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Synthesis of All 16 Stereoisomers of Pinesaw Fly Sex Pheromones − Tools and Tactics for Solving Problems in Fluorous Mixture Synthesis

Sivaraman Dandapani, Mario Jeske, and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

curran@pitt.edu

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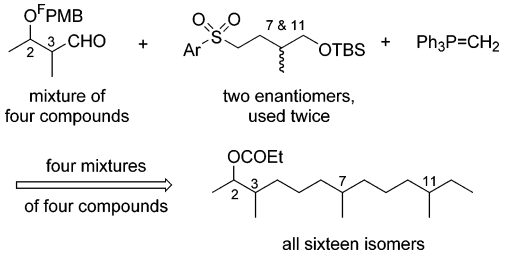

The application of fluorous mixture synthesis (FMS) for accessing natural products and their stereoisomers was validated by the total synthesis of all 16 stereoisomers of the pine sawfly sex pheromone. Four fluorous *p*-methoxybenzyl groups were used as tags, and a "4-mix-4-split" approach was employed in a divergent synthesis. This paper presents the details of the FMS of pine sawfly sex pheromones with an emphasis on identification and solving of problems encountered when working with fluorous mixtures.

Introduction

The emerging technique of fluorous mixture synthesis (FMS)[1,2] allows solution-phase organic synthesis to be carried out on mixtures of compounds with predictable separation of the products and hence offers unique advantages for library generation. FMS has three stages: pre-mix, mixture synthesis, and post-mix (Figure 1). The pre-mix stage consists of synthesis of required precursors, their tagging with a unique fluorous tag, and mixing of the resulting tagged precursors. The fluorous-tagged compounds are taken through a series of synthetic steps during the mixture synthesis phase. Splitting is sometimes used to further leverage the tags and provide additional products. At the end of the synthesis, the mixture is subjected to chromatography over fluorous silica gel in a process called demixing.[3] This provides the individual pure compounds in order of fluorous tag from smallest to largest. In the post-mix stage, the fluorous tags are removed in separate detagging steps and the individual target compounds are purified.

In solution-phase mixture synthesis methods based on separation tagging, the structure of the tag "encodes" a key structural feature of the molecule to which it is attached.[1,4] This feature is "decoded" during demixing by the order of elution. Proof-of-principle work on fluorous mixture synthesis with the natural product mappicine used fluorous tags to encode absolute configuration at a single stereocenter (enantiomers) and to encode the structure of a substituent (analogues), as shown in Figure 2.[1c] When enantiomers are tagged, the order of demixing has to be controlled by the tag so decoding cannot go wrong. When analogues are tagged, the final detagged products have different molecular weights, so the decoding process can be confirmed by mass spectroscopy.

The coding of diastereomers with fluorous tags presents a problem because the final detagged diastereomers all have the same molecular weight. Of course, their structures could be confirmed by other spectroscopic means, but the exercise then becomes circular because the goal in making multiple diastereomers of a compound

(1) (a) Luo, Z. Y.; Zhang, Q. S.; Oderatoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769. (b) Curran, D. P.; Oderaotoshi, Y. *Tetrahedron* **2001**, *57*, 5243−5253. (c) Zhang, W.; Luo, Z.; Chen, C. H. T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443−10450. (d) Curran, D. P.; Furukawa, T. *Org. Lett.* **2002**, *4*, 2233−2235. (e) Manku, S.; Curran, D. P. *J. Comb. Chem.* **2005**, *7*, 63−68.

(2) Short review: Zhang, W. *Arkivoc* **2004**, 101−109.

(3) For reviews of chromatography with fluorous silica gel, see: (a) Curran, D. P. *Synlett* **2001**, 1488−1496. (b) Curran, D. P. In *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Horvath, I. T., Curran, D. P., Eds.; Wiley-VCH: Weinheim, 2004; pp 128−156. (c) Zhang, W. *Tetrahedron* **2003**, *59*, 4475−4489.

(4) Wilcox, C. S.; Turkyilmaz, S. *Tetrahedron Lett.* **2005**, *46*, 1827−1829.

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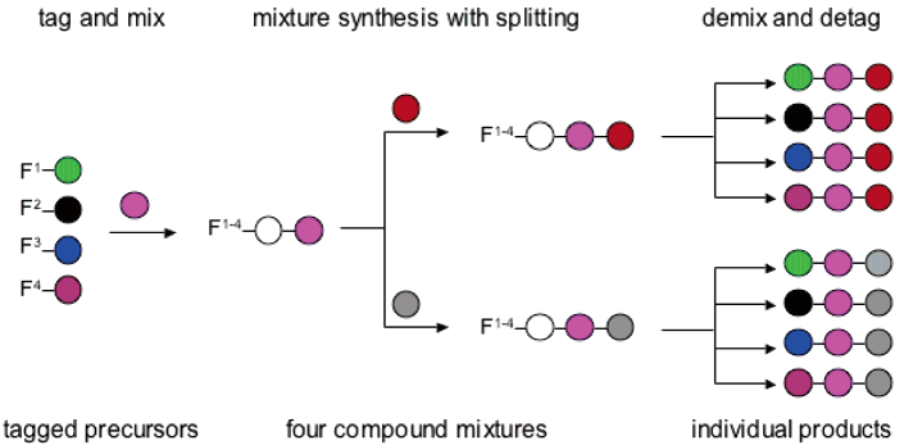


FIGURE 1. The stages of fluorous mixture synthesis.

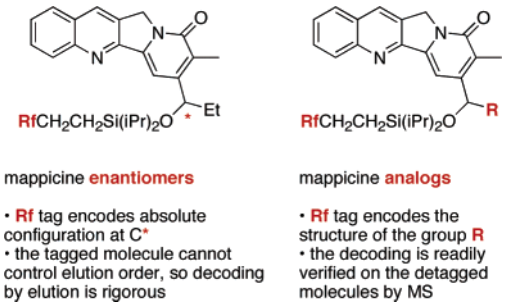


FIGURE 2. Fluorous tags encode absolute configuration or substituent information in mappicine syntheses.

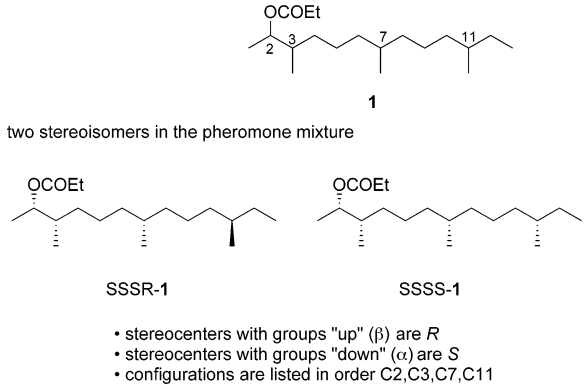


FIGURE 3. Structures of the pine sawfly sex pheromones.

is to assign spectra from a known structure, not the reverse. The decoding of a set of diastereomers with homologous fluorous tags should be possible by demixing coupled with mass spectrometric analysis because all of the tagged compounds have the same molecular weight but the tags are different. In principle, the independent verification of the decoding on the detagged products should not be needed.

To confirm this proposition and to show the utility of fluorous mixture synthesis in a diastereomer setting, we decided to make all 16 diastereomers of a natural product and then to confirm the success of the exercise by comparing the products with known samples. This requires that the complete set of stereoisomers of the target compound, hereafter called the stereoisomer library, already be known. Outside of the simple sugars, very few natural products with four stereocenters have complete stereoisomer libraries. This reflects the difficulties of making multiple isomers by traditional solution-phase syntheses; a large amount of effort is required even for relatively simple compounds.

The female sex pheromone of the minor sawfly *Microdiprion pallipes* comprises at least two stereoisomers of the propionate esters of 3,7,11-trimethyl-2-tridecanol **1** (Figure 3).[5] Pine sawflies are serious pests on pine trees, and pheromones **1** can be used for pest control by placing them in suitable traps in an infested area.[6] Mori and co-workers synthesized two diastereomers (2*S*,3*S*,7*S*,11*R* and 2*S*,3*R*,7*R*,11*R*) of **1**.[7,8] Hedenstrom and co-workers synthesized the complete 16-stereoisomer library of **1** as a mixture and in pure form. Both syntheses relied heavily on lipase-catalyzed diastereoselective acylations.

We recently communicated the total synthesis of all 16 stereoisomers of pine sawfly sex pheromone **1** by a combination of FMS and parallel synthesis.[9] By comparison of our data with Hedenstrom's,[5b] we were able to validate that FMS is a useful technique for the rapid synthesis of natural product stereoisomer libraries.[10] That communication focused on conceptual and strategic aspects of FMS. In this full paper, we report a detailed account of our split-parallel FMS approach to the total

(5) (a) Bergstrom, G.; Wassgren, A.-B.; Anderbrant, O.; Hedenstrom, E.; Hogberg, H.-E. *Naturwissenschaften* **1998**, *85*, 244−249 (b) Larsson, M.; Nguyen, B.-V.; Hogberg, H.-E.; Hedenstrom, E. *Eur. J. Org. Chem.* **2001**, 353−363.

(6) (a) Smith, D. R. In *Sawfly Life History Adaptations to Woody Plants*; Wagner, M. R., Raffa, K. F., Eds.; Academic Press: San Diego, 1993; pp 3−32. (b) Tai, A.; Higashiura, Y.; Kakizaki, M.; Naito, T.; Tanaka, T.; Fukita, M.; Sugimura, T.; Hara, H.; Hayashi, N. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 607−608.

(7) Nakamura, Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, *2175*, 5−2182.

(8) The phermone structures are consistently drawn such that a stereocenter with an "up" group is *R* and a stereocenter with a "down" group is *S*. Configurations are always listed in the order C2, C3, C7, C11.

(9) Dandapani, S.; Jeske, M.; Curran, D. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12008−12012.

(10) (a) Fluorous mixture synthesis has recently been used to make a 16-member stereoisomer library of murisolins for rigorous structure assignment. See: Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36−37. (b) For a recent Concept Article and quasi-enantiomers and other quasi-isomers, see: Zhang, Q.; Curran, D. P. *Chem.-Eur. J.* **2005**, *11*, 4866−4880.

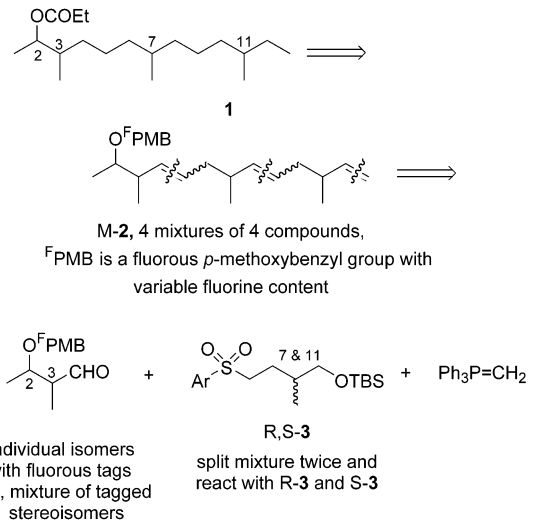


FIGURE 4. Retrosynthesis for FMS of all 16 stereoisomers of pine sawfly sex pheromone **1**.

synthesis of all 16 stereoisomers of the pine sawfly sex pheromone. We provide the customary descriptions of chemical reactions and complete characterization data for intermediates and products. In addition, we focus on practical methods for identifying and solving problems in FMS.

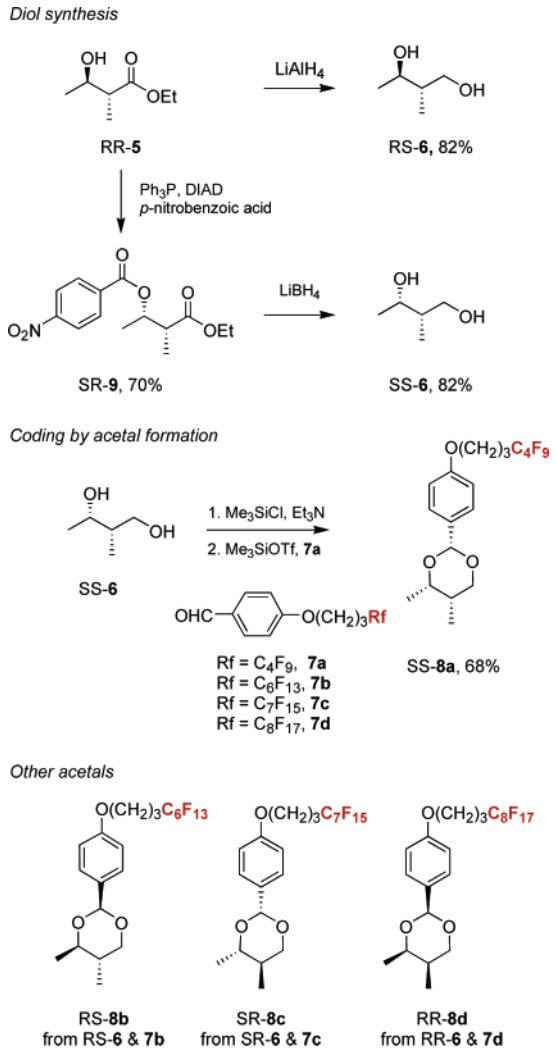
Because we needed reliable access to all stereoisomers of **1** in high ee, the retrosynthesis in Figure 4 was designed such that all of the stereocenters come directly from the precursors and are not introduced during the course of the synthesis. Desaturation of **1** with introduction of three double bonds leads to triene **2**. This triene can be readily assembled from aldehyde **4** by iterative application of Julia olefinations[11] with sulfone **3**, followed by deprotection, oxidation, and capping with methylene triphenylphosphorane ($Ph_3P{=}CH_2$).

To make all 16 isomers, we envisioned tagging each of the four stereoisomers of **4** with fluorous *p*-methoxybenzyl (^{F}PMB) protecting groups differing in fluorine content.[12] The mixture of aldehydes M-**4**[13] is split in half for separate coupling with each enantiomer of **3** by Julia olefination. The resulting two mixtures of alkenes (not shown) are carried forward in parallel to a second split and Julia olefination with the enantiomeric pair **3**. Finally, the Wittig reaction with $Ph_3P{=}CH_2$ then gives four mixtures of trienes M-**2** that fully encode all 16 stereoisomers. Each of the four mixtures contains molecules with one of the four possible configurations at C7 and C11 and all four possible configurations at C2 and C3. These mixtures are reduced, demixed, detagged, and acylated to give the 16 individual isomers of **1**.

