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Synthesis and NMR Analysis of a Conformationally Controlled β-Turn Mimetic Torsion Balance

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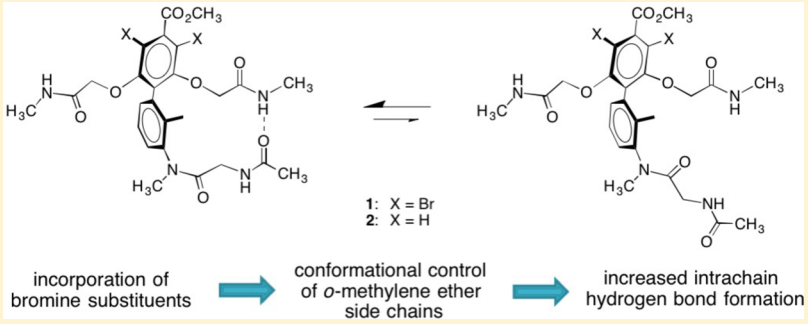
Supporting Information



ABSTRACT: The molecular torsion balance concept was applied to a new conformationally controlled scaffold and synthesized to accurately evaluate pairwise amino acid interactions in an antiparallel β-sheet motif. The scaffold's core design combines (*ortho*-tolyl)amide and *o*,*o*,*o*′-trisubstituted biphenyl structural units to provide a geometry better-suited for intramolecular hydrogen bonding. Like the dibenzodiazocine hinge of the traditional torsion balance, the (*ortho*-tolyl)amide unit offers restricted rotation around an N-aryl bond. The resulting two-state folding model is a powerful template for measuring hydrogen bond stability between two competing sequences. The aim of this study was to improve the alignment between the amino acid sequences attached to the upper and lower aromatic rings in order to promote hydrogen bond formation at the correct distance and antiparallel orientation. Bromine substituents were introduced *ortho* to the upper side chains and compared to a control to test our hypothesis. Hydrogen bond formation has been identified between the NH amide proton of the upper side chain (proton donor) and glycine acetamide of the lower side chain (proton acceptor).

INTRODUCTION

Thoughtful evaluations of new experimental data can enhance our understanding of the various molecular forces that influence biological phenomena. The "molecular torsion balance" was first conceived as a model for biomolecule folding that would serve as a tool to measure the relative free energy of two conformationally distinct thermodynamic states.[1−3]

Enzyme and drug-receptor binding rely upon many inter- and intramolecular interactions. Efforts have been made to design secondary protein mimetic structures such as antiparallel β-sheet mimics that accurately model protein folding.[4−6] Gellman's β-hairpin motif[5] was developed to measure the folding and stability of β-sheets in water. That study provided valuable NMR data to relate the thermodynamic parameters between two conformational states. β-Sheet mimics developed by Nowick and co-workers[6] are based on a combination of natural and synthetic amino acids to induce peptide interactions of a protein folded state. Folding within a β-strand resulted from the insertion of an artificial amino acid, "Orn(*i*-PrCO-Hao)", into a peptide sequence that acts to replace the β-turn motif.

A peptide torsion balance hybrid (Figure 1) was designed to support an investigation of pairwise amino acid interactions in an antiparallel orientation of a β-sheet and the effects of changes in amino acids on a short β-strand.[7] During the design stage we determined that the original dibenzodiazocine torsion balance scaffold was not useful. Molecular modeling showed that the scaffold did not have the correct shape (1) to match the ends of an antiparallel β-sheet and (2) to establish the distances and orientations required for intramolecular peptidomimetic hydrogen bond formation. We therefore turned to an (*ortho*-tolyl)amide core structure. The desired barrier between the two competing folded states (Figure 1) would be imposed by the restricted rotation around an aryl−nitrogen bond.[7,8]

The final design also incorporated an *o*,*o*,*o*′-trisubstituted biphenyl unit. Thus, both the aryl−aryl[9] and N−aryl[8] bonds are sites having restricted single bond rotation.[7] Although *ortho*-substituents are mostly responsible for the biaryl bond restriction, the incorporation of additional *meta*-substituents is known to introduce further rotational restriction due to a "buttressing effect".[9a,b] An *ortho* substituent is well-known to constrain rotation about the N−aryl bond.[8,10] This was reported by Mislow[8] for acyclic and cyclic (*ortho*-tolyl)amides and has been employed by the Curran group[10] in their development of *o*-haloanilide atropisomer selective reactivity.

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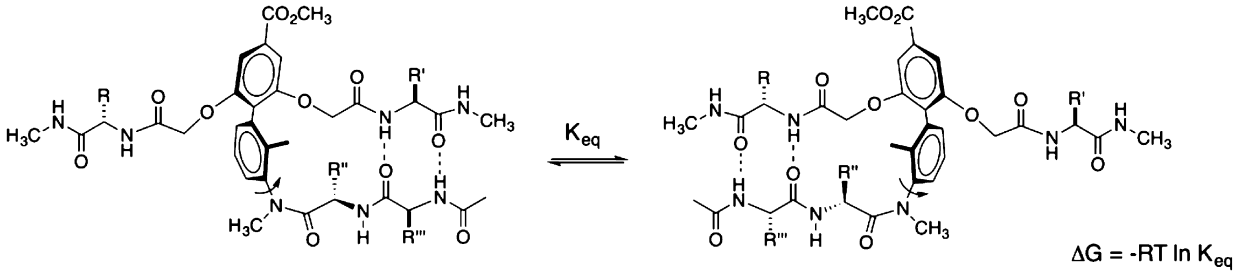


Figure 1. Example of two conformers of the β-turn mimetic torsion balance. The R groups are different, and each represents an amino acid side chain.

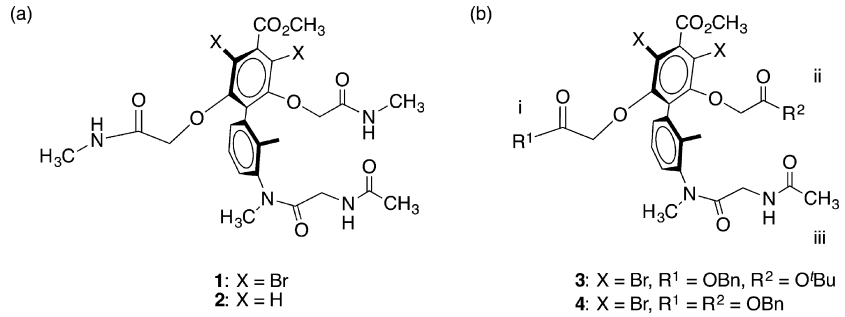
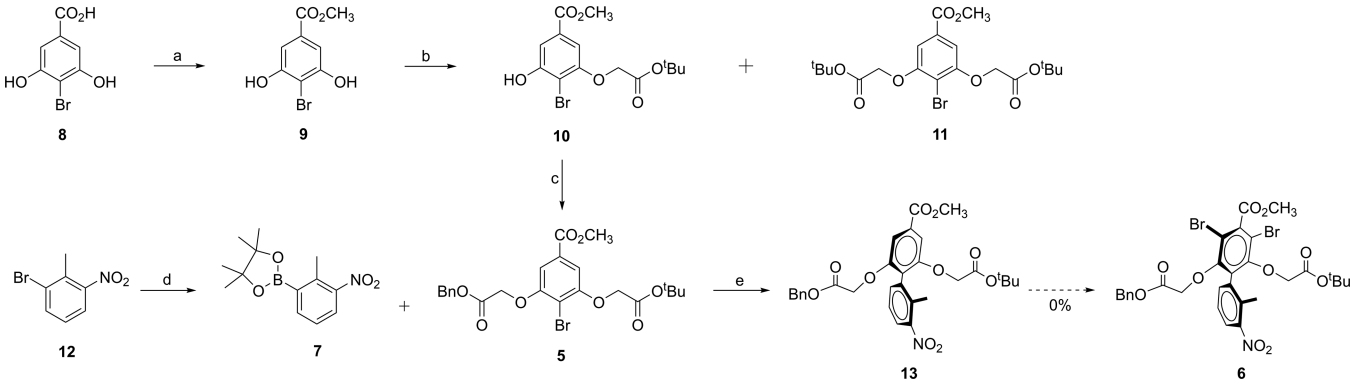


Figure 2. (a) β-Turn molecular torsion balances of interest. (b) Primary targets for the biaryl core. i, ii, and iii are positions for orthogonal protection.

