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Enantioselective Synthesis of SNAP-7941: Chiral Dihydropyrimidone Inhibitor of MCH1-R

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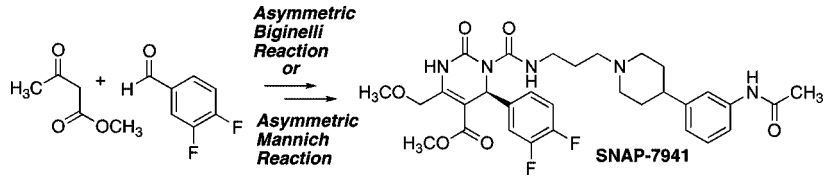

An enantioselective synthesis of SNAP-7941, a potent melanin concentrating hormone receptor antagonist, was achieved by using two organocatalytic methods. The first method utilized to synthesize the enantioenriched dihydropyrimidone core was the *Cinchona* alkaloid-catalyzed Mannich reaction of β-keto esters to acylimines and the second was the chiral phosphoric acid-catalyzed Biginelli reaction. Completion of the synthesis was accomplished via selective urea formation at the N3 position of the dihydropyrimidone with the 3-(4-phenylpiperidin-1-yl)propylamine side chain fragment. The synthesis of SNAP-7921 highlights the utility of asymmetric organocatalytic methods in the construction of an important class of chiral heterocycles.

Introduction

Dihydropyrimidones (DHPMs) are a class of heterocyclic compounds[1] that possess wide ranging biological activity[2] such as calcium channel modulators,[3] antihypertensive agents,[4] mitotic kinesin Eg5 inhibitors,[5] and melanin concentrating hormone receptor (MCH1-R) antagonists (Figure 1).[6] In most cases only one enantiomeric form of the heterocycle is often determined to be biologically active.[7] While racemic DHPMs are easily constructed via the Biginelli reaction, a 3-component condensation reaction of ureas, β-keto esters, and aldehydes,[8] a limited number of asymmetric methods exist to access the

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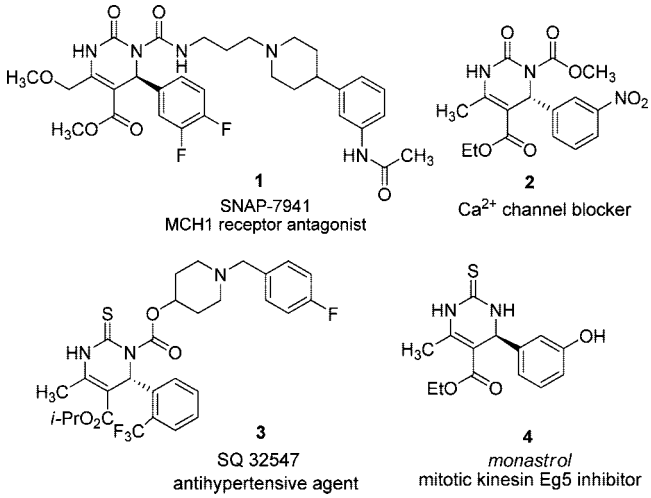
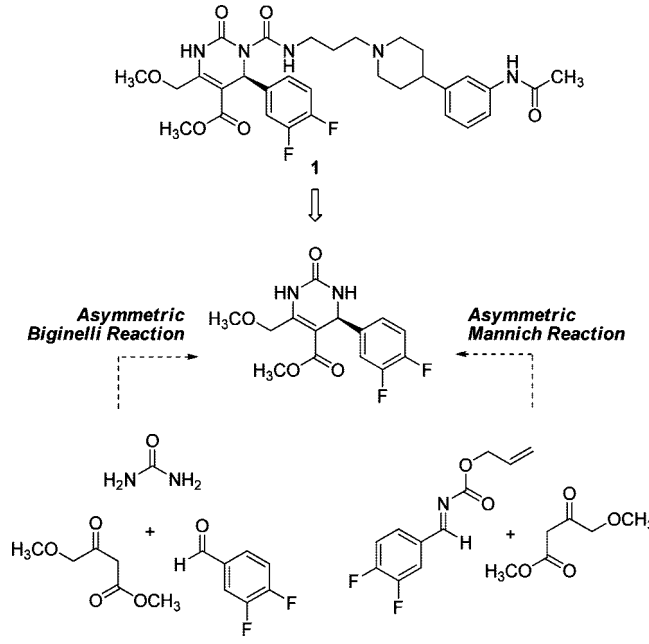


FIGURE 1. Biologically Active DHPMs.

