JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Total Synthesis of Atisane-Type Diterpenoids: Application of Diels–Alder Cycloadditions of Podocarpane-Type Unmasked *ortho*-Benzoquinones

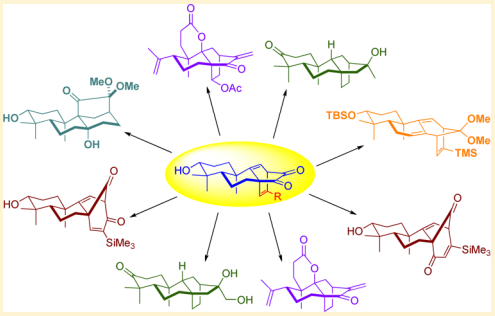
Liqiang Song,[†,§] Guili Zhu,[†,§] Yongjiang Liu,[†] Bo Liu,[*,†,‡] and Song Qin[†]

[†]Key Laboratory of Green Chemistry & Technology of the Ministry of Education, College of Chemistry, Sichuan University, Chengdu, Sichuan 610064, China

[‡]State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China

Supporting Information

ABSTRACT: Few examples of [4 + 2] cycloaddition with unmasked *ortho*-benzoquinones (UMOBs) as carbodiene have been reported in complex molecule synthesis. Herein we report that this cycloaddition with podocarpane-type UMOB was developed and applied to construct fully functionalized bicyclo[2.2.2]octanes. Based on this methodology, divergent total syntheses of atisane-type diterpenoids, including (±)-crotobarin, crotogoudin, atisane-3β,16α-diol, and 16*S*,17-dihydroxy-atisan-3-one, were accomplished in 14, 14, 12, and 16 steps, respectively. Key elements in these total syntheses include: (1) $FeCl_3$-catalyzed cationic cascade cyclization to construct podocarpane-type skeleton; (2) Mn(III)/Co(II)-catalyzed radical hydroxylation of alkene with high regio-, diastereo-, and chemoselectivities; (3) and a ketal-deprotection/lactone-opening/deprotonation/lactonization cascade. Additionally, the synthetic utility of the fully functionalized bicyclo[2.2.2]octane framework was further elucidated by applying ring distortion strategy to afford different skeleton-rearranged natural product-like compounds.



INTRODUCTION

Inspired by the biogenetic connection between tricyclic and tetracyclic diterpenoids via a carbocation intermediate, synthetic chemists speculate that a podocarpane-type intermediate could chemically provide a generalizable synthetic pathway to both tricyclic and tetracyclic diterpenoids, through dearomatization of podocarpane and subsequent appropriate functionalization. Although the feasibility of this tactic toward tricyclic diterpenoids has already been demonstrated,[1] the transformation from the podocarpane-type diterpenoids to tetracyclic diterpenoids is underdeveloped and we believe it merits additional exploration (Scheme 1).

Notably, the atisane-type diterpenoid or its enantiomeric natural counterpart is a special member among the tetracyclic diterpenoid family. It is biosynthetically related to abietane, beyerane, kaurane, and other types of diterpenoids, all of which are generated in a carbocation-based mechanism catalyzed by diterpene cyclase.[2] Architectures including atisane occur frequently in the C_{20}-diterpenoid alkaloid family.[3] And the unique bicyclo[2.2.2]octane skeleton within C_{20}-diterpenoid alkaloids can be transformed to the bicyclo[3.2.1]octane skeleton in C_{18}- and C_{19}- diterpenoid alkaloids,[4,5] based on Overton's conversion of atisane to aconane.[6]

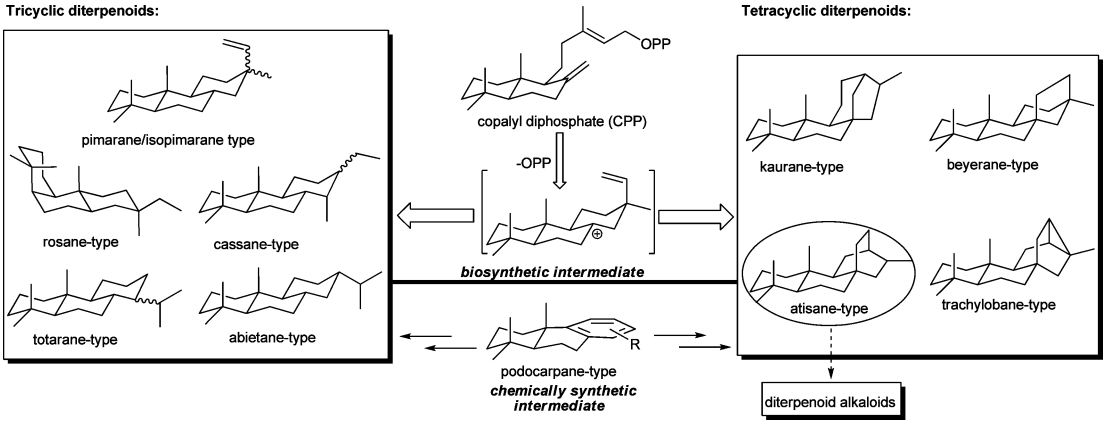
Due to their structural diversity and biogenetic importance, atisane-related diterpenoids and diterpenoid alkaloids, as well as their *ent*-family members, have been the focus of numerous synthetic studies and total syntheses.[7] Four principal approaches have been explored to construct the bicyclo[2.2.2]-octane substructure in atisane-type natural products: (1) intramolecular nucleophilic cyclization, including aldol, double Michael, or S_N2 reactions;[8] (2) intramolecular radical cyclization of alkyne;[9] (3) rearrangement from a kaurane- or trachylobane-type skeleton;[10] and (4) intra- or intermolecular Diels–Alder cycloaddition.[11] However, to the best of our knowledge, no one has reported attempts to use unmasked *ortho*-benzoquinone as carbodiene in Diels–Alder cycloaddition to construct bicyclo[2.2.2]octane architecture in natural product synthesis.

Besides these developed synthetic strategies, Wiesner's group and Baran's group installed this bicyclo[2.2.2]octane architecture from a podocarpane-type intermediate, using a sequential dearomatization/allene [2 + 2] cycloaddition/ozonolysis/acidic rearrangement strategy.[8a,f] Here we describe an alternative strategy involving a dearomatization/[4 + 2] cycloaddition sequence, in which unmasked *ortho*-benzoquinone is used as carbodiene in [4 + 2] cycloaddition. To further demonstrate synthetic significance of this Diels–Alder cycloaddition of podocarpane-type unmasked *ortho*-benzoquinone, a [4 + 2] cycloadduct in our strategy was converted to the counterparts of several representative *ent*-atisane-type and *ent*-3,4-*seco*-atisane

Received: August 28, 2015
Published: October 4, 2015

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706–13714

Scheme 1. Biosynthetic and Chemically Synthetic Connections among Tricyclic and Tetracyclic Diterpenoids[a]



[a]Applicable to *ent*-family diterpenoids as well.

natural products, as well as other skeleton-rearranged diterpenoids.

In 2010, crotobarin (**1**) and crotogoudin (**2**) were isolated from *Croton barorum* and *Croton goudotii* (Figure 1).[12] They are cytotoxic to several human cancer cell lines (IC_{50} 0.49−2.5 μM) and effectively induce apoptosis. Both molecules belong to the rare *ent*-3,4-*seco*-atisane family of diterpenoids[13] and possess a unique tetracyclic framework with five stereocenters. The interesting bioactivity and challenging molecular architecture of crotobarin and crotogoudin make them attractive targets for synthetic chemists, and these efforts have culminated in total synthesis of *ent*-crotogoudin by Carreira's group,[14] as well as several synthetic studies.[15] Carreira's total synthesis includes a baker's yeast-catalyzed desymmetrization of *meso*-[2.2.2] diketone, a rhodium-catalyzed cyclopropanation and a SmI_2-promoted radical cyclopropane-opening/annulation/elimination cascade to access the tetracyclic skeleton. As a result of this total synthesis, the absolute configuration of natural crotogoudin was determined, and the compound was classified into the *ent*-atisane family. Compounds **3** and **4** were isolated and characterized more than 20 years ago.[16] They embrace typical atisane-type skeleton with multiple stereocenters and thus were selected as our synthetic targets to illustrate the diversity of our synthetic strategy.

