Determination of Absolute Configuration of Stereogenic Carbinol Centers in Annonaceous Acetogenins by ^{1}H- and ^{19}F-NMR Analysis of Mosher Ester Derivatives

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Abstract: The absolute configuration of the stereogenic carbinol centers in nine annonaceous acetogenins has been determined by careful ^{1}H- and ^{19}F-NMR analysis of (*S*)- and (*R*)-Mosher ester [methoxy(trifluoromethyl)phenylacetate or MTPA] derivatives. These acetogenins include five adjacent bis-tetrahydrofuran acetogenins [uvaricin (**3**), bullatacin (**4**), bullatacinone (**5**), asimicin (**6**), and rolliniastatin 1 (**7**)] and four mono-tetrahydrofuran acetogenins [reticulatacin (**8**), isoannonacin-10-one (**9**), annonacin-10-one (**10**), and annonacin (**11**)]. Importantly, the configuration at the C(4) carbinol center in all of the biologically most significant acetogenins examined here is *R*. The validity of the refined Mosher methodology[8c] for assigning absolute carbinol stereochemistry in several specific substructural regions of these acetogenins was established by analysis of the MTPA esters of appropriate synthetic model compounds. These possessed unambiguous absolute (as well as relative) stereochemistry. It was demonstrated that the analysis of proton and fluorine NMR data from atoms flanking carbinol centers is always a valid strategy for assigning absolute configuration at any of the carbinol centers, given the availability of suitable model compounds of known absolute configuration. The interpretation of the fluorine NMR data, however, must be performed with caution. Although there are clearly identifiable trends among the fluorine data, whether they are indicative of *R* or *S* absolute configuration is dependent upon quite subtle local structural features.

Introduction

Annonaceous acetogenins are a rapidly growing class of new naturally occurring polyketide-derived fatty acid derivatives isolated from a number of plants in the Annonaceae. A review[1a] has been published describing the sources, isolation, chemistry, biogenesis, and biological activities[1b] of these new compounds. Because of their multiple stereogenic centers and the likely importance of stereochemistry for their bioactivities, the determination of all the stereochemical issues in this type of compound is an important concern. The waxy, amorphous, or microcrystalline nature of these compounds has, thus far, usually rendered them unsuitable for direct X-ray crystallographic studies.[2] Methodology has been developed previously to determine the *relative* stereochemical relationships among the stereogenic carbon atoms around the THF rings,[3,4] and a technique has been published previously for determining the *relative* stereochemistry of a stereogenic carbinol center adjacent to a tetrahydrofuran ring.[2b] The *absolute* configuration at C(36) of uvaricin and desacetyluvaricin has been determined by ozonolysis and subsequent chromatographic comparison with the appropriate derivatives of (*R*)- and (*S*)-lactic acid.[5] The *absolute* configuration at C(4) for bullatacinone and bullatalicinone has been suggested by comparisons of the CD spectra of these compounds with those of the model compound, rubrenolide.[6,7] However, there is ambiguity associated with the last of these methods.[1a] Among the reported adjacent bis-tetrahydrofuran acetogenins, at least ten structures (uvaricin, asimicin, bullatacin, rolliniastatin 1, 4-hydroxy-25-desoxyneorollinicin, annonin VI, annonareticin, 14-hydroxy-25-desoxyrollinicin (revised), rollinicin 2, and laherradurine)[1a] have the same skeleton of contiguous carbon atoms. Determination of the relative stereochemistries has differentiated some of the C(15)–C(24) diastereomeric relationships in this series, such as those found in uvaricin, asimicin, bullatacin, rolliniastatin 1, and 4-hydroxy-25-desoxyneorollinicin. In this paper we describe the determination of the *absolute* configurations of stereogenic carbinol centers in several annonaceous acetogenins using Mosher ester methodology.[8]

The Mosher ester technique is an empirically derived method to determine the absolute configuration[8a-c] (and enantiomeric excess)[8e] of stereogenic centers bearing hydroxyl (or amino) groups. The chiral alcohol (or amine) is first coupled with each of the individual enantiomers of the Mosher acid chloride. The optically pure Mosher acid of *R* configuration [(*R*)-MTPA] is converted to the acid chloride of *S* configuration [(*S*)-MTPA-Cl] and then on to the MTPA ester of *R* configuration.[9] The ^{1}H-

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(1) (a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (b) It has been determined recently that acetogenins such as asimicin act as inhibitors (IC_{50} in the subnanomolar range) of complex I in the mitochondrial electron transport systems: Lewis, M. A.; Arnason, J. T.; Philogene, B. J. R.; Rupprecht, J. K.; McLaughlin, J. L. *Pestic. Biochem. Physiol.*, in press.

(2) Exceptions for which single-crystal X-ray data have been successfully obtained are (a) the 15-*O*-(*p*-bromophenyl)urethane derivative of rolliniastatin 1 (Pettit, G. R.; Cragg, G. M.; Polonsky, J.; Herald, D. L.; Goswami, A.; Smith, C. R.; Meretti, C.; Schmidt, J. M.; Wiesleder, D. *Can. J. Chem.* **1987**, *65*, 1433) and (b) the dihydro and lactone-hydrolyzed carboxylate salt of annonin I Born, L.; Lieb, F.; Lorentzen, J. P.; Moeschler, H.; Nonfon, M.; Söllner, R.; Wendisch, D. *Planta Med.* **1990**, *56*, 312).

(3) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4402.

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(5) (a) 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. (b) Jolad, S. D.; Hoffmann, J. J.; Cole, J. R.; Barry, C. E., III; Bates, R. B.; Linz, G. S.; Konig, W. A. *J. Nat. Prod.* **1985**, *48*, 644.

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(7) Hui, Y. H.; Rupprecht, J. K.; Anderson, J. E.; Wood, K. V.; McLaughlin, J. L. *Phytother. Res.* **1991**, *5*, 124.

(8) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (d) For reasons other than determination of absolute stereochemistry, the recommendation has been made to routinely record MTPA data on all newly isolated acetogenins: Fujimoto, Y.; Murasaki, C.; Kakinuma, K.; Eguchi, T.; Ikekawa, N.; Furuya, M.; Hirayama, K.; Ikekawa, T.; Sahai, M.; Gupta, Y. K.; Ray, A. B. *Tetrahedron Lett.* **1990**, *31*, 535. (e) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

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Table I. ^{1}H-NMR Chemical Shift Data[a] for H(14)–H(25) from the (*S*)- and (*R*)-Per-MTPA Mosher Ester Derivatives of the (Synthetic) Model Bis-Tetrahydrofuran **12**, (Synthetic) *hexepi*-Uvaricin (**13**), and the (Natural) Acetogenins Containing th/t/th/t/... Relative Stereochemistry among C(15)–C(24) (**3–6**) and the Mono-Mosher Ester Derivatives of **5** and **12**

entry	Per-MTPA Derivative (carbinol)	MTPA config	Proton Chemical Shifts ($\Delta\delta_H = \delta_S - \delta_R$)					Carbinol Configuration
			H(14) $\Delta\delta_H$	H(16) $\Delta\delta_H$	H(19)/H(20) $\Delta\delta_H$	H(23) $\Delta\delta_H$	H(25) $\Delta\delta_H$	C(15) C(24)
1	Model bis-THF (**12**)	*S*	1.62, 1.58 } pos	3.96, 4.06 } neg	3.63, 3.81 } neg	3.96, 4.06 } neg	1.62, 1.58 } pos	*R* *R*
	er/t/th/t/er	*R*						
2	Hexepi-Uvaricin (**13**)	*S*	1.50, 1.62 } neg	4.03, 4.03 } zero	3.87-3.92, 3.79-3.86 } pos	3.92, 3.91 } na[b]	na[b]	*S* (*R*)[b]
	th/t/th/t/er	*R*						
3	Uvaricin (**3**)	*S*	1.62, 1.50 } pos	4.03, 4.03 } zero	3.79-3.86, 3.87-3.92 } neg	3.91, 3.92 } na[b]	na[b]	*R* (*S*)[b]
	th/t/th/t/er	*R*						
4	Bullatacin (**4**)	*S*	1.59, 1.45 } pos	4.03, 3.97 } pos	3.76-3.83, 3.83/3.65 } [c]	3.99, 3.90 } pos	1.53, 1.57 } neg	*R* *S*
	th/t/th/t/er	*R*						
5	Bullatacinone (**5**)	*S*	[d]	4.04, 4.00 } pos	3.80, 3.83/3.65 } [c]	3.99, 3.94 } pos	[d]	*R* *S*
	th/t/th/t/er	*R*						
6	Asimicin (**6**)	*S*	1.56, 1.45 } pos	3.93, 3.97 } neg	3.76, 3.92 } neg	3.93, 3.97 } neg	1.56, 1.45 } pos	*R* *R*
	th/t/th/t/th	*R*						
	mono-MTPA Derivative (carbinol)							
7	Model bis-THF (**12**)	*S*	1.63, 1.59 } pos	4.05, 4.13 } neg	3.60/3.81-3.87, 3.80/3.89-3.92 } neg	3.81-3.87, 3.89-3.92 } neg	1.37, 1.37 } zero	*R* *R*
	15-mono-MTPA ester	*R*						
8	Bullatacinone (**5**)	*S*	[d]	4.083, 4.075 } ~zero	[d]	[d]	[d]	*R* *S*
	15-MTPA ester	*R*						
9	Bullatacinone (**5**)	*S*	[d]	[d]	[d]	4.11, 4.03 } pos	[d]	*R* *S*
	24-MTPA ester	*R*						

[a] All chemical shifts > δ 2.0 are determined directly from the 1D ^{1}H-NMR spectrum whereas, because of the large degree of overlap among the resonances, all shifts < δ 2.0 are carefully estimated from the center of the relevant COSY off-diagonal peaks. [b] Not applicable since the C(24) hydroxyl is acetylated in **13** and **3**. [c] Effects from both ends are in opposition. [d] ^{1}H/^{1}H COSY data were not acquired.

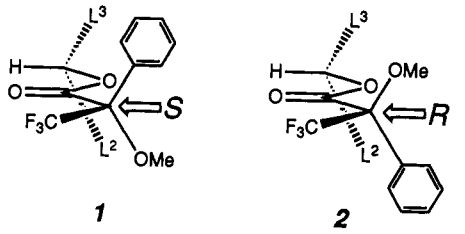


Figure 1.

NMR and ^{19}F-NMR spectra of the Mosher ester derivatives are then obtained. The absolute configuration of the carbinol (or amine) center can then be deduced by comparison of the chemical shifts in the ^{1}H-NMR or ^{19}F-NMR spectra of the (*R*)-MTPA and (*S*)-MTPA esters.

The recent refinement of the Mosher method developed by Kakisawa and Kashman[8c] points out the advantages of analysis based upon the more reliable proton NMR chemical shifts as well as ambiguity inherent in the use of fluorine chemical shift data for the assignment of configuration. The Mosher argument assumes that the most stable conformation of the (*S*)-MTPA ester is as shown in **1** (Figure 1). Protons in the L^3 portion of this molecule are, therefore, more highly shielded (and appear further upfield), and those in the L^2 moiety are less highly shielded (and appear further downfield). The reverse is true for the (*R*)-MTPA ester **2** (Figure 1). The difference in chemical shift of any set of like protons in the diastereomeric (*S*)- and (*R*)-MTPA esters ($\Delta\delta_H = \delta_S - \delta_R$) will therefore be positive in value when associated with L^2 and negative in value when associated with L^3. This method gives greater reliability, in part, because modern NMR techniques often permit the identification of a number of like sets of protons within L^n, thereby reinforcing the assignment made by a comparison of the chemical shifts of only a single set.[8c]

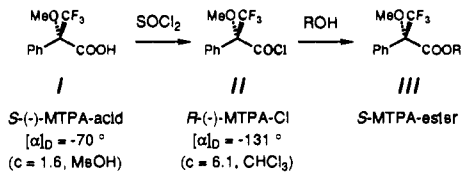
In contrast the fluorine shift data necessarily allow only a single point comparison. Moreover, it requires that one know confidently which of the diastereomers **1** and **2** has a greater population of the most stable conformation having the CF_3 group in the deshielding plane of the carbonyl (as shown in Figure 1). The relative energies of the various conformers generated upon rotation about the carbonyl carbon to benzylic carbon bond, in turn, is dependent upon sometimes subtle differences in through-space steric (and electronic) effects between L^n and Ph or MeO.

We have used this refined Mosher ester strategy[8c] to examine the absolute stereochemistries of certain stereogenic centers of several annonaceous acetogenins [uvaricin (**3**), bullatacin (**4**), bullatacinone (**5**), asimicin (**6**), rolliniastatin 1 (**7**), reticulatacin (**8**), isoannonacinon-10-one (**9**), annonacin-10-one (**10**), and annonacin (**11**)] and describe the results here.

Results and Discussion

MTPA Proton Data for Carbinol Centers Flanked by THF Rings: Validation of Synthetic Model Compounds and Application to Uvaricin. Uvaricin (**3**), bullatacin (**4**), bullatacinone (**5**), and asimicin (**6**) [and rolliniastatin 1 (**7**)] (Figure 2) belong to the subgroup of adjacent, or 2,5-linked, bis-tetrahydrofuran acetogenins. Each of **3–6** is now (vide infra for **4** and **5**) known to

(9) A referee has commented on the possible confusion that arises over a nomenclature issue first clearly noted by Mosher (ref 8a, footnote 46). Namely, Cahn–Ingold–Prelog priority interchange accompanies each of the chemical conversions of the MTPA acid to MTPA-Cl and of MTPA-Cl to the MTPA ester. That is, the *S* acid (I) gives rise to the *S* ester (III) but by way of the *R* acid chloride (II), and vice versa. This is a particularly crucial detail now that both enantiomers of MTPA-Cl (as well as the MTPA acid) are commercially available (e.g., Aldrich Catalog, 1992–1993).



