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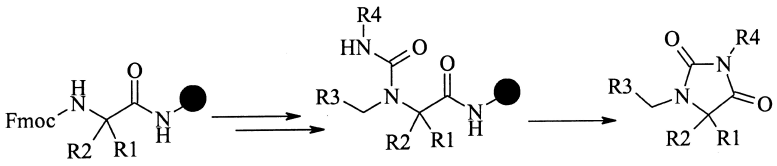

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Solid-Phase Preparation of Hydantoins through a New Cyclization/Cleavage Step

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An efficient process for the solid-phase synthesis of hydantoins has been developed. The amino acid starting material is anchored to the resin from its carboxylic acid end through formation of a very stable amide bond. After introduction of different functional groups, the cleavage/cyclization step can be performed in acidic or basic conditions.

Hydantoins constitute an important class of heterocycles in medicinal chemistry because many derivatives have been identified that display interesting activities against a broad range of biological targets.[1] For example, fosphenytoin is a sodium channel antagonist used in the treatment of epilepsy and nilutamide is an androgen antagonist used in anticancer therapy (Figure 1). The observed activities do not arise from the heterocycle but from the different ligands that have been attached to it. Therefore, this small and rigid heterocycle illustrates an interesting scaffold in combinatorial chemistry because it represents a three-point diversity backbone. Several methods for the solid-phase preparation of hydantoin libraries have already been reported,[2,3] and today, we report a new method that we found by serendipity in a program of modified dipeptide library preparation.

Indeed, we were surprised to find that cleavage of resin **3** using the mild and basic conditions reported by Snieckus and co-workers[4] did not release the modified dipeptide but instead hydantoin **1a** (Scheme 1). A transient intermediate could be observed by HPLC but was too unstable to allow full identification. Hydantoin **1a** was also obtained upon acidic cleavage. Surprisingly, in this operation the first amino acid was lost through the cleavage of an amide bond. There have been some reports of such a process under homogeneous conditions.[5] The cyclization can occur under acidic or basic conditions but with distinct mechanisms (Figure 2). Under acidic conditions, the amide is protonated prior to the cyclization. Under basic conditions, the mechanism is more complex because two pathways can be involved. In the first path, cyclization and cleavage are concomitant, whereas in the second path, cleavage and cyclization occur in two separate steps. This latter hypothesis could account for the transient intermediate that was observed by HPLC. However, Machacek and co-workers[5b] have shown that hydantoins can sometimes be hydrolyzed into hydantoate ions, so the first path cannot be ruled out.

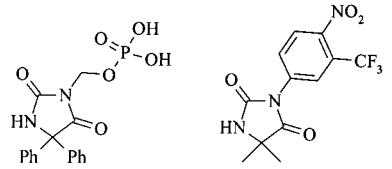
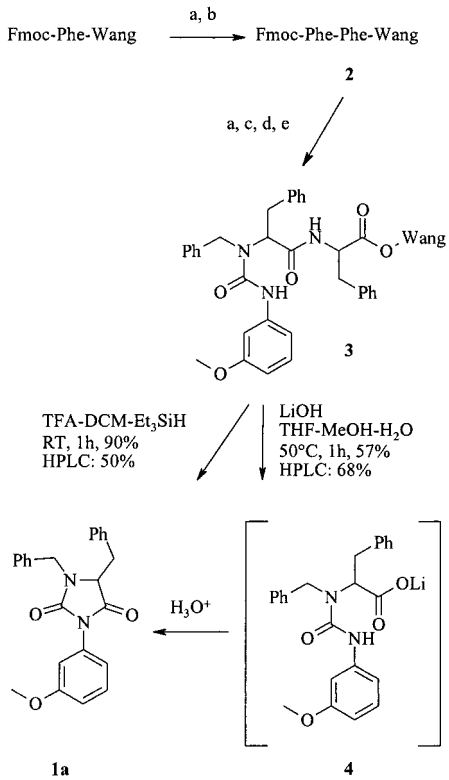


Figure 1. Examples of biologically active hydantoins.

Scheme 1[a]



[a] (a) 20% piperidine/DMF, 1 h. (b) 1.5 equiv of Fmoc-Phe-OH, 4 equiv of DIEA, 4 equiv of BOP, NMP, 18 h, 100% (HPLC, 97%).[5] (c) 4 equiv of PhCHO, 4 equiv of AcOH, $(CH_2Cl)_2$, 18 h. (d) 4 equiv of $NaBH(OAc)_3$, 4 equiv of AcOH, $(CH_2Cl)_2$, 18 h. (e) 5 equiv of 3-methoxyphenylisocyanate, CH_2Cl_2, 18 h.

