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Fluorous Mixture Synthesis of Stereoisomer Libraries: Total Syntheses of (+)-Murisolin and Fifteen Diastereoisomers

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Rigorous structure proof of compounds with features such as nearly symmetric subunits or remote stereocenters can be difficult. Many acetogenin natural products couple these features with a resistance to crystallize.[1] Figure 1 shows the structures assigned to the three known members of the murisolin class of monotetrahydrofuran acetogenins: (+)-murisolin (**1**), (+)-16,19-*cis*-murisolin (**2**), and (+)-murisolin A (**3** or **4**).[2,3] The murisolins exhibit powerful cell killing effects (with reported IC_{50}'s as low as 1 fM), yet differ from each other in relative potencies by factors of up to 1 billion.[2b]

We communicate herein a 4-mix/4-split strategy for the synthesis of a stereoisomer library of (+)-murisolin and 15 of its isomers. This relies on the recently introduced solution phase technique of fluorous mixture synthesis[4] to leverage synthetic effort through much of the synthesis. There is excellent evidence that all three murisolins have the 4(*R*) and 34(*S*) configurations in the hydroxy butenolide (right) fragment,[2] so we focused on making the 16 stereoisomers of the dihydroxy tetrahydrofuran (left) fragment with these two centers fixed. Figure 2 summarizes the synthetic strategy.

Initially, two pairs of enantiomers are prepared, tagged with different fluorous PMB tags, and mixed to give M-**5**.[5] Advancement of this single mixture to alkene M-**6** is then followed by two splits. First, each of two mixtures is subjected to a Shi epoxidation with enantiomeric ketone catalysts.[6] Later, these two mixtures are split again with half being subjected to a Mitsunobu reaction and the other half not. Ultimately, we obtain four mixtures M-**7a**−**d**, each containing four isomers, which are demixed and detagged to provide all 16 target isomers.

The premix stage of the fluorous mixture synthesis is summarized in Scheme 1. Homoallyllic alcohol (*S*,*S*)-**8** was prepared in 95% ee by Brown allylation,[7] and half of this sample was inverted by Mitsunobu reaction to provide (*R*,*S*)-**8**. Likewise, (*S*,*R*)-**8** and (*R*,*R*)-**8** were made from the enantiomeric borane (not shown). Each of these compounds **5** was tagged with a corresponding fluorous PMB-bromide ($BrPMB^F$),[8] and the resulting compounds were then mixed in roughly equimolar proportions to give M-**5**. In this mixture, the fluorine content of the tag serves as a code for the configurations at C19 and C20 (murisolin numbering).

The mixture stage of the synthesis is summarized in Scheme 2. For brevity, we describe herein only the synthesis of M-**14d** (series **d**), which contains the proposed structures of murisolin **1** and 16,19-*cis*-murisolin **2** and one of the proposed structures (**4**) of murisolin A. Initial mixture M-**5** is subjected to hydroboration and oxidation, and the resulting alcohol is converted to the iodide prior to Negishi coupling[9] with a vinyl iodide to give M-**9**. Protecting group exchange to give M-**10** is then followed by Shi epoxidation with the 3-keto-(L)-fructose diacetonide[6] (first split), closure to the tetrahydrofuran, Mitsunobu inversion (second split), and hydrolysis. Diol M-**11** is then bis-silylated and mono-desilylated to give alcohol M-**12**. Conversion to the sulfonyl tetrazole M-**13**, Kocienski-Julia coupling[10] with aldehyde **15**,[11] and hydrogenation of the resulting alkene with Wilkinson's catalyst provide the final mixture M-**14d**.

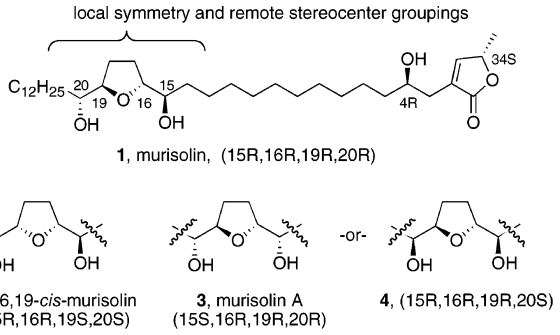


Figure 1. Structures of the murisolin family of acetogenins.