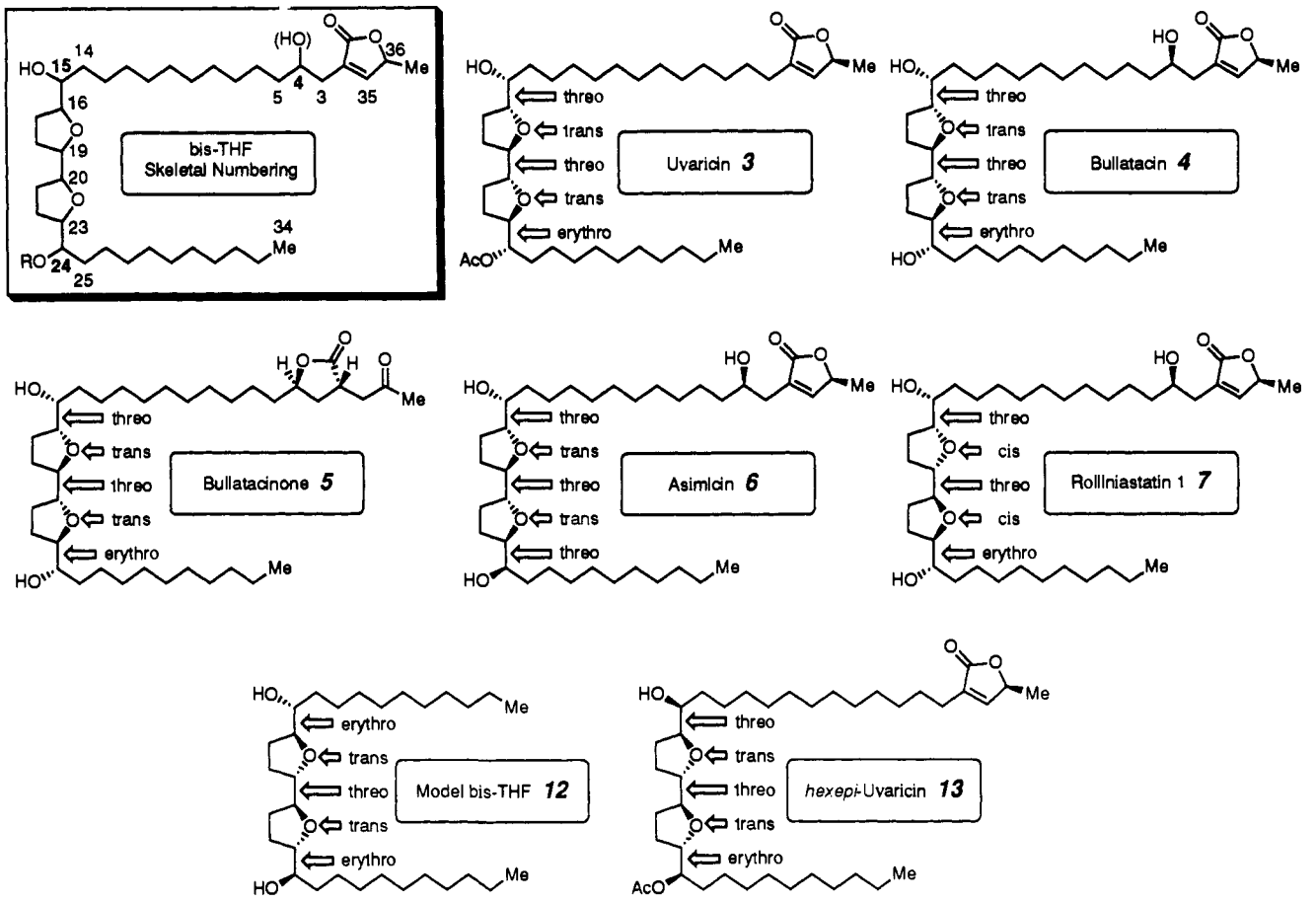


Figure 2.

have relative stereochemical relationships of threo between C(15) and C(16), trans between (or across) C(16) and C(19), threo between C(19) and C(20), and trans between (or across) C(20) and C(23). These relationships are denoted by th/t/th/t/er for **3–5** and th/t/th/t/th for **6**. Preliminary verification of the Mosher methodology to this substructural unit was obtained by analysis of the two synthetically prepared bis-tetrahydrofurans **12**[10a] and **13**[10b] (15,16,19,20,23,24-*hexepi*-uvaricin) (Figure 2). Because of the means of their preparation, these two compounds possess the unambiguous relative and absolute stereochemistry shown.

Relevant proton NMR data for the bis-(*R*)- and bis-(*S*)-Mosher esters of the C_2-symmetric bis-THF diol **12** having er/t/th/t/er relative stereochemistry are summarized in entry 1 of Table I. Note that the carbon skeleton numbering for **12** (as well as for other model compounds described later) follows that of uvaricin and the other bis-THF acetogenins. The synthetic derivatives *S*-MTPA-**12** and *R*-MTPA-**12** are known to have the *R* configuration at both C(15) and C(24). Therefore, the methylene protons H(14) reside in L[2] (cf. Figure 1), and the methine protons H(16) and H(19) lie within L[3]. As shown in Figure 3, the sign of $\Delta\delta_H$ [$=(\delta_S - \delta_R)$] is therefore positive for H(14) [and H(25)], negative for H(16) [and H(23)], and negative for H(19) [and H(20)]. In other words, H(16) and H(19) are relatively more shielded, and H(14) is relatively less shielded, in *S*-MTPA-**12** because of their various proximities to the phenyl ring.

All of the proton NMR data reported here were collected at 500 MHz. A comparison of a few random spectra at both 500 and 300 MHz suggested that the great majority of information can be extrapolated at both field strengths, even when the $\Delta\delta$

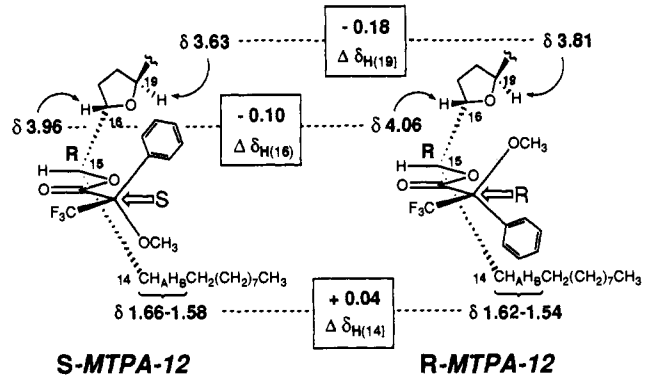


Figure 3.

values are as small as ~0.02 ppm. One potential limitation to 300-MHz data is that the additional field dispersion is very useful in permitting confident assignment of small chemical shift differences of protons residing in the aliphatic envelope [i.e., H(5), H(14), H(17–18), H(21–22), and H(25)]. These were identified by ^{1}H–^{1}H COSY techniques.

For synthetic *hexepi*-uvaricin (**13**)[10b] (entry 2, Table I), which has the unambiguous relative and absolute stereochemistry shown in Figure 2, C(15) is of *S* configuration. As expected, then, $\Delta\delta_H$ for H(14) is negative and $\Delta\delta_H$ for H(19)/H(2) is positive. Unexpectedly, $\Delta\delta_H$ for H(16) is ~0 (vide infra). ^{1}H-NMR data arising from the C(14)–C(25) region of the MTPA derivatives of natural uvaricin (**3**) (entry 3, Table I) clearly indicate the mirror image relationship between the C(14)–C(25) portions of uvaricin and *hexepi*-uvaricin (**13**). In fact, it was only upon comparison of these MTPA data from **3** and **13** that their stereochemical differences were revealed.[10b] That fact, in turn, permitted the entire stereo structure of uvaricin to be assigned as **3** for the first time.

(10) (a) Prepared analogously to the compound numbered **11c** in Hoye and Suhadolnik (Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855); i.e., the bis primary tosylate related to the compound numbered **5** in ref 10b was coupled with lithium di-*n*-nonylcuprate. (b) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *114*, 9369.

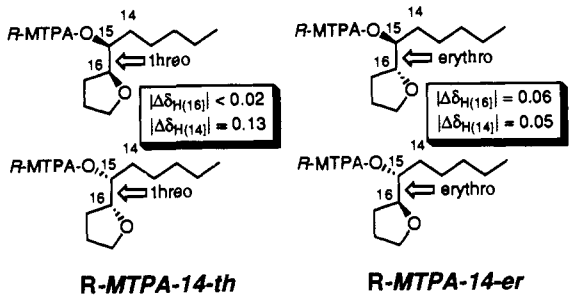


Figure 4.

That $\Delta\delta_H$ for H(16) in both MTPA-3 and MTPA-**13** is 0 was surprising. It was therefore necessary to identify a set of compounds of known stereochemistry which would be suitable to model these circumstances. Thus, we prepared the (*R*)-Mosher esters *R*-MTPA-**14**-th and *R*-MTPA-**14**-er from a racemic mixture of each of the two (threo and erythro) diastereomers of the corresponding mono-tetrahydrofuran carbinols (Figure 4).[11a,b] The $\Delta\delta_H$ for H(16) in the C(15)/C(16)-threo diastereomers *R*-MTPA-**14**-th is also approximately 0 (overlapping resonances in the spectrum of the mixture, with $\Delta\delta_H < 0.02$ ppm). Although the reason(s) for a ~0 value of $\Delta\delta_H$ for H(16) in the threo isomers is not clear, it is reassuring that this outcome is reproduced in the model compounds. Incidentally, note that there is good correlation of the remaining $\Delta\delta_H$ values shown in Figure 4 with the relevant H(14) and H(16) data in entries 1–3 of Table I. This point is further supported by data obtained from the mono-MTPA ester derivatives of **12** and bullatacinone (**5**) (entries 7–9). Once again, the $\Delta\delta_H$ for H(16) having a C(15)/C(16)-erythro relationship and H(23) having a C(23)/C(24)-erythro relationship is 0.08 (entries 7 and 9), whereas the $\Delta\delta_H$ for H(16) having a C(15)/C(16)-threo relationship is ~0 (entry 8).

MTPA Fluorine Data for All Carbinol Centers Flanked by THF Rings. Fluorine NMR analysis has frequently been used for making assignments of the configuration of MTPA esters.[8b] However, Kakisawa and Kashman have cautioned that conclusions based on ^{19}F-NMR analysis are often in error and must be scrutinized with care.[8c] The fundamental arguments are again based on the assumption of the preferred conformations **1** and **2** (Figure 1). The trifluoromethyl group prefers the illustrated rotamer, in which it is eclipsed with the carbonyl group and is, therefore, within its deshielding cone. The relative extent of this preference for conformers **1** and **2** is assumed to be largely dependent upon the magnitude of the steric interaction between the large phenyl group and the carbinol substituents L^2 and L^3. For example, if L^3 in **1** and **2** is larger than L^2, the destabilizing L^3/phenyl interaction in conformer **1** of the (*S*)-MTPA ester will result in the trifluoromethyl group spending less time in the carbonyl deshielding plane (relative to conformer **2** for the (*R*)-MTPA ester). Consequently, $\Delta\delta_F$ [$=(\delta_S - \delta_R)$] for the CF_3 resonance in the ^{19}F-NMR spectra will be negative. Alternatively, if L^3 in **1** and **2** is smaller than L^2, $\Delta\delta_F$ will be positive.

The ^{19}F-NMR data at C(15) and C(24) for the MTPA ester derivatives of **12**, **13**, and **3**–**6** are summarized in Table II. In synthetic *hexepi*-uvaricin (**13**) the configuration at C(15) is *S*. Thus, L^3 contains the smaller, unbranched C(14)–C(1) subunit, and L^2 comprises the larger, α-branched bis-THF moiety commencing with C(16). As expected from the arguments presented in the last paragraph, $\Delta\delta_F$ is positive for CF_3(15) in the MTPA esters of **13** (entry 2, Table II). Similarly, the MTPA esters of synthetic, C_2-symmetric model compound **12** have the *R* configuration at C(15) and C(24). Accordingly, the $\Delta\delta_F$ values are negative (entry 1, Table II). Thus, ^{19}F-based assignments of configuration of those carbinol centers directly flanking a THF ring in these systems are valid.

(11) (a) Unpublished results of P. R. Hanson. (b) Details of the synthesis of the carbinol precursors to **14**-th and **14**-er will be reported elsewhere. (c) Unpublished results of Z. Zhuang. (d) Details of the synthesis of **15** and its related stereoisomers will be reported elsewhere.

TAble II. ^{19}F-NMR Chemical Shift Data for CF_3(15) and CF_3(24) from the (*S*)- and (*R*)-Per-MTPA Mosher Ester Derivatives of the (Synthetic) Model Bis-Tetrahydrofuran **12**, (Synthetic) *hexepi*-Uvaricin (**13**), and the (Natural) Acetogenins Containing th/t/th/t/... Relative Stereochemistry among C(15)–C(24) (**3**–**6**) and the C(15)- and C(24)-Mono-Mosher Ester Derivatives of **5**

entry	per-MTPA Derivative	MTPA Config	Fluorine Chemical Shifts		Carbinol Configuration	
			CF_3(15)	CF_3(24)	H(15)	H(24)
1	Model bis-THF (12) er/t/th/t/er	*S*	4.37	4.37	*R*	*R*
		R	4.40 } neg	4.40 } neg		
2	*hexepi*-Uvaricin (13) 1h/t/th/t/er	*S*	4.37	na	*S*	(*R*)[a]
		R	3.97 } pos	na		
3	Uvaricin (3) 1h/t/th/t/er	*S*	3.97	na	*R*	(*S*)[a]
		R	4.41 } neg	na		
4	Bullatacin (4) th/t/th/t/er	*S*	4.06	4.45	*R*	*S*
		R	4.42 } neg	4.38 } pos		
5	Bullatacinone (5) th/t/th/t/er	*S*	4.11	4.48	*R*	*S*
		R	4.45 } neg	4.41 } pos		
6	Asimicin (6) 1h/t/th/t/1h	*S*	4.09	4.05	*R*	*R*
		R	4.42 } neg	4.42 } neg		
	mono-MTPA Derivatives of 5					
7	Bullatacinone (5) 15-MTPA ester	*S*	4.14	X	*R*	*S*
		R	4.46 } neg			
8	Bullatacinone (5) 24-MTPA ester	*S*	X	4.45	*R*	*S*
		R		4.39 } pos		

[a] Not applicable since the C(24) hydroxyl is acetylated in **13** and **3**.

The $\Delta\delta_F$ for uvaricin (**3**) MTPA esters is negative, reinforcing the C(15) *R* assignment (entry 3, Table II). Likewise, the negative $\Delta\delta_F$ values in bullatacin (**4**), bullatacinone (**5**), and asimicin (**6**) MTPA esters suggest an associated *R* configuration, and the postive $\Delta\delta_F$ values an *S* configuration, at the pertinent carbinol centers (entries 4–8, Table II).

