Mixture Synthesis

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Solution-Phase Mixture Synthesis with Fluorous Tagging En Route: Total Synthesis of an Eight-Member Stereoisomer Library of Passifloricins**

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Fluorous mixture synthesis is a new solution-phase technique that permits the synthesis of mixtures of compounds—with the attendant savings in effort—but at the same time provides for the isolation of individual, pure products through a sorting process called demixing.[1,2] This symphony of reactions and separations is orchestrated by fluorous tags, which are typically attached to substrates in the guise of protecting groups bearing a homologous series of perfluoroalkyl groups ($-(CF_2)_nCF_3$). A mixture of compounds encoded with different fluorous tags can be kept together or pulled apart (demixed) during a separation depending on whether a fluorous or a non-fluorous separation method is used. Demixing is generally accomplished by chromatography over fluorous silica gel.[3]

Fluorous tags have been used to encode enantiomers[1c] (so-called quasiracemic synthesis), diastereomers,[1c] and analogues.[1b] While limitless in principle, the number of fluorous tags is limited in practice by the availability of suitable fluoroalkyl precursors and more importantly by the increasing molecular weights and unusual properties that very large fluorous groups confer on molecules that bear them. It is thus an important goal to leverage available tags by developing tagging methods in which the number of tagged compounds exceeds the number of tags.[4]

We report herein the total synthesis of an eight-member stereoisomer library of passifloricins[5–7] in which the stereocenters are introduced and tagged en route during the synthesis. The library comprises the enantiomer of passifloricin A and all seven epimers at C5, C7, and C9. The synthesis contrasts with all prior mixture work, in which building blocks with coded stereocenters were premade and pretagged. Further, the total fluorine content of each tagged molecule is defined by two tags, whereas a lone fluorous tag has been used in all prior work.

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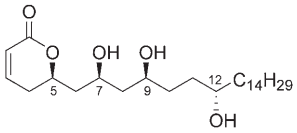


passifloricin A
(5*R*,7*S*,9*S*,12*S*)-**1**

The en route approach is doubly attractive because it saves steps over serial or parallel approaches and because it naturally enables the use of fewer fluorous tags than the number of stereoisomers in the library. These two points are illustrated by the synthetic pathway diagrams in Figure 1. In the traditional serial or parallel synthesis of stereoisomer libraries, the reaction products must be divided into two parts prior to the introduction of each new stereocenter and then carried along separately. The unavoidable doubling of work that attends the introduction of each stereocenter explains why stereoisomer libraries have received little attention to date.

In fluorous mixture synthesis, the division and complementary reactions to introduce a new stereocenter in both possible configurations are followed by tagging and remixing. Thus, the synthesis never diverges if there are sufficient tags to accommodate the isomers. Further, whereas two new tags are needed to encode the first stereocenter, only one new tag is needed for each of the successive stereocenters. Thus, a library of n molecules is uniquely encoded with $2/n + 1$ tags. The pairwise combination of tags T^1–T^3 provides four products with differing numbers of fluorine atoms provided only that T^1, T^2, and T^3 have a different fluorine content. One of the tags does not need to have any fluorine atoms, thereby further economizing the available perfluoroalkyl groups. If the effect of the fluorine content of the tags is additive on fluorous chromatography, then these products can be unambiguously demixed and their configurations decoded.

