

Ring-Closing Metathesis of Allylsilanes/Electrophilic Desilylation To Prepare *exo*-Methylidenecycloalkanes. Short Syntheses of Teucladiol and Poitediol

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Most polycyclic terpene natural products incorporate alkenes as a vestige of their biosynthetic construction via cationic cyclization.¹ While most of these alkenes are the thermodynamically preferred endocyclic isomers, the less stable, exocyclic alkenes are still frequently encountered. The sesquiterpenes teucladiol,² poitediol,³ caryophyllene,⁴ and echinopine B⁵ (Figure 1) showcase a few of the different ring systems present within this large group of natural products.

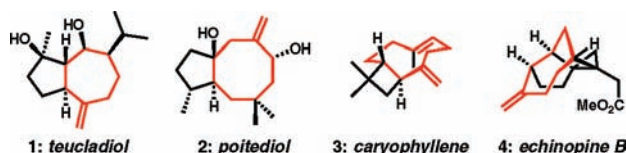
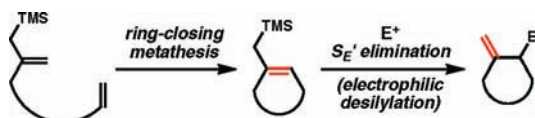


Figure 1. Representative sesquiterpene natural products bearing the *exo*-methylidenecycloalkane motif.

Among the many methods to generate cycloalkenes, ring-closing metathesis has proven its utility in applications to complex molecule synthesis.⁶ Excellent functional group tolerance and broad applicability to many ring sizes led us to consider its use for the indirect generation of *exo*-methylidenecycloalkanes such as those found in Figure 1. In this communication, we disclose that allylsilane ring-closing metathesis/*S_E'* electrophilic desilylation (Scheme 1) constitutes an effective strategy for the synthesis of these motifs; the power of ring-closing metathesis is critical to the short syntheses of teucladiol and poitediol described below.

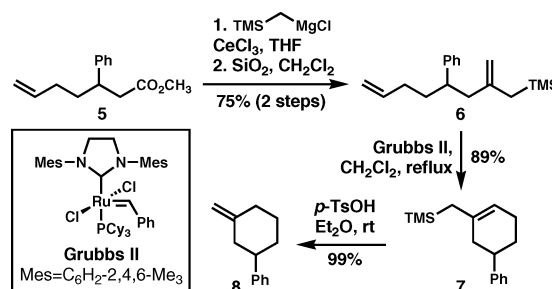
Scheme 1. Strategy To Access *exo*-Methylidenecycloalkanes



Although precedents for both alkene ring-closing metathesis of allylsilanes⁷ and allylsilane protodesilylation with alkene transposition (*S_E'*) are plentiful,^{8,9} the combination of these two simple reactions into a cohesive strategy for the synthesis of *exo*-methylidenecycloalkanes has never, to our knowledge, been reported. To prove that this sequence was viable, we embarked on the model study shown in Scheme 2. Known alkene **5** was prepared by conjugate addition of butenylmagnesium bromide to methyl cinnamate;¹⁰ its ester function was then transformed to the allylsilane of **6** via Peterson olefination.¹¹ Ring-closing metathesis with the Grubbs second-generation ruthenium catalyst¹² proceeded uneventfully, and the final protodesilylation reaction provided *exo*-methylidene product **8** in nearly quantitative yield.

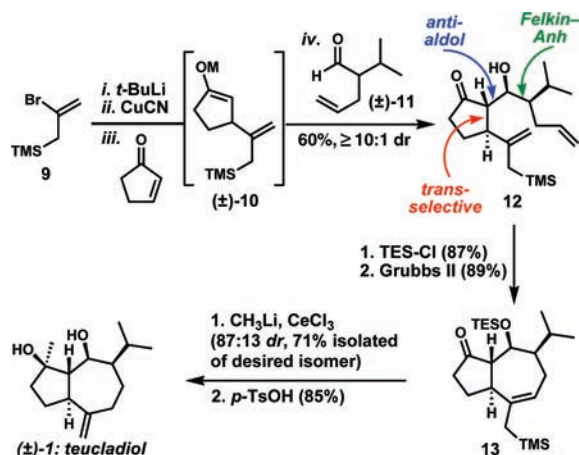
Rather than define the scope and limitations of this strategy with simple substrates, we elected to explore its potential in complex contexts with syntheses of the natural products teucladiol (**1**) and poitediol (**2**). Teucladiol was isolated from the plant *Teucrium*

