JOC The Journal of Organic Chemistry

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Macrocyclizations for Medicinal Chemistry: Synthesis of Druglike Macrocycles by High-Concentration Ullmann Coupling

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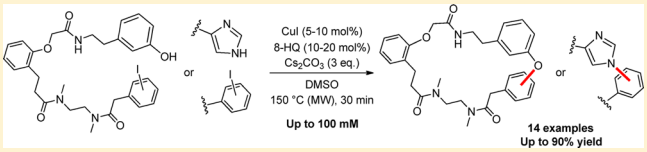
Supporting Information

ABSTRACT: Conditions have been identified for the efficient Ullmann macrocyclization of phenol and imidazole nucleophiles with aryl iodides at high reaction concentrations of up to 100 mM and using 5−10 mol % loading of an inexpensive copper catalyst. A range of substitution patterns and ring sizes are tolerated, and the method has been exemplified by the synthesis of a set of druglike macrocycles.



INTRODUCTION

Despite increasing interest in the use of macrocycles as an important, yet relatively unexploited, class of potential new drugs,[1] the corresponding synthetic methodology is lacking in two key respects. First, only a small number of reactions are generally considered to be readily applicable to macrocyclization, limiting both the range of potential targets and the flexibility of the synthesis.[2] Furthermore, these reactions are typically run at low concentration, which is both inefficient and impractical in an industrial setting.[3] We recently proposed a macrocyclization efficiency index, Emac, which allows a quantitative assessment of the practicality of macrocyclizations by consideration of both reaction concentration and yield,[2] revealing a wide range of efficiencies (over six orders of magnitude) for reactions published in the recent literature. We plan to use this metric to judge the success of our own efforts toward development of further macrocyclization methodologies, because the key assumption underlying our work in this area has been that these issues are largely the consequence of a lack of optimization, and that it may be possible to find practical and efficient macrocyclization conditions for a wide range of reactions.[4]

The Ullmann reaction has been one of the main beneficiaries of the significant recent progress in the field of metal-catalyzed cross-coupling, with highly optimized catalytic systems allowing efficient and mild coupling of a wide range of nucleophiles and (hetero)aryl halides.[5] Development of an Ullmann macrocyclization was pioneered by Boger toward the synthesis of complex biaryl ether natural products,[6] albeit requiring sensitive reagents and high dilutions. Milder and more practical variants were established by Nicolaou,[7] and more recently Ma,[8] which require activating groups ortho to the aryl halide. This trend continued further, with Ullmann coupling in complex natural product synthesis largely being superseded by efficient metal-free S_NAr cyclizations using highly activated aryl fluorides.[9] Although isolated examples of Ullmann macrocyclizations in total synthesis continue to be reported,[10] there remains a need for general, practical macrocyclization conditions, coupling unactivated aryl halides with a range of nucleophiles without resorting to high dilutions, that are suitable for both rapid, diverse analogue synthesis and efficient scale-up, to facilitate the rapidly growing pharmaceutical interest in the special properties of druglike macrocycles.

In this study, phenols and imidazoles were chosen to represent two distinct types of heteroatom nucleophile, for which optimized coupling conditions might be more widely applicable. Furthermore, these functionalities also comprise the side chains of tyrosine and histidine, potentially allowing application of Ullmann macrocyclization methodology to the side chain to side chain bridging strategy for peptide stabilization.[11]

RESULTS AND DISCUSSION

The initial design of macrocyclization substrates emphasized flexible, rapid synthesis of relatively conformationally mobile linear precursors, containing the phenol and imidazole nucleophiles and a *meta* aryl iodide. We anticipated that *meta*-substitution would provide the optimal balance between product ring strain and steric hindrance in the macrocyclization. Ring-opening of dihydrocoumarin (**1**) with mono-Boc propylenediamine and alkylation of the resulting phenol resulting in the bifunctional intermediate **2** in excellent yield. Sequential deprotection and amide coupling of the ester and amine termini of this linker led rapidly to the desired precursors **3a** and **3b**, again in high overall yield (Scheme 1).

An iterative, small-scale array optimization of the Ullmann macrocyclization was performed (selected results shown in Table 1 and Supporting Information), varying ligand, base, solvent and temperature, initially with conditions reported to be effective for intermolecular couplings.[5] Interestingly, while yields for the phenol arylation were largely independent of the

Received: October 2, 2012
Published: November 20, 2012

Scheme 1. Synthesis of Macrocyclization Precursors 3a and 3b

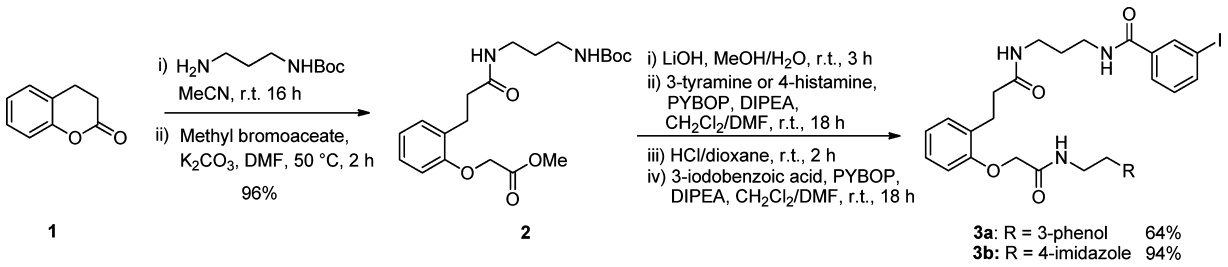
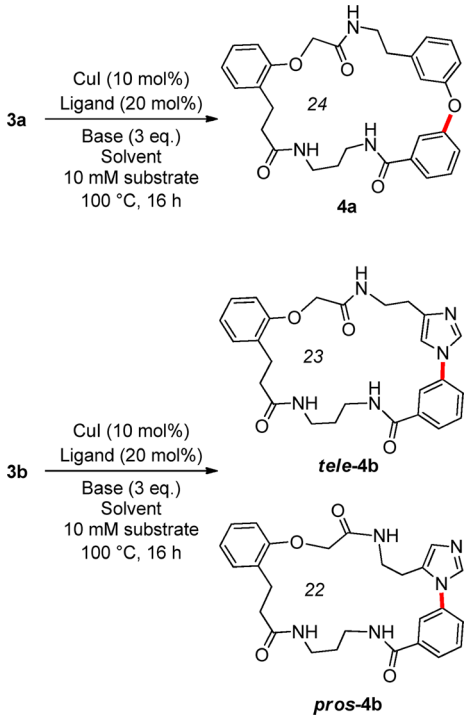


Table 1. Optimization of Conditions for Ullmann Macrocyclization of 3a and 3b[a]



entry	product	ligand	base	solvent	LC yield (%)[b]
1	**4a**	8-HQ	Cs_2CO_3	DMSO	80
2	**4a**	8-HQ	K_3PO_4	DMSO	82
3	**4a**	$Me_2NCH_2CO_2H$	Cs_2CO_3	DMSO	78
4	**4a**	8-HQ	Cs_2CO_3	DMF	–
5	**4b**	8-HQ	Cs_2CO_3	DMSO	25
6	**4b**	$Me_2NCH_2CO_2H$	Cs_2CO_3	DMSO	–
7	**4b**	8-HQ	Cs_2CO_3	DMF	26
8	**4b**	8-HQ	Cs_2CO_3	DMSO	50[c]
9	**4b**	8-HQ	Cs_2CO_3	DMSO	84[d]
10	**4a**	8-HQ	Cs_2CO_3	DMSO	95[e] (90)
11	**4b**	8-HQ	Cs_2CO_3	DMSO	97[e] (82[f])

[a]Ring size is denoted by number within the macrocyclic ring. [b]Yield calculated as percentage of total UV absorption (210 nm). Isolated yield in parentheses. [c]Microwave heating, 190 °C, 15 min. [d]200 °C, 20 min. [e]Optimized conditions: 5 mol % CuI, 10 mol % 8-HQ, 3 equiv of Cs_2CO_3, 100 mM in DMSO, 150 °C, 30 min (for **4a**) or 190 °C, 15 min (for **4b**). [f]Isolated as a 5:1 mixture of imidazole regioisomers *tele*-**4b** and *pros*-**4b**.

ligand or base, solvent choice (DMSO) proved critical (entries 1–4). However, the analogous imidazole arylation was instead highly dependent upon the choice of ligand, with only 8-hydroxyquinoline (8-HQ)[12] proving effective, and similar results being obtained in DMF (entries 5–7). While initial screening found K_3PO_4 and Cs_2CO_3 to be almost equally effective, it was subsequently found that the latter gave more reproducible results. Microwave heating also proved beneficial for the imidazole arylation, increasing the yield and purity of the target macrocycles (entries 8 and 9) and ultimately allowing lower catalyst loading. In accordance with the aims of this study, the final round of optimization looked at increasing reaction concentration, and we were pleased to discover that both coupling reactions gave high conversion to the macrocycle products at 100 mM. The optimized conditions (entries 10 and 11) result in excellent isolated yields of macrocycles **4a** and **4b** at high concentration, short reaction times, and low loading of inexpensive catalyst, with best results obtained using a lower microwave reaction temperature for the phenol arylation. Overall, these conditions are the only ones tested that gave reliable, batch-independent reactivity.

Two regioisomeric products were obtained from macrocyclization of imidazole **3b.** The major regioisomer in intermolecular imidazole N-arylation reactions has been exclusively reported (although usually assumed) to be the *tele*-isomer, via attack from the less sterically hindered distal nitrogen atom.[13] However, in intramolecular reactions, this product likely exhibits additional ring strain imposed by the *meta*-cyclophanic imidazole ring, and therefore we sought to confirm the identity of the major product. The few imidazole N-arylation macrocyclization examples reported provide no comment.[14] Separation of the isomers and HMBC analysis concluded that *tele*-**4b** was indeed the major product (Figure 1), which can be rationalized by observations that Ullmann couplings are highly sensitive to steric hindrance.[15]

Before undertaking further analysis of the scope of the successful macrocyclization conditions, the structure of the linker was altered to that as shown in compounds **7a–g** (Scheme 2), using DMEDA in place of propylenediamine and iodophenylacetic instead of iodobenzoic acid. These changes were expected to improve the solubility of the compound series and provide a more stringent test of the general applicability of the optimized conditions, by employing a less electron-deficient aryl halide electrophile. Synthesis of the macrocyclization precursors proceeded in fashion very similar to those in Scheme 1, with some divergence of the sequence of amide couplings to achieve the most efficient overall route.

Figure 2 shows the results of applying the optimized macrocyclization conditions to precursors **7a–g**, as a test of the tolerance to various substitution patterns, with the macrocycles identified by the same letter as the corresponding precursors in Scheme 2. For the phenol nucleophile, reaction with a hindered *ortho*-iodide was unsuccessful (**9a**), but the potentially strained *para-meta* biaryl ether **9b** and the *meta-meta* biaryl ether product **9e** were formed in moderate and excellent

dx.doi.org/10.1021/jo302089f | J. Org. Chem. 2012, 77, 11079–11090

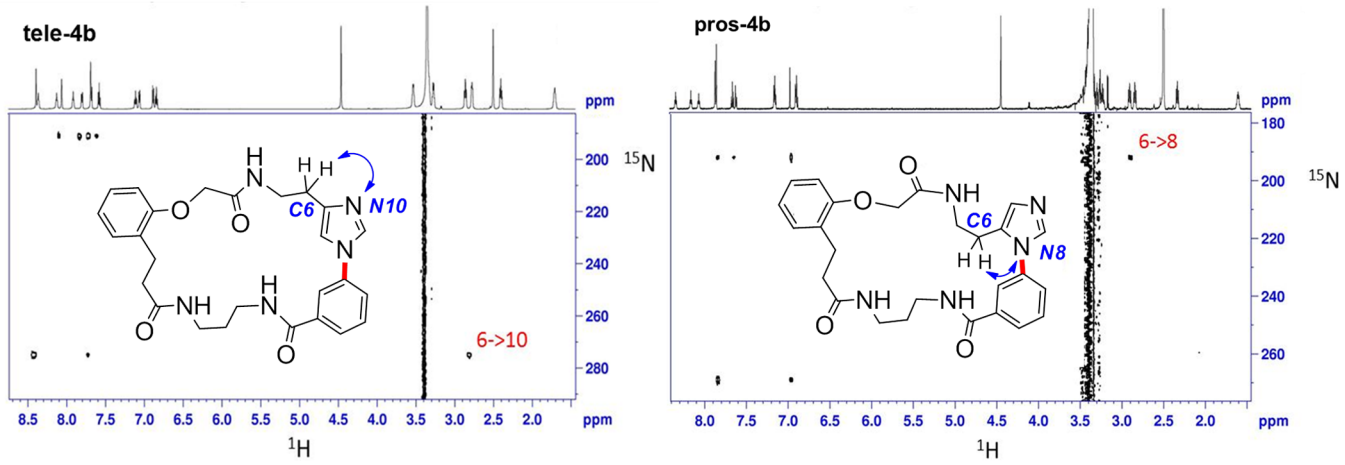
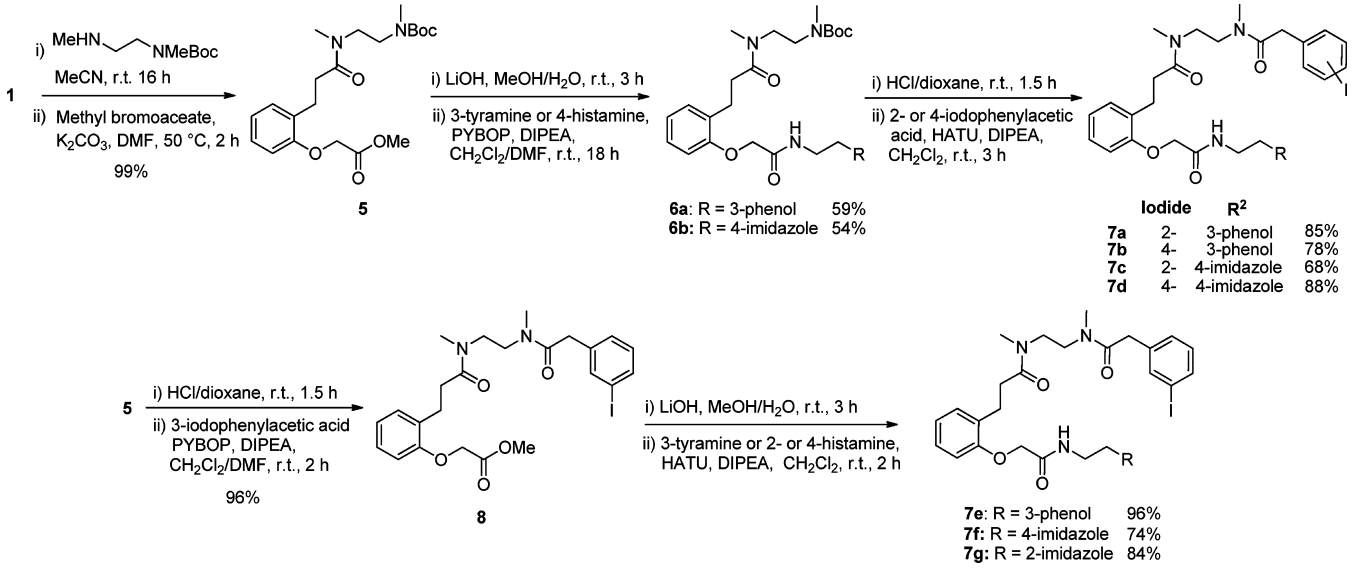


Figure 1. HMBC correlation observed between C6 and N10 (isomer *tele*-**4b**) and between C6 and N8 (isomer *pros*-**4b**).

