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Total Synthesis of *cis*-Solamin

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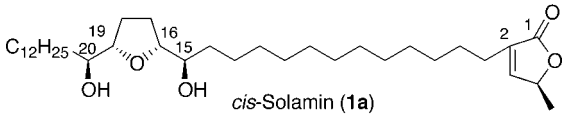
ABSTRACT



A convergent total synthesis of *cis*-solamin and its diastereomer was accomplished using $VO(acac)_2$-catalyzed diastereoselective epoxidation followed by cyclization of bis-homoallylic alcohol as the key step. By comparison of the optical rotation of two possible diastereomers, it is suggested that the absolute configuration of natural *cis*-solamin is 1a.

The Annonaceous acetogenins, which are isolated from a number of plants of *Annonaceae*, have attracted much attention in recent years due to a wide variety of biological activities, i.e., cytotoxic, antitumoral, antimalarial, immunosuppressive, pesticidal, and antifeedant. So far, over 350 compounds have been isolated.[1] Their unique structures are characterized by one or more tetrahydrofuran rings, together with a terminal γ-lactone moiety on a C-35 or C-37 carbon chain.[1] *cis*-Solamin (**1**, Figure 1) is a mono-tetrahydrofuran acetogenin,[2] isolated from *Annona muricata* in 1998.[3] A similar compound corresponding to the well-known solamin (**2**)[4] was synthesized by Keinan[5a] and Trost[5b] and by us.[5c] The absolute configuration of natural **1** has not been reported. However, because the *cis-threo-cis* stereochemistry of the tetrahydrofuran ring of **1** has been determined by A. Laurens et al.,[3] and the (*S*) configuration of the secondary methyl group of the γ-lactone moiety is well-known, it follows that the absolute stereochemistry of **1** is (15*R*,16*R*,19*S*,20*S*) or (15*S*,16*S*,19*R*,20*R*). Two possible structures, **1a** and **1b**, would be difficult to differentiate by ^{1}H NMR or ^{13}C NMR spectroscopic data, since two stereogenic regions, that is, the THF ring core part and the γ-lactone moiety are separated

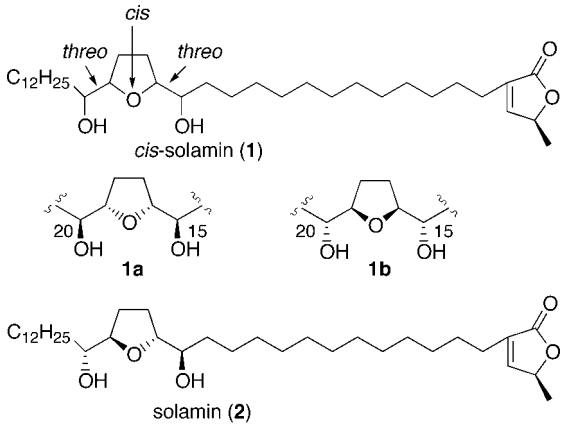


Figure 1.

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(1) For recent reviews for annonaceous acetogenins, see: (a) Alali, F. Q.; Liu, X. -X,; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (b) Zafra-Polo, M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117. (c) Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products: Acetogenins from Annonaceae*; Herz, W., Eds; Springer-Verlag: New York, 1997; Vol. 70, pp 81−288.

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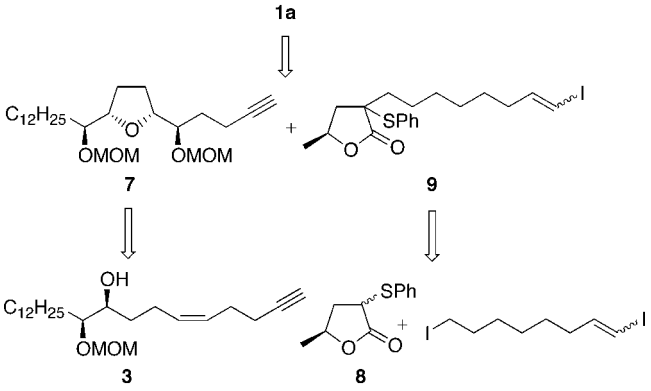
Scheme 1

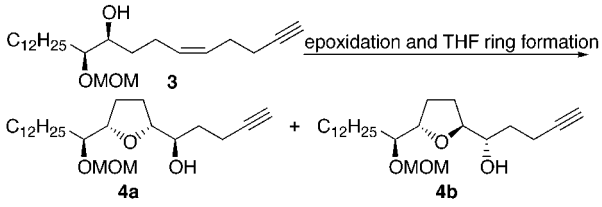


by a long carbon chain. X-ray analysis is also very difficult due to the waxy nature of this compound. To establish the absolute configuration of *cis*-solamin, we planned to synthesize the two candidates **1a** and **1b**, employing a TBHP−$VO(acac)_2$ diastereoselective epoxidation[6] followed by a cyclization strategy.

