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On the Proof and Disproof of Natural Product Stereostructures: Characterization and Analysis of a Twenty-Eight Member Stereoisomer Library of Murisolins and Their Mosher Ester Derivatives

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Abstract: Characterizing a stereoisomer library of 28 of the 64 possible isomers of the acetogenin murisolin, including 24 of the 32 possible diastereomers, provides a complete picture of the spectra of this class of molecules. Remarkably, each of the 32 diastereomers exhibits one of only six sets of substantially identical ^{1}H NMR spectra under standard conditions. These spectra follow directly from a local symmetry analysis of the dihydroxy−THF fragment of the molecule and provide no information about the configuration about the hydroxybutenolide. Eighteen tris-Mosher ester derivatives of library members have been made, and their spectra were analyzed to give a complete picture of the usefulness of chiral derivatives. The tris-Mosher esters of the 64 isomers of murisolin will exhibit 40 sets of spectra: 16 isomers have unique spectra whereas 24 isomers share an identical spectrum with one other isomer. This identity occurs even though the pairs of compounds were already diastereomers (not enantiomers) before the derivatization. The complete set of spectra allows any murisolin or closely related compound to be narrowed to one or two structures by simple matching and without recourse to assignment and subtraction of resonances. The structure of murisolin was proved to be the 4*R*,15*R*,16*R*,19*R*,20*R*,34*S* isomer, whereas the assignment of 16,19-*cis*-murisolin as *RRRSSS* was changed to the *RSSRRS* diastereomer and murisolin A is suggested to be *RSRRRS*.

Introduction

What constitutes rigorous proof of the structure of a natural product? The gold standard is X-ray crystallography, which has an outstanding—though not blemish-free[1]—track record. However, there are large classes of natural products that are oils, waxes, or powders that do not readily yield crystalline derivatives. In such cases, total or semisynthesis of a candidate structure coupled with demonstration of identity of various physical and spectral data is generally accepted to constitute a structure proof. This type of exercise frequently uncovers errors in structure assignments based on spectroscopic methods.[2] Two assumptions underlying such a comparative proof are often neglected. These are: (1) that the synthesis provided the target structure[3] and (2) that there is no other candidate structure with substantially identical physical and spectral data to those of target.

In cases where several potentially indistinguishable structure possibilities exist, the burden shifts from proof to disproof—it must be shown that all likely structural possibilities but one are materially different from the proposed structure in one or more ways. The logic here is not unlike that applied to analysis of competing reaction mechanism postulates, where the goal is to disprove all but one.[4] The rigorous way to disprove structural identity is to synthesize all the similar candidates for comparison.[5]

The likelihood of compounds with similar or identical spectra often arises in complex natural products with local symmetry or remote stereocenters or groups of stereocenters. The members of the acetogenins, a large and important family of biologically active natural products, often exhibit both local symmetry and remote stereocenter problems. And they typically exist as waxy solids that are not amenable to X-ray crystallography.[6] The murisolin group of acetogenins consists of murisolin itself, 16,-19-*cis*-murisolin, and murisolin A[7] and an assortment of other analogues, and these compounds have assignment problems typical of many acetogenins. The structures as assigned by Cavé[7a] and McLaughlin[7b] are shown in Figure 1.

(1) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770−4773.
(2) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.
(3) As shown by the famous case of patchouli alcohol, even this bedrock assumption may not always be correct: (a) Dobler, M. D.; Dunitz, J. D.; Gubler, B.; Weber, H. P.; Büchi, G.; Padilla, O. J. *Proc. Chem. Soc. London* **1963**, 383. (b) Büchi, G.; MacLeod, W. D.; Padilla, O. J. *J. Am. Chem. Soc.* **1964**, *86*, 4438−4444.
(4) Hine, J. *Physical Organic Chemistry*; MacGraw-Hill: New York, 1962; p 75.
(5) For a systematic and rigorous approach to assigning structures by building NMR databases, see among others: (a) Higashibayashi, S.; Kishi, Y. *Tetrahedron* **2004**, *60*, 11977−11982. (b) Ghosh, I.; Zeng, H.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4715−4718. (c) Ghosh, I.; Kishi, Y.; Tomoda, H.; Omura, S. *Org. Lett.* **2004**, *6*, 4719−4722. (d) Adams, C. M.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4723−4726.

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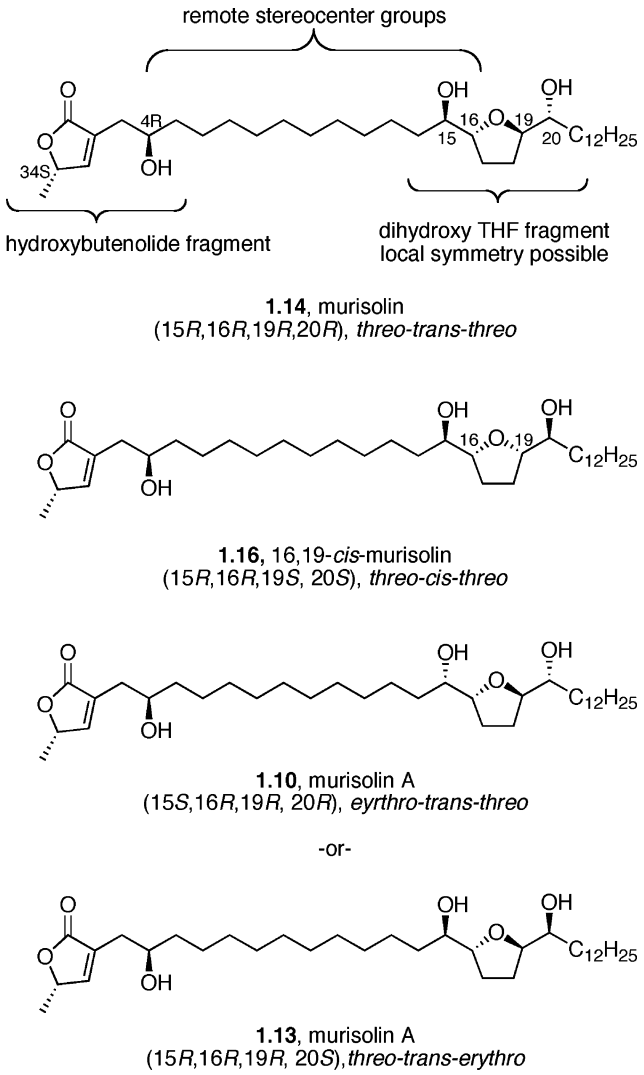


Figure 1. Proposed structures for murisolin (**1.14**), 16,19-*cis*-murisolin (**1.16**), and murisolin A (**1.10** or **1.13**)

We recently described the syntheses of two 16-member stereoisomer libraries of murisolin isomers that provided 24 of the 32 possible diastereomers, including all of the compounds in Figure 1 and other structure candidates for the three natural products.[8] Having so many closely related stereoisomers in hand affords unique opportunities for comparisons. How similar are these isomers? How can they be differentiated? It turns out that none of the murisolin isomers has a unique ^{1}H or ^{13}C NMR spectrum under standard recording conditions. Accordingly, are the structures of the murisolins in Figure 1 correct? And what can we learn more generally about how to rigorously solve structure problems in the acetogenin class of natural products? We address these questions herein by comparing spectral and physical data of the members of the stereoisomer library and their Mosher acid derivatives with each other and with data reported for the natural products.

Results and Discussion

Symmetry and Structural Classifications. Figure 2 classifies the stereostructures of the murisolins according to the symmetries of the model dihydroxytetrahydrofuran molecules **2** bearing identical, achiral substituents (Bu) on either end of the molecule (C15 and C20 in murisolin numbering).[9] These classifications aid in the understanding of spectral comparisons in both murisolins and their Mosher ester derivatives. The stereostructures of both mono-THF and di-THF classes of acetogenins have been extensively discussed[6,9] (see especially refs 6d,h,9e), and we use here the prevailing terminology for consistency.

Starting with the relative configuration, the C15 and C20 hydroxy groups can be *threo* (th) or *erythro* (er) with respect to the adjacent stereocenter on the THF ring, and the two substituents on the THF ring can be cis (c) or trans (t). This leads to six diastereomers of **2**, classed as the parents of murisolin isomer Groups 1−6, with the configurations as indicated in Figure 2.[9] Two of the diastereomers of **2** are achiral (*meso*) compounds due to a plane of symmetry passing down through the middle of the THF ring (Groups 3 and 4). Two of the compounds are C2 symmetric (Groups 2 and 5), and two compounds have no symmetry at all (Groups 1 and 6). These four compounds have enantiomers, resulting in a total of 10 stereoisomers for **2**.

Making the two side chains of **2** different but lacking in stereocenters (or other stereogenic elements) increases the number of possible diastereomers from 6 to 8 (no isomer has symmetry), and adding two stereocenters on the side chain provides 32 diastereomers of murisolin, all of which are chiral (64 total isomers). The 16 possible stereoisomers of the murisolins (**1.1**−**1.16**) arising from the dihydroxy−THF portion of the molecule are shown in their respective groups in Figure 2. There are four sets of these isomers due to the four possible configurations at the two stereocenters in the hydroxybutenolide fragment of the molecule, murisolin belonging to the set with 4*R*,34*S*. Perhaps counterintuitively, it is the breaking of the local symmetry of the dihydroxy−THF fragment of model **2**, and not the presence of remote hydroxybutenolide stereocenters in **1**, that proves to be the most difficult assignment problem for murisolin and by extension scores of other acetogenins that have similar structures.

(6) Reviews: (a) Zafra-Polo, M. C.; González, M. C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry* **1996**, *42*, 253−271. (b) Zafra-Polo, M. C.; Figadère, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117. (c) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306. (d) Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Seglich, W., Tamm, Ch., Eds.; Springer-Verlag: Wienberg, 1997; Vol. 70, pp 281−288. (e) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (f) Tormo, J. R.; Gallardo, T.; González, M. C.; Bermejo, A.; Cabedo, N.; Andreu, I.; Estornell, E. *Curr. Top. Phytochem.* **1999**, *2*, 69−90. (g) Bermejo, A.; Figadère, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269−303. (h) Ramirez, E. A.; Hoye, T. R. In *Studies in Natural Products Chemistry*, Vol. 17; Rahman, A., Ed.; Elsevier: Amsterdam, 1995; pp 251−282.

(7) (a) Myint, S. H.; Laurens, A.; Hocquemiller, R.; Cavé, A.; Davoust, D.; Cortes, D. *Heterocycles* **1990**, *31*, 861−867. (b) Woo, M. H.; Zeng, L.; Ye, Q.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1135−1140. (c) To the best of our knowledge, McLaughlin and co-workers have not published the data for this analysis.

