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Syntheses of Acetogenins of Annonaceae: A New Class of Bioactive Polyketides

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Introduction

This Account deals with an emerging new class of natural products, the linear acetogenins. These compounds are isolated from a worldwide spread family of tropical plants, the Annonaceae (2300 species within 130 genera) and possess interesting cytotoxic activities against several cell lines.[1] The name "linear acetogenins" was proposed because of their polyketide origin through an acetyl coenzyme A elongation process.[2] The first compound to be isolated and characterized was uvaricin,[3] extracted from *Uvaria acuminata*, and since then about 132 related compounds have been found in the Annonaceae and exclusively from this family. These molecules have in common several structural features such as a long alkyl chain (35 or 37 carbon atoms) ending in a γ-lactone and possessing oxygenated functions such as tetrahydrofuran rings (one to three), epoxides, hydroxyl groups, ketonic groups, and/or double bonds (Chart 1). We classified these compounds as a function of the number and position of THF rings (types A–E corresponding to one, two contiguous, two isolated, three contiguous, and lack of THF rings, respectively) and as a function of the nature of the γ-lactone ring (subtypes 1–3 for an α,β-unsaturated γ-methyl-γ-lactone, a saturated γ-lactone, and a β-hydroxy-γ-methyl-γ-lactone, respectively).[1] We have shown in Châtenay-Malabry that in fact compounds of subtype 2 are not natural ones but are artifacts due to a *trans*-lactonization followed by a rearrangement of the allylic alcohol so obtained, occurring during the isolation and purification steps.[4] Obviously the rare subtype 3 is a natural precursor of products of subtype 1 through dehydration. In spite of these simple structural criteria, it is now obvious that all acetogenins isolated so far possess varying degree of *in vitro* cytotoxicity against a large variety of carcinogenic cell lines.[5] Furthermore, some acetogenins have *in vivo* antitumor properties, ranking them among potentially antineoplastic drugs.[5] The mechanism of action of these compounds is still not completely understood, even though several hypotheses have been proposed. The study of the acetogenins in our group and elsewhere has brought to light many important results concerning the extraction, structural elucidation, total synthesis, biological properties, mechanism of action, and biogenesis of these new bioactive and unique natural products. But the growing inter-

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(1) Cavé, A.; Cortes, D.; Figadère, B.; Hocquemiller, R.; Laprévote, O.; Laurens, A.; Lebœuf, M. Recent advances in the acetogenins of Annonaceae. In *Phytochemical Potential of Tropical Plants*; Downum, K. R., Romeo, J. T., Stafford, H. E., Ed.; Plenum Press: New York, 1993; pp 167–202.
(2) Dabrah, T. T.; Sneden, A. T. *Phytochemistry* **1984**, *23*, 2013–2016.
(3) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, G. R; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151–3153.
(4) Duret, P.; Laurens, A.; Hocquemiller, R.; Cortes, D.; Cavé, A. *Heterocycles* **1994**, *39*, 741–749.
(5) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237–278.

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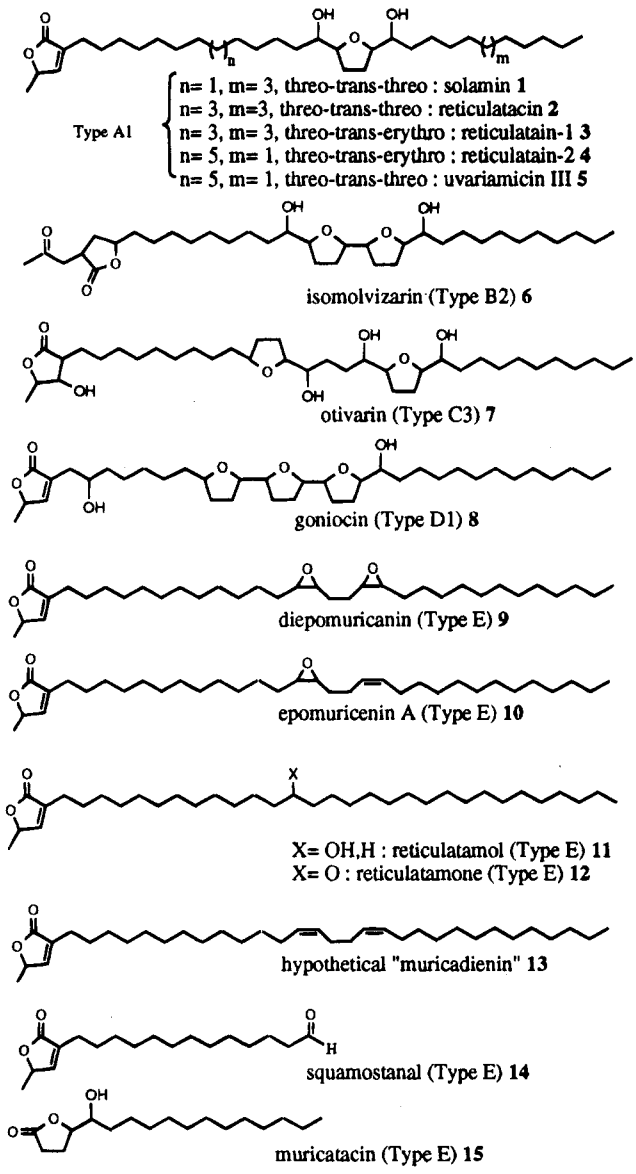
Chart 1



est in this family, illustrated by the increasing number of publications during the last two years, could be a sign that acetogenins might soon play a role in certain pathological conditions.