Considering the inherent relationship between *ent*-atisane and *ent*-3,4-*seco*-atisane, we formulated a hypothesis for biogenesis of *ent*-3,4-*seco*-atisane by taking crotogoudin as an example (Scheme 2). The C3 carbonyl in compound **A** can

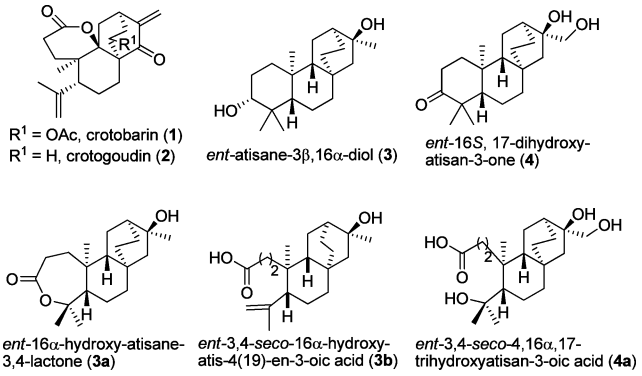
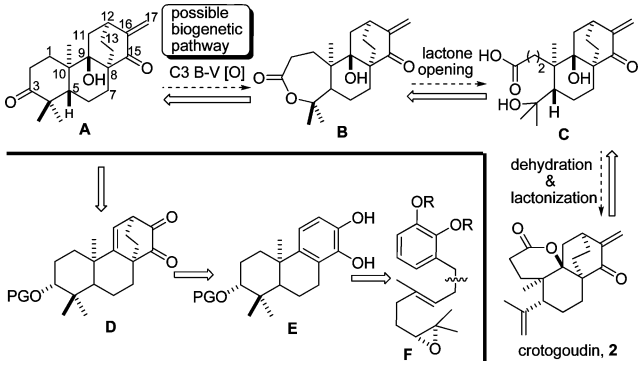


Figure 1. Structures of representative atisane-type diterpenoids.

Scheme 2. Hypothesis for Biogenesis of *ent*-3,4-*seco*-Atisane and Retrosynthetic Analysis



undergo Baeyer−Villiger oxidation to give **B**, a possible biosynthetic process catalyzed by Baeyer−Villiger monooxygenase (BVMO) in Nature.[17,18] This oxidation can be followed by lactone opening in the presence of lactone hydrolase to afford compound **C**.[19] Subsequent dehydration and lactonization catalyzed by enzyme afford crotogoudin in a streamlined fashion.[20] The proposed biohypothesis can be partly evidenced by co-occurrence of compound **3** and its natural siblings, **3a** and **3b**, in *Excoecaria agallocha*,[13c] and co-occurrence of compounds **4** and **4a** in *Euphorbia acaulis*.[21]

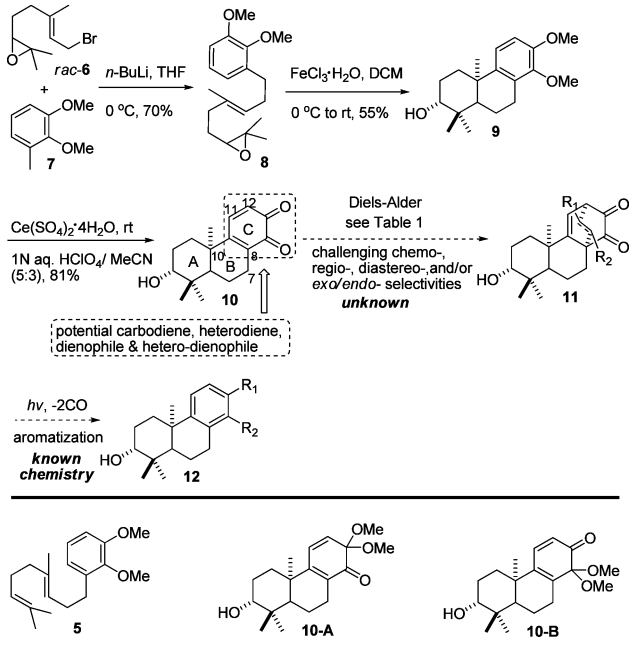
Retrosynthetic analysis suggested that we could obtain compound **A** from compound **D** via multistep functional group transformations. Oxidative dearomatization of compound **E** would give *ortho*-benzoquinone, which could undergo [4 + 2] cycloaddition to yield compound **D**. Compound **E**, a podocarpane-type diterpenoid analogue, could be prepared from compound **F** via cationic cascade cyclization.

RESULTS AND DISCUSSION

Synthesis of the Unmasked Benzoquinone 10. Since site-selective epoxidation at the terminal trisubstituted alkene in the polyene **5** was unsuccessful,[22] we initiated the total synthesis by coupling epoxy geranyl bromide (**6**)[23] with functionalized benzyl anion, generated *in situ* from the commercially available compound **7** (Scheme 3). This coupling approach to compound **8** was exploited as a straightforward entry to precursor of podocarpane-type diterpenoids. Then a biomimetic, Lewis acid-catalyzed cascade polycyclization of

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706−13714

Scheme 3. Synthesis of 10

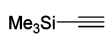
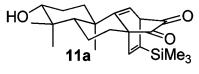
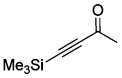
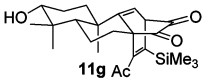
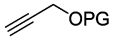
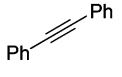
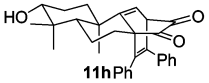
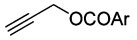
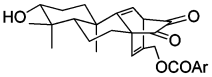
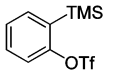
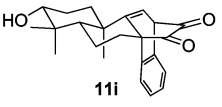
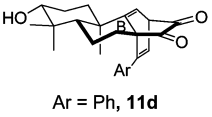
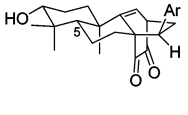


epoxy substrate **8** was developed.[23b,24] Extensive screening identified cheap and environment-friendly iron(III) chloride as the optimal catalyst, affording compound **9** as the sole isolable diastereomer in 55% yield.[8a] This cascade reaction generated two new stereogenic centers in a substrate-controlled fashion and formed two C−C bonds simultaneously. While oxidation of **9** with CAN gave **10** in only 43% yield, using $Ce(SO_4)_2 \cdot 4H_2O$ increased the yield to 81%.

