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Enantioselective Organocatalytic Friedel–Crafts Alkylation Reaction of Indoles with 5-Hydroxyfuran-2(5*H*)-one: Access to Chiral γ-Lactones and γ-Lactams via a Ugi 4-Center 3-Component Reaction

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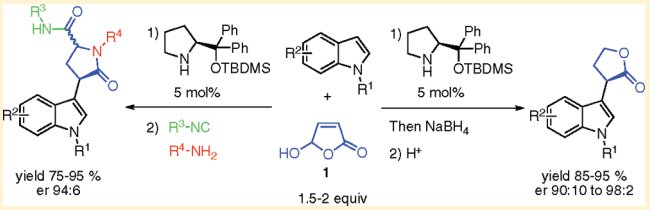
Supporting Information

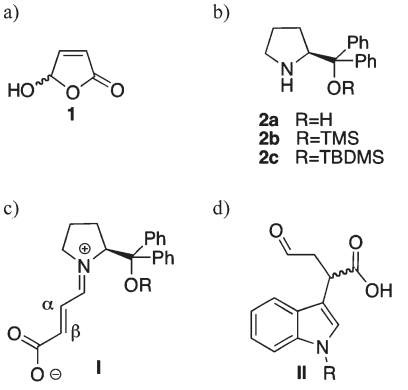
ABSTRACT: 5-Hydroxyfuran-2(5*H*)-one **1**, a readily available renewable resource, was used as an electrophile in the Friedel–Crafts alkylation of indoles catalyzed by a diphenylprolinol silyl ether. Moderate catalyst loading was achieved because of the high reactivity of 5-hydroxyfuran-2(5*H*)-one **1** in this process. Reduction of the Friedel–Crafts adduct (FC adduct) afforded indoyl lactones in high yield and enantioselectivity. Moreover, the FC adduct was used as a chiral synthon in a diversity-oriented synthesis, as illustrated by its successful engagement in a 4-center 3-component Ugi reaction (U-4C-3CR) to afford chiral five-membered lactams in high yield and enantioselectivity.



INTRODUCTION

The indole moiety has long been a privileged structure in drug discovery because of its presence in numerous biologically active natural products.[1−3] Construction of a substituted indole ring can be carried out by de novo synthesis from simpler starting material[4] or by direct functionalization of a preformed indole ring.[5] Friedel–Crafts alkylation is one of the most powerful strategies for direct functionalization of the indole ring especially when applied to catalytic asymmetric transformations.[6,7] The emergence of organocatalysis has considerably increased the methodology available for achieving catalytic enantioselective Friedel–Crafts alkylation.[8−10] Imidazolidinone was introduced in the pioneering work by MacMillan and co-workers as a highly efficient catalyst for iminium activation of α,β-unsaturated aldehydes.[11] When applied to indole alkylation, fine-tuning of the imidazolidinone catalyst has proven to be effective, with attack of the indole on the β position of the iminium activated α,β-unsaturated aldehyde in a geometrically controlled manner.[12] Since the first introduction of diphenylprolinol silyl ether in organocatalysis,[13,14] its high catalytic efficiency in numerous asymmetric transformations involving iminium or enamine intermediates has elevated it to the class of privileged catalysts. The use of diphenylprolinol silyl ether in the Friedel–Crafts alkylation of indole with α,β-unsaturated aldehydes was recently reported.[15−17] The use of 20 mol % catalyst loading and 0.5 equiv of triethylamine allowed addition of indole to α,β-unsaturated aldehydes in good yield (67–95%) and enantioselectivity (92–98% ee) when the reaction was carried out at −20 °C in MTBE for 36 h.[15] When cinamaldehyde derivatives were used as electrophiles, good yield (60–87%) and enantioselectivity (86–93% ee) were also obtained using the same catalyst loading without the use of any additive when carried out in methanol. However, in spite of optimized reaction conditions, long reaction times (4 days) and the use 2 equiv of indole were required.[16] Very recently, higher enantioselectivity was obtained (up to 99% ee) with modified diphenylprolinol silyl ether derivatives. However, only moderate yields (37–65%) were obtained after a prolonged reaction time (45 h).[17]

Scheme 1. (a) 5-Hydroxyfuran-2(5*H*)-one 1, (b) Diphenylprolinol Catalyst 2, (c) Putative Zwitterionic Iminium Intermediate I, (d) Friedel–Crafts Adduct II



The use of more functionalized electrophiles would allow an efficient increase of structural diversity after initial Friedel–Crafts indole alkylation. 5-Hydroxyfuran-2(5*H*)-one **1** (Scheme 1) is a readily available renewable resource which can be obtained on large scale by photooxygenation of furfural.[18] The synthetic

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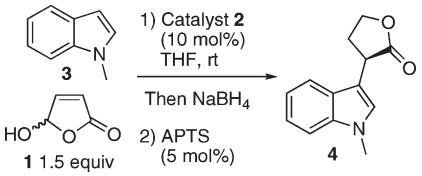
Table 1. Organocatalytic Friedel–Crafts Reaction of *N*-Methylindole with 5-Hydroxyfuran-2(5*H*)-one 1[a]



entry	catalyst	time[b] (h)	yield (%)	er[c] (%)
1	**2a**	20	81	90:10
2	**2b**	7	96	94:6
3	**2c**	14	93	96:4

[a] The reactions were carried out with 0.5 mmol of indole **3**, 0.75 mmol of 5-hydroxyfuran-2(5*H*)-one **1**, and 0.05 mmol of **2** in THF (0.5 mL). [b] Reaction time needed for the total consumption of indole **2** in the Friedel–Crafts alkylation step. [c] Determined by chiral HPLC analysis; absolute configuration determined by chemical correlation to a known compound (see the Experimental Section).

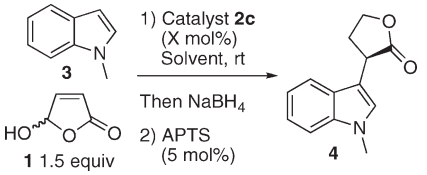
utility of 5-hydroxyfuran-2(5*H*)-one **1** has been demonstrated by its use as a synthon in numerous natural product syntheses.[19] The use of **1** in asymmetric transformations has essentially been performed via derivatization with a chiral auxiliary such as 5-menthyoxyfuran-2(5*H*)-one.[20,21] In contrast, the use of 5-hydroxyfuran-2(5*H*)-one **1** or a simple analogue in a catalytic enantioselective transformation has only rarely been reported.[22] Herein we describe the use of 5-hydroxyfuran-2(5*H*)-one **1** in a highly enantioselective Friedel–Crafts alkylation of indole catalyzed by diphenylprolinol derivatives **2** (Scheme 1). The prerequisite for a successful alkylation is the efficient formation of the zwitterionic iminium **I**. Stereoselective nucleophilic addition of the indole in the β position should then afford a Friedel–Crafts adduct (FC adduct) **II**.

RESULTS AND DISCUSSION

Preliminary experiments were conducted with *N*-methyl indole **3** and 1.5 equivalents of 5-hydroxyfuran-2(5*H*)-one **1** in the presence of 10 mol % of prolinol catalyst **2a** or the diphenylprolinol silyl ethers **2b** and **2c** (Table 1). When the reaction was conducted in THF, full conversion to the Friedel–Crafts adduct (FC adduct) was observed in 7–20 h. This adduct, which was not easy to purify,[23] was directly converted to the chiral lactone **4** by in situ reduction followed by lactonization using a catalytic amount of *p*-toluenesulfonic acid.

