Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201509160
German Edition: DOI: 10.1002/ange.201509160

Total Synthesis of Crotophorbolone

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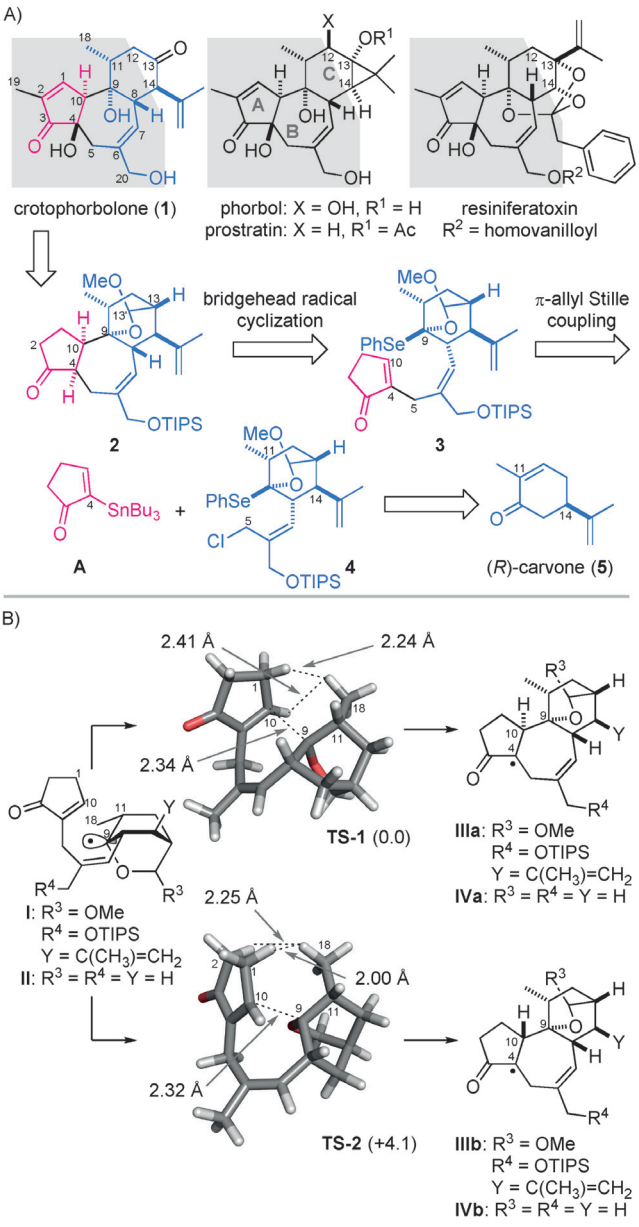
Abstract: *The complex ABC-tricyclic structure of crotophorbolone, a derivative of the tigliane diterpenoids, was assembled by coupling of simple fragments. The six-membered C-ring fragment, having five contiguous stereocenters, was stereoselectively constructed from (R)-carvone. After attachment of the five-membered A-ring through the π-allyl Stille coupling reaction, the α-alkoxy bridgehead radical reaction effected the endo-cyclization of the seven-membered B-ring by forming the sterically congested bond at C9 and C10 stereospecifically and stereoselectively, respectively. Finally, the functional groups on the 5/7/6-membered ring system were manipulated by rhodium-catalyzed C2 olefin isomerization, C13 decarboxylative oxidation, and C4 hydroxylation, thus completing the first total synthesis of crotophorbolone.*

More than one hundred tigliane and daphnane diterpenoids have been identified from the plant families of Euphorbiaceae and Thymelaeaceae,[1] and have been shown to exhibit a remarkably broad range of biological activities. For instance, the tiglianes diacylated phorbol[2] and prostratin[3] show tumor-promoting and latent HIV-activating activities,[4] respectively, while the daphnane resiniferatoxin[5] possesses an analgesic effect (Scheme 1 A). These natural products share a highly oxygenated 5/7/6-fused ABC-ring system, and only differ in the substitution patterns at the C12,C13,C14 positions. As the C1–C11 substructure highlighted in gray is identical among these compounds, the C12,C13,C14 functionalities are likely to function as important structural elements for diversifying their biological functions.