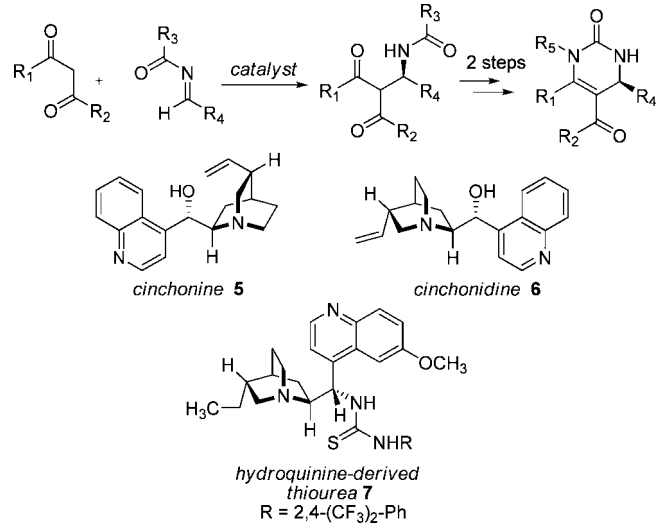
chiral heterocycle in high enantiomeric purity. Early approaches include chemical resolution,[9] enzymatic synthesis,[10] and chiral Yb-[11] or Ce/In-complex[12] catalyzed Biginelli reactions. More recently, asymmetric organocatalytic approaches have emerged as effective methods to construct enantioenriched DHPMs. We developed the asymmetric Mannich reaction[13] of β-ketoesters to acylimines catalyzed by the *Cinchona* alkaloids as a way to construct chiral DHPM heterocycles.[14] Subsequent to our initial communication, Gong and co-workers reported the first asymmetric organocatalytic Biginelli reaction catalyzed by a BINOL-derived chiral phosphoric acid catalyst, yielding chiral DHPMs in high enantiomeric ratios.[15] These methods could be readily applied to asymmetric synthesis due to the accessibility of the reagents and catalysts, as well as the useful levels of enantioselectivity.

SNAP-7941 is a chiral DHPM identified as a small molecule inhibitor of MCH1-R in a G protein-coupled receptor (GPCR) biased library screening. Inhibition of MCH1-R promotes weight loss in obese rats, and decreases anxiety and depression in both guinea pigs and rats, as shown in social interaction studies.[6] SNAP-7941 exhibits a K_d of 0.18 nM with specific binding of 98% in COS-7 cells expressing human MCH1-R. However, synthesis of SNAP-7941 in enantioenriched form relies on a chiral separation of the racemic dihydropyrimidone synthon.[16] In an effort to synthesize chiral DHPMs and apply these methods toward the synthesis of a relevant target, SNAP-7941, we investigated using both the *Cinchona* alkaloid-catalyzed asymmetric Mannich reaction and the chiral phosphoric acid-catalyzed Biginelli reaction as the key enantioselective step in the synthesis. Our goal was to illustrate the utility of both the asymmetric Mannich reaction and the asymmetric Biginelli reaction in the synthesis of SNAP-7941.

SCHEME 1. Retrosynthetic Analysis of SNAP-7941



SCHEME 2. Synthesis of DHPMs via Asymmetric Mannich Reaction



SNAP-7941 consists of two main structural components, a chiral DHPM and a 3-(4-phenylpiperidin-1-yl)propylamine side chain linked as a urea (Scheme 1). The two approaches to the chiral DHPM require different building blocks to construct the amine stereocenter. The *Cinchona* alkaloid-catalyzed asymmetric Mannich addition of methoxy methylacetoacetate to *N*-alloc-3,4-difluorophenyl aldimine results in the amine precursor that is ultimately converted to the heterocycle with microwave irradiation.[17] The chiral phosphoric acid-catalyzed multicomponent Biginelli reaction results in direct formation of the chiral DHPM. Both methods proved to be equally effective in accessing the desired heterocycle for the synthesis of enantioenriched SNAP-7941.