Lactone **4** was obtained in high yield (81 to 93%) for the overall process and high enantiomeric ratio (90:10 to 96:4). The diphenylprolinol silyl ethers **2b** and **2c** are better catalysts than the simple diphenylprolinol **2a** both in terms of conversion rate and enantioselectivity (er 94:6 and 96:4). Further reactions were consequently performed with catalyst **2c**. In order to optimize the reaction conditions, solvent effects were then studied (Table 2). In 2-methylTHF, the Friedel–Crafts reaction proceeded slowly (12 h), albeit in good yield (84%) and high enantiomeric ratio (96:4) (entry 3). Interestingly, a significant rate increase was observed in a large variety of solvents. The use of protic solvents such as ethanol or water (with a minimal amount of THF required to achieved a homogeneous mixture) led to full conversion in only 2 h. It is noteworthy that a good enantiomeric ratio (95:5) for lactone **4** was obtained in such polar protic solvents (entries 1 and 2). When the reaction was carried out in dichloromethane, a short reaction time (1 h) gave full conversion, although with a lower enantiomeric ratio for lactone **4** (89:11) (entry 5).

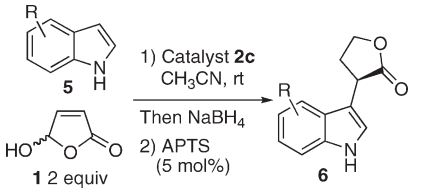
Table 2. Effect of Solvent and Catalyst Loading on Friedel–Crafts Reaction of *N*-Methylindole with 5-Hydroxyfuran-2(5*H*)-one 1[a]



entry	**2c** (mol %)	solvent	time[b] (h)	yield (%)	er[c]
1	10	H_2O/THF (9/1)	2	96	95:5
2	10	EtOH	2	97	95:5
3	10	2-methyl THF	12	84	96:4
4	10	THF	14	93	96:4
5	10	CH_2Cl_2	1	97	89:11
6	10	CH_3CN	1	93[d]	95:5
7	5	CH_3CN	1.5	90[d]	94:6
8	1	CH_3CN	4	90[d]	88:12

[a] The reactions were carried out with 0.5 mmol of indole **3**, 0.75 mmol of 5-hydroxyfuran-2(5*H*)-one **1**, and 0.05 mmol of **2c** in solvent (0.5 mL). [b] Reaction time needed for the total consumption of indole **2** in the Friedel–Crafts alkylation step. [c] Determined by chiral HPLC analysis. [d] Reaction was performed on 1 mmol scale.

Table 3. Scope of the Organocatalytic Friedel–Crafts Reaction of Indole with 5-Hydroxyfuran-2(5*H*)-one 1 Catalyzed by 2c[a]



entry	**2c** (mol %)	indole	time[b] (h)	yield (%)	er[c]
1	5	**5a**, 1*H*-indole	3	89	93:7
2	10	**5a**, 1*H*-indole	2	93	97:3
3	5	**5b**, 5-methyl-1*H*-indole	3	93	93:7
4	10	**5b**, 5-methyl-1*H*-indole	2	90	95:5
5	5	**5c**, 7-methyl-1*H*-indole	3	84	94:6
6	5	**5d**, 5-methoxy-1*H*-indole	2	86	93:7
7	5	**5e**, 5-fluoro-1*H*-indole	6	84	96:4
8	5	**5f**, 6-chloro- 1*H*-indole	10	80	95:5
9	10	**5f**, 6-chloro-1*H*-indole	15	83	98:2
10	5	**5g**, 1*H*-indole-4-carbonitrile	36	45	91:9

[a] The reactions were carried out with 1 mmol of indole **5**, 2 mmol of 5-hydroxyfuran-2(5*H*)-one **1**, and 0.05 mmol of **2c** in acetonitrile (1 mL). [b] Reaction time needed for the total consumption of indole **5** in the Friedel–Crafts alkylation step. [c] Determined by chiral HPLC analysis; absolute configuration assigned by analogy.

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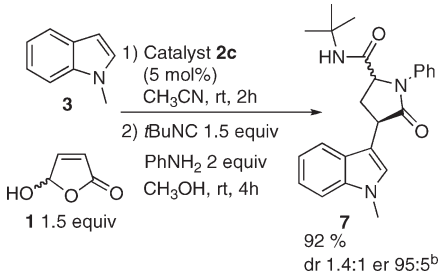
Best results were obtained in acetonitrile, combining both a short reaction time to get full conversion to the FC adduct (1 h) and a high enantiomeric ratio for lactone **4** (95:5) (entry 6). The short reaction time then prompted us to assess catalyst loading in this process. The use of 5 mol % of **2c** led to a full conversion to the FC adduct after only 1.5 h while maintaining a high enantiomeric ratio for lactone **4** (entry 7). Interestingly, in the presence of only 1% of catalyst **2c** the Friedel−Crafts alkylation proceeded in a relatively short reaction time (4 h), but with a significant decrease of the enantiomeric ratio of lactone **4** (88:12). This optimized methodology was then applied to several 1*H*-indole derivatives on a 1 mmol scale (Table 3). In the presence of 5 mol % of catalyst **2c**, 1*H*-indole **5a** was uneventfully converted to lactone **6a** in good yield (83%) and enantiomeric ratio (93:7) (entry 1).

The corresponding Friedel−Crafts adducts were obtained in short reaction times with 5- or 7-methylindole (3 h) (entries 3 and 5) as well as 5-methoxyindole (2 h) (entry 6). In all cases, the lactones **6** were obtained in good enantiomeric ratio (up to 95:5). Electron-deficient indoles were also successfully engaged in the alkylation reaction, 6-chloro-1*H*-indole **5f** (80%, er 95:5) and 5-fluoro-1*H*-indole **5e** (84%, er 96:4), giving good yields and excellent enantioselectivity (entries 7 and 8). As illustrated in entry 10, indoles with a strong electron-withdrawing group can also be used. The 4-cyano-substituted indole **5g** was slowly converted to the corresponding lactone in a moderate yield (45%) and good enantiomeric ratio (91:9) (entry 10). As observed in entries 2, 4, and 9, the enantiomeric ratio was slightly increased by using 10 mol % of catalyst **2c**.

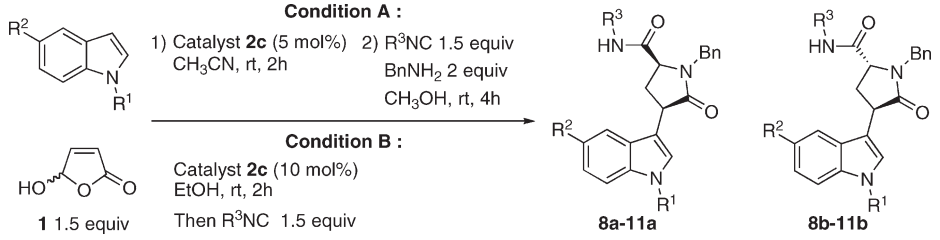
Having demonstrated the usefulness of 5-hydroxyfuran-2(5*H*)-one **1** as an electrophile in the enantioselective organocatalytic Friedel−Crafts alkylation, we wished to take advantage of the polyfunctional nature of the FC adduct to quickly increase the structural diversity of the indole scaffold. Application of multicomponent reactions (MCR) is obviously the archetypal strategy in a diversity-oriented synthesis.[24] Among the well-established multicomponent reactions, the Ugi reaction is widely recognized as an efficient tool in assembling library of pharmacologically relevant structures.[25−27] Since the pioneering work on the Ugi reaction, the use of bifunctional starting material has been explored in order to increase structural diversity and overcome bioavailability problems of normal Ugi products, which are peptide-like, by nature. Simple achiral oxo-carboxylic acids have been widely used in this context.[28−33] However, to the best of our knowledge, strategies based on chiral oxo-carboxylic acids have not been reported. We thus thought that the combination of a highly enantioselective Friedel−Crafts reaction producing chiral indoyl oxo-carboxylic acids and Ugi 4-center 3-component reaction should be a fruitful diversity-oriented synthetic strategy. A model experiment was conducted with *N*-methylindole **3**. The Friedel−Crafts reaction was carried out using the optimized conditions. After full conversion to the FC adduct, the solvent was switched to methanol, a more usual solvent for the Ugi reaction. When *tert*-butyl isocyanide and aniline were used as Ugi partners, the expected lactam **7** was obtained in 92% yield for the two steps (scheme 2).

