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Stereocontrolled Synthesis of Key Intermediates in the Total Synthesis of Acetogenins of Annonaceae

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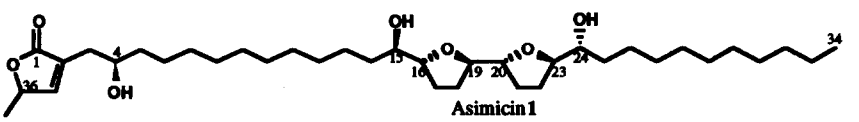
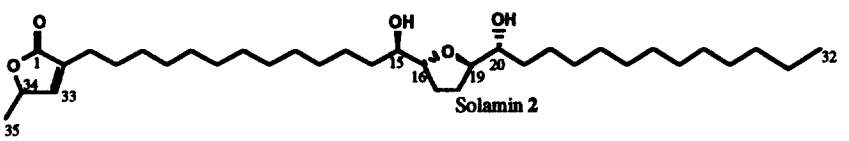
Key words: stereospecific synthesis; γ-lactones; acetogenin; stereochemical relationship assignment.

Abstract: *: (4S, 5S, 8S, 9S)-* and *(4R, 5S, 8S, 9S)-9-hydroxy-5,8-epoxy-henicosabutanolides 3b and 4b, respectively, have been successfully synthesized from very inexpensive L-glutamic acid. The key step of the synthetic sequence is an alkylation of lactol acetates 5a,b with 2-(trimethylsilyloxy)-furan. Stereochemical relationship assignment of the obtained products were deduced from NMR data, and by chemical correlation.*

About 100 acetogenins of Annonaceae have now been discovered since 1982[1], and are potently bioactive as antitumoral, pesticide, antiparasitic compounds.[2] But the mode of action of these natural products remains unclear, eventhough some preliminary observations of an effective inhibition of the mitochondrial oxidative phosphorylation have been reported lately[3]. Asimicin **1**, a cytotoxic adjacent bis-tetrahydrofuran (bis-THF) acetogenin extracted from several plants[4], contains 8 stereogenic centres whose absolute configurations have been elucidated recently by high field nuclear magnetic resonance analysis of its methoxyfluoromethylphenylacetic acid esters (Mosher's esters).[5] Solamin **2**, a cytotoxic mono-THF acetogenin isolated from *A. muricata*[6] possesses 5 asymmetric centres whose absolute configurations have been established as all *R* across the THF ring.[7]



Asimicin 1

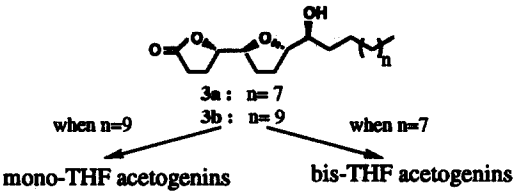


Solamin 2

We report in this communication a stereocontrolled approach which led to the synthesis of lactones **3a,b** (and their epimers **4a,b**; compounds of "a" series possess an alkyl chain of 11 carbon atoms, and those of "b" series an alkyl chain of 13 carbon atoms) as single enantiomers (Scheme 1) with the desired relative configuration (*threo-trans-threo*), found in the natural acetogenins **1**[5] and **2**[7], across

either the C19-C24 or C15-C20 carbon skeleton, respectively. Indeed lactones **3a** and **3b** are key intermediates for the preparation of enantiomers of natural acetogenins of both series (mono- or bis-THF).

Scheme 1



L-glutamic acid **4** was chosen as an inexpensive and suitable starting material for our synthetic pathway. In 7 steps and 45% overall yield, **4** was converted to a 1:1 anomeric mixture of either acetates **5a** or **5b** as described earlier.[8] Reaction of anomeric acetates with trimethylsilyl enol ether of various carbonyl compounds in the presence of a catalytic amount of trityl perchlorate ($TrClO_4$) gives an almost quantitative yield of C-glycosides with variable α/β ratios, depending on the nature of the substrate.[9a,b] Therefore **5a** and **5b** separately reacted with 2-(trimethylsilyloxy)-furan (TMSOF)[10] in ethyl ether at 0°C with a catalytic amount of $TrClO_4$. Among the four possible isomers, only two (in each series) **6a/7a** and **6b/7b**, in 40:60 ratio and 90% combined yield, were observed and separated by flash chromatography (Scheme 2).