Scheme 2. Synthesis of Macrocyclization Precursors 7a–g



yields respectively, demonstrating that the aryl iodide does not require an electron-withdrawing substituent. The imidazole nucleophile proved much more tolerant of structural variation, with the 4-imidazole cyclizing in good to excellent yields with *ortho*-, *para*-, and *meta*-iodides (**9c**, **9d**, and **9f**). Furthermore, reaction with the sterically hindered 2-imidazolyl analogue was also successful, resulting in *N*-arylimidazole **9g**, an isostere of the heterobiaryl linkage observed in 4-imidazolyl macrocycle *pros*-**4b**. Increasing the reaction concentration to 100 mM in the synthesis of **9e** and **9f** resulted in moderate yields of the desired products (Figure 2, yields in parentheses). In contrast to the results obtained for macrocycle **4b**, only one *N*-arylimidazole isomer was obtained for **9c**, **9d**, and **9f**.

The inclusion of two tertiary amides proved to greatly impede the purification and characterization of this set of compounds, as each was isolated as a mixture of at least three rotamers. This was confirmed by VT-NMR analysis of **9f** (see Supporting Information), which showed the expected peak coalescence at elevated temperature.

To demonstrate the applicability of this methodology to the synthesis of more druglike and conformationally constrained macrocycles, a range of precursors was prepared from readily available chiral pool amino alcohols as shown in Scheme 3. Selective O-alkylation of ephedrine (**10**) was achieved using KHMDS, and the amine product **11** was coupled with Boc-protected amino acids *m*-tyrosine and histidine to give precursors **12a** and **12b**. A protecting-group strategy was used for the synthesis of **15a** and **15b** from tetrahydroisoquinoline **13** by a similar route. The selective O-alkylation of this amino alcohol was subsequently achieved, thereby avoiding the need for protection, to give **16** en-route to linker-extended precursors **18a** and **18b**.

Using the optimized conditions, these precursors were cyclized in good to excellent yields, and at relatively high concentration (20 mM), to give the six corresponding macrocycles (Figure 3). These results exemplify the synthesis of smaller ring sizes than in the original optimization, with the macrocyclic products likely now exhibiting a higher degree of conformational restriction. These compounds represent excellent examples of small, druglike macrocycles, with calculated properties in the desired ranges: M_r 338–442; ClogP 1.82–4.74; tPSA 50.8–71.2.[16] Another feature is the potential for additional elaboration from the primary amine groups in **19a,b** and **20a,b**; these amines were Boc-protected in the linear

dx.doi.org/10.1021/jo302089f | *J. Org. Chem.* 2012, 77, 11079–11090

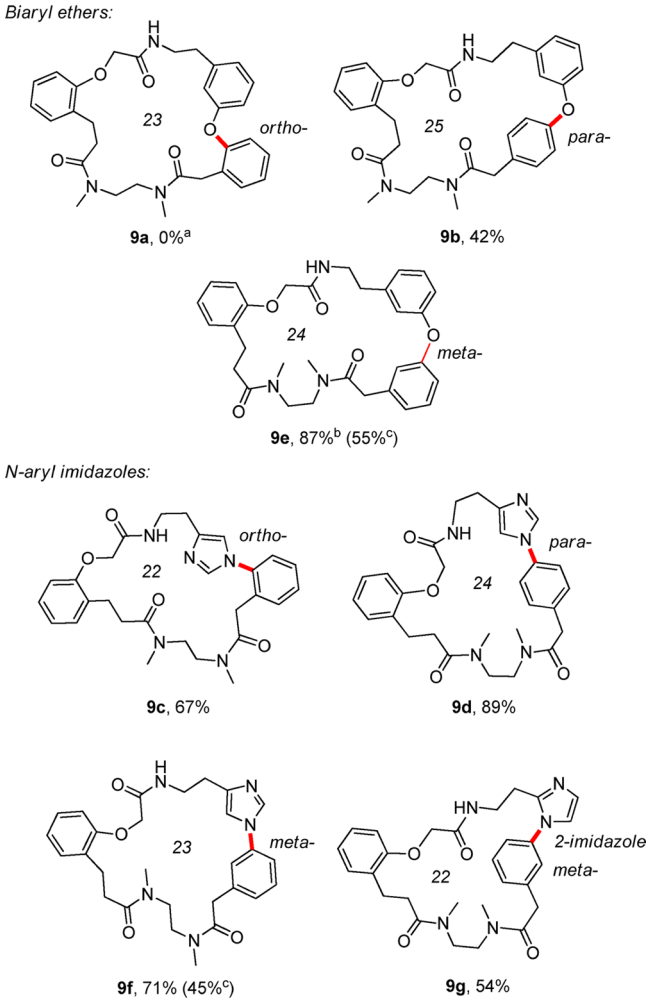


Figure 2. Scope of Ullmann macrocyclization−substitution pattern. Ring size is denoted by number within the macrocyclic ring. Macrocyclizations were conducted using 10 mol % CuI, 20 mol % 8-HQ, 3 equiv of Cs_2CO_3 in DMSO (20 mM) at 150 °C for 30 min. [a]Trace product detected. [b]40 mM reaction concentration. [c]100 mM.

precursors and were cleanly unmasked under the high-temperature reaction conditions. While this does illustrate one potential functional group incompatibility, the amine product clearly does not interfere with the macrocyclization, despite its high nucleophilicity.

Calculation of the Emac values for these reactions provides quantitative support for our assessment that the Ullmann macrocyclization methodology presented here is highly effective. The most efficient example in this study, biaryl ether **4a**, has an Emac value of 7.86, placing it in the top 2% most efficient macrocyclizations of any type (and this study in the top five reports) published over the last 3 years. All the druglike macrocycles in Figure 3 also score highly (Emac 6.89−7.15), illustrating the practicality of this methodology for potential use in a drug discovery setting.

CONCLUSION

In summary, we have developed conditions for a highly efficient Ullmann macrocyclization of phenols and imidazoles with unactivated aryl iodides at practical concentrations. A range of substitution patterns are tolerated, and the utility for medicinal chemistry has been exemplified by the synthesis of a set of druglike macrocycles. These macrocyclizations are among the most efficient reported over the last three years and open the way to construction of a variety of novel macrocycles with potentially unique 3D pharmacophores.

EXPERIMENTAL SECTION

General Considerations. All reagents and solvents were used as received. Anhydrous CH_2Cl_2 was obtained by passing through activated alumina columns. NMR spectra were recorded on 500 or 600 MHz instruments using residual solvent peak as a reference. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatography was performed using silica columns and CH_2Cl_2−MeOH gradients.

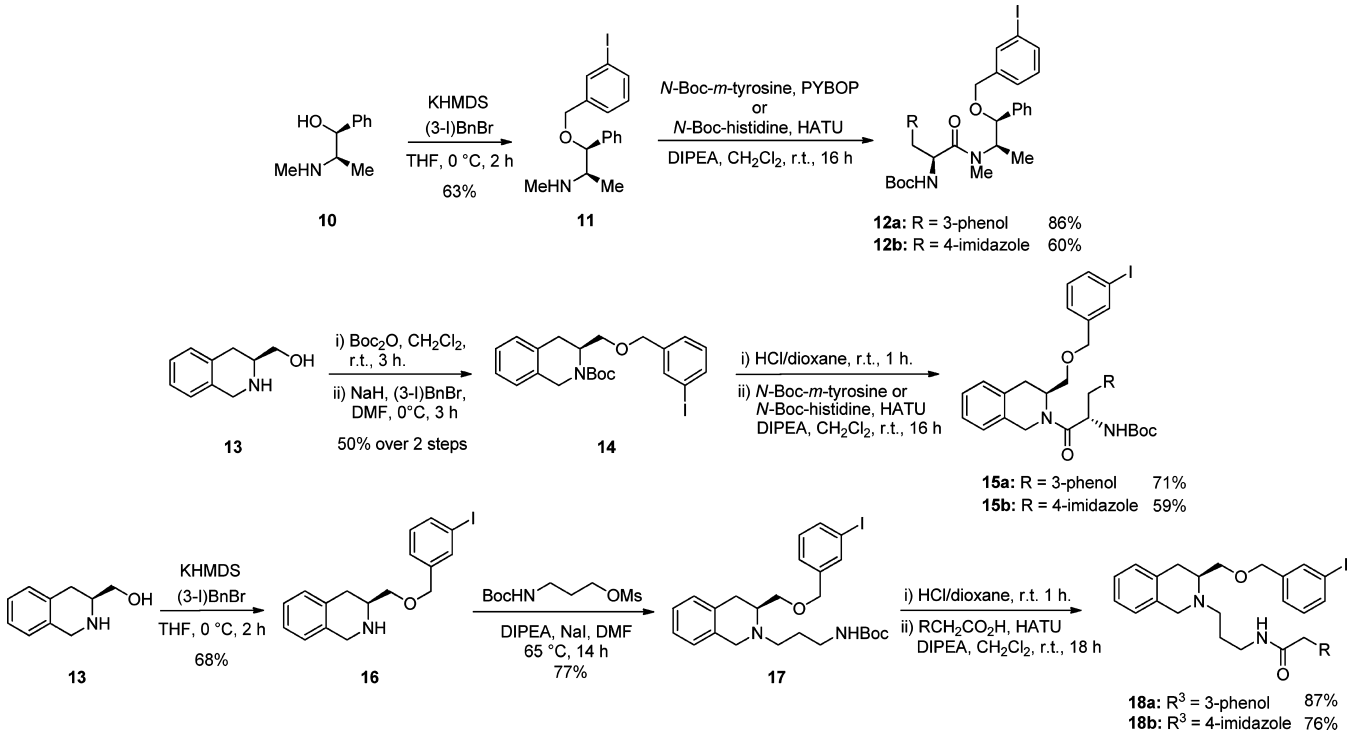
Methyl 2-(2-(3-((3-((tert-Butoxycarbonyl)amino)propyl)amino)-3-oxopropyl)phenoxy)acetate, ***2****.* To a solution of dihydrocoumarin (3.13 mL, 24.7 mmol) in MeCN (200 mL) was added *tert*-butyl (3-aminopropyl)carbamate (4.30 g, 24.7 mmol), and the resulting solution stirred at rt for 16 h. The solvent was removed in vacuo and the resulting residue taken up in DMF (100 mL). Following addition of K_2CO_3 (10.2 g, 74.0 mmol) and methyl 2-bromoacetate (3.04 mL, 32.1 mmol), the resulting suspension was heated to 50 °C for 2 h. After cooling, the solvent was removed in vacuo and the resulting residue taken up in EtOAc (100 mL) and extracted with H_2O (3 × 50 mL). The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The resulting residue was purified by column chromatography to give the title compound as a white semisolid (9.29 g, 96%), δ_H (500 MHz, $CDCl_3$) 7.16−7.08 (m, 3H), 6.86 (t, *J* 7.4, 1H), 6.66 (d, *J* 8.4, 1H), 6.55 (br s, 1H), 5.08 (br s, 1H), 4.69 (s, 2H), 3.78 (s, 3H), 3.16 (q, *J* 6.0, 2H), 2.95 (t, *J* 6.4, 2H), 2.89−2.81 (m, 2H), 2.54 (t, *J* 6.5, 2H), 1.45−1.41 (m, 2H), 1.39 (s, 9H); δ_C (126 MHz, $CDCl_3$) 173.4, 170.1, 156.3, 155.4, 131.0, 129.3, 127.7, 121.7, 110.5, 78.9, 64.5, 52.4, 36.9, 36.5, 35.9, 29.8, 28.5, 28.3; HRMS (ESI) for $C_{20}H_{30}N_2O_6$, MH^+ 395.2177; found 395.2182 (Δ 1.3 ppm).

N-(3-(3-(2-(2-((3-Hydroxyphenethyl)amino)-2-oxoethoxy)-phenyl)propanamido)propyl)-3-iodobenzamide, ***3a****.* To a stirred solution of **2** (9.27 g, 23.5 mmol) in MeOH (40 mL) at rt was added slowly a solution of LiOH·H_2O (2.59 g, 61.7 mmol) in H_2O (20 mL), and the reaction mixture was stirred for 3 h, before being washed with CH_2Cl_2 (20 mL) and acidified to ca. pH 2 with 0.5 M HCl. The solution was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried (Na_2SO_4), and the solvent removed in vacuo to give the carboxylic acid as a thick white semisolid (8.92 g), used in this crude form in subsequent reactions. To a solution of this carboxylic acid (2.00 g, 5.26 mmol) in CH_2Cl_2 (50 mL) and DMF (2.5 mL) were added PyBOP (3.01 g, 5.78 mmol) and DIPEA (1.84 mL, 10.5 mmol), and the resulting solution was stirred at rt for 15 min before addition of *m*-tyramine (870 mg, 6.31 mmol). The reaction mixture was stirred at rt for 18 h before being washed with 1 M HCl (100 mL) and sat. aq $NaHCO_3$ (100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue partially purified by column chromatography to give the intermediate phenol as a white semisolid (1.93 g), δ_H (400 MHz, $CDCl_3$) 8.50 (br s, 1H, NH), 7.11 (dt, *J* 11.8, 7.4, 3H, ArH), 7.05 (br s, 1H, NH), 6.87 (t, *J* 7.4, 1H, ArH), 6.75 (s, 2H, ArH), 6.71−6.62 (m, 3H, ArH), 6.54 (s, 1H, NH), 4.90 (br s, 1H, OH), 4.38 (s, 2H, OCH_2), 3.59 (q, *J* 6.1, 2H, CH_2), 3.20 (q, *J* 6.0, 2H, CH_2), 3.02 (q, *J* 6.0, 2H, CH_2), 2.90−2.86 (m, 2H, CH_2), 2.78 (t, *J* 6.5, 2H, CH_2), 2.40 (t, *J* 7.6, 2H, CH_2), 1.52 (p, *J* 6.3, 2H, CH_2), 1.38 (s, 9H, ^{t}Bu).