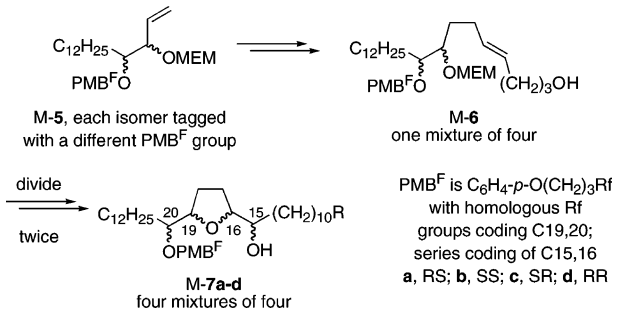
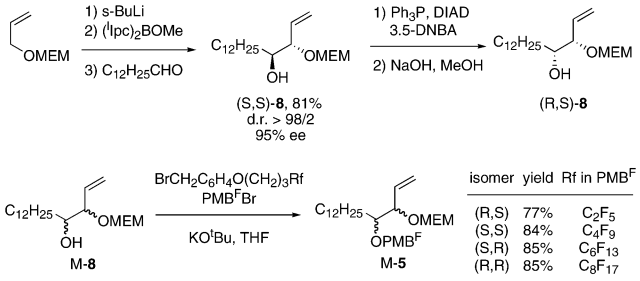


Figure 2. Strategy for the 16-member murisolin stereoisomer library.

Scheme 1



While only the series **d** reactions are shown in Scheme 2, a total of 39 synthetic steps were required to make all four final mixtures (series **a**−**d**). This is a considerable savings over the 156 steps that would be required to do the same transformations on individual samples.

In the postmix stage, preparative demixing of M-**14d** over FluoroFlash[8b] silica gel provided the four pure components of the mixture. Each was subjected to rapid two step detagging and HPLC purification to provide >95% isomerically pure **16** (not shown, from the C_2F_5 tag), **2** (from the C_4F_9 tag), **4** (from the C_6F_{13} tag), and **1**

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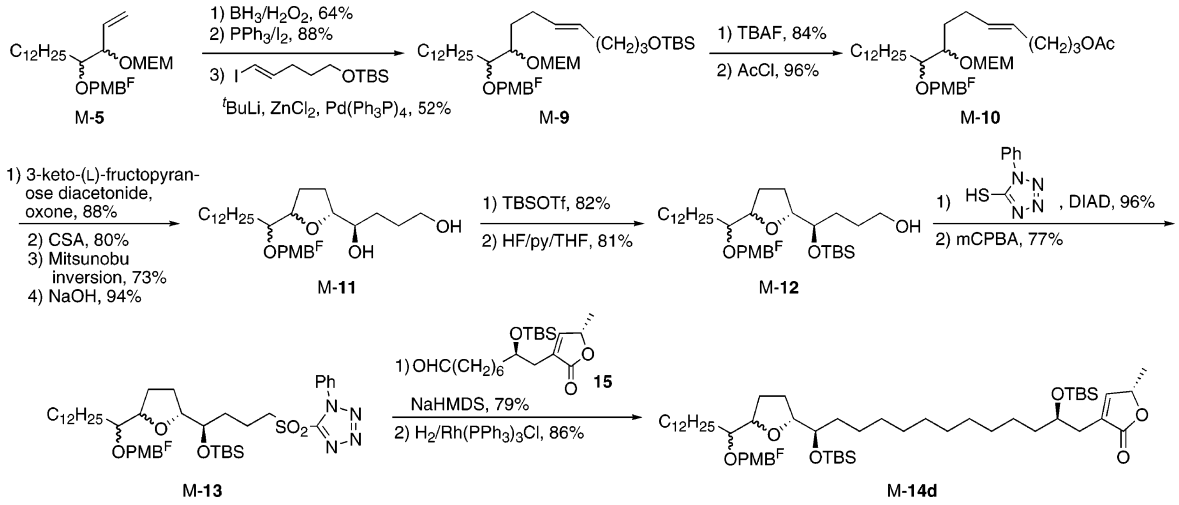
Scheme 2



