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A Relay Ring-Closing Metathesis Synthesis of Dihydrooxasilines, Precursors of (*Z*)-Iodo Olefins

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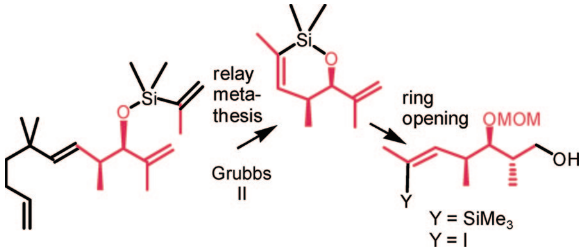
ABSTRACT



A convenient Grubbs II metathesis provides dihydrooxasilines by relay RCM (RRCM). Dihydrooxasilines undergo ring opening to give *Z*-vinyl silanes. These can then be converted to *Z*-vinyl iodides. This sequence provides a short, high yield, and convenient route to trisubstituted *Z*-vinyl iodides, useful intermediates for the preparation of polypropionate antibiotics.

Iodo olefins are important intermediates in organic synthesis. As key reactants in the convergent steps of many total syntheses, they are often the reagents of choice in Heck, Stille and Suzuki, Sonogashira, and Negishi coupling methods[1] as well as in the popular Nozaki−Hiyama−Kishi (NHK) addition reaction.[2] Stereochemical homogeneity in the products of these transformations depends on the availability of geometrically clean iodo olefins as starting materials.

We have been interested in the preparation of a 2-iodo (*Z*)-olefin of general structure **1** (Figure 1) and, in particular, the iodoolefinic alkyne **2**,[3] which we projected as a key intermediate in the synthesis of discodermolide (**3**).[4]

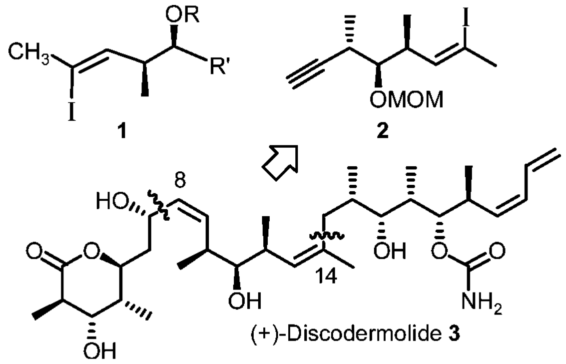


Figure 1. Functional group pattern in target intermediates and relationship to the structure of discodermolide.

Given the small number of approaches to vinyl iodides of this substitution pattern,[5] we considered the design of a new method that might be high yielding and that would be easy to implement.

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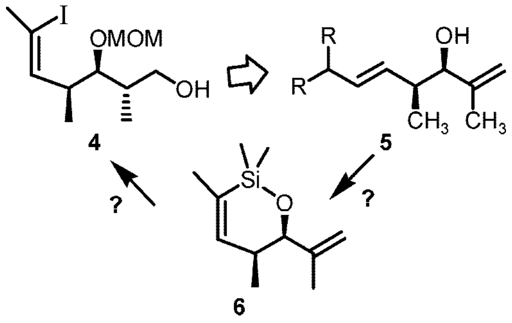
[1] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

[2] For a review, see: (a) Fuerstner, A. *Chem. Rev.* **1999**, *99*, 991. For the asymmetric NHK reaction, see: (b) Choi, H.-w.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435. See also: (c) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroder, M.l.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032.

[3] Parker, K. A.; Cao, H. US Patent Applications, Serial No. 11/421,290 and Serial No. 11/697,340. We had prepared alkyne **2** by a scheme that employed the Stork−Zhao conversion, a transformation that is low-yielding for the preparation of trisubstituted olefins. See: Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qiu, Y.; Smith, A. B., III. *Synlett* **1998**, *7*, 765.

