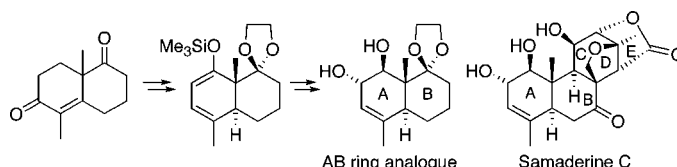


Stereocontrolled Synthesis of the AB  
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## ABSTRACT

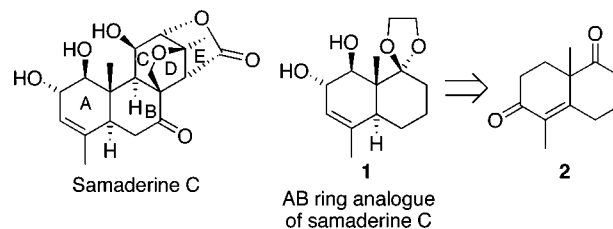


A concise synthesis of the AB rings of samaderine C (12 steps, 8 isolation steps, 7.8% overall yield), a quassinoid with antifeedant and insecticidal activity, is described. The development of the first general approach to the *trans*-1,2-diol A-ring motif in samaderine C and other quassinoids is a key feature. The *trans*-1,2-diol is crafted *via* stereoselective  $\alpha$ -hydroxylation (of a silyl enol ether) and reduction, a strategy that has much potential for quassinoid synthesis.

Samaderine C (Scheme 1) is a highly oxygenated, polycyclic quassinoid isolated from the bark and seed kernels of the *samadera indica* plant found primarily in Madagascar and southeast Asia.<sup>1,2</sup> One of eight isolated samaderines, our interest in samaderine C was initiated by its reported antifeedant and insecticidal properties.<sup>3</sup> To date, there have been rather limited synthetic efforts on the samaderines, with only two reported total syntheses. In 1994, Grieco et al. disclosed a racemic total synthesis (> 30 steps) of samaderine B.<sup>4</sup> More, recently, Shing and co-workers reported a 21-step synthesis of (–)-samaderine Y starting from (+)-carvone.<sup>5</sup>

As there have been no previous synthetic studies on samaderine C, and to explore possible agrochemical structure–activity relationships, we focused on the synthesis of analogues of the AB rings of samaderine C. In particular,

Scheme 1. Samaderine C and **1**, an AB Ring Analogue



we sought a general strategy for constructing the *trans*-1,2-diol A-ring motif present in samaderine C and other quassinoids. Indeed, we could find no previous syntheses of such *trans*-1,2-diols in the quassinoid literature. Diol **1** was chosen as a suitable AB ring analogue of samaderine C, and herein we describe a concise, stereocontrolled synthesis starting from the known<sup>6</sup> bicyclic enone **2** (Scheme 1).

Our retrosynthetic analysis of diol **1** is summarized in Scheme 2. Our long-term plan had protected enone **3** serving as an advanced intermediate from which the CDE rings of samaderine C would be elaborated. Enone **3** would

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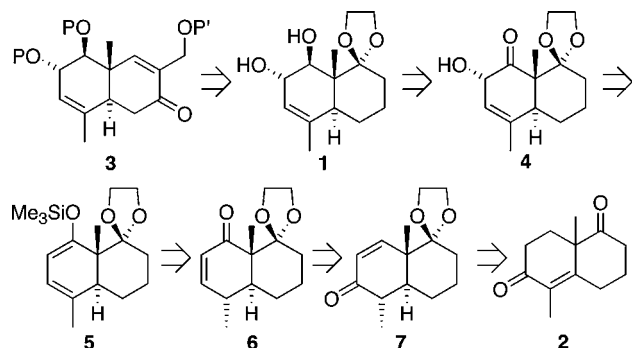
<sup>‡</sup> Syngenta.

(1) Zylber, J.; Polonsky, J. *Bull. Chim. Soc. Fr.* **1964**, 2016.  
(2) Malathi, R.; Rajan, S. S.; Suresh, G.; Krishnakumari, G. N.; Gopalakrishnan, G. *Acta Crystallogr.* **2003**, C59, 416.  
(3) Govindachari, T. R.; Krishnakumari, G. N.; Gopalakrishnan, G.; Suresh, G.; Wesley, S. D.; Sreelatha, T. *Fitoterapia* **2001**, 72, 568.  
(4) Grieco, P. A.; Pineiro-Nunez, M. M. *J. Am. Chem. Soc.* **1994**, 116, 7606.  
(5) Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, 44, 7981.

