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Stereocontrolled Synthesis of 2,5-Linked Monotetrahydrofuran Units of Acetogenins

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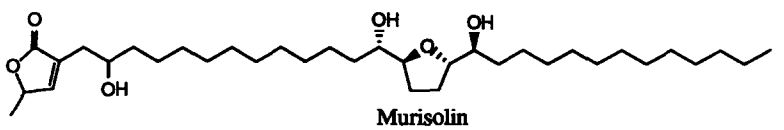
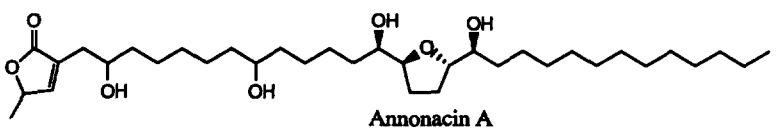
Key words: Stereospecific Synthesis; Tetrahydrofurans; Relative Stereochemistry; Acetogenins.

Abstract: *An approach to the stereocontrolled monotetrahydrofuran units of acetogenins is described. The NMR data of the two synthesized diastereoisomers 11 and 12 allow us to define the relative configuration of the monotetrahydrofuran acetogenins.*

We were in need of methods to allow us to define the absolute configuration of natural monotetrahydrofuran acetogenins with the hope to use the information so obtained in a synthetic approach. This prompted us to elaborate a facile route to the preparation of functionalized unsymmetrical 2,5-linked tetrahydrofurans. Up to now, most of the monotetrahydrofuran acetogenins reported in the literature[1] present the same relative stereochemical relationship across the tetrahydrofuran skeleton as murisolin[2] : *threo-trans-threo*. So far, only two acetogenins, annonacin A[3] and jetein[4], have been described with a *erythro-trans-threo* relative configuration.



Murisolin



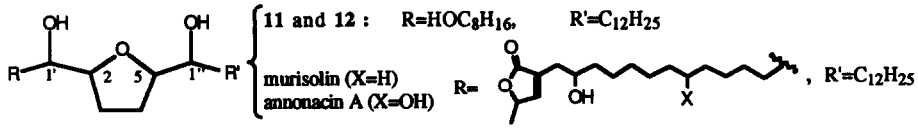
Annonacin A

(in both structures the absolute configurations represented might be inverted)

To confirm these determinations and compare with different known absolute configurations across the tetrahydrofuran ring, we prepared the 9(*S*),10(*S*),13(*S*),14(*S*) and 9(*R*),10(*S*),13(*S*),14(*S*) isomers **11** and **12** of 1,9,14-trihydroxy 10,13-epoxyhexacosane with therefore the relative configurations chemically fixed as *threo-trans-threo* and *erythro-trans-threo*, respectively. The strategy developed was to establish each new stereogenic center in an absolute sense, starting from L-glutamic acid. Each step of the sequence described was chosen for its high degree of stereoselectivity, with in mind a possible large scale synthetic application. The synthetic pathway we used is represented on Figure 1. The key intermediate is the *trans*

nitrile **7a** prepared from (+)-muricatacin **3**[5]. After protection of (+)-muricatacin **3** as a silyl ether **4** with TBDMSCl in DMF and imidazole, the lactone **4** was quantitatively reduced by one equivalent of DIBAL in toluene at -78°C to afford lactol **5**. The latter was then acetylated with acetic anhydride to produce quantitatively acetals **6**. The 1:1 anomeric mixture of acetals **6** was purified by flash chromatography on silica gel (CH_2Cl_2 with 1% of diethylamine). The acetals **6**, treated with TMSCN in the presence of a Lewis acid[6] ($TrClO_4$, 5% mol) afforded a 1:1 mixture of the *cis* and *trans* nitriles **7** in quantitative yield. After separation on silica gel, the *trans* nitrile **7a**[7] was converted into the corresponding ketone **8** in good yield with 2.5 eq. of the desired Grignard reagent in the presence of 4 eq. of TMSCl. The reduction of the carbonyl group was performed with high diastereoselectivity, by using L-Selectride as the reductive reagent to afford only the 9(*S*),10(*S*),13(*S*),14(*S*) isomer **9**. When the reaction was performed with sodium borohydride, its epimer 9(*R*),10(*S*),13(*S*),14(*S*) **10** was obtained along with **9** in an *erythro/threo* ratio of 15:85. Deprotection of the two hydroxyl groups of compounds **9** and **10** was readily effected with *n*-Bu_4NF at room temperature in THF in 12 hours to afford **11** and **12**, respectively[8]. Therefore, the compounds 9(*S*),10(*S*),13(*S*),14(*S*) **11** and 9(*R*),10(*S*),13(*S*),14(*S*) **12** were obtained in high optical purity and in 12 steps with 10% and 2% overall yield respectively from L-glutamic acid. In the following Table, the ^1H and ^{13}C NMR data for the four stereogenic centers of compounds **11** and **12** as well as for murisolin and annonacin A are reported.

