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Thiol additions to acrylates by fluorous mixture synthesis: relative control of elution order in demixing by the fluorous tag and the thiol substituent

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Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

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Abstract—All possible combinations of a series of three fluorous benzyl tags and three acrylates have been made. The resulting acrylate esters were combined in groups of three (one of each tag) and the resulting mixtures were reacted with a mixture of four thiols under standard conditions to effect conjugate addition. Analysis of the resulting libraries by fluorous hplc showed a primary separation based on the tag and revealed reliable secondary separations based on the thiol and the acrylate. The primary and secondary separations were used together in a preparative 'mixture of mixtures' experiment in which one of the tagged acrylate mixtures was reacted with a mixture of three thiols. The resulting nine component mixture was demixed by fluorous and reverse phase hplc and then detagged to give all nine final products in pure form.

1. Introduction

The purposeful synthesis of mixtures of organic compounds is a recent development. The inherent efficiency of making more than one compound in one reaction vessel is the primary attraction of mixture synthesis, but this is offset by difficulties in analyzing, separating and identifying mixture components. Split-mix synthesis on the solid phase addresses the separation and identification problems,[1] but a price is paid at the reaction stage since standard solution phase reaction conditions are not directly applicable. Existing solution phase mixture techniques tend to sidestep the separation and identification problems by directly subjecting organized mixtures to biological assays in a process called deconvolution.[2] No attempts are made to isolate individual pure components in these techniques.

A conceptual solution to the separation and identification problems inherent in solution phase mixture synthesis involves the use of a 'separation tag' as shown in Fig. 1. Separation tags (T) are chosen such that they dominate over tagged molecules in a complementary separation technique.

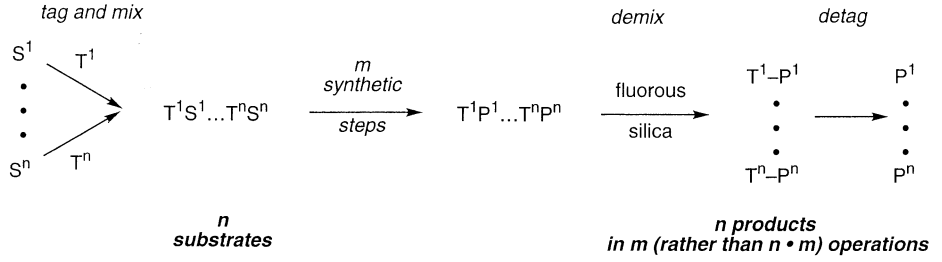

Figure 1.

Keywords: mixture synthesis; fluorous synthesis; solution phase combinatorial chemistry.

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In other words, the separation of a mixture of tagged molecules is dictated by the tag, not the molecule that is tagged. In tag-based mixture synthesis, a series of organic substrates ($S^1 \ldots S^n$) is attached to a series of incrementally different tags ($T^1 \ldots T^n$). The tagged substrates ($T^1S^1 \ldots T^nS^n$) are then mixed and taken through a series of reaction steps to produce a tagged product mixture ($T^1P^1 \ldots T^nP^n$). This mixture is then subjected to the appropriate separation technique that complements the tag to generate the individual pure products in a process called demixing. Identification of the tagged products follows directly from the original tag-substrate pairings. Finally, the tag is removed to give individual final products ($P^1 \ldots P^n$).

To reduce this conceptual approach to practice, we recently introduced 'fluorous mixture synthesis (FMS)'.[3] In FMS, the tags are fluorinated (fluorous) groups with increasing numbers of fluorines, and the complementary tag-based separation method is fluorous reverse phase chromatography.[4]

An example of FMS in the context of a synthesis of a combinatorial library of mappicine analogs is shown in Fig. 2. Four different alcohols were tagged with fluorous silyl tags of increasing fluorine content, and the resulting tagged products **1** were mixed to give **M-1** and carried through four steps to provide a mixture of tagged mappicines **M-2**. This mixture was then demixed by chromatography over silica gel with a fluorocarbon bonded phase to give the individual pure products. More than 25 mixtures were made, and in each case, the products eluted in order of increasing fluorine content of the tag.

To further extend FMS as a useful tool, much more information is needed about the relative effects of tags and tagged components on retention time in fluorous chromatography. For example, tags and substrates were paired arbitrarily in the experiment in Fig. 2, so we could not analyze the effect of the tag vs the tagged substrate on retention time. Indeed, while it seems improbable, we could not rigorously rule out the possibility that it was the substrate and not the tag that determined the order of demixing.

This paper describes a series of experiments designed to glean additional information about the effects of tags vs tagged substrates on demixing. While the tag shows the predominant effect, clear structural effects of tagged substrates are identified. These effects are leveraged to allow the synthesis of a mixture with three times more components than the number of tags. This 'mixture of mixtures' experiment is the first example of tag-based mixture synthesis where the number of pure products that are isolated exceeds the number of tags that are used.

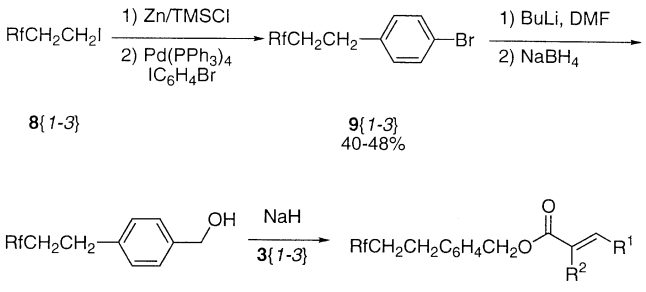
2. Results and discussion

2.1. Mixture plan

Fig. 3 shows the plan for the mixture syntheses described in this paper.[5] Three acrylates **3**{*1–3*} were tagged with three fluorous tags **4**{*1–3*} to give nine fluorous-tagged benzyl esters **5** {*tag 1–3, acrylate 1–3*}. These were then mixed in groups of three—one of each tag—and reacted with four thiols **6**{*1–4*} under standard conditions to give mixtures of 12 adducts **7** {*tag 1–3, acrylate 1–3, thiol 1–4*}, which were then analyzed by fluorous hplc. Three libraries were prepared with different combinations of tags and acrylates and the resulting three mixtures of 12 compounds each provided significant information about factors effecting retention time on fluorous hplc.

2.2. Synthesis of starting materials and authentic product samples

The preparation of the benzyl alcohol tags **4** and their coupling to the acrylates are summarized in Eq. (1). Palladium-catalyzed coupling of the zinc reagents derived from perfluoroalkylethyl iodides **8**{*1–3*} provided coupled products **9**{*1*} (48%), **9**{*2*} (46%) and **9**{*3*} (40%) after purification by silica gel chromatography.[6] Metalation of these products with BuLi followed by addition of DMF and workup provided an intermediate aldehyde (not shown) which was directly reduced with sodium borohydride. Flash chromatographic purification provided **4**{*1*} (81%), **4**{*2*} (68%), and **4**{*3*} (75%) as colorless solids.



	Rf	R^1	R^2	yield
5{*1,1*}	C_6F_{13}	Me	H	73%
5{*2,2*}	C_8F_{17}	Pr	H	82%
5{*3,3*}	$C_{10}F_{21}$	H	Me	97%
5{*1,2*}	C_6F_{13}	Pr	H	65%
5{*2,3*}	C_8F_{17}	H	Me	43%
5{*3,1*}	$C_{10}F_{21}$	Me	H	57%
5{*1,3*}	C_6F_{13}	H	Me	58%
5{*2,1*}	C_8F_{17}	Me	H	56%
5{*3,2*}	$C_{10}F_{21}$	Pr	H	56%

(1)

All possible combinations (nine) of the three benzyl alcohols **4**{*1–3*} with the three acrylate esters **3**{*1–3*} were then prepared individually by heating a benzene solution of the alcohol, the acrylate and sodium hydride with azeotropic distillation to remove methanol. Yields of purified products ranged from 43–97%, as summarized in Eq. (1).

