Pergamon

Tetrahedron Letters 39 (1998) 8077–8080

TETRAHEDRON LETTERS

Study of Butyrolactones Related to Sub-type 3 Annonaceous Acetogenins. Structure Revision of Itrabin, Jetein, Laherradurin and Otivarin.

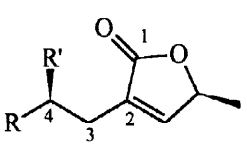
Erwin Warmerdam, Isabelle Tranoy, Brigitte Renoux and Jean-Pierre Gesson*

Laboratoire de Chimie 12, Université de Poitiers et CNRS, 40, Avenue du Recteur Pineau, F-86022 Poitiers (France)

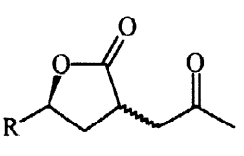
Received 17 August 1998; accepted 24 August 1998

Abstract : Starting from 5(*S*)-hydroxymethyl-γ-butyrolactone **1**, lactones related to title acetogenins have been prepared in few steps. This study leads to a structure revision of the lactone configurations of these acetogenins.

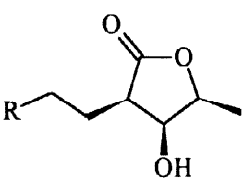
Annonaceous acetogenins represent a large class (*c.a.* 300) of natural products which display potent cytotoxic, immunosuppressive, pesticidal and insecticidal properties.[1] The main structural features of these fatty acid derived compounds are the presence of one to three tetrahydrofuran rings (or in one case a tetrahydropyran) and a terminal lactone moiety. Four different lactones are usually found: sub-types 1a and 1b are 2,4-disubstituted butenolides (1b bears an extra hydroxyl group at C-4),[2] sub-type 2, an alleged artifact which has been shown to result from base-catalysed rearrangement of sub-type 1b (a 2/1 cis-trans ratio is usually obtained after extraction and purification)[2] and the more scarce sub-type 3, only present in otivarin, laherradurin,[3] itrabin and jetein.[4] Indeed, several other naturally ocurring 2-alkyl-3-hydroxy (or acyloxy)-4-methyl butyrolactones are known, such as grandinolide,[5] blastmycinone,[6] antimycinone,[7] NFX-2, NFX-4[8] and some other lipid metabolites.[9]



sub-type 1a R= H
sub-type 1b R= OH

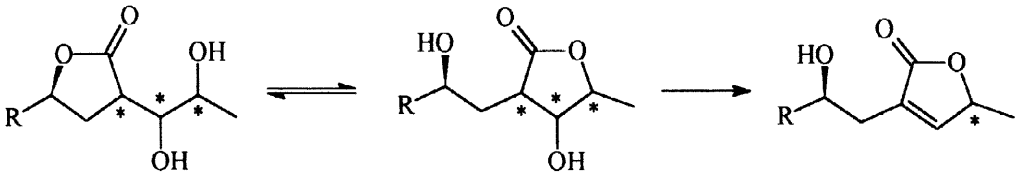


sub-type 2 (*cis* + *trans*)



sub-type 3

Several strategies have been already developped to prepare lactone synthons related to sub-types 1a,b[1] and 2.[10] Indeed, we became interested in preparing lactones **A** which should be in equilibrium with lactones **B** related to sub-type 3 wih hydroxyl group at C-2'. The effect of relative configurations on this equilibrium and,

