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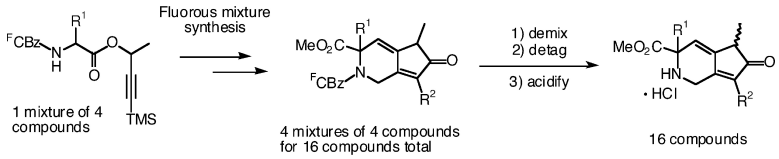

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Fluorous Mixture Synthesis of 4-Alkylidene Cyclopentenones via a Rhodium-Catalyzed [2+2+1] Cycloaddition of Alkynyl Allenes

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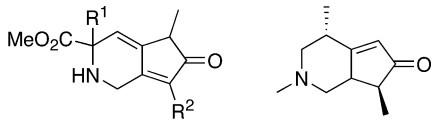
Fluorous mixture synthesis was used to prepare a library of 4-alkylidene cyclopentenones starting from a mixture of four α-amino acid derivatives tagged with different fluorous benzyl carbamates (^{F}CBz) of varying fluorine content. The amino acids were converted to the corresponding propargyl esters and then subjected to an ester-enolate Claisen rearrangement to give a mixture of allenic amino esters. The allenes were then split four ways and propargylated with different propargyl bromides to give four mixtures of alkynyl allenes. The 4-alkylidene cyclopentenones were formed by a formal [2+2+1] cycloaddition of the alkynyl allenes using catalytic $[Rh(CO)_2Cl]_2$ under CO atmosphere. Demixing by fluorous preparative HPLC, removal of the fluorous benzyl carbamates, and then exposure to HCl/ether gave the hydrochloride salts of 16 compounds as diastereomeric mixtures in 69−99% purity. Thus, after just 26 chemical steps, a library of 16 cyclopentenones was prepared by using fluorous mixture synthesis. By comparison, the same library would have required 112 steps if each compound were made individually by parallel synthesis.

Introduction

The synthesis and biological testing of small-molecule libraries resembling natural products has become increasingly important for studying the function of biological macromolecules and holds potential in medicinal chemistry for the discovery of new lead compounds.[1−4] To this end, we have begun examining the use of fluorous mixture synthesis (FMS)[5,6] to produce small-molecule libraries that may otherwise prove too difficult to access using standard solid-phase or solution-phase combinatorial chemistry. FMS is a solution-phase technique that allows libraries to be made as mixtures, thereby increasing the efficiency over traditional parallel syntheses, while still having the advantages associated with solution chemistry, such as straightforward analyses of intermediates, reaction monitoring, and purification of the final products. It also has its advantages in syntheses over a large number of steps, for multistep syntheses become impractical using standard parallel techniques.

The key to FMS is the use of fluorous tags of varying fluorine content on each of the mixture components. These tags not only serve as protective groups but also allow each component to be separated from the others, or demixed, by fluorous HPLC (F-HPLC). This type of chromatography separates compounds mainly on the tag's fluorine content: the greater the number of fluorines, the greater the retention.[7] Furthermore, organic compounds are poorly retained on the fluorous stationary phase, as compared to fluorous compounds, allowing for easy purification from organic impurities. In certain cases, secondary separation of fluorous impurities from the desired compounds can also be achieved during preparative F-HPLC.

Herein, we describe the results of our fluorous mixture synthesis combined with an allenic Pauson−Khand-type reaction[8,9] for the production of small-molecule libraries possessing a unique architecture. The target structures are designed around the 4-alkylidene cyclopentenone scaffold (**1**, Figure 1) and are reminiscent of naturally occurring alkaloids containing cyclopentanopyridine and cyclopentanopiperidine skeletons.[10] One example from this alkaloid family is tecomanine **2**, a substance shown to have powerful hypoglycemic activity.[11] In addition, cyclopentenones **1** can be considered novel bicyclic α-amino acid derivatives that can potentially be useful in the synthesis of peptidomimetics.[12]



1 tecomanine, **2**

Figure 1. The 4-alkylidene cyclopentenone scaffold **1** compared to tecomanine **2**.