Diels−Alder Cycloaddition of the Unmasked Benzoquinone 10. Masked *ortho*-benzoquinone (MOB) is widely used in intermolecular and intramolecular Diels−Alder reaction in organic synthesis including natural product synthesis.[25] Recently, Fukuyama and Yokoshima's group successfully realized intermolecular Diels−Alder cycloaddition between a complex MOB and ethylene in total synthesis of lepenine, a diterpenoid alkaloid containing bicyclo[2.2.2]octane architecture.[11e] To our surprise, reacting traditional MOB surrogates (**10-A** and **10-B**) of compound **10** in an atmosphere of ethylene (7 MPa) did not deliver any detectable [4 + 2] cycloadduct even at 70 °C for 48 h. Application of trimethylsilylacetylene (20 equiv) instead of ethylene in thermal conditions did not afford the desired cycloadducts either. We then resorted to Diels−Alder cycloaddition of **10-A** and **10-B** with trimethylsilylacetylene (20 equiv) in the presence of different Lewis acids, including $AlCl_3$, $MeAlCl_2$, Et_2AlCl, $ZnCl_2$, $Bi(OTf)_3$, and $Fe(OTf)_3$. However, no cycloadducts could be detected, while decomposition of **10-A** and **10-B** was observed. Actually, the reactivity discrepancy between our MOBs (**10-A** and **10-B**) and Fukuyama and Yokoshima's MOB could be ascribed to the difference among their molecular conformation, since the polycyclic skeleton of Fukuyama and Yokoshima's MOB substrate is distinctly distorted by an additional nitrogen-containing heterocycle, compared to those of our MOBs.[11e]

Our failure in MOB cycloaddition prompted us to fall back on an unmasked *ortho*-benzoquinone (UMOB) Diels−Alder methodology. Theoretically and experimentally, UMOB shows versatile reactivity, acting as a carbodiene, heterodiene, dienophile, and heterodienophile.[26] Moreover, the cycloadducts from UMOB are labile to light-driven decarbonylation and

Table 1. Substrate Scope of the Diels−Alder Cyclization[a]

entry	dienophile	major product	M: Σisom.[b]	yield[c]	entry	dienophile	major product	M: Σisom	yield
1		 **11a**	7:1	78%	7		 **11g** Ac	3:1	79%
2[d]	 PG = TBDPS	 PG = TBDPS, **11b**	5:1	97%	8[d]		 **11h** Ph	3:1	96%
3	 Ar = 4-$C_6H_4NO_2$	 Ar = 4-$C_6H_4NO_2$, **11c**	3:1	>99%	9[e]		 **11i**	6:1	>99%
4	 Ar = Ph	 Ar = Ph, **11d**	3:1	96%	10	 Ar = Ph	 Ar = Ph, **11j**	3:1	99%
5	Ar = 4-$MeOC_6H_4$	Ar = 4-$MeOC_6H_4$, **11e**	3:1	96%	11	Ar = 4-$MeOC_6H_4$	Ar = 4-$MeOC_6H_4$, **11k**	3:1	94%
6	Ar = 4-FC_6H_4	Ar = 4-FC_6H_4, **11f**	3:1	98%	12	Ar = 4-FC_6H_4	Ar = 4-FC_6H_4, **11l**	2:1	99%

[a]Unless otherwise stated, reactions were performed in dichloromethane in sealed tubes wrapped in aluminum foil at 140 °C for 2−6 h with **10** (1 equiv), dienophile (20 equiv), and freshly activated MnO_2 (4 equiv). [b]M:∑isom. = major isomer:sum of minor isomers. These ratios were determined by ^{1}H NMR analysis. [c]Isolated yield combining all isomers. [d]These reactions were performed at 150 °C. [e]KF (2.5 equiv), 18-crown-6 (2.5 equiv), and **10** (1 equiv) were dissolved in THF at 0 °C, then dienophile (1.2 equiv) was added dropwise at 0 °C, and the reaction was stirred for 3 h before quenching.

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706−13714

aromatization.[27a,b] Thus, there are only sporadic reports on Diels–Alder cycloaddition involving UMOB and alkyne or alkene.[27] It may help explain why, to the best of our knowledge, Diels–Alder cycloaddition with UMOB has not been reported in natural product synthesis yet. Accordingly, applying such an UMOB as compound **10** solely as carbodiene presents a challenge for fulfilling requirements for chemo-, regio-, diastereo-, and *exo*/*endo* selectivities. Herein we endeavor to demonstrate the realizability and synthetic applicability of such type of intermolecular Diels–Alder reactions.

Scrupulous screening of reaction conditions led us to intermolecular Diels–Alder cycloaddition involving **10** and different alkynes and alkenes (Table 1). Notably, these reactions were performed in the presence of MnO_2 to prevent reduction of **10** to the corresponding 1,2-phen-diol. When functionalized terminal alkynes were used, the cycloadducts formed in satisfactory selectivities and yields (Table 1, entries 1–3). In all three major products, the bulky substituents (TMS, CH_2OR) were positioned outside the polycyclic skeleton. However, while no selectivity was observed in the cycloaddition between structurally simple reactants, i.e., 3,5-di-*tert*-butyl-*o*-benzoquinone and phenylacetylene,[27a] aromatic rings were directed inward to ring B in the major cycloadduct when phenylacetylene and its derivatives were reacted as dienophile with **10** (entries 4–6).

Reacting **10** with 4-trimethylsilyl-3-butyn-2-one, an electron-deficient internal alkyne, afforded the corresponding diastereomers in the ratio of 3:1 in 79% combined yield (entry 7). Steric hindrance from the TMS group might cause it to project outward in the major cycloadduct (entry 1 vs entry 7). Using a symmetric internal alkyne showed excellent reactivity and medium diastereoselectivity (entry 8). The highly reactive benzyne, generated *in situ*, delivered the desired cycloadduct at 0 °C (entry 9). Interestingly, *α*-facial selectivity predominated in cycloaddition reactions with alkyne as dienophile (entries 1–9). However, *β*-facial selectivity was observed with aromatically substituted terminal alkene as dienophile, and the corresponding *endo*-type cycloadducts were found to be predominant (entries 10–12).

To probe insightful information on the unexpected regioselectivities in entries 4–6 and facial-selectivities in entries 10–12, DFT calculation on three typical Diels–Alder reactions (entries 1, 4, and 10) was executed by employing M06-2X method combined with the 6-31G(d,p) basis set. Calculation shows that the major cycloadducts in these three entries are the most energy-favored among all four (entries 1 and 4) or eight (entry 10) possible isomers.[28a]

For entry 1, compared to the stable conformation of **10** in ground state, single-point energy calculation indicates less geometric distortion of the diene motif in *α-anti*-TS than that in *β-anti*-TS. This makes *α*-facial selectivity favorable with alkyne as the dienophile.[28a] Moreover, theoretical calculation reveals the different regioselectivities between entries 1 and 4 could be ascribed to different HOMO–LUMO interactions between diene and dienophile in different transition states. Greater HOMO–LUMO interaction usually leads to lower Gibbs free energy in transition state and thus benefits formation of the major cycloadduct. For the cycloadditions in both entries 1 and 4, NBO analysis implies the migration of electron from the HOMOs of alkynes to the LUMO of **10** in transition states (Figure 2A). The more charge transfer in *anti*-TSs than that in *syn*-TSs (0.07 e vs 0.06 e) suggests that *anti*-TSs possess greater HOMO–LUMO interaction, which satisfactorily accounts for