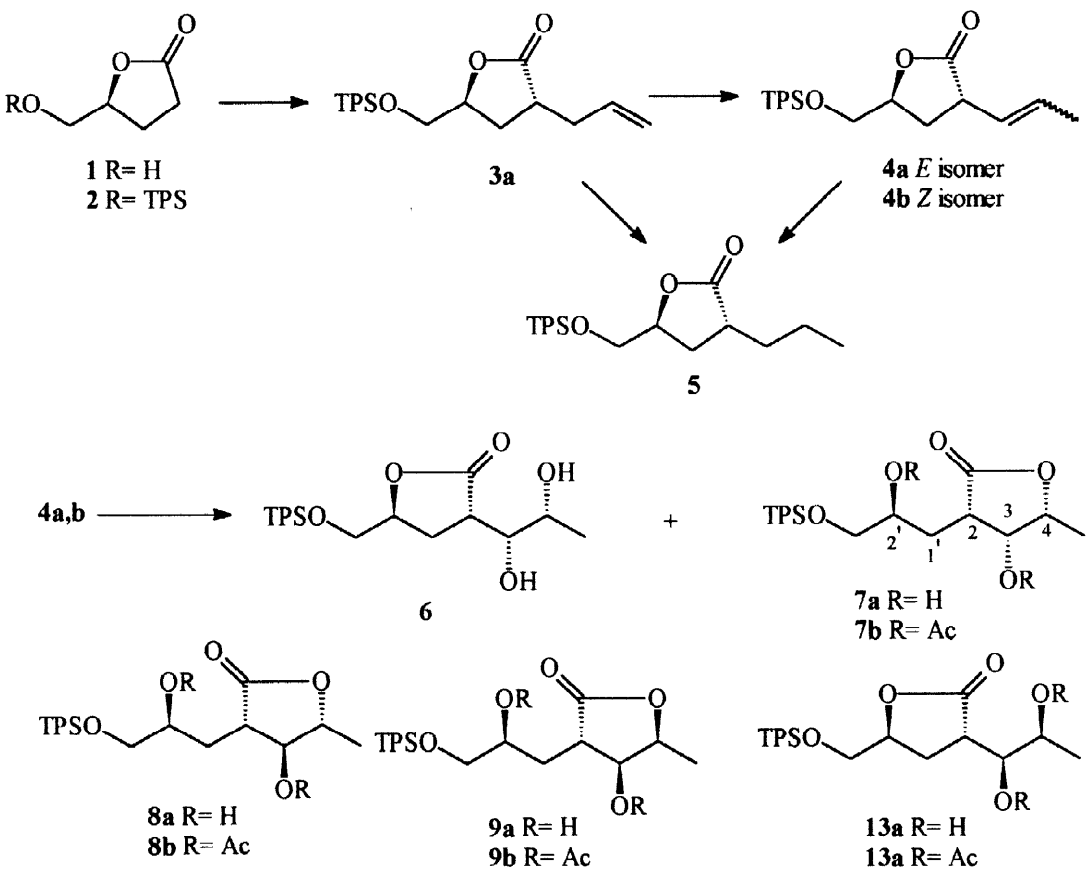


A **B** sub-type 1b

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01786-9

later, conversion of **B** to sub-type 1b lactones and analogs will be studied.

Preliminary results are now reported starting from the commercially available 5(*S*)-hydroxymethyl-γ-butyrolactone **1** (ee 98%) as a model of the 5(*R*)-alkyl butyrolactone moiety of annonaceous acetogenins. After protection as a TPS ether (91%), alkylation of the lithium enolate of **2** with 1.5 eq of allyl iodide (LDA 1.05 eq., -78 to -40°C, THF) gave the *trans* lactone **3a** (81%) together with the *cis* isomer **3b** (9.5%) in agreement with previous reports.[11] Upon heating in EtOH-H_2O in presence of cat. $(PPh_3)_3RhCl$ for 5 h, **3a** afforded in 70-80% yield a 8/1 mixture of *E* and *Z* lactones **4a** and **4b** (together with 7-10% of unchanged starting material). The *trans* configuration of lactones **4a** and **4b** was secured by hydrogenation over Pd/C to **5** which turned out to be identical to the compound obtained from **3a** by similar reduction. Since separation of these lactones was difficult using flash-chromatography over silica (**4a** and **4b** were isolated respectively in only 39% and 5% isolated yields), asymmetric dihydroxylation was carried on the 8/1 mixture obtained above for higher efficiency.