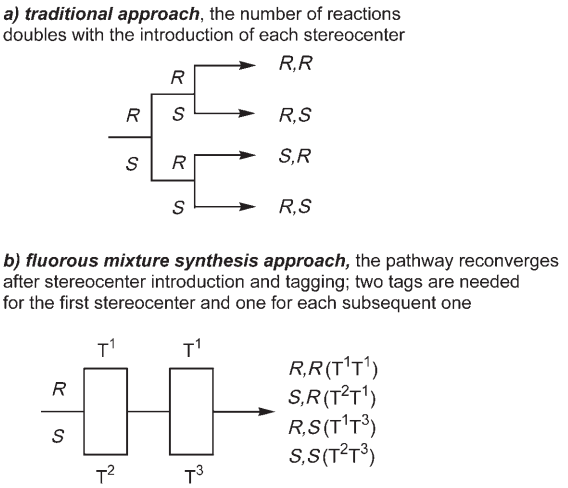
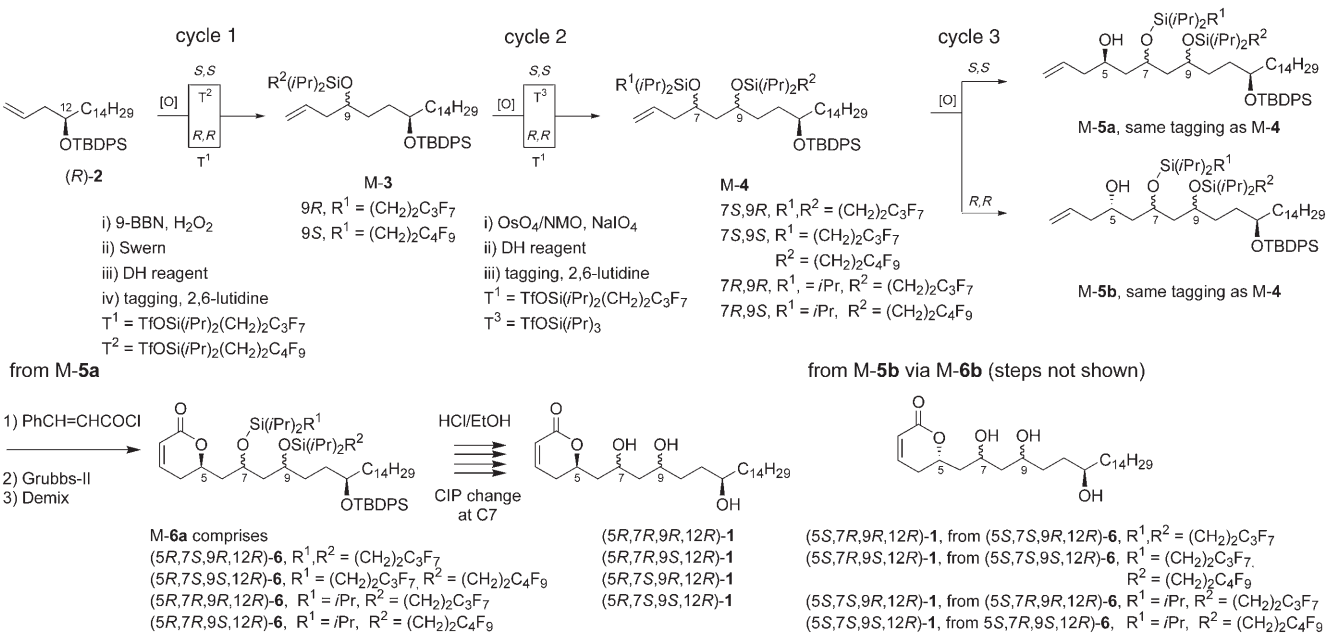


Figure 1. Strategies for the synthesis of stereoisomer libraries with the formation of stereocenters en route. Each branch represents the division of a product and introduction of a new stereocenter in both possible configurations.

The synthesis of the passifloricin stereoisomer library follows in the footsteps of syntheses of individual passifloricins by Marco[6a,b,7] and Cossy[6c,d] and is summarized in Scheme 1. The reaction path involves three similar iterative cycles of 1) oxidation to an aldehyde, 2) division and reagent-controlled asymmetric allylation of the aldehyde with both enantiomers of the Duthaler–Hafner reagent (hereafter called the DH reagent),[6c,d,8] 3) fluorous tagging of the isomeric products, and 4) remixing. We chose to make the enantiomer of passifloricin A because Marco and co-workers had already prepared natural passifloricin A and three



Scheme 1. Synthesis of passifloricins. 9-BBN = 9-borabicyclo[3.3.1]nonane, TBDPS = *tert*-butyldiphenylsilyl.

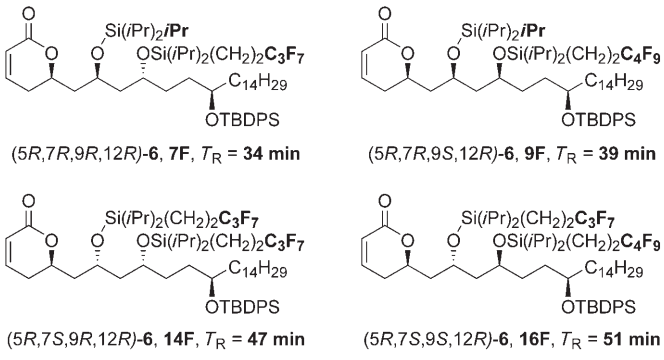
isomers.[7] These four compounds served as controls for the success of our exercise.

