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Simultaneous Preparation of Four Truncated Analogues of Discodermolide by Fluorous Mixture Synthesis

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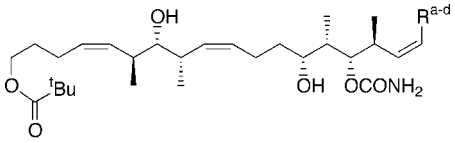
ABSTRACT



Four analogues made in one synthesis

Four truncated analogues of the natural product discodermolide were synthesized in a single synthetic sequence. Precursors bearing four different groups at C22, each with a unique fluorous *p*-methoxybenzyl substituent on the C17 hydroxy group, were mixed and taken through an nine-step sequence. Demixing by fluorous chromatography followed by deprotection and purification provided the individual analogues in 3–7% overall yields and with a savings of 24 synthetic steps. Fluorous mixture synthesis is recommended as a new technique to make multiple natural product analogues in a single multistep synthesis.

The preparation of analogues of small organic molecules for detailed structure/function analysis is a common goal in natural products synthesis, medicinal chemistry, and other areas. Parallel techniques are convenient for syntheses with only a few steps, but the effort involved increases in direct proportion to the number of reaction and separation steps. For syntheses longer than two or three steps, mixing of intermediates is economical.[1] However, the economies in the collective preparation of several organic compounds by solution-phase mixture synthesis are generally thought to be negated by difficulties in analyzing, separating, and identifying mixture components.

We have recently introduced the concept of mixture synthesis with separation tags and implemented this with fluorous tags.[2] Briefly, members of a series of substrates are tagged with homologous fluorous tags. The tagged compounds are mixed and taken through a series of steps to make a mixture of tagged products. These are then demixed (separated by tag structure) and identified by chromatography over fluorous silica gel[3] prior to detagging to give the individual target products.

Proof-of-principle experiments for fluorous mixture synthesis followed a short, well-worn synthetic path to analogues of mappicine.[2] Is extensive reaction development and rehearsal a prerequisite, or can fluorous mixture synthesis be used in an exploratory fashion to make multiple compounds in a new multistep synthesis? We are addressing this question in the synthesis of analogues of the potent anticancer agent (+)-discodermolide **1**[4] and now communicate the

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(2) (a) Luo, Z. Y.; Zhang, Q. S.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766. (b) Curran, D. P.; Oderaotoshi, Y. *Tetrahedron* **2001**, *57*, 5243. (c) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774.

(3) Curran, D. P. *Synlett* **2001**, 1488.

(4) Leading references for prior synthetic work: (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621. (b) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (c) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054. (d) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (e) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (f) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

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preparation of four truncated analogues **2a**−**d** by fluorous mixture synthesis. A new fluorous analogue of the popular *p*-methoxybenzyl protecting group enables this mixture synthesis.[5]

Our approach to analogues of discodermolide **1** is shown in Figure 1. The natural product is divided into a central

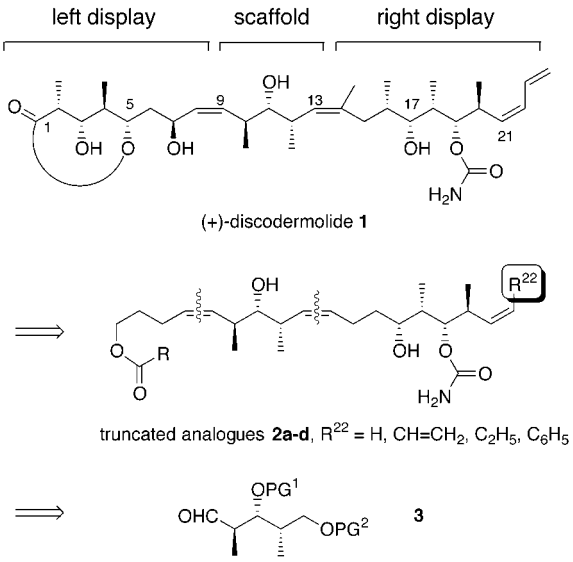
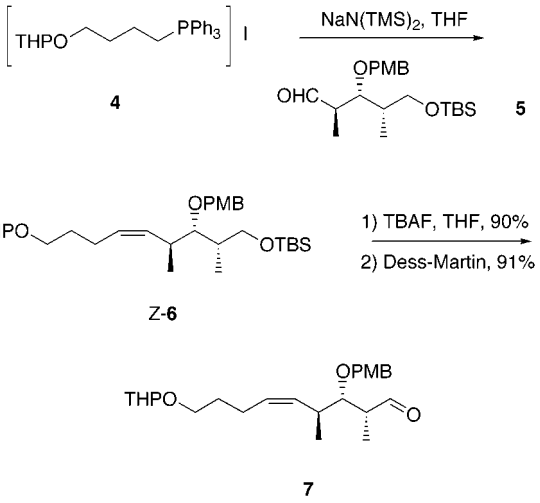


Figure 1. Structures of discodermolide and truncated analogues.