Scheme 2. Synthesis of *exo*-Methylidenecyclohexane **8**



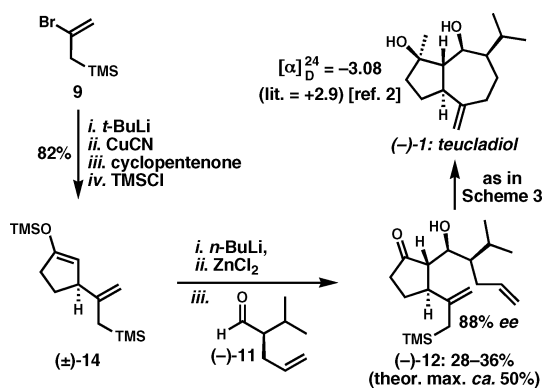
leucocladum in 1993² and was later shown to exhibit moderate activity against two human breast cancer cell lines;¹³ no synthesis of this sesquiterpene has been reported. We synthesized racemic teucladiol by the sequence shown in Scheme 3. Conjugate addition of the higher-order cyanocuprate derived from **9**¹⁴ to cyclopentenone presumably led to enolate (\pm)-**10**, which was trapped with aldehyde (\pm)-**11**¹⁵ to afford **12** in 60% yield (d.r. \geq 10:1) in an interesting case of double diastereodifferentiation¹⁶ between racemic reaction partners. The stereochemical result, which was confirmed by transformation of **12** into teucladiol, is consistent with trans-selective tandem vicinal difunctionalization of the enone¹⁷ and anti-selective aldol addition of the ring-constrained *E*-enolate via closed transition state,¹⁸ which is known to favor formation of Felkin-Anh-type products with α -chiral aldehydes.¹⁹ After silylation of the secondary hydroxyl, our strategy for *exo*-methylidenecycloalkane synthesis was applied: ring-closing metathesis afforded **13**;²⁰ methylcerium addition to the ketone followed by acid-mediated allylsilane protodesilylation/silyl ether cleavage delivered synthetic (\pm)-teucladiol, which displayed spectral data consistent with those previously reported.² The silyl ether was required for success of the metathesis reaction and likely governs the diastereoselectivity

Scheme 3. Synthesis of (\pm)-Teucladiol



of the nucleophilic methylation reaction. Teucladiol is thus available in five steps from cyclopentenone and (\pm)-**11** in 28% overall yield.

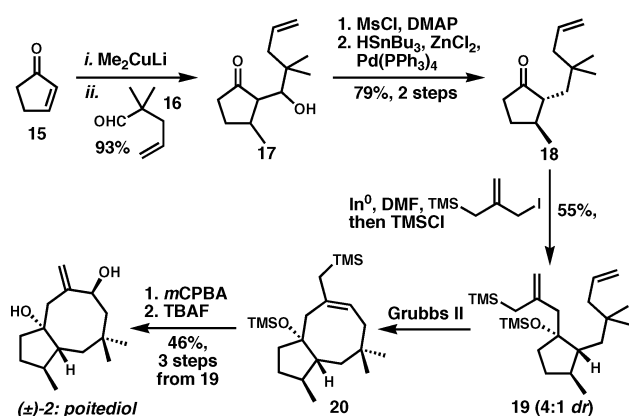
Scheme 4. Enantioselective Synthesis of (–)-Teucladiol



The synthesis of teucladiol could be rendered enantioselective by incorporation of enantioenriched aldehyde (–)-**11** into the three-component coupling.^{15,21,22} Enolsilane (\pm)-**14** was generated from **9** and cyclopentenone and was subsequently transformed into its zinc enolate for reaction with (–)-**11** (1.1 equiv). The resulting product (–)-**12** was isolated in 28–36% yield²³ (max. possible ca. 50%) and in 88% *ee*. Transformation to (–)-teucladiol followed the sequence in Scheme 3 and proved that the absolute configuration of teucladiol is opposite that depicted in Figure 1 and Scheme 4.