MTPA Proton Data for Carbinol Centers Flanking THF Rings in Bullatacin (4), Bullatacinone (5), and Asimicin (6). Bullatacinone (**5**) and bullatacin (**4**) contain nonidentical vicinal stereochemical relationships between C(15) and C(16) and between C(23) and C(24).[6] Which of these is erythro and which is threo (i.e., the "endedness", or distinction between er/t/th/t/th and th/t/th/t/er) was previously ambiguous for these unsymmetrical C(15), C(24)-diols. In the course of generating and interpreting NMR data for the bis- and tris-MTPA esters of **5** and **4**, respectively, it became useful to prepare various bis- and mono-MTPA esters, respectively. After separation it was possible to determine the position of esterification by analysis of mass spectral fragmentation patterns, which are summarized in Figure 5a–c for C(15),C(24)-bis- and C(15)- and C(24)-mono-MTPA esters of bullatacinone and in Figure 6a–c for C(4),C(15),C(24)-tris- and C(4),C(15)- and C(4),C(24)-bis-MTPA esters of bullatacin, respectively. These clearly establish the positional nature of these partial MTPA derivatives. Analysis of ^{13}C- and ^{1}H-NMR data from some of these derivatives unambiguously allowed the assignment of the *relative* configurations between C(15) and C(16) as threo [unesterified carbinol carbon and proton resonances for, e.g., the ester shown in Figure 5b: δ 71.45, C(24), and 3.8–4.0, H(24)][11a,12] and between C(23) and C(24) as erythro [unesterified carbinol carbon and proton resonances for, e.g., the ester shown in Figure 5c: δ 74.03, C(15), and 3.37, H(15)].[11a,12] Thus, the C(15)–C(24) *relative* stereochemistry in both bullatacin (**4**) and bullatacinone (**5**) is th/t/th/t/er and not er/t/th/t/th. Note that bullatacin has been chemically converted into bullatacinone, thereby establishing stereochemical identity throughout C(15)–C(24).[6] Also note that the endedness issue for uvaricin (**3**) was naturally solved as a consequence of the presence of the C-(24)-acetate in **3**.

The ^{1}H as well as ^{19}F $\Delta\delta$ values for bullatacin (**4**) and bullatacinone (**5**) per-MTPA esters (entries 4 and 5 of Tables I and II, respectively) suggest the assignment of the *S* configuration

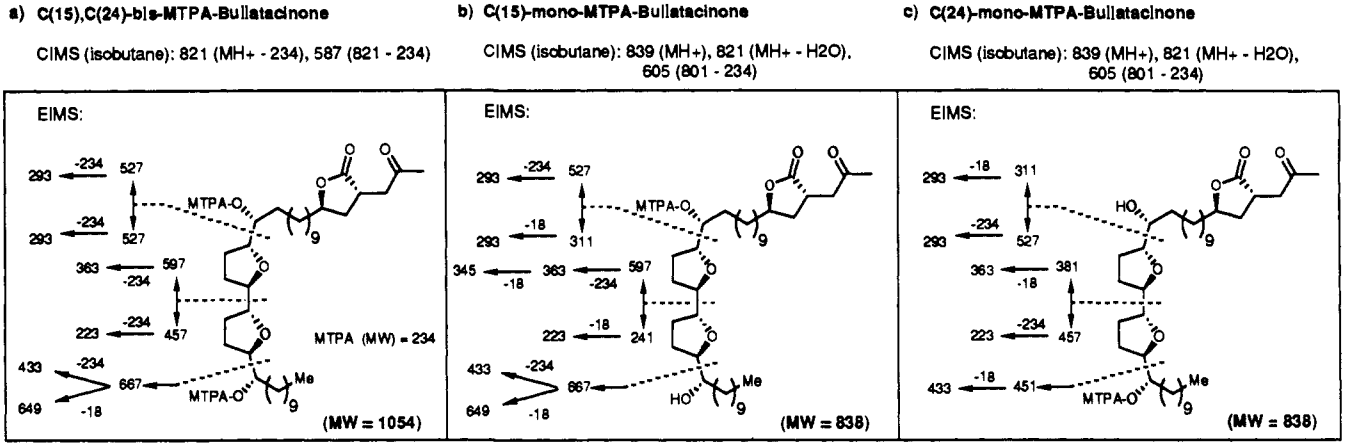


Figure 5.

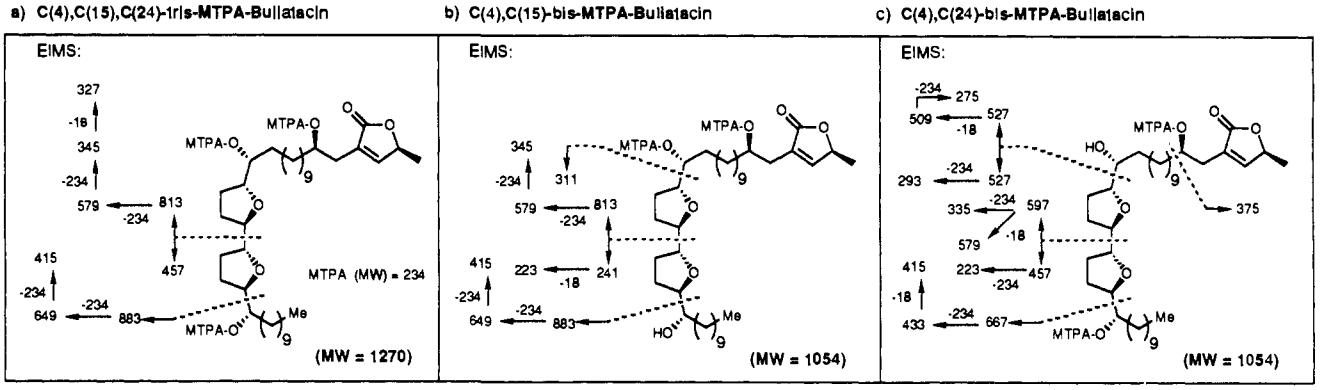


Figure 6.

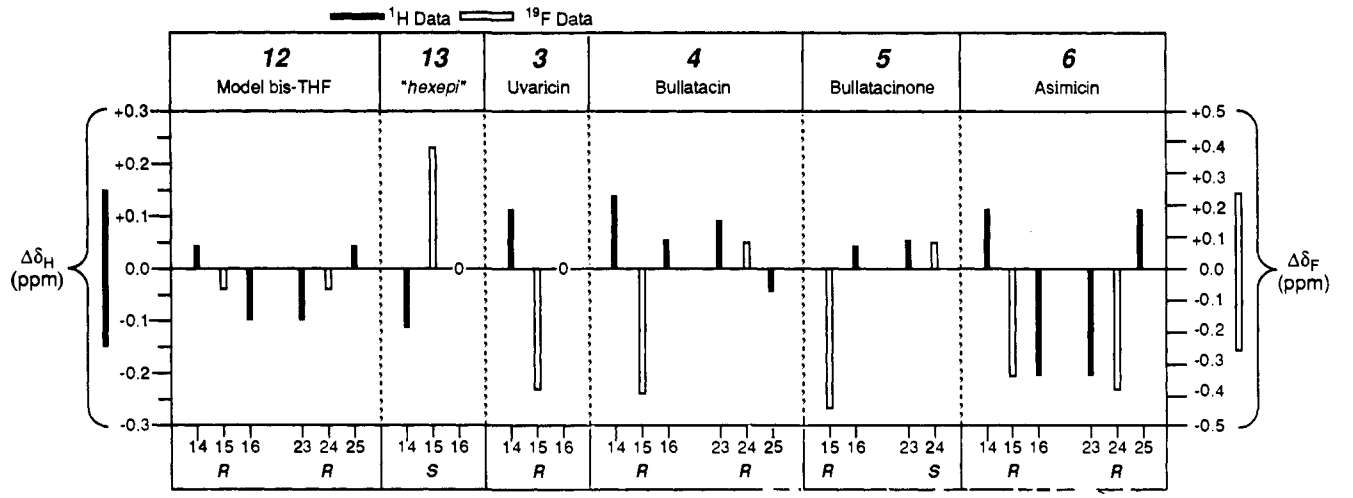


Figure 7.

to C(24) [$\Delta\delta_H$ for H(23) is positive, and $\Delta\delta_F$ for CF_3(24) is positive]. Given the relative th/t/th/t/er stereochemistry, it follows that C(15) has the *R* configuration. This is supported by the positive $\Delta\delta_H$ value for H(14) is the tris-MTPA derivatives of **4** (entry 4, Table I). The careful reader may be troubled at this juncture by the apparent inconsistency created by the positive $\Delta\delta_H$ value for H(16) in entries 4 and 5 of Table I. Notice, however, that $\Delta\delta_H$ for H(16) in the 15-mono-MTPA derivatives of **5** (entry 8, Table I) is ~0. This is entirely consistent with the C(15)/C(16)-threo relationship as discussed earlier. Thus, the anomalous positive $\Delta\delta_H$ value for H(16) noted above is a consequence of the presence of the additional Mosher ester at C(24). That is, there are long-range, through-space influences superimposed on the more local anisotropic effects. We see these effects elsewhere among the data, they are internally consistent, and we intend to comment upon them elsewhere when additional model mono-MTPA derivative data are in hand.

Asimicin (**6**) is known to have the locally symmetrical relative stereochemistry th/t/th/t/th among C(15)–C(24).[1a,4] The ^1H and ^{19}F $\Delta\delta$s for asimicin (**6**) per-MTPA esters (entry 6 of Tables I and II, respectively) definitively prove that the configuration of both C(15) and C(24) is *R*. Note that the entire set of both $\Delta\delta_H$ and $\Delta\delta_F$ values for the MTPA derivatives of the symmetrical model bis-THF **12**, which also contains 15*R*,24*R* stereochemistry, are of identical sign to those of asimicin (**6**).

In order to provide a more simplistic, yet useful, representation of the data in Tables I and II, we have graphed the ^1H and ^{19}F $\Delta\delta$ values for the diagnostic protons surrounding the C(15) and C(24) carbinol centers (Figure 7). The graphic representation clearly shows the change in the sign of $\Delta\delta_H$ on either side of the

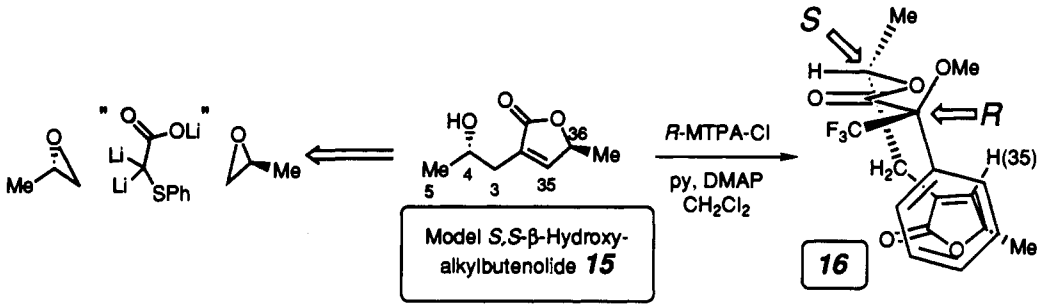


Figure 8.

Table III. ^{1}H- and ^{19}F-NMR Chemical Shift Data for H(5)–H(37)[a] and CF_3(4) from the (*S*)- and (*R*)-Per-MTPA Mosher Ester Derivatives of the (Synthetic) Model Butenolide **15** and the Relevant Acetogenins Containing a C(4) Carbinol Center (**4**, **6**, **7**, **10**, and **11**)

entry	Per-MTPA Derivative	MTPA Config	Proton Chemical Shifts ($\Delta\delta_H = \delta_S - \delta_R$)					Carbinol Config	^{19}F Chemical Shifts ($\Delta\delta_F = \delta_S - \delta_R$)
			H(5) $\Delta\delta_H$	H(3) $\Delta\delta_H$	H(35)[a] $\Delta\delta_H$	H(36)[a] $\Delta\delta_H$	H(37)[a] $\Delta\delta_H$	C(4)	CF_3(4)
1	*S*,*S*-Synthetic Model Butenolide (**15**)	*S*	1.35	2.60/2.68	6.98	4.90	1.34	*S*	4.33
		R	1.42 } neg	2.57 } pos	6.66 } pos	4.73 } pos	1.28 } pos		4.46 } neg
2	Bullatacin (**4**)	*S*	1.64	2.56	6.72	4.86	1.29	*R*	4.87
		R	1.61 } pos	2.61/2.69 } neg	6.97 } neg	4.91 } neg	1.32 } neg		4.59 } pos
3	Asimicin (**6**)	*S*	1.63	2.56	6.70	4.84	1.26	*R*	4.90
		R	1.61 } pos	2.58/2.66 } neg	6.96 } neg	4.88 } neg	1.29 } neg		4.63 } pos
4	Rolliniastatin 1 (**7**)	*S*	~1.67	2.58	6.73	4.86	1.28	*R*	4.87
		R	~1.64 } pos	2.60/2.69 } neg	6.97 } neg	4.91 } neg	1.31 } neg		4.60 } pos
5	Annonacin-10-one (**10**)	*S*	[b]	2.56/2.60	6.70	4.86	1.28	*R*	4.73
		R		2.59/2.68 } neg	6.94 } neg	4.91 } neg	1.31 } neg		4.36 } pos
6	Annonacin (**11**)	*S*	1.61	2.57	6.70	4.84	1.26	*R*	4.87
		R	1.56 } pos	2.62 } neg	6.94 } neg	4.88 } neg	1.28 } neg		4.67 } pos

[a] The numbering of the carbon skeleton is different for annonacin-10-one (**10**) and annonacin (**11**); thus, C(35)–C(37) are actually C(33)–C(35). [b] ^{1}H/^{1}H COSY data were not acquired.

carbinol center in question. Notice how the graphic representation clearly displays the C_2 symmetry of the synthetic model compound (**12**) as well as the local C_2 symmetry of asimicin (**6**). The mirror relationship about C(15)–C(24) in *hexepi*-uvaricin (**13**) and uvaricin (**3**) is also highlighted with such a graph.