Scheme 1. Synthesis of Asymmetrical Biaryl 13[a]



[a]Reagents and conditions: (a) H_2SO_4, MeOH, reflux, 99%; (b) *tert*-butyl bromoacetate, K_2CO_3, 18-crown-6, acetone, reflux, 35%; (c) benzyl bromoacetate, K_2CO_3, 18-crown-6, acetone, reflux, 80%; (d) $(Bpin)_2$, $Pd(dppf)Cl_2$·DCM, KOAc, DMSO, 90 °C, 14 h, 70%; (e) $Pd_2(dba)_3$, SPhos, K_3PO_4·H_2O, toluene, 100 °C, 34%.

The design relied on the two *ortho* sites of the top aromatic ring of the biaryl structure carrying different amino acid sequences. These sequences would compete for interaction with the lower side chain attached to the *N*-aryl amine. The equilibrium established by rotation would reveal which upper side chain formed stronger attractive interactions with the lower side chain.

The present paper reports the synthesis and preliminary structural analysis of this new molecular torsion balance. After developing the synthetic pathway, we investigated the alignment of the *o*-methylene ether side chains of the top half of the balance to promote hydrogen bonding. We hypothesized that the ether side chains would most effectively promote intrachain hydrogen bonding when oriented at 90° (perpendicular) to the plane of the aromatic ring. To enforce this orientation and further preorganize the side chains for hydrogen bonding, bromine atoms were incorporated *ortho* to the aryl ether and *o*-methylenes. The torsion balances prepared for this study are shown in Figure 2a.

The structure of **1** and **2** differ by the presence or absence of the bromines on the top ring. Derivative **2** serves as a control for this study to evaluate conformational effects of the two bromines. Our hypothesis was that torsion balance **1** will support better upper-to-lower side chain hydrogen bonding than will torsion balance **2**.

RESULTS AND DISCUSSION

Biaryl analogue **3** (Figure 2b) was the primary target for our synthesis of a conformationally controlled β-turn mimetic torsion balance. The design featured the same conformational features of the des-bromo balance shown in Figure 1 and allowed for independent amino acid couplings at three orthogonally protected positions (i, ii, and iii). The synthetic route requires the installation of two different upper side chains

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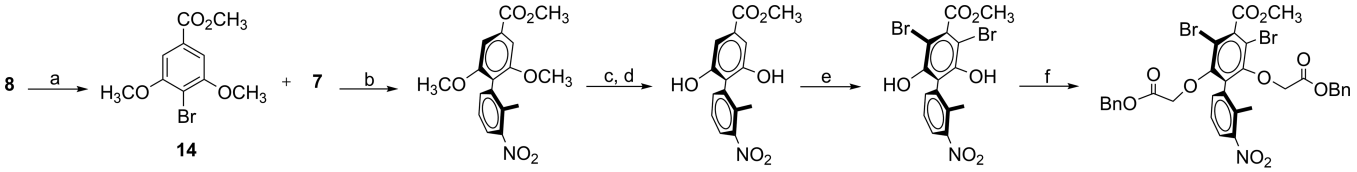
Scheme 2. Synthesis of Symmetrical Biaryl 18[a]



[a]Reagents and conditions: (a) DMS, K_2CO_3, acetone, reflux, 99%; (b) $Pd_2(dba)_3$, SPhos, $K_3PO_4·H_2O$, toluene, 100 °C, 74%; (c) BBr_3, DCM, 0 °C→ rt; (d) H_2SO_4, MeOH, reflux, 78% over two steps; (e) Br_2, CCl_4, 76%; (f) benzyl bromoacetate, K_2CO_3, 18-crown-6, acetone, reflux, 80%.

to form an asymmetrical top rotamer (**5**) before aryl coupling and bromination to give an asymmetrical biaryl (**6**; Scheme 1).

Synthesis of Asymmetrical Biaryl Core. The synthetic effort began with individual preparations of the asymmetrical top (**5**) and the bottom (**7**) halves. Bromide **5**, which was required for the Suzuki coupling, was generated according to the protocol shown in Scheme 1.[7] Fischer esterification[11] of commercially available 4-bromo-3,5-dihydroxybenzoic acid **8** afforded the methyl benzoate **9** in 99% yield. Ether **10** was synthesized by alkylation[12] on **9** with 1 equiv of commercially available *tert*-butyl bromoacetate in 35% yield. Asymmetrical product **10** was separated from the symmetrical ether **11** via flash chromatography. The alkylation protocol[12] was again utilized to generate asymmetrical coupling fragment **5**. The product was afforded by coupling **10** with commercially available benzyl bromoacetate in 80% yield. The bottom half of the balance **7** was provided in 70% yield by subjecting commercially available 2-bromo-6-nitrotoluene **12** to Miyaura boration conditions[13] with bis(pinacolato)diboron ($(Bpin)_2$) as the boron nucleophile. A similar procedure using additional 1,1′-bis(diphenylphosphino)ferrocene (dppf) in dioxane also gave boronic ester **7** but with a significantly lower yield.[13b]

The Suzuki–Miyaura cross-coupling reaction[14] of **5** and **7** furnished biaryl **13**, which could then be brominated to afford the dibromo derivative **6**. We anticipated that the coupling step should be done before bromination because of the coupling fragments exhibiting a total of three *ortho*-substituents and a *meta*-substituent; dibromination of **5** would not only increase the difficulty of the coupling reaction due to the presence of two additional *meta*-substituents but also decrease the yield because of competing cross-coupling reactions. In addition, cleavage of *tert*-butyl ester could be observed if longer reaction times needed to be employed. Treatment of fragments **5** and **7** with tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) in toluene accompanied by Buchwald's phosphine ligand[14] afforded the Suzuki–Miyaura cross-coupled product **12** with a yield of 34%.

Methods attempted to achieve dibromination *ortho* to the side chains to produce **6** from **13** were unsuccessful. Employment of Br_2 in AcOH[15] resulted in decomposition and cleavage of the *tert*-butyl ester, indicated by the formation of *tert*-butyl alcohol in ^{1}H NMR spectra. Addition of sodium acetate to buffer the system prevented decomposition but failed to provide dibromide **6**. Increased reaction times resulted in a complex mixture of products. The unsuccessful dibromination may be due to the steric hindrance of the bulky side chains as well as the inductively diminished activating effects of the α-benzyloxycarbonyl ethers. Experiments using model compounds revealed evidence (^{1}H NMR and HRMS) of undesirable aromatic bromination occurring on the benzyl ester group. We concluded that the reaction rate for dibromination of **13** was very slow and would not be easily achieved without simultaneous aromatic bromination of the benzyl ester or cleavage of the *tert*-butyl ester.

Preparation of Symmetrical Biaryl Core. We developed a modified route to our goal (Scheme 2). The new pathway featured the addition of the upper side chains after the aryl coupling and after bromination. Bromination on the phenol substrate before side chain attachment would be more readily achieved because of the enhanced activation and diminished steric hindrance of the phenol substrate in comparison with **13**. Although this synthesis does not include the attachment of differential acetoxy side chains, our central question regarding the effect of dibromination on conformation could be answered more quickly using the simpler symmetrical balance **4** that would be prepared with this new path.

The synthesis of coupling fragment **14** was straightforward and began by using 3 equiv of dimethylsulfate (DMS) to methylate commercially available 4-bromo-3,5-dihydroxybenzoic acid **8** in quantitative yield following recrystallization.[16a] An alternative procedure using methyl iodide (MeI) also gave **14** from the esterification product **9**, but with a slightly lower yield of 85%.[16b] Cross-coupling of bromide **14** with boronic ester **7** using the same conditions[14] for the Suzuki–Miyaura reaction as before afforded **15** with an exceptional yield of 74%. The increase in percent yield compared to formation of **13** (a yield of 34% in Scheme 1) is most likely due to the less sterically hindered nature of **14**.

We were unsuccessful in our attempts to couple diphenol **9** with **7** under the same conditions.[14] Protection of the phenols was necessary, but coupling of the *tert*-butyldimethylsilyl ether of **9** (not shown) with **7** was also unsuccessful. The methyl ether was the preferred protecting group for the diphenol due to its convenient preparation and the exceptional yield of the cross-coupling reaction.

The next challenge was methyl ether cleavage and functionalization of the top portion of the balance. We envisioned a selective ether cleavage using magnesium iodide (MgI_2) in an ionic liquid following the method of Lee and coworkers[17a] in order to obtain the dihydroxy-biaryl **16**. Treatment of biaryl **15** with 3 equiv of freshly prepared MgI_2[17b] in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) at 50 °C for 7 to 24 h resulted only in isolation of starting material.[17] Consideration of the drawbacks of aryl methyl ether cleavage procedures[18] led us to conclude that ether cleavage without ester cleavage was unlikely. A two-step reaction sequence of nonselective demethylation of **15** by BBr_3 and subsequent Fischer re-esterification[11] of the acid afforded dihydroxy-biaryl ester **16** in 78% overall yield.