Biosynthesis of Acetogenins

Despite the presence of numerous asymmetric centers due to the oxygenated groups, biosynthesis of such natural products seems obviously derived from straightforward enzymatic processes: *e.g.*, dehydrogenation and oxidation. For instance, the α,α′-dihydroxylated tetrahydrofuran pattern of solamin (**1**) must be derived from a $\Delta^{15,19}$ diunsaturated precursor **13**, *via* an oxidation step leading to a bisepoxide (isolated from *Annona muricata* and named diepomuricanin (**9**)[6]) which rearranges in acidic medium to a dihydroxylated THF. Therefore one of the early precursors might be a very long chain fatty acid (VLCFA) which could be firstly transformed to a butanolide probably from a glycerol derivative. Then the first enzymatic step is probably a dehydrogenation, introducing either the Δ^{15} or the Δ^{19} double bond, and then the other. This $\Delta^{n,n+4}$ pattern is practically unknown in mammalian species where fatty acid unsaturations separated only by a methylene group ($\Delta^{n,n+3}$) are found. In fact the $\Delta^{n,n+4}$ pattern has been found in marine organisms, principally in marine sponges,[7] and recently in sea anemones.[8] These common biogenetic intermediates with very primitive living organisms such as these marine invertebrates led us to confirm the archaism of the Annonaceae family. Hutchinson[9] and Takhtajan[10] already have reported that the Annonaceae family is an archaic family of angiosperms related to the Magnoliales which are considered "living fossils". The fact that we successfully isolated the bisepoxide **9**[6,11] and the unsaturated epoxide **10**[6] (the double bond being separated by an ethylene group from the epoxide function) from *A. muricata* confirmed our hypothesis for the biogenetic pathway. But so far the diunsaturated derivative precursor (already named "muricadienin" (**13**)) remains hypothetical. During our search for such a precursor, we isolated reticulatamol (**11**)[12] and reticulatamone (**12**),[13] which are only functionalized at C-15 with a hydroxyl and a ketonic group, respectively. Reticulatamol (**11**) could be obtained by an enzymatic hydroxylation of the corresponding saturated precursor, which will lead either to the Δ^{15} double bond through an enzymatic dehydration or to more oxidized metabolites such as reticulatamone (**12**) or squamostanal (**14**).[14] The same sequence can be envisaged for acetogenins possessing two contiguous THF rings, but involving in this case a $\Delta^{n,n+4,n+8}$ unsaturated precursor which will lead to a triepoxide (which we have isolated from the hexanic extract of the seeds of *Annona reticulata*[11]), and then after acidic rearrangement to a bisTHF acetogenin. Muricatacin (**15**), which also has been isolated from *A. muricata* but in an almost racemic mixture,[15] is probably an oxidative metabolite of mono-THF acetogenins probably formed during the isolation procedure.

If in marine invertebrates the presence of elaborated compounds can be envisaged as a long process of evolution for the defense of the organisms, in plants many tentative hypotheses justifying the presence of such complex substances have always led to unsatisfactory explanations. Therefore, we shall not discuss the role of the acetogenins in the Annonaceae.

Isolation and Structural Elucidation of Acetogenins of Annonaceae

After the first isolation of uvaricin by Jolad[3] in 1982, identification of new acetogenins from the methanolic extract of either the seeds, bark, leaves, or roots of different species of Annonaceae occurred almost si-

(6) Roblot, F.; Laugel, T.; Leboeuf, M.; Cavé, A.; Laprévote, O. *Phytochemistry* **1993**, *34*, 281–285.

(7) Djerassi, C.; Lam, W.-K. *Acc. Chem. Res.* **1991**, *24*, 69.

(8) Carballeira, N. M.; Medina, J. R. *J. Nat. Prod.* **1994**, *57*, 1688–1695.

(9) Hutchinson, J. *Evolution and Phylogeny of Flowering Plants*; Academic Press: New York, 1969.

(10) Takhtajan, A. *Flowering Plants, Origin and Dispersal*; Oliver and Boyd Ltd.; Edinburgh, 1969.

(11) Vu Thi Tam; Phan-Quan Chi Hieu; Chappe, B.; Roblot, F.; Laprévote, O.; Figadère, B.; Cavé, A. *Nat. Prod. Lett.* **1994**, *4*, 255–262.