(8) (a) Curran, D. P.; Zhang, Q.; Richard, C.; Lu, H.; Gudipati, V. Wilcox, C. S. *J. Am. Chem. Soc.* **2006**, ASAP article. (b) The structures and numbers in this paper parallel those in ref 8a.

(9) Butyl groups are shown as substituents of **2** because all six of these compounds are known: (a) Gale, J. B.; Yu, J.-G.; Khare, A.; Hu, X. E.; Ko, D. K.; Cassady, J. M. *Tetrahedron Lett.* **1993**, *34*, 5851−5854. (b) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175−1184. (c) *Bis*-Mosher esters of two models: Shimada, H.; Nishioka, S.; Singh, S.; Sahai, M.; Fujimoto, Y. *Tetrahedron Lett.* **1997**, *35*, 3961−3964. (d) Several of the dimethyl-substituted isomers of **2** are known: Walba, D. M.; Haltiwanger, R. C.; Wand, M. D.; Wilkes, M. C. *Tetrahedron* **1981**, *37*, 1663−1668. (e) For the dihydroxy-bis-tetrahydrofuran ring analysis, see: Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4403−4404.

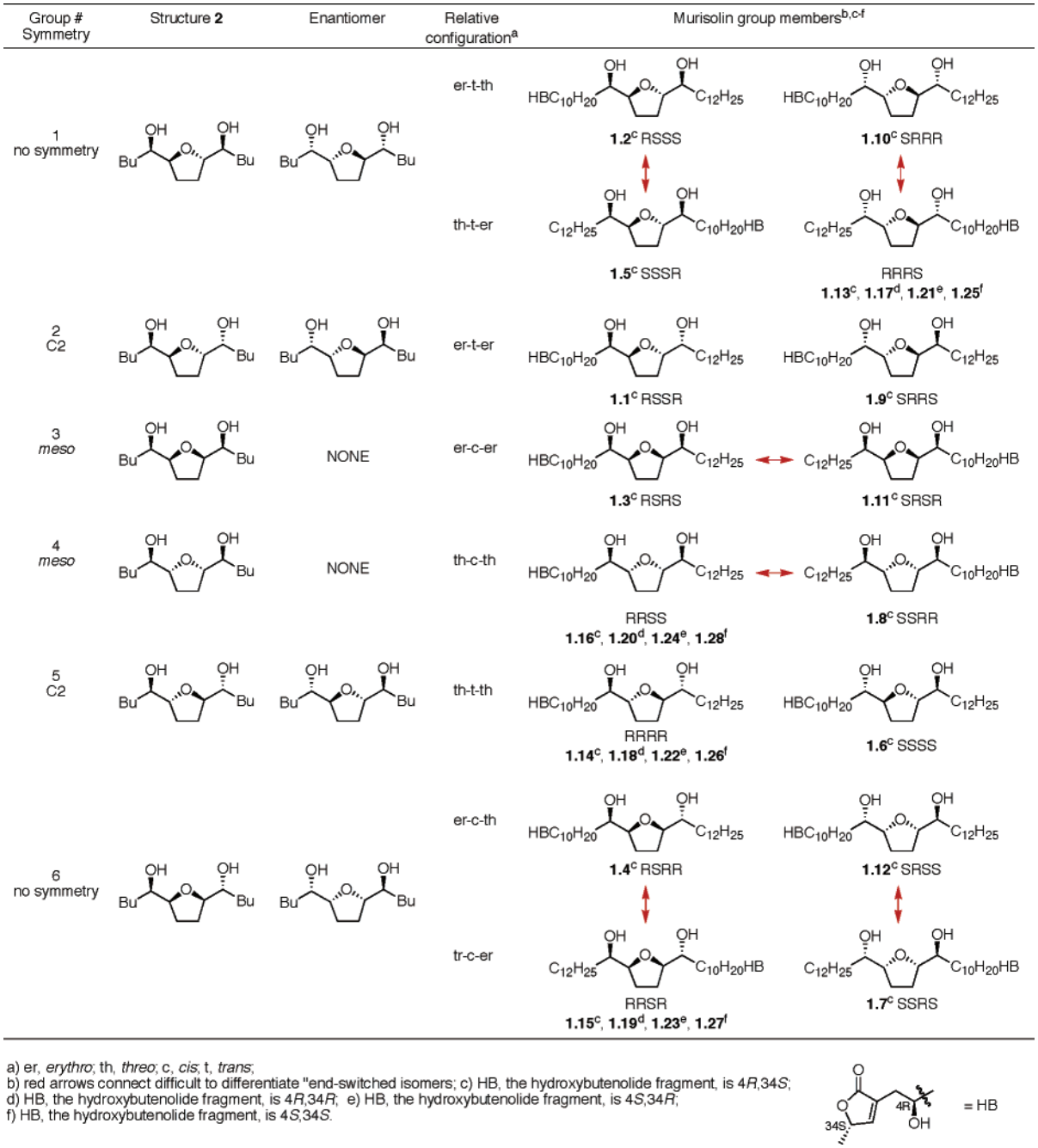


Figure 2. Group classifications of murisolin isomers **1** on the basis of symmetric model compound **2**.

Assignments of Acetogenin Stereocenter Configurations. Following the assignment of a two-dimensional (2D) structure (constitution) of a typical mono-THF acetogenin, the two subunits are then addressed independently for configuration assignment. It is now relatively straightforward to place a given murisolin **1** into one of the six groups of diastereomers about the dihydroxy−THF fragment by comparison of its ^{1}H and ^{13}C NMR spectra with those of symmetrical models **2**.[6d,h,9] The syn/anti relative configuration of the hydroxybutenolide has not to date been assigned directly without derivatization, but a reliable Mosher ester analysis is available.[10]

With the relative configurations of the dihydroxy-THF and hydroxybutenolide fragments in hand, it might now appear that the rest of the assignment can be completed by independently assigning the absolute configurations of the two fragments. This is of course true, yet it is much easier said than done. Assigning the absolute configuration of the hydroxybutenolide fragment of the molecule—for example, by making a Mosher ester or other chiral derivative of the C4 hydroxy group—is straightforward.[10] However, assigning the absolute configuration of the dihydroxy-THF fragment may or may not be straightforward, depending on the local symmetry.

To understand the assignment problems, consider the two murisolin members **1.1** and **1.9** of Group 2, which have C2 local symmetry. The two isomers have either *RR* (**1.1**) or *SS* (**1.9**) configurations at the alcohol-bearing carbons C15 and C20. On

(10) Because the syn and anti-isomers at C4, C34 give substantially identical spectra, the relative and absolute configurations of this part of the molecule are often determined simultaneously through Mosher esters: Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. E.; Ramirez, E. A.; Zhuang, Z. P. *Tetrahedron Lett.* **1994**, *35*, 8529−8532.

paper, one isomer can be generated from the other either by inverting all four stereocenters or by keeping all four stereocenters the same but switching the C15 side chain to C20 and the C20 side chain to C15. Because of this redundancy, it suffices to assign only the absolute configuration at C15 and C20; it is not necessary to assign which side chain is where. (In practice, this means that in analysis of pairs of chiral derivatives such as Mosher esters, one does not need to assign which proton is H15 and which is H20 because both stereocenters have the same configuration, see below.) The same situation pertains to the related C2-symmetic Group 5.

Now consider the two murisolins **1.3** and **1.11** in Group 3, which has a local plane of symmetry. The two isomers have either *RS* (**1.3**) or *SR* (**1.11**) configurations at C15 and C20. Superficially, the problem looks the same as the Group 2 (C2) class above because either inverting the four stereocenters of **1.3** or interchanging the side chains at C15 and C20 provides **1.11**. However, the configurations at C15 and C20 are now different, so we do not need to know what the configurations are (one is *R*, the other *S*) but, instead, which side chain is where. Ramirez and Hoye called this the "endedness problem".[6h] (In practice, this translates to assigning H15 and H20 in chiral derivatives.) Because the two side chains are so similar (10 methylene groups must be traversed to find a difference), this knowledge is not easy to come by. The same analysis applies to related *meso* Group 4.

Groups 1 and 6 lack local symmetry and again one needs to know where the side chains are located to unambiguously assign the structure. In Group 1, inversion of the four stereocenters of **1.2** provides **1.10**, and these two can in principle be differentiated by making a chiral derivative even though C15 and C20 have opposite configurations (**1.2** is 15*R*,20*S* whereas **1.10** is 15*S*,20*R*). This is because one of the 15/16 or 19/20 pairs has the *erythro* relative configuration while the other is *threo*. (In practice, this means that the H15 and H20 can be assigned in chiral derivatives.) In contrast, interchanging the side chains of **1.2** provides **1.5**, and to differentiate these compounds, we need to know not only what the two configurations are but which side chain is where. This is because the alcohol-bearing stereocenters in the *erythro* unit (C15 in **1.2** and C20 in **1.5**) are both *R*-configured, whereas the alcohol bearing stereocenters in the *threo* unit (C20 in **1.2** and C15 in **1.5**) are both *S*-configured.

A similar analysis applies for the other pair compounds linked by red arrows in Group 1 and for the two pairs of compounds in Group 6; such pairs of compounds cannot be differentiated without knowledge of which side chain is where. The assignment problems posed by local symmetry have been recognized by Hoye, McLaughlin, and others for compounds in the nonsymmetric Groups 1 and 6,[6h] but they do not seem to have been recognized for compounds in the *meso* Groups 3 and 4.

Notice how the problems emanate directly from local symmetry considerations. There is an unambiguous one-to-one match between the number of isomers of model compounds **2** in Groups 2 and 5 and the number of murisolins **1** that they give rise to. But there is a one-to-two match between the model compounds **2** in Groups 1, 3, 4, and 6 and the derived murisolins. Simply stated, the structure problem is underdetermined because the same isomer of model compound **2** cannot be used to differentiate the two isomers of **1** that it models. This symmetry analysis provides an essential foundation for understanding the following spectral observations of both the murisolins themselves and the derived Mosher esters.

Comparison of the ^{1}H and ^{13}C NMR Spectra of the Murisolin Stereoisomers—the Dihydroxy−THF Subunit. In a prior paper, we described the synthesis of a library of 28 stereoisomers of murisolin that included 24 of the 32 possible diastereomers.[8a] Having these compounds in hand allows us to turn the above spectroscopic analysis problem upside down. We can now assign the spectra from the structures, not the reverse. And we can compare the authentic samples with the natural products to establish which one is identical and which ones are not. But what kinds of comparisons are useful, and where are the limitations imposed by the structural similarities discussed above?