10.1021/ol802063h CCC: $40.75

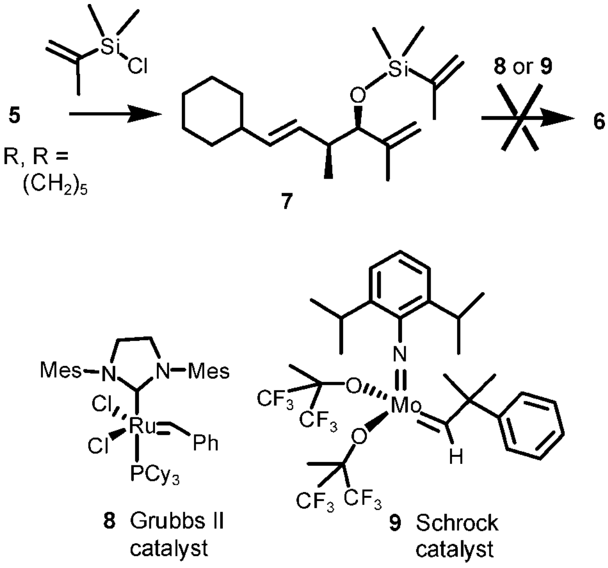
Scheme 1. Desired Iodo Olefin-Containing Polyketide Building Block, Readily Available Potential Precursor, and Possible Intermediate



We were especially motivated to prepare alcohol **4**, an obvious precursor to alkyne **2** and a generally useful intermediate, from a precursor of general structure **5**. Alcohols **5** are readily available from a short scheme based on asymmetric catalysis.[6] Thus, we considered the possibility that the dihydrooxasiline **6** might serve as an intermediate in the desired conversion.

Imagining the silyl ether **6** to be the product of a ring-closing metathesis (RCM) reaction, we set out to attempt this cyclization.[7] Silylation of the known alcohol **5** (R, R = (CH$_2$)$_5$, Scheme 2) with isopropenyldimethylsilyl chloride provided the desired **7**. In this metathesis substrate, the functional group pattern should allow RCM to favor the formation of a 6-membered ring containing a trisubstituted olefin (not a cyclobutane and not a 5-membered ring containing a tetrasubstituted olefin).[8]

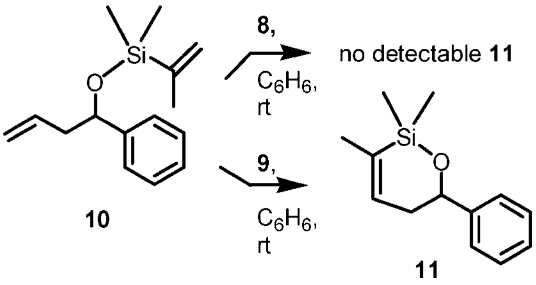
Scheme 2. Initial Plan for the Ring-Closing/Ring-Opening Strategy for the Preparation of Alcohol **6**



Attempted RCM with Grubbs's second-generation catalyst (**8**) or with Schrock's catalyst **9** resulted in the recovery of starting material. We repeated both the Grubbs II and Schrock experiments under an atmosphere of ethylene,[9] recovering silyl ether **7** in both cases.

In order to find conditions that would effect the desired closure, we prepared the model substrate **10** and subjected it to metathesis conditions (Scheme 3). Material recovered from the Grubbs II reaction showed two spots on tlc, one of which represented the starting material **10** and the other a new compound(s), which was clearly not the cyclized **11**.[10] This result was not particularly surprising. The literature sports no examples of ruthenium catalyst-promoted ring closing olefin metathesis to 1,2-dihydrooxasilines; both Grubbs generation I catalyst[11] and Grubbs generation II catalyst (**8**)[11c] are reported to fail with the relevant substrates.[12] On the other hand, the Schrock catalyst converted silyl ether **10** to the RCM product in 97% yield.

Scheme 3. Test of Metathesis Conditions with Model Silyl Ether



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(4) (a) Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342. (b) Smith, A. B.; Freeze, B. S. *Tetrahedron* **2008**, *64*, 261. (c) Mickel, S. J. *Pure Appl. Chem.* **2007**, *79*, 685, and references therein.