Proton and Fluorine MTPA Data of the Acetogenins Containing C(4) Carbinol Centers. The assignment of configuration at C(4) to the subset of 4-hydroxylated acetogenins was initially confounded by the fact that ^{1}H- and ^{19}F-based analyses led to conflicting outcomes. It was again necessary to prepare a model substrate of unambiguous absolute (and relative) stereochemistry for the 2-(β-hydroxyalkyl)-4-methylbutenolide subunit of the relevant acetogenins. Therefore, the butenolide **15**, having *S* configuration at both C(4) and C(36), was synthesized using two (*S*)-propylene oxide molecules through the strategy summarized in Figure 8.[11c,d] The relevant ^{1}H and ^{19}F chemical shift data for **15** (bis-THF acetogenin numbering) and the other C(4)-hydroxylated acetogenins (**4**, **6**, **7**, **10**, and **11**; see Figures 2 and 10) are summarized in Table III.

Given that the C(4) carbinol configuration is *S*, the MTPA esters of butenolide **15** clearly show the expected sign of the $\Delta\delta_H$ values for H(5) (negative), H(3) (positive), and H(35–37) (positive) (entry 1, Table III). The large positive magnitude of the $\Delta\delta_H$ for H(35) is particularly diagnostic. However, the $\Delta\delta_F$ is negative for CF_3(4). This is the opposite of that expected for the *S* configuration, assuming that the C(3)-containing substituent is larger than the C(5) methyl group (vide supra). Apparently there are additional subtle factors which dictate the carbonyl carbon to α-carbon bond conformation preferences within **1** and **2** for cases where L^2 and L^3 are both *unbranched at the attachment carbon*. Such is the case in **15**. The conformation of the (*R*)-MTPA derivative of **15**, which is shown as **16** (Figure 8), suggests that a possible favorable π–π interaction between the phenyl and butenolide groups might be sufficient to override the presumably small steric difference between L^2 and L^3 in **15**. Therefore, for the assignment of the C(4) stereochemistry using ^{19}F data, a negative value of $\Delta\delta_F$ implies the *S* configuration, and vice versa. All of the $\Delta\delta_H$ and $\Delta\delta_F$ data for C(4) of bullatacin (**4**), asimicin (**6**), rolliniastatin 1 (**7**), annonacin-10-one (**10**), and annonacin (**11**) (entries 2–6 of Table III) are internally consistent. Moreover, they allow the assignment of *R* configuration to C(4) of all of the 4-hydroxylated natural acetogenins we have examined.

Recall that the relative stereochemistry within rolliniastatin 1 (**7**) was determined through X-ray analysis.[2a] Given that the absolute configuration at C(4) is *R*, the entire stereo structure of the molecule can now be drawn as represented by **7** in Figure 2. We did not include a discussion of the C(15)–C(24) NMR data derived from Mosher MTPA derivatives of **7**, because the analysis is not straightforward, and we do not yet have access to any synthetic derivatives with a cis–cis relationship across the two THF rings [as is the case for rolliniastatin 1 (**7**)].

We have depicted the configuration of the methyl-bearing butenolide carbon [C(36) or C(34)] as *S* for acetogenins **3**, **4**, **6**, **7**, **10** and **11**. This was known previously for uvaricin (**3**) because of the degradation study in which **3** was converted to a lactic acid derivative,[5b] and it follows for rolliniastatin 1 (**7**) because of the X-ray structure, which defines all relative relationships.[2a] Further spectroscopic observations with MTPA esters of additional stereoisomers of the model butenolide **15** [i.e., the 4*R**(*S**),36*S**(*R**) isomers] allow us to conclude that this relationship also exists in the 4-hydroxy acetogenins **4**, **6**, **10**, and **11**. Discussion of those details will be presented elsewhere.[11a,c,d]

In order to highlight the data in Table III, we have again provided a graphic representation of the ^{1}H and ^{19}F $\Delta\delta$ values for the diagnostic protons surrounding the C(4) carbinol center in the model (*S*,*S*)-butenolide (**15**) and in bullatacin (**4**) (Figure 9).

Table IV. ^{1}H- and ^{19}F-NMR Chemical Shift Data for H(14)[a]–H(21)[a] from the (*S*)- and (*R*)-Per-MTPA Mosher Ester Derivatives of the Mono-Tetrahydrofuran-Based Acetogenins Containing th/t/th Relative Stereochemistry among C(15)[a]–C(20)[a] (**8–11**)

entry	Per-MTPA Derivative	MTPA Config	Proton Chemical Shifts ($\Delta\delta_H = \delta_S - \delta_R$)					Carbinol Configuration		^{19}F chemical shift ($\Delta\delta_F = \delta_S - \delta_R$)	
			H(14)[b] $\Delta\delta_H$	H(16)[b] $\Delta\delta_H$	H(17)[b] $\Delta\delta_H$	H(19)[b] $\Delta\delta_H$	H(21)[b] $\Delta\delta_H$	C(15)[b]	C(20)[b]	CF_3(15)[b]	CF_3(20)[b]
1	Reticulatacin (**8**)[a] th/t/th	*S*	c	4.01, 4.06 neg	c	4.01, 4.06 neg	c	*R*	*R*	4.27, 4.53 neg	4.27, 4.53 neg
		R									
2	Isoannonacin-10-one (**9**) th/t/th	*S*	c	3.86, 3.98 neg	c	3.86, 3.98 neg	c	*R*	*R*	4.03, 4.29 neg	3.93, 4.25 neg
		R									
3	Annonacin-10-one (**10**) th/t/th	*S*	c	3.92, 4.01 neg	c	3.92, 4.00 neg	c	*R*	*R*	3.99, 4.31 neg	3.89, 4.27 neg
		R									
4	Annonacin (**11**) th/t/th	*S*	1.53/1.46, 1.48/1.42 pos	3.89, 3.98 neg	1.61/1.47, 1.89/1.58 neg	3.89, 3.98 neg	1.53/1.46, 1.48/1.42 pos	*R*	*R*	4.11, 4.53 neg	4.19, 4.53 neg
		R									

[a] The numbering of the carbon skeleton is different for reticulatacin (**8**); thus, C(15)/C(16)/C(19)/C(20) are actually C(17)/C(18)/C(21)/C(22). [b] Due to local C_2 symmetry, the protons H(14)/H(21); H(16)/H(19); and H(17)/H(18) are interchangeable. [c] ^{1}H/^{1}H COSY data were not acquired.

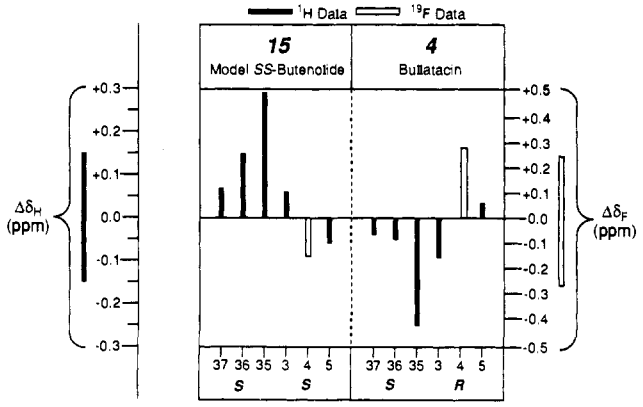


Figure 9.

This representation again clearly shows the change in the sign of $\Delta\delta_H$ on either side of the C(4) carbinol center, as well as the opposite configuration of the C(4) carbinol centers in **15** (4*S*,36*S*) and **4** (4*R*,36*S*). Notice the differences in the magnitides of the $\Delta\delta$ values between **15** and **4**. The graphical representation clearly shows the differences between the set of like configurations at C(4) and C(36) contained in **15** and the set of unlike configurations contained in **4** (as well as in the other acetogenins of Table III, i.e., **6**, **7**, **10**, and **11**). As mentioned in the previous paragraph, these details will be presented elsewhere.[11a,c,d]

Proton and Fluorine MTPA Data for the Mono-THF-Containing Acetogenins Reticulatacin (8), Isoannonacin-10-one (9), Annonacin-10-one (10), and Annonacin (11). Several acetogenins containing a single tetrahydrofuran ring have also been examined (Figure 10). We have confidently assigned the absolute configuration of the carbinol centers flanking this THF ring in four of them, namely, reticulatacin (**8**), isoannonacin-10-one (**9**), annonacin-10-one (**10**), and annonacin (**11**). Both the proton and fluorine NMR data are summarized in Table IV. Note that the numbering of the carbon skeleton in reticulatacin (**8**) is different. The relative th/t/th relationships for these four acetogenins were known from previous work.[11a,12] The negative values of $\Delta\delta_H$ for H(16) and $\Delta\delta_F$ for CF_3(15) both support the assignment of *R* configuration for C(15); those for $\Delta\delta_H$ for H(19) and $\Delta\delta_F$ for CF_3(20) both support the assignment of *R* configuration for C(20). Therefore, the stereo structures shown in Figure 10 for **8–11** represent all of the unambiguous assignments that are known to date for these mono-THF-containing acetogenins.

Conclusion

The absolute configuration of the stereogenic carbinol centers in the five adjacent bis-tetrahydrofuran acetogenins uvaricin (**3**), bullatacin (**4**), bullatacinone (**5**), asimicin (**6**), and rolliniastatin 1 (**7**) and in the four mono-tetrahydrofuran acetogenins reticulatacin (**8**), isoannonacin-10-one (**9**), annonacin-10-one (**10**), and annonacin (**11**) has been determined. When taken in conjunction with established *relative* stereochemical information, the approach used here allows the assignment of the previously unknown absolute configuration of these natural products. This strategy will clearly be applicable to future structural studies among the annonaceous acetogenins. Finally, it is reassuring that a number of the independent assignments of *absolute* configuration made here within a given molecule reinforce the *relative* assignments of stereochemistry made in our earlier studies based solely upon analyses of proton chemical shift data.

Experimental Section

General Information. The seven annonaceous acetogenins bullatacin,[6] bullatacinone,[6] asimicin,[13] reticulatacin,[14] annonacin,[15] annonacin-10-one,[16] and isoannonacin-10-one,[16] were isolated in one of our laboratories from plants in the Annonaceae. Uvaricin was provided by Professors J. R. Cole and J. J. Hoffmann (University of Arizona), and rolliniastatin 1 was provided by Dr. C. R. Smith (of Professor G. R. Pettit's laboratory at Arizona State University).

^{1}H-NMR, 2D-COSY, and ^{13}C-NMR spectra were recorded on a Varian VXR-500S spectrometer, and ^{19}F-NMR spectra were recorded on a Varian VXR-300 spectrometer. Proton chemical shifts are referenced to either TMS (δ 0.00) or residual $CHCl_3$ (δ 7.25) as indicated; carbon chemical shifts are referenced to $CDCl_3$ (δ 77.00). ^{19}F-NMR spectra were recorded in $CDCl_3$ with 0.25% TFA (δ 0.00) as an external standard. Mass spectral data were obtained on a Finnigan 4000 or VG 7070-HF spectrometer.

Preparation and Purification of Mosher Esters. A mixture of the starting acetogenin (usually 4–10 mg) and a 10-fold millimolar excess over starting material of (*R*)- or (*S*)-MTPA, 1-hydroxybenzotriazole hydrate (HOBT), and 4-(dimethylamino)pyridine (DMAP) in 1 mL of CH_2Cl_2 containing 3 drops of *N*,*N*-dimethylformamide (DMF) was stirred at room temperature until everything was dissolved. An excess of 1,3-dicyclohexylcarbodiimide (DCC) was rapidly added, and the resulting mixture was stirred at room temperature overnight (a white precipitate formed after several minutes). The reaction mixture was filtered, and the filtrate was concentrated and chromatographed over a silica gel microcolumn (eluted with 0 → 50% EtOAc in hexane in 10% increments) to give the purified Mosher ester products. For the monoesters of bullatacinone, H refers to the purified compound having the higher R_f and L refers to the purified compound having the lower R_f in a TLC system of hexane/EtOAc (6:4) on silica gel. The TLC solvent system of $CHCl_3$/MeOH (9:1) over silica gel was used to check for the disappearance of the starting acetogenin, and the TLC solvent system of

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(16) (a) Xu, L.; Chang, C.-J.; Yu, J.-G.; Cassady, J. M. *J. Org. Chem.* **1989**, *54*, 5418. (b) The relative stereochemistry for annonacin-10-one and isoannonacin-10-one has been determined (unpublished results of M. J. Rieser).

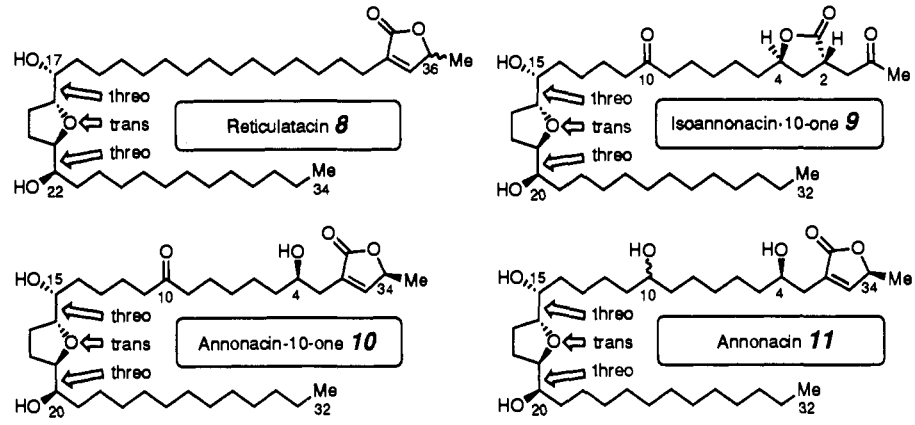

Figure 10.

hexane/EtOAc (6:4) over silica gel was used to check for the degree of derivatization for mono-, di-, and triesterification.

A more efficient preparation involves direct acylation of the carbinols with MTPA-Cl.[8,9,17] A detailed example of such a preparation including the preparation of MTPA-Cl is described below for uvaricin (3).

