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Ring-Closing Metathesis of Allylsilanes As a Flexible Strategy toward Cyclic Terpenes. Short Syntheses of Teucladiol, Isoteucladiol, Poitediol, and Dactylol and an Attempted Synthesis of Caryophyllene

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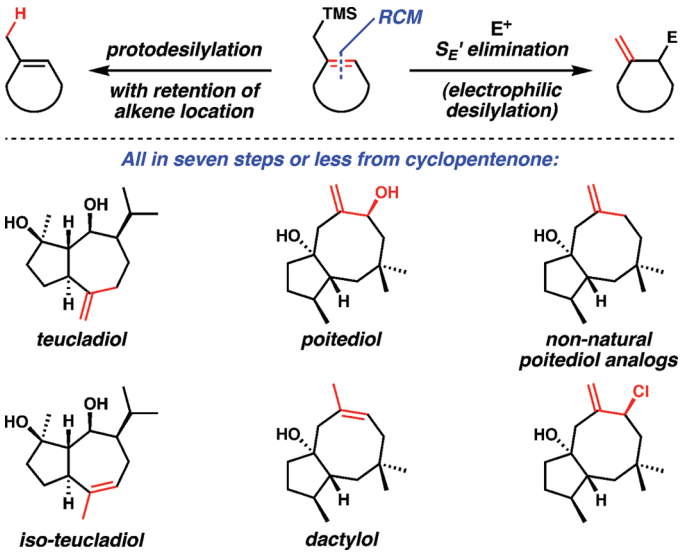

The development of a strategy consisting of allylsilane ring-closing metathesis and subsequent S_E' electrophilic desilylation (allylsilane RCM/S_E') to construct *exo*-methylidenecycloalkanes is described. Its utility is documented in short syntheses of teucladiol and poitediol. A key transformation in the synthesis of teucladiol is an aldol addition that establishes three stereochemical relationships in one step with ≥10:1 diastereoselectivity and provides a fascinating example of double stereodifferentiation/kinetic resolution with racemic reaction partners in the context of natural product synthesis. The synthesis of (±)-teucladiol required five steps from cyclopentenone and proceeded in 28% overall yield; adaptation of this route to an enantioselective synthesis of (−)-teucladiol enabled the determination of the absolute configuration of this terpene natural product. The use of fluoride-mediated conditions in the final desilylation step preserves the location of the alkene, delivering the natural product (±)-isoteucladiol (five steps and 21% yield from cyclopentenone). The synthesis of poitediol showcases the power of RCM for constructing eight-membered rings and features a highly diastereoselective epoxidation/fluoride-mediated fragmentation sequence for installing the *exo*-methylidene group with an adjacent hydroxyl-bearing stereocenter. The synthesis of (±)-poitediol required seven steps and proceeded in 18% overall yield. Again, fluoride-mediated desilylation of a late-stage intermediate (with retention of double-bond location) delivered the natural product (±)-dactylol (seven steps and 24% yield). Efforts directed toward incorporating the RCM/S_E' sequence into a synthesis of caryophyllene are also disclosed. While ultimately unsuccessful, these efforts resulted in the identification of a novel metal alkylidene-promoted deallylation reaction of terminal 1,4-dienes. A possible mechanism for this unexpected deallylation reaction of 1,4-dienes is provided.

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Introduction

Because of their impressive structural diversity,[1,2] terpenes have long served as a source of inspiration for the development of strategies and tactics in organic synthesis; however, this same diversity of architectures also renders the development of a completely general strategy for the synthesis of terpenes difficult. Inspired by the unusual tetracyclic architecture of echinopine A[3] (**1**, Figure 1), we sought to develop an efficient method for synthesizing the *exo*-methylidenecycloheptane function (highlighted in red) present in this natural product. While contemplating potential solutions to this problem, we recognized that *exo*-methylidenecycloalkanes occur frequently in terpene natural products. To the best of our knowledge, no truly general strategy has been reported for the synthesis of this functional group arrangement that is characterized by the presence of a thermodynamically less stable exocyclic alkene. The majority of the reported routes to natural products containing *exo*-methylidenecycloalkanes utilize either ketone olefination processes,[4] the elimination of a suitable leaving group,[5] or an annulation sequence involving a vinyl organometallic reagent or intermediate[6] to install the exocyclic alkene.

Exemplary *exo*-methylidenecycloalkane-bearing terpenes include echinopine A (**1**),[3] caryophyllene (**2**),[7] teucladiol (**3**),[8] poitediol (**4**),[9] eupahualin D (**7**),[10] and cladiellisin (**8**)[11] (Figure 1); these natural products demonstrate the variety of ring sizes and substitution patterns found in this large subset of terpenes. Many terpenes that contain *exo*-methylidenecycloalkanes are coproduced with their thermodynamically more stable endocyclic isomers as a consequence of their biogenetic derivation from cationic cyclization reactions[12] (see isoteucladiol [**5**][13] and dactylol [**6**],[14] Figure 1, and Scheme 1). An ideal strategy for accessing *exo*-methylidenecycloalkanes would also provide the flexibility to generate these endocyclic isomers from late-stage intermediates; moreover, the ability to introduce diverse functional groups adjacent to the exocyclic alkene would be substantially useful.

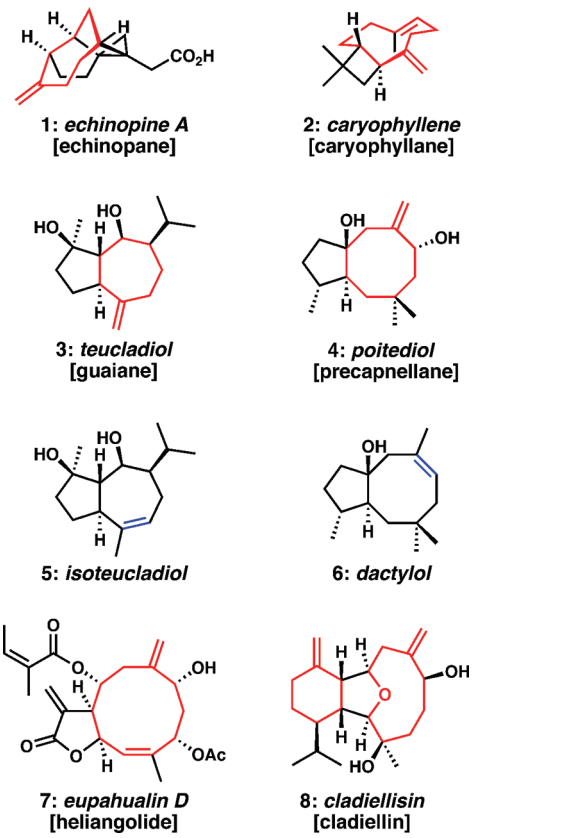
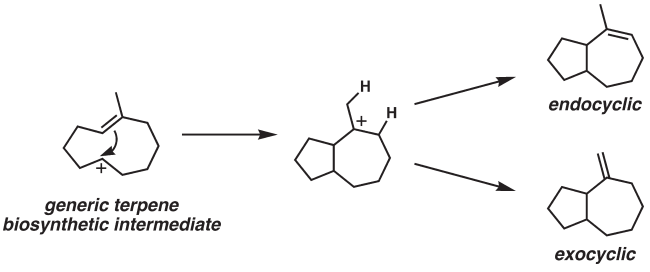


FIGURE 1. Representative terpenes bearing the *exo*-methylidenecycloalkane motif (in red) and two closely related natural products bearing the corresponding endocyclic alkene.

SCHEME 1. Generic Polycyclic Terpene Biosynthesis Showing the Origin of Both the Endocyclic and Exocyclic Alkene Isomers



We recently conceived of a straightforward strategy for constructing *exo*-methylidenecycloalkanes.[15] Our two-step approach involves ring-closing olefin metathesis[16] of allylsilanes of type **9**, with subsequent S_E' electrophilic desilylation of the resultant trisubstituted allylsilane **10** to generate the *exo*-methylidenecycloalkane motif (**11**, Scheme 2a).

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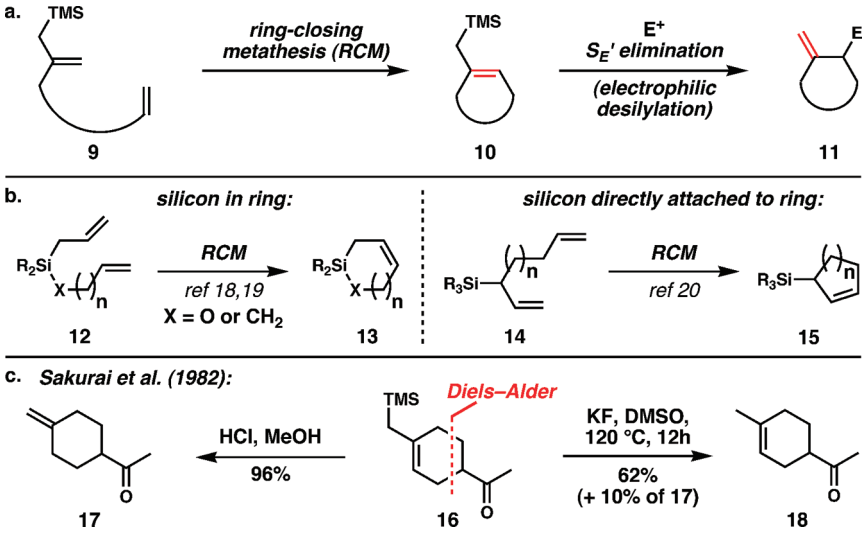
SCHEME 2. (a) Strategy to Access *exo*-Methylidenecycloalkanes (E = electrophile (H, Cl, OH, carbon electrophiles, etc.)); (b) Known RCM-Based Allylsilane Syntheses; (c) Sakurai's Precedent for Accessing Both Exocyclic and Endocyclic Alkenes from a Common Cyclic Allylsilane



Ring-closing metathesis of allylic silanes has been reported;[17] for example, silacycles have been forged according to the metathesis process **12** → **13**[18,19] (Scheme 2b), and cyclic allylsilanes with the silicon atom attached directly to the ring have also been made by RCM (see **14** → **15**).[20] Examples of allylsilane cross-metathesis are also known (not shown).[21] In spite of all of these precedents, prior to our work, cyclic allylsilanes of specific type **10** had never been made by RCM. With respect to the second key step in our strategy, myriad examples of electrophilic desilylation of allylsilanes are known.[22] Given these literature precedents, it was surprising that the combination of these simple reaction types into a cohesive strategy to access the *exo*-methylidenecycloalkane motif common to many terpene natural products had never been reported. The closest precedent that shares the spirit of our design is the strategy reported by Sakurai in 1982,[23] which involved the Diels−Alder reaction of 2-trimethylsilylmethylbutadiene with typical dienophiles to afford compounds of type **16**, followed by S_E' electrophilic desilylation to afford the exocyclic alkene (Scheme 2c). Conditions for desilylation that retained the location (endocyclic) of the alkene were also reported. This report clearly documented the versatility of cyclic allylsilanes of type **10** that we hoped to use in our work. However, because of the requisite cycloaddition step, this earlier work was limited to the generation of six-membered rings.