In comparison to asymmetrical biaryl **13**, compound **16** was considered to be an improved substrate for dibromination due to the more strongly electron-donating hydroxyl groups that

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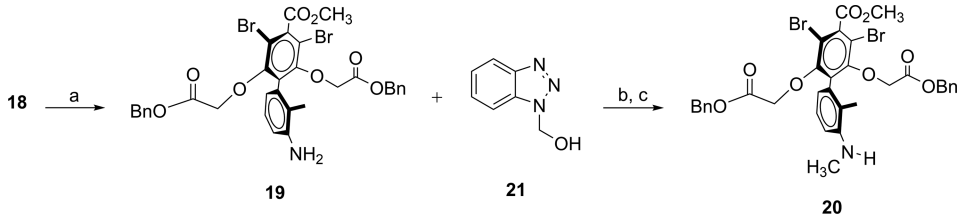
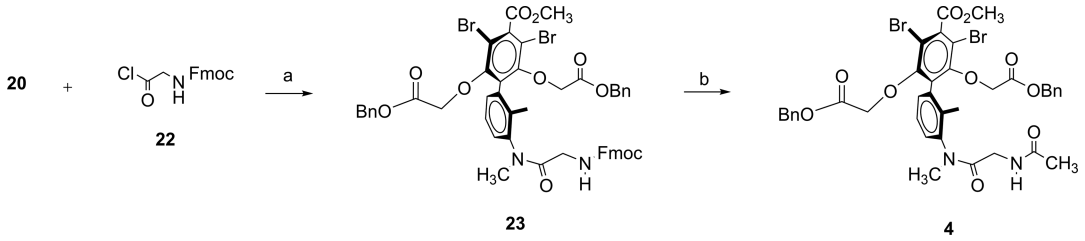
Scheme 3. Synthesis of Toluidine 20[a]



[a]Reagents and conditions: (a) Zn, HCl, EtOAc, 0 °C→ rt, 82%; (b) EtOH, THF; (c) $NaBH_4$, THF, 53% over two steps.

Scheme 4. Synthesis of Primary Target 4[a]



[a]Reagents and conditions: (a) $NaHCO_3$, $CHCl_3/H_2O$, 67%; (b) Piperidine, DMF; (b) Ac_2O, pyridine, DCM, 76% over two steps.

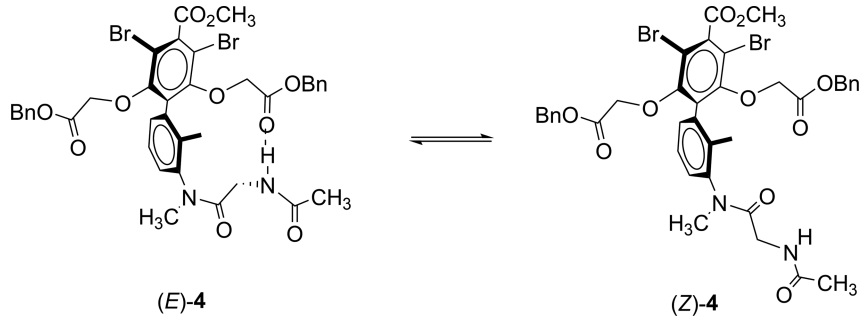


Figure 3. Two conformers of glycine torsion balance **4** by rotation around the (aryl)-N--CO amide bond.

replaced the inductively less activating α-benzyloxycarbonyl ether groups and due to diminished steric hindrance. Treatment of **16** with 2.5 equiv of Br_2 in carbon tetrachloride (CCl_4) afforded dibromination product **17** in 76% yield.[19] The symmetrical intermediate **18** was isolated in 80% yield after side chain attachment[12] using **17** with 2 equiv of commercially available benzyl bromoacetate.

With the top portion in hand, we directed our efforts toward functionalizing the bottom portion of the balance. Reduction of biaryl **18** by Zn/HCl gave an 80% yield of **19** (Scheme 3).[20] In an initial attempt to prepare *N*-methyl toluidine **20**, we employed an indirect method based on alkylation of the boc protected aniline.[7] Reaction of di-*tert*-butyl dicarbonate (Boc_2O) with **19** generated the protected derivative, but subsequent alkylation by treatment with MeI and NaH in DMF resulted in a complex mixture of products. Boc group cleavage of this mixture with TFA and purification afforded **20** in only 20% yield. Attempts to methylate **19** by treatment of its sulphonamide derivative with diazomethane were also unsuccessful.[21−23]

With the *N*-methylation proving more difficult than anticipated, we turned to an approach based on Katritzky's methods for the mono-*N*-alkylation of anilines by Mannich reaction.[24] The Katritzky conditions were modified by employing a separate preliminary condensation of 1-hydroxymethylbenzotriazole (**21**) with **19** (Scheme 3).[25] This modification removed the uncertainty of the formalin reaction and related equilibria. Treatment of **19** with **21**, followed by reduction with $NaBH_4$,afforded the methylated biaryl **20** in 53% yield. Effects of catalysis by pyridinium *p*-toluenesulfonate on the alkylation were also examined, but no significant improvement was observed.

Only the amidation step remained en route to the torsion balance core (Scheme 4). The approach used was based on Carpino's conditions.[26] Commercially available 9-fluorenylmethyloxycarbonyl-glycine (Fmoc-gly) was converted to its corresponding acid chloride **22** with thionyl chloride, which was immediately coupled with biaryl **20** due to susceptibility of **22** to hydrolysis. Amide **23** was isolated in 67% yield. The final step to synthesize torsion balance **4** involved treatment of **23** with piperidine in DMF to deprotect the amino acid, followed by immediate acylation with acetic anhydride (Ac_2O) and pyridine (76% yield).

Analysis of *E* and *Z* Amide Conformers. We investigated the conformational freedom of torsion balance **4**. The symmetry of the top portion of this analogue leads only to enantiomers by rotation around the N−aryl bond when all side chains have only achiral elements; however, rotation around the (aryl)-N--CO amide bond does lead to two conformations (Figure 3).

The presence of (aryl)-N--CO bond rotational conformers of torsion balance **4** is evident from the two *N*-methyl group

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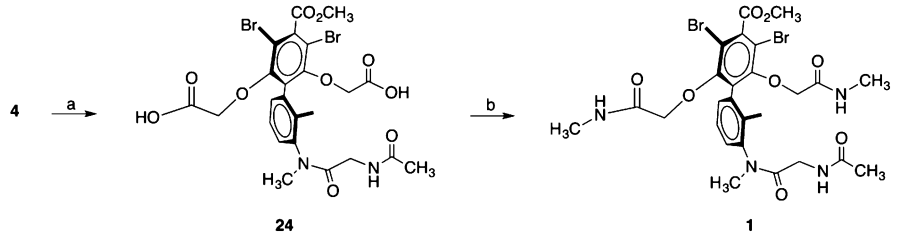
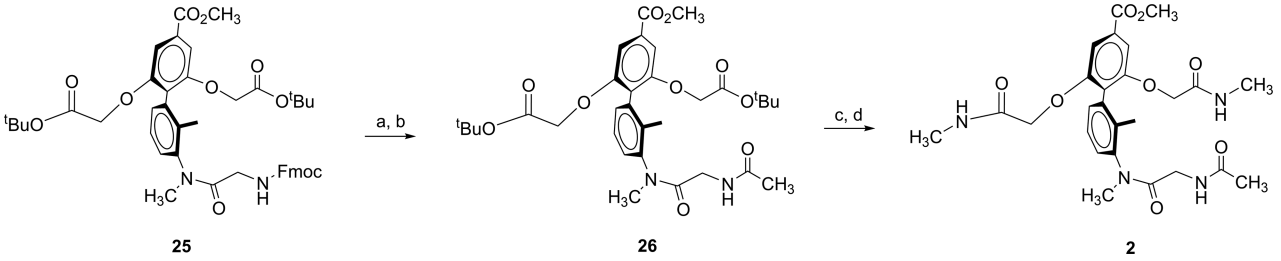
Scheme 5. Synthesis of Torsion Balance Derivative 1[a]



[a]Reagents and conditions: (a) H_2, PtO_2, EtOAc, 95%; (b) CH_3NH_2·HCl, EDCI, HOBT, DIEA, DCM, 63%.

Scheme 6. Synthesis of Control Target 2[a]



[a]Reagents and conditions: (a) Piperidine, DMF; (b) Ac_2O, pyridine, DCM, 90% over two steps; (c) TFA, DCM; (d) CH_3NH_2·HCl, EDCI, HOBT, DIEA, DCM, 24% over two steps.

