

# Fluorous Parallel Synthesis of a Piperazinedione-Fused Tricyclic Compound Library

Stefan Werner,<sup>†</sup> Simon D. Nielsen,<sup>†</sup> Peter Wipf,<sup>†</sup> David M. Turner,<sup>†</sup>  
Peter G. Chambers,<sup>†</sup> Steven J. Geib,<sup>†</sup> Dennis P. Curran,<sup>†</sup> and Wei Zhang<sup>\*,‡,§</sup>

Center for Chemical Methodologies and Library Development (UPCMLD), Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, Fluorous Technologies, Inc., 970 William Pitt Way, Pittsburgh, Pennsylvania 15238, and Department of Chemistry, University of Massachusetts, 100 Morrissey Boulevard, Boston, Massachusetts 02125

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A fluorous-linker-assisted solution-phase protocol has been developed and applied to parallel synthesis of a piperazinedione-fused tricyclic compound library. The one-pot [3 + 2] cycloaddition of fluorous amino esters, aldehydes, and maleimides afforded bicyclic proline derivatives. The intermediates were subjected to N-acylation with chloroacetyl chloride, followed by displacement reactions with amines. Linker cleavage with concomitant lactamization yielded the final products. Microwave heating was employed to facilitate several reaction steps and fluorous solid phase extraction (F-SPE) was employed to purify the intermediates. During the method development, a small library containing sixteen analogs was prepared. The optimized conditions were applied to the synthesis of a production library containing ninety analogs.

## Introduction

Multicomponent reactions (MCRs) represent a convergent and atom economical way to construct molecules with complex structures.<sup>1</sup> These reactions are increasingly popular in the synthesis of chemical libraries for lead generation programs at pharmaceutical companies.<sup>2</sup> In MCRs, one or more components are usually used in excess to drive the reaction to completion. The excess of starting materials may complicate the product purification. Having one of the building blocks attached to solid support<sup>3</sup> or attached to a fluorous linker<sup>4</sup> can facilitate the separation of MCR products.

Fluorous separations are based on highly selective fluorophilic interactions between the fluorous molecules and the separation media.<sup>5</sup> Fluorous solid phase extraction (F-SPE) separates a mixture based on the presence or absence of fluorinated components.<sup>6</sup> In contrast to molecules bound to a solid support, fluorous molecules are soluble in many organic solvents, reactions can be monitored by techniques like TLC, NMR, LC-MS, fluorous reagents can be used in equimolar ratios, and conventional solution phase protocols can be applied to fluorous chemistry without significant optimization.

We recently reported a fluorous diversity-oriented synthesis of three novel heterocyclic scaffolds.<sup>7</sup> The common bicyclic proline intermediates **4** were prepared by a one-pot, three-component [3 + 2] cycloaddition involving fluorous amino esters, aldehydes, and maleimides.<sup>8</sup> The

intermediates then underwent different postcondensation modifications to form hydantoin-fused tricyclic compounds **2**, piperazinedione-fused tricyclic compounds **1**, and benzodiazapinedione-fused tricyclic compounds **3**, respectively (Scheme 1). A 420-membered library of **2** and a 60-membered library of **3** have been prepared by fluorous mixture synthesis.<sup>9</sup> Described in this paper is the development and production of a 90-membered library of **1** by fluorous parallel synthesis.

Tricyclic piperazinediones library **1** is structurally comparable to tricyclic thrombin inhibitors **5**<sup>10</sup> and diketopiperazine-based inhibitors **6** of human hormone-sensitive lipase (Scheme 2).<sup>11</sup> Synthesis and screening of tricyclic piperazinedione analogs may provide additional QSAR information.

## Results and Discussion

**Library Development.** The synthesis of tricyclic piperazinediones has four steps: (1) one-pot [3 + 2] cycloaddition of fluorous amino ester **7**, aldehyde **8**, and maleimide **9** to afford bicyclic proline derivative **4**; (2) N-acylation of **4** with chloroacetyl chloride to form **11**; (3) displacement of chloride on **11** with amine **10** to form **12**; and (4) linker cleavage with concomitant lactamization to yield final product **1**. Each reaction step was optimized during the library development. Sixteen final products **1** were prepared during the method development by combining a selection of building blocks **7**, **8**, **9**, and **10**, as shown in Scheme 3.

The one-pot, three component [3 + 2] cycloaddition reactions of **7**, **8**, and **9** were performed under microwave irradiation at 150 °C for 30 min to give four fluorous proline derivatives **4**{1-2,1-2,1}.<sup>7</sup> The use of oil bath heating was also tested but resulted in lower yields. For example, compound **4**{1,1,1} was produced in 94% yield under

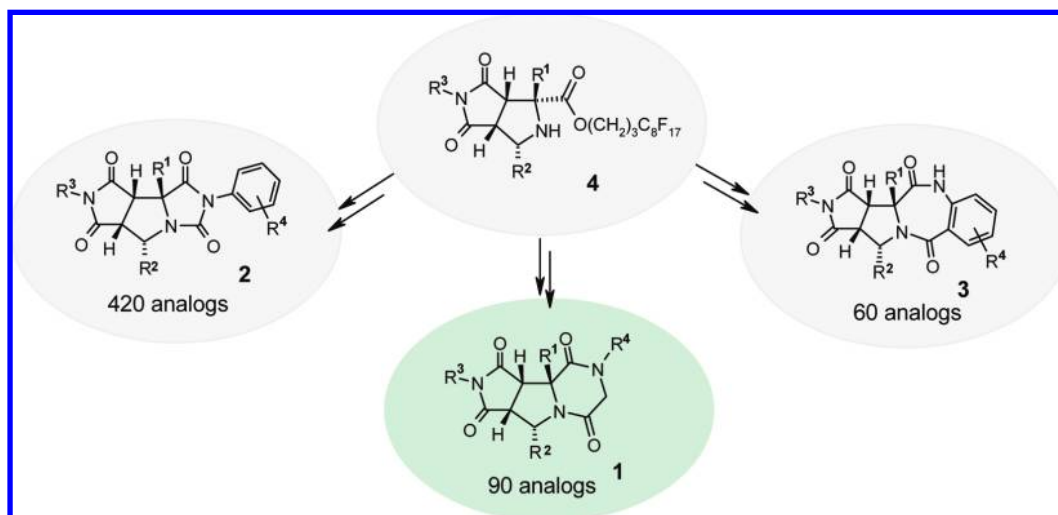
\* To whom correspondence should be addressed. E-mail: wei2.zhang@umb.edu.