The synthesis of cyclopentenone **1** is based on an established route described by Brummond et al.[8] beginning from amino acid **3** (see Scheme 1). For a fluorous mixture synthesis, it was envisioned that a set of amino acids can be individually tagged with a fluorous N-protective group prior to mixing. To this end, the application of fluorous versions of benzyl[13] and *t*-butyl carbamates,[14] recently developed in our laboratories, as tags for the amino acids was appropriate for planned mixture synthesis. Conversion of the amino acids into a mixture of allenic derivatives **5** could be accomplished by the rearrangement of the propargyl ester mixture **4**. This rearrangement can be achieved via the zinc chelate-controlled ester enolate Claisen reaction, reported by Kazmaier and Görbitz,[15] for it has been shown to be general for a variety of carbamate derivatized α-amino acids and provides high levels of allene diastereoselectivities.

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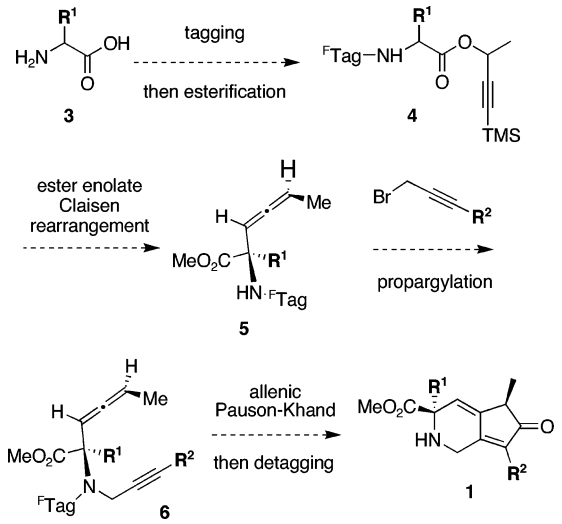
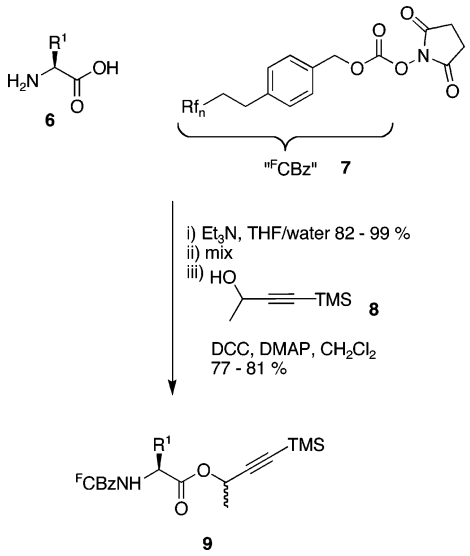
Scheme 1

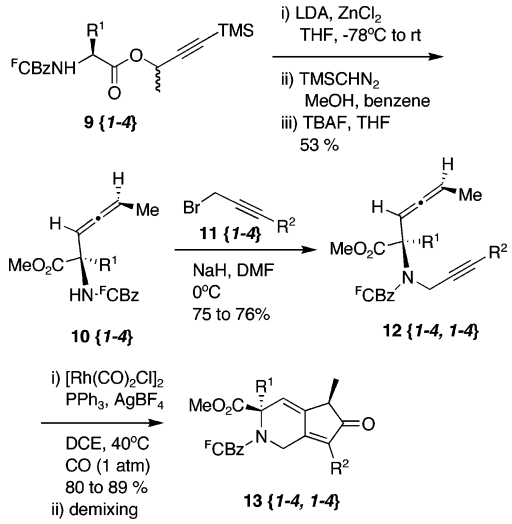


Scheme 2



An additional point of diversity can be incorporated into the library by N-propargylation of allenes **5** with a set of different propargyl bromides to provide mixtures of alkynyl allenes **6**. Transformation to the cyclopentenone can be performed by a rhodium (I) catalyzed allenic [2+2+1] cycloaddition under a carbon monoxide atmosphere. As reported by Brummond et al.,[8] this allenic cycloaddition is highly regioselective toward the terminal π bond of the allene function to give exclusively the 4-alkylidene cyclopentenone scaffold. Furthermore, the diastereomeric ratio from the alkynyl allene is retained in the cyclopentenone. The final mixtures can then be demixed by preparative F-HPLC,

Scheme 3



9	{1}	{2}	{3}	{4}
R^1	Me	*n*-Pr	Bn	*i*-Bu
Rf_n	C_4F_7	C_6F_{13}	C_8F_{17}	C_9F_{19}

11	{1}	{2}	{3}	{4}
R^2	Me	Ph	C_5H_{11}	*i*-Bu

affording the indivdual tagged compounds, which are each detagged to afford a library of **1**.

