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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, 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 antiretroviral 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

Total synthesis of crotophorbolone†‡

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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 C_{20} and C_4 .

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.

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

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Accompanied by successful chemical syntheses of tiglianetype 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 C_{20} and the $C_6 = C_7$ 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 sixmembered 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

RCN

allylic

Opa

Opa

nucleophilic

addition

Scheme 2 Retrosynthetic analysis.

crotophorbolone (1)

(-)-carvone

alkene

MeO₂C

isomerization HO HO



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, "BuLi, 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; (I) 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($C_8 - C_{10}$) 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 1,4reduction 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 fivemembered ring **17**. In the presence of $CeCl_3$, 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 C_6F_6 (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 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



Scheme 4 Total synthesis of crotophorbolone. Reagents and conditions: (a) ^{*n*}BuLi, CeCl₃, **12**, THF, -78 °C, 1 h; (b) TFA/THF/H₂O (3/4/4), rt, 4 h, 86% over two steps; (c) TPAP, NMO, DCM, 0 °C, 2.5 h, 78%; (d) cat. **19**, C₆F₆, reflux, 3 h, 96%; (e) DBU, MeOH, 0 °C to rt, 1.5 h, 94%; (f) Sml₂, THF, 0 °C, 20 min, 63% (brsm 90%); (g) TPP, O₂, *hv*, DCE, 12 h, PPh₃; and then Re₂O₇, 15 min, 32% (brsm 45%) after two cycles; (h) TMSOTf, Et₃N, 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, NaHCO₃, DCM, rt, 3 h, quant.; and (k) ^{*n*}Bu₄N·BH₄, 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 $Ba(OH)_2$ 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 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 SeO₂ and ^tBuOOH 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 Re₂O₇-mediated rearrangement.³⁰ Notably, allylic positions adjacent to C1=C2 and C15=C16 were inert, probably due to the electron-deficient properties of $C_1 = C_2$ and the shielding effect of neighbouring TBDPS ether near C15=C16 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 MeReO₃/H₂O₂, 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 °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 ₂ O ₂ (2.5 equiv.), MeCN/AcOH (19/1), 0 °C	28' (57%)
3	NaHCO ₃ (2 equiv.), DCM, dropwise addition of ^m CPBA (1.05 equiv.) in DCM, -78 °C	N. R. ^b
4	NaHCO ₃ (2 equiv.), DCM, dropwise addition of ^m CPBA (1.05 equiv.) in DCM, -40 °C	28/28' (1/1.4) 67%
5	NaHCO ₃ (2 equiv.), DCM, dropwise addition of ^m CPBA (1.05 equiv.) in DCM, 0 $^{\circ}$ C	28/28' (1.4/1) 59%
6	NaHCO ₃ (2 equiv.), DCM, one-batch addition of ^m 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. ^mCPBA = meta-chloroperbenzoic acid.



Scheme 5 Thermodynamic stability of 25 over 30'. Reagents and conditions: (a) Sml₂, 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 SmI₂ 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 C₄.

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 C₂₀ and C₄ 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.

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