and B. Liu, *Nat. Commun.*, 2019, **10**, 1892.
- 18 A. Leticia Garcia-Cabeza, R. Marin-Barrios, R. Azarken, F. Javier Moreno-Dorado, M. J. Ortega, H. Vidal, J. M. Gatica, G. M. Massanet and F. M. Guerra, *Eur. J. Org. Chem.*, 2013, **2013**, 8307–8314.
- 19 F. Camps, J. Coll and J. Guitart, *Tetrahedron*, 1986, **42**, 4603–4609.
- 20 H. J. Reich and F. Chow, *J. Chem. Soc., Chem. Commun.*, 1975, 790–791.
- 21 C. J. Kowalski and J. S. Dung, *J. Am. Chem. Soc.*, 1980, **102**, 7950–7951.
- 22 R. Naef and D. Seebach, *Angew. Chem., Int. Ed.*, 1981, **20**, 1030–1031.
- 23 (a) A. I. Meyers and B. A. Lefker, *Tetrahedron Lett.*, 1987, **28**, 1745–1748; (b) A. I. Meyers and B. A. Lefker, *Tetrahedron*, 1987, **43**, 5663–5676; (c) A. I. Meyers and C. A. Busacca, *Tetrahedron Lett.*, 1989, **30**, 6977–6980.
- 24 (a) L. A. Paquette, F. Gallou, Z. Zhao, D. G. Young, J. Liu, J. Yang and D. Friedrich, *J. Am. Chem. Soc.*, 2000, **122**, 9610–9620; (b) T. V. Ovaska, S. E. Reisman and M. A. Flynn, *Org. Lett.*, 2001, **3**, 115–117; (c) O. L. Epstein and J. K. Cha, *Angew. Chem., Int. Ed.*, 2005, **44**, 121–123.
- 25 C. Samojlowicz, M. Bieniek, A. Zarecki, R. Kadyrov and K. Grell, *Chem. Commun.*, 2008, 6282–6284.
- 26 L. Jafarpour, H. J. Schanz, E. D. Stevens and S. P. Nolan, *Organometallics*, 1999, **18**, 5416–5419.
- 27 X. Huang, L. Song, J. Xu, G. Zhu and B. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 952–955.
- 28 (a) M. S. Chen and M. C. White, *J. Am. Chem. Soc.*, 2004, **126**, 1346–1347; (b) M. S. Chen, N. Prabakaran, N. A. Labenz and M. C. White, *J. Am. Chem. Soc.*, 2005, **127**, 6970–6971.
- 29 A. A. Ghogare and A. Greer, *Chem. Rev.*, 2016, **116**, 9994–10034.
- 30 I. Volchkov and D. Lee, *Chem. Soc. Rev.*, 2014, **43**, 4381–4394.