(6) Ziegler, F. E.; Hwang, K.-J.; Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Org. Chem.* **1986**, 51, 4573.

in turn be prepared from diol **1** by diol protection, ketal deprotection, 1,3-carbonyl transposition, enone formation, and enone  $\alpha$ -functionalization. It was our intention that the bridgehead axial methyl group would control the configuration of the diol functionality in **1**: reduction of hydroxy ketone **4** ( $\rightarrow$  **1**) and  $\alpha$ -hydroxylation of silyl enol ether **5** ( $\rightarrow$  **4**) should both occur on the face opposite to the axial methyl group to deliver the requisite *trans*-1,2-diol motif. Silyl enol ether **5** would be derived from enone **6** (by  $\gamma$ -enolization), itself obtained from enone **7** via a 1,3-carbonyl transposition (Wharton rearrangement of an epoxy ketone<sup>7</sup> was envisaged). Previously, Grieco had developed an approach for the  $\alpha$ -hydroxylation of enones such as **6**,<sup>8</sup> and the preparation of enone **7** from bicyclic enone **2** has been described.<sup>9</sup>

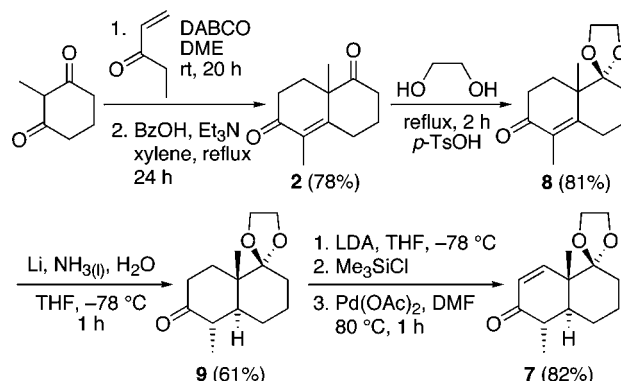
**Scheme 2.** Detailed Retrosynthetic Analysis of Diol **1**



Multigram quantities of racemic enone **7** were prepared as outlined in Scheme 3. First, 2-methyl-1,3-cyclohexanedione and ethyl vinyl ketone were reacted in a DABCO-mediated Robinson annelation<sup>6</sup> to give, after elimination, bicyclic enone **2** in 78% yield. Ketal formation to give **8** (81% yield) was accomplished using ethylene glycol and catalytic *p*-TsOH under Dean–Stark conditions. Next, stereoselective reduction of enone **8** using lithium in ammonia (in the presence of 1 equiv of H<sub>2</sub>O) gave ketone **9** in 61% yield. Over-reduction to the secondary alcohol was a complicating factor although the alcohol could be isolated and oxidized to give additional quantities of **9**. Finally, the enone in **7** was constructed using a stoichiometric Pd(OAc)<sub>2</sub>-mediated oxidation<sup>10</sup> of an intermediate silyl enol ether (formed by regioselective deprotonation of ketone **9** using LDA), as developed by Saegusa.<sup>9</sup> This delivered a single diastereomer of enone **7** in 82% yield. Using the Larock modification<sup>11</sup> of the Saegusa oxidation

(catalytic Pd(OAc)<sub>2</sub>/oxygen), none of **7** was formed and a Nicolaou-style<sup>12</sup> IBX-mediated oxidation of ketone **9** gave only a 14% yield of enone **7**.

**Scheme 3.** Synthesis of Bicyclic Enone **7**



Next, we needed to carry out a 1,3-carbonyl transposition on enone **7** to place the ketone adjacent to the bridgehead methyl group (as in **6**). For this, a nucleophilic epoxidation of enone **7** and a Wharton rearrangement–oxidation were planned. However, all attempts at directly epoxidizing **7** (e.g., H<sub>2</sub>O<sub>2</sub> and NaOH or Triton B) met with failure, presumably due to steric hindrance from the neighboring methyl and ketal groups. Instead, we resorted to a three-step reduction, *m*-CPBA epoxidation, and oxidation which, although it involved more steps, was efficient and was ultimately telescoped successfully.

