

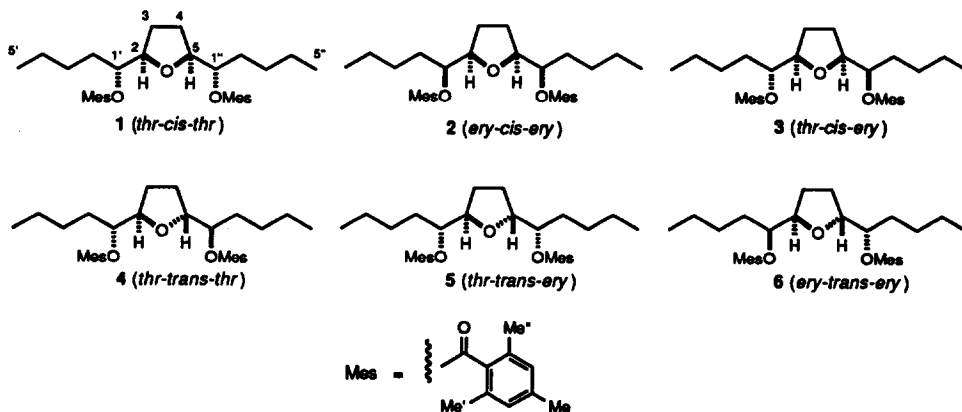
## STEREOCHEMISTRY OF MONO-TETRAHYDROFURANYL MOIETY IN CYTOTOXIC POLYKETIDES. PART B: APPLICATION OF PROTON CHEMICAL SHIFT PATTERNS

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**Abstract.** Dimesitoate esters of  $\alpha,\alpha$ -dibutyl-2,5-tetrahydrofuran dimethanols of different relative stereochemistry showed unique chemical shift patterns in benzene- $d_6$ , which is applicable to the assignment of relative stereochemistry of the mono-tetrahydrofuran moiety of cytotoxic polyketides.

A novel  $^1\text{H-NMR}$ -based approach is devised to assign the relative stereochemistry about mono-tetrahydrofuran (mono-THF) moiety of cytotoxic polyketides.<sup>1</sup> While the synthesis of the model compounds 1 - 6 is reported in the previous letter,<sup>2</sup> the application of this method is elaborated in this letter.



The dimesitoates 1 - 6 represent all the possible relative stereochemical relationship between the dihydroxyl groups and the mono-THF ring. It was found that the proton chemical shifts of the dimesitoates 1 - 6 observed in  $\text{C}_6\text{D}_6$  resulted in diagnostic patterns (Table 1).

Compound	Stereochemistry	$\delta$ H(2, 5)	$\delta$ H(1', 1'')	$\delta$ H (Me', Me'')
1	<i>threo-cis-threo</i>	3.97	5.29	2.45
2	<i>erythro-cis-erythro</i>	3.93	5.45	2.40
3	<i>threo-cis-erythro</i>	3.89, 3.97	5.37, 5.43	2.39, 2.48
4	<i>threo-trans-threo</i>	4.09	5.35	2.45
5	<i>threo-trans-erythro</i>	4.00, 4.11	5.30, 5.52	2.39, 2.51
6	<i>erythro-trans-erythro</i>	4.05	5.48	2.40

Table 1. Selected  $^1\text{H-NMR}$  Shifts of 1 - 6

A *threo* relationship between the methine carbinol group and the mono-THF ring results in: (A) a chemical shift of  $\leq \delta$  5.37 for the ester methine proton of the dimesitoate; and (B) a chemical shift of  $\geq \delta$  2.45 for the methyl groups at the 2,6-positions of the aryl rings of the dimesitoates.

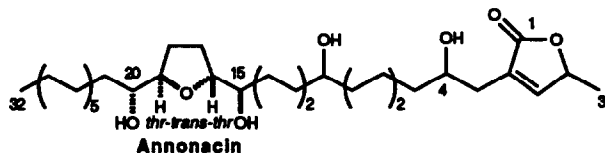
An *erythro* relationship between the methine carbinol group and the mono-THF ring results in: (A) a chemical shift of  $\geq \delta$  5.43 for the ester methine proton of the dimesitoate; and (B) a chemical shift of  $\leq \delta$  2.40 for the methyl groups at the 2,6-positions of the aryl rings of the dimesitoates.

A *cis* relationship of the alkyl groups will result in chemical shifts of  $\delta$  3.89 - 3.97 for the 2,5-protons. On the other hand, a *trans* relationship will result in shifts of  $\delta$  4.00 - 4.11 for the 2,5 protons.

