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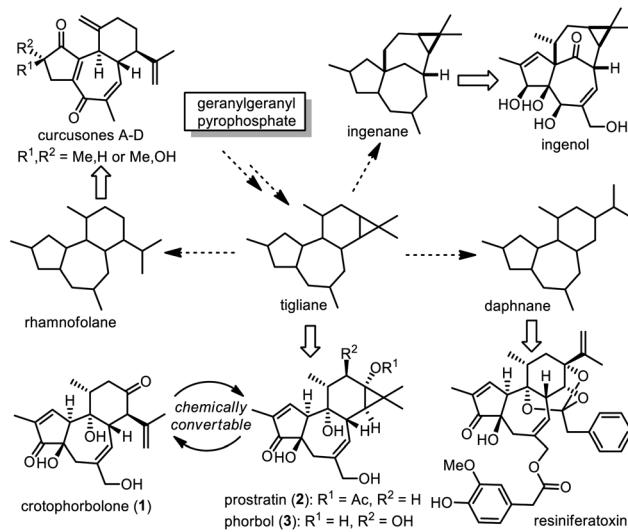
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Introduction

Diterpenoid natural products are structurally versatile and can be classified into different families, many of which are biogenetically correlated. Hecker proposed that among them, tiglane might be regarded as the biosynthetic precursor of ingenane, daphnane and rhamnofolane (Scheme 1),⁴ and this hypothesis was partially supported by co-occurrence of these diterpenoids in the plant families Euphorbiaceae and Thymelaeaceae.² Tiglane 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 tiglane, 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 tiglane-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 tiglane-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, tiglane-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 tiglane-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 tiglane-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.



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‡ 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

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



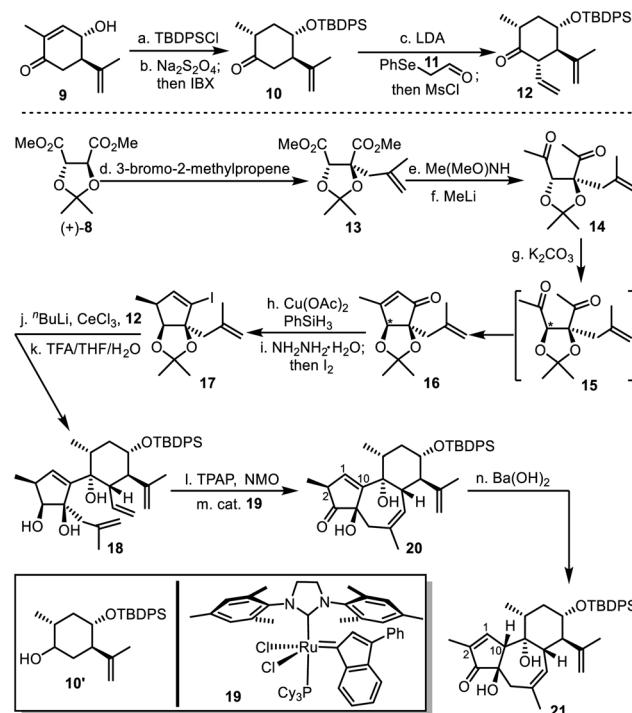
Accompanied by successful chemical syntheses of tiglane-type diterpenoids including prostratin and phorbol,^{5,11,12} the first total synthesis of crotophorbolone was achieved by the Inoue group.¹³ In their pioneering work, an impressive strategy was accomplished in thirty four linear steps, featuring 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-(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**.

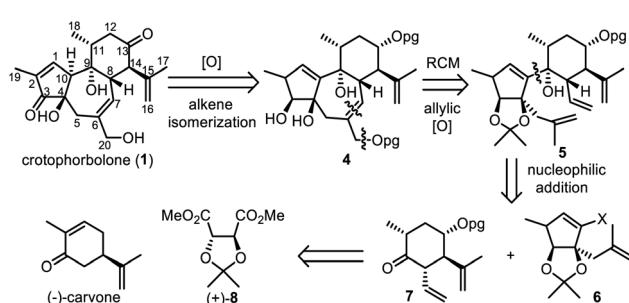
Then synthesis of the five-membered fragment **17** began with methallylation of compound (+)-**8** with high yield and diastereoselectivity.²² Sequential Weinreb amidation and nucleophilic addition with methyl lithium led to compound **14**. The following treatment with potassium carbonate resulted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



Scheme 3 Synthesis of 5/7/6 tricyclic intermediate **21**. Reagents and conditions: (a) TBDPSCl, imidazole, DCM, rt, 3 h, 78%; (b) Na₂S₂O₄, NaHCO₃, 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, ⁿBuLi, 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) ⁿBuLi, 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.