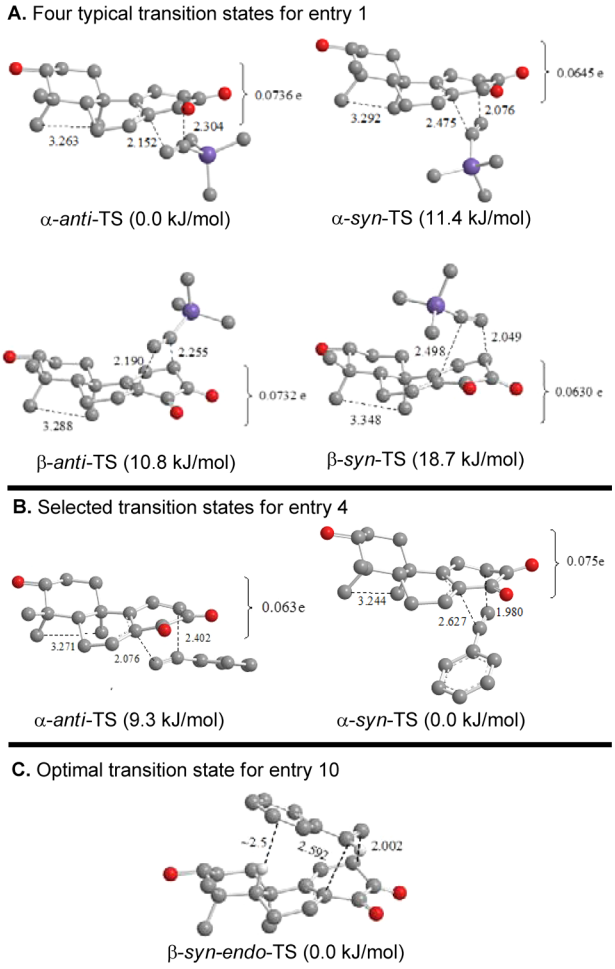


Figure 2. Selected transition states (optimized by DFT calculation) for cycloadditions in entries 1, 4, and 10. Bond lengths are in angstroms, and relative energies are in parentheses. *Syn*/*anti* denotes different position of the substituent on dienophiles with respect to ring B of **10**.

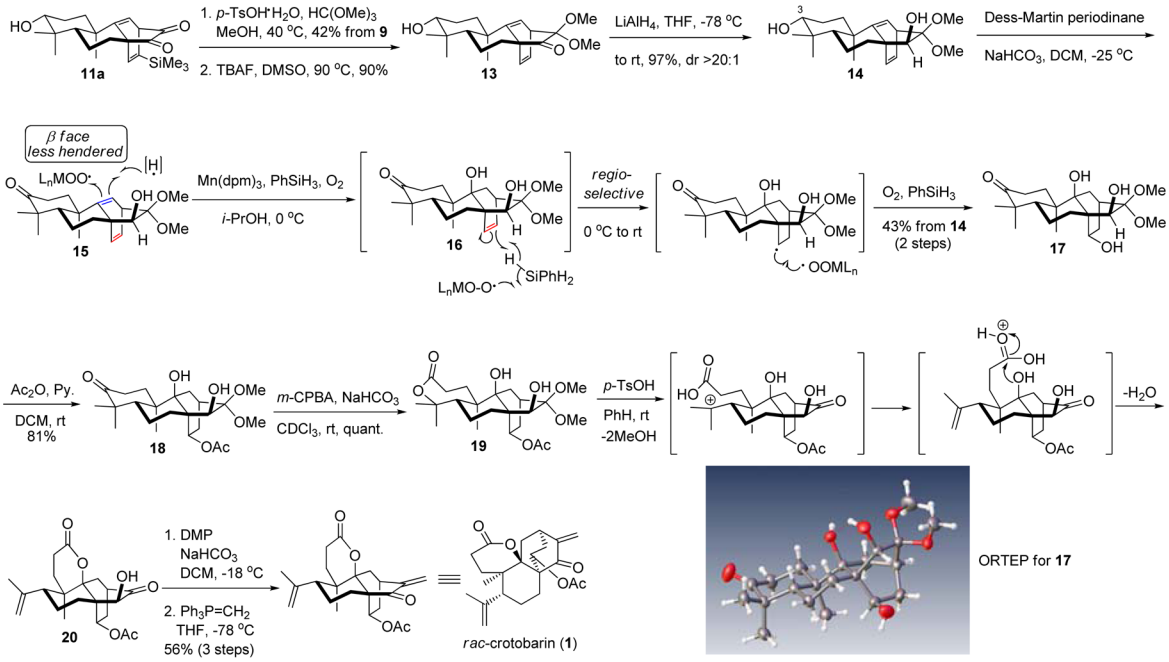
the regioselectivity in entry 1. However, for the cycloaddition in entry 4, the *syn*-TSs possess greater HOMO–LUMO interaction than the *anti*-TSs (charge-transfer: 0.07 e vs 0.06 e), which affords the opposite regioselectivity to that in entry 1 (Figure 2B).[28a]

As for the cycloaddition in entry 10, the most energy-favored *β-syn-endo*-TS is featured by the unique geometry that C–H bond at C5 of compound **10** is vertical to the phenyl ring of styrene with the distance of ca. 2.5 Å (Figure 2C), suggesting a strong *σ*–*π* interaction between two reactants in this transition state. This C–H···*π* interaction therefore stabilizes *β-syn-endo*-TS and leads to **11j** as the major product.[28b–e]

Attempts to react **10** with alkenes other than styrene derivatives, including ethylene even under high pressure, failed to afford significant amounts of Diels–Alder cycloadducts,[11e] which is different from the reactivity with structurally simple UMOB as diene.[27e,f] The relative stereochemistry of major cycloadducts in Table 1 was confirmed by X-ray crystallography or NOESY experiments after purifying them from isomeric mixtures by recrystallization and/or chemical derivation. Although the products decompose upon standing in sunlight, they are stable under thermal reaction condition in the dark and in the purification process. Undoubtedly, our developed cycloaddition with podocarpane-type UMOB will further

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706–13714

Scheme 4. Total Synthesis of *rac*-Crotobarin



extend applicable scope of Diels–Alder chemistry in natural product synthesis.[29]

Synthesis of *rac*-Crotobarin. With mixture of **11a** and its inseparable diastereomers in hand, we selectively protected the less hindered ketone moiety in **11a** as a ketal to enhance its stability and thereby to facilitate subsequent transformations. Gram-scale synthesis of the ketal of **11a** from compound **9** was carried out over three steps in 42% overall yield, with just one purification operation (Scheme 4). Desilylation with TBAF afforded compound **13** in 90% yield. Diastereoselective reduction of the carbonyl group in **13** with $LiAlH_4$ afforded compound **14** with a β-oriented hydroxyl group. This diastereoselectivity was achieved by reducing **13** at −78 °C first and then increasing reaction temperature. Reduction of the ketone in **13** is necessary because otherwise the skeleton rearrangement in the subsequent Mn (III)-mediated Mukaiyama hydroxylation would be unavoidable in the presence of C15 carbonyl (see also Scheme 7A). Then C3-hydroxyl was selectively oxidized to the ketone **15** at low temperature with Dess–Martin periodinane.

