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Asymmetric Total Synthesis of Crotophorbolone: Construction of the 5/7/6-Fused Ring System via an α-Alkoxy Bridgehead Radical Reaction

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Abstract

This account describes the development of a synthetic route to crotophorbolone (**1**). Compound **1** is classified as a derivative of the tigliane diterpenoids, and possesses a highly oxygenated 5/7/6-fused ABC ring system. First, the six-membered C-ring fragment with five contiguous stereocenters was stereoselectively constructed from (*R*)-carvone. Nucleophilic addition of the three-carbon unit to the C-ring and stereoselective attachment of the five-membered A-ring through the π-allyl Stille coupling reaction provided the substrate for the key radical cyclization. Next, treatment of the O,Se-acetal with V-40 and $(TMS)_3SiH$ in refluxing toluene generated the α-alkoxy bridgehead radical, which participated in the *endo*-cyclization of the seven-membered B-ring with formation of the sterically congested bond in C9-stereospecific and C10-stereoselective manners. The C11-methyl group controlled the C10-stereochemical outcome via a long-range steric interaction, which was supported by the calculated transition state of the abbreviated α-alkoxy bridgehead radical structure. Finally, the functional groups on the 5/7/6-membered ring system were manipulated by Rh-catalyzed C2-olefin isomerization, C13-decarboxylative oxidation and C4-hydroxylation, completing the first total synthesis of **1** in 33 steps from (*R*)-carvone.

1. Introduction

Plants of the Euphorbiaceae and Thymelaeaceae families contain diverse isoprenoids.[1] Diterpenoids occurring in these plants attract significant attention as a source of drugs and probes due to their pharmacologically useful bioactivities. A considerable number of isolated diterpenoids are classified into more than 20 skeletal types including tigliane, daphnane, ingenane, jatrophane, lathyrane, and myrsinane.

To date, more than one hundred tigliane and daphnane diterpenoids have been identified from Euphorbiaceae and Thymelaeaceae, and many of them have been shown to exhibit a remarkably broad range of selective biological activities.[1] For instance, C12,13-diacylated derivative of phorbol,[2] a tigliane, expresses tumor promoting activity (Figure 1), while prostratin,[3] 12-deoxyphorbol-13-acetate, shows latent HIV-activating activity.[4] The daphnane resiniferatoxin[5] is a potent activator of TRPV1,[6] an ion channel protein in the plasma membrane of sensory neurons, and possesses an analgesic effect. These natural products share a highly oxygenated 5/7/6-fused tricyclic ABC-ring system, and only differ in the substitution patterns at the C12,13,14-positions. Since the C1-11 substructure highlighted in gray is identical among these compounds, the C12,13,14-functionalities are

likely to function as important structural elements for diversifying their biological functions.

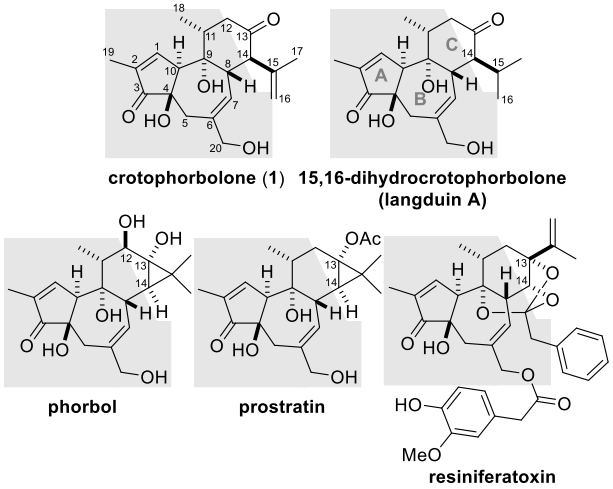


Figure 1. Structures of crotophorbolone (**1**) and related natural products

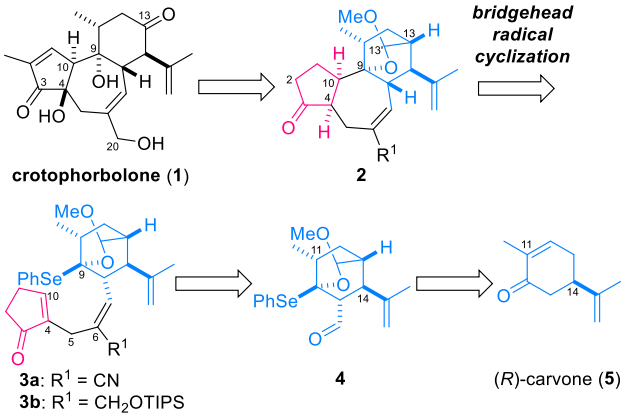
Crotophorbolone (**1**, Figure 1) was isolated as a degraded compound of phorbol in 1934, and its structure was determined in 1969.[7] In 2010, **1** was identified from the dried plant roots of *Euphorbia fischeriana* Steud, which has been used as a traditional Chinese medicine for treatment of edema, ascites and cancer.[8] 15,16-Dihydrocrotophorbolone, designated as langduin A, was also identified from the same plant source.[9] The structures of **1** and langduin A are the same as those of phorbol, prostratin and resiniferatoxin except for the C12,13,14-substitutions on the C-ring. Recently, Wender demonstrated efficient conversion of **1** to prostratin through a four-step manipulation of the C13,14-stereocenters.[4]