Results and Discussion

Synthesis of SNAP-7941 DHPM Core via the Mannich Reaction. Synthesis of the SNAP-7941 DHPM using the

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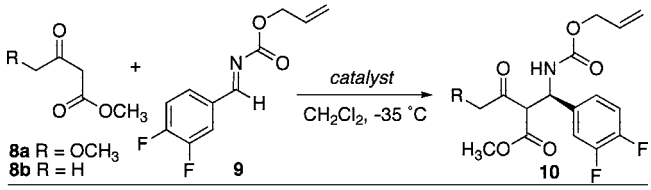
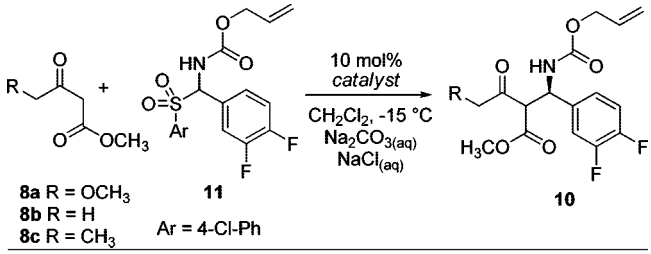
TABLE 1. Asymmetric Mannich Reactions with *N*-Alloc-3,4-difluorophenylimine[a]



entry	catalyst	ketoester	% yield[b]	er[c]
1	**5**	**8a**	72	71:29
2	**5**	**8b**	68	91:9
3	**7**	**8b**	77	85:15
4	**5**[d]	**8b**	88	93:7
5	**5**[e]	**8b**	89	93.5:6.5

[a] Reactions were run with imine **9** (1.00 mmol), β-ketoesters **8a** and **8b** (3.00 mmol), and catalyst (0.10 mmol) in CH_2Cl_2 (10 mL) at −35 °C for 24 h, followed by flash chromatography on silica gel. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Reaction run at −50 °C with 0.20 mmol of catalyst in CH_2Cl_2 (5 mL). [e] Reaction run at −50 °C with 0.20 mmol of catalyst in CH_2Cl_2 (10 mL).

TABLE 2. Asymmetric Mannich Reactions with α,α-Allylcarbamate-3,4-difluorophenyl Sulfone[a]



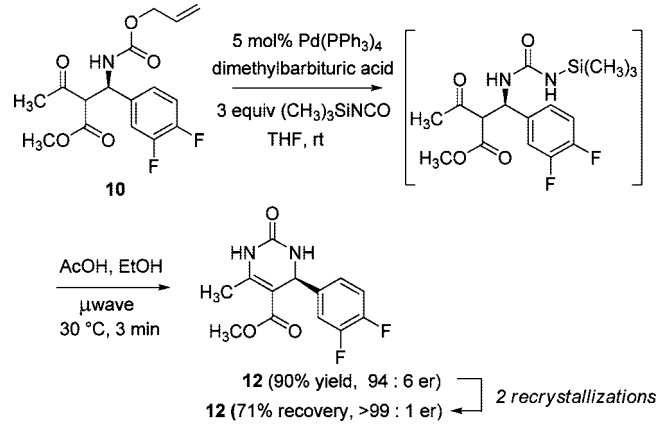
entry	catalyst	ketoester	% yield[b]	er[c]
1	**5**	**8a**	67	78:22
2	**7**	**8a**	81	82:18
3	**5**	**8b**	95	94:6
4	**7**	**8b**	67	85:15
5	**5**	**8c**	98	89:11

[a] Reactions were run with amido sulfone **11** (1.00 mmol), β-ketoesters **8a**−**c** (3.00 mmol), and catalyst (0.10 mmol) in CH_2Cl_2 (10 mL) and Na_2CO_3 in brine (10 mL) at −15 °C for 24 h, followed by flash chromatography on silica gel. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

asymmetric Mannich reaction required the addition of a β-ketoester to an acylimine, followed by urea formation and subsequent ring closure (Scheme 2). On the basis of our previous work, cinchonine would be the preferred catalyst for the asymmetric Mannich reaction; however, additional catalysts were evaluated in the reaction including other *Cinchona* alkaloids and thiourea *Cinchona* alkaloid derived catalyst **7**.[18] A catalyst screen was conducted to identify the optimal catalyst for the reaction.