<sup>†</sup> University of Pittsburgh.

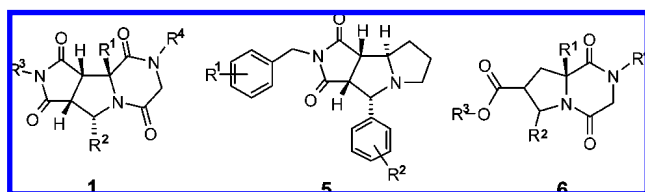
<sup>‡</sup> Fluorous Technologies, Inc.

<sup>§</sup> University of Massachusetts.

## Scheme 1. Diversity-Oriented Synthesis of Three Heterocyclic Library Scaffolds



## Scheme 2. Library Scaffold 1 and Related Biologically Active Molecules



microwave heating at 130 °C for 30 min, whereas the same compound was produced in 72% under oil bath heating at 130 °C for 1 h. We found that the yield of these [3 + 2] cycloaddition reactions could be improved by reacting the aldehyde and amine first in the presence of triethylamine, followed by the addition of the corresponding maleimide and continued heating in the microwave at 150 °C for 30 min. The fluoros amino esters **7** {1–2} were used as the limiting reagents, and the other two building blocks were used in slight excess to ensure the consumption of the fluoros component so that the unreacted starting material, as well as base and solvent, could be easily removed by F-SPE. Nonfluorous components were eluted with 4:1 MeOH/H<sub>2</sub>O, and the fluoros product **4** was eluted with MeOH. In the case of R<sup>1</sup> being a benzyl substituent, flash chromatography was used for additional purification. The purity of all four products was >90% as determined by <sup>1</sup>H NMR.

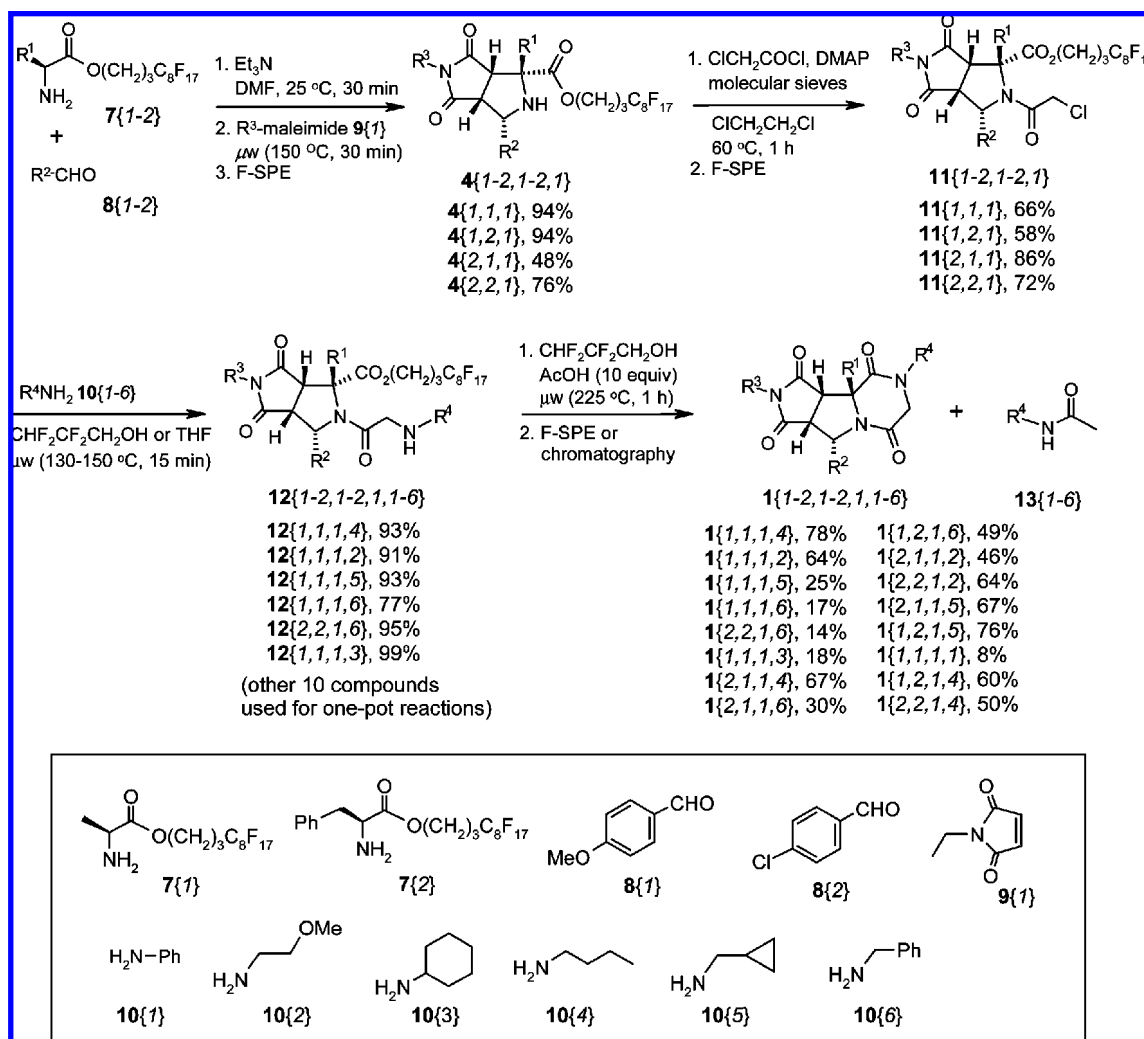
The acylation of **4** with chloroacetyl chloride was performed under conventional heating at 60 °C for 1 h. High yields were obtained in dichloroethane in the presence of molecular sieves and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP). The addition of 15 equiv of chloroacetyl chloride was completed in two portions and the starting material was usually consumed after 1 h. Purification by flash chromatography gave four products **11** {1–2, 1–2, 1} in 58–86% yields and ELS purities >90%.