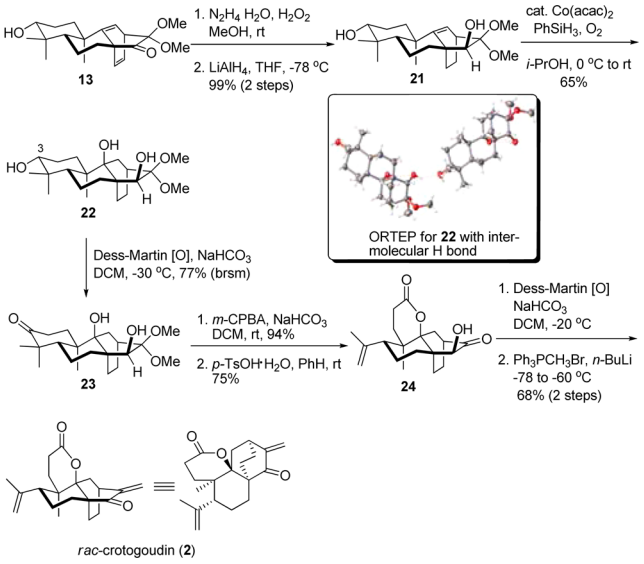
In the condition developed by Mukaiyama's group with $Mn(dpm)_3$,[30] silane, and oxygen, **15** was first converted into the intermediate **16** at 0 °C by introducing a tertiary alcohol at the trisubstituted alkene from the less hindered β face. Increasing the temperature from 0 °C to room temperature resulted in formation of compound **17** in regio- and diastereoselective style, through the second radical hydroxylation on the disubstituted alkene (red color in **16**). The relative configuration of **17** was confirmed by X-ray crystallography. The reactive priority of the trisubstituted alkene over the disubstituted alkene in **15** can be ascribed to the kinetic priority of formation of the more stable tertiary radical leading to **16**. Application of $Co(acac)_2$ delivered lower yield than that of $Mn(dpm)_3$ (28% vs 43%), while using $Fe(acac)_3$ afforded neither **16** nor **17**. Chemoselective protection with acetic anhydride yielded compound **18** in the presence of pyridine, although employing triethylamine as the base afforded inferior result with only 22% yield of **18**. The ketone in **18** was subsequently transformed into a lactone through Baeyer–Villiger rearrangement. To our delight, treating **19** under acidic condition triggered a cascade reaction, involving ketal deprotection, lactone opening, isopropene formation, and final lactonization, to afford **20**. The feasibility of transformations from **18** to **20** indicates the possibility of the biohypothesis for formation of *ent*-3,4-*seco*-atisane (Scheme 2). Finally, subjection of compound **20** to Dess–Martin periodinane, followed by selective Wittig olefination on the less hindered C16 carbonyl in the resultant diketone intermediate, afforded racemic crotobarin. Characterization data of our synthetic *rac*-**1** were in good agreement with those of natural **1**.[12] Thus, we accomplished the first total synthesis of crotobarin in racemic form.

Synthesis of *rac*-Crotogoudin. Enlightened by the above successful total synthesis of *rac*-crotobarin, we turned our attention to total synthesis of *rac*-crotogoudin. Thus, the less hindered disubstituted alkene of compound **13** was selectively saturated under diimide reduction condition, and the following diastereoselective reduction of ketone afforded compound **21** (Scheme 5). Regioselective radical hydration in the presence of cobalt(II) catalyst, phenyl silane, and oxygen gave compound **22** as the sole isolable diastereomer (Scheme 5),[31] while employing $Mn(dpm)_3$ or $Fe(acac)_3$ as the catalyst just resulted in complex mixture. The relative stereochemistry of **22** was confirmed by X-ray crystallography. Chemoselective Dess–Martin oxidation of the C3-hydroxyl in **22** afforded compound **23** in 77% yield based on the recovery of starting material. The same biomimetic strategy in the conversion from **18** to **20**, involving Baeyer–Villiger rearrangement and acid-catalyzed cascade, delivered compound **24**. It was smoothly converted to *rac*-crotogoudin through oxidation of secondary alcohol and final selective Wittig reaction. Characterization data of our synthetic *rac*-**2** were in good agreement with those of natural **2** and Carreira's *ent*-**2**.[12,14]

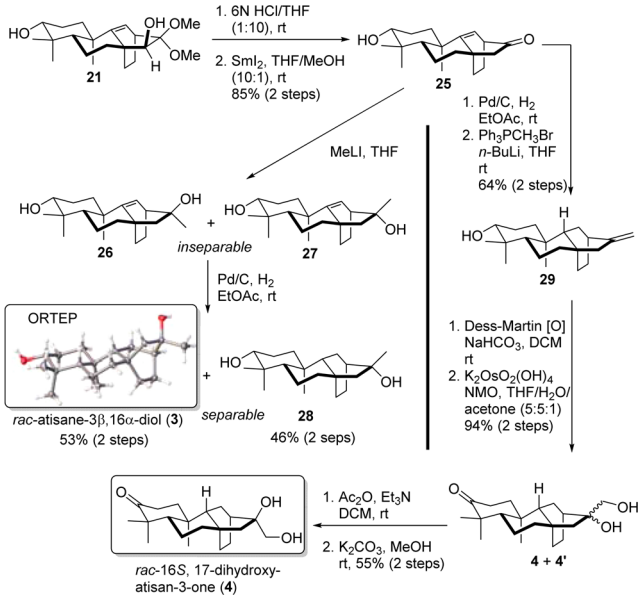
Synthesis of *rac*-Atisane-3β, 16α-Diol, and 16*S*,17-Dihydroxy-atisan-3-one. On the basis of total syntheses of these two 3,4-*seco* atisane diterpenoids, we turned our attention

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706–13714

Scheme 5. Total Synthesis of *rac*-Crotogoudin



Scheme 6. Syntheses of *rac*-Atisane-3β,16α-Diol, and 16*S*,17-Dihydroxy-atisan-3-one



to total syntheses of representative atisane-type diterpenoids, i.e., **3** and **4**. Deprotection of the ketal moiety of **21** and SmI_2-mediated dehydroxylation delivered the ketone **25**. Nucleophilic addition with methyl lithium produced two inseparable diastereomers, **26** and **27**. Then diastereoselective hydrogenation of the double bond with palladium on activated carbon afforded racemic atisane-3β,16α-diol (**3**) in 53% yield and compound **28** in 46% yield over two steps (Scheme 6). At this stage, *rac*-**3** and **28** were separable on silica column. The molecular structure of *rac*-**3** was confirmed by X-ray crystallography. Characterization data of our synthetic sample were in agreement with those of natural **3** except one of ^{13}C NMR signals, indicating that it be inadvertently misreported in the isolation literature.[16a,b]

Alternatively, compound **25** was subjected to diastereoselective hydrogenation and Wittig olefination to afford compound **29** in 64% yield over two steps. Oxidation of the secondary hydroxyl to ketone and dihydroxylation of the *gem*-disubstituted alkene afforded our desired target molecule **4**, accompanied by the inseparable diastereomer **4**′ at nearly 1:1 ratio. Acetylation of the primary alcohols in the diastereomeric mixture facilitated column separation of these two resultant acetates. Hydrolysis of the desired acetate resulted in smooth formation of racemic 16*S*,17-dihydroxy-atisan-3-one (**4**), whose characterization data were in good accordance with those of natural **4**.[13f,16c]

Ring Distortion Strategy. Based on the resultant fully functionalized bicyclo[2.2.2]octane scaffold from complex UMOB, our Diels–Alder methodology facilitates divergent and collective synthesis of atisane-type diterpenoids for screening bioactive lead compounds.[32] In addition, we show here that these atisane-type intermediates can also undergo rearrangement to produce other types of diterpenoids with potentially useful skeleton by applying a ring-distortion strategy (Scheme 7).[33]

For example, under Yamada's condition,[31] a tertiary radical was generated from compound **30**, which was prepared from compound **13** through diimide reduction of the disubstituted alkene.[34] It then induced transfer of the adjacent carbonyl to form a radical bicyclo[3.2.1]octane through a cyclopropyl intermediate. Trapping the radical in the presence of oxygen and silane afforded racemic compound **31** in 67% yield, which embraces the substructure of scopadulane-type diterpenoids (Scheme 7A). Scopadulane-type diterpenoids feature complex tetracyclic architecture and interesting bioactivities. Scopadulciol and thyrsiflorin A are representative molecules in this family.[35]

Treating compound **11a** with boron trifluoride activated either carbonyl group and thus initiated transfer of the alkene attached to trimethylsilyl in two reaction pathways, i.e., paths a and b. These two concomitant rearrangements led to compounds **32** and **33** in 57% and 38% yield, respectively, with functionalized bicyclo[3.2.1]octane skeletons different from that of compound **31** (Scheme 7B). Notably, architecture of compounds **32** and **33** matches the highlighted substructure with red color in andilesin A and thus can be regarded as potential synthetic precursors to andilesin A and its natural siblings. These natural products belong to fungal meroterpenoids isolated from *Aspergillus* sp.[36]