Enantiopure allyl silyl ether (*R*)-**2** (>99% *ee*) was subjected to a sequence of hydroboration and oxidation. Half of the resulting aldehyde was treated with the (*R*,*R*)-DH reagent, and the resulting alcohol (82%, d.r. = 98:2) was tagged with fluorous triisopropylsilyl trifluoromethanesulfonate (^{F}TIPSOTf) bearing a C_4F_9 group (81%).[9] The other half was treated with the (*S*,*S*)-DH reagent, and the alcohol (83%, d.r. = 2:98) was tagged with the ^{F}TIPS group bearing C_3F_7 (95%). The resulting quasi-diastereomers were mixed to make M-**3** for the second cycle.

The terminal carbon atom of the allyl group is not needed in cycle 2, so the aldehyde was generated by oxidative cleavage (OsO_4/*N*-methylmorpholine *N*-oxide (NMO), then $NaIO_4$, 73%) of M-**3**. Now division and allylation as above (91 and 88%, respectively) were followed by tagging; the product from the (*R*,*R*)-DH reagent received the new "null" (non-fluorous) TIPS tag (90%), and the product from the (*S*,*S*)-DH reagent received the repeat C_3F_7 tag. The resulting pair of two-compound mixtures was mixed to make a four-compound mixture of quasi-diastereomers M-**4** in preparation for cycle 3.

Cycle 3 was identical to cycle 2 through oxidation (73%) and allylation (93 and 80%) but was then interrupted to complete the synthesis. The resulting two mixtures of four compounds M-**5a**,**b** were acylated with cinnamoyl chloride (83 and 78%), and the crude products were directly subjected to ring-closing metathesis with the second-generation Grubbs catalyst[6,7] (85 and 92%). This process provided the full stereoisomer library of protected passifloricins as two mixtures of four compounds M-**6a**,**b**.

The product structures and retention times for the preparative demixing of M-**6a** are shown in Scheme 2. The



Scheme 2. Demixing of M-**6a** by fluorous HPLC: the quasi-diastereomers emerge in order of increasing total fluorine content.

samples were injected on a PF-C8 fluorous HPLC column,[9] which was eluted over 60 minutes with a gradient from 80% MeCN/water to 100% MeCN. The approximate additivity of the fluorine content of the tags was indeed observed, with the quasi-isomer of **6** bearing 7 fluorine atoms emerging first, followed in turn by those with 9, 14, and 16 fluorine atoms. These four major fractions were collected and concentrated to provide the four individual, protected quasi-isomers of passifloricin. Demixing of M-**6b** provided the other four isomers (not shown). All eight isomers of **6** were deprotected individually by exposure to 3 N HCl in EtOH. Products **1** were purified by flash chromatography and normal-phase HPLC to provide the eight-member library including (*ent*)-passifloricin A (5*S*,7*R*,9*R*,12*R*-**1**) and its seven diastereomers with *R* configurations at C12 and all the possible configurations at C5, C7, and C9.[10]

Unlike previous libraries that we have made with remote stereocenters,[1c] each member of this library exhibited unique ^{1}H and ^{13}C NMR spectra. Samples of passifloricin and three isomers from Marco and co-workers[7b] were identical to the four expected products **1** in our library, thus demonstrating that the tagging and demixing process was successful. The exercise confirms the stereostructure of passifloricin by rigorously proving that it is not any of the other seven possible stereoisomers.

This strategy of fluorous mixture synthesis with the introduction and tagging of stereocenters en route is a powerful new approach to making stereoisomer libraries with significant savings in effort. The mixture synthesis phase of this work required only 18 chemical reactions, whereas the same synthesis conducted in serial fashion would have required 44 reactions. The route also economizes tags, as four pairs of isomers were made by using three tags, only two of which were fluorous. Eight isomers could be made in a single mixture with five tags, 16 isomers with 9 tags, and so on. Central to this approach is the approximate additivity of the fluorine content of the tags as expressed by elution order in the demixing. Although demonstrated in an en route setting, the tactic of using multiple tags is equally applicable in settings in which pretagged building blocks are assembled.[11]

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[9] Reagents and fluorous silica products were purchased from Fluorous Technologies, Inc; D.P.C. holds an equity interest in this company.
[10] Note the change in Cahn–Ingold–Prelog (CIP) priorities at C7 between **6** and **1**.
[11] The Supporting Information contains copies of the NMR spectra for all of the eight isomers of **6** and **1**.

