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Fluorous "Racemic" Mixture Synthesis: Simultaneous Strategy for Demixing and Enantioseparation of Racemic Fluorous-Tagged Products

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Reported herein is the concept of fluorous "racemic" mixture synthesis (FRMS), which is applied to two types of proof-of-concept experiments. Mixtures of racemic *O*-benzoylmandelate derivatives and prochiral crotonamide derivatives, respectively, bearing different lengths of fluorous-cleavable tags are taken through a segmented reaction sequence to provide their enantiomers, as well as their individual derivatives, by virtue of chiral β-cyclodextrin columns.

In modern organic synthesis, pharmaceutical and agrochemical compounds are frequently required in an enantiopure form rather than in a racemic form for "chiral switch" regulation.[1] Even in their combinatorial syntheses, enantioseparation of drug candidates and their analogues in the simultaneous demixing step should, in principle, be so efficient as to diversify the library[2–4] in an enantiopure form.

In this paper, we introduce the principles of fluorous "racemic" mixture synthesis (FRMS) (see Scheme 1). This starts from two types of starting materials, racemic [R′/S^1...R^n/S^n, see (1)] and prochiral [P$_c$^{1}...P$_c$^{n}, see (2)] substrates, with cleavable tags (F^1...F^n) and terminates with enantiopure products (R^1, ..., R^n; S^1, ..., S^n). Therefore, this method simultaneously solves the enantioseparation, demixing and identification problems associated with conventional solution-phase mixture synthesis.[5]

Fluorous techniques, such as Curran's excellent "quasiracemic synthesis"[6] of small organic molecules, are based on enantiopure starting materials where the respective enantiomers have been tagged with different fluorous ponytails. In this way, 1) the separation of enantiomers is guaranteed by the tags, and 2) the structure of the enantiomers is known by the order of elution. However, as Curran reported, racemization occurring during the synthesis can often be problematic.[6e]

In sharp contrast, racemization is not an obstacle at all in our FRMS. β-Cyclodextrin (β-CD) as a chiral HPLC column[7] (SUMICHIRAL OA-7000 series[8]) efficiently performs enantioseparation of racemates by the introduction of fluorous tags.[5] β-Cyclodextrin columns efficiently demix and enantioseparate racemic products simultaneously. The salient points of this FRMS strategy are (Table 1): 1) enantiopure starting materials are not necessary, 2) two enantiomeric products can be simultaneously obtained by single fluorous tagging, 3) racemization during the course of the reaction sequence can be disregarded, and 4) the efficiency of the present FRMS can be further maximized by the auxiliary use of optical rotation (OR) (JASCO OR-1590) or circular dichroism (CD) [JASCO CD-995 (1595)] HPLC spectroscopy to determine the specific configuration of the enantiomeric products.[9,10]

Table 1. Comparison between FRMS and quasiracemic synthesis.

	FRMS	"Quasiracemic" Synthesis
Starting material	Even racemic	Enantiopure only
The number of fluorous tag	One fluorous tag for a pair of racemates	Two fluorous tags for a pair of racemates
Enantioseparation	No problem	Problematic (Racemization can occur)
Enantiomer identification	Auxiliary methods are required	Identified by the order of elution

As a proof-of-concept experiment, this FRMS method was first applied to racemic starting materials, in the context of the synthesis of *O*-benzoylmandelate derivatives with important biological properties (Scheme 2).[11] Racemic mandelic acid derivatives as starting materials were tagged with different fluorous alcohols, $C_nF_{2n+1}CH_2OH$ (n = 1, 3, 7) by the standard method [DCC/DMAP, see (2) in Scheme 2].

In order to directly produce fluorous-tagged mandelic acid derivatives, Friedel–Crafts alkylation[12] of aromatic compounds such as isobutylbenzene was also exploited with fluorous-tagged glyoxylate in the presence of a Lewis acid; see (1) in Scheme 2. Each tagged compound was mixed and split into m (three) portions and then reacted with n (three) types of benzoyl chloride derivatives to give $m \times n$ (3-mix/3-split) tagged products (**1a**–**c**, **2a**–**c**, **3a**–**c**).

