JOC Article

Fluorous Mixture Synthesis of Fused-Tricyclic Hydantoins. Use of a Redundant Tagging Strategy on Fluorinated Substrates

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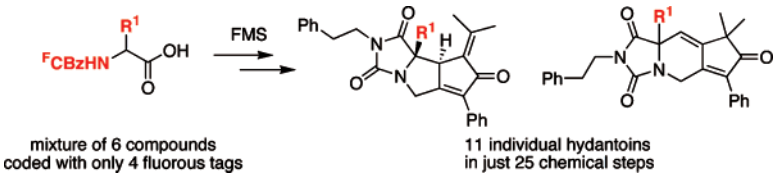
Received February 8, 2005



Simple HPLC experiments were used to identify a redundant tagging scheme wherein six different amino acids were tagged with only four fluorous tags. The tagged amino acids were converted to regiosiomeric mixtures of tricyclic hydantoins. Despite the lack of selectivity, the mixtures were demixed and detagged to give 11 individual pure products in just 25 steps.

Introduction

We have recently introduced the technique of fluorous mixture synthesis and highlighted its usefulness in the simultaneous synthesis of multiple analogues of natural products and other small organic molecules.[1] Briefly, each member of a series of precursors is coded with a member of a homologous series of fluorous tags. The tagged compounds are mixed, taken through a series of steps, and then demixed prior to detagging to provide the final set of analogues in individual, pure form. Demixing entails HPLC separation on fluorous silica gel,[2] a process that resolves the mixture in an orchestrated fashion on the basis of the fluorine content of the tags. The technique captures the inherent efficiency of solution-phase mixture synthesis by overcoming its traditional separation liabilities.

The incorporation of fluorine atoms is a popular tactic in medicinal chemistry for modulating polarity, solubility, metabolism, hydrogen bonding capabilities, and other features of druglike small molecules.[3] Accordingly, the design of analogue libraries in medicinal chemistry often incorporates fluorinated members. On the analytical side, small molecules bearing fluorine atoms typically have a stronger affinity toward perfluoroalkyl stationary phases than those lacking fluorine.[2,4]

Combining the medicinal and analytical features of the element fluorine, we envisioned that fluorous mixture synthesis would be ideal in preparing focused libraries containing fluorine atoms and that we could leverage the separation properties of the fluorinated library members by the use of "redundant tags", that is, by having more components in a mixture synthesis than there are tags. In all past fluorous mixture syntheses, the number of tagged components and the number of tags were the same (typically 2−7).[1] Here we tag six components with four tags (two pairs of redundant tags) and capitalize on the separation features of the fluorinated components to allow demixing despite the redundancies.

Results and Discussion

Pairing Tags and Amino Acids. In a recent mixture synthesis of the 4-alkylidene cyclopentenones,[5] we selected favorable pairings of fluorous tags with amino acid side chains by tagging individual amino acids **1** with

(1) For other examples of fluorous mixture syntheses, see: (a) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769. (b) Zhang, W.; Luo, Z.; Hiu-Tung Chen, C.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443−10450. (c) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.*, **2004**, *126*, 36−37. (d) Dandapani, S.; Jeske, M.; Curran, D. P. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 12008−12012. (e) Short review: Zhang, W. *Arkivoc* **2004**, 101−109.

(2) (a) Curran, D. P. *Synlett* **2001**, 1488−1496. (b) Curran, D. P. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I., Eds.; Wiley-VCH: Weinheim, 2004; pp 101−128.

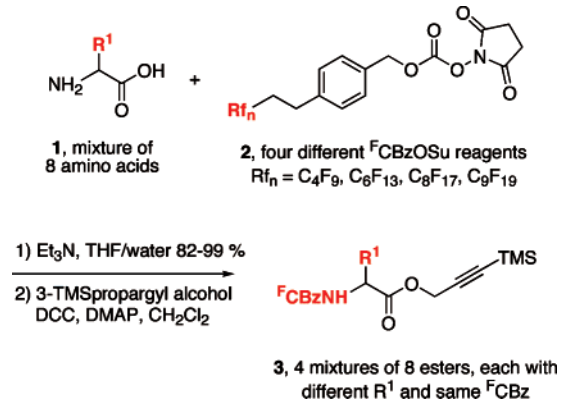
(3) (a) Böhm, H.-J.; Banner, D.; Bendals, S.; Kansey, M.; Kuhn, K.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643. (b) Biffinger, J. C.; Kim. H. W.; DiMagno, S. G. *ChemBioChem* **2004**, *5*, 622−627. (c) Ojima, I. *ChemBioChem* **2004**, *5*, 628−635. This issue of *ChemBioChem* also contains other articles and reviews regarding fluorine in the life sciences.

