Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: T. Yu, Y. Sun, C. Tu, T. Chen, S. Fu and B. Liu, *Chem. Sci.*, 2020, DOI: 10.1039/D0SC02829K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemical-science

ARTICLE

View Article Online
DOI: 10.1039/D0SC02829K

ARTICLE TYPE

Cite this: DOI: 00.0000/xxxxxxxxxx

Received Date
Accepted Date

DOI: 00.0000/xxxxxxxxxx

Total Synthesis of Crotophorbolone

Tianzi Yu[1], Ying Sun[1], Canhui Tu[1], Ting Chen[1], Shaomin Fu[1], and Bo Liu [1]*

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

As a natural diterpenoid, crotophorbolone possesses a challenging *trans,trans*-5/7/6 framework decorated with six contiguous stereogenic centers, which is structurally and biogenetically related to tigliane-type diterpenoids with intriguing bioactivities such as phorbol and prostratin. On the basis of convergent strategy, we completed an eighteen-step total synthesis of crotophorbolone starting from (-)-carvone and (+)-dimethyl-2,3-*O*-isopropylidene-*L*-tartrate. Key elements of the synthesis involve expedient installation of the six-membered ring and the five-membered ring with multiple functional groups at early stage, cyclization of the seven-membered ring through alkenylation of ketone between the five-membered ring and the six-membered ring, functional group-sensitive ring-closing metathesis and final selective introduction of hydroxyls at C_{20} and C_4.

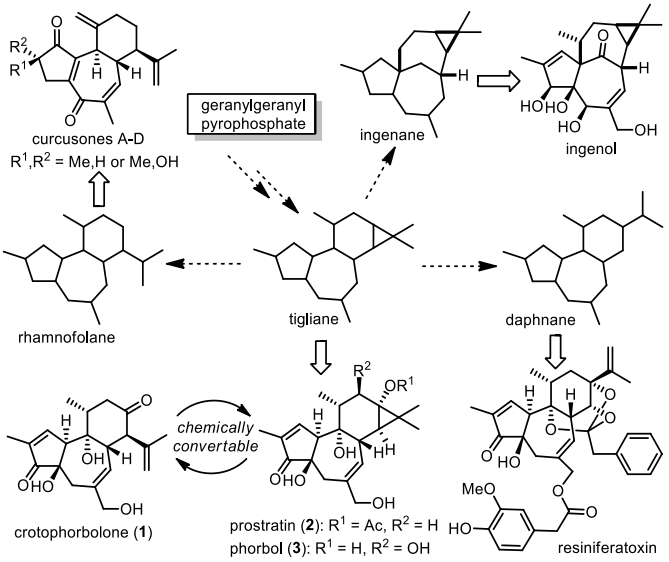
Introduction

Diterpenoid natural products are structurally versatile and can be classified into different families, many of which are biogenetically correlated. Among them, Hecker proposed that tigliane might be regarded as 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 of Euphorbiaceae and Thymelaeaceae.[2] Biosynthetically, tigliane could be achievable initially from the 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 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 antiretroviral therapy (HAART) against HIV.[5] Interestingly, acidic 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 source 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 embrace 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 involving 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 similar carbon skeleton with rhamnofolane-type diterpenoids.

Accompanied by successful chemical syntheses of tigliane-type diterpenoids involving prostratin and phorbol,[5,11,12] the Inoue group fulfilled the first total synthesis of crotophorbolone.[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

Scheme 1. Biogenic correlationship among tigliane, ingenane, daphnane and rhamnofolane.

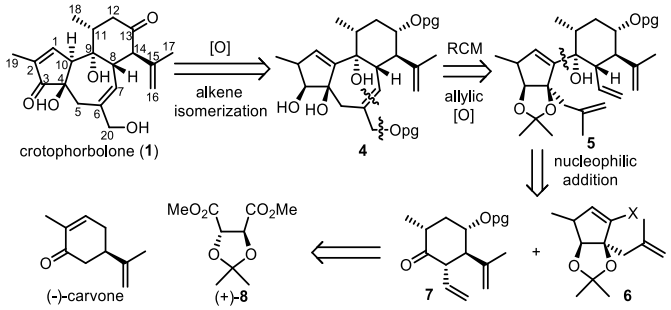


[1] *Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University 29 Wangjiang Rd., Chengdu, Sichuan 610064 (China). Correspondence and requests for materials should be addressed to B.L.(E-mail: chembliu@scu.edu.cn)*