Crotophorbolone (**1**) was isolated as a degraded compound of phorbol in 1934, and its structure was determined in 1969.[6] In 2010, **1** was identified from the dried plant roots of *Euphorbia fischeriana* Steud, which has been used as a traditional Chinese medicine for the treatment of edema, ascites, and cancer.[7] The structure of **1** is the same as those of prostratin and resiniferatoxin except for the C13,C14 substitutions. Recently, Wender and co-workers demonstrated efficient conversion of **1** into prostratin through a four-step manipulation of these two stereocenters.[4]

Tiglianes, daphnanes, and their derivatives, collectively, have attracted a great deal of attention from the synthetic community for many decades because of their significant biological activities and architecturally complex structures.[8] However, even to date, only the groups of Wender[9] and Cha[10] have reported successful total syntheses of this class of molecules. In this context, we became interested in establishing a new and efficient strategy for assembly of the C1–C12 motif which is common to these natural products. Development of such a strategy would provide access to a number of structurally related targets by minimum modifications of



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

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509160.

substrates and reaction sequences. As the initial phase of this campaign, we selected crotophorbolone (**1**) as a target molecule. Herein we report the total synthesis of **1** from (*R*)-carvone (**5**) by employing a π-allyl Stille coupling reaction and an α-alkoxy bridgehead radical mediated cyclization for stereoselective construction of the common C1–C12 tricycle.

The three rings of **1**, having five various oxygen-based functionalities, present a daunting synthetic challenge (Scheme 1 A). Crucial to the success of the total synthesis would be efficient formation of the sterically congested C9–C10 bond between the A- and C-rings. To realize this connection, we decided to incorporate the intramolecular α-alkoxy bridgehead radical reaction of **3**, which was designed to possess the cyclopentenone and O,Se-acetal moieties as the radical acceptor and donor, respectively.[11] The stereochemically defined and highly reactive bridgehead radical generated from the oxabicyclo[2.2.2]octane **3** would undergo a 7-*endo* cyclization into **2** with a C9 stereospecific connection of the hindered bond. Appropriate C2 and C4 functionalizations of the A-ring and oxidative cleavage of the C13–C13′ bond would transform **2** into the target molecule **1**. Accordingly, this radical-based strategy would simplify the stereochemical issues, because only two stereocenters (C4,C10) out of six need to be introduced upon conversion from **3** into **1**. The skipped diene structure of the key intermediate **3** would be synthesized from the achiral A-ring **A** and the chiral C-ring **4** by applying the π-allyl Stille coupling reaction. Pattern recognition of the β-oriented isopropenyl cyclohexane substructure within **4** led us to utilize (*R*)-carvone (**5**) as the starting material.[12]