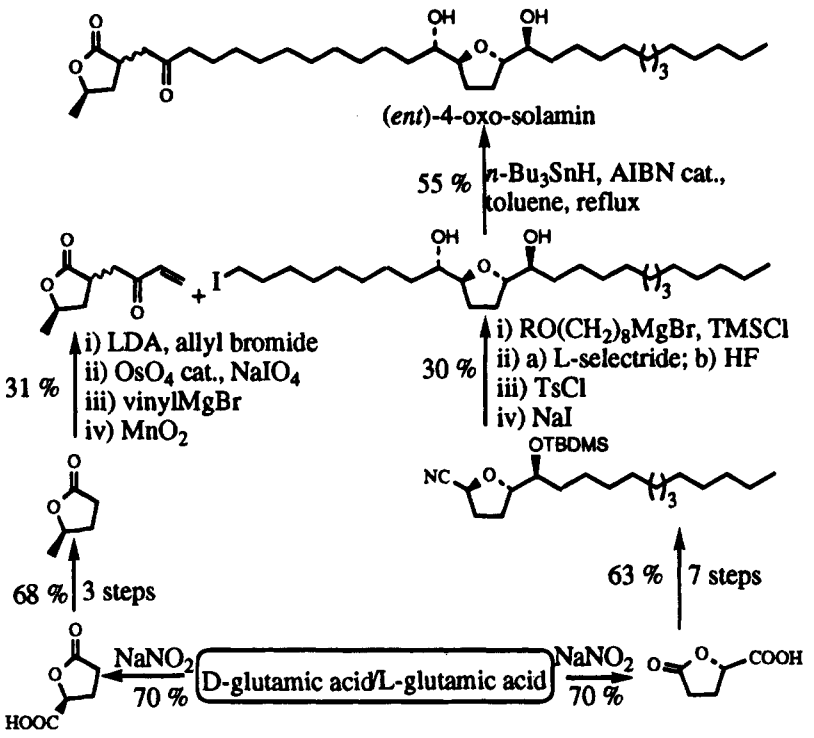
(12) Vu Thi Tam; Chaboche, C.; Figadère, B.; Chappe, B.; Bui Chi Hieu; Cavé, A. *Tetrahedron Lett.* **1994**, *35*, 883–886.

(13) Vu Thi Tam; Phan-Quan Chi Hieu; Chappe, B.; Roblot, F.; Figadère, B.; Cavé, A. *Bull. Soc. Chim. Fr.* **1995**, *132*, 324–329.

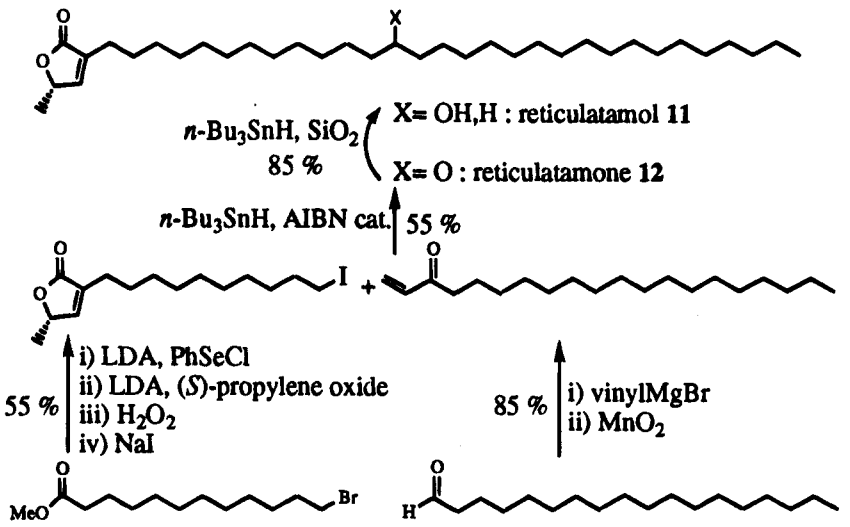
(14) Araya, H.; Hara, N.; Fujimoto, Y.; Sahai, M. *Biosci., Biotechnol., Biochem.* **1994**, *58*, 1146–1147.

(15) Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137–1140.