A solution of this phenol (320 mg, 0.642 mmol) in 4 M HCl/dioxane (1.60 mL, 6.41 mmol) was stirred at rt for 2 h. The solvent was removed in vacuo, and a premixed solution of 3-iodobenzoic acid (159 mg, 0.642 mmol), PyBOP (333 mg, 0.642 mmol), and DIPEA (450 μL, 2.56 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred at rt for 6 h before being poured into brine (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a white semisolid (346 mg, 64% over three steps), as a mixture of rotamers, δ_H (400 MHz,

dx.doi.org/10.1021/jo302089f | J. Org. Chem. 2012, 77, 11079−11090

Scheme 3. Synthesis of Macrocyclization Precursors 12a,b, 15a,b, and 18a,b



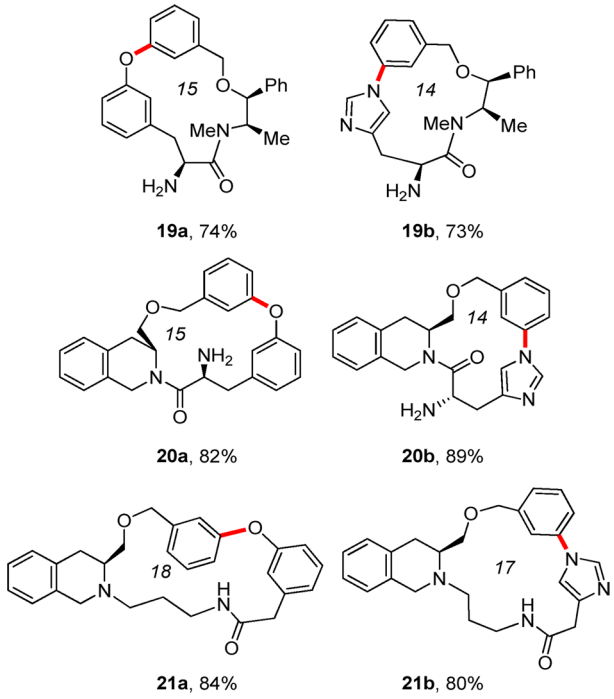


Figure 3. Scope of Ullmann macrocyclization: small, druglike macrocycles. Ring size is denoted by number within the macrocyclic ring. Macrocyclizations were conducted using 10 mol % CuI, 20 mol % 8-HQ, and 3 equiv of Cs_2CO_3 in DMSO (20 mM) at 150 °C for 30 min.

CD_3OD) 8.11 (s, 1H), 8.07 (t, *J* 5.5, 1H), 7.79 (d, *J* 7.8, 1H), 7.74 (d, *J* 7.8, 1H), 7.17–7.08 (m, 3H), 7.02 (t, *J* 7.8, 1H), 6.85 (t, *J* 7.4, 1H), 6.75 (d, *J* 8.4, 1H), 6.65–6.57 (m, 3H), 4.45 (s, 2H), 3.47 (t, *J* 7.0, 2H), 3.19 (t, *J* 6.7, 2H), 3.13 (t, *J* 6.7, 2H), 2.91 (t, *J* 7.2, 2H), 2.73 (t, *J* 7.2, 2H), 2.43 (t, *J* 7.3, 2H), 1.61 (p, *J* 6.6, 2H); δ_C (101 MHz, CD_3OD) 174.6, 169.8, 169.8, 167.2, 157.4, 155.6, 140.6, 140.4, 136.4, 136.2, 130.3, 130.2, 129.4, 129.2, 127.7, 126.3, 121.5, 119.9, 115.5, 113.2, 111.5, 93.7, 67.0, 40.5, 40.4, 37.1, 36.6, 36.4, 35.2, 28.9, 26.7; HRMS (ESI) for $C_{29}H_{32}IN_3O_5$, MH^+ 630.1459; found 630.1460 (Δ 0.2 ppm)

N-(3-(3-(2-(2-((2-(1H-Imidazol-4-yl)ethyl)amino)-2-oxoethoxy)-phenyl)propanamido)propyl)-3-iodobenzamide, ***3b.*** To a solution of the intermediate carboxylic acid from the synthesis of **3a** (2.00 g, 5.26 mmol) in CH_2Cl_2 (50 mL) and DMF (2.5 mL) were added PyBOP (3.01 g, 5.78 mmol) and DIPEA (3.67 mL, 21.0 mmol), and the resulting solution was stirred at rt for 15 min before addition of histamine·2HCl (1.16 g, 6.31 mmol). The reaction mixture was stirred at rt for 18 h before being washed with 1 M HCl (100 mL) and sat. aq $NaHCO_3$ (100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue partially purified by column chromatography to give the intermediate imidazole as a white semisolid (2.46 g), which was used in this crude form in the subsequent reactions, δ_H (400 MHz, $CDCl_3$) 7.74 (br s, 1H), 7.59 (s, 1H), 7.42 (br s, 2H), 7.12 (t, *J* 7.0, 2H), 6.88 (t, *J* 7.3, 2H), 6.79 (s, 1H), 6.69 (d, *J* 8.2, 1H), 4.41 (s, 2H), 3.61 (q, *J* 6.2, 2H), 3.18–3.09 (m, 2H), 3.01–2.84 (m, 6H), 2.45 (t, *J* 7.3, 2H), 1.50–1.43 (m, 2H), 1.38 (s, 9H).

A solution of this imidazole (284 mg, 0.600 mmol) in 4 M HCl/dioxane (1.50 mL, 6.00 mmol) was stirred at rt for 2 h. The solvent was removed in vacuo, and a premixed solution of 3-iodobenzoic acid (149 mg, 0.600 mmol), PyBOP (312 mg, 0.600 mmol), and DIPEA (420 μL, 2.40 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred at rt for 6 h before being poured into brine (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a white semisolid (344 mg, 94% over three steps), δ_H (400 MHz, $CDCl_3$) 10.74 (br s, 1H), 8.16 (s, 1H), 8.01 (t, *J* 5.8, 1H), 7.84 (t, *J* 4.8, 1H), 7.76 (t, *J* 9.0, 2H), 7.55–7.49 (m, 2H), 7.16–7.05 (m, 3H), 6.88 (t, *J* 7.4, 1H), 6.79 (s, 1H), 6.69 (d, *J* 8.5, 1H), 4.42 (s, 2H), 3.58 (q, *J* 5.6, 2H), 3.25 (q, *J* 5.7, 2H), 3.19 (q, *J* 5.6, 2H), 2.98 (t, *J* 7.2, 2H), 2.86 (t, *J* 5.9, 2H), 2.51 (t, *J* 7.2, 2H), 1.62–1.51 (m, 2H); δ_C (101 MHz, $CDCl_3$) 173.9, 168.7, 166.6, 155.1, 140.4, 136.4, 136.4, 134.8, 134.7, 130.6, 130.3, 129.1, 128.0, 126.3, 121.9, 117.5, 111.4, 94.4, 67.2, 39.2, 37.3, 36.6,

dx.doi.org/10.1021/jo302089f | J. Org. Chem. 2012, 77, 11079–11090

36.2, 29.5, 27.0, 26.3; HRMS (ESI) for $C_{26}H_{30}IN_5O_4$, MH^+ 604.1415; found 604.1416 (Δ 0.2 ppm).

General Procedure for Ullmann Macrocyclization. A suspension of macrocycle precursor (20.0 μmol), CuI (0.38 mg, 2.00 μmol), 8-hydroxyquinoline (0.58 mg, 4.00 μmol), and Cs_2CO_3 (19.6 mg, 60.0 μmol) in degassed DMSO (1 mL, 20 mM reaction concentration) was heated to 150 °C in a Biotage Initiator microwave with air-cooling and an external temperature sensor. After 30 min at this temperature, the reaction mixture was cooled, poured into sat. aq $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the macrocycle product.

*Macrocycle **4a**.* Macrocyclization carried out as per the general procedure using **3a**. Carried out on 100 μmol scale with 5 mol % CuI and 10 mol % 8-HQ in 1 mL of DMSO (100 mM reaction concentration). Obtained as a white solid (45 mg, 90%), δ_H (500 MHz, DMSO-d_6) 8.46 (t, *J* 6.0, 1H), 8.23 (t, *J* 5.9, 1H), 7.91 (t, *J* 6.0, 1H), 7.64 (d, *J* 7.7, 1H), 7.57−7.55 (m, 1H), 7.53 (t, *J* 8.0, 1H), 7.37 (t, *J* 7.9, 1H), 7.35−7.32 (m, 1H), 7.18−7.12 (m, 2H), 7.05 (dd, *J* 8.1, 2.0, 1H), 7.01 (d, *J* 7.6, 1H), 6.91−6.86 (m, 1H), 6.79 (s, 1H), 4.47 (s, 1H), 3.38−3.32 (m, 2H), 3.25−3.20 (m, 2H), 3.06−3.00 (m, 2H), 2.84−2.79 (m, 2H), 2.79−2.75 (m, 2H), 2.31−2.26 (m, 2H), 1.61−1.54 (m, 2H); δ_C (126 MHz, DMSO-d_6) 172.0, 167.6, 165.3, 156.5, 155.7, 155.0, 141.2, 136.1, 130.4, 130.3, 129.7, 129.6, 127.5, 123.6, 122.7, 122.5, 121.0, 116.8, 116.7, 116.4, 111.8, 66.7, 40.2, 36.4, 36.4, 36.2, 35.1, 29.2, 26.7; HRMS (ESI) for $C_{29}H_{31}N_3O_5$, MH^+ 502.2336; found 502.2342 (Δ 1.2 ppm).

*Macrocycle **4b**.* Macrocyclization carried out as per the general procedure using **3b** on 100 μmol scale with 5 mol % CuI and 10 mol % 8-HQ in 1 mL of DMSO (100 mM reaction concentration) and heated to 190 °C in a microwave for 15 min. Obtained as a white solid as a mixture of regioisomers (39 mg, 82%); HRMS (ESI) for $C_{26}H_{29}N_5O_4$, MH^+ 476.2292; found 476.2300 (Δ 1.7 ppm). The regioisomers were separated by supercritical fluid chromatography using normal-phase conditions on a 150 mm × 21.2 mm 5 μm column with a gradient of 5−50% A over 5.6 min with a flow rate of 60 mL/min. Mobile phase A was MeOH, and mobile phase B was CO_2, with monitoring at UV 260 nm. QC was orthogonally analyzed by LC using a 50 × 4.6 mm 3.5 μm column with 10 mM NH_4OAC in H_2O and MeCN.

tele-**4b**: δ_H (600 MHz, DMSO-d_6); 8.40 (s, 1H), 8.37 (t, *J* 5.1, 1H), 8.13 (t, *J* 5.5, 1H), 8.06 (s, 1H), 7.93 (t, *J* 5.3, 1H), 7.80 (d, *J* 7.9, 1H), 7.70 (s, 1H), 7.67 (d, *J* 7.6, 1H), 7.57 (t, *J* 7.8, 1H), 7.11 (t, *J* 7.6, 1H), 7.06 (d, *J* 7.3, 1H), 6.88 (d, *J* 8.2, 1H), 6.84 (t, *J* 7.4, 1H), 4.46 (s, 2H), 3.53 (q, *J* 5.3, 2H), 3.33−3.30 (m, 2H), 3.27 (q, *J* 5.8, 2H), 2.86 (t, *J* 7.6, 2H), 2.79−2.75 (m, 2H), 2.40 (t, *J* 7.7, 1H), 1.74−1.68 (m, 2H); δ_C (151 MHz, DMSO-d_6) 172.5, 167.6, 165.8, 155.0, 141.0, 136.9, 136.7, 135.4, 130.0, 129.1, 128.8, 127.2, 125.3, 121.5, 121.0, 118.5, 114.1, 111.6, 67.1, 37.7, 36.5, 35.7, 34.8, 27.7, 27.3, 25.2.

pros-**4b**: δ_H (500 MHz, DMSO-d_6) 8.33 (t, *J* 5.5, 1H), 8.15 (t, *J* 5.9, 1H), 8.09−8.03 (m, 1H), 7.89−7.84 (m, 3H), 7.68−7.60 (m, 2H), 7.18−7.13 (m, 2H), 6.97 (s, 1H), 6.93−6.87 (m, 2H), 4.45 (s, 2H), 3.45−3.39 (m, 2H), 3.28−3.21 (m, 4H), 2.91 (t, *J* 8.0, 2H), 2.84 (t, *J* 7.3, 2H), 2.33 (t, *J* 7.6, 2H), 1.65−1.57 (m, 2H); δ_C (126 MHz, DMSO-d_6) 172.9, 167.6, 165.4, 154.8, 137.7, 136.4, 135.9, 130.2, 129.9, 129.5, 129.3, 127.9, 127.6, 127.5, 127.0, 123.3, 121.1, 111.8, 66.6, 37.3, 36.8, 35.3, 34.9, 28.4, 27.0, 24.1.

*Methyl 2-(2-(3-((2-((tert-Butoxycarbonyl)(methyl)amino)ethyl)-(methyl)amino)-3-oxopropyl)phenoxy)acetate, **5**.* To a solution of dihydrocoumarin (3.37 mL, 26.6 mmol) in MeCN (150 mL) was added *tert*-butyl methyl(2-methylamino)ethyl)carbamate (5.00 g, 26.6 mmol), and the resulting solution was stirred at rt for 16 h. The solvent was removed in vacuo and the resulting residue taken up in DMF (100 mL). Following addition of K_2CO_3 (11.0 g, 80.0 mmol) and methyl 2-bromoacetate (3.27 mL, 34.5 mmol), the resulting suspension was heated to 50 °C for 2 h. After cooling, the solvent was removed in vacuo and the resulting residue taken up in EtOAc (100 mL) and extracted with H_2O (5 × 50 mL). The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The resulting residue was purified by column chromatography to give the title compound as a thick yellow oil (10.7 g, 99%) as a mixture of rotamers, δ_H (400 MHz, $CDCl_3$) 7.16−7.11 (m, 1H), 7.10−7.04 (m. 1H), 6.87−6.80 (m, 1H), 6.65−6.61 (m, 1H), 4.61−4.57 (m, 2H), 3.70 (s, 3H), 3.48−3.19 (m, 4H), 2.97−2.86 (m, 5H), 2.81−2.72 (m, 3H), 2.62−2.54 (m, 2H), 1.41−1.30 (m, 9H); δ_C (101 MHz, $CDCl_3$) 172.7, 169.2, 155.6, 130.6, 130.0, 127.3, 121.5, 110.8, 79.8, 79.6, 79.2, 65.0, 52.0, 47.7, 47.2, 46.4, 46.1, 45.6, 45.1, 36.2, 35.7, 34.7, 33.6, 32.8, 28.3, 26.8, 26.6; HRMS (ESI) for $C_{21}H_{32}N_2O_6$, MH^+ 408.2333; found 408.2335 (Δ 0.5 ppm).