Two different approaches were developed for the last two steps. We only prepared sixteen of possible twenty-four compounds of **12** {1–2, 1–2, 1, 1–6}. Among them, six were isolated and then used for the next round of cyclization reactions to produce the final products. Ten were used in a one-pot procedure for the synthesis of the final products. For

the approach involving the isolation of **12**,  $\alpha$ -chloroamide **11** and primary amine **10** in THF were heated under microwave irradiation at 150 °C for 15 min. The crude product was purified by F-SPE. The first elution solvent 4:1 MeOH/H<sub>2</sub>O contained 10 equiv of tetramethylguanidine to remove the HCl formed in the displacement reaction and to ensure that the product **12** was obtained as the free amine. The products **12** were produced in high yields with excellent purities. The lactamization of **12** to form the final products **1** proved to be a difficult step, and a screening of a range of different reaction conditions was carried out with substrate **12** {1,1,1,4}. This compound was converted to **1** {1,1,1,4} by heating in isopropanol under microwave at 180 °C for 12 h. For the lactamizations of other substrates **12**, they were heated in 2,2,3,3-tetrafluoropropanol with 10 equiv of acetic acid at 250 °C for 1 h. The acetic acid prevented the decomposition of the starting material. The products were purified by F-SPE to give corresponding tricyclic piperazinediones **12** in modest to good yield and excellent purity.

For the one-pot displacement and lactamization reactions, a solution of  $\alpha$ -chloroamide **11** and primary amine **10** in 2,2,3,3-tetrafluoropropanol were heated under microwave conditions at 150 °C for 15 min, then 10 equiv of acetic acid were added, and the mixture was heated in the microwave at 250 °C for 1 h. The corresponding tricyclic piperazinediones **1** were isolated in modest to good yields after chromatography. However, in this one-pot procedure acetylamine **13** was observed as a side product and sometimes coeluted with the final compound.

Compounds **4**, **11**, **12**, and **1** were prepared during the library development stage and were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and mass spectrometry. The aromatic resonances in the <sup>1</sup>H NMR spectra of compounds **11**, **12**, and **1** (see Supporting Information) displayed various stages of coalescence. Resonances for pairs of symmetry related protons on the aryl ring of R<sup>2</sup> (H2/H5 and H3/H4) appeared as either broad two-proton signals or more or less broad pairs of one-proton signals. Clearly the rotation of the CH–Ar bond of the R<sup>2</sup> substituent is occurring on the NMR time scale at 300 MHz.<sup>12</sup> We will report in more detail on this unusual phenomenon in a later paper.

**Scheme 3.** Sixteen-Member Development Library of **1** and Building Blocks (7–10)

**Library Production.** The synthesis of a 90-compound library of piperazinedione-fused tricyclic compounds **1** was undertaken. Four sets of building blocks were selected which included two fluorous amino esters **7**{1–2}, three aldehydes **8**{3–5}, three maleimides **9**{2–4}, and five amines **10**{5–9} (Scheme 4). With the exception of compounds **7**{1–2} and **10**{5–6}, all other building blocks are different from those used in the library development stage.