Tiglianes, daphnanes and their derivatives collectively have attracted a great deal of attention from the synthetic community due to their significant biological activities and architecturally complex structures.[10] Despite numerous studies, fully chemical construction of tiglianes and daphnanes has been hampered for many decades. Successful total syntheses of this class of molecules were only reported by Wender's group[11] and Cha's group,[12] before our laboratory disclosed the total synthesis of **1** in 2015.[13] Most recently, Baran's group described the biosynthesis-inspired elegant total synthesis of phorbol.[14]

Our primary synthetic interest focused on establishing a new efficient strategy for assembly of the C1-11 common motif of the tigliane and daphnane diterpenoids. Development of such a strategy would provide access to a number of structurally related targets by minimum modifications of substrates and reaction sequences. As the initial phase of this campaign, we selected crotophorbolone (**1**) as the target molecule. In this account, we describe the development of the strategy and tactics for the total synthesis of **1**. The complex 5/7/6-tricyclic structure of **1** was constructed by efficient coupling of simple fragments and powerful 7-*endo* cyclization of a specifically designed α-alkoxy bridgehead radical intermediate.

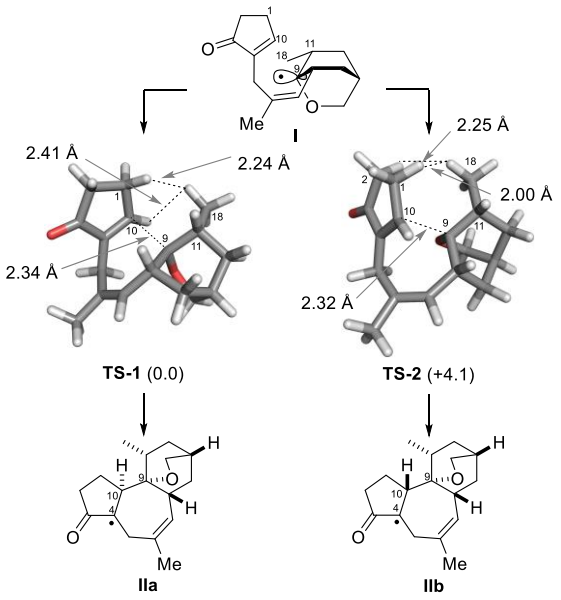
2. Synthetic plan of crotophorbolone

The three *trans*-fused rings of **1** with the two tertiary hydroxy (C4, 9), allylic hydroxy (C20), ketone (C13) and enone groups (C3) present a daunting synthetic challenge (Scheme 1). Crucial to success of the total synthesis would be efficient formation of the sterically congested C9-10 bond between the A- and C-rings. To realize this, we decided to incorporate the intramolecular α-alkoxy bridgehead radical reaction of **3a**/**b**, which was designed to possess the cyclopentenone and O,Se-acetal moieties as the radical acceptor and donor, respectively.[15] The stereochemically defined and highly reactive bridgehead radical generated from oxabicyclo[2.2.2]octane **3a**/**b** would undergo 7-*endo* cyclization into **2** with C9-stereospecific connection of the hindered bond. Installation of the C2-methyl group embedded in the enone system, C4-hydroxylation of the A-ring and oxidative cleavage of the C13-13' bond would transform **2** to the target molecule **1**. Accordingly, this radical-based strategy would simplify the stereochemical issues, because only two stereocenters (C4,10) out of six would need to be introduced upon conversion from **3a**/**b** to **1**. Two substrates **3a** and **3b** with the skipped diene structure were planned to be assembled from the C-ring **4** and the appropriately functionalized five-membered A-ring fragment by Horner-Wadsworth-Emmons olefination and π-allyl Stille coupling reaction, respectively. Pattern recognition of the β-oriented isopropenyl cyclohexane substructure within **4** led us to utilize (*R*)-carvone as the starting material.[16]



Scheme 1. Synthetic plan of crotophorbolone (**1**)

In this approach, the C10-stereocenter must be established during the key radical cyclization (Scheme 2). Since the five chiral centers are concentrated on the C-ring moiety, the stereochemical information of the C-ring of **3** must be transmitted to the achiral A-ring to produce the correct isomer **2** instead of its C10-diastereomer. Computational modeling studies were thus performed to predict the C10-stereoselectivity. To simplify the calculation, the radical intermediate **I** was used as an abbreviated structure of **3a**, whose methoxy, isopropenyl, and OTIPS groups were replaced with H atoms. The two transition states **TS-1** and **TS-2** from **I** were simulated at the UM06-2X/6-31G(d) level of theory.[17] **TS-1**, which leads to the desired **IIa**, was found to be more stable than **TS-2** by 4.1 kcal/mol. Close inspection of the three-dimensional structures of **TS-1** and **TS-2** suggested that the equatorially oriented C11-methyl group influenced the energy difference. While the distances from H18 of the C11-methyl group of **TS-2** to H1 (2.00 Å) and H2 (2.25 Å) are both within the sum of the van der Waals radii (2.40 Å),[18] **TS-1** possesses only one such close contact [H18-1 (2.24 Å), H18-10 (2.41 Å)]. On the basis of the DFT calculations, we expected that the C10-stereocenter would be controlled by the remote C11-stereocenter in a 1,9-relationship.