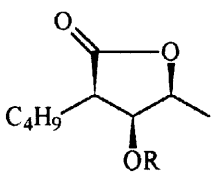
Upon treatment with $K_2OsO_2(OH)_4$ (0.002 eq.), hydroquinidine 1,4-phthalazinediyl diether (0.01 eq.), $K_3Fe(CN)_6$ (3 eq.) and K_2CO_3 (3 eq.) [AD-mix-β],[12] **4a,b** (*E*/*Z*: 8/1) gave mainly lactones **6** (16%) and **7a** (54%) together with minor amounts of **8a** (4%) and **9a** (3%). The rearranged structure of **7a** was deduced from ^1H-^1H COSY experiments. At this stage examination of *J* between H-3 and H-4 was not possible due to signal overlap and this was done after acetylation to **7b**. ^1H NMR data of **7a** and **7b** were identical,

respectively, to those reported by Node[13] for (-)-3-*epi*-blastmycinol **10a** and (-)-3-*epi*-blastmycinone **10b**. Furthermore, the observed ^3J between H-2, H-3 and H-4 were found to be similar to those of the 2,4-dimethyl-3-hydroxy–γ-butyrolactone possessing the same relative configurations and clearly different from data of the three other diastereoisomers.[14] This result is in agreement with the expected formation of the *R,R* diol with AD-mix-β. Then, the structure of **6** could be easily deduced since upon exposure to cat. PTSA in CH_2Cl_2 (rt, overnight), a 3.5/1 thermodynamic mixture of **7a** and **6** was obtained starting either from **6** or **7a**.

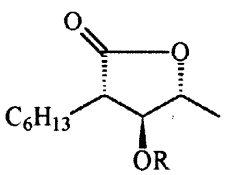
Table 1. Selected δ (ppm) and *J* values (in Hz) for lactones **7-12**.

Compound	**7a**	**10a**[13]	**7b**	**10b**[13]	**8a**	**11a**[13]	**8b**	**11b**[13]	**9a**	**12a**[15]	**9b**	**12b**[15]
δ H-3	4.45	4.32	5.49	5.62	3.73	3.84	5.06	4.94	4.28	4.20	5.32	5.17
δ H-4	4.45	4.45	4.51	4.57	4.25	4.21	4.38	4.37	4.74	4.64	4.75	4.76
$J_{H\text{-}2,H\text{-}3}$	4.7	4.7	5.3	5.3	*a*	8.6	6.0	5.6	8.5	3.2	3.3	2.7
$J_{H\text{-}3,H\text{-}4}$	*a*	3.0	3.6	3.4	6.0	7.3	4.8	4.6	7.0	4.8	5.1	4.8

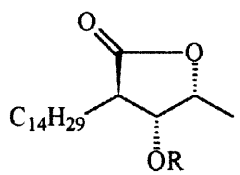
a: not observed.



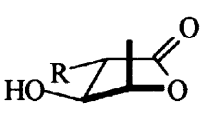
10a R= H
10b R= CO*i*Bu



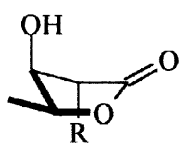
11a R= H
11b R= CO*i*Bu



12a R= H
12b R= Ac



A

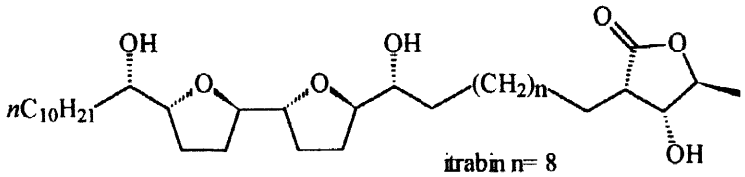


B

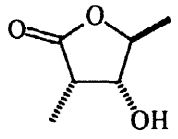
Similarly, the structures of the minor isomers **8a** and **9a** (and their acetates **8b**, **9b**) were determined by comparison to the known lactones NFX-2 **11a**, antimycinone **11b** and **12a,b** (see Table 1). **8a** arising from dihydroxylation of the minor *Z* isomer **4b** is a 2,4-disubsituted *cis* lactone (as **7a**). The *trans* lactone **9a** proved to be rather instable and gave a 1/1 mixture with **13a** on standing (*vide infra*). Although a good agreement of NMR data was found between acetates **9b** and **12b**, the observed ^3J between H-2, H-3 and H-4 (Table 1) for alcohol **9a** were larger than those of **12a**. This may be explained by a conformational bias between these lactones. MM2 calculations and *J* analysis carried out by Jaime *et al.*[14] have shown that the corresponding dimethyl lactone exists as a 26/74 mixture of degenerate envelope conformations **A** and **B** (R= Me). The calculated $J_{H\text{-}2,H\text{-}3}$ and $J_{H\text{-}3,H\text{-}4}$ being respectively 8.9 and 7.1 Hz for conformer **A** and 0.5 and 3.8 Hz for conformer **B**, it may be assumed that lactone **9a** exists mainly as conformer **A**.