(4) Curran, D. P.; Oderaotoshi, Y. *Tetrahedron* **2001**, *57*, 5243−5253.

(5) Manku, S.; Curran, D. P. *J. Comb. Chem.* **2005**, *7*, 63−68. In this work, secondary propargyl esters [RCOOCH(Me)C≡CTMS] were studied.

10.1021/jo0502596 CCC: $30.25
Published on Web 05/04/2005

SCHEME 1. Tagging Four Mixtures of Eight Compounds



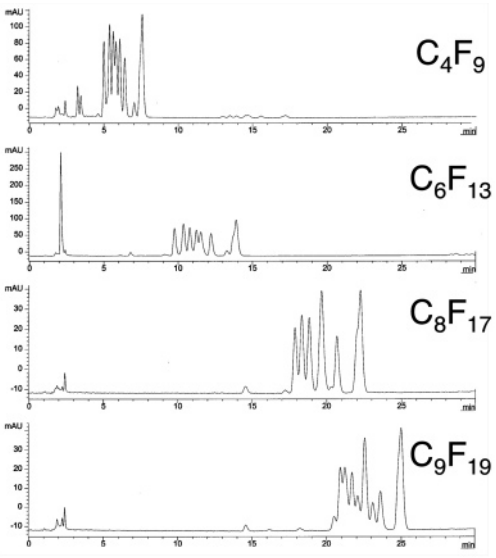
different fluorous Cbz (^{F}CBz) tags[6] followed by conversion to propargyl esters such as **3**[5] and measurement of retention times on fluorous HPLC. To more quickly identify suitable redundant tag pairings, we first treated each of four identical mixtures of eight amino acids **1** (alanine, leucine, norvaline, phenylalanine, 4-fluorophenylalanine, 3,4-difluorophenyl-alanine, 4-CF_3-phenylalanine, and 3-CF_3-phenyl-alanine) with one of four different fluorous carbobenzyloxy succidinyl esters **2** (^{F}CBzOSu, Rf_n = C_4F_9, C_6F_{13}, C_8F_{17}, and C_9F_{19}) (Scheme 1).

The tagged acids were then esterified with 3-trimethylsilylpropargyl alcohol, giving four mixtures of esters **3**, each mixture containing eight different amino acids bearing the same ^{F}CBz tag. These propargyl mixtures were analyzed by LCMS with a fluorous column, and the resulting four chromatograms are shown in Figure 1.

The retention of each of the 32 fluorous esters **3** can be influenced by many features,[2] but the chromatograms show the expected importance of the fluorine content of tag. For example, all eight C_4F_9-tagged esters elute before the first C_6F_{13}-tagged ester. In turn, all eight of the C_6F_{13}-tagged esters elute before the first C_8F_{17}-tagged ester. However, there is some overlap between the late eluting members bearing the C_8F_{17} tag and the early eluting ones bearing the C_9F_{19} tag. This is expected because these tags differ only by one CF_2 group and because some of the component members are fluorinated amino acids.

Within each series of derivatives bearing the same tag, there was a secondary separation wherein members bearing different amino acid side chains eluted in the same order (Me < Bn < 4-F−Bn < *i*-Bu ≈ Pr < 3,4-diF−Bn < 3-CF_3−Bn ≈ 4-CF_3−Bn). As expected, the analogues with the polyfluorinated side chains eluted at the end of each tag series.