Results and Discussion

Pre-Mix Stage. Fluorous PMP (*para*-methoxyphenyl) acetals **8a**−**d** proved to be suitable precursors of aldehydes **4**, and the syntheses of these acetals are shown in Scheme 1. Ester RR-**5** was prepared in 20:1 anti selectivity by Frater−Seebach alkylation.[14] Direct ^{F}PMB protection of the secondary alcohol in RR-**5** by the trichloroacetimidate[15] route was low yielding, so RR-**5** was reduced by lithium aluminum hydride to the anti diol RS-**6** in 82% yield. To prepare syn diol SS-**6**, ester RR-**5** was inverted by a Mitsunobu reaction with *p*-nitrobenzoic acid to give SR-**9** (70%), followed by reductive cleavage with $LiBH_4$ (82%).

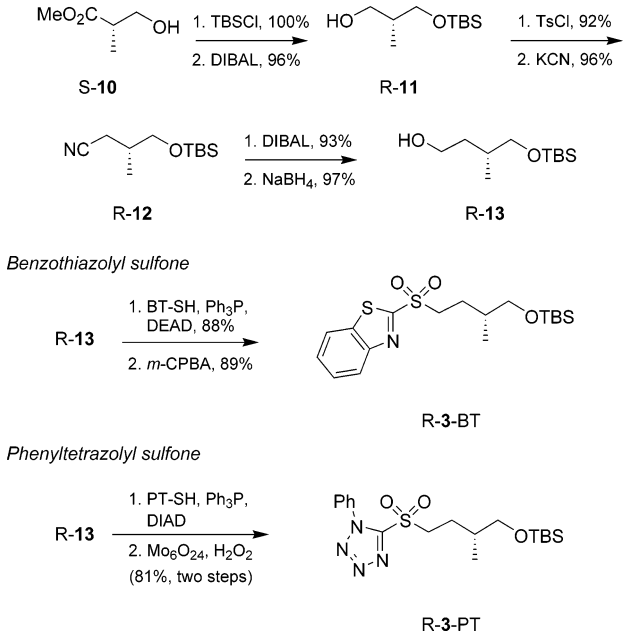
SCHEME 1. Synthesis of Fluorous Acetals 8a−d



Formation of the fluorous PMP acetal was accomplished by using Noyori's protocol.[16] Diol SS-**6** was silylated with TMSCl, and then ^{F}PMB aldehyde **7a** bearing the perfluorobutyl (C_4F_9) group[17] was added along with TMSOTf to provide SS-**8a** in 68% yield. (Hereafter, the letters **a**−**d** designate the fluorous tags, as shown in Scheme 1.) Likewise, the anti diol RS-**6** was converted to the anti acetal RS-**8b** bearing the perfluorohexyl group (C_6F_{13}) in two steps in 86% overall

(11) Review: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585.
(12) ^{F}PMB tags have been previously employed for the synthesis of discodermolide [ref 1d] and murisolin analogues [ref 10a].
(13) The prefix M denotes mixture of fluorous-tagged compounds.
(14) (a) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269−1277. (b) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1983**, *63*, 109−120.
(15) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 86−87.
(16) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357−1358.
(17) Fluorous compounds and FluoroFlash silica gel were purchased from Fluorous Technologies, Inc. (www.fluorous.com). D.P.C. holds an equity interest in the company.

SCHEME 2. Synthesis of Sulfones R-3-BT and R-3-PT



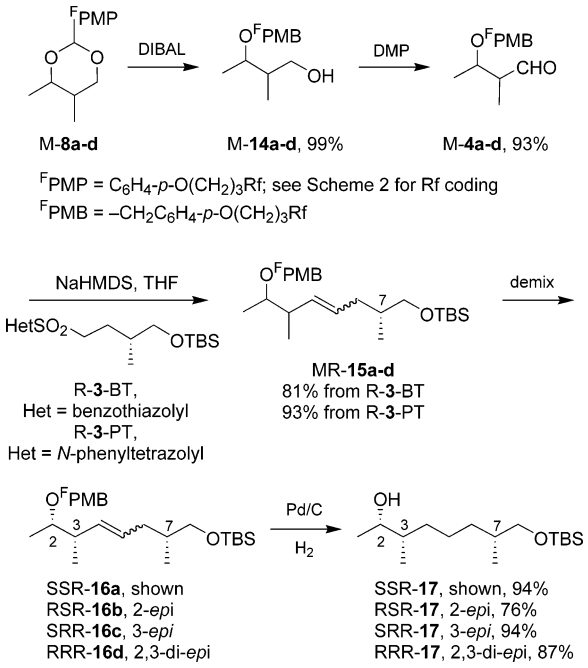
yield. An identical sequence of reactions was used to prepare SR-**6** and RR-**6** (not shown), and these were reacted with **7c** and **7d**, respectively, to provide the quasi-enantiomeric[10b] acetals SR-**8c** and RR-**8d**.

The diastereomeric purities of all of the acetals **8** were determined by a single GC experiment immediately after mixing. Both the syn acetals SS-**8a** and RR-**8d** were diastereomerically pure, while the two anti acetals RS-**8b** and SR-**8c** had diastereomeric ratios (anti/syn) of 25:1 and 29:1, respectively. Details of this mixture analysis method are provided below in the section on analytical tools for FMS.

The Kocienski–Julia coupling was initially tested with both benzothiazolyl (BT) sulfone[11] R-**3**-BT and *N*-phenyltetrazolyl (PT) sulfone R-**3**-PT,[18] and the syntheses of these reagents are outlined in Scheme 2. Primary alcohol R-**13** was prepared according to Kitahara[19] with some modifications (see Supporting Information for details). TBS protection (100% yield) of primary alcohol of S-**10** followed by DIBAL reduction gave the alcohol R-**11** in 96% yield. This was converted to the corresponding tosylate in 92% yield. Cyanide displacement gave R-**12** in 96% yield. The nitrile in R-**12** was first reduced by DIBAL to the corresponding aldehyde (93% yield), which in turn was further reduced by sodium borohydride to alcohol R-**13** in 97% yield. The ee of alcohol R-**13** was determined to be greater than 95% by ^{1}H NMR spectroscopic analysis of a Mosher ester of a derivative of R-**13** (see Supporting Information).

Alcohol R-**13** was coupled with benzothiazolyl sulfide (BT-SH) under Mitsunobu conditions to give the intermediate sulfide (88% yield). This was directly oxidized by *m*-CPBA to sulfone R-**3**-BT in 89% yield. Correspondingly, R-**13** was converted with *N*-phenyltetrazolyl sulfide (PT-SH) to R-**3**-PT in 84% yield by a one-pot Mitsunobu/oxidation process developed by Kocienski.[20]

SCHEME 3. Julia Olefinations with BT and PT Sulfones R-3



Enantiomeric sulfones S-**3**-BT and S-**3**-PT (not shown) were synthesized by the same reactions starting from R-**10**. The ee of intermediate alcohol S-**13** was determined to be 96% from ^{1}H NMR analysis as above.

Kocienski–Julia Olefination with BT and PT Sulfones 3. Prior to starting the mixture synthesis in earnest, we carried out Julia olefinations with sulfones R-**3**-BT and R-**3**-PT to probe for epimerization of the α-stereocenter of aldehyde M-**4a**–**d**. Mixture M-**8a**–**d**, prepared by blending equimolar amounts of the four fluorous acetals SS-**8a**, SR-**8b**, RS-**8c**, and RR-**8d**, was reduced with DIBAL to give M-**14a**–**d** in 99% yield (Scheme 3). This alcohol mixture was subsequently oxidized to aldehyde M-**4a**–**d** in 93% yield by using Dess–Martin periodinane (DMP). Portions of M-**4a**–**d** were subjected to Kocienski–Julia olefination[11] with sulfones R-**3**-BT and R-**3**-PT to give two mixtures M-**15a**–**d** in 81% and 93% yield, respectively.

Mixture M-**15a**–**d** from coupling with benzothiazolyl sulfone R-**3**-BT was demixed by using a FluoroFlash semiprep column under gradient elution (80:20 acetonitrile:water to 100% acetonitrile in 30 min) to give the four individual fluorous PMB ethers **15a**–**d**. However, these were difficult to characterize because it was not clear whether minor peaks in the their ^{13}C NMR spectra arose from *E*/*Z* isomers or epimers. Accordingly, each of the crude ethers **16** was directly hydrogenated to reduce the double bond and remove the fluorous PMB group. The resulting alcohols SSR-**17**, RSR-**17**, SRR-**17**, and RRR-**17** were analyzed by ^{1}H and ^{13}C NMR spectroscopy. In a similar way, mixture M-**15a**–**d** obtained from R-**3**-PT was also demixed. The alkenes SRR-**16a** and RRR-**16b**

(18) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

(19) (a) Kitahara, T.; Shimizu, H. *J. Nat. Prod.* **1998**, *61*, 551–554. (b) Eguchi, T.; Arakawa, K.; Terachi, T.; Kakinuma, K. *J. Org. Chem.* **1997**, *62*, 1924–1933.

(20) Bellingham, R.; Jarowicki, K.; Kocienski, P. J.; Martin, V. *Synthesis* **1996**, 285–296.

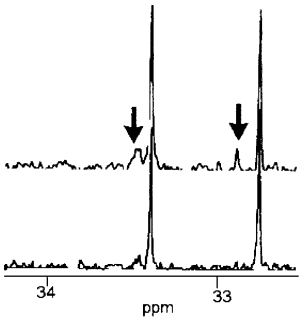


FIGURE 5. Expanded regions of ^{13}C NMR spectra of SRR-**17** pbtained from R-**3**-BT (top) and R-**3**-PT (bottom). Arrows show the additional peaks attributed to epimers formed in Julia olefinations with BT sulfone R-**3**-BT.

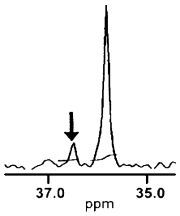


FIGURE 6. Expanded region of the ^{13}C NMR spectrum of SRR-**17** obtained from R-**3**-PT. Arrow shows the additional peak attributed to an epimer formed in Pd-mediated hydrogenation.

were isolated in pure form,[21] and each was hydrogenated to give alcohols SRR-**17** and RRR-**17**, respectively.

Analysis of the two sets of samples **17** by ^{13}C NMR spectroscopy showed that none of the samples was pure. However, the spectra from samples derived from the *N*-phenyltetrazolyl sulfones R-**3**-PT were clearly superior to those from the benzothiazolyl sulfone R-**3**-BT. Figure 5 compares expanded parts of the ^{13}C NMR spectra (32.5−33.5 ppm) of SRR-**17** obtained from R-**3**-BT (top) and R-**3**-PT (bottom). The top spectrum exhibits two pairs of major peaks and minor peaks, while the bottom spectrum exhibits only the major pair. The chemical shifts of these and several other minor peaks match those of the corresponding major peaks of alcohol SSR-**17**, so we conclude that the side product is a C3 epimer. This is present only in the spectra of **17** derived from the R-**3**-BT sulfone, so we conclude that partial epimerization during the Julia olefination occurred with this sulfone only and not with phenyltetrazolyl sulfone R-**3**-PT.

Importantly, the products **17** from the PT sulfones also had small additional peaks in their ^{13}C NMR spectra. For example, an expanded region of the ^{13}C NMR spectrum of SRR-**17** obtained from R-**3**-PT shows a minor peak at 36.7 ppm adjacent to a major peak at 35.7 ppm (Figure 6). All of the additional peaks present in the sample obtained from R-**3**-PT were also present in the corresponding samples obtained from R-**3**-BT, and the minor peaks in the spectrum did not appear to match the major peaks of any of the four isomers of **17** in hand. These results suggest that epimerization was also occurring during Pd-catalyzed hydrogenations, presumably at C7. It is known that metal-catalyzed hydrogenations of an alkene can epimerize stereocenters at the allylic carbon through reversible hydrometalation.[22] We decided to postpone investigating this problem until later in the synthesis when all stereocenters were present. Hence, our efforts turned toward a large-scale synthesis of triene **M2**.

These results show the power of using mixture synthesis methods to solve common problems in mixture synthesis. With only two Kocienski−Julia olefinations of the four-compound mixtures, we learned that all four aldehydes M-**4a**−**d** produced two sets of minor products when reacted with R-**3**-BT. The larger of the two minor products is readily attributed to the C3 epimer because the mixture is "self-indexed". In other words, all epimers at C2 and C3 are present, so the minor peaks from one spectrum can simply be aligned with the major peaks of another spectra for identification. The smaller set of minor peaks from R-**3**-BT was also in the spectra from R-**3**-PT; these peaks are not in the index (that is, they do not arise from epimers at C2 or C3), and their origin is not known. The experiments show that *N*-phenyltetrazolyl sulfone R-**3**-PT is clearly the superior reagent. Even though the problem of the presence of a minor product (<10%) still remains, that problem has been identified for later solution.

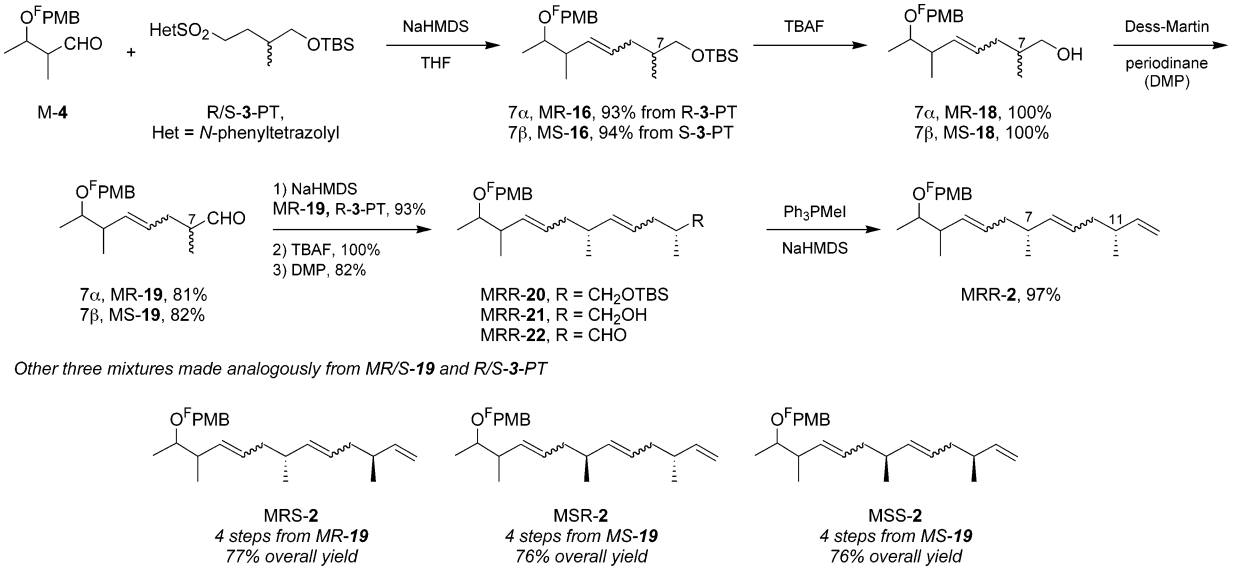
Split-Parallel Mixture Synthesis Stage. The split-parallel stage of the synthesis from aldehyde M-**4** through to four mixtures containing all 16 stereoisomers of triene **2** is summarized in Scheme 4. Aldehyde M-**4** (6.0 g) was split into two portions, and the first portion (3.1 g) was coupled with sulfone R-**3**-PT to give alkene MR-**16** in 93% yield. This was subjected to TBS deprotection to give alcohol MR-**18** (100% yield), which was oxidized by Dess−Martin periodinane to give aldehyde MR-**19** (87% yield, 2.6 g). In parallel, the second portion of aldehyde M-**4** (2.8 g) was subjected to Julia olefination with S-**3**-PT to give MS-**16** in 94% yield. TBS deprotection (100% yield) and oxidation (81% yield) gave aldehyde MS-**19** (2.6 g).