Scheme 2. Friedel−Crafts/Ugi Reaction Sequence with 5-Hydroxyfuran-2(5*H*)-one 1, Aniline, and *tert*-Butyl Isocyanide[a]



[a] Friedel−Crafts reactions were carried out with 1 mmol of indole **5**, 2 mmol of 5-hydroxyfuran-2(5*H*)-one 1, and 0.05 mmol of **2c** in acetonitrile (1 mL). Ugi reactions were achieved by addition of aniline (2 mmol) and *tert*-butyl isocyanide (1.5 mmol) to a methanol solution (1 mL) of the crude FC adduct. [b] Determined by chiral HPLC analysis.

Table 4. Friedel−Crafts/Ugi Reaction Sequence[a]



entry	R^1	R^2	R^3	cond	compd	yield (%)	er[b]	compd	yield (%)	er[b]
1	CH_3	H	*t*-Bu	A	**8a**	43	94:6	**8b**	34	94:6
2	CH_3	H	Cycl	A	**9a**	44	92:8	**9b**	38	94:6
3	CH_3	H	Bn	A	**10a**	42	94:6	**10b**	35	94:6
4	CH_3	H	*t*-Bu	B	**8a**	37	89:11	**8b**	30	89:11
5	H	F	*t*-Bu	B	**11a**	29	91:9	**11b**	30	nd[c]

[a] Conditions A: Friedel−Crafts reactions were carried out with 1 mmol of indole **3**, 1.5 mmol of 5-hydroxyfuran-2(5*H*)-one **1**, and 0.05 mmol of **2c** in acetonitrile (1 mL). Ugi reactions were achieved by addition of benzylamine (2 mmol) and isocyanide (1.5 mmol) to a methanol solution (1 mL) of the crude FC adduct. Conditions B: Friedel−Crafts reactions were carried out with 1 mmol of indole **3** and **5e**, 1.5 mmol of 5-hydroxyfuran-2(5*H*)-one 1, and 0.1 mmol of **2c** in ethanol (1 mL) after total consumption of indole. Benzylamine (2 mmol) and *tert*-butyl isocyanide (1.5 mmol) were added to the reaction mixture. [b] Determined by chiral HPLC analysis. [c] Not determined; expected to be the same as compound **11a**.

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As expected, lactam **7** was obtained as a mixture of two diastereoisomers, inseparable by usual flash chromatography, with virtually no diastereoisomeric excess (dr 1.4:1). However, the high enantiomeric ratio (95:5) obtained for both diastereoisomeric lactams **7** attests that no racemization of the initially created stereogenic center occurred in the subsequent Ugi reaction. The scope of the reaction was then demonstrated using benzylamine and various isocyanides.

As previously observed, all reactions proceeded with virtually no diasteroselectivity during the Ugi step. However, the diastereosisomers were easily separated by silica gel flash chromatography in good yields (Table 4, entries 1−3). As expected, the products were obtained with the same high enantiomeric ratio (94:6). X-ray crystallography of compound **8a** allowed the unambiguous assignment of the relative stereochemistry of compounds **8a** and **8b** (see the Supporting Information).[34]

The reaction sequence involving a solvents change was clearly not optimal. Consequently, the feasibility of carrying out the Friedel−Crafts and Ugi reaction in a sequential one-pot process was then evaluated. Ethanol appeared to be the most appropriate solvent for the overall process. The reaction was conducted with indole **3** and 1.5 equiv of 5-hydroxyfuran-2(5*H*)-one **1** in the presence of 10 mol % of catalyst **2c**. After full conversion to the FC adduct, benzylamine and *tert*-butylisonitrile were added (Table 4, entry 4). The reaction gave the expected products **8a** and **8b** in good yields (37% and 30%, respectively). Slightly lower enantiomeric ratios were obtained using these reaction conditions (89:11). Finally, the Friedel−Crafts/Ugi sequence was successfully applied to an NH indole (Table 4, entry 5). Compounds **11a** and **11b** were obtained from 5-fluoro-1*H*-indole **5e** in good yield (29% and 30%, respectively) and good enantiomeric ratios (91:9).

■ CONCLUSION

In summary, the use of 5-hydroxyfuran-2(5*H*)-one **1** in asymmetric transformations has previously been restricted to chiral auxiliary-based approachs. We have demonstrated here that 5-hydroxyfuran-2(5*H*)-one **1** can also be efficiently used in an organocatalyzed enantioselective transformation. The proposed methodology allows efficient access to chiral lactones in high yield and enantioselectivity. The synthetic utility of 5-hydroxyfuran-2(5*H*)-one was further illustrated in the context of a multicomponent reaction by development of a sequence involving an enantioselective Friedel−Crafts alkylation followed by a Ugi 4-center 3-component reaction (U-4C-3CR). The use of 5-hydroxyfuran-2(5*H*)-one in an enantioselective Friedel−Crafts reaction with other aromatic compounds and more generally in organocatalyzed multicomponent reactions is currently under investigation.

■ EXPERIMENTAL SECTION

General Information. Thin-layer chromatography (TLC) analyses were done using aluminum sheets coated with silica gel 60 F_{254}. Flash column chromatography (FC) was carried out using silica gel 60 Å (0.015−0.04 mm). Commercially available products were used without further purification. NMR spectra were recorded with 500 MHz (BBFO + Z-GRD Probe) (^{1}H: 500 and ^{13}C: 125 MHz) and 600 MHz (CPTCI Z-GRD CryoProbe) (^{1}H: 600 and ^{13}C: 151 MHz) spectrometers in $CDCl_3$, CD_3CN and $(CD_3)_2SO$. Chemical shifts are given in ppm, calibrated to the residual solvent peak,[35] and coupling constants "*J*" are expressed in hertz (multiplicity: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, m = multiplet). Optical rotations were determined at 20 °C in the specified solvents. High-resolution mass spectra (HRMS) were performed on Q-TOF Micro micromass positive ESI (CV = 30 V). Enantiomeric ratios were determined by high-performance liquid chromatography (HPLC) with a chiral column.

General Procedure for Synthesis of Lactone 4 and 6a−g. The indole (1 mmol) and 5-hydroxyfuran-2(5*H*)-one **1** (2 mmol) were dissolved in acetonitrile. Catalyst **2c** (0.05 mmol) was then added, and the reaction was stirred until total consumption of the indole (TLC analysis). The reaction mixture was then diluted with 4 mL of THF, and $NaBH_4$ (2 mmol) was added. When reduction was complete (30 min), 15 mL of 1 M HCl solution was carefully added. The reaction mixture was extracted twice with ethyl acetate (2 × 15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was dissolved in a mixture of THF/$CHCl_3$ (1 mL/2 mL), and *p*-toluenesulfonic acid was added (0.05 mmol). The reaction mixture was then stirred for 4 h. The solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography to yield the desired product.