An initial pairing of tags and esters **5**{*1,1*}, **5**{*2,2*}, **5**{*3,3*} was selected arbitrarily and studied in some detail. First, a

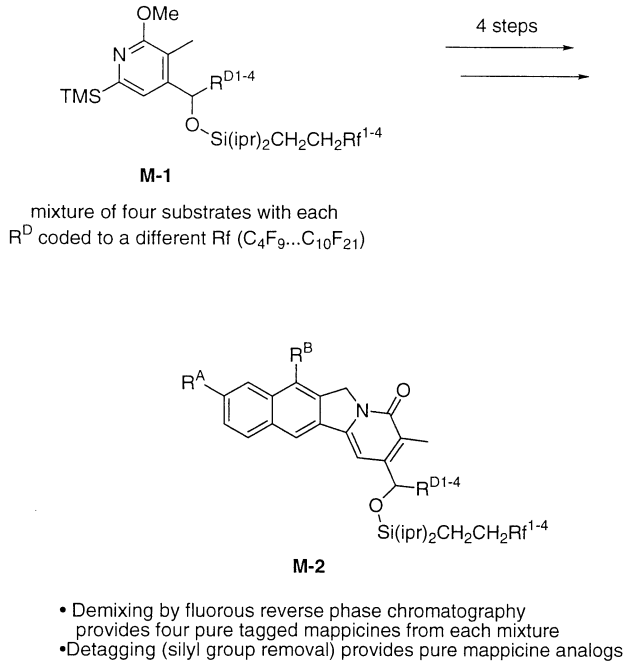
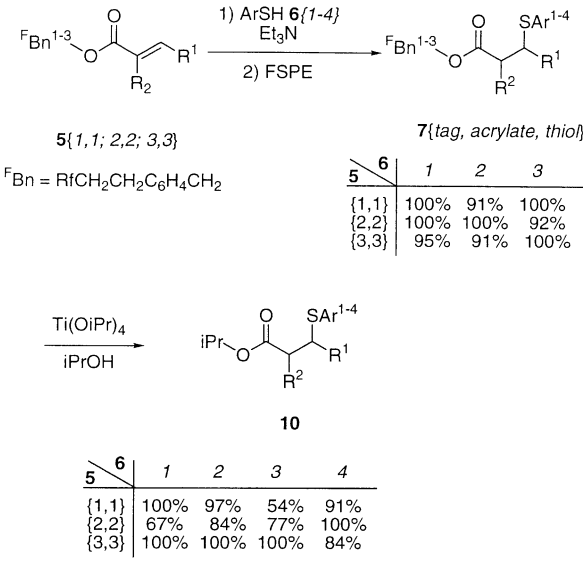


Figure 2. Making mappicine analogs by fluorous mixture synthesis

library of authentic samples of all 12 adducts was made in individual, parallel experiments by reaction of thiols **6**{*1–4*} (5 equiv.), triethylamine (1 equiv.) and tagged esters **5** (1 equiv.) in THF for 15 h (Eq. (2)). The crude products **7** were purified by solid phase extraction over fluorous reverse phase silica gel.[7] An initial pass with 4/1 methanol/water provided an organic fraction (amine, thiols), which was discarded. A second pass with ethyl acetate provided a fluorous fraction, which contained substantially pure Michael products **7**. Crude yields of these products are shown in Eq. (2). This experiment provides a nice example of how fluorous solid phase extraction can be used to purify tag compounds in a parallel synthesis experiment.[7b]



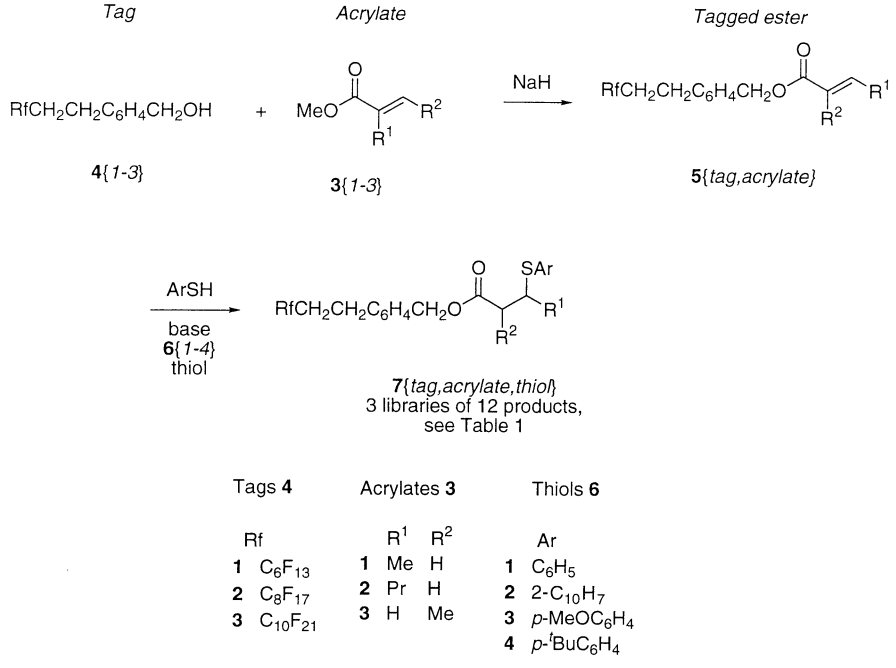
5 \ 6	*1*	*2*	*3*	*4*
{1,1}	100%	91%	100%	100%
{2,2}	100%	100%	92%	91%
{3,3}	95%	91%	100%	100%

5 \ 6	*1*	*2*	*3*	*4*
{1,1}	100%	97%	54%	91%
{2,2}	67%	84%	77%	100%
{3,3}	100%	100%	100%	84%

(2)

The tags were then removed individually by treating the products, again in parallel, with titanium isopropoxide in isopropanol. Workup and solid phase extraction through fluorous silica gel (4/1 methanol/water) provided the isopropyl esters **10** in the indicated overall yields. Further elution with ethyl acetate provided the starting benzyl alcohol tags **4**, which were reused for subsequent experiments. The yields of the recovered tags were close to quantitative.

Mixture Experiments: Three mixture libraries were then made by adding 0.2 mmol of each of the four thiols



Tags **4**	
	Rf
1	C_6F_{13}
2	C_8F_{17}
3	$C_{10}F_{21}$

Acrylates **3**		
	R^1	R^2
1	Me	H
2	Pr	H
3	H	Me

Thiols **6**	
	Ar
1	C_6H_5
2	2-$C_{10}H_7$
3	*p*-$MeOC_6H_4$
4	*p*-$^tBuC_6H_4$

Figure 3. Synthesis of three mixture libraries and separation by tag

Table 1. Retention times (in min) of the adducts in Libraries 1–3

Library 1[a]		Library 2[b]		Library 3[c]	
{*1,1,3*}	18.5	{*1,2,3*}	20.3	{*1,3,3*}	18.1
{*1,1,2*}	18.9	{*1,2,2*}	20.8	{*1,3,2*}	18.5
{*1,1,1*}	19.3	{*1,2,1*}	21.0	{*1,3,1*}	18.7
{*1,1,4*}	23.8	{*1,2,4*}	25.3	{*1,3,4*}	23.2
{*2,2,3*}	28.7	{*2,3,3*}	26.4	{*2,1,3*}	27.0
{*2,2,2*}	28.7	{*2,3,2*}	26.4	{*2,1,2*}	27.0
{*2,2,1*]	29.5	{*2,3,1*}	27.0	{*2,1,1*}	27.6
{*2,2,4*}	32.6	{*2,3,4*}	30.8	{*2,1,4*}	31.2
{*3,3,3*}	34.1	{*3,1,3*}	34.2	{*3,2,3*}	35.6
{*3,3,2*}	34.1	{*3,1,2*}	34.2	{*3,2,2*}	35.6
{*3,3,1*}	35.1	{*3,1,1*}	35.1	{*3,2,1*}	36.5
{*3,3,4*}	37.7	{*3,1,4*}	37.8	{*3,2,4*}	38.8

[a] From **5**{*1,1*}, **5**{*2,2*}, **5**{*3,3*}.
[b] From **5**{*1,2*}, **5**{*2,3*}, **5**{*3,1*}.
[c] From **5**{*1,3*}, **5**{*2,1*}, **5**{*3,2*}.

6{*1–4*} to three separate mixtures of the three tagged acrylates **5** (0.05 mol) and triethylamine (0.15 mol) in THF. After purification by solid phase extraction as above, the fluorous fraction of each of the three mixture libraries containing 12 products **7** was analyzed by injection onto a Fluofix column (gradient of 80/20 MeOH/water to 100% methanol over 40 min) with analysis by mass spectroscopy. The retention times of the components of the three libraries are listed in Table 1. No effort was made to quantify the reactions at this point, although it is clear from TLC and LC analysis that all the starting acrylates were consumed.

The 12 products of Library 1 were identified against the individual pure products from Eq. (2) by LC retention time and co-injection and by comparison of the mass spectra. Since all the products were readily identified and eluted in an order primarily dictated by the tag, we deemed it unnecessary to prepare authentic samples of the products in Libraries 2 and 3. These compounds were unambiguously identified by the LCMS analysis of the mixtures.

The HPLC chromatogram of a mixture similar to Library 1 is shown in Fig. 4 and the retention times of all three libraries are tabulated in Table 1. The compounds elute in order of the tag; a first group of peaks is all the products with the C_6F_{13} tag (18–25 min); a second group of peaks is all the products with the C_8F_{17} tag (26–33 min), and a third group of peaks is all the products with the $C_{10}F_{21}$ tag (34–39 min). Within these groups, the separation of peaks was much better than expected; indeed, up to 11 of the 12 possible peaks could be resolved with only two compounds partially overlapping. The adducts **7** bearing the same Rf group eluted reliably in order based on the appended thiol: **6**{*3*} before **6**{*2*} before **6**{*1*} before **6**{*4*}. The *t*-butyl-bearing compounds **7**{*tag, acrylate,4*} always eluted well after the other three, which were closely spaced.