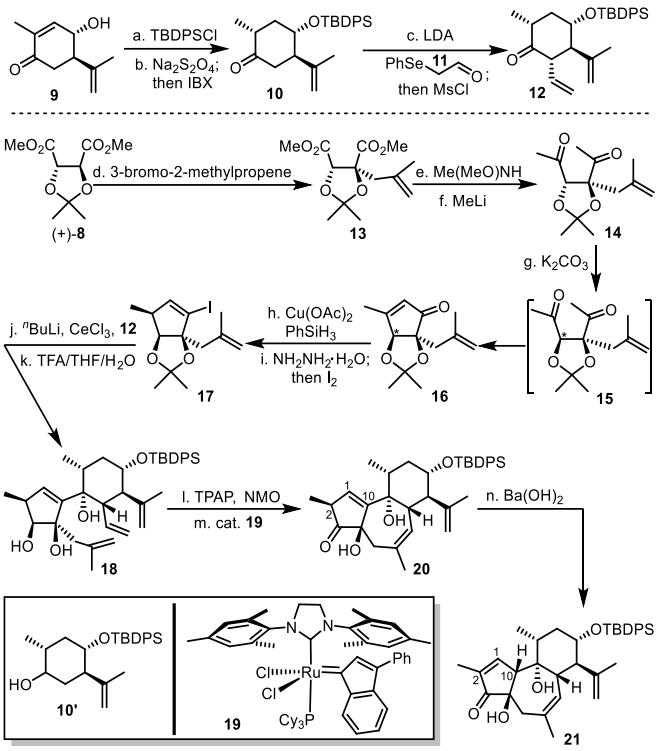
† Electronic supplementary information (ESI) available: Experimental procedures and details of the electrochemical apparatus employed. See DOI: 00.0000/xxxxxxxxxx

View Article Online
DOI: 10.1039/D0SC02829K

Scheme 2. Retrosynthetic analysis.



Scheme 3. Synthesis of 5/7/6 tricyclic intermediate **21**.[a]



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] on the basis of our persistent research on total synthesis of terpenoids.[17] Herein, we would like to present our efforts on convergent total synthesis of crotophorbolone.

Retrosynthetically, crotophorbolone could be derived from compound **4** after oxidation of alcohols and alkene isomerization (Scheme 2). Cleavage of the allylic alcohol at C_{20} and the C_6=C_7 double bond in **4** would lead to its precursor **5**, which could be coupled from **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-(phenylselenyl)-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 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 the fragment **6** after formation of hydrazone and subsequent iodination.

Inspired by precedent synthetic studies,[24] we attempted connection between the six-membered ring **12** and the five-membered ring **17**. In the presence of $CeCl_3$, the alkenyl lithium generated from **17** and butyl lithium was added to the ketone **12** to afford a diastereoselective adduct, 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 C_6F_6[25] using Nolan's ruthenium