*tert-Butyl (2-(3-(2-(2-((3-Hydroxyphenethyl)amino)-2-oxoethoxy)phenyl)-N-methylpropanamido)ethyl)(methyl)-carbamate, **6a**.* To a stirred solution of **5** (2.00 g, 4.90 mmol) in MeOH (8 mL) at rt was added slowly a solution of $LiOH·H_2O$ (510 mg, 12.2 mmol) in H_2O (4 mL), and the reaction mixture was stirred for 3 h. The reaction mixture was acidified to approximately pH 2 with 0.5 M HCl and extracted with EtOAc (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to give the carboxylic acid as a colorless oil (1.75 g), which was used crude in the following reactions. To a solution of this carboxylic acid (830 mg, 2.09 mmol) in CH_2Cl_2 (25 mL) were added PyBOP (1.20 g, 2.30 mmol) and DIPEA (730 μL, 4.18 mmol), and the resulting solution was stirred at rt for 15 min before addition of *m*-tyramine (340 mg, 2.51 mmol). The reaction mixture was stirred at rt for 18 h before being washed with sat. aq citric acid (100 mL) and sat. aq $NaHCO_3$ (100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue purified by column chromatography to give the title compound as a thick colorless oil (710 mg, 59% over two steps) as a mixture of rotamers, δ_H (600 MHz, CD_3OD) 7.16−7.12 (m, 2H), 7.04−7.00 (m, 1H), 6.90−6.86 (m, 1H), 6.78 (d, *J* 8.2, 1H), 6.64−6.60 (m, 2H), 6.58 (d, *J* 8.1, 1H), 4.46 (s, 2H), 3.51−3.46 (m, 2H), 3.46−3.41 (m, 1H), 3.37−3.33 (m, 1H), 3.28−3.23 (m, 2H), 2.94−2.85 (m, 5H), 2.81−2.72 (m, 5H), 2.62−2.53 (m, 2H), 1.39 (d_{app}, *J* 9.1, 5H), 1.34 (s, 4H); δ_C (151 MHz, CD_3OD) 170.0, 157.6, 155.9, 140.8, 130.4, 130.3, 129.8, 129.8, 129.5, 129.5, 127.9, 127.9, 121.9, 121.8, 120.0, 120.0, 115.7, 115.7, 113.4, 111.9, 111.8, 67.4, 40.6, 40.6, 35.4, 33.2, 27.8, 27.7, 26.2; HRMS (ESI) for $C_{28}H_{39}N_3O_6$, MH^+ 514.2911; found 514.2915 (Δ 0.8 ppm).

*tert-Butyl (2-(3-(2-(2-((2-(1H-Imidazol-4-yl)ethyl)amino)-2-oxoethoxy)phenyl)-N-methylpropanamido)ethyl)(methyl)-carbamate, **6b**.* To a solution of the intermediate carboxylic acid from the synthesis of **6a** (830 mg, 2.09 mmol) in CH_2Cl_2 (25 mL) were added PyBOP (1.20 g, 2.30 mmol) and DIPEA (1.46 mL, 8.37 mmol), and the resulting solution was stirred at rt for 15 min before addition of histamine·2HCl (280 mg, 2.51 mmol). The reaction mixture was stirred at rt for 18 h before being washed with sat. aq citric acid (100 mL) and sat. aq $NaHCO_3$ (100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue purified by column chromatography to give the title compound as a thick colorless oil (600 mg, 54% over two steps), δ_H (600 MHz, CD_3OD) 7.54 (s, 1H), 7.17−7.10 (m, 2H), 6.91−6.86 (m, 1H), 6.80−6.74 (m, 2H), 4.48 (s, 2H), 3.53−3.49 (m, 2H), 3.46−3.42 (m, 1H), 3.37−3.33 (m, 1H), 3.27−3.24 (m, 2H), 2.95−2.86 (m, 5H), 2.82−2.74 (m, 5H), 2.65−2.55 (m, 2H), 1.39 (d_{app}, *J* 8.6 5H), 1.33 (s, 4H); δ_C (151 MHz, CD_3OD) 174.9, 170.5, 156.9, 156.3, 135.6, 135.2, 130.8, 130.3, 128.3, 122.3, 117.5, 112.2, 81.0, 80.7, 80.3, 67.8, 46.7, 46.3, 46.1, 45.8, 39.4, 36.2, 36.0, 35.5, 34.6, 34.3, 34.0, 33.7, 28.1, 27.1, 26.6; HRMS (ESI) for $C_{25}H_{37}N_5O_5$, MH^+ 488.2867; found 488.2866 (Δ 0.2 ppm).

*3-(2-(2-((3-Hydroxyphenethyl)amino)-2-oxoethoxy)phenyl)-N-(2-(2-(2-iodophenyl)-N-methylacetamido)ethyl)-N-methylpropanamide, **7a**.* A 4 M HCl/dioxane (2.30 mL, 9.20 mmol) solution was added to **6a** (591 mg, 1.15 mmol) and the resulting solution stirred at rt for 1.5 h. The solvent was removed in vacuo and the crude product amine used in subsequent reactions. To a premixed solution of 2-(2-iodophenyl)acetic acid (157 mg, 0.600 mmol), HATU (274 mg, 0.720 mmol), and DIPEA (314 μL, 1.80 mmol) in CH_2Cl_2 (5 mL) was added this amine (238 mg, 0.58 mmol). The reaction mixture was stirred at rt for 3 h, before being poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the

resulting residue was purified by column chromatography to give the title compound as a thick colorless oil (322 mg, 85% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 8.12−8.08 (m, 0.4H), 7.85−7.79 (m, 1H), 7.31−7.26 (m, 1H), 7.24−7.11 (m, 4H), 7.01−6.90 (m, 3H), 6.81−6.71 (m, 2H), 6.71−6.66 (m, 2H), 4.69 (s, 0.3H), 4.45 (s, 1.7H), 3.86−3.74 (m, 2H), 3.64 (s, 3H), 3.62−3.57 (m, 1.8H), 3.56−3.40 (m, 1.2H), 3.15 (s, 2H), 3.11−2.91 (m, 6H), 2.85−2.73 (m, 2H), 2.70−2.56 (m, 2H); δ_C (151 MHz, $CDCl_3$) 174.2, 174.0, 173.8, 171.2, 171.0, 170.7, 168.8, 168.5, 168.5, 165.4, 157.6, 157.4, 157.3, 154.9, 154.7, 140.2, 140.1, 140.0, 139.5, 139.5, 138.6, 138.4, 138.2, 133.9, 130.5, 130.4, 130.4, 130.2, 130.2, 130.2, 130.1, 130.0, 129.9, 129.2, 129.1, 129.0, 129.0, 128.8, 128.8, 128.6, 128.1, 128.0, 128.0, 122.1, 120.1, 119.9, 119.8, 115.8, 115.7, 115.6, 114.1, 114.1, 113.9, 111.6, 111.5, 101.5, 101.3, 101.3, 67.2, 67.0, 62.9, 47.8, 47.4, 47.3, 47.2, 45.8, 45.8, 45.5, 45.4, 40.4, 40.3, 40.2, 37.3, 37.1, 36.3, 36.2, 35.0, 35.0, 34.4, 34.3, 34.2, 34.0, 33.0, 25.7, 25.3, 25.2; HRMS (ESI) for $C_{31}H_{36}IN_3O_5$, MH^+ 658.1772; found 658.1772 (Δ 0.0 ppm).

3-(2-(2-((3-Hydroxyphenethyl)amino)-2-oxoethoxy)phenyl)-N-(2-(2-(4-iodophenyl)-N-methylacetamido)ethyl)-N-methylpropanamide, ***7b***. To a premixed solution of 2-(4-iodophenyl)acetic acid (157 mg, 0.600 mmol), HATU (274 mg, 0.720 mmol), and DIPEA (314 μL, 1.80 mmol) in CH_2Cl_2 (5 mL) was added the intermediate amine from the synthesis of **7a** (238 mg, 0.580 mmol). The reaction mixture was stirred at rt for 3 h, before being poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a thick colorless oil (295 mg, 78% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 8.85 (s, 0.7H), 8.61 (s, 0.1H), 8.48 (s, 0.1H), 7.64−7.53 (m, 2H), 7.21−7.08 (m, 4H), 6.99−6.89 (m, 3H), 6.80−6.72 (m, 2H), 6.71−6.65 (m, 2H), 4.44 (s, 0.5H), 4.43 (s, 1.5H), 3.65−3.53 (m, 7H), 3.44−3.33 (m, 1H), 3.04 (s, 2H), 2.97−2.89 (m, 6H), 2.83−2.75 (m, 2H), 2.60−2.48 (m, 2H); δ_C (151 MHz, $CDCl_3$) 173.8, 173.7, 173.4, 171.3, 171.1, 171.0, 168.4, 168.2, 157.5, 157.4, 157.3, 154.9, 154.8, 154.7, 140.3, 140.2, 140.1, 137.8, 137.7, 137.7, 134.6, 134.4, 133.8, 131.2, 131.0, 130.9, 130.1, 130.1, 130.0, 129.9, 129.3, 129.1, 128.9, 128.0, 127.9, 121.9, 121.9, 120.0, 119.9, 119.8, 115.7, 115.6, 113.9, 113.9, 113.7, 111.5, 111.5, 111.4, 92.5, 92.4, 92.3, 67.3, 67.1, 67.1, 47.4, 47.2, 47.2, 47.1, 45.2, 45.1, 40.3, 40.3, 40.2, 40.2, 39.7, 37.2, 36.9, 36.2, 35.9, 35.2, 35.2, 34.1, 33.8, 33.8, 33.1, 25.9, 25.5, 25.4; HRMS (ESI) for $C_{31}H_{36}IN_3O_5$, MH^+ 658.1772; found 658.1771 (Δ 0.2 ppm).

3-(2-(2-((2-(1H-Imidazol-4-yl)ethyl)amino)-2-oxoethoxy)phenyl)-N-(2-(2-(2-iodophenyl)-N-methylacetamido)ethyl)-N-methylpropanamide, ***7c***. A 4 M HCl/dioxane (2.30 mL, 9.20 mmol) solution was added to **6b** (561 mg, 1.15 mmol) and the resulting solution stirred at rt for 1.5 h. The solvent was removed in vacuo and the crude product amine used in subsequent reactions. To a premixed solution of 2-(2-iodophenyl)acetic acid (157 mg, 0.600 mmol), HATU (274 mg, 0.720 mmol), and DIPEA (314 μL, 1.80 mmol) in CH_2Cl_2 (5 mL) was added this amine (223 mg, 0.580 mmol). The reaction mixture was stirred at rt for 3 h, before being poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a thick colorless oil (247 mg, 68% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 10.30 (br s, 1H), 7.74−7.71 (m, 1H), 7.69−7.31 (m, 1H), 7.28−7.16 (m, 2H), 7.14−7.07 (m, 3H), 6.89−6.83 (m, 2H), 6.71−6.59 (m, 2H), 4.41 (s, 0.3H), 4.40 (s, 1.2H), 4.38 (s, 0.5H), 3.73−3.62 (m, 2H), 3.56−3.50 (m, 2H), 3.50−3.25 (m, 4H), 3.06−2.82 (m, 8H), 2.80−2.72 (m, 2H), 2.62−2.46 (m, 2H); δ_C (151 MHz, $CDCl_3$) 173.3, 173.2, 170.7, 170.3, 168.4, 168.2, 155.1, 155.0, 139.4, 138.7, 138.3, 135.0, 134.9, 133.8, 130.5, 130.5, 130.3, 130.2, 130.2, 129.4, 129.2, 128.9, 128.9, 128.6, 128.5, 128.0, 127.9, 127.9, 121.8, 118.2, 111.3, 101.4, 101.3, 67.3, 67.2, 47.6, 47.3, 47.2, 46.8, 45.7, 45.7, 45.5, 45.3, 45.0, 38.9, 38.7, 37.0, 36.8, 36.2, 36.0, 34.3, 34.2, 33.9, 33.2, 26.5, 26.3, 26.1, 25.9, 25.9; HRMS (ESI) for $C_{28}H_{34}IN_5O_4$, MH^+ 632.1728; found 632.1730 (Δ 0.3 ppm).

3-(2-(2-((2-(1H-Imidazol-4-yl)ethyl)amino)-2-oxoethoxy)phenyl)-N-(2-(2-(4-iodophenyl)-N-methylacetamido)ethyl)-N-methylpropanamide, ***7d***. To a premixed solution of 2-(4-iodophenyl)acetic acid (157 mg, 0.600 mmol), HATU (274 mg, 0.720 mmol), and DIPEA (314 μL, 1.80 mmol) in CH_2Cl_2 (5 mL) was added the intermediate amine from the synthesis of **7c** (223 mg, 0.580 mmol). The reaction mixture was stirred at rt for 3 h, before being poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a thick colorless oil (320 mg, 88%) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 10.80 (br s, 1H), 7.87 (t, *J* 5.7, 0.25H), 7.81 (t, *J* 5.7, 0.15H), 7.73 (t, *J* 5.7, 0.6H), 7.59−7.39 (m, 3H), 7.19−7.12 (m, 2H), 6.97−6.84 (m, 3H), 6.77−6.68 (m, 2H), 4.46 (s, 0.35H), 4.45 (s, 1.15H), 4.44 (s, 0.5H), 3.63−3.53 (m, 4H), 3.48 (s, 2.5H), 3.40−3.29 (m, 1.5H), 3.01−2.82 (m, 10H), 2.60 (t, *J* 7.2, 0.3H), 2.56 (t, *J* 7.3, 0.4H), 2.49 (t, *J* 7.3, 1.3H); δ_C (151 MHz, $CDCl_3$) 173.4, 173.3, 171.2, 171.0, 170.9, 168.4, 168.3, 155.1, 155.1, 155.0, 137.9, 137.8, 137.7, 134.9, 134.8, 134.5, 133.9, 131.2, 131.0, 131.0, 130.8, 130.3, 130.2, 129.4, 129.4, 129.2, 128.0, 127.9, 121.8, 121.8, 118.0, 111.4, 111.3, 92.5, 92.4, 92.3, 67.3, 67.2, 67.2, 47.4, 47.2, 47.1, 47.0, 45.3, 44.9, 40.3, 40.2, 39.6, 38.8, 38.8, 37.1, 36.9, 36.3, 35.9, 34.2, 34.1, 33.8, 33.3, 26.6, 26.5, 26.3, 26.2, 25.9; HRMS (ESI) for $C_{28}H_{34}IN_5O_4$, MH^+ 632.1728; found 632.1733 (Δ 0.8 ppm).

