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Synthesis of (−)-Pinolidoxin: Divergent Synthetic Strategy Exploiting a Common Silacyclic Precursor

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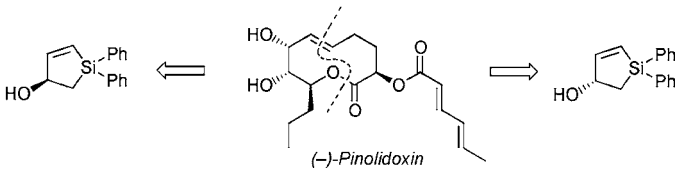
ABSTRACT



We describe a highly convergent and efficient synthesis of (−)-pinolidoxin, a potent modulator of plant pathogenesis, providing unambiguous determination of the relative and absolute stereostructure of this highly oxygenated fungal metabolite. Our unique strategy highlights the applications of novel silacyclic precursors for stereocontrolled polyol synthesis and features the finding of the reversible ring-closing metathesis.

Occurrence of diverse polyol-containing motifs in many complex synthetic targets stimulates the development of efficient chemical methods for their construction. Recently, we have introduced a new strategy for stereocontrolled polyol synthesis exploiting a highly enantioselective, catalytic desymmetrization of readily available silacyclopentene oxides.[1] In this letter, we extend this concept to the synthesis of (−)-pinolidoxin, a potent modulator of plant pathogenesis, providing unambiguous stereochemical determination of this highly oxygenated fungal metabolite. The synthesis further highlights our independent finding of the reversibility of the ring-closing metathesis.[2,3]

Small molecule regulation of plant defense responses during pathogenesis has important mechanistic and practical implications. Isolated from the fungus *Ascochyta pinodes* in 1993,[4] pinolidoxin (**1**, Scheme 1) was shown to possess potent suppression of phenylalanine ammonia-lyase (PAL) activity, a key regulatory enzyme in the phenylpropanoid metabolic pathway activated following the pathogen attack.[4] Interestingly, pinolidoxin had no phytotoxic effects on cell growth and respiration, suggesting a specific mechanism of action.[5] Structure elucidation of pinolidoxin (**1**) entailed extensive spectroscopic investigation combined with degradation−reconstitution studies.[6] While the relative stereochemistry of the three stereogenic centers at C_7, C_8, and C_9 was firmly established, the configuration at the C_2 remained unknown.[6]

Our strategy to pinolidoxin (Scheme 1) was designed to explore two pivotal tactical issues. First, we envisioned a convergent disconnection of the macrolide exploiting esterification and ring-closing metathesis. Second, we designed a divergent assembly of the two required advanced fragments **2** and **3** starting from a common silacyclic precursor **8**. Thus,

(1) Liu, D.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4757.

(2) For another synthesis of pinolidoxin reported during submission of the present manuscript, see: (a) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddrad, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069. For an earlier communication, see: (b) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671.

(3) For previous observations pertaining to the reversibility of large ring-closing olefin metathesis, see: (a) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984. (b) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145. (c) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990. (d) Smith, A. B. III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990. (e) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449.

(4) Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34*, 999.

(5) Vurro, M.; Ellis, B. E. *Plant Sci.* **1997**, *126*, 29.

(6) Napoli, L.; Messere, A.; Palomba, D.; Piccialli, V. *J. Org. Chem.* **2000**, *65*, 3432.