To address these questions, we first discuss the analysis of a 16-member sublibrary of murisolins whose members have 4*R*,-34*S* configurations fixed with all possible configurations at the remaining stereocenters in the dihydroxy−THF fragment (**1.1**−**1.16**). The analyses of the other isomers follow directly from this group (see below). We first recorded a complete set of ^{1}H NMR spectra at 600 MHz ($CDCl_3$) and ^{13}C NMR spectra at 151 MHz ($CDCl_3$) and then carefully compared and contrasted these spectra by reviewing printouts of chemical shifts and by overlaying sets of expansions of relevant regions of all the spectra.

None of these 16 isomers of **1** exhibits a unique ^{1}H or ^{13}C NMR spectrum. Indeed, every spectrum belongs to one of only six groups, and the spectra within each group are *substantially identical*. By this, we mean that we could not identify any difference in chemical shift or peak shape that could reliably (or even tentatively) be attributed to a real difference in the spectrum rather than a feature of an individual experiment.[11] To provide a more rigorous standard for "substantially identical", we compared unlabeled spectra of the four pairs of true enantiomers in the library (**1.5**/**1.21**; **1.6**/**1.22**; **1.7**/**1.23**; **1.8**/**1.24**) with their diastereomers in the same groups (**1.13**/**1.2**/**1.5**/**1.10**; **1.14**/**1.6**; **1.15**/**1.4**/**1.7**/**1.12**; **1.16**/**1.8**). In this blind exercise, it was not possible for us to identify which spectra belonged to enantiomers and which spectra belonged to diastereomers.

The six groups of spectra assemble without exception following the analysis of relative configuration in Figure 2. There are two groups of four compounds (Groups 1 and 6) that share identical spectra and cannot be differentiated, and four groups of two compounds (Groups 2−5) cannot be differentiated either. Expansions of portions of two ^{1}H NMR spectra of the Group 5 isomers are representative and are shown in Figure 3. The spectrum of the natural product murisolin **1.14** (see below for assignment) is shown in Figure 3 (top), and its spectrum is substantially identical to the spectrum of its diastereomer **1.6**, Figure 3 (bottom), with the same configuration in the hydroxybutenolide ring but opposite configurations in the dihydroxy−THF ring. In turn, the enantiomer of **1.6**, compound **1.22**, has identical spectra to both **1.6** and **1.14** (not shown). The same

(11) ^{1}H (600 MHz) and ^{13}C (150 MHz) spectra were recorded in $CDCl_3$ with residual $CHCl_3$ as the standard. In ^{1}H spectra, chemical shifts within groups differed by = 0.01 pm. In the ^{13}C NMR spectra, chemical shifts within groups differed by = 0.03 ppm, with one exception. The THF ring carbon (C^{15}/C^{20}) of **1.3** (δ 72.76) differed from that of its Group 3 partner **1.11** (δ 72.85) by 0.09 ppm. Although this small difference may be real, it is certainly not sufficient for a structure assignment given that all other H's and C's are chemical shift equivalent.

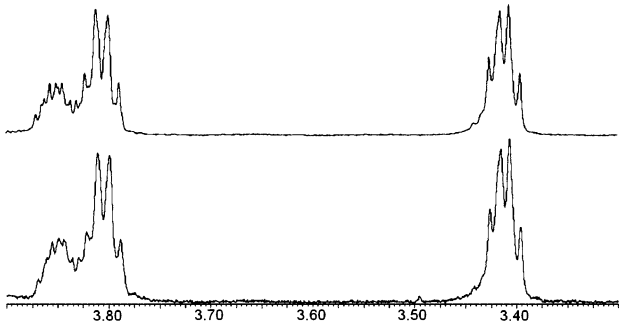


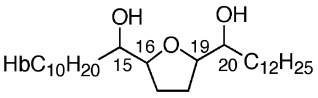
Figure 3. Representative expansions of the 600 MHz ^{1}H NMR spectra of **1.14** (top) and **1.6** (bottom) illustrate that diastereomers exhibit substantially identical spectra.

situation pertains to the other compounds in Group 1−4 and Group 6. Complete printouts with standardized expansions of the ^{1}H and ^{13}C NMR spectra of all 28 samples are provided for comparison in the Supporting Information.

We do not contend that the spectral identities that we have observed here at high field under common experimental conditions will extend to all NMR experiments. Indeed, it is probable that the isomers could be further differentiated under chiral conditions,[12] and they could perhaps even be differentiated under achiral conditions, especially if the hydroxybutenolide and dihydroxy-THF fragments of the molecule can be induced to interact with each other. However, were such experiments to be undertaken, it would be essential to have the members of this stereoisomer library as a reference to ensure that any change that was observed was not the same for two (or four) isomers. Having the isomers in hand renders such studies unnecessary for structure assignment—there are much simpler ways to differentiate compounds that share identical spectra (see below).

A number of guidelines have been put forth to assign relative configuration to the dihydroxy-THF ring stereocenters,[6d,h,9] and most of these rely on chemical shifts in the ^{1}H NMR spectrum either alone or in combination with ^{13}C NMR shifts. These guidelines typically focus on assigning *threo*/*erythro* and *cis*/*trans* configurations. The existing guidelines are accurate because we found no exceptions in our library. But likewise, we found that the relative configurations of murisolins can be rapidly classed starting from a local symmetry perspective by looking at the chemical shifts of only two or four key resonances in the ^{13}C NMR spectra. These guidelines are summarized in Figure 4. The six carbons bearing oxygen resonate in region δ 70−84. Carbons 4 and 34 of the hydroxybutenolide are constant ($\pm$ 0.02 ppm) at δ 70.09 and 78.05, so these resonances are ignored. If there are two remaining resonances in this region, then the compound belongs in one of the Groups with local symmetry (2−5), whereas if there are four resonances, it belongs in one of the Groups lacking local symmetry (1 or 6).

Within the four locally symmetric groups, the compounds can be reliably classed on the basis of the chemical shifts of the carbinyl carbons (C15,20) and the oxygen-bearing carbons of the THF ring (C16,C19). The only close call is differentiating Groups 4 and 5, where the assignment based on a small (0.3 ppm) difference between the resonances of C15,20 should be confirmed by other means. A spectrum from a nonsymmetric



Step 1: Remove peaks at δ 70.09 and 78.05, then count the remaining peaks between δ 70–84
- if two peaks remain, then Groups 2-5
- if four peaks remain, then Group 1 or 6

Step 2a: Two peaks remain; compare δ of both peaks

Group	δ C15,20	δ C16,19	config
2	72.0	83.0	er-t-er
3	72.8	82.4	er-c-er
4	74.4	82.7	th-c-th
5	74.1	82.7	th-t-th

Step 2b: Four peaks remain; compare δ of most downfield peak

Group	δ C16 or 19	config
1	83.3	er-t-th or th-t-er
6	82.8	er-c-th or th-c-er

Figure 4. Rapid classification of the relative configuration of the dihydroxy−THF fragment of murisolins by comparing ^{13}C NMR resonances of the carbons bearing oxygen, δ 70−84 ppm.

compound can be classed by looking at the most downfield of the two THF-carbon resonances, which is at δ 82.8 for Group 6 and δ 83.3 for Group 1. Because the spectra within the groups are identical, no further information about what a compound is within an individual group is available.[11]

Synthesis and Analysis of Mosher Esters Derivatives. Mosher esters and related chiral derivatives are frequently used to help assign configurations of secondary alcohol centers in acetogenin natural products.[6d,h,9c,13,14] With a full set of 16 dihydroxy-THF isomers of murisolin of known configurations in hand, we are in a unique position to test the reliability and limits of using Mosher esters to assign configurations in these systems.

In the standard approach, typically called an "advanced Mosher analysis",[13c] a secondary alcohol of unknown absolute configuration is reacted with both (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chlorides (hereafter called Mosher acid chlorides) to generate diastereomeric (*S*)- or (*R*)-Mosher esters (due to a CIP change, the Mosher esters have opposite absolute configurations to the acid chlorides).

Subtraction of the chemical shifts of the protons of the (*R*)-Mosher ester from the (*S*)-Mosher ester in the vicinity of the ester-bearing stereocenter then provides differences ($\Delta\delta$), the signs of which are used to assign the configuration of the stereocenter. We applied this standard approach to two isomers by converting **1.15** and **1.7** in Group 6 (*threo-cis-erythro*) to

(12) The analysis for which isomers can and cannot be differentiated in principle is parallel to that of the analysis of the Mosher esters in the following section.

(13) (a) Dale, J. A.; Mosher, H. S., *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Sullivan, G. R.; Dale, G. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147. (c) Advanced Mosher ester use: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (d) 2-Naphthylmethoxy acetic acid esters have been used less frequently but give larger and more reliable chemical shift differences. See, Duret, P.; Waechter, A.-I.; Figadère, B.; Hocquemiller, R.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 4717−4720.

(14) Reviews: (a) Seco, J. A.; Quinoa, E.; Riguera, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2781−2791. (b) Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, 104, 17−117.

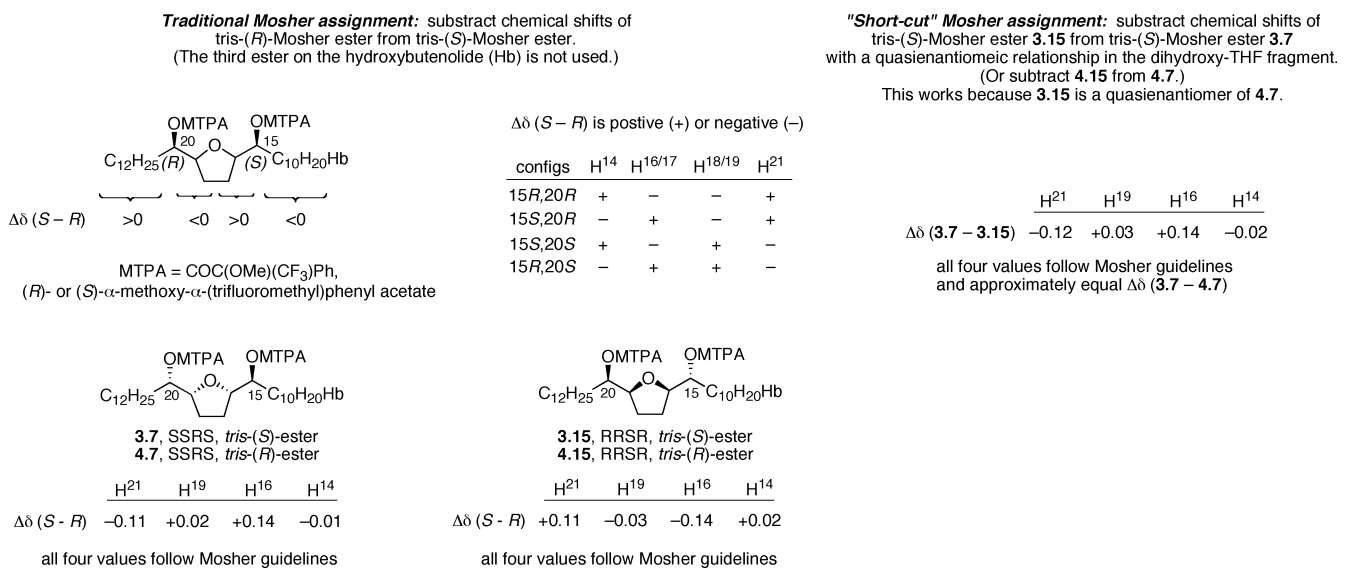


Figure 5. Traditional and "short-cut" assignments of configuration by advanced Mosher ester subtraction.