General Procedure for Synthesis of Friedel−Crafts/Ugi Reaction Sequence: Procedure with a Solvent Change (Conditions A). The indole (1 mmol) and 5-hydroxyfuran-2(5*H*)-one **1** (2 mmol) were dissolved in acetonitrile. Catalyst **2c** (0.05 mmol) was then added, and the reaction was stirred until total consumption of the indole (TLC analysis). A 1 M HCl solution (10 mL) was added, and the reaction mixture was extracted twice with dichloromethane (15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was dissolved in methanol (2 mL), and benzylamine (2 mmol) and isocyanide (1.5 mmol) were then added. The reaction mixture was stirred for 6 h and then concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to yield the desired products.

General Procedure for Synthesis of Friedel−Crafts/Ugi Reaction Sequence: One-Pot Sequential Procedure (Condition B). The indole (1 mmol) and 5-hydroxyfuran-2(5*H*)-one **1** (1.5 mmol) were dissolved in ethanol. Catalyst **2c** (0.1 mmol) was then added, and the reaction was stirred until total consumption of the indole (TLC analysis). Benzylamine (2 mmol) and *tert*-butyl isocyanide (1.5 mmol) were then added to the reaction mixture. The reaction mixture was stirred for 6 h and concentrated under reduce pressure. The crude residue was purified by silica gel column chromatography to yield the desired products.

(R)-3-(1-Methyl-1H-indol-3-yl)dihydrofuran-2(3H)-one ***(4)*** *(Table 2, Entry 6).* The title compound (200 mg, 0.93 mmol, 93%) was prepared as a pale yellow oil by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.8 CH_2Cl_2/EtOAc (90:10)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 4.49 (td, *J* = 8.5, 3.5 Hz, 1H), 4.40 (dt, *J* = 8.5, 7.0 Hz, 1H), 4.09 (t, *J* = 9.5 Hz, 1H), 3.76 (s, 3H), 2.79 (m, 1H), 2.47 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 137.3, 126.9, 126.8, 122.1, 119.4, 118.9, 109.7, 109.6, 66.9, 37.5, 32.9, 31.2; IR (KBr plate) ν_{max} 3121, 3052, 2990, 2937, 2914, 1764, 1616, 1553, 1477, 1427, 1375, 1333, 1240, 1215, 1151, 1072, 1023 (cm^{-1}); ESI-HRMS: *m*/*z*: calcd for $C_{13}H_{14}NO_2$ ($[M + H]^+$) 216.1025, found 216.1032; $[\alpha]^{20}_D$ = +74.5 (*c* 1, $CHCl_3$), er (95:5). The enantiomeric ratio was determined by HPLC with a CHIRALCEL OD-H column (hexane/EtOH = 75:25, 254 nm, 0.8 mL/min), t_R (major) = 26.0 min, t_R (minor) = 19.7 min.

(R)-3-(1H-Indol-3-yl)dihydrofuran-2(3H)-one ***6a*** *(Table 3, Entry 2).* The title compound (188 mg, 0.93 mmol, 93%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.6 CH_2Cl_2/EtOAc (90:10)): mp 146−148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.21 (td, *J* = 7.5, 1.0 Hz, 1H), 7.14 (td, *J* = 7.5, 1.0 Hz,

1H), 7.09 (d, J = 2.0 Hz, 1H), 4.49 (td, J = 8.5, 3.5 Hz, 1H), 4.40 (td, J = 8.5, 7.0 Hz, 1H), 4.08 (t, J = 9.5 Hz, 1H), 2.77 (m, 1H), 2.48 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 136.6, 126.3, 122.6, 122.4, 120.0, 118.8, 111.7, 111.1, 67.0, 37.6, 31.0; IR (KBr plate) ν_{max} 3402, 3021, 2967, 2910, 2841, 1761, 1457, 1426, 1370, 1338, 1272, 1214,1161, 1098, 1020 (cm^{-1}); ESI-HRMS m/z calcd for $C_{12}H_{11}NNaO_2^+$ ($[M + Na]^+$) 224.0687, found 224.0677; $[\alpha]^{20}_D$ = +94.2 (c 0.5, $CHCl_3$), er (97:3). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/i-PrOH = 77:23, 254 nm, 0.8 mL/min), t_R(major) = 34.4 min, t_R(minor) = 36.6 min

(R)-3-(5-Methyl-1H-indol-3-yl)dihydrofuran-2(3H)-one ***(6b)*** *(Table 3, Entry 3).* The title compound (195 mg, 0.90 mmol, 90%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.6 CH_2Cl_2/EtOAc (90:10)): mp 142−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.34 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.03 (dd, J = 8.5, 1.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 4.47 (td, J = 8.5, 4.0 Hz, 1H), 4.38 (td, J = 8.5, 7.0 Hz, 1H), 4.03 (t, J = 9.5 Hz, 1H), 2.74 (m, 1H), 2.52−2.41 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 135.1, 129.2, 126.7, 124.2, 122.6, 118.4, 111.4, 110.7, 66.9, 37.7, 31.0, 21.6; IR (KBr plate) ν_{max} 3430, 3401, 3126, 3088, 3014, 2912, 2861, 1751, 1482, 1457, 1426, 1371, 1303, 1268, 1248, 1205, 1157,1100, 1097, 1021 (cm^{-1}); ESI-HRMS m/z calcd for $C_{13}H_{13}NNaO_2^+$ ($[M + Na]^+$) 238.0844, found 238.0838; $[\alpha]^{20}_D$ = +74.3 (c 1, $CHCl_3$), er (93:7). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (Hexane/i-PrOH = 77:23, 254 nm, 0.8 mL/min), t_R (major) = 30.8 min, t_R (minor) = 35.2 min.

(R)-3-(7-Methyl-1H-indol-3-yl)dihydrofuran-2(3H)-one ***(6c)*** *(Table 3, Entry 5).* The title compound (180 mg, 0.84 mmol, 84%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.6 CH_2Cl_2/EtOAc (90:10)): mp 132−134 °C; ^{1}H NMR (500 MHz, DMSO) δ 10.99 (s, 1H), 7.33 (dd, J = 7.0, 2.0 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 6.98−6.81 (m, 2H), 4.46 (td, J = 9.0, 3.0 Hz, 1H), 4.34 (td, J = 9.0, 7.0 Hz, 1H), 4.15 (t, J = 9.5 Hz, 1H), 2.65 (m, 1H), 2.48−2.37 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 177.6, 135.9, 125.8, 122.8, 121.7, 120.7, 118.8, 116.2, 110.8, 66.5, 36.8, 30.1, 16.6; IR (KBr plate) ν_{max} 3297, 3055, 3018, 2992, 2923, 2858, 1758, 1617, 1591, 1497, 1442, 1378, 1344, 1314, 1274, 1217, 1160, 1126, 1102,1072, 1024 (cm^{-1}); ESI-HRMS m/z calcd for $C_{13}H_{13}NNaO_2^+$ ($[M + Na]^+$) 238.0844, found 238.0832; $[\alpha]^{20}_D$ = +81.7 (c 0.5, $CHCl_3$) −30.3 (c 0.5, CH_3CN), er (94:6). Enantiomeric ratio was determined by HPLC with a Chirex (R)-NGLY and DNB column (hexane/EtOH = 60:40, 254 nm, 1 mL/min), t_R (major) = 11.6 min, t_R (minor) = 16.7 min.