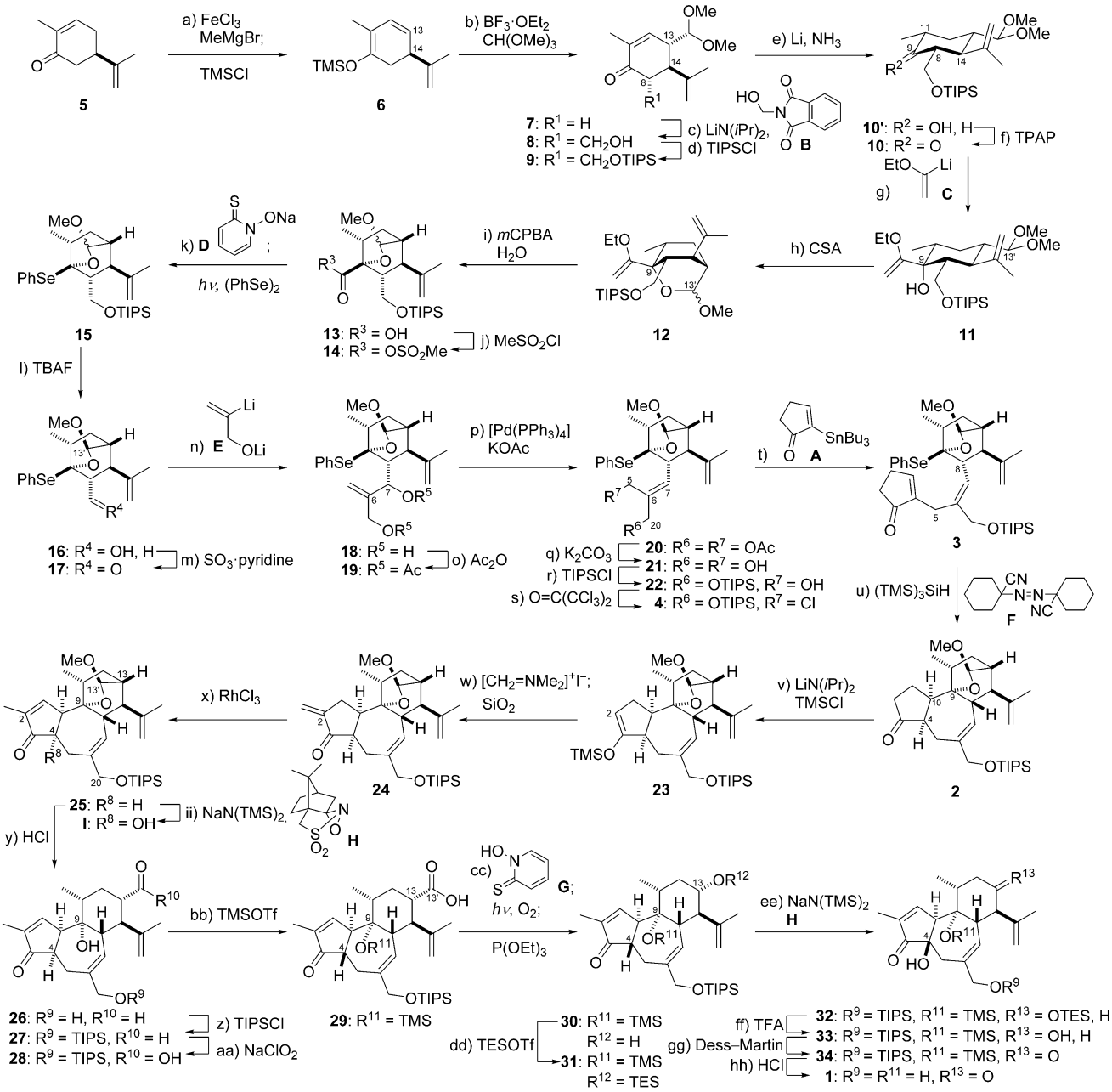
In this approach, the C10 stereocenter must be established upon cyclization of the radical **I** (Scheme 1 B). Since the five chiral centers are concentrated on the C-ring moiety, the stereochemical information of the C-ring of **I** must be transmitted to the achiral A-ring to produce the correct isomer **IIIa** instead of **IIIb**. Computational modeling studies of **II**, an abbreviated structure of **I**, were thus performed to predict the C10 stereoselectivity. Specifically, the two transition-states, **TS-1** and **TS-2**, from **II** were simulated at the UM06-2X/6-31G(d) level of theory.[13] **TS-1**, which leads to the desired **IVa**, was found to be more stable than **TS-2** by 4.1 kcal mol^{-1}. Close inspection of the three-dimensional structures of **TS-1** and **TS-2** suggested that the equatorially oriented C11 methyl group influenced their 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),[14] **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.

