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First Synthesis of a New Acetogenin of Annonaceae, Reticulatamol : Activated Tin Hydride with Enhanced Reducing Ability

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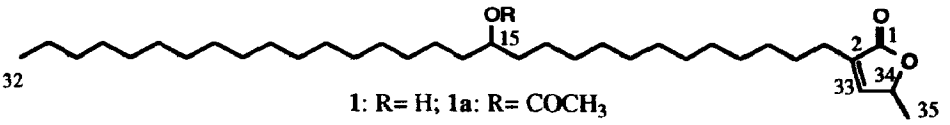
Key words: acetogenins; Annonaceae; isolation; synthesis; radicals; reduction of ketones

Abstract: *A new annonaceous acetogenin, reticulatamol 1, is described. In order to confirm its structure, its total synthesis has been performed, using as a key step a radical coupling reaction between an alkyl iodide and an enone, followed by an original reduction of the so obtained ketone to yield the desired natural product.*

Acetogenins of Annonaceae belong to a rapidly growing family of bioactive natural compounds, which are characterized by the presence of typical structural features such as tetrahydrofuran rings (THF), γ-methyl-γ-lactone, hydroxy groups and an alkyl chain of 35 to 37 carbon atoms[1]. In addition to these now well known acetogenins, new natural products have been isolated in which tetrahydrofuran rings have been replaced by epoxides and/or double bonds[2]. We have demonstrated that such compounds can rank among the natural precursors of acetogenins, because of their chemical transformations to the corresponding mono- or bis-THF acetogenins[3,4]. In continuation of our investigation of the natural precursors of such cytotoxic products[1], we succeeded in the isolation of a new Annonaceous acetogenin from *A. reticulata*, reticulatamol **1**. Its structure has been determined by classical spectroscopic means (^1H, ^{13}C NMR, MS and FAB-Li MS) and confirmed by its total synthesis.

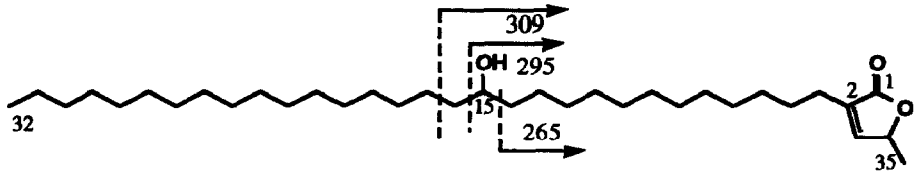


1: R= H; **1a**: R= $COCH_3$

Reticulatamol **1** was isolated from the seeds of *A. reticulata* as an amorphous white solid ($[\alpha]_D$=+2 c=1, $CHCl_3$). The molecular weight was indicated by a peak at m/z 541 $[M+Li]^+$ in FAB-Li MS[2] and m/z 535 $[MH]^+$ in CIMS, corresponding to the molecular formula, $C_{35}H_{66}O_3$. The existence of the hydroxyl group was indicated by an IR absorption at 3350 cm^{-1} and loss of H_2O from MH^+ in both the FABMS and CIMS, and by the preparation of the acetate **1a**. The presence of the γ-methyl substituted unsaturated γ-lactone was confirmed by IR (absorption at ν_{max} 1750 cm^{-1}), UV (EtOH, λ_{max} 206 nm, log ε= 1.011) and the typical chemical shifts of the corresponding proton and carbon resonances in the ^1H and ^{13}C NMR spectra of **1**[5]. The lack of tetrahydrofuran, epoxide and double bonds was indicated by the absence of any typical pattern for the resonances of the

corresponding proton and carbon in the ^{1}H and ^{13}C NMR spectrum, respectively. MS fragmentation analyses of **1** and **1a** demonstrated that the OH was located at C-15 (Scheme 1).