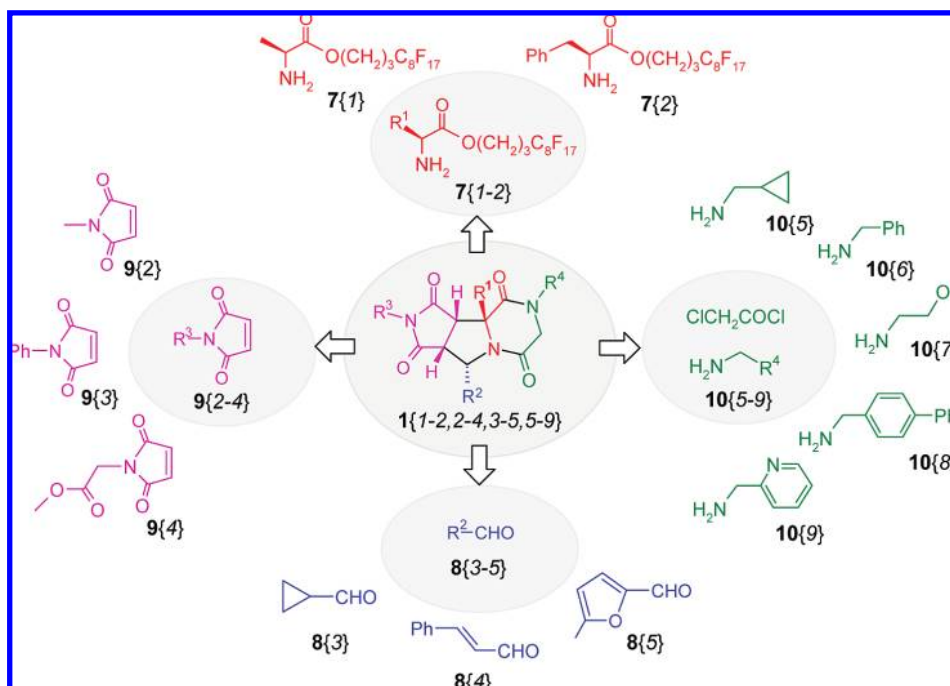
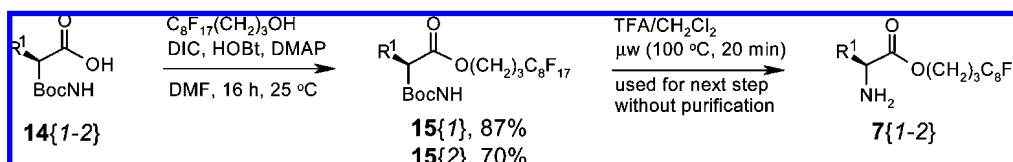
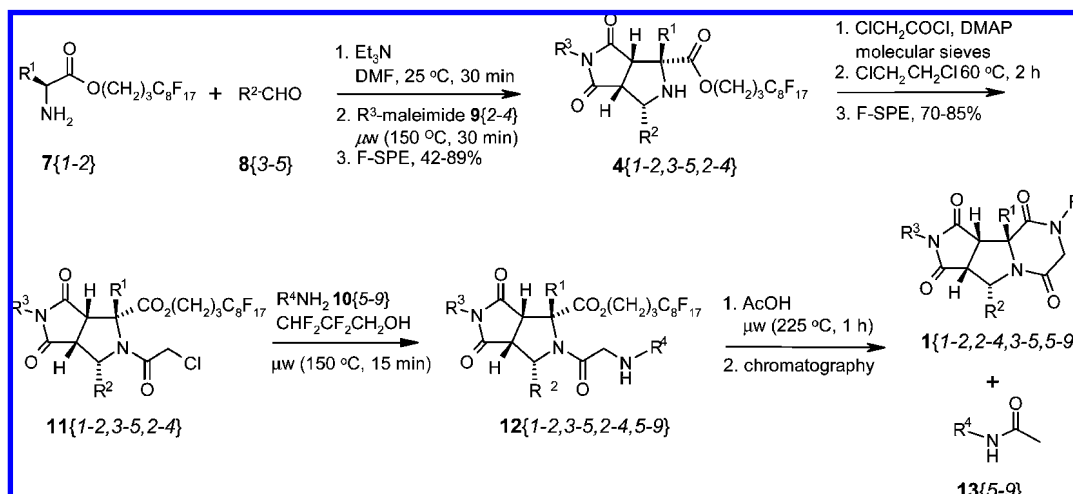
Fluorous amino esters **7**{1–2} were prepared from the corresponding amino acids. 3-(Perfluorooctyl)propanol as the fluorous linker was attached to the Boc-protected amino acids **14**{1–2} to form esters **15**{1–2} under standard conditions using *N,N'*-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) as the coupling agents. The Boc groups were removed from **15**{1–2} with 10% TFA/CH<sub>2</sub>Cl<sub>2</sub> solution under microwave heating at 100 °C for 20 min to yield amino esters **7**{1–2} (Scheme 5).

The [3 + 2] cycloaddition reactions for the preparation of compound **4** were performed using the optimized conditions (Scheme 6 and Table 1). Aldehydes **8** and amines **7** were first reacted in the presence of triethylamine, followed by addition of maleimides **9**. The mixtures were heated in the microwave reactor at 150 °C for 30 min and the products were purified by F-SPE. The fluorophilic fraction contained only the fluorous addition products **4**{1–2, 3–5, 2–4}. With

all alanine derivatives, bicycles **4**{1, 3–5, 2–4} were obtained as single diastereomers in good yields (average 75%, including Boc-deprotection) and excellent purities (average 94%). The benzyl substituent at R<sup>1</sup> led to a mixture of diastereomers and lower yields (average 49%, including Boc-deprotection). Traditional chromatography was used in several cases to obtain intermediates in sufficient purity (average 94%).

The acylation reactions of **4** were performed in the presence of molecular sieves and catalytic amounts of DMAP under conventional heating at 60 °C for 1 h. The addition of 15 equiv of chloroacetyl chloride was completed in two portions. While the acylation of alanine derivatives led again to good yields and purities (average yield 70% and average purity 93% after F-SPE), it was observed that for R<sup>1</sup> = benzyl only the major diastereomer of **4**{2, 3–5, 2–4} could be acylated, probably because of steric reasons (Table 2). In the case of **4**{2, 4, 2}, the two diastereomers had been separated. Acylation of the major diastereomer led to **11**{2, 4, 2} in 88% yield (100% purity), while no conversion was observed for the minor diastereomer under otherwise identical reaction conditions. The minor diastereomer could be recovered from the reaction mixture.