Results and Discussion

The amino acids initially chosen were alanine, phenylalanine, valine, and isoleucine due to their simplicity and their previous success as starting materials in the rhodium catalyzed allenic [2+2+1] cycloaddition.[8] To apply the FMS technology, each amino acid was individually tagged with a fluorous benzyl carbamate (^{F}CBz)[13] prior to mixing. The ^{F}CBz tags were selected over the *tert*-butyl carbamates because of successful previous results with the nonfluorous analogues and their high UV absorbances making detection easier during HPLC analysis of the mixtures.

Although the fluorine content of the tag will have the major influence on the separation of compounds over fluorous silica gel, we have observed during past fluorous mixture syntheses that the polarity of the substrate bearing the tag can have a significant effect on the retention times.[7b,16] In other words, the polarity of the amino acid side chains can either improve or compromise the separation of mixture components at the demixing stage by moving them further apart or bringing them closer together. Therefore, rather than

Table 1. Retention Times (R_T) of **9**[a]

matched case			mismatched case			optimized case		
Rf_n	R^1	R_T (min)[b]	Rf_n	R^1	R_T (min)[b]	Rf_n	R^1	R_T (min)[b]
C_4F_9	Me	5.4	C_4F_9	*i*-Bu	6.9	C_4F_9	Me	5.3
C_6F_{13}	CH_2Ph	10.4	C_6F_{13}	*i*-Pr	11.6	C_6F_{13}	*n*-Pr	11.3
C_8F_{17}	*i*-Pr	19.6	C_8F_{17}	CH_2Ph	17.4	C_8F_{17}	CH_2Ph	17.3
C_9F_{19}	*i*-Bu	23.4	C_9F_{19}	Me	20.1	C_9F_{19}	*i*-Bu	23.0

[a] Done on a Fluofix 4.6 × 150 mm column using 80/20 acetonitrile/water to 100% acetonitrile in 30 min at 1.0 mL/min with detection by UV at 254 nm and MS. [b] Taken as an average between two diastereomeric chromatographic signals.

