

Synthesis of *cis*-Solamin Using a Permanganate-Mediated Oxidative Cyclization

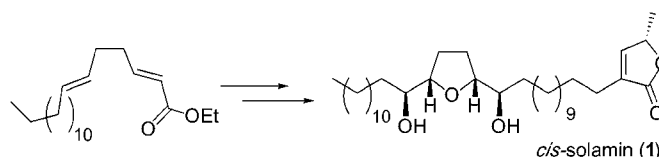
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Received August 5, 2002

ABSTRACT



cis-Solamin (**1**) and its diastereoisomer **14** have been synthesized in 13 steps using the diastereoselective permanganate-promoted oxidative cyclization of 1,5-dienes to create the tetrahydrofuran diol core. Notably, no protecting groups are required during the stages of fragment assembly.

Since the identification of the Annonaceous acetogenin uvaracin,¹ isolated from the roots of *Uvaria accuminata*, as an in vivo active antitumor agent, there has been significant interest in the isolation and biological evaluation of acetogenins from Annonaceae (custard-apple family).² In addition to potent cytotoxic antitumor activity, Annonaceous acetogenins have also displayed a variety of other interesting biological effects that include anthelmintic, antimalarial, antimicrobial, antiprotazoal, and pesticidal activities.² Consequently, significant effort has been devoted toward their synthesis and a number of total syntheses have appeared in the literature.^{3–5} However, the vast majority of these synthetic approaches have focused on the natural products containing trans-2,5-disubstituted tetrahydrofuran (THF) rings. In contrast, there has been relatively little published on the stereoselective synthesis of the corresponding *cis*-THF compounds.^{4,5}

cis-Solamin (**1**), is a mono-THF acetogenin isolated from the roots of a tropical fruit tree *Annona muricata*, which possesses *cis*-2,5-disubstitution of the THF core (Figure 1).⁶ The relative stereochemical relationship of the THF-diol

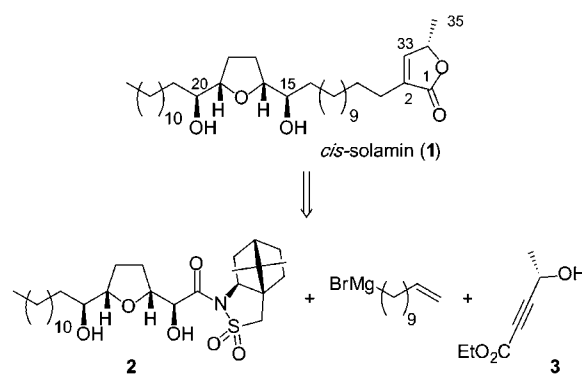


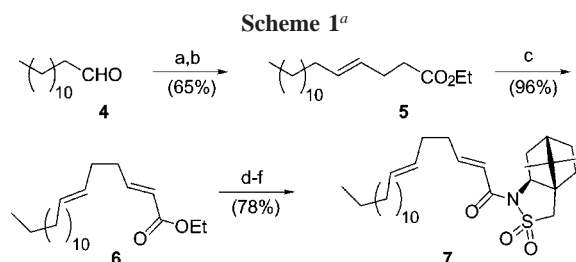
Figure 1. Approach to the synthesis of mono-THF acetogenin *cis*-solamin (**1**).

portion of **1** was determined to be threo/*cis*/threo from analysis of the NMR data, although the absolute stereochemistry of this part of the molecule could not be defined. Recently, syntheses of **1** and its diastereoisomer **14** were reported, and the structure of *cis*-solamin was assigned as **1** on the basis of the optical rotation data obtained.^{4c} Here we report the total synthesis of **1** and **14**.

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(2) For a recent review, see: Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540.

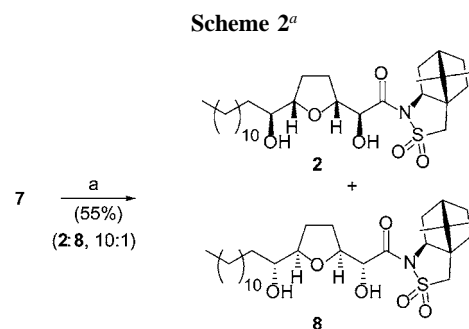
Our strategy for the synthesis of *cis*-solamin was centered around the permanganate-promoted oxidative cyclization of a 1,5-diene to introduce all the stereochemistry into the THF-diol fragment **2** in a single step (Figure 1).⁷ A number of elegant approaches to the butenolide portion of the acetogenins had already been devised, and we chose to employ one of them, Trost's ruthenium-catalyzed Alder-ene reaction, in our synthesis.^{3c,8}



^a Reagents and conditions: (a) $\text{CH}_2=\text{CHMgBr}/\text{THF}$; (b) $\text{CH}_3\text{C}(\text{OEt})_3$, 135°C ; (c) DIBAL-H; toluene, -60°C , then added to $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$, NaH, THF, from -60°C to room temperature; (d) NaOH, NaHCO_3 , $\text{MeOH}-\text{H}_2\text{O}$; (e) $(\text{COCl})_2$, DMF; (f) (2*S*)-10,2-camphorsultam, *n*-BuLi, THF.