Virtues of the strategy outlined in Scheme 2a for the synthesis of *exo*-methylidenecycloalkanes include the following: (1) Ring-closing olefin metathesis is an efficient and functional-group-tolerant method for constructing normal, medium, and large rings.[16] (2) Allylsilanes are readily introduced by a variety of reliable procedures (see below)[24] and are relatively stable species that can be carried through multistep reaction sequences. (3) In addition to simple protodesilylation of allylsilane **10** to give **19** (Scheme 3), this versatile intermediate is amenable to multiple productive transformations to other motifs frequently found in terpene natural products, including (1) epoxidation/fluoride-mediated olefination to produce allylic alcohols of type **20**;[22a,b] (2)

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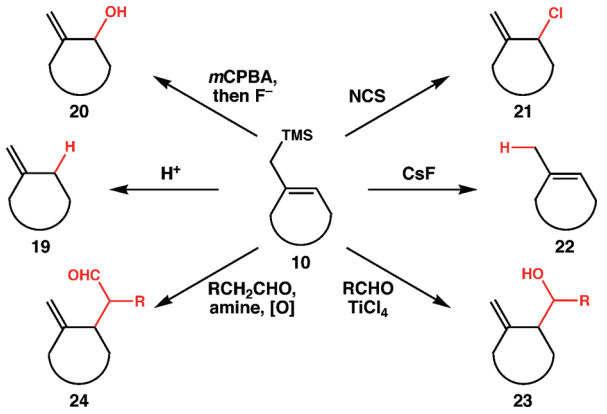
SCHEME 3. Versatility of RCM-Derived Cyclic Allylsilanes



halogenation via an S_E' mechanism to deliver allylic halides with exocyclic alkenes (**10** → **21**);[25] (3) fluoride-mediated desilylation to provide the endocyclic alkene (**22**) from the same allylsilane precursor (enabling the synthesis of either the more stable or the less stable alkene regioisomer at will);[23b] and (4) the generation of new carbon−carbon bonds via Sakurai reactions (**10** → **23**)[26] or potential oxidative coupling with enamines according to MacMillan's procedure for organocatalytic SOMO catalysis (**10** → **24**),[27] which would both ultimately deliver much more complex structures.[28]

There are a wide variety of methods for incorporting allylsilanes into organic substrates, which adds to the overall flexibility of this approach. They can generally be divided into methods that bring in the allylsilane unit via a nucleophilic reagent (Scheme 4a)[29] and methods that construct the allylsilane from other functional groups (Scheme 4b).[30] Of particular importance to the work described in this report are the conjugate addition reactions of cuprates derived from 2-(3-trimethysilyl-1-propenyl)magnesium bromide (**26**) as developed by Trost,[29a] the indium-mediated allylation of carbonyl electrophiles starting from allylic iodide **30** as described by Remuson,[29c] and the method of Bunnelle that treats esters with excess trimethylsilylmethylmagnesium chloride and cerium trichloride followed by a Peterson elimination (see **35** to **37**).[30a]

Full details describing the incorporation of the strategy shown in Scheme 2a into syntheses of teucladiol (**3**, Figure 1)[8] and poitediol (**4**)[9] are included below, along with a previously undisclosed account of the synthesis of the natural products isoteucladiol (**5**)[13] and dactylol (**6**)[14] from intermediates originally used to make **3** and **4**, respectively, and attempted application of this strategy to a synthesis of caryophyllene (**2**),[7] which yielded some unanticipated findings.

Results and Discussion

Although published examples of cross and ring-closing metathesis reactions involving allylsilanes are numerous, as are cases of allylsilane S_E' electrophilic desilylation, to the best of our knowledge the synthesis of an *exo*-methylidenecycloalkane using the two-step sequence shown in Scheme 2a had not been reported. In order to establish the feasibility of this two-step reaction sequence, a model substrate, **43**, was constructed as shown in Scheme 5. Conjugate addition of butenylmagnesium bromide to methyl cinnamate afforded known ester **42**,[31] which was converted into allylsilane **43** according to Bunnelle's protocol.[30a] Exposure of **43** to the Grubbs first-generation catalyst (see Grubbs I, Scheme 5)[32] in dichloromethane at reflux afforded the homodimer **44** in 65% yield. The desired cyclic trisubstituted allylsilane **45** was not detected in the crude reaction mixture. This result was not surprising, because it is known that this relatively unreactive catalyst often fails to effect the formation of cyclic trisubstituted olefins.[33] Exposure of **43** to the Grubbs second-generation catalyst (Grubbs II)[34] furnished allylsilane **45** in 89% yield, which underwent smooth S_E' protodesilylation[23a] in the presence of *p*-TsOH. The *exo*-methylidenecyclohexane product (**46**) proved to be very stable to *p*-TsOH in Et_2O; exposure of this compound to excess acid for 24 h did not lead to isomerization to the more stable endocyclic alkene. With success in this simple model system, we aimed to demonstrate its utility in complex contexts by incorporating this two-step strategy into discrete syntheses of teucladiol (**3**), poitediol (**4**), and caryophyllene (**2**), rather than demonstrating the scope of the strategy with a series of simple and uninteresting substrates.

Teucladiol: Background. Teucladiol (**3**, Figure 1) is a guaiane sesquiterpene that was first isolated in 1993 by de la Torre and co-workers[8] from the aerial parts of *Teucrium leucocladum*, a flowering plant found in Egypt. The structure and relative stereochemistry of teucladiol were determined using a combination of one- and two-dimensional NMR techniques. Since this initial disclosure, teucladiol has been isolated from a variety of terrestrial sources[35] including the Egyptian weed *Pluchea dioscoridis*,[13] the green rabbitbrush (*Chrysothamnus viscidiflorus*) in the western United States,[35a] the aerial parts of the plant *Croton arboreous* in Mexico,[35b] the stem of the peacock flower (*Caesalpinia pulcherrima*) in Thailand,[35c] the rhizome of the plant *Notopterygium incisum*

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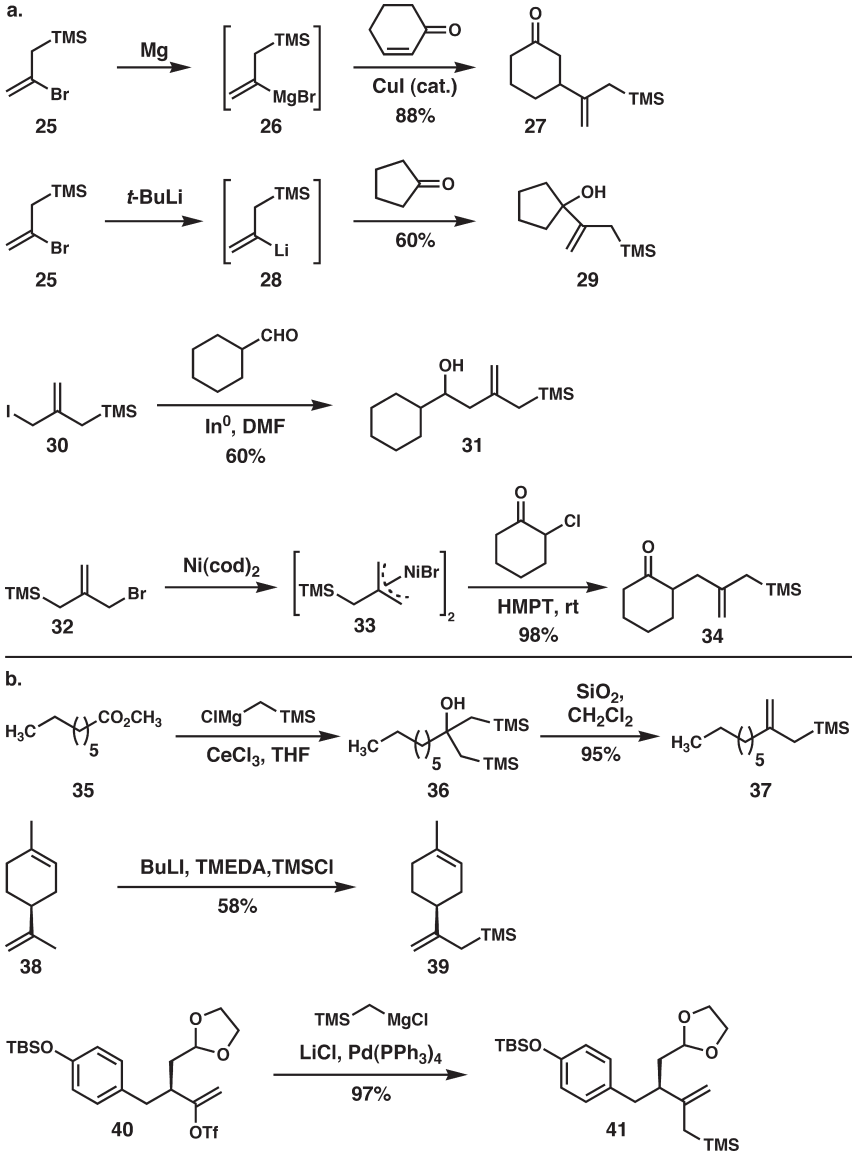
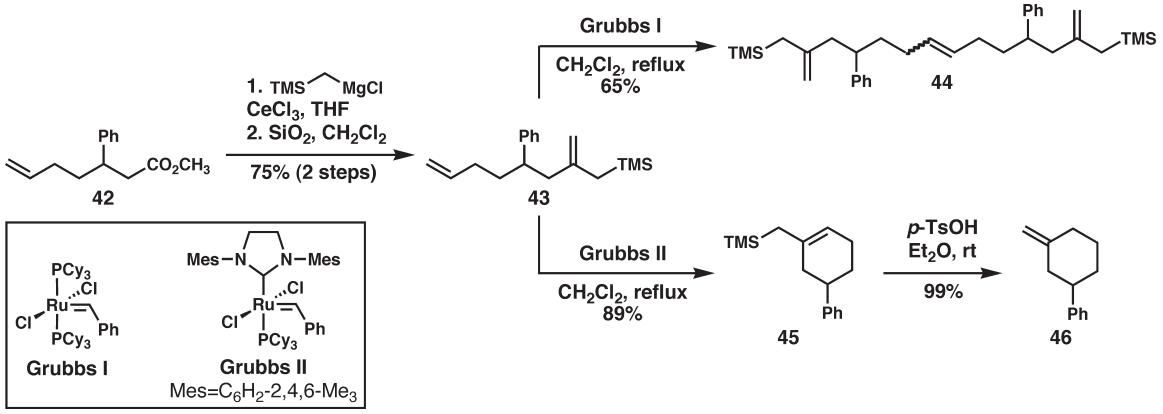
SCHEME 4. Representative Methods for the Synthesis of 2-Substituted-3-trimethylsilyl-1-propenes