their tris-(*S*)- and tris-(*R*)-Mosher esters **3.15/4.15** and **3.7/4.7**,[15] recording the ^{1}H NMR spectra of these esters, and then subtracting the chemical shifts of the related resonances as usual. The signs of the $\Delta\delta$ are shown in Figure 5.[16] For **1.7**, subtractions of the relevant four pairs of resonances provided differences that were consistent with the known 15*S*,20*S* configuration. Likewise, the data for **1.15** point to the known 15*R*,20*R* configurations. The other protons on the THF ring (17,-17′,18,18′) can also be assigned and included in the analysis, and this is described in the Supporting Information.

Compounds such as **1.15** and **1.7** (and **1.4**/**1.12**) with opposite configurations at all four stereocenters in the dihydroxy-THF fragment can be differentiated by the Mosher ester method if enough resonances can be assigned for subtraction. But can **1.7** be differentiated from **1.12** (both 15*S*,20*S*) or **1.15** from **1.4** (both 15*R*,20*R*)? To address this question for all 16 isomers, we ostensibly need to make 32 Mosher esters; however, to minimize effort, we instead validated a "shortcut" Mosher ester method.

Typically, only one stereoisomer of a chiral alcohol is available, so it is converted to two diastereomeric Mosher esters. In contrast, we have available 16 stereoisomers of the dihydroxy-THF ring groups in eight pairs with opposite absolute configurations at C15,16,19,20. Accordingly, rather than making two pairs of Mosher esters from each murisolin, we can simply make a single Mosher ester from each and subtract the resonances of that from its appropriate diastereomer with the locally enantiomeric configurations in the dihydroxy-THF fragment. To test this idea, we subtracted the appropriate resonances of **3.15** (15*R*,-20*R*) from **3.7** (15*S*,20*S*).[17] As projected, both the signs and magnitudes of the differences in chemical shifts (Figure 5) were identical within experimental error to the subtractions of the appropriate tris-(*R*)- and tris-(*S*)-Mosher esters. The same holds for the other pair of Mosher esters **4.15** and **4.7**.

Having demonstrated that making pairs of tris-(*R*)/(*S*)-Mosher esters from each compound provided redundant information, we next prepared the tris-(*S*)-Mosher ester derivatives from the other 14 murisolin isomers and then subtracted the chemical shifts of the relevant resonances to provide signs and magnitudes for each $\Delta\delta$. Tables S1−S6 in the Supporting Information show the complete results of this exercise. In six of the eight pairs with locally enantiomeric conformations in the dihydroxy-THF fragment (including **3.7** and **3.15** above), the subtraction rule was followed. However, the two other pairs of spectra (**3.8** and **3.16**; **3.3** and **3.11**) were substantially identical! Accordingly, subtraction of resonances of these pairs of spectra is pointless. Furthermore, four pairs of spectra (**3.2** and **3.5**; **3.10** and **3,13**; **3.4** and **3.15**; **3.7** and **3.12**) were identical to each other even though these pairs of compounds are not locally enantiomeric in the dihydroxy-THF fragment! A summary of the compounds exhibiting identical Mosher spectra is presented in Figure 6.

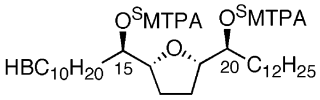
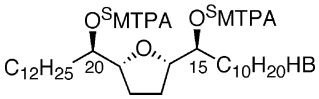
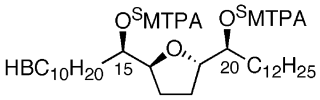
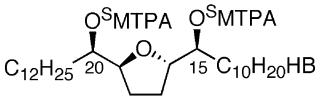
Thus, each of the 16 tris-(*S*)-Mosher esters **3.1**−**3.16** of murisolin isomers exhibits one of only 10 sets of ^{1}H NMR spectra; four compounds have unique spectra, whereas six pairs of compounds have spectra that are identical (though still different from all the rest). This identity may seem surprising, but it is actually predicted from the local symmetry groupings in Figure 2. Each pair of compounds connected by arrows in Figure 2 shares identical tris-Mosher ester spectra. These compounds share the feature that one can be converted to the other by interchanging the two side chains on C15 and C20.

The spectral identity is not a result of a flaw with the Mosher esters; it is a fundamental property of the local symmetry of the molecules, and we predict that other chiral derivatives of these pairs will also exhibit identical spectra. Consider the pair of local C2-symmetric Groups 2 (or 5). The parent of these groups is chiral, and accordingly, a Mosher ester can be used to assign the configuration of its enantiomers. Accordingly, tris-(*S*)-Mosher esters **3.1** and **3.9** have different spectra, and this

(15) Compounds beginning with the number **1** are murisolin triols, whereas those beginning with **3** are tris-(*S*)-Mosher esters (from the (*R*)-Mosher acid chloride) and those beginning with **4** are tris-(*R*)-Mosher esters (from the (*S*)-Mosher acid chloride).

(16) Protons H20 and H15 are assigned by using the guideline that carbinyl protons in *erythro* relationships resonate downfield from those in *threo* relationships. The other assignments follow from the H, H COSY spectra.

(17) In this experiment, **3.15** (tris-(*S*)-Mosher ester, RRSR) can be considered as a surrogate for **4.7** (tris-(*R*)-Mosher ester, SSRS). (Or **3.7** can be considered as a surrogate for **4.15**.) These pairs of compounds have opposite configurations in the dihydroxy−THF region of the spectrum (including the two Mosher esters), and thus, the associated resonances are identical. However, the compounds have opposite Mosher ester but the same (4*R*, 34*S*) configurations in the hydroxybutenolide fragment, so resonances from this region differ, as detailed in ref 10.

Entry	Isomer **3**[a,b]	Isomer **3**[a,b]	Group,[c] local sym
1			4, *meso*
	3.16, RRSS, *tris*-(*S*)-Mosher ester	**3.8**, SSRR, *tris*-(*S*)-Mosher ester	
2	**3.3**, RSRS, *tris*-(*S*)-Mosher ester	**3.11**, SRSR, *tris*-(*S*)-Mosher ester	3, *meso*
3			1, none
	3.2, RSSS, *tris*-(*S*)-Mosher ester	**3.5**, SSSR, *tris*-(*S*)-Mosher ester	
4	**3.10**, SRRR, *tris*-(*S*)-Mosher ester	**3.13**, RRRS, *tris*-(*S*)-Mosher ester	1, none
5	**3.4**, RSRR, *tris*-(*S*)-Mosher ester	**3.15**, RRSR, *tris*-(*S*)-Mosher ester	6, none
6	**3.12**, SRSS, *tris*-(*S*)-Mosher ester	**3.7**, SSRS, *tris*-(*S*)-Mosher ester	6, none

a) ^{S}MTPA is the (*S*)-Mosher ester, C(O)C(CF_3)(OMe)Ph; b) representative structures are shown for enties 1 and 3; the other structures follow directly from Figure 2; c) the Group numbers correspond to those in Figure 2

Figure 6. Tris-(*S*)-Mosher ester pairs **3** that exhibit substantially identical ^{1}H NMR spectra in the dihydroxy−THF region.

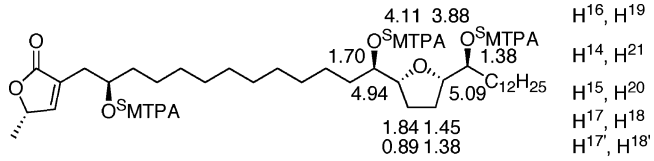
means that the configuration of **1.1** or **1.9** could be assigned by making tris-(*S*)- and tris-(*R*)-Mosher esters and subtracting as usual.

In contrast, consider the pairs of compounds in the local *meso* Groups 3 (or 4). Here, the parents of the Groups are achiral, so making a chiral derivative is pointless. Likewise, the chiral derivatives of **1.3** and **1.11** (or **1.8** and **1.16**) are of course diastereomers because of the two different side chains, but their spectra are still identical because the side chains are so similar.

Ironically, although we cannot use the advanced Mosher rule to assign structures from spectra for such pairs (because the spectra are identical), we can use the rule to assign spectra from structures. This is because we already know the structures and because the differential shifts of the paired protons (H^{14}/H^{21}, H^{16}/H^{19}, H^{17}/H^{18}) as assessed by the Mosher rule tell us which protons are adjacent to the S stereocenter of the 15/20 pair and which are adjacent to the R stereocenter. The representative assignment of **3.16** of Group 4 (16,19-*cis*-murisolin group) is illustrated in Figure 7; three of the proton pairs follow the Mosher guidelines and there is one exception—H^{14} should be upheld of H^{21} but it is downfield. The assignments of H^{14} and H^{21} cannot be independently reversed because the connectivity is known from the H,H−COSY spectrum. Reversing all of the assignments provides three exceptions and only one accord.

The other isomer in Group 4, **3.8**, has the same Mosher spectrum as **3.16**, but all the paired assignments are interchanged. Similar reasoning can be used to assign the protons of the other meso Group 3, and this is shown in the Supporting Information. For this Group, there are four accords and no exceptions to the Mosher rule.

The same identity of Mosher spectra (or lack thereof) holds for the relevant pairs of compounds in Groups 1 and 6. For example, compound **3.2** with *RSSS* configurations can be



3.16
(15*R*,16*R*,19*S*,20*S*)

The advanced Mosher rule predicts...