Parallel Synthesis Approach

The known procedures for such library syntheses start with the anchoring of an amino acid on the solid support through the formation of an ester bond[2] (from the carboxylic end) or a carbamate bond[3] (from the amino end), and each time the

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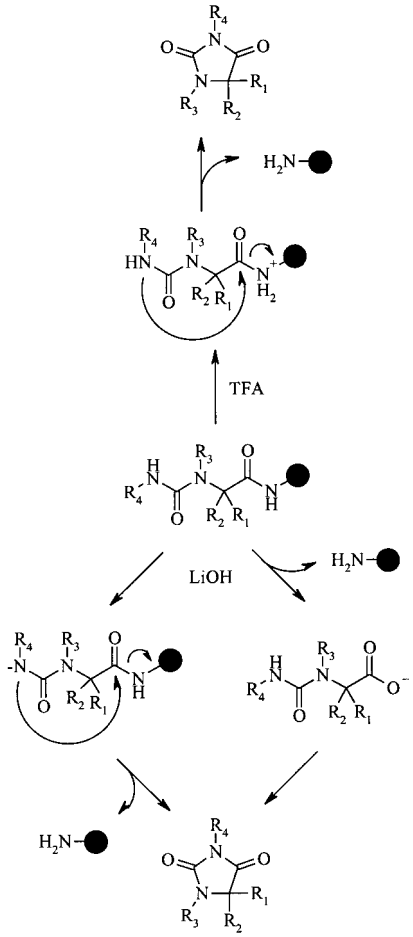
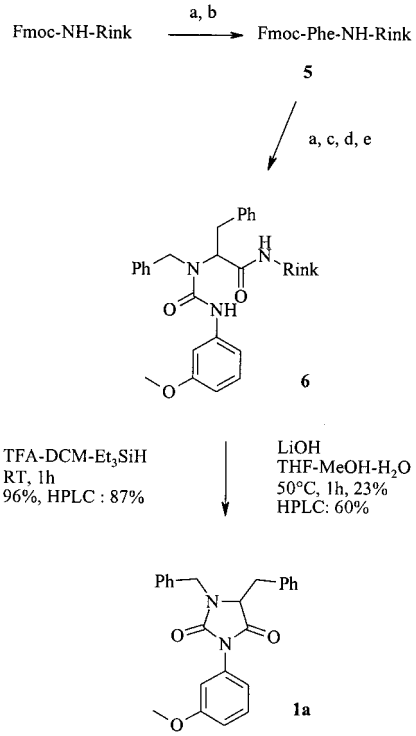


Figure 2. Proposed mechanism.

cyclization occurs through the breakage of a CO−O bond (ester or carbamate). Anchorage via an ester bond formation is usually performed using a large excess of amino acid[7] (5−10 equiv) to ensure complete loading on the resin, which can be a severe drawback when using in-house, nonnatural amino acids. In this new method, the amino acid is linked to the support from its carboxylic acid end through the formation of an amide bond. The loading of the amino acid on the amino resin is a more efficient process and can be completed with only a small excess of amino acid as shown in the preparation of resin **2** (Scheme 1). This hydantoin formation was first observed serendipitously using a Fmoc-Phe-Wang resin, but the use of preloaded Wang resin was not an ideal setting because the phenylalanine linker was lost in the process and contaminated the hydantoin at the end of the synthesis. We thought that Rink amide resin would be a more appropriate choice, but we needed to verify that the amide bond generated in that case would also be broken under such mild conditions.

Therefore, resin **6** was prepared in six steps from Rink amide (Scheme 2). Loading on Rink resin was completed in one cycle using only 1.5 equiv of amino acid. Then, reductive amination had to be performed in two steps to avoid formation of the dialkylated side product. Finally we were able to validate our strategy and found that the acidic treatment of resin **6** was able to cleanly produce the desired reaction. In that case, hydantoin **1a** was obtained in almost quantitative yield. Conversely, resin **6** was very resistant to

Scheme 2[a]

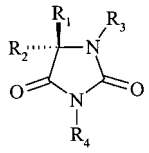


[a] (a) 20% piperidine/DMF, 1 h. (b) 1.5 equiv of Fmoc-Phe-OH, 4 equiv of DIEA, 4 equiv of BOP, NMP, 18 h, 98% (HPLC, 97%).[5] (c) 4 equiv of PhCHO, 4 equiv of AcOH, $(CH_2Cl)_2$, 18 h. (d) 4 equiv of $NaBH(OAc)_3$, 4 equiv of AcOH, $(CH_2Cl)_2$, 24 h. (e) 5 equiv of 3-methoxyphenylisocyanate, CH_2Cl_2, 24 h.

the lithium hydroxide treatment, unveiling a markedly different behavior for Rink and Wang supports. It was then necessary to reduce the length of this protocol in order to make it more practical for library production. Starting from resin **5**, the entire five-step procedure could be performed in 30 h. The primary amine alkylation and the urea formation steps each could be completed in 4 h, whereas the imine reduction with $NaBH(OAc)_3$ had to be left overnight.

By use of this methodology, a small library of hydantoins was prepared (Table 1). The efficacy of the syntheses was determined by fast RP-HPLC, and structure elucidation of the products was accomplished using mass spectroscopy and ^{1}H NMR. For UV-transparent compounds (**1p**−**t**), purities were determined by ^{1}H NMR. Some hydantoins were purified by flash chromatography to allow yield calculation and validation of this methodology. An interesting feature of this chemistry is that it gives access to fully substituted hydantoins. Indeed, the reaction proceeded well with both mono- and disubstituted amino acids, as exemplified with the synthesis of **1a**, **1u**, and **1w**. A high level of diversity can also be obtain for R_3 because aliphatic, aromatic, and heterocyclic aldehydes reacted equally well. However, the reaction was more sensitive to the steric hindrance of the isocyanate as shown by the decreasing purity and mass recovery observed in the quinolin series. A second interesting feature of this whole process is that it does not epimerize the amino acid enantiomeric center. Two pairs of enantiomers were synthesized (**1a**/**1i** and **1c**/**1o**) and were obtained with high enantiomeric excess (ee) (>96%). An attempt was also made to use this methodology for the preparation of