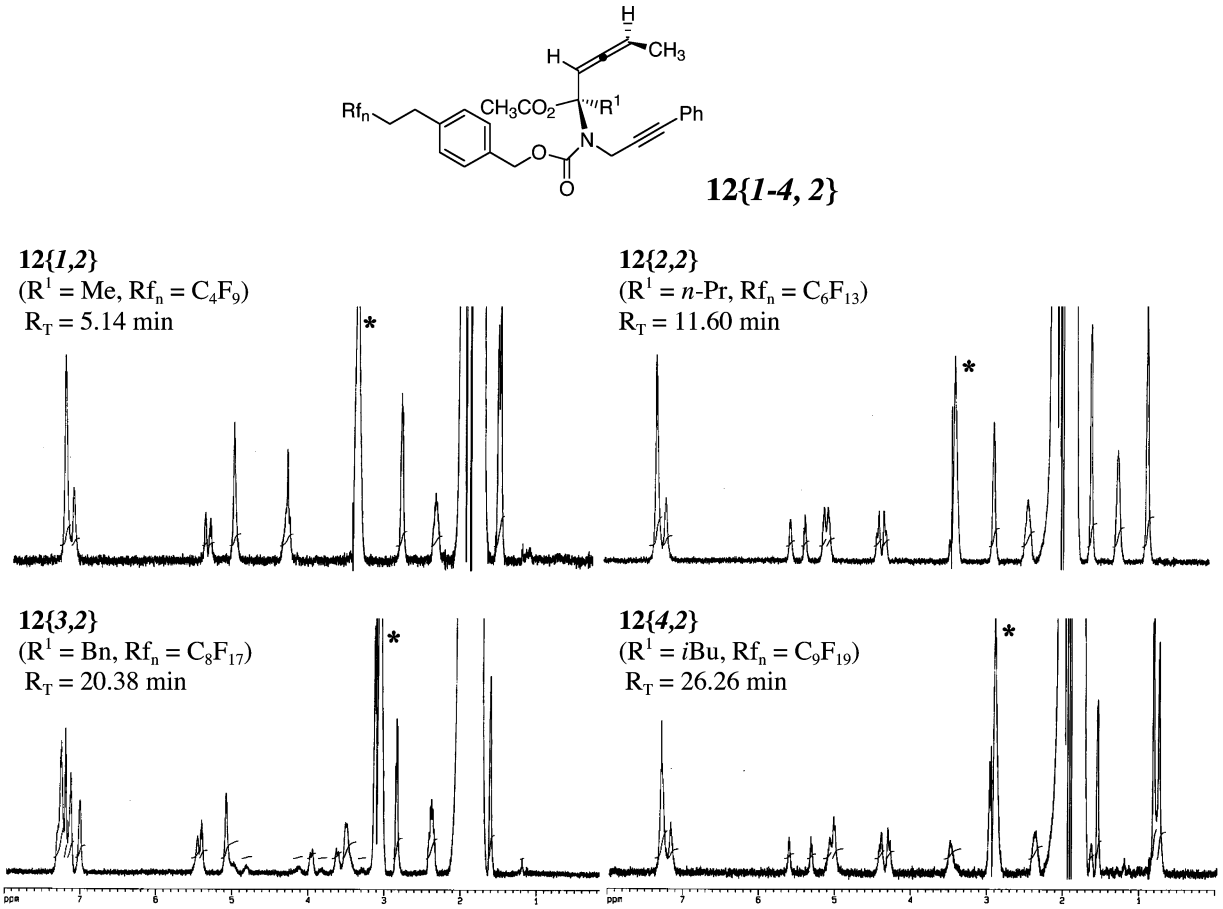


Figure 2. Sample 600-MHz LC/NMR taken from alkynyl allene mixture **12**{*1*−*4,2*} eluted with 80/20 to 95/5 acetonitrile/D_2O in 30 min at 1 mL/min through a FluoroFlash 4.6 × 150 mm column. Note: the star indicates the location of the water signal.

assigning tags to the amino acids randomly, a systematic approach was taken whereby the polarity of the side chain was taken into account to optimize the separation of the mixture components.

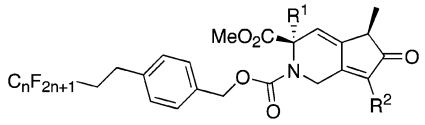
To find the right balance between substrate polarity and fluorine content, a series of propargyl ester mixtures **9** (Scheme 2) was prepared, and their retention times on a fluorous HPLC column were obtained.[17] For one mixture, the polarity of the side chain matched the polarity of fluorous chain; that is, the most polar amino acid (alanine, R^1 = Me) was coupled to the benzyl carbamate with the fewest fluorines (C_4F_9), whereas the least polar amino acid (isoleucine, R^1 = *i*Bu) was coupled with the tag having the most fluorines (C_9F_{19}). The tagged amino acids were then mixed and reacted with 4-trimethylsilanyl-but-3-yn-2-ol **8** to give the esters **9**, which were analyzed by F-HPLC. For the second mixture, a mismatched case was created whereby the least polar amino acid was coupled to the tag having the fewest fluorines and vice versa before they were mixed and converted to **9** for analysis. Retention times of these mixtures were measured by HPLC, and these data are shown in Table 1.

With the matched case, the elution of all the mixture components occurred over a longer period (18 min) from the first peak to the last, as compared to the mismatched case (13 min). There was also a wide variation in the spaces between peaks of the two mixtures. For instance, in the matched case, the largest space of 9.2 min was observed between C_6F_{13} and C_8F_{17} components, whereas the shortest space of 3.2 min occurred between the last two peaks, with the C_8F_{17} and C_9F_{19} tags. With the mismatched case, the peaks were generally closer together, ranging from 5.8 min between the C_6F_{13}- and C_8F_{17}-tagged propargyl esters to only 2.7 min between the C_8F_{17} and C_9F_{19} esters.