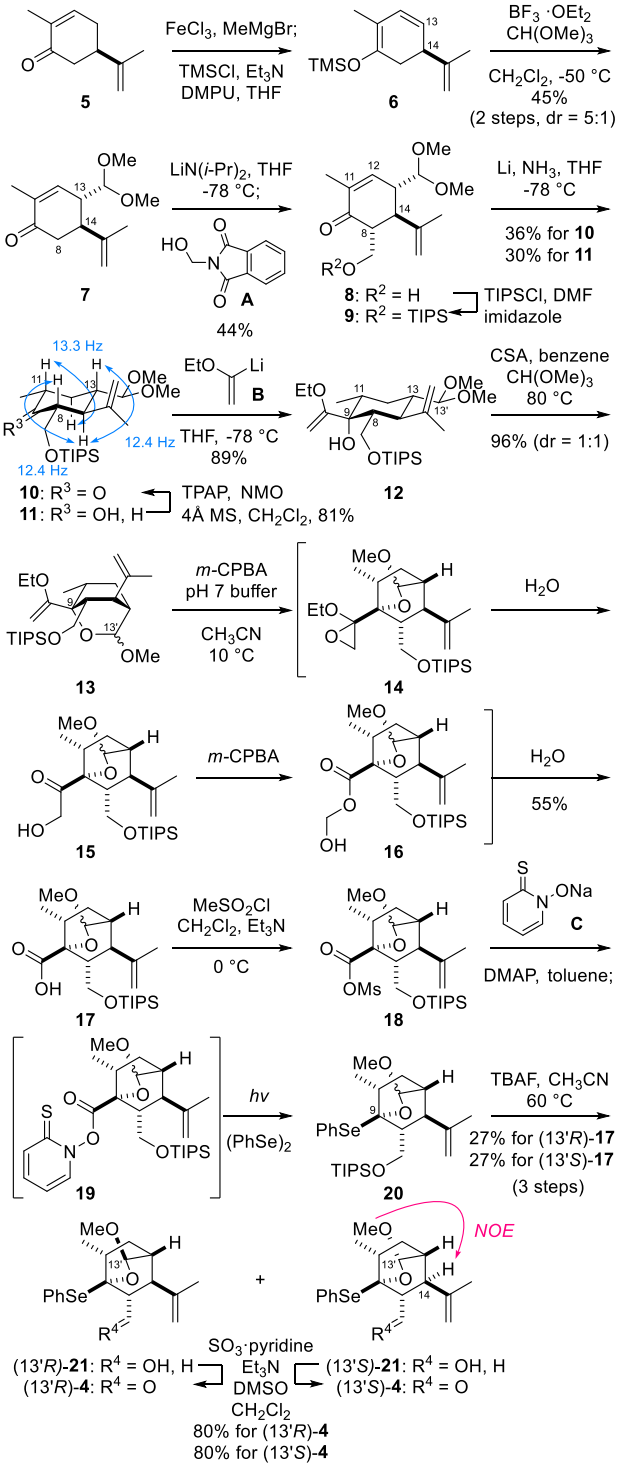


Scheme 2. Calculated transition states of the cyclization at the UM06-2X/6-31G(d) level. Values in parentheses are relative free energies (ΔG in kcal mol^{-1}, 1 atm, 298 K)

3. Construction of the 5/7/6-fused ABC-ring system

3-1. Stereoselective synthesis of the C-ring fragment

The synthesis commenced with conversion of (*R*)-carvone **5** to **12** via introduction of the four new stereocenters (C8, 9, 11, 13) (Scheme 3). Treatment of **5** with TMSCl and MeMgBr in the presence of catalytic $FeCl_3$ regioselectively produced dienoxysilane **6**.[19] Subsequent vinylogous Mukaiyama aldol reaction of **6** by the action of $BF_3{\cdot}OEt_2$ and $CH(OMe)_3$[20] attached the dimethyl acetal group at the C13-position in an anti-selective manner to the bulky C14-isopropenyl group, leading to **7** as the major product (dr = 5:1 at C13). The kinetic enolate generated from **7** by LiN(*i*-Pr)$_2$ underwent the second aldol reaction at -78 ºC with formaldehyde that was released in situ from **A** (2 equiv) and excess LiN(*i*-Pr)$_2$.[21] The exclusive stereoselectivity in forming the C8-center of **8** was again controlled by the C14-substituent. Importantly, the double hydroxymethylation or the elimination of the hydroxy group were not observed under these mild conditions. After TIPS-protection of the primary hydroxy group of **8**, the conjugated C11-12 double bond was reduced under Birch conditions to produce ketone **10** and alcohol **11** with the thermodynamically stable equatorial C11-methyl group. Over-reduced **11** was in turn oxidized to **10** by TPAP.[22] The three large coupling constants among the C8, 11, and 13-protons (J = 12.4, 13.3, 12.4 Hz) confirmed the stereostructure of **10**. The sterically demanding lithiated vinyl ether **B** in turn approached the C9-ketone of **10** equatorially, furnishing the pentasubstituted cyclohexane **12**.



