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Stereocontrolled Synthesis of the AB Rings of Samaderine C

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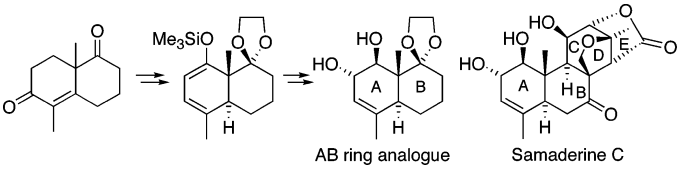
ABSTRACT

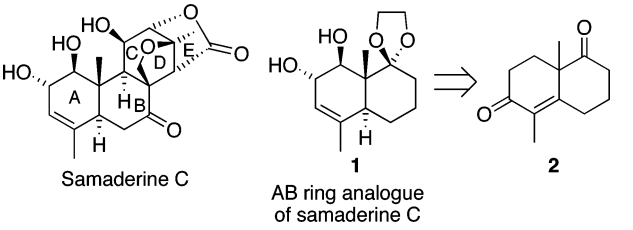


A concise synthesis of the AB rings of samaderine C (12 steps, 8 isolation steps, 7.8% overall yield), a quassinoid with antifeedant and insecticidal activity, is described. The development of the first general approach to the *trans*-1,2-diol A-ring motif in samaderine C and other quassinoids is a key feature. The *trans*-1,2-diol is crafted *via* stereoselective α-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.[1,2] One of eight isolated samaderines, our interest in samaderine C was initiated by its reported antifeedant and insecticidal properties.[3] 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.[4] More, recently, Shing and co-workers reported a 21-step synthesis of (−)-samaderine Y starting from (+)-carvone.[5]

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[6] 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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(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.

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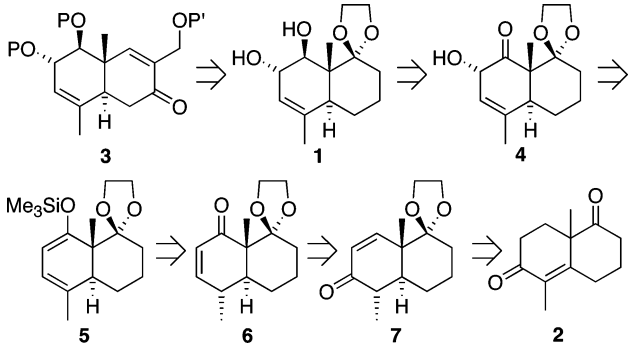
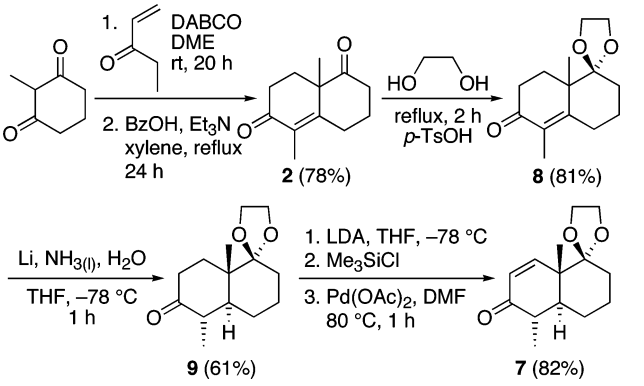
in turn be prepared from diol **1** by diol protection, ketal deprotection, 1,3-carbonyl transposition, enone formation, and enone α-functionalization. It was our intention that the bridgehead axial methyl group would control the configuration of the diol functionality in **1**: reduction of hydroxy ketone **4** (→ **1**) and α-hydroxylation of silyl enol ether **5** (→ **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 γ-enolization), itself obtained from enone **7** *via* a 1,3-carbonyl transposition (Wharton rearrangement of an epoxy ketone[7] was envisaged). Previously, Grieco had developed an approach for the α-hydroxylation of enones such as **6**,[8] and the preparation of enone **7** from bicyclic enone **2** has been described.[9]

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-cyclohexadione and ethyl vinyl ketone were reacted in a DABCO-mediated Robinson annelation[6] 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_2O) 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 $Pd(OAc)_2$-mediated oxidation[10] of an intermediate silyl enol ether (formed by regioselective deprotonation of ketone **9** using LDA), as developed by Saegusa.[9] This delivered a single diastereomer of enone **7** in 82% yield. Using the Larock modification[11] of the Saegusa oxidation (catalytic $Pd(OAc)_2$/oxygen), none of **7** was formed and a Nicolaou-style[12] IBX-mediated oxidation of ketone **9** gave only a 14% yield of enone **7**.