Comparison of the results of Libraries 2 and 3 with Library 1 again shows that the primary separation is by the fluorous tag with a secondary separation by thiol. A close inspection of the data also shows that there is a small effect of the ester as well (comparison of retention times across libraries is needed for this); methacrylates eluted before crotonates which in turn eluted before hexanoates.

2.3. Preparative mixture experiment

In addition to showing that the primary separation is based

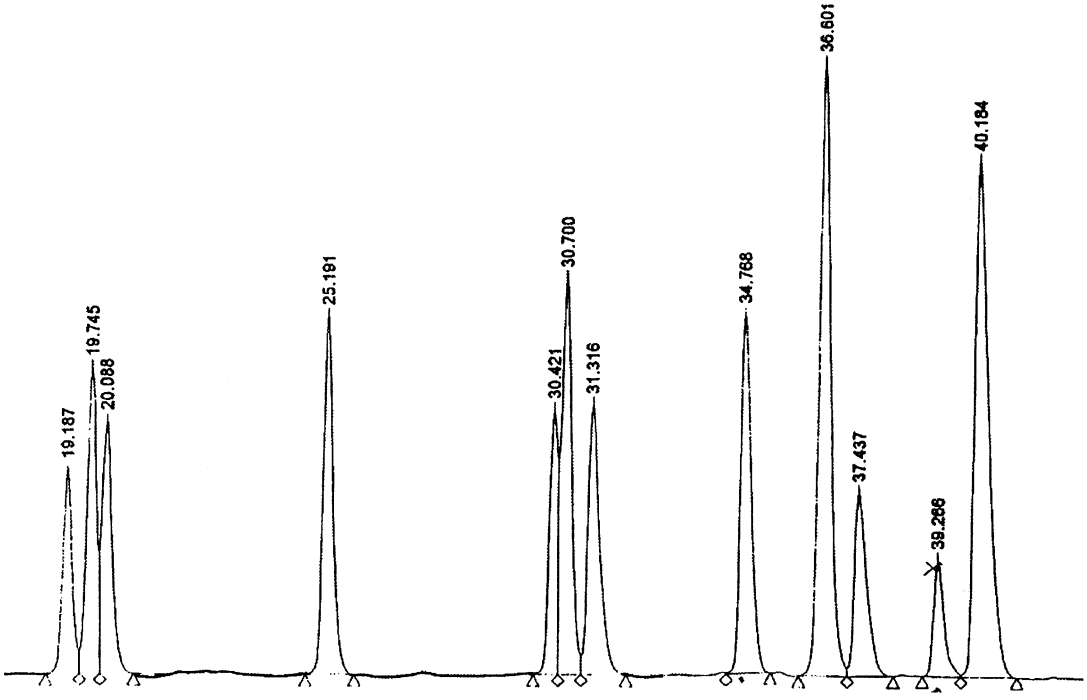


Figure 4. An HPLC trace of a mixture of compounds similar to Library 1. Retention times are listed in minutes; Fluofix column eluting with a gradient of 80% methanol/water increased to 100% methanol over 40 min. The order of peaks is **5**{*1,1,3* then *2* then *1* then *4*}, **5**{*1,1,3* then *2* then *1* then *4*}; **5**{*1,1,3* then *2* then *1* then *4*}. Peaks **5**{*3,3,3/2*} overlap at 36.5 min. The peak at 39 min is an unknown impurity. The mixture was made from individual pure components in ratios roughly proportional to the UV extinction coefficients at 254 nm to give similar peak heights.

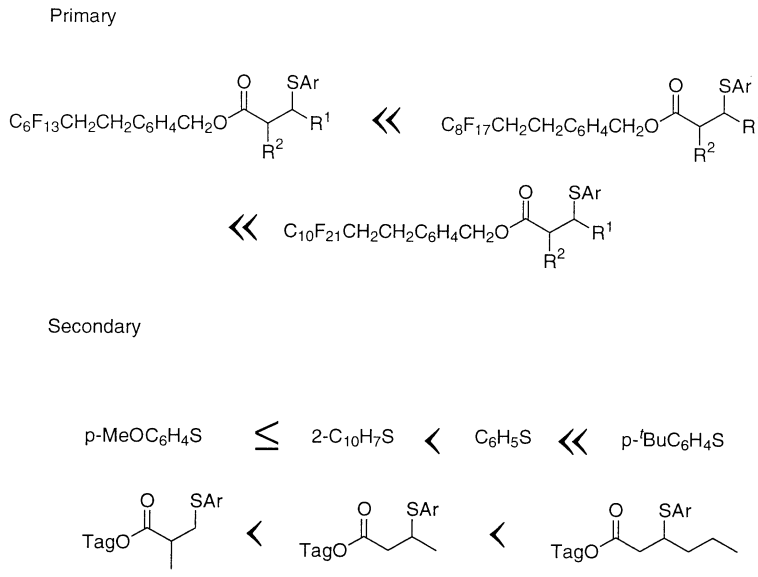
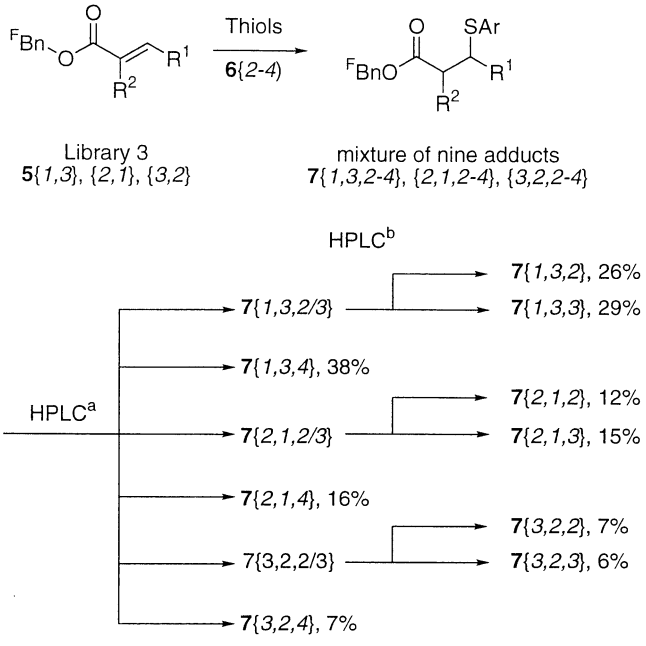


Figure 5. Effects of tags and substituents on retention times.

on the tag, these experiments identified a reliable separation based on the thiol. This suggests a way to leverage mixture library synthesis experiments in a combinatorial setting by reacting each mixture with more than one reagent in a diversity generating step. Inspection of the data Libraries 1–3 showed that the *t*-butylthiol adducts were well separated from the other three thiols. However, even though the other three thiols eluted in the same order, they were very closely spaced, sometimes even overlapping. By conducting a few experiments with pure tagged adducts **7** on regular silica gel, we learned that the *p*-methoxy adducts **7**{*tag,acrylate,3*} emerged well before the naphthyl adducts **7**{*tag,acrylate,2*}. In contrast, the phenyl adducts **7**{*tag, acrylate,1*} were not readily separated so thiol **6**{*1*} was dropped from the preparative experiment.

These analytical experiments lead the synthesis and purification of a prototype nine compound mixture as shown in Eq. (3). The three thiols **6**{*2–4*} (0.075 mmol each) were reacted with the acrylate mixture used to make Library 3 (0.05 mmol each) and DBU (0.05 mmol). The mixture was then preparatively separated over a Fluofix column to provide six fractions: a mixture of **7**{*1,3,2/3*} and pure **7**{*1,3,4*}, a mixture of **7**{*2,1,2/3*} pure **7**{*2,1,4*}, a mixture of **7**{*3,2,2/3*}, and finally pure **7**{*3,2,4*}. As presaged by the analytical experiments, the separation occurred in order by tag with the *t*-butylthiol adducts {*tag, acrylate,4*} following the *p*-methoxythiol and napthylthiol adducts {*tag,acrylate,2/3*}. No effort was made to separate the later pairs at this stage. The three remaining two-component mixtures were separated on regular reverse phase (C18) silica gel to give the other six pure products.

The yields of each product based on 100% for each tagged precursor **5** are listed in Eq. (3). These reflect a reactivity difference for the three precursors; the combined yield of products from the methacrylate (**7**{*1,3,thiol*}) was 93% while the crotonate (**7**{*2,1,thiol*}) gave 43% yield and the hexanoate (**7**{*3,2,thiol*}) gave only 20% combined yield. These yields reflect the expected relative reactivities of the Michael acceptors, but tags also differ (largest tag gives lowest yeld) so the relative effects cannot be disentangled from this experiment. Among each group of three thiol adducts, the ratio was close to statistical (1/1/1).