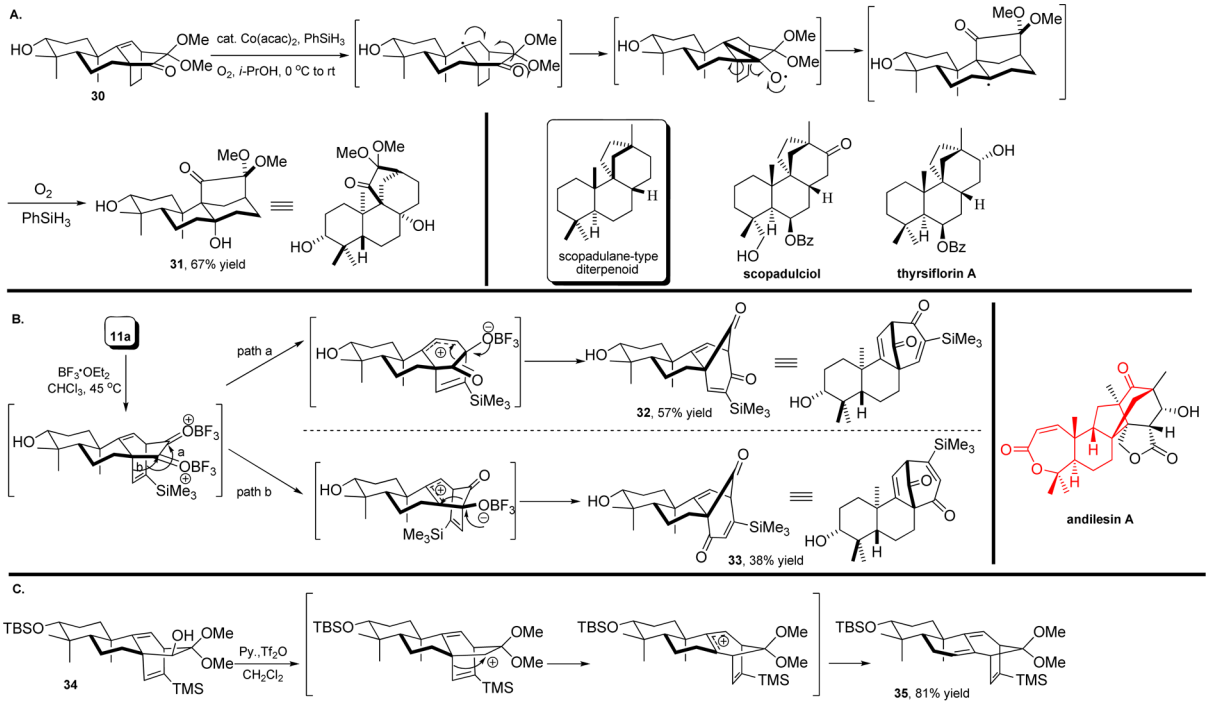
Alternatively, treating alcohol **34** with Tf_2O initiated Wagner–Meerwein-type 1,2-shift of the double bond with TMS to generate a tertiary allylic carbocation (Scheme 7C). Compound **34** could be facilely prepared from compound **11a** through selective ketal protection of the C16 ketone, silyl protection of the C3 hydroxyl, and diastereoselective DIBAL-H reduction of the C15 ketone.[34] Its deprotonation afforded compound **35** with functionalized bicyclo[3.2.1]octane skeleton, a molecular structure different from those of compounds **31**–**33**.

CONCLUSION

In conclusion, we have developed an intermolecular Diels–Alder reaction involving unmasked *ortho*-benzoquinone containing a complex tricycle to efficiently construct fully functionalized bicyclo[2.2.2]octanes. The use of this methodology was demonstrated by converting the bicyclo[2.2.2]octane intermediate to different complex molecules, such as atisane-type diterpenoids (**1**–**4**), scopadulane-type diterpenoid core (**31**), and other natural product-like compounds (**32**, **33**, and **35**). Besides the Diels–Alder cycloaddition with UMOB, key

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706–13714

Scheme 7. Ring Distortion Strategy to Convert Functionalized Bicyclo[2.2.2]octenes To Natural Product-Like Compounds



elements in these total syntheses include: (1) $FeCl_3$-catalyzed cationic cascade cyclization to construct podocarpane-type skeleton; (2) Mn(III)/Co(II)-catalyzed radical hydroxylation of alkene with high chemo-, regio-, and diastereoselectivities; (3) and a ketal-deprotection/lactone-opening/deprotonation/lactonization cascade in total syntheses of *rac*-crotobarin and crotogoudin. In principle, a general synthetic pathway can be constructed from podocarpane-type diterpenoids (such as **9**) to different tricyclic and tetracyclic diterpenoids and potentially to diterpenoid alkaloids. In this regard, our work shows that after generating the first stereogenic center in compound **6**, the remaining centers can be generated in a substrate-controlled fashion. As a result, both atisane-type and *ent*-atisane-type diterpenoids can be synthesized smoothly when either antipode of enantiopure **6** is used.[23] Moreover, application of ring distortion strategy (Scheme 7) into the total synthesis of other terpenoids is under development in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08958.

X-ray data for **3** (CIF)
Crystallographic data for **11c** (CIF)
Crystallographic data for **11d** (CIF)
Crystallographic data for **11f** (CIF)
Crystallographic data for **11g-3**, the derivative of **11g** (CIF)
Crystallographic data for **11i** (CIF)
Crystallographic data for **11j-1**, the derivative of **11j** (CIF)
Crystallographic data for compound **11k-1**, the derivative of **11k** (CIF)
Crystallographic data for **11l-1**, the derivative of **11l** (CIF)
Crystallographic data for **17** (CIF)
Crystallographic data for **22** (CIF)
Crystallographic data for **31** (CIF)
Crystallographic data for **S1a**,the derivative of **11a** (CIF)
Crystallographic data for **S5**, the derivative of **33** (CIF)
Characterization data, DFT calculation details, ^{1}H NMR and ^{13}C NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*chembliu@scu.edu.cn

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the NSFC (21290180, 21322205, 21321061). We also thank the comprehensive training platform of the Specialized Laboratory in the College of Chemistry at Sichuan University for compound testing.

■ REFERENCES

(1) For examples, see: (a) Zhou, B.; Li, X.; Tang, H.; Miao, Z.; Feng, H.; Li, Y. *Org. Biomol. Chem.* **2011**, *9*, 3176. (b) Cambie, R. C.; Rutledge, P. S.; Stevenson, R. J.; Woodgate, P. D. *J. Organomet. Chem.* **1995**, *486*, 199. (c) Matsumoto, T.; Imai, S.; Mimura, K.; Aiba, K. *Chem. Lett.* **1988**, *17*, 1399.

(2) For cyclase-catalyzed diterpenoid biosynthesis, see: (a) Dickschat, J. S. *Nat. Prod. Rep.* **2011**, *28*, 1917. (b) Dewick, P. M. *Nat. Prod. Rep.* **2002**, *19*, 181. (c) Gao, W.; Hillwig, M. L.; Huang, L.; Cui, G.; Wang, X.; Kong, J.; Yang, B.; Peters, R. J. *Org. Lett.* **2009**, *11*, 5170. for computational chemistry of carbocation intermediates, see: (d) Tantillo, D. J. *Nat. Prod. Rep.* **2011**, *28*, 1035. (e) Tantillo, D. J. *Chem. Soc. Rev.* **2010**, *39*, 2847. (f) Hong, Y. J.; Tantillo, D. J. *Nat. Chem.* **2014**, *6*, 104. (g) Hong, Y. J.; Tantillo, D. J. *Chem. Sci.* **2013**, *4*, 2512. (h) Hong, Y. J.; Tantillo, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 5375.