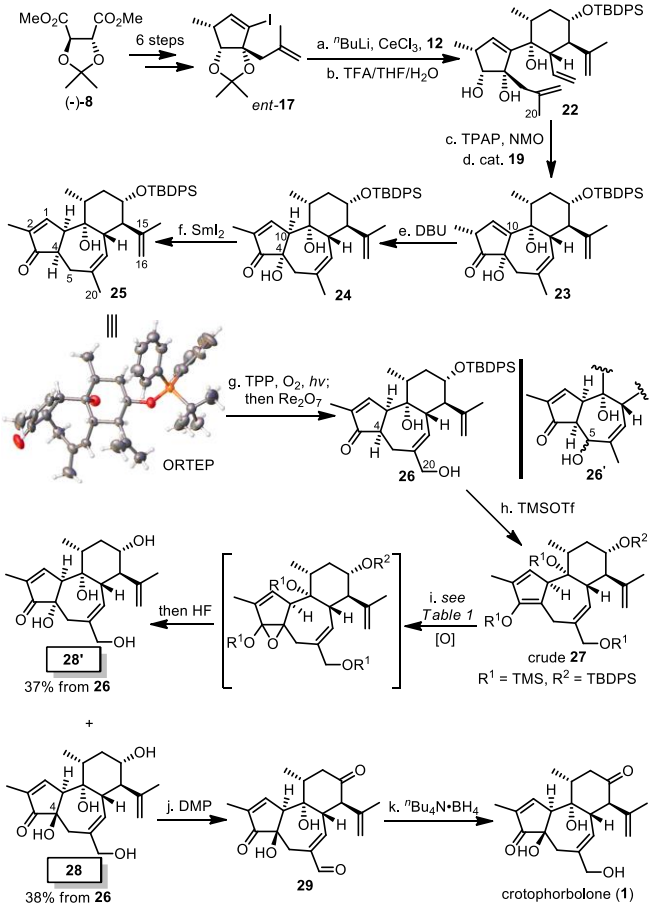
[a]Reagents and conditions: (a) TBDPSCl, imidazole, DCM, rt, 3 h, 78%; (b) $Na_2S_2O_4$, $NaHCO_3$, Adogen® 464, PhMe/H_2O (1/1), reflux, 1.5 h; then IBX, EtOAc, 80 ℃, 12 h, 77%, dr 3.3:1; (c) LDA, $PhSeCH_2CHO$, THF, -78 ℃ to -55 ℃, 2 h; then MsCl, Et_3N, DCM, 0 ℃, 2 h, 59%; (d) LiHMDS, 3-bromo-2-methylpropene, HMPA, THF, -78 ℃, 4 h, quant., dr > 20:1; (e) Me(MeO)NH•HCl, ^{n}BuLi, THF, -55 ℃, 1 h; (f) MeLi, THF, -78 to rt, 1.5 h, 72% over two steps; (g) K_2CO_3, MeOH/EtOH (2/1), rt, 13 h, 72%; (h) $Cu(OAc)_2$, PPh_3, $PhSiH_3$, PhMe, rt, 5 h, 69%; (i) NH_2NH_2•H_2O, Et_3N, EtOH, 80 ℃, 20 h; then I_2, Et_3N, THF, 0 ℃, 0.5 h, 85%; (j) ^{n}BuLi, $CeCl_3$, **12**, THF, -78 ℃, 1 h; (k) TFA/THF/H_2O (3/4/4), rt, 3 h, 65% over two steps; (l) TPAP, NMO, DCM, 0 ℃, 3 h, 72%; (m) cat. **19**, C_6F_6, reflux, 2 h, 88%; (n) $Ba(OH)_2$, MeOH/toluene (2/1), 55 ℃, 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, NMO = N-methylmorpholine N-oxide.

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 C_{10} would be constructed after alkene isomerization from C_1=C_{10} to C_1=C_2,[15a, 27] at least co-existing with the *cis*-5,7-fused ring 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 inverse absolute configuration of the five-membered fragment by starting synthesis from (-)-**8** (Scheme 4). Thus compound *ent*-**17**, prepared in the same synthetic procedure as compound **17**, was coupled with compound **12**. The resultant intermediate was converted into compound **22** after acidic removal of 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

View Article Online
DOI: 10.1039/D0SC02829K

Scheme 4. Total synthesis of crotophorbolone.[a]



[a]Reagents and conditions: (a) ^{n}BuLi, $CeCl_3$, **12**, THF, -78 ℃, 1 h; (b) TFA/THF/H_2O (3/4/4), rt, 4 h, 86% over two steps; (c) TPAP, NMO, DCM, 0 ℃, 2.5 h, 78%; (d) cat. **19**, C_6F_6, reflux, 3 h, 96%; (e) DBU, MeOH, 0 ℃ to rt, 1.5 h, 94%; (f) SmI_2, THF, 0 ℃, 20 min, 63% (brsm 90%); (g) TPP, O_2, *hv*, DCE, 12 h, PPh_3; then Re_2O_7, 15 min, 32% (brsm 45%) after two cycles; (h) TMSOTf, Et_3N, DCM, 0 ℃,3 h, 72%;; (i) see table 1, then 40% HF/MeCN (1/4), 60 ℃, 4 h, **28**/**28′** = 38%/37%; (j) Dess-Martin periodinane, $NaHCO_3$, DCM, rt, 3 h, quant.; (k) $^{n}Bu_4N$ • BH_4, MeOH, -40 ℃, 10 min, 92%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TPP = 5,10,15,20-tetraphenylporphyrin, DCE = 1,2-dichloroethane, brsm = based on recovery of starting material.