Low yield and selectivity was observed for the asymmetric Mannich addition of methoxy methylacetoacetate **8a** to *N*-alloc-3,4-difluorophenylimine **9** catalyzed by cinchonine **5** (Table 1, entry 1). We suspected that the C4 methoxy substituent was problematic as better reaction rates and selectivities were

SCHEME 3. DHPM Formation from Mannich Adduct



observed in the absence of a C4 substituent on the β-ketoester (Table 1, entry 2). Mannich addition of methylacetoacetate **8b** catalyzed by cinchonine proceeded in moderate yield and good enantiomeric ratio (Table 1, entry 2). The addition with methylacetoacetate **8b** was further optimized by increasing catalyst loading to 20 mol % while reducing the reaction temperature, to afford the desired chiral amine **10b** in high yield with an enantiomeric ratio of 93.5:6.5 (Table 1, entry 5). While the additions of methylacetoacetate **8b** to acylimine **9** provided enantioenriched Mannich products, we investigated a method utilizing α,α-allylcarbamate-3,4-difluorophenyl sulfone and generating the corresponding acylimine in situ. The α-amido sulfones are bench stable and easily synthesized,[19] and we have previously illustrated the utility of the α-amido sulfones in the asymmetric Mannich reaction.[14b]

Addition of C4 methoxy substituted β-ketoester **8a** to α-amido sulfone **11** again provided the Mannich adduct **10a** in low yields and moderate enantioselectivities (Table 1, entries 1 and 2). We hypothesized that the C4 substituent plays a crucial role. The observed decrease in reactivity may be attributed to a disruption of hydrogen bonding nature between the catalyst and the β-ketoester, as additions with methoxy methylacetoacetate **8a** generally provided lower yields and selectivities when compared to the unsubstituted methylacetoacetate **8b**. To determine whether the change in reactivity and selectivity was a steric or electronic effect, the Mannich reaction with C4 methyl substituted β-ketoester **8c** was examined. Mannich addition of **8c** to α-amido sulfone **11** catalyzed by cinchonine did not significantly decrease selectivity or yield (Table 2, entry 5). We reasoned that an intramolecular hydrogen bond of the tautomer alcohol and the C4 methoxy substituent of **8a** interrupts the hydrogen-bonding nature. To overcome the low selectivity, we sought to synthesize the DHPM core with β-ketoester **8b** and install the methoxy substituent at a later stage. Best results were obtained for the Mannich reaction of β-ketoester **8b** and α,α-allylcarbamate-3,4-difluorophenyl sulfone **11** catalyzed by cinchonine, providing chiral amine **10b** in high yield and high enantiomeric ratio (Table 2, entry 3).

Conversion of the chiral imine to the desired enantioenriched DHPM proceeded via a two-step process. Exposure of Mannich adduct **10b** to a catalytic amount of $Pd(PPh_3)_4$, an excess of trimethylsilyl isocyanate, and 3,5-dimethylbarbituric acid as an allyl scavenger affords the desired silyl urea (Scheme 3).

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SCHEME 4. Synthesis of the C4 Methoxy-Substituted DHPM

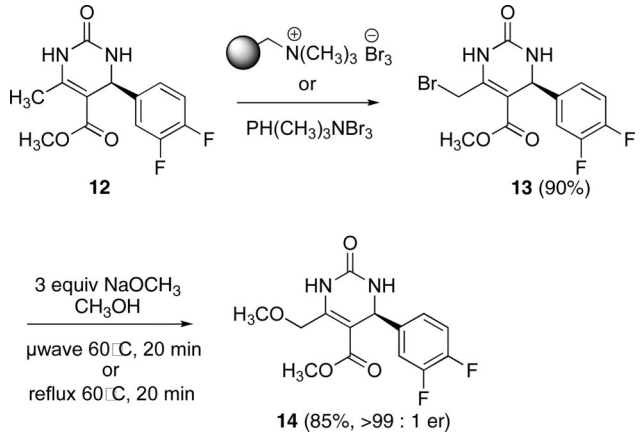
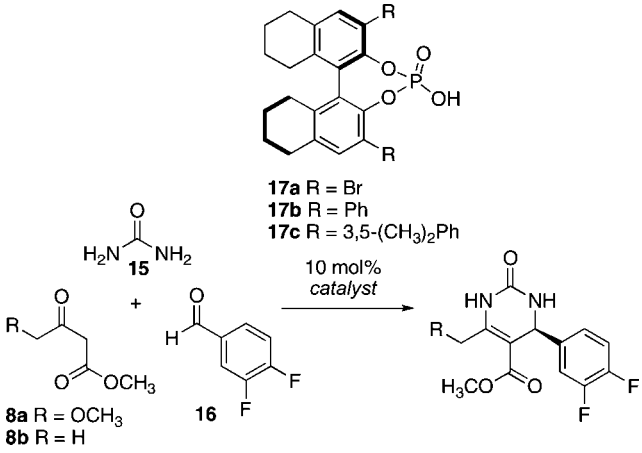