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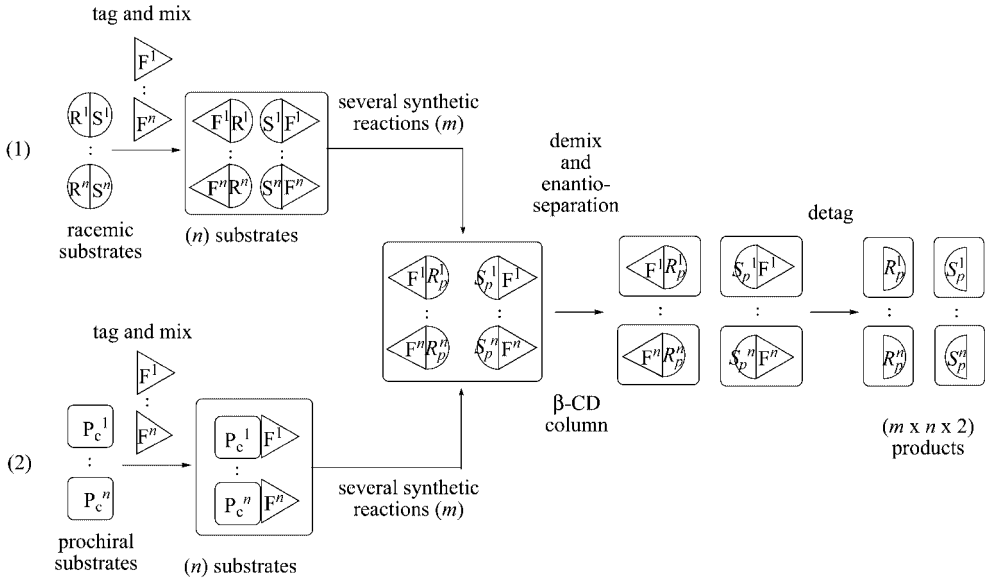
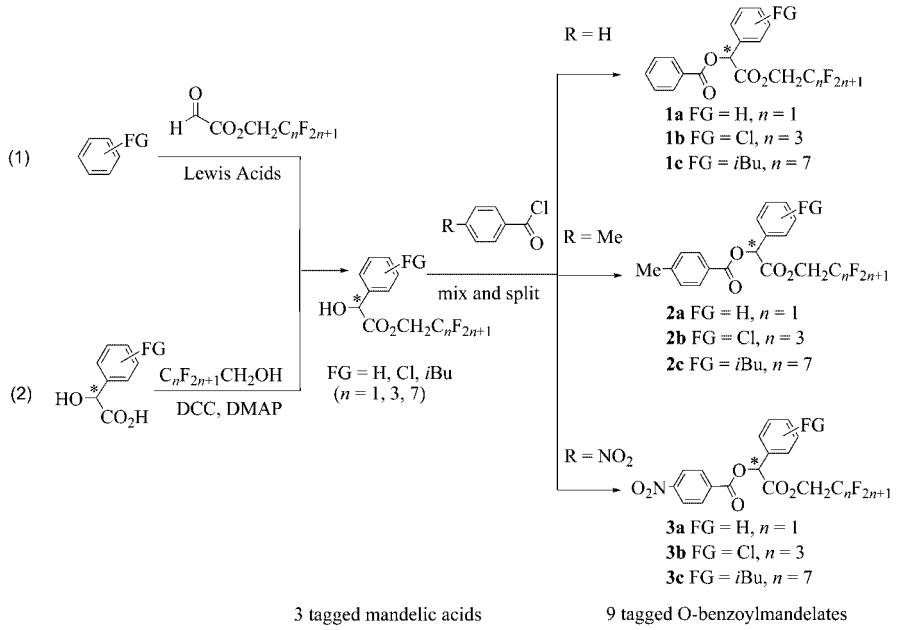