Scheme 1

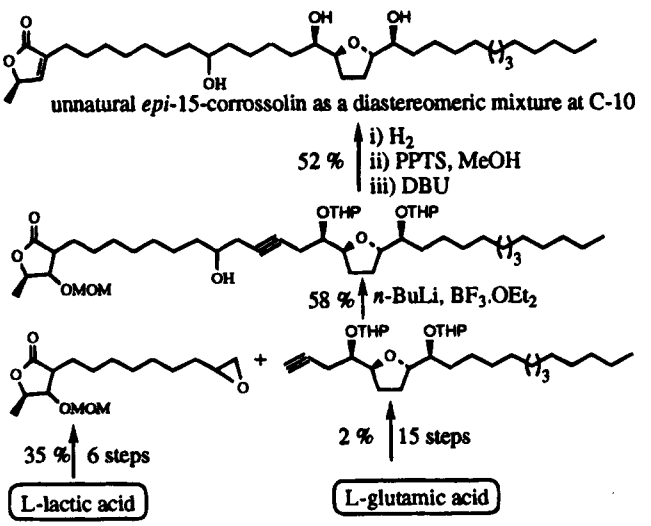


Scheme 2



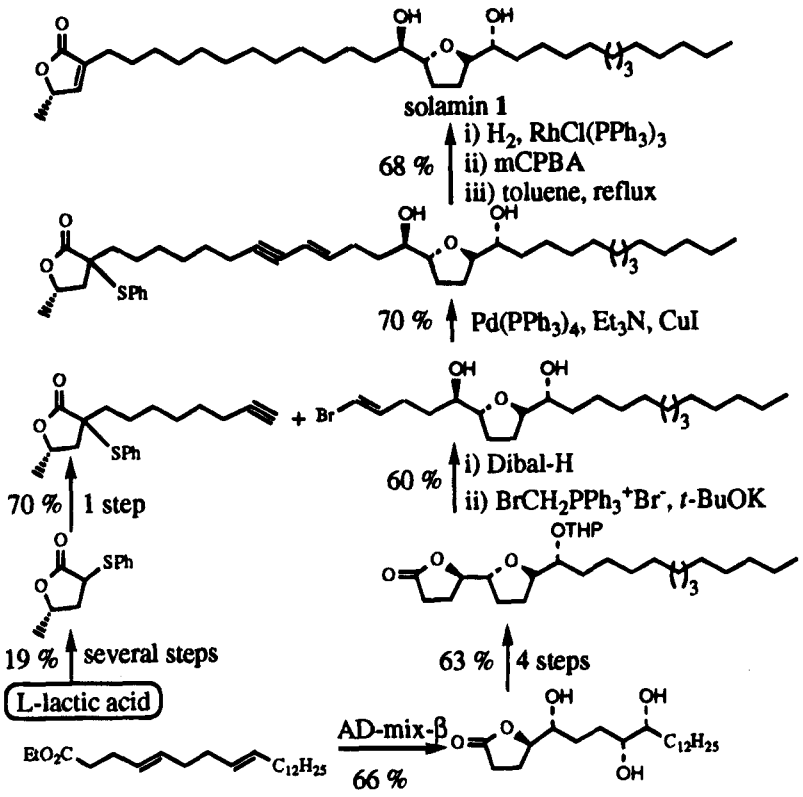
multaneously in Châtenay and by Jerry L. McLaughlin's team at Purdue. For about 25 years, André Cavé's group in Châtenay studied the alkaloids[16] and secondarily neutral compounds such as terpenes, fatty acids, and flavonoids found in the Annonaceae before becoming interested in the isolation of tetrahydrofuranoid fatty acid lactones, which finally were found to be responsible for the pesticide and antiparasitic activities already observed by the populations in South America. The standard protocol for the extraction of the acetogenins of Annonaceae is to apply several liquid–liquid extractions (for instance with hexane, dichloromethane) after maceration of the dry plant material in cold methanol. Then several adsorption chromatographies (at different pressures) guided by simple bioassays (toxicity test on brine shrimp larvae) give bioactive subfractions which display a single spot

Scheme 3

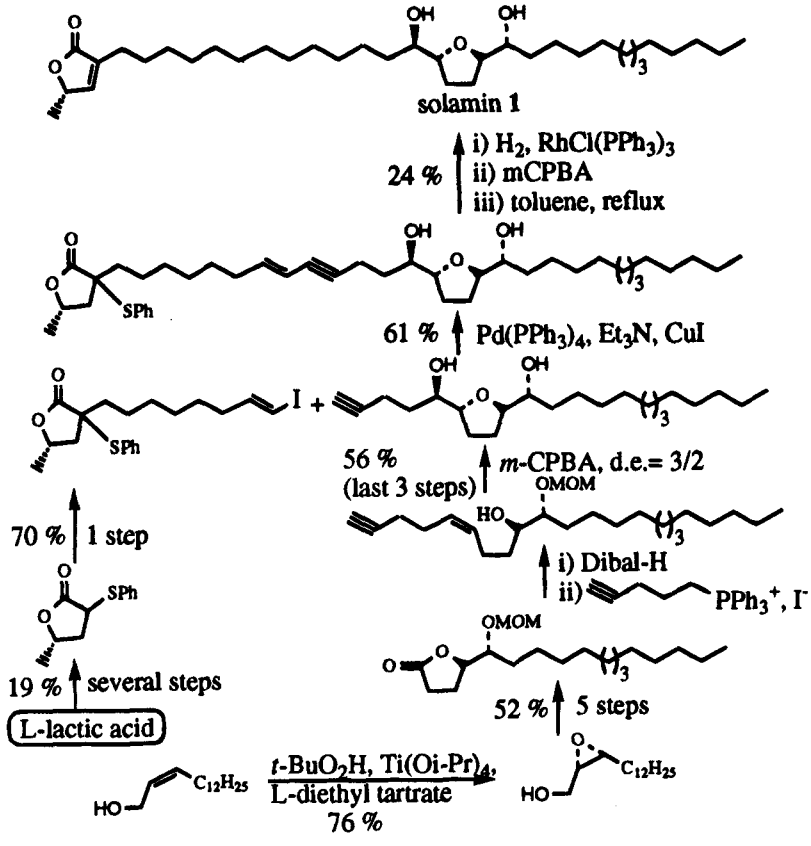


(16) Lebœuf, M.; Cavé, A.; Bhaumik, P. K.; Mukherjee, B.; Mukherjee, R. *Phytochemistry* **1982**, *21*, 2783–2813.