Each of the two aldehydes MR/S-**19** was split into two portions, and these were taken through the same sequence of olefination, deprotection, and oxidation; Scheme 4 shows exemplary reactions in the "MRR" series. Coupling of the appropriate mixture of **19** with sulfones S-**3**-PT or R-**3**-PT gave four alkenes MRR-**20** (1.4 g, 93% yield, shown in Scheme 4), MRS-**20** (1.6 g, 92% yield, not shown), MSR-**20** (1.1 g, 92% yield, not shown), and MSS-**20** (1.4 g, 92% yield, not shown). Alkene MRR-**20** was subjected to TBS deprotection (100% yield) to give alcohol MRR-**21**, which was oxidized in 82% yield to the aldehyde MRR-**22**. Aldehyde MRR-**22** was subjected to a Wittig reaction with methylene triphenylphosphorane to give triene MRR-**2** (612 mg) in 95% yield. Following the same protocol, the other three mixtures MRS-**20**, MSR-**20**, and MSS-**20** were transformed in parallel to the corresponding mixtures of trienes **2** shown at the bottom of Scheme 4 (MRS-**2**, 625 mg; MSR-**2**, 520 mg; MSS-**2**, 544 mg).

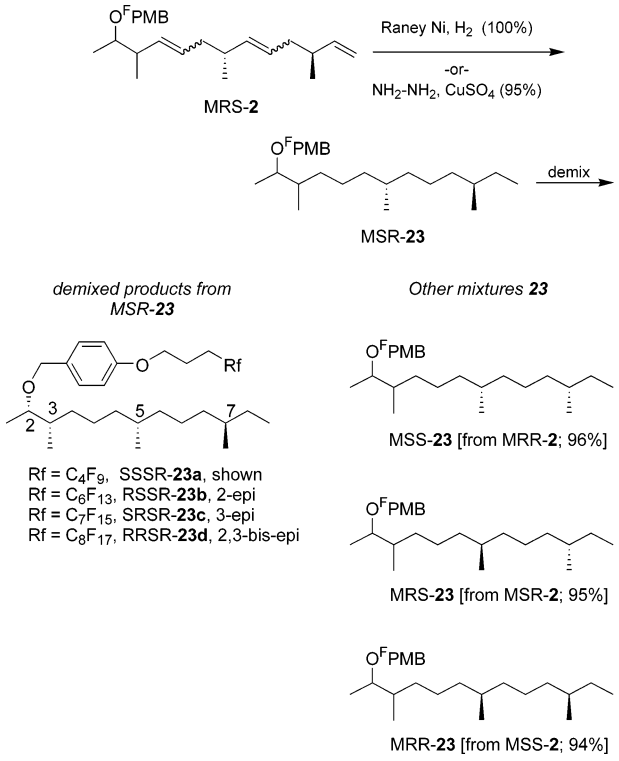
(21) The other two fractions (SSR-**17** and RSR-**17**) obtained during this demixing were contaminated with diol by partial deprotection of the TBS group. The source of this deprotection was not investigated.

(22) (a) Chan K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497−3505. (b) Schwartz, B. D.; Hayes, P. Y.; Kitching, W.; De Voss, J. J. *J. Org. Chem.* **2005**, *70*, 3054−3065.

SCHEME 4. Split-Parallel Fluorous Mixture Synthesis



SCHEME 5. Reduction of MRS-2 and Demixing of MSR-23



Triene Reduction and Demixing. The model study in Scheme 3 identified potential problems in the hydrogenation step, so this was initially investigated with a single mixture. Small amounts of triene MRS-**2** were reduced to the saturated analogue MSR-**23** with Raney Ni (100% yield) and diimide (95% yield) (Scheme 5, note the change in CIP priorities at C7 and C11 in going from **2** to **23**). Unlike the Pd/C reaction, hydrogenation by Raney Ni or diimide did not result in hydrogenolysis of the fluorous PMB group. The two mixtures MRS-**23** were individually demixed by using a FluoroFlash semiprep HPLC column (20 × 250 mm) under a gradient elution from 95:5 acetonitrile:water to 100% acetonitrile in 30 min followed by isocratic acetonitrile to 50 min to give individual compounds SSSR-**23a**, RSSR-**23b**, SRSR-**23c**, and RRSR-**23d**, all of which were analyzed by ^{1}H and ^{13}C NMR spectroscopy.

Samples of fluorous PMB ethers **23** obtained from Raney Ni-catalyzed reduction were found to have additional minor peaks in their ^{13}C NMR spectra, while the ^{13}C NMR spectra of the corresponding samples from diimide reduction showed only the expected number of resonances. Expanded segments of the ^{13}C NMR spectra (150 MHz) of RSSR-**23b** obtained from both of the reduction procedures are shown in Figure 7. The top spectrum is from the sample of RSSR-**23b** obtained from Raney Ni reduction, while the bottom spectrum corresponds to the same compound obtained from diimide reduction. Minor peaks can clearly be seen in the top spectrum (shown with downward arrows), while the bottom spectrum is clean. These results suggest that Raney Ni epimerizes the allylic stereocenters in competition with hydrogenation, while diimide does not.

Having established a reliable procedure for reduction of the triene, we preparatively reduced all four mixtures of M-**2** with diimide to the corresponding saturated analogues M-**23**, each of which was subjected to demixing. The results of all four demixings are summarized in Table 1. For example, mixture MSS-**23** (451 mg) was demixed by using a FluoroFlash semiprep HPLC column (20 × 250 mm) under a gradient elution from 95:5 acetonitrile:water to 100% acetonitrile in 30 min and

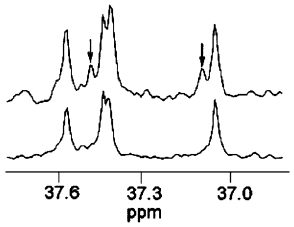


FIGURE 7. Segments of the ^{13}C NMR spectrum of RSSR-**23b** obtained from Raney Ni (top) and diimide (bottom) reductions. Arrows show the additional peaks attributed to epimers formed in Raney Ni-mediated hydrogenation.

TABLE 1. Summary of Four Semiprep Demixings of 23

entry	mixture (amount)	overall mass recovery	overall recovery of desired products	structure of product (amount)	fluorous tag
1	MSS-**23** (451 mg)	93%	91%	SSSS-**23a** (86 mg)	C_4F_9
				RSSS-**23b** (103 mg)	C_6F_{13}
				SRSS-**23c** (108 mg)	C_7F_{15}
				RRSS-**23d** (113 mg)	C_8F_{17}
2	MSR-**23** (471 mg)	94%	91%	SSSR-**23a** (92 mg)	C_4F_9
				RSSR-**23b** (106 mg)	C_6F_{13}
				SRSR-**23c** (111 mg)	C_7F_{15}
				RRSR-**23d** (119 mg)	C_8F_{17}
3	MRS-**23** (460 mg)	94%	89%	SSRS-**23a** (81 mg)	C_4F_9
				RSRS-**23b** (103 mg)	C_6F_{13}
				SRRS-**23c** (108 mg)	C_7F_{15}
				RRRS-**23d** (117 mg)	C_8F_{17}
4	MRR-**23** (476 mg)	98%	96%	SSRR-**23a** (96 mg)	C_4F_9
				RSRR-**23b** (113 mg)	C_6F_{13}
				SRRR-**23c** (120 mg)	C_7F_{15}
				RRRR-**23d** (128 mg)	C_8F_{17}

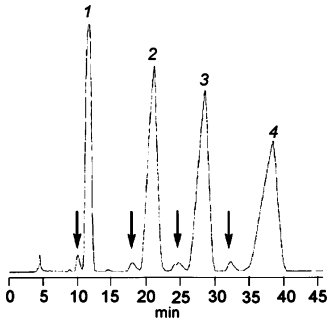


FIGURE 8. Chromatogram for the semiprep demixing of MSS-**23**. Peak 1 SSSS-**23a**, peak 2, RSSS-**23b**, peak 3, SRSS-**23c**, peak 4 RRSS-**23d**.

isocratic acetonitrile to 50 min to give four fluorous PMB ethers SSSS-**23a**, RSSS-**23b**, SRSS-**23c**, and RRSS-**23d** (Table 1, entry 1). Up to 86 mg of the mixture was demixed in a single injection.

A typical chromatogram of semiprep demixing of MSS-**23** is shown in Figure 8. In addition to the four major peaks labeled 1−4, the four minor peaks (highlighted by arrows) were also collected. The products from each of the major peaks were identified by spectroscopic methods to be the desired fluorous PMB ethers **23**. Proton NMR analysis of the fractions from the minor peaks revealed the presence of alkene protons. Hence, these side products are probably partially reduced alkenes carried over from MSS-**2**. The ability to separate under-reduced byproducts from the desired fully reduced products demonstrates that demixing is more than simple separation of tagged compounds. Ancillary separations observed during demixing enable purification of the each of the compounds.

The overall mass recovery during the demixing of MSS-**23** was 93%. The four saturated fluorous PMB ethers accounted for 97−98% of the recovered mass, while byproducts accounted for the remaining 2−3%. The mole ratio of the tagged compounds (C_4F_9:C_6F_{13}:C_7F_{15}:C_8F_{17}) isolated from demixing of MSS-**23** was 1:1:1:1. This is same as the composition of the four acetals in the first mixture M-**8**, indicating that all of the fluorous compounds showed similar reactivities in all of the steps involved in the FMS.

The other three mixtures **23** were similarly demixed, and the results are summarized in entries 2−4 of Table 1. The total recovery of the desired products from all three mixtures was 89−96%. Mixture MRS-**23** had the highest amount of byproducts (5%), while the other two mixtures had 2−3% byproducts. The molar composition of the tagged products isolated from all of the demixings was close to 1:1:1:1.

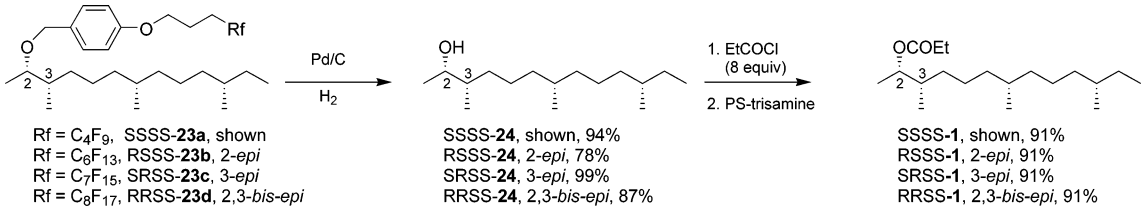
Post-Mix Stage. The four fluorous PMB ethers SSSS-**23a**, RSSS-**23b**, SRSS-**23c**, and RRSS-**23d** were detagged by hydrogenolysis to give the corresponding alcohols **24**, which were then acylated to give the corresponding propionates **1** (Scheme 6). The acylation reactions were carried out with excess propionyl chloride, and the excess was quenched with polymer-supported trisamine (PS-trisamine).[23] Filtration of the crude reaction mixture then provided pure **1**. The purity of the resulting propionates was excellent as assayed by ^{1}H and ^{13}C NMR spectroscopy. The rest of the 12 ^{F}PMB ethers **23** were also detagged and propionylated (not shown) to provide all 16 isomers of **1**. The corresponding alcohols **24** were synthesized in 24−36 mg scale, and roughly half of each alcohol was acylated to the corresponding esters **1** (16−23 mg each).

Spectral data (^{1}H and ^{13}C NMR) obtained for all 32 compounds (16 alcohols **24** and the corresponding 16 propionates **1**) matched well with Hedenstrom's published data.[5b] We were also able to identify unique sets of methyl group resonances in the ^{1}H NMR spectra (600 MHz) of the eight diastereomeric alcohols of **24** (shown elsewhere[9]) and the corresponding propionates **1**. These resonances are shown in expanded NMR spectra of **1** in Figure 9, which originate from the family of enantiomers having *R* configuration at C2 carbon.

The patterns of lines in the spectra of Figure 9 emanate from four of the five methyl groups: the three methyl groups attached to C3, C7, C11 and the C13 methyl group (the doublet of the C1 methyl group is further downfield). A total of nine lines are expected from these four methyl groups (three doublets and one triplet). The partial overlap of these resonances from the four methyl groups generates unique patterns in the region between 0.92 and 0.82 ppm in the 600 MHz ^{1}H NMR spectrum of each of the diastereomers. The resonance of the methyl group at C3 carbon atom of the esters **1** is easily recognizable as the most downfield doublet in all nine spectra. This

(23) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882−4886. PS-trisamine was purchased from Argonaut Technologies (www.argotech.com).

SCHEME 6. Detagging and Acylation in the (7*S*,11*S*) Series



group resonates at about 0.90 ppm in the four C2,C3 syn isomers, and 0.88 ppm in the four C2,C3 anti isomers. In the propionate ester series, the spectra for the four anti isomers are well resolved and clearly different; all nine lines can be identified in each spectrum. The patterns of the syn isomers are much more similar, and typically only seven lines can be identified because the doublets for the methyl groups on C7 and C11 overlap. The resonances of the syn isomers are better resolved in the alcohol **24**, while the resonances of the anti isomers are better resolved in the ester **1**. This allows each of the eight isomers to be readily identified.