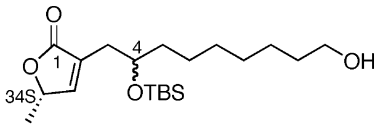
H^{14} is upfield of H^{21}, not observed
H^{16} is downfield of H^{19}, observed
H^{17} is downfield of H^{18}, observed
$H^{17'}$ is downfield of $H^{18'}$, observed

Figure 7. Representative assignment of ^{1}H resonances in meso Group 4 by the Mosher rule.

differentiated from compound **3.10** (*SRRR*), which has a locally enantiomeric relationship at the four dihydroxy−THF ring stereocenters (recall that Mosher esters differentiate enantiomers), but **3.2** cannot be differentiated from the Mosher ester **3.5** (*SSSR*), which has the same local configurations at the two THF ring carbons (C16,19) but opposite configurations at the hydroxy-bearing carbons (C15,20).

In another view of the same phenomenon, all of the isomers that have identical Mosher ester spectra have opposite absolute configurations at C15 and C20 and, accordingly, give the same spectra. Thus, the identical spectra for pairs of diastereoisomers result because different protons in the two isomers give rise to the same sets of resonances.

Comparison of the ^{1}H and ^{13}C NMR Spectra of the Murisolin Stereoisomers—the Hydroxybutenolide Subunit. Synthesis of a second 16-member library of murisolins by double mixture synthesis provided new isomers of murisolin at the hydroxybutenolide fragment.[8] This library's members had



	C1	C2	C3	C5	C35
4*R*,34*S*, anti	174.60	151.82	70.00	33.46	19.13
4*S*,34*S*, syn	174.57	151.89	69.90	33.41	19.10

anti, $\Delta\delta$ C2 – C4 = 81.8 ppm
syn, $\Delta\delta$ C2 – C4 = 82.0 ppm

Figure 8. Assigning the relative configuration of the hydroxybutenolide fragment by small differences in ^{13}C NMR spectra.

fixed configurations at C15 (*R*) and C16 (*R*) and had all possible isomers at the other four stereocenters (Figure 2). Four isomers in this library were identical to four in the prior one (**1.13**−**1.16**), and four were enantiomers (**1.21**−**1.24** are enantiomers of **1.5**−**1.8**). As expected, these eight pairs of compounds exhibited identical ^{1}H NMR spectra.

The other eight compounds (**1.17**−**1.20** and **1.25**−**1.28**) are new diastereomers, and their ^{1}H NMR spectra are compiled in the Supporting Information. As expected, they collate readily into Groups 1−6 in Figure 2, showing identical resonances to the prior compounds that have the same local symmetry in the dihydroxy-THF portion of the molecule. Even though these eight compounds have the syn relative configuration of C4 and C34 in the hydroxybutenolide, their ^{1}H NMR spectra are substantially identical to the isomers with the anti configuration. This identity has been recognized previously.[10]

In contrast, we were able to identify small yet reliable differences in the ^{13}C NMR spectra of the syn and anti isomers.[18] These differences are illustrated with the hydroxybutenolide fragment shown in Figure 8. Individual samples of the 4*R*,34*S* (anti) and 4*S*,34*S* (syn) isomers of this compound exhibited ^{13}C NMR spectra that were very similar. However, when the samples were mixed in a 2/1 ratio, the doubling of five resonances originating from the hydroxybutenolide region of the molecule was evident. Differences in chemical shifts ranged from about 0.03 ppm (peak doubling observed) up to 0.1 ppm (near baseline separation observed).

Given these small differences, how can the configuration of an unknown compound be assigned by ^{13}C NMR spectroscopy without recourse to mixing with the other isomer? This can be done by capitalizing on the observation that one of the peaks of the anti isomer is upfield of the syn isomer whereas the other peaks are downfield. Subtracting the peak at about 70 ppm from the corresponding peak at about 152 ppm effectively doubles the $\Delta\delta$ compared to the usual method of comparing individual peaks to a reference standard rather than to each other. If the difference between the resonances at about 152 ppm (C33) and 70 ppm (C4) is 82.0 ppm, then the compound is a syn isomer, whereas if this difference is 81.8 ppm, then it is an anti isomer.

We did not record any Mosher spectra of these compounds because these spectra can be readily predicted on the basis of those already in hand.[10] It is not necessary to make any of the missing eight compounds to determine their spectral data either because these data will be identical to those from one (or more) current members of the library.

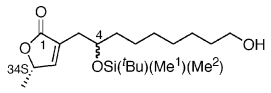
In summary, each of the 32 diastereomers of murisolin exhibits *one of only six* sets of ^{1}H NMR spectra under standard conditions! The six groups of spectra are organized according to the local symmetry of the dihydroxy-THF ring. In contrast, there are two very closely related pairs of six ^{13}C NMR spectra that are identical in the dihydroxy-THF region but have very small (≤ 0.1 ppm) differences in the hydroxybutenolide region based on the syn/anti relative configurations at C4,C34.

The chiral tris-derivatives (as exemplified by tris-Mosher esters) of the 32 isomers in a given enantiomeric series will give rise to 20 ^{1}H NMR spectra, falling into two groups of 10 based on the C4,C34 configuration and the local symmetry of the hydroxybutenolide. In turn, the full complement of chiral tris-derivatives of 64 isomers prepared with one enantiomer of a chiral derivatizing agent (or 32 isomers prepared with both enantiomers of the chiral derivatizing reagent) will give rise to 40 spectra. Within broad limits, the 24 pairs of redundancies do not depend on the power of the chiral derivatizing agent to shift nearby resonances (because the closest differences are 10 or more atoms away from the centers being derivatized).

Structure Assignments of Murisolin, 16,19-*cis*-Murisolin and Murisolin A. With 28 of the isomers of murisolin in hand and well characterized, we can assess the structure assignments of the three known murisolin natural products. The relative configurations of any murisolin in the dihydroxy-THF fragment are readily assigned from the high field NMR spectra. This provides a group of either four or eight diastereomers as candidate structures, to which must then be added the enantiomers of these structures. The logic problem then becomes to collect a set of data that is fully consistent with one of the candidate structures, but more importantly is materially inconsistent with all of the other structures in the group. Many structure assignments to date in the acetogenin class have addressed only the "proof" aspect of the logic problem and neglected the "disproof" aspect. This is often of necessity because only one candidate structure is in hand. And with such similar compounds, it can be very difficult to disprove structures that are not available for comparison.

To further refine the structure from a collection of candidates, the proper use of a chiral derivative can eliminate one enantiomeric series and narrow the other candidate isomers down to two or even one, depending on the group. So derivatization is a powerful structure tool. Beyond that, by far the most used tool has been optical rotation. However, we concur with

(18) Interestingly, the epimers of TBS ethers at C4 can be differentiated by both ^{1}H and ^{13}C NMR spectroscopy. The resonances of H33 are very slightly different in chemical shift, although this was not apparent to us until the isomers were mixed. However, the diastereotopic methyl groups of the *t*-butyldimethylsilyl group were clearly different both before and after mixing. Again, we feel that $\Delta\delta$ is most useful in assessing this difference in single samples of unknown configuration. The $\Delta\delta$ of the syn isomer is about 0.055 ppm, whereas that of the anti isomer is about 0.020 ppm. The following chemical shifts are taken from the mixture spectra with residual $CHCl_3$ as the standard; all other resonances overlap.



	C1	C2	C4	C5	C6	C35	
4*R*,34*S*, anti	174.11	151.61	70.23	36.96	25.09	19.02	$\Delta\delta$ C2 – C4 = 81.38 ppm
4*S*,34*S*, syn	174.05	151.84	69.96	37.17	25.03	19.21	$\Delta\delta$ C2 – C4 = 81.88 ppm

	H33	Me^1	Me^2	
4*R*,34*S*, anti	7.126	0.045	0.018	$\Delta\delta$ Me1 – Me2 = 0.020 ppm
4*S*,34*S*, syn	7.106	0.029	–0.026	$\Delta\delta$ Me1 – Me2 = 0.055 ppm

Figadère and co-workers[19] that optical rotation is a very blunt tool of little utility in these compounds. The rotations of all the murisolins are small and somewhat variable.[8a] The differences in magnitudes of rotations between enantiomers measured under similar conditions are often comparable to the differences in rotations between diastereomers. In our view, the use of rotation in a "proof" sense (the rotations of two samples "match" so they must have the same structure) with these structures is not valid. The combination of a "proof" with a "disproof" (the rotation of a sample matches the rotation of isomer A, but not B, C, D) may be valid, but only if the rotations of all the candidate isomers are measured carefully under strictly identical conditions. Melting points could also be useful, but again they must be accurately known for all isomers.

If all the candidate isomers are available, then chiral hplc is superior to either optical rotation or melting point comparison to prove and disprove structures. In the prior paper,[8] we showed that the murisolin isomers were widely dispersed on a Chiralcel-OD column and that members of any given group were separated from other members of the group by at least 2 min. Thus, when a natural sample and all reasonable candidate isomers are available, a compound within any group (as indicated by NMR experiments) can be assigned simply by conducting several hplc co-injections.

The connectivity of murisolin and its *threo-trans-threo* relative stereochemistry were assigned early on by Cavé and co-workers.[7a] This places murisolin in the local C2 symmetric Group 5, with candidate structures **1.6** and **1.14** and their enantiomers along with the four isomers with C4,34 syn relative configuration. McLaughlin later represented murisolin as **1.14**,[7b] presumably following the standard analysis of tris-(*R*)- and tris-(*S*)-Mosher esters.[7c] We now know that this Mosher analysis should rule out all possible isomers but one. Three groups of isomers at the hydroxybutenolide (4*R*,34*R*, 4*S*,34*S*, 4*S*,34*R*) are eliminated by applying Hoye's application of the Mosher method for assigning both relative and absolute configurations at these centers.[10] (Alternatively, the $\Delta\delta$ C33−C4 can now also be used to assign the relative configuration of the hydroxybutenolide.) This reduces the possibilities from eight to two, **1.6** and **1.14**. Isomers in Group 5 can be differentiated by chiral derivatives, so the application of the Mosher method to eliminate **1.6** and select **1.14** is proper.