TABLE 3. Asymmetric Biginelli Reaction Catalyzed by Chiral Binapthol-Derived Phosphoric Acid[a]



entry	15:8:16	catalyst	ketoester	% yield[b]	er[c]
1	1.0:5.0:2.0	**17b**	**8a**	27	64.5:35.5
2	1.2:5.0:1.0	**17a**	**8b**	50	63:37
3	1.2:5.0:2.0	**17b**	**8b**	42	83:17
4	1.0:5.0:2.0	**17b**	**8b**	96	94.5:5.5
5	1.0:5.0:2.0	**17c**	**8b**	65	77.5:22.5
6[d]	1.0:5.0:2.0	**17b**	**8b**	27	64.5:35.5

[a] Reactions were run with urea **15**, phosphoric acid catalysts **17a**−**c** (0.02 mmol), aldehyde **16** in CH_2Cl_2 (3 mL) for 2 h. β-Ketoesters **8a** and **8b** (1.00 mmol) were added, and the mixture was stirred at room temperature for 6 days, and subsequently purified by flash chromatography on silica gel. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The reaction was run at 0.5 M.

Formation of the heterocycle proceeds without purification of the silyl urea with subsequent ring closure under acidic conditions. The desired DHPM was achieved in 80% yield with retention of stereochemistry (Scheme 3). The heterocycle was purified by recrystallization to provide DHPM **12** in an enantiomeric ratio of >99:1.

Installation of the C4 methoxy substituent proceeded through bromination and subsequent methanolysis of DHPM **12**. Monobromination of the C4 methyl of the DHPM was achieved in high yield by using a solid supported brominating agent reported by Kappe and co-workers (Scheme 4).[20] The monobrominated DHPM was also synthesized by using brominating reagent

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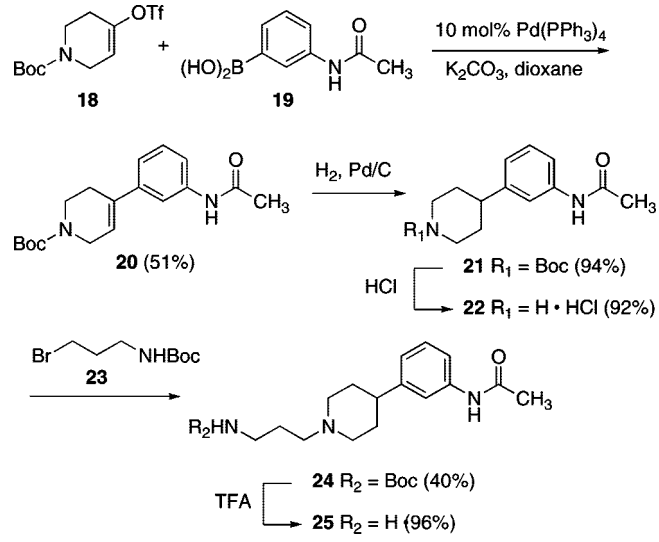
SCHEME 5. Synthesis of 3-(4-Phenylpiperidin-1-yl)propylamine Side Chain



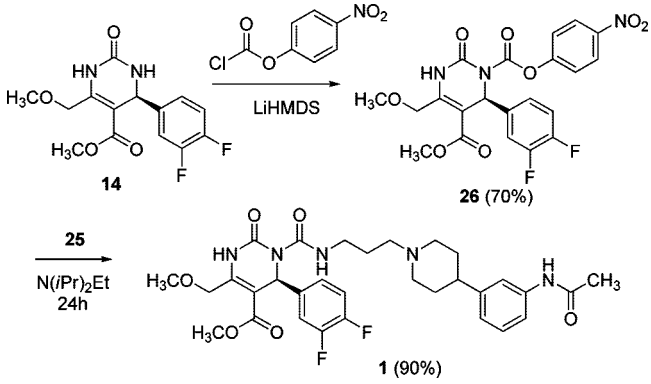
$Ph(CH_3)_3NBr_3$, providing DHPM **13** in equally high yield. Installation of the methoxy substituent proceeded through nucleophilic substitution with sodium methoxide. Use of either microwave or thermal conditions provided the heterocyclic core of SNAP-7941 **14** in 85% yield with retention of enantioenrichment.