Analytical Tools for FMS. Effective use of spectroscopic and chromatographic methods, both modern and traditional, is crucial for troubleshooting problematic reactions and products in any total synthesis, and fluorous mixture synthesis is no exception. How can one follow reactions, assess purities, and characterize products when molecular mixtures are involved? This section highlights the various techniques used in this project that are also broadly applicable for other FMS projects as well. These techniques can be classified as nonfluorous (mixture NMR and normal phase TLC) or fluorous (LC−MS, LC NMR, and GC).

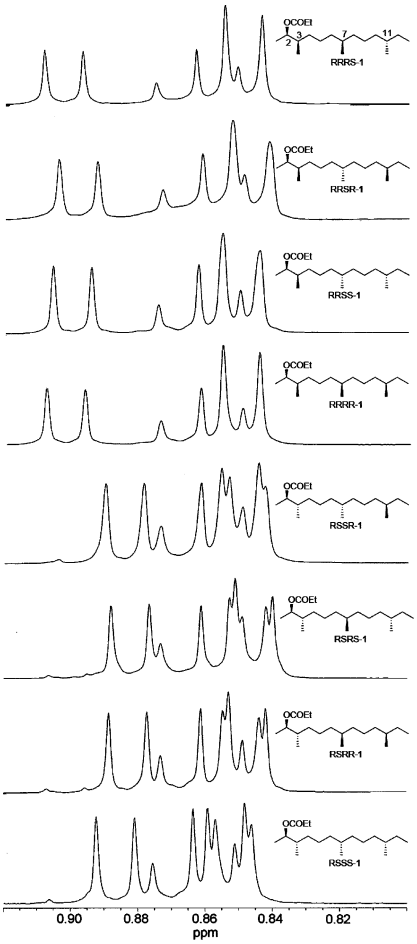


FIGURE 9. Fingerprint resonances in the ^{1}H NMR spectra of pine sawfly sex pheromones **1**.

Nonfluorous Techniques. Just as in standard solution-phase transformations of single compounds, the relative retention factors (R_f) of the starting and product mixtures on thin-layer chromatography (TLC) can be a valuable guide for evaluating the progress of a reaction. Although every mixture in this work consisted of four compounds (two quasidiastereomeric pairs of quasi-enantiomers, neglecting the geometric isomers around double bonds), each mixture behaved like a single compound during normal phase TLC analysis. "Spot-to-spot" conversions were observed in clean reactions, and the components of mixtures containing the same functionalities but different configurations and fluorous tags never separated either on TLC analysis or on flash chromatography on normal silica gel. Thus, reactions were routinely followed by TLC, and crude product mixtures were typically chromatographed to provide pure product mixtures. However, this ideal behavior of fluorous mixtures is not always observed when structurally diverse starting materials are tagged with different fluorous protecting groups.[1e]

The conversion of a starting fluorous mixture to a product mixture was also followed by comparing the ^{1}H NMR spectra of the starting and the product samples. Although a complete analysis of the NMR spectra of these mixture spectra is complicated by the presence of quasi-diastereomers having different chemical shifts (and also by the presence of alkene isomers in some mixtures), the partial analysis of key resonances of functional groups involved in the transformation was frequently informative. For example, the conversion of an aldehyde mixture to an alkene mixture in the Julia olefinations was readily assessed by mixture NMR by looking for the appearance/disappearance of characteristic resonances.

Fluorous Techniques. The single most useful tool for following reactions in FMS is LC−MS. All of the mixtures involved in this project were characterized by LC−MS over a Fluofix column with APCI ionization. In all of the cases, tag-based separation (demixing) was observed. When mixtures were impure, secondary separations of products with different functionalities were often observed. For example, the product of an incomplete reaction might exhibit eight peaks in four pairs each for starting material and product. The identity of the eluting compounds could be readily ascertained by the presence of molecular ion in the associated mass spectrum. In a given pure mixture, the tagged products are all quasi-isomers and every CF_2 group has MW = 50 amu, making

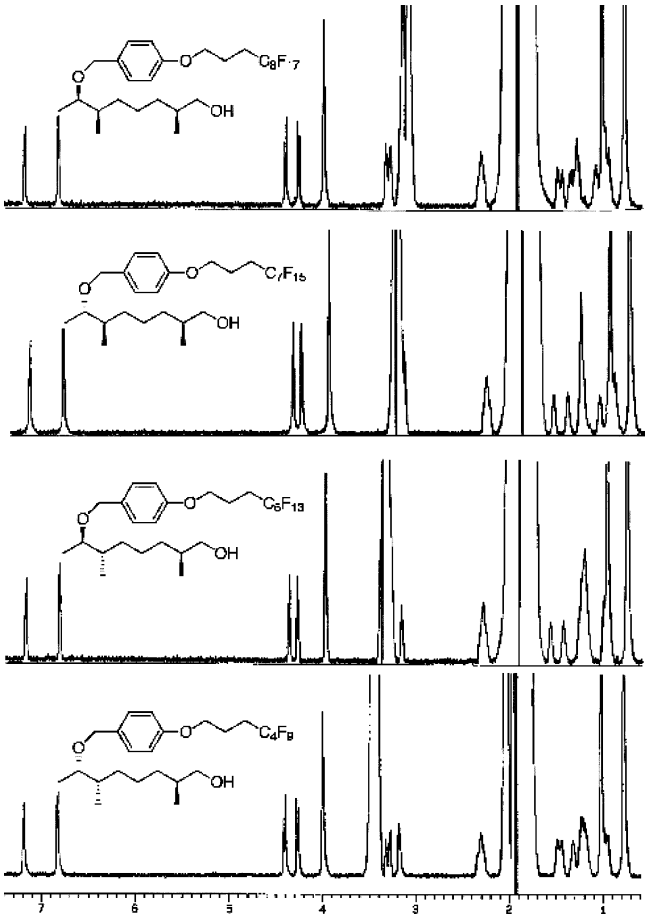


FIGURE 10. ^{1}H NMR spectra from LC NMR analysis of an intermediate derived from diimide reduction of MS-**18**.

interpretation especially easy; each mass spectrum is essentially identical to its predecessor, but the peaks are shifted to either 50 or 100 atomic mass units higher depending on whether the tag size increases by one or two CF_2 groups.

LC NMR spectroscopy was also used to characterize seven of the intermediate mixtures. Alcohol M-**14** (Scheme 3) was analyzed directly, while small quantities of the subsequent alkenes were reduced first by diimide to the corresponding saturated analogues prior to LC NMR analysis to eliminate complications emanating from the presence of alkene isomers. A representative set of 600 MHz LC NMR spectra derived from the diimide reduction of MS-**18** is shown in Figure 10. Copies of other LC NMR spectra are given in the Supporting Information.

A typical LC NMR experiment of a four-compound mixture needed about 0.8 mg per injection. A gradient of CH_3CN/H_2O was used for the separation, and the peaks were collected and transferred directly to the probe for data acquisition with a standard routine including solvent suppression. Experiments took about 4 h for LC separation and NMR data collection, and the quality of the spectra was adequate for standard analyses of chemical shift, multiplicity, and integration. The later-emerging compounds required more acquisition time because peaks broaden and the sample injected into the NMR probe is more dilute, but satisfactory spectra were obtained for all four components of all seven mixtures.

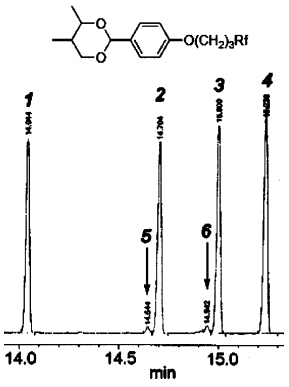


FIGURE 11. GC chromatogram showing separation of a mixture of fluorous acetals M-**8**. Peak 1 SS-**8a**, peak 2 RS-**8b**, peak 3 SR-**8c**, peak 4 RR-**8d**, peak 5 RR-**8b**, peak 6 SS-**8c**.

Although these NMR spectra were adequate for our purposes, even the best NMR spectrum obtained from LC NMR experiments was poorly resolved as compared to a standard spectrum of the same quantity of sample dissolved in $CDCl_3$. Over the same 4 h period of an LC NMR experiment, it is possible to semipreparatively demix a 0.8 mg sample, evaporate and dry the fractions, dissolve in $CDCl_3$, and collect data for all four spectra. While there is more sample handling in this procedure, that extra effort is more than compensated for by the better quality of the spectra that are obtained. These spectra exhibit both better resolution and better sensitivity because the entire sample from the demixing fraction is in the probe in every case and because no solvent suppression is needed.

Despite the added mass of the fluorous tags, gas chromatography (GC) with a flame ionization detector (FID) was also routinely used for the analysis of fluorous mixtures. Most components of the quasi-isomeric fluorous mixtures eluted in order of increasing tag size. In effect, GC provides an alternative to fluorous LC for analytical demixing, and it is now the regular increase in molecular weight that provides the basis for the demixing.

The GC analysis of the starting mixture M-**8** shown in Figure 11 is representative of conditions and results. Injection of M-**8** into a [HP-1 methyl siloxane (length 30 m, diameter 320 μm, film thickness 0.25 μm)] GC column [50 °C (2 min); 15 °C/min, 300 °C] provided four major peaks (labeled 1−4) and two minor peaks (5 at 14.6 and 6 at 14.9 min, highlighted with downward arrows in Figure 11). The major peaks in order are SS-**8a** (syn), RS-**8b** (anti), SR-**8c** (anti), and RR-**8d** (syn). The minor peaks were assigned as syn isomers RR-**8b** and SS-**8c**, and in this case the assignment was confirmed by preparation of authentic samples. Generally speaking, this is not necessary because the library is "self-indexed"; in other words, RR-**8b** can be identified by comparison to its higher homologue RR-**8d** and its lower quasi-enantiomer SS-**8a**.

From these GC chromatograms, the diastereomeric purities of anti acetals RS-**8b** and SR-**8c** were determined to be 25:1 and 29:1, respectively. The syn acetals SS-**8a** and RR-**8a** show a single peak in GC, so they are not contaminated with corresponding anti acetals. Because the starting compounds **5** for the Mitsunobu reaction to

make these compounds (Scheme 1) were not diastereopure, the minor anti diastereomer must have been removed during the chromatographic purification of syn diesters SR-**9** and RS-**9**.

Conclusions

All 16 stereoisomers of the sex pheromone of the pinesaw fly have been synthesized by split-parallel fluorous mixture synthesis. Spectral data (^{1}H and ^{13}C NMR) obtained for all 32 compounds (16 alcohols **24** and the corresponding propionates **1**) matched well with Hedenstrom's data.[5b] The 4-mix/4-split approach successfully encoded the configurations of all of the library members, and hence FMS is recommended for expedient synthesis of stereoisomers of the natural products.

It is a common practice to synthesize several stereoisomers of chiral compounds for structural identification or for biological testing. When high purity and reliability are required, solution-phase synthesis is the method of choice. Traditionally, each stereoisomer is synthesized in sequence or in parallel, but such efforts are time-consuming. For example, consider the traditional parallel synthesis of 16 stereoisomeric alcohols **24** by the same synthetic scheme outlined above. Each of the alcohols requires 11 steps to make from one of the four acetals **8**. Hence, a traditional approach would require 176 reaction steps to synthesize all 16 stereoisomers. However, the split-parallel fluorous mixture approach with four fluorous tags in this work needed only 44 steps to make all 16 isomers.

Unlike previous "proof-of-principle" fluorous mixture syntheses,[1] the steps involved in the mixture syntheses of this project were never rehearsed on a single compound. Problems were identified and solved directly on fluorous mixtures. This represents an important technical advance because rehearsals on single compounds are time-consuming and in effect require two syntheses to be conducted in serial or parallel, one on the single compound and one on the mixture. In this work, modern tools such as LC−MS and LC NMR were used to characterize mixtures of compounds. Even the time-honored analytical tools of TLC and GC were found to be routinely useful for analyzing fluorous mixtures. A total of 132 steps were saved in FMS as compared to a traditional one-compound/one-flask approach. The efficiency and ease of fluorous mixture synthesis can be used to leverage effort in both diversity-oriented synthesis and total synthesis by providing more compounds per unit work.

Experimental Section

Pre-Mix Stage. General Procedure 1. Reduction of *β*-Hydroxy Ester to Diol. (2*R*,3*S*)-2-Methylbutane-1,3-diol (RS-6). A solution of lithium aluminum hydride in ether (1 M, 23 mL, 23 mmol) was slowly added to a solution of ethyl (2*R*,3*R*)-3-hydroxy-2-methylbutanoate RR-**5** at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 3 h and quenched with ethyl acetate (10 mL) and methanol (1 mL). Water (8.4 mL), 30% NaOH (8.4 mL), and water (17 mL) were added and stirred for 30 min. The solution was then decanted from the white crystalline precipitate and separated using a separatory funnel. The aqueous layer was added to the white crystalline precipitate and extracted with ethyl acetate (2 × 100 mL) and dichloromethane (2 × 100 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (1:1 hexane:ethyl acetate) gave (2*R*,3*S*)-2-methylbutane-1,3-diol RS-**6** as a colorless viscous oil (1.77 g, 82%). $[\alpha]_D$ +3.2 (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 3.78−3.69 (m, 2H), 3.61 (dd, *J* = 8.0, 10.7 Hz, 1H), 1.74−1.60 (m, 1H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) *δ* 72.9, 67.4, 41.6, 21.5, 13.4; IR (thin film) 3307 (b), 2970, 1455, 1028 cm^{-1}; LRMS 89 ((M − Me)$^+$, 17%), 71 (100%), 56 (91%); HRMS calculated (for $C_5H_{10}O$ (M − H_2O)) 86.0732, found 86.0727.

(2*S*,3*R*)-2-Methylbutane-1,3-diol (SR-6). Synthesized by General Procedure 1. Yield 84%; $[\alpha]_D$ −2.2 (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 3.79−3.71 (m, 2H), 3.64 (dd, *J* = 7.8, 10.8 Hz, 1H), 1.75−1.62 (m, 1H), 1.25 (d, *J* = 6.2 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) *δ* 73.3, 67.8, 41.7, 21.7, 13.5; IR (thin film) 3356 (b), 2971, 1455, 1028 cm^{-1}; LRMS 89 ((M − Me)$^+$, 9%), 73 (100%), 61 (80%); HRMS calculated (for $C_5H_{13}O_2$ (M^+ + H)) 105.0913, found 105.0916.