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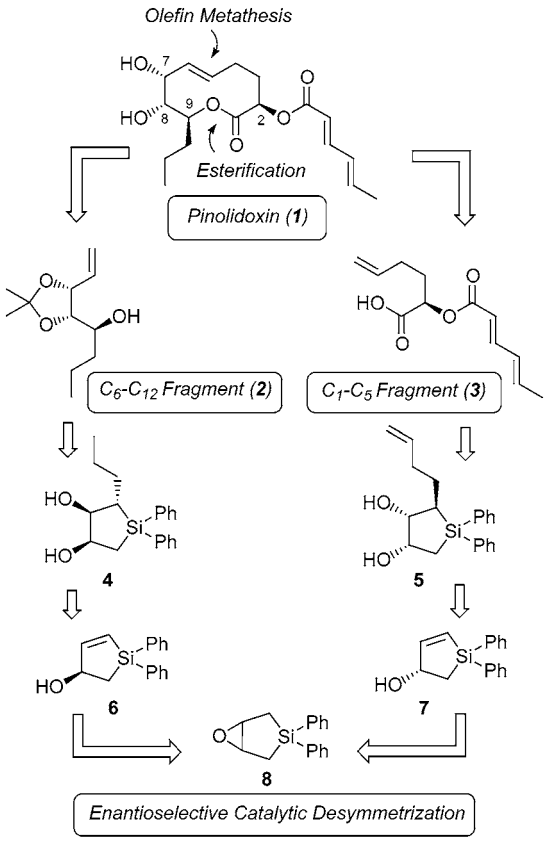
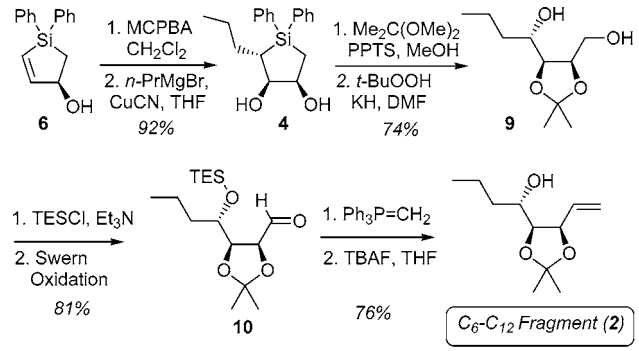
Scheme 1



creation of all stereogenic centers of the target would rely on diastereoselective functionalization of silacyclic alcohols **6** and **7** assembled via our recent catalytic enantioselective desymmetrization of meso silacyclic epoxides.[1]

Construction of the C_6-C_{12} fragment (**2**, Scheme 2) began

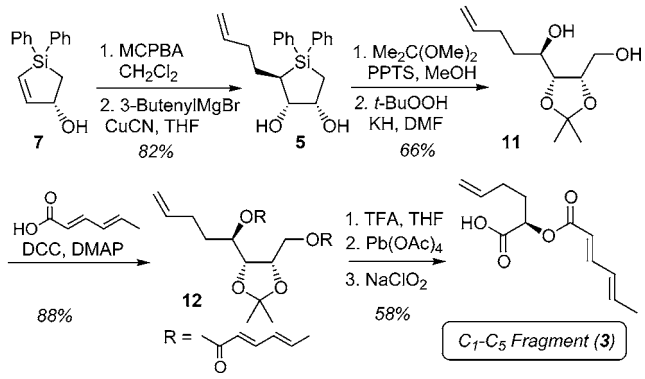
Scheme 2



with highly diastereoselective and efficient epoxidation−cuprate opening sequence starting with alcohol **6**, available in high enantiomeric purity via enantioselective isomerization of epoxide **8**.[1] Installation of the acetonide protection and oxidative cleavage of the silacyclic scaffold (*t*-BuOOH, KH, DMF) revealed acyclic diol **9**.[7] Bis-silylation (TESCl, Et_3N), followed by chemoselective Swern oxidation of the primary silyl ether afforded aldehyde **10**.[8] Final elaboration entailed Wittig methylenation and proto-desilylation furnishing the C_6-C_{12} subunit (**2**) with excellent overall efficiency (nine steps from known epoxide **8**,[9] 42% overall yield).

The synthesis of the C_1-C_5 segment (**3**) was commenced with another diastereoselective opening of the epoxide derived from silane **7**[1] utilizing 3-butenyl cuprate (Scheme 3). Acetonide formation, followed by Woerpel oxidation gave

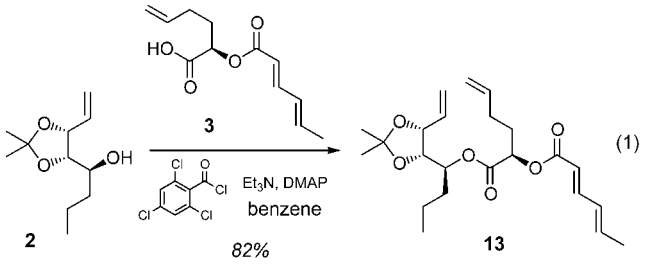
Scheme 3



1,4-diol **11**.[7] Bis-acylation with sorbic acid (DCC, DMAP) afforded acetonide **12**. Final elaboration entailed oxidative cleavage with $Pb(OAc)_4$, followed by oxidation of the resulting aldehyde ($NaClO_2$, NaH_2PO_4), to give fully functionalized C_1-C_5 fragment **3** (nine steps, 28% overall yield).