Scheme 3. Stereoselective synthesis of the C-ring fragment **4**

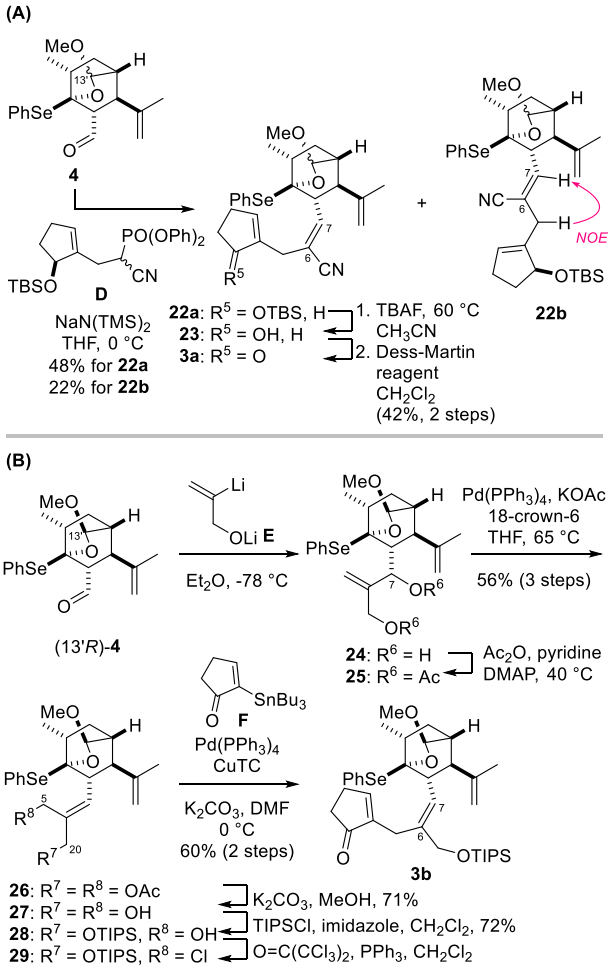
Next, the caged C9,13'-bis-acetal structure **4** was built from **12** through a six-step functional group manipulation. Upon activation with CSA, the axial C9-alcohol of **12** participated in acetal exchange with the C13'-dimethyl acetal to provide oxabicyclo[2.2.2]octane **13** (dr = 1:1 at C13'). The C9-O,Se-acetal was then constructed by conversion of the C9-vinyl ether of **13**.[15a] Vinyl ether **13** was chemoselectively oxidized by *m*-CPBA to carboxylic acid **17**. This single step included a series of reactions in one flask. Thus, the vinyl ether was first epoxidized with *m*-CPBA to generate **14**, the hydrolysis of which afforded the hydroxy ketone intermediate **15**. The highly electrophilic hydroxy ketone **15** rapidly

underwent Baeyer-Villiger oxidation in situ with excess *m*-CPBA, and the resultant hemiacetal **16** was hydrolyzed into carboxylic acid **17**. After mesylation of **17**, the mesyloxycarbonyl group of **18** was converted to the PhSe group of **20** in one-pot by Barton ester formation[23] and subsequent photo-irradiation in the presence of $(PhSe)_2$.[24] Remarkably, the seven events from vinyl ether **13** to O,Se-acetal **20** were realized in three steps, thereby shortening the synthetic route to **20**. Removal of the TIPS group of **20**, followed by chromatographic separation, gave rise to (13'*R*)-**21** and (13'*S*)-**21**. Finally, (13'*R*)-**21** and (13'*S*)-**21** were subjected to SO_3·pyridine oxidation, yielding the C-ring fragments (13'*R*)-**4** and (13'*S*)-**4**, respectively. The C13'-configuration of (13'*S*)-**4** was assigned by NOE experiments.