General Procedure 2. Mitsunobu Reaction of *β*-Hydroxy Ester. 4-Nitrobenzoic Acid (1*S*,2*R*)-2-Ethoxycarbonyl-1-methylpropyl Ester (SR-9). A solution of diisopropyl azodicarboxylate (11.1 mL, 56.3 mmol) in THF (50 mL) was added dropwise from an addition funnel to a solution of ethyl (2*R*,3*R*)-3-hydroxy-2-methylbutanoate (RR-**5**) (6 g, 41.7 mmol), triphenylphosphine (14.2 g, 54.2 mmol), and 4-nitrobenzoic acid (9.4 g, 56.3 mmol) in THF (100 mL). After being stirred at room temperature for 12 h, the reaction mixture was concentrated. Flash column chromatography on silica gel (hexane:ethyl acetate 6:1) gave 4-nitrobenzoic acid (1*S*,2*R*)-2-ethoxycarbonyl-1-methylpropyl ester SR-**9** as a yellow oil (8.55 g, 70%). $[\alpha]_D$ +17.7 (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 8.31−8.27 (m, 2H), 8.21−8.17 (m, 2H), 5.47 (dq, *J* = 5.5, 6.4 Hz, 1H), 4.22−4.08 (m, 2H), 2.80 (dq, *J* = 5.6, 7.1 Hz, 1H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) *δ* 173.3, 163.9, 150.5, 135.7, 130.7, 123.5, 72.9, 60.8, 44.4, 17.5, 14.2, 12.2; IR (thin film) 2254, 1727, 1277 cm^{-1}; LRMS 295 (M^+, 12%), 279 (11%), 150 (100%), 104 (36%), 83 (52%), 75 (100%); HRMS calculated 295.1063, found 295.1056.

4-Nitrobenzoic Acid (1*R*,2*S*)-2-Ethoxycarbonyl-1-methylpropyl Ester (RS-9). Synthesized by General Procedure 2. Yield 79%; yellow liquid; $[\alpha]_D$ −19.4 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 8.32−8.28 (m, 2H), 8.21−8.17 (m, 2H), 5.47 (dq, *J* = 5.6, 6.4 Hz, 1H), 4.23−4.08 (m, 2H), 2.80 (dq, *J* = 5.6, 7.1 Hz, 1H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) *δ* 173.1, 163.8, 150.6, 135.8, 130.6, 123.4, 72.8, 60.6, 44.4, 17.4, 14.1, 12.1; IR (thin film) 2254, 1731, 1275 cm^{-1}; LRMS 295 (M^+, 12%), 251 (17%), 150 (100%); HRMS calculated 295.1056, found 295.1059.

(2*R*,3*R*)-2-Methylbutane-1,3-diol (RR-6). A solution of DIBAL in hexanes (1 M, 125 mL, 125 mmol) was slowly added to a solution of 4-nitrobenzoic acid (1*R*,2*S*)-2-ethoxycarbonyl-1-methylpropyl ester (RS-**9**) in dicholoromethane (120 mL) at −65 °C. The reaction mixture was warmed to −25 °C and stirred at that temperature for 5 h. After warming to room temperature, the reaction mixture was quenched by the addition of ethyl acetate (5 mL), water (10 mL), and 3 M NaOH solution (15 mL). The reaction mixture was extracted with refluxing ethyl acetate (5 × 200 mL), and the layers were separated. The organic layers were combined, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (3:1 hexane:ethyl acetate) gave (2*R*,3*R*)-2-methylbutane-1,3-diol (RR-**6**) as a viscous oil (2.86 g, 88%). $[\alpha]_D$ −10.2 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 4.06 (dq, *J* = 2.9, 7.0 Hz, 1H), 3.77−3.68 (m, 2H), 1.89−1.77 (m, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) *δ* 69.7, 65.7, 40.1, 19.2, 10.6; IR (thin film) 3354 (b), 2971, 1459, 1027 cm^{-1}; LRMS 89 ((M − Me)$^+$, 6%), 73 (100%), 61 (96%); HRMS calculated for (M − Me)$^+$ 89.0603, found 89.0604.

(2*S*,3*S*)-2-Methylbutane-1,3-diol (SS-6). A solution of lithium borohydride in THF (2 M, 35.7 mL, 71.5 mmol) was slowly added to a solution of 4-nitro-benzoic acid (1*S*,2*R*)-2-ethoxycarbonyl-1-methylpropyl ester (SR-**9**) (5.24 g, 17.87 mmol) in THF (60 mL) and stirred at room temperature for 1 d. The reaction was then quenched by slow addition of saturated NH_4Cl solution (20 mL) and stirred at room temperature for 1 h. The crude reaction mixture was then extracted with refluxing ethyl acetate (5 × 100 mL). The organic layers were then combined, dried, and concentrated. Most of the *p*-nitrobenzyl alcohol was removed by recrystallization from aqueous ethanol, and the remainder of the crude product was subjected to column chromatography. After flash column chromatography on silica gel (1:1 hexane:ethyl acetate), (2*S*,3*S*)-2-methylbutane-1,3-diol (SS-**6**) was isolated as a colorless viscous oil (1.42 g, 77%); $[\alpha]_D$ +11.4 (*c* 0.51, $CHCl_3$); ^{1}H NMR δ 4.05 (dq, J = 3.1, 6.5 Hz, 1H), 3.77−3.67 (m, 2H), 1.89−1.77 (m, 1H), 1.21 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 69.7, 65.7, 40.1, 19.2, 10.6; IR (thin film) 3362 (b), 2971, 1459, 1027 cm^{-1}; LRMS 89 ((M − Me)$^+$, 17%), 71 (100%), 59 (92%); HRMS calculated (M − Me)$^+$ 89.0603, found 89.0605.

General Procedure 3. Noyori Ketalization. (4*R*,5*S*)-(4,5-Dimethyl-2-[4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)phenyl]-[1,3]dioxane (RS-8b). (2*R*,3*S*)-2-Methylbutane-1,3-diol RS-**6** (1.1 g, 10.6 mmol) was dissolved in THF (100 mL) and cooled to 0 °C using an ice-bath. Triethylamine (11.8 mL, 84.6 mmol) was added. Chlorotrimethylsilane (10.7 mL, 84.6 mmol) was slowly added, and the reaction mixture was warmed to room temperature. After 16 h at room temperature, the reaction was quenched with saturated sodium bicarbonate solution (50 mL) and the layers were separated. The aqueous layer was extracted with ether (2 × 50 mL). The organic layers were combined, washed with brine, and concentrated. A fast flash column chromatography on silica gel (hexane:ethyl acetate:triethylamine = 20:1:0.1) gave (2*R*,3*S*)-2-methyl-1,3-bis(trimethylsilanyloxy)butane (2.20 g, 84%), which was used in the next step without characterization.

Trimethylsilyltriflate (60 μL, 0.33 mmol) was added to dichloromethane (75 mL) and cooled to −78 °C. A solution of (2*R*,3*S*)-2-methyl-1,3-bis(trimethylsilanyloxy)butane (1.98 g, 7.97 mmol) in dichloromethane (15 mL) was added. A solution of 4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzaldehyde **7b** (3.2 g, 6.64 mmol) in dichloromethane (30 mL) was then slowly added. After beingstirred at −78 °C for 12 h, the reaction was quenched by adding pyridine (0.3 mL) and warmed to room temperature. Ethyl acetate (100 mL) and saturated sodium bicarbonate (100 mL) were added and stirred for 10 min. The phases were separated, and the aqueous layer was extracted with ether (3 × 25 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (20:1 hexane:ethyl acetate) gave (4*R*,5*S*)-(4,5-dimethyl-2-[4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)phenyl]-[1,3]dioxane (RS-**8b**) as a white solid (3.06 g, 81%). mp 84−85 °C; $[\alpha]_D$ +2.1 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46−7.38 (m, 2H), 6.93−6.88 (m, 2H), 5.46 (s, 1H), 4.1 (dd, J = 4.7, 11.4 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.59−3.45 (m, 2H), 2.40−2.19 (m, 2H), 2.14−2.05 (m, 2H), 1.86−1.71 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.8, 131.7, 127.5, 121.5−106.0 (m), 114.2, 101.1, 79.5, 73.0, 66.3, 35.8, 27.9 (t, J = 22.1 Hz), 20.5, 19.1, 12.4; ^{19}F NMR ($CDCl_3$) −81.3 (3F), −114.9 (2F), −122.4 (2F), −123.4 (2F), −124.0 (2F), −126.7 (2F); IR (thin film) 2985, 1265, 1241 cm^{-1}; LRMS 567 ((M − H)$^+$, 12%), 482 (22%), 121 (100%); HRMS calculated 568.1283, found 568.1262.

(4*S*,5*S*)-(4,5-Dimethyl-2-[4-(4,4,5,5,6,6,7,7,7-nonafluorononyloxy)phenyl]-[1,3]dioxane (SS-8a). This compound was synthesized by general procedure 3. Yield 86% (two steps); white solid mp 77 °C; $[\alpha]_D$ +5.1 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46−7.41 (m, 2H), 6.90−6.86 (m, 2H), 5.50 (s, 1H), 4.14−4.00 (m, 5H), 2.43−2.19 (m, 2H), 2.17−2.05 (m, 2H), 1.53−1.45 (m, 1H), 1.23 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.9, 131.9, 127.4, 121−114 (m), 114.2, 101.8, 75.6, 73.8, 66.3, 32.9, 27.7 (t, J = 22.2 Hz), 20.5 (t, J = 3.5 Hz), 18.8, 10.9; ^{19}F NMR ($CDCl_3$) −81.5 (3F), −115.0 (2F), −124.9 (2F), −126.5 (2F); IR (thin film) 2981, 1265, 1238 cm^{-1}; LRMS 467 ((M − H)$^+$, 18%), 382 (45%), 121 (100%); HRMS calculated 467.1269, found 467.1264.

(4*S*,5*R*)-4,5-Dimethyl-2-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-pentadecafluorodecyloxy)-phenyl]-[1,3]dioxane (SR-8c). This compound was synthesized by general procedure 3. Yield 82% (two steps); white solid mp 89−90 °C; $[\alpha]_D$ −1 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46−7.38 (m, 2H), 6.91−6.86 (m, 2H), 5.46 (s, 1H), 4.09 (dd, J = 6.6, 11.2 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.59−3.45 (m, 2H), 2.40−2.18 (m, 2H), 2.13−2.05 (m, 2H), 1.80−1.77 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.8, 131.7, 127.5, 121−115 (m), 114.2, 101.1, 79.5, 73.0, 66.3, 35.8, 27.9 (t, J = 22.1 Hz), 20.5, 19.1, 12.5; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.9 (2F), −122.2 (2F), −122.6 (2F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2985, 1265, 1242 cm^{-1}; LRMS 617 ((M − H)$^+$, 24%), 532 (28%), 121 (100%); HRMS calculated 617.1173, found 617.1174.

(4*R*,5*R*)-2-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)-phenyl]-4,5-dimethyl-[1,3]dioxane (RR-8d). Yield 86% (two steps); mp 106−107 °C; $[\alpha]_D$ −3.2 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46−7.39 (m, 2H), 6.91−6.86 (m, 2H), 5.47 (s, 1H), 4.11 (dd, J = 2.4, 6.5 Hz, 1H), 4.08−3.99 (m, 4H), 2.80−2.45 (m, 2H), 2.31−2.10 (m, 2H), 1.53−1.49 (m, 1H), 1.23 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.9, 131.9, 127.5, 121.5−106.0 (m), 114.2, 101.8, 75.6, 73.8, 66.3, 32.9, 27.9 (t, J = 22.1 Hz), 20.4 (t. J = 3.4 Hz), 18.7, 10.8; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.8 (2F), −122.1 (2F), −122.4 (6F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2985, 1265, 1243 cm^{-1}; LRMS 667 ((M − H)$^+$, 25%), 582 (45%), 121 (100%); HRMS calculated 667.1141, found 667.1111.

Syntheses of Intermediates 10−13 and General Procedure 4, Determination of ee of Alcohol 13, Are Described in the Supporting Information. (3*R*)-2-[4-(*tert*-Butyldimethylsilanyloxy)-3-methylbutane-1-sulfonyl]-benzothiazole (R-3-BT). Diethylazodicarboxylate (0.16 mL, 1.0 mmol) was added to a solution of (3*R*)-4-(*tert*-butyldimethylsilanyloxy)-3-methylbutan-1-ol (R-**13**) (145 mg, 0.67 mmol), triphenylphosphine (262 mg, 1 mmol), and benzothiazole-2-thiol (167 mg, 1.0 mmol) in THF (10 mL) at 0 °C. After being stirred at room temperature for 2 d, the reaction mixture was quenched by the addition of saturated sodium bicarbonate solution (30 mL). The reaction mixture was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. After flash column chromatography on silica gel (20:1 hexane:ethyl acetate), (3*R*)-2-[4-(*tert*-butyldimethylsilanyloxy)-3-methyl-butylsulfanyl]benzothiazole was isolated as a colorless liquid (213 mg, 88%). ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.42 (dd, J = 7.4, 7.4 Hz, 1H), 7.30 (dd, J = 7.7, 7.7 Hz, 1H), 3.53−3.32 (m, 4H), 2.02−1.93 (m, 1H), 1.89−1.76 (m, 1H), 1.69−1.57 (m, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

m-Chloroperbenzoicacid (284 mg, 1.64 mmol) was added to a solution of (3*R*)-2-[4-(*tert*-butyldimethylsilanyloxy)-3-methylbutylsulfanyl]benzo-thiazole (213 mg, 0.66 mmol) in dichloromethane (20 mL) at 0 °C. After being stirred at room temperature for 36 h, the reaction mixture was quenched with saturated sodium bicarbonate solution (20 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (5:1 hexane:ethyl acetate) gave (3*R*)-2-[4-(*tert*-butyldimethylsilanyloxy)-3-methylbutane-1-sulfonyl]benzo-thiazole (R-**3**-BT)

as a white solid (206 mg, 89%). mp 39−40 °C; $[\alpha]_D$ +4.6 (*c* 0.26, $CHCl_3$); ^1H NMR ($CDCl_3$) 8.24−8.16 (m, 1H), 8.04−8.00 (m, 1H), 7.65−7.55 (m, 2H), 3.61−3.54 (m, 2H), 3.48 (dd, J = 4.0, 8.3 Hz, 1H), 3.35 (dd, J = 6.3, 10.0 Hz, 1H), 2.05−1.89 (m, 1H), 1.82−1.68 (m, 2H), 0.88 (d, J = 6.5 Hz, 3H), 0.80 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.7, 152.7, 136.8, 127.9, 127.6, 125.5, 122.3, 67.4, 53.1, 34.7, 26.1, 25.7, 18.1, 16.3, −5.5, −5.6; IR (thin film) 2955, 2856, 1329, 1148, 1089 cm^{-1}; LRMS 384 $(M - Me)^+$ (10%), 342 (100%), 256 (46%); HRMS calculated 384.11123, found 384.1114.