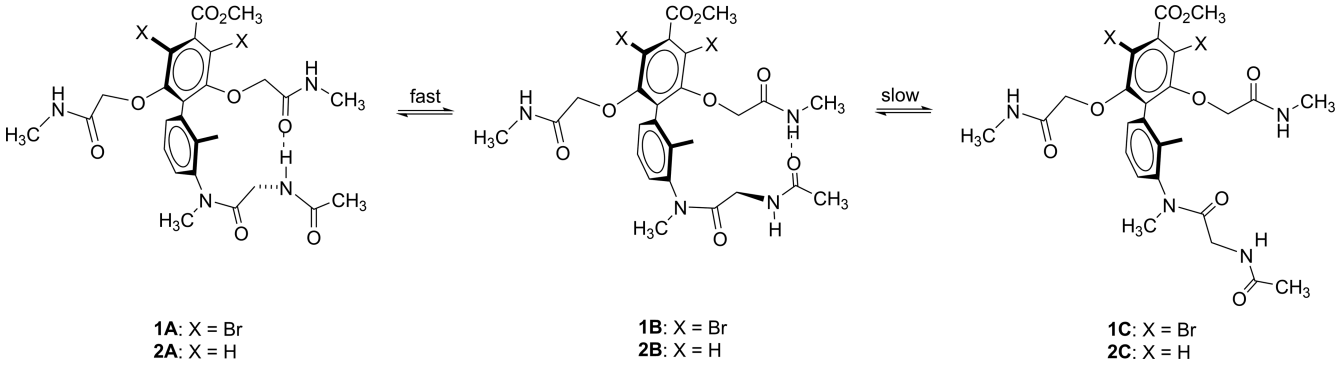


Figure 4. Three conformers of **1** and **2** (enantiomers not shown).

singlets in the ^{1}H NMR spectra of **4** at 298 K in both $CDCl_3$ and CD_2Cl_2. The two signals arise due to rotation around the bond, and ^{1}H NMR data reveal the ratio of *E*/*Z* rotamers to be 94:6. The 2D ROESY data confirm that (*E*)-**4** is the major rotamer and (*Z*)-**4** is the minor rotamer.

Preparation of Torsion Balances with Competing Intramolecular Hydrogen Bond Patterns. To examine conformational effects of bromine installation on potential hydrogen bonding between the upper and lower side chains, we prepared target amides **1** (Scheme 5) and **2** (Scheme 6). Debenzylation of amide **4** by H_2/PtO_2 reduction generated diacid **24** in an excellent yield of 95% without any debromination product observed.[20] Amide coupling of diacid **24** using 1-hydroxybenzotriazole (HOBT) with methylamine hydrochloride, 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (EDCI), and *N*,*N*′-diisopropylethylamine (DIEA) afforded the desired target **1** in 63% yield.[27]

Synthesis of the control compound (**2**) is shown in Scheme 6. Amide **26** was afforded in 90% yield using the same conditions as previously described for Fmoc deprotection and acylation of the amino acid. Treatment of **26** with TFA and subsequent employment of the same amidation protocol as earlier mentioned provided control amide **2** in 24% yield.[27]

NMR Studies of Torsion Balances 1 and 2. Core target **1** was designed to demonstrate increased conformational control of the ether side chains in comparison with amide **2**. The purpose of this increased control was to improve the opportunities for hydrogen bonding between the upper and lower side chains. Comparison of **1** with control amide **2** might provide insight into the degree of control the bromines contribute to the torsion balance structure. Furthermore, we hoped to establish the identity of the hydrogen bond donor/acceptor pairs (two arrangements are possible) between the upper and lower side chains.

NMR Assignments and Initial Comparison of 1 and 2. The three most relevant conformers of **1** and **2** to this study are shown in Figure 4. The mixture is racemic, and only one enantiomer each for these chiral molecules is shown. Conformers **a** and **b** arise from two alternative arrangements of hydrogen bonding: In **a**, the top side chain is the hydrogen bond acceptor and the glycine acetamide acts as the hydrogen bond donor. In **b**, the top side chain is the hydrogen bond donor and the glycine acetamide acts an acceptor. Conformer **c**

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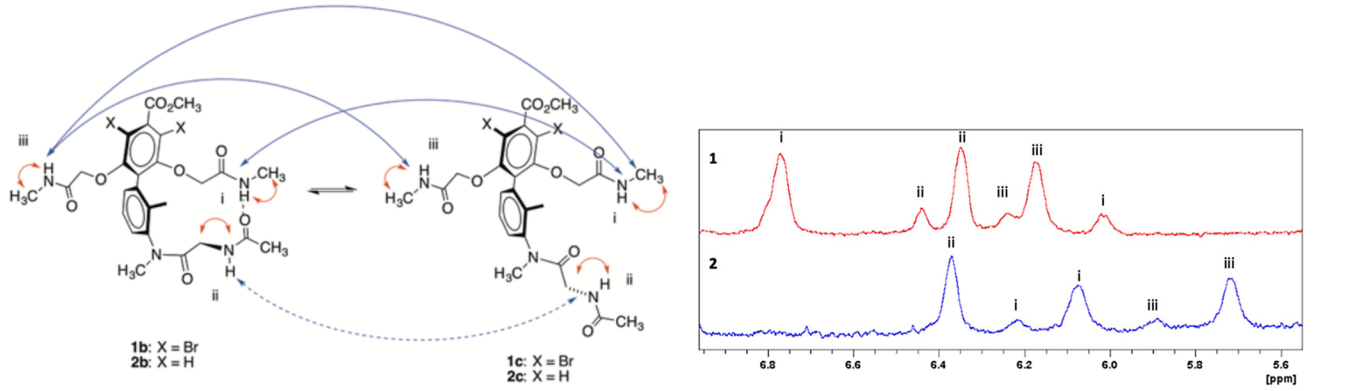

Figure 5. Summary of ROESY/EXSY data (left) and ^{1}H NMR spectra (right) for 1 mM solutions of **1** and **2** in CD_2Cl_2 at 298 K for amide proton ^{1}H NMR assignments of the major (**b**) and minor (**c**) conformers of **1** and **2**. Original 2D ROESY/EXSY data are provided in Supporting Information.

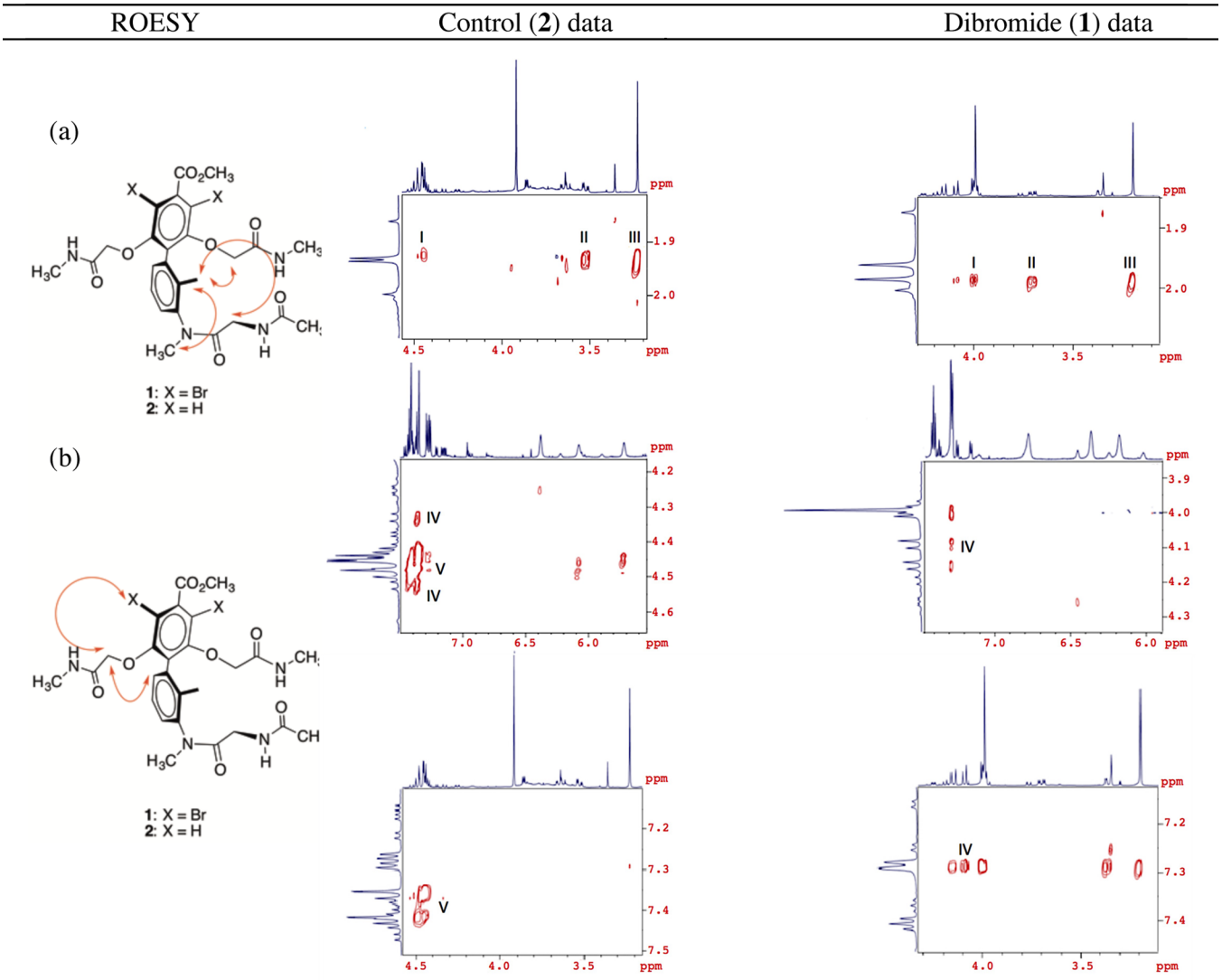

Figure 6. Selected ROESY data for 1 mM solutions of **1** (right) and **2** (left) in CD_2Cl_2 at 298 K for (a) aryl methyl protons and (b) upper side chain methylene protons.