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



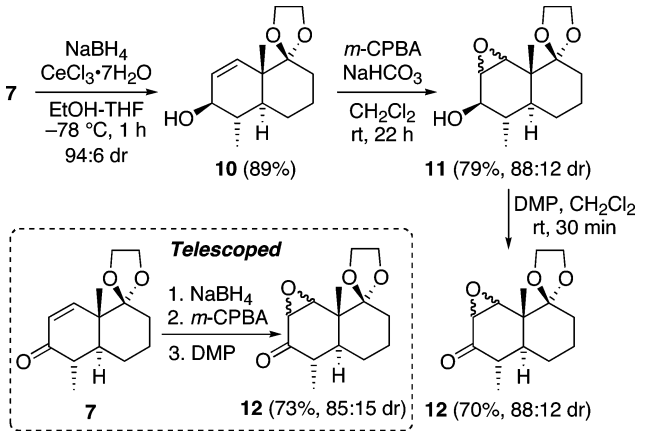
Next, we needed to carry out a 1,3-carbonyl transposition on enone **7** to place the ketone adjacent to the bridgehead methyl group (as in **6**). For this, a nucleophilic epoxidation of enone **7** and a Wharton rearrangement–oxidation were planned. However, all attempts at directly epoxidizing **7** (e.g., H_2O_2 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 ($NaBH_4/CeCl_3 \cdot 7H_2O$) of enone **7** gave a 94:6 mixture of diastereomeric alcohols from which an 89% yield of alcohol **10**[13] 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.[14] Oxidation with Dess-Martin periodinane (DMP) delivered an 88:12 mixture of epoxy-ketones **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 epoxy-ketones **12** was obtained after chromatography (73% yield from **7**) (Scheme 4).

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

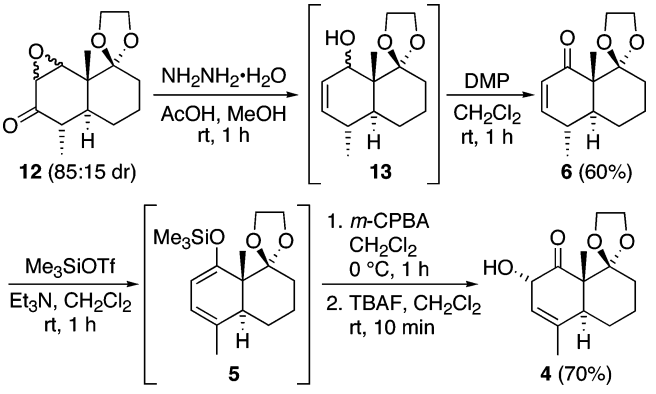
(7) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.
(8) (a) Spohn, R. F.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491. (b) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.
(9) Poigny, S.; 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 ^3J coupling between the C*H*OH and C*H*Me protons in the ^{1}H NMR spectrum (^3J = 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**



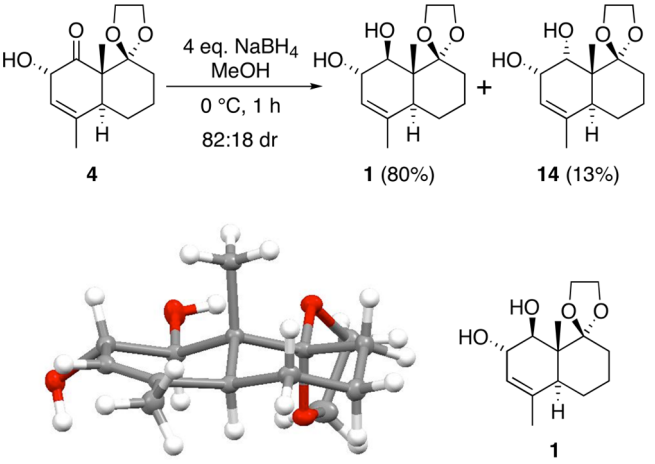
in a separate experiment) *via* a Wharton rearrangement (Scheme 5).[7] Workup and subjection of the crude allylic alcohols **13** to Dess-Martin periodinane oxidation gave enone **6** in 60% yield over the two steps. γ-Enolization of enone **6** was achieved using Et_3N and Me_3SiOTf and gave extended silyl enol ether **5**. Based on Grieco's precedent,[8] *in situ* oxidation with purified *m*-CPBA followed by stirring with TBAF generated α-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 α-Hydroxy Ketone **4**

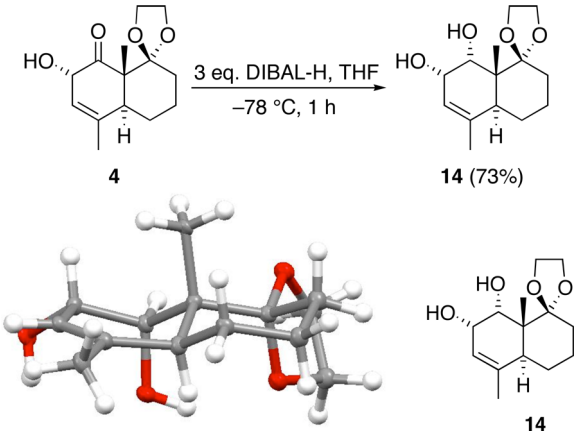


Finally, the reduction of α-hydroxy ketone **4** was explored. Using 4 equiv of $NaBH_4$ in MeOH at 0 °C, an 82:18 mixture of alcohols **1** and **14** were generated. After chromatography, *trans*-1,2-diol **1** was isolated in 80% yield and *cis*-1,2-diol **14** in 13% yield. As predicted, steric hindrance 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 α-hydroxy ketone **4** using 3 equiv of DIBAL-H in THF at −78 °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 $NaBH_4$ 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 α-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,[15] has also been discovered. We believe that these new aspects have great potential for quassinoid total synthesis.

(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 ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.