Synthesis of the DHPM Core via the Asymmetric Biginelli Reaction. The asymmetric Biginelli reaction catalyzed by BINOL-derived phosphoric acids was also investigated to produce the desired SNAP-7941 DHPM core. Use of methoxy methylacetoacetate **8a** in the multicomponent reaction provided DHPM **14** in low yield and enantioselectivity (Table 3, entry 1). This observation is again attributed to an unfavorable hydrogen-bonding nature as the use of methylacetoacetate **8b** greatly improved yield and selectivity (Table 3, entries 2 and 3). Optimal reaction conditions were achieved with a limiting amount of urea and an excess of both aldehyde and methylacetoacetate (Table 3, entries 4, 5, and 6). DHPM **12** was synthesized in 96% yield with 94.5:5.5 er, utilizing 3,3′-diphenyl-substituted BINOL-derived phosphoric acid catalyst **17b.** The Biginelli product was recrystallized and functionalized via the previously described bromination and methanolysis procedures to provide the enantioenriched SNAP-7941 core.

Synthesis of 3-(4-Phenylpiperidin-1-yl)propylamine Side Chain. Piperidine **18** and boronic acid **19** were synthesized according to previously reported literature procedures.[21] Suzuki coupling of **18** and **19** provided the desired piperidinyl amide **20** in 51% yield. Subsequent hydrogenation followed by acid deprotection of **20** afforded the piperidinyl phenyl acetamide hydrochloride salt **22** in 86% overall yield. Nucleophilic substitution of *N*-Boc propyl bromide **23**[19] with piperidinyl hydrochloride salt **22** yielded the Boc protected amide side chain **24**. Deprotection of the Boc group with TFA and subsequent pH adjustment afforded the desired amine **25** (Scheme 5).

Synthesis of SNAP-7941. Synthesis of *N*-substituted DHPM carbamate **26** via addition of *p*-nitrophenyl chloroformate was achieved in 70% yield (Scheme 6). The urea moiety of SNAP-7941 was constructed via addition of piperidine side chain **25** to *N*-substituted DHPM carbamate **26**. Optimal yield and

SCHEME 6. Synthesis of SNAP-7941



reaction time was obtained with Hünig's base, providing the enantioenriched form of SNAP-7941 in 90% yield.

Conclusion

We have developed two organocatalytic enantioselective approaches to SNAP-7941 that focus on the synthesis of the chiral dihydropyrimidone core. The asymmetric Mannich reaction catalyzed by *Cinchona* alkaloids and the asymmetric Biginelli reaction catalyzed by chiral phosphoric acids were equally effective at producing the desired heterocycle. The additional steps required by the Mannich route are offset by the time required for the enantioselective Biginelli reaction. Despite the progress to date, some challenges still remain. However, these approaches are the first highly enantioselective routes to this important class of biologically and pharmaceutically relevant compounds. The development of effective synthetic approaches will hopefully facilitate future efforts to characterize the activity and biological properties of these chiral heterocycles.

Experimental Section

General Procedure for Asymmetric Mannich Reaction of α-Amido Sulfones. To an oven-dried 50-mL round-bottomed flask equipped with a stir bar was added α-amido sulfone **11** (0.40 g, 1.00 mmol), (+)-cinchonine (0.029 g, 0.10 mmol), and CH_2Cl_2 (10 mL). The solution was cooled to −15 °C. The dicarbonyl compound (**8a**−**c**) (3.00 mmol) and 10 mL of a solution of Na_2CO_3/NaCl were sequentially added dropwise. The reaction was stirred for 24 h at −15 °C and then diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was quickly separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography over silica gel (elution with 30% to 40% ethyl acetate in hexanes) to afford the Mannich reaction products as white solids.

General Procedure for Conversion from Mannich Adduct to Dihydropyrimidone. To an oven-dried 50-mL round-bottomed flask equipped with stir bar was added **10b** (0.34 g, 1.00 mmol), 3,5-dimethylbarbituric acid (0.156 g, 1.00 mmol), and THF (10 mL). To another oven-dried 50-mL round-bottomed flask equipped with stir bar was added $Pd(PPh_3)_4$ (0.060 g, 0.050 mmol), trimethylsilyl isocyanate (0.346 g, 3.00 mmol), and THF (10 mL). The solution containing the **10b** and 3,5-dimethylbarbituic acid was transferred via cannula to the palladium and isocyanate mixture. The reaction mixture was stirred for 4 h. The solution was then concentrated under reduced pressure, and a solution of 75% acetic acid in ethanol (3 mL) was added. The solution was transferred to a 10 mL microwave tube, and irradiated for 3 min at 30 °C. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography over silica gel (elution with 80% to 100% EtOAc in hexanes) to afford the dihydropyrimidone reaction product as a white solid.