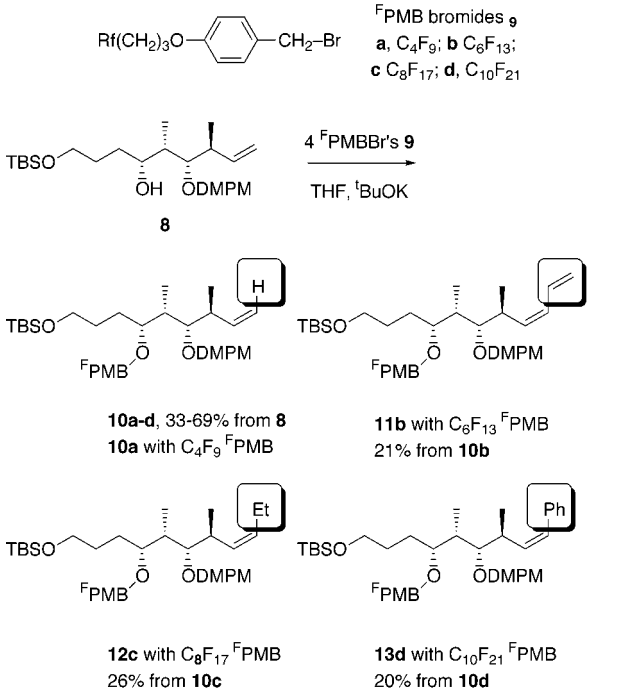
"scaffold" bearing left and right "displays". The scaffold has limited conformational freedom by virtue of the stereotriad C10−12 and the (*Z*)-alkenes,[6] and this controls the presentation of the displays to any binding site.[7] For this exercise, we omitted the methyl groups at C14 and C16 and the hydroxy group at C7[8] and truncated the left display to a simple alkyl chain terminating with an ester. To accompany these simplifications, we added a complication, namely, the preparation of four analogues R^{22} of the vinyl group of the (21*Z*)-diene. Thus, the target molecules become **2a**−**d**. The plan takes maximum advantage of symmetry[4] by using a common intermediate **3** for C9−13, C17−C20, and (ultimately) C1−C5. In this work, both the left and right displays are grafted to the scaffold by Wittig reactions.

The coupling of the truncated left display to the scaffold is summarized in eq 1. Wittig reaction of the ylide derived from **4** and aldehyde **5** provides exclusively (*Z*)-**6** in 85% yield. Desilylation followed by oxidation provides aldehyde **7** ready for the second Wittig coupling to append the right display.



Four different right displays were made from the common intermediate **8**, as summarized in Scheme 1.[9] Alcohol **8** was

Scheme 1

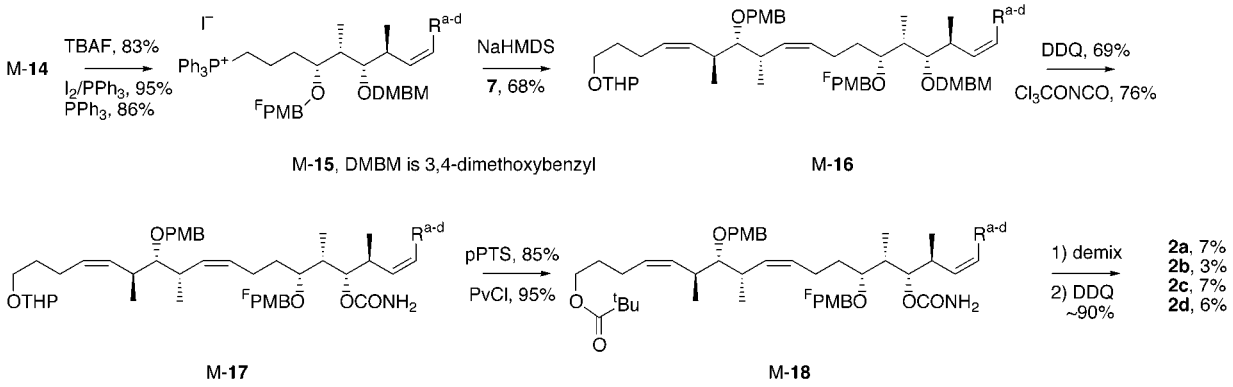


divided into four portions, each of which was coupled with one of four homologous fluorous PMB-bromides **9a**−**d**[5] to give **10a**−**d**, respectively. The F9-tagged substrate **10a** was used as is. The F13-substrate **10b** was ozonized, and the derived aldehyde was coupled with 3-bromo-3-trimethylsilylpropene and $CrCl_2$ followed by base treatment to produce the (*Z*)-diene **11b**.[4f] Wittig reaction of the same aldehyde but with the F17 tag provided (*Z*)-alkene **12c**. Finally, conversion of the aldehyde with the F21 tag to the (*Z*)-vinyl iodide and coupling with phenylzinc iodide provided (*Z*)-styrene analogue **13d**.