The observed patterns of the model compounds 1 - 6 can be readily applied to the assignment of the relative stereochemistry about the mono-THF moiety of cytotoxic polyketides. First, the polyketide to be studied is converted to its permesitoate.<sup>3</sup> Second, the  $^1\text{H-NMR}$  of the permesitoate is performed in  $\text{C}_6\text{D}_6$  and the data are compared with those of the model mesitoates 1 - 6. The 2,5-protons are indicative of the *cis* versus *trans* relationship, while the 1',1''-protons of the *threo* versus *erythro* relationship.

For symmetrical mono-THF systems, there will be one signal from the ring methine protons (2,5) and one from the ester methine protons (1',1''). Examination of the chemical shift of the tetrahydrofuran ring methine protons in comparison to the range of shifts in the model compounds allows differentiation of *cis* and *trans* stereochemistry. Examination of the ester methine proton chemical shift compared to the model compounds allows assignment to *threo* or *erythro*. For unsymmetrical mono-THF systems, there will be two signals from the ring methine protons and two from the ester methine protons. For assigning the *cis/trans* relationship, only the two signals from the ring methine protons (2,5) should be used for comparison.

Using annonacin as an example, the ring methine protons ( $\delta$  4.13) and the ester methine protons ( $\delta$  5.32) of its mesitoate can be utilized in the assignment. Since there is only one signal from each position, it can be said that annonacin has a symmetrical mono-THF moiety. The chemical shift of  $\delta$  4.13 implies a *trans* relationship, and that of  $\delta$  5.32 a *threo* relationship.



An approach using  $^1\text{H}$  NMR chemical shift data from a set of model diastereomeric bis-tetrahydrofuran acetate derivatives was used by Hoye et al<sup>4a</sup> for determining the relative stereochemistry of the bis-tetrahydrofuran series of polyketides. One can also use the following simple equation to assign the stereochemistry of the mono-tetrahydrofuran series by comparing methine proton signals with the model compounds 1-6. The absolute values of the differences of chemical shifts at each position are added and assignment of stereochemistry is based on the model which exhibits the smallest sum of differences in comparison with the natural product.<sup>4b</sup> The use of this equation in the assignment of annonacin is illustrated in Table 2.

$$\Sigma\Delta\delta\text{H} = |\delta\text{H}_{\text{observed}} - \delta\text{H}_{\text{model}}|_{\text{Ring Methine}} + |\delta\text{H}_{\text{observed}} - \delta\text{H}_{\text{model}}|_{\text{Ester Methine}}$$

Annonacin	Ring Methine		Ester Methine		Assignment	
C15/C16 and C20/C19	$\delta\text{H}_{\text{observed}} = 4.13$		$\delta\text{H}_{\text{observed}} = 5.32$		<i>threo-trans</i>	
Possible Stereochemistry	$\delta\text{H}_{\text{Model}}$	$ \Delta\delta\text{H} $	$\delta\text{H}_{\text{Model}}$	$ \Delta\delta\text{H} $	$\Sigma\Delta\delta\text{H}$	Best Fit
<i>threo-cis</i>	3.97	0.16	5.29	0.03	0.19	
<i>erythro-cis</i>	3.93	0.20	5.45	0.13	0.33	
<i>threo-trans</i>	4.09	0.04	5.35	0.03	0.07	←
<i>erythro-trans</i>	4.05	0.08	5.48	0.16	0.24	

Table 2. Application of Equation to the Assignment of Annonacin.

We have employed the above method to establish the relative stereochemistries about the  $\alpha,\alpha$ -dialkyl-2,5-tetrahydrofurandimethanol moiety for annonacin,<sup>1a</sup> annonacin-10-one,<sup>1c</sup> isoannonacin,<sup>1c</sup> and isoannonacin-10-one<sup>1c</sup> (Table 3). In addition, this method can also be applied to systems with only one hydroxyl group  $\alpha$  to the mono-THF ring as in the case of densicomacins.<sup>5</sup> Therefore, this  $^1\text{H-NMR}$ -based method is applicable to all mono-THF moiety assignments. A complementary study has recently been completed by Hoye and co-workers.<sup>6</sup>

Polyketide	$\delta H_{\text{observed}}$ Of Ring Methine	$\delta H_{\text{observed}}$ Of Ester Methine	Assignment
Annonacin	4.13	5.32	<i>threo-trans</i>
Annonacin-10-one	4.11	5.30	<i>threo-trans</i>
Isoannonacin	4.13	5.33	<i>threo-trans</i>
Isoannonacin-10-one	4.11	5.31	<i>threo-trans</i>
10,13- <i>trans</i> -13,14- <i>erythro</i> -Densicomacin	4.12	5.54	<i>erythro-trans</i>
10,13- <i>trans</i> -13,14- <i>threo</i> -Densicomacin	4.09	5.36	<i>threo-trans</i>

Table 3. Application of Method to Various Polyketides

### Acknowledgments

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