Scheme 1: MS-EI Fragmentation of **1**



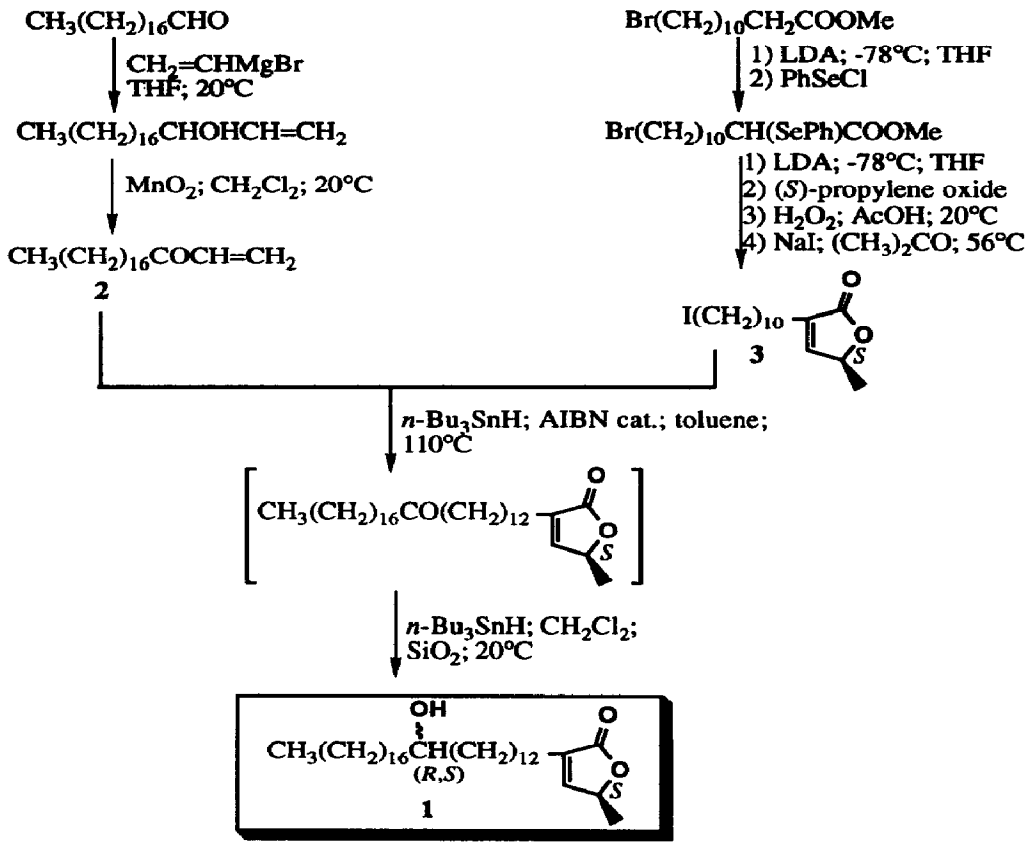
To confirm the location of the hydroxyl group and to tentatively attribute absolute configurations to the asymmetric centres, we decided to stereospecifically synthetize **1**. The configuration at the methyl carbinol was anticipated to be 34*S* on the basis of a possible analogy to other acetogenins[1]. The pathway we used is depicted on scheme 2 and is based on the key step : namely a radical coupling of a primary alkyl iodide with an electron deficient double bond[6]. This required to prepare enone **2** and iodo lactone **3** as a single enantiomer.

Enone **2** was obtained from octadecanal after addition of one equivalent of vinylmagnesium bromide, followed by oxidation of the allylic alcohol so obtained with MnO_2 to afford **2** in 83% overall yield (2 steps).

Lactone **3** was prepared as a single enantiomer from methyl 12-bromododecanoate, which after enolization with one equivalent of LDA followed by addition of phenylselenium chloride, gave the desired selenoderivative in 88% yield. A second enolization with LDA, followed by addition of (*S*)-propylene oxide afforded the desired lactone which upon oxidation with H_2O_2 gave rise to the α,β-unsaturated γ-lactone in 50% yield for the last 3 steps. Displacement of bromine by iodine in acetone gave the iodo compound **3** ($[\alpha]_D$=+9, c= 0.62, $CHCl_3$) in quantitative yield which is used for the next step without further purification. The coupling reaction of 2 eq. of enone **2** with 1 eq. of iodo lactone **3** was performed under standard free radical-generating conditions[7], by slow addition (in 2 h) of 3 eq. of tri-*n*-butyltin hydride and a catalytic amount of AIBN, in toluene under reflux. After 3 more hours, the reaction mixture was cooled down to room temperature and the solvent evaporated under reduced pressure. The crude material was analyzed by ^{1}H NMR (presence of typical triplet at δ 2.38 ppm corresponding to the methylenes at C-14 and C-16, α to the carbonyl of the ketone) which confirms the presence of the coupled product. The residue was then submitted to a purification by column chromatography on silica gel with CH_2Cl_2 as eluent. *Surprisingly*, instead of the oxo-derivative we isolated the reduced compound(s) in 56% yield from **3**, without any product resulting of the reduction of the unsaturated γ-lactone. Indeed we assume that *n*-Bu_3SnH in the presence of SiO_2 in CH_2Cl_2 can reduce a carbonyl of a ketone, by complexation of SiO_2 with tin atom which increases the reducing ability of *n*-Bu_3SnH, as it has been reported for the complexation with tetraalkyl amonium halides[8]. Therefore, in order to confirm this unexpected result we submitted a ketone ((4*S*)-5-acyl-heptadecabutanolide **4**) to different reducing procedures with *n*-Bu_3SnH in CH_2Cl_2 (Scheme 3 and table 1) without catalyst (entry 1), with *n*-Bu_4NF (entry 2) and with SiO_2 (entry 3); in the latter case we observed a clean reduction of the carbonyl of the ketone to afford the natural product (+)-muricatacin **5**[9] and its epimer **6** in a 28/72 ratio and 80% combined yield[10], whereas no reaction was observed in the lack of any catalyst and over reduction with *n*-Bu_4NF.