(3)

3. Conclusions

The effects of the tag, the thiol and the analysis of retention times are summarized in Fig. 5. The systematic tagging of the three different acrylates with three different tags and the synthesis and demixing of the resulting libraries clearly show the dominance of tag in this series of compounds. Tagged products eluted in groups based on the fluorine content of the tag, from lowest to highest. Secondary

separations based on both the thiol and ester components were also observed and these effects also are reliable across the series of tags. The *t*-butyl group has an especially strong effect in retaining compounds on the fluorous silica gel. The effect is probably stronger than the CF_2 group but is clearly less than two. Other groups had much smaller effects which cannot yet be fully interpreted. Polarity may play a role[8] (for example, hexanoates are better retained than methacrylates and crotonates), but it is not the only effect since the orders of elution of some of the thiol adducts differ on fluorous and regular reverse phase columns.

The generality of tag dominance still requires further study. The compounds described herein are closely related analogs, and it is premature to conclude that the tag dominance observed in this and the prior mappicine series[3] will translate to mixtures whose components have vastly different structural types of sizes. More information will be needed before we can assess the broad bounds of tag vs substrate dominance.

Given that the organic components do have some effect on the retention of tagged products, the arbitrary pairing of tags and substrates will not always be desirable. While each of the three different libraries described herein provided reasonable separations, the tag substrate pairing in Library 3 maximized the space between the components, so this pairing would probably be preferred for broader library experiments. Because the effects of the organic components translate across the different tags, it will be possible to plan favorable pairings by attaching a single tag to a series of different substrates or products from a planned library. The tagged adducts should then be analyzed by fluorous hplc and products that elute faster should be given shorter tags while those that elute slower should be given longer tags. This will help to ensure the tag-substrate pairing expands rather than contracts available chromatographic space between mixture components.

Perhaps most importantly, the work suggests that reliable secondary separations based on organic components can be identified by simple hplc experiments on representative compounds. Once identified, these separations can be used to make mixtures of mixtures by reacting each mixture of tagged compounds with a mixture of organic reactants. Primary and secondary separations can be accomplished either by the fluorous chromatography or a standard chromatography, or a combination. This approach leverages fluorous mixture synthesis by providing additional products without additional tags or a proportional increase in effort. In the mixture of mixtures experiment in Eq. (3), nine pure products emanated from one reaction and four hplc separations.

4. Experimental

4.1. General

4.1.1. 1-Bromo-4-(2-perfluorohexyl)ethylbenzene 9{*1*}. To zinc powder (1.63 g, 25.0 mmol) under argon was added THF (4 ml) and 1,2-dibromoethane (0.100 ml). The mixture was heated at reflux for 5 min and then cooled to room temperature. Chlorotrimethylsilane (0.100 ml) was added and the resulting mixture was stirred for 15 min at room temperature. A THF solution (20 ml) of 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorooctane (10.0 g, 21.00 mmol) was added to the reaction mixture at 30°C. The reaction mixture was stirred for 15 h at room temperature. The mixture was added to a THF solution (20 ml) of tetrakis(triphenylphosphine)palladium (0.850 g, 0.735 mmol) and 1-bromo-4-iodobenzene (6.09 g, 21.5 mmol). The mixture was heated at 45°C for 12 h, cooled, and partitioned between dichloromethane (20 ml) and FC-72 (40 ml). The organic layer was washed twice with FC-72 and evaporated. Purification of the residue by distillation under high vacuum (0.2 mmHg, 120°C) afforded 5.06 g (48%) of desired product as colorless solid: mp 33–34°C; IR (KBr) 2954, 1485, 1236, 1145, 1004, 974, 851, 697, 570, 535, and 507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (d, J=8.3 Hz, 2H), 7.11 (d, J=8.3 Hz, 2H), 2.90–2.85 (m, 2H), and 2.45–2.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 138.15, 131.99, 130.15, 120.69, 120–110 (m), 32.83 (t), and 26.05; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.61 (3F), −113.45 (2F), −120.73 (2F), −121.71 (2F), −122.34 (2F), and −124.99 (2F); Mass (EI) (rel intensity, %) *m/z* 505 (6), 504 (33), 503 (7), 502 (32, M^+), 423 (7), 172 (7), 171 (base peak), 170 (8), 169 (99), 153 (6), 133 (5), 109 (37), 104 (10), 103 (5), 90 (20), and 89 (7); HRMS Calcd for $C_{14}H_8F_{13}Br$: *m/z* 501.9602. Found: *m/z* 501.96134.

4.1.2. 1-Bromo-4-(2-perfluorooctyl)ethylbenzene 9{*2*}. The compound was prepared according to the procedure for the preparation of 1-bromo-4-(2-perfluorooctyl)ethylbenzene. A THF solution (40 ml) of 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorodecane (12.1 g, 21.00 mmol) was added to the suspension of zinc. After workup, removal of palladium residue from the crude product by column chromatography on silica gel with hexane/ethyl acetate=19/1 gave a mixture of product and 1-bromo-4-iodobenzene (6.75 g, product/starting compound =75/25, 46% yield). This mixture was used for the following transformation: Colorless solid; mp 45–48°C; IR (KBr) 2998, 1723, 1370, 1224, 998, 804, 669, and 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (d, J=8.3Hz, 2H), 7.11 (d, J=8.3Hz, 2H), 2.90–2.86 (m, 2H), and 2.45–2.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 138.16, 132.00, 130.14, 120.70, 120.00–100.00 (m), 32.85 (t), and 26.06; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.52 (3F), −113.39 (2F), −120.47 (2F), −120.69 (4F), −121.51 (2F), −122.25 (2F), and −124.89 (2F); Mass (EI) (rel intensity, %) *m/z* 606 (6), 602 (7, M^+), 523 (7), 172 (6), 171 (98), 170 (6), 169 (base peak), 153 (7), 133 (5), 109 (42), 104 (9) 91 (6), 90 (14), 89 (5), and 69 (6); HRMS Calcd for $C_{16}H_8F_{17}Br$: *m/z* 601.9538. Found: *m/z* 601.951328.

4.1.3. 1-Bromo-4-(2-perfluorodecyl)ethylbenzene 9{*3*}. This was prepared according to the procedure for the preparation of 1-bromo-4-(2-perfluorooctyl)ethylbenzene. A THF solution (40 ml) of 1-iodo-1*H*,1*H*,2*H*,2*H*-perfluorododecane (14.2 g, 21.00 mmol) was added to a suspension of zinc. After workup, removal of palladium residue from the crude product by column chromatography on silica gel with hexane/ethyl acetate=19/1 gave a mixture of product and 1-bromo-4-iodobenzene (8.09 g, product/starting compound=52/48, 40% yield). This mixture was used for

the following transformation: Colorless solid; mp 64–69°C; IR (KBr) 2951, 1489, 1347, 1204, 1145, 1073, 1018, 883, 808, 756, 650, 562, and 523 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (d, J=8.4 Hz, 2H), 7.11 (d, J=8.4 Hz, 2H), 2.92–2.79 (m, 2H), and 2.45–2.26 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 138.16, 132.00, 130.16, 120.69, 120.00–100.00 (m), 32.84 (t), and 26.05; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.54 (3F), −113.41 (2F), −120.86 (10F), −121.52 (2F), −122.27 (2F), and −124.92 (2F); Mass (EI) (rel intensity, %) m/z 705 (15), 704 (83), 703 (20), 702 (91, M^+), 682 (8), 683 (10), 623 (13), 314 (26), 169 (43), 153 (17), 152 (base peak), 151 (29), 150 (13), 126 (13), 109 (14), 76 (7), and 75 (5); HRMS Calcd for $C_{18}H_8F_{21}Br$: m/z 701.9474. Found: m/z 701.9536.

4.1.4. 4-(2-Perfluorohexyl)ethylbenzylalcohol 4{*1*}. A 1.7 M solution of *n*-butyllithium in hexane (1.17 ml, 1.99 mmol) was added dropwise to THF solution (2 ml) of 1-bromo-4-(2-perfluorohexyl)ethylbenzene (0.500 g, 1.99 mmol) at −40°C under argon. The resulting mixture was stirred for 20 min at −40°C. *N*,*N*-Dimethylformamide (0.154 ml, 1.99 mmol) was added dropwise to the mixture. After 30 min, diluted hydrochloric acid was added, and the mixture was extracted with dichloromethane three times. The organic layer was dried with anhydrous sodium sulfate, and evaporated.

To the above residue was added ethanol (2 ml) and sodium borohydride (75.2 mg, 1.99 mmol). This mixture was stirred at 25°C for 16 h. The mixture was diluted with hydrochloric acid, and then extracted with dichloromethane three times. The organic layer was dried over sodium sulfate and evaporated. Purification of the residue by column chromatography on silica gel with hexane/ethyl acetate=3/1 afforded 0.366 g (81%) of product: Colorless solid; mp 33–35° C; IR (neat) 3889, 2954, 2871, 1367, 1318, 1235, 1140, 1083, 1101, 837, and 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 4.96 (s, 2H), 2.96–2.90 (m, 2H), 2.47–2.28 (m, 2H), and 1.80–1.50 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 139.47, 138.71, 128.63, 127.62, 120.00–103.00 (m), 65.17, 33.07 (t), and 26.27; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.54 (3F), −13.46 (2F), −120.73 (2F), −121.71 (2F), −122.34 (2F), and −124.97 (2F); Mass (EI) (rel intensity, %) m/z 454 (21, M^+), 121 (18), 109 (7), 106 (13), 107 (base peak), 105 (5), 93 (7), 91 (31), 79 (47), 78 (7), 77 (22), and 60 (5); HRMS Calcd for $C_{15}H_{11}F_{13}O$: m/z 454.0602. Found: m/z 454.0589.

