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Catalytic Hydrogenation of Annonaceous Acetogenins

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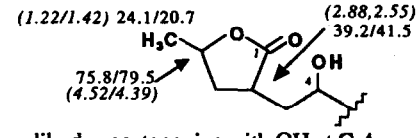
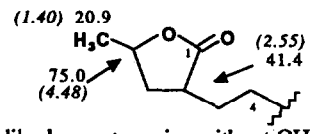
Key Words: catalytic hydrogenation; tetrahydrofuranic γ-lactone acetogenins; diastereoselection.

***Abstract:** Catalytic hydrogenation of cytotoxic Annonaceous acetogenins afforded two or one diastereomers whether the γ-unsaturated lactone acetogenin possesses or not an hydroxyl group at the 4-position.*

In order to confirm and attribute fragment ions in MS experiments of some bioactive tetrahydrofuran (THF) α,β-unsaturated γ-lactones acetogenins[1], corossolin, solamin, annonacin and annonacinone (mono-THF/C35)[2], and motrilin, cherimolin-1, squamocin and rolliniastatin-2 (bis-THF/C37)[3], were hydrogenated over Pd/C. Therefore each peak involving the lactone ring increases its mass by 2 a.m.u. after hydrogenation. The catalytic hydrogenation was performed in a methanolic solution with 10% Pd/C at room temperature under an atmospheric pressure of H_2 for 2 hours in quantitative yields. Examination of ^1H and ^{13}C NMR spectra of hydrogenated acetogenins shows that whenever there is an OH at position 4, a 1:1 mixture of two diastereomers (the *cis* and the *trans* products) are obtained, whereas only one of them is obtained with acetogenins non-hydroxylated at C-4. ^{13}C NMR and ^1H NMR (in bracked) of either diastereomer are reported below (assignments were deduced by 2D, COSY 45 and XH CORR, experiments).

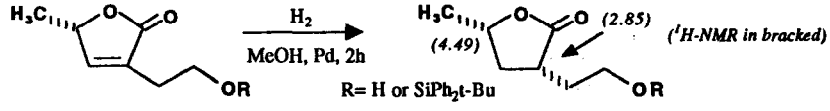


dihydro-acetogenins with OH at C-4

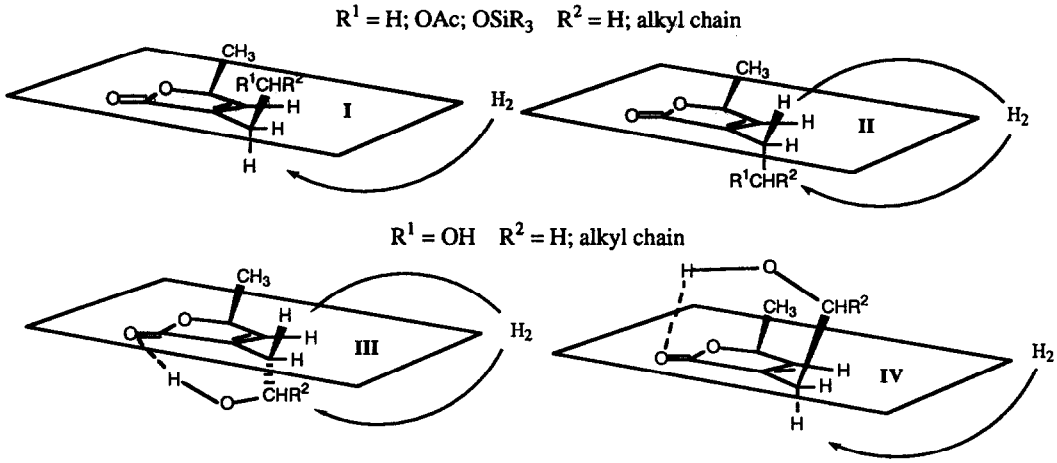


dihydro-acetogenins without OH at C-4

When the γ-lactones **1a,b** [4] are hydrogenated in the same conditions than described above, we obtained in both cases only the *cis* isomer.



The *cis* relationships was established by NMR and confirmed by comparison with our own results [4] and those observed by Hoye *et al.* [5]. The stereospeficity of the reaction may be explained by the methyl influence and the H-bonding between the hydroxyl at C-4 position and the carbonyl of the lactone. To tentitatively rationalize those observations, we represented 4 more favorable conformers of the starting materials, due to 1,3-allylic strain, and assume than after complexation of the less hindered face with palladium they produce the corresponding hydrogenated compounds.



Undoubtedly, conformers (I) and (IV) present one of the two faces more accessible, while in conformers (II) and (III) both faces are similarly hindered at both allylic positions by CH_3 at C-34 (or C-36) and by CHR^2OH at C-3. In fact when there is no H-bonding possible (R^1 is either H or OAc or $OSiR_3$ and R^2 is H or an alkyl chain) the two conformers (I) and (II) are in equilibrium but (I) with one face more accessible can better complex palladium and therefore affords a single isomer after hydrogenation. Stabilization of the molecules by H-bonding, can be represented by conformers (III) and (IV). When R^1 is OH and R^2 equal to H, then (III) and (IV) are within 0.1 kcal/mole, but complexation being probably more feasable with (IV), produces only the *cis*-isomer after hydrogenation. When R^1 is OH and R^2 an alkyl chain, because of steric hindrance conformer (IV) is higher in energy than (III) which affords a mixture of both isomers after hydrogenation. In order to confirm the influence of the possible hydrogen bonding, hydroxyl groups of natural acetogenins were acetylated prior to hydrogenation. As expected, a single diastereoisomer was obtained after hydrogenation.

It is interesting to note here the published results of Born *et al.*[6]. In the X-ray crystallographic study of hydrogenated squamocin (acetogenin without OH at C-4), crystallized as potassium salt, they found only one hydrogenated product. These observations may be used as a very useful method to confirm the presence (or the lack) of an hydroxyl group at the 4 position of unknown mono- or bis-THF acetogenins. By extending these results, if we assume the absolute configuration at C-36 to be *S* for these accetogenins, as it is the case for desacetyluvaricin[7], the configurations of hydrogenated acetogenins 4-OH-free are 2R,36S for C_{37} compounds and 2R,34S for C_{35} compounds; and for hydrogenated 4-OH-acetogenins 2R,36S and 2S,36S for C_{37} compounds and 2R,34S and 2S,34S for C_{35} compounds.

References and Notes

1. Rupprecht, J.R; Hui, Y.-H.; McLaughlin, J.L. *J. Nat. Prod.* **1990**, *53*, 237-278.
2. Myint, S.H.; Cortes, D; Laurens, A.; Hocquemiller, R.; Lebœuf, M.; Cavé, A.; Cotte, J.; Quéro, A.M. *Phytochemistry* **1991**, *30*, 3335-3338.
3. Cortes, D.; Myint, S.H.; Hocquemiller, R. *Tetrahedron* **1991**, *47*, 8195-8202.
4. Harmange, J.C; Figadère, B; Hocquemiller, R. *Tetrahedron : Asymmetry* **1991**, *2*, 347-350.
5. Hoye, T.R; Hanson, P.R. *J. Org. Chem.* **1991**, *56*, 5092-5095.
6. Born, L.; Lieb, F.; Lorentzen, J.P., Moeschler, H.; Nonfon, M.; Söllner, R.; Wendisch, D. *Planta Med.* **1990**, *56*, 312-316.
7. Jolad, S.D.; Hoffmann, J.J.; Cole, J.R.; Barry III, C.E.; Bates, R.B.; Linz, G.S.; Konig, W. *J. Nat. Prod.* **1985**, *48*, 644-645.

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