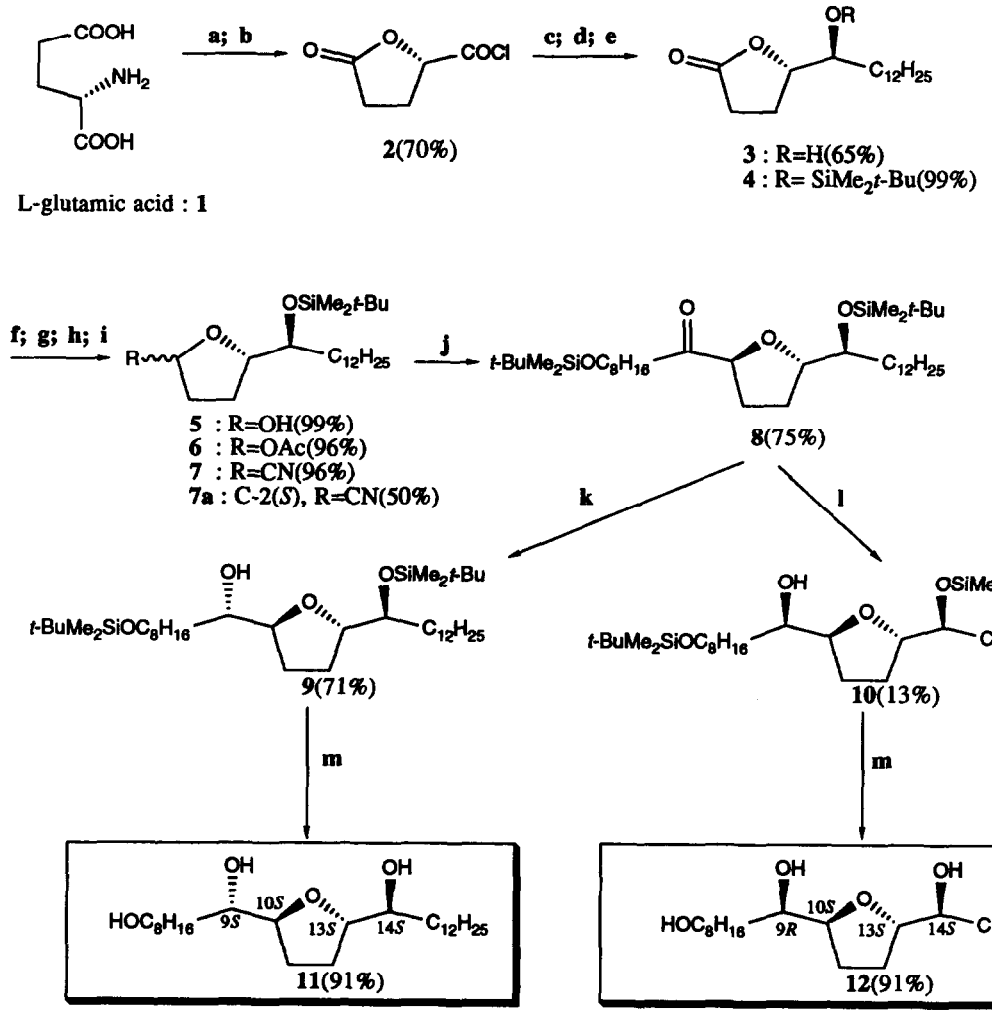
Chemical shifts ^1H NMR (200 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$)



	HC-1'		HC-2		HC-5		HC-1''	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
11 (*threo-trans-threo*)	3.41	74.04	3.80	82.71	3.80	82.71	3.41	74.01
12 (*erythro-trans-threo*)	3.82	71.56	3.82	83.24	3.82	82.15	3.38	74.33
murisolin (*threo-trans-threo*)	3.38	74.2	3.76	82.7	3.76	82.7	3.38	74.2
annonacin A (*erythro-trans-threo*)	3.82	71.62	3.82	83.32	3.82	82.31	3.40	74.36