These simple experiments (four reactions and four HPLC injections) provide much information for selecting tag/side pairings. From among many possibilities, we matched norvaline to the C_4F_9 group and alanine to the C_8F_{17} group. In the redundant taggings, both phenylalanine and 4-trifluoromethylphenylalanine were paired with the C_6F_{13} group and both 4-fluorophenylalanine and 3-trifluoromethylphenylalanine were paired with the



Selected tag/side chain pairings

	3{1}	3{2}	3{3}	3{4}	3{5}	3{6}
R	*n*Pr	Bn	3(4)CF_3	Me	4-F-Bn	4(3)CF_3
Rf_n	C_4F_9	C_6F_{13}	C_6F_{13}	C_8F_{17}	C_9F_{19}	C_9F_{19}
R_T(min)	5.7	10.4	13.9	17.8	21.5	24.7

FIGURE 1. Chromatograms of the 4 eight-compound mixtures of **3**. Conditions: FluoroFlash PF-C8 (4.6 × 150 mm) column using a gradient from 80/20 acetonitrile in water to 100% acetonitrile in 30 min at 1 mL/min. UV signal at 254 nm is shown.

C_9F_{19} group. The HPLC retention times of the six tagged compounds are listed at the bottom of Figure 1. A comfortable separation of 3−4 min between each pair of peaks was observed.

Fluorous Mixture Synthesis of Tricyclic Hydantoins. Will the separation based on redundant tags reliably translate through a series of different substrates in a multistep synthesis? To address this question, we conducted a six-compound mixture synthesis of tricyclic hydantoins that is summarized in Schemes 2 and 3.[7] The synthesis is related to a previous fluorous mixture synthesis of sixteen 4-alkylidene cyclopentenones via a [2 + 2 + 1] cycloaddition of an alkynyl allene. In that case, a Rh(I) catalyst in the presence of a CO atmosphere was used to give the exclusively the 4-alkylidene cyclopentenone scaffold.[5,8] Here, we effect the cycloaddition with $Mo(CO)_6$ to give regioisomeric 4- and α-alkylidene cyclopentenones.[8,9]

The six fluorous carbobenzyloxy amino acids were prepared individually and mixed to give acids **4**{***1***−***6***}

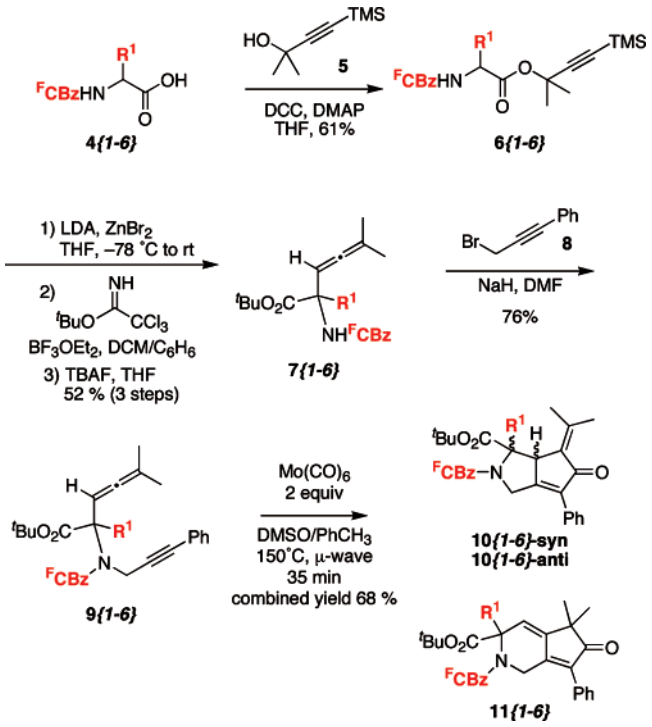
(6) (a) Curran, D. P.; Amatore, M.; Guthrie, D.; Campbell, M.; Go, E.; Luo, Z. *J. Org. Chem.*, **2003**, *68*, 4643−4647. (b) The fluorous reagents and columns were purchased from Fluorous Technologies, Inc. (www.fluorous.com). (c) DPC holds an equity interest in this company.

(7) For another example of fluorous synthesis of hydantoins, see: Zhang, W.; Lu, Y. *Org. Lett.* **2003**, *5*, 2555−2558. For a review on the use of fluorous reagents for the synthesis of heterocycles, see: Zhang, W. *Chem. Rev.* **2004,** *104*, 2531−2556.