Scheme 4



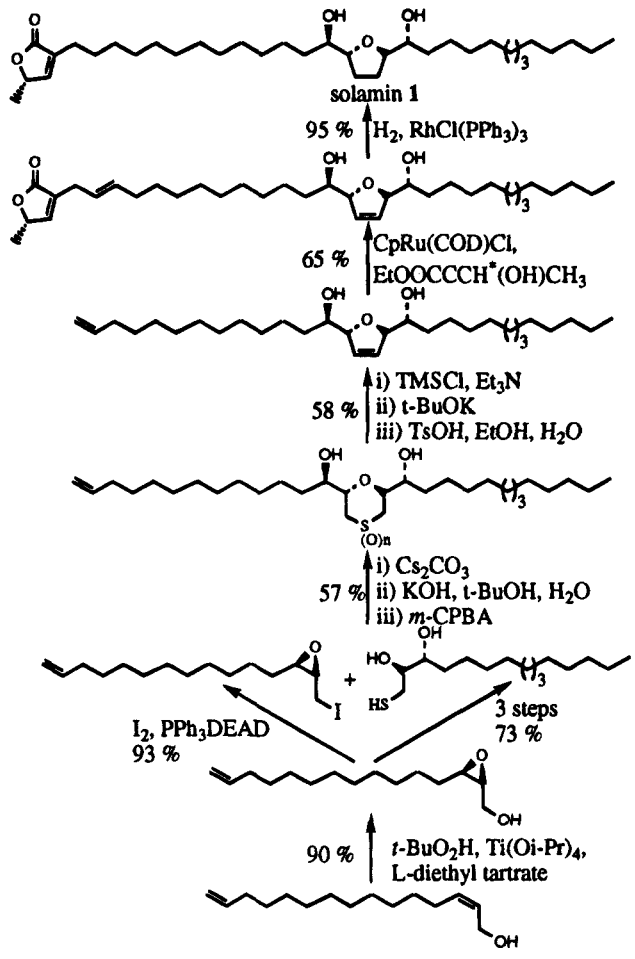
Scheme 5



by CCM, but still give a mixture of components by analytical HPLC. Therefore, preparative HPLC must be performed in order to separate compounds' positional isomers or diastereomers.[17,18] IR, UV, and ^1H and ^{13}C NMR techniques allow us to characterize the oxygenated functions present in the molecule, but

(17) Gromek, D.; Figadère, B.; Hocquemiller, R.; Cavé, A.; Cortes, D. *Tetrahedron* **1993**, *49*, 5247–5252.
(18) Gromek, D.; Hocquemiller, R.; Cavé, A. *Phytochem. Anal.* **1994**, *5*, 133–140.

Scheme 6



mass spectroscopy permits us to determine both the molecular weight and the relative positions of the different groups. Indeed, mass-tandem and collision-induced dissociation (CID) of the $[M + Li]^+$ ion using linked scan analysis at constant *B/E* are very helpful techniques for the determination of the positions of THF rings or epoxides along the chain.[19] Relative configurations of the asymmetric centers are determined by NMR analyses, and absolute configurations by applying Yamaguchi's method[20] based on analysis by ^1H NMR of Mosher's esters.[21] However, many stereogenic centers remain undetermined, because of the intrinsic limitations of Mosher's technique and because of the waxy nature of acetogenins, which do not allow direct X-ray crystallography.

Biological Properties and Mechanism of Action of Acetogenins

The cytotoxicity observed for all acetogenins measured as a lethal concentration for 50% of mortality of the cells (LD_{50}) range among 10^{-1}–10^{-12} μg/mL according to the acetogenins and the cell lines.[5] In some cases these extraordinarily low values are correlated with a relatively good effective dose (ED_{50}) corresponding to a 50% diminution of a grafted tumor on mice, making these compounds excellent candidates for antitumor drugs.[5] In addition to this antineoplastic activity, acetogenins have shown very interesting pesticide properties, as well as antiparasitic activities, confirming their traditional uses in South America.[1] Recently, annonacin was found to inhibit an immunosuppressive activity on mixed lymphocytes on mouse system cells, with a $IC_{50} = 3$ nM for this model (compared to cyclosporin with 10 nM for the same model).[22]

Concerning the mechanism of action of such compounds, several hypotheses have been proposed. In collaboration with Prof. G. Jeminet it has been shown that annonacin improved extrusion of K^+ from the lymphocytes, through a mechanism similar to that of antibiotic ionophores.[23] This ability to complex a metallic cation (mono- or bivalent) was confirmed by mass spectroscopy in experiments performed in a matrix with *m*-nitrobenzyl alcohol and in the presence of LiCl, by collision with argon. Nevertheless, this chelating property is still under investigation to obtain further information about the site and the thermodynamic constants of the complexation.[24]