General Procedure for the Chiral Phosphoric Acid-Catalyzed Asymmetric Biginelli Reaction. An oven-dried 10-mL round-bottomed flask equipped with stir bar was charged with urea **15** (0.012 g, 0.20 mmol), phosphoric acid catalyst (**17a**−**c**) (0.02 mmol), 3,4-difluorobenzaldehyde (**16**) (44 μL, 0.40 mmol), and CH_2Cl_2 (3 mL). The flask was sealed with a Teflon cap (caplug), and the solution was stirred for 2 h at room temperature. The dicarbonyl compound (**8a**, **8b**) (1.0 mmol) was slowly added, and the solution was stirred for 6 days. Silica gel was added to the reaction mixture, and the mixture was concentrated under reduced pressure. The resulting solid was purified by flash chromatography over silica gel (with 80−100% EtOAc in hexanes) to afford the Biginelli reaction products as white solids.

Synthesis of SNAP-7941. A solution of **25** (0.050 g, 0.10 mmol), **24** (0.083 g, 0.30 mmol), DIPEA (0.078, 0.60 mmol), and anhydrous CH_2Cl_2 (3 mL) was stirred at room temperature under argon atmosphere for 24 h. The mixture was concentrated and the resulting residue was purified by flash chromatography over silica gel (elution with 1−5% methanol in ethyl acetate) to provide the desired final compound as a yellow oil.

Characterization Data for Selected Compounds: (a) 2-[(*R*)-Allyloxycarbonylamino-3,4-difluorophenylmethyl)-3-oxo-4-methoxybutyric Acid Methyl Ester (10a). Clear viscous oil (0.25 g, 67% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, both diastereomers reported): δ 7.10 (m, 8H), 6.41 (d, J = 9.2 Hz, 1H), 6.33 (d, J = 8.8 Hz, 1H), 5.86 (m, 2H), 5.53 (m, 1H), 5.43 (m, 1H), 5.30 (s, 1H), 5.27 (s, 1H), 5.23 (s, 1H), 5.20 (s, 1H), 4.50 (d, J = 5.6 Hz, 4H), 4.32 (m, 2H), 4.08 (dd, J = 7.2, 6.8 Hz, 2H), 3.87 (dd, J = 14.8, 6.0 Hz, 2H), 3.69 (s, 3H), 3.62 (s, 3H), 3.44 (s, 3H), 3.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.0 MHz, both diastereomers reported): δ 204.5, 202.2, 171.4, 169.0, 167.4, 156.0, 155.8, 151.7, 149.3 (d, $^1J_{CF}$ = 212.0 Hz), 136.9, 132.7, 122.8 (d, $^2J_{CF}$ = 80.0 Hz), 117.8 (d, $^2J_{CF}$ = 60.0 Hz), 116.1 (d, $^2J_{CF}$ = 72.0 Hz), 66.3, 60.1, 59.6, 57.5, 53.4, 53.2, 52.8, 51.9. IR (thin film, cm^{-1}): 3425, 2956, 1722, 1612, 1519, 1503, 1437, 1345, 1284, 1222, 1118, 1059. High resolution mass spectrum m/z 394.1095 [(M + Na$^+$) calcd for $C_{17}H_{19}NO_6NaF_2^+$: 394.1078]. [α]$^{23}_D$ −28.7 (c 4.0, $CHCl_3$). 78:22 er; HPLC analysis, t_r major (of single diastereomer) 9.7 min, t_r minor (of single diastereomer) 11.2 min [ChiralcelAD column, hexanes:IPA 90:10, 1.0 mL/min].