Table 1. Small Hydantoin Library from Combination of Amino Acids, Aldehydes, and Isocyanates



					results (%)	
compound	R_1	R_2	R_3	R_4	purity[a]	mass recovery (yield)[b]
1a	H	Bn	Bn	3-methoxyphenyl	93	100 (52)
1b	H	Bn	Bn	*tert*-Bu	0	15
1c	H	Bn	cyclohexylmethyl	3-methoxyphenyl	93	100 (48)
1d	H	Bn	quinolin-3-ylmethyl	*n*Pr	82	72
1e	H	Bn	quinolin-3-ylmethyl	*i*Pr	71	39 (10)
1f	H	Bn	quinolin-3-ylmethyl	cyclohexyl	57	32 (6)
1g	H	Bn	quinolin-3-ylmethyl	allyl	90	100
1h	H	Bn	quinolin-3-ylmethyl	3-chloropropyl	90	100
1i	Bn	H	Bn	3-methoxyphenyl	90	100 (58)
1j	Bn	H	Bn	*n*Pr	92	87
1k	Bn	H	Bn	*i*Pr	92	70
1l	Bn	H	Bn	cyclohexyl	80	81
1m	Bn	H	Bn	allyl	91	87
1n	Bn	H	Bn	3-chloropropyl	90	100
1o	Bn	H	cyclohexylmethyl	3-methoxyphenyl	90	100 (54)
1p	Bn	H	cyclopropylmethyl	*n*Pr	90[c]	81
1q	Bn	H	cyclopropylmethyl	*i*Pr	90[c]	74
1r	Bn	H	cyclopropylmethyl	cyclohexyl	90[c]	87
1s	Bn	H	cyclopropylmethyl	allyl	90[c]	85
1t	Bn	H	cyclopropylmethyl	3-chloropropyl	90[c]	77
1u[d]	Ph	H	Bn	3-methoxyphenyl	90	100 (50)
1v[d]	Ph	H	cyclohexylmethyl	3-methoxyphenyl	94	100 (47)
1w	Me	Me	Bn	3-methoxyphenyl	85	100 (53)
1x	Me	Me	cyclohexylmethyl	3-methoxyphenyl	84	100 (62)

[a] Purities were determined at 220 nm, on a C18 symmetry column (4.6 mm × 50 mm; 5 μm), using a linear gradient from 100% water (0.05% TFA) to 100% CH_3CN (0.05% TFA) in 8 min (flow rate, 2.5 mL/min). [b] Percentages of mass recovery are based on the theoretical recovery of product starting from Fmoc-AA-NH−Rink [load of resins: 0.63 mmol/g (L-Phe); 0.63 mmol/g (D-Phe); 0.64 mmol/g (Phg); 0.66 mmol/g (α-Me-Ala).]. Yields were determined after purification by flash chromatography and based on the theoretical recovery of product. [c] The purity of the compounds was determined by ^{1}H NMR. [d] The starting amino acid was racemic.

thiohydantoins using 3-nitrophenylisothiocyanate but failed to give any trace of the desired heterocycle. Instead, 3-nitrophenylthiourea was recovered in all cases as the major product.

Conclusion

An efficient process for the solid-phase synthesis of hydantoins has been developed. The amino acid starting material can be very efficiently anchored to Rink resin, using a small excess of amino acid, with the formation of a very stable amide bond. After construction of the amidourea hydantoin precursor, cleavage and cyclization can be performed under standard TFA conditions. This methodology allows the preparation of fully substituted hydantoins.

Experimental Section

General Methods. Materials obtained from commercial suppliers were used as received. The dichloromethane used in the syntheses was HPLC grade and stabilized with amylene. Fmoc-Phe-Wang and Rink resins were purchased respectively from Senn Chemical (Dielsdorf, Switzerland) and Advanced ChemTech (Louisville, KY). Analytical thin layer chromatography (TLC) was performed with Merck glass-backed silica gel 60 F 254 plates. Data from fast RP-HPLC were recorded at 220 nm using the following set of conditions: C18 symmetry column (Waters; 4.6 mm × 50 mm, 5 μm), flow rate 2.5 mL/min, linear gradient from 100% water (0.05% TFA) to 100% CH_3CN (0.05% TFA) in 8 min. Chiral HPLC data were recorded at 220 nm using a Chiralpack AD column (Daicel Chemical Industries; 250 mm × 4.6 mm, 10 μm). The composition of the eluent varied with the compound nature (flow rate: 1 mL/min). ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtained from a Bruker DPX-400 spectometer. Proton and carbon spectral chemical shifts are reported in ppm using, respectively, tetramethylsilane and residual solvent as internal standards. When peak multiplicity is reported, the following abbreviation is used: s (singlet), d (doublet), t (triplet), spt (septet), M (multiplet), br (broad), dd (doublet of doublets), ddd (doublet of doublets of doublets), dt (doublet of triplets), ddt (doublet of doublets of triplets), dq (doublet of quartets), td (triplet of doublets), m (undefined pattern). Coupling constants are reported in hertz. Elemental analyses were performed on a Fison EA 1108 CHN instrument, and the determined values are within 0.4% of theory. Mass spectra were recorded on a Finnigan MAT TSQ 7000. Parallel syntheses were performed on a Quest 210 organic synthesizer (Argonaut Technologies, San Carlos, CA). Flash chroma-

tography was performed on a CombiFlash Optix 10 parallel purification system (Isco, Lincoln, NE) using 4 g of silica columns (Isco) and a linear gradient from 0% methanol to 10% methanol in CH_2Cl_2.