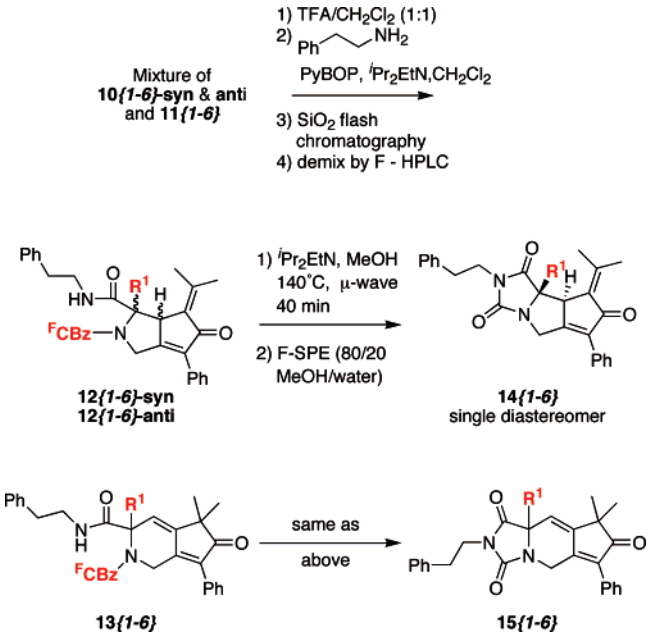
(8) For the use of Rh(I) catalysts on alkynyl allenes, see: (a) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245−2248. (b) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Gein, S. J. Org. Lett. **2002**, 4, 1931−1934. (c) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186−15187.

(9) Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535−6545.

SCHEME 2. Fluorous Mixture Synthesis



SCHEME 3. Formation of Hydantoins



(Scheme 2). These acids were converted to allenes by esterification with alcohol **5**[10] to the propargyl esters **6**-{***1***–***6***}, followed by a zinc-chelated ester enolate Claisen rearrangement.[11] The carboxylic acid on the resulting allene was converted to the *tert*-butyl ester with *tert*-butyl 2,2,2-trichloroacetimidate, and the trimethylsilyl group was removed to give mixture **7**{***1***–***6***} in 52% yield from the propargyl esters **6**. The alkynyl allenes **9**{***1***–***6***} were then obtained by N-propargylation with bromide **8**. The fluorous HPLC chromatograms of mixtures **6**–**9** each exhibited six clean peaks (see Supporting Information), and the components were characterized by LCMS.

The allenic Pauson–Khand reaction was performed by heating **9**{***1***–***6***} with $Mo(CO)_6$ (2 equiv) and catalytic DMSO in toluene to 150 °C under microwave conditions. A relatively complex 24-component mixture resulted; however, analytical demixing showed that each component precursor had been partially converted to three new products. The conversions were about 67% for each component, and three products, α-alkylidenecyclopentenone stereoisomers **10-syn** and **10-anti** along with 4-alkylidenecyclopentanone regioisomer **11**, were formed. Due to overlapping of HPLC peaks, we could only make crude estimates of product ratios at this stage. Ratios of **10-syn/10-anti/11** were about 1/0.5/1 for the components with larger R substituents, while the methyl analogue showed only a trace amount of **11**{***4***} and gave a higher ratio of **10**{***4***}**-syn/10**{***4***}**-anti**.[12]

This complex mixture showed only three main spots in standard silica TLC analysis, and it was purified by flash chromatography over regular silica gel eluting with 10% EtOAc/hexane. The least polar spot containing the starting materials **9**{***1***–***6***} was separated, and the other two overlapping fractions containing the cyclized products were collected and combined. The resulting mixture contained all but one of the 18 cyclized products by LCMS analysis. The minor diastereomer of **10**{***4***}**-anti** (R = Me) was missing, and we believe that this is more polar and was retained on the column.

Moving ahead with the single 17-compound mixture of **10**{***1***–***6***}**-syn**, **10**{**1**–***6***}**-anti**, and **11**{***1***–***3,5,6***}, we cleaved the *tert*-butyl ester with TFA, and the resulting acid mixture was coupled with phenethylamine (Scheme 3). At this stage, three main spots were observed on silica TLC, and the mixture was preparatively separated to give three submixtures containing predominately **12**{***1***–***6***}**-syn**, **12**{***1***–***6***}**-anti**, and **13**{***1***–***3,5,6***}. These submixtures were then demixed by fluorous HPLC to give 17 crude individual products **12** and **13**. These crude products were not cross contaminated with compounds bearing other fluorous tags, yet they were still not isomerically pure in most cases. Combined yields of the products were *n*-Pr {***1***}, 67%; Bn {***2***}, 66%; 4-CF_3–Bn {***3***}, 68%; Me {***4***}, 61%; 4-F–Bn {***5***}, 61%; and 3-CF_3–Bn {***6***}, 94%.