4.1.5. 4-(2-Perfluorooctyl)ethylbenzylalcohol 4{*2*}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzylalcohol. Use of 1.7 M of *n*-butyllithium in hexane (14.6 ml, 24.9 mmol), *N*,*N*-dimethylformamide (1.93 ml, 24.9 mmol), THF (16 ml), and sodium borohydride (0.941 g, 24.9 ml) for treatment of the mixture (5.00 g) of 1-bromo-4-(2-perfluorooctyl)ethylbenzene/1-bromo-4-iodobenzene =75:25) afforded 2.70 g (68%) of product: Colorless solid; mp 68–69°C; IR (KBr) 3394, 2996, 1612, 1343, 1152, 1081, 1006, 883, 646, and 554 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 4.96 (s, 2H), 2.96–2.90 (m, 2H), 2.47–2.28 (m, 2H), and 1.90–1.70 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 139.47, 138.70, 128.63, 127.62, 120.00–103.00 (m), 65.16, 33.06 (t), and 26.25; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.55 (3F), −113.39 (2F), −120.53 (2F), −121.71 (2F), −122.29 (2F), and −124.91 (2F); Mass (EI) (rel intensity, %) m/z 555 (24), 554 (base peak, M^+), 553 (23), 552 (15), 551 (30), 537 (10), 536 (8), 535 (27), 525 (5), 167 (5), 121 (16), 109 (10), 108 (8), 107 (94), 105 (8), 91 (29), 79 (18), and 77 (6); HRMS Calcd for $C_{17}H_{11}F_{17}O$: m/z 554.0538. Found: m/z 554.0527.

4.1.6. 4-(2-Perfluorodecyl)ethylbenzylalcohol 4{*3*}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzylalcohol. Use of 1.7 M of *n*-butyllithium in hexane (15.1 ml, 25.6 mmol), *N*,*N*-dimethylformamide (1.98 ml, 25.6 mmol), THF (16 ml), and sodium borohydride (0.968 g, 25.6 ml) for treatment of the mixture (6.00 g) of 1-bromo-4-(2-perfluorodecyl)ethylbenzene/1-bromo-4-iodobenzene=52:48) afforded 3.04 g (75%) of product: Colorless solid; mp 95–97°C; IR (KBr) 3366, 2958, 1706, 1370, 1335, 1208, 1149, 1081, 1013, 828, 700, 653, and 558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 4.70 (s, 2H), 3.00–2.90 (m, 2H), 2.47–2.19 (m, 2H), and 1.80–1.50 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 139.47, 138.72, 128.63, 121.00–100.00 (m), 65.17, 33.06 (t), and 26.26; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.51 (3F), −113.41 (2F), −120.54 (2F), −121.48 (10F), −122.25 (2F), and −124.91 (2F); Mass (EI) (rel intensity, %) m/z 655 (6), 654 (30, M^+), 653 (7), 652 (20), 635 (11), 121 (18), 109 (9), 108 (7), 107 (base peak), 105 (8), 91 (28) and 79 (18); HRMS Calcd for $C_{19}H_{11}F_{21}O$: m/z 654.0474. Found: m/z 654.0463.

4.1.7. 4-(2-Perfluorohexyl)ethylbenzyl crotonate 5{*1,1*}. Sodium hydride (about 1 mg) and ethyl crotonate (27.4 μl, 1.10 mmol) were added to a benzene solution (2 ml) of 4-(2-perfluorohexyl)ethylbenzylalcohol (0.100 g, 0.220 mmol), and then the mixture was heated at reflux for 1 h. Benzene was distilled out at atmospheric pressure to give a residue. The residue was quenched with dilute hydrochloric acid, and this mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated. Purification of the residue by column chromatography on silica gel with hexane/ethyl acetate=19/1 afforded 84 mg (73%) of product: Colorless oil; IR (neat) 2953, 1724, 1654, 1448, 1320, 1243, 1177, 1142, 1022, 975, 847, 808, and 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H), 7.03 (dq, J=15.3 Hz and J=7.0 Hz, 1H), 5.90 (dq, J=15.3 Hz and J=1.6 Hz, 1H), 5.18 (s, 2H), 2.96–2.85 (m, 2H), 2.47–2.28 (m, 2H), and 1.89 (dd, J=7.0 Hz and J=1.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.43, 145.38, 139.24, 134.85, 128.60, 128.60, 122.54, 120.00–103.00 (m), 65.74, 33.02 (t), 26.28, and 18.10; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.62 (3F), −113.51 (2F), −120.75 (2F), −121.73 (2F), −122.38 (2F), and −125.01 (2F); Mass (EI) (rel intensity, %) m/z 522 (13, M+), 477 (10), 439 (26), 117 (10), 104 (13), 91 (12), and 69 (base peak); HRMS Calcd for $C_{19}H_{15}F_{13}O_2$: m/z 522.0864. Found: m/z 522.0873.

4.1.8. 4-(2-Perfluorohexyl)ethylbenzyl 2-hexenoate 5{*1,2*}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless oil; IR (neat) 2960, 1724, 1654, 1464, 1375, 1239, 1173, 1014, 975, 812, 707, and 653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H),

7.02 (dt, J=15.5 Hz and J=7.0 Hz, 1H), 5.87 (d, J=15.5 Hz, 1H), 5.16 (s, 2H), 2.96–2.86 (m, 2H), 2.50–2.30 (m, 2H), 2.29–2.05 (m, 2H), 1.65–1.44 (m, 2H), and 0.94 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.66, 150.20, 139.25, 134.84, 128.88, 128.62, 121.10, 120.00–105.00 (m), 65.79, 34.38, 33.01 (t), 26.27, 21.33, and 13.78; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.60 (3F), −113.48 (2F), −120.72 (2F), −121.70 (2F), −122.35 (2F), and −124.97 (2F); Mass (EI) (rel intensity, %) *m/z* 550 (28, M+), 494 (10), 438 (19), 437 (base peak), 117(25), 104 (29), 97 (99), 91 (32), 77 (10), and 56 (11); HRMS Calcd for $C_{21}H_{19}F_{13}O_2$: *m/z* 550.1177. Found: *m/z* 550.1202.

4.1.9. 4-(2-Perfluorohexyl)ethylbenzyl methacrylate 5{1,3}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless oil; IR (KBr) 2959, 1720, 1634, 1456, 1320, 1243, 1014, 940, 816, 704, and 650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J=8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 6.17 (s, 1H), 5.60 (s 1H), 5.19 (s, 2H), 2.97–2.64 (m, 2H), 2.47–2.29 (m, 2H), and 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.44, 139.34, 136.44, 134.90, 128.79, 128.70, 126.03, 120.00–105.00 (m), 66.28, 33.10 (t), 26.37, and 18.52; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.73 (3F), −113.55 (2F), −120.78 (2F), −121.77 (2F), −122.41 (2F), and −125.06 (2F); Mass (EI) (rel intensity, %) *m/z* 523 (15), 522 (73, M+), 504 (10), 478 (13), 477 (61), 453 (18), 451 (13), 438 (21), 437 (base peak), 118 (16), 104 (18), 91 (29), and 69 (80); HRMS Calcd for $C_{19}H_{15}F_{13}O_2$: *m/z* 522.0864. Found: *m/z* 522.0852.

4.1.10. 4-(2-Perfluorooctyl)ethylbenzyl crotonate 5{2,1}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless solid; mp 33–34°C; IR (KBr) 2934, 1710, 1651, 1450, 1378, 1200, 1145, 1105, 1022, 986, 804, 741, 665, and 554 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H), 7.03 (dq, J=15.5 Hz and J=6.9 Hz, 1H), 5.90 (dq, J=15.5 Hz and J=1.4 Hz, 1H), 5.14 (s, 2H), 2.96–2.89 (m, 2H), 2.46–2.28 (m, 2H), and 1.89 (dd, J=6.9 Hz and J=1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.45, 145.42, 139.24, 134.83, 128.84, 128.61, 122.53, 120.00–105.00 (m), 65.76, 33.03 (t), 26.47, and 18.13; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.55 (3F), −13.46 (2F), −120.52 (2F), −120.73 (4F), −121.54 (2F), −122.30 (2F), and −124.94 (2F); Mass (EI) (rel intensity, %) *m/z* 627 (14), 622 (27, M$^+$), 604 (13), 577 (23), 553 (13), 551 (11), 538 (16), 537 (72), 309 (20), 308 (75), 265 (43), 223 (44), 180 (28), 179 (21), 178 (34), 165 (19), 117 (14), 104 (12), 91 (16), 69 (base peak), and 57 (12); HRMS Calcd for $C_{21}H_{15}F_{17}O_2$: *m/z* 622.0800. Found: *m/z* 622.0808.