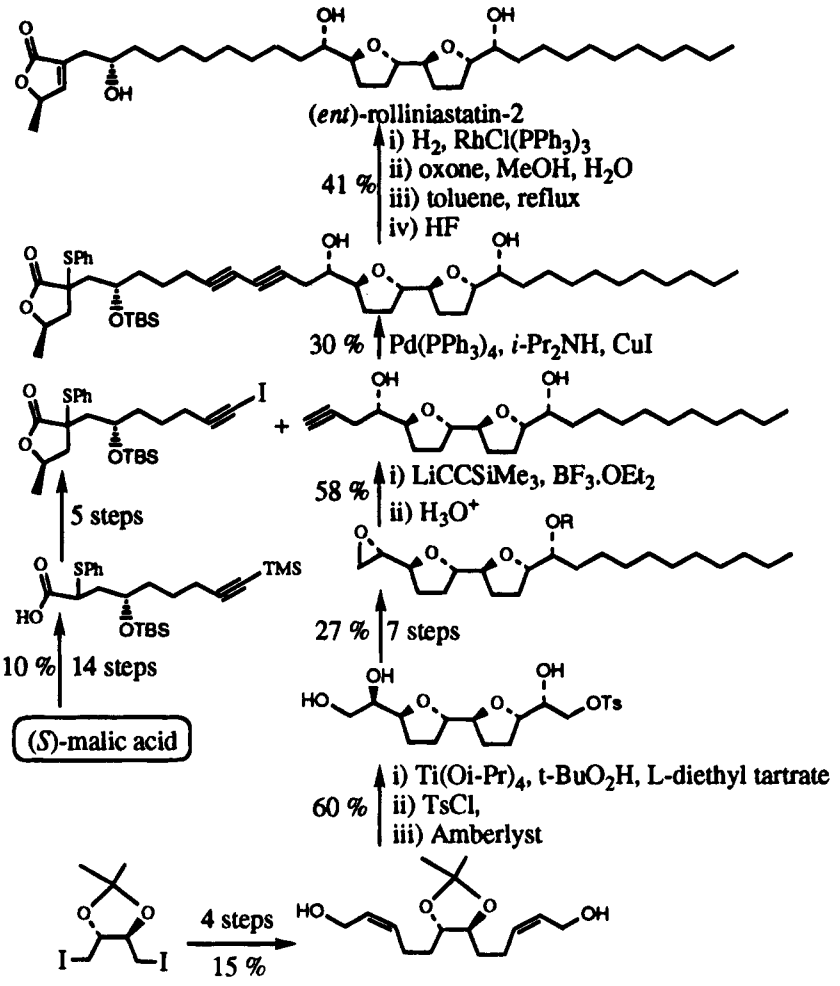
It also has been shown that acetogenins inhibit mitochondrial electron transport through the NADH–ubiquinone oxidoreductase (respiratory complex I) and consequently inhibit the energy-conserving function.[25,26] In collaboration with Prof. D. Cortes and Prof. M. D. Esposti it was found that several acetogenins are more potent than rotenone and piericidin (piericidin is the most powerful inhibitor of complex I reported so far) in bovine heart submitochondrial particles.[25] Since then, J. L. McLaughlin has shown that bullatacin remarkably reduced the NADH oxidase activity of HeLa and HL-60 plasma membranes (ED_{50}: 5–10 nM), whereas plasma membranes of rat liver were unaffected over the concentration range of 1 nM to 10 μM.[27] Prof. M. Schwaller (from the Châtenay group) has already observed that multi drug resistant cells (MDR cells), even more dependent on ATP concentration than normal cells, respond to the presence of acetogenins by an inhibition of proliferation. Further developments in this area are needed to better understand the bioactivity of these compounds.[28]

Total Synthesis of Acetogenins

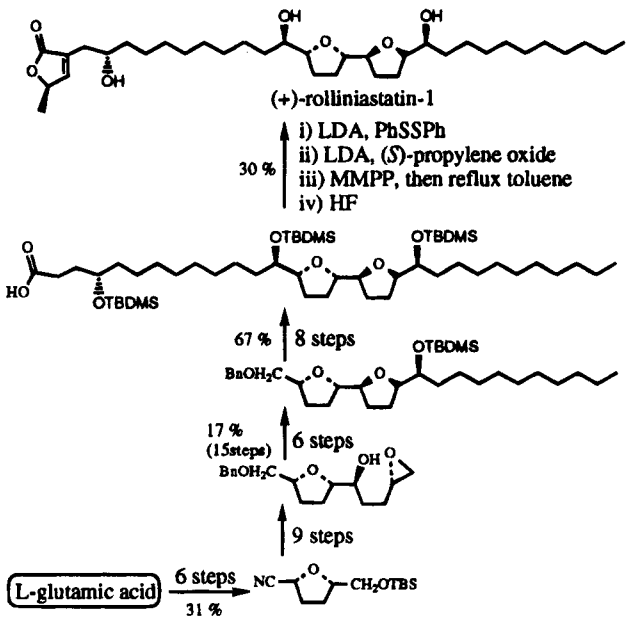
Total asymmetric syntheses of acetogenins of type A or type B have been reported in the literature only recently. Most of the approaches are based on a convergent strategy which consisted of preparing both the tetrahydrofuran part and the lactonic moiety in a stereocontrolled way and finally the cross-coupling of the two synthons. For the tetrahydrofuran fragment,