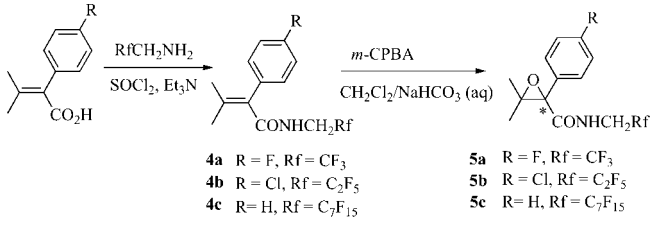
Scheme 1. Fluorous 'racemic' mixture synthesis.



Scheme 2. Fluorous "racemic" mixture synthesis of *O*-benzoylmandelate derivatives.

The resulting 3-mix/3-split mixture of *O*-benzoylmandelate derivatives and their enantiomers were simultaneously demixed and enantioseparated by using a β-CD column to give $3 \times 3 \times 2$ enantiopure *O*-benzoylmandelate derivatives (Figure 1). Each mixture of *O*-benzoylmandelate derivatives was eluted in the order of increasing length of the fluorous tags from CF_3 to C_7F_{15} (**a**, **b**, **c**). Each enantiomer pair was simultaneously resolved with an OA-7500 column with the (*S*)(–)-enantiomers as the faster eluents. The configuration of the enantiomers can be determined by CD or OR spectroscopy [e.g. Figure 1 (1′)].[9,10] Thus, $m \times n \times 2$ of enantiopure *O*-benzoylmandelate derivatives and their enantiomers were separated.

Simultaneous demixing and enantioseparation of the products was next examined with a prochiral starting material, in the context of epoxidation of crotonamide deriva-



Scheme 3. Epoxidation of crotonamide derivatives for FRMS.

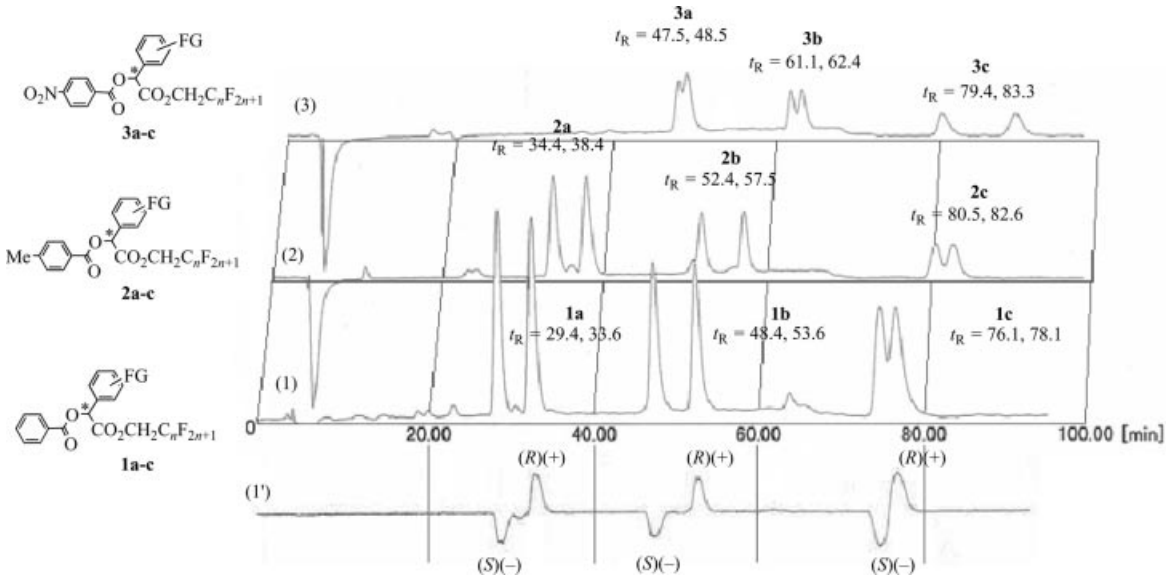


Figure 1. Demixing and enantioseparation of *O*-benzoylmandelate derivatives (**1a**–**c**, **2a**–**c**, **3a**–**c**). Column: OA-7500, mobile phase: methanol/water (0 to 60 min, 65:35 to 85:15, v/v), flow rate: 0.7 mL min^{-1}, detector: 254 nm UV (1),(2),(3) and 235 nm CD (1′), column temperature: 20 °C.