The synthesis of diene **6**, required for the key oxidative cyclization, started from commercially available aldehyde **4** and followed a modification of a published procedure.⁹ Addition of vinyl Grignard to **4** proceeded in an unoptimized

72% yield to afford an allylic alcohol, which underwent a Johnson–Claisen rearrangement to afford enoate **5** in excellent yield (Scheme 1). Conversion of **5** to the known dienolate **6** was best achieved without isolation of the intermediate aldehyde, in a one-pot reduction–olefination reaction.¹⁰ The synthesis of precursor **7** for the oxidative cyclization reaction



^a Reagents and conditions: (a) KMnO_4 (1.4 equiv), AcOH (8 equiv), Adogen 464 (0.1 equiv), EtOAc, from -30 to 0°C .

was completed by hydrolysis of **6** and activation of the resulting unsaturated acid as the acid chloride followed by reaction with lithiated (2*S*)-10,2-camphorsultam.

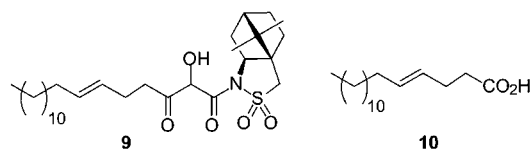


Figure 2. Byproducts from the KMnO_4 oxidation of diene **7**.

The key oxidative cyclization reaction proved to be somewhat more problematic than we had anticipated on the

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(4) For stereoselective syntheses of *cis*-mono-THF acetogenins, see the following. 15,20-Di-*epi*-*cis*-solamin: (a) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975–1981. Muricatetrocin A: (b) Bäurle, S.; Peters, U.; Friedrich, T.; Koert, U. *Eur. J. Org. Chem.* **2000**, *65*, 2207–2217. *cis*-Solamin: (c) Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett.* **2002**, *4*, 1083–1085.

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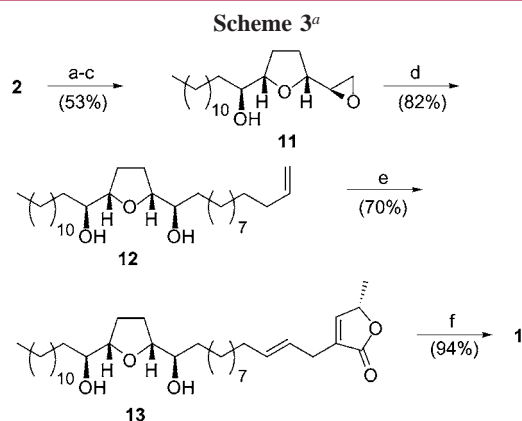
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basis of results previously obtained in our group for related oxidations.¹¹ The conventional acetone–water system returned the desired THF diol **2** in a disappointing 18% yield, with the major isolated product being α -hydroxy- β -ketoester **9** (Figure 2). Similarly poor yields have been observed by others for the oxidative cyclization of 1,5-diene substrates where the olefins were either mono- or disubstituted.^{7b,12}

Fortunately, conducting the oxidation under phase-transfer conditions¹³ led to an improved yield (55%) for this pivotal transformation that introduces the C15, C16, C19, and C20 stereocenters present in *cis*-solamin in one step. A small amount of the diastereoisomeric THF-diol **8** was also produced in the oxidation (**2**:**8** = 10:1 as estimated from crude ¹H NMR spectrum). We were pleased to discover that the minor isomer was readily separated from **2** by column chromatography. The major byproduct isolated from the phase-transfer oxidative cyclization was the cleavage product **10** (Figure 2), which probably arose from further oxidation of α -hydroxy- β -ketoester **9**, or rather its enol tautomer.