(19) Laprévote, O.; Das, B. C. *Tetrahedron* **1994**, *50*, 8479–8490.
(20) Yamaguchi, S. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, pp 125–152.
(21) Rieser, M. J.; Hui, Y. H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203–10213.
(22) Laurens, A.; Dutartre, P.; Cortes, D.; Hocquemiller, R.; Cavé, A. Immunomodulating Activity of Annonacin Isolated from *A. muricata* Seeds. Poster session, 18th IUPAC Symposium, Strasbourg, France, 30 Aug 1992.
(23) Jeminet, G. Personal communication.
(24) Sasaki, S.; Naito, H.; Maruta, K.; Kawahara, E.; Maeda, M. *Tetrahedron Lett.* **1994**, *35*, 3337–3340.
(25) Degli Esposti, M.; Ghelli, A.; Ratta, M.; Cortes, D.; Estornell, E. *Biochem. J.* **1994**, *301*, 161–167.
(26) Friederich, T.; van Heek, P.; Leif, H.; Ohnishi, T.; Forche, E.; Kunze, B.; Jansen, R.; Trowitzsch-Kienast, W.; Höfle, G.; Reichenbach, H.; Weiss, H. *Eur. J. Biochem.* **1994**, *219*, 691–698.
(27) Morré, D. J.; de Cabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci.* **1995**, *56*, 343–348.
(28) Schwaller, M. Personal communication.

Scheme 7



Scheme 8



two different approaches have been chosen: either to use a compound from the chiral pool (*e.g.*, α-amino acid, L-tartaric acid) as starting material or to apply an asymmetric catalyzed reaction (*e.g.*, Sharpless asymmetric epoxidation, Sharpless asymmetric dihydroxylation). The γ-methyl-γ-lactone is prepared either from L-glutamic acid, from L-lactic acid, or from (*S*)-propylene oxide. In most cases the authors have used the very efficient Stille reaction based on a palladium-catalyzed reaction of a vinyl bromide with an acetylenic compound for the coupling. Trost *et al.* have used a very elegant strategy based on a ruthenium-catalyzed butenolide annelation on a monosubstituted double bond with a chiral ynoate. In Châtenay, we prefer a Michael type addition of a primary alkyl radical with an α,β-unsaturated ketone.

We prepared *ent*-4-oxosolamin as a mixture of distereomers at C-2, in 14 steps and 6.4% overall yield from L-glutamic acid.[29,30] Two more steps, reduction of the carbonyl at C-4 and introduction of the unsaturation in the lactone ring, will lead to *ent*-solamin (Scheme 1). Using the same strategy we have successfully synthesized reticulatamone (**12**)[13] and reticulatamol (**11**)[12] (Scheme 2) in a few steps and in high overall yield (30% and 26%, respectively, from commercially available starting materials). This strategy has the advantage over competitive approaches of being easily applied to the synthesis of bis-tetrahydrofuranic acetogenins, as well as to the preparation of epimers or the enantiomer of almost any natural acetogenin.

Yao and Wu[31] reported the synthesis of a diastereomeric mixture of corossolin at C-10 with the wrong

(29) Figadère, B.; Harmange, J.-C.; Hai, L. X.; Cavé, A. *Tetrahedron Lett.* **1992**, *33*, 5189–5192.
(30) Harmange, J.-C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1992**, *33*, 5749–5752.
(31) Yao, Z. J.; Wu, Y. L. *Tetrahedron Lett.* **1994**, *35*, 157–160.

relative stereochemical relationship across the THF ring. Starting materials were L-glutamic acid for the THF fragment and L-lactic acid for the lactone moiety. The cross-coupling reaction was based on a nucleophilic opening of a terminal epoxide by a lithium acetylide in the presence of a Lewis acid (Scheme 3). The synthesis was achieved in 20 steps and 1.14% overall yield, but the strongest disadvantage of this approach is the access to a mixture of compounds having the wrong relative and absolute configurations at C-15/16/19/20.

Sinha and Keinan[32] in their synthesis of solamin (**1**) and reticulatacin (**2**) used the very efficient Sharpless asymmetric dihydroxylation (AD-mix) for the preparation of the THF part. The lactone fragment was prepared from L-lactic acid with the desired (*S*) configuration at C-36, and the cross-coupling reaction of the two synthons was performed *via* a palladium-catalyzed reaction of an acetylenic derivative with a vinyl bromide. This synthesis was achieved in 14 steps and 7.7% overall yield (Scheme 4).