The nucleophilic substitution of the α-chloro amides **11**{1–2, 3–5, 2–4} with primary amines **10**{5–9}, followed

Scheme 4. Ninety-Member Production Library of **1** and Building Blocks (7–10)Scheme 5. Preparation of Fluorous Amino Esters **7**{1–2}Scheme 6. Preparation of Tricyclic Piperazinediones **1**{1–2,2–4,3–5,5–9}

by lactamization of **11**{1–2,3–5,2–4,5–9} to form final products **1**{1–2,3–5,2–4,5–9} was performed using the one-pot procedure.  $\alpha$ -Chloroamides **11** and primary amine **10** in 2,2,3,3-tetrafluoropropanol were heated under microwave conditions at 150 °C for 15 min; then 10 equiv of acetic acid was added, and the mixture was heated in the microwave reactor at 250 °C for 1 h. Acylated amines **13**{5–9} were observed as side products and coeluted with the target compounds in several cases. To solve this problem, the protocol was changed halfway through the library synthesis (see footnotes in Table 3). Insertion of a third F-SPE purification after the  $S_N$  reaction removed the excess amine

**Table 1.** Yields [%] for the Synthesis of Fluorous Bicycles **4**{1–2,3–5,2–4} from **7**{1–2}, **8**{3–5}, and **9**{2–4} (Purity by ELSD [%])

<b>4</b> {1–2,3–5,2–4}	<b>7</b> {1}	<b>7</b> {1}	<b>7</b> {1}	<b>7</b> {2}	<b>7</b> {2}	<b>7</b> {2}
	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}
<b>8</b> {3}	75 (93)	79 (89)	75 (98)	78	64 (86) <sup>a</sup>	35 (87) <sup>a</sup>
<b>8</b> {4}	85 (92)	42 (86)	84 (96)	30 (94) <sup>b</sup>	19 (99) <sup>a</sup>	27 <sup>a</sup>
<b>8</b> {5}	69 (97)	81 (98)	82 (96)	50 (97) <sup>a</sup>	50 (98) <sup>a</sup>	80 (100)

<sup>a</sup> Yield after chromatography; a single diastereomer was obtained after chromatography. <sup>b</sup> Major diastereomer (second eluting).

and prevented the formation of amides **15**{5–9} after addition of acetic acid in the last step. Although the additional

**Table 2.** Yields [%] for the Synthesis of Amides **11**{1-2,3-5,2-4} from **4**{1-2,3-5,2-4} (Purity by ELSD in [%])

<b>11</b> {1-2,3-5,2-4}	<b>7</b> {1}	<b>7</b> {1}	<b>7</b> {1}	<b>7</b> {2}	<b>7</b> {2}	<b>7</b> {2}
	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}
<b>8</b> {3}	43 (89)	76 (93)		80 (83)	72 (84)	77 (93)
<b>8</b> {4}	73 (88)	80 (97)	85 (99)	88 (100) <sup>a</sup>	44 (98)	74 (100)
<b>8</b> {5}	62 (96)	75 (99)	61 (81)	80 (100)	10 (98)	74 (100)

<sup>a</sup>From the second eluting diastereomer of **7**{2,4,2}, acylation of minor diastereomer failed.

purification step led to lower isolated yields (average 30% instead 53% for the one-pot protocol, R<sup>1</sup> = Me), the target compounds **1**{1-2,3-5,2-4,5-9} were no longer contaminated with **13**{5-9} (average purity 97% instead of 92% for the one-pot protocol, R<sup>1</sup> = Me). These results emphasize the power of F-SPE as an orthogonal purification strategy to traditional chromatography on silica. Although thirty-eight out of forty-five benzyl derivatives **1**{2,3-5,2-4,5-9} could be isolated in excellent purities (average 96%), the yields were low for this branch of the library (average 28%).

The configuration of the library members was determined with the help of a crystal structure analysis. The three-component [3 + 2] cycloaddition reaction was diastereoselective in the case of the alanine derivatives (R<sup>1</sup> = Me), and the stereochemistry has been confirmed by an X-ray structure analysis described in our previous paper.<sup>7</sup> A mixture of diastereomers was obtained in the case of the phenylalanine derivatives (R<sup>1</sup> = Bn). Only the major diastereomer underwent the subsequent acylation and ring closure. This diastereomer shows the same configuration as the one obtained from the alanine series (Figure 1), so we conclude that all final library members have the same core configuration.

**Purity Analysis.** Altogether seventy-two tricyclic piperazinediones **1**{1-2,3-5,2-4,5-9} were synthesized. All compounds were analyzed by LC/MS-ELSD (Tables 1-3). Sixty-three compounds passed the purity criteria of 85% by ELSD for the UPCMLD compound collection. The average purity by ELSD of the accepted library members was 98% (Table 3).

## Conclusions

With the help of the fluoros linker and F-SPE for intermediate purification, a library containing 90 tricyclic piperazinediones was synthesized, and 63 final products were obtained with in greater than 85% purity. The key steps of three-component [3 + 2] cycloaddition reaction and detag lactamization cyclization have been optimized for library production. All compounds have been submitted to the NIH repository and are currently being evaluated in several high-throughput screening programs. Results on their biological activities can be found in PubChem (<http://pubchem.ncbi.nlm.nih.gov>).

## Experimental Section

**General.** All solvents or reagents were used without further purification. Reactions were monitored by TLC analysis (EM Science precoated silica gel 60 F<sub>254</sub> plates, 250 mm layer thickness), and visualization was accomplished with a 254 nm UV light and by staining with Vaughn's

reagent (4.8 g (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub>·4H<sub>2</sub>O, 0.2 g Ce(SO<sub>4</sub>)<sub>2</sub>·4H<sub>2</sub>O in 10 mL conc. H<sub>2</sub>SO<sub>4</sub> and 90 mL H<sub>2</sub>O) and KMnO<sub>4</sub> (1.0 g KMnO<sub>4</sub>, 1.0 g K<sub>2</sub>CO<sub>3</sub>, 2 mL 5% aqueous NaOH, 100 mL H<sub>2</sub>O). NMR spectra were recorded in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> (298 K) at 300.1 MHz (<sup>1</sup>H) or 75.5 MHz (<sup>13</sup>C) using a Bruker Avance 300 with XWIN-NMR software. Chemical Shifts (δ) are reported in parts per million (ppm). Tetramethylsilane (<sup>1</sup>H), chloroform-*d* (<sup>13</sup>C), or DMSO-*d*<sub>6</sub> (<sup>13</sup>C) were used as internal standards. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, app = apparent), integration and coupling constants. IR spectra were obtained on a Nicolet AVATAR 360 FTIR ESP Spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument (EI) or a Waters Q-ToF mass spectrometer (ESI). Compounds were analyzed by reverse-phase HPLC (Alltech Prevail C-18, 100 × 4.6 mm, 1 mL/min, 20-80% MeCN, 80-20% H<sub>2</sub>O) with UV (210 and 254 nm), ELS (Nebulizer 45 °C, Evaporator 45 °C, N<sub>2</sub> flow 1.25 SLM), and MS detection using a Thermo Finnigan Surveyor LC and LCQ Advantage MS system (ESI positive mode) or a Waters LC-MS system.