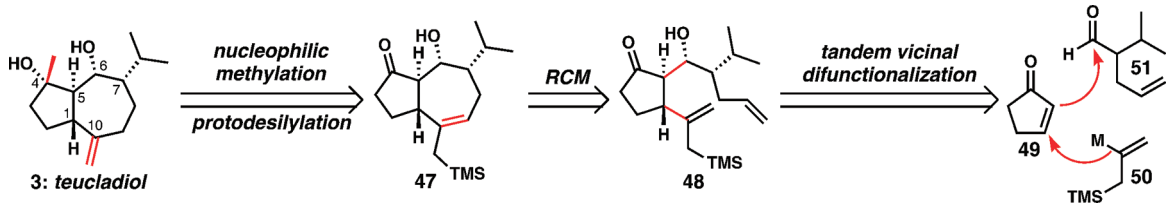


SCHEME 5. Synthesis of Model *exo*-Methylidenecyclohexane 46

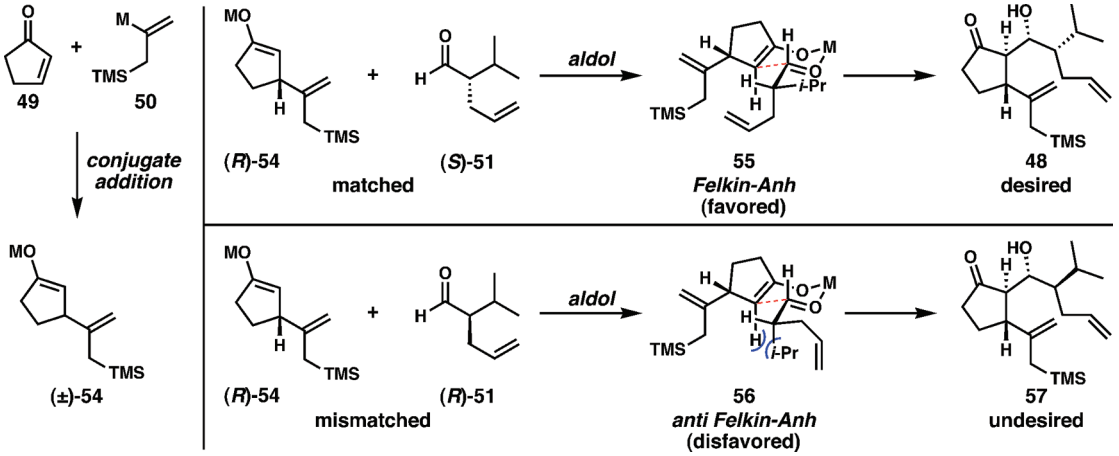


in China,[35d] and the aerial parts of the flowering plant *Cleome droserifolia* in Saudi Arabia.[35e] Mabry and co-workers have shown teucladiol to be moderately cytotoxic against the MCF-7 and MDA-MB-435 breast cancer cell lines with $EC_{50} = 50\ \mu g/mL$.[35a] No synthesis of teucladiol has been reported prior to (or since) our initial communication in 2009.[15]

SCHEME 6. Retrosynthetic Analysis of Teucladiol

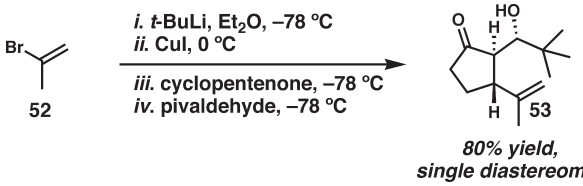


SCHEME 7. Anticipated Stereochemical Course of Aldol Coupling between (±)-54 and (±)-51



The major synthetic challenge posed by teucladiol involves the controlled installation of five contiguous stereogenic centers, four of which are present on the seven-membered ring embedded in teucladiol's bicyclo[5.3.0]decane framework.[36]

Teucladiol: Retrosynthetic Analysis and Synthetic Planning. Our general retrosynthetic plan for teucladiol is shown in Scheme 6. It was anticipated that teucladiol could be generated from ketone **47** in two steps via substrate-controlled methylcerium addition followed by allylsilane protodesilylation. Ketone **47**, in turn, would be derived from diene **48** through a ring-closing olefin metathesis reaction.[37] This compound (**48**) was envisioned to arise from a diastereoselective tandem vicinal difunctionalization reaction[38] between cyclopentenone (**49**), an organometallic reagent (**50**) derived from 2-bromoallyltrimethylsilane (**25**, Scheme 4a), and aldehyde **51**.[39] If successful, this three-component coupling process[38a] would set four of the five stereogenic centers found in teucladiol and assemble all but one of the necessary carbon atoms.



(1)

With respect to the proposed three-component coupling reaction (**49** + **50** + **51** → **48**), Snider has shown that conjugate addition of the organocuprate derived from metalation of 2-bromopropene to cyclopentenone and trapping of the resulting enolate with pivaldehyde gives **53** as a single diastereomer in 80% yield (eq 1).[40] The stereochemical result of this reaction is consistent with *trans*-addition of the nucleophile and electrophile and *anti*-selective aldol addition of the ring-constrained *E*-enolate proceeding via a closed transition state. The three contiguous stereocenters found in **53** map directly onto teucladiol (**3**) with the correct relative configuration, which indicated that a related three-component coupling process might be suitable for a synthesis of teucladiol. It was further anticipated that aldol coupling of the racemic enolate (±)-**54** (Scheme 7), derived from conjugate addition of cyclopentenone (**49**) and organometallic **50**, with aldehyde (±)-**51**, might proceed with a high level of double diastereodifferentiation[41] to provide the desired stereoisomer (±)-**48** with the correct relative configuration at the isopropyl-bearing C7. The pertinent aldol addition is anticipated to proceed through a closed transition state; this prediction is supported by the stereochemical outcome of Snider's three-component coupling reaction. The transition-state assembly between enolate (*R*)-**54** and aldehyde (*S*)-**51** depicted as **55** at the top of Scheme 7 (or the enantiomeric pair of (*S*)-**54** and (*R*)-**51**, not shown) corresponds to a Felkin−Anh addition, a preference that is known to be enhanced when *E*-enolates are employed,[42] and would

(36) For a recent review on synthetic approaches to this ring system, see: Foley, D. A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 1131–1175.

(37) Nakashima, K.; Fujisaki, N.; Inoue, K.; Minami, A.; Nagaya, C.; Sono, M.; Tori, M. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1955–1962.

(38) For pertinent reviews, see: (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (b) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847–876. (c) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225–653.

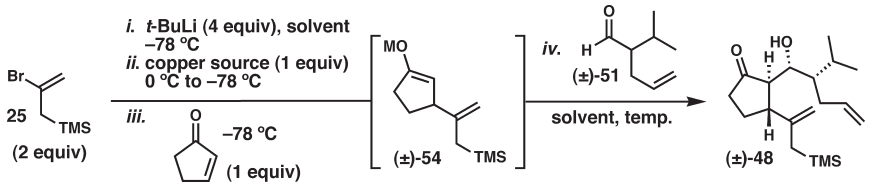
(39) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952–1956.

(40) Snider, B. B.; Yank, K. *J. Org. Chem.* **1992**, *57*, 3615–3626.

(41) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30. (b) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953–6018.

(42) For a discussion, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.

TABLE 1. Optimization of the Three-Component Coupling Sequence to Generate 48



entry	copper source	solvent	temperature (°C)	equivalents (±)-**51**	yield[a]
1	CuI	Et_2O	−78	1.0	15−28%
2[b]	Li(2-thienyl)CuCN	Et_2O	−78 to −50	1.2	trace
3	$CuBr \cdot SMe_2$	Et_2O	−78	1.2	30%
4	$CuBr \cdot SMe_2$	THF	−78	1.5	0%
5[b]	$CuI \cdot PBu_3$	Et_2O	−78	1.3	trace
6[b]	$CuI \cdot PBu_3$	Et_2O	−78	2.0	15%
7[c]	CuCN	Et_2O	−78	1.0	35%
8[c]	CuCN	Et_2O	−78	2.1	39%
9[c]	CuCN	Et_2O/hexanes (3:1)	−78	2.0	34%
10[c]	CuCN	Et_2O/THF (19:1)	−78	2.1	60%[d]

[a]Isolated yield after column chromatography. [b]1 equiv of **25** and 2 equiv of *t*-BuLi were used in this reaction. [c]2.2 equiv of **25**, 4.2 equiv of *t*-BuLi, and 1.05 equiv of CuCN were used in this reaction. [d]dr of reaction as determined from crude ^{1}H NMR: ≥10:1.

produce the diastereomer required for a synthesis of teucladiol. In contrast, aldol coupling between (*R*)-**54** and (*R*)-**51** corresponding to **56** (or the enantiomeric pair (*S*)-**54** and (*S*)-**51**, not shown) should be disfavored due to the presence of a destabilizing interaction between the bulky isopropyl group and the vinyl hydrogen of the cyclopentene in the pretransition-state assembly. This predicted preference of reactivity of one enantiomer of enolate with one enantiomer of aldehyde would represent an interesting and unusual example of double stereodifferentiation/kinetic resolution of two chiral but racemic reaction partners.

Trost first demonstrated the utility of 2-metalated allylsilane reagents in organic synthesis in the early 1980s. For example, the Grignard reagent **26** (Scheme 4) derived from 2-bromoallyltrimethylsilane (**25**) was shown to add in a conjugate manner to cyclohexenone in high yields in the presence of catalytic copper(I) iodide.[29a] Attempts to form and utilize stoichiometric cuprates derived from reductively metalated derivatives of 2-bromoallyltrimethylsilane were reported to be unsuccessful,[29a] because the desired reactivity was complicated by competitive oxidative dimerization of the cuprate. This result caused us some concern regarding the feasibility of the proposed three-component coupling reaction (**49** + **50** + **51** → **48**) because the majority of high-yielding tandem vicinal difunctionalization reactions that are triggered by the addition of an organocuprate to a cyclic conjugate acceptor utilize stoichiometric cuprates.[38,40]

Teucladiol: Synthesis. Table 1 outlines our attempts to develop a one-pot tandem vicinal difunctionalization sequence to access **48**. Initial experiments adhered closely to the procedure used by Snider in his synthesis of **53** (eq 1),[40] which involved reductive lithiation[43] of 2-bromoallyltrimethylsilane in diethyl ether, forming the stoichiometric Gilman reagent, treating the resultant cuprate with cyclopentenone, and trapping the resulting enolate with aldehyde (±)-**51** at −78 °C (entry 1, Table 1). ^{1}H NMR analysis of the crude reaction mixture suggested that the reaction had proceeded with a useful level of diastereoselectivity to provide **48** (see below); however, it was isolated in low and variable yields (15−28%). The major identifiable side products resulted from oxidative dimerization of the cuprate and 1,2-addition to cyclopentenone. Subsequent experiments examined the use of other copper sources, and copper cyanide emerged as the reagent of choice for this reaction, routinely affording the desired product in 35% yield (entry 7). Utilizing two equivalents of the readily available aldehyde (±)-**51** provided a modest improvement in yield (entry 8). Optimization of solvent demonstrated that a 19:1 mixture of diethyl ether/THF proved ideal among those examined, furnishing the desired product in ≥10:1 diastereoselectivity as determined by ^{1}H NMR analysis of the crude reaction product and in 60% isolated yield after column chromatography (entry 10). These results suggest that small quantities of THF help to suppress oxidative dimerization of the cyanocuprate; on the other hand, when used as the sole solvent, THF appears detrimental to aldol addition (entry 4). The high level of diasteroselection observed in this three-component coupling reaction indicates that there is a strong kinetic preference for aldol coupling between (*R*)-**54** and (*S*)-**51** (and its enantiomeric pair) relative to that between (*R*)-**54** and (*R*)-**51** (and its enantiomeric pair), as predicted by the analysis shown in Scheme 7.