Methyl 2-(2-(3-((2-(2-(3-Iodophenyl)-N-methylacetamido)ethyl)-(methyl)amino)-3-oxopropyl)phenoxy)acetate, ***8***. A solution of **5** (1.00 g, 2.45 mmol) in 4 M HCl/dioxane (4.90 mL, 19.6 mmol) was stirred at rt for 1.5 h. The solvent was removed in vacuo, and a premixed solution of 3-iodophenylacetic acid (770 mg, 2.94 mmol), PyBOP (1.53 g, 2.94 mmol), and DIPEA (2.14 mL, 12.2 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred at rt for 2 h before being washed with sat. aq citric acid (100 mL) and sat. aq $NaHCO_3$ (50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue purified by column chromatography to give the title compound as a thick colorless oil (1.30 g, 96%) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 7.61 (s, 0.2H), 7.53−7.46 (m, 1.8H), 7.23−7.05 (m, 3H), 7.01−6.89 (m, 1H), 6.88−6.82 (m, 1H), 6.64 (d, *J* 8.1, 1H), 4.61 (s, 0.5H), 4.59 (s, 1.4H), 4.58 (s, 0.1H), 3.71 (s, 0.7H), 3.69 (s, 2.3H), 3.64 (s, 0.4H), 3.51 (s, 1.6H), 3.47−3.30 (m, 4H), 3.01−2.83 (m, 8H), 2.67−2.62 (m, 0.4H), 2.60−2.55 (m, 1.6H); δ_C (151 MHz, $CDCl_3$) 174.3, 174.2, 173.6, 171.9, 171.5, 171.3, 170.3, 170.2, 156.5, 138.8, 138.7, 138.6, 138.1, 137.8, 136.7, 136.6, 131.6, 131.6, 131.4, 131.1, 130.8, 130.5, 130.5, 129.5, 129.2, 128.5, 128.4, 122.6, 122.5, 111.9, 111.8, 111.7, 95.4, 95.3, 95.3, 65.9, 65.8, 53.0, 48.2, 48.0, 47.8, 46.1, 45.8, 40.9, 40.7, 40.4, 37.8, 37.7, 37.4, 36.9, 34.8, 34.7, 34.4, 34.3, 33.8, 27.8, 27.6, 27.2; HRMS (ESI) for $C_{24}H_{29}IN_2O_5$, MH^+ 553.1194; found 553.1197 (Δ 0.5 ppm).

3-(2-(2-((3-Hydroxyphenethyl)amino)-2-oxoethoxy)phenyl)-N-(2-(2-(3-iodophenyl)-N-methylacetamido)ethyl)-N-methylpropanamide, ***7e***. To a stirred solution of **8** (1.30 g, 2.45 mmol) in MeOH (8 mL) at rt was added slowly a solution of $LiOH·H_2O$ (260 mg, 6.12 mmol) in H_2O (4 mL), and the reaction mixture was stirred for 2 h. The reaction mixture was acidified to approximately pH 2 with 0.5 M HCl and extracted with EtOAc (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to give a quantitative recovery of the title compound as a colorless oil that was used crude in the following reactions. To a stirred solution of this carboxylic acid (323 mg, 0.600 mmol), HATU (274 mg, 0.720 mmol), and DIPEA (419 μL, 2.40 mmol) in CH_2Cl_2 (5 mL) was added *m*-tyramine hydrochloride (146 mg, 0.840 mmol), and the reaction was stirred at rt for 2 h. The reaction mixture was poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a thick colorless oil (380 mg, 96% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 8.81 (d, *J* 1.2, 0.7H), 8.49 (d, *J* 1.4, 0.1H), 8.41 (d, *J* 1.4, 0.1H), 7.63−7.51 (m, 1.9H), 7.37−7.31 (m, 0.1H), 7.23−7.05 (m, 5H), 7.05−6.97 (m, 1H), 6.97−6.90 (m, 1H), 6.82−6.63 (m, 4H), 4.46−4.42 (m, 2H), 3.66−3.58 (m, 3.8H), 3.58−3.55 (m, 3H), 3.44−3.33 (m, 1.2H), 3.07−3.04 (s, 2H), 3.01−2.87 (m, 6H), 2.83−2.77 (m,

dx.doi.org/10.1021/jo302089f | J. Org. Chem. 2012, 77, 11079−11090

2H), 2.61−2.56 (m, 0.6H), 2.55−2.50 (m, 1.4H); δ_C (151 MHz, $CDCl_3$) 173.9, 173.8, 173.5, 171.2, 171.0, 170.8, 168.4, 168.2, 157.5, 157.4, 157.3, 154.9, 154.8, 154.8, 140.4, 140.2, 140.1, 138.0, 137.9, 137.6, 137.4, 137.1, 136.5, 136.2, 136.1, 136.1, 130.5, 130.5, 130.4, 130.2, 130.2, 130.1, 130.1, 130.0, 129.3, 129.1, 129.0, 128.5, 128.3, 128.3, 128.1, 127.9, 122.0, 121.9, 120.00, 119.9, 119.8, 115.8, 115.8, 115.6, 114.0, 113.9, 113.8, 111.5, 111.4, 94.7, 94.6, 94.6, 67.3, 67.1, 67.1, 47.4, 47.3, 47.2, 45.3, 45.2, 40.3, 40.3, 40.2, 40.2, 39.8, 37.3, 37.0, 36.3, 36.0, 35.3, 35.2, 34.2, 34.1, 33.9, 33.8, 33.1, 25.8, 25.5, 25.4; HRMS (ESI) for $C_{31}H_{36}IN_3O_5$, MH^+ 658.1772; found 658.1774 (Δ 0.3 ppm).

3-(2-(2-((2-(1H-Imidazol-4-yl)ethyl)amino)-2-oxoethoxy)phenyl)-N-(2-(2-(3-iodophenyl)-N-methylacetamido)ethyl)-N-methylpropanamide, ***7f.*** To a stirred solution of the intermediate carboxylic acid from the synthesis of **7e** (1.29 g, 2.40 mmol), HATU (1.00 g, 2.64 mmol), and DIPEA (2.10 mL, 12.0 mmol) in CH_2Cl_2 (15 mL) was added histamine dihydrochloride (530 mg, 2.88 mmol), and the reaction was stirred at rt for 2 h. The reaction mixture was poured into sat. aq $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a thick colorless oil (1.12 g, 74% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 7.96−7.90 (m, 0.2H), 7.85 (t, *J* 5.6, 0.2H), 7.80 (t, *J* 5.4, 0.5H), 7.52−7.44 (m, 2H), 7.43−7.36 (m, 1H), 7.14−7.04 (m, 3H), 6.93 (t, *J* 7.8, 1H), 6.90−6.82 (m, 1H), 6.72−6.66 (m, 2H), 4.42 (s, 0.5H), 4.41 (s, 1.1H), 4.39 (s, 0.4H), 3.59−3.52 (m, 2.5H), 3.52−3.42 (m, 4H), 3.34−3.23 (m, 1.5H), 2.96 (s, 2H), 2.94−2.86 (m, 3H), 2.84 (s, 2H), 2.82−2.75 (m, 3H), 2.57 (t, *J* 7.2, 0.4H), 2.53 (t, *J* 7.3, 0.4H), 2.47 (t, *J* 7.2, 1.2H); δ_C (151 MHz, $CDCl_3$) 173.2, 173.0, 170.8, 170.7, 170.5, 168.2, 168.1, 154.9, 154.9, 154.8, 137.9, 137.7, 137.5, 137.3, 137.0, 136.5, 135.9, 135.8, 134.8, 134.7, 130.2, 130.2, 130.1, 130.1, 129.3, 129.2, 129.1, 128.4, 128.2, 128.1, 127.8, 127.7, 127.7, 121.6, 121.6, 121.5, 111.2, 111.2, 111.1, 94.4, 94.4, 94.4, 67.1, 67.1, 67.0, 47.2, 47.0, 46.9, 46.8, 45.1, 44.7, 39.9, 39.9, 39.3, 38.8, 38.8, 36.9, 36.7, 36.1, 35.8, 33.9, 33.9, 33.6, 33.5, 33.1, 26.6, 26.5, 26.3, 26.1, 25.7; HRMS (ESI) for $C_{28}H_{34}IN_5O_4$, MH^+ 632.1728; found 632.1728 (Δ 0.0 ppm).

3-(2-(2-((2-(1H-Imidazol-2-yl)ethyl)amino)-2-oxoethoxy)phenyl)-N-(2-(2-(3-iodophenyl)-N-methylacetamido)ethyl)-N-methylpropanamide, ***7g.*** To a stirred solution of the intermediate carboxylic acid from the synthesis of **7e** (323 mg, 0.600 mmol), HATU (274 mg, 0.720 mmol), and DIPEA (419 μL, 2.40 mmol) in CH_2Cl_2 (5 mL) was added 2-(1*H*-imidazol-2-yl)ethanamine dihydrochloride (155 mg, 0.840 mmol), and the reaction was stirred at rt for 2 h. The reaction mixture was poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a thick colorless oil (318 mg, 84% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 8.32−7.98 (m, 2H), 7.59−7.48 (m, 2H), 7.22−7.09 (m, 3H), 7.02−6.95 (m, 1H), 6.95−6.84 (m, 3H), 6.77−6.67 (m, 1H), 4.46 (s, 0.5H), 4.44 (s, 1.1H), 4.43 (s, 0.4H), 3.78−3.67 (m, 2H), 3.61−3.37 (m, 5H), 3.37−3.27 (m, 1H), 3.08−2.85 (m, 10H), 2.66−2.52 (m, 2H); δ_C (151 MHz, $CDCl_3$) 173.7, 173.6, 173.6, 171.0, 170.9, 170.7, 169.0, 168.9, 168.8, 155.1, 155.0, 154.9, 146.1, 145.9, 145.8, 138.1, 137.9, 137.7, 137.5, 137.1, 136.6, 136.2, 136.0, 136.0, 130.6, 130.4, 130.4, 130.3, 130.3, 129.4, 129.3, 129.3, 128.6, 128.4, 128.2, 128.0, 128.0, 121.9, 121.8, 121.8, 121.5, 111.4, 111.4, 111.3, 94.6, 94.6, 94.5, 67.2, 67.1, 67.0, 47.5, 47.3, 47.2, 47.1, 45.2, 44.9, 40.2, 40.1, 39.6, 37.6, 37.5, 37.4, 37.2, 37.1, 36.3, 36.1, 34.2, 34.1, 34.1, 33.9, 33.4, 28.5, 28.4, 28.3, 26.5, 26.1, 26.1; HRMS (ESI) for $C_{28}H_{34}IN_5O_4$, MH^+ 632.1728; found 632.1726 (Δ 0.3 ppm).

Macrocycle ***9b.*** Macrocyclization carried out as per the general procedure using **7b**. Obtained as a colorless oil (4.4 mg, 42%) as a mixture of at least four rotamers, δ_H (600 MHz, DMSO-d_6) 8.16 (t, *J* 6.0, 0.3H), 7.99 (t, *J* 5.8, 0.2H), 7.94 (t, *J* 5.8, 0.2H), 7.86 (t, *J* 5.9, 0.3H), 7.37−7.27 (m, 1H), 7.26−7.04 (m, 4H), 7.03−6.77 (m, 5H), 6.76−6.63 (m, 1H), 6.62−6.32 (m, 1H), 4.40 (s, 0.6H), 4.38 (s, 0.65H), 4.37 (s, 0.45H), 4.25 (s, 0.3H), 3.67−3.63 (m, 1H), 3.63−3.56 (m, 1H), 3.56−3.34 (m, 4.5H), 3.33−3.20 (m, 2.5H), 3.01−2.88 (m, 2H), 2.84 (d, *J* 7.8, 1H), 2.82−2.74 (m, 2H), 2.74−2.60 (m, 3.5H), 2.58−2.51 (m, 2H), 2.43−2.38 (d, *J* 7.5, 0.5H); δ_C (151 MHz, DMSO-d_6) 172.2, 171.9, 171.7, 170.8, 170.7, 170.2, 168.0, 167.7, 157.6, 157.1, 156.8, 156.7, 156.0, 155.8, 155.3, 155.2, 155.1, 154.7, 141.5, 141.4, 141.4, 141.3, 131.0, 130.8, 130.7, 130.5, 130.4, 130.3, 130.2, 130.2, 130.1, 130.1, 130.0, 129.8, 129.5, 127.3, 127.3, 127.2, 123.9, 123.8, 123.4, 121.0, 120.9, 120.8, 119.7, 119.3, 118.8, 118.5, 118.1, 117.9, 117.3, 117.2, 116.9, 116.6, 111.8, 111.6, 111.2, 110.8, 67.0, 67.0, 66.3, 47.8, 47.0, 46.7, 46.4, 45.9, 44.6, 44.1, 36.7, 36.0, 35.6, 35.1, 35.0, 34.9, 34.5, 33.8, 33.4, 33.1, 32.8, 32.7, 32.4, 32.2, 26.0, 25.8, 25.4, 25.0; HRMS (ESI) for $C_{31}H_{35}N_3O_5$, MH^+ 530.2649; found 530.2650 (Δ 0.2 ppm).

Macrocycle ***9c.*** Macrocyclization carried out as per the general procedure using **7c**. Obtained as a colorless oil (6.7 mg, 67%) as a mixture of at least four rotamers, δ_H (600 MHz, DMSO-d_6) 9.32−9.18 (m, 0.6H), 8.77 (s, 0.4H), 8.66 (t, *J* 5.9, 0.4H), 8.34−8.24 (m, 0.6H), 7.61−7.39 (m, 4H), 7.32−7.10 (m, 2H), 6.98 (td, *J* 7.8, 2.1, 0.3H), 6.93−6.75 (m, 2H), 6.60 (td, *J* 7.5, 2.9, 0.2H), 6.36 (td, *J* 7.4, 2.5, 0.5H), 4.58 (s, 0.8H), 4.57 (s, 0.5H), 4.52 (s, 0.4H), 4.50 (s, 0.3H), 3.71−3.50 (m, 3H), 3.49−3.36 (m, 3H), 3.35 (t, *J* 6.3, 0.5H), 3.29 (t, *J* 5.9, 0.5H), 3.22 (t, *J* 6.3, 0.5H), 3.01−2.76 (m, 9H), 2.68−2.60 (m, 2.5H), 2.53 (t, *J* 7.5, 1H); δ_C (151 MHz, DMSO-d_6) 173.0, 172.8, 172.2, 172.1, 170.0, 169.1, 169.1, 168.5, 168.4, 168.3, 158.4, 158.2, 158.1, 155.4, 155.0, 155.0, 154.8, 136.0, 135.8, 135.7, 135.2, 135.1, 135.1, 135.0, 134.4, 132.8, 132.3, 132.3, 132.2, 132.1, 132.0, 132.0, 130.8, 130.5, 130.3, 130.3, 130.2, 130.1, 129.9, 129.8, 129.7, 129.4, 129.2, 128.2, 128.2, 128.2, 128.1, 127.5, 127.4, 127.3, 127.0, 127.0, 126.9, 126.8, 126.6, 121.0, 120.8, 120.6, 120.5, 120.5, 120.2, 120.1, 119.3, 117.4, 115.4, 113.5, 111.7, 111.4, 111.0, 110.4, 66.8, 66.8, 66.3, 65.8, 48.8, 47.0, 46.7, 46.4, 45.9, 45.3, 44.7, 44.2, 40.1, 38.3, 38.1, 37.3, 36.3, 35.8, 35.4, 35.1, 34.8, 34.3, 33.9, 33.8, 33.5, 33.2, 33.1, 32.9, 32.6, 32.4, 26.5, 25.6, 25.3, 24.7, 24.5, 24.5, 24.3, 24.2; HRMS (ESI) for $C_{28}H_{33}N_5O_4$, MH^+ 504.2605; found 504.2605 (Δ 0.0 ppm).