3-2. Attachment of the A-ring

Attachment of the A-ring substructure was realized by two different coupling methods, resulting in preparation of substrates **3a** and **3b** with CN and CH_2OTIPS groups at C6, respectively. Scheme 4A illustrates the synthesis of **3a** from the C13'-diastereomeric mixture of **4**. In this approach, the *E*-selective Horner-Wadsworth-Emmons olefination[25] was accomplished by using the C-ring aldehyde **4** and the A-ring phosphonate **D**. Use of diphenyl phosphonate **D** instead of its dialkyl phosphate counterpart was crucial for the requisite *E*-C6-7 regiochemistry.[26] Specifically, the phosphonium ylide derived from **D** and $NaN(TMS)_2$ reacted with **4** at 0 °C to yield a 2.2:1 *E*/*Z*-mixture of **22**, providing desired **22a** and its isomer **22b** in 48% and 22% yields, respectively, after separation by HPLC. An NOE experiment of **22b** established the *Z*-geometry of its C6-7 double bond. The TBS group of the thus obtained *E*-isomer **22a** was removed with TBAF in CH_3CN at 60 °C, and the resultant hydroxy group of **23** was oxidized with the Dess-Martin reagent[27] to the ketone of **3a**. Hence, the developed sequence established the *cis*-relationship of the radical donor (C-ring) and acceptor (A-ring), and constructed the skipped diene structure. Despite the coupling efficiency, the inevitable HPLC-purification of *E*-olefin **22a** limited the scalable synthesis of **3a** (below 50 mg), and the C6-cyanide moiety remained to be reduced at a later stage of the total synthesis. Accordingly, an alternative route was planned for preparation of **3b** with the C6-oxidation level corresponding to the targeted **1**.

Compound **3b** with the trialkyl-substituted C6-7 double bond was prepared from (13'*R*)-**4** by employing a stereoselective π-allyl Stille coupling reaction (Scheme 4B). Although not shown, the diastereomeric (13'*S*)-**4** was also utilized as an intermediate for the total synthesis of crotophorbolone (**1**). Before the pivotal Stille reaction, (13'*R*)-**4** was regioselectively converted to allylic chloride **29** in six steps. Aldehyde (13'*R*)-**4** was transformed to diol **24** (dr = 14:1 at C7) by nucleophilic addition of vinyl lithium **E**. The two hydroxy groups of **24** were then acetylated to afford bis-acetate **25**. A reagent combination of Pd(0) and KOAc isomerized disubstituted olefin **25** into trisubstituted olefin **26** via π-allyl formation and site-selective addition of acetate to the less congested primary position.[28] After saponification of **26**, the more exposed C20-hydroxy group of the resultant diol **27** was regioselectively capped with the bulky TIPS group, and the remaining C5-hydroxy group of **28** was chlorinated to give **29**. These two transformations enabled selective activation of C5 over C20 for the π-allyl Stille coupling reaction.[29] However, the resulting C6-7 geometry[30] was partially isomerized under the standard thermal conditions for coupling with **F**. For example, the π-allyl Stille coupling of the corresponding allyl carbonate by using catalytic $Pd(PPh_3)_4$ and stoichiometric CuCl, LiCl and Et_3N in DMSO at 80 ºC resulted in the formation of a 1:1 mixture of **3b** and its stereoisomer in 26% combined yield. The application of the same reaction conditions to the more reactive **29** again was ineffective, leading to decomposition of **29** without isolable products. After screening of additives to avoid the unwanted side reactions and decomposition, copper(I)-thiophene-2-carboxylate (CuTC)[31] was found to significantly accelerate and selectively promote the π-allyl Stille coupling reaction. When **29** was treated with **F**, CuTC and K_2CO_3 in the presence of catalytic $Pd(PPh_3)_4$ in DMF, the C-C bond formation proceeded even at 0 °C to afford **3b** with no geometrical alteration.



Scheme 4. Synthesis of substrates **3a** and **3b** for the key cyclization

3-3. Stereoselective 7-*endo* radical cyclization

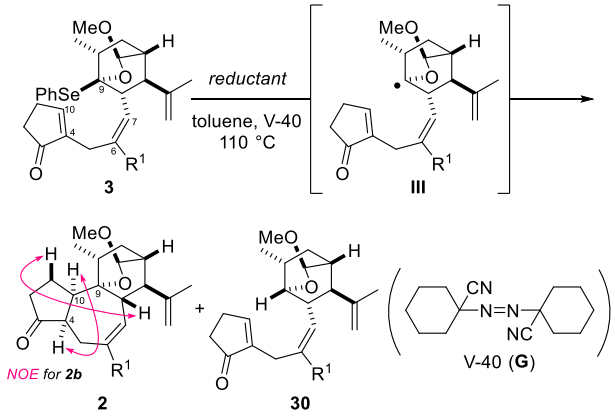
As shown in Schemes 3 and 4, the O,Se-acetal structure at the bridgehead position was retained from **20** to **3a** and **3b**. Despite its inertness towards nucleophilic, oxidative and transition metal reagents, the O,Se-acetal in both **3a** and **3b** served as the reactive radical generating functional group (Table 1). For instance, treatment of **3a** with Ph_3SnH and AIBN in refluxing benzene afforded the α-alkoxy bridgehead radical **III**, which stereospecifically reacted in a 7-*endo* manner according to the electronic guidance of the α,β-unsaturated ketone to afford **2a** (entry 1). As expected from the calculations, the C10-stereocenter was completely controlled to deliver the tricyclic ring system **2a** as the sole isomer after the C4-stereoselective hydrogen transfer from Ph_3SnH. However, the premature reduction of radical **III** occurred to generate **30a**