We have available the two key candidate isomers **1.6** and **1.14**, and we compared a sample of natural murisolin provided by Dr. Bruno Figadère to these compounds by chiral hplc and found that murisolin coeluted with **1.14** and eluted about 2 min before **1.6**. Likewise, three other isomers in Group 5 with differing configurations at C4 and C34 (**1.18**, **1.22** and **1.26**) were different by chiral hplc from both murisolin **1.14** and **1.6**. Among the eight candidate isomers, three are absent in the library, but it is unreasonable to expect that any of these isomers could coelute with murisolin. Thus, the co-injections prove that murisolin is not **1.6** (or other less likely hydroxybutenolide isomers) and prove that it is **1.14**. Likewise, a synthetic sample prepared independently by Prof. T. Tanaka matched Cavé's natural murisolin and **1.14** but not **1.6**.[20]

By whatever means they used, McLaughlin and co-workers deduced the correct structure of murisolin **1.14** as isolated by Cavé. Ironically, it is not rigorously clear that they deduced the correct structure for the murisolin that they isolated. Because we could not obtain either a sample of murisolin or a copy of the derived Mosher ester spectra for comparison,[17] we cannot disprove that McLaughlin's murisolin is different from ours, Cavé's, and Tanaka's. Because McLaughlin's murisolin and Cavé's murisolin were isolated from different sources, the possibility that they are isomers in the same Group 5 merits consideration.[21] However, because the correct application of the Mosher method does provide a unique structure in Group 5, it seems highly probable that McLaughlin's murisolin is also **1.14**.

Unfortunately, assigning secure structures to 16,19-*cis*-murisolin and murisolin A is not straightforward because samples of these natural compounds are no longer available and because not enough data were collected on the samples when they were available to disprove that they were not at least one other isomer. What can we say about the structures of these two compounds on the basis of the available data of natural and synthetic samples?

16,19-*cis*-Murisolin belongs to local *meso* Group 4, and thus, inspection of the published NMR spectra[7b] reduces the candidate structures to **1.8**, **1.16**, and their enantiomers. The four associated C4,34-syn isomers are ruled out because $\Delta\delta$ C33 − C4 = 81.8 ppm. McLaughlin made the tris-(*R*)- and tris-(*S*)-Mosher esters from the natural product,[7b] and these derivatives eliminate the enantiomers (and also the syn-isomers) from consideration by showing that the configuration of C4 is *R* and C34 is *S*. McLaughlin further subtracted pairs of resonances in the vicinity of H15 and H20 of the two Mosher esters to deduce structure **1.16**. As indicated above, *this is not a meaningful analysis*. Just as the spectra of **3.8** and **3.16** formed from a single enantiomer of the Mosher ester were identical, so should the spectra of products of reaction of **1.8** or **1.16** with both enantiomers of the Mosher ester (**3.8**/**4.8** and **3.16**/**4.16**) be identical in the dihydroxy-THF region of the molecule. Subtraction of one set of resonances from the other is simply a gauge of the error of measurement of ppm values under a given set of experimental conditions; neither the sign nor the magnitude of the differences has any meaning. Indeed, the $\Delta\delta$ values recorded by McLaughlin for this analysis were tiny (<0.003 ppm), and measurement errors in this range are expected because most resonances overlap in one-dimensional (1D) spectra and must be assigned chemical shifts from cross-peaks in 2D spectra.

We stress again that this problem arises from local symmetry and not from a failure of the Mosher derivative to induce a sufficient shift. The inapplicability of chiral derivatives to differentiate structures such as this (without proton assignment) has not been widely recognized, and by perusing recent

(19) For a discussion on problems with optical rotation of acetogenins, see: Duret, P.; Figadère, B.; Hocquemiller, R.; Cavé, A. *Tetrahedron Lett.* **1997**, *38*, 8849−8852.

(20) (a) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Ueki, R.; Tanaka, T.; Yamori, T. *Chem. Commun.* **2004**, 406−407. (b) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem.−Eur. J.* **2005**, *11*, 6237−6245.

(21) Others have also reported the isolation of murisolin, and these samples should be compared with existing ones by chiral hplc or Mosher analysis to prove that they have structure **1.14** and are not one of the seven other isomers in Group 5.

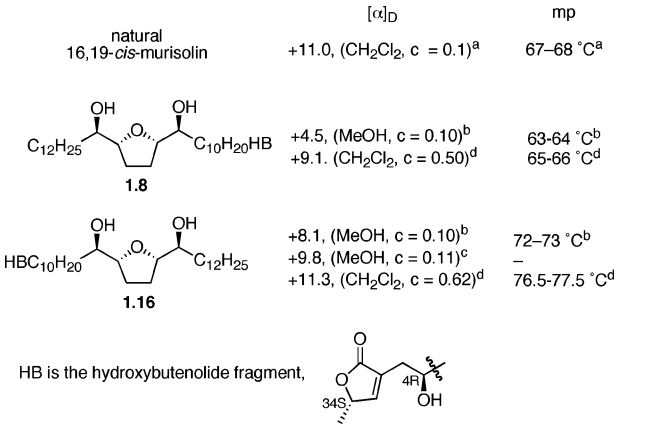


Figure 9. Comparison of optical rotation and melting point data for natural 16,19-*cis*-murisolin and synthetic **1.8** and **1.16**.

acetogenin literature, we quickly identified several analogous improper uses of Mosher esters (see below); there are likely to be others.

With no sample of 16,19-*cis*-mursiolin for chiral hplc analysis, we can only resort to comparing other available data. Murisolin **1.14** and 16,19-*cis*-murisolin were isolated from the same source, so a stereochemical resemblance is likely. But both candidate isomers **1.8** and **1.16** share two stereocenters with murisolin and differ at two, so this comparison provides no help.

Recently, synthetic samples of both **1.8** and **1.16** have also been made by Tanaka by appropriate variants of his efficient synthesis.[20b] Because we know that Tanaka's sample of murisolin has the correct structure, we can be confident that his samples of **1.8** and **1.16** are also correct. (Tanaka mentions that the 1D ^{1}H and ^{13}C spectra of **1.8** and **1.16** are "very similar"; we contend that they are substantially identical.) Melting points and optical rotations for the two pairs of synthetic samples and the natural sample are shown in Figure 9. As mentioned above, optical rotation measurements give little guidance toward a secure structure. However, on the basis of the melting point measurements, we tentatively assign structure **1.8** to 16,19-*cis*-murisolin. During the review of this paper, Figadère and Brown made the surprising discovery that *cis*-solamin is a mixture of two compounds with locally enantiomeric dihydroxy−THF fragments (see below),[22] and this in turn suggests that natural 16,19-*cis*-murisolin might actually be a mixture of **1.8** and **1.16**. Because the Mosher ester derivatives of these compounds are identical, this mixture could not be identified by Mosher analysis of the natural sample.

Lacking in natural 16,19-*cis*-murisolin, it may never be possible to confirm whether the natural product is a single compound or a mixture unless the sample is reisolated from the same source. Even if another 16,19-*cis*-murisolin of Group 4 is someday isolated from a different source and its structure is rigorously proved, it will not be possible to prove whether this was or was not different from the originally isolated sample (other than by comparisons of rotation and melting point as above). Because natural samples all have finite shelf lives, it becomes especially important for workers in this field to collect data that can conclusively disprove that a structure is one of several closely related molecules in a group. Currently, there is no reliable spectroscopic means to do this for murisolins, but the monoderivatization approach deployed by Hoye and coworkers is certainly feasible in principle.[23] Until more direct methods are developed, this procedure should be implemented whenever practical for new or existing acetogenins that cannot be differentiated from their end-switch isomers by chiral derivatives for local symmetry reasons.

Murisolin A belongs to Group 1, so four candidate structures along with their enantiomers and the eight C4,C34 syn isomers (16 in total) remain following standard 1D NMR analysis. Again, there is no natural sample available for comparison with the synthetic samples. However, McLaughlin made pairs of tris-(*S*)- and tris-(*R*)-Mosher ester derivatives of the natural product, and their spectra rule out all isomers at C4,C34 except *R*,*S*. This leaves the four isomers shown in Group 1. Two of these can be ruled out because it is possible to assign *erythro* and *threo* carbinol protons in this group; the Mosher analysis suggests that the *erythro* unit is *S*-configured and the *threo* unit is *R*-configured. This eliminates **1.2** and **1.5** and leaves the two end-switched isomers **1.10** and **1.13**. McLaughlin recognized that these could not be differentiated by the chiral derivative method.

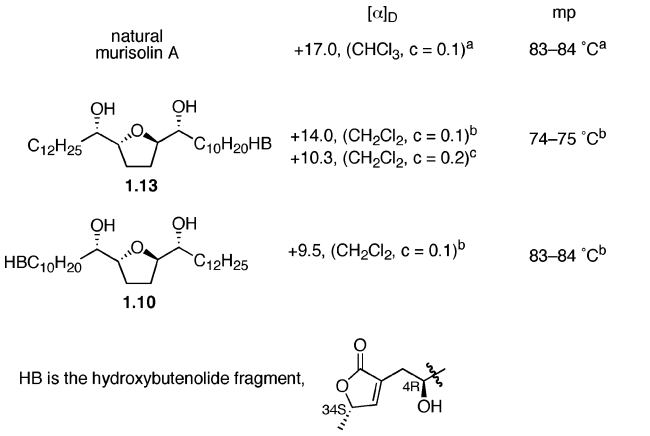
We have made the tris-(*S*)-Mosher esters of these four compounds, and the data from these samples concur with McLaughlin's assignment of murisolin A as either **1.10** or **1.13**. These two compounds (**3.10** and **3.13**) have identical tris-(*S*)-Mosher ester spectra that match well with the tris-(*S*)-Mosher ester spectrum reported by McLaughlin. In turn, the spectra of tris-(*S*)-Mosher esters **3.5** and **3.2** are identical to each other and to McLaughlin's tris-(*R*)-Mosher ester of murisolin A (in the dihydroxy-THF region). Accordingly, this proves that murisolin A is neither **1.5** nor **1.2**. As an aside, we discovered that by far the poorest performance of the "advanced Mosher rule" occurs in this *threo-trans-erythro* series, where subtraction trends for only 5 of 8 assignable resonances are correctly predicted. (Other groups have subtraction trends of 7 or all 8 of 8 resonances correctly predicted, see Supporting Information.) However, this shortcoming is of no consequence to us because we know the configuration of our synthetic compounds, so we simply match spectra with those of McLaughlin's. The matches are independent of assignment or subtraction of resonances.

Melting points and optical rotations of synthetic and natural samples are compared in Figure 10, but the optical rotation comparison is not conclusive. However, if **1.8** is the correct structure of 16,19-*cis*-murisolin, then we suggest that **1.10** is the more likely structure for murisolin A. This is because **1.10** differs in configuration at only one center from both murisolin (C15) and 16,19-*cis*-murisolin (C16). In contrast, **1.13** differs from murisolin by one stereocenter but from 16,19-*cis*-murisolin by three. This suggestion is supported by melting point measurements, so we tentatively assign structure **1.10** to murisolin A.