Scheme 1 outlines our synthetic strategy. One of the key steps is TBHP−$VO(acac)_2$ diastereoselective epoxidation[6] followed by cyclization in the presence of 4A molecular sieves. The starting material is bis-homoallylic alcohol **3**, whose enantiomer had been reported earlier by us.[5c]

The results of diastereoselective epoxidation of **3** and spontaneous cyclization are summarized in Table 1. The

Table 1. Epoxidation and Subsequent Cyclization of Bis-homoallyl Alcohol **3**[a]



Reagent	Solvent	Additive	Yield (**4a** +**4b**)%	**4a** : **4b**
*m*CPBA	CH_2Cl_2	–	83	37 : 63
TBHP-10 mol% Ti(O*i*-Pr)$_4$	CH_2Cl_2	–	24	49 : 51
TBHP-10 mol% $MoO_2(acac)_4$	CH_2Cl_2	–	trace	–
TBHP-5 mol% $VO(acac)_2$	C_6H_5Cl	–	trace	–
TBHP-5 mol% $VO(acac)_2$	CH_2Cl_2	–	43	78 : 22
TBHP-5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	–	51	87 : 13
TBHP-5 mol% $VO(acac)_2$	$(CH_2Cl)_2$	MS 4A	75	89 : 11

[a] The reactions were carried out at room temperature.

results shown in Table 1 indicate the following. $VO(acac)_2$ in the presence of 4A molecular sieves can serve as the most effective catalyst system in the diastereoselective epoxidation. On the other hand, Ti and Mo catalysts were ineffective. Halogenic solvents, especially 1,2-dichloroethane, gave a good stereoselectivity and yield. Determination of the relative stereochemistry of **4a** and **4b** was performed J. M. Cassady's method as we have previously reported (Figure 2).[5c,7]

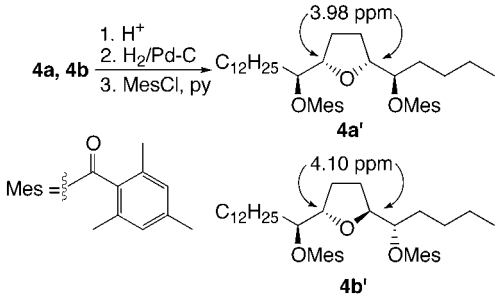
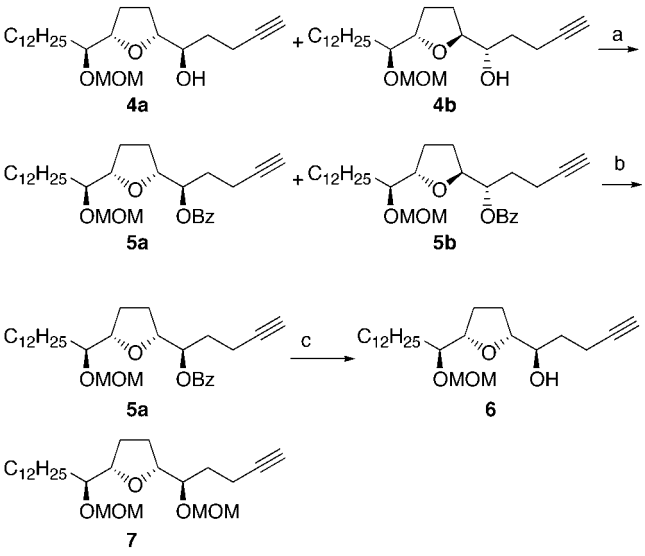


Figure 2.

Diastereoisomers **4a** and **4b** were separated by column chlomatography (benzene−AcOEt = 20:1) after the hydroxy group of **4a** and **4b** had been protected as a benzoate ester (**5a** and **5b**). Hydrolysis of the benzoate ester gave **6** and protection of the hydroxyl group as MOM ether afforded tetrahydrofuran moiety **7** (Scheme 2).

Scheme 2[a]



[a] Reagent and conditions: (a) BzCl, pyridine (94%); (b) separation (81%); (c) NaOH, MeOH (92%); (d) MOMCl, *i*-Pr_2NEt (94%).

As shown in Figure 3, the γ-lactone moiety **9** was constructed as we had reported earlier starting from γ-lactone **8**.[5c,8]

Both segments were coupled by the Sonogashira cross coupling[9] reaction mediated by $Cl_2Pd(PPh_3)_2$/CuI in the THF