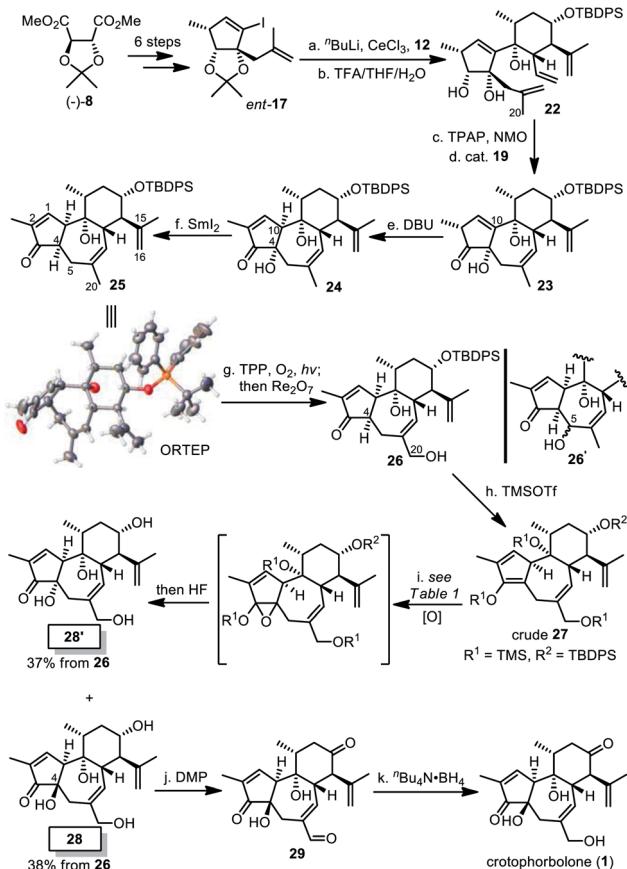
stable *cis*-fused 5/5 bicyclic ring system. Copper-catalyzed 1,4-reduction delivered an intermediate, which was transformed to compound **17** as a surrogate of fragment **6** after formation of hydrazone and subsequent iodination.

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 2 Retrosynthetic analysis.





Scheme 4 Total synthesis of crotophorbolone. Reagents and conditions: (a) $n\text{BuLi}$, CeCl_3 , 12, THF, -78°C , 1 h; (b) TFA/THF/ H_2O (3/4/4), rt, 4 h, 86% over two steps; (c) TPAP, NMO, DCM, 0°C , 2.5 h, 78%; (d) cat. 19, C_6F_6 , reflux, 3 h, 96%; (e) DBU, MeOH, 0°C to rt, 1.5 h, 94%; (f) SmI_2 , THF, 0°C , 20 min, 63% (brsm 90%); (g) TPP, O_2 , $h\nu$, DCE, 12 h, PPh_3 , and then Re_2O_7 , 15 min, 32% (brsm 45%) after two cycles; (h) TMSOTf, Et_3N , DCM, 0°C , 3 h, 72%; (i) see Table 1, then 40% HF/MeCN (1/4), 60°C , 4 h, $28/28' = 38\% / 37\%$; (j) Dess–Martin periodinane, NaHCO_3 , DCM, rt, 3 h, quant.; and (k) $n\text{Bu}_4\text{N}\cdot\text{BH}_4$, MeOH, -40°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 $\text{Ba}(\text{OH})_2$ in hot methanol only led to compound 21 in 44% yield, while

