Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8529-8532, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01888-X

Stereostructural Studies on the 4-Hydroxylated Annonaceous Acetogenins: A Novel Use of Mosher Ester Data for Determining *Relative* Configuration [Between C(4) and C(36)]

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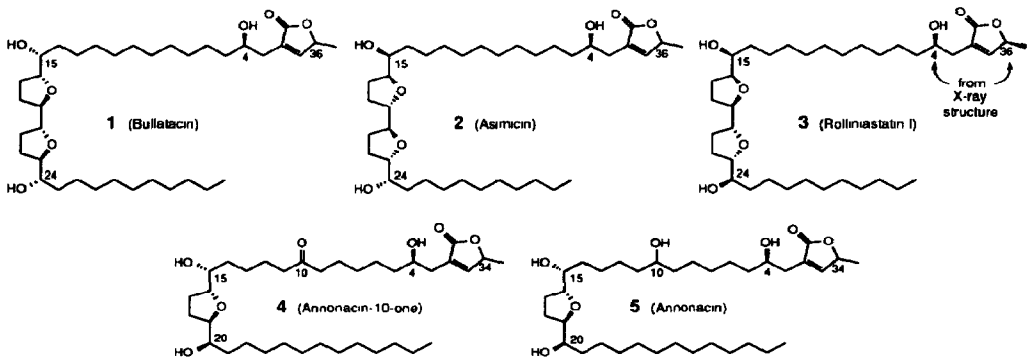
Abstract: *Analysis of MTPA (Mosher) esters of model butenolides 7 vs. the MTPA derivatives of 4-hydroxylated acetogenins provides the first general method for assignment of C(4)/C(36) relative configuration.*

The Annonaceous acetogenins are a group of naturally occurring antitumor compounds that have received much attention of late. These molecules are stereochemically complex, but most have proven unsuitable for X-ray crystallographic studies. General methods for determining the relative configuration of the tetrahydrofuranyl portion of these natural products have been developed;[2] more recently, a method was developed for determining the absolute configuration of carbinol centers at C(4) and adjacent to the THF rings, using Mosher ester methods.[3] An important remaining stereochemical feature to be solved, common to nearly all members of this class, is the absolute configuration at C(36) in the butenolide, which has been directly determined only for uvaricin.[4] Although this is a remote, isolated stereogenic center in many Annonaceous acetogenins, in those bearing a hydroxyl group at C(4) it is conceivable that through-space interaction between sites C(4) and C(36) could lead to a method for deducing their relative configuration. Examples of Annonaceous acetogenins bearing a hydroxyl group at C(4)--often among the most potent of these cytotoxins--are shown in Figure 1.

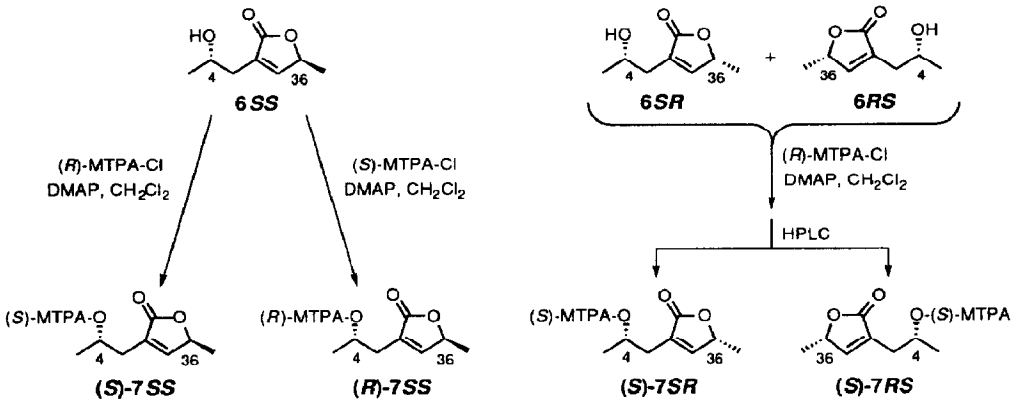
Figure 1



We report here a method for assigning the relative configuration between C(4) and C(36) in the C(4) hydroxylated acetogenins. This method relies on examination of the NMR spectral data of Mosher esters at C(4) and comparison with appropriate model compounds. While conventional Mosher ester technology involves comparing the *sign* of differences in chemical shift ($\Delta\delta$'s) between pairs of diastereomeric esters, the work described here makes use of trends in the *magnitude* of these differences, which to our knowledge is a novel use of Mosher data in structure determination.

The synthesis of enantiomerically enriched (+)-**6*SS*** (*like*) and of racemic (±)-**6*R**S*** (*unlike*) model butenolides was described in the previous Letter. Their ^{1}H and ^{13}C NMR spectral data were virtually identical.[5] Mosher esters at C(4) (acetogenin numbering) of **6** were prepared (Figure 2),[6] and the diastereomers (*S*)-**7*SR*** and (*S*)-**7*RS*** were separated by HPLC.