Structure Assignments of Related Mono-THF Acetogenins. The problems outlined above with assigning structures

(22) (a) Hu, Y.; Cecil, A. R. L.; Frank, X.; Gleye, C.; Figadère, B.; Brown, R. C. D. *Org. Biomol. Chem.* **2006**, *4*, 1217−1219. (b) Gleye, C. PhD Thesis, Université Paris-Sud, 1998. See also the Supporting Information associated with the above paper.

(23) Rieser, M. J.; Hui, Y.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hansen, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203−10213.



Footnotes: a) from McLaughlin, ref 7b; b) this work, first library sample; c) this work, second library sample

Figure 10. Comparison of optical rotation and melting point data for natural murisolin A and synthetic **1.13** and **1.10**.

from spectra are not unique to murisolin and extend to scores of other acetogenins with remote stereocenters and local symmetry in the mono- or bis-tetrahydrofuran portion of the molecule. We briefly revisit several typical structure assignments in the dihydroxy-THF class of acetogenins related to murisolin and show that some choices between structures within the same local symmetry group may be without a firm basis.

Solamin and *cis*-solamin are 4-deoxy analogues of the corresponding murisolins. Cavé and co-workers assigned solamin as *threo-trans-threo*; this is in Group 5 with local C2 symmetry.[24] This leaves four possible structures. Because *cis*-solamin has been shown to have the 34*S* configuration (see below), we eliminate the 34*R* isomers of solamin, leaving **5.14** and **5.6** as candidates (Figure 10). Structure **5.14** has been prepared by total synthesis four times, and each time it has been shown to match either natural solamin or a prior synthetic sample by spectra, melting point, and optical rotation.[25] Accordingly, **5.14** is now the accepted structure of solamin. However, we see no basis in published data for differentiating structures **5.14** and **5.6**. We now know that these compounds will have substantially identical spectra. And proofs based on matching between melting point and optical rotations are not valid because the data are only known for **5.14** and not **5.6**. On the basis of our data above, it would not be at all surprising if the melting point and optical rotation of **5.6** fell within the range of observations for existing synthetic samples of **5.14**.

In short, although it is clear that the total syntheses have provided **5.14** in all cases, these endeavors do not show whether natural solamin is **5.14** or **5.6** because none of the data collected to date disproves one of the structures. Furthermore, natural solamin has been isolated from several different sources, and it is not at all clear that these compounds have the same structure.[26] Though it seems unlikely because the plants are all related, for all we know there could be two (**5.6** and **5.14**), or even four (epimers at C34), natural solamins.

We recently learned that the bis-(*S*)- and bis-(*R*)-Mosher ester spectra of natural solamin are contained in the thesis of Dr. C. Gleye,[22b] and Dr. B. Figadère kindly provided copies of the original spectra. Mosher subtraction of these spectra suggests that solamin is **5.14**,[22a] and this is confirmed by matching to the relevant spectra in our collection; the ^{1}H NMR spectrum of the bis-(*S*)-Mosher ester of solamin maps with the spectrum of the tris-(*S*)-Mosher ester **3.14** of murisolin in the dihydroxy−THF region, whereas the bis-(*R*)-Mosher ester of solamin maps with the locally enantiomeric tris-(*S*)-Mosher ester **3.6**. Thus, the structure of solamin is confirmed as **5.14** (4-deoxymurisolin) with identical configurations to murisolin **1.14** at all five shared stereocenters.

Laurens and co-workers described the isolation of *cis*-solamin in 1998 and ascribed it the *threo-cis-threo* relative configuration.[26c] It is thus in *meso* Group 4 and is 4-deoxy-16,19-*cis*-murisolin. Later, Figadère and co-workers used a chiral shift reagent to assign the 34*S* configuration.[27] This information leaves two candidate structures standing for 16,19-*cis*-solamin, **5.16** and **5.8**. Both of these compounds have been synthesized independently by the groups of Makabe[28a] and Brown,[28b] and the latter group also prepared the two enantiomers. None of these compounds could be differentiated from each other by standard NMR analyses. The reported melting points and optical rotations of the natural and synthetic samples are summarized in Figure 11. The collective rotation data support the conclusion that *cis*-solamin is 34*S*, but the choice of the two possible THF configurations is ambiguous. Makabe and co-workers concluded that *cis*-solamin was **5.16** based on their rotations,[28a] but the later rotations of Brown[27b] seem accurate (enantiomers give equal and opposite rotations) and are nearly equal. The melting points for all the samples are scattered in a narrow range and are not helpful.

Makabe and co-workers made bis-Mosher ester derivatives of both **5.16** and **5.8** to show that the Mosher analysis could be used to differentiate them. However, we submit that these Mosher spectra are substantially identical and that the small differences in chemical shift observed (0.01 ppm or less) are of experimental origin; their signs and magnitudes have no meaning. Accordingly, the synthesis of a bis-Mosher esters of this natural product is not a worthwhile exercise unless some secure method can be established to differentiate them by assigning resonances.[29]

During the review of this paper, Figadère and Brown made the remarkable suggestion on the basis of chiral HPLC experiments that natural *cis*-solamin is an (approximately) equimolar mixture of **5.8** and **5.16**.[22a] This suggestion is fully consistent with available and expected spectroscopic information. Compounds **5.8** and **5.16** exhibit identical spectra, and the spectra of all four Mosher esters (bis-(*R*)- and bis-(*S*)- of both isomers)

(24) Myint, S. H.; Cortes, D.; Laurens, A.; Hocquemiller, R.; Leboeuf, M.; Cavé, A.; Cotte, J.; Quero, A. M. *Phytochem.* **1991**, *30*, 3335−3338.

(25) (a) Kuriyama, W.; Ishigami, K.; Kitahara, T. *Heterocycles* **1999**, *50*, 981−988. (b) Trost, B. M.; Shi, Z. P. *J. Am. Chem.* Soc. **1994**, *116*, 7459−7460. (c) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975−1981. (c) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891−4892.

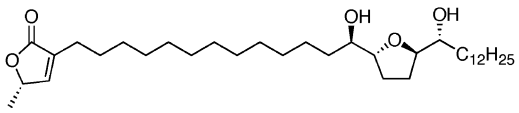
(26) (a) das Chagas do Naseimento, F.; Boaventura, M. A. D.; Assuncao, A. C. S.; Pimenta, L. P. S. *Quim. Nova* **2003**, *26*, 319−322. (b) Fall, D.; Gleye, C.; Franck, X.; Laurens, A.; Hocquemiller, R. *Nat. Prod. Lett.* **2002**, *16*, 315−321. (c) Gleye, C.; Duret, P.; Laurens, A.; Hocquemiller, R.; Cavé, A. *J. Nat. Prod.* **1998**, *61*, 576−579. (d) Qin, Y.; Pan, X.; Chen, R.; Yu, D. *Yaoxue Xuebao* **1996**, *31*, 381−386. (e) Duret, P.; Waechter, A. I.; Hocquemiller, R.; Cavé, A.; Batten, D. *Nat. Prod. Lett.* **1996**, *8*, 89−95. (f) Chen, W.-S.; Yao, Z.-J.; Wu, Y.-J. *Youji Huaxue* **1995**, *15*, 85−88.

(27) Latypov, S.; Franck, X.; Jullian, J.-C.; Hocquemiller, R.; Figadère, B. *Chem.−Eur. J.* **2002**, *8*, 5262−5266.

(28) (a) Cecil, A. R. L.; Hu, Y. L.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368−3374. (b) Makabe, H.; Hattori, Y.; Kimura, Y.; Konno, H.; Abe, M.; Miyoshi, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **2004**, *60*, 10651−10657.

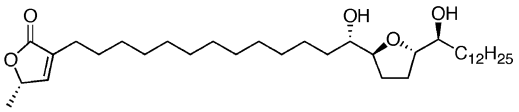
(29) For example, H15 and H20 and the other nearby nuclei are chemical-shift equivalent in **5.16** and **5.8** but different in thier bis-Mosher ester derivatives. If any of these nuclei could be reliably assigned, then a secure structure would result.

solamin is threo-trans-threo, Group 5 (C2), and could be



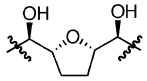
5.14, (15*R*,16*R*,19*R*,20*R*,34*S*)

-or-



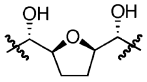
5.6, (15*S*,16*S*,19*S*,20*S*,34*S*)

cis-solamin is threo-cis-threo, Group 4 (meso), and could be

	$[\alpha]_D$	mp
	+11.3, (MeOH, c = 0.87)[a]	67–69 °C[a]
	+26 (MeOH, c = 0.45)[b]	71–72°C[b]
	–11.7, (MeOH, c = 0.85) (ent-**5.16**)[a]	66–68 °C[a]

5.16, (15*R*,16*R*,19*S*,20*S*,34*S*)

-or-

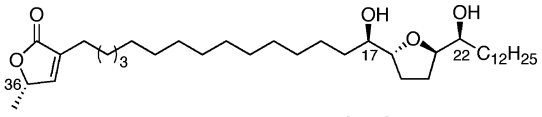
	+11.8, (MeOH, c = 0.85)[a]	67–69 °C[a]
	+42 (MeOH, c = 0.50)[b]	71–72°C[b]
	–11.3, (MeOH, c = 0.68) (ent-**5.8**)[a]	66–68 °C[a]

5.8, (15*S*,16*S*,19*R*,20*R*,34*S*)

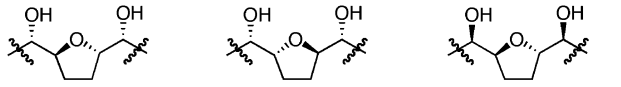
natural cis-solamin	+22, (MeOH, c = 0.55)[c]	63-66 °C[c]

a) ref 28a; b) ref 28b; c) ref 25c

Figure 11. Candidate structures for solamin and *cis*-solamin.



6.13, (17*R*,18*R*,21*R*,22*S*,36*S*)

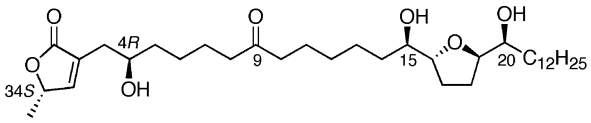


6.5 (17*S*,18*S*,21*S*,22*R*,36*S*) **6.10** (17*S*,18*R*,21*R*,22*R*,36*S*) **6.2** (17*R*,18*S*,21*S*,22*S*,36*S*)

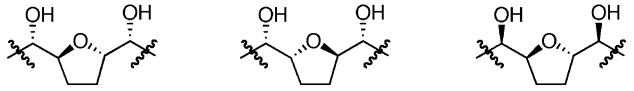
Figure 12. Candidate structures for reticulatain-1, *threo-trans-erythro*, Group 1 (no symmetry).

will also be identical. Chiral HPLC is accordingly the only method presently available that can identify that such natural samples are mixtures. As mentioned above, the structure resemblance of murisolins and solamins suggests that *cis*-murisolin might also be a mixture of two isomers.