Preparation of Resins 2 and 5. Both resins were prepared using the following procedure, starting with 1.54 g of resin in each case (loading of Fmoc-Phe-Wang, 0.65 mmol/g; loading of Rink, 0.7 mmol/g). The resin was treated at room temperature with a solution of piperidine in DMF (20%; 10 mL) for 1 h. The reaction mixture was then drained, and the beads were sequentially washed with DMF (2×), CH_2Cl_2 (2×), MeOH (2×), and finally CH_2Cl_2 (2×). Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (1.9 g; 4.3 mmol), Fmoc-Phe-OH (620 mg; 1.6 mmol), diisopropylethylamine (740 μL; 4.3 mmol), and *N*-methylpiperidinone (10 mL) were added, and the suspension was stirred at room temperature overnight. The reaction mixture was then drained, and the beads were sequentially washed with DMF (2×), CH_2Cl_2 (2×), MeOH (2×), CH_2Cl_2 (2×), and finally MeOH (2×). The resin was dried at 40 °C under vacuum (30 mbar) until a constant weight was attained (resin **2**, 1.71 g; resin **5**, 1.67 g). The Kaiser test was negative on both resins.[8]

A small fraction of resin **2** (100 mg) was treated with a solution of trifluoroacetic acid (TFA) and triethylsilane (TES) in CH_2Cl_2 (TFA/DCM/TES = 50/50/10 v/v/v; 4 mL) at room temperature for 1 h. The solution was then drained and collected, and the beads were washed with CH_2Cl_2 (2×). The filtrates were combined and concentrated under low pressure to give Fmoc-Phe-Phe-OH as a white solid (32 mg; 100%). HPLC: RT = 7.95 min (97.7%). ^{1}H NMR (DMSO-d_6): δ 2.71 (dd, J = 10, 24.8, 1H), 2.85−3.05 (m, 2H), 3.08 (dd, J = 5, 13.6, 1H), 4.05−4.2 (m, 2H), 4.27 (td, J = 3.6, 10, 1H), 4.46 (dd, J = 8, 13.6, 1H), 7.1−7.5 (m, 15H), 7.58 (d, J = 9.2; 1H), 7.62 (d, J = 9.1, 1H), 7.87 (d, J = 7.6, 2H), 8.26 (d, J = 7.8, 1H), 12.78 (brs, 1H). ^{13}C NMR (CD_3-OD): δ 38.5, 39.0, 48.3, 55.0, 57.7, 68.1, 120.9 (2C), 126.3, 126.4, 127.7, 127.8 (2C), 128.2 (2C), 128.8 (2C), 129.5 (3C), 130.39 (2C), 130.43 (2C), 138.1, 138.7, 142.6 (2C), 145.2 (2C), 158.2, 173.9, 174.3. Anal. Calcd for $C_{33}H_{30}N_2O_5 \cdot 0.4H_2O$: C, 73.15; H, 5.73; N, 5.17. Found: C, 73,26; H, 5.78; N, 5.03. MS (ESI) *m*/*z*: 535 (M + H^+).

A small fraction of resin **5** (195 mg) was treated with a solution of trifluoroacetic acid (TFA) and triethylsilane (TES) in CH_2Cl_2 (TFA/DCM/TES = 20/80/10 v/v/v; 4 mL) at room temperature for 1 h. The solution was then drained and collected, and the beads were washed with CH_2Cl_2 (2×) and MeOH (2×). The filtrates were combined and concentrated under low pressure to give Fmoc-Phe-NH_2 as a white solid (42 mg; 87%). HPLC: RT = 6.69 min (97%). ^{1}H NMR (CD_3OD): δ 2.85 (dd, J = 9.9, 13.2, 1H), 3.14 (dd, J = 4.6, 14, 1H), 4.05−4.45 (m, 4H), 7.1−7.35 (m, 7H), 7.38 (t, J = 7.1, 2H), 7.56 (brs, 2H), 7.78 (d, J = 7.5, 2H). Anal. Calcd for $C_{24}H_{22}N_2O_3 \cdot 0.3H_2O$: C, 73.56; H, 5.81; N, 7.15. Found: C, 73,67; H, 5.89; N, 6.77. MS (ESI) *m*/*z*: 387 (M + H^+).