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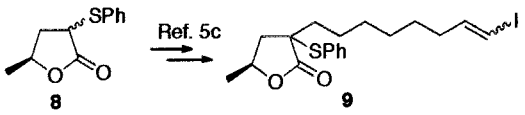
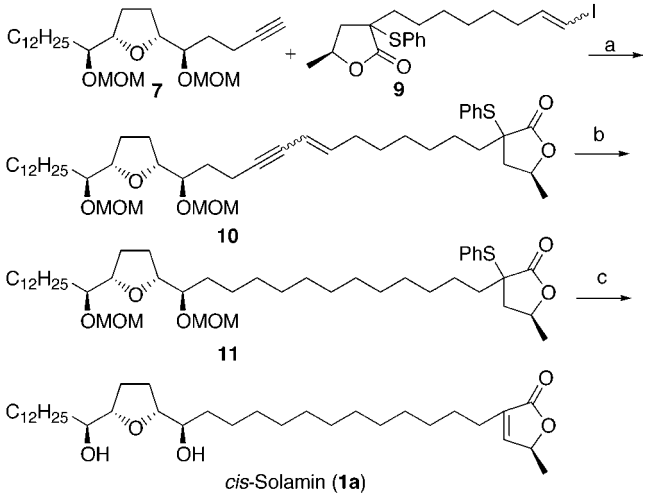


Figure 3.

solvent system to give compound **10** (Scheme 3). Catalytic hydrogenation of **10** using Wilkinson's catalyst afforded saturated product **11**. Oxidation of the sulfur with *m*CPBA followed by thermal elimination and deprotection of MOM ethers with $BF_3{\cdot}Et_2O$ in DMS[10] afforded the candidate **1a**. On the other hand, the other candidate **1b** was synthesized from the enantiomer of compound **2** using the same procedure as that employed for **1a**.

Scheme 3[a]



[a] Reagent and conditions: (a) 5% $Cl_2Pd(PPh_3)_2$, 10% CuI, Et_3N (74%); (b) H_2/$ClRh(PPh_3)_3$ (68%); (c) (i) *m*CPBA, toulene reflux; (ii) $BF_3{\cdot}Et_2O$/dimethyl sulfide (60%).

The two synthetic samples (**1a**, **1b**) could not be differentiated by the spectral data (^{1}H NMR, ^{13}C NMR). On the other hand, their specific rotations showed a sharp contrast. While the specific rotation of synthetic **1a** ($[\alpha]^{21}_D$ = +26, *c* 0.45, MeOH) is similar to the reported value of the naturally occurring *cis*-solamin ($[\alpha]_D$ = +22, *c* 0.55, MeOH), that of **1b** ($[\alpha]^{21}_D$ = +42, *c* 0.50, MeOH) showed a much higher value.[11,12] As shown in Table 2, the ^{1}H NMR spectra of the carbinol centers of the corresponding bis (*R*)- and (*S*)-MTPA esters of synthetic **1a** and **1b** showed a slight chemical shift difference. According to the sign of $\Delta\delta_H$ [= ($\delta_S - \delta_R$)] values of each carbinol center, the absolute configuration of **1a** is assigned as C-15*S*, C-16*S*, C-19*R*, and C-20*R*. Similarly, the absolute configuration of **1b** is assigned as C-15*R*, C-16*R*, C-19*S*, and C-20*S*. This indicates that if natural **1** is available, we can determine the absolute stereochemistry of *cis*-solamin by applying advanced Mosher methodology.[13]

Table 2. ^{1}H NMR Chemical Shifts of the Bis (*R*)- and (*S*)-MTPA Esters of **1a** and **1b**[a]

MTPA ester	15-H	16-H	19-H	20-H
(*R*)-MTPA-**1a**	5.06	3.87	4.08	4.92
(*S*)-MTPA-**1a**	5.06	3.86	4.09	4.93
δ (*S*)-(*R*)-**1a**		0.01	−0.01	−0.01
abs confign	*S*	*S*	*R*	*R*
(*R*)-MTPA-**1b**	5.06	3.86	4.09	4.93
(*S*)-MTPA-**1b**	5.06	3.87	4.08	4.92
δ (*S*)-(*R*)-**1b**		-0.01	0.01	0.01
abs confign	*R*	*R*	*S*	*S*

[a] Proton chemical shifts are referenced to *CH*Cl_3 (δ 7.25).

In conclusion, the first total synthesis of *cis*-solamin (**1a**) and its diastereomer **1b** was accomplished using $VO(acac)_2$-catalyzed diastereoselective epoxidation followed by spontaneous cyclization. On the basis of the present data, it is strongly suggested that the natural *cis*-solamin is **1a**.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **4a**, **5**, **6**, **8**, **1a**, and **1b** and ^{1}H NMR spectra for compounds **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Physical and spectroscopic data for **1a**: mp 66−68 °C, $[\alpha]^{21}_D$ +26 (*c* 0.45, MeOH). ^{1}H and ^{13}C NMR spectra were identical with those reported in ref 3. HREIMS: calcd for $C_{35}H_{64}O_5$ 564.4753, found 564.4720.

(12) Physical and spectroscopic data for **1b**: mp 61−63 °C, $[\alpha]^{21}_D$ +42 (*c* 0.50, MeOH). ^{1}H and ^{13}C NMR spectra were identical with those reported in ref 3. HRFABMS (M + Na): calcd for $C_{35}H_{64}O_5Na$ 587.4651, found 587.4650.

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