The synthesis commenced with conversion of (*R*)-carvone (**5**) into **11** by introduction of the four new stereocenters (C8, C9, C11, and C13; Scheme 2). Treatment of **5** with TMSCl and MeMgBr in the presence of catalytic $FeCl_3$ regioselectively produced the dienoxysilane **6**.[15] Subsequent vinylogous Mukaiyama aldol reaction of **6** by the action of $BF_3{\cdot}OEt_2$ and $CH(OMe)_3$[16] 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 (d.r. = 5:1). The kinetic enolate generated from **7** by $LiN(i\text{Pr})_2$ underwent the second aldol reaction with formaldehyde, which was released in situ from **B**.[17] The exclusive stereoselectivity in forming the C8 center of **8** was again controlled by the C14 substituent. After TIPS-protection of the primary hydroxy group of **8**, the conjugated C11–C12 double bond was reduced under Birch conditions to produce the ketone **10** and alcohol **10′** with the thermodynamically stable equatorial C11 methyl group. The over-reduced **10′** was in turn oxidized to **10** by TPAP.[18] Then, the sterically demanding lithiated vinyl ether **C** added to the C9 ketone of **10** equatorially, furnishing the pentasubstituted cyclohexane **11**.

Next, the caged C9,C13′ bis(acetal) structure **16** was built from **11** through a five-step functional-group manipulation. Upon activation with CSA, the axial C9 alcohol of **11** participated in acetal exchange with the C13′ dimethyl acetal to provide the oxabicyclo[2.2.2]octane **12** (d.r. = 1:1 at C13′). The C9 O,Se-acetal was then constructed by conversion of the C9 vinyl ether of **12**.[8j] Thus, the vinyl ether **12** was chemoselectively oxidized by *m*CPBA to the carboxylic acid **13** via the intermediacy of the hydroxy ketone. After mesylation of **13**, the mesyloxycarbonyl group of **14** was converted into the PhSe group in a one-pot by Barton ester formation[19] and subsequent photoirradiation in the presence of $(PhSe)_2$.[20] Removal of the TIPS group of **15**, followed by chromatographic separation, gave rise to (13′*R*)-**16** and (13′*S*)-**16**.

The key intermediate **3** was prepared from (13′*R*)-**16**[21] by stereoselective construction of the skipped diene structure. The three-carbon extension from the aldehyde **17**, which was obtained by $SO_3{\cdot}$pyridine oxidation, was realized by nucleophilic addition of the vinyl lithium **E**, resulting in formation of **18**. The two hydroxy groups of **18** were simultaneously acetylated to afford **19**. A reagent combination of Pd^0 and KOAc isomerized the disubstituted olefin **19** into the trisubstituted olefin **20** by π-allyl formation and site-selective addition of acetate to the less-congested primary position.[22] After saponification of **20**, the more exposed C20 hydroxy group of the resultant diol **21** was regioselectively capped with a bulky TIPS group, and the remaining C5 hydroxy group of **22** was chlorinated to give **4**. These two transformations enabled selective activation of C5 over C20 for the π-allyl Stille coupling reaction.[23] However, the resulting C6–C7 geometry[24] of **4** was partially isomerized under the standard thermal conditions for coupling with **A**.[25] After screening of additives to avoid this unwanted reaction, CuTC[26] was found to significantly accelerate and selectively promote the π-allyl Stille coupling reaction. When **4** was treated with **A**, 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 **3** with no geometrical alteration. Hence, the requisite *cis* relationship between the radical donor (C-ring) and acceptor (A-ring) was secured at this stage.

Most importantly, the O,Se-acetal structure tolerated various nucleophilic and transition-metal reagents from **15** to **3**, yet functioned as the radical-generating functional group. Treatment of **3** with $(TMS)_3SiH$ and V-40 (**F**) in