The structure assignment of reticulatain-1 presents another twist on the structure problem. This was isolated by Figadère and co-workers, who showed that it has an *erythro-trans-threo* relative configuration (Figure 12).[30] Reticulatain-1 is thus in Group 1 with murisolin A, but it has two more methylene groups in the hydroxybutenolide side chain than either the murisolins



7.13, (15*R*,16*R*19*R*,20*S*)



7.5 (15*S*,16*S*,19*S*,20*R*) **7.10** (15*S*,16*R*,19*R*,20*R*) **7.2** (15*R*,16*S*,19*S*,22*S*)

Figure 13. Candidate structures for mosin B, *threo-trans-erythro*, Group 6 (no symmetry).

or the solamins. As is usual with C4-deoxy acetogenins, we assume a 36*S* configuration.

Makabe and co-workers prepared candidates **6.13** and **6.5** for reticulatain-1 and could not differentiate these by standard spectroscopic means (because the spectra are substantially identical) or by rotation or melting point.[31] However, they could properly differentiate these two structures by making bis-(*R*)-Mosher esters, whose data were consistent with **6.13** and not **6.5**.[32] Accordingly, it was concluded that **6.13** is reticulatain-1.

This assignment is inconclusive because **6.13** is in Group 1, so four isomers must be considered as structure candidates. The two missing isomers are **6.10** and **6.2**. Although the Mosher data clearly disprove structure **6.2**, they do not disprove structure **6.10**. Indeed, we now know that **6.10** and **6.13** will have substantially identical Mosher spectra. Thus, the structure of reticulatain-1 cannot be considered to be proved until one of structures **6.10** or **6.13** is disproved. Again, if the assignment of murisolin A as **1.10** proves correct, then reticulatain-1 is probably **6.10**.

The last case is mosin B. Isolated by McLaughlin and assigned the *threo-trans-erythro* configuration, mosin B is a 9-oxo murisolin A falling into Group 1.[33] The 4*R*,34*S* configurations were supported by Mosher ester analysis, but this analysis did not provide a firm assignment of configuration in the dihydroxy-THF ring.[34] We can now understand that this is because the *threo-trans-erythro* isomers are not the best actors in the advanced Mosher analysis (see above). Accordingly, there are four candidate isomers to consider, as shown in Figure 13. Tanaka and co-workers made two of the four isomers, **7.13** and **7.2**, and concluded that **7.13** was mosin B based on optical rotation and systematic subtraction of ^{13}C NMR resonances.[35] But this conclusion again rests on shaky ground. First, structures **7.5** and **7.10** were not considered. Second, the optical rotation

(30) a) Duret, P.; Waechter, A. I.; Hocquemiller, R.; Cavé, A.; Batten, D. *Nat. Prod. Lett.* **1996**, *8*, 89−95. b) Tam, V. T.; Hieu, P. Q. C.; Chappe, B.; Roblot, F.; Figadère, B.; Cavé, A. *Bull. Soc. Chim. France* **1995**, *132*, 324−329.

(31) (a) Makabe, H.; Hattori, Y.; Kimura, Y.; Konno, H.; Abe, M.; Miyoshi, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **2004**, *60*, 10651−10657. (b) Makabe, H.; Miyawaki, A.; Takahashi, R.; Hattori, Y.; Konno, H.; Abe, M.; Miyoshi, H. *Tetrahedron Lett.* **2004**, *45*, 973−977.

(32) Makabe reached the conclusion by comparing chemical shifts of the bis-(*R*)-Mosher esters with those of the Mosher esters derived from the standard model shown in Table 1 (see ref 9c). However, the same conclusion can be reached without reference to models or bis-(*S*)-Mosher esters by subtracting the relevant resonances of the two spectra from each other.

(33) Hopp, D. C.; Zeng, L.; Gu, Z.-M.; Kozlowski, J. F.; McLaughlin, J. L. *J. Nat. Prod.* **1997**, *60*, 581−586.

(34) If we had access to the unpublished spectra mentioned ref 33, then we could rule out two of the four possible isomers by comparison to our set of Mosher spectra.

(35) (a) Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C.; Tanaka, T. *Org. Lett.* **2001**, *3*, 429−432. (b) Maezaki, N.; Kojima, N.; Sakamoto, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdensuren, B.; Nakamori, S. *Chem.−Eur. J.* **2003**, *9*, 389−399.

data are not conclusive. And third, the ^{13}C NMR analysis is not meaningful because the ^{13}C NMR data for **7.13** and **7.2** will be substantially identical even though these compounds are diastereomers. Thus, none of the data collected to date disproves any of the four structures for mosin B.[34] Based on its similarity to murisolin A, mosin B might be **6.10**. But this is only an analogy and not a proof, or more importantly, not a disproof.

Finally, the natural product mosin C (not shown) was also isolated in this paper,[33] and this has the *threo-cis-threo* relative configuration of the dihydroxy-THF ring (Group 4, like 16,-19-*cis*-murisolin and *cis*-solamin) and the C4,34-anti configuration (also like 16,19-*cis*-murisolin). However, the reported subtraction of resonances of Mosher ester spectra to assign the *RRSS* configuration to mosin C is not proper because these spectra are identical, so there is no basis for choosing the *RRSS* isomer over the *SSRR* isomer. Mosin C could still be either one of these two pure compounds or a mixture.[22a]

Conclusions

Characterizing a stereoisomer library of 28 of the 64 possible isomers of the acetogenin murisolin including 24 of the 32 possible diastereomers has provided a complete picture of the spectra of this class of molecules. Remarkably, each of the 32 diastereomers exhibits one of only six sets of substantially identical ^{1}H NMR spectra under standard conditions. These spectra follow directly from a local symmetry analysis of the dihydroxy−THF fragment of the molecule and provide no information about the hydroxybutenolide. In contrast, the ^{13}C NMR spectra fall into 1 of 12 sets consisting of 6 very closely related pairs grouped by the local symmetry of the dihydroxy−THF fragment (set of 6) and the relative configuration of the hydroxybutenolide (set of 2). The small differences observed in the hydroxybutenolide resonances now allow the assignment of the relative configuration of this fragment of many acetogenins without derivatization. No isomer has a unique ^{1}H or ^{13}C NMR spectrum, so the spectra of the eight missing isomers are already known with confidence.

Making tris-Mosher esters of the library reduces but does not eliminate the redundancies. The tris-Mosher esters of the 64 isomers of murisolin will exhibit 40 sets of spectra: 16 isomers have unique spectra whereas 24 isomers share an identical spectrum with one other isomer. Spectra are available for 10 of the 40 possible tris-(*S*)-Mosher ester combinations. These and published[10] spectra cover all possible local configurations of both fragments of the molecule, so the other 30 spectra can be readily assembled by extracting appropriate resonances from spectra of the relevant dihydroxy-THF- and hydroxybutenolide-containing molecules and adding them together. Accordingly, *it is no longer necessary to use the advanced Mosher rule to assign configurations of murisolins and related molecules*. Instead, one simply matches resonances of a single Mosher ester spectrum of an unknown isomer with the fragments of spectra from the complete library of dihydroxy-THF and hydroxybutenolide spectra. Matching of the second Mosher ester spectrum, as we did with solamin **5.14**, can be useful to confirm the assignment, but is probably not necessary in most cases.

The problem of redundant Mosher ester spectra is not the result of a fault or anomaly with Mosher esters as chiral shift reagents. Instead, it arises because the (necessary) use of a symmetrical model to analyze the Mosher ester spectra is an underdetermined solution to the problem. There are only 10 stereoisomers of the model, and these cannot model the 16 dihydroxy-THF isomers in murisolin without redundancy. Mosher esters can always be used to differentiate a compound from others with locally enantiomeric configurations in the dihydroxy-THF ring, but "end-switched" diastereomers cannot be differentiated. At the highest level, the pairs of spectra are not truly "identical". Instead, different protons (for example H15 in one isomer and H20 in another) give rise to identical resonances. A distance experiment that spanned the 10 methylene groups to identify the different ends of the two side chains would provide different results for each of the otherwise identical pairs of spectra and thereby break their coincidence.

With all the data of the library in hand, we confirmed by spectroscopic analysis and hplc co-injection that **1.14** is murisolin and that all other candidates that share identical spectra with **1.14** are not murisolin. Samples of 16,19-*cis*-murisolin and murisolin A are not available, and comparison of spectroscopic data of the compounds and derivatives still matches two compounds for each structure. However, the melting point data are more consistent with structure **1.8** for 16,19-*cis*-murisolin and with structure **1.10** for murisolin A. Clearly these assignments are tentative and await further confirmation to rigorously rule out one of the two candidate structures in each case. Indeed, recent results with *cis*-solamin suggest that natural 16,19-*cis*-murisolin might be a mixture of two isomers.[22a] Because the natural product samples no longer exist and because not enough data was collected on them while they did to differentiate them from one other isomer, their original structures will probably never be known with certainty.

The problems with structure assignment in the murisolins multiply across many other acetogenins in both the mono- and dihydroxy-THF classes. It is now clear that for certain types of diastereomers, standard "matching" of spectral data is of no help in differentiating structures because there are multiple matches. Mixture synthesis methods provide a valuable approach to the structure problem because all candidate isomers can be made for comparison with a natural product. The problem in logic then becomes finding a method that can disprove that all but one of the isomers is identical to the natural product. Toward this end, chiral hplc analysis appears to be much more valuable than melting point or optical rotation comparisons.

Finally, traditional "one at a time" synthesis is commonly pursued with the aim of assigning a stereostructure of a natural product. The usual method is to apply the best assumptions to select a likely "correct" structure and then to synthesize that structure and prove by comparison that it is the natural product. In the acetogenins, this approach should be reversed. Most acetogenins are now readily classed in groups of 2, 4, or more candidate isomers without recourse to synthesis. Once the most likely structure of a compound from a group of candidate isomers is selected, this structure should be tabled and the other isomer (or isomers) in the same group should be synthesized. Once the supposed incorrect isomer is in hand, experiments should then be undertaken to disprove that it the natural product. When all the isomers but one have been disproved, then a solid structure assignment is in hand. It may, of course, be desirable to make the natural product for biological testing or other ends, but it is not necessary to make it for structure proof.

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Supporting Information Available: Contains copies of 1D and 2D spectra of murisolin isomers and their derived Mosher esters (150 pages, print/PDF). This material is available free of charge via the Internet at http://www.acs.org.

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