arises when rotation around the (aryl)-N--CO amide bond affords the more extended *Z* amide. Note that hydrogen bonded *E* amide conformers (**a** and **b**) and non-hydrogen bonded *E* amide conformers (not shown) will appear as an

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averaged ^{1}H NMR signal due to their rapid interconversion. NMR analysis of the dibenzyl derivative **4** reveals that **c** is a minor component in solution.

In the assignment of NMR resonances observed in **1** and **2**, 2D NMR spectroscopy (COSY, NOESY, ROESY, HMQC, and HMBC) was utilized to identify the ^{1}H and ^{13}C peaks of each conformer. The ROESY data were most useful in assigning the amide proton shifts and the acetyl methyl and aryl methyl proton chemical shifts (Figures 5and 6).

EXSY data recorded at 298 K in CD_2Cl_2 (0.1 mM) used to assign the amide protons are shown in Figure 5. The major and minor conformers of **1** and **2** are identifiable among the broad singlets appearing between 5.4 δ and 6.5 δ. The ^{1}H NMR spectrum of the control (Figure 5) exhibits apparent overlap of NH signals. Only five NH signals are observed, rather than the six possible for three amide NH protons of the two observable conformers.

The most downfield amide proton signal of control **2** belongs to that of glycine proton "ii". This conclusion is based on the ROESY crosspeak between the NH proton and glycine α-protons (as shown by the red arrow in Figure 5). Major and minor conformers, **2b** and **2c** respectively, appear to overlap for this proton (as shown by the dashed blue arrow; Figure 5). In comparison the data for the dibromo balance **1** (Figure 5) clearly show that it is the middle NH signal that corresponds to proton "ii" of the major glycine conformer **1b**, while the most downfield major NH peak belongs to the methylamide proton "i" of **1b**. The most upfield NH signal corresponds to methylamide proton "i" of the minor conformer **1c**. This assignment for "i" is evident from the ROESY crosspeak between the NH proton and *N*-methyl protons (as shown by the red arrow in Figure 5).

We interpret the large change in chemical shift for proton "i" in **1** versus **2** as evidence of a hydrogen bond that is present in **1** but not in **2**. Since the glycine NH signal for "ii" barely moves, we believe introduction of bromine substituents has only minor effects on its environment. This insensitivity to bromine addition supports our conclusion that the topside chain is the hydrogen bond donor and the glycine acetamide is the hydrogen bond acceptor.

Other observations were also useful for comparing the degree of conformational change between the target balance and the control. ROESY data allowed assignments of the acetyl and aryl methyl protons (Figure 6). These two signals are very close in chemical shift. The aryl methyl protons of both **1** and **2** show three strong ROESY effects (Figure 6a) due to the ether methylene protons on the upper side chains (crosspeak I), the glycine methylene protons (crosspeak II), and aryl *N*-methyl protons (crosspeak III). These ROESYs correspond to the more upfield methyl signal for control **2**. This establishes that the upfield methyl of **2** is the aryl methyl and the downfield methyl of **2** is the acetyl methyl. The alternative is seen for the dibromo case. The crosspeaks correspond to the more downfield methyl signal of **1** (Figure 6a). These data support our ^{1}H NMR assignment for the methyl protons. The downfield shift observed for the aryl methyl protons between **2** and **1** indicates a conformational change upon bromine installation.

The ROESY data for **1** and **2** also show off-diagonal peaks between the ether methylene protons on the upper side chains and the aromatic proton *ortho* to the top aryl group (Figure 6b). This crosspeak signal (IV) is much more significant for dibromide **1** than for control **2**. ROESY data show a notably stronger crosspeak (V) between the upper side chain methylene protons of **2** and the *ortho* aromatic protons of the upper ring (Figure 6b). This confirms that the upper side chains of **2** are coplanar or close to coplanar with the upper aromatic ring. The stronger crosspeak IV in **1** points to a perturbation in the orientation of the upper side chains caused by introduction of bromine substituents.

Analysis of Torsion Balance 1 Conformers. NMR data for **1** were collected at concentrations between 0.1 and 10 mM in $CDCl_3$, C_7D_8, and CD_2Cl_2 at 298 K. The presence of two conformations is again evident from the two *N*-methyl group singlets in the ^{1}H NMR spectra in all solvents. A ratio of the two *N*-methyl group singlets can be observed in all solvents as was seen for torsion balance **4** (Figure 3). ROESY data confirm that rotation around the (aryl)-N--CO amide bond is responsible for both conformers. Results of NMR dilution studies reveal that the broadening of N−H amide proton signals is not due to self-aggregation.

CONCLUSIONS

We report herein the synthesis of a new conformationally controlled torsion balance to use as a molecular tool for comparing the energy of pairwise amino acid interactions in antiparallel orientation and the effects of amino acid changes on short β-strand stability. The design incorporates a two-state folding model imposed by restricted rotation about an N−aryl bond. The dibromo scaffold incorporates an additional degree of conformational control to optimize intrachain hydrogen bonding by the introduction of bromine substituents *ortho* to the upper side chains. With this synthesis we successfully realized our goal to promote hydrogen bond formation by improving chain alignment between the top and bottom side chains.

2D ROESY data clearly indicated a perturbation in the orientation of the upper side chains for the dibromo case compared to the control balance (**2**). Based on our ^{1}H and 2D ROESY NMR analyses, we have found that our scaffold has improved the balance's shape toward enforcing the correct distance and antiparallel orientation of amino acid recognition points of two β-strands. Hydrogen bond formation has been identified, in which the NH amide proton of the upper side is the hydrogen bond donor and the glycine acetamide is the hydrogen bond acceptor.

EXPERIMENTAL SECTION

General Experimental Methods. Dry solvents were obtained by distilling the solvents from the appropriate drying agent under a nitrogen atmosphere shortly before use. References to "removal of volatile components from the filtrate under reduced pressure" refer to rotary evaporation of the sample at 25−65 °C at a pressure of 18−25 mmHg and then overnight under high vacuum (0.1 mmHg) at room temperature. Reaction progress was monitored by thin-layer chromatography (TLC) on glass silica gel plates (60 F_{254} 0.25 mm) and components visualized by UV radiation and $KMnO_4$ or phosphomolybdic acid developing reagents. Melting points were determined using a capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with FT-IR and are expressed in cm^{-1}. NMR measurements (^{1}H and ^{13}C) were recorded in $CDCl_3$, CD_2Cl_2, or MeOD at room temperature (21−27 °C) using 300, 400, 500, 600, and 700 MHz spectrometers. Chemical shifts are expressed in parts per million (δ) using TMS or a residual deuterated solvent peak as the reference value. Coupling constants (J) are valued in hertz (Hz). ^{1}H NMR multiplicity are designated as follows: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of

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doublets); m (multiplet); ABq (AB quartet); qd (quartet of doublets). High-resolution mass spectra (HRMS) were obtained via EI or ESI using a QTOF, mass spectrometer.

