Fluorous diastereomeric mixture synthesis (FDMS) of hydantoin-fused hexahydrochromeno[4,3-*b*]pyrroles†‡

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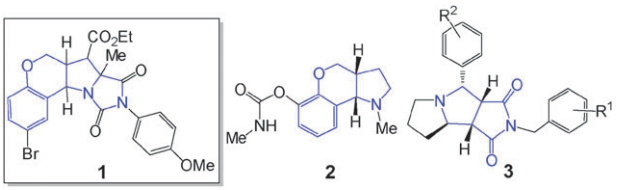
Fluorous diastereomeric mixture synthesis (FDMS) is introduced and demonstrated in the synthesis of six diastereomers of hydantoin-fused hexahydrochromeno[4,3-*b*]pyrroles.

Since it was introduced by the Curran group in 2001, fluorous mixture synthesis (FMS)[1] has become a powerful tool for solution-phase synthesis of natural product analogs,[2] diastereomers,[3] enantiomers[4] as well as drug-like compound libraries,[5] glycosides,[6] oligomers,[7] and dendrimers.[8] FMS requires a set of different length fluorous tags to be attached to a set of analogous reactants and relies on fluorous liquid chromatography (LC) to separate the mixture. In the fluorous racemic mixture synthesis (FRMS) developed by the Mikami group, two enantiomers are attached to a single fluorous tag and chiral LC is used to separate the racemic mixture.[9] Introduced in this paper is fluorous diastereomeric mixture synthesis (FDMS) which employs a single fluorous tag to attach to diastereomers. The diastereomeric intermediates are isolated from the reaction mixture by fluorous solid-phase extraction (F-SPE). The tag-cleaved diastereomeric products are separated by reverse-phase LC instead of fluorous or chiral LC.

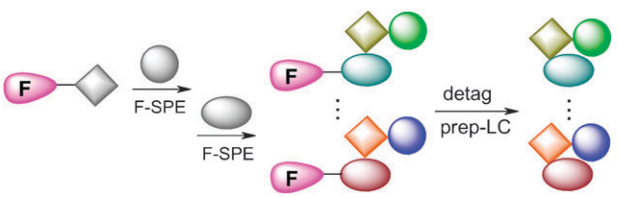
In diversity-oriented synthesis, generation of stereoisomers is equally important to skeleton and substitution variations.[10] Preparation of diastereomers for QSAR studies is one of the major tasks in medicinal and agricultural chemistries. Traditionally, diastereomers are prepared in parallel and handled individually from start to finish. Mixture synthesis of diastereomeric products is possible in principle since the final product isomers can often be separated by prep-LC; however, it is unclear how to purify diastereomeric intermediates without separating them from each other. FDMS addresses this problem by collecting all the fluorous intermediates in a single F-SPE fraction.[11] The diastereomeric mixture can be treated as a single component in the multistep synthesis (Scheme 1).

Hydantoin-fused hexahydrochromeno[4,3-*b*]pyrrole **1** was selected as the target molecule for the proof-of-principle experiment of FDMS. This compound has four stereogenic centres on the central pyrrolidine ring which could have many diastereomers. The hexahydrochromeno[4,3-*b*]pyrrole moiety in **1** can be found in compound **2** which is as potent as physostigmine against human acetylcholinesterase and butyrylcholinesterase for potential treatment of Alzheimer's disease.[12] Compound **1** is also related to tricyclic thrombin inhibitor **3**.[13]



A stereoselective solution-phase synthesis of hydantoin-fused hexahydrochromeno[4,3-*b*]pyrrole **8** has been developed by the Kurth group (Scheme 2).[14] It has the following three steps: (1) AgOAc-promoted intramolecular 1,3-dipolar cycloaddition of **4** with **5** to form hexahydrochromeno[4,3-*b*]pyrrole **6** as a single *trans*-fused compound;[15] (2) reaction of **6** with an isocyanate to form urea **7**; and (3) cyclization of **7** to form **8** as a single diastereomer or a pair of epimers.

In order to generate more stereoisomers, we made the following two modifications to Kurth's route: (1) The 1,3-dipolar cycloaddition of **9** and fluorous L-alanine ester **10** was carried out under microwave heating without using a metal salt. It is known in the literature that both metal-free and microwave heating generate *cis*- and *trans*-fused cycloaddition products.[16,17] (2) We used alanine ester **10** to afford cycloaddition products with an additional steric variation at the pyrrolidine 2-position (Scheme 3). The LC-MS analysis of the reaction mixture gave four major peaks in a ratio of 9 : 4 : 59 : 28 together with a minor peak (less than 1%) which could be an epimer of one of the four major components. The reaction mixture was loaded directly onto an F-SPE cartridge and eluted with 80 : 20 MeOH–H_2O to remove all the non-fluorous components and then eluted with MeOH to collect the mixture of **11a–d** in a single fraction.[11,18]



Scheme 1 FDMS (diastereomers are shown in different colours).