To equalize the spaces between the chromatographic peaks, the C_4F_9- and C_9F_{19}-tagged esters in the matched mixture were combined with the C_6F_{13} and C_8F_{17} esters in the mismatched case. In addition, the valine amino acid was replaced with norvaline due to the former's relatively poor reactivity in the esterification with the proparyl alcohol. This combination resulted in an optimized tagging scheme, as shown in Table 1, where all peaks were ~6 min from each other. Using this optimized tag pairing, we expect during the demixing stage four nicely separated components on the preparative chromatographic column allowing us to inject large amounts of material without risking cross-contamination. Furthermore, secondary purifications from fluorous impurities can more easily be achieved between desired mixture components, ensuring high purity of individual compounds.

With an optimized tagging strategy in hand, we set out to prepare a small library of tagged 4-alkylidene cyclopentenones (Scheme 3). The allenic amino acid mixture was obtained through the Claisen rearrangement[12] on 6.8 mmol (5.24 g) of propargyl esters **9**{*1*−*4*} via their corresponding zinc enolates. The resulting carboxylic acids were then methylated to the methyl esters and desilylated using TBAF

Table 2. Demixing of 4-Alkylidene Cyclopentenones, **13**{*1−4, 1−4*}



13 {*1-4, 1-4*}

	$R^2 = CH_3$ **13**{*1−4,1*}	$R^2 = Ph$ **13**{*1−4,2*}	$R^2 = C_5H_{11}$ **13**{*1−4,3*}	$R^2 = i$-Pr **13**{*1−4,4*}
crude cyclization yield, %	80	81	86	89
amt demixed, mg	197	226	240	247
	Molar Ratio			
$R^1 = CH_3$; **13**{*1,1−4*}	0.52	0.57	0.40	0.42
$R^1 = n$-Pr; **13**{*2,1−4*}	0.70	0.79	0.69	0.73
R^1 = Bn; **13**{*3,1−4*}	1.00	1.00	1.00	1.00
$R^1 = i$-Bu; **13**{*4,1−4*}	0.43	0.46	0.44	0.43
mass recovery, %	91	89	81	85

to give a mixture of allenes **10**{*1−4*} in 53% yield from the esters. At this point, a small portion of the allene mixture **10**{*1−4*} was demixed to determine the individual yields of each component. It was found that the relative proportion of the C_9F_{19}-tagged component **10**{*4*} (that is, $R^1 = i$-Bu) was significantly reduced in the mixture, as compared to the initial propargyl ester mixture. Its individual yield after the three steps from the ester and the demixing was only 28%. The C_8F_{17}-tagged component, **10**{*3*} (R^1 = Bn), had the highest relative proportion in the allene mixture and was recovered in 67% yield from the propargyl ester after demixing. Yields of **10**{*1*} and **10**{*2*} (R^1 = Me and *n*-Pr, respectively) were found be similar, at 51 and 48%, respectively. These differences in the relative amounts of the mixture components are likely due to reactivity differences in the ester enolate Claisen rearrangement.

Next, the allene mixture was split into four portions of ∼0.55 mmol (400 mg) and reacted with one of four different propargyl bromides **11**{*1−4*}[18] to give four mixtures of alkynyl allenes **12**{*1−4,1−4*}. The yields of each reaction ranged between 75 and 78%, as calculated on the basis of the weighted average molecular mass of the allenes **10**{*1−4*}. At this stage, the diastereomeric products arising from the Claisen rearrangement of the propargyl esters **9**{*1−4*} could be observed by F-HPLC for the **12**{*2,1−4*} and **12**{*3,1−4*} mixture components (the other two components were poorly resolved). The diastereomeric ratios for the resolved compounds were found to be in the range of 9/1 and 18/1, and the major product was assigned the syn configuration by analogy to Kazmaier and Görbitz.[15]

During the synthesis, LC/MS was frequently used to verify the success of all transformations for each mixture component. We were able to further characterize the alkynyl allene mixtures **12**{*1−4,1−4*} by LC/NMR. An example of the four 600 MHz ^{1}H NMR spectra obtained from the elution of mixture **12**{*1−4,2*} (R^2 = Ph) through a fluorous analytical column is shown in Figure 2. The signals in each spectrum were generally broad due to hindered rotation of the benzyl carbamate and were most pronounced whenever R^1 was a benzyl substituent. Despite this broadening and the presence of a strong acetonitrile signal from the mobile phase, the characteristic chemical resonances arising from the R^1 and R^2 substituents were still clearly visible.