Scheme 2. Total synthesis of crotophorbolone (**1**). Reagents and conditions: a) $FeCl_3$, MeMgBr, TMSCl, Et_3N, *N*,*N*′-dimethylpropyleneurea, THF; b) $CH(OMe)_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −50 °C, 45%, (d.r. = 5:1, 2 steps); c) $LiN(iPr)_2$, THF, −78 °C; **B**, 44%; d) TIPSCl, imidazole, DMF; e) Li, NH_3, THF, −78 °C, 30% for **10′**, 36% for **10** (2 steps); f) TPAP, *N*-methylmorpholine *N*-oxide, 4 Å MS, CH_2Cl_2, 81%; g) **C**, THF, −78 °C, 89%; h) CSA, benzene, $CH(OMe)_3$, 80 °C, 96% (d.r. = 1:1); i) *m*CPBA, pH 7 buffer, CH_3CN, 10 °C, 55%; j) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; k) **D**, DMAP, toluene; *hν*, $(PhSe)_2$; l) TBAF, CH_3CN, 60 °C, 54% [27% for (13′*R*)-**16**, 27% for (13′*S*)-**16**, 3 steps]; m) $SO_3{\cdot}$pyridine, Et_3N, DMSO, CH_2Cl_2, 80%; n) **E**, Et_2O, −78 °C; o) Ac_2O, DMAP, pyridine, 40 °C; p) $[Pd(PPh_3)_4]$, KOAc, 18-crown-6, THF, 65 °C, 56% (3 steps); q) K_2CO_3, MeOH, 71%; r) TIPSCl, imidazole, CH_2Cl_2, 72%; s) $O{=}C(CCl_3)_2$, PPh_3, CH_2Cl_2; t) **A**, $[Pd(PPh_3)_4]$, CuTC, K_2CO_3, DMF, 0 °C, 60% (2 steps); u) $(TMS)_3SiH$, **F**, toluene, 110 °C, 69%; v) $LiN(iPr)_2$, THF, −78 °C; TMSCl, −78 °C to 0 °C; w) $[CH_2{=}NMe_2]^+I^-$, CH_2Cl_2; SiO_2, *n*-hexane/EtOAc (10:1), 63% (2 steps); x) $RhCl_3{\cdot}nH_2O$, EtOH/pH 7 buffer (5:1), 110 °C, 68%; y) HCl aq., 1,4-dioxane, 35 °C; z) TIPSCl, imidazole, DMF, 10 °C; aa) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O; bb) TMSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 54% (4 steps); cc) **G**, EDCI·HCl, toluene; *hν*, O_2, *t*BuSH; $P(OEt)_3$; dd) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 35% (2 steps); ee) $NaN(TMS)_2$, THF, −78 °C; **H**, 43% (brsm 62%); ff) TFA, THF/H_2O (5:1), 0 °C; gg) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2, 80% (2 steps); hh) HCl, MeOH/H_2O (3:1), 70 °C, 83%; ii) $NaN(TMS)_2$, THF, −78 °C; **H**, −78 °C, 31%. brsm = based on recovered starting material, CSA = 10-camphorsulfonic acid, CuTC = copper(I)-thiophene-2-carboxylate, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, EDCI·HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, *m*CPBA = *m*-chloroperbenzoic acid, TBAF = tetra-*n*-butylammonium fluoride, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TIPS = triisopropylsilyl, TMS = trimethylsilyl, TPAP = tetra-*n*-propylammonium perruthenate.

refluxing toluene indeed afforded the α-alkoxy bridgehead radical **I** (see Scheme 1 B), which stereospecifically reacted in a 7-*endo* manner according to the electronic guidance of the α,β-unsaturated ketone. As expected from the calculations, the C10 stereocenter was completely controlled to deliver the tricyclic ring system **2** as the sole isomer after the C4 stereoselective hydrogen transfer to intermediate **IIIa**. Therefore, this single step successfully connected the tetrasubstituted and trisubstituted carbon atoms of **1**, and installed the three contiguous C4,C9,C10 stereocenters. Notably, the alternative diastereomers, the 6-*exo* cyclization adduct or the isomerized product of the skipped olefin were not observed, thus demonstrating the high stereo-, regio-, and chemoselectivities of the radical cyclization.