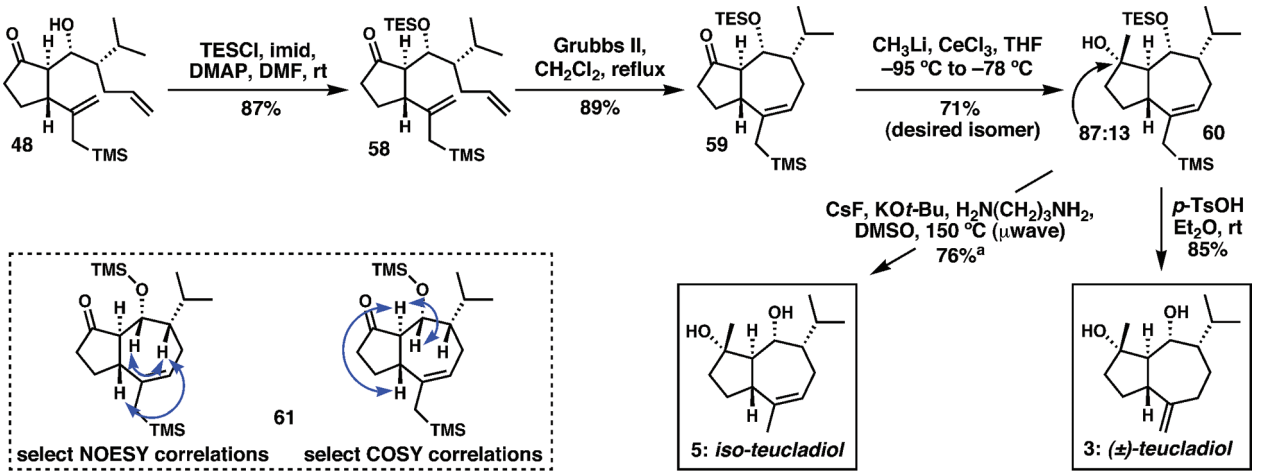
With a reliable route to aldol adduct **48** in hand, subsequent efforts focused on converting this material into teucladiol (Scheme 8). Attempted ring-closing olefin metathesis of **48** failed, likely due to coordination of the intermediate ruthenium alkylidene with the pendant alcohol.[44] While *in situ* protection of the hydroxy group with Lewis acids was considered,[45] we opted to mask the secondary alcohol with a triethylsilyl ether to aid in both the ring-closing metathesis reaction and a later step. Silyl ether **58** underwent smooth ring-closing olefin metathesis in the presence of the Grubbs

(43) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1–46.

(44) For other examples of unsuccessful RCM in the presence of a free alcohol, see: (a) Rhee, H. J.; Beom, H. Y.; Kim, H.-D. *Tetrahedron Lett.* **2004**, *45*, 8019–8022. (b) Fujiwara, K.; Koyama, Y.; Doi, E.; Shimawaki, K.; Ohtaniuchi, Y.; Takemura, A.; Souma, S.-I.; Murai, A. *Synlett* **2002**, 1496–1499.

(45) For the *in situ* protection of a carbonyl function that interfered with ring-closing metathesis, see: Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

SCHEME 8. Synthesis of (±)-Teucladiol and (±)-*iso*-Teucladiol



[a]contaminated with *ca.* 15% teucladiol.

second-generation catalyst (see Grubbs II in Scheme 5) to furnish bicyclic **59** in 89% yield. NOESY and COSY NMR analysis of **61** (the TMS congener of **59**) confirmed the expected and desired stereochemical outcome of the three-component coupling reaction.

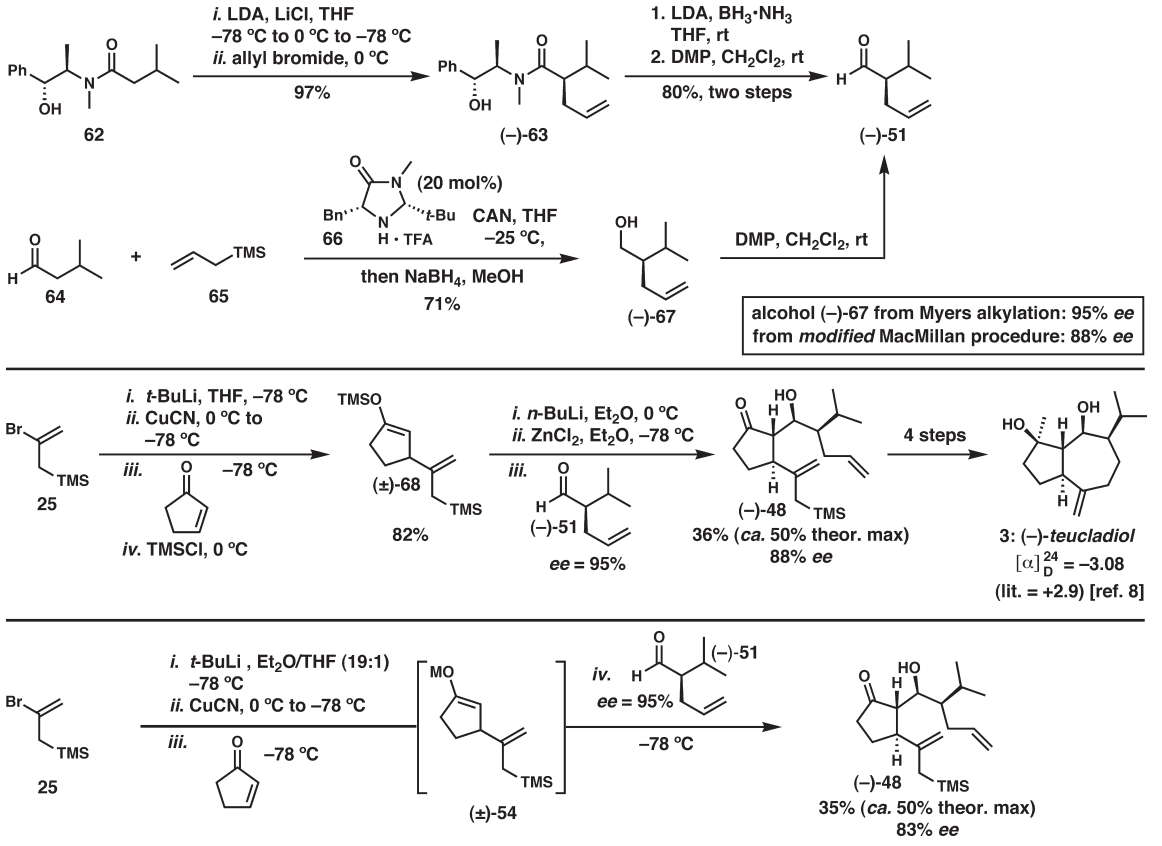
It was anticipated that addition of a methyl nucleophile to ketone **59** would proceed with a high level of diastereoselection to give **60** as a result of steric shielding of the *re*-face of the ketone by the adjacent triethylsilyl ether. Slow addition of **59** as a solution in THF to the organocerium reagent[46] derived from methyllithium at −95 °C with gradual warming to −78 °C afforded an 87:13 mixture of diastereomers at C4, which were isolated in a combined 92% yield. These two isomers were separable, and the desired diastereomer was isolated in 71% yield. Exposure of **60** to *p*-toluenesulfonic acid in diethyl ether led to protodesilylation of both the allylsilane and the silyl ether to afford racemic teucladiol (**3**) in 85% yield. Alternatively, exposure of **60** to CsF, KO*t*-Bu, and 1,3-diaminopropane in DMSO at 150 °C under microwave irradiation afforded the natural product 4β,6β-dihydroxy-1α,5β(*H*)-guai-9-ene (*iso*-teucladiol, **5**)[13] in 76% yield and in moderate purity (contaminated with small quantities of teucladiol), thus demonstrating the versatility of cyclic allylsilane **60** in particular and this strategy for terpene synthesis in general.

The optimized route to racemic teucladiol required a total of five operations from cyclopentenone and known aldehyde **51** and proceeded in 28% overall yield. Besides featuring a high level of step[47] and redox[48] economy, this synthesis constitutes one of the most concise synthetic routes to a guaiane sesquiterpene. Notable features include a highly diastereoselective three-component coupling reaction that establishes four contiguous stereogenic centers, the use of an allylsilane RCM/S_E' sequence to construct the *exo*-methylidenecycloalkane motif, and the efficient use of a TES protecting group, which served to enable the key ring-closing olefin metathesis reaction, likely influenced the diastereoselectivity of the methylcerium addition reaction, and was efficiently removed under conditions required for S_E' protodesilylation of the allylsilane.

Enantioselective Synthesis of (−)-Teucladiol. A synthesis of enantiomerically enriched teucladiol was realized by incorporating enantiomerically enriched aldehyde (−)-**51** into a modified version of the three-component coupling sequence shown above (Scheme 9). Aldehyde (−)-**51** could be prepared in enantiomerically enriched form through utilization of the Myers pseudoephedrine amide alkylation technology[49] or in fewer steps through organocatalytic SOMO α-allylation of isovaleraldehyde using a modified version of MacMillan's procedure.[26,50] Enolsilane (±)-**68** was produced in racemic form through conjugate addition of the cyanocuprate derived from 2-bromoallyltrimethylsilane **25** to cyclopentenone followed by trapping of the resulting enolate with TMSCl. Regeneration of the corresponding lithium enolate from enolsilane (±)-**68** was achieved through treatment with *n*-BuLi; addition of anhydrous zinc chloride[51] presumably led to the zinc enolate, which was trapped with enantiomerically enriched aldehyde (−)-**51** (precursor alcohol (−)-**67** had 95% ee) to give (−)-**48** in 36% yield (theoretical maximum ca. 50%) and 88% ee.[52] Conversion of (−)-**48** into (−)-teucladiol (**3**) was achieved using the same four-step sequence from our synthesis of (±)-teucladiol (Scheme 8) and proved that the absolute configuration of natural teucladiol is that depicted in Figure 1 and Scheme 8. Incorporating aldehyde (−)-**51** into the identical one-pot, three-component coupling sequence utilized for the synthesis of (±)-**48** delivered (−)-**48** in 35% yield (theoretical maximum ca. 50%) and 83% ee. Although the yields for these two procedures are essentially the same, it appears that the use of the zinc enolate generated from enolsilane (±)-**68** in the stepwise procedure leads to slightly better retention of enantioselectivity. While an ideal enantioselective synthesis

(46) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.
(47) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505–7511.
(48) Burns, N. Z.; Baran, P. S.; Hoffman, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854–2867.
(49) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
(50) Because of isolation difficulties related to the volatility of the product, we used THF as solvent instead of the recommended DME; presumably this protocol change led to the slightly depressed enantioselectivity (88% ee) of this transformation relative to those reported in ref 26.
(51) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324.
(52) Under these conditions, other diastereomers, presumably from the mismatched combination, are observed in the crude reaction mixture.

SCHEME 9. Synthesis of (−)-Teucladiol[a]



[a]DMP = Dess−Martin periodinane.

of (−)-**48** would incorporate enantioenriched enolate (*R*)-**54**, the asymmetric conjugate addition of sp^2-hybridized organometallics to cyclopentenone with productive use of the resulting enolate is not a well-developed process.[53] Our goal was simply to use inexpensive materials to rapidly determine the absolute configuration of teucladiol.