4.1.11. 4-(2-Perfluorooctyl)ethylbenzyl 2-hexenoate 5{2,2}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless solid; mp 33–34°C; IR (neat) 2950, 2712, 1653, 1460, 1373, 1330, 1217, 1145, 978, 704, 656 and 561 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 7.03 (dt, J=15.6 Hz and J=7.0 Hz, 1H), 5.97 (d, J=15.6 Hz, 1H), 5.17 (s, 2H), 2.96–2.90 (m, 2H), 2.47–2.28 (m, 2H), 2.23–2.09 (m, 2H), 1.57–1.44 (m, 2H), and 0.95 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.64, 150.16, 139.25, 134.85, 128.86, 128.59, 121.10, 120.00–103.00 (m), 65.77, 34.36, 33.01 (t), 26.26, 21.32, and 13.72; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.80 (3F), −113.60 (2F), −120.64 (2F), −120.87 (4H), −121.68 (2F), −122.41 (2F), and −125.10 (2F); Mass (EI) (rel intensity, %) *m/z* 650 (3, M$^+$), 594 (5), 590 (5), 551 (9), 538 (17), 537 (base peak), 178 (15), 177 (10), 176 (13), 115 (7), 102 (5), and 98 (5); HRMS Calcd for $C_{23}H_{19}F_{17}O_2$: *m/z* 650.1113. Found: *m/z* 650.1125.

4.1.12. 4-(2-Perfluorooctyl)ethylbenzyl methacrylate 5{2,3}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless oil: IR (neat) 2953, 1724, 1638, 1456, 1371, 1200, 1154, 944, 812, and 657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 6.17 (s, 1H), 5.60 (s 1H), 5.19 (s, 2H), 2.96–2.80 (m, 2H), 2.48–2.28 (m, 2H), and 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.44, 139.34, 136.44, 134.90, 128.79, 128.69, 126.02, 124.00–106.00 (m), 66.28, 33.11 (t), 26.38, and 18.51; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.74 (3F), −113.56 (2F), −120.60 (2F), −120.83 (4H), −121.64 (2F), −122.38 (2F), and −125.06 (2F); Mass (EI) (rel intensity, %) *m/z* 622 (8, M$^+$), 577 (33), 551 (23), 538 (20), 537 (base peak), 165 (13), 129 (17), 128 (23), 116 (12), 115 (26), 103 (34), 89 (23), 84 (12), and 83 (17); HRMS Calcd for $C_{21}H_{15}F_{17}O_2$: *m/z* 622.0800. Found: *m/z* 622.0804.

4.1.13. 4-(2-Perfluorodecyl)ethylbenzyl crotonate 5{3,1}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless solid; mp 46–48°C; IR (KBr) 2939, 1715, 1655, 1450, 1196, 1149, 986, 887, 646, 558, and 531 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H), 6.98 (dq, J=15.7 Hz and J=7.0 Hz, 1H), 5.90 (dq, J=15.7 Hz and J=1.5 Hz, 1H), 5.15 (s, 2H), 2.96–2.90 (m, 2H), 2.60–2.44 (m, 2H), and 1.88 (dd, J=7.0 Hz and J=1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.45, 145.41, 139.25, 134.84, 128.84, 128.60, 122.53, 120.00–105.00 (m), 65.75, 33.01 (t), 26.25, and 18.11; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.67 (3F), −113.52 (2F), −120.65 (10F), −121.59 (2F), −122.35 (2F), and −125.02 (2F); Mass (EI) (rel intensity, %) *m/z* 722 (11, M$^+$), 704 (14), 678 (13), 677 (53), 676 (14), 654 (23), 651 (25), 638 (22), 637 (base peak), 171 (14), 167 (18), 166 (11), 165 (28), 163 (10), 154 (10), 148 (14), 147 (15), 144 (15), 133 (17), 130 (14), 129 (11), 128 (26), 127 (12), 126 (16), 125 (12), 105 (11), 104 (43), 103 (19), 102 (13), and 89 (22); HRMS Calcd for $C_{23}H_{15}F_{21}O_2$: *m/z* 722.0736. Found: *m/z* 722.0729.

4.1.14. 4-(2-Perfluorodecyl)ethylbenzyl 2-hexenoate 5{3,2}. This was prepared according to the procedure for the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless solid; mp 36–38°C; IR (neat) 2958, 1719, 1655, 1465, 1382, 1223, 1150, 978, 879, 645, and 554 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 7.03 (dt, J=15.5 Hz and J=7.0 Hz, 1H), 5.88 (dd, J=15.6 Hz and J=1.5 Hz, 1H), 5.16 (s, 2H), 2.96–2.85 (m, 2H), 2.50–2.33 (m, 2H), 2.23–2.13 (m, 2H), 1.56–1.40 (m, 2H), and 0.95 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.58, 150.10, 139.19, 134.76, 128.80, 128.52, 121.02, 120.00–105.00 (m), 65.71, 34.30, 32.94 (t),

26.20, 21.25, and 13.66; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.58 (3F), −113.46 (2F), −120.58 (10F), −121.53 (2F), −122.30 (2F), and −124.95 (2F); Mass (EI) (rel intensity, %) *m/z* 750 (5, M^+), 725 (6), 653 (10), 638 (18), 637 (91), 537 (9), 223 (6), 179 (28), 178 (base peak), 164 (43), 121 (23), 117 (18), 115 (12), 104 (14), 97 (59), 91 (32), 68 (15), and 56 (14); HRMS Calcd for $C_{25}H_{19}F_{21}O_2$: *m/z* 750.1049. Found: *m/z* 750.1054.

4.1.15. 4-(2-Perfluorodecyl)ethylbenzyl methacrylate 5{*3,3*}. This was prepared according to the procedure of the preparation of 4-(2-perfluorohexyl)ethylbenzyl crotonate: Colorless solid; mp 55–56°C; IR (KBr) 2950, 1897, 1723, 1652, 1450, 1374, 1212, 1149, 1081, 880, 642, and 558 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, *J*=8.0 Hz, 2H), 7.23 (d, *J*=8.0 Hz, 2H), 6.17 (s, 1H), 5.60 (s, 1H), 5.19 (s, 2H), 2.97–2.90 (m, 2H), 2.45–2.28 (m, 2H), and 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.37, 139.24, 136.31, 134.77, 128.70, 128.61, 125.99, 122.00–100.00 (m), 66.19, 33.01 (t), 26.27, and 18.45; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.59 (3F), −113.50 (2F), −120.59 (10H), −121.56 (2F), −122.31 (2F), and −124.96 (2F); Mass (EI) (rel intensity, %) *m/z* 722 (19, M^+), 677 (15), 637 (27), 537 (10), 177 (19), 178 (68), 169 (17), 167 (16), 166 (10), 165 (44), 121 (18), 199 (13), 117 (31), 104 (31), and 69 (base peak); HRMS Calcd for $C_{23}H_{15}F_{21}O_2$: *m/z* 722.0736. Found: *m/z* 722.0719.

4.2. General procedure for the synthesis of individual Michael adducts

Twelve separate acceptor solutions (4 each of **5**{*1,1*}, **5**{*2,2*}, **5**{*3,3*}) were prepared by diluting an acceptor (0.05 mmol) with THF (50 μl). One of the four thiols **6**{*1–4*} (0.25 mmol, benzenethiol, 2-naphthalenethiol, *4*-methoxybenzenethiol, and *4-tert*-butylbenzenethiol) was added to each of the 12 acceptor solutions such that all possible combinations of three acceptors and four thiols were generated. Triethylamine (6.1 μl, 0.05 mol) was added to each mixture. The mixtures were stirred for 15 h at room temperature. The reaction mixtures were charged on to 3.00 g of fluorous reverse phase silica gel in 12 short columns with methanol/water=4/1. The columns were eluted with methanol/water=4/1 (12 ml), and then they were eluted with ethyl acetate (12 ml). Removal of solvent of the ethyl acetate fractions gave the 12 individual Michael adducts. These were used as standards to characterize the mixture library. The characterization data of 4-(2-perfluorodecyl)ethylbenzyl 2-methyl-3-phenylthiopropanate **7**{*3,1,1*} are representative: Colorless solid; mp 51–52°C; IR (KBr) 2954, 1731, 1592, 1236, 887, 816, 737, 650, and 554 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.17 (m, 9H), 5.10 (s, 2H), 3.29 (dd, *J*=13.2 Hz and *J*=7.3 Hz, 1H), 2.96 (dd, *J*=13.2 Hz and *J*=7.0 Hz, 1H), 2.95–2.85 (m, 2H), 2.80–2.70 (s, 1H), 2.50–2.25 (m, 2H), and 1.30 (d, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.86, 139.33, 135.76, 134.52, 130.19, 129.10, 128.76, 128.62, 126.61, 120.00–105.00 (m), 66.25, 39.92, 37.47, 32.98 (t), 26.28, and 16.88; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.60 (3F), −113.46 (2F), −120.59 (10H), −121.55 (2F), −122.31 (2F), and −124.96 (2F); Mass (EI) (rel intensity, %) *m/z* 833 (10), 832 (30, M^+), 638 (16), 637 (93), 205 (14), 196 (13), 195 (base peak), 177 (12), 152 (31), 149 (37), 139 (16), 137 (19), 131 (21), 124 (46), 120 (12), 118 (40), 110 (16), 109 (49), 107 (12), 105 (21), and 104 (35); HRMS Calcd for $C_{29}H_{21}F_{21}O_2S$: *m/z* 832.0944. Found: *m/z* 832.0947.