Finally, [2+2+1] cyclization of the alkynyl allenes to the 4-alkylidene cyclopentenones **13**{*1−4,1−4*} was performed on ∼0.34 mmol (270 mg) scale using $[Rh(CO)_2Cl]_2$ as the metal catalyst (5−10 mol %) in the presence of $AgBF_4$ and triphenylphosphine under one atmosphere of carbon monoxide.[8] Upon completion of the reaction, each mixture was chromatographed through standard silica gel to remove the rhodium and other nonfluorous materials. The crude yields for each cyclization ranged from 80 to 89% (See Table 2).

The four mixtures were then demixed by preparative F-HPLC to give 16 individual compounds. In a typical demixing, 200−250 mg of material was injected onto the F-HPLC column in four to five portions, and 81−91% of the material was recovered (see Table 2 and Figure 3). The final ratio of each cyclopentenone within each mixture revealed a significant loss of both the **13**{*1,1−4*} and

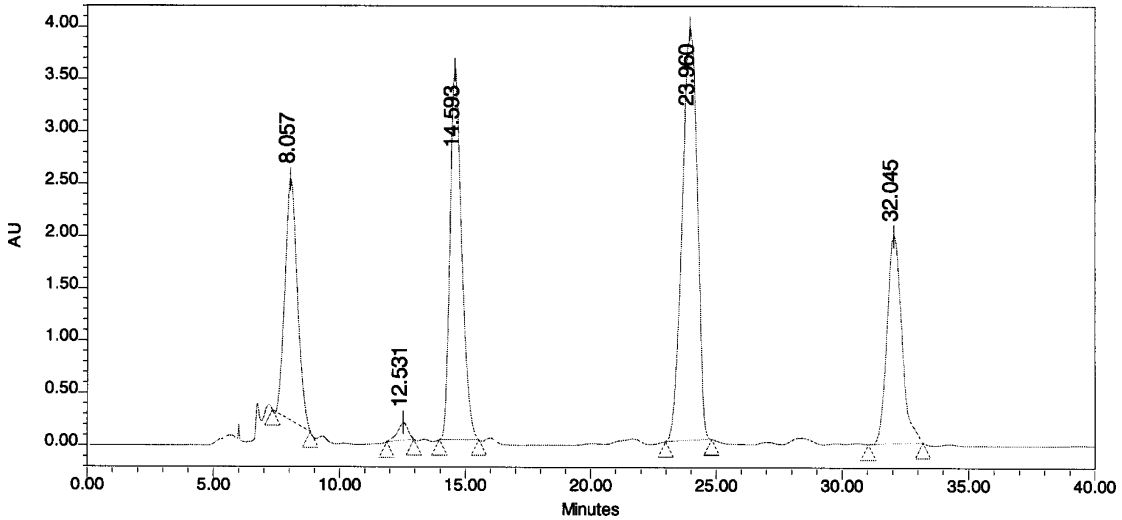


Figure 3. Sample of a chromatograph taken from the demixing of **13**{*1−4,1*}. The order of elution is: **13**{*1,1*}/C_4F_9, **13**{*2,1*}/C_6F_{13}, **13**{*3,1*}/C_8F_{17}, and **13**{*4,1*}/C_9F_{19} at 8.1, 14.6, 24.0, and 32.0 min, respectively. Performed on a FluoroFlash PF-C8 preparative column (20 × 250 mm) using 10 mL/min of 90/10 acetonitrile/water to 100% acetonitrile in 30 min, continued at 100% acetonitrile for an additional 10 min.