Macrocycle ***9d.*** Macrocyclization carried out as per the general procedure using **7d**. Obtained as a colorless oil (9.0 mg, 89%) as a mixture of at least three rotamers, δ_H (500 MHz, $CDCl_3$) 7.99−7.79 (m, 1H), 7.56−7.47 (m, 2H), 7.39−7.35 (m, 1H), 7.29−7.12 (m, 2H), 7.10−7.01 (m, 1H), 7.00−6.65 (m, 3H), 6.54−6.40 (m, 1H), 4.53−4.46 (m, 2H), 3.88−3.56 (m, 5.7H), 3.43−3.38 (m, 0.3H), 3.21−3.17 (m, 2.6H), 3.06 (s, 0.4H), 3.01 (s, 1H), 2.91 (s, 2H), 2.83 (br s, 1H), 2.74−2.64 (m, 2H), 2.59−2.38 (m, 3H), 1.84−1.74 (m, 1H); δ_C (151 MHz, $CDCl_3$) 172.2, 171.8, 171.4, 171.3, 170.8, 168.2, 168.1, 167.8, 155.3, 154.6, 154.5, 135.9, 135.8, 134.5, 134.5, 133.6, 130.5, 130.1, 129.9, 129.3, 129.1, 128.8, 128.6, 127.7, 127.6, 127.4, 127.4, 121.8, 121.7, 121.3, 120.8, 120.7, 111.3, 111.1, 111.0, 67.9, 67.4, 67.4, 49.8, 47.5, 45.8, 45.5, 43.3, 43.0, 41.0, 40.8, 40.6, 40.3, 37.4, 37.4, 37.3, 37.1, 36.4, 35.6, 34.2, 32.7, 32.5, 32.4, 31.4, 29.7, 29.5, 28.6, 28.3, 23.4, 23.0, 22.8; HRMS (ESI) for $C_{28}H_{33}N_5O_4$, MH^+ 504.2605; found 504.2601 (Δ 0.8 ppm).

Macrocycle ***9e.*** Macrocyclization carried out as per the general procedure using **7e**. Carried out on 80 μmol scale in 2 mL of DMSO (40 mM reaction concentration). Obtained as a thick colorless oil (37 mg, 87%) as a mixture of at least four rotamers, δ_H (600 MHz, DMSO-d_6) 8.12 (t, *J* 5.6, 0.4H), 7.99 (t, *J* 5.7, 0.1H), 7.93 (t, *J* 5.4, 0.35H), 7.80 (t, *J* 5.6, 0.15H), 7.38−6.79 (m, 10H), 6.79−6.43 (m, 2H), 4.47 (br s, 0.1H), 4.42 (s, 1H), 4.39 (s, 0.7H), 4.36 (s, 0.2H), 3.63−3.54 (m, 2H), 3.47−3.37 (m, 5H), 3.34−3.19 (m, 3H), 2.93−2.90 (s, 2H), 2.86−2.80 (m, 2H), 2.78−2.66 (m, 5H), 2.38 (t, *J* 7.2, 0.5H), 2.18 (t, *J* 7.5, 0.5H);δ_C (151 MHz, $CDCl_3$) 173.5, 173.1, 173.0, 171.5, 171.3, 171.2, 168.4, 168.1, 158.1, 157.6, 157.4, 157.4, 156.9, 156.2, 155.3, 155.0, 155.0, 141.4, 141.1, 136.9, 136.8, 135.4, 130.6, 130.5, 130.3, 130.3, 130.3, 130.2, 130.1, 130.0, 129.6, 129.4, 129.3, 128.1, 128.1, 127.8, 124.7, 124.5, 124.1, 123.8, 123.5, 123.2, 121.8, 121.7, 121.6, 121.2, 119.3, 119.3, 118.7, 118.4, 118.3, 118.2, 117.2, 116.9, 116.6, 111.3, 111.2, 111.1, 67.1, 67.0, 66.9, 48.5, 47.9, 47.8, 47.7, 44.7, 43.9, 41.3, 41.0, 40.9, 40.3, 40.1, 40.1, 38.1, 37.4, 36.0, 35.7, 35.4, 35.1, 33.9, 33.7, 33.7, 33.5, 33.0, 29.8, 27.6, 25.7, 25.6; HRMS (ESI) for $C_{31}H_{35}N_3O_5$, MH^+ 530.2649; found 530.2645 (Δ 0.8 ppm).

Macrocycle ***9f.*** Macrocyclization carried out as per the general procedure using **7f**. Obtained as a colorless oil (7.2 mg, 71%) as a

mixture of at least three rotamers, δ_H (500 MHz, $CDCl_3$) 8.65−8.58 (m, 1H), 8.24 (t, *J* 6.4, 0.15H), 7.97 (t, *J* 6.1, 0.3H), 7.89 (t, *J* 6.1, 0.55H), 7.68 (d, *J* 7.8, 0.3H), 7.59−7.40 (m, 2.7H), 7.34−7.28 (m, 0.5H), 7.25−7.18 (m, 2.1H), 7.16−7.10 (m, 1.4H), 6.97 (t, *J* 7.4, 0.55H), 6.90 (t, *J* 7.4, 0.3H), 6.86 (t, *J* 7.3, 0.15H), 6.72 (d, *J* 8.3, 0.5H), 6.69 (d, *J* 8.3, 0.3H), 6.52 (d, *J* 8.1, 0.2H), 4.54 (s, 0.6H), 4.52 (s, 0.4H), 4.37 (s, 1H), 3.78 (s, 1.6H), 3.65 (s, 0.4H), 3.61−3.55 (m, 1H), 3.54−3.39 (m, 4H), 3.36 (q, *J* 6.2, 1H), 3.19 (s, 0.5H), 3.10 (s, 0.9H), 3.06 (s, 1.6H), 2.96 (s, 0.7H), 2.94−2.87 (m, 2.8H), 2.83−2.76 (m, 2.1H), 2.76 (s, 1.4H), 2.65 (t, *J* 7.6, 0.6H), 2.59 (t, *J* 7.3, 0.4H), 2.45 (t, *J* 6.8, 1H); δ_C (151 MHz, $CDCl_3$) 174.8,174.3, 172.8, 170.8, 170.5, 169.1, 168.5, 162.0, 155.2, 154.8, 138.5, 138.0, 137.2, 135.9, 135.7, 135.4, 133.9, 133.5, 133.3, 133.0, 132.5, 132.1, 131.5, 131.1, 130.9, 130.5, 130.4, 129.8, 129.1, 128.9, 128.3, 128.1, 127.6, 127.4, 127.2, 124.4, 124.3, 124.1, 122.3, 121.9, 121.8, 119.2, 119.0, 118.5, 117.3, 115.3, 111.3, 111.2, 111.0, 67.3, 67.1, 66.5, 47.7, 47.5, 47.4, 46.5, 46.1, 45.9, 40.0, 39.8, 39.7, 37.7, 37.5, 36.7, 36.5, 36.3, 35.9, 35.5, 34.6, 34.4, 34.3, 34.2, 33.6, 26.9, 26.6, 26.0, 24.5, 24.1, 23.8; HRMS (ESI) for $C_{28}H_{33}N_5O_4$, MH^+ 504.2605; found 504.2605 (Δ 0.0 ppm).

Macrocycle ***9g***. Macrocyclization carried out as per the general procedure using **7g**. Obtained as a colorless oil (5.4 mg, 54%) as a mixture of at least three rotamers, δ_H (600 MHz, DMSO-d_6) 8.35−8.03 (m, 1H), 7.92−7.78 (m, 2H), 7.59−7.50 (m, 1H), 7.47−7.30 (m, 2.5H), 7.27−7.12 (m, 2.5H), 6.90−6.78 (m, 2H), 4.43 (s, 1H), 4.41 (s, 0.3H), 4.38 (s, 0.7H), 3.57−3.37 (m, 5H), 3.19 (t, *J* 6.0, 0.5H), 3.11−3.02 (m, 3H), 3.00 (s, 0.5H), 2.94−2.75 (m, 4H), 2.72−2.51 (m, 4H), 2.25−2.17 (m, 1H); δ_C (151 MHz, DMSO-d_6) 173.0, 173.0, 172.2, 172.1, 170.1, 169.9, 169.6, 169.6, 168.4, 168.3, 168.2, 167.8, 158.5, 158.2, 158.0, 157.8, 155.4, 155.2, 155.1, 154.9, 145.7, 145.6, 145.0, 138.2, 138.0, 137.7, 137.6, 134.4, 134.4, 134.3, 134.2, 131.7, 131.1, 130.8, 130.3, 130.2, 130.0, 130.0, 130.0, 129.7, 129.7, 129.6, 129.6, 129.4, 129.4, 129.0, 127.7, 127.6, 127.5, 127.4, 127.1, 126.9, 126.7, 126.3, 124.3, 124.1, 124.0, 123.8, 123.7, 123.5, 123.3, 123.3, 121.2, 121.1, 121.0, 120.9, 119.3, 119.2, 119.2, 117.4, 115.5, 113.5, 111.7, 111.6, 111.3, 111.1, 66.7, 66.5, 66.4, 66.3, 48.0, 47.1, 46.7, 46.1, 45.7, 44.3, 43.7, 38.5, 38.2, 36.5, 36.4, 36.4, 36.2, 36.2, 35.9, 35.1, 34.2, 33.8, 33.5, 33.3, 32.3, 32.1, 26.8, 26.7, 26.0, 25.6, 25.3, 25.2, 25.1; HRMS (ESI) for $C_{28}H_{33}N_5O_4$, MH^+ 504.2605; found 504.2607 (Δ 0.4 ppm).

(1S,2R)-1-((3-Iodobenzyl)oxy)-N-methyl-1-phenylpropan-2-amine, ***11***. To a solution of ephedrine (826 mg, 5.00 mmol) in THF (20 mL) at 0 °C was slowly added KHMDS (0.5 M in PhMe, 11.0 mL, 5.50 mmol). After 15 min, 1-(bromomethyl)-3-iodobenzene (1.63 g, 5.50 mmol) was added and the reaction stirred at rt for 2 h before being poured into sat. aq $NaHCO_3$ (50 mL). This was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layers dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue purified by column chromatography to give the title compound as a pale brown oil (1.19 g, 63%), δ_H (600 MHz, $CDCl_3$) 7.67 (s, 1H), 7.60 (d, *J* 7.8, 1H), 7.40−7.36 (m, 2H), 7.35−7.29 (m, 3H), 7.26 (d, *J* 7.4, 1H), 7.06 (t, *J* 7.7, 1H), 4.44 (d, *J* 12.1, 1H), 4.32 (d, *J* 5.4, 1H), 4.24−4.20 (d, *J* 12.1, 1H), 2.81−2.76 (m, 1H), 2.34 (s, 3H), 1.28 (br s, 1H), 1.09 (d, *J* 6.4, 3H); δ_C (151 MHz, $CDCl_3$) 141.8, 140.4, 137.4, 137.4, 130.9, 129.4, 128.7, 128.3, 127.7, 95.2, 84.9, 70.7, 60.9, 34.8, 16.0; HRMS (ESI) for $C_{17}H_{20}INO$, MH^+ 382.0662; found 382.0670 (Δ 2.1 ppm).

tert-Butyl ((S)-3-(3-Hydroxyphenyl)-1-(((1S,2R)-1-((3-iodobenzyl)oxy)-1-phenylpropan-2-yl)(methyl)amino)-1-oxopropan-2-yl)carbamate, ***12a***. To **11** (189 mg, 0.490 mmol) were added a premixed solution of *N*-Boc-*m*-Tyr-OH (138 mg, 0.490 mmol), PyBOP (255 mg, 0.490 mmol), and DIPEA (171 μL, 0.981 mmol) in CH_2Cl_2 (4 mL) and the resulting solution stirred at rt for 16 h. Further *N*-Boc-*m*-Tyr-OH (69 mg, 0.245 mmol), PyBOP (127 mg, 0.245 mmol), and DIPEA (85 μL, 0.490 mmol) were added in DMF (2 mL), and the solution was heated to 80 °C for 1 h before being cooled to rt and washed with sat. aq citric acid (50 mL) and sat. aq $NaHCO_3$ (50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue purified by column chromatography to give the title compound as a thick colorless oil (271 mg, 86%) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 8.07 (d, *J* 8.3, 0.5H), 7.88 (d, *J* 8.4, 0.5H), 7.61−7.54 (m, 3H), 7.48−7.43 (m, 0.5H), 7.35−7.29 (m, 3.5H), 7.26−7.24 (m, 1H), 7.21−7.17 (m, 1H), 7.13−7.07 (m, 1H), 7.04 (t, *J* 7.8, 1H), 6.74−6.70 (m, 2H), 6.69−6.65 (m, 1H), 5.37 (d, *J* 9.0, 0.7H), 5.22 (d, *J* 8.3, 0.3H), 4.78−4.62 (m, 1H), 4.40−4.32 (m, 1H), 4.32−4.28 (m, 0.7H), 4.25 (d, *J* 6.6, 0.3H), 4.12−4.07 (m, 1H), 3.86−3.78 (m, 0.3H), 2.96−2.91 (m, 0.3H), 2.83−2.73 (m, 2H), 2.73−2.69 (m, 1H), 2.57−2.52 (m, 0.7H), 2.51−2.44 (m, 0.7H), 1.45 (s, 3H), 1.36 (s, 6H), 1.20 (d, *J* 6.8, 2.1H), 0.73 (d, *J* 6.5, 0.9H); δ_C (151 MHz, $CDCl_3$) 172.3, 172.1, 157.1, 156.8, 155.4, 154.8, 143.5, 140.7, 140.4, 139.0, 138.1, 138.0, 137.7, 136.7, 136.7, 136.6, 136.5, 130.2, 130.2, 129.9, 129.7, 129.1, 128.9, 128.5, 128.4, 128.2, 128.0, 127.1, 126.9, 126.9, 125.5, 121.0, 120.9, 120.3, 116.6, 116.5, 114.3, 114.2, 109.4, 105.0, 94.4, 94.4, 84.2, 83.8, 80.0, 79.7, 70.1, 70.0, 57.9, 51.5, 41.1, 39.3, 29.0, 28.5, 28.4, 13.6, 12.1; HRMS (ESI) for $C_{31}H_{37}IN_2O_5$, MH^+ 645.1820; found 645.1809 (Δ 1.7 ppm).