4.3. Library 1. Representative procedure for Michael addition of four thiols with three acceptors (LC-mass analysis)

Benzenethiol (20.6 μl, 0.200 mmol), naphthalenethiol (32.1 mg, 0.200 mmol), 4-methoxybenzenethiol (24.6 μl, 0.200 mmol), 4-*tert*-butylbenzenethiol (33.6 μl, 0.200 mmol), and triethylamine (18.3 μl, 0.15 mmol) were added to a THF solution (150.0 μl) of the three acceptors (**5**{*1,1*}, **5**{*2,2*}, **5**{*3,3*}, 0.05 mmol each). The mixture was stirred for 15 h at room temperature. The reaction mixture was then charged on to 5.00 g of fluorous reverse phase silica gel in short column wetted with methanol/water=4/1. The column was eluted first with 20 ml of methanol/water=4/1, and then with 20 ml of ethyl acetate. Evaporation of the ethyl acetate fraction gave the mixture of Michael adducts. The mixture was analyzed by LC-MS (APCI, positive mode) with a Fluofix 120E (1E415, 150× 4.6 mm) column ($MeOH/H_2O$=4/1 gradient to MeOH only for 40 min, flow rate 1.0 ml/min). All 12 adducts were present as evidenced by the presence of the molecular ions in the MS. Retention times for the peaks are shown in Table 1.

4.4. General procedure for Michael addition of three thiols with three acceptors to form a mixture library (separation by HPLC)

Naphthalenethiol (8.0 mg, 0.050 mmol), 4-methoxybenzenethiol (6.2 μl, 0.050 mmol), 4-*tert*-butylbenzenethiol (8.4 μl, 0.050 mmol), and DBU (7.5 μl, 0.050 mmol) were added to a THF solution (150.0 μl) of three acceptors (0.05 mmol of **5**{*2,1*}, **5**{*3,2*}, **5**{*1,3*}). The mixture was stirred for 5 h at room temperature. The reaction mixture was then charged onto 5.00 g of fluorous reverse phase silica gel in short column wetted with methanol/water=4/1. The column was eluted with 20 ml of methanol/water=4/1, and then with 20 ml of ethyl acetate. Evaporation of the ethyl acetate fraction gave the mixture of Michael adducts.

This mixture was separated into six fractions [(1) a mixture of **7**{*1,3,2/3*}, (2) **7**{*1,3,4*}, (3) a mixture of **7**{*2,1,2/3*}, (4) **7**{*2,1,4*}, (5) a mixture of **7**{*3,2,2/3*}, (6) **7**{*3,2,4*}] by HPLC (Fluofix 120E, 1EW125, 250×10.0 mm, NEOS Co. Ltd.) ($MeOH/H_2O$=9/1 gradient to MeOH only for 30 min, flow rate 3.0 ml/min). The mixtures (1), (3), and (5) were further separated by HPLC (Nova-pack 250×100 mm, Waters Corp.) ($MeOH/H_2O$=19/1 to MeOH only for 20 min, flow rate 5.0 ml/min) into the individual components.

Two other libraries were prepared similarly using different combinations of tags and esters, as shown in Fig. 1. Data for the products follow:

7{*1,1,1*}: ^{1}H NMR ($CDCl_3$) δ 7.46–7.20 (m, 9H), 5.10 (s,2H), 3.66–3.60 (m, 1H), 2.96–2.90 (m, 2H), 2.69 (dd, *J*=15.7 Hz and *J*=6.1 Hz, 1H), 2.49 (dd, *J*=15.7 Hz and *J*=8.5 Hz, 1H), 2.45–2.30 (m, 2H), and 1.33 (d, *J*=6.9 Hz, 3H).

7{*1,1,2*}: ^{1}H NMR ($CDCl_3$) δ 8.00–7.19 (m, 11H), 5.09

(s, 2H), 3.80–3.74 (m, 1H), 2.95–2.89 (m, 2H), 2.74 (dd, J=15.6 Hz and J=6.2 Hz, 1H), 2.54 (dd, J=15.6 Hz and J=8.3 Hz, 1H), 2.49–2.30 (m, 2H), and 1.38 (d, J=6.8 Hz, 3H).

7{*1,1,3*}: ^{1}H NMR ($CDCl_3$) δ 7.43–7.21 (m, 6H), 6.87–6.79 (m, 2H), 5.06 (s, 2H), 3.81 (s, 3H), 3.49–3.42 (m, 1H), 2.96–2.88 (m, 2H), 2.64 (dd, J=15.5 Hz and J=6.3 Hz, 1H), 2.44 (dd, J=15.5 Hz and J=8.2 Hz, 1H), 2.48–2.28 (m, 2H), and 1.21 (d, J=6.9 Hz, 3H).

7{*1,1,4*}: ^{1}H NMR ($CDCl_3$) δ 7.47–7.17 (m, 8H), 5.10 (s, 2H), 3.63–3.58 (m, 1H), 2.96–2.90 (m, 2H), 2.70 (dd, J=15.6 Hz and J=6.1 Hz, 1H), 2.47 (dd, J=15.6 Hz and J=8.4 Hz, 1H), 2.52–2.34 (m, 2H), 1.32 (d, J=6.8 Hz, 3H), and 1.31 (s, 9H).

7{*2,2,1*}: ^{1}H NMR ($CDCl_3$) δ 7.52–7.10 (m, 9H), 5.09 (s, 2H), 3.53–3.48 (m, 1H), 2.95–2.89 (m, 2H), 2.70–2.55 (m, 2H), 2.45–2.30 (m, 2H), 1.70–1.40 (m, 4H), and 0.90 (t, J=6.9 Hz, 3H).

7{*2,2,2*}: ^{1}H NMR ($CDCl_3$) δ 7.90–7.17 (m, 11H), 5.07 (s, 2H), 3.70–3.61 (m, 1H), 2.95–2.88 (m, 2H), 2.69–2.60 (m, 2H), 2.49–2.30 (m, 2H), 1.70–1.27 (m, 4H), and 0.92 (t, J=7.0 Hz, 3H).

7{*2,2,3*}: ^{1}H NMR ($CDCl_3$) δ 7.42–7.20 (m, 6H), 6.85–6.78 (m, 2H), 5.10 (s, 2H), 3.80 (s, 3H), 3.33–3.29 (m, 1H), 2.96–2.89 (m, 2H), 2.60–2.49 (m, 2H), 2.48–2.30 (m, 2H), 1.70–1.40 (m, 4H), and 0.89 (t, J=6.8 Hz, 3H).

7{*2,2,4*}: ^{1}H NMR ($CDCl_3$) δ 7.47–7.20 (m, 8H), 5.09 (s, 2H), 3.50–3.43 (m, 1H), 2.96–2.90 (m, 2H), 2.70–2.55 (m, 2H), 2.50–2.30 (m, 2H), 1.70–1.40 (m, 4H), 1.31 (s, 9H), and 0.90 (t, J=6.6 Hz, 3H).

7{*3,3,1*}: Colorless solid; mp 51–52°C; IR (KBr) 2954, 1731, 1592, 1236, 887, 816, 737, 650, and 554 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.17 (m, 9H), 5.10 (s, 2H), 3.29 (dd, J=13.2 Hz and J=7.3 Hz, 1H), 2.96 (dd, J=13.2 Hz and J=7.0 Hz, 1H), 2.95–2.85 (m, 2H), 2.80–2.70 (s, 1H), 2.50–2.25 (m, 2H), and 1.30 (d, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.86, 139.33, 135.76, 134.52, 130.19, 129.10, 128.76, 128.62, 126.61, 120.00–105.00 (m), 66.25, 39.92, 37.47, 32.98 (t), 26.28, and 16.88; ^{19}F NMR ($CDCl_3$, relative to CCl_3F) δ −79.60 (3F), −113.46 (2F), −120.59 (10H), −121.55 (2F), −122.31 (2F), and −124.96 (2F); Mass (EI) (rel intensity, %) *m/z* 833 (10), 832 (30, M^+), 638 (16), 637 (93), 205 (14), 196 (13), 195 (base peak), 177 (12), 152 (31), 149 (37), 139 (16), 137 (19), 131 (21), 124 (46), 120 (12), 118 (40), 110 (16), 109 (49), 107 (12), 105 (21), and 104 (35). HRMS Calcd for $C_{29}H_{21}F_{21}O_2S$: *m/z* 832.0944. Found: *m/z* 832.0947.