Poitediol: Background. Poitediol (**4**) was isolated by Fenical and Clardy from the red seaweed *Laurencia poitei* in 1978 in the waters off the coast of the Florida Keys.[9] This unusual cyclooctane-containing natural product is thought to arise from a halogen solvolysis/rearrangement sequence of a more typical sesquiterpene skeleton, although no specific biogenetic postulate has been put forth.[54] As a result, and unlike most sesquiterpenes that display *exo*-methylidenecycloalkanes, poitediol's exocyclic alkene is not directly adjacent to a ring junction. The structure of poitediol was secured by X-ray crystallographic analysis. Gadwood reported the only prior synthesis of poitediol in 1984.[55] While his synthesis elegantly exploits an oxy-Cope rearrangement to forge poitediol's eight-membered ring, the entire route required 26 steps and proceeded in approximately 1% overall yield. Five syntheses of the related cyclooctene natural product dactylol (**6**, Scheme 10) have been reported;[55b,56] Fürstner's efficient 1996 synthesis of this sesquiterpene[56e] was one of the first to showcase the effectiveness of RCM for medium-ring formation (see below) and served as an inspiration for our study toward poitediol. It is also noteworthy that Gadwood was able to transform synthetic poitediol into dactylol under dissolving metal reducing conditions.[55b,56a]

Poitediol: Retrosynthetic Analysis and Synthetic Planning. Eight-membered rings are widely considered to be the most difficult ring size to construct due to the presence of destabilizing transannular interactions and ring strain.[57] Over the past decade and a half, however, ring-closing metathesis has emerged as a useful method for directly forming eight-membered rings.[58] In this context, poitediol was viewed as an attractive target, as it would allow us to test the applicability of our allylsilane RCM/S_E' strategy for the synthesis of *exo*-methylidenecyclooctenes, in this case with the simultaneous stereoselective introduction of an adjacent hydroxyl group. Thus, poitediol (**4**) would be derived from allylsilane

(53) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823.

(54) The fascinating conversion of africanol into a molecule with the precapnellane skeleton by Matsumoto presents a possible biosynthetic link between "normal" sesquiterpene architectures and that of poitediol. See: Hayasaka, K.; Ohtusuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1985**, *26*, 873–876.

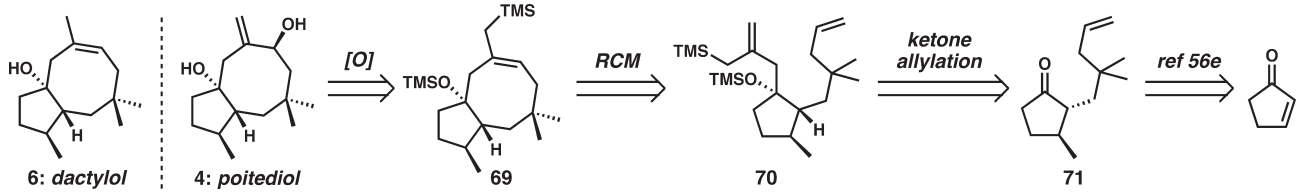
(55) (a) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3869–3870. (b) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343–6350.

(56) (a) Gadwood., R. C. *J. Chem. Soc., Chem. Commun.* **1985**, 123–124. (b) Paquette, L. A.; Ham, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 3025–3036. (c) Feldman, K. S.; Wu, M.-J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490–8496. (d) Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559–4565. (e) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746–8749.

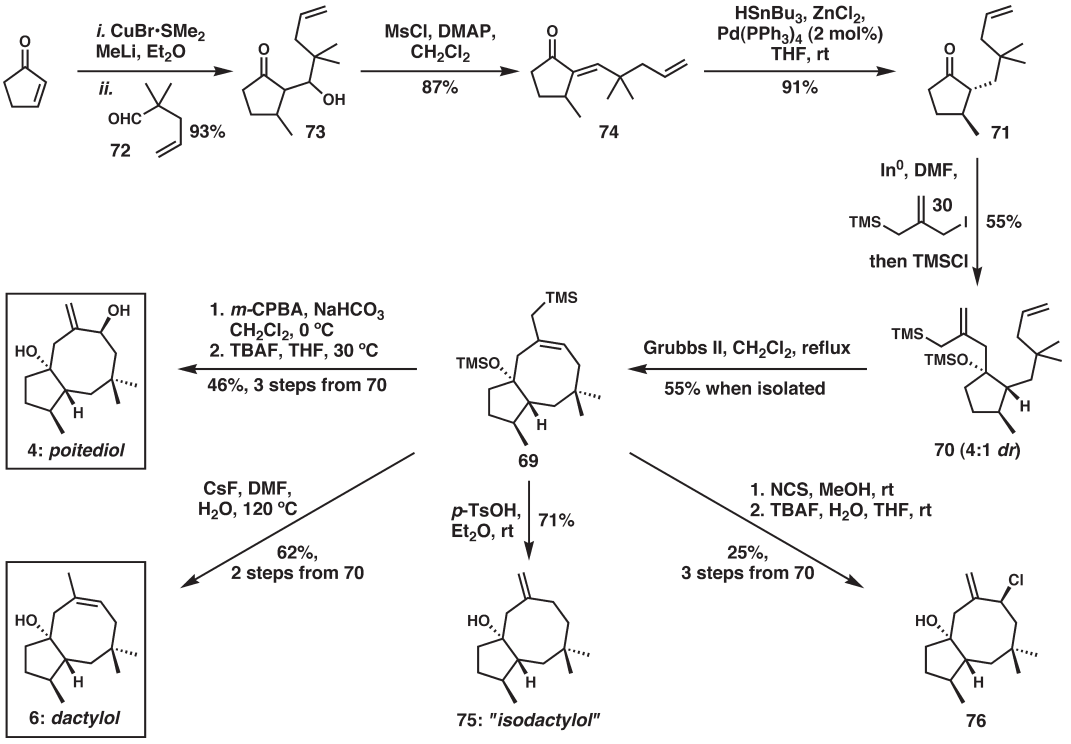
(57) (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930. (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821.

(58) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740–5750.

SCHEME 10. Structure of Dactylol and Synthetic Approach to Poitediol



SCHEME 11. Synthesis of Poitediol (4), Dactylol (6), "*iso*-Dactylol" (75), and Chlorinated Analogue 76

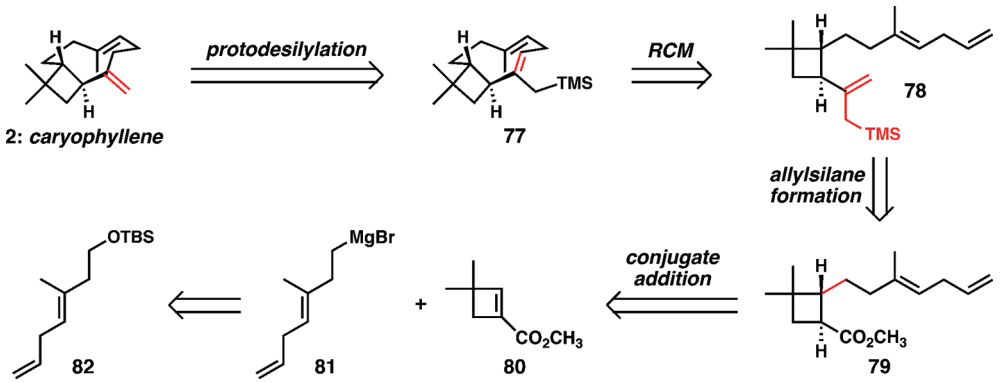


69 (Scheme 10), which molecular models suggest should undergo diastereoselective allylsilane oxidation in the desired sense, as the *re*-face appears to be blocked by the adjacent OTMS moiety as a result of the conformational bias of the cyclooctene ring. Allylsilane **69** would be produced through RCM of diene **70**, which would be derived from ketone **71** through an allylation reaction.[29c] Ketone **71** is known; it was a key intermediate in Fürstner's synthesis of dactylol (**6**).[56e]

Poitediol: Synthesis. Our synthesis of poitediol makes use of a slight modification of Fürstner's procedure for producing ketone **71**, an important intermediate in his dactylol synthesis. Tandem vicinal difunctionalization of cyclopentenone with dimethylcuprate and the commercially available aldehyde **72** gave adduct **73** in 93% yield (Scheme 11). In our hands, the use of copper bromide·dimethylsulfide complex in this three-component coupling reaction afforded a much better yield of **73** than we obtained using Fürstner's procedure, which utilized copper iodide·tributylphosphine complex. The aldol adduct **73** was dehydrated with methanesulfonyl chloride in the presence of DMAP and triethylamine to furnish enone **74**. Chemo- and stereoselective reduction of the enone was achieved with tributyltin hydride in the presence of catalytic $Pd(PPh_3)_4$ and zinc chloride to afford ketone **71** as a single diastereomer in 79% yield over two steps. The stereochemical result of this reaction is consistent with the known tendency of 2,3-disubstituted cyclopentenone-derived enols to give the thermodynamically preferred *trans*-product following kinetic protonation.[59] Indium-mediated reductive allylation of ketone **71** with allyl iodide **30** followed by *in situ* silylation gave **70** in 55% yield as a 4:1 mixture of diastereomers in favor of the isomer shown. This method of allylsilane introduction is distinct from that employed in our teucladiol synthesis and represents the third different method for introducing this key functionality showcased in this report. Exposure of the diastereomeric mixture of **70** to the Grubbs second-generation catalyst (see Grubbs II in Scheme 5) in refluxing dichloromethane gave crude cyclooctene **69**, which was epoxidized with buffered *m*-CPBA. Fluoride-promoted fragmentation of this crude silyl epoxide with TBAF furnished pure poitediol (**4**) in 46% yield over three steps from **70**. While this sequence does not technically make use of the S_E' reactivity of the allylsilane, the net transformation accomplished just such an oxidation. The structure of synthetic poitediol was confirmed by X-ray crystallographic analysis, since a complete set of NMR data was not available.[9] The versatility of cyclic allylsilane **69** was demonstrated by its transformation into the natural product dactylol

(59) Zimmerman, H. E.; Wang, P. *J. Org. Chem.* **2003**, *68*, 9226–9232.

SCHEME 12. Retrosynthetic Analysis of Caryophyllene



(**6**) through fluoride-mediated protodesilylation, the formation of the "*iso*-dactylol" (**75**, not a known natural product) by S_E' protodesilylation, and the synthesis of a chlorinated congener of poitediol (**76**).