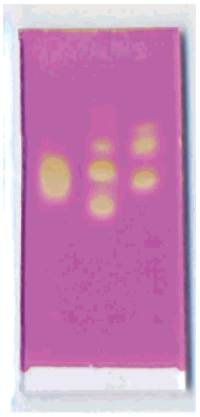


Figure 4. A normal-phase silica gel TLC of fluorous mixture intermediates eluted with 20% ethyl acetate in hexanes and stained with $KMnO_4$. Lane a: alkynyl allenes **12**{*1*−*4*,*1*}; lane b: allenes **10**{*1*−*4*}; lane c: propargyl esters **9**{*1*−*4*}.

13{*4*,*1*−*4*} compounds (that is, R^1 = Me and *i*-Bu, respectively) with a modest loss of the **13**{*2*,*1*−*4*} (R^1 = *n*Pr) components. The loss of the **13**{*4*,*1*−*4*} compounds was attributed mainly to the Claisen rearrangement, whereas the **13**{*1*,*1*−*4*} compounds seem to decrease more gradually throughout the synthesis either because of "accidental demixing" during flash chromatography (see below for discussion) or consistently poor reactivity as compared to others. Characterization of the individual compounds was accomplished by standard ^{1}H NMR, ^{19}F NMR, and mass spectrometry, and ^{13}C NMR spectra were obtained whenever large amounts of sample were available.

By normal silica gel thin-layer chromatography, most of the mixtures of fluorous-tagged intermediates in Scheme 3 eluted as three distinct spots. Three examples are depicted in Figure 4 with the alkynyl allenes **12**{*1*−*4*,*1*}, allenes **10**{*1*−*4*}, and the propargyl esters **9**{*1*−*4*}. Isolation of some of the spots by flash chromatography revealed that the R^1 = *i*-Bu components were often the highest spot; followed by the R^1 = Bn and *n*-Pr components together in the middle; and finally, the trailing R^1 = Me components. With the alkynyl allene mixtures, the components merge closer together, as compared to the other intermediates, making them sometimes appear as a single spot or two very close spots. As a consequence of this "accidental demixing" on normal-phase silica gel, small impurities eluting very close to the mixture could not be easily removed by standard flash chromatography because removing them risked compromising the yield of some the components. However, in the final demixing, all organic impurities were easily removed while small amounts of fluorous impurities were removed by secondary separations on the fluorous silica gel.

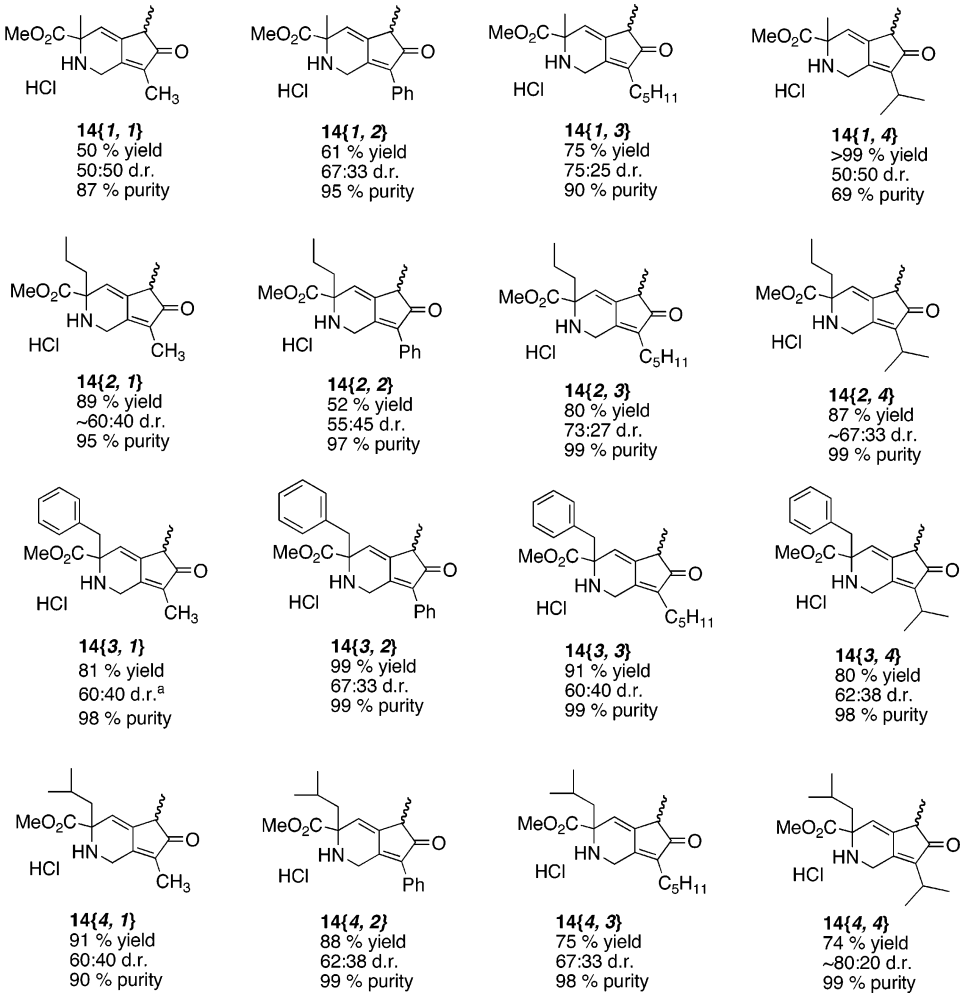
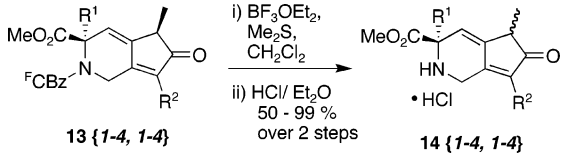