(5) Those that are generally appropriate for introduction of the vinyl iodide moiety into advanced intermediates include: (a) The Stork−Zhao reaction: Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827. (b) Iododemetalation: de Lemos, E.; Poree, F.-H.; Commercon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1917. Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (c) The Tanino−Miyashita olefination: Tanino, K.; Arakawa, K.; Satoh, M.; Iwata, Y.; Miyashita, M. *Tetrahedron Lett.* **2006**, *47*, 861.

(6) (a) Parker, K. A.; Cao, H. *Org. Lett.* **2006**, *8*, 3541. See also: (b) Tsai, D. J. S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1842.

(7) All exploratory reactions were carried out with racemic materials. Structures **14**−**20**, **6**, and **4** in Schemes 4 and 5 represent chiral compounds.

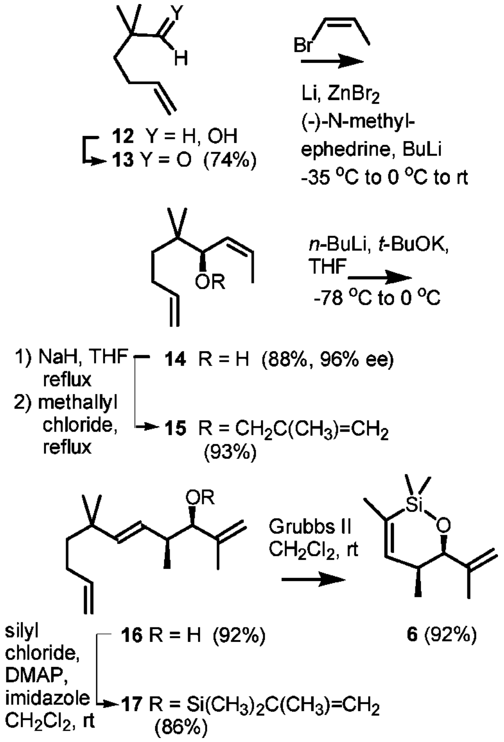
(8) Denmark and Yang have shown that, in simple systems, dihydrooxasilines with di- and trisubstituted olefins were formed with the Schrock catalyst. However, an attempt to effect closure to a tetrasubstituted olefin was not successful. See: Denmark, S. E.; Yang, S.-M. *Tetrahedron* **2004**, *60*, 9695.

(9) Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett.* **2004**, *6*, 4077.

(10) The NMR spectrum of the compound represented by the second spot (approximately 10% of the recovered material) contained absorptions in the silylmethyl, vinylmethyl, allyl, vinyl, and aromatic regions (as does silyl ether **10**); however, the integral of the aromatic region was enhanced. Metathesis of the catalyst with the substrate is the likely origin of this minor product.

(11) (a) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508. (b) Ahmed, M.; Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A.; Salter, M. M. *Tetrahedron* **1999**, *55*, 3219. (c) Denmark, S. E.;Yang, S.-M.;*Org. Lett.* **2001**, *3*, 1749, and ref 8. See also entry 2 in Table I in: (d) Kroell, R. M.; Schuler, N.; Lubbad, S.; Buchmeiser, M. R. *Chem. Commun.* **2003**, 2742.

Scheme 4. Relay Metathesis-Based Synthesis of Dihydooxasiline **6**



All of the above suggested that the Grubbs II catalyst would not effect RCM to dihydrooxasilines (as is believed), that the Schrock catalyst would effect such a closure, but that the Schrock catalyst was not generating the critical metal carbene by metathesis with our substrate **7**, even when the reaction was run under ethylene.