*Methyl 3′-(2-Acetamido-N-methylacetamido)-3,5-dibromo-2′-methyl-2,6-bis(2-(methylamino)-2-oxoethoxy)-[1,1′-biphenyl]-4-carboxylate (**1**).* To a round-bottom flask equipped with a condenser and nitrogen gas inlet were added 0.015 g (0.023 mmol) of diacid **24**, 0.005 g (0.068 mmol) of methylamine hydrochloride, 0.013 g (0.068 mmol) of EDCI, 0.010 g (0.068 mmol) of HOBT, 0.015 mL (0.084 mmol) of DIEA, and 0.46 mL of DCM. The reaction mixture was stirred at room temperature for 16 h and diluted with ethyl acetate (10 mL) and washed with 1.0 M NaOH (5 mL), water (10 mL), and then brine (10 mL). The organic layers were combined, dried over $MgSO_4$ and filtered, and the volatile components were removed from the filtrate under reduced pressure to give a crude brown oil. The oil was purified twice by flash chromatography (SiO_2, (first column: hexanes/ethyl acetate/MeOH elution gradient 1:1:0/2:3:0/0:1:0/0:9:1); (second column: DCM/MeOH elution gradient 1:0/49:1/19:1)) to give 0.009 g (63%) of **1** as a white foam: R_f 0.15 (100% ethyl acetate); ^{1}H NMR (700 MHz, CD_2Cl_2) δ One proton of conformers: [7.43 (t, J = 15.4 Hz), 7.39 (t, J = 15.4 Hz)], one proton of conformers: [7.30 (d, J = 7.7 Hz), 7.17 (d, J = 7.7 Hz)], one proton of conformers: [7.30 (d, J = 7.7 Hz), 7.26 (d, J = 7.7 Hz)], one proton of conformers: [6.80 (broad s), 6.03 (broad s)], one proton of conformers: [6.36 (broad s), 6.46 (broad s)], one proton of conformers: [6.19 (broad s), 6.26 (broad s)], two protons of conformers: [4.30, 4.27 (qd, J = 18.2, 6.3 Hz), 3.72, 3.36 (ABq, J = 6.3 Hz)], two protons of conformers: [4.18−4.00 (ABq, J = 6.3 Hz), 4.56−3.79 (ABq, J = 14.7 Hz)], two protons of conformers: [4.10,4.00 (ABq, J = 10.5 Hz), 4.20,4.00 (ABq, J = 10.5 Hz)], 4.00 (s, 3H), three protons of conformers: [3.36 (s), 3.21 (s)], 2.65 (d, J = 4.9 Hz, 3H), three protons of conformers: [2.59 (d, J = 4.9 Hz), 2.47 (d, J = 4.9 Hz)], three protons of conformers: [2.02 (s), 1.98 (s)], three protons of conformers: [2.00 (s), 1.88 (s)]; ^{13}C NMR (700 MHz, CD_2Cl_2) δ 168.7, 167.4, 165.9, 153.5, 153.2, 143.4, 142.0, 140.0, 135.8, 135.3, 134.4, 133.6, 132.1, 132.0, 131.0, 129.3, 128.2, 127.8, 111.4, 111.1,72.2, 72.0, 42.0, 41.8, 36.5, 30.0, 26.2, 25.8, 23.2, 15.7, 15.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{31}N_4O_8Br_2$ 687.0488, found 687.0477.

*Methyl 3′-(2-Acetamido-N-methylacetamido)-2′-methyl-2,6-bis-(2-(methylamino)-2-oxoethoxy)-[1,1′-biphenyl]-4-carboxylate (**2**).* To a solution of 0.015 g (0.028 mmol) of **26** in DCM (0.045 mL) at room temperature was added 0.009 mL (0.111 mmol) of TFA and the reaction mixture was stirred for 2 h. The volatile components were removed under reduced pressure to give a brown crude oil. To this crude oil, in a vial equipped with a condenser and nitrogen gas inlet were added 0.007 g (0.108 mmol) of methylamine hydrochloride, 0.021 g (0.108 mmol) of EDCI, 0.016 g (0.108 mmol) of HOBT, 0.023 mL (0.132 mmol) of DIEA, and 0.72 mL of DCM. The reaction mixture was stirred at room temperature for 80 h, and the volatile components were removed under reduced pressure to give a crude brown oil. The oil was purified by flash chromatography (SiO_2, (first column: hexanes/ethyl acetate/MeOH elution gradient 1:1:0/2:3:0/0:1:0/0:9:1); (second column: DCM/MeOH elution gradient 1:0/49:1/19:1)) to give 0.004 g (24%) of **2** as a white foam: R_f 0.1 (100% ethyl acetate); ^{1}H NMR (700 MHz, CD_2Cl_2) δ one proton of conformers: [7.44 (t, J = 7.7 Hz), 7.43 (t, J = 7.7 Hz)], 7.39 (d, J = 0.7 1H), 7.38 (d, J = 0.7 Hz, 1H), one proton of conformers: [7.29 (d, J = 7.7 Hz), 7.22 (d, J = 7.7 Hz)], one proton of conformers: [7.27 (d, J = 7.7 Hz), 7.17 (d, J = 7.7 Hz)], 6.38 (broad s, 1H), one proton of conformers: [6.08 (broad s), 6.23 (broad s)], one proton of conformers: [5.89 (broad s), 5.72 (broad s)], two protons of conformers: [4.54, 4.34 (ABq, J = 14.0 Hz), 4.45, 4.44 (qAB, J = 4.9, 3.5 Hz)], two protons of conformers: [4.46, 4.42 (ABq, J = 14.7 Hz), 4.39, 4.37 (ABq, J = 7.0 Hz)], two protons of conformers: [4.25, 4.23 (qd, J = 18.2, 4.2 Hz), 3.66, 3.54 (ABq, J = 17.5, 4.2 Hz)], 3.93 (s, 3H), three protons of conformers [3.37 (s), 3.24 (s)], three protons of conformers: [2.71 (d, J = 4.9 Hz), 2.66 (d, J = 4.9 Hz)], 2.63 (d, J = 4.9 Hz, 3H), three protons of conformers: [2.1 (s), 1.96 (s)], three protons of conformers: [1.95 (s), 1.88 (s)]; ^{13}C NMR (700 MHz, CD_2Cl_2) δ168.7, 168.0, 166.2, 155.9, 155.5, 141.7, 136.1, 135.9, 132.5, 131.1, 128.2, 127.7, 123.7, 108.7, 108.2, 69.0, 68.5, 42.0, 36.5, 30.1, 25.8, 23.1, 14.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{33}N_4O_8$ 529.2298, found 529.2289.

*Dibenzyl 2, 2′-((3′-(2-Acetamido-N-methylacetamido)-3,5-dibromo-4-(methoxycarbonyl)-2′-methyl-[1, 1′-biphenyl]-2,6-diyl)bis-(oxy))diacetate (**4**).* To 0.01 g (0.01 mmol) of **23** in a round-bottom flask was added 0.045 mL of a 20% piperidine/DMF solution, and the reaction mixture was stirred at room temperature for 20 min. Then 0.24 mL (mmol) of acetic anhydride and 0.71 mL (mmol) of pyridine were added, and the solution was stirred at room temperature for 30 min. The volatile components were removed from the filtrate under reduced pressure to give a yellow oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate/methanol elution gradient 1:1:0/2:3:0/0:1:0/0:9:1) to give 0.007 g (76%) of **4** as a white foam: R_f 0.34 (100% ethyl acetate); IR (thin film, cm^{-1}) 3338, 2932, 1751, 1723, 1655, 1580, 1423, 1393, 1369, 1329, 1235, 1193, 1135, 1029, 996, 844, 806, 733; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34−7.27 (m, 8H), 7.22−7.19 (m, 4H), 7.14−7.13 (m, 1H), 6.26 (broad s, 1H), 5.07 (s, 2H), 5.02 (s, 2H), four protons of conformers: [4.25, 3.96 (qAB, J = 15 Hz), 4.20, 4.15 (qAB, J = 15 Hz)], 4.02 (s, 3H), two protons of conformers: [3.65 (qd, J = 4.9 Hz), 3.35 (s)], 3.15 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.0, 169.0, 167.2, 167.1, 166.1, 153.5, 141.6, 139.6, 136.4, 135.6, 135.3, 133.9, 131.4, 131.3, 127.8, 111.7, 111.3, 69.5, 67.4, 67.1, 53.7, 42.2, 36.3, 23.4, 15.3; HRMS (ESI-TOF) m/z: $[M + CHO_2]^-$ calcd for $C_{39}H_{37}O_{12}N_2Br_2$ 885.0700, found 885.0709.