as a side product (19% yield), and the cyclization to the desired **2a** was inefficient (19% yield). When a higher temperature was applied to the reaction [Ph_3SnH, V-40 (**G**), toluene, 110 ºC, entry 2], the yield of **2a** was increased to 31%, and that of **30a** was decreased to 15% yield. Switching Ph_3SnH to less reactive hydrogen donors Bu_3SnH (entry 3) and $(TMS)_3SiH$ (entry 4) decelerated the direct reduction of radical **III**, resulting in formation of **2a** in 39% and 62% yields, respectively. Remarkably, formation of **30a** was completely suppressed upon the use of $(TMS)_3SiH$. The same reaction conditions [$(TMS)_3SiH$, V-40 (**G**), toluene, 110 ºC, entry 5] were successfully applied to the alternative substrate **3b**, leading to the tricycle **2b** in even higher yield (69%). The stereochemistries at C4, 9 and 10 of **2b** were assigned based on NOE experiments.

Whereas the C10-stereochemical outcome was consistent throughout the entries, the C6-substituents of **3a** and **3b** affected the yields of the products **2a** and **2b** (62% in entry 4 vs. 69% in entry 5). The bulkier TIPS-protected hydroxymethyl group of **3b** in comparison to the CN group of **3a** would preorganize the reacting A-ring to be proximal to the C9-radical by destabilizing the non-productive linear conformation, and/or kinetically protecting the potentially reactive C6-7 double bond.[32]

Most importantly, the present cyclization connected the tetrasubstituted and trisubstituted carbons of **1**, and established the three contiguous stereocenters (C4,9,10) in a single step. The alternative diastereomers, the 6-*exo* cyclization adduct, or the isomerized product of the skipped olefin were not observed in any entries, demonstrating the high stereo-, regio- and chemoselectivities of the radical reaction.

Table 1. Optimization of the radical cyclization



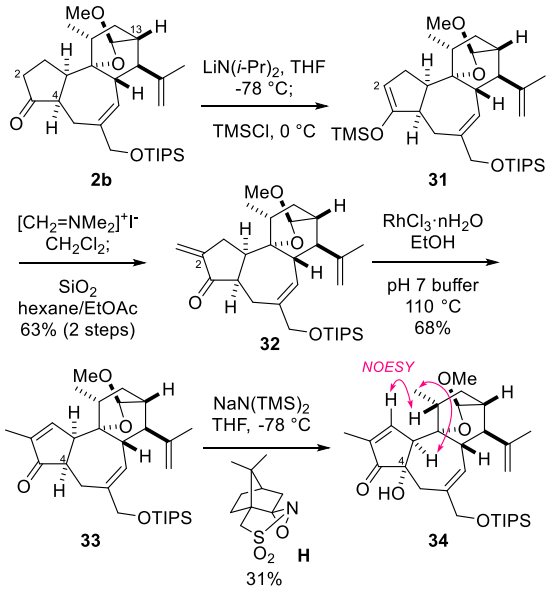
entry	substrate	reductant	products
1[a,b]	**3a**: R^1 = CN	Ph_3SnH	**2a**: 19% **30a**: 19%
2[a]	**3a**: R^1 = CN	Ph_3SnH	**2a**: 31% **30a**: 15%
3[a]	**3a**: R^1 = CN	*n*-Bu_3SnH	**2a**: 39% **30a**: 15%
4[a]	**3a**: R^1 = CN	$(TMS)_3SiH$	**2a**: 62%
5	**3b**: R^1 = CH_2OTIPS	$(TMS)_3SiH$	**2b**: 69%

[a] A 1:1 diastereomixture at C13' was used. [b] The reaction was performed in refluxing benzene using AIBN as a radical initiator.

4. Total synthesis of crotophorbolone

4-1. Functionalization of the A-ring

With the tricyclic framework **2b** in hand, the C2-, C4- and C13-functionalizations from **2b** were explored to complete the total synthesis of **1**. Installations of the olefinic C2-methyl and C4-hydroxy groups of **1** to the A-ring were first investigated (Scheme 5). Ketone **2b** was regioselectively transformed to TMS-enol ether **31**, which was homologated with Eshenmoser's reagent to provide enone **32** after β−elimination of the dimethyl amino group with silica gel.[33] Internalization of the *exo*-olefin of **32** into the more stable *endo*-olefin of **33** was effectively catalyzed by $RhCl_3$.[34] The next C4-hydroxylation was problematic, because it was necessary to perform the oxidation at the sterically shielded angular position without touching the three other potentially oxidizable olefins. After screening hydroxylating reagents, Davis' reagent **H**[35] was found to serve as the oxidant of the enolate derived from **33** and $NaN(TMS)_2$.[36] However, the hydroxy group was exclusively introduced from the α-face, providing the undesired *cis*-fused isomer **34** (31% yield). The structure of **34** was determined by NOESY experiments. Therefore, the C4-reduction (**3** → **2**) and C4-oxidation (**33** → **34**) both took place from the α-faces of the molecules, indicating that the C4-stereochemical outcome originated from the intrinsic three-dimensional structure of the acetal-bridged ring system. According to these data and considerations, we planned to open the C13'-acetal and install a bulky protecting group at the C9-hydroxy group prior to the C4-hydroxylation in order to block the α-face and reverse the C4-stereoselectivity.