^a Reagents and conditions: (a) NaBH₄, THF, H₂O; (b) TsCl, Et₃N, CH₂Cl₂; (c) DBU, CH₂Cl₂; (d) CH₂=CH(CH₂)₉MgBr, CuI, THF, –60 °C; (e) **3**, CpRu(cod)Cl, MeOH, reflux; (f) TsNHNH₂, NaOAc, THF–H₂O, 60 °C.

We found that the auxiliary was best removed from **2** by reduction using NaBH₄, whereas LiAlH₄ surprisingly gave a complex mixture of products (Scheme 3). The resulting diol was taken forward by conversion to the epoxide **11**, prior to addition of the C3–C13 fragment in a copper-catalyzed Grignard reaction. Notably, there was no need for protection of the C20 hydroxyl group. The butenolide ring in 4,5-dehydro-*cis*-solamin (**13**) was put in place using a ruthenium-catalyzed Alder-ene reaction, which was also tolerant of the free hydroxyl groups present in the starting materials. The

final selective reduction of the 4,5-double bond could be achieved according to the literature method by hydrogenation over Wilkinson's catalyst,^{3–5} although great care had to be exercised in order to avoid over reduction of the butenolide ring. We found that diimide reduction was easier to control¹⁴ and ultimately used this method to complete the synthesis of **1**.¹⁵

Due to uncertainties relating to the exact stereochemical assignment of *cis*-solamin, we also synthesized diastereoisomeric structure **14** following the route described above but using the (2*R*)-10,2-camphorsultam (Figure 3). As

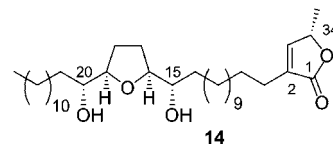


Figure 3. Structure of compound **14**.

reported by Makabe et al., the NMR spectra of diastereoisomers **1** and **14** were not distinguishable from each other and data reported for *cis*-solamin.^{4c} However, in contrast to the results of Makabe, we also found that the optical rotations of the two synthetic compounds were quite similar,^{16,17} although the data for **1** more closely matched the reported value for the natural product. Therefore, we believe that structure **1** probably corresponds to the natural product *cis*-solamin; however, it is not possible to unambiguously confirm the assignment on the basis of the optical rotation data alone.

In summary, concise total syntheses of two *cis*-diastereoisomers of solamin **1** and **14** have been achieved, both giving spectroscopic data consistent with that of the natural product *cis*-solamin. The key step in the syntheses involved oxidative cyclization of a 1,5-diene **7** or *ent*-**7** using permanganate under phase-transfer conditions. Hydroxyl protecting groups were not required during the final assembly of the fragments. Our current efforts are extending the oxidative cyclization methodology to the synthesis of adjacent and nonadjacent bis-THF acetogenins.

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(15) It is interesting to note that one of our samples of **14**, prepared by hydrogenation over Wilkinson's catalyst, displayed two peaks in a 1:1 ratio when run down a Chiralcel OD-H HPLC column, eluting with 5:95 *i*-PrOH/hexane. The same sample only showed one set of signals in the ¹³C NMR spectrum. We concluded that the new peak corresponded to a C34 epimer of **14** (*ent*-**1**). Epimerization of C34 has previously been reported to occur under basic conditions (see ref 17).

(16) Optical rotation was measured on an Optical Activity, Ltd., Automatic Polarimeter. Compound **1**: [α]_D²⁴ +22.6 (c 0.12, MeOH) (lit.^{4c} [α]_D²¹ +26 (c 0.45, MeOH)). Compound **14**: [α]_D²⁴ +14 (c 0.19, MeOH) (lit.^{4c} [α]_D²¹ +42.0 (c 0.50, MeOH)). The optical rotation for a natural sample of *cis*-solamin was reported as +22 (c 0.55, MeOH).⁶ Both of our samples of **1** and **14**, for which the optical rotation data are reported, gave single peaks by chiral HPLC under the conditions given above (see ref 15).

(17) It has previously been observed that the optical rotation value of acetogenins is largely due to the stereochemistry of the butenolide and, to a lesser extent, due to the stereochemistry of the THF diol portion: Duret, P.; Figadère, B.; Hocquemiller, R.; Cavé, A. *Tetrahedron Lett.* **1997**, 38, 8849–8852.

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Acknowledgment. We thank the Royal Society for a University Fellowship (R.C.D.B.). Merck Sharp & Dohme, Syngenta, and Pfizer Central Research are also gratefully acknowledged for unrestricted grants.

Supporting Information Available: Copies of ^1H and ^{13}C NMR for **1**, **2**, **8**, and **12–14**. This material is available free of charge via the Internet at <http://pubs.acs.org>.
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