tives (Scheme 3). Prochiral crotonamide derivatives as starting materials bearing different length of fluorous tags (CF_3, C_2F_5 and C_7F_{15}) were synthesized (**4a**–**c**). Equimolar portions of these crotonamides were mixed and underwent epoxidation with achiral *m*-chloroperbenzoic acid (*m*-CPBA) to give a racemic mixture of three fluorous-tagged compounds (**5a**–**c**). The mixture thus obtained was demixed by a β-CD column to give six enantiomers in the order of increasing length of fluorous tags (**5a**, **b**, **c**) (Figure 2).

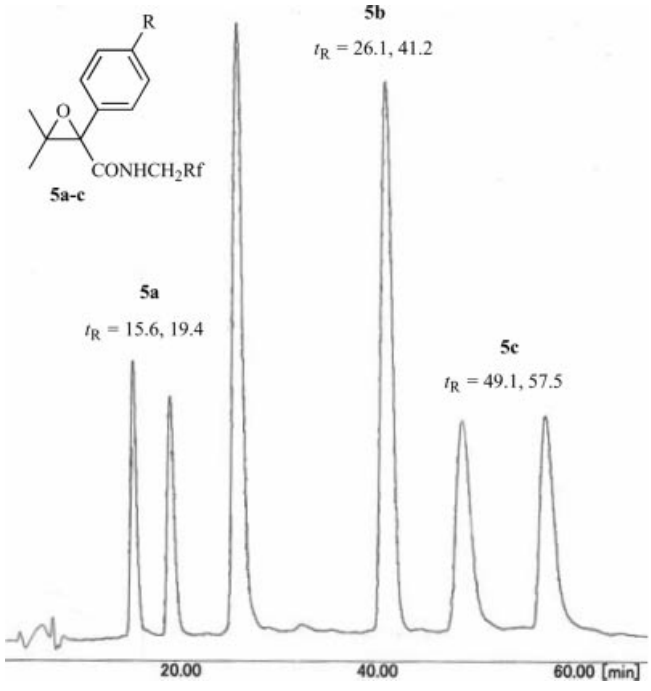


Figure 2. Demixing and enantioseparation of racemic epoxide derivatives with β-CD column. Column: OA-7500, mobile phase: methanol/water (0 to 50 min, 65:35 to 75:25, v/v), flow rate: 0.4 mL min^{-1}, detector: absorption at 220 nm, column temperature: 20 °C.

In conclusion, we have thus reported the concept of FRMS and demonstrated the two types of proof-of-concept experiments. Each mixture of racemic *O*-benzoylmandelate derivatives and prochiral crotonamide derivatives bearing different length of fluorous cleavable tags were taken through a segmented reaction to provide their enantiomers as well as their individual derivatives by virtue of chiral β-CD columns. Further applications of FRMS are now in progress.

Experimental Section

HPLC analysis was performed with β-CD columns (OA-7500, 25 cm × 4.6 mm i.d.) with a GL cart (0.5 cm × 4.6 mm i.d.) as a guard column and a JASCO HPLC system [pump: PU-1580, gradient unit: LG-1580-04, degasser: DG-1580-54, column oven: CO-1560, UV and CD detector: CD-995 (1595), auto sampler: AS-1555]. Peak area was calculated by JASCO-BORWIN as an automatic integrator. HPLC-grade methanol and water were purchased from Kanto Chemical.

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