Caryophyllene: Background, Retrosynthetic Analysis, and Synthetic Planning. Caryophyllene (**2**) is a widely distributed natural product that is most abundantly produced by the clove tree *Eugenia caryophyllata*.[7] This sesquiterpene has attracted a significant amount of interest from synthetic chemists as a result of its intriguing *trans*-fused bicyclo-[7.2.0]decane carbon framework, which incorporates both an *exo*-methylidene function and an endocyclic trisubstituted *E*-alkene.[60] Our interest in this natural product is derived from the presence of the *exo*-methylidenecyclononene, which suggested that a concise approach to caryophyllene might be possible through utilization of our allylsilane RCM/S_E' desilylation strategy. Thus, the key step in our proposed sequence toward caryophyllene would be ring-closing olefin metathesis of **78** to generate cyclononene **77** (Scheme 12). Examination of molecular models suggested that this transformation is feasible, and several examples of successful cross-metathesis[61] and ring-closing[62] olefin metathesis reactions of 1,4-dienes have been reported; however, there was some concern regarding the viability of this key ring-closing metathesis reaction because it is known that the formation of trisubstituted olefins in nine- to 12-membered rings using ring-closing olefin metathesis can be difficult, especially when one of the alkenes in the substrate is α-branched.[63−66] Despite these concerns, we reasoned that the substrate for the key ring-closing metathesis reaction, triene **78**, should be relatively easy to construct; the allylsilane function in this triene would be derived from the corresponding ester **79** using Bunnelle's methodology.[30a] The ester precursor to the allylsilane would, in turn, enable its formation via conjugate addition reaction of the organocuprate derived from Grignard reagent **81** to known cyclobutene **80**. Diene **82** is a known, easily prepared compound that should serve as a reasonable precursor to an organometallic reagent such as **81**.

Caryophyllene: Attempted Synthesis. The known cyclobutene ester **80** was prepared using a modification of Fleming's procedure (Scheme 13).[67] Thermal [2+2] cycloaddition between methyl acrylate and enamine **83** derived from pyrrolidine and isobutyraldehyde gave cyclobutane **84**, which was quaternized with methyl iodide. The resulting ammonium salt was treated with methanolic sodium methoxide in pentane to furnish cyclobutene ester **80** in 84% yield over four steps. Although this sequence of reactions is identical to Fleming's original route to this useful cyclobutene,[67] the overall yield is much improved, and the total time for the sequence is dramatically decreased.

The known TBS-protected alcohol **82** was prepared using a nickel-catalyzed three-component coupling process developed by Ikeda and co-workers.[68] Treatment of **82** with bromine/triphenylphosphine afforded alkyl bromide **86** directly[69] in nearly quantitative yield, which was transformed into the corresponding Grignard reagent (**81**) under standard conditions. In the presence of trimethylsilyl chloride, DMPU, and a catalytic amount of copper bromide·dimethylsulfide complex, Grignard reagent **81** underwent smooth conjugate addition to cyclobutene ester **80** to give **79** in 67% yield as a 5:1 mixture of diastereomers in which the major isomer was tentatively assigned the *trans*-configuration.[70] Conversion of the ester function in **79** into

(60) (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485–492. (b) Ohtsuka, Y.; Niitsuma, S.; Tadokoro, H.; Hayashi, T.; Oishi, T. *J. Org. Chem.* **1984**, *49*, 2326–2332. (c) McMurry, J. E.; Miller, D. D. *Tetrahedron Lett.* **1983**, *24*, 1885–1888. (d) Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954–2955.

(61) Yoshimura, T.; Yakushiji, F.; Kondo, S.; Wu, X.; Shindo, M.; Shishido, K. *Org. Lett.* **2006**, *8*, 475–478.

(62) (a) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Chou, T.-C.; Dong, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 10913–10922. (b) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. *J. Nat. Prod.* **2004**, *67*, 139–143.

(63) For an example involving a failed nine-membered ring closure, see: Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, *72*, 7135–7147.

(64) (a) Helmboldt, H.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1698–1708. (b) Helmboldt, H.; Köhler, D.; Hiersemann, M. *Org. Lett.* **2006**, *8*, 1573–1576.

(65) One potential problem is formal excision of a methylene unit via alkene isomerization and subsequent ring-closure (see: Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635–8638.), although the eight-membered ring corresponding to caryophyllene would likely be prohibitively strained to close.

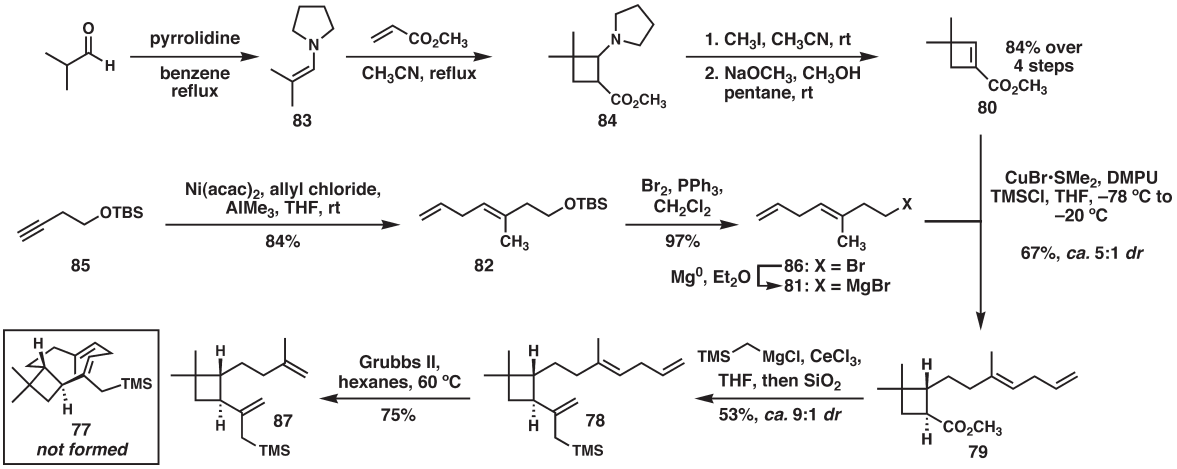
(66) For the successful generation of trisubstituted olefin-containing nine-membered rings, see: (a) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200–17201. (b) Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649–1660. (c) Gurjar, M. K.; Nayak, S.; Ramana, C. V. *Tetrahedron Lett.* **2005**, *46*, 1881–1884. (d) Ramírez-Fernández, J.; Collado, I. G.; Hernández-Galán, R. *Synlett* **2008**, 339–342. (e) Becker, J.; Bergander, K.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1654–1657. (f) Hamel, C.; Prusov, E. V.; Gertsch, J.; Schweizer, W. B.; Altmann, K.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 10081–10085.

(67) Fleming, I.; Rowley, M. *Tetrahedron* **1986**, *42*, 3181–3198.

(68) Ikeda, S.-I.; Miyashita, H.; Sato, Y. *Organometallics* **1998**, *17*, 4316–4318.

(69) Aizpurua, J. M.; Cossío, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941–4943.

SCHEME 13. Attempted Synthesis of the Caryophyllene Bicyclo[9.2.0]undecane Ring System Leads to Deallylation under Alkene Metathesis Conditions



an allylsilane was accomplished via Peterson olefination to give allylsilane **78** in 53% unoptimized yield as an apparent 9:1 mixture of diastereomers. With the key intermediate in hand, efforts were focused on effecting the challenging ring-closing olefin metathesis reaction to generate the cyclononene ring (**78** → **77**). Unfortunately, and despite extensive evaluation of various metathesis initiators (Grubbs second-generation catalyst, Hoveyda–Grubbs second-generation catalyst,[71] Schrock catalyst,[72] and several others) under various sets of conditions (dichloromethane, toluene, or hexanes at reflux, all at ca. 1 mM), the desired cyclononene **77** was never detected. Instead, the major identifiable product of the reactions was **87**, the result of a deallylation reaction. The highest yield of this compound was achieved when **78** was exposed to the Grubbs second-generation catalyst (see Grubbs II in Scheme 5) in hexanes at reflux (75%). Attempts to circumvent this destructive process included masking the trisubstituted alkene as its corresponding epoxide (which would have ultimately provided caryophyllene oxide, not shown). While the deallylation process was certainly prevented, this substrate decomposed apparently without ring closure upon exposure to Grubbs II at 100 °C in toluene.

To the best of our knowledge, the metal alkylidene-promoted deallylation of 1,4-dienes is a novel process. A potential mechanism for the transformation of **78** into **87** is shown in Scheme 14. According to this proposal, dimerization of starting material is followed by metathetical cleavage of one of the trisubstituted olefins of dimer **89** to afford one equivalent of **87** and metal carbene **91**. In the case where the dimer was produced with the new alkene *Z*-configured, ring-closing olefin metathesis with the remaining trisubstituted alkene within **91** would generate a molecule of 1,4-cyclohexadiene (**92**)[73] and eventually a second molecule of **87** (via metal alkylidene **93**). In order to provide further circumstantial evidence for this mechanistic proposal with another, simpler substrate, the trisubstitued skipped diene **86** was exposed to the Grubbs second-generation catalyst in $CDCl_3$ in a closed reaction vessel and heated to 40 °C. After 2 h, ^1H NMR analysis of the reaction mixture showed a 0.4:1 mixture of **92** and **95**. Another mechanistic scenario that cannot be ruled out at this time involves direct catalyst attack on the trisubstituted alkene of the starting material: in effect, a cross-metathesis deallylation procedure that could certainly eventuate molecules of 1,4-cyclohexadiene. The simplest and most direct mechanistic possibility, involving ring-closing metathesis of **88** to generate cyclopropene, is unlikely from an energetic standpoint. All mechanistic scenarios that we have entertained to this point are troubling in one way or another. For example, the dimerization-based mechanism shown in Scheme 14 requires selective intermolecular metathesis of a trisubstituted alkene in the presence of a disubstituted one. Clearly, more experiments are required to gain a better mechanistic understanding of this interesting deallylation reaction that apparently becomes operative with 1,4-dienes when more kinetically favored metathetical processes are not available.

Conclusions

Allylsilane ring-closing metathesis/S_E' electrophilic desilylation is a powerful strategy for synthesizing *exo*-methylidenecycloalkanes that are embedded in numerous terpene natural products. The power of this strategy has enabled concise syntheses of teucladiol (racemic: five steps, 28% overall yield; enantioenriched: five steps, 16% overall yield) and poitediol (seven steps, 18% overall yield). Syntheses of the natural products *iso*-teucladiol and dactylol, as well as unnatural analogues, were realized using advanced intermediates en route to teucladiol and poitediol, respectively. Attempted incorporation of this strategic combination of

(70) This stereochemical assignment is based on two observations from subsequent experiments (see Scheme 13): (1) Conversion of the ester function in **79** (with dr = ca. 5:1) into the corresponding allylsilane (**78**), in a reaction that is known to be sensitive to steric hindrance, affords a 9:1 mixture of diastereomers, suggesting that the major diastereomer is less hindered than the minor diastereomer. (2) Diene **87** does not appear to undergo ring-closing metathesis to form the corresponding bicyclo[4.2.0]octane, which should be possible if the stereochemistry is *cis*. Unfortunately, all attempts to confirm this stereochemical assignment with NOE experiments provided ambiguous results.