**General Procedure for the Preparation of Fluorous Esters **15**{1-2}.** A solution of Boc-L-alanine **14**{1} (11.0 g, 58.3 mmol, 1.5 equiv) in DMF (85 mL) was treated with 3-(perfluorooctyl)propanol (18.9 g, 38.9 mmol, 1.0 equiv), *N,N'*-diisopropylcarbodiimide (7.36 g, 58.3 mmol, 1.5 equiv), HOBt (7.88 g, 58.3 mmol, 1.5 equiv), and DMAP (0.713 g, 5.83 mmol, 0.15 equiv) and was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and washed three times with water (100 mL). The organic fraction was washed with brine (100 mL), dried over magnesium sulfate, and concentrated. Purification by chromatography over SiO<sub>2</sub> provided 21.9 g (34.0 mmol, 87%) of fluoros ester **15**{1}, while 1.67 g of 3-(perfluorooctyl)propanol (3.50 mmol, 9%) was recovered.

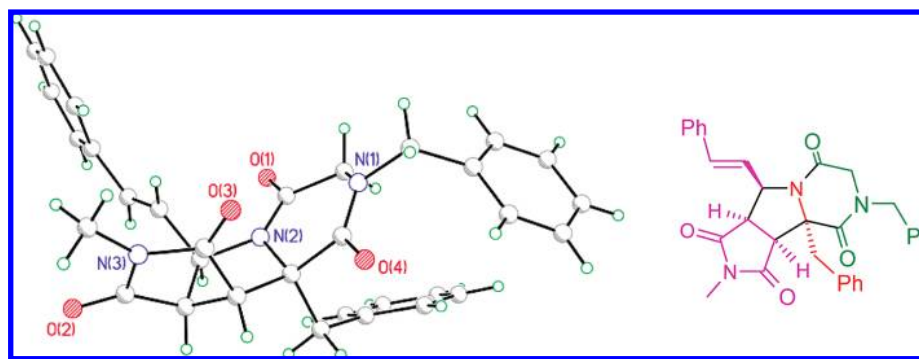
**General Procedure for the Preparation of Bicycles **4**{1-2,3-5,2-4}.** Fluorous ester **15**{1} (2.49 g, 4.54 mmol, 1.0 equiv) was dissolved in a solution of TFA in DCM (10 wt%, 15 mL) and irradiated at 100 °C for 20 min in a Biotage Initiator microwave reactor. All volatile components were removed in a Genevac HT-4 parallel evaporation system, and the residue was dissolved in DMF (15 mL). Cinnamaldehyde **8**{4} (0.720 g, 5.45 mmol, 1.2 equiv) and triethylamine (1.38 g, 13.6 mmol, 3.0 equiv) were added, and the reaction mixture was stirred for 30 min at room temperature. Then, *N*-methylmaleimide **9**{2} (0.757 g, 6.81 mmol, 1.5 equiv) was added, and microwave irradiation was continued at 150 °C for 30 min.

**F-SPE Purification.** A plastic SPE cartridge (150 mL volume) was filled with FluoroFlash silica gel (50 g)<sup>13</sup> and preconditioned with 80:20 MeOH/H<sub>2</sub>O. The crude reaction mixture was loaded in DMF onto the cartridge. Elution with 80:20 MeOH/H<sub>2</sub>O (200 mL) provided all nonfluorous materials, including the DMF, these fractions were discarded. Next, the cartridge was eluted with diethylether (200 mL). The resulting ether fraction was concentrated to provide the bicycle **4**{1,2,1} (2.97 g, 3.84 mmol) in 85% yield and 92% purity by ELS detection. The cartridge was washed with THF

**Table 3.** Yields [%] for the Synthesis of Piperazindiones **1**{1-2,3-5,2-4,5-9} from **11**{1-2,3-5,2-4} and Amines **10**{5-9} (Purity by ELSD [%], if the Purity Was Less than 50% the Reaction Was Considered As Failed)