compound **24** in 94% yield, as a *cis*-5/7 ring system with identical stereochemistry at C_{10} to that of **1**. At this stage, directly inverting stereochemistry of the quaternary stereogenic center at C_4 was infeasible. So the α-OH at C_4 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 C_{20} be selectively introduced to generate compound **26** in the presence of other two alkenes. However, oxidation with stoichiometric selenium dioxide in THF at 50 ℃ resulted in **26′** instead, while its application in other solvents, as well as 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 facilitated by means of Schenk ene reaction with singlet oxygen,[29] followed by Re_2O_7-mediated

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

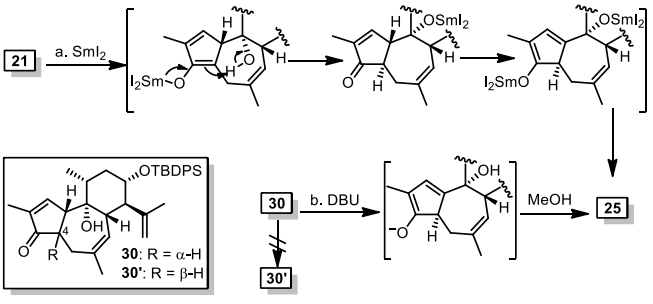
Entry	Conditions in the epoxidation step	Result[a]
1	Oxone (1.5 equiv.), $NaHCO_3$ (3.0 equiv.) acetone, 0 ℃	**28′** (67%)
2	$MeReO_3$ (0.25 equiv.), pyridine (2.5 equiv.), H_2O_2 (2.5 equiv.), MeCN/AcOH (19/1), 0 ℃	**28′** (57%)
3	$NaHCO_3$ (2 equiv.), DCM, dropwise addition of ^{m}CPBA (1.05 equiv.) in DCM, -78 ℃	N. R.[b]
4	$NaHCO_3$ (2 equiv.), DCM, dropwise addition of ^{m}CPBA (1.05 equiv.) in DCM, -40 ℃	**28**/**28′** (1/1.4) 67%
5	$NaHCO_3$ (2 equiv.), DCM, dropwise addition of ^{m}CPBA (1.05 equiv.) in DCM, 0 ℃	**28**/**28′** (1.4/1) 59%
6	$NaHCO_3$ (2 equiv.), DCM, one-batch addition of ^{m}CPBA (1.05 equiv.), 0 ℃	**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.

rearrangement.[30] Notably, allylic positions adjacent to C_1=C_2 and C_{15}=C_{16} were inert, probably due to electron-deficient property of C_1=C_2 and shielding effect of neighbouring TBDPS ether near C_{15}=C_{16} respectively.

To introduce hydroxyl at C_4, we decided to examine feasibility of a three-step sequence involving silyl enolation, diastereoselective epoxidation and global deprotection to afford the desired compound **28**. Crude **27** was firstly *in situ* obtained 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 1-2). Although application of *meta*-chloroperbenzoic acid (^{m}CPBA) at -78 ℃ afforded no reaction (entry 3), epoxidation with it at higher temperature did take place, which was followed by global desilylation to afford a mixture of diastereomers **28** and **28′** with almost 1:1 ratios (entries 4-5). To our delight, we found direct addition of ^{m}CPBA in one batch into the DCM solution of crude **27** at 0 ℃ 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 total synthesis of crotophorbolone (**1**).