(R)-3-(5-Methoxy-1H-indol-3-yl)dihydrofuran-2(3H)-one ***(6d)*** *(Table 3, Entry 6).* The title compound (200 mg, 0.86 mmol, 86%) was prepared as a pale purple oil by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.4 CH_2Cl_2/EtOAc (90:10)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.24 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 9.0, 2.5 Hz, 1H), 4.49 (td, J = 8.5, 3.5 Hz, 1H), 4.40 (td, J = 8.5, 7.0 Hz, 1H), 4.04 (t, J = 9.0 Hz, 1H), 3.85 (s, 3H), 2.75 (m, 1H), 2.46 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 154.2, 131.8, 126.7, 123.22, 123.19, 112.5, 110.5, 100.8, 67.1, 56.1, 37.6, 30.7; IR (film) ν_{max} 3405, 2994, 2940, 2909, 2832, 1759, 1626, 1584, 1486, 1456, 1375, 1301, 1276, 1253, 1210, 1173, 1102, 1022 (cm^{-1}); ESI-HRMS m/z calcd for $C_{13}H_{13}NNaO_3^+$ ($[M + Na]^+$) 254.0793, found 254.0800; $[\alpha]^{20}_D$ = +63.6 (c 0.5, $CHCl_3$), er (93:7). Enantiomeric ratio was determined by HPLC with a CHIRALCEL OD-H column (hexane/i-PrOH = 65:35, 254 nm, 0.8 mL/min), t_R (major) = 24.1 min, t_R (minor) = 29.5 min.

(R)-3-(5-Fluoro-1H-indol-3-yl)dihydrofuran-2(3H)-one ***(6e)*** *(Table 3, Entry 7).* The title compound (184 mg, 0.84 mmol, 84%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.5 CH_2Cl_2/EtOAc (90:10)): mp 125−127 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 9.42 (s, 1H), 7.39 (dd, J = 9.0, 4.5 Hz, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.25 (dd, J = 10.0, 2.5 Hz, 1H), 6.95 (td, J = 9.0, 2.5 Hz, 1H), 4.46 (td, J = 8.5, 3.0 Hz, 1H), 4.35 (td, J = 8.5, 7.0 Hz, 1H), 4.13 (t, J = 9.0 Hz, 1H), 2.69 (m, 1H), 2.44 (m, 1H); ^{13}C NMR (126 MHz, CD_3CN) δ 178.7, 158.3 (d, J_{C-F}= 230.5 Hz), 134.1, 127.6 (d, J_{C-F} = 9.5 Hz), 125.9, 113.5 (d, J_{C-F} = 8.5 Hz), 112.1 (d, J_{C-F} = 5.5 Hz), 110.8 (d, J_{C-F} = 25.5 Hz), 104.3 (d, J_{C-F} = 24.0 Hz), 67.7, 37.9, 30.9; ^{19}F NMR (235 MHz, CD_3CN) δ −126.8 (td, J = 10.0, 4.5 Hz); IR (KBr plate) ν_{max} 3381, 3130, 3088, 3055, 2992, 2940, 2912, 1746, 1631, 1583, 1490, 1459, 1433, 1375, 1343, 1304, 1297, 1244, 1224, 1176, 1138, 1107, 1022 (cm^{-1}); ESI-HRMS m/z calcd for $C_{12}H_{10}FNNaO_2^+$ ($[M + Na]^+$) 242.0593, found 242.0587; $[\alpha]^{20}_D$ = −31.5 (c 0.5, CH_3CN), er (96:4). Enantiomeric ratio was determined by HPLC with a CHIRALCEL OD-H column (hexane/i-PrOH= 65:35, 254 nm, 0.8 mL/min), t_R (major) = 12.1 min, t_R (minor) = 16.0 min.

(R)-3-(6-Chloro-1H-indol-3-yl)dihydrofuran-2(3H)-one ***(6f)*** *(Table 3, Entry 9).* The title compound (195 mg, 0.83 mmol, 83%) was prepared as a white solid by general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.5 CH_2Cl_2/EtOAc (90:10)): mp 200−202 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 9.47 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 1.5 Hz, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.10 (dd, J = 8.5, 1.5 Hz, 1H), 4.49 (td, J = 9.0, 3.0 Hz, 1H), 4.38 (td, J = 9.0, 6.5 Hz, 1H), 4.13 (t, J = 9.5 Hz, 1H), 2.73 (m, 1H), 2.48 (m, 1H); ^{13}C NMR (126 MHz, CD_3CN) δ 178.8, 138.0, 128.2, 126.2, 124.9, 121.1, 121.0, 120.6, 112.4, 67.9, 38.0, 31.1; IR (KBr plate) ν_{max} 3358, 3128, 3000, 2962, 2905, 1765, 1614, 1572, 1454, 1408, 1374, 1338, 1135, 1113, 1055, 1022 (cm^{-1}); ESI-HRMS m/z calcd for $C_{12}H_{10}ClNNaO_2^+$ ($[M + Na]^+$) 258.0298, found 258.0308; $[\alpha]^{20}_D$ = −37.3 (c 0.5, CH_3CN) er (98:2). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/i-PrOH = 70:30, 254 nm, 0.8 mL/min), t_R (major) = 12.0 min, t_R (minor) = 13.7 min.

*(R)-3-(2-Oxotetrahydrofuran-3-yl)-1H-indole-4-carbonitrile (****6g****) (Table 3, Entry 10).* The title compound (100 mg, 0.44 mmol, 44%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.9 CH_2Cl_2/EtOAc (90:10)): mp 167−169 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.71 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 4.59- 4.20 (m, 3H), 2.68 (m, 1H), 2.49 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 177.2, 136.6, 127.1, 125.9, 125.5, 121.2, 119.2, 117.2, 110.0, 100.5, 66.3, 36.6, 30.6; IR (KBr plate) ν_{max} 3416, 3125, 3068, 2999, 2947, 2888, 2214, 1765, 1495, 1430, 1377, 1348, 1308, 1264, 1214, 1153, 1112, 1047, 1021 (cm^{-1}); ESI-HRMS m/z calcd for $C_{13}H_{10}N_2NaO_2^+$ ($[M + Na]^+$) 249.0640, found 249.0636; $[\alpha]^{20}_D$ = −13.6 (c 0.5, CH_3CN) er (91:9). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/EtOH = 70:30, 254 nm, 0.8 mL/min), t_R (major) = 11.6 min, t_R (minor) = 10.5 min.