(a) reaction of <b>11</b> {1-2,1-3,1-3} with cyclopropylmethanamine <b>10</b> {5}						
<b>1</b> {1-2,3-5,2-4,5}	<u>7{1}</u>	<u>7{1}</u>	<u>7{1}</u>	<u>7{2}</u>	<u>7{2}</u>	<u>7{2}</u>
	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}
<b>8</b> {3}	59 (97) <sup>a</sup>	69 (97) <sup>a</sup>		failed <sup>b</sup>	23 (100) <sup>b</sup>	failed <sup>b</sup>
<b>8</b> {4}	56 (99) <sup>a</sup>	24 (93) <sup>a</sup>	40 (100) <sup>a</sup>	54 (100) <sup>b</sup>	34 (100) <sup>b</sup>	16 (100) <sup>b</sup>
<b>8</b> {5}	59 (100) <sup>b</sup>	59 (94) <sup>a</sup>	18 (100) <sup>b</sup>	21 (100) <sup>b</sup>	20 (90) <sup>b</sup>	21 (100) <sup>b</sup>
(b) reaction of <b>11</b> {1-2,1-3,1-3} with ethanolamine <b>10</b> {6}						
<b>1</b> {1-2,3-5,2-4,5}	<u>7{1}</u>	<u>7{1}</u>	<u>7{1}</u>	<u>7{2}</u>	<u>7{2}</u>	<u>7{2}</u>
	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}
<b>8</b> {3}	64 (97) <sup>a</sup>	60 (83) <sup>a</sup>		failed <sup>b</sup>	failed <sup>b</sup>	failed <sup>b</sup>
<b>8</b> {4}	55 (100) <sup>a</sup>	45 (100) <sup>a</sup>	54 (89) <sup>a</sup>	25 (100) <sup>b</sup>	failed <sup>b</sup>	20 (100) <sup>b</sup>
<b>8</b> {5}	46 (100) <sup>b</sup>	42 (95) <sup>a</sup>	29 (99) <sup>b</sup>	22 (100) <sup>b</sup>	89 (89) <sup>b</sup>	30 (98) <sup>b</sup>
(c) reaction of <b>13</b> {1-2,1-3,1-3} with benzylamine <b>10</b> {7}						
<b>1</b> {1-2,3-5,2-4,5}	<u>7{1}</u>	<u>7{1}</u>	<u>7{1}</u>	<u>7{2}</u>	<u>7{2}</u>	<u>7{2}</u>
	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}
<b>8</b> {3}	failed <sup>a</sup>	62 (78) <sup>a</sup>		19 (100) <sup>b</sup>	24 (89) <sup>b</sup>	20 (100) <sup>b</sup>
<b>8</b> {4}	35 (100) <sup>a</sup>	39 (100) <sup>a</sup>	23 (78) <sup>a</sup>	33 (100) <sup>b</sup>	26 (100) <sup>b</sup>	16 (100) <sup>b</sup>
<b>8</b> {5}	12 (96) <sup>b</sup>	40 (62) <sup>a</sup>	18 (98) <sup>b</sup>	11 (100) <sup>b</sup>	9 (98) <sup>b</sup>	12 (100) <sup>b</sup>
(d) reaction of <b>11</b> {1-2,1-3,1-3} with 4-phenylbenzylamine <b>10</b> {8}						
<b>1</b> {1-2,3-5,2-4,5}	<u>7{1}</u>	<u>7{1}</u>	<u>7{1}</u>	<u>7{2}</u>	<u>7{2}</u>	<u>7{2}</u>
	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}
<b>8</b> {3}	68 (95) <sup>a</sup>	failed <sup>b</sup>		57 (68) <sup>b</sup>	6 (100) <sup>b</sup>	62 (98) <sup>b</sup>
<b>8</b> {4}	58 (100) <sup>a</sup>	33 (100) <sup>b</sup>	26 (100) <sup>b</sup>	30 (90) <sup>b</sup>	88 (61) <sup>b</sup>	32 (100) <sup>b</sup>
<b>8</b> {5}	51 (100) <sup>b</sup>	42 (94) <sup>b</sup>	25 (94) <sup>b</sup>	39 (95) <sup>b</sup>	78 (73) <sup>b</sup>	failed <sup>b</sup>
(e) reaction of <b>11</b> {1-2,1-3,1-3} with 2-pyridylmethanamine <b>10</b> {9}						
<b>1</b> {1-2,3-5,2-4,5}	<u>7{1}</u>	<u>7{1}</u>	<u>7{1}</u>	<u>7{2}</u>	<u>7{2}</u>	<u>7{2}</u>
	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}	<b>9</b> {2}	<b>9</b> {3}	<b>9</b> {4}
<b>8</b> {3}	failed <sup>a</sup>	96 (74) <sup>a</sup>		24 (100) <sup>b</sup>	20 (94) <sup>b</sup>	24 (100) <sup>b</sup>
<b>8</b> {4}	57 (95) <sup>a</sup>	19 (79) <sup>b</sup>	failed <sup>a</sup>	35 (99) <sup>b</sup>	20 (100) <sup>b</sup>	25 (100) <sup>b</sup>
<b>8</b> {5}	30 (100) <sup>b</sup>	21 (100) <sup>b</sup>	23 (97) <sup>b</sup>	17 (100) <sup>b</sup>	23 (73) <sup>b</sup>	17 (98) <sup>b</sup>

<sup>a</sup> Protocol D: no FSPE on intermediate. <sup>b</sup> Protocol E: FSPE on intermediate prior to ring closure.

**Figure 1.** Crystal structure analysis of **1**{2,4,2,6}.

(200 mL) and diethylether (100 mL) prior to reuse; it was reused up to 15 times.

**(1R,3R,3aR,6aS)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptafluoroundecyl 1,5-Dimethyl-4,6-dioxo-3-styryloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate 4{1,4,2}**: IR (film) 3336, 2982, 2953, 1703, 1437, 1208 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.43–7.20 (m, 5 H), 6.69 (d, 1 H, *J* = 15.9 Hz), 6.29 (dd, 1 H, *J* = 15.9, 6.9 Hz), 4.37–4.25 (m, 3 H), 3.47 (app. t, 1 H, *J* = 8.0 Hz), 3.25 (d, 1 H, *J* = 7.5 Hz), 2.93 (s, 3 H), 2.40–2.15 (m, 2 H), 2.15–2.00 (m, 2 H), 1.58 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 175.7, 174.9, 172.1, 136.4, 132.4,

128.5, 127.9, 126.7, 125.0, 68.2, 64.5, 60.5, 56.4, 50.2, 27.9 (t, *J* = 20.3 Hz), 25.0, 24.0, 19.8 (t, *J* = 3.8 Hz); MS (ES) *m/z* (rel. intensity) 775 ([M + 1]<sup>+</sup>, 100), 671 (60); HRMS (ES) *m/z* calculated for C<sub>28</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>F<sub>17</sub> 775.1465, found 775.1431.