Scheme 5. Thermodynamic stability of **25** over **30′**.[a]

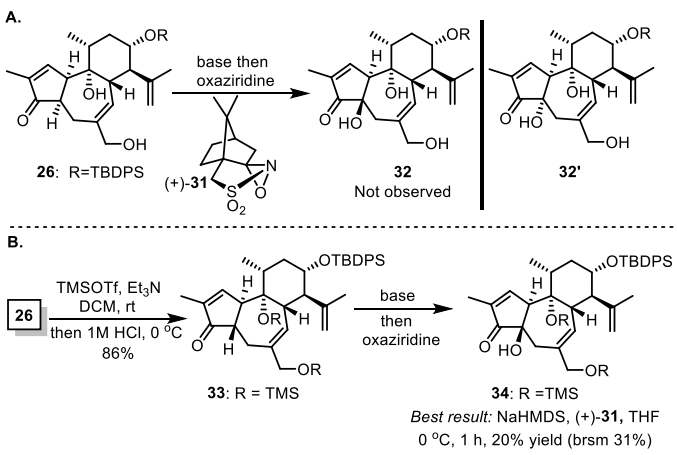


[a]Reagents and conditions: (a) SmI_2, THF, 0 ℃, 20 min, 74%; (b) DBU, MeOH, rt-40 ℃, 16 h, 63%.

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

Actually, to properly install the hydroxyl at C_4, we first attempted deprotonation of compound **26** and coupled the resulting enolate with different oxaziridines involving the Davis' reagent (+)-**31** (Scheme 6A). Unfortunately, under those conditions, either no reaction was observed, or only trace amount of **32′** with *cis*-5/7 ring system was generated instead of the desired **32**. 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 compound **34** was achieved when **33** was subjected to sodium hexamethyldisilazide (NaHMDS) and (+)-**31** in THF at 0 ℃. Fortunately, a three-step manipulation was developed to successfully transform **26** to **28** as illustrated in scheme 4.

Scheme 6. Attempts to install β-OH at C4.



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 C20 and C4 proved challenging but accessible. Undoubtedly, our discovery on stability of **25** over **30′** would benefit design of concise routes in future total synthesis of crotophorbolone and other structurally and biosynthetically related diterpenoids.

Conflicts of interest

The authors declare no competing interests.

View Article Online
DOI: 10.1039/D0SC02829K

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

[1] a) E. Hecker, *Pure Appl. Chem.,* 1977, **49,** 1423-1431; b) W. Adolf, E. Hecker, *Isr. J. Chem.,* 1977, **16,** 75-83.

[2] a) H. B. Wang, X. Y. Wang, L. P. Liu, G. W. Qin, T. G. Kang, *Chem. Rev.,* 2015, **115,** 2975-3011; b) G. Appendino, *Progress in the chemistry of organic natural products.,* 2016, **102,** 1-90; c) Y. X. Jin, L. L. Shi, D. P. Zhang, H. Y. Wei, Y. Si, G. X. Ma, J. Zhang, *Molecules.,* 2019, 24; d) S. G. Liao, H. D. Chen, J. M. Yue, *Chem. Rev.,* 2009, **109,** 1092-1140; e) H. A. Abdelgadir, J. Van Staden, *South African Journal of Botany.,* 2013, **88,** 204-218; f) R. K. Devappa, H. P. S. Makkar, K. Becker, *J. Am. Oil Chem. Soc.,* 2011, **88,** 301-322; g) F. J. Evans, C. J. Soper, *Lloydia-the Journal of Natural Products.,* 1978, **41,** 193-233.

[3] R. J. Schmidt, *Bot. J. Linn. Soc.,* 1987, **94,** 221–230.

[4] G. A. Miana, M. Riaz, S. Shahzad-ul-Hussan, R. Z. Paracha, U. Z. Paracha, *Mini-Reviews in Medicinal Chemistry.,* 2015, **15,** 1122-1130.

[5] P. A. Wender, J. M. Kee, J. M. Warrington, *Science.,* 2008, **320,** 649-652.

[6] G. Goel, H. P. S. Makkar, G. Francis, K. Becker, *International Journal of Toxicology.,* 2007, **26,** 279-288.

[7] a) B. Flaschentrager, F. F. Falkenhausen, *Justus Liebigs Ann. Chem.,* 1934, **514,** 252-260; b) H. W. Thielmann, 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, G. W. Qin, *J. Asian Nat. Prod. Res.,* 2010, **12,** 1038-1043.