Figure 2



The absolute configurations at C(4) in the four Mosher esters **7** were assigned by standard Mosher analysis.[3] However, we also observed that the *magnitudes* of the $\Delta\delta$ values for the ^{1}H and ^{19}F nuclei in **7** were different depending on the *relative* configuration between C(4) and C(36) in these models. Most diagnostically, the absolute value of $\Delta\delta$ for H(35) (i.e., $|\Delta\delta_{H(35)}|$) was 0.23 ppm for the "unlike" diastereomeric pair (*S*)-**7*SR***/(*S*)-**7*RS***, while the value for the pair of "like" models (*S*)-**7*SS***/(*R*)-**7*SS*** was 0.32 ppm. Also, for H(36), $|\Delta\delta_{H}|$ was 0.06 ppm for the "unlike" model but 0.17 ppm for its "like" diastereomer (Table 1). The $|\Delta\delta_{H}|$ values for H(35) and H(36) in the natural acetogenins in Figure 1 were 0.24-0.26 ppm and 0.04-0.06 ppm, respectively (Table 1), which strongly suggests an "unlike" relative configuration for all of these compounds. Furthermore, $|\Delta\delta_{19F}|$ data were also diagnostic and consistent with this conclusion. Since C(4) in these molecules has the *R* absolute configuration,[3] it follows that all of the natural products examined here possess a 4*R*,36*S* configuration.

These features are shown graphically in Figure 3. Absolute values of the magnitudes of the chemical shift differences (i.e., $|\Delta\delta|$) for relevant ^{1}H and ^{19}F nuclei in "like" and "unlike" models **7** are plotted, along with those from the Mosher esters of bullatacin as a representative C(4)-hydroxylated acetogenin. From this graph the trend in magnitude is clearly seen; indeed, the pattern of $|\Delta\delta|$'s for bullatacin is much more similar to that of the "unlike" model. All acetogenins examined in the present study give similar results.

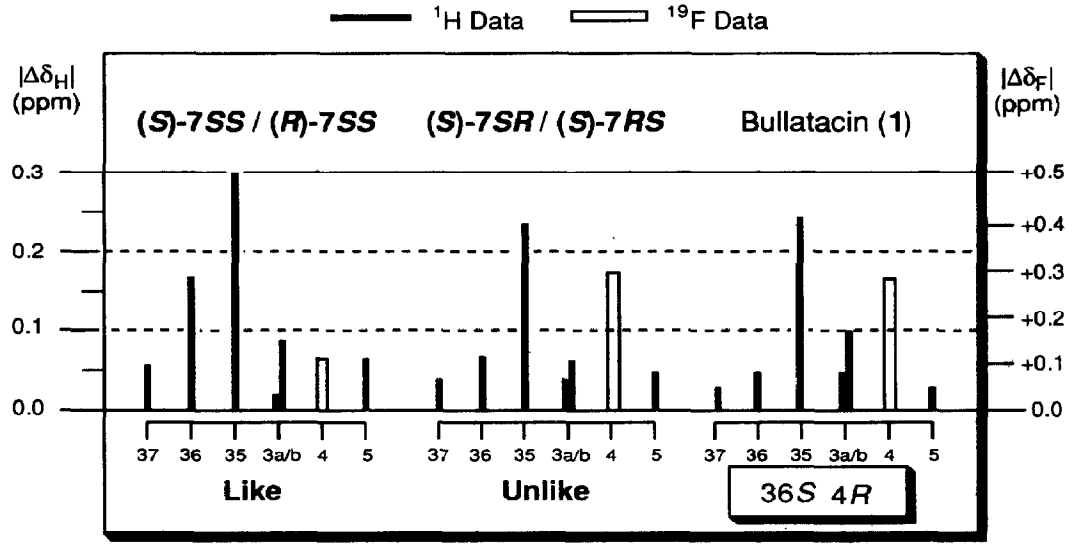
The magnitude of chemical shift differences has not previously been used to deduce the stereochemical features of molecules. The conclusion of unlike configuration between C(4)/C(36) in rolliniastatin I (**3**) and bullatacin (**1**) is validated by the X-ray crystallograpic structure of a rolliniastatin I derivative[7] and the recent total syntheses of *ent*-bullatacin[8] and rolliniastatin I (**3**).[9] We are confident that other opportunities for application of this strategy exist.

Table 1. ^{1}H and ^{19}F NMR Chemical Shift Data for H(5)-H(37)[a] and CF_3(4) from the perMTPA Mosher Esters of the (Synthetic) "Like" Model Butenolide (7*SS*), the Relevant Acetogenins Containing a C(4) Carbinol Center (*i.e.*, 1, 2, 3, 4, and 5), and the (Synthetic) "Unlike" Model Butenolides (7*SR* and 7*RS*).