Preparation of Mosher Acid Chloride.[9,17] Into a 10-mL round-bottom flask equipped with a reflux condenser, a magnetic stirring bar, and a drying tube were placed *S*(or *R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1.0 g, 4.3 mmol), thionyl chloride (3.5 mL, 5.7 g, 47.9 mmol), and sodium chloride (15.9 mg, 0.27 mmol). The reaction mixture was refluxed at 90 °C (bath temperature) for 2 days and then cooled. The thionyl chloride was removed by using a water aspirator (equipped with a dry ice/acetone trap to minimize back diffusion of moisture) while the reaction mixture was stirred in a water bath at room temperature. The Mosher acid chloride was purified by Kugelrohr (bulb to bulb) distillation (40–45 °C at 0.6 mmHg) as a clear colorless liquid. Yield: 0.96 g, 89% [(*S*)-(+)-MTPA-Cl, prepared from the (*R*)-(+)-MTPA acid,[9] had $[\alpha]^{24}_{D} = +129.8°$ (c = 1.92, CCl_4)]. The product was stored under nitrogen in a desiccator. It is convenient to store the MTPA-Cl in a Teflon-lined, septum-capped vial (like various Wheaton vials); a Teflon-lined, screw-capped, 13-mm culture tube (like Corning No. 9826); or a Mininert vial fitted with a Mininert slider valve (e.g., Supelco 3-3300).

Preparation of the C(15)-(*S*)-MTPA Ester of Natural (+)-Uvaricin (3). To a stirred solution of (+)-uvaricin (3, 1.0 mg, 1.5 μmol) in CH_2Cl_2 (200 μL) at room temperature in a 10-mL pear-shaped flask (or screw-capped culture tube) was sequentially added pyridine [predried over activated (~350 °C, ≥4 h) 4-Å molecular sieves; 100 μL], 4-(dimethylamino)pyridine (0.5 mg, 4 μmol, 2.5 equiv), and (*R*)-MTPA-Cl[9] (~5 μL, 0.027 mmol, 17 equiv). (The extent of excess MTPA-Cl can usually be substantially reduced, particularly more so as the reaction scale is increased). After the mixture was allowed to sit for 3 h at room temperature (reaction progress can be conveniently monitored by TLC), saturated $NaHCO_3$ (~3 mL) and Et_2O (~3 mL) were added. This mixture was stirred vigorously for 30 min to allow for the efficient hydrolysis of the excess MTPA-Cl. The organic phase was separated, and the aqueous phase was extracted with Et_2O (~5 mL, 2×). The organic phases were combined, washed three times with $NaHSO_4$ (5% aqueous solution, to remove pyridine) and brine, dried ($MgSO_4$), and concentrated under reduced pressure to leave a crude yellow oil. If pyridine remained, benzene was added (~10 mL) and removed by rotary evaporation to azeotropically remove the last traces of pyridine. Flash chromatography through a $^1/_4$- × ~2.5-in. bed of silica gel in a disposable pipet (3:1 hexane/EtOAc) gave 1.2 mg (90%) of (*S*)-MTPA-3 as a light yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.61 (m, 2 H, Ar*H*), 7.40 (m, 3 H, Ar*H*), 6.99 [d, 1 H, J = 1.5 Hz, C=C(35)*H*], 5.05 [ddd, 1 H, J ~ 6, 6, 6 Hz, C(15)*H*O_2C], 5.00 [dtq, 1 H, J ~ 1.5, 1.5, 7.0 Hz, C(36)*H*CH_3], 4.89 [ddd, 1 H, J ~ 9.0, 4.5, 4.5 Hz, C(24)*H*OAc], 4.03 [ddd, 1 H, J ~ 7, 7, 7 Hz, C(16)*H*O], 3.91 [ddd, 1 H, J ~ 6, 6, 6 Hz, C(23)HO], 3.83 [m, 2 H, C(19)*H*O, C(20)*H*O], 3.56 (s, 3 H, OCH_3), 2.26 [dt, 2 H, J ~ 1.5, 7 Hz, CH_2C(3)H_2], 2.038 (s, 3 H, CH_3CO), 1.93 [m, 1 H, C(17)H_aH_b, from COSY], 1.90–1.55 [m, 6 H, C(18,21,22)H_2, from COSY], 1.62 [m, 2 H, C(14)H_aH_b, from COSY], 1.55 [m, 1 H, C(17)H_aH_b, from COSY], 1.54 [m, 2 H, C(4)H_2, from COSY], 1.52 [m, 2 H, C(25)H_aH_b, from COSY], 1.40 [d, 3 H, J = 7 Hz, C(37)H_3], 1.36–1.20 [m, 34 H, C(5–13)H_2, C(26–33)H_2], 0.89 [t, 3 H, J = 6.7 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 3.97 [CF_3(15)]; IR ($CDCl_3$) 2928, 2856, 1747, 1602, 1467, 1456, 1374, 1320, 1257, 1242, 1171, 1120, 1081, 1025, 1025 cm^{-1}; TLC R_f = 0.3 (3:1 hexane/EtOAc).

C(15)-(*R*)-MTPA ester of natural (+)-uvaricin (3): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.64 (m, 2 H, Ar*H*), 7.39 (m, 3 H, Ar*H*), 6.99 [d, 1 H, J = 1.5 Hz, C=C(35)*H*], 5.05 [ddd, 1 H, J ~ 7, 7, 7 Hz, C(15)*H*O_2C], 4.99 [dtq, 1 H, J ~ 1.5, 1.5, 7.0 Hz, C(36)-*H*CH_3], 4.90 [ddd, 1 H, J ~ 9.0, 4.5, 4.5 Hz, C(24)*H*OAc], 4.03 [ddd, 1 H, J ~ 7, 7, 7 Hz, C(16)*H*O], 3.92 [ddd, 1 H, J ~ 6, 6, 6 Hz, C(23)HO], 3.89 [m, 2 H, C(19)*H*O, C(20)*H*O], 3.64 (s, 3 H, OCH_3), 2.26 [dt, 2 H, J = 1.3, 6.8 Hz, C(3)H_2], 2.045 (s, 3 H, CH_3CO), 2.03 [m, 1 H, C(17)H_aH_b, from COSY], 1.96–1.64 [m, 6 H, C(18,21,22)H_2, from COSY], 1.60 [m, 1 H, C(17)H_aH_b, from COSY], 1.52 [m, 4 H, C(4)H_2 and C(25)H_aH_b, from COSY], 1.50 [m, 2 H, C(14)H_aH_b, from COSY], 1.40 [d, 3 H, J = 7.0 Hz, C(37)H_3], 1.34–1.14 [m, 34 H, C(5–13)H_2, C(26–33)H_2], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.41 [CF_3(15)]; IR (solution, $CDCl_3$) 3693, 3606, 2928, 2855, 1747, 1602, 1467, 1371, 1320, 1251, 1172, 1120, 1081, 1026 cm^{-1}; HRMS (FAB) calcd for $C_{49}H_{76}O_9F_3$ (M + H$^+$) 865.5441, found 865.5406; calcd for $C_{49}H_{75}O_9F_3$Na (M + Na) 887.5261, found 887.5257; TLC R_f = 0.3 (3:1 hexane/EtOAc).

C(15)-(*S*)-MTPA ester of synthetic (+)-15,16,19,20,23,24-*hexepi*-uvaricin (13): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.64 (m, 2 H, Ar*H*), 7.39 (m, 3H, Ar*H*), 6.99 [d, 1 H, J = 1.5 Hz, C=C(35)*H*], 5.05 [ddd, 1 H, J ~ 7, 7, 7 Hz, C(15)*H*O_2C], 4.99 [brq, 1 H, J ~ 7 Hz, C(36)*H*CH_3], 4.90 [ddd, 1 H, J ~ 9.0, 4.5, 4.5 Hz, C(24)*H*OAc], 4.03 [ddd, 1 H, J ~ 7, 7, 7 Hz, C(16)*H*O], 3.92 [ddd, 1 H, J ~ 6, 6, 6, Hz, C(23)*H*O], 3.89 [m, 2 H, C(19)*H*O, C(20)*H*O], 3.64 (s, 3 H, OCH_3), 2.26 [brt, 2 H, J ~ 7 Hz, C(3)H_2], 2.044 (s, 3 H, CH_3CO), 2.03 [m, 1 H, C(17)H_aH_b, from COSY], 1.96–1.64 [m, 6 H, C(18,21,22)H_2, from COSY], 1.60 [m, 1 H, C(17)H_aH_b, from COSY], 1.52 [m, 4 H, C(4)H_2, C(25)H_aH_b, from COSY], 1.50 [m, 2 H, C(14)H_aH_b, from COSY], 1.40 [d, 3 H, J = 7.0 Hz, C(37)H_3], 1.34–1.14 [m, 34 H, C(5–13)H_2, C-(26–33)H_2], and 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.37 [CF_3(15)]; IR ($CDCl_3$) 2929, 2856, 1750, 1602, 1467, 1450, 1371, 1320, 1251, 1172, 1122, 1081, 1026 cm^{-1}; HRMS (FAB) calcd for $C_{49}H_{76}O_9F_3$ (M + H$^+$) 865.5441, found 865.5438; calcd for $C_{49}H_{75}O_9$-F_3Na (M + Na) 887.5261, found 887.5314; TLC R_f = 0.3 (3:1 hexane/EtOAc).

C(15)-(*R*)-MTPA ester of synthetic (+)-15,16,19,20,23,24-*hexepi*-uvaricin (13): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.61 (m, 2 H, Ar*H*), 7.40 (m, 3 H, Ar*H*), 6.99 [d, 1 H, J = 1.5 Hz, C=C(35)*H*], 5.05 [ddd, 1 H, J ~ 6, 6, 6 Hz, C(15)*H*O_2C], 5.00 [brq, 1 H, J ~ 7 Hz, C(36)*H*CH_3], 4.89 [ddd, 1 H, J ~ 9.0, 4.5, 4.5 Hz, C(24)*H*OAc], 4.03 [ddd, 1 H, J ~ 7, 7, 7 Hz, C(16)*H*O], 3.91 [ddd, 1 H, J ~ 6, 6, 6 Hz, C(23)*H*O], 3.83 [m, 2 H, C(19)*H*O, C(20)*H*O], 3.56 (s, 3 H, OCH_3), 2.26 [brt, 2 H, J ~ 7 Hz, C(3)H_2], 2.037 (s, 3 H, CH_3CO), 1.93 [m, 1 H, C(17)H_aH_b, from COSY], 1.90–1.50 [m, 6 H, C(18,21,22)H_2, from COSY], 1.62 [m, 2 H, C(14)H_aH_b, from COSY], 1.55 [m, 1 H, C-(17)H_aH_b, from COSY], 1.54 [m, 2 H, C(4)H_2, from COSY], 1.52 [m, 2 H, C(25)H_aH_b, from COSY], 1.40 [d, 3 H, J = 7.0 Hz, C(37)H_3], 1.25 [m, 34 H, C(5–13)H_2 and C(26–33)H_2], 0.88 [t, 3 H, J = 6.7 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 3.97 [CF_3(15)]; IR ($CDCl_3$) 2928, 2855, 1747, 1602, 1467, 1450, 1372, 1320, 1251, 1172, 1120, 1081, 1026 cm^{-1}; HRMS (FAB) calcd for $C_{49}H_{76}O_9F_3$ (M + H$^+$) 865.5441, found 865, 5453; calcd for $C_{49}H_{75}O_9F_3$Na (M + Na) 887.5261, found 887.5287; TLC R_f = 0.3 (3:1 hexane/EtOAc).

C(15),C(24)-Bis-(*S*)-MTPA ester of synthetic model bis-THF (12): ^{1}H NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.55 (4 H, Ar*H*), 7.44–7.37 (6 H, Ar*H*), 5.23 [ddd, 2 H, J ~ 6, 6, 6 Hz, C(15)*H*O,

(17) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165 and references cited therein.

C(24)*HO*], 3.96 [ddd, 2 H, $J \sim 6, 6, 6$ Hz, C(16)*HO*, C(23)*HO*], 3.63 [m, 2 H, C(19)*HO*, C(20)*HO*], 3.55 (s, 6 H, MeO-15, MeO-24), 1.80 [m, 2 H, C(17)H_aH_b, C(22)H_aH_b], 1.75 [m, 2 H, C(18)H_aH_b, C(21)H_aH_b], 1.64 [m, 2 H, C(17)H_aH_b, C(22)H_aH_b], 1.62 [m, 4 H, C(14)H_aH_b, C(25)H_aH_b], 1.60 [m, 2 H, C(18)H_aH_b, C(21)H_aH_b], 1.31–1.19 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 0.88 [t, 3 H, J = 7.3 Hz, C(5)H_3, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.37 [CF_3(15)], [CF_3(24)].

C(15),C(24)-Bis-(*R*)-MTPA ester of synthetic model bis-THF (12): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.58 (4 H, Ar*H*), 7.42–7.38 (6 H, Ar*H*), 5.28 [ddd, 2 H, J = 7.9, 4.0, 4.0 Hz, C(15)*HO*, C(24)*HO*], 4.06 [m, 2 H, C(16)*HO*, C(23)*HO*], 3.81 [m, 2 H, C(19)-*HO*, C(20)*HO*], 3.54 (s, 6 H, MeO-15, MeO-24), 1.94 [m, 2 H, C-(17)H_aH_b, C(22)H_aH_b], 1.85 [m, 2 H, C(18)H_aH_b, C(21)H_aH_b], 1.76 [m, 2 H, C(17)H_aH_b, C(22)H_aH_b], 1.70 [m, 2 H, C(18)H_aH_b, C-(21)H_aH_b], 1.58 [m, 4 H, C(14)H_aH_b, C(25)H_aH_b], 1.36–1.14 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 0.88 [t, 3 H, J = 6.7 Hz, C(5)H_3, C-(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.40 [CF_3(15)], [CF_3(24)].

C(15)-Mono-(*S*)-MTPA ester of synthetic model bis-THF (12): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.57 (2 H, Ar*H*), 7.39 (3 H, Ar*H*), 5.29 [ddd, 1 H, $J \sim 6, 6, 6$ Hz, C(15)*HO*], 4.05 [ddd, 1 H, $J \sim 6, 6, 6$ Hz, C(16)*HO*], 3.87–3.81 [m, 3 H, C(19)*HO* or C(20)*HO*, C(23)*HO*, C(24)*HO*], 3.60 [ddd, 1 H, $J \sim 7, 7, 7, 7$ Hz, C(19)*HO* or C(20)*HO*], 3.57 (s, 3 H, MeO-15), 1.95–1.48 [m, 6 H, from among C(18,21,22)H_2], 1.86 [m, 1 H, C(17)H_aH_b], 1.72 [m, 1 H, C(17)H_aH_b], 1.63 [m, 2 H, C(14)H_aH_b], 1.37 [m, 2 H, C(25)H_aH_b] 1.40–1.21 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 0.881 [t, 3 H, J = 7.0 Hz, C(5)H_3 or C(34)H_3], 0.879 [t, 3 H, J = 6.7 Hz, C(5)H_3 or C(34)H_3].