General Procedure 5. Synthesis of PT-Sulfones. (3*R*)-5-[4-(*tert*-Butyldimethylsilanyloxy)-3-methylbutane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (R-3-PT). Diisopropylazodicarboxylate (3.8 mL) was added via a syringe to a solution of (3*R*)-4-(*tert*-butyldimethylsilanyloxy)-3-methylbutan-1-ol (R-**13**) (3.47 g, 15.9 mmol), triphenylphosphine **8** (5.0 g, 19.1 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (3.4 g, 19.1 mmol) in THF (120 mL). After being stirred at room temperature for 3 h, the reaction mixture was diluted with ethanol (120 mL) and cooled to 0 °C. $(NH_4)_6Mo_7O_2 \cdot 4H_2O$ (2.97 g, 2.4 mmol) and 30% hydrogen peroxide (24.2 mL, 237 mmol) were added, and the reaction mixture was warmed to room temperature. After the mixture was stirred at room temperature for 14 h, water (200 mL) was added and the reaction mixture was extracted with dichloromethane (5 × 70 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. After flash column chromatography on silica gel (5:1 hexane:ethyl acetate), (3*R*)-5-[4-(*tert*-butyldimethylsilanyloxy)-3-methylbutane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (R-**3**-PT) was isolated as a colorless oil (5.28 g, 81%). $[\alpha]_D$ +8.7 (*c* 0.61, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.71−7.51 (m, 5H), 3.86−3.81 (m, 2H), 3.56 (dd, J = 4.6, 10.0 Hz, 1H), 3.43 (dd, J = 6.4, 10.0 Hz, 1H), 2.12−2.04 (m, 1H), 1.91−1.76 (m, 2H), 0.95 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) 153.4, 133.0, 131.4, 129.6, 125.0, 67.5, 54.4, 34.6, 25.8, 18.2, 16.3, −5.5; IR (thin film) 2956, 2857, 1343, 1153, 1095 cm^{-1}; LRMS 353 $(M - {}^tBu)^+$ (18%), 175 (95%), 117 (100%); HRMS calculated 353.1104, found 353.1120.

(3*S*)-5-[4-(*tert*-Butyldimethylsilanyloxy)-3-methylbutane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (S-3-PT). This compound was synthesized by general procedure 5. Yield 3.76 g, 84%; $[\alpha]_D$ −8.5 (*c* 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.71−7.51 (m, 5H), 3.87−3.81 (m, 2H), 3.56 (dd, J = 4.7, 10.1 Hz, 1H), 3.43 (dd, J = 6.4, 10 Hz, 1H), 2.12−2.01 (m, 1H), 1.91−1.76 (m, 2H), 0.95 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) 153.4, 133.0, 131.4, 129.7, 125.1, 67.5, 54.5, 34.6, 25.8, 18.2, 16.3, −5.4; IR (thin film) 2956, 2857, 1343, 1153, 1095 cm^{-1}; LRMS 353 $(M - {}^tBu)^+$ (20%), 175 (95%), 117 (100%); HRMS calculated 353.1104, found 353.1114.

Fluorous Mixture Synthesis Stage. Some of the steps involved in the FMS were carried out on smaller and larger scales. In those cases, yields from both of the runs are reported.

Mixing (M-8a−d). Mixture M-**8a**−**d** was generated by mixing acetals SS-**8a** (1.30 g, 2.79 mmol), RS-**8b** (1.58 g, 2.79 mmol), SR-**8c** (1.72 g, 2.79 mmol), and RR-**8d** (1.86 g, 2.79 mmol).

3-(Fluorous-4-methoxybenzyloxy)-2-methylbutan-1-ol (M-14a−d). A solution of DIBAL in hexanes (1 M, 33.4 mL, 33.4 mmol) was slowly added to a solution of M-**8a**−**d** (6.47 g, 11.14 mmol, calculated on the basis of average molecular weight of the mixtures) in dichloromethane (340 mL) at 0 °C. After being stirred at 0 °C for 3 h, the reaction mixture was quenched by the addition of saturated ammonium chloride solution (50 mL) and saturated sodium potassium tartarate solution (300 mL), and the resulting suspension was vigorously stirred for 1 h. The crude reaction mixture was extracted with ether (4 × 100 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (3:1 hexane:ethyl acetate) gave alcohol M-**14a**−**d** (6.45 g. 99%). LC−MS (APCI) for M-**14a**−**d**: **14a** *m/z* 469 $(M - 1)^+$, **14b** *m/z* 569 $(M - 1)^+$, **14c** *m/z* 619 $(M - 1)^+$, **14d** *m/z* 669 $(M - 1)^+$.

General Procedure 6. Dess−Martin Oxidation. 3-(Fluorous-4-methoxybenzyloxy)-2-methylbutyraldehyde (M-4a−d). Dess−Martin periodinane (5.6 g, 13.2 mmol) was added to a solution of M-**14a**−**d** (6.42 g, 11.0 mmol) in dichloromethane (300 mL). After being stirred at room temperature for 3 h, the reaction mixture was quenched by the addition of saturated sodium bicarbonate solution (200 mL) and sodium thiosulfate solution (200 mL) and stirred for 30 min. The phases were separated, and the aqueous layer was extracted with ether (3 × 100 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (7:3 hexane:ethyl acetate) gave aldehyde M-**4a**−**d** (5.98 g, 94%). LC−MS (APCI) for M-**4a**−**d**: **4a** *m/z* 467 $(M - 1)^+$, **4b** *m/z* 567 $(M - 1)^+$, **4c** *m/z* 617 $(M - 1)^+$, **4d** *m/z* 667 $(M - 1)^+$.

General Procedure 7. Julia Olefination. *tert*-Butyl-[7-(fluorous-4-methoxybenzyloxy)-2,6-dimethyloct-4-enyloxy]-dimethyl-silane MS-16. A solution of sodiumhexamethyldisilazide in THF (1 M, 6.1 mL, 6.1 mmol) was slowly added to a solution of sulfone S-**3**-PT (2.71 g, 6.62 mmol) in THF (100 mL) at −78 °C. After the mixture was stirred at −78 °C for 30 min, a solution of M-**4** (2.83 g, 4.87 mmol) in THF (20 mL) was slowly added via a syringe. After being stirred at −78 °C for 2 h, the reaction mixture was quenched with saturated ammonium chloride (100 mL), water (100 mL), and warmed to room temperature. The reaction mixture was extracted with ether (5 × 100 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (10:1 hexane:ethyl acetate) gave alkene MS-**16** (3.505 g, 94%). LC−MS (APCI) for MS-**16**: S-**16a** *m/z* 653 $(M - 1)^+$, S-**16b** *m/z* 753 $(M - 1)^+$, S-**16c** *m/z* 803 $(M - 1)^+$, S-**16d** *m/z* 853 $(M - 1)^+$.

***tert*-Butyl-[7-(fluorous-4-methoxybenzyloxy)-2,6-dimethyloct-4-enyloxy]dimethylsilane MR-16. Synthesized by General Procedure 7.** Yield 3.753 g, 93%. LC−MS (APCI) for MR-**16**: R-**16a** *m/z* 653 $(M - 1)^+$, R-**16b** *m/z* 753 $(M - 1)^+$, R-**16c** *m/z* 803 $(M - 1)^+$, R-**16d** *m/z* 853 $(M - 1)^+$.

General Procedure 8. TBS Deprotection. 7-(Fluorous-4-methoxybenzyloxy)-2,6-dimethyloct-4-en-1-ol MS-18. A solution of TBAF in THF (1 M, 9 mL, 9.0 mmol) was slowly added to a solution of MS-**16** (3.437 g, 4.49 mmol) in THF (120 mL). After the mixture was stirred at room temperature for 3 h, brine (100 mL) was added and the reaction mixture was extracted with ether (5 × 100 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (3:1 hexane:ethyl acetate) gave alcohol MS-**18** (2.90 g, 100%). LC−MS (APCI) for MS-**18**: S-**18a** *m/z* 537 $(M - 1)^+$, S-**18b** *m/z* 637 $(M - 1)^+$, S-**18c** *m/z* 687 $(M - 1)^+$, S-**18d** *m/z* 737 $(M - 1)^+$.

7-(Fluorous-4-methoxybenzyloxy)-2,6-dimethyloct-4-en-1-ol MR-18. This mixture was synthesized by general procedure 8. Yield 3.09 g, 99%. LC−MS (APCI) for MR-**18**: R-**18a** *m/z* 537 $(M - 1)^+$, R-**18b** *m/z* 637 $(M - 1)^+$, R-**18c** *m/z* 687 $(M - 1)^+$, R-**18d** *m/z* 737 $(M - 1)^+$.

7-(Fluorous-4-methoxybenzyloxy)-2,6-dimethyloct-4-enal MS-19. This mixture was synthesized by general procedure 6. Yield 2.32 g, 82%. LC−MS (APCI) for MS-**19**: S-**19a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, S-**19b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, S-**19c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, S-**19d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

7-(Fluorous-4-methoxybenzyloxy)-2,6-dimethyloct-4-enal MR-19. This mixture was synthesized by general procedure 6. Yield 2.62 g, 81%. LC−MS (APCI) for MR-**19**: R-**19a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, R-**19b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, R-**19c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, R-**19d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

***tert*-Butyl-[11-(fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dienyloxy]dimethylsilane MSS-20.** This mixture was synthesized by general procedure 7. Yield 923 mg, 92%; 485 mg, 92%. LC−MS (APCI) for MSS-**20**: SS-

20a *m/z* 721 $(M - 1)^+$, SS-**20b** *m/z* 821 $(M - 1)^+$, SS-**20c** *m/z* 871 $(M - 1)^+$, SS-**20d** *m/z* 921 $(M - 1)^+$.

***tert*-Butyl-[11-(fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dienyloxy]dimethylsilane MSR-20.** This mixture was synthesized by general procedure 7. Yield 747 mg, 92%; 475 mg, 91%. LC−MS (APCI) for MSR-**20**: SR-**20a** *m/z* 721 $(M - 1)^+$, SR-**20b** *m/z* 821 $(M - 1)^+$, SR-**20c** *m/z* 871 $(M - 1)^+$, SR-**20d** *m/z* 921 $(M - 1)^+$.

***tert*-Butyl-[11-(fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dienyloxy]dimethylsilane MRS-20.** This mixture was synthesized by general procedure 7. Yield 1.57 g, 92%. LC−MS (APCI) for MRS-**20**: RS-**20a** *m/z* 721 $(M - 1)^+$, RS-**20b** *m/z* 821 $(M - 1)^+$, RS-**20c** *m/z* 871 $(M - 1)^+$, RS-**20d** *m/z* 921 $(M - 1)^+$.

***tert*-Butyl-[11-(fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dienyloxy]dimethylsilane MRR-20.** This mixture was synthesized by general procedure 7. Yield 1.366 g, 93%. LC−MS (APCI) for MRR-**20**: RR-**20a** *m/z* 721 $(M - 1)^+$, RR-**20b** *m/z* 821 $(M - 1)^+$, RR-**20c** *m/z* 871 $(M - 1)^+$, RR-**20d** *m/z* 921 $(M - 1)^+$.

11-(Fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dien-1-ol MSS-21. This mixture was synthesized by general procedure 8. Yield 1.12 g 100%. LC−MS (APCI) for MSS-**21**: SS-**21a** *m/z* 607 $(M - 1)^+$, SS-**21b** *m/z* 707 $(M - 1)^+$, SS-**21c** *m/z* 757 $(M - 1)^+$, SS-**21d** *m/z* 807 $(M - 1)^+$.

11-(Fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dien-1-ol MSR-21. This mixture was synthesized by general procedure 8. Yield 1.03 g (100%). LC−MS (APCI) for MSR-**21**: SR-**21a** *m/z* 607 $(M - 1)^+$, SR-**21b** *m/z* 707 $(M - 1)^+$, SR-**21c** *m/z* 757 $(M - 1)^+$, SR-**21d** *m/z* 807 $(M - 1)^+$.

11-(Fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dien-1-ol MRS-21. This mixture was synthesized by general procedure 8. Yield 1.33 g (100%). LC−MS (APCI) for MRS-**21**: RS-**21a** *m/z* 607 $(M - 1)^+$, RS-**21b** *m/z* 707 $(M - 1)^+$, RS-**21c** *m/z* 757 $(M - 1)^+$, RS-**21d** *m/z* 807 $(M - 1)^+$.

11-(Fluorous-4-methoxybenzyloxy)-2,6,10-trimethyldodeca-4,8-dien-1-ol MRR-21. This mixture was synthesized by general procedure 8. Yield 1.09 g (100%). LC−MS (APCI) for MRR-**21**: RR-**21a** *m/z* 607 $(M - 1)^+$, RR-**21b** *m/z* 707 $(M - 1)^+$, RR-**21c** *m/z* 757 $(M - 1)^+$, RR-**21d** *m/z* 807 $(M - 1)^+$.

11-(Fluorous-4-methoxy-benzyloxy)-2,6,10-trimethyldodeca-4,8-dienal MSS-22. This mixture was synthesized by general procedure 6. Yield 908 mg, 81%. LC−MS (APCI) for MSS-**22**: SS-**22a** *m/z* 605 $(M - 1)^+$, SS-**22b** *m/z* 705 $(M - 1)^+$, SS-**22c** *m/z* 755 $(M - 1)^+$, SS-**22d** *m/z* 805 $(M - 1)^+$.

11-(Fluorous-4-methoxy-benzyloxy)-2,6,10-trimethyldodeca-4,8-dienal MSR-22. This mixture was synthesized by general procedure 6. Yield 833 mg (84%). LC−MS (APCI) for MSR-**22**: SR-**22a** *m/z* 605 $(M - 1)^+$, SR-**22b** *m/z* 705 $(M - 1)^+$, SR-**22c** *m/z* 755 $(M - 1)^+$, SR-**22d** *m/z* 805 $(M - 1)^+$.