tert-Butyl ((S)-3-(1H-Imidazol-4-yl)-1-(((1S,2R)-1-((3-iodobenzyl)oxy)-1-phenylpropan-2-yl)(methyl)amino)-1-oxopropan-2-yl)carbamate, ***12b***. To **11** (381 mg, 1.00 mmol) was added a premixed solution of *N*-Boc-His-OH (511 mg, 2.00 mmol), HATU (760 mg, 2.00 mmol), and DIPEA (699 μL, 4.00 mmol) in CH_2Cl_2 (5 mL), and the resulting solution was stirred at rt for 16 h. The reaction mixture was washed with sat. aq citric acid (50 mL) and sat. aq $NaHCO_3$ (50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue purified by column chromatography to give the title compound as a thick colorless oil (371 mg, 60%) as a mixture of rotamers, δ_H (500 MHz, $CDCl_3$) 8.44 (br s, 1H), 7.64−7.56 (m, 2H), 7.51 (s, 1H), 7.37−7.27 (m, 5H), 7.21 (d, *J* 7.5, 1H), 7.05 (t, *J* 7.7, 1H), 6.77 (s, 0.3H), 6.67 (s, 0.7H), 5.47 (d, *J* 8.2, 0.7H), 5.47 (d, *J* 8.2, 0.3H), 4.90−4.74 (m, 0.7H), 4.74−4.68 (m, 0.3H), 4.61−4.49 (m, 0.7H), 4.38−4.32 (m, 2H), 4.19−4.11 (m, 1H), 4.01−3.94 (m, 0.3H), 2.94−2.85 (m, 0.6H), 2.80 (s, 2.1H), 2.77 (s, 0.9H), 2.43−2.31 (m, 1.4H), 1.42 (s, 2H), 1.36 (s, 7H), 1.29 (d, *J* 6.8, 2.4H), 1.10 (d, *J* 6.3, 0.6H); δ_C (151 MHz, $CDCl_3$) 172.6, 156.3, 155.9, 141.3, 141.1, 139.6, 138.9, 137.6, 137.5, 137.4, 137.4, 135.9, 135.7, 131.0, 131.0, 129.7, 129.3, 129.3, 129.2, 128.2, 127.7, 127.7, 95.2, 95.2, 84.6, 84.6, 80.8, 80.5, 70.9, 70.7, 58.2, 51.1, 32.5, 31.9, 30.6, 29.9, 29.2, 29.1, 15.0, 14.2; HRMS (ESI) for $C_{28}H_{35}IN_4O_4$, MH^+ 619.1776; found 619.1777 (Δ 0.2 ppm).

(S)-tert-Butyl 3-(((3-Iodobenzyl)oxy)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate, ***14***. To a solution of (*S*)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (750 mg, 4.60 mmol) in CH_2Cl_2 (10 mL) was added Boc_2O (2.39 g, 4.60 mmol), and the reaction mixture was stirred at rt for 3 h before being washed with 0.5 M HCl (100 mL) and brine (50 mL), dried (Na_2SO_4) and the solvent removed in vacuo. To a solution of this crude Boc-protected amine in DMF (20 mL) at 0 °C was added NaH (95%, 165 mg, 6.90 mmol). The reaction mixture was stirred for 15 min before addition of 1-(bromomethyl)-3-iodobenzene (2.05 g, 6.90 mmol). The solution was allowed to warm to rt and stirred for 3 h before being partitioned between EtOAc (50 mL) and sat. aq $NaHCO_3$ (50 mL). The organic layer was washed with H_2O/brine (1:1, 5 × 30 mL), the combined aqueous layers were extracted with CH_2Cl_2 (30 mL), the combined organic layers were dried (Na_2SO_4), and the solvent removed in vacuo. The resulting residue was purified by column chromatography to give the title compound as a colorless oil (1.10 g, 50% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 7.67−7.55 (m, 2H), 7.24−7.17 (m, 3H), 7.17−7.06 (m, 2H), 7.04 (s, 3H), 4.79 (s, 0.5H), 4.71 (d, *J* 16.8, 1H), 4.54 (s, 0.5H), 4.47−4.37 (m, 2H), 4.28 (d, *J* 16.8, 1H), 3.45 (s, 1H), 3.22 (m, 1H), 3.12−3.00 (m, 1H), 2.97−2.84 (m, 1H), 1.55−1.47 (m, 9H); δ_C (151 MHz, $CDCl_3$) 155.3, 140.9, 140.8, 136.7, 136.6, 136.3, 133.4, 133.1, 133.0, 130.1, 129.2, 128.9, 126.9, 126.6, 126.4, 126.1, 94.4, 80.1, 72.1, 71.9, 69.9, 69.6, 49.8, 48.1, 43.8, 43.4, 30.4, 30.1, 28.6; HRMS (ESI) for $C_{22}H_{26}INO_3$, MH^+ 480.1030; found 480.1030 (Δ 0.0 ppm).

tert-Butyl ((S)-3-(3-Hydroxyphenyl)-1-((S)-3-(((3-iodobenzyl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)-1-oxopropan-2-yl)carbamate, ***15a***. To **14** (192 mg, 0.400 mmol) was added 4 M HCl/dioxane (5 mL), and the solution was stirred for 1 h. The solvent was removed in vacuo to give the crude amine. To this amine was added a premixed solution of *N*-Boc-*m*-Tyr-OH (225 mg, 0.800 mmol), HATU (304 mg, 0.800 mmol), and DIPEA (279 μL, 1.60 mmol) in CH_2Cl_2 (5 mL), and the resulting solution was stirred at rt for 16 h.

The reaction mixture was washed with sat. aq citric acid (20 mL) and sat. aq $NaHCO_3$ (50 mL). Each aqueous layer was extracted with CH_2Cl_2 (30 mL), the combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a very pale brown oil (182 mg, 71% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 7.60 (s, 0.5H), 7.57 (dd, *J* 13.6, 7.9, 1H), 7.49 (s, 0.5H), 7.21−7.06 (m, 5H), 7.05−6.94 (m, 2.5H), 6.83 (dd, *J* 15.5, 7.5, 1H), 6.78 (s, 1H), 6.75−6.69 (m, 1.5H), 5.59 (d, *J* 8.5, 0.6H), 5.51 (d, *J* 8.7, 0.4H), 5.12−5.06 (m, 0.6H), 4.97−4.92 (m, 0.4H), 4.74 (d, *J* 17.6, 0.6H), 4.62 (d, *J* 15.7, 0.4H), 4.42 (s, 0.8H), 4.30−4.25 (m, 1.2H), 4.08−4.00 (m, 0.6H), 3.72 (d, *J* 15.6, 0.4H), 3.39 (dd, *J* 9.5, 6.5, 0.4H), 3.20 (t, *J* 8.6, 0.6H), 3.08−2.83 (m, 4H), 2.82 (s, 1H), 2.51 (d, *J* 15.9, 0.5H), 2.15 (dd, *J* 6.0, 4.9, 1H), 1.42−1.35 (m, 9H); δ_C (151 MHz, $CDCl_3$) 173.2, 172.6, 157.5, 157.3, 156.0, 155.9, 141.2, 141.2, 138.7, 138.7, 137.6, 137.4, 137.4, 137.1, 133.5, 132.5, 132.4, 132.3, 131.0, 131.0, 130.7, 130.6, 129.6, 129.3, 128.1, 127.8, 127.7, 127.4, 127.4, 127.3, 127.2, 126.8, 122.2, 122.1, 117.6, 117.2, 115.2, 115.1, 95.2, 95.1, 80.9, 80.7, 72.9, 72.6, 70.1, 69.7, 52.8, 52.8, 52.4, 48.4, 45.7, 43.8, 41.8, 41.1, 39.6, 30.6, 30.5, 29.2; HRMS (ESI) for $C_{31}H_{35}IN_2O_5$, MH^+ 643.1663; found 643.1660 (Δ 0.5 ppm).

tert-Butyl ((S)-3-(1H-Imidazol-4-yl)-1-((S)-3-(((3-iodobenzyl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)-1-oxopropan-2-yl)carbamate, ***15b****.* To **14** (192 mg, 0.400 mmol) was added 4 M HCl/dioxane (5 mL), and the solution was stirred for 1 h. The solvent was removed in vacuo to give the crude amine. To this amine was added a premixed solution of *N*-Boc-His-OH (204 mg, 0.800 mmol), HATU (304 mg, 0.800 mmol), and DIPEA (279 μL, 1.60 mmol) in CH_2Cl_2 (5 mL), and the resulting solution was stirred at rt for 16 h. The reaction mixture was washed with sat. aq citric acid (20 mL) and sat. aq $NaHCO_3$ (50 mL). Each aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a very pale brown oil (146 mg, 59% over two steps) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 9.18 (br s, 0.5H), 7.60−7.47 (m, 2.5H), 7.37 (s, 0.5H), 7.20−6.95 (m, 6H), 6.83 (s, 0.5H), 6.78 (s, 0.5H), 5.77 (d, *J* 7.9, 0.5H), 5.62 (d, *J* 8.0, 0.5H), 5.23−5.15 (m, 0.5H), 5.14−5.04 (m, 0.5H), 5.01−4.93 (m, 0.5H), 4.89 (d, *J* 17.7, 0.5H), 4.80 (d, *J* 15.9, 0.5H), 4.43−4.27 (m, 3H), 4.19 (d, *J* 17.8, 0.5H), 3.75−3.57 (m, 0.5H), 3.48−3.41 (m, 0.5H), 3.37−3.27 (m, 1H), 3.27−3.18 (m, 0.5H), 3.14−2.94 (m, 2.5H), 2.81−2.64 (m, 1H), 1.41−1.35 (m, 9H); δ_C (151 MHz, $CDCl_3$) 172.3, 171.3, 155.3, 140.4, 139.9, 137.0, 136.7, 136.6, 136.2, 135.2, 135.1, 132.5, 131.7, 131.5, 131.4, 130.3, 130.2, 129.1, 128.8, 127.4, 127.0, 126.7, 126.6, 126.4, 126.1, 94.5, 94.3, 80.0, 79.8, 72.2, 72.1, 71.2, 69.3, 53.7, 53.7, 52.3, 51.2, 50.9, 47.5, 44.4, 42.7, 42.0, 38.7, 31.9, 30.2, 30.0, 29.7, 29.7, 29.5, 28.4, 28.4, 18.1, 12.3; HRMS (ESI) for $C_{28}H_{33}IN_4O_4$, MH^+ 617.1619; found 617.1615 (Δ 0.6 ppm).

(S)-3-(((3-Iodobenzyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline, ***16****.* To a solution of (*S*)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (920 mg, 5.64 mmol) in THF (20 mL) at 0 °C was slowly added KHMDS (0.5 M in PhMe, 12.4 mL, 6.20 mmol). After 45 min, 1-(bromomethyl)-3-iodobenzene (2.18 g, 7.33 mmol) was added and the reaction stirred at rt for 2 h before being poured into 1 M HCl (50 mL). This was washed with CH_2Cl_2 (50 mL), and the aqueous layer basified with $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a colorless oil (1.45 g, 68%), δ_H (500 MHz, $CDCl_3$) 7.82 (s, 1H), 7.72 (d, *J* 7.9, 1H), 7.41 (d, *J* 7.6, 1H), 7.25−7.20 (m, 2H), 7.20−7.15 (m, 2H), 7.15−7.10 (m, 1H), 4.59 (s, 2H), 4.19 (d, *J* 15.6, 1H), 4.13 (d, *J* 15.7, 1H), 3.70 (dd, *J* 9.2, 3.8, 1H), 3.58 (dd, *J* 8.9, 7.7, 1H), 3.27 (ddd, *J* 14.4, 7.6, 3.8, 1H), 2.78 (dd, *J* 16.0, 4.2, 1H), 2.73 (dd, *J* 16.0, 10.6, 1H), 2.27, (br s, 1H); δ_C (126 MHz, $CDCl_3$) 141.1, 137.2, 137.0, 136.0, 134.5, 130.7, 129.7, 127.3, 126.7, 126.6, 126.2, 95.0, 74.9, 72.9, 53.7, 48.6, 32.0; HRMS (ESI) for $C_{17}H_{18}INO$, MH^+ 380.0506; found 380.0510 (Δ 1.1 ppm).

(S)-tert-Butyl (3-(3-(((3-Iodobenzyl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)propyl)carbamate, ***17****.* A solution of **16** (379 mg, 1.00 mmol), 3-((*N*-Boc)amino)propyl methanesulfonate (507 mg, 2.00 mmol), NaI (300 mg, 2.00 mmol), and DIPEA (697 μL, 4.00 mmol) in DMF (10 mL) was stirred at 65 °C for 14 h. After cooling, the reaction mixture was partitioned between EtOAc (50 mL) and sat. aq $NaHCO_3$ (50 mL). The organic layer was washed with H_2O/brine (1:1, 2 × 30 mL), the combined aqueous layers were extracted with EtOAc (3 × 30 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting residue was purified by column chromatography to give the title compound as a pale yellow oil (412 mg, 77%), δ_H (500 MHz, $CDCl_3$) 7.75 (s, 1H), 7.69 (d, *J* 7.9, 1H), 7.38−7.34 (m, 1H), 7.27−7.20 (m, 2H), 7.20−7.09 (m, 3H), 5.41 (br s, 1H), 4.55, 4.54 (ABq, J_{AB} 12.4, 1H), 3.98−3.84 (m, 2H), 3.71 (dd, *J* 9.4, 6.0, 1H), 3.57−3.49 (m, 1H), 3.39−3.33 (m, 1H), 3.33−3.23 (m, 2H), 3.04 (dd, *J* 16.5, 5.0, 1H), 2.90−2.80 (m, 3H), 1.89−1.78 (m, 2H), 1.49 (s, 9H); δ_C (151 MHz, $CDCl_3$) 156.3, 140.7, 136.8, 136.6, 133.5, 130.3, 129.0, 126.8, 126.7, 126.1, 94.5, 79.0, 72.5, 70.1, 57.0, 51.5, 39.4, 29.8, 29.6, 28.6, 27.0; HRMS (ESI) for $C_{25}H_{33}IN_2O_3$, MH^+ 537.1609; found 537.1607 (Δ 0.4 ppm).