With the tricyclic framework **2** in hand, the C2, C4, and C13 functionalizations from **2** were explored to complete the total synthesis of **1**. The olefinic C2 methyl group of **1** was first constructed in three steps. The ketone **2** was regioselectively transformed into the TMS enol ether **23**, which was homologated with Eschenmoser's reagent to provide the enone **24** after β-elimination of the dimethyl amino group with silica gel.[27] Isomerization of the *exo*-olefin of **24** into the more stable *endo*-olefin of **25** was effectively catalyzed by $RhCl_3$.[28] Next, the extra carbon C13′ was exchanged to the C13 hydroxy group by radical oxidation. Before doing so, the cyclic acetal of **25** was opened by acid hydrolysis, and the partially deprotected C20 hydroxy group was re-capped with a TIPS group to afford **27**. Oxidation of the aldehyde **27** to the carboxylic acid **28** and subsequent silylation of the C9 tertiary hydroxy group with TMSOTf gave rise to **29**. The latter reaction concomitantly induced the C4 epimerization through TMS enol formation and protonation. Finally, the carboxylic acid **29** was stereoselectively transformed into the C13 secondary alcohol **30** by the following one-pot sequence: a) Barton ester formation with **G** and EDCI·HCl; b) peroxide formation by photoirradiation in the presence of oxygen and *t*BuSH; and c) reductive alcohol formation by $P(OEt)_3$.[29] The thus constructed C13 hydroxy group of **30** was protected as the TES ether to afford **31**.

The C4 hydroxylation, C13 oxidation and deprotection ultimately furnished the target molecule **1** from **31**. Among these requisite transformations, stereoselective implementation of the C4 hydroxy group was most problematic, because the oxidation was required to be performed at the sterically shielded angular position without touching the three potentially oxidizable olefins. In fact, proper choice of the substrates and reagents was crucial to the success.[30] When the tricyclic ketone **31** was subjected to $NaN(TMS)_2$, the resultant sodium enolate reacted with Davis' reagent (**H**)[31] to deliver the desired C4 stereoisomer **32** as a single isomer. In contrast, treatment of the tetracyclic ketone **25** with $NaN(TMS)_2$ and **H** resulted in sole formation of the undesired C4 stereoisomer **I**. These contrasting results would originate from the C9 oxygen-based functional groups of **25** and **31**. As the C4 stereochemical outcomes were consistent in the reduction (**3**→**2**) and oxidation (**25**→**I**), the α-face of the intermediates appeared to be less shielded. The bulky OTMS group at C9 of **31** would override this intrinsic steric bias by blocking the α-face, thus allowing installation of the β-oriented C4 hydroxy group. In the subsequent reaction with TFA, the TES group of the trisilylated **32** was chemoselectively removed, and the liberated C13 alcohol of **33** was oxidized using the Dess–Martin reagent to the corresponding ketone of **34**. Lastly, deprotection of disilylated **34** using a methanolic solution of hydrochloric acid gave rise to crotophorbolone (**1**). Analytical data of the fully synthetic **1**, including the specific rotation, IR, NMR, and HRMS, matched those of natural **1**.

In summary, we achieved the first total synthesis of the highly complex diterpenoid crotophorbolone (**1**) with the 5/7/6-ring system from (*R*)-carvone (**5**) in 33 linear steps. Design of the unique oxabicyclo[2.2.2]octane **3**, as the key intermediate, enabled us to utilize the stereochemically predestined α-alkoxy bridgehead radical for cyclization of the central seven-membered ring of **2**. 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: 1) stereoselective installations of four stereocenters from **5**; 2) chemoselective construction of the bicyclic bis(acetal) structure **16** equipped with the PhSe group; 3) regioselective formation of the differentially functionalized C6 trisubstituted olefin **4**; 4) efficient coupling of the A-ring **A** and C-ring **4** by the π-allyl Stille coupling using CuTC; and 5) highly optimized C2, C4, and C13 functionalization protocols for conversion of **2** into **1**. Further synthetic studies of biologically active tiglianes and daphnanes, which possess the same C1–C12 moiety as **1**, are currently being explored based on the present synthetic strategy.

Acknowledgements

This research was financially supported by the Funding Program a Grant-in-Aid for Scientific Research (A) (JSPS) to M.I., and (C) (JSPS) and on Innovative Areas (MEXT) to D.U. A fellowship to T.A. from Graduate Program for Leaders in Life Innovation (MEXT) is gratefully acknowledged.

Keywords: cross-coupling · natural products · radical reactions · terpenoids · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14457–14461
Angew. Chem. **2015**, *127*, 14665–14669

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Received: September 30, 2015
Published online: October 22, 2015