*(R)-N-tert-butyl-4-(1-methyl-1H-indol-3-yl)-5-oxo-1-phenylpyrrolidine-2-carboxamide (****7****).* The title compound (mixture of two diastereoisomers) (360 mg, 0.92 mmol, 92%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = CH_2Cl_2/EtOAc (95:5)): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.61−7.55 (m), 7.43 (m), 7.38−7.31 (m), 7.31−7.20 (m), 7.21−7.10 (m), 7.10−7.08 (m, 1H), 5.67 (s, 1H, minor dia), 5.51 (s, 1H, major dia), 4.70 (t, J = 8.0 Hz, 1H, major dia), 4.59 (dd, J = 9.0, 3.0 Hz, 1H, minor dia), 4.33 (t, J = 9.0 Hz, 1H, minor dia), 4.18 (t, J = 9.0 Hz, 1H, major dia), 3.79 (s, 3H, major dia), 3.77 (s, 3H, minor dia), 3.03 (m, 1H, major dia), 2.77 (m, 1H, minor dia), 2.68 (m, 1H, minor dia), 2.44 (m, 1H, major dia), 1.31 (s, 9H, minor dia), 1.09 (s, 9H, major dia); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 175.0, 170.3, 170.1, 138.5, 138.2, 137.53, 137.48, 129.35, 129.28, 127.1, 127.0, 126.8, 125.8, 125.7, 122.2, 122.1, 121.6, 121.3, 119.5, 119.4, 119.2, 111.4, 111.3, 109.7, 62.3, 62.2, 51.9, 51.4, 40.5, 40.1, 32.9, 32.86, 32.85, 31.7, 28.7, 28.3; IR (KBr plate) ν_{max} 3319, 3060, 2968, 2933, 2882, 1674, 1599, 1548, 1497, 1456, 1390, 1363, 1332, 1299, 1262, 1218,

1160, 1123, 1072, 1047, 1013 (cm^{-1}); ESI-HRMS m/z calcd for $C_{24}H_{27}N_3NaO_2^+$ ($[M + Na]^+$) 412.2001, found 412.1999; $[\alpha]^{20}_D$ = +59.8 (mixture of 2 diastereoisomers) (c 0.5, $CHCl_3$), er (91:9). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (Hexane/EtOH = 65:35, 254 nm, 0.8 mL/min), t_R (major, major dia) = 10.9 min, t_R (minor, major dia) = 15.7 min; t_R (major, minor dia) = 9.9 min, t_R (minor, minor dia) = 20.1 min.

*(2S,4R)-1-Benzyl-N-tert-butyl-4-(1-methyl-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**8a**).* The title compound (172 mg, 0.43 mmol, 43%) was prepared as a pale orange solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.5 CH_2Cl_2/EtOAc (80:20)): mp 102 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 1H), 7.39−7.28 (m, 6H), 7.23 (t, J = 8.0 Hz, 1H), 7.14−7.09 (m, 2H), 5.36 (s, 1H), 5.04 (d, J = 14.5 Hz, 1H), 4.16 (d, J = 14.5 Hz, 1H), 3.96 (t, J = 9.0 Hz, 1H), 3.80 (t, J = 8.0 Hz, 1H), 3.75 (s, 3H), 2.81 (dt, J = 13.0, 9.0 Hz, 1H), 2.26 (dt, J = 13.0, 8.0 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 170.0, 137.4, 136.5, 129.0, 128.9, 128.0, 127.0, 127.98, 122.0, 119.4, 119.3, 112.0, 109.6, 60.8, 51.4, 46.6, 39.3, 32.8, 32.1, 28.5; IR (KBr plate) ν_{max} 3356, 3317, 3084, 3059, 2991, 2964, 2921, 1668, 1554, 1476, 1450, 1417, 1363, 1331, 1275, 1224, 1172, 1073, 1049 (cm^{-1}); ESI-HRMS m/z calcd for $C_{25}H_{29}N_3NaO_2^+$ ($[M + Na]^+$) 426.2157, found 426.2148; $[\alpha]^{20}_D$ = +57.8 (c 0.5, $CHCl_3$), er (94:6). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/EtOH = 55:45, 254 nm, 0.8 mL/min), t_R (major) = 7.4 min, t_R (minor) = 15.7 min.

*(2R,4R)-1-Benzyl-N-tert-butyl-4-(1-methyl-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**8b**).* The title compound (137 mg, 0.34 mmol, 34%) was prepared as a pale orange solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (90:10) (R_f = 0.3 CH_2Cl_2/EtOAc (80:20)): mp 200 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 1H), 7.39−7.27 (m, 6H), 7.22 (t, J = 8.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 7.02−6.99 (m, 1H), 5.43 (s, 1H), 5.09 (d, J = 14.5 Hz, 1H), 4.18 (t, J = 9.0 Hz, 1H), 4.06 (d, J = 14.5 Hz, 1H), 3.80 (dd, J = 9.0, 3.0 Hz, 1H), 3.73 (s, 3H), 2.57 (ddd, J = 13.0, 9.0, 3.0 Hz, 1H), 2.40 (dt, J = 13.0, 9.0 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 170.4, 137.5, 136.4, 129.0, 128.9, 128.1, 127.1, 126.8, 121.9, 119.2, 111.9, 109.6, 60.1, 51.8, 46.6, 38.7, 32.85, 32.81, 28.8; IR (KBr plate) ν_{max} 3273, 3065, 2969, 1761, 1554, 1431, 1363, 1331, 1259, 1227, 1201, 1130, 1074, 1039 (cm^{-1}); ESI-HRMS m/z calcd for $C_{25}H_{30}N_3O_2^+$ ($[M + H]^+$) 404.2338, found 404.2339; $[\alpha]^{20}_D$ = −63.9 (c 0.5, $CHCl_3$), er (94:6). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/*i*-PrOH= 55:45, 254 nm, 0.8 mL/min), t_R (major) = 13.7 min, t_R (minor) = 11.5 min.

*(2S,4R)-1-Benzyl-N-cyclohexyl-4-(1-methyl-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**9a**).* The title compound (189 mg, 0.44 mmol, 44%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f= 0.4 CH_2Cl_2/EtOAc (80:20)): mp 210 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.38−7.27 (m, 6H), 7.23 (td, J = 7.5, 1.0 Hz, 1H), 7.12 (td, J = 7.5, 1.0 Hz, 1H), 7.09 (s, 1H), 5.44 (d, J = 7.5 Hz, 1H), 5.14 (d, J = 14.5 Hz, 1H), 4.05 (d, J = 14.5 Hz, 1H), 3.99 (t, J = 9.0 Hz, 1H), 3.87 (dd, J = 8.0, 7.0 Hz, 1H), 3.76 (s, 3H), 3.70 (m, 1H), 2.82 (dt, J = 13.0, 9.0 Hz, 1H), 2.29 (ddd, J = 13.0, 8.0, 7.0 Hz, 1H), 1.79−1.72 (m, 2H), 1.68−1.54 (m, 3H), 1.42−1.22 (m, 2H), 1.16−1.01 (m, 1H), 0.98−0.83 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 169.9, 137.4, 136.2, 129.0, 128.9, 128.1, 127.0, 126.96, 122.0, 119.41, 119.40, 111.9, 109.5, 59.9, 48.4, 46.4, 39.3, 32.94, 32.90, 32.8, 31.9, 25.5, 24.8; IR (KBr plate) ν_{max} 3281, 3085, 3062, 3016, 2931, 2853, 1686, 1653, 1552, 1477, 1448, 1413, 1347, 1309, 1274, 1245, 1206, 1179, 1155, 1092 1074, 1018 (cm^{-1}); ESI-HRMS m/z calcd for $C_{27}H_{32}N_3O_2^+$ ($[M + H]^+$) 430.2495, found 430.2500; $[\alpha]^{20}_D$ = +57.4 (c 0.5, $CHCl_3$), er (94:6). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/EtOH = 50:50, 254 nm, 0.8 mL/min), t_R (major) = 7.8 min, t_R (minor) = 16.0 min.

