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Synthesis of 2,33-Dihydro-4-Oxo-Murisolin : Conjugate Addition of Primary Alkyl Iodides to α,β-Unsaturated Ketones

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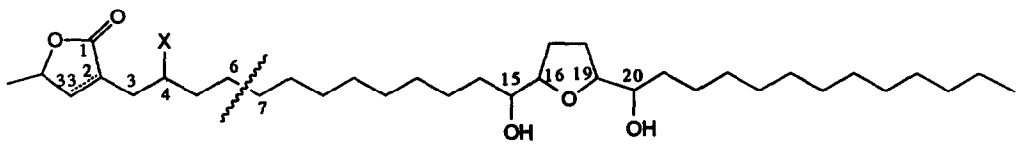
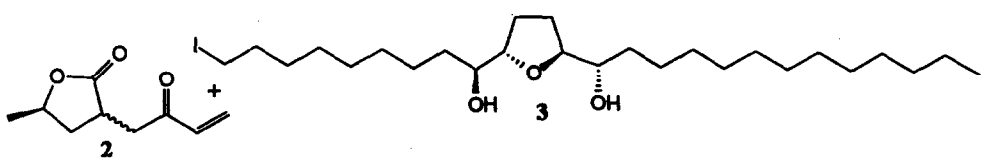
Key words: Free Radicals; Conjugate Addition; Tetrahydrofurans; Acetogenins.

Abstract: *A synthesis of the title compound is described. The conjugate addition of highly functionalized primary alkyl iodide to enone allows us to obtain a precursor of the monotetrahydrofuran acetogenin murisolin.*

During the past few years we were currently engaged in a synthetic program to prepare cytotoxic monotetrahydrofuran γ-lactone acetogenins[1]. So far, we have been working on the preparation of the tetrahydrofuran ring and reported a very efficient stereocontrolled synthesis of 9(*S*),10(*S*),13(*S*),14(*S*) 1,9,14-trihydroxy 10,13-epoxyhexacosane[2], as well as a preparation of opticaly pure γ-lactones substituted at C-2 position[3]. The remaining problem was to couple the two synthons in order to obtain **1**, the oxo-precursors of monotetrahydrofuran γ-lactone acetogenins, which after further reduction of the carbonyl group will produce either 2,33-dihydrosolamin[4] or 2,33-dihydromurisolin[5]. The retrosynthetic approach used was to create the last carbon-carbon bond between C-6 and C-7 of the acetogenin. This method required to prepare in a stereocontrolled manner the two synthons **2** and **3** with the desired configurations at the chiral centers.

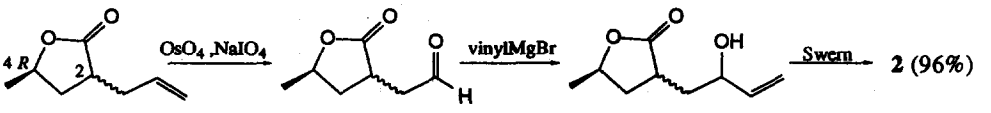


X= O : **1**; X= OH : murisolin; X= H : solamin

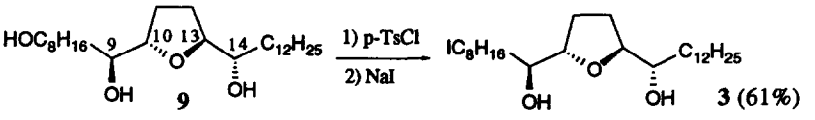


2 was obtained as a 90/10 *cis-trans* mixture from the mixture of (2*R*,4*R*) and (2*S*,4*R*) 2-(3-propenyl)-4-methyl-4-butanolides **6**[3] in three steps. Oxidation of **6** with $OsO_4/NaIO_4$, followed by addition of one equivalent of vinylmagnesium bromide afforded the desired allylic alcohols **8** which upon treatment

under Swern conditions[7] gives **2** as an inseparable mixture of (2*R*,4*R*) and (2*S*,4*R*) 2-(2-oxo-3butenyl)-4-methyl-4-butanolides.

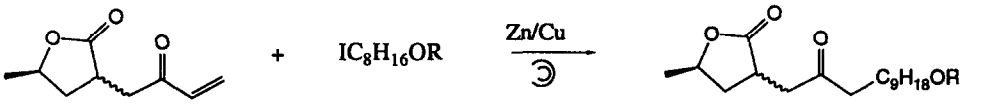


3 was prepared from the corresponding triol **9** (namely 9(*S*),10(*S*),13(*S*),14(*S*) 1,9,14-trihydroxy 10,13-epoxyhexacosane)[2] after mono-tosylation of the primary hydroxyl group at low temperature (+4°C), followed by iodine displacement of the tosylate function by NaI.



With **2** and **3** in hand, we then studied the coupling reaction between these two synthons in order to obtain **1** the oxo-precursors of monotetrahydrofuran γ-lactone acetogenins of Annonaceae.