The NMR data show without any ambiguity that the two compounds **11** and **12** present large

Figure 1



a : $NaNO_2$, H_3O^+, 20°C; **b** : $(COCl)_2$, DMF cat., 20°C; **c** : $C_{12}H_{25}MgBr$, THF, -78°C; **d** : L-Selectride,THF -78°C; **e** : TBDMSCl, imidazole, DMF, 20°C; **f** : DIBAL, toluene, -78°C; **g** : $(Ac)_2O$, Et_3N, 20°C; DMAP **h** : TMSCN, $TrClO_4$ cat., Et_2O, 0°C; **i** : Silica gel separation; **j** : t-Bu$(Me)_2SiO(CH_2)_8MgBr$,toluene, -78°C; **k** : L-Selectride,THF,-78°C; **l** : $NaBH_4$, EtOH, 4°C; **m** : TBAF, THF, 20°C.

differences for the chemical shifts for C-1' both in $^{1}H(\Delta\delta=0.41)$ and ^{13}C NMR($\Delta\delta=2.6$). With these observations in hand it is possible to confirm for the first time the relative stereochemistry of the known monotetrahydrofuran acetogenins as *threo-trans-threo* for most of the natural products, except for annonacin A and jetein which present the same relative stereochemical relationship *erythro-trans-threo* across the tetrahydrofuran ring.

The coupling reaction of these two synthons **11** and **12** with the lactone fragment[9] bearing the desired absolute configuration at C-34 has thus been sucessfully performed. This approach allows us to obtain the monotetrahydrofuran acetogenins with all the possible *absolute* stereochemical relationships across the tetrahydrofuran ring and the lactone fragment in a sufficient amount for biological assays and structure-activity relationship studies[10].

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References and notes

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6) Other Lewis acids ($LiClO_4$, $BF_3.OEt_2$) give the desired products in lower yields.

7) The trans relationship has been proved by ^{1}H NMR (Noe). The *cis* nitrile afforded in the same conditions the desired *cis* ketone as the major product.

8) All intermediates gave spectroscopic data in agreement with the proposed structures. Selected data for compounds **11** and **12** are given. **11** : $[\alpha]^{25}_{D}$=+10 (c=2.5, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, ref. to $CHCl_3$) δ ppm; 0.87 (t, J=6.3Hz, 3H), 1.20-1.60 (m, 36H), 1.62 (m, 2H), 1.90 (m, 2H), 1.80-2.50 (OH), 3.41 (q, J=5.3Hz, 2H), 3.63 (t, J=6.5Hz, 2H), 3.80 (q, J=6.8Hz, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm; 14.06, 22.63, 25.49, 25.54, 25.67, 28.75, 29.30, 29.46, 29.56, 29.60, 29.68, 31.87, 32.71, 33.35, 62.86, 74.01, 74.04, 82.71. IR(solution in $CHCl_3$) cm^{-1} : 3500-3200, 1480, 1400, 1050. MS-ci-NH_3 (%) : 446 ($M+NH_4^+$, base), 429 (MH^+, 87), 393 (2), 269 (5), 176 (24). **12** : $[\alpha]^{25}_{D}$=+9 (c=0.53, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$, ref. to $CHCl_3$) δ ppm; 0.87 (t, J=6.3Hz, 3H), 1.20-1.40 (m, 32H), 1.60 (m, 6H), 1.90 (m, 4H), 2.00-2.40 (OH), 3.38 (q, J=5.5Hz, 1H), 3.62 (t, J=6.5Hz, 2H), 3.82 (m, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm; 14.08, 22.66, 25.29, 25.56, 25.67, 25.91, 28.58, 29.31, 29.43, 29.62, 31.89, 32.52, 32.75, 33.24, 63.00, 71.56, 74.33, 82.15, 83.24.IR(solution in $CHCl_3$) cm^{-1} : 3500-3200, 1480, 1400, 1050.

9) Harmange J.-C., Figadère B., Hocquemiller R., *Tetrahedron : Asymmetry*, **1991**, *2*, 347-350.

10) The details and experimental procedures will be published in a forthcoming paper.

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