Preparation of Resins 3 and 6 from Resins 2 and 5, Respectively. Resins **2** and **5** (200 mg of each resin, 0.11−0.12 mmol approximately) were separately treated at room temperature with a solution of piperidine in DMF (20%; 4.5 mL) for 1 h. The reaction mixtures were then drained, and the beads were sequentially washed with DMF (2×), MeOH (2×), and finally CH_2Cl_2 (2×). 1,2-Dichloroethane (4.5 mL), benzaldehyde (50 μL; 0.48 mmol), and acetic acid (27 μL; 0.48 mmol) were added, and the suspensions were stirred overnight at room temperature. The reaction mixtures were then drained, and the beads were washed with CH_2Cl_2 (2×). 1,2-Dichloroethane (4.5 mL), sodium triacetoxyborohydride (102 mg; 0.48 mmol), and acetic acid (27 μL; 0.48 mmol) were added, and the suspensions were stirred for 1 day at room temperature. The reaction mixtures were then drained, and the beads were sequentially washed with MeOH (2×), CH_2Cl_2 (2×), MeOH (2×), H_2O (2×), MeOH (2×), and finally CH_2Cl_2 (2×). 3-Methoxyphenylisocyanate (80 μL; 0.6 mmol) and CH_2Cl_2 (4.5 mL) were added, and the suspensions were stirred for 1 day at room temperature. The reaction mixtures were then drained, and the beads were sequentially washed with CH_2Cl_2 (2×), MeOH (2×), and finally CH_2Cl_2 (2×). Resins **3** and **6** thus obtained were cleaved directly afterward.

Cleavage of Resins 3 and 6 under Basic Conditions. Resins **3** and **6** were separately treated with a solution of lithium hydroxyde (1 M in water) in MeOH and THF (LiOH/MeOH/THF = 1/2/5 v/v/v; 4.5 mL) at 55 °C for 1 h. The solution was then drained and collected, and the beads were washed with MeOH (2×). The filtrates were combined and concentrated under low pressure to give hydantoin **1a**. From resin **3**: quantity = 48 mg; HPLC purity = 50%. From resin **6**: quantity = 16 mg; HPLC purity = 68%.

Cleavage of Resin 3 under Acidic Conditions. Resin **3** was treated with a solution of trifluoroacetic acid (TFA) and triethylsilane (TES) in CH_2Cl_2 (TFA/DCM/TES = 50/50/10 v/v/v; 4.5 mL) at room temperature for 1 h. The solution was then drained and collected, and the beads were washed with CH_2Cl_2 (2×). The filtrates were combined and concentrated under low pressure to give hydantoin **1a** (64 mg; HPLC purity = 60%).

Cleavage of Resin 6 under Acidic Conditions. Resin **6** was treated with a solution of trifluoroacetic acid (TFA) and triethylsilane (TES) in CH_2Cl_2 (TFA/DCM/TES = 20/80/10 v/v/v; 4.5 mL) at room temperature for 1 h. The solution was then drained and collected, and the beads were washed with CH_2Cl_2 (2×). The filtrates were combined and concentrated under low pressure to give hydantoin **1a** (51 mg; HPLC purity = 87%).

Hydantoin Library Preparation. 1. Loading of Fmoc-Protected Amino Acids on Rink resin. The four Fmoc-AA-Rink resins involved in the hydantoin library were prepared from Fmoc-L-Phe-OH, Fmoc-D-Phe-OH, Fmoc-PHG-OH, and Fmoc-αMe-Ala-OH following the procedure described for the preparation of resin **5**.

2. Parallel Preparation of Hydantoins. The Fmoc-AA-Rink resins (150 mg of resin per reactor; 0.09−0.10 mmol approximately) were separately treated at room temperature with a solution of piperidine in DMF (20%; 3 mL) for 1 h. The reaction mixtures were then drained, and the beads were sequentially washed with DMF (2×), MeOH (2×), and finally CH_2Cl_2 (2×). The aldehydes (2 M solutions in 1,2-

dichloroethane; 0.3 mmol), 1,2-dichloroethane (3 mL), and acetic acid (3 M solution in 1,2-dichloroethane; 0.4 mmol) were added, and the suspensions were stirred for 4 h at room temperature. The reaction mixtures were then drained, and the beads were washed with CH_2Cl_2 (2×). 1,2-Dichloroethane (3 mL), sodium triacetoxyborohydride (0.4 mmol), and acetic acid (3 M solution in 1,2-dichloroethane; 0.4 mmol) were added, and the suspensions were stirred overnight at room temperature. The reaction mixtures were then drained, and the beads were sequentially washed with a solution of 50% MeOH in CH_2Cl_2 (2×), then MeOH (2×), H_2O (2×), MeOH (2×), and finally CH_2Cl_2 (3×). The isocyanate (2 M solutions in CH_2Cl_2; 0.3 mmol) and CH_2Cl_2 (3 mL) were added, and the suspensions were stirred for 4 h at room temperature. The reaction mixtures were then drained, and the beads were sequentially washed with CH_2Cl_2 (2×), MeOH (2×), and finally CH_2Cl_2 (2×). A solution of trifluoroacetic acid (TFA) and triethylsilane (TES) in CH_2Cl_2 (TFA/DCM/TES = 20/80/10 v/v/v; 3 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. The solution was then drained and collected, and the beads were washed with CH_2Cl_2 (2×). The filtrates were combined and concentrated under low pressure to give hydantoins **1a**−**x**.