^{1}H, ^{13}C NMR, IR and UV spectra of the synthesized product(s) are identical with spectroscopic data of reticulatamol **1**. Comparison of the FAB-Li MS of compounds obtained either by extraction or total synthesis allows us to confirm the hydroxyl position at C-15. The optical rotation of synthesized reticulatamol ($[\alpha]_D$= +3,

Scheme 2



Scheme 3

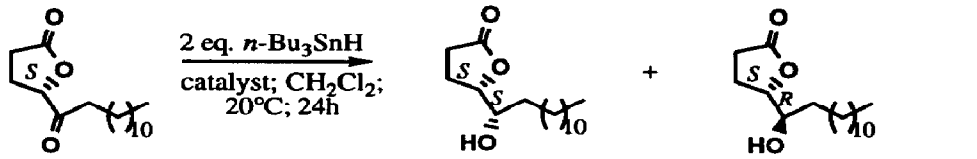


Table 1

entry	catalyst	Ratio 5/6	Yield (%)
1	none	-	0[a]
2	*n*-Bu_4NF[b]	-	0[c]
3	SiO_2[d]	28/72	80[e]

a) 4 is recovered unchanged; b) 1 eq.; c) complex mixture; d) SiO_2/4=20g/1g; e) not optimized

c= 0.3, $CHCl_3$) differs from the $[\alpha]_D$ of natural reticulatamol **1**, since we suppose we obtained a diastereomeric mixture at C-15 (mixture of (15*S*, 36*S*) and (15*R*, 36*S*) compounds)[11].

In conclusion we have succeeded in (i) isolating the first acetogenin which does not possess any of the usual structural features (THF, epoxide, double bonds), (ii) synthesizing this new natural product as a supposed diastereomeric mixture[12] and (iii) developing an improved procedure for the chemoselective reduction of the carbonyl group of a ketone in mild conditions with *n*-Bu_3SnH in CH_2Cl_2 (no additives such as Bu_3PO, Lewis acid, neither high temperatures in polar solvents)[10].

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5 **1** : $[\alpha]_D$ =+2, c= 1, $CHCl_3$; mp : 92-94°C (heptane); IR (ν_{max} cm^{-1}): 3350, 1750; UV (EtOH): λ_{max} 206 nm, logε= 1.011 ; ^1H NMR (200MHz, in $CDCl_3$, ref. to $CHCl_3$, δ ppm): 6.98 (d, J=1.5Hz), 5.00 (qd, J=6.7, J=1.5Hz), 3.58 (m), 2.26 (t, J=7.2Hz), 1.42 (d, J=6.7Hz), 1.35-1.20 (m), 0.88 (t, J=6.6Hz); ^{13}C NMR (50MHz, in $CDCl_3$, ref. to $CHCl_3$, δ ppm): 173.9, 148.9, 134.5, 77.5, 72.2, 37.7, 32.1, 29.8, 29.4, 29.3, 27.6, 25.8, 25.3, 22.8, 19.3, 14.2; EIMS (70 ev) 534 (M^+), 516, 309, 295 (base), 281, 266; CIMS (isobutane) 535 (MH^+), 517 (M-H_2O), 489; FAB-Li MS: 545 (M+Li).

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10 Developments of this improved reducing procedure of ketones with *n*-Bu_3SnH are under way in our laboratory.

11 ^1H and ^{13}C NMR spectra do not allow us to conclude about the stereoselectivity of the reaction. It is therefore impossible to conclude about the absolute configuration at C15 of naturally occuring or synthesized reticulatamol **1**.

12 Following the same strategy, we have also succeeded in the synthesis of **7** ($C_{37}H_{70}O_3$, $[\alpha]_D$= +4, c= 6, $CHCl_3$), a natural analog of reticulatamol **1**, but possessing 37 carbon atoms and an OH at C-15, that we have noticed in trace amount with **1**, in a natural extract from the seeds of *A. reticulata*. Spectroscopic data of **7** are in accord with those obtained for **1**.

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