11-(Fluorous-4-methoxy-benzyloxy)-2,6,10-trimethyldodeca-4,8-dienal MRS-22. This mixture was synthesized by general procedure 6. Yield 1.11 g (86%). LC−MS (APCI) for MRS-**22**: RS-**22a** *m/z* 605 $(M - 1)^+$, RS-**22b** *m/z* 705 $(M - 1)^+$, RS-**22c** *m/z* 755 $(M - 1)^+$, RS-**22d** *m/z* 805 $(M - 1)^+$.

11-(Fluorous-4-methoxy-benzyloxy)-2,6,10-trimethyldodeca-4,8-dienal MRR-22. This mixture was synthesized by general procedure 6. Yield 858 mg (82%). LC−MS (APCI) for MRR-**22**: RR-**22a** *m/z* 605 $(M - 1)^+$, RR-**22b** *m/z* 705 $(M + 1)^+$, RR-**22c** *m/z* 755 $(M - 1)^+$, RR-**22d** *m/z* 805 $(M - 1)^+$.

General Procedure 9. Wittig Reaction. 1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodeca-3,7,11-trienyloxymethyl)benzene MSS-2. A solution of sodiumhexamethyldisilazide (1 M, 2.3 mL, 2.3 mmol) was added to a suspension of methyl triphenylphosphonium iodide (1.56 g, 3.85 mmol) in THF (10 mL) at −78 °C. After the mixture was stirred at −78 °C for 30 min, a solution of MSS-**22** (555 mg, 0.77 mmol) in THF (10 mL) was added. After being stirred at −78 °C for 2 h, the reaction mixture was warmed to room temperature over a period of 3 h and quenched with brine (30 mL) and water (50 mL). The reaction mixture was extracted with ether (5 × 50 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (15:1 hexane:ethyl acetate), gave alkene MSS-**2** (544 mg, 97%). LC−MS (APCI) for MSS-**2**: MSS-**2a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, MSS-**2b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, MSS-**2c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, MSS-**2d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodeca-3,7,11-trienyloxymethyl)benzene MSR-2. This mixture was synthesized by general procedure 9. Yield 520 mg (98%). LC−MS (APCI) for MSR-**2**: SR-**2a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SR-**2b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SR-**2c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SR-**2d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodeca-3,7,11-trienyloxymethyl)benzene MRS-2. This mixture was synthesized by general procedure 9. Yield 625 mg (97%). LC−MS (APCI) for MRS-**2**: RS-**2a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RS-**2b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RS-**2c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RS-**2d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodeca-3,7,11-trienyloxymethyl)benzene MRR-2. This mixture was synthesized by general procedure 10. Yield 612 mg (95%). LC−MS (APCI) for MRR-**2**: RR-**2a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RR-**2b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RR-**2c** *m/z* 687 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RR-**2d** *m/z* 737 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

General Procedure 10. Diimide Reduction. 1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodecyloxymethyl)-benzene MRR-23. Anhydrous hydrazine (7.1 mL, 0.23 mol) was added to a suspension of triene MSS-**2** (544 mg, 0.76 mmol) and copper sulfate (5.66 g, 22.67 mmol) in ethanol (10 mL). After being stirred at room temperature for 15 min, the reaction mixture was warmed to 70 °C. (These reaction conditions sometimes resulted in incomplete reduction of starting triene. In those cases, the crude product was resubjected to the same reaction conditions. Bubbling air through the reaction mixture also helped improve conversion.) After being stirred at 70 °C for 20 h, the reaction was cooled to room temperature. Water (50 mL) was added, and the reaction mixture was extracted with ether (5 × 50 mL). The organic layers were combined, washed with brine, dried with magnesium sulfate, and concentrated. Flash column chromatography on silica gel (10:1 hexane:ethyl acetate) gave MRR-**23** (514 mg, 94%). LC−MS (APCI) for MRR-**23**: RR-**23a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RR-**23b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RR-**23c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RR-**23d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene MRS-23. This mixture was synthesized by general procedure 10. Yield 473 mg (90%). LC−MS (APCI) for MRS-**23**: RS-**23a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RS-**23b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RS-**23c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, RS-**23d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene MSR-23. This mixture was synthesized by general procedure 10. Yield 432 mg (95%). LC−MS (APCI) for MSR-**23**: SR-**23a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SR-**23b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SR-**23c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SR-**23d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

1-Fluorous Methoxy-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene MSS-23. This mixture was synthesized by general procedure 10. Yield 460 mg (96%). LC−MS (APCI) for MSS-**23**: SS-**23a** *m/z* 367 $(C_4F_9(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SS-**23b** *m/z* 467 $(C_6F_{13}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SS-**23c** *m/z* 517 $(C_7F_{15}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$, SS-**23d** *m/z* 567 $(C_8F_{17}(CH_2)_3O\text{-}p\text{-}C_6H_4CH_2)^+$.

General Procedure 11. Demixing. Demixing MRR-23. The separation conditions were as follows: FluoroFlash HPLC column (20 mm × 250 mm), gradient 95:5 acetonitrile:water to 100% acetonitrile in 30 min, then isocratic acetonitrile to 50 min with a flow rate of 12 mL/min. UV detector (230 nm) was used to manually identify peaks. A mixture of MRR-**23** (476 mg, 0.66 mmol), acetonitrile (9 mL), and THF (2 mL) was sonicated for about 15 s and filtered through a Wattman filter paper (0.45 μm pore size). Five separations using 2 mL (86 mg of MRR-**23**) each and two separations using 1 mL (43 mg of MRR-**23**) each were carried out to give SSRR-**23a** (96 mg, 0.16 mmol), RSRR-**23b** (113 mg, 0.16 mmol), SRRR-**23c** (120 mg, 0.16 mmol), and RRRR-**23d** (128 mg, 0.16 mmol).

(1*S*,2*S*,6*R*,10*R*)-1-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SSRR-23a. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30−7.28 (m, 2H), 6.89−6.86 (m, 2H), 4.52 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 4.9, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.64−1.58 (m, 1H), 1.46−1.07 (m, 16H), 1.14 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 157.9, 132.0, 129.1, 114.2, 121−105 (m), 78.3, 70.2, 66.3, 38.0, 37.6, 37.3, 37.0, 34.4, 32.8, 32.4, 29.5, 27.8 (t, J = 21.9 Hz), 24.8, 24.5, 20.6, 19.7, 19.2, 16.1, 15.2, 11.3; ^{19}F NMR ($CDCl_3$) −81.5 (3F), −115.1 (2F), −124.9 (2F), −126.6 (2F); IR (thin film) 2928, 1238 cm^{-1}; LRMS 608 (M^+, 5%), 564 (15%), 367 (100%); HRMS calculated 608.3276, found 608.3291.

(1*R*,2*S*,6*R*,10*R*)-1-(1,2,6,10-Tetramethyldodecyloxymethyl)-4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzene RSRR-23b. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.28 (m, 2H), 6.89−6.87 (m, 2H), 4.50 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.05 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 6.2, 6.2 Hz, 1H), 2.37−2.29 (m, 2H), 2.13−2.08 (m, 2H), 1.75−1.71 (m, 1H), 1.40−1.08 (m, 16H), 1.12 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 131.9, 129.1, 114.3, 121−105 (m), 78.3, 70.0, 66.4, 37.5, 37.3 (2C), 37.0, 34.5, 33.4, 32.7, 29.6, 28.0 (t, J = 22.5 Hz), 24.8, 24.5, 20.6, 19.7, 19.2, 15.3, 14.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.3 (3F), −114.9 (2F), −122.4 (2F), −123.4 (2F), −124.0 (2F), −126.7 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 708 (M^+, 10%), 664 (15%), 467 (100%); HRMS calculated 708.3212, found 708.3222.

(1*S*,2*R*,6*R*,10*R*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Pentadecafluorodecyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SRRR-23c. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30−7.28 (m, 2H), 6.89−6.87 (m, 2H), 4.50 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 5.4, 5.4 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.75−1.71 (m, 1H), 1.41−1.05 (m, 16H), 1.11 (d, J = 6.3 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 131.9, 129.1, 114.3, 125−105 (m), 78.3, 70.0, 66.4, 37.4 (2C), 37.3, 37.0, 34.4, 33.5, 32.8, 29.5, 28.0 (t, J = 26.1 Hz), 24.8, 24.5, 20.6, 19.8, 19.2, 15.2, 14.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.3 (3F), −114.9 (2F), −122.2 (2F), −122.6 (2F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 758 (M^+, 5%), 714 (15%), 517 (100%); HRMS calculated 758.3180, found 758.3193.

(1*R*,2*R*,6*R*,10*R*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl-oxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene RRRR-23d. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.28 (m, 2H), 6.88−6.87 (m, 2H), 4.52 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 4.8, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.63−1.58 (m, 1H), 1.50−1.06 (m, 16H), 1.14 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (d, J = 5.5 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 132.0, 129.1, 114.3, 125−105 (m), 78.3, 70.2, 66.4, 38.1, 37.4, 37.4, 37.0, 34.4, 32.8, 32.5, 29.5, 28.0 (t, J = 22.3 Hz), 24.8, 24.5, 20.6, 19.8, 19.2, 16.1, 15.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.8 (2F), −122.2 to −122.4 (6F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 808 (M^+, 3%), 764 (10%), 567 (60%), 121 (100%); HRMS calculated 808.3148, found 808.3112.

Demixing of MRS-23. Mixture MRS-**23** (460 mg, 0.64 mmol) was demixed by general procedure 11 to give compounds SSRS-**23a** (81 mg, 0.13 mmol), RSRS-**23b** (103 mg, 0.15 mmol), SRRS-**23c** (108 mg, 0.14 mmol), and RRRS-**23d** (117 mg, 0.15 mmol).

(1*S*,2*S*,6*R*,10*S*)-1-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SSRS-23a. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30−7.28 (m, 2H), 6.89−6.87 (m, 2H), 4.52 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.05 (t, J = 6.0 Hz, 2H), 3.38 (dq, J = 4.9, 6.3 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.08 (m, 2H), 1.63−1.60 (m, 1H), 1.48−1.10 (m, 16H), 1.14 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 157.9, 132.0, 129.1, 114.3, 125−105 (m), 78.3, 70.2, 66.3, 38.0, 37.5, 37.4, 37.0, 34.4, 32.8, 32.4, 29.6, 27.9 (t, J = 22.1 Hz), 24.8, 24.5, 20.6, 19.6, 19.2, 16.1, 15.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.5 (3F), −115.1 (2F), −124.9 (2F), −126.6 (2F); IR (thin film) 2928, 1242 cm^{-1}; LRMS 608 (M^+, 10%), 564 (15%), 367 (100%); HRMS calculated 608.3276, found 608.3291.

(1*R*,2*S*,6*R*,10*S*)-1-(1,2,6,10-Tetramethyldodecyloxymethyl)-4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzene RSRS-23b. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30−7.28 (m, 2H), 6.89−6.87 (m, 2H), 4.49 (d, J = 11.5 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 5.4, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.74−1.71 (m, 1H), 1.41−1.09 (m, 16H), 1.11 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 131.9, 129.1, 114.3, 125−105 (m), 78.4, 70.0, 66.3, 37.5, 37.4, 37.3, 37.0, 34.4, 33.4, 32.8, 29.6, 27.8 (t, J = 22.1 Hz), 24.8, 24.5, 20.6, 19.6, 19.2, 15.3, 14.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.3 (3F), −114.9 (2F), −122.4 (2F), −123.4 (2F), −124.0 (2F), −126.7 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 708 (M^+, 4%), 664 (10%), 467 (100%); HRMS calculated 708.3212, found 708.3185.

(1*S*,2*R*,6*R*,10*S*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Pentadecafluorodecyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SRRS-23c. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30−7.28 (m, 2H), 6.88−6.86 (m, 2H), 4.49 (d, J = 11.3 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 6.7, 6.7 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.73−1.71 (m, 1H), 1.41−1.07 (m, 16H), 1.11 (d, J = 6.2 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 131.9, 129.1, 114.3, 125−105 (m), 78.3, 70.0, 66.4, 37.5, 37.4, 37.3, 37.0, 34.4, 33.4, 32.8, 29.6, 28.0 (t, J = 22.4 Hz), 24.8, 24.5, 20.6, 19.7, 19.2, 15.2, 14.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.3 (3F), −114.9 (2F), −122.2 (2F), −122.6 (2F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 758 (M^+, 6%), 714 (10%), 517 (100%); HRMS calculated 758.3180, found 758.3143.

(1*R*,2*R*,6*R*,10*S*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene RRRS-23d. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.28 (m, 2H), 6.88−6.87 (m, 2H), 4.52 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 6.1, 6.1 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.63−1.59 (m, 1H), 1.51−1.09 (m, 16H), 1.14 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H), 0.87 (d, J = 5.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 132.0, 129.1, 114.3, 125−105 (m), 78.3, 70.2, 66.4, 38.1, 37.5, 37.3, 37.0, 34.4, 32.8, 32.5, 29.6, 28.0 (t, J = 22.5 Hz), 24.8, 24.5, 20.6, 19.7, 19.2, 16.1, 15.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.8 (2F), −122.2 to −122.4 (6F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin

film) 2928, 1242 cm^{-1}; LRMS 808 (M$^+$, 3%), 764 (10%), 567 (45%), 91(100%); HRMS calculated 808.3148, found 808.3172.

Demixing of MSR-23. Mixture MSR-**23** (471 mg, 0.65 mmol) was demixed by general procedure 11 to give compounds SSSR-**23a** (92 mg, 0.15 mmol), RSSR-**23b** (106 mg, 0.15 mmol), SRSR-**23c** (111 mg, 0.15 mmol), and RRSR-**23d** (119 mg, 0.15 mmol).

(1*S*,2*S*,6*S*,10*R*)-1-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SSSR-23a. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.28−7.27 (m, 2H), 6.87−6.86 (m, 2H), 4.51 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.37 (dq, J = 6.2, 6.2 Hz, 1H), 2.36−2.27 (m, 2H), 2.12−2.08 (m, 2H), 1.62−1.58 (m, 1H), 1.50−1.05 (m, 16H), 1.13 (d, J = 6.3 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 157.9, 132.0, 129.1, 114.3, 125−105 (m), 78.3, 70.2, 66.3, 38.0, 37.5, 37.3, 36.9, 34.4, 32.8, 32.4, 29.6, 27.9 (t, J = 23.2 Hz), 24.8, 24.5, 20.6, 19.7, 19.2, 16.2, 15.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.5 (3F), −115.1 (2F), −124.9 (2F), −126.5 (2F); IR (thin film) 2928, 1242 cm^{-1}; LRMS 608 (M$^+$, 6%), 564 (10%), 367 (100%); HRMS calculated 608.3276, found 608.3284.