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

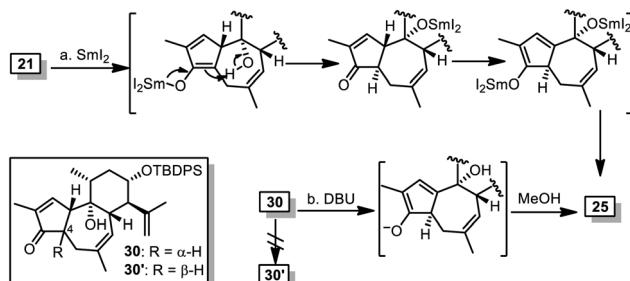
To introduce proper stereochemistry at C_{10} , we decided to invert the absolute configuration of the five-membered fragment by starting the synthesis from (*-*)-8 (Scheme 4). Thus compound *ent*-17, prepared by the same synthetic procedure as compound 17, was coupled with compound 12. The resultant 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 $\text{Ba}(\text{OH})_2$, 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 C_{10} to 1. At this stage, directly inverting the stereochemistry of the quaternary stereogenic center at C_4 was unfeasible. 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 the other two alkenes. However, oxidation with stoichiometric selenium dioxide in THF at 50°C resulted in 26' instead, while its application in other solvents and the combination of catalytic SeO_2 and $^n\text{BuOOH}$ led to decomposition of 25. Then White's protocol with $\text{Pd}(\text{OAc})_2$ -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 $\text{C}_1=\text{C}_2$ and $\text{C}_{15}=\text{C}_{16}$ were inert, probably due to the electron-deficient properties of $\text{C}_1=\text{C}_2$ and the shielding effect of neighbouring TBDPS ether near $\text{C}_{15}=\text{C}_{16}$ respectively.

To introduce a hydroxyl group at C_4 , 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 $\text{MeReO}_3/\text{H}_2\text{O}_2$, epoxidation of crude 27 only resulted in the undesired *cis*-product 28' after desilylation (entries 1 and 2). Although application of *meta*-chloroperbenzoic acid ($^m\text{CPBA}$) at -78°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°C	28' (67%)
2	MeReO_3 (0.25 equiv.), pyridine (2.5 equiv.), H_2O_2 (2.5 equiv.), MeCN/AcOH (19/1), 0°C	28' (57%)
3	NaHCO_3 (2 equiv.), DCM, dropwise addition of $^m\text{CPBA}$ (1.05 equiv.) in DCM, -78°C	N. R. ^b
4	NaHCO_3 (2 equiv.), DCM, dropwise addition of $^m\text{CPBA}$ (1.05 equiv.) in DCM, -40°C	28/28' (1/1.4) 67%
5	NaHCO_3 (2 equiv.), DCM, dropwise addition of $^m\text{CPBA}$ (1.05 equiv.) in DCM, 0°C	28/28' (1.4/1) 59%
6	NaHCO_3 (2 equiv.), DCM, one-batch addition of $^m\text{CPBA}$ (1.05 equiv.), 0°C	28 (38%) ^c
		28' (37%) ^c

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

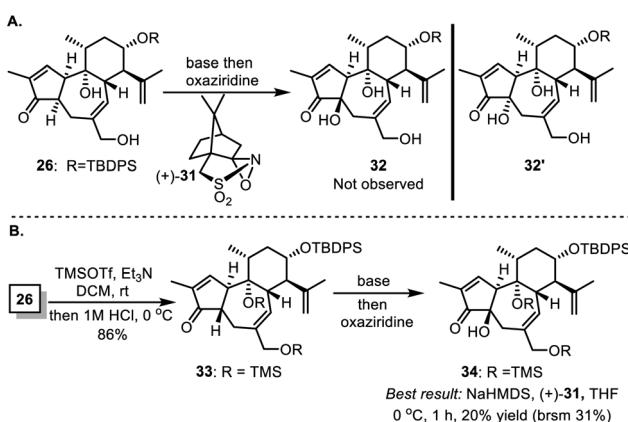


Scheme 5 Thermodynamic stability of **25** over **30'**. Reagents and conditions: (a) SmI_2 , THF, 0 °C, 20 min, 74%; and (b) DBU, MeOH, rt-40 °C, 16 h, 63%.

To our delight, we found that direct addition of $^m\text{CPBA}$ 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 $\beta\text{-OH}$ 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

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