1a. HPLC: RT = 7.16 min. ^{1}H NMR (DMSO-d_6): δ 3.10 (dd, J = 3.6, 14.2, 1H), 3.32 (covered by water peak, 1H), 3.71 (s, 3H), 4.40 (t, J = 4.0, 1H), 4.49 (d, J = 15.6, 1H), 4.89 (d, J = 15.6, 1H), 6.45 (t, J = 1.9, 1H), 6.55 (d, J = 8, 1H), 6.93 (dd, J = 2, 8.2, 1H), 7.13 (dd, J = 1.7, 7.5, 2H), 7.2−7.45 (m, 9H). ^{13}C NMR (DMSO-d_6): δ 33.7, 44.0, 55.2, 59.5, 112.3, 113.6, 118.7, 126.9, 127.5, 128.0 (2C), 128.1 (2C), 128.6 (2C), 129.4, 129.6 (2C), 132.7, 134.5, 136.2, 154.8, 159.2, 170.8. MS (ESI) m/z: 387 (M + H$^+$). Enantiomer of **1i**: chiral HPLC (hexanes/EtOH = 75/25), RT = 15.5 min, ee = 98.4%.

1c. HPLC: RT = 7.71 min. ^{1}H NMR (DMSO-d_6): δ 0.75−1.05 (m, 2H), 1.05−1.30 (m, 3H), 1.55−1.75 (m, 6H), 3.09 (d, J = 14, 2H), 3.32 (covered by water peak, 1H), 3.46 (dd, J = 8.8, 14, 1H), 3.70 (s, 3H), 4.61 (t, J = 4.0, 1H), 6.39 (s, 1H), 6.52 (d, J = 7.6, 1H), 6.91 (dd, J = 1.9, 8.2, 1H), 7.16 (d, J = 6.6, 2H), 7.2−7.4 (m, 4H). MS (ESI) m/z: 393 (M + H$^+$). Enantiomer of **1o**: chiral HPLC (hexane/*i*PrOH = 93/7), RT = 23.0 min, ee = 97.8%.

1d. HPLC: RT = 5.19 min. ^{1}H NMR (DMSO-d_6): δ 0.53 (t, J = 7.6, 3H), 1.1−1.35 (m, 2H), 3.07 (dd, J = 4, 14.8, 1H), 3.15 (dd, J = 6.8, 14, 1H), 3.25 (dd, J = 6.4, 13.6, 1H), 3.32 (dd, J = 4.4, 14.4, 1H), 4.42 (t, J = 4.0, 1H), 4.67 (d, J = 16, 1H), 5.04 (d, J = 16, 1H), 7.1−7.3 (m, 5H), 7.71 (t, J = 7.8, 1H), 7.85 (t, J = 8.0, 1H), 8.04 (d, J = 8.1, 1H), 8.08 (d, J = 8.4, 1H), 8.40 (s, 1H), 8.93 (s, 1H). MS (ESI) m/z: 374 (M + H$^+$).

1e. HPLC: RT = 5.25 min. ^{1}H NMR (DMSO-d_6): δ 1.06 (d, J = 6.8, 6H), 3.04 (dd, J = 3.6, 14, 1H), 3.30 (dd, J = 4.4, 14, 1H), 3.98 (spt, J = 6.8, 1H), 4.35 (t, J = 4, 1H), 4.64 (d, J = 16, 1H), 4.98 (d, J = 15.6, 1H), 7.05−7.15 (m, 2H), 7.15−7.30 (m, 3H), 7.63 (t, J = 7.5, 1H), 7.77 (td, J = 1.2, 7.6, 1H), 7.98 (d, J = 8, 1H), 8.03 (d, J = 8.4, 1H), 8.22 (s, 1H), 8.84 (d, J = 1.9, 1H). MS (ESI) m/z: 374 (M + H$^+$).

1f. HPLC: RT = 5.89 min. ^{1}H NMR (DMSO-d_6): δ 0.9−1.35 (m, 5H), 1.45−1.85 (m, 5H), 3.05 (dd, J = 3.6, 14.4, 1H), 3.30 (dd, J = 4.4, 14.4, 1H), 3.57 (br t, J = 12.4, 1H), 4.36 (t, J = 4, 1H), 4.64 (d, J = 16, 1H), 4.98 (d, J = 16, 1H), 7.05−7.15 (m, 2H), 7.15−7.30 (m, 3H), 7.66 (t, J = 7.4, 1H), 7.80 (t, J = 7.2, 1H), 8.00 (d, J = 8, 1H), 8.05 (d, J = 8.4, 1H), 8.28 (s, 1H), 8.87 (s, 1H). MS (ESI) m/z: 414 (M + H$^+$).

1g. HPLC: RT = 5.06 min. ^{1}H NMR (DMSO-d_6): δ 3.09 (dd, J = 4, 14.8, 1H), 3.34 (dd, J = 4.4, 14.4, 1H), 3.79 (dd, J = 4.8, 18, 1H), 3.92 (dd, J = 4.8, 18, 1H), 4.49 (t, J = 4, 1H), 4.54 (dd, J = 0.8, 17.2, 1H), 4.70 (d, J = 16, 1H), 4.87 (dd, J = 0.8, 10.4, 1H), 5.05 (d, J = 16, 1H), 5.49 (ddd, J = 19, 10.4, 2.6, 1H), 7.05−7.15 (m, 2H), 7.15−7.30 (m, 3H), 7.74 (t, J = 7.6, 1H), 7.89 (t, J = 7.2, 1H), 8.07 (d, J = 8.1, 1H), 8.11 (d, J = 8.6, 1H), 8.46 (s, 1H), 8.96 (s, 1H). MS (ESI) m/z: 372 (M + H$^+$).