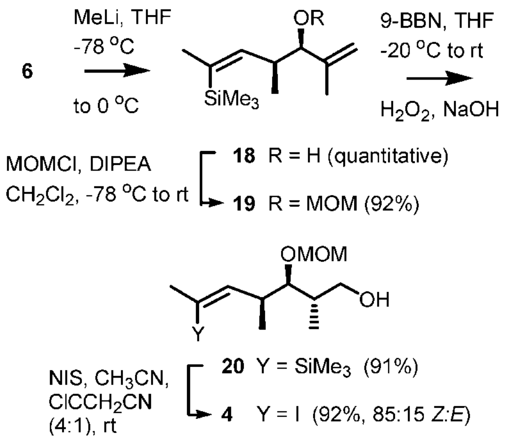
In an effort to drive the initiation of the metathesis reaction, we resolved to prepare substrate **17**, designed so that it would participate in a Hoye-type "relay."[13] In our design, the tether between the initiating terminal olefin and the site of desired reactivity was to be three carbons long, setting up a cascade in which the first ring formed would be a cyclopentene. Also, the tether would contain, adjacent to the internal olefin, two methyl substituents. This design would promote ring closure in the first step of the metathesis reaction by the famous "gem dimethyl effect."[14] Furthermore, substitution at this position would be advantageous in the synthesis of the substrate precursor **16**, the product of a 2,3-Wittig rearrangement,[6] by favoring the syn relationship of the adjacent methyl and hydroxyl substituents.

Synthesis of the "relay substrate" **17** relied on methods already established. Preparation of aldehyde **13**, which would supply the excisable tether, followed the strategy of Ashby[15] (see the Supporting Information for details). Addition of the chiral zinc reagent[16] from *cis*-1-bromopropene[17] and (−)-*N*-methylephedrate afforded the (*S*)-alcohol **14**, which was converted to the methallyl ether **15**. Treatment with the *n*-BuLi/KO-*t*-Bu reagent effected the expected stereoselective 2,3-Wittig rearrangement. Silylation of the resulting (3*S*,4*S*)-undecatrienol **16** afforded the relay metathesis susbstrate **17**.

When exposed to the Grubbs II catalyst **8**, silyl ether **17** underwent the relay RCM (RRCM) reaction to provide the desired cyclic silyl ether **6** in high yield. The surprising but welcome success of this reaction provides another example[18] of the power of the relay metathesis strategy.

With **6** in hand, we studied methods for effecting the desired conversion to a linear vinyl iodide such as our target **4** (Scheme 5). Ring cleavage of silyl ether **6** with methyllithium[19] proved to be a high yield transformation, giving vinyl silane **18**. Then protection of the alcohol (**18** → **19**) and hydroboration with 9-BBN gave silane **20**.[20] Iododesilylation of silane **20** with recrystallized NIS in CH_3CN/CCl_3CN[21] gave a high yield of the known alcohol **4** as an 85:15 *Z*/*E* mixture.[22]

Scheme 5. Ring Cleavage, Modification, and Iododesilylation



A small amount of a byproduct was also isolated. The NMR spectrum of this compound showed the MOM and

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(12) A related enyne RCM proceeds with catalyst **8**. See Miller, R. L.; Maifeld, S. V.; Lee, D. *Org. Lett.* **2004**, *6*, 2773.

(13) (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210. (b) For a review, see: Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912.

(14) (a) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735. (b) For a discussion of this effect in ring-closing enyne metathesis, see: Kim, Y. J.; Grimm, J. B.; Lee, D. *Tetrahedron Lett.* **2007**, *48*, 7961.

(15) Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424.

(16) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.

(17) *cis*-1-Bromopropene is conveniently prepared in multigram quantities by the method of: Fuller, C. E.; Walker, D. G. *J. Org. Chem.* **1991**, *56*, 4066.

(18) Hoye's original paper (ref 13a) describes several different cases in which the relay strategy proved advantageous. For others, see: (a) Zakarian, J. E.; El-Azizi, Y.; Collins, S. K. *Org. Lett.* **2008**, 2027. (b) Cho, E. J.; Lee, D. *Org. Lett.* **2008**, *10*, 257. (c) Dudley, G. B.; Engel, D. A.; Ghiviriga, I.; Lam, H.; Poon, K. W. C.; Singletary, J. A. *Org. Lett.* **2007**, *9*, 2839. (d) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960. (e) Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122. (f) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369. (g) For an example of the use of relay strategy in macrocyclic enyne metathesis, see: Collins, S. K.; El-Azizi, Y.; Schmitzer, A. R. *J. Org. Chem.* **2007**, *72*, 6397.