Initially, the steps were separately explored (Scheme 4). Luche reduction (NaBH<sub>4</sub>/CeCl<sub>3</sub>·7H<sub>2</sub>O) of enone **7** gave a 94:6 mixture of diastereomeric alcohols from which an 89% yield of alcohol **10**<sup>13</sup> was isolated. Then, *m*-CPBA epoxidation of allylic alcohol **10** gave an inseparable 88:12 mixture of epoxides **11** in 79% yield. The relative stereochemistry of epoxides **11** is of no consequence (*vide infra*) and remains unassigned.<sup>14</sup> Oxidation with Dess–Martin periodinane (DMP) delivered an 88:12 mixture of epoxyketones **12** (70% yield). A more efficient synthesis of **12** was achieved by telescoping these three reactions. By working-up the first two reactions and carrying the crude products forward without purification, an 85:15 mixture of epoxyketones **12** was obtained after chromatography (73% yield from **7**) (Scheme 4).

Treatment of the 85:15 mixture of diastereomeric epoxyketones **12** with hydrazine hydrate (50% aqueous solution) and acetic acid led to the allylic alcohols **13** (characterized

(7) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.

(8) (a) Spohn, R. F.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491. (b) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.

(9) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 5890.

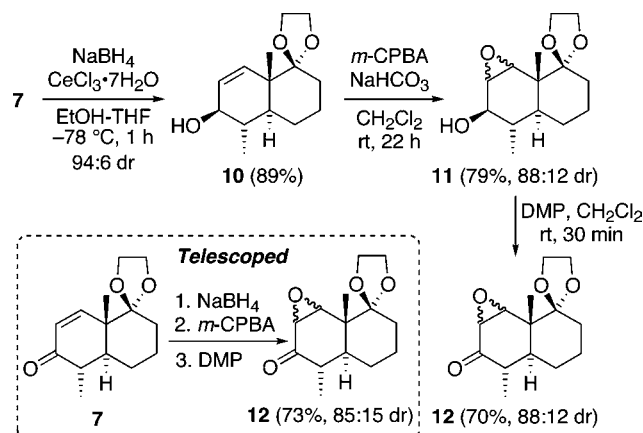
(10) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(11) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423.

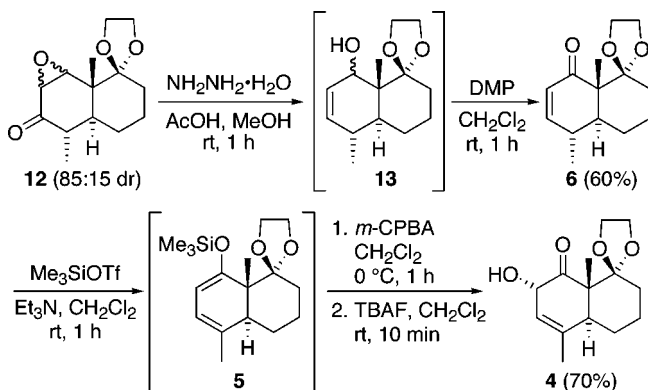
(12) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

(13) The relative configuration of alcohol **10** was assigned as shown due to the presence of a characteristic *trans*-diaxial <sup>3</sup>*J* coupling between the CHOH and CHMe protons in the <sup>1</sup>H NMR spectrum (<sup>3</sup>*J* = 8.5 Hz).

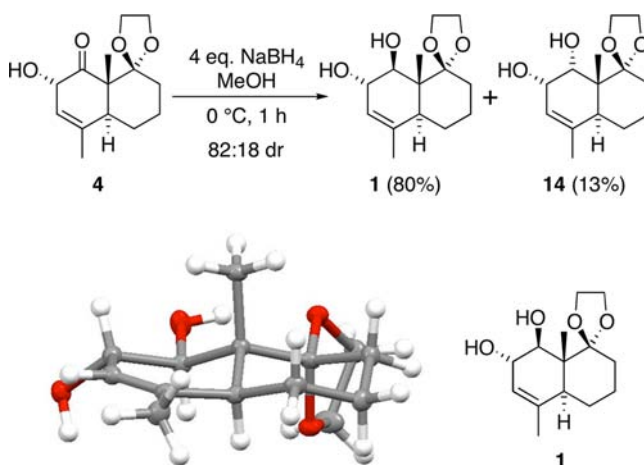
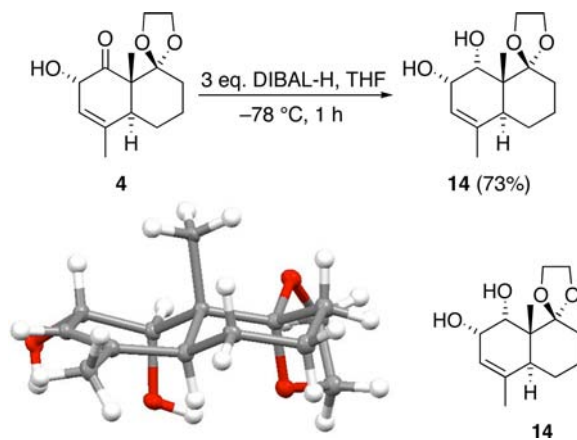
(14) It is tempting to assign the major epoxide as being *trans* to the axial methyl group in a sterically controlled epoxidation of **10**. However, there is also the potential of hydrogen-bonded directed epoxidation *cis* to the hydroxyl group (and hence *cis* to the methyl group), and this should not be ruled out given the enhanced *cis*-directing potential of an equatorial hydroxyl group. See: (a) Chamberlain, P.; Roberts, M. L.; Whitham, G. G. *J. Chem. Soc. (B)* **1970**, 1374. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