Removal of the fluorous tag with concomitant hydantoin formation was achieved by exposing the individual amides **12-syn/anti** and **13** to diisopropylethylamine (DIPEA) in the microwave at 140 °C for 40 min (Scheme 3). The crude hydantoins **14**{***1***–***6***} and **15**{***1***–***6***} were then purified by fluorous solid-phase extraction (F-SPE)[2a] to remove the fluorous benzyl alcohol. The DIPEA could be removed either by adding a layer of Amberlite CG-50 ion-exchange resin to the top of the F-SPE cartridge[13] or by an aqueous acid–base extraction after the F-SPE. With the C_4F_9-tagged substrates, **14**{***1***} and **15**{***1***}, the relatively low fluorine content (C_4F_9) of the tag made

(10) Trimethylsilylpropargyl alcohol, which was used in the initial tag assignments, failed to undergo the ester–enolate Claisen rearrangement cleanly.

(11) Kazmaier, U.; Görbitz, C. H. *Synthesis* **1996**, 1489–1493.

(12) This estimate was aided by a study of cyclization of two nonfluorous analogues. The standard CBz analogue of **9**{***2***} (R^1 = Bn) provided a 0.9/0.5/1 ratio of the corresponding products **10-syn/10-anti/11**, while the CBz analogue of **9**{***4***} (R^1 = Me) gave a 4/1 mixture of **10-syn/10-anti** with little or no **11**. Full details can be found in Supporting Information.

(13) Zhang, W. *Org. Lett.* **2003**, *5*, 1011–1013.

TABLE 1. Yields and Purities of Hydantoins from Detagging Either Crude or after Semipreparative HPLC

	14		15	
R	yield (%)[a]	purity (%)[a,b]	yield (%)	purity (%)[b]
nPr {***1***}	e	e	44[a]	99[a]
Bn {***2***}	74	99	90[c]	86[c]
4-CF_3−Bn {***3***}	59	91	38[a]	94[a]
Me {***4***}	40	99	d	d
4-F−Bn {***5***}	57	91	99[c]	85[c]
3-CF_3−Bn {***6***}	25	90	86[c]	87[c]

[a] After normal-phase semipreparative HPLC. [b] Purity determined by C18-HPLC at 254 nm. [c] Yield and purity after F-SPE. [d] Not obtained. [e] Isolated but difficult to remove fluorous benzyl alcohol.

removal of the fluorous byproduct difficult by F-SPE. However, with compound **15**{***1***}, the byproduct could be removed by preparative TLC.

The cyclative cleavage reactions of **12-syn** and **12-anti** provided not different products but the same ones. Crystal structures of **14**{***2***} and **14**{***4***} showed that these were anti isomers, and we assigned all the others as anti by analogy. Evidently, the syn isomers isomerized to the more stable anti isomers during the base-promoted reaction.

This "reconvergence" of two pairs of products then left 11 total products, whose yields and purities are shown in Table 1. All of the 5−5−5-fused ringed hydantoins **14**-{***1***−***6***} were purified by normal phase semipreparative HPLC to increase their purities above 90%. During this chromatography, any remaining 4-alkylidene product that survived the flash chromatography of the amide mixtures **12**{***1***−***6***} and **13**{***1***−***6***} was removed. For the 5−6−5 hydantoin tricycles, good purities were obtained simply after F-SPE.

Conclusion

After only 25 chemical steps, including the 6 tagging reactions and the 11 detaggings, 11 complex hydantoins were obtained by using fluorous mixture synthesis with two pairs of redundant tags. In addition, we also developed a rapid method for coding fluorous tags to building blocks prior to the fluorous mixture synthesis. The redundant tagging strategy and methods for tagging introduced herein should be applicable not only to fluorinated substrates but to other substrates that exhibit reliable secondary separations on fluorous HPLC.

Acknowledgment. Financial support has been provided by the National Institutes of Health and the Natural Sciences and Engineering Research Council of Canada (postdoctoral fellowship to S.M.). The authors also thank Prof. Kay M. Brummond and Mr. Branko Mitasev for helpful discussions and Dr. Steven Geib for X-ray crystallography.

Supporting Information Available: Experimental procedures and characterization data for all compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0502596