*(2R,4R)-1-Benzyl-N-cyclohexyl-4-(1-methyl-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**9b**).* The title compound (165 mg, 0.38 mmol, 38%) was prepared as a pale brown solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (90:10) (R_f = 0.2 CH_2Cl_2/EtOAc (80:20)): mp 200 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.27 (m, 7H), 7.22 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.98 (s, 1H), 5.92 (bs, 1H), 5.17 (d, J = 14.5 Hz, 1H), 4.15 (t, J = 9.5 Hz, 1H), 3.96 (d, J = 14.5 Hz, 1H), 3.90 (dd, J = 9.0, 3.0 Hz, 1H), 3.83−3.74 (m, 1H), 3.73 (s, 3H), 2.56 (ddd, J = 13.0, 9.0, 3.0 Hz, 1H), 2.40 (dt, J = 13.0, 9.5 Hz, 1H), 1.93−1.80 (m, 2H), 1.74−1.65 (m, 2H), 1.64−1.57 (m, 1H), 1.50−1.22 (m, 2H), 1.17−0.73 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 170.1, 137.4, 136.1, 129.0, 128.8, 128.1, 127.1, 126.7, 122.0, 119.20, 119.16, 111.8, 109.6, 59.4, 48.6, 46.5, 38.8, 33.1, 33.05, 33.01, 32.8, 25.5, 25.0; IR (KBr plate) ν_{max} 3308, 3109, 3064, 3028, 2928, 2854, 1690, 1650, 1548, 1477, 1450, 1418, 1377, 1333, 1306, 1247, 1181, 1097, 1011 (cm^{-1}); ESI-HRMS m/z calcd for $C_{27}H_{32}N_3O_2^+$ ($[M + H]^+$) 430.2495, found 430.2491; $[\alpha]_D^{20}$ = −59.2 (c 0.5, $CHCl_3$), er (94:6). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/EtOH = 50:50, 254 nm, 0.8 mL/min), t_R (major) = 28.6 min, t_R (minor) = 16.7 min.

*(2S,4R)-N,1-Dibenzyl-4-(1-methyl-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**10a**).* The title compound (186 mg, 0.42 mmol, 42%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (95:5) (R_f = 0.6 CH_2Cl_2/EtOAc (80:20)): mp 55 °C dec; ^{1}H NMR (600 MHz, DMSO) δ 8.67 (t, J = 6.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.37−7.17 (m, 9H), 7.15 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.01 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 5.00 (d, J = 15.0 Hz, 1H), 4.39 (dd, J = 15.0, 6.0 Hz, 1H), 4.25 (dd, J = 15.0, 5.5 Hz, 1H), 4.08 (t, J = 8.0 Hz, 1H), 4.02 (t, J = 10.0 Hz, 1H), 3.91 (d, J = 15.0 Hz, 1H), 3.74 (s, 3H), 2.73 (ddd, J = 12.5, 9.5, 8.0 Hz, 1H), 2.09 (ddd, J = 12.5, 10.0, 8.0 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 174.6, 170.3, 138.9, 136.7, 136.2, 128.4, 128.1, 127.7, 127.6, 127.15, 127.11, 126.7, 126.5, 121.0, 119.2, 118.3, 111.9, 109.4, 57.5, 44.7, 42.1, 38.4, 32.1, 31.1; IR (KBr plate) ν_{max} 3291, 3083, 3057, 2932, 1677, 1657, 1561, 1456, 1437, 1419, 1332, 1277, 1249, 1159, 1076, 1032 (cm^{-1}); ESI-HRMS m/z calcd for $C_{28}H_{28}N_3O_2^+$ ($[M + H]^+$) 438.2182, found 438.2181; $[\alpha]^{20}_D$ = +67.2 (c 0.5, $CHCl_3$), er (92:8). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/EtOH = 55:45, 254 nm, 0.8 mL/min), t_R (major) = 8.2 min, t_R (minor) = 16.2 min.

*(2R,4R)-N,1-Dibenzyl-4-(1-methyl-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**10b**).* The title compound (155 mg, 0.35 mmol, 35%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (90:10) (R_f = 0.4 CH_2Cl_2/EtOAc (80:20)): mp 200 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.17 (m, 13H), 7.08 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.98 (s, 1H), 6.46 (s, 1H), 5.18 (d, J = 14.5 Hz, 1H), 4.41 (d, J = 6 Hz, 2H), 4.18 (t, J = 9.5 Hz, 1H), 3.98 (dd, J = 9.5, 3.0 Hz, 1H), 3.95 (d, J = 14.7 Hz, 1H), 3.74 (s, 3H), 2.62 (ddd, J = 13.0, 9.5, 3.0 Hz, 1H), 2.42 (dt, J = 13.0, 9.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 171.1, 138.0, 137.4, 135.9, 129.0, 128.9, 128.7, 128.1, 127.95, 127.86, 127.1, 126.7, 122.0, 119.2, 119.2, 111.7, 109.7, 59.2, 46.4, 43.7, 38.8, 33.0, 32.8; IR (KBr plate) ν_{max} (cm^{-1}) 3288, 3060, 3030, 2925, 1667, 1550, 1450, 1423, 1379, 1356, 1330, 1243, 1177, 1159, 1129, 1075, 1023 (cm^{-1}); ESI-HRMS m/z calcd for $C_{28}H_{28}N_3O_2^+$ ($[M + H]^+$) 438.2182; found 438.2170. $[\alpha]_D^{20}$ = −56.3 (c 0.5, $CHCl_3$) er (94:6). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/EtOH = 55:45, 254 nm, 0.8 mL/min), t_R (major) = 17.9 min, t_R (minor) = 15.7 min.

*(2S,4R)-1-Benzyl-N-tert-butyl-4-(5-fluoro-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**11a**).* The title compound (135 mg, 0.33 mmol, 33%) was prepared as white solid by general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (90:10) (R_f= 0.3 CH_2Cl_2/EtOAc (80:20)): mp 95 °C dec; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.40−7.27 (m, 6H), 7.21 (dd, J = 9.0, 4.5 Hz, 1H), 7.08 (s, 1H), 6.89 (td, J = 9.0, 2.5 Hz,

1H), 5.39 (s, 1H), 5.08 (d, J = 14.5 Hz, 1H), 4.15 (d, J = 14.5 Hz, 1H), 3.87 (t, J = 9.0 Hz, 1H), 3.79 (t, J = 8.0 Hz, 1H), 2.74 (dt, J = 13.0, 9.0 Hz, 1H), 2.21 (dt, J = 13.0, 8.5 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.3, 169.8, 157.9 (d, J_{C-F} = 234.5 Hz), 136.3, 133.2, 129.1, 128.8, 128.1, 126.8 (d, J_{C-F} = 9.5 Hz), 124.6, 113.2 (d, J_{C-F} = 5.0 Hz), 112.3 (d, J_{C-F} = 10.0 Hz), 110.6 (d, J_{C-F} = 26.0 Hz), 104.0 (d, J_{C-F} = 24.0 Hz), 60.5, 51.7, 46.6, 39.4, 31.6, 28.6; ^{19}F NMR (235 MHz, $CDCl_3$) δ −124.7 (td, J = 9.0, 4.5 Hz); IR (KBr plate) ν_{max} 3302, 3270, 3084, 2972, 2929, 1666, 1557, 1489, 1454, 1421, 1392, 1362, 1270, 1225, 1168, 1103 (cm^{-1}); ESI-HRMS m/z calcd for $C_{24}H_{27}FN_3O_2^+$ ([M + H]$^+$) 408.2087, found 408.2097; $[\alpha]^{20}_D$ = +63.8 (c 0.5, $CHCl_3$), er (94:6). Enantiomeric ratio was determined by HPLC with a CHIRALPAK IC column (hexane/EtOH = 70:30, 254 nm, 0.8 mL/min), t_R (major) = 6.3 min, t_R (minor) = 8.4 min.