**Scheme 4.** Telescoped Synthesis of Epoxy-Ketone **12**

in a separate experiment) *via* a Wharton rearrangement (Scheme 5).<sup>7</sup> Workup and subjection of the crude allylic alcohols **13** to Dess-Martin periodinane oxidation gave enone **6** in 60% yield over the two steps.  $\gamma$ -Enolization of enone **6** was achieved using  $\text{Et}_3\text{N}$  and  $\text{Me}_3\text{SiOTf}$  and gave extended silyl enol ether **5**. Based on Grieco's precedent,<sup>8</sup> *in situ* oxidation with purified *m*-CPBA followed by stirring with TBAF generated  $\alpha$ -hydroxy ketone **4** as a single diastereomer in 70% yield. The stereochemistry of **4** was confirmed by X-ray crystal structures of diols **1** and **14** (*vide infra*) which indicated that the oxidation had, as expected, occurred opposite to the bridgehead axial methyl group.

**Scheme 5.** Synthesis of  $\alpha$ -Hydroxy Ketone **4**

Finally, the reduction of  $\alpha$ -hydroxy ketone **4** was explored. Using 4 equiv of  $\text{NaBH}_4$  in MeOH at  $0^\circ\text{C}$ , an 82:18 mixture of alcohols **1** and **14** were generated. After chromatography, *trans*-1,2-diol **1** was isolated in 80% yield and *cis*-1,2-diol **14** in 13% yield. As predicted, steric hindrance led to a preferred hydride attack on the face opposite to the methyl group. Unequivocal proof of the structure of *trans*-1,2-diol **1** was obtained by X-ray crystallography (Scheme 6).

**Scheme 6.** Stereoselective Synthesis and X-ray Crystal Structure of *trans*-1,2-Diol **1****Scheme 7.** Stereoselective Synthesis and X-ray Crystal Structure of *cis*-1,2-Diol **14**

In contrast, and somewhat surprisingly, reduction of  $\alpha$ -hydroxy ketone **4** using 3 equiv of DIBAL-H in THF at  $-78^\circ\text{C}$  led to the preferred formation of *cis*-1,2-diol **14** which was isolated in 73% yield. Structural proof was obtained by X-ray crystallography (Scheme 7). There was no evidence of the formation of *trans*-1,2-diol **1** in this reaction. Our conjecture is that, with DIBAL-H, an aluminum alkoxide forms which, if it adopts an axial position, can coordinate to the axial oxygen of the ketal group. This would lead to a conformational change of the A-ring, exposing the other carbonyl face to the excess DIBAL-H that is present. Notably, the complementary diastereoselectivity produced with  $\text{NaBH}_4$  and DIBAL-H facilitates synthetic access to either *trans*- or *cis*-1,2-diols in the quassinoid family of natural products.

In summary, a concise synthesis of the AB rings of samaderine C has been developed (12 steps, 8 isolation steps, 7.8% overall yield). In particular, we have successfully implemented a strategy for the stereoselective synthesis of the *trans*-1,2-diol motif present in samaderine C (and a range

of other quassinoids). Our approach includes a stereoselective  $\alpha$ -hydroxylation (of an extended silyl enol ether) and a reduction. A complementary route to a *cis*-1,2-diol, a motif that is present in other quassinoid natural products such as castelanolide,<sup>15</sup> has also been discovered. We believe that these new aspects have great potential for quassinoid total synthesis.

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(15) Grieco, P. A.; Lis, R.; Ferrino, S.; Yan, J. *J. Org. Chem.* **1984**, *49*, 2342.

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**Supporting Information Available.** Full experimental procedures, characterization data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.