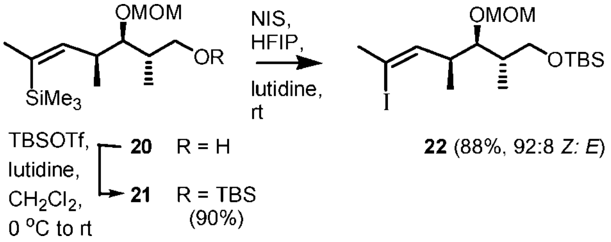
(19) For a cleavage of a related cyclic silyl ether with phenyllithium, see Barrett's synthesis of glycosphingolipids; see reference 11a.

TMS groups but no vinyl proton and its infrared spectrum showed no absorption for a hydroxyl group.

We attempted to improve the ratio of isomers in the iododesilylation product of alcohol **20** by adopting hexafluoro isopropanol (HFIP) as solvent.[23] This experiment afforded a crude product, which contained many compounds (as indicated by tlc). Only minor amounts of the desired vinyl iodide **4** (both E and Z, as judged by analysis of the NMR spectrum) could be seen; furthermore, the aforementioned byproduct appeared to be the major component of the product mixture. We suspect that this byproduct results from an iodoetherification reaction and that the use of HFIP in iododesilylations may be limited to substrates that cannot take part in this type of pathway.[24]

Improved results were obtained when TBS ether **21** was subjected to the iododesilylation conditions in HFIP. This reaction afforded an 88% yield of the known vinyl iodide **22** (a key intermediate in Smith's fourth-generation discodermolide synthesis)[22] as a 92:8 mixture of (*Z*)- and (*E*)-isomers.

Scheme 6. Protection and Stereoselective Iododesilylation



Overall, the preparation depicted in Schemes 4−6 provides the original target, iodo olefin **4**, in 29% yield (corrected for the presence of the *E*-isomer) and the vinyl iodide building block **22** in 27% yield (likewise corrected for the presence of *E*-isomer) from alcohol **12**. Thus, the relay RCM preparation of dihydrooxasilines followed by ring opening and iododesilylation provides efficient access to (*Z*)-vinyl iodides. As it is generally accepted that the Schrock catalyst is required for the closure of vinyl silane metathesis substrates, the effectiveness of the Grubbs II catalyst in the relay RCM reaction (**17** → **6**) is noteworthy and will be the subject of further examination.

Acknowledgment. This work was supported by the Army Breast Cancer Initiative (BC 051816), the National Institutes of Health (GM 74776), and the National Science Foundation (CHE-0131146, NMR instrumentation). We thank Professor Richard Franck of Hunter College for valuable discussions.

Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The corresponding TBS ether is a known compound, prepared in 11 steps including a chiral resolution; see: (a) Arefolov, A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397. (b) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (c) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1998**, *75*, 78.

(21) (a) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647. A detailed protocol for NIS iododesilylation in acetonitrile/chloroacetonitrile can be found in the Supporting Information of reference 20a.

(22) Smith, A. B., III.; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett.* **2005**, *7*, 1825.

(23) (a) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822. (b) Iardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.

(24) Iodoetherification by addition to vinyl silanes to form tetrahydropyrans has not been reported. However, iodolactonization in vinyl silane substrates is known; see: (a) Kira, K.; Hamajima, A.; Isobe, M. *Tetrahedron* **2002**, *58*, 1875. (b) Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem.* **2001**, 1873. (c) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821. (d) Kitano, Y.; Okamoto, S.; Sato, F. *Chem. Lett.* **1989**, 2163. Also, Zakarian (ref 23b) noted the isolation of products derived from addition to a vinylsilane of iodonium and the carbonyl of a benzoate by way of a 5-membered ring.