7{*3,3,2*}: ^{1}H NMR ($CDCl_3$) δ 8.00–7.05 (m, 11H), 5.07 (s, 2H), 3.40 (dd, J=13.3 Hz and J=7.2 Hz, 1H), 3.07 (dd, J=13.3 Hz and J=6.8 Hz, 1H), 2.94–2.90 (m, 2H), 2.90–2.75 (m, 1H), 2.50–2.25 (m, 2H), and 1.33 (d, J=7.0 Hz, 3H).

7{*3,3,3*}: ^{1}H NMR ($CDCl_3$) δ 7.39–7.20 (m, 6H), 6.86–6.79 (m, 2H), 5.08 (s, 2H), 3.80 (s, 3H), 3.16 (dd, J=13.3 Hz and J=7.5 Hz, 1H), 2.96–2.80 (m, 3H), 2.72–2.63 (m, 1H), 2.51–2.30 (m, 2H), and 1.26 (d, J=7.0 Hz, 3H).

7{*3,3,4*}: ^{1}H NMR ($CDCl_3$) δ 7.51–7.19 (m, 8H), 5.09 (s, 2H), 3.26 (dd, J=13.3 Hz and J=7.3 Hz, 1H), 2.97–2.90 (m, 3H), 2.80–2.70 (m, 1H), 2.60–2.34 (m, 2H), 1.31 (s, 9H), and 1.27 (d, J=6.7 Hz, 3H).

7{*1,3,2*}: ^{1}H NMR ($CDCl_3$) δ 7.82–7.15 (m, 11H), 5.09 (s, 2H), 3.38 (dd, J=13.3 Hz and J=7.2 Hz, 1H), 3.05 (dd, J=13.3 Hz and J=6.8 Hz, 1H), 2.95–2.90 (m, 2H), 2.90–2.75 (m, 1H), 2.50–2.30 (m, 2H), and 1.32 (d, J=7.0 Hz, 3H).

7{*1,3,3*}: ^{1}H NMR ($CDCl_3$) δ 7.38–7.21 (m, 6H), 6.85–6.80 (m, 2H), 5.09 (s, 2H), 3.80 (s, 3H), 3.16 (dd, J=13.4 Hz and J=7.4 Hz, 1H), 2.96–2.90 (m, 2H), 2.84 (dd, J=13.4 Hz and J=6.7 Hz, 1H), 2.72–2.63 (m, 1H), 2.50–2.30 (m, 2H), and 1.20 (d, J=7.1 Hz, 3H).

7{*1,3,4*}: ^{1}H NMR ($CDCl_3$) δ 7.38–7.20 (m, 8H), 5.08 (s, 2H), 3.25 (dd, J=13.3 Hz and J=7.2 Hz, 1H), 2.95–2.88 (m, 3H), 2.80–2.70 (m, 1H), 2.50–2.30 (m, 2H), 1.30 (s, 9H), and 1.27 (d, J=7.0 Hz, 3H).

7{*2,1,2*} ^{1}H NMR ($CDCl_3$) δ 7.90–7.00 (m, 11H), 5.08 (s, 2H), 3.80–3.72 (m, 1H), 2.95–2.88 (m, 2H), 2.73 (dd, J=15.6 Hz and J=6.1 Hz, 1H), 2.53 (dd, J=15.6 Hz and J=8.3 Hz, 1H), 2.39–2.20 (m, 2H), and 1.37 (d, J=6.9 Hz, 3H).

7{*2,1,3*}: ^{1}H NMR ($CDCl_3$) δ 7.43–7.20 (m, 6H), 6.88–6.79 (m, 2H), 5.09 (s, 2H), 3.81 (s, 3H), 3.50–3.40 (m, 1H), 2.96–2.89 (m, 2H), 2.63 (dd, J=15.5 Hz and J=6.4 Hz, 1H), 2.44 (dd, J=15.5 Hz and J=8.0 Hz, 1H), 2.55–2.37 (m, 2H), and 1.27 (d, J=7.1 Hz, 3H).

7{*2,1,4*}: ^{1}H NMR ($CDCl_3$) δ 7.39–7.20 (m, 8H), 5.09 (s, 2H), 3.62–3.53 (m, 1H), 2.96–2.89 (m, 2H), 2.47 (dd, J=15.6 Hz and J=8.1 Hz, 1H), 2.38 (dd, J=15.6 Hz and J=7.9 Hz, 1H), 2.37–2.20 (m, 2H), 1.31 (d, J=7.0 Hz, 3H), and 1.31 (s, 9H).

7{*3,2,2*}: ^{1}H NMR ($CDCl_3$) δ 7.89–7.10 (m, 11H), 5.07 (s, 2H), 3.66–3.60 (m, 1H), 2.94–2.88 (m, 2H), 2.70–2.59 (m, 2H), 2.50–2.30 (m, 2H), 1.70–1.40 (m, 4H), and 0.90 (t, J=7.0 Hz, 3H).

7{*3,2,3*}: ^{1}H NMR ($CDCl_3$) δ 7.41–7.10 (m, 6H), 6.85–6.80 (m, 2H), 5.09 (s, 2H), 3.80 (s, 3H), 3.33–3.28 (m, 1H), 2.96–2.89 (m, 2H), 2.57–2.50 (m, 2H), 2.50–2.20 (m, 2H), 1.70–1.40 (m, 4H), and 0.89 (t, J=7.0 Hz, 3H).

7{*3,2,4*}: ^{1}H NMR ($CDCl_3$) δ 7.38–7.20 (m, 8H), 5.09 (s, 2H), 3.50–3.40 (m, 1H), 2.96–2.89 (m, 2H), 2.70–2.50 (m, 2H), 2.50–2.30 (m, 2H), 1.70–1.40 (m, 4H), 1.31 (s, 9H), and 0.90 (t, J=6.8 Hz, 3H).

LC-Mass (M+1) of **7**

1,1,1=633; *1,1,2*=683; *1,1,3*=663; *1,1,4*=689
2,2,1=761; *2,2,2*=811; *2,2,3*=791; *2,2,4*=817
3,3,1=833; *3,3,2*=883; *3,3,3*=863; *3,3,4*=889

1,2,1=661; *1,2,2*=711; *1,2,3*=691; *1,2,4*=717
2,3,1=733; *2,3,2*=783; *2,3,3*=763; *2,3,4*=789
3,1,1=833; *3,1,2*=883; *3,1,3*=863; *3,1,4*=889
1,3,1=633; *1,3,2*=683; *1,3,3*=663; *1,3,4*=689
2,1,1=733; *2,1,2*=783; *2,1,3*=763; *2,1,4*=789
3,2,1=861; *3,2,2*=911; *3,2,3*=891; *3,2,4*=917

4.5. General procedure for the deprotection of the Michael adducts

Titanium tetraisopropoxide (12.5 mg, 0.0439 mmol) was added to a suspension of each Michael adduct (0.0240 mmol) in anhydrous 2-propanol (0.5 ml) under argon. The mixture was heated at reflux temperature for 6 h, cooled to room temperature, and was quenched with dilute hydrochloric acid. The resulting mixture was extracted with ethyl ether three times. The organic layer was dried over sodium sulfate and evaporated. The residue in a minimum amount of acetonitrile was charged on to 2.00 g of fluorous reverse phase silica gel in a short column wetted with methanol/water=4/1. The column was eluted with 8 ml of methanol/water=4/1 and then it was eluted with 8 ml of ethyl acetate to give fluorous tagged benzylalcohols. Removal of solvent from the first eluate and the second eluate afforded deprotected product and fluorous tagged benzylalcohol, respectively. 1-Methylethyl 2-methyl-3-phenylthiopropanate is a representative deprotected product.

4.5.1. 1-Methylethyl 2-methyl-3-phenylthiopropanoate. Colorless oil; IR (KBr) 2979, 2929, 1728, 1585, 1458, 1315, 1211, 1170, 739, and 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.20 (m, 5H), 5.08–5.00 (m, 1H), 3.26 (dd, J=13.2 Hz and J=7.3 Hz, 1H), 2.92 (dd, J=13.2 Hz and J=6.9 Hz, 1H), 2.69–2.58 (m, 1H), and 1.27–1.22 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.59, 136.02, 130.04, 129.07, 126.50, 68.11, 40.01, 37.46, 21.94, and 16.94; Mass (EI) (rel intensity, %) *m/z* 238 (7, M^+), 123 (8), 88 (14), 86 (71), and 84 (base peak); HRMS Calcd for $C_{13}H_{18}O_2S$: *m/z* 238.1044. Found: *m/z* 238.1016.

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