Treatment of **4a,b** with AD-mix-α[12] was more complex, giving **9a** and **13a** which could not be separated by chromatography due to a very fast equilibrium between these lactones. Therefore, the crude mixture was acetylated to give **9b** and **13b**, respectively in 36 and 6% from **4a,b**. If acetylation is carried out after exposure of diols to cat. PTSA or silica, then a 1/1 ratio of **9b**/**13b** is obtained in similar overall yield.

In conclusion, this study has shown that lactones related to sub-type 3 acetogenins may be prepared in few steps from 5-alkyl butyrolactones and it may be assumed that this methodology can be extended to the preparation of all diastereomers starting from both enantiomers. Conversion to sub-type 1b lactones should be possible after protection as MOM ethers and treatment with DBU,[16] although care should be taken to avoid the easy epimerisation at C-4 recently demonstrated by Figadère for such insaturated lactones.[2] Finally, ^{1}H NMR data of the all cis isomer **7a**, as well as the other lactones **8a** and **9a**, do not correspond to the reported values for naturally occurring sub-type 3 acetogenins. Indeed, the observed (numbering as above) $J_{H\text{-}2,H\text{-}3}$ (5.5 Hz) and $J_{H\text{-}3,H\text{-}4}$ (<1Hz) of these acetogenins better agree with those reported for lactone **14**[15] (respectively: 5.6 and 1.1 Hz) and we propose that the structures of itrabin, jetein, laherradurin and otivarin should now be revised in their lactone moiety as shown below for itrabin and laherradurin.



itrabin n= 8
laherradurin n= 10



14

Acknowledgements

We thank ADIR and the Ligue Nationale contre le Cancer, Comité de Charente-Maritime, for financial support.

References and Notes

1. Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. Acetogenins from Annonaceae. In *Progress in the Chemistry of Organic Natural Products*, Vol 70, Herz, W.; Kirby, G.W.; Moore, R.E.; Steglich, W.; Tamm, Ch. Eds.; Springer: Wien, New-York, 1997, pp 81-288. Zeng, L.; Ye, Q.; Oberlies, N.H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J.L. *Nat. Prod. Reports*, **1996**, *13*, 275-306.
2. Duret, P.; Figadère, B.; Hocquemiller, R.; Cavé, A. *Tetrahedron Lett.* **1997**, *38*, 8849-8852.
3. Cortes, D.; Rios, J.L.; Villar, A.; Valverde, S. *Tetrahedron Lett.* **1984**, *25*, 3119-3203. Rios, J.L.; Cortes, D.; Valverde, S. *Planta Med.* **1989**, *55*, 321-323.
4. Cortes, D.; Myint, S.H.; Leboeuf, M.; Cavé, A. *Tetrahedron Lett.* **1992**, *32*, 6133-6134.
5. Vieira, P.C.; Yoshida, M.; Gottlieb, O.R.; Filho, H.F.P.; Nagem, T.J.; Filho, R.B. *Phytochem.* **1983**, *22*, 711-713.
6. Kinoshita, M.; Aburaki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373-376 and references cited therein.
7. Nishida, T.; Nihira, T.; Yamada, Y. *Tetrahedron*, **1991**, *47*, 6623-6634.
8. Li, W.; Nihira, T.; Sakuda, S.; Nishida, T.; Yamada, Y. *J. Ferment. Bioeng.* **1992**, *74*, 214-217.
9. Ravi, B.N.; Wells, R.J. *Aust. J. Chem.* **1982**, *35*, 105-112.
10. Bertrand, P.; Gesson, J.-P. *Synlett*, **1992**, 889-890.
11. Harmange, J.C.; Figadere, B.; Hocquemiller R.; *Tetrahedron Asymmetry*. **1991**, *5*, 347-350.
12. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771.
13. Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron*, **1994**, *50*, 8337-8346.
14. Jaime, C.; Segura, C.; Dinarés, I.; Font, J. *J. Org. Chem.* **1993**, *58*, 154-158.
15. Sibi, M.; Lu, J.; Talbacka, C.L. *J. Org. Chem.* **1996**, *61*, 7848-7855.
16. Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157-160.