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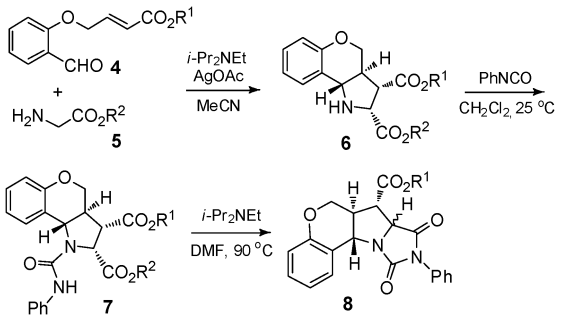
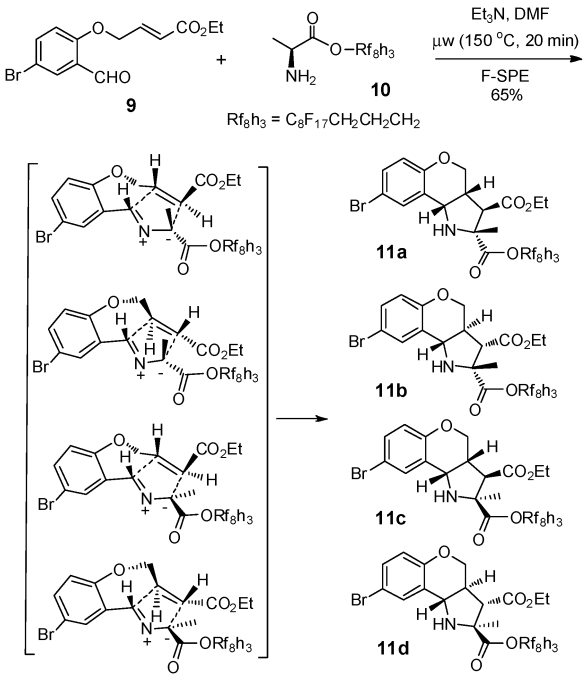


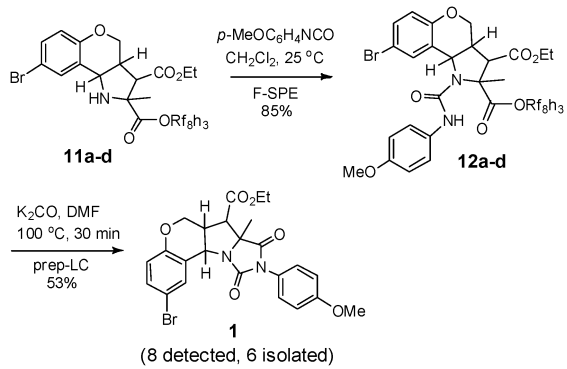
Scheme 2 Kurth's route for diastereoselective synthesis.

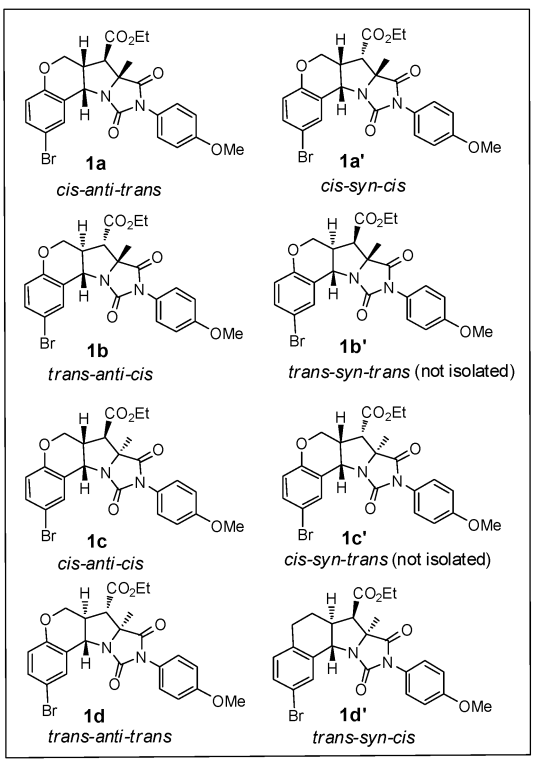


Scheme 3 Formation of four diastereomers of **11**.

The mixture of compounds **11a–d** was reacted with an isocyanate to form ureas **12a–d** (Scheme 4). No new diastereomers were generated at this step. After F-SPE purification, the mixture of **12a–d** was subjected to K_2CO_3-promoted cyclization to cleave the fluorous tag and form the hydantoin ring. A total of eight diastereomers were detected by LC-MS. Among them, six diastereomers (**1a** : **1b** : **1c** : **1d** : **1a′** : **1d′** = 24 : 39 : 19 : 4 : 4 : 10) were separated by prep-scale reverse-phase LC in a combined yield of 53%. Compounds **1b′** and **1c′** were present in trace amounts and could not be isolated.

The structures of six isolated diastereomers were established by analysis of a battery of ^{1}H NMR spectra. From the 1D spectra, the compounds were classed into two groups of three with either a *cis* ($J_{2,7}$ = 6–8 Hz) or *trans* ($J_{2,7}$ = 12 Hz) hexahydrochromeno[4,3-*b*]pyrrole ring fusion. From there, analysis of the 2D-NOE spectra provided the assignments of the remaining stereocenters. To support this spectroscopic analysis, a single crystal of **1a** was obtained for X-ray crystal structure analysis to confirm that it is the *cis–anti–trans* isomer (Fig. 1). Diastereomers **1a–d** are the expected products. Diastereomers **1a′** and **1d′** in small amounts (4% and 10%) were generated by the epimerization of the ester group at the





Scheme 4 Formation of eight diastereomers of **1**.