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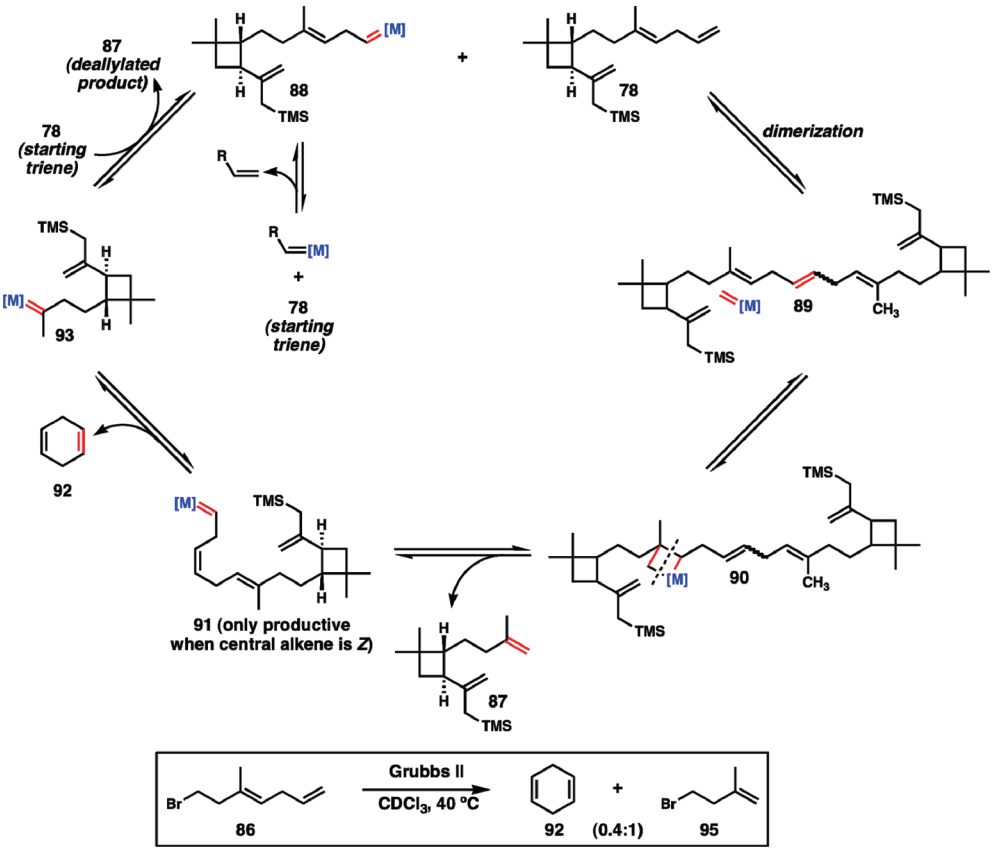
(73) For generation of 1,4-cyclohexadiene in a related manner, see: Guiard, S.; Santelli, M.; Parrain, J.-L. *Synlett* **2001**, 553–556.

SCHEME 14. Possible Mechanism for the Metal Alkylidene-Promoted Deallylation of Skipped Dienes and Circumstantial Evidence for the Proposed Mechanism



reactions into a synthesis of caryophyllene failed to deliver the natural product because a novel deallylation reaction of the starting 1,4-diene preempted the challenging ring closure. Because of the ubiquity of the *exo*-methylidenecycloalkane motif in terpene natural products, many more applications of the allylsilane RCM/S_E' strategy in natural product synthesis are likely.

Experimental Section

General Experimental Details. All reactions were performed under a nitrogen or argon atmosphere using oven-dried glassware. All solvents were dried by passing through activated alumina columns. ^{1}H and ^{13}C NMR spectra were obtained on 500 or 600 MHz spectrometers at 298 K, unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) using the internal solvent residual of $CDCl_3$ at 7.26 for ^{1}H NMR and 77.23 for ^{13}C NMR as the internal reference. Coupling constants are reported in hertz (Hz), and the peak multiplicity is listed as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. Column chromatography was performed using 230−400 mesh silica gel (SiO_2) or 230−400 mesh high-preformance silica gel with the indicated solvent system. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm coated commercial silica gel plates (F_{254} precoated glass plates) using iodine as visualizing agent and vanillin or $KMnO_4$ and heat as a developing agent. Melting points are uncorrected. *p*-Toluenesulfonic acid monohydrate was dried by azeotropic removal of water with toluene and recrystallized from hexanes/ethyl acetate prior to use. DMPU was distilled from CaH under reduced pressure. Chlorotrimethylsilane was distilled from CaH at atmospheric pressure. Compounds not included in this Experimental Section have been previously documented in ref 15.

Isoteucladiol (5). Argon was bubbled through a mixture of **60** (7.00 mg, 0.017 mmol), CsF (25.0 mg, 0.165 mmol), KO*t*-Bu (18.0 mg, 0.165 mmol), and 1,3-diaminopropane (0.013 mL, 0.165 mmol) in DMSO (0.6 mL) for 20 min. The reaction mixture was sealed and heated to 150 °C in a microwave for 45 min. The cooled black reaction mixture was poured into saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to afford an apparent 4:1 mixture of isoteucladiol/teucladiol by ^{1}H NMR as a clear oil. The crude material was purified by column chromatography (HP SiO_2, 98:2 to 92:8 hexanes/EtOAc) to afford **5** (3 mg, ca. 85% pure, 76% yield) as a clear oil. R_f = 0.28 (65:35 hexanes/EtOAc); spectral data were obtained on a cut fraction and were consistent with those reported previously for the natural product.[13] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, J = 9.3 Hz, 1H), 4.14 (m, 1H), 2.44 (s, 1H), 2.25−2.35 (m, 2H), 2.26 (d, J = 3.0 Hz, 1H), 2.09 (dd, J = 12.0, 9.5 Hz, 1H), 1.88−1.60 (m, 6H), 1.66 (s, 3H), 1.32 (s, 3H), 1.25−1.30 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 126.4, 81.4, 72.6, 57.7, 50.7, 42.5, 40.1, 28.7, 26.8, 24.5, 24.4, 23.4, 21.7, 21.6; IR (thin film) ν 2958, 1455 cm^{-1}; HRMS (ESI) m/z calc for $C_{15}H_{26}O_2Na$ $(M + Na)^+$ 261.1830, found 261.1837.

Dactylol (6). A solution of crude allylsilane **69** (27.0 mg, 0.074 mmol) [from the ring-closing metathesis reaction of **70**] and CsF (11.3 mg, 0.074 mmol) in a mixture of H_2O (0.05 mL) and DMF (0.75 mL) was heated to 120 °C for 4 h. The cooled reaction mixture was treated with more CsF (40.0 mg, 0.263 mmol) and again heated to 120 °C. After an additional 3.5 h, the cooled

reaction mixture was poured into NH_4Cl (15 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude material was purified by column chromatography (SiO_2, 100:0 to 98:2 hexanes/EtOAc) to afford **6** (8 mg, 62% from **70**) as a white solid with mp = 45−47 °C [lit.[14] 50.3−51.5 °C]. Spectral data were consistent with those reported previously.[56e] R_f = 0.38 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51−5.55 (m, 1H), 2.40 (d, J = 13.5 Hz, 1H), 2.19 (d, J = 13.5 Hz, 1H), 1.98 (dd, J = 12.9, 10.5 Hz, 1H), 1.88−1.95 (m, 1H), 1.84 (s, 3H), 1.71−1.76 (m, 3H), 1.59 (dd, J = 6.7, 13.2 Hz, 1H), 1.39 (dd, J = 7.84, 14.6 Hz, 1H), 1.13−1.20 (m, 1H), 1.10 (dd, J = 7.8, 11.3 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.83 (d, J = 14.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 125.1, 83.4, 53.0, 42.9, 40.1, 39.32, 39.26, 36.6, 35.3, 29.4, 28.9, 27.9, 19.3; IR (thin film) ν 2951, 2866, 1469, 1015, 859 cm^{-1}; HRMS (NH_3-CI GCMS) m/z calc for $C_{15}H_{30}NO$ $(M + NH_4)^+$ 240.2327, found 240.2335.

Isodactylol (75). [Note: As described below, this reaction was worked up several times in order to monitor the progress of the reaction by ^{1}H NMR, because TLC analysis was not possible.] A solution of **69** (30.0 mg, 0.082 mmol) in Et_2O (1.6 mL) was treated with *p*-TsOH (28.0 mg, 0.162 mmol), and the solution was stirred at rt. After 1.66 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to afford a clear oil, which was diluted with Et_2O (1.6 mL) and treated with *p*-TsOH (28.0 mg, 0.162 mmol). After 2.25 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to afford a clear oil, which was diluted with Et_2O (1.2 mL) and treated with *p*-TsOH (28.0 mg, 0.162 mmol). After 4 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to afford a clear oil. The crude material was purified by column chromatography (SiO_2, 100:0 to 98:2 hexanes/EtOAc) to afford **75** (13 mg, 71%) as a white solid with mp = 37−39 °C. R_f = 0.45 (9:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.79 (s, 1H), 2.40−2.47 (m, 3H), 2.20−2.56 (m, 1H), 2.17 (d, J = 12.9 Hz, 1H), 1.97 (ddt, J = 7.4, 9.1, 13.0 Hz, 1H), 1.80−1.85 (m, 1H), 1.65−1.78 (m, 3H), 1.34 (dd, J = 14.9, 6.9 Hz, 1H), 1.10−1.20 (m, 2H), 1.02 (dd, J = 6.9, 11.3 Hz, 1H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (s, 3H), 0.87 (d, J = 14.9 Hz, 1H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 113.4, 79.0, 51.9, 43.4, 39.01, 38.99, 36.4, 35.4, 34.2, 33.3, 31.1, 29.8, 28.2, 19.0; IR (thin film) ν 2951, 2865, 1458, 1251, 1042, 894; HRMS (NH_3-CI GCMS) m/z calc for $C_{15}H_{30}NO$ $(M+NH_4)^+$ 240.2327, found 240.2324.

Allyl Chloride (76). A solution of crude allylsilane **69** (23.0 mg, 0.063 mmol) [from the ring-closing metathesis reaction of **70**] in MeOH (2.5 mL) was treated with NCS (67.0 mg, 0.508 mmol) and stirred at rt. After 1 h, the reaction mixture was poured into a solution of saturated aqueous sodium sulfite (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to afford a clear oil. The crude product was immediately treated with water (0.05 mL) and a solution of TBAF (1 mL, 1 M in THF) and stirred at rt. After 20 h, the reaction mixture was poured in saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude material was purified by column chromatography (SiO_2, 100:0 to 97:3 hexanes/EtOAc) to afford **76** (4.0 mg, 25% from **70**) as an oily residue. R_f = 0.43 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 1H), 5.10 (s, 1H), 4.74 (dd, J = 4.0, 12.6 Hz, 1H), 2.47 (d, J = 13.7 Hz, 1H), 2.38 (d, J = 13.7 Hz, 1H), 2.06 (t, J = 13.6 Hz, 1H), 1.95−2.02 (m, 1H), 1.94 (s, 1H), 1.70−1.85 (m, 5H), 1.35 (dd, J = 6.9, 15.1 Hz, 1H), 1.17−1.25 (m, 1H), 1.04 (dd, J = 7.3, 11.5 Hz, 1H), 0.97 (s, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 118.8, 79.3, 65.6, 51.9, 45.9, 39.2, 39.0, 38.7, 35.6, 33.5, 31.4, 29.6, 28.3, 18.9; IR (thin film) ν 2952, 2866, 1471, 1016, 916; HRMS (NH_3-CI GCMS) m/z calc for $C_{15}H_{29}ClNO$ $(M + NH_4)^+$ 274.1938, found 274.1948.