Entry	Per-MTPA Derivative	MTPA Config	C(4)-C(36) Relationship	Proton Chemical Shifts ($\Delta\delta_H = \delta_S - \delta_R$)					^{19}F Chemical Shifts ($\lvert\Delta\delta_F\rvert = \lvert\delta_S - \delta_R\rvert$)
				H(5) $\lvert\Delta\delta_H\rvert$	H(3) $\lvert\Delta\delta_H\rvert$	H(35)[a] $\lvert\Delta\delta_H\rvert$	H(36)[a] $\lvert\Delta\delta_H\rvert$	H(37)[a] $\lvert\Delta\delta_H\rvert$	CF_3(4)
1	*S,R*-Synthetic Model Butenolide (7*SR*)	*S*	*SR*	1.36	2.60/2.69	7.00	4.94	1.33	4.22
	R,S-Synthetic Model Butenolide (7*RS*)	*S* (*R*)[b]	*RS* (*SR*)[b]	1.41 **0.05**	2.56/2.63 **0.04-0.06**	6.77 **0.23**	4.87 **0.07**	1.29 **0.04**	4.52 **0.30**
2	*S,S*-Synthetic Model Butenolide (7*SS*)	*S*	*SS*	1.35	2.60/2.68	6.98	4.90	1.34	4.33
		R		1.42 **0.07**	2.56/2.59 **0.04-0.09**	6.66 **0.32**	4.73 **0.17**	1.28 **0.06**	4.46 **0.13**
3	Bullatacin (1)	*S*	*RS*	1.64	2.56/2.59	6.72	4.86	1.29	4.87
		R		1.61 **0.03**	2.61/2.69 **0.05-0.10**	6.97 **0.25**	4.91 **0.05**	1.32 **0.03**	4.59 **0.28**
4	Asimicin (2)	*S*	*RS*	1.63	2.56	6.70	4.84	1.26	4.90
		R		1.61 **0.02**	2.58/2.66 **0.02-0.10**	6.96 **0.26**	4.88 **0.04**	1.29 **0.03**	4.63 **0.27**
4	Rolliniastatin 1 (3)	*S*	*RS*	~1.67	2.58	6.73	4.86	1.28	4.87
		R		~1.64 **0.03**	2.60/2.69 **0.02-0.11**	6.97 **0.24**	4.91 **0.05**	1.31 **0.03**	4.60 **0.27**
5	Annonacin-10-one (4)	*S*	*RS*	c	2.56/2.60	6.70	4.86	1.28	4.73
		R			2.59/2.68 **0.03-0.08**	6.94 **0.24**	4.91 **0.05**	1.31 **0.03**	4.36 **0.37**
6	Annonacin (5)	*S*	*RS*	1.61	2.57	6.70	4.84	1.26	4.87
		R		1.56 **0.05**	2.62 **0.05**	6.94 **0.24**	4.88 **0.04**	1.28 **0.02**	4.67 **0.20**

a) The numbering of the carbon skeleton is different for annonacin-10-one (4) and annonacin (5); thus, C(35)-C(37) are actually C(33)-C(35). b) Note that the ^{1}H and ^{19}F NMR data determined for (*S*)-7*RS* are identical to the set of data that could have been extracted from its enantiomer (*R*)-7*SR*. c) $^{1}H/^{1}H$ COSY data were not acquired.

Figure 3



Acknowledgments. This investigation was supported by grant GM-34492 awarded by the DHHS.

References and Notes

1. a) University of Minnesota Graduate School Dissertation Fellow, 1991-92. b) NSF-Lando Undergraduate Research Fellow, 1992.
2. For a review of recent advances in the three-dimensional structure determination of the Annonaceous acetogenins, see: Ramirez, E. A.; Hoye, T. R. in Rahman, A., ed. *Studies in Natural Products*, Amsterdam: Elsevier, in press.
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5. In some of our earliest efforts to synthesize appropriate model butenolides for this study we independently prepared the *like*- and *unlike*- isomers of structure **2** in the preceding Letter. These as well as diastereomers (±)-**6*R**R*** and (±)-**6*R**S*** had virtually identical ^{1}H and ^{13}C NMR spectra. The differences were so slight ($\Delta\delta \leq 0.01$ ppm in ^{1}H NMR and $\Delta\delta \leq 0.2$ ppm in ^{13}C NMR) that we were reluctant to rely upon the comparison of absolute chemical shift values for one or the other model diastereomer with a given natural C(4)-hydroxylated acetogenin having, of course, only a single C(4)/C(36) relationship. Moreover, acetate and benzoate derivatives of **2** were also only barely distinguishable by NMR analysis.
6. For experimental detail, see, e.g., reference 3. Note that *R*-MTPA-Cl provides the *S*-MTPA ester due to Cahn-Ingold-Prelog priority changes.
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(*Received in USA* 16 *August* 1994; *revised* 13 *September* 1994; *accepted* 21 *September* 1994)