Determining Absolute Configurations of Stereocenters in Annonaceous Acetogenins through Formaldehyde Acetal Derivatives and Mosher Ester Methodology

Zhe-ming Gu, Lu Zeng, Xin-ping Fang, Trina Colman-Saizarbitoria, Mei Huo, and Jerry L. McLaughlin*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

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Formaldehyde (methylene) acetal derivatives can be conveniently prepared, on a small scale, using parent Annonaceous acetogenins which have 1,2-, 1,4-, and/or 1,5-diols along their aliphatic chains. The resulting cyclic acetal protons give NMR signals which allow characterization of the relative stereochemistries of the two stereogenic centers that originated from the diols. Less complicated (vs the parent acetogenins) per-Mosher ester [methoxy(trifluoromethyl)phenyl acetate or MTPA] derivatives of the acetal derivatives can then be prepared and used to determine absolute configurations of the chiral positions which bear the remaining free hydroxyls. Prior knowledge of relative stereochemical relationships then permits assignments of absolute configurations to additional chiral centers along the chain of the molecules. This method has been particularly useful in solving the absolute configurations of several nonadjacent bis-THF and mono-THF acetogenins, *viz.* bullatanocin (**1**), (2,4-*cis* and *trans*)-bullatanocinones (**2** and **3**), bullatalicin (**4**), (2,4-*cis* and *trans*)-bullatalicinones (**5** and **6**), squamostatin A (**7**), squamocin (**8**), gigantetrocin A (**9**), and goniothalamicin (**10**). Most of the resulting acetals (vs the parent acetogenins) show enhanced bioactivities, and their mode of action is, likewise, by mitochondrial inhibition.

Introduction

The Annonaceous acetogenins are γ-lactone derivatives of C-32 or C-34 long chain fatty acids; most possess one or two tetrahydrofuran rings and a combination of double bonds, hydroxyls, ketones, epoxides, or acetoxyls as functional groups. Since their discovery in 1982, they have attracted considerable interest among natural product chemists because of their stereochemical diversities and their broad spectrum of bioactivities.[1] These compounds act biologically, at least in part, as highly potent mitochondrial inhibitors.[2] A recent review revealed that 61 acetogenins, out of a total of *ca.* 90, have been discovered in the 3 year period of 1990–92 and demonstrate the rapid growth of recent scientific information regarding this relatively new class of bioactive natural compounds.[1b]

Annonaceous acetogenins are mainly composed of three groups, *i.e.*, the adjacent bis-tetrahydrofuran, nonadjacent bis-THF, and mono-THF subclasses.[1] All of the acetogenins in these subclasses have multiple stereogenic centers, and, indeed, some are differentiated from each other only by their stereochemistries. Consequently, the determination of the relative and absolute stereochemistries of these stereocenters has become a major concern in the elucidation of the structures of new, as well as previously reported, acetogenin compounds; in addition, the stereochemistries, in many cases, influence the relative potencies and biological specificities.[1,2] Because of their waxy nature, the acetogenins and their derivatives do not readily produce crystals suitable for X-ray crystallographic analysis. Relative stereochemistries around the THF ring(s) and those of the keto lactone moieties have typically been determined by comparisons with synthetic model compounds of known relative stereochemistry.[3] The absolute stereochemistry of none of the Annonaceous acetogenins had been defined until recently when Mosher ester methodology was applied and demonstrated to be very helpful.[4] So far, the absolute configurations of the carbinol centers of several adjacent bis-THF and some mono-THF acetogenins have been determined by the use of this methodology.[4,5]

The nonadjacent bis-THF acetogenins are the newest subclass of the THF-bearing Annonaceous acetogenins,[1a,b] and some, *e.g.*, bullatalicin (**4**), show promising *in vivo* antitumor activities although their potencies are less than those of the adjacent bis-THF compounds.[2c] Their nonadjacent bis-THF rings have made their structural elucidations and assignments of their relative stereochemistries more difficult than the adjacent bis-THF and mono-THF subclasses. Bullatalicin (**4**), whose structure

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(1) Reviews on Annonaceous acetogenins include: (a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (b) Fang, X.-P.; Rieser, M. J.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, *4*, 27. (c) Cave, A.; Cortes, D.; Figadere, B.; Hocquemiller, R.; Laprevote, O.; Laurens, A.; Leboeuf, M. In *Recent Advances in Phytochemistry*; Downum, K. R., Romeo, J., Stafford, H. P., Eds.; Plenum Press: New York, 1993; Vol. 27, pp 167–202.

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