Figure 5. Structures of 16 4-alkylidene cyclopentenones as their HCl salts with yields, diastereoselectivities (as determined by ^{1}H NMR), and purities (by HPLC with 254-nm UV detection). [a]Diastereomeric ratio determined by HPLC.

Scheme 4



Detagging the 16 individual cyclopentenones **13**{*1*−*4*,*1*−*4*} from the fluorous benzyl carbamates was achieved by treatment with dimethyl sulfide in the presence of $BF_3 \cdot Et_2O$ (Scheme 4). After aqueous workup, the free amines were separated from the fluorous benzyl sulfonium salt by passage through normal silica gel. To ensure greater stability over long-term storage, the free amines were acidified with anhydrous HCl to give the hydrochloride salts **14**{*1*−*4*,*1*−*4*}. However, it was discovered that the detagging conditions led to the epimerization of the cyclopentenones, leading to a severe loss of diastereomeric purity (Figure 5). The diastereomers were poorly resolved chromatographically (TLC and reversed-phase HPLC), making their separation very difficult. As an effort to avoid this epimerization, other methods for removing of benzyl carbamates[19] were attempted, but they all failed to give clean product.

Figure 5 shows the structures of each of the 16 4-alkylidene cyclopentenone hydrochloride salts along with their yields, diastereomeric ratios, and purities. The yields from the detagging and acidification ranged from 50 to 99%, affording between 12 and 2 mg of final compounds. The diastereomeric ratios were determined by HPLC analysis or by integration in the ^{1}H NMR spectra of the epimerized methyl substituents or the vinylic protons. Purities listed in Figure 5 were determined by HPLC with 254-nm UV detection. These purities correlated well with purities as estimated by ^{1}H NMR and LC/MS.

Conclusions

The synthesis of the alkylidene cyclopentenones demonstrated the application of fluorous mixture synthesis toward a library of small, drug-like molecules. The time-saving advantage of FMS was considerable because only 26 chemical steps, including the fluorous tagging steps and each detagging/acidification, were required to prepare all 16 compounds. By comparison, 112 steps would be needed if each compound were made individually. In addition, already established solution-phase reactions were used, and no effort was required in reoptimizing them for a library synthesis. With a basic strategy for fluorous mixture synthesis established for the alkynyl allenes, we are currently attempting to expand the library by subjecting these intermediates to alternative transition-mediated reactions to provide different scaffolds whereupon further diversity can be incorporated.[8] This diversity-oriented synthesis from fluorous-tagged substrates can provide a significant number of the natural-product-like compounds with potential biological activity.

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Supporting Information Available. Experimental procedures, HPLC/MS and LC NMR chromatographs, and all ^{1}H NMR spectra for demixed compounds are given in the Supporting Information. This material is available via the Internet at http://pubs.acs.org.

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