To establish the relative stereochemistry of the compounds so formed, NOE-NMR experiments were performed on **6a**. H4 and H5 showed a strong NOE effect as well as H8 and H9, while H5 and H8 showed no NOE enhancement. These data suggest that H8 and H5 are *anti* to each other, which means that **6a**, and by correlation **6b**, have a *trans* relationship across the THF ring.

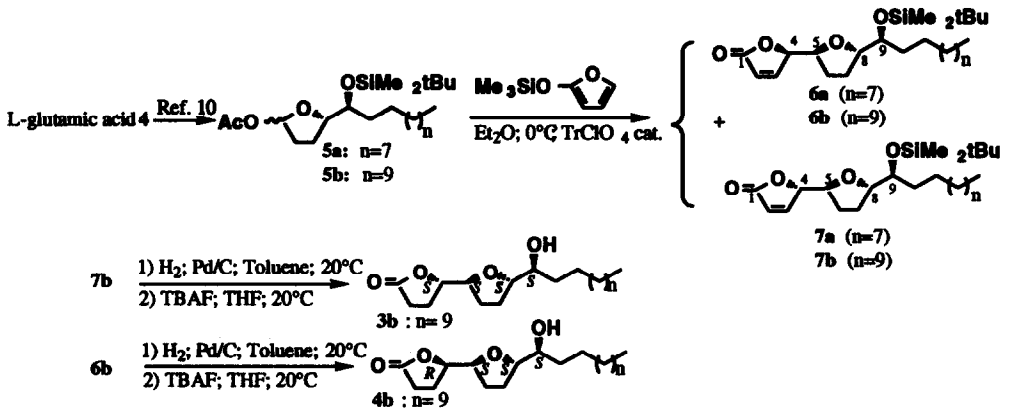
Because the resonance frequencies of protons H5, H8 in **7a** (or **7b**) were very similar for selective irradiation, NOE spectra could not give the stereochemical relationship across the lactone-THF skeleton. The *trans* stereochemical assignment of **7a** was mainly based on the clean Et_3N-catalyzed epimerization of **7a** into **6a** (**7a/6a**=40:60 equilibrium ratio at 45°C).[11] Therefore, **7b** is assumed to have the same *trans* relationship across the THF ring.

The relative configurations across C4-C5, were assigned by comparison of the chemical shifts of protons at C3, and confirmed later by chemical correlation. *Erythro* butenolides **6a,b** where distinguished from the *threo* isomers **7a,b** by the downfield chemical shift of the C3 proton ($\Delta\delta$= 0.2 ppm) as observed earlier.[12] Indeed, chemical shifts of carbon and proton atoms of **6a,b** and **7a,b** were deduced from 2D-^1H (COSY 45) NMR experiments as well as ^1H-^{13}C correlated (XH CORR) spectra.

It is noteworthy that a dominant *threo* diastereoselectivity in such a transformation has already been observed by others in a related reaction.[11,12] Whereas it should be noted that a >98:2 selectivity in favour of the *trans* isomers is observed for the first time[13], eventhough the starting materials **5a** and **5b**

do not bear any substituent at 2,3-positions (numerotation in the furanose series). Indeed *cis* isomers (across the THF ring) were not detected by NMR analysis.

Scheme 2



Partial NMR data for **6a,b** and **7a,b***

	C2	H2	C3	H3	C4	H4	C5	H5	C8	H8	C9	H9
6a	122.05	6.15	155.04	7.60	85.18	4.88	79.30	3.88	83.05	3.98	74.93	3.54
7a	122.67	6.18	153.53	7.40	84.73	5.05	77.54	4.26	83.28	3.90	74.80	3.52
6b	122.10	6.15	155.00	7.58	85.21	4.86	79.32	3.88	83.12	3.98	75.00	3.53
7b	122.61	6.15	153.56	7.39	84.72	5.04	77.50	4.23	83.26	3.88	74.79	3.52