**General Procedure for the Preparation of Acylated Bicycles 11{1-2,3-5,2-4}**. To a solution of bicycle **4**{1,5,3} (1.17 g, 1.44 mmol, 1.0 equiv) in dichloroethane (35 mL) was added DMAP (0.018 g, 0.144 mmol, 0.1 equiv), molecular sieves (2.93 g), and chloroacetyl chloride (1.63 g, 14.4 mmol, 10.0 equiv). The reaction mixture was heated

for at 70 °C for 1 h; 5 more equiv of chloroacetyl chloride was added, and heating was continued for 1 h. It was proven to be advantageous to add the chloroacetyl chloride in two portions. The molecular sieves were filtered off, and the reaction mixture was concentrated and redissolved in DMF (15 mL). The DMF reaction mixture was purified by F-SPE as described in Protocol B. Concentration of the ether fraction provided the acylated bicycle **13**{1,5,3} (962 mg, 1.08 mmol) in 75% yield and 99% purity by ELS detection.

**(1R,3S,3aR,6aS)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl 2-(2-Chloroacetyl)-1-methyl-3-(5-methylfuran-2-yl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate 13{1,5,3}**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40–7.33 (m, 3 H), 6.97–6.92 (m, 2 H), 6.64 (d, 1 H, *J* = 3.0 Hz), 5.97 (dd, 1 H, *J* = 3.0, 0.9 Hz), 5.71 (d, 1 H, *J* = 10.5 Hz), 4.40–4.20 (m, 2 H), 4.12 (dd, 1 H, *J* = 10.2, 9.0 Hz), 3.83 (d, 1 H, *J* = 13.2 Hz), 3.65 (d, 1 H, *J* = 12.9 Hz), 3.52 (d, 1 H, *J* = 9.0 Hz), 2.21 (s, 3 H), 2.22–2.08 (m, 2 H), 2.08–1.95 (m, 2 H), 1.82 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) *d* 172.4, 171.3, 168.9, 165.4, 153.7, 147.5, 131.1, 129.0, 128.8, 126.0, 111.4, 107.1, 69.2, 64.6, 57.8, 54.2, 48.7, 41.8, 27.7 (t, *J* = 22.5 Hz), 23.6, 19.7 (t, *J* = 3.4 Hz), 13.3.

**General Procedure for One-Pot Displacement/Lactamization Reaction to Form 1{1-2,3-5,2-4,5-9}**. A solution of the acylated bicycle **11**{1,3,2} (0.201 g, 0.261 mmol, 1.0 equiv) in 2,2,3,3-tetrafluoropropanol (TEFPO) was treated with 4-phenylbenzylamine **10**{8} (0.191 g, 1.04 mmol, 4.0 equiv), and microwave irradiation was continued for 15 min at 150 °C. After the mixture was cooled to room temperature, acetic acid (0.105 g, 1.82 mmol, 7.0 equiv) was added, and the reaction mixture was irradiated at 225 °C for 1 h under microwave. All volatile components were removed in vacuo, and the residue was purified by chromatography over SiO<sub>2</sub> to provide 0.0809 g (0.177 mmol, 68%) of the target compound **1**{1,3,2,8} in 95% purity by ELS detection.

In several cases, the acylated amine **13**{5-9} coeluted with the target compound **1**{1-2,3-5,2-4,5-9}. This problem was solved by introducing a F-SPE purification prior to the addition of acetic acid. After the first microwave irradiation, all volatile components were removed in vacuo, and the residue was loaded in THF (0.5 mL) on a pre-conditioned F-SPE cartridge (5 g FluoroFlash silica gel). Elution with 80:20 MeOH/H<sub>2</sub>O provided **12**{1-2,3-5,2-4,5-9} containing fraction. Methanol was removed in vacuo and the aqueous fraction was extracted with ethyl acetate (2 × 20 mL). Both organic fractions were combined, washed with brine, dried over magnesium sulfate, and concentrated. The residue was dissolved in 2,2,3,3-tetrafluoropropanol and treated with acetic acid in the microwave as described above.

**(3aR,4R,9aR,9bS)-8-Aza-8-(biphenyl-4-ylmethyl)-4-cyclopropyl-2,9a-dimethyltetrahydro-1H-pyrrolo[3,4-a]indolizine-1,3,6,9(2H,9aH,9bH)-tetraone 1{1,3,2,8}**: IR (film) 3007, 1712, 1673 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.62–7.55 (m, 4 H), 7.47–7.39 (m, 4 H), 7.38–7.33 (m, 1 H), 4.82 (d, 1 H, *J* = 14.4 Hz), 4.56 (d, 1 H, *J* = 14.4 Hz), 3.88 (d, 1 H, *J* = 18.0 Hz), 3.79 (d, 1 H, *J* = 18.0 Hz), 3.58–3.50 (m, 2 H), 3.35 (app. t, 1 H, *J* = 9.3 Hz), 2.98 (s, 3 H), 1.51 (s, 3 H), 0.88–0.78 (m, 1 H), 0.78–0.70 (m, 2 H), 0.50–0.40 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.8, 173.5, 166.2, 163.6,

140.9, 140.4, 134.1, 129.0, 128.7, 127.5, 127.3, 126.9, 65.9, 65.4, 53.2, 50.3, 48.4, 46.2, 25.1, 24.8, 11.3, 9.4, 5.9; MS (ES) *m/z* (rel. intensity) 458 ([M + 1]<sup>+</sup>, 100); HRMS (ES) *m/z* calculated for C<sub>27</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub> 458.2080, found 458.2079.

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**Supporting Information Available.** NMR spectra of representative compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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