Conjugate addition of organometallic or radical species to α,β-unsaturated ketones are particulary attractive methods. Indeed these methods retained our attention for their efficiency, since both of our synthons were highly functionalized and bearing several chiral centers with their absolute configurations unambigously fixed. Recently Luche *et all.* have shown that alkyl halides add smoothly to α,β-unsaturated carbonyl compounds in the presence of zinc-copper couple in an alcoholic-water medium under sonication[6]. These authors have studied the influence of the solvents (in particular the need of water) on the rate of the reaction and furthermore found that primary halides are less reactive than secondary halides. Therefore, in order to optimize these reaction conditions, we studied the coupling reaction between enone **2** and alkyl halides **4a-b**, before to apply this method to our highly valuable starting material **3**.



2

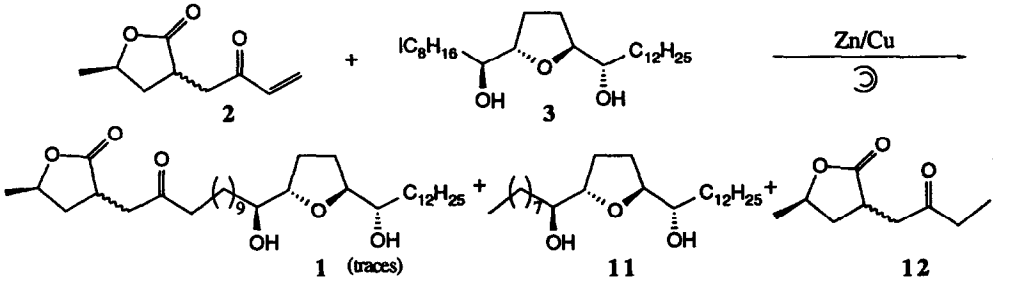
4a : R= H
4b : R= $SiPh_2t$-Bu

5a : R= H
5b : R= $SiPh_2t$-Bu

We found that the best conditions for the above reaction was to use a mixture of **4a** and **2** with Zn and CuI in the ratio : 1:1.5:1:1.5, respectively, with the binary system EtOH/H_2O (7:3). Indeed, after 1.5 h of sonication, **5a** was obtained in 53% yield. This result is noteworthy since Luche *et all.* have shown that primary iodides give low yields of the adduct products. Furthermore, we found there were no need to use a large excess of enone **2** (1.5 eq.) neither to protect the hydroxyl group since we obtained **5b** in the same

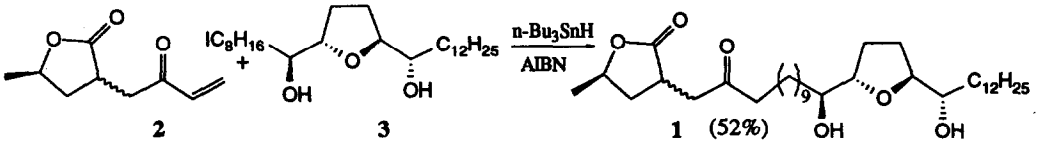
yield than **5a**. After these promising results, we thus decided to apply this procedure to the conjugate addition of our synthon **3** to the enone **2**.

Unfortunately several attempts to realize the coupling between **2** and **3** under the same conditions than described above failed to give the desired product in reasonable yields.



Instead, the products resulting of the reduction of the starting materials were obtained in high yields. This can can be rationalized by the formation of chelated species of the metallated intermediate **3'** lowering drastically its reactivity toward the enone, which then in a protic medium is finally hydrolysed to produce the reduced compound **11**[8a]. In the other hand, it is quite surprinsing to observe the clean reduction of the double bond of the enone, since it never has been reported as a side reaction by others[8b].

We then decided to study the coupling reaction under standard free radical-generating conditions with tri-*n*-butyltin hydride with a catalytic amount of AIBN[9]. In our case, the best reaction conditions were the following : compound **3** (0.21mmol) and **2** (0.62mmol) in toluene (6mL) were heated to reflux. Then a diluted solution of *n*-Bu_3SnH (0.031M, 0.74mmol, 24mL) with a catalytic amount of AIBN was added dropwise (over a period of 3 h). After one more hour under reflux, the reaction mixture was cooled down to room temperature. After evaporation of the solvents, the residue, after flash chromatography on silica gel (MeOH/AcOEt/C_6H_{12}; 10:20:70), gave **1**[10] ($[\alpha]_D$=+17 c=1.0,$CHCl_3$) in 52% yield. We found that the rate of the addition and the concentration were crucial for the yield of the reaction. Optimization of this procedure is still under investigations, since some unreacted enone is recovered along with polymers at the end of the reaction.