[9] a) R. Liu, J. Feng, B. Liu, *Acta Chim. Sinica.,* 2016, **74,** 24-43 and references cited therein; b) Y. Li, M. Wei, M. Dai, *Tetrahedron.,* 2017, **73,** 4172-4177; c) L. V. Nguyen, A. B. Beeler, *Org. Lett.,* 2018, **20,** 5177-5180; d) Z. G. Brill, Y.-M. Zhao, V. H. Vasilev, T. J. Maimone, *Tetrahedron.,* 2019, **75,** 4212-4221; e) K. Watanabe, Y. Suzuki, K. Aoki, A. Sakakura, K. Suenaga, H. Kigoshi, *J. Org. Chem.,* 2004, **69,** 7802-7808; f) X. Liu, J. Liu, J. Zhao, S. Li, C. C. Li, *Org. Lett.,* 2017, **19,** 2742-2745; g) K. Murai, S.-i. Katoh, D. Urabe, M. Inoue, *Chem. Sci.,* 2013, **4,** 2364-2368; h) J. K. Cha, O. L. Epstein, *Tetrahedron.,* 2006, **62,** 1329-1343; i) S. Chow, T. Krainz, P. V. Bernhardt, C. M. Williams, *Org. Lett.*, 2019, **21,** 8761-8764; j) A. Pascual-Escudero, M. González-Esguevillas, S. Padilla, J. Adrio, J. C. Carretero, *Org. Lett.*, 2014, **16,** 2288-2231; k) A. J. Catino, A. Sherlock, P. Shieh, J. S. Wzorek, D. A. Evans, *Org. Lett.*, 2013, **15,** 3330-3333; l) C. Stewart, R. McDonald, F. G. West, *Org. Lett.*, 2011, **13,** 720-723; m) G. L. Carroll, R. D. Little, *Org. Lett.*, 2000, **2,** 2873-2876.

[10] a) J. D. Winkler, M. B. Rouse, M. F. Greaney, S. J. Harrison, Y. T. Jeon, *J. Am. Chem. Soc.,* 2002, **124,** 9726-9728; b) K. Tanino, K. Onuki, K. Asano, M. Miyashita, T. Nakamura, Y. Takahashi, I. Kuwajima, *J. Am. Chem. Soc.,* 2003, **125,** 1498-1500; c) A. Nickel, T. Maruyama, H. Tang, P. D. Murphy, B. Greene, N. Yusuff, J. L. Wood, *J. Am. Chem. Soc.,* 2004, **126,**

16300-16301; d) I. Kuwajima, K. Tanino, *Chem. Rev.,* 2005, **105,** 4661-4670; e) T. Ohyoshi, S. Funakubo, Y. Miyazawa, K. Niida, I. Hayakawa, H. Kigoshi, *Angew. Chem. Int. Ed.,* 2012, **51,** 4972-4975; f) L. Jorgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding, P. S. Baran, *Science.,* 2013, **341,** 878-882; g) S. J. McKerrall, L. Jorgensen, C. A. Kuttruff, F. Ungeheuer, 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, 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, P. D. Williams, *J. Am. Chem. Soc.,* 1989, **111,** 8957-8958; b) P. A. Wender, F. E. McDonald, *J. Am. Chem. Soc.,* 1990, **112,** 4956-4958; c) P. A. Wender, K. D. Rice, M. E. Schnute, *J. Am. Chem. Soc.,* 1997, **119,** 7897-7898; d) K. Lee, J. K. Cha, *J. Am. Chem. Soc.,* 2001, **123,** 5590-5591; e) S. Kawamura, H. Chu, J. Felding, P. S. Baran, *Nature.,* 2016, **532,** 90-93.

[12] a) G. Tong, Z. Liu, P. Li, *Chem.,* 2018, **4,** 2944-2954. b) G. Tong, Z. Ding, Z. Liu, Y. Ding, L. Xu, H. Zhang, P. Li, *J. Org. Chem.,* 2020, **85,** 4813-4837.

[13] a) P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe, 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, K. E. Longcore, *Nat. Chem.,* 2011, **3,** 615-619; c) S. Hashimoto, S.-i. Katoh, T. Kato, D. Urabe, M. Inoue, *J. Am. Chem. Soc.,* 2017, **139,** 16420-16429.

[14] A. Vasas, J. Hohmann, *Chem. Rev.,* 2014, **114,** 8579-8612

[15] a) T. Asaba, Y. Katoh, D. Urabe, M. Inoue, *Angew. Chem. Int. Ed.,* 2015, **54,** 14457-14461; b) D. Urabe, T. Asaba, M. Inoue, *Bull. Chem. Soc. Jpn.,* 2016, **89,** 1137-1144.