*Methyl 3-(2-(Benzyloxy)-2-oxoethoxy)-4-bromo-5-(2-tert-butoxy-2-oxoethoxy) Benzoate (**5**).* In a round-bottom flask, 0.49 g (1.36 mmol) of benzoate **10**, 0.26 mL (1.63 mmol) of benzyl bromoacetate, 0.22 g (1.63 mmol) of K_2CO_3, and 0.08 g (0.33 mmol) of 18-crown-6 were dissolved in acetone (35.4 mL), and the reaction mixture was refluxed for 24 h. The volatile components were removed under reduced pressure, and the residue was diluted with DCM (25 mL) and water (25 mL); the organic layer was extracted, and the aqueous layer was washed with additional DCM (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the volatile components were removed from the filtrate under reduced pressure to give a crude yellow oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, elution gradient 7:1/6:1/3:1) to yield 0.55 g (80.2%) of **5** as a white solid: R_f 0.48 (hexanes/ethyl acetate 3:2); mp 68−70 °C; IR (thin film, cm^{-1}) 2978, 1753, 1724, 1587, 1423, 1369, 1337, 1241, 1194, 1133, 1029, 1000, 844, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 5H), 7.04 (d, J = 4 Hz, 2H), 5.14 (s, 2H), 4.70 (s, 2H), 4.56 (s, 2H), 3.77 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.8, 166.9, 165.9, 155.8, 155.7, 149.9, 149.1, 143.4, 141.7, 140.0, 135.0, 130.5, 130.0, 128.7, 128.6, 128.6, 128.5, 128.5, 108.2, 107.4, 107.2, 82.9, 67.3, 67.2, 66.6, 66.3, 60.7, 52.5, 28.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{25}O_8NaBr$ 531.0630, found 531.0663.

*4,4,5,5-Tetramethyl-2-(2-methyl-3-nitrophenyl)-1,3,2-dioxaborolane (**7**).* To a third flame-dried 200 mL round-bottom flask, 3.00 g (13.9 mmol) of **12**, 5.29 g (20.8 mmol) of $(Bpin)_2$, 4.09 g (41.7 mmol) of KOAc, and 0.45 g of [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with DCM ($Pd(dppf)Cl_2$·DCM; 0.56 mmol) were added. The reaction flask was then placed on a vacuum line for 5 min and backfilled with nitrogen and repeated. DMSO (83.2 mL) was then added, and the solution was degassed using the freeze−pump−thaw method three times under a nitrogen atmosphere. The flask was sealed; the reaction mixture was stirred at 90 °C for 20 h and then cooled to room temperature. The reaction mixture was then diluted with DCM (100 mL) and H_2O (100 mL). The organic layer was extracted and washed with H_2O (3 × 100 mL). The aqueous layer was washed with additional DCM (2 × 100 mL). Organic extracts were combined, and the volatile components were removed from the filtrate under reduced pressure to give a brown crude oil. The oil was purified twice by flash column chromatography (SiO_2, hexanes/ethyl acetate, elution gradient (2 columns) 10:1/6:1; then 30:1) to give 2.7 g (76%) of **7** as a pale yellow solid: R_f 0.89 (hexanes/ethyl acetate, 4:1); mp 52−53 °C; IR (thin film, cm^{-1}) 3055, 2982, 2933, 1603, 1569, 1527, 1474, 1439, 1344, 1267, 1214, 1144,

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1109, 1026, 1078, 963, 786, 739, 669, 579. 463; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7 Hz, 1H), 7.77 (d, J = 8 Hz, 1H), 7.27 (t, J = 8 Hz, 1H), 2.67 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 151.3, 139.9, 138.2, 126.3, 126.0, 84.4, 25.0, 18.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{19}BNO_4$ 264.1407, found 264.1405.[13b]

*Methyl 4-Bromo-3,5-dihydroxybenzoate (**9**).* To 1.0 g (4.4 mmol) of carboxylic acid **8** in 6.8 mL of methanol was added 0.41 mL (7.6 mmol) of H_2SO_4 dropwise, and the reaction mixture was refluxed for 16 h. The reaction was quenched by addition of $NaHCO_3$ (1.2 g, 14.8 mmol), and the volatile components were removed under reduced pressure. The residue was diluted with ethyl acetate (25 mL) and water (25 mL); the organic layer was extracted, and the aqueous layer was washed with additional ethyl acetate (3 × 25 mL). The organic layers were dried over $MgSO_4$ and filtered, and the volatile components were removed from the filtrate under reduced pressure to give 1.05 g (99%) of **9** as a white solid: R_f 0.34 (hexanes/ethyl acetate 3:2); mp 225−227 °C; IR (thin film, cm^{-1}) 3416, 3329, 1701, 1594, 1421, 1353, 1270, 1233, 1118, 1033, 990, 907, 857, 760, 705; ^{1}H NMR (300 MHz, MeOD) δ 7.03 (s, 2H), 4.85 (broad s, 2H), 3.85 (s, 3H); ^{13}C NMR (600 MHz, MeOD) δ 168.1, 156.7, 131.0, 108.6, 105.1, 52.7; HRMS (EI) m/z calcd for $C_8H_7O_4Br$ 245.9528, found 245.9519.

*Methyl 4-Bromo-3-(-2-tert-butoxy-2-oxoethoxy)-5-hydroxybenzoate (**10**).* In a round-bottom flask, 1.0 g (4.2 mmol) of benzoate **9**, 0.62 mL (4.2 mmol) of *tert*-butyl bromoacetate, 1.2 g (8.8 mmol) of K_2CO_3, and 0.05 g (0.2 mmol) of 18-crown-6 were dissolved in acetone (21.0 mL), and the reaction mixture was refluxed for 24 h. The volatile components were removed under reduced pressure, and the residue was diluted with ethyl acetate (50 mL) and water (50 mL); the organic layer was extracted, and the aqueous layer was washed with additional ethyl acetate (2 × 50 mL). The organic layers were dried over $MgSO_4$ and filtered, and the volatile components were removed from the filtrate under reduced pressure to give a crude yellow oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, elution gradient 5:1/3:2/0:1) to give 0.49 g (32.4%) of **10** as a white solid: R_f 0.44 (hexanes/ethyl acetate 3:2); mp 117−118 °C; IR (thin film, cm^{-1}) 3393, 2923, 2852, 1724, 1590, 1497, 1438, 1354, 1247, 1158, 1117, 1011, 904, 870, 843, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.92 (s, 1H), 6.41 (s, 1H), 4.57 (s, 2H), 3.81 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.9, 166.0, 154.9, 153.7, 130.6, 110.4, 105.8, 105.2, 82.9, 66.4, 52.5, 28.0; HRMS (EI) m/z calculated for $C_{14}H_{17}BrO_6$ 360.0209, found 360.0205. Benzoate **11** was generated as the major product (48%) en route to benzoate **10**. HRMS (EI) m/z calcd for $C_{14}H_{17}O_6Br$ 360.0209, found 360.0205.

*Methyl 2,6-Dimethoxy-2′-methyl-3′-nitro-[1,1′-biphenyl]-4-carboxylate (**13**).* In a round-bottom flask, 0.17 g (0.34 mmol) of benzoate **5**, 0.14 g (0.55 mmol) of boronic ester **7**, 0.013 g (0.014 mmol) of $Pd_2(dba)_3$, 0.022 g (0.055 mmol) of 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos), and 0.24 g (1.03 mmol) of (ground) $PO_4{\cdot}H_2O$ were added and dried under reduced pressure for 5 min and backfilled with nitrogen two times. Toluene (3 mL) was added, and the solution was degassed using the freeze−pump−thaw method three times under a nitrogen atmosphere. The flask was sealed; the reaction mixture was stirred at 90 °C for 18 h, and cooled to room temperature. The mixture was diluted with DCM (30 mL) and H_2O (30 mL); the organic layer was extracted, and the aqueous layer was washed with additional DCM (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and volatile components were removed from the filtrate under reduced pressure to give a brown crude oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, 5:1) to afford 0.13 g (67.6%) of **13** as a white foam: R_f 0.36 (hexanes/ethyl acetate, 4:1); IR (thin film, cm^{-1}) 3442, 2979, 1751, 1725, 1581, 1528, 1437, 1422, 1354, 1330, 1236, 1194, 1136; 1082, 1029, 999, 867, 844, 810, 771, 741, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8 Hz, 1H), 7.42 (d, J = 7 Hz, 1H), 7.33 (broad s, 4H), 7.27 (broad s, 2H), 7.19 (s, 2H), 5.16 (s, 2H), 4.67 (s, 2H), 4.49 (s, 2H), 3.91 (s, 3H), 2.27 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.2, 167.4, 166.2, 156.2, 155.9, 150.8, 136.2, 135.3, 135.1, 132.8, 131.5, 128.8, 128.6, 126.0, 123.9, 122.5, 106.5, 106.0, 82.9, 67.3, 66.0, 65.4, 52.6, 28.2, 16.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{31}NO_{10}Na$ 588.1840, found 588.1854.