C(15)-Mono-(*R*)-MTPA ester of synthetic model bis-THF (12): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.61–7.57 (2 H, Ar*H*), 7.39 (3 H, Ar*H*), 5.33 [ddd, 1 H, J = 7.7, 4.5, 4.5 Hz, C(15)*HO*], 4.13 [m, 1 H, C(16)*HO*], 3.92–3.89 [m, 3 H, C(19)*HO* or C(20)*HO*, C(23)*HO*, C(24)*HO*], 3.80 [ddd, 1 H, $J \sim 7, 7, 7$ Hz, C(19)*HO* or C(20)*HO*], 3.54 (s, 3 H, MeO-15), 2.01–1.55 [m, 6 H, from among C(18,21,22)H_2], 1.94 [m, 1 H, C(17)H_aH_b], 1.81 [m, 1 H, C(17)H_aH_b], 1.59 [m, 2 H, C-(14)H_aH_b], 1.37 [m, 2 H, C(25)H_aH_b], 1.41–1.15 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 0.883 [t, 3 H, J = 6.8 Hz, C(5)H_3 or C(34)H_3], 0.878 [t, 3 H, J = 7.0 Hz, C(5)H_3 or C(34)H_3].

C(4),C(15),C(24)-Tris-(*S*)-MTPA ester of (+)-bullatacin (4): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.63–7.51 (6 H, Ar*H*), 7.43–7.36 (9 H, Ar*H*), 6.72 [d, 1 H, J = 1.1 Hz, C(35)*H*], 5.32 [m, 1 H, C(4)*HO*], 5.26 [ddd, 1 H, J = 4.7, 4.2, 6.2 Hz, C(15)*HO*], 5.07 [q, 1 H, J = 6.2 Hz, C(24)*HO*], 4.86 [qq, 1 H, J = 6.7, 1.2 Hz, C(36)-*H*CH_3], 4.03 (q, 1 H, J = 6.2 Hz, C(16)*HO*], 3.99 [m, 1 H, C(23)*HO*], 3.83–3.76 [m, 2 H, C(19)*HO*, C(20)*HO*], 3.55 (s, 3 H, MeO-24), 3.53 (s, 3 H, MeO-15), 3.52 (s, 3 H, MeO-4), 2.58–2.53 [m, 2 H, C(3)H_aH_b], 2.00–1.11 [m, 40 H, C(6–13)H_2, C(17,18,21,22)H_2, C(26–33)H_2], 1.64 [m, 2 H, C(5)H_aH_b], 1.59 [m, 2 H, C(14)H_aH_b], 1.53 [m, 2 H, C-(25)H_aH_b], 1.29 [d, 3 H, J = 6.8 Hz, C(37)H_3], 0.88 [t, 3 H, J = 6.9 Hz, C(34)H_3], 0.88 [t, 3 H, J = 6.9 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.87 [CF_3(4)], 4.45 [CF_3(24), 4.06 [CF_3(15)].

C(4),C(15),C(24)-Tris-(*R*)-MTPA ester of (+)-bullatacin (4): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.7–7.5 (6 H, Ar*H*), 7.45–7.30 (9 H, Ar*H*), 6.97 [d, 1 H, J = 1.7 Hz, C(35)*H*], 5.39 [ddd, 1 H, C(4)*HO*], 5.24 [q, 1 H, J = 6.2 Hz, C(24)*HO*], 5.03 [q, 1 H, J = 6.2 Hz, C(15)*HO*], 4.91 [qq, 1 H, J = 6.7, 1.2 Hz, C(36)*H*CH_3], 3.97 (q, 1 H, J = 7.4 Hz, C(16)*HO*], 3.90 [ddd, 1 H, J = 7.2, 6.3, 5.1 Hz, C(23)*HO*], 3.83 [ddd, 1 H, J = 8.1, 6.7, 4.0 Hz, C(19)*HO* or C(20)*HO*], 3.65 [m, 1 H, C(19)*HO* or C(20)*HO*], 3.62 (s, 3 H, MeO-24), 3.55 (s, 3 H, MeO-15), 3.50 (s, 3 H, MeO-4), 2.69 [ddt, 1 H, J = 15.0, 8.0, 1.4 Hz, C(3)H_aH_b], 2.61 [dddd, 1 H, J = 15.0, 4.0, 1.5, 1.1 Hz, C(3)H_aH_b], 2.05–1.00 [m, 40 H, C(6–13)H_2, C(17,18,21,22)H_2, C(26–33)H_2], 1.61 [m, 2 H, C(5)H_aH_b], 1.57 [m, 2 H, C(25)H_aH_b], 1.45 [m, 2 H, C-(14)H_aH_b], 1.32 [d, 3 H, J = 6.8 Hz, C(37)H_3], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.59 [CF_3(4)], 4.42 [CF_3(15)], 4.38 [CF_3(24)].

C(15),C(24)-Bis-(S)-MTPA ester of (+)-Bullatacinone (5): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.62–7.59 (2 H, Ar*H*), 7.59–7.56 (2 H, Ar*H*), 7.41–7.36 (6 H, Ar*H*), 5.25 [ddd, 1 H, J = 8.2, 4.2, 4.2 Hz, C(24)*HO*], 5.07 [q, 1 H, J = 6.2 Hz, C(15)*HO*], 4.55 [dddd, 1 H, C(4)*HO*CO, minor], 4.39 [dddd, 1 H, C(4)*HO*CO, major], 4.04 (q, 1 H, J = 6.2 Hz, C(16)*HO*], 3.99 [ddd, 1 H, J = 8.1, 6.1, 3.8 Hz, C(23)*HO*], 3.80 [m, 2 H, C(19)*HO*, C(20)*HO*], 3.55 (s, 3 H, MeO-15), 3.53 (s, 3 H, MeO-24), 3.14–2.98 [m, 2 H, C(2)*H*CO_2, C-(35)H_aH_bCOCH_3], 2.71–2.57 [m, 2 H, C(3)H_aH_bC*H*CO_2, C-(35)H_aH_bCOCH_3], 2.20 [m, 1 H, C(3)H_aH_bC*H*CO_2], 2.20 [s, 3 H, COC(37)H_3], 2.05–1.05 [m, 40 H, C(5–14)H_2, C(17,18,21,22)H_2, C-(25–33)H_2], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.48 [CF_3(24)], 4.11 [CF_3(15)].

C(15),C(24)-Bis-(*R*)-MTPA ester of (+)-bullatacinone (5): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.63 (2 H, Ar*H*), 7.56 (2 H, Ar*H*), 7.40–7.36 (6 H, Ar*H*), 5.24 [ddd, 1 H, J = 6.3, 6.3, 4.7 Hz, C(24)*HO*$_2$C], 5.03 [ddd, 1 H, J = 7.6, 6.4, 6.4 Hz, C(15)*HO*$_2$C], 4.55 [dddd, 1 H, C(4)*HO*CO, minor], 4.40 [dddd, 1 H, C(4)*HO*CO, major], 4.00 [q, 1 H, J = 7.6 Hz, C(16)*HO*], 3.94 [ddd, 1 H, J = 7.3, 6.3, 5.1 Hz, C(23)*HO*], 3.83 [ddd, 1 H, J = 8.1, 6.6, 4.1 Hz, C(19)*HO* or C(20)*HO*], 3.65 [ddd, 1 H, J = 6.5, 6.4, 4.1 Hz, C(19)*HO* or C(20)*HO*], 3.62 (s, 3 H, MeO-15), 3.55 (s, 3 H, MeO-24), 3.14–2.99 [m, 2 H, C(2)*H*CO_2, C(35)H_aH_bCOCH_3], 2.71–2.57 [m, 2 H, C(3)H_aH_bC*H*CO_2, C(35)H_aH_bCOCH_3], 2.20 [m, 1 H, C(3)H_aH_bC*H*CO_2], 2.20 [s, 3 H, COC(37)H_3], 2.05–1.05 [m, 40 H, C(5–14)H_2, C(17,18,21,22)H_2, C-(25–33)H_2], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.41 [CF_3(24)].

C(15)-Mono-(*S*)-MTPA ester of (+)-bullatacinone (5): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3, reference) δ 7.63–7.55 (2 H, Ar*H*), 7.41–7.37 (3 H, Ar*H*), 5.07 [q, 1 H, J = 6.5 Hz, C(15)*HO*$_2$C], 4.55 [dddd, 1 H, C(4)*HO*CO, major], 4.39 [dddd, 1 H, C(4)*HO*CO, minor], 4.083 (q, 1 H, J = 7.0 Hz, C(16)*HO*], 4.05–3.75 [m, 4 H, C(19,20,23,24)*HO*], 3.57 (s, 3 H, MeO-15), 3.14–3.00 [m, 2 H, C(2)*H*CO_2, C(35)H_aH_bCOCH_3], 2.71–2.57 [m, 2 H, C(3)H_aH_bC*H*CO_2, C(35)H_aH_bCOCH_3], 2.20 [m, 1 H, C(3)H_aH_bC*H*CO_2], 2.20 [s, 3 H, COC(37)H_3], 2.05–1.00 [m, 40 H, C(5–14)H_2, C(17,18,21,22)H_2, C(25–33)H_2], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.14 [CF_3(15)].

C(15)-Mono-(*R*)-MTPA ester of (+)-bullatacinone (5): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.63–.7.55 (2 H, Ar*H*), 7.41–7.37 (3 H, Ar*H*), 5.08 [q, 1 H, J = 6.5 Hz, C(15)*HO*$_2$C], 4.55 [dddd, 1 H, C(4)*HO*CO, major], 4.40 [dddd, 1 H, C(4)*HO*CO, minor], 4.075 (q, 1 H, J = 7.1 Hz, C(16)*HO*], 3.95–3.78 [m, 4 H, C(19,20,23,24)*HO*], 3.63 (s, 3 H, MeO-15), 3.14–2.98 [m, 2 H, C(2)*H*CO_2, C(35)H_aH_bCOCH_3], 2.71–2.57 [m, 2 H, C(3)H_aH_bC*H*CO_2, C(35)H_aH_bCOCH_3], 2.20 [m, 1 H, C(3)H_aH_bC*H*CO_2], 2.20 [s, 3 H, COC(37)H_3], 2.05–1.05 [m, 40 H, C(5–14)H_2, C(17,18,21,22)H_2, C(25–33)H_2], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 205.43, 178.75, 166.37, 154.11, 149.63, 132.50, 129.37, 128.16, 127.46, 106.51, 82.47, 81.44, 81.24, 79.71, 79.37, 78.92, 78.05, 71.44 [C(24)], 55.59, 44.26, 43.82, 39.05, 36.71, 33.59, 35.49, 35.41, 24.44, 33.28, 32.58, 31.93, 30.39, 30.03, 29.98, 29.73, 29.63, 29.58, 29.53, 29.51, 29.46, 29.41, 29.36, 29.30, 28.51, 28.45, 28.24, 26.04, 25.33, 25.25, 24.90, 24.71, 22.72, 14.17; ^{19}F-NMR ($CDCl_3$) δ 4.46 [CF_3(15)].

C(24)-Mono-(*S*)-MTPA ester of (+)-bullatacinone (5): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.62–7.58 (2 H, Ar*H*), 7.42–7.38 (3 H, Ar*H*), 5.32 [ddd, 1 H, J = 8.8, 4.1, 4.0 Hz, C(24)*HO*], 4.55 [dddd, 1 H, C(4)*HO*CO, minor], 4.39 [dddd, 1 H, C(4)*HO*CO, major], 4.11 (q, 1 H, J = 7.0 Hz, C(23)*HO*], 3.89–3.78 [m, 3 H, C(16,19,20)*HO*], 3.54 (s, 3 H, MeO-24), 3.37 [m, 1 H, C(15)*HO*], 3.14–2.99 [m, 2 H, C(2)*H*CO_2, C(35)H_aH_bCOCH_3], 2.71–2.57 [m, 2 H, C(3)H_aH_bC*H*CO_2, C(35)H_aH_bCOCH_3], 2.20 [m, 1 H, C(3)H_aH_bC*H*CO_2], 2.20 [s, 3 H, COC(37)H_3], 2.05–1.05 [m, 40 H, C(5–14)H_2, C(17,18,21,22)H_2, C-(25–33)H_2], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.45 [CF_3(24)].

C(24)-Mono-(*R*)-MTPA ester of (+)-bullatacinone (5): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.58–7.54 (2 H, Ar*H*), 7.41–7.38 (3 H, Ar*H*), 5.29 [q, 1 H, J = 6.5 Hz, C(24)*HO*], 4.55 [dddd, 1 H, C(4)*HO*CO, minor], 4.39 [dddd, 1 H, C(4)*HO*CO, major], 4.03 (m, 1 H, C(23)*HO*], 3.78 [m, 2 H, C(19,20)*HO*], 3.64 [m, 1 H, C(16)*HO*], 3.56 (s, 3 H, MeO-24), 3.37 [m, 1 H, C(15)*HO*], 3.14–2.95 [m, 2 H, C(2)*H*CO_2, C(35)H_aH_bCOCH_3], 2.71–2.57 [m, 2 H, C(3)H_aH_bC*H*CO_2, C(35)H_aH_bCOCH_3], 2.20 [m, 1 H, C(3)H_aH_bC*H*CO_2], 2.20 [s, 3 H, COC(37)H_3], 2.05–1.05 [m, 40 H, C(5–14)H_2, C(17,18,21,22)H_2, C-(25–33)H_2], 0.88 [t, 3 H, J = 6.8 Hz, C(34)H_3]; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 205.50, 178.23, 165.86, 154.10, 149.70, 132.29, 129.34, 128.21, 127.39, 106.51, 83.05, 81.72, 81.53, 79.94, 79.39, 78.93, 77.42, 74.03 [C(15)], 55.41, 44.27, 43.84, 39.05, 36.71, 35.60, 35.48, 35.40, 34.44, 33.45, 33.28, 31.92, 31.39, 30.04, 29.98, 29.76, 29.74, 29.66, 29.65, 29.62, 29.60, 29.57, 29.53, 29.51, 29.50, 29.48, 29.46, 29.45, 29.36, 29.34, 29.30, 28.80, 28.39, 28.36, 28.27, 26.78, 25.66, 25.44, 25.33, 25.24, 24.98, 24.84, 22.71, 14.17; ^{19}F-NMR ($CDCl_3$) δ 4.39 [CF_3(24)].