While the union of the two advanced fragments **2** and **3** proved to be initially problematic, this highly convergent step was successfully executed using the Yamaguchi protocol to give the coupling product **13** in 82% yield (Scheme 4).[10]

Scheme 4

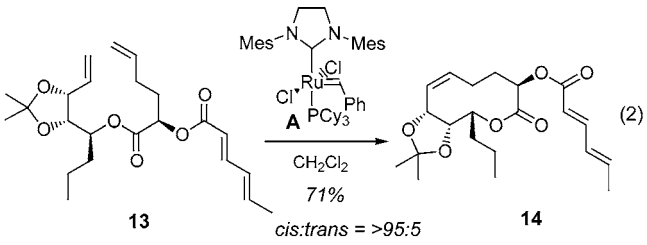


Incorporation of the unsaturated side chain prior to cyclization was envisioned to enhance the overall efficiency of the synthesis by avoiding the additional protection−deprotection manipulations. The caveat, however, was the risk of competitive participation of the sorbate moiety in the metathesis step.

(7) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.
(8) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161.
(9) Manuel, G.; Boukherroub, R. *J. Organomet. Chem.* **1993**, *447*, 167.
(10) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Treatment of tetraene **13** with the Grubbs dihydroimidazolylidene catalyst **A** (10 mol %)[11] resulted in efficient ring closure to afford 10-membered lactone **14** as a single, albeit undesired, *cis*-olefin isomer (Scheme 5).[12] Subjection of **13**

Scheme 5



to $Cl_2(PCy_3)_2Ru{=}CHPh$[13] afforded a mixture of *cis*- and *trans*-olefin isomers in ca. 1:1 ratio. A complete conformational search[14] revealed that *cis*-isomer **14** was 2.7 kcal/mol lower in energy compared to the *trans*-alkene suggesting that the outcome of the ring-closing metathesis employing catalyst **A** can be a result of thermodynamic control.[12]

Additional molecular modeling revealed that removal of the acetonide in silico reversed the thermodynamic stability of the two isomeric macrocycles, favoring the *trans*-alkene by 1.0−1.3 kcal/mol.[14] This theoretical study suggested the possibility of obtaining pinolidoxin directly by subjecting diol **15** (see Scheme 6) to the ring-closing metathesis under thermodynamic control.

To this end, acid-mediated hydrolysis of acetonide **13** (TFA, THF−H_2O) proceeded to give diol **15** in 81% yield. Subjection of diol **15** to the Grubbs catalyst **A** (10 mol %) indeed afforded predominantly the desired trans isomer, providing direct access to pinolidoxin (**1**), albeit with modest

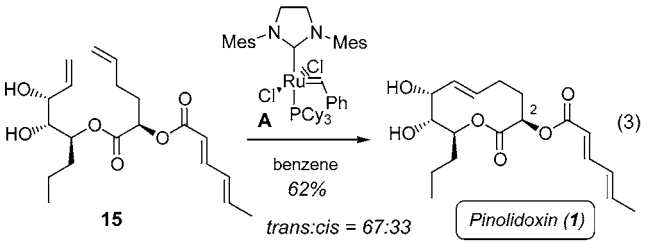
(11) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(12) For similar independent observations, see ref 2a.

(13) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(14) Conformational search was carried out using MMFF force field, followed by AM1 energy minimization; Mac Spartan Pro 1.0.4, Wavefunction, Inc.; www.wavefun.com.

Scheme 6



diastereoselectivity (Scheme 6).[15] Interestingly, treatment of the cis product of this reaction with catalyst **A** resulted in formation of the two alkene isomers in the same ratio, providing additional support for the reversible nature of this cyclization. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra of synthetic pinolidoxin (**1**) were in excellent agreement with those reported in the literature,[4] firmly establishing the relative stereochemistry at C_2. Optical rotation of **1** ($[\alpha]_D^{28}$ −140°) indicated its enantiomeric relationship to the natural product (lit. $[\alpha]_D^{25}$ 142.9°),[4] necessitating the revision of the originally postulated absolute configuration.[6]

In closing, we have described a highly convergent and efficient synthesis of (−)-pinolidoxin, providing unambiguous stereochemical determination of this fungal metabolite. Our unique strategy highlighted the utilization of novel silacyclic platforms for stereocontrolled polyol synthesis and featured the design of the final reversible ring-closing metathesis.

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Supporting Information Available: Characterization of new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Higher diastereoselectivity was observed under the same conditions in the absence of the sorbate side chain (trans:cis = 83:17).