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706−13714

(3) (a) Wang, F.-P.; Liang, X.-T. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Science: New York, 2002; Vol. *59*, pp 1−280. (b) Wang, F.-P.; Chen, Q.-H.; Liu, X.-Y. *Nat. Prod. Rep.* **2010**, *27*, 529.
(4) Wang, F.-P.; Chen, Q.-H.; Liang, X.-T. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Science: New York, 2009; Vol. *67*, pp 1−78.
(5) Wang, F.-P.; Chen, Q.-H. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Science: New York, 2010; Vol. *69*, pp 1−577.
(6) (a) Johnston, J. P.; Overton, K. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1490. (b) Johnston, J. P.; Overton, K. H. *J. Chem. Soc. Chem. Commun.* **1969**, 329.
(7) For seminal reviews, see: (a) Zhu, G.; Liu, R.; Liu, B. *Synthesis* **2015**, *47*, 2691. (b) Hamlin, A. M.; Kisunzu, J. K.; Sarpong, R. *Org. Biomol. Chem.* **2014**, *12*, 1846. (c) Cherney, C. C.; Baran, P. S. *Isr. J. Chem.* **2011**, *51*, 391.
(8) (a) Cherney, E. C.; Green, J. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9019. (b) Hamin, A. M.; Cortez, F. J.; Lapointe, D.; Sarpong, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 4854. (c) Hamlin, A. M.; Lapointe, D.; Owens, K.; Sarpong, R. *J. Org. Chem.* **2014**, *79*, 6783. (d) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T.; Kabuto, C. *J. Am. Chem. Soc.* **1988**, *110*, 1963. (e) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164. (f) Guthrie, R. W.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett.* **1966**, *7*, 4645. (g) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T.; Hayase, Y. *J. Am. Chem. Soc.* **1963**, *85*, 2342.
(9) (a) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2006**, *62*, 7093. (b) Toyota, M.; Wada, T.; Ihara, M. *Org. Lett.* **1999**, *1*, 1627.
(10) (a) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916. (b) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565. (c) Toyota, M.; Asano, T.; Ihara, M. *Org. Lett.* **2005**, *7*, 3929. (d) Abad, A.; Agulló, C.; Cuñat, A. C.; Navarro, I. *Tetrahedron Lett.* **2001**, *42*, 8965. (e) Abad, A.; Agulló, C.; Cuñat, A. C.; Navarro, I.; de Arellano, M. C. R. *Synlett* **2001**, 349. (f) Abad, A.; Agulló, C.; Cuñat, A. C.; de Alfonso Marzal, I.; Navarro, I.; Gris, A. *Tetrahedron* **2006**, *62*, 3266. (g) Abad, A.; Agulló, C.; Cuñat, A. C.; de Alfonso Marzal, I.; Gris, A.; Navarro, I.; de Arellano, C. R. *Tetrahedron* **2007**, *63*, 1664. (h) Ungur, N.; Kulcițki, V.; Chetraru, O.; Grinco, M.; Vlad, P. F. *Helv. Chim. Acta* **2013**, *96*, 864. (i) Cherney, E. C.; Lopchuk, J. M.; Green, J. C.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 12592.
(11) (a) Peese, K. M.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 8734. (b) Peese, K. M.; Gin, D. Y. *Chem. - Eur. J.* **2008**, *14*, 1654. (c) Liu, X.-Y.; Cheng, H.; Li, X.-H.; Chen, Q.-H.; Xu, L.; Wang, F.-P. *Org. Biomol. Chem.* **2012**, *10*, 1411. (d) Singh, V.; Bhalerao, P.; Sahu, B. C.; Mobin, S. M. *Tetrahedron* **2013**, *69*, 137. (e) Nishiyama, Y.; Han-ya, Y.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2014**, *136*, 6598.
(12) Rakotonandrasana, O. L.; Raharinjato, F. H.; Rajaonarivelo, M.; Dumontet, V.; Martin, M.-T.; Bignon, J.; Rasoanaivo, P. *J. Nat. Prod.* **2010**, *73*, 1730.
(13) (a) Liu, J.-H.; Latif, A.; Ali, M.; Zhang, G.-P.; Xiang, W.-J.; Ma, L.; Arfan, M.; Hu, L.-H. *Phytochemistry* **2012**, *75*, 153. (b) Li, Y.; Liu, J.; Yu, S.; Proksch, P.; Gu, J.; Lin, W. *Phytochemistry* **2010**, *71*, 2124. (c) Wang, Z. C.; Lin, Y. M.; Feng, D. Q.; Ke, C. H.; Lin, P.; Yan, C. L.; Chen, J. D. *Molecules* **2009**, *14*, 414. (d) Wang, J.-D.; Li, Z.-Y.; Xiang, W.-S.; Guo, Y.-W. *Helv. Chim. Acta* **2006**, *89*, 1367. (e) Wang, J.-D.; Li, Z.-Y.; Guo, Y.-W. *Helv. Chim. Acta* **2005**, *88*, 979. (f) Lal, A. R.; Cambie, R. C.; Rutledge, P. S.; Woodgate, P. D. *Phytochemistry* **1990**, *29*, 1925.
(14) Breitler, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11168.
(15) (a) Guo, Y.; Liu, Q.; Jia, Y. *Chem. Commun.* **2015**, *51*, 889. (b) Behera, T. K.; Singh, V. *Tetrahedron* **2014**, *70*, 7983. (c) Ushakov, D. B.; Maier, M. E. *Synlett* **2013**, *24*, 705.
(16) For isolation and characterization of **3**, see: (a) Schmitz, F. J.; Vanderah, D. J.; Hollenbeak, K. H.; Enwall, C. E. L.; Gopichand, Y. *J. Org. Chem.* **1983**, *48*, 3941. (b) Cafieri, F.; Fattorusso, E.; Mahajnah, Y.; Mangoni, A. *Magn. Reson. Chem.* **1995**, *33*, 286. For isolation and characterization of **4**, see: (c) Satti, N. K.; Suri, O. P.; Dhar, K. L. *J. Nat. Prod.* **1987**, *50*, 790.
(17) For elegant reviews on BVMO, see: (a) Leisch, H.; Morley, K.; Lau, P. C. K. *Chem. Rev.* **2011**, *111*, 4165. (b) Alphand, V.; Wohlgemuth, R. *Curr. Org. Chem.* **2010**, *14*, 1928. For Baeyer−Villiger oxidation of monoterpenoid in the presence of BVMO, see: (c) Wang, Y.; Lim, L.; Madilao, L.; Lah, L.; Bohlmann, J.; Breuil, C. *Appl. Environ. Microbiol.* **2014**, *80*, 4566. (d) Cernuchova, P.; Mihovilovic, M. D. *Org. Biomol. Chem.* **2007**, *5*, 1715. (e) Van der Werf, M. J. *Biochem. J.* **2000**, *347*, 693. For Baeyer−Villiger oxidation of meroterpenoid in the presence of BVMOs, see: (f) Matsuda, Y.; Wakimoto, T.; Mori, T.; Awakawa, T.; Abe, I. *J. Am. Chem. Soc.* **2014**, *136*, 15326. (g) Matsuda, Y.; Awakawa, T.; Wakimoto, T.; Abe, I. *J. Am. Chem. Soc.* **2013**, *135*, 10962.
(18) For insightful study on catalytic mechanism of BVMO, see: Yachnin, B. J.; Sprules, T.; McEvoy, M. B.; Lau, P. C. K.; Berghuis, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 7788.
(19) (a) Van der Vlugt-Bergmans, C. J. B.; Van der Werf, M. J. *Appl. Environ. Microbiol.* **2001**, *67*, 733. (b) Van der Werf, M. J.; Boot, A. M. *Microbiology* **2000**, *146*, 1129.
(20) (a) Liu, C.; Tagami, K.; Minami, A.; Matsumoto, T.; Frisvad, J. C.; Suzuki, H.; Ishikawa, J.; Gomi, K.; Oikawa, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 5748. (b) Citron, C. A.; Brock, N. L.; Tudzynsk, B.; Dickschat, J. S. *Chem. Commun.* **2014**, *50*, 5224.
(21) Suri, O. P.; Satti, N. K.; Suri, K. A.; Dhar, K. L.; Kachroo, P. L.; Kawasaki, T.; Miyahara, K.; Tsunehiro, T.; Fumiko, Y. *J. Nat. Prod.* **1990**, *53*, 470.
(22) Lichter, P. A.; Millller, S. J. *Nat. Chem.* **2012**, *4*, 990.
(23) (a) Racemic **6** was prepared in two steps from geraniol and used as a crude compound without purification; see Supporting Information for details. For recent accounts of preparing enantiopure **6**, see: (b) Xu, S.; Gu, J.; Li, H.; Ma, D.; Xie, X.; She, X. *Org. Lett.* **2014**, *16*, 1996. (c) Topczewski, J. J.; Kodet, J. G. *J. Org. Chem.* **2011**, *76*, 909.
(24) (a) Yu, L.-G.; Ni, T.-F.; Gao, W.; He, Y.; Wang, Y.-Y.; Cui, H.-W.; Yang, C.-G.; Qiu, W.-W. *Eur. J. Med. Chem.* **2015**, *90*, 10. (b) Onyango, E. O.; Fu, L.; Gribble, G. W. *Org. Lett.* **2014**, *16*, 322. (c) Kim, M. B.; Shaw, J. T. *Org. Lett.* **2010**, *12*, 3324. (d) Zhao, J.-F.; Zhao, Y.-J.; Loh, T.-P. *Chem. Commun.* **2008**, 1353.
(25) For selected reviews, see: (a) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. (b) Liao, C.-C. *Pure Appl. Chem.* **2005**, *77*, 1221.
(26) (a) Nair, V.; Menon, R. S.; Biju, A. T.; Abhilash, K. G. *Chem. Soc. Rev.* **2012**, *41*, 1050. (b) Kumar, V.; Ramanathan, S.; Sang, D.; Chen, X.; Lemal, D. M. *J. Org. Chem.* **2012**, *77*, 966.
(27) (a) Thomas, A.; Anilkumar, G.; Nair, V. *Tetrahedron* **1996**, *52*, 2481. (b) Nair, V.; Maliakal, D. *Res. Chem. Intermed.* **2002**, *28*, 337. (c) Kaicharia, T.; Bhojgude, S. S.; Biju, A. *Org. Lett.* **2012**, *14*, 6238. (d) Nair, V.; Maliakal, D.; Treesa, P. M.; Rath, N. P.; Eigendorf, G. K. *Synthesis* **2000**, *2000*, 850. (e) Müller, G. H.; Lang, A.; Seithel, D. R.; Waldmann, H. *Chem. - Eur. J.* **1998**, *4*, 2513. (f) Nair, V.; Kumar, S. *Synlett* **1996**, *1996*, 1143. (g) Liao, C. C.; Lin, H. S. *J. Chin. Chem. Soc.* **1986**, *33*, 73.
(28) (a) See Supporting Information for details on DFT calculation. (b) Hong, Y. J.; Tantillo, D. J. *Chem. Sci.* **2013**, *4*, 2512. (c) Shibasaki, K.; Fujii, A.; Mikami, N.; Tsuzuki, S. *J. Phys. Chem. A* **2006**, *110*, 4397. (d) Ugozzoli, F.; Arduini, A.; Massera, C.; Pochini, A.; Secchi, A. *New J. Chem.* **2002**, *26*, 1718. (e) Mo, Y.; Subramanian, G.; Gao, J.; Ferguson, D. M. *J. Am. Chem. Soc.* **2002**, *124*, 4832.
(29) For recent reviews on the Diels−Alder reaction in natural product synthesis, see: (a) Nawrat, C. C.; Moody, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2056. (b) Parvatkar, P. T.; Kadam, H. K.; Tilve, S. G. *Tetrahedron* **2014**, *70*, 2857. (c) Wan, C. Y.; Deng, J.; Liu, H.; Bian, M.; Li, A. *Sci. China: Chem.* **2014**, *57*, 926. For recent application of Diels−Alder reaction in natural product synthesis in our group, see: (d) Yuan, C.; Du, B.; Yang, L.; Liu, B. *J. Am. Chem. Soc.* **2013**, *135*, 9291. (e) Du, B.; Yuan, C.; Yu, T.; Yang, L.; Liu, B.; Qin, S. *Chem. - Eur. J.* **2014**, *20*, 2613. (f) Yang, L.; Yue, G.; Yuan, C.; Du, B.; Deng, H.; Liu, B. *Synlett* **2014**, *25*, 2471.