*(2R,4R)-1-Benzyl-N-tert-butyl-4-(5-fluoro-1H-indol-3-yl)-5-oxopyrrolidine-2-carboxamide (**11b**).* The title compound (122 mg, 0.30 mmol, 30%) was prepared as a white solid by the general procedure and eluted from silica gel with CH_2Cl_2/EtOAc (80:20) (R_f = 0.1 CH_2Cl_2/EtOAc (80:20)): mp 220 °C dec; ^{1}H NMR (600 MHz, DMSO) δ 11.04 (s, 1H), 7.80 (s, 1H), 7.40−7.33 (m, 3H), 7.33−7.28 (m, 2H), 7.24 (d, J = 9.0 Hz, 2H), 7.07 (dd, J = 10.0, 2.5 Hz, 1H), 6.92 (td, J = 9.0, 2.5 Hz, 1H), 4.89 (d, J = 15.0 Hz, 1H), 4.06 (dd, J = 8.5, 3.0 Hz, 1H), 4.01 (t, J = 9.0 Hz, 1H), 3.78 (d, J = 15.0 Hz, 1H), 2.35- 2.19 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (151 MHz, DMSO) δ 175.0 170.2, 156.5 (d, J_{C-F} = 231.0 Hz), 136.8, 133.2, 128.6, 127.9, 127.4, 126.2 (d, J_{C-F} = 10.0 Hz), 125.4, 113.2 (d, J_{C-F} = 4.5 Hz), 112.5 (d, J_{C-F} = 10.0 Hz), 109.2 (d, J_{C-F} = 26.0 Hz), 103.5 (d, J_{C-F} = 23.0 Hz), 58.1, 50.4, 45.0, 38.2, 31.4, 28.4; ^{19}F NMR (235 MHz, $CDCl_3$) δ −125.9 (td, J = 10.0, 4.5 Hz); IR (KBr plate) ν_{max} 3447, 3414, 3297, 3226, 3065, 2963, 2924, 2888, 1681, 1668, 1583, 1552, 1520, 1488, 1452, 1428, 1361, 1292, 1257, 1222, 1165, 1128, 1089 (cm^{-1}); ESI-HRMS m/z calcd for $C_{24}H_{26}FN_3O_2Na^+$ ([M + Na]$^+$) 430.1907, found 430.1894; $[\alpha]_D^{20}$ = −121.2 (c 0.5, DMSO)

*(R)-Methyl 2-(1-Methyl-1H-indol-3-yl)-4-oxobutanoate **12** (Determination of Absolute Configuration of Compound **4**).* The indole (0.5 mmol) and 5-hydroxyfuran-2(5*H*)-one **1** (0.75 mmol) were dissolved in acetonitrile (0.5 mL). Catalyst **2c** (0.05 mmol) was then added, and the reaction was stirred until total consumption of indole (TLC analysis). A 1 M HCl solution (10 mL) was added, and the reaction mixture was extracted twice with dichloromethane (15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was dissolved in methanol (2 mL), a catalytic amount (5 mol %) of *p*-TSA was added, and the reaction mixture was stirred at reflux for 6 h. The methanol was then removed by concentrating in vacuo. The crude residue was then refluxed with a catalytic amount of *p*-TSA in H_2O (1 mL)/acetone (1 mL) for 5 h. The reaction was then treated with an excess of saturated aqueous sodium bicarbonate, extracted with CH_2Cl_2 (2 × 10 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel chromatography (10:90 CH_2Cl_2/hexanes) to provide the known (*R*)-methyl 2-(1-methyl-1*H*-indol-3-yl)-4-oxobutanoate **12** (85 mg, 0.34 mmol, 68%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.37−7.20 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.99 (s, 1H), 4.45 (dd, J = 9.5, 5.0 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.48 (dd, J = 18.5, 9.5 Hz, 1H), 2.94 (dd, J = 18.5, 5.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.3, 173.8, 137.1, 127.0, 126.6, 122.2, 119.6, 119.2, 110.8, 109.6, 52.5, 46.7, 36.5, 32.9; ESI-HRMS m/z calcd for $C_{14}H_{15}NNaO_3$ ([M + Na]$^+$) 268.0950, found 268.0953; $[\alpha]^{20}_D$ = −148 (c 1, $CHCl_3$); reported rotation for (*R*)-methyl 2-(1-methyl-1*H*-indol-3-yl)-4-oxobutanoate **12** (ee 91) $[\alpha]^{20}_D$ = −123.6 (c 1, $CHCl_3$).[12]

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra and HPLC chromatograms of all compounds. X-ray structural data (CIF) of compound **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. *J. Med. Chem.* **1988**, *31*, 2235.
(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(3) Alves, F. R. d. S.; Barreiro, E. J.; Fraga, C. A. M. *Mini Rev. Med. Chem.* **2009**, *9*, 782.
(4) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
(5) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.
(6) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199.
(7) Liu, X.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2011**, DOI: 10.1021/ar200015s.
(8) Zeng, M.; You, S.-L. *Synlett* **2010**, 1289.
(9) Terrasson, V.; Marcia de Figueiredo, R.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635.
(10) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449.
(11) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(12) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.
(13) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.
(14) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
(15) Hong, L.; Wang, L.; Chen, C.; Zhang, B.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 772.
(16) Wang, Z.-J.; Yang, J.-G.; Jin, J.; Lv, X.; Bao, W. *Synthesis* **2009**, 3994.
(17) Shi, Z.-H.; Sheng, H.; Yang, K.-F.; Jiang, J.-X.; Lai, G.-Q.; Lu, Y.; Xu, L.-W. *Eur. J. Org. Chem.* **2011**, *2011*, 66.
(18) Schenck, G. O. *Liebigs Ann. Chem.* **1953**, *584*, 156.
(19) Esser, P.; Pohlmann, B.; Scharf, H.-D. *Angew. Chem., Int. Ed.* **1994**, *33*, 2009.
(20) Feringa, B. L.; De Lange, B.; Jansen, J. F. G. A.; De Jong, J. C.; Lubben, M.; Faber, W.; Schudde, E. P. *Pure Appl. Chem.* **1992**, *64*, 1865.
(21) Marinković, S.; Brulé, C.; Hoffmann, N.; Prost, E.; Nuzillard, J.-M.; Bulach, V. *J. Org. Chem.* **2004**, *69*, 1646.
(22) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090.
(23) NMR spectra of the crude product showed the presence of the expected FC-adduct in equilibrium with its acetal form: 5-hydroxy-3-(1-methyl-1*H*-indol-3-yl)dihydrofuran-2(3*H*)-one.
(24) Zhu, J., Bienayme, H., Eds. *Multicomponent Reactions*; Wiley: Weinheim, 2005.

(25) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321.
(26) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300.
(27) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(28) Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591.
(29) Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron* **1997**, *53*, 6653.
(30) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725.
(31) Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem.* **1999**, *64*, 1074.
(32) Wang, W.; Ollio, S.; Herdtweck, E.; Dömling, A. *J. Org. Chem.* **2010**, *76*, 637.
(33) Mehta, V. P.; Modha, S. G.; Ruijter, E.; Van Hecke, K.; Van Meervelt, L.; Pannecouque, C.; Balzarini, J.; Orru, R. V. A.; Van der Eycken, E. *J. Org. Chem.* **2011**, *76*, 2828.
(34) The relative stereochemistry of compounds **9a**, **9b**, **10a**, **10b**, **11a**, and **11b** were assigned by comparison of their NMR spectrum to NMR spectrum of compounds **8a** and **8b**.
(35) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.