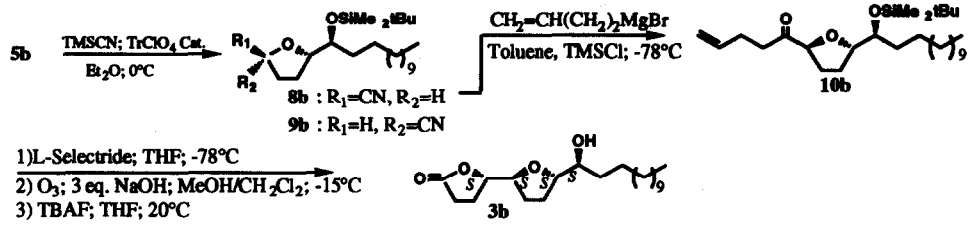
*: δ deduced from XH CORR, 2D-^{1}H COSY 45 and Noe NMR experiments

Hydrogenation on Pd/C of the double bond of compound **7b**, followed by deprotection of the hydroxyl group with tetrabutylamonium fluoride (TBAF), allowed us to obtain the desired lactone **3b** $[\alpha]_D$= +8 (c=1.33, $CHCl_3$)[7,14], whereas the same sequence applied to **6b** afforded the epimeric lactone **4b** $[\alpha]_D$= +15 (c=1.33, $CHCl_3$)[14,15] (scheme 2).

To confirm our stereochemical relationship assignments of **6a,b** and **7a,b** and so of **3a,b** and **4a,b**, comparison of spectroscopic data of **3b** obtained by a second route, as depicted on scheme 3, was performed. Therefore reaction of acetate **5b** with TMSCN in Et_2O at 0°C, with a catalytic amount of $TrClO_4$, afforded a nearly 1:1 *trans:cis* mixture of separable nitriles **8b** and **9b** in 96% yield. Addition of 3-butenylmagnesium bromide on *trans* nitrile **8b** in the presence of TMSCl in toluene at -78°C afforded ketone **10b** in 83% yield, which after reduction by L-Selectride® at -78°C, gave rise to the sole *threo* alcohol **11b** in 80% yield.[8] The double bond was then readily cleaved by ozonolysis at -15°C in the presence of 3eq. of NaOH in a MeOH/CH_2Cl_2 (1/8 vol.) solution[16], to afford after deprotection of the hydroxyl group at C-9 with TBAF, the expected lactone **3b** in 90% yield for the last two steps.

Spectroscopic data (MS, IR, ^1H and ^{13}C NMR) as well as specific rotation of compound **3b** obtained by either way are identical, and confirm the stereochemical assignments for **6a,b** and **7a,b** made in scheme 2. Use of **3a** and **3b** as key intermediates for the synthesis of asimicin **1** and solamin **2**, respectively, will be demonstrated in a subsequent report from this laboratory.

Scheme 3



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References and notes

1 Cortes D., Figadère B., Cavé A., *Phytochemistry* **1993**, *14*, 1467-1473.

2 Cavé A., Cortes, D. Figadère B., Hocquemiller R., Laprévote O., Laurens A., LeBoeuf M., "Phytochemical Potential of Tropical Plants; Recent Advances in Phytochemistry". 27, Downum K.R., Romeo J., Stafford HH.A., Eds., Plenum Press, New-York, **1993**, pp167-202.

3 Londershausen M., Leicht W., Lieb F., Moeschler H., Weiss H., *Pestic. Sci.*, **1991**, *33*, 427-438.

4 Rupprecht J.K., Liu Y.H., McLaughlin J.L., *J. Nat. Prod.*, **1990**, *53*, 237-278.

5 Rieser M.J., Hui Y.H., Rupprecht J.K., Kozlowski J.F., Wood K.V., McLaughlin J.L., Hanson P.R., Zhuang Z., Hoye T.R., *J. Am. Chem. Soc.*, **1992**, *114*, 10203-10213

6 Myint S.H., Cortes D., Laurens A., Hocquemiller R., LeBœuf M., Cavé A., Cotte J., Quéro A.M., *Phytochemistry*, **1991**, *30*, 3335-3338.