Cyclobutene Ester 80. The preparation of **80** is based on a modified version of a procedure described by Fleming.[67] A mixture of isobutyraldehyde (6.30 mL, 69.3 mmol) and pyrrolidine (5.20 mL, 62.4 mmol) in benzene (150 mL) was heated to reflux in a flask outfitted with a Dean−Stark trap and a reflux condenser. After 6 h, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was diluted with acetonitrile (100 mL), and methyl acrylate (6.20 mL, 68.6 mmol) was added; the resulting mixture was heated at reflux for 3 h. The cooled reaction mixture was concentrated under reduced pressure to afford an amber oil (10.16 g), which was diluted with CH_3CN (24 mL). The resulting solution was treated with iodomethane (7.48 mL, 120 mmol) and allowed to stir at rt. After 14 h at rt, the reaction mixture was concentrated to afford a brown solid. This solid was dissolved in MeOH (100 mL) and added to a two-phase mixture of sodium methoxide (11.40 g, 211.7 mmol) dissolved in methanol (300 mL) and pentane (400 mL). The reaction mixture was stirred vigorously for 1 h, at which point the two phases were separated. The methanol phase was extracted with pentane (2 × 150 mL), then diluted with water (150 mL) and extracted with pentane/Et_2O (2:1, 3 × 150 mL). The combined organic layers were washed with 0.5 N HCl (50 mL), water (200 mL), and brine (2 × 200 mL) and dried over $MgSO_4$. Filtration through SiO_2, followed by evaporation *in vacuo*, afforded **80** as an amber oil (7.33 g, 84% from pyrrolidine). The spectral properties of **80** were consistent with those reported previously.[1] R_f = 0.48 (92:8 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 3.72 (s, 3H), 2.42 (s, 2H), 1.22 (s, 6H).

Diene 82. We adopted the procedure reported by Ikeda and co-workers, who previously described the preparation of diene **82**.[68] ^{1}H NMR data reported for this compound in Ikeda's publication appear to correspond to a lower homologue of **82** (their compound **5c**); therefore, we fully characterized this diene. To a cooled (0 °C) solution of $Ni(acac)_2$ (493 mg, 1.91 mmol) in THF (191 mL) was added trimethylaluminum (27.6 mL, 49.6 mmol, 15% in hexane) over the course of 10 min. The resulting black reaction mixture was stirred at 0 °C for 5 min, then treated with alkyne **85** (7.40 g, 40.2 mmol) followed by allyl chloride (3.12 mL, 38.3 mmol). The reaction mixture was stirred at 0 °C for an additional 30 min, then allowed to warm to rt and stirred for an additional 1.5 h. The reaction mixture was poured into 0.5 N HCl (350 mL) and extracted with pentane (3 × 250 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered through a plug of SiO_2, eluting with pentane. Concentration *in vacuo* afforded **82** as a 92:8 mixture of regioisomers (9.81 g, >99%). R_f = 0.45 (9:1 hexanes/CH_2Cl_2). Spectral data for the major isomer, **82**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.20 (t, J = 7.2 Hz, 1H), 5.02 (dt, J = 17.2, 1.6 Hz, 1H), 4.95 (d, J = 20.1 Hz, 1H), 3.68 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.22 (t, J = 7.0 Hz, 2H), 1.62 (s, 3H), 0.90 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 133.8, 123.5, 114.4, 62.6, 43.2, 32.5, 26.1, 16.5, −5.1; IR (thin film) ν 2929, 2857, 1472, 1255, 1099, 836 cm^{-1}; HRMS (NH_3-CI GCMS) m/z calc for $C_{14}H_{29}OSi$ $(M + H)^+$ 241.1988, found 241.1984.

Bromide 86. To a cooled (0 °C) solution of PPh_3 (6.68 g, 25.5 mmol) in CH_2Cl_2 (100 mL) was added bromine (1.29 mL, 25.0 mmol). The ice water bath was removed, and the reaction was allowed to slowly warm to rt over 20 min, which resulted in

the formation of a white precipitate. The reaction mixture was then treated with neat **82** (1.2 g, 5.0 mmol, 92:8 mixture of regioisomers) and allowed to stir at rt for 1 h. The reaction mixture was filtered through SiO_2 eluting with hexanes (300 mL), and the filtrate was evaporated *in vacuo*. The resulting residue was subjected to column chromatography eluting with pentane to afford **86** as a clear oil (923 mg, 97%). R_f = 0.41 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.1, 10.8, 6.1 Hz, 1H), 5.28 (t, J = 7.3 Hz, 1H), 5.04 (dd, J = 17.1, 1.7 Hz, 1H), 4.98 (dd, J = 10.8, 1.7 Hz, 1H), 3.44 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.0 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 1.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 133.4, 124.9, 114.7, 43.0, 32.3, 31.7, 15.7; IR (thin film) ν 2975, 1638, 1434, 1266, 912 cm^{-1}; HRMS (EI GCMS) m/z calc for $C_8H_{13}Br$ $(M)^+$ 188.0201, found 188.0196.

Grignard Reagent 81. To solid Mg^0 ribbons (83.0 mg, 3.43 mmol) in THF (5.2 mL) was added **86** (500 mg, 2.64 mmol). The reaction mixture was stirred at rt, and the magnesium was clearly being consumed after ca. 20 min. After stirring at rt for 2 h, the solution of putative Grignard reagent **81** was used directly in the next step.

Cyclobutane 79. A suspension of $CuBr \cdot SMe_2$ (44.0 mg, 0.216 mmol) in THF (2 mL) was cooled to −78 °C and treated sequentially with DMPU (0.52 mL, 4.32 mmol), TMSCl (0.658 mL, 5.18 mmol), and **80** (302 mg, 2.16 mmol). The reaction mixture was stirred at −78 °C for 10 min, then treated with the Grignard reagent **81** prepared above dropwise over 5 min, which caused the reaction mixture to become viscous. The reaction mixture was allowed to stir at −78 °C for 1 h and then slowly warm to −20 °C over the course of 1 h. The reaction mixture was then poured into 1 N HCl (40 mL). The product was extracted with pentane (3 × 45 mL), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude product, which was subjected to column chromatography on SiO_2 (hexanes/Et_2O, 100:0 to 97:3) to provide **79** (364 mg, 67%, ca. 5:1 mixture of diastereomers) as a clear oil. R_f = 0.55 (9:1, hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.1, 11.1, 6.1 Hz, 1H), 5.13 (t, J = 7.1 Hz, 1H), 5.02 (d, J = 17.1 Hz, 1H), 4.95 (d, J = 10.1 Hz, 1H), 3.67 (s, 3H), 2.74 (t, J = 6.7 Hz, 2H), 2.61 (q, J = 9.2 Hz, 1H), 2.16 (q, J = 8.2 Hz, 1H), 1.85−1.95 (m, 3H), 1.78 (t, J = 9.7 Hz, 1H), 1.59 (s, 3H), 1.44−1.52 (m, 2H), 1.09 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 137.6, 136.6, 121.5, 114.3, 51.7, 48.2, 39.5, 37.4, 36.5, 34.8, 32.4, 30.6, 29.1, 22.4, 16.1; IR (thin film) ν 2951, 2863, 1736, 1434, 1168 cm^{-1}; HRMS (ESI) m/z calc for $C_{16}H_{26}O_2Na$ $(M + Na)^+$ 273.1830, found 273.1834.

Triene 78. $CeCl_3 \cdot 7H_2O$ (3.24 g, 8.73 mmol) was pulverized with a mortar and pestle, placed under high vacuum (0.5 mmHg), and slowly heated to 150 °C over the course of 2 h. The solid was maintained at 150 °C under vacuum with vigorous stirring for 14 h and then allowed to cool to rt under N_2. The white solid was cooled to 0 °C and treated with THF (14.5 mL), the ice water bath was removed, and the suspension was stirred at rt for 2 h, producing a thick white slurry. The slurry was cooled to −78 °C and treated with a freshly prepared solution of trimethylsilylmethylmagnesium chloride (1.0 M in Et_2O, 7.9 mL, 7.9 mmol) dropwise via syringe over 15 min. The reaction mixture was stirred at −78 °C for 1.5 h, and ester **79** (364 mg, 1.45 mmol) in THF (2.5 mL) was added to the reaction mixture. The reaction mixture was stirred at −78 °C for 2 h and rt for 48 h. The reaction mixture was then poured into saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford an oil, which was dissolved in CH_2Cl_2 (20 mL) and treated with SiO_2 (2 g). The slurry was stirred at rt for 4 h, the solvents were removed *in vacuo*, and the crude material was purified by column chromatography (SiO_2, 100:0 to 95:5 hexanes/EtOAc) to afford allylsilane **78** (237 mg, 53%, ca. 9:1 mixture of diastereomers) as a clear oil. R_f = 0.41 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.1, 10.5, 6.2 Hz, 1H), 5.15 (t, J = 7.0 Hz, 1H), 5.02 (dd, J = 17.1, 1.4 Hz, 1H), 4.95 (dd, J = 10.5, 1.4 Hz, 1H), 4.60 (s, 1H), 4.52 (s, 1H), 2.75 (t, J = 6.6 Hz, 2H), 2.25 (q, J = 9.1 Hz, 1H), 1.1.80−2.00 (m, 4H), 1.77 (t, J = 8.5 Hz, 1H), 1.61 (s, 3H), 1.43−1.50 (m, 3H), 1.40 (t, J = 10.0 Hz, 1H), 1.06 (s, 3H), 1.04 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 137.7, 137.1, 121.2, 114.3, 104.9, 48.9, 43.0, 40.2, 38.4, 33.5, 32.5, 31.6, 29.7, 25.4, 22.6, 16.2, −0.9; IR (thin film) ν 2952, 1634, 1248, 852 cm^{-1}; HRMS (NH_3-CI GCMS) m/z calc for $C_{20}H_{37}Si$ $(M + H)^+$ 305.2664, found 305.2666.

Diene 87. A solution of **78** (20.0 mg, 0.066 mmol) in deoxygenated hexanes (44 mL) was treated with the Grubbs second-generation catalyst (11.1 mg, 0.013 mmol). The reaction mixture was stirred at rt for 15 min, then heated to 60 °C for 1 h. The cooled reaction mixture was filtered through a plug of silica gel, eluting with hexanes. Concentration of the filtrate afforded **87** (13 mg, 75%) as a clear oil. The ^{1}H NMR spectrum of **87** provided in the Supporting Information was taken after chromatography on silica gel (pentane). R_f = 0.46 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.66 (s, 1H), 4.60 (s, 1H), 4.51 (s, 1H), 2.25 (q, J = 8.9 Hz, 1H), 1.94 (q, J = 8.4 Hz, 1H), 1.87 (m, 1H), 1.78 (t, J = 10.0 Hz, 1H), 1.71 (s, 3H), 1.55 (m, 3H), 1.46 (d, J = 9.4 Hz, 2H), 1.40 (t, J = 10.1 Hz, 1H), 1.07 (s, 3H), 1.04 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 146.4, 109.4, 104.8, 48.6, 42.8, 39.9, 36.3, 33.3, 31.3, 29.3, 25.2, 22.5, 22.4, −1.1; IR (thin film) ν 2952, 1247, 851 cm^{-1}; HRMS (NH_3-CI GCMS) m/z calc for $C_{17}H_{33}Si$ $(M + H)^+$ 265.2352, found 265.2349.

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Supporting Information Available: NMR spectra for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.