1h. HPLC: RT = 5.36 min. ^{1}H NMR (DMSO-d_6): δ 1.5−1.75 (m, 2H), 3.07 (dd, J = 3.6, 14.4, 1H), 3.22 (t, J = 6.4, 2H), 3.25−3.45 (m, 3H), 4.43 (t, J = 4, 1H), 4.70 (d, J = 16, 1H), 5.05 (d, J = 16, 1H), 7.05−7.15 (m, 2H), 7.15−7.30 (m, 3H), 7.72 (t, J = 7.6, 1H), 7.87 (t, J = 7.8, 1H), 8.05 (d, J = 8.1, 1H), 8.09 (d, J = 8.4, 1H), 8.45 (s, 1H), 8.96 (s, 1H). MS (ESI) m/z: 408 (M + H$^+$).

1i. HPLC: RT = 7.18 min. ^{1}H NMR (DMSO-d_6): δ 3.10 (dd, J = 3.6, 14.4, 1H), 3.32 (covered by water peak, 1H), 3.71 (s, 3H), 4.40 (t, J = 4, 1H), 4.50 (d, J = 15.6, 1H), 4.89 (d, J = 15.6, 1H), 6.45 (t, J = 1.9, 1H), 6.55 (br d, J = 7.4, 1H), 6.93 (dd, J = 2.1, 8.3, 1H), 7.13 (dd, J = 1.9, 7.6, 2H), 7.20−7.45 (m, 9H). MS (ESI) m/z: 387 (M + H$^+$). Enantiomer of **1a**: chiral HPLC (hexanes/EtOH = 75/25), RT = 18.2 min; ee = 96.8%.

1j. HPLC: RT = 7.09 min. ^{1}H NMR (DMSO-d_6): δ 0.50 (t, J = 7.4, 3H), 1.10−1.30 (m, 2H), 3.02 (dd, J = 3.7, 13.6, 1H), 3.05−3.30 (m, 3H), 4.19 (t, J = 4, 1H), 4.38 (d, J = 15.6, 1H), 4.83 (d, J = 15.6, 1H), 7.05−7.45 (m, 10H). MS (ESI) m/z: 323 (M + H$^+$).

1k. HPLC: RT = 7.18 min. ^{1}H NMR (DMSO-d_6): δ 1.03 (d, J = 6.8, 6H), 2.99 (dd, J = 3.6, 14.4, 1H), 3.20 (dd, J = 4.8, 14.4, 1H), 3.95 (spt, J = 7.2, 1H), 4.14 (t, J = 4, 1H), 4.37 (d, J = 15.6, 1H), 4.80 (d, J = 15.2, 1H), 7.00−7.45 (m, 10H). MS (ESI) m/z: 323 (M + H$^+$).

1l. HPLC: RT = 7.95 min. ^{1}H NMR (DMSO-d_6): δ 0.95−1.35 (m, 5H), 1.45−1.9 (m, 5H), 3.00 (dd, J = 3.6, 14.4, 1H), 3.20 (dd, J = 4, 14, 1H), 3.54 (br t, J = 12.4, 1H), 4.14 (t, J = 4, 1H), 4.37 (d, J = 15.6, 1H), 4.80 (d, J = 15.6, 1H), 7.06 (dd, J = 2.2, 7.6, 2H), 7.15−7.45 (m, 8H). MS (ESI) m/z: 363 (M + H$^+$).

1m. HPLC: RT = 6.88 min. ^{1}H NMR (DMSO-d_6): δ 3.04 (dd, J = 4, 14.4, 1H), 3.23 (dd, J = 4.8, 14.4, 1H), 3.70−3.95 (m, 2H), 4.25 (t, J = 4.4, 1H), 4.38 (d, J = 15.6, 1H), 4.47 (d, J = 17.2, 1H), 4.75−4.90 (m, 2H), 5.46 (ddt, J = 4.9, 10, 15.3, 1H), 7.00−7.45 (m, 10H). MS (ESI) m/z: 321 (M + H$^+$).

1n. HPLC: RT = 7.18 min. ^{1}H NMR (DMSO-d_6): δ 1.50−1.70 (m, 2H), 3.02 (dd, J = 3.6, 14.4, 1H), 3.1−3.45 (m, 5H), 4.22 (t, J = 4, 1H), 4.41 (d, J = 15.2, 1H), 4.84 (d, J = 15.6, 1H), 6.95−7.40 (m, 10H). MS (ESI) m/z: 357 (M + H$^+$).

1o. HPLC: RT = 7.71 min. ^{1}H NMR (DMSO-d_6): δ 0.75−1.05 (m, 2H), 1.05−1.30 (m, 3H), 1.55−1.75 (m, 6H), 3.00−3.15 (m, 2H), 3.35 (covered by water peak, 1H), 3.46 (dd, J = 9.2, 14, 1H), 3.70 (s, 3H), 4.61 (t, J = 4, 1H), 6.40 (br s, 1H), 6.52 (d, J = 7.9, 1H), 6.92 (dd, J = 1.7, 8.2, 1H), 7.17 (d, J = 6.7, 2H), 7.25−7.40 (m, 4H). MS (ESI) m/z: 393 (M + H$^+$). Enantiomer of **1c**: chiral HPLC (hexane/*i*PrOH = 93−7), RT = 25.9 min; ee = 98.4%.