Poitediol is an unusual, rearranged sesquiterpene that was isolated by Fenical, Clardy, and co-workers in 1978 from the red seaweed *Laurencia poitei*³ and has been synthesized once by the Gadwood group.²⁴ Its *exo*-methylidencyclooctane, which incorporates allylic oxygenation, provided an excellent opportunity to test our strategy for generation of the exocyclic alkene with concomitant introduction of new functionality. Our synthesis shown in Scheme 5 borrows substantially from Fürstner and Langemann's elegant synthesis of the related natural product dactyol;²⁵ our key contribution is the strategy for introduction of the exocyclic alkene, in this case with the simultaneous stereoselective introduction of a hydroxyl group. The synthesis of **18** is adapted from the earlier dactyol synthesis. Indium-mediated allylation²⁶ of this ketone followed by *in situ* silylation afforded diene **19**. Grubbs second-generation catalyst generated cyclooctene **20**,²⁷ which was epoxidized stereoselectively. The resultant silyl epoxide was decomposed via fluoride-mediated elimination²⁸ with concomitant silyl ether cleavage to afford poitediol, which provided X-ray diffraction-quality crystals.¹⁵ This seven-step synthesis (18% overall yield) exploits the cyclic allyl-

Scheme 5. Synthesis of Poitediol



silane for the introduction of the secondary hydroxyl group using the conformational bias of the cyclooctene ring for stereocontrol.

Allylsilane ring-closing metathesis followed by electrophilic desilylation is a powerful strategy for the synthesis of *exo*-methylidencycloalkane motifs that are found in many terpene natural products. We have described three different ways to introduce the precursor allylsilanes, demonstrated that this process can make six-, seven-, and eight-membered rings, and completed short syntheses of teucladiol and poitediol using this method as a centerpiece.

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Supporting Information Available: Complete experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Cane, D. E. In *Comprehensive Natural Products Chemistry. Isoprenoids, Including Carotenoids and Steroids*; Cane, D. E., Ed.; Elsevier: Oxford, 1999; Vol. 2, pp 154–200.
- (2) Bruno, M.; de la Torre, M. C.; Rodríguez, B.; Omar, A. A. *Phytochemistry* **1993**, *34*, 245–247.
- (3) Fenical, W.; Schulte, G. R.; Finer, J.; Clardy, J. *J. Org. Chem.* **1978**, *43*, 3628–3630.
- (4) Collado, I. G.; Hanson, J. R.; Macías-Sánchez, A. *J. Nat. Prod. Rep.* **1998**, *15*, 187–204.
- (5) Dong, M.; Cong, B.; Yu, S.-H.; Sauriol, F.; Huo, C.-H.; Shi, Q.-W.; Gu, Y.-C.; Zamir, L. O.; Kiyota, H. *Org. Lett.* **2008**, *10*, 701–704.
- (6) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.
- (7) (a) Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693–1696. (b) Adam, J.-M.; de Fays, L.; Laguerre, M.; Ghosez, L. *Tetrahedron* **2004**, *60*, 7325–7344.
- (8) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 355–358.
- (9) Of course, the allylsilane can also be used for installation of functionality by reaction with heteroatom or carbon electrophiles.
- (10) Aggarwal, V. K.; Daly, A. M. *Chem. Commun.* **2002**, 2490–2491.
- (11) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261–6264.
- (12) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.
- (13) Ahmed, A. A.; Hegazy, M.-E., F.; Hassan, N. M.; Wojcinska, M.; Karchesy, J.; Pare, P. W.; Mabry, T. J. *Phytochemistry* **2006**, *67*, 1547–1553.
- (14) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 6879–6881.
- (15) Please see Supporting Information for details.
- (16) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30.
- (17) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed.* **1984**, *23*, 847–876. (b) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225–653.
- (18) Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615–3626, and references therein.
- (19) For a discussion, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.
- (20) Nakashima, K.; Fujisaki, N.; Inoue, K.; Minami, A.; Nagaya, C.; Sono, M.; Tori, M. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1955–1962.
- (21) Enantioselective conjugate addition to cyclopentenone would provide access to enantioenriched enolate **10**, but methods for asymmetric conjugate addition of *sp*²-hybridized organometallics with productive use of the resulting enolate are poorly developed, especially with cyclopentenones.
- (22) (–)-**11** was made by Myers pseudoephedrine amide enolate alkylation, LAB reduction (Mosher ester analysis of the alcohol intermediate showed ca. 95% *ee*), and oxidation: (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511. The recent SOMO activation procedure of MacMillan for organocatalytic asymmetric aldehyde allylation delivered (–)-**11** in fewer operations. (b) Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585.
- (23) Other diastereomers, presumably from the mismatched combination, are observed in the crude reaction mixture.
- (24) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343–6350. This instructive first synthesis proceeded in 26 steps and ca. 1% overall yield from commercially available materials.
- (25) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746–8749. For the structure of dactyol, see the Supporting Information.
- (26) Bardot, V.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Synlett* **1996**, 37–38.
- (27) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740–5750.
- (28) Many examples of allylsilane epoxidation/silanol elimination can be found in: Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192.

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