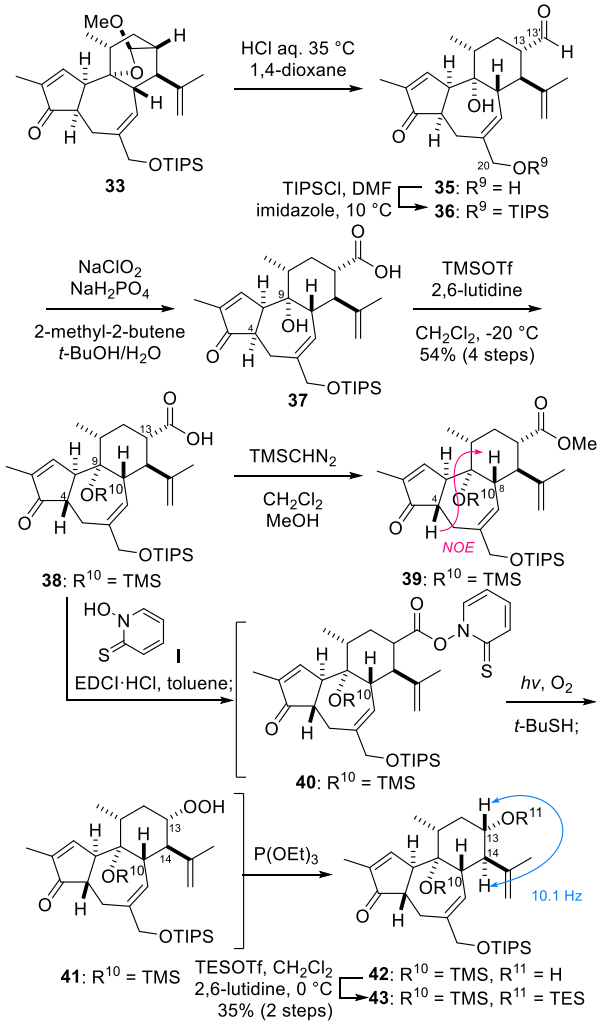
Scheme 5. Functionalization of the A-ring

4-2. C13-decarboxylative oxidation

Acid hydrolysis of **33** opened the cyclic acetal and partially deprotected the C20-hydroxy group, which was re-capped with the TIPS group to afford **36** (Scheme 6). The extra carbon C13' was exchanged to the C13-hydroxy group by radical oxidation. Thus, oxidation of aldehyde **36** to carboxylic acid **37** and subsequent silylation of the C9-tertiary hydroxy group with TMSOTf gave rise to **38**. The latter reaction concomitantly induced the C4-epimerization through TMS-enol formation and protonation from the β-face. The *trans*-fused AB-ring system was elucidated by the NOE correlation of the methylated **39**. Although the C4-epimerization was not a

prerequisite for construction of the targeted **1**, this result implied higher accessibility of reagents from the β-face of the molecule as compared to the cyclic acetal intermediates.

Carboxylic acid **38** was stereoselectively transformed to C13-secondary alcohol **42** by the following one-pot sequence: i) Barton ester formation with **I** and EDCI·HCl; ii) peroxide formation by photo-irradiation in the presence of oxygen and *t*-BuSH; and iii) reductive alcohol formation by $P(OEt)_3$.[37] The adjacent C14-isopropenyl group directed oxygen to approach from the less hindered α-face, producing the α-oriented C13-hydroxy group having a large coupling constant between the two axial protons H13 and H14 (J = 10.1 Hz). The thus constructed hydroxy group of **42** was protected as the TES ether, affording **43**.



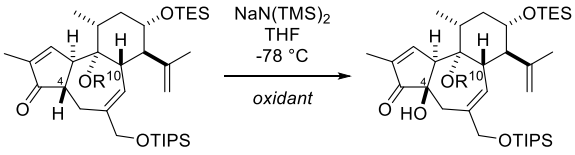
Scheme 6. Installation of the C13-oxygen functionality

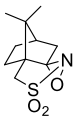
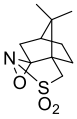
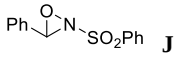
4-3. C4-Hydroxylation

The C4-hydroxylation was re-examined by using **43** as a new substrate (Table 2). Gratifyingly, the sodium enolate derived from **43** and $NaN(TMS)_2$ reacted with Davis' reagent **H** at -78 °C to deliver the desired C4-stereoisomer **44** in 43% yield without forming the undesired C4-epimer (entry 1). It was worthy of note that the yield of **44** was greatly affected by the oxidant. The use of the enantiomer of **H** (*ent*-**H**) resulted in no detectable formation of **44**, and 52% of the starting **43** was recovered (entry 2), while the simple oxidant **J**[38] afforded **44** in 27% yield (entry 3). These results clarified that the three-dimensional structures of both the substrate and the oxidant were crucial to the efficient C4-hydroxylation.