(1*R*,2*S*,6*S*,10*R*)-1-(1,2,6,10-Tetramethyldodecyloxymethyl)-4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzene RSSR-23b. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.27 (m, 2H), 6.87−6.86 (m, 2H), 4.48 (d, J = 11.4 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.37 (dq, J = 6.2, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.08 (m, 2H), 1.73−1.69 (m, 1H), 1.40−1.06 (m, 16H), 1.10 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 157.9, 131.9, 129.1, 114.3, 125−105 (m), 78.2, 70.0, 66.4, 37.5, 37.3, 37.3, 36.9, 34.4, 33.4, 32.8, 29.6, 28.0 (t, J = 22.8 Hz), 24.8, 24.5, 20.6, 19.7, 19.2, 15.2, 14.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.3 (3F), −114.9 (2F), −122.4 (2F), −123.4 (2F), −124.0 (2F), −126.6 (2F); IR (thin film) 2928, 1242 cm^{-1}; LRMS 708 (M$^+$, 6%), 664 (10%), 467 (100%); HRMS calculated 708.3212, found 708.3215.

(1*S*,2*R*,6*S*,10*R*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Pentadecafluorodecyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SRSR-23c. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.27 (m, 2H), 6.88−6.86 (m, 2H), 4.48 (d, J = 11.4 Hz, 1H), 4.41 (d, J = 11.4 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.37 (dq, J = 6.2, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.08 (m, 2H), 1.73−1.68 (m, 1H), 1.38−1.08 (m, 16H), 1.10 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 157.9, 131.9, 129.1, 114.3, 125−105 (m), 78.4, 70.0, 66.4, 37.5, 37.4, 37.3, 36.9, 34.4, 33.4, 32.8, 29.6, 28.0 (t, J = 22.2 Hz), 24.8, 24.5, 20.6, 19.6, 19.2, 15.3, 14.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.9 (2F), −122.2 (2F), −122.6 (2F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 758 (M$^+$, 8%), 714 (15%), 517 (100%); HRMS calculated 758.3180, found 758.3155.

(1*R*,2*R*,6*S*,10*R*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene RRSR-23d. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.28−7.27 (m, 2H), 6.88−6.86 (m, 2H), 4.51 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.37 (dq, J = 4.8, 6.2 Hz, 1H), 2.36−2.28 (m, 2H), 2.13−2.08 (m, 2H), 1.63−1.57 (m, 1H), 1.40−1.05 (m, 16H), 1.13 (d, J = 6.3 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 157.9, 132.0, 129.1, 114.2, 125−105 (m), 78.3, 70.2, 68.3, 38.0, 37.5, 37.4, 37.0, 34.4, 32.8, 32.3, 29.6, 28.0 (t, J = 22.2 Hz), 24.8, 24.5, 20.6, 19.6, 19.2, 16.2, 15.3, 11.4; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.8 (2F), −122.2 to −122.4 (6F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2928, 1242 cm^{-1}; LRMS 808 (M$^+$, 10%), 764 (15%), 567 (100%); HRMS calculated 808.3148, found 808.3144.

Demixing of MSS-23. Mixture MSS-**23** (451 mg, 0.62 mmol) was demixed by general procedure 11 to give compounds SSSS-**23a** (86 mg, 0.14 mmol), RSSS-**23b** (103 mg, 0.15 mmol), SRSS-**23c** (108 mg, 0.14 mmol), and RRSS-**23d** (113 mg, 0.14 mmol).

(1*S*,2*S*,6*S*,10*S*)-1-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SSSS-23a. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.28 (m, 2H), 6.88−6.87 (m, 2H), 4.52 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 4.8, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.63−1.59 (m, 1H), 1.51−1.08 (m, 16H), 1.14 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (d, J = 5.3 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 132.0, 129.2, 114.3, 125−105 (m), 78.4, 70.3, 66.4, 38.1, 37.5, 37.5, 37.1, 34.5, 32.9, 32.5, 29.6, 28.0 (t, J = 22.4 Hz), 24.9, 24.6, 20.7, 19.9, 19.3, 16.2, 15.4, 11.5; ^{19}F NMR ($CDCl_3$) −81.5 (3F), −115.1 (2F), −124.9 (2F), −126.6 (2F); IR (thin film) 2928, 1242 cm^{-1}; LRMS 608 (M$^+$, 5%), 564 (10%), 367 (100%); HRMS calculated 608.3276, found 608.3283.

(1*R*,2*S*,6*S*,10*S*)-1-(1,2,6,10-Tetramethyldodecyloxymethyl)-4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzene RSSS-23b. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.28 (m, 2H), 6.89−6.87 (m, 2H), 4.50 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 5.5, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.75−1.70 (m, 1H), 1.42−1.07 (m, 16H), 1.11 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.1, 132.0, 129.2, 114.4, 125−105 (m), 78.3, 70.1, 66.4, 37.5 (2C), 37.4, 37.1, 34.5, 33.5, 32.9, 29.6, 28.1 (t, J = 22.5 Hz), 24.8, 24.6, 20.7, 19.8, 19.3, 15.3, 14.4, 11.4; ^{19}F NMR ($CDCl_3$) −81.3 (3F), −114.9 (2F), −122.4 (2F), −123.4 (2F), −124.0 (2F), −126.7 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 708 (M$^+$, 6%), 567 (3%), 467 (100%); HRMS calculated 708.3212, found 708.3218.

(1*S*,2*R*,6*S*,10*S*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Pentadecafluorodecyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene SRSS-23c. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.28 (m, 2H), 6.89−6.87 (m, 2H), 4.49 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.37 (dq, J = 5.5, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.74−1.69 (m, 1H), 1.41−1.06 (m, 16H), 1.11 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.1, 132.0, 129.2, 114.3, 125−105 (m), 78.5, 70.1, 66.5, 37.6, 37.4, 37.4, 37.1, 34.5, 33.5, 32.9, 29.6, 28.1 (t, J = 22.3 Hz), 24.8, 24.6, 20.7, 19.8, 19.3, 15.4, 14.4, 11.5; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.9 (2F), −122.2 (2F), −122.6 (2F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2928, 1241 cm^{-1}; LRMS 758 (M$^+$, 9%), 714 (15%), 517 (100%); HRMS calculated 758.3180, found 758.3183.

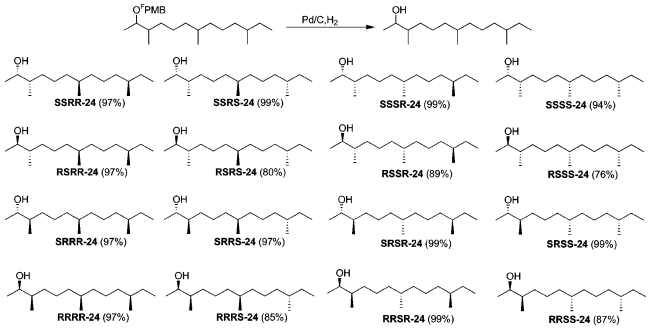
(1*R*,2*R*,6*S*,10*S*)-1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyloxy)-4-(1,2,6,10-tetramethyldodecyloxymethyl)benzene RRSS-23d. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29−7.28 (m, 2H), 6.88−6.87 (m, 2H), 4.52 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.04 (t, J = 5.9 Hz, 2H), 3.38 (dq, J = 4.8, 6.2 Hz, 1H), 2.37−2.28 (m, 2H), 2.13−2.09 (m, 2H), 1.63−1.59 (m, 1H), 1.49−1.09 (m, 16H), 1.14 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) 158.0, 132.1, 129.2, 114.3, 125−105 (m), 78.4, 70.3, 66.4, 38.1, 37.7, 37.4, 37.1, 34.5, 32.9, 32.5, 29.6, 28.1 (t, J = 22.3 Hz), 24.9, 24.6, 20.7, 19.7, 19.3, 16.2, 15.4, 11.4; ^{19}F NMR ($CDCl_3$) −81.2 (3F), −114.9 (2F), −122.2 to −122.4 (6F), −123.2 (2F), −123.9 (2F), −126.6 (2F); IR (thin film) 2928, 1242 cm^{-1}; LRMS 808 (M$^+$, 6%), 764 (15%), 567 (100%); HRMS calculated 808.3148, found 808.3122.

Post-Mix Stage. General Procedure 12. Detagging. (2*S*,3*S*,7*R*,11*R*)-3,7,11-Trimethyltridecan-2-ol SSRR-24. (1*S*,2*S*,6*R*,10*R*)-1-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)-4-(1,2,6,10-tetramethyl-dodecyloxymethyl)-benzene SSRR-**23a**

(76 mg, 0.125 mmol) and Pd/C (10 wt %) (10 mg) was taken up in ethanol (2 mL) and water (0.2 mL). The reaction flask was degassed using aspirator and filled with hydrogen from a balloon. After being stirred at room temperature for 12 h, the reaction mixture was filtered through Celite. After flash column chromatography on silica gel (10:1 hexane:ethyl acetate to remove fluorous toluene and then 2:1 hexane:ethyl acetate to remove the product), (2*S*,3*S*,7*R*,11*R*)-3,7,11-trimethyltridecan-2-ol SSRR-**24** was isolated as a colorless oil (30 mg, 97%).

All of the other 15 fluorous PMB ethers of **23** were detagged by general procedure 12. The yields of all 15 reactions are as follows: (2*R*,3*S*,7*R*,11*R*)-3,7,11-trimethyltridecan-2-ol RSRR-**24** (31 mg, 89%), (2*S*,3*R*,7*R*,11*R*)-3,7,11-trimethyltridecan-2-ol SRRR-**24** (33 mg, 96%), (2*R*,3*R*,7*R*,11*R*)-3,7,11-trimethyltridecan-2-ol RRRR-**24** (29 mg, 87%), (2*S*,3*S*,7*R*,11*S*)-3,7,11-trimethyltridecan-2-ol SSRS-**24** (28 mg, 98%), (2*R*,3*S*,7*R*,11*S*)-3,7,11-trimethyltridecan-2-ol RSRS-**24** (24 mg, 80%), (2*S*,3*R*,7*R*,11*S*)-3,7,11-trimethyltridecan-2-ol SRRS-**24** (30 mg, 97%), (2*R*,3*R*,7*R*,11*S*)-3,7,11-trimethyltridecan-2-ol RRRS-**24** (26 mg, 85%), (2*S*,3*S*,7*S*,11*R*)-3,7,11-trimethyltridecan-2-ol SSSR-**24** (36 mg, 96%), (2*R*,3*S*,7*S*,11*R*)-3,7,11-trimethyltridecan-2-ol RSSR-**24** (35 mg, 99%), (2*S*,3*R*,7*S*,11*R*)-3,7,11-trimethyltridecan-2-ol SRSR-**24** (35 mg, 99%), (2*R*,3*R*,7*S*,11*R*)-3,7,11-trimethyltridecan-2-ol RRSR-**24** (35 mg, 99%), (2*S*,3*S*,7*S*,11*S*)-3,7,11-trimethyltridecan-2-ol SSSS-**24** (31 mg, 94%), (2*R*,3*S*,7*S*,11*S*)-3,7,11-trimethyltridecan-2-ol RSSS-**24** (27 mg, 78%), (2*S*,3*R*,7*S*,11*S*)-3,7,11-trimethyltridecan-2-ol SRSS-**24** (32 mg, 99%), (2*R*,3*SR*,7*S*,11*S*)-3,7,11-trimethyltridecan-2-ol RRSS-**24** (28 mg, 87%).

The structures and yields of all of the stereoisomers of **24** obtained by the detagging reactions are shown below.



^{1}H and ^{13}C NMR data for all 16 isomers of **24** are given in Appendix 1 of the Supporting Information. Copies of the ^{1}H and ^{13}C NMR spectra of the eight different diastereomers of **24** are reproduced in Appendix 4 of the Supporting Information.

General Procedure 13. Propionylation. (1*S*,2*S*,6*R*,10*R*)-Propionic Acid 1,2,6,10-Tetramethyldodecyl Ester SSRR-1. Propionyl chloride (49 μL, 0.56 mmol) was added to a solution of (2*S*,3*S*,7*R*,11*R*)-3,7,11-trimethyltridecan-2-ol SSRR-**24** (16 mg, 0.07 mmol) in dichloromethane (3 mL). After the mixture was stirred at room temperature for 12 h, PS-trisamine (4.11 mmol/g, 476 mg, 1.96 mmol) was added. After gentle stirring at room temperature for 4 h, the reaction mixture was filtered, concentrated, and dried to get (1*S*,2*S*,6*R*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SSRR-**1** as a colorless oil (20 mg, 100%).

All of the other 15 stereoisomers of **24** were propionylated by general procedure 13. The yields of all 15 reactions are as follows: (1*R*,2*S*,6*R*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RSRR-**1** (18 mg, 98%), (1*S*,2*R*,6*R*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SRRR-**1** (18 mg, 98%), (1*R*,2*R*,6*R*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RRRR-**1** (20 mg, 96%), (1*S*,2*S*,6*R*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SSRS-**1** (18 mg, 97%), (1*R*,2*S*,6*R*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RSRS-**1** (17 mg, 99%), (1*S*,2*R*,6*R*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SRRS-**1** (16 mg, 93%), (1*R*,2*R*,6*R*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RRRS-**1** (17 mg, 99%), (1*S*,2*S*,6*S*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SSSR-**1** (23 mg, 98%), (1*R*,2*S*,6*S*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RSSR-**1** (23 mg, 98%), (1*S*,2*R*,6*S*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SRSR-**1** (21 mg, 90%), (1*R*,2*R*,6*S*,10*R*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RRSR-**1** (19 mg, 91%), (1*S*,2*S*,6*S*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SSSS-**1** (18 mg, 91%), (1*R*,2*S*,6*S*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RSSS-**1** (18 mg, 91%), (1*S*,2*R*,6*S*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester SRSS-**1** (18 mg, 91%), (1*R*,2*R*,6*S*,10*S*)-propionic acid 1,2,6,10-tetramethyldodecyl ester RRSS-**1** (18 mg, 91%).

^{1}H and ^{13}C NMR data for all 16 stereoisomers of **1** are given in Appendix 3 of the Supporting Information. Copies of the ^{1}H and ^{13}C NMR spectra of the eight different diastereomers of **1** are reproduced in Appendix 5 of the Supporting Information.

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Supporting Information Available: Additional experimental and characterization details for all of the intermediates described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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