C(4),C(15),C(24)-Tris-(*S*)-MTPA ester of (+)-asimicin (6): ^{1}H-NMR (500 MHz, $CDCl_3$, C*H*Cl_3 reference) δ 7.62–7.52 (6 H, Ar*H*), 7.45–7.35 (9 H, Ar*H*), 6.70 [q, 1 H, $J \sim 1$ Hz, C(35)*H*], 5.29 [m, 1 H, C(4)*HO*], 4.94 [ddd, 2 H, J = 6.4, 6.4, 6.4 Hz, C(15)*HO*, C(24)*HO*], 4.84 [qq, 1 H, J = 6.7, ~1 Hz, C(36)*H*CH_3], 3.93 (ddd, 2 H, J = 6.5 Hz, C(16)*HO*, C(23)*HO*], 3.76 [m, 2 H, C(19)*HO*, C(20)*HO*], 3.53 (s, 6 H, MeO-15, MeO-24), 3.40 (s, 3 H, MeO-4), 2.56 [m, 2 H, C-(3)H_aH_b], 1.80 [m, 2 H, C(17)H_aH_b, C(22)H_aH_b], 1.68 [m, 2 H, C-(18)H_aH_b, C(21)H_aH_b], 1.63–1.62 [m, 4 H, C(5)H_aH_b, C(18)H_aHb, C(21)H_aH_b, 1.56 [m, 4 H, C(14)H_aH_b, C(25)H_aH_b], 1.43 [m, 2 H, C(17)H_aH_b, C(22)H_aH_b], 1.32–1.10 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 1.26 [d, 3 H, J = 6.8 Hz, C(37)H_3], 0.86 [t, 3 H, J = 6.7 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.90 [CF_3(4)], 4.09 [CF_3(15) or CF_3-(24)], 4.05 [CF_3(24) or CF_3(15)].

C(4),C(15),C(24)-Tris-(*R*)-MTPA ester of (+)-asimicin (6): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.65–7.5 (6 H, Ar*H*), 7.4–7.3 (9 H, Ar*H*), 6.96 [q, 1 H, $J \sim 1$ Hz, C(35)*H*], 5.36 [m, 1 H, C(4)*HO*], 5.04 [ddd, 2 H, J = 6.5, 6.5, 6.5 Hz, C(15)*HO*, C(24)*HO*], 4.88 [qq, 1 H, J = 6.0, 1.0 Hz, C(36)*H*CH_3], 3.97 (ddd, 2 H, J = 7.2 Hz, C(16)*HO*, C(23)*HO*], 3.92 [m, 2 H, C(19)*HO*, C(20)*HO*], 3.58 (s, 6 H, MeO-15, MeO-24), 3.40 (s, 3 H, MeO-4), 2.66 [m, 1 H, C-(3)H_aH_b], 2.58 [m, 1 H, C(3)H_aH_b], 1.95–1.90 [m, 4 H, C(17)H_aH_b, C(18)H_aH_b, C(21)H_aH_b, C(22)H_aH_b], 1.82 [m, 2 H, C(18)H_aH_b, C-(21)H_aH_b], 1.61 [m, 2 H, C(5)H_aH_b], 1.53 [m, 2 H, C(17)H_aH_b, C-(22)H_aH_b], 1.45 [m, 4 H, C(14)H_aH_b, C(25)H_aH_b, 1.32–1.10 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 1.29 [d, 3 H, J = 6.7 Hz, C(37)H_3], 0.86 [t, 3 H, J = 6.7 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.63 [CF_3(4)], 4.42 [CF_3(15), CF_3(24)].

C(4),C(15),C(24)-Tris-(*S*)-MTPA ester of (+)-rolliniastatin 1 (7): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.64–7.37 (15 H, Ar*H*), 6.73 [q, 1 H, $J \sim 1$ Hz, C(35)*H*], 5.33 [m, 1 H, C(4)*HO*], 5.18 [ddd, 2 H, $J \sim 6$, 6, 6 Hz, C(15)*HO* or C(24)*HO*], 5.08 [ddd, 2 H, J = 8.4, 4.6, 4.6 Hz, C(15)*HO* or C(24)*HO*], 4.86 [brq, 1 H, J = 6.2, C(36)-*H*CH_3], 4.04 (ddd, 1 H, $J \sim 6$, 6, 6 Hz, C(16)*HO* or C(23)*HO*], 3.97 (ddd, 1 H, $J \sim 6$, 6, 6 Hz, C(16)*HO* or C(23)*HO*], 3.69 [m, 2 H, C(19)*HO*, C(20)*HO*], 3.57 (s, 3 H, MeO-4 or MeO-15 or MeO-24), 3.53 (s, 3 H, MeO-4 or MeO-15 or MeO-24), 3.52 (s, 3 H, MeO-4 or MeO-15 or MeO-24), 2.58 [m, 2 H, C(3)H_aH_b], 1.88–1.42 [m, 8 H, from among C(17,18)H_2, C(21,22)H_2], 1.67 [m, 2 H, C(5)H_aH_b], 1.65 [m, 2 H, C(14)H_aH_b or C(25)H_aH_b], 1.60 [m, 2 H, C(25)H_aH_b or C(14)H_aH_b], 1.42–1.11 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 1.28 [d, 3 H, J = 6.8 Hz, C(37)H_3], 0.88 [t, 3 H, J = 7.0 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.87 [CF_3(4)], 4.40 [CF_3(24)], 4.02 [CF_3(15)].

C(4),C(15),C(24)-Tris-(*R*)-MTPA ester of (+)-rolliniastatin 1 (7): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.69–7.37 (15 H, Ar*H*), 6.97 [q, 1 H, $J \sim 1$ Hz, C(35)*H*], 5.38 [m, 1 H, C(4)*HO*], 5.15 [ddd, 2 H, J = 6.1, 6.1, 6.1 Hz, C(15)*HO* or C(24)*HO*], 5.07 [ddd, 2 H, $J \sim$ 6.5, 6.5, 6.5 Hz, C(15)*HO* or C(24)*HO*], 4.91 [brq, 1 H, J = 6.5 Hz, C(36)*H*CH_3], 3.96 (ddd, 1 H, $J \sim 7$, 7, 7 Hz, C(16)*HO* or C(23)*HO*], 3.89 (ddd, 1 H, $J \sim 6.5$, 6.5, 6.5 Hz, C(16)*HO* or C(23)*HO*], 3.69 [m, 1 H, C(19)*HO* or C(20)*HO*], 3.61 (s, 3 H, MeO-4 or MeO-15 or MeO-24), 3.58 [m, 1 H, C(19)*HO* or C(20)*HO*], 3.55 (s, 3H, MeO-4 or MeO-15 or MeO-24), 3.51 (s, 3 H, MeO-4 or MeO-15 or MeO-24), 2.69 [m, 1 H, C(3)H_aH_b], 2.60 [m, 1 H, C(3)H_aH_b], 1.94–1.38 [m, 8 H, from among C(17,18)H_2, C(21,22)H_2], 1.65 [m, 2 H, C(14)H_aH_b or C(25)H_aH_b], 1.64 [m, 2 H, C(5)H_aH_b], 1.52 [m, 2 H, C(25)H_aH_b or C(14)H_aH_b], 1.38–1.10 [m, 32 H, C(6–13)H_2, C(26–33)H_2], 1.31 [d, 3 H, J = 6.8 Hz, C(37)H_3], 0.88 [t, 3 H, J = 6.7 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.60 [CF_3(4)], 4.56 [CF_3(15) or CF_3(24)], 4.48 [CF_3(24) or CF_3(15)].

C(17),C(22)-Bis-(*S*)-MTPA ester of (+)-reticulatacin (8): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.65–7.37 (10 H, Ar*H*), 6.97 [q, 1 H, J = 1.5 Hz, C(35)*H*], 5.06 [ddd, 2 H, J = 6.4, 6.4, 6.4 Hz, C-(17)*HO*, C(22)*HO*], 5.00 [qq, 1 H, J = 6.7, 1.4 Hz, C(36)*H*CH_3], 4.01 (m, 2 H, C(18)*HO*, C(21)*HO*], 3.56 (s, 6 H, MeO-17, MeO-22), 2.28 [t, 2 H, J = 7.7 Hz, C(3)H_aH_b], 2.05–1.09 [m, 52 H, C(4–16)H_2, C-(19–20)H_2, C(23–33)H_2], 1.40 [d, 3 H, J = 6.8 Hz, C(37)H_3], 0.88 [t, 3 H, J = 6.9 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.27 [CF_3(17) and CF_3(22)].

C(17),C(22)-Bis-(*R*)-MTPA ester of (+)-reticulatacin (8): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.65–7.37 (10 H, Ar*H*), 6.97 [q, 1 H, J = 1.5 Hz, C(35)*H*], 5.08 [ddd, 2 H, J = 6.7, 6.7, 6.7 Hz, C-(17)*HO*, C(22)*HO*], 5.01 [qq, 1 H, J = 6.7, 1.4 Hz, C(36)*H*CH_3], 4.06 (m, 2 H, C(18)*HO*, C(21)*HO*], 3.62 (s, 6 H, MeO-17, MeO-22), 2.28 [t, 2 H, J = 7.7 Hz, C(3)H_aH_b], 2.05–1.09 [m, 52 H, C(4–16)H_2, C-(19,20)H_2, C(23–33)H_2], 1.40 [d, 3 H, J = 6.8 Hz, C(37)H_3], 0.88 [t, 3 H, J = 6.9 Hz, C(34)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.53 [CF_3(17) and CF_3(22)].

C(15),C(20)-Bis-(*S*)-MTPA ester of (+)-isoannonacin-10-one (9): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.6–7.5 (4 H, Ar*H*), 7.4–7.3 (6 H, Ar*H*), 4.90 [overlapping m, 2 H, C(15)*HO*, C(20)*HO*], 4.55 [dddd, 1 H, C(4)*HOCO*, trans], 4.39 [dddd, 1 H, C(4)*HOCO*, cis], 3.86 (overlapping m, 2 H, C(16)*HO*, C(19)*HO*], 3.47 (s, 3 H, MeO-15 or MeO-20), 3.46 (s, 3 H, MeO-15 or MeO-20), 3.03 [dddd, 1 H, C-(2)*H*CO_2], 3.02 [dd, 1 H, C(33)H_aH_b], 2.70–2.55 [m, 2 H, C(33)H_aH_b, C(3)H_aH_b(cis)], 2.34–2.27 [t, 4 H, C(9)H_aH_b, C(11)H_aH_b], 2.23 [m, 1 H, C(3)H_aH_b, trans], 2.20 [s, 3 H, COC(35)H_3], 2.0–1.4 [m, 11 H, from among C(3)H_aH_b, C(5)H_2, C(14)H_2, C(17,18)H_2, C(21)H_2], 1.4–1.1 [m, 33 H, from among C(6–8)H_2, C(12,13)H_2, C(22–31)H_2, C(35)H_3], 0.88 [t, 3 H, C(32)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.03 [CF_3(15) or CF_3(20)], 3.93[CF_3(20) or CF_3(15)].

C(15),C(20)-Bis-(*R*)-MTPA ester of (+)-isoannonacin-10-one (9): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.6–7.5 (4 H, Ar*H*), 7.4–7.3 (6 H, Ar*H*), 5.00 [overlapping m, 2 H, C(15)*HO*, C(20)*HO*], 4.55 [dddd, 1 H, C(4)*HOCO*, trans], 4.39 [dddd, 1 H, C(4)*HOCO*, cis], 3.98 (overlapping m, 2 H, C(16)*HO*, C(19)*HO*], 3.52 (s, 3 H, MeO-15 or MeO-20), 3.50 (s, 3 H, MeO-15 or MeO-20), 3.03 [dddd, 1 H, C-(2)*H*CO_2], 3.02 [dd, 1 H, C(33)H_aH_b], 2.70–2.55 [m, 2 H, C(33)H_aH_b, C(3)H_aH_b(cis)], 2.33 [t, 2 H, C(9)H_aH_b or C(11)H_aH_b], 2.24 [t, 2 H, C(9)H_aH_b or C(11)H_aH_b], 2.23 [m, 1 H, C(3)H_aH_b, trans], 2.20 [s, 3 H, COC(35)H_3], 2.0–1.4 [m, 11 H, from among C(3)H_aH_b, C(5)H_2, C(14)H_2, C(17,18)H_2, C(21)H_2], 1.4–1.1 [m, 33 H, from among C(6–8)H_2, C(12,13)H_2, C(22–31)H_2, C(35)H_3], 0.88 [t, 3 H, C(32)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.29 [CF_3(15) or CF_3(20)], 4.25 [CF_3(20) or CF_3(15)].

C(15),C(20)-Bis-(*S*)-MTPA ester of (+)-annonacin-10-one (10): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.63–7.56 (6 H, Ar*H*), 7.43–7.30 (9 H, Ar*H*), 6.70 [ddd, 1 H, C(33)*H*], 5.24 [ddd, 1 H, C-(4)*HO*], 4.95 [ddd, 2 H, C(15)*HO*, C(20)*HO*], 4.86 [qd, 1 H, C(34)-*H*CH_3], 3.92 (dd, 2 H, C(16)*HO*, C(19)*HO*], 3.52 (s, 3 H, MeO-4 or MeO-15 or MeO-20), 3.513 (s, 3 H, MeO-4 or MeO-15 or MeO-20), 3.511 (s, 3 H, MeO-4 or MeO-15 or MeO-20), 2.60 [m, 1 H, C(3)H_aH_b], 2.56 [m, 1 H, C(3)H_aH_b], 2.34 [t, 2 H, C(9)H_aH_b or C(11)H_aH_b], 2.33 [t, 2 H, C(9)H_aH_b or C(11)H_aH_b], 1.8–1.4 [m, 10 H, from among C-(5)H_2, C(14)H_2, C(17,18)H_2, C(21)H_2], 1.4–1.1 [m, 30 H, from among C(6–8)H_2, C(12,13)H_2, C(22–31)H_2], 1.28 [d, 3 H, J = 6.7 Hz, C-(35)H_3], 0.88 [t, 3 H, C(32)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.73 [CF_3(4)], 3.99 [CF_3(15) or CF_3(20)], 3.89 [CF_3(20 or CF_3(15)].