1p. ^{1}H NMR (DMSO-d_6): δ 0.20 (dq, J = 4.3, 9.2, 1H), 0.33 (dq, J = 4.3, 9.2, 1H), 0.38−0.60 (m, 5H), 1.00 (M, 1H), 1.05−1.25 (m, 2H), 2.95−3.15 (m, 3H), 3.15−3.30 (m, 2H), 3.49 (dd, J = 9.7, 14.5, 1H), 4.55 (t, J = 4, 1H), 7.11 (br d, J = 5.2, 2H), 7.15−7.3 (m, 3H). MS (ESI) m/z: 287 (M + H$^+$).

1q. ^{1}H NMR (DMSO-d_6): δ 0.20 (dq, J = 4.3, 9.2, 1H), 0.33 (dq, J = 4.3, 9.2, 1H), 0.38−0.60 (m, 2H), 0.95−1.10 (m, 7H), 2.95−3.05 (m, 2H), 3.20 (dd, J = 4.6, 14.3, 1H), 3.47 (dd, J = 6.8, 14.6, 1H), 3.90 (spt, J = 7.0, 1H), 4.47 (t, J = 3.8, 1H), 7.09 (br d, J = 5.9, 2H), 7.15−7.3 (m, 3H). MS (ESI) m/z: 287 (M + H$^+$).

1r. ^{1}H NMR (DMSO-d_6): δ 0.20 (dq, J = 4.3, 9.2, 1H), 0.33 (dq, J = 4.3, 9.2, 1H), 0.40−0.60 (m, 2H), 0.80−1.3 (m, 6H), 1.45−1.85 (m, 5H), 2.95−3.10 (m, 2H), 3.20 (dd, J = 4.8, 14.4, 1H), 3.35−3.55 (m, 2H), 4.47 (t, J = 3.6, 1H), 7.05−7.3 (m, 5H). MS (ESI) m/z: 327 (M + H$^+$).

1s. ^{1}H NMR (DMSO-d_6): δ 0.20 (dq, J = 4.5, 9.4, 1H), 0.33 (dq, J = 4.6, 9.4, 1H), 0.44 (dq, J = 3.8, 12.2, 1H), (dq, J = 4, 13.3, 1H), 1.01 (M, 1H), 3.02 (dd, J = 7.3, 14.6, 1H), 3.06 (dd, J = 4.6, 14.3, 1H), 3.24 (dd, J = 4.7, 14.3, 1H), 3.50 (dd, J = 6.9, 14.6, 1H), 3.74 (dd, J = 4.1, 15.6, 1H), 3.84 (dd, J = 4.7, 15.6, 1H), 4.44 (d, J = 17.2, 1H), 4.61 (t, J = 4, 1H), 4.82 (d, J = 10.5, 1H), 5.42 (ddt, J = 6.7, 11, 18, 1H), 7.00 (br d, J = 8.1, 2H), 7.15−7.3 (m, 3H). MS (ESI) m/z: 285 (M + H$^+$).

1t. ^{1}H NMR (DMSO-d_6): δ 0.21 (dq, J = 4.4, 9.2, 1H), 0.33 (dq, J = 4.4, 9.2, 1H), 0.45 (dq, J = 4.4, 8.8, 1H), 0.52 (dq, J = 4.4, 8.8, 1H), 1.01 (M, 1H), 1.50−1.65 (m, 2H), 2.95−3.10 (m, 2H), 3.13 (t, J = 6.4, 2H), 3.20−3.40 (m, 3H), 3.51 (dd, J = 6.4, 14.4, 1H), 4.55 (t, J = 3.6, 1H), 7.05−7.30 (m, 5H). MS (ESI) m/z: 321 (M + H$^+$).

1u. HPLC: RT = 7.14 min. ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H), 3.99 (d, J = 15.6, 0.7H), 4.16 (d, J = 16, 0.3H), 4.47 (d, J = 15.6, 0.3H), 4.84 (d, J = 15.6, 0.73H), 5.19 (s, 0.7H), 7.0−7.5 (m, 14H). MS (ESI) m/z: 373 (M + H$^+$).

1v. HPLC: RT = 7.75 min. ^{1}H NMR (DMSO-d_6): δ 0.65−0.95 (m, 2H), 0.95−1.20 (m, 3H), 1.35−1.70 (m, 6H), 2.69 (dd, J = 6.4, 14, 1H), 3.37 (dd, J = 8.4, 14, 1H), 3.78 (s, 3H), 5.36 (s, 1H), 6.90−7.05 (m, 3H), 7.35−7.55 (m, 6H). MS (ESI) m/z: 379 (M + H$^+$).

1w. HPLC: RT = 6.63 min. ^{1}H NMR (DMSO-d_6): δ 1.35 (s, 6H), 3.78 (s, 3H), 4.59 (s, 2H), 6.95−7.05 (m, 3H), 7.30−7.50 (m, 6H). MS (ESI) m/z: 325 (M + H$^+$).

1x. HPLC: RT = 7.33 min. ^{1}H NMR (DMSO-d_6): δ 0.80−1.00 (m, 2H), 1.10−1.3 (m, 3H), 1.42 (s, 6H), 1.55−1.85 (m, 6H), 3.12 (d, J = 7.2, 2H), 3.76 (s, 3H), 6.85−7.00 (m, 3H), 7.37 (t, J = 8.9, 1H). MS (ESI) m/z: 331 (M + H$^+$).

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