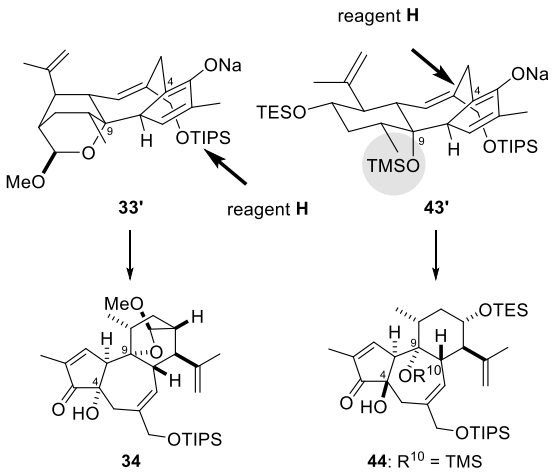
The contrasting stereoselective outcomes of the C4-hydroxylation of **33** and **43** were considered to originate from the C9-oxygen-based functional groups (Scheme 7). As discussed in Section 4-1, while the oxidant approached from the less hindered α-face of the tricyclic framework of **33'**, the bulky TMS-group at C9-O of **43'** would override this intrinsic steric bias by blocking the α-face, thereby allowing installation of the β-oriented C4-OH.

Table 2. Optimization of C4-hydroxylation



entry	oxidant	yield[a]
1	 **H**	43% (62%)
2	 ***ent*-H**	0%[b]
3	 **J**	27% (34%)

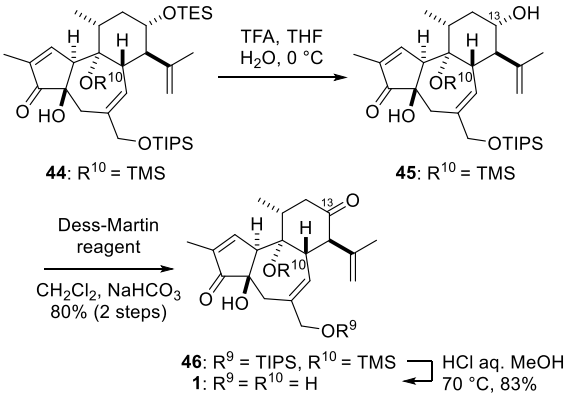
[a] The yields in parentheses are calculated based on recovered **43**. [b] 52% of **43** was recovered.



Scheme 7. Explanation for the stereoselectivity of the C4-hydroxylation

4-4. Completion of the total synthesis

Crotophorbolone (**1**) was synthesized from **44** in three additional steps (Scheme 8). In the reaction of **44** with TFA in a mixture of H_2O and THF at 0 ºC, the most labile TES group of trisilylated **44** was chemoselectively removed, and the liberated C13-alcohol of **45** was oxidized to the corresponding ketone of **46** using the Dess-Martin reagent. Finally, HCl in aqueous MeOH deprotected disilylated **46**, giving rise to crotophorbolone (**1**). Analytical data of the fully synthetic **1** including the specific rotation, IR, NMR, and HRMS, matched those of natural **1**.



Scheme 8. Total synthesis of crotophorbolone (**1**)

5. Summary

In summary, we achieved the first total synthesis of the highly complex diterpenoid crotophorbolone (**1**) with the 5/7/6-ring system in 33 total steps from (*R*)-carvone. Design of the unique oxabicyclo[2.2.2]octane **3b** as the key intermediate enabled us to utilize the stereochemically predestined α-alkoxy bridgehead radical for cyclization of the central seven-membered ring of **2b**. This transformation proved the power and generality of the bridgehead radical reaction for stereoselective construction of the hindered bond within the densely functionalized natural product. Other notable methodological features of the synthesis include: i) stereoselective installations of four stereocenters from (*R*)-carvone **5**; ii) chemoselective construction of the bicyclic bisacetal structure **20** equipped with the PhSe group; iii) regioselective formation of the differentially functionalized C6-trisubstituted olefin **29**; iv) efficient coupling of A-ring **F** and C-ring **29** by the π–allyl Stille coupling using CuTC; and v) highly optimized C2, C4- and C13-functionalization protocols for conversion of **2b** to **1**. The present strategy would be applicable to the unified synthesis of biologically active tiglianes and daphnanes that possess the same C1-11 moiety as **1**. Future investigations in our laboratory will involve such studies.

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Graphical Abstract

Asymmetric Total Synthesis of Crotophorbolone: Construction of the 5/7/6-Fused Ring System via an α-Alkoxy Bridgehead Radical Reaction

Daisuke Urabe, Taro Asaba, Masayuki Inoue*

This account details the asymmetric total synthesis of crotophorbolone with a highly oxygenated 5/7/6-fused ABC ring system. The assembly of the complex structure is highlighted by two key C-C bond formations: the π-allyl Stille coupling between the five-membered A- and six-membered C-rings, and α-alkoxy bridgehead radical cyclization of the seven-membered B-ring.