[16] a) J. Feng, H. Yin, Y. Man, S. Fu, B. Liu, *Chin. J. Chem.,* 2018, **36,** 831-836; b) J. Feng, T. Yu, Z. Zhang, J. Li, S. Fu, J. Chen, B. Liu, *Chem. Commun.,* 2018, **54,** 7665-7668.

[17] a) C. Yuan, B. Du, L. Yang, B. Liu, *J. Am. Chem. Soc.,* 2013, **135,** 9291-9294; b) L. Song, G. Zhu, Y. Liu, B. Liu, S. Qin, *J. Am. Chem. Soc.*, 2015, **137,** 13706-13714; c) H. Deng, W. Cao, R. Liu, Y. Zhang, B. Liu, *Angew. Chem. Int. Ed.,* 2017, **56,** 5849-5852; d) C. Yuan, B. Du, H. Deng, Y. Man, B. Liu, *Angew. Chem. Int. Ed.,* 2017, **56,** 637-640; e) B. Du, Z. Huang, X. Wang, T. Chen, G. Shen, S. Fu, 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, F. M. Guerra, *Eur. J. Org. Chem.,* 2013, **2013,** 8307-8314.

[19] F. Camps, J. Coll, J. Guitart, *Tetrahedron.,* 1986, **42,** 4603-4609.

[20] H. J. Reich, F. Chow, *J. Chem. Soc., Chem. Commun.,* 1975, 790-791.

[21] C. J. Kowalski, J. S. Dung, *J. Am. Chem. Soc.,* 1980, **102,** 7950-7951.

[22] R. Naef, D. Seebach, *Angew. Chem. Int. Ed.,* 1981, **20,** 1030-1031.

[23] a) A. I. Meyers, B. A. Lefker, *Tetrahedron. Lett.*, 1987, **28**, 1745-1748; b) A. I. Meyers, B. A. Lefker, *Tetrahedron.*, 1987, **43**, 5663-5676; c) A. I. Meyers, 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, D. Friedrich, *J. Am. Chem. Soc.,* 2000, **122,** 9610-9620; b) T. V. Ovaska, S. E. Reisman, M. A. Flynn, *Org. Lett.,* 2001, **3,** 115-117; c) O. L. Epstein, J. K. Cha, *Angew. Chem. Int. Ed.,* 2005, **44,** 121-123.

[25] C. Samojlowicz, M. Bieniek, A. Zarecki, R. Kadyrov, K. Grela, *Chem. Commun.,* 2008, 6282-6284.

[26] L. Jafarpour, H. J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics.,* 1999, **18,** 5416-5419.

[27] X. Huang, L. Song, J. Xu, G. Zhu, B. Liu, *Angew. Chem. Int. Ed.,* 2013, **52,** 952-955.

[28] a) M. S. Chen, M. C. White, *J. Am. Chem. Soc.,* 2004, **126,** 1346-1347; b) M. S. Chen, N. Prabagaran, N. A. Labenz, M. C. White, *J. Am. Chem. Soc.,* 2005, **127,** 6970-6971.

[29] A. A. Ghogare, A. Greer, *Chem. Rev.,* 2016, **116,** 9994-10034.

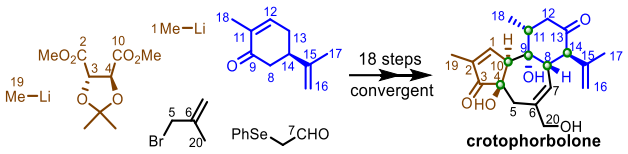
[30] I. Volchkov, D. Lee, *Chem. Soc. Rev.*, 2014, **43,** 4381-4394.

View Article Online
DOI: 10.1039/D0SC02829K

ARTICLE

Entry for the Table of Contents

View Article Online
DOI: 10.1039/D0SC02829K



Convergent total synthesis of crotophorbolone was accomplished in 18 longest linear steps by combining all facilely accessible fragments. Unexpected thermodynamic stability of a *cis,trans*-5/7/6 tricycle was observed, benefiting future synthetic design of rhamnofolane-, tigliane- and daphnane-type diterpenoids.