(5) Solimini, M. M.S. Thesis, University of Pittsburgh, Pittsburgh, PA, 2000. We thank Mr. S. Dandapani for preparing the FPMB bromides.
(6) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2055.
(7) (a) Smith, A. B.; LaMarche, M. J.; FalconeHindley, M. *Org. Lett.* **2001**, *3*, 695. (b) Monteagudo, E.; Cicero, D. O.; Cornett, B.; Myles, D. C.; Snyder, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 6929.
(8) Martello, L. A.; LaMarche, M. J.; He, L.; Beauchamp, T. J.; Smith, A. B.; Horwitz, S. B. *Chem. Biol.* **2001**, *8*, 843.

(9) See Supporting Information for syntheses of precursors **5** and **8**.

Scheme 2



The four analogues (**10a**, **11b**, **12c**, **13d**) were then mixed in roughly equimolar ratios to give M-**14a**−**d**, and the next eight steps of the synthesis were conducted on mixtures (denoted by the prefix "M"), as summarized in Scheme 2. Desilylation provided a primary alcohol, which was converted via an iodide to phosphonium salt M-**15**. Wittig reaction then grafted the left display mixture to the aldehyde to provide M-**16** in 68% yield.[10] The DMB group was removed with DDQ, and the resulting alcohol was converted to the carbamate M-**17**. Removal of the THP group and acylation of the alcohol with pivaloyl chloride then completed the mixture synthesis and provided protected analogues M-**18**.

The final mixture M-**18** was easily demixed[11] into the four underlying components by fluorous chromatography.[2,3] As expected, products eluted in the order of increasing fluorine content of the tag: **18a**, **b**, **c**, and **d**. Finally, both the standard and fluorous PMB groups were removed by DDQ oxidation, and the individual products **2a**−**d** were purified by flash chromatography. The overall yield for the mixture portion of the synthesis (Scheme 2) was about 19%, while the individual yields for the demixing/detagging stage were about 90%. Isolated yields over all steps (11−14, depending on the substituent) in Schemes 1 and 2 from common precursor alkene **8** were 6−7% for **2a**,**c**,**d**, while the yield of **2b** was about 3%.[12] Compound **2b** had been made previously by a another route in our labs, and the sample made by fluorous mixture synthesis was identical to this.[13]

The value of fluorous mixture synthesis is evident from this exercise: four analogues were prepared in a single synthetic sequence with only a little more effort than that required for one. Overall, 24 steps were saved by the mixing. Intermediate mixtures were generally treated like pure compounds; for example, most intermediate mixtures were single spots on regular silica gel and purified by flash chromatography. LCMS and LCNMR techniques were used coupled with fluorous columns when data on individual components were needed.

We conclude that fluorous mixture synthesis can be used directly as an exploratory synthesis technique. It is not necessary to rehearse for a fluorous mixture synthesis with a nonfluorous synthesis or even a fluorous synthesis of a single component. Certainly, problems will arise in conducting syntheses for the first time on fluorous mixtures as reactions will need to be optimized or even fail entirely and necessitate the redesign of the plan. Encountering and solving such problems is part and parcel of synthetic chemistry. But the tools (fluorous silica, LCMS, LCNMR) now exist to identify and solve these problems directly on fluorous mixtures. We recommend that fluorous mixture synthesis techniques now be considered for exploratory multistep synthesis of natural products and other organic molecules. Why should you make one final product when you can make two, or four, or more?

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Supporting Information Available: Detailed experimental procedures for syntheses of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Mixture yields are calculated on the basis of average molecular weights. For example, the theoretical quantity of M-**16** at 100% yield was calculated in the following manner: mmol expected × [(MW **16a** + **16b** + **16c** +**16d**)/4].

(11) Demixing was conducted on a Fluophase-RP column with the following gradient: from 80% MeOH/water to 100% MeOH over 30 min and then to 90% MeOH/10% THF over 15 min. Retention times (min) were 17.3, 22.5, 28.1, and 30.1.

(12) A major side product bearing the C_6F_{13} tag was isolated during demixing and tentatively assigned as the (21*E*)-diene by LC MS and LC NMR. The estimated overall yield of this product is 3−4%; however, we were not able to purify and characterize the expected (*E*)-isomer of **2b** after detagging.

(13) Minguez, J.; Curran, D. P., unpublished results.