(S)-2-(3-Hydroxyphenyl)-N-(3-(3-(((3-iodobenzyl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)propyl)acetamide, ***18a****.* A 4 M HCl/dioxane (1.60 mL, 6.40 mmol) solution was added to **17** (429 mg, 0.800 mmol), and the resulting solution was stirred at rt for 1.5 h. The solvent was removed in vacuo to give the crude amine. To a portion of this amine (175 mg, 0.400 mmol) was added a premixed solution of 2-(3-hydroxyphenyl)acetic acid (122 mg, 0.800 mmol), HATU (304 mg, 0.800 mmol), and DIPEA (279 μL, 1.60 mmol) in CH_2Cl_2/DMF (1:1, 4 mL), and the resulting solution was stirred at rt for 16 h. The reaction mixture was added to excess $LiOH·H_2O$ in MeOH/H_2O (10 mL) and stirred at rt for 1 h. The reaction mixture was partitioned between EtOAc (30 mL) and 2 M HCl (20 mL), and the organic layer was washed with sat. aq $NaHCO_3$ (50 mL). Each aqueous layer was extracted with EtOAc (30 mL), the combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a pale yellow oil (199 mg, 87% over two steps), δ_H (600 MHz, $CDCl_3$) 7.64 (s, 1H), 7.60 (d, *J* 7.9, 1H), 7.23 (d, *J* 7.5, 2H), 7.20−7.14 (m, 2H), 7.09 (d, *J* 6.6, 1H), 7.07−7.00 (m, 3H), 6.73 (s, 1H), 6.69 (dd, *J* 8.1, 2.0, 1H), 6.56 (d, *J* 7.4, 1H), 4.40 (s, 2H), 3.80 (d, *J* 15.9, 1H), 3.64 (d, *J* 15.9, 1H), 3.53 (dd, *J* 10.0, 6.5, 1H), 3.42 (dd, *J* 10.0, 5.6, 1H), 3.37−3.29 (m, 3H), 3.30−3.23 (m, 2H), 2.90 (dd, *J* 16.8, 5.4, 1H), 2.77−2.67 (m, 3H), 1.70 (p, *J* 6.0, 2H); δ_C (151 MHz, $CDCl_3$) 172.4, 157.1, 140.3, 137.0, 136.6, 136.5, 132.9, 132.3, 130.4, 130.1, 129.1, 127.2, 127.0, 126.5, 120.9, 116.3, 114.8, 94.6, 72.5, 69.9, 57.3, 51.4, 50.8, 43.7, 39.0, 28.6, 25.4; HRMS (ESI) for $C_{28}H_{31}IN_2O_3$, MH^+ 571.1452; found 571.1454 (Δ 0.4 ppm).

(S)-2-(3-Hydroxyphenyl)-N-(3-(3-(((3-iodobenzyl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)propyl)acetamide, ***18b****.* A 4 M HCl/dioxane (1.60 mL, 6.40 mmol) was added to **17** (429 mg, 0.800 mmol), and the resulting solution was stirred at rt for 1 h. The solvent was removed in vacuo to give the crude amine. To a portion of this amine (175 mg, 0.400 mmol) was added a premixed solution of 2-(1*H*-imidazol-4-yl)acetic acid (101 mg, 0.800 mmol), HATU (304 mg, 0.800 mmol), and DIPEA (279 μL, 1.60 mmol) in CH_2Cl_2/DMF (1:1, 4 mL), and the resulting solution was stirred at rt for 16 h. The reaction mixture was partitioned between EtOAc (30 mL) and 1 M HCl (20 mL), and the organic layer was washed with sat. aq $NaHCO_3$ (50 mL). Each aqueous layer was extracted with EtOAc (30 mL), the combined organic layers were dried (Na_2SO_4), the solvent was removed in vacuo, and the resulting residue was purified by column chromatography to give the title compound as a pale yellow oil (330 mg, 76% over two steps), δ_H (500 MHz, $CDCl_3$); 7.63 (s, 1H), 7.60−7.53 (m, 2H), 7.43 (s, 1H), 7.22 (d, *J* 7.6, 1H), 7.17−7.10 (m, 3H), 7.10−7.06 (m, 1H), 7.04 (t, *J* 7.7, 1H), 7.02−6.98 (m, 1H), 6.70 (s, 1H), 4.42, 4.39 (ABq, J_{AB} 12.4, 1H), 3.76 (d, *J* 15.8, 1H), 3.68 (d, *J* 15.8, 1H), 3.58 (dd, *J* 9.6, 6.0, 1H), 3.40 (s, 2H), 3.38 (d, *J* 6.3, 1H), 3.32 (p, *J* 6.4, 2H), 3.18 (p, *J* 5.8, 1H), 2.88 (dd, *J* 16.4, 5.2, 1H), 2.75−2.65 (m, 3H), 1.70 (p, *J* 6.4, 2H); δ_C (126 MHz, $CDCl_3$) 170.6, 140.6, 136.8, 136.5, 135.3, 134.0, 133.7, 131.9, 130.3, 129.1, 126.8, 126.7, 126.6, 126.0, 117.5, 94.5, 72.4, 70.3, 57.0, 51.7, 51.3, 39.0, 35.0,

dx.doi.org/10.1021/jo302089f | *J. Org. Chem.* 2012, 77, 11079−11090

29.7, 26.4; HRMS (ESI) for $C_{25}H_{29}IN_4O_2$, MH^+ 545.1408; found 545.1403 (Δ 0.9 ppm).

Macrocycle ***19a***. Macrocyclization carried out as per the general procedure using **12a**. Obtained as a pale brown oil (6.2 mg, 74%), δ_H (600 MHz, $CDCl_3$) 7.38 (t, *J* 7.8, 1H), 7.36−7.32 (m, 2H), 7.29−7.24 (m, 3H), 7.17 (t, *J* 7.8, 1H), 7.15 (d, *J* 7.7, 1H), 7.09−7.05 (m, 2H), 6.72 (m, 1H), 6.68 (m, 1H), 6.45 (d, *J* 7.4, 1H), 4.67 (d, *J* 13.6, 1H), 4.48 (s, 1H), 4.45−4.39 (m, 1H), 4.19 (d, *J* 13.5, 1H), 3.08−2.90 (m, 2H), 2.62−2.60 (m, 4H), 2.08 (br s, 2H),1.06 (d, *J* 7.0, 3H); δ_C (151 MHz, $CDCl_3$) 158.9, 157.5, 140.4, 139.4, 138.3, 130.6, 129.9, 128.4, 127.7, 127.5, 125.0, 123.0, 119.4, 119.2, 118.9, 115.9, 81.2, 68.5, 55.3, 41.1, 30.9, 9.5; HRMS (ESI) for $C_{26}H_{28}N_2O_3$, MH^+ 417.2173; found 417.2173 (Δ 0.0 ppm).

Macrocycle ***19b***. Macrocyclization carried out as per the general procedure using **12b**. Obtained as a pale brown oil (5.8 mg, 73%) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 7.67 (s, 1H), 7.40−7.32 (m, 6H), 7.28 (s, 1H), 6.97−6.91 (m, 2H), 6.90 (s, 1H), 5.00 (s, 1H), 4.85 (d, *J* 16.6, 1H), 4.76−4.69 (m, 1H), 4.35 (d, *J* 16.7, 0.9H), 4.28 (d, *J* 16.1, 0.1H), 4.07 (br s, 0.9H), 3.95 (br s, 0.1H), 3.25−3.16 (m, 1H), 3.04−2.95 (m, 1H), 2.90 (s, 0.3H), 2.80 (s, 2.7H), 1.85 (brs, 1H), 1.06 (d, *J* 7.7, 2.7H), 1.01 (d, *J* 7.5, 0.3H); δ_C (151 MHz, $CDCl_3$) 177.9, 140.8, 140.2, 139.9, 138.9, 138.3, 129.8, 128.6, 127.8, 127.0, 126.7, 126.3, 124.7, 124.3, 120.1, 83.2, 66.3, 55.8, 54.3, 35.7, 32.1, 9.6; HRMS (ESI) for $C_{23}H_{26}N_4O_2$, MH^+ 391.2128; found 391.2131 (Δ 0.8 ppm).

Macrocycle ***20a***. Macrocyclization carried out as per the general procedure using **15a**. Obtained as a pale brown oil (8.4 mg, 82%), δ_H (500 MHz, $CDCl_3$) 7.43−7.36 (m, 1H), 7.32−7.27 (m, 1H), 7.23−7.13 (m, 4H), 7.08−7.01 (m, 3H), 6.85 (d, *J* 7.0, 1H), 6.80 (s, 2H), 4.79 (br s, 1H), 4.64−4.53 (m, 2H), 4.43−4.06 (m, 3H), 3.66−3.57 (m, 1H), 3.26−3.19 (m, 1H), 3.15 (br s, 1H), 3.11−3.02 (m, 1H), 3.02−2.81 (m, 2H), 1.75 (br s, 2H); δ_C (151 MHz, $CDCl_3$) 173.9, 158.1, 156.3, 139.7, 139.3, 134.7, 133.6, 130.3, 130.0, 128.7, 127.6, 126.4, 125.4, 125.2, 121.7, 120.4, 119.1, 118.1, 115.2, 71.7, 70.0, 53.0, 48.9, 45.6, 42.2, 30.0; HRMS (ESI) for $C_{26}H_{26}N_2O_3$, MH^+ 415.2016; found 415.2013 (Δ 0.7 ppm).

Macrocycle ***20b***. Macrocyclization carried out as per the general procedure using **15b**. Obtained as a pale brown oil (6.9 mg, 89%) as a mixture of rotamers, δ_H (600 MHz, $CDCl_3$) 7.65 (s, 1H), 7.43−7.38 (m, 1H), 7.38−7.34 (m, 1H), 7.20−7.15 (m, 1H), 7.15−7.10 (m, 2H), 7.08−7.01 (m, 2H), 6.93 (s, 2H), 4.93−4.82 (m, 1H), 4.73 (d, *J* 16.8, 0.1H), 4.67 (d, *J* 15.2, 0.9H), 4.57 (d, *J* 16.2, 1H), 4.45 (d, *J* 16.3, 0.9H), 4.40 (d, *J* 16.0, 0.1H), 4.20 (br s, 1H), 4.13−4.06 (m, 1H), 3.88 (d, *J* 10.2, 1H), 3.54 (d, *J* 10.1, 1H), 3.26−3.14 (m, 2H), 3.09−2.93 (m, 2H), 2.16 (s, 1H); δ_C (151 MHz, $CDCl_3$) 176.2, 141.0, 140.2, 139.8, 138.5, 135.1, 129.9, 128.5, 127.6, 126.5, 125.6, 124.7, 124.5, 124.2, 119.6, 72.3, 68.7, 53.9, 51.3, 46.6, 34.4, 30.8, 29.8; HRMS (ESI) for $C_{23}H_{24}N_4O_2$, MH^+ 389.1972; found 389.1974 (Δ 0.5 ppm).

Macrocycle ***21a***. Macrocyclization carried out as per the general procedure using **18a**. Obtained as a pale brown oil (7.5 mg, 84%), δ_H (600 MHz, $CDCl_3$) 7.37 (t, *J* 7.8, 1H), 7.31 (t, *J* 7.8, 1H), 7.17−7.12 (m, 2H), 7.10 (dd, *J* = 8.2, 2.4, 1H), 7.08−7.02 (m, 2H), 7.01−6.94 (m, 3H), 6.81 (s, 1H), 6.57 (br s, 1H), 6.51 (s, 1H), 4.46 (s, 2H), 3.77 (d, *J* 15.1, 1H), 3.57−3.48 (m, 2H), 3.47 (s, 1H), 3.44 (m, 2H), 3.24 (dd, *J* 9.4, 6.6, 1H), 3.16−3.06 (m, 2H), 3.01−2.94 (m, 1H), 2.84 (dd, *J* 16.2, 5.6, 1H), 2.74−2.55 (m, 3H), 1.78−1.67 (m, 1H), 1.67−1.56 (m, 1H); δ_C (151 MHz, DMSO-d_6) 169.8, 157.4, 156.5, 140.8, 138.8, 134.8, 133.7, 130.1, 128.6, 126.2, 126.1, 125.5, 125.1, 122.4, 118.4, 118.3, 118.1, 115.9, 71.6, 68.9, 56.8, 51.6, 50.8, 42.8, 36.7, 30.8, 27.4; HRMS (ESI) for $C_{28}H_{30}N_2O_3$, MH^+ 443.2329; found 443.2349 (Δ 4.5 ppm).

Macrocycle ***21b***. Macrocyclization carried out as per the general procedure using **18b**. Obtained as a colorless oil (6.7 mg, 80%), δ_H (600 MHz, DMSO-d_6) 8.22 (s, 1H), 8.11 (t, *J* 5.3, 1H), 7.59 (dd, *J* 7.8, 2.2, 1H), 7.48−7.43 (m, 2H), 7.37 (s, 1H), 7.17−7.13 (m, 2H), 7.12−7.09 (m, 2H), 7.04 (d, *J* 7.3, 1H), 4.79 (d, *J* 15.3, 1H), 4.45 (d, *J* 15.3, 1H), 3.76 (d, *J* 15.7, 1H), 3.71 (dd, *J* 9.0, 4.4, 1H), 3.56 (d, *J* 15.7, 1H), 3.44−3.39 (m, 1H), 3.32−3.24 (m, 3H), 3.24−3.17 (m, 1H), 3.17−3.10 (m, 1H), 3.03 (dd, *J* 16.1, 5.8, 1H), 2.86−2.78 (m, 1H), 2.73 (d, *J* 16.2, 1H), 2.72−2.66 (m, 1H), 1.82−1.73 (m, 1H), 1.69−1.61 (m, 1H); δ_C (151 MHz, DMSO-d_6) 169.8, 141.5, 139.1, 137.0, 134.9, 134.8, 133.3, 130.0, 128.9, 126.3, 126.2, 125.5, 124.0, 117.7, 117.0, 114.7, 70.1, 68.4, 57.5, 53.9, 49.4, 40.1, 37.4, 37.2, 30.9, 27.9; HRMS (ESI) for $C_{25}H_{28}N_4O_2$, MH^+ 417.2285; found 417.2286 (Δ 0.2 ppm).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Selected iterative array screening results, HPLC traces, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Bill Farrell and Loanne Chung (Pfizer) for SFC purification and Pfizer Worldwide R&D for funding.

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