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706−13714

(30) Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 1869.
(31) (a) Kato, K.; Yamada, T.; Takai, T.; Inoki, S.; Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 179. (b) Inoki, S.; Kato, K.; Takai, T.; Isayama, S.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1989**, 515.
(32) (a) Hao, X. *Huaxue Jinzhan* **2009**, *21*, 84. (b) Kume, T.; Katuski, H.; Akaike, A. *Biol. Pharm. Bull.* **2004**, *27*, 964. (c) Hao, X.; Shen, Y.; Li, L.; He, H. *Curr. Med. Chem.* **2003**, *10*, 2253. (d) Kume, T.; Asai, N.; Nishikawa, H.; Mano, N.; Terauchi, T.; Taguchi, R.; Shirakawa, H.; Osakada, F.; Mori, H.; Asakawa, N.; Yonaga, M.; Nishizawa, Y.; Sugimoto, H.; Shimohama, S.; Katsuki, H.; Kaneko, S.; Akaike, A. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 3288.
(33) (a) Rafferty, R. J.; Hicklin, R. W.; Maloof, K. A.; Hergenrother, P. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 220. (b) Huigens, R. W., III; Morrison, K. C.; Hicklin, R. W.; Flood, T. A., Jr; Richter, M. F.; Hergenrother, P. J. *Nat. Chem.* **2013**, *5*, 195.
(34) For the related synthesis, see Supporting Information.
(35) For recent isolation and characterization of scopadulane-type diterpenoids, see: (a) Fuentes, R. G.; Toume, K.; Arai, M. A.; Sadhu, S. K.; Ahmed, F.; Ishibashi, M. *J. Nat. Prod.* **2015**, *78*, 864. (b) Munoz, M. A.; Chamy, C.; Bucio, M. A.; Hernandez-Baragan, A.; Joseph-Nathan, P. *Tetrahedron Lett.* **2014**, *55*, 4274. (c) Liu, Q.; Yang, Q.-M.; Hu, H.-J.; Yang, L.; Yang, Y.-B.; Chou, G.-X.; Wang, Z.-T. *J. Nat. Prod.* **2014**, *77*, 1594. (d) Ahsan, M.; Islam, SK. N.; Gray, A. I.; Stimson, W. H. *J. Nat. Prod.* **2003**, *66*, 958.
(36) (a) Matsuda, Y.; Wakimoto, T.; Mori, T.; Awakawa, T.; Abe, I. *J. Am. Chem. Soc.* **2014**, *136*, 15326. (b) Dunn, A. W.; Johnstone, R. A. W.; Sklarz, B. *J. Chem. Soc., Chem. Commun.* **1978**, 533.

DOI: 10.1021/jacs.5b08958
J. Am. Chem. Soc. 2015, 137, 13706−13714