In conclusion, the free radical method provides good yields of the desired adduct of the conjugate addition of a highly functionalized alkyl iodide bearing several chiral centers to an α,β-unsaturated ketone. Thus, the desired oxo-precursors **1** of murisolin was obtained in fairly good yield, as a 58/42 diastereomeric mixture. The coupling reactions of epimers of **2** and **3** have been performed with sucess so

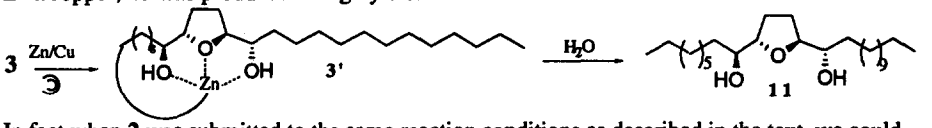
far. Stereoselective reduction of the carbonyl and introduction of the unsaturation in the lactone ring, in order to obtain murisolin and solamin, are curently under way in this laboratory. These results, with the structure-activity relationship of natural and un-natural acetogenins so obtained, will be published somewhere else in due course.

Acknowledgment : This work was sponsored by the CNRS and the Direction de la Recherche et des Etudes Doctorales through a biennial contract with the Réseau de Recherche de Pharmacochimie. We wish to thank Mrs. J. Mahuteau for NMR experiments and Pr. D. Cortes for fruitful discussions.

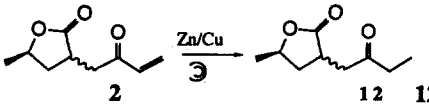
References and notes

1) For a review on acetogenins see : Rupprecht J.K., Hui Y.H., McLaughlin J.L., *J. Nat. Prod.*, **1990**, *53*, 237-278.
2) Harmange J.-C., Figadère B., Cavé A., *Tetrahedron Lett.*, in press.
3) Harmange J.-C., Figadère B., Hocquemiller R., *Tetrahedron : Asymmetry*, **1991**, *2*, 347-350.
4) Myint S.H., Cortes D., Laurens A., Hocquemiller R., Leboeuf M., Cavé A., Cotte J., Quero A.-M., *Phytochemistry*, **1991**, *30*, 3335-3338.
5) Myint S.H., Laurens A., Hocquemiller R., Cavé A., Davoust D., Cortes D., *Heterocycles*, **1990**, *31*, 861-867.
6) Petrier C., Dupuy C., Luche J.-L., *Tetrahedron Lett.*, **1986**, *27*, 3149-3152; Luche J.-L., Allavena C., *ibid.*, **1988**, *29*, 5369-5372; Einhorn C., Einhorn J., Luche J.-L., *Synthesis*, **1989**, 787.
7) Mancuso A.J., Swern D., *Synthesis*, **1981**, 165-185.

8a) When **3** was sonicated for several hours in a mixture alcohol/water in the presence of the couple zinc/copper, **11** was produced in high yield.



b) In fact when **2** was submitted to the same reaction conditions as described in the text, we could isolate, after 1 h, the corresponding reduced products **12** in quantitative yield. The generalization of this method to reductions of other α,β-unsaturated ketones is under investigation in this laboratory.



2 **12** **12** (as a 90/10 diastereomeric mixture) : [in bracked are given the values for the minor isomer.] ^{1}H-NMR (200 MHz, $CDCl_3$, ref. to $CHCl_3$) δ ppm; 1.05 (t, J=7.5Hz, 3H), 1.38 (d, J=6.3Hz, 3H), [1.43(d, J=5Hz, 3H)], 1.90-2.20 (m, 2H), 2.45 (m, 2H), 2.55 (m, 2H), 3.05 (m, 1H), 4.73 (m, 1H), [4.52, (m, 1H)]. ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm; 7.63, [20.76], 21.14, 34.31, 34.76, 35.95, [37.13, 37.22, 42.34], 42.63, 75.02, [75.51], 178.73, 208.34. IR(solution in $CHCl_3$) cm^{-1} : 1760, 1715.

9) Giese B., *Radicals in Organic Synthesis : Formation of Carbon-Carbon Bonds*, Ed. J. E. Baldwin, Pergamon, Oxford, **1986**.

10) All new compounds gave satisfactory analytical and spectral data; Selected data for compound **1**, as 58/42 diastereomeric mixture, are given : $[\alpha]^{25}_D$=+17 (c=1.0, $CHCl_3$); Mp : 89°C; ^{1}H-NMR (200 MHz, $CDCl_3$, ref. to $CHCl_3$) δ ppm; 0.86 (t, J=6.5Hz, 3H), 1.08-1.80 (m, 46H), 1.87-2.28 (m, 3H), 2.32-2.73 (m, 5H), 2.90-3.19 (m, 2H), 3.28 (m, 2H), 3.70-3.90 (m, 2H), 4.44-4.61 (m, 2H), 4.64-4.80 (m,1H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ ppm; 14.1, 20.8, 21.2, 22.7, 23.8, 25.6, 28.7, 29.1, 29.3, 29.5, 29.6, 31.9, 33.5, 34.3, 34.8, 37.1, 37.3, 42.8, 43.1, 74.0, 75.1, 75.5, 82.6, 178.4, 178.8, 208.1. IR(in KBr) cm^{-1} : 3600-3100, 3060-2800, 1750, 1700. MS-ci-NH_3 (%) : 598 ($M+NH_4^+$, 31), 363 (11), 328 (52), 311 (base), 156 (14), 113 (8).

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