(b) 2-[(*R*)-Allyloxycarbonylamino-3,4-difluorophenylmethyl)-3-oxo-butyric Acid Methyl Ester (10b). White solid (0.97 g, 97% yield). Mp: 97−100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, both diastereomers reported): δ 7.12 (m, 6H), 6.99 (s, 2H), 6.41 (d, J = 8.8 Hz, 1H), 6.25 (d, J = 9.2 Hz, 1H), 5.85 (m, 2H), 5.47 (m, 1H), 5.37 (dd, J = 6.8, 2.0 Hz, 1H), 5.21 (m, 5H), 4.49 (d, J = 1.6 Hz, 4H), 4.00 (d, J = 5.6 Hz, 1H), 3.94 (d, J = 4.0 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 2.23 (s, 3H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.0 MHz, both diastereomers reported): δ 202.0, 199.6, 170.5, 168.2, 166.6, 155.0, 154.8, 150.6 (d, $^1J_{CF}$ = 220.0 Hz), 148.1 (d, $^1J_{CF}$ = 220.0 Hz), 131.8, 121.6 (d, $^2J_{CF}$ = 24.0 Hz), 117.2 (d, $^2J_{CF}$ = 44.0 Hz), 115.2 (d, $^2J_{CF}$ = 72.0 Hz), 65.4, 63.0, 59.7, 52.1, 51.7, 30.0, 29.5, 22.0. IR (thin film, cm^{-1}): 3423, 2996, 1720, 1649, 1612, 1519, 1503, 1437, 1363, 1284, 1219, 1147, 1119, 1061. High resolution mass spectrum m/z 364.0954 [(M + Na$^+$) calcd for $C_{16}H_{17}NO_5NaF_2^+$: 364.0972]. [α]$^{23}_D$ −32.4 (c 4.0, $CHCl_3$). 94:6 er; HPLC analysis, t_r major (of single diastereomer) 23.7 min, t_r

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minor (of single diastereomer) 31.9 min [ChiralcelAD-H column, hexanes:IPA 95:5, 1.0 mL/min].

(c) (*S*)-Methyl-4-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (12). White solid (0.254 g, 90% yield). Mp: 204−206 °C. ^{1}H NMR (DMSO, 400 MHz): δ 9.31 (s, 1H), 7.82 (s, 1H), 7.35 (d and dd$_{CF}$, J = 6.4 Hz, $^4J_{CF}$ = 8.4 Hz, $^4J_{CF}$ = 10.8 Hz, 1H), 7.20 (d and dd$_{CF}$, J = 6.0 Hz, $^4J_{CF}$ = 8.0 Hz, $^4J_{CF}$ = 10.8 Hz, 1H), 7.07 (m, 1H), 5.15 (d, J = 3.6 Hz, 1H), 3.52 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (DMSO, 75.0 MHz): δ 165.9, 152.2, 149.7, 147.9 (d, $^1J_{CF}$ = 236.3 Hz), 142.6 (d, $^2J_{CF}$ = 16.0 Hz), 123.1, 117.8 (d, $^2J_{CF}$ = 68.3 Hz), 115.5 (d, $^2J_{CF}$ = 68.0 Hz), 98.5, 53.3, 51.1, 18.3. IR (thin film, cm^{-1}): 3328, 2922, 2850, 1696, 1645, 1516, 1434, 1279, 1228, 1093. High resolution mass spectrum m/z 283.0912 [(M + H$^+$) calcd for $C_{13}H_{13}N_2O_3F_2^+$: 283.0894]. $[\alpha]^{23}_D$ +10.0 (*c* 2.0, CHCl3). >99:1 er HPLC analysis, t_r minor 18.2 min, t_r major 27.0 min [ChiralcelOD column, hexanes: IPA 95:5, 1.0 mL/min].

(d) SNAP-7941 (1). Yellow oil (0.055 g, 0.090 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.90 (s, 1H), 8.11 (s, 1H), 7.79 (s, 1H), 7.50 (d, J = 8.00 Hz, 1H), 7.26 (s, 1H), 7.20 (s, 1H), 7.13 (m, 2H), 7.02 (m, 2H), 6.84 (d, J = 8.00 Hz, 1H), 6.56 (s, 1H), 4.61 (s, 2H), 3.65 (s, 3H), 3.42 (s, 3H), 3.31 (m, 3H), 2.82 (m, 2H), 2.54 (m, 2H), 2.18 (m, 2H), 2.12 (s, 3H), 1.99 (m, 4H), 1.83 (d, J = 16.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 171.5, 169.2, 153.9, 152.6, 149.2, 146.5, 144.6, 139.0, 137.7, 129.5, 123.3, 122.8, 118.0, 117.8 (d, $^2J_{CF}$ = 68.0 Hz), 116.6 (d, $^2J_{CF}$ = 72.0 Hz), 101.7, 68.3, 59.5, 55.5, 53.6, 53.5, 52.1, 40.9, 38.6, 30.6, 25.0, 24.9, 21.4. IR (thin film, cm^{-1}): 3291, 2950, 2501, 1713, 1647, 1409, 1517, 1436, 1394, 1313, 1280, 1219, 1117, 1083, 964, 912. $[\alpha]^{23}_D$ +130 (*c* 2.0, $CHCl_3$).

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Supporting Information Available: Experimental procedures, characterization data, and chiral chromatographic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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