C(15),C(20)-Bis-(*R*)-MTPA ester of (+)-annonacin-10-one (10): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.63–7.56 (6 H, Ar*H*), 7.43–7.30 (9 H, Ar*H*), 6.94 [ddd, 1 H, C(33)*H*], 5.25 [ddd, 1 H, C-(4)*HO*], 5.026 [ddd, 2 H, C(15)*HO* or C(20)*HO*], 5.021 [ddd, 2 H, C(15)*HO* or C(20)*HO*], 4.91 [qd, 1 H, C(34)*H*CH_3], 4.01 [dd, 1 H, C(16)*HO* or C(19)*HO*], 4.00 [dd, 1 **H**, C(16)*HO* or C(19)*HO*], 3.54 (s, 3 H, MeO-4 or MeO-15 or MeO-20), 3.52 (s, 3 H, MeO-4 or MeO-15 or MeO-20), 3.50 (s, 3 H, MeO-4 or MeO-15 or MeO-20), 2.68 [m, 2 H, C(3)H_aH_b], 2.59 [m, 2 H, C(3)H_aH_b], 2.30 [t, 2 H, C(9)H_aH_b or C(11)H_aH_b], 2.25 [t, 2 H, C(9)H_aH_b or C(11)H_aH_b], 1.8–1.4 [m, 10 H, from among C(5)H_2, C(14)H_2, C(17,18)H_2, C(21)H_2], 1.4–1.1 [m, 30 H, from among C(6–8)H_2, C(12,13)H_2, C(22–31)H_2], 1.31 [d, 3 H, J = 6.7 Hz, C(35)H_3], 0.88 [t, 3 H, C(32)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.36 [CF_3(4)], 4.31 [CF_3(15) or CF_3(20)], 4.27 [CF_3(20) or CF_3(15)].

C(15),C(20)-Bis-(*S*)-MTPA ester of (+)-annonacin (11): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.54 (6 H, Ar*H*), 7.46 (4 H, Ar*H*), 7.36 (12 H, Ar*H*), 6.70 [q, 1 H, J = 1.0 Hz, C(33)*H*], 5.28 [m, 1 H, C(4)*HO*], 5.01 [m, 1 H, C(10)*HO*], 4.93 [ddd, 1 H, J = 6.5, 6.5, 5.5 Hz, C(15)*HO* or C(20)*HO*], 4.88 [ddd, 1 H, J = 6.5, 6.5, 5.5 Hz, C(15)*HO* or C(20)*HO*], 4.84 [qq, 1 H, J = 6.7, 1.0 Hz, C(34)*H*CH_3], 3.89 (ddd, 1 H, J = 6.1 Hz, C(16)*HO* or C(19)*HO*], 3.87 [m, 1 H, C(16)*HO* or C(19)*HO*], 3.50 (s, 3 H, from among MeO-4, MeO-10, MeO-15, MeO-20), 3.48 (s, 9 H, from among MeO-4, MeO-10, MeO-15, MeO-20), 2.57 [m, 2 H, C(3)H_aH_b], 1.70–1.42 [m, 4 H, C(9,11)H_2], 1.61 [m, 4 H, C(17)H_aH_b, C(18)H_aH_b, C(5)H_aH_b], 1.53 [m, 2 H, C-(14)H_aH_b, C(21)H_aH_b], 1.47 [m, 2 H, C(17)H_aH_b, C(18)H_aH_b], 1.46 [m, 2 H, C(14)H_aH_b, C(21)H_aH_b], 1.32–1.10 [m, 30 H, C(6–8)H_2, C(12,13)H_2, C(22–31)H_2], 1.26 [d, 3 H, J = 6.7 Hz, C(35)H_3], 0.86 [t, 3 H, J = 6.7 Hz, C(32)H_3]; ^{19}F-NMR ($CDCl_3$)δ 4.87 [CF_3(4)], 4.19 [CF_3(15) or CF_3(20)], 4.11 [CF_3(20) or CF_3(15)].

C(15),C(20)-Bis-(*R*)-MTPA ester of (+)-annonacin (11): ^{1}H-NMR (500 MHz, $CDCl_3$, $CHCl_3$ reference) δ 7.55 (4 H, Ar*H*), 7.49 (4 H, Ar*H*), 7.34 (12 H, Ar*H*), 6.94 [q, 1 H, J = 1.0 Hz, C(33)*H*], 5.33 [m, 1 H, C(4)*HO*], 5.02–4.94 [overlapping m, 3 H, C(10)*HO*, C(15)*HO*, C(20)*HO*], 4.88 [qq, 1 H, J = 6.7, 1.0 Hz, C(34)*H*CH_3], 3.98 (overlapping ddd, 2 H, J = 6.0, 5.5, 5.5 H, C(16)*HO*, C(19)*HO*], 3.51 (s, 6 H, MeO-15, MeO-20), 3.50 (s, 3 H, MeO-10), 3.47 (s, 3 H, MeO-4), 2.62 [m, 2 H, C(3)H_aH_b], 1.89 [m, 2 H, C(17)H_aH_b, C(18)H_aH_b], 1.58 [m, 2 H, C(17)H_aH_b, C(18)H_aH_b], 1.56 [m, 2 H, C(5)H_aH_b], 1.48 [m, 6 H, C(9,11)H_2, C(14)H_aH_b, C(21)H_aH_b], 1.42 [m, 4 H, C(14)H_aH_b, C(21)H_aH_b], 1.32–1.10 [m, 30 H, C(6–8)H_2, C(12,13)H_2, C(22–31)H_2], 1.28 [d, 3 H, J = 6.7 Hz, C(35)H_3], 0.86 [t, 3 H, J = 6.7 Hz, C(32)H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.67 [CF_3(4)], 4.53 [CF_3(15)], [CF_3(20)].

(*R*)-MTPA ester of synthetic (±)-threo model mono-THF (14-th): ^{1}H-NMR (500 MHz, $CDCL_3$, TMS reference) δ 7.65–7.60 (2 H, Ar*H*), 7.39 (3 H, Ar*H*), 5.07 [m, 1 H, C(15)*HO*, C(15′)*HO*], 3.99–3.93 [m, 1 H, C(16)*HO*, C(16′)*HO*], 3.83–3.75 [m, 1 H, C(19)H_aO, C(19′)H_aO], 3.70 [m, 1 H, C(19)H_bO, C(19′)H_bO], 3.62 (s, 1.5 H, MeO-15 or MeO-15′), 3.57 (s, 1.5 H, MeO-15′ or MeO-15), 2.00–1.83 [m, 2 H, from among C(17,18)H_2 or C(17′,18′)H_2], 1.78–1.63 [m, 1 H, from among C(17,18)H_2 or C(17′,18′)H_2], 1.65 [m, 1 H, C(14)H_aH_b or C-(14′)H_aH_b], 1.60–1.44 [m, 1 H, from among C(17,18)H_2 or C-(17′,18′)H_2], 1.52 [m, 1 H, C(14) H_aH_b or C(14′)H_aH_b], 1.38–1.14 [m,

6 H, C(11-13)H_2, C(11'-13')H_2], 0.88 [t, 1.5 H, J = 6.7 Hz, C(10)H_3 or C(10')H_3], 0.83 [t, 1.5 H, J = 7.3 Hz, C(10)H_3 or C(10')H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.36, 4.06.

(*R*)-MTPA ester of synthetic (±)-erythro model mono-THF (14-er): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.59-7.56 (2 H, Ar*H*), 7.40 (3 H, Ar*H*), 5.31-5.25 [m, 1 H, C(15)*HO*, C(15')*HO*], 3.96 [m, 0.5 H, C(16)*HO* or C(16')*HO*], 3.90 [m, 0.5 H, C(16)*HO* or C(16')*HO*], 3.82 [m, 0.5 H, C(19)H_aO or C(19')H_aO], 3.73 [m, 0.5 H, C(19)H_bO or C(19')H_bO], 3.64 [m, 1 H, C(19)H_aH_bO or C(19')H_aH_bO], 3.57 (s, 1.5 H, MeO-15 or MeO-15'), 3.55 (s, 1.5 H, MeO-15' or MeO-15), 1.92-1.62 [m, 4 H, C(17,18)H_2, C(17',18')H_2], 1.64 [m, 1 H, C(14)H_aH_b or C(14')H_aH_b], 1.59 [m, 1 H, C(14)H_aH_b or C(14')H_aH_b], 1.38-1.20 [m, 6 H, C(11-13)H_2, C(11'-13')H_2], 0.88 [t, 1.5 H, J = 7.0 Hz, C(10)H_3 or C(10')H_3], 0.85 [t, 1.5 H, J = 7.1 Hz, C(10)H_3 or C(10')H_3]; ^{19}F-NMR ($CDCl_3$) δ 4.46, 4.37.

(S)-MTPA ester of synthetic model (β-hydroxyalkyl)butenolide (15): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.48 (2 H, Ar*H*), 7.41 (3 H, Ar*H*), 6.98 [brd, 1 H, J = 1.2 Hz, C(35)*H*], 5.41 [m, 1 H, C(4)*HO*], 4.90 [qq, 1 H, J = 6.8, 1.3 Hz, C(36)*H*CH_3], 3.48 (d, 3 H, J = 1.0 Hz, MeO-4), 2.68 [dddd, 1 H, J = 15.4, 7.8, 1.2, 1.2 Hz, C(3)H_aH_b], 2.60 [dddd, 1 H, J = 15.4, 4.6, 1.7, 1.7 Hz, C(3)H_aH_b], 1.35 [d, 3 H, J = 6.3 Hz, C(5)H_3], 1.34 [d, 3 H, J = 6.8 Hz, C(37)H_3]; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.27, 165.81, 152.21, 131.84, 129.65, 128.98, 128.46, 127.44, 123.26 (q, J = 289 Hz, *C*F_3), 77.67, 71.52, 55.18, 31.22, 19.45, 18.84; ^{19}F-NMR ($CDCl_3$) δ 4.33; IR (neat) 3072, 2985, 2938, 2849, 1755, 1655, 1493, 1452, 1377, 1320, 1271, 1169, 1121, 1081, 1022 cm^{-1}; TLC R_f = 0.3 (2:1 hexane/EtOAc).

(*R*)-MTPA ester of synthetic model (β-hydroxyalkyl)butenolide (15): ^{1}H-NMR (500 MHz, $CDCl_3$, TMS reference) δ 7.52 (2 H, Ar*H*), 7.41 (3 H, Ar*H*), 6.66 [br d, 1 H, J = 1.2 Hz, C(35)*H*], 5.34 [m, 1 H, C(4)*HO*], 4.73 [qq, 1 H, J = 6.8, 1.2 Hz, C(36)*H*CH_3], 3.56 (d, 3 H, J = 1.2 Hz, MeO-4), 2.57 [m, 2 H, C(3)H_aH_b], 1.42 [d, 3 H, J = 6.3 Hz, C(5)H_3], 1.28 [d, 3 H, J = 6.8 Hz, C(37)H_3]; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.30, 165.75, 152.26, 132.42, 129.54, 128.63, 128.40, 127.06, 123.26 (q, J = 289 Hz, *C*F_3), 77.58, 71.49, 55.41, 30.99, 19.77, 18.72; ^{19}F-NMR ($CDCl_3$) δ 4.46; IR (neat) 3070, 2985, 2950, 2850, 1752, 1655, 1492, 1452, 1377, 1320, 1271, 1169, 1121, 1081, 1024 cm^{-1}; TLC R_f = 0.3 (2:1 hexane/EtOAc).

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The Pagodane Route to Dodecahedranes: Highly Functionalized, Saturated, and Unsaturated Pentagonal Dodecahedranes via Aldol-Type Cyclizations

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Abstract: Pentagonal dodecahedranes with four (**69**), six (**67** and **83**), and eight (**79**) skeletal positions being functionalized are made available from dimethyl 14,19-dioxopagodane-4-*syn*,9-*syn*-dicarboxylate **7** as a common precursor. Key steps are the installation of the two carbonyl functions of **7** into the expeditiously available pagodane 4-*syn*,7-*syn*-diester, the $2\sigma \rightarrow 2\pi$ pagodane isomerization into the respective bissecododecahedradiene (**46**), and two transannular C,C bond formations. The implied oxidation of two unactivated methylene groups is brought about by a Barton reaction of unusual complexity (at least 14 bond breaking/bond forming events), conveniency (one-pot reaction), and performance (nearly quantiative yield). The subsequent cyclobutane opening ($2\sigma \rightarrow 2\pi$) in **7** and several model systems by bromine addition and bromine elimination is found to be complicated by heavy skeletal substitution but is efficiently effected for **7** by an intriguing detour (isododecahedranes **48**, secododecahedradienes **50**). Thus, for the 20(21) steps between isodrin and the various dodecahedranes, total yields of 12-16% are achieved. Under acid catalysis the two (exothermic) cyclization steps are kinetically sufficiently differentiated to allow the selective generation of intermediate secododecahedranes (**66** and **78**). Limitations of this aldol type route are the cyclizations calculated to be endothermic and which could not be executed irreversibly. Dodecahedrenes (**67**) with their highly bent C=C double bond (ψ ca. 46°) are found to be kinetically surprisingly stable; from mass spectra, indications for the existence of even higher unsaturated dodecahedranes and leads for further functional group manipulations are derived. In the X-ray determinations, the doubly epoxyannulated dodecahedrane **79a** is found to be slimmer by ca. 0.5 Å than the parent dodecahedrane skeleton of **69a**.

Introduction

The $(CH)_{20}$ pentagonal dodecahedrane (**C**)—here synonymously called dodecahedrane—has been an outstanding target in organic synthesis.[1] Of the numerous strategies perceived for the construction of this fascinating molecular skeleton, to date only two have been successfully completed. In the pioneering synthesis by the group of Paquette,[2] the readily available [C10(C5 + C5) + C4] cycloadduct **A** is linearly transformed into C_{20} seco precursor **B**, which for the ultimate cyclization **B** → **C** necessitated dehydrogenative C,C bond forming methodology. The synthesis developed in our laboratory[3] starts from the commercial [C7(C5 + C2) + C5] composite **D** (isodrin), from which the C_{20} [1.1.1.1]pagodane framework **E** is built up by making inter alia use of an earlier discovered [6 + 6] photocyclization reaction.[4] Thanks to a highly optimized protocol, a remarkable 24% yield of parent pagodane was accomplished in large scale preparations.[5]

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