Tanaka *et al.*[33] prepared **1** and **2** using the Sharpless asymmetric epoxidation of an allylic alcohol as a key step for the synthesis of the THF fragment. The lactonic moiety was prepared again from L-lactic acid in a few steps, and the cross-coupling reaction of the two synthons was based on the Stille reaction. The synthesis was performed in 16 steps and 1.5% overall yield (Scheme 5).

Trost and Shi's synthesis[34] of solamin (**1**) is particularly innovative, since the THF fragment was prepared *via* a Ramberg–Backlund olefination (this being the first report of the preparation of a THF ring using this methodology), and the lactone moiety was obtained by a ruthenium-catalyzed butenolide annelation. The asymmetric centers were introduced by the Sharpless asymmetric epoxidation of an allylic alcohol. The synthesis was achieved in 14 steps and 11.7% overall yield (Scheme 6).

Hoye *et al.*[35,36] synthesized *ent*-rolliniastatin-2 from L-tartaric acid, using the Sharpless asymmetric epoxidation of an allylic alcohol for the preparation of the THF fragment, taking advantage of a pseudo C-2 symmetry of the molecule. The lactonic part was prepared from L-malic acid and (*S*)-propylene oxide. The cross-coupling reaction between the two synthons was performed *via* a Stille reaction of an acetylide with an iodoalkyne. The synthesis was then achieved in 20 steps and 0.8% overall yield (Scheme 7).

Koert[37] reported the total synthesis of (+)-rolliniastatin-1 from L-glutamic acid, for the THF part, and from (*S*)-propylene oxide for the lactonic fragment. The strategy used was a sequential approach in 30 steps and 2.1% overall yield (Scheme 8).

Besides the total syntheses of tetrahydrofuranic acetogenins, several preparations of muricatacin (**15**), a metabolite of acetogenins, have been described in the literature.[38–45] Muricatacin (**15**) appears also in different approaches as a key intermediate leading to natural acetogenins.[29–31,33]

It is also interesting to note that some hemisyntheses of natural or unnatural acetogenins have been reported, starting from natural precursors.[6,11,17,46–47]

Conclusion

Acetogenins of Annonaceae are a relatively new class of bioactive naturally occurring products. The difficulty of isolating these compounds and elucidating their structures makes them a challenging target for chemists. But their wide spectrum of biological properties is probably the most intriguing and exciting domain. Unfortunately, the natural abundance of most acetogenins is minute (except, for instance, rolliniastatin-2 extracted from the seeds of *Annona squamosa* in gram quantities), and therefore total synthesis is required for the preparation of large amounts of the natural product for further studies on structure–activity relationships. It will not be surprising if acetogenins of Annonaceae or related compounds with structural modifications might, in the near future, play a significant role in cancer therapy *via* an original mechanism of action.

I wish to thank all of my collaborators whose names appear in the cited articles, and particularly Prof. André Cavé for his enthusiasm and personal support. By their dedication and talented contribution to the study of the acetogenins of Annonaceae, they have allowed us to explore and better understand these relatively new natural products possessing an intriguing large spectrum of biological properties.

AR9500168

(32) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891–4892.
(33) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. I* **1994**, 1975–1981.
(34) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 7459–7460.
(35) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369–9371.
(36) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043–5046.
(37) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517–2520.
(38) Figadère, B.; Harmange, J.-C.; Laurens, A.; Cavé, A. *Tetrahedron Lett.* **1991**, *32*, 7539–7542.
(39) (a) Scholz, G.; Tochtermann, W. *Tetrahedron Lett.* **1991**, *32*, 5535–5538. (b) Tochtermann, W.; Scholz, G.; Bunte, G.; Wolff, C.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Liebigs Ann. Chem.* **1992**, 1069–1080.
(40) (a) Marshall, J. A.; Welmaker, G. S. *Synlett* **1992**, 537, 538. (b) Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1994**, *59*, 4122–4125.
(41) Wang, Z. M.; Zhang, X. L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407–6410.
(42) Kang, S. K.; Cho, H. S.; Sim, H. S.; Kim, B. K. *J. Carbohydr. Chem.* **1992**, *11*, 807–812.
(43) Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1993**, *34*, 1597–1598.
(44) Liu, Z. Y.; Zhang, J. J.; Chen, W. *Chin. Chem. Lett.* **1993**, *4*, 663–664.
(45) (a) Gravier-Pelletier, C.; Sanière, M.; Charvet, I.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 115–118. (b) Sanière, M.; Charvet, I.; LeMerrer, Y.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 1653–1662.
(46) Gu, Z. M.; Fang, X. P.; Zeng, L.; Song, R.; Ng, J. H.; Wood, K. V.; Smith, D. L.; McLaughlin, J. L. *J. Org. Chem.* **1994**, *59*, 3472–3479.
(47) Sahpaz, S.; Figadère, B.; Saez, J.; Hocquemiller, R.; Cavé, A.; Cortes, D. *Nat. Prod. Lett.* **1993**, *2*, 301–308.