7 Sinha S.C., Keinan E., *J. Am. Chem. Soc.*, **1993**, *115*, 4891-4892.

8 Harmange J.-C., Figadère B., Cavé A., *Tetrahedron Lett.*, **1992**, *33*, 5749-5752.

9 a) Mukaiyama T., Kobayashi S, *Carbohydrate Res.*, **1987**, *171*, 81-87.
b) For a review on the synthesis of 2,5-disubstituted tetrahydrofurans see : Harmange J.-C., Figadère B., *Tetrahedron: Asymmetry*, **1993**, *4*, 1711-1754.

10 Casiraghi G., Colombo L., Rassu G., Spanu P., *J. Org. Chem.*, **1990**, *55*, 2565-2567.

11 Casiraghi G., Colombo L., Rassu G., Spanu P., *Tetrahedron Lett.*, **1989**, *30*, 5325-5328.

12 Jefford C. W., Jaggi D., Boukouvalas J., *Tetrahedron Lett.*, **1987**, *28*, 4037-4040.

13 Koert U., Stein M., Harms K., *Tetrahedron Lett.*, **1993**, *34*, 2299-2302.

14 **3b**: $[\alpha]_D$= +8 (c=1.33, $CHCl_3$); IR (ν_{max} cm^{-1}): 3880, 3600, 1780; UV (Et_2OH): λ_{max} 204 nm, logε= 0.228 ; ^1H NMR (200MHz, in $CDCl_3$, ref. to $CHCl_3$, δ ppm): 4.47 (ddd, J=8.0, 5.0, 3.0Hz, 1H), 4.06 (dt, J=7.4, 2.9Hz, 1H), 3.84 (dt, J=7.8 5.6Hz, 1H), 3.39 (m, 1H), 2.65 (ddd, J=16.7, 10.1, 6.6Hz, 1H), 2.47 (ddd, J=16.7, 9.8, 6.8Hz, 1H), 2.25 (m, 3H), 2.00 (m, 3H), 1.72 (m, 1H), 1.54-1.18 (br, 22H), 0.88 (t, J=6.8Hz, 3H); ^{13}C NMR (50MHz, in $CDCl_3$, ref. to $CHCl_3$, δ ppm): 176.6, 83.5, 81.3, 80.8, 73.7, 33.8, 31.9, 29.6, 29.3, 28.2, 25.6, 24.6, 23.8, 22.7, 19.6, 14.1, 13.5; EIMS (70 ev, %) 337 (MH^+-H_2O, 1), 269 (M^+-$C_4H_5O_2$[lactone ring], 20), 155 (54), 138 (base), 111 (55), 97 (24), 83 (34), 71 (37); CIMS (NH_3) 372 (M+NH_4^+), 337 (MH^+-H_2O) .**4b**: $[\alpha]_D$= +15 (c=1.33, $CHCl_3$); IR (ν_{max} cm^{-1}): 3900, 3600, 1780; UV (Et_2OH): λ_{max} 202 nm, logε= 0.424 ; ^1H NMR (200MHz, in $CDCl_3$, ref. to $CHCl_3$, δ ppm): 4.44 (dt, J=6.7, 4.9Hz, 1H), 4.10 (dt, J=7.5, 6.3Hz, 1H), 3.83 (dt, J= 7.6, 6.4Hz, 1H), 3.38 (m, 1H), 2.53 (m, 1H), 2.32 (m, 1H), 2.25 (m, 3H), 2.11 (m, 3H), 1.73 (m, 1H), 1.40-1.00 (br, 22H), 0.87 (t, J=6.0Hz, 3H); ^{13}C NMR (50MHz, in $CDCl_3$, ref. to $CHCl_3$, δ ppm): 177.0, 83.5, 81.6, 79.9, 73.9, 33.5, 31.9, 29.6, 29.3, 28.5, 28.1, 25.5, 23.6, 22.6, 14.1; EIMS (70 ev) 337 (MH^+-H_2O, 1), 269 (M^+-$C_4H_5O_2$[lactone ring], 15), 155 (69), 138 (base), 111 (47), 97 (22), 83 (29), 71 (30); CIMS (NH_3) 372 (M+NH_4^+), 337 (MH^+-H_2O).

15 The same sequence applied to **6a** and **7a** have afforded the corresponding lactones **3a** and **4a**.

16 Marshall J.A., Garofalo A.W., *J. Org. Chem.*, **1993**, *58*, 3675-368.

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