(from the C_8F_{17} tag). Likewise, the other 12 isomers were isolated from the appropriate series **a**−**c** syntheses. Amounts of final products isolated varied from series to series from 1 to 20 mg, with an average of 6 mg. The identity of each stereoisomer is provided by its series coupled with its elution order (fluorous tag) on demixing. Table 1 in the Supporting Information summarizes the configurations of the products and the tagging scheme and provides optical rotations and retention times on a chiral column (see below).

The 16 isomers are substantially similar, and there are only six different sets of ^{1}H (600 MHz) and ^{13}C (151 MHz) NMR spectra; two sets of four compounds exhibit identical spectra as do four sets of two compounds. Optical rotations at the sodium D-line are not reliable indicators for murisolins (see Supporting Information). Despite the spectral similarities, the 16 isomers are well resolved on a Chiracel-OD HPLC column. Accordingly, candidate murisolin isomers can now be assigned by direct comparison to this stereoisomer library by ^{1}H and ^{13}C NMR spectroscopy and chiral HPLC co-injection.

Two compounds in the stereoisomer library, the *SSSS* isomer from series **b** and *RRRR* isomer from series **d**, exhibit spectra identical to that of the natural product murisolin. Dr. Bruno Figadère kindly provided us with a sample of natural murisolin, which was identical to *RRRR*-**1** by co-injection on a Chiracel OD column and different from the *SSSS* isomer. Thus, we have confirmed that the stereochemical assignment of murisolin is correct. We have not been able to secure samples of 16,19-*cis*-murisolin (spectra match two isomers) or murisolin A (spectra match four isomers), and efforts to confirm their configurations will be described in a full paper.

This work shows that tag-based mixture synthesis strategies are powerful tools for making suitable stereoisomer libraries for comparison to a natural or synthetic product of uncertain configuration. Beyond their use in assignment of configuration, the members of the stereoisomer library will provide rich information on all sorts of stereostructure/function relationships.

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Supporting Information Available: A table with rotation and retention data and copies of ^{1}H and ^{13}C NMR spectra of all 16 murisolin isomers (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) See: Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540, and prior reviews in this series.
(2) (a) Myint, S. H.; Laurens, A.; Hocquemiller, R.; Cave, 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.
(3) (a) Hoye, T. R.; Zhuang, Z. *J. Org. Chem.* **1988**, *53*, 5580−5582. (b) Duret, P.; Waechter, A.-I.; Figadère, B.; Hocquemiller, R.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 4717−4720. (c) Latypov, S.; Franck, X.; Jullian, J.-C.; Hocquemiller, R.; Figadere, B. *Chem.-Eur. J.* **2002**, *8*, 5662−5666.
(4) (a) Luo, Z. Y.; Zhang, Q. S.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769. (b) Curran, D. P.; Oderaotoshi, Y. *Tetrahedron* **2001**, *57*, 5243−5253. (c) Zhang, Q. S.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774−5781. (d) Zhang, W.; Luo, Z.; Chen, C. H. T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443−10450. (e) Curran, D. P.; Amatore, M.; Guthrie, D.; Campbell, M.; Go, E.; Luo, Z. Y. *J. Org. Chem.* **2003**, *68*, 4643−4647.
(5) The prefix "M" denotes a mixture of fluorous-tagged compounds.
(6) (a) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979−2000. (b) Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
(7) (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. L. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.
(8) (a) Curran, D. P.; Furukawa, T. *Org. Lett.* **2002**, *4*, 2233−2235. (b) The PMB alcohols and FluoroFlash HPLC columns are commercially available from Fluorous Technologies, Inc. (www.fluorous.com). DPC holds an equity interest in this company.
(9) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823.
(10) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28.
(11) Avedissian, H.; Sinha, S.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035−6051.

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