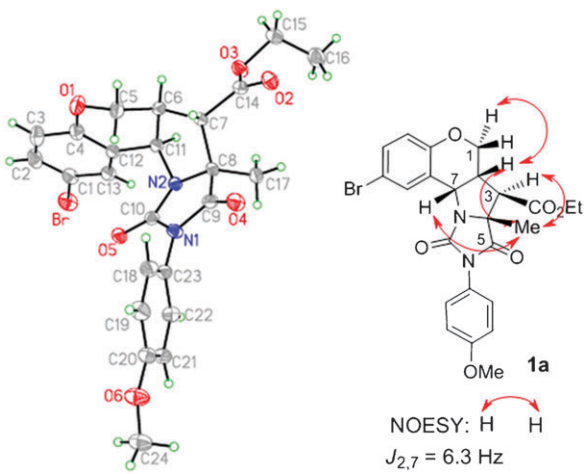


Fig. 1 X-ray structure and ^{1}H NMR (NOESY) of **1a**.[19]

3-position of the pyrrolidine. Compound **1a′** is the epimer of **1a** and compound **1d′** is the epimer of **1d**. Another two

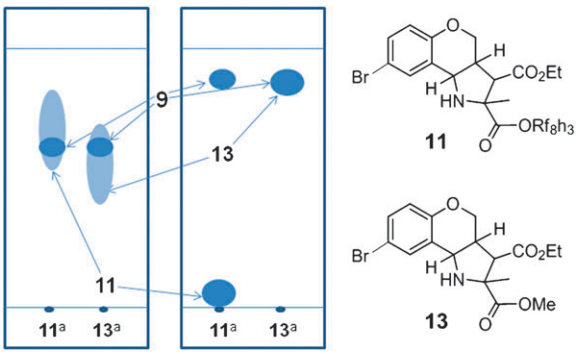


Fig. 2 TLC of crude compounds **11** and **13**. Left, on normal silica gel developed with 2 : 1 hexanes-EtOAc; right, on fluorous silica gel developed with 4 : 1 MeOH–H_2O. [a]Crude sample containing unreacted compound **9**.

diastereomers detected by LC-MS but unable to be isolated due to the very small amount could be **1b′** and **1c′** which are the epimers of **1b** and **1c**, respectively.

To confirm the epimerization could happen at the hydantoin formation step, a major 1,3-dipolar cycloaddition product **11a** isolated from the reaction mixture was used for urea formation and subsequent cyclization reactions. A single urea compound **12a** was formed, but two hydantoin-fused compounds **1a** and **1a′** were detected in a ratio of 2 : 1.

To show the advantage of FDMS, a non-fluorous diastereomeric mixture **13** prepared by the reaction of **9** and L-alanine methyl ester was tested side-by-side with fluorous diastereomeric mixture **11** on normal and fluorous TLC plates, respectively (Fig. 2). On the normal silica gel, crude reaction mixtures **11** and **13** both gave tailed spots because the diastereomers in each mixture have slightly different polarities. Compounds **11** and **13** could not be separated from unreacted compound **9**. However, on the fluorous TLC, crude sample **11** gave a spot at the baseline and it was well-separated from **9**. Because it is a fluorous tag-based separation, diastereomers bearing the same tag should have the same retention on fluorous TLC. On the other hand, crude sample **13** had almost no retention on fluorous TLC and gave a mixture spot close to the solvent front. This TLC experiment explains why fluorous-tagged diastereomeric mixture **11** can be collected as a single fraction and separated from non-fluorous component **9** by F-SPE.

In summary, FDMS is developed as a new solution-phase method for the synthesis of diastereomeric products. The mixture of fluorous-tagged diastereomeric intermediates could be easily isolated by F-SPE without separation from each other, which overcomes the major separation issue and increases the efficiency of mixture synthesis of diastereomers. In this project, eight possible diastereomers of hydantoin-fused hexahydrochromeno[4,3-*b*]pyrroles were synthesized by FDMS and six of them were isolated for structure characterizations. Use of FDMS to prepare compound libraries with substitution, skeleton, and stereochemistry diversities is in progress and will be reported in due course.

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18 (*a*) Fluorous media available from Fluorous Technologies, Inc; (*b*) WZ and DPC hold an equity interest in this company.

19 Crystal data for compound **1a**: $C_{24}H_{23}BrN_2O_6$, M = 515.35, monoclinic, a = 13.396(2), b = 6.8114(12), c = 24.048(4) Å, β = 90.825(4)°, V = 2194.1(7) Å^3, T = 173 K, space group $P2_1/c$ (no. 14), Z = 4, 26 044 reflections measured, 7225 unique (R_{int} = 0.054) which were used in all calculations. The final wR(F2) was 0.1345 (using all data).