*Methyl 4-Bromo-3,5-dimethoxybenzoate (**14**).* To a stirred solution of 2.50 g (10.7 mmol) of carboxylic acid **8** and 6.2 g (45.1 mmol) of K_2CO_3 in acetone (67.0 mL), 3.46 mL (36.5 mmol) of dimethyl sulfate was added. The mixture was stirred at reflux for 4.5 h and cooled to room temperature. Volatile components were removed under reduced pressure. The residue was then diluted with ethyl acetate (75 mL) and H_2O (75 mL); the organic layer was extracted, and the aqueous layer was washed with additional ethyl acetate (2 × 75 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and filtered, and the volatile components were removed from the filtrate under reduced pressure to yield a white solid. The solid was purified by recrystallization to give 2.9 g (100%) of benzoate **14** as white crystals: R_f 0.45 (hexanes/ethyl acetate, 4:1); mp 121−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 2H), 3.95 (s, 6H), 3.93 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.7, 157.3, 130.4, 106.9, 105.8, 56.9, 52.7; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{11}O_4Br$ 273.9841, found 273.9829.

*Methyl 2,6-Dimethoxy-2′-methyl-3′-nitro-[1,1′-biphenyl]-4-carboxylate (**15**).* In a round-bottom flask, 1.45 g (5.29 mmol) of benzoate **14**, 2.08 g (7.94 mmol) of boronic ester **7**, 0.19 g (0.21 mmol) of $Pd_2(dba)_3$, 0.35 g (0.85 mmol) of SPhos, and 3.66 g (15.87 mmol) of $K_3PO_4{\cdot}H_2O$ (ground) were added and dried under reduced pressure for 5 min and backfilled with nitrogen two times. Toluene (30 mL) was added, and the solution was degassed using the freeze−pump−thaw method three times under a nitrogen atmosphere. The flask was sealed; the reaction mixture was stirred at 90 °C for 18 h and cooled to room temperature. The mixture was diluted with DCM (150 mL) and H_2O (150 mL); the organic layer was extracted, and the aqueous layer was washed with additional DCM (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and filtered. Volatile components were removed from the filtrate under reduced pressure to give a reddish brown crude oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, elution gradient, 8:1/6:1) to give 1.19 g (74%) of **15** as a pale yellow solid: R_f 0.28 (hexanes/ethyl acetate, 4:1); mp 119−120 °C; IR (thin film, cm^{-1}) 3436, 2919, 2881, 1721, 1580, 1527, 1456, 1434, 1409, 1351, 1326, 1242, 1126, 997, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 6, 3 Hz, 1H), 7.36−7.34 (m; 4H), 3.97 (s, 3H), 3.78 (s, 6H), 2.20 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.0, 157.7, 150.9, 137.0, 135.4, 132.6, 131.8, 126.1, 123.8, 121.8, 105.4, 56.3, 52.7, 16.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{18}NO_6$ 332.1134, found 332.1124.

*Methyl 2,6-Dihydroxy-2′-methyl-3′-nitro-[1,1′-biphenyl]-4-carboxylate (**16**).* In a third-flame-dried round-bottom flask, 5.35 g (21.36 mmol) of a 1.0 M solution of BBr_3 in DCM was added dropwise over 30 min to a stirred solution of 1.18 g (3.56 mmol) of **15** in DCM (8 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and gradually warmed to room temperature and stirred for an additional 21 h. The volatile components were removed under reduced pressure. The residue was charged with nitrogen and slowly diluted with MeOH (7 mL). 0.33 mL (6.14 mmol) of H_2SO_4 was added dropwise at 0 °C. The reaction mixture was then heated to reflux for 20 h. After cooling to room temperature, the reaction was quenched by addition of $NaHCO_3$ (1.03 g, 12.3 mmol), and the volatile components were removed under reduced pressure. The residue was diluted with ethyl acetate (75 mL) and H_2O (75 mL); the organic layer was extracted, and the aqueous layer was washed with additional ethyl acetate (2 × 75 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and filtered. Volatile components were removed from the filtrate under reduced pressure to yield a brown oil. The oil was purified by flash column chromatography (SiO_2, hexanes/ethyl acetate, elution gradient, 2:1) to give 0.84 g (78%) of **16** as a white solid: R_f 0.22 (hexanes/ethyl acetate, 2:1); mp 160−161 °C; IR (thin film, cm^{-1}) 3310, 2524, 2219, 2043, 1653, 1451, 1113, 1034; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 6 Hz, 1H), 7.49−7.47 (m, 2H), 7.31 (s, 2H), 5.71 (broad s, 2H), 3.92 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.4, 151.7, 135.53, 134.6, 133.7, 131.9, 127.5, 125.2, 118.6, 109.5, 53.0,

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16.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO_6$ 304.0821, found 304.0837.

*Methyl 3,5-Dibromo-2,6-dihydroxy-2′-methyl-3′-nitro-[1,1′-biphenyl]-4-carboxylate (**17**).* In an oven-dried round-bottom flask, 0.26 mL (4.12 mmol) of Br_2 in CCl_4 (2.9 mL) was added dropwise over 30 min to a stirred solution of 0.52 g (1.72 mmol) of **16** in CCl_4 (7 mL) in the dark. The reaction mixture was stirred for 1 h. Saturated $NaHSO_3$ was then added until the red color dissipated. The mixture was diluted with ether (30 mL), and the organic layer was extracted. The aqueous layer was washed with additional ether (2 × 30 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and filtered, and the volatile components were removed from the filtrate under reduced pressure to yield a brown oil. The oil was purified by flash column chromatography to give 0.60 g (76%) of **17** as an off-white foam: R_f 0.36 (hexanes/ethyl acetate, 4:1); mp 158−159 °C; IR (thin film, cm^{-1}) 3431, 2101, 1642, 1264, 790; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7, 2 Hz, 1H), 7.44−7.39 (m, 2H), 5.91 (broad s, 2H), 4.02 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 166.0, 151.1, 150.5, 137.0, 135.0, 134.6, 132.9, 126.8, 124.9, 115.7, 99.3, 53.7, 16.4; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{11}NO_6Br_2$ 461.8900, found 461.8882.

*Dibenzyl 2,2′-((3,5-Dibromo-4-(methoxycarbonyl)-2′-methyl-3′-nitro-[1,1′-biphenyl]-2,6-diyl)bis(oxy))diacetate (**18**).* In an oven-dried round-bottom flask, 0.46 g (1.0 mmol) of **17**, 0.38 mL (2.4 mmol) of benzyl bromoacetate, 0.42 g (3.0 mmol) of K_2CO_3, and 0.10 g (0.40 mmol) of 18-crown-6 were dissolved in acetone (11.1 mL), and the reaction mixture was refluxed for 24 h. The volatile components were removed from the filtrate under reduced pressure, and the residue was diluted with DCM (30 mL) and water (30 mL); the organic layer was extracted, and the aqueous layer was washed with additional DCM (3 × 30 mL). The combined organic layers were washed with brine (90 mL), dried over $MgSO_4$, and filtered, and the volatile components were removed from the filtrate under reduced pressure to give a crude yellow oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, elution gradient 6:1) to yield 0.60 g (80%) of **18** as a light yellow foam: R_f 0.48 (hexanes/ethyl acetate 2:1); ^1H NMR (400 MHz, CD_2Cl_2) δ 7.82 (d, J = 8 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 7.36−7.34 (m, 6H), 7.30−7.24 (m, 5H), 5.02 (q, J = 4 Hz, 4H), 4.22, 4.10 (ABq, J_{AB} = 15 Hz, 4H), 2.30 (s, 3H); ^{13}C NMR (400 MHz, CD_2Cl_2) δ 167.2, 166.1, 154.0, 151.3, 140.4, 135.8, 135.5, 134.5, 133.1, 131.0, 129.1, 129.0, 128.9, 127.1, 125.5, 111.7, 70.0, 67.4, 17.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{33}H_{28}NO_{10}Br_2$ 758.01052, found 758.0080.

*Dibenzyl 2,2′-((3′-Amino-3,5-dibromo-4-(methoxycarbonyl)-2′-methyl-[1, 1′-biphenyl]-2,6-diyl)bis(oxy))diacetate (**19**).* 0.5 g (0.67 mmol) of **18** was dissolved in ethyl acetate (11 mL) and concentrated HCl (0.33 mL). The solution was cooled to 0 °C, and Zn powder (0.21 g, 3.3 mmol) was added in portions over 20 min with stirring. The mixture was gradually warmed to room temperature and stirred for 15 h. The reaction mixture was passed through a Celite plug and washed with ethyl acetate (5 mL). The filtrate was washed with saturated $NaHCO_3$ solution (1 × 5 mL), water (1 × 5 mL), and brine (1 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and volatile components were removed from the filtrate under reduced pressure to give a crude yellow oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, elution gradient 3:1/2:1) to yield 0.41 g (82%) of **19** as a light yellow foam: R_f 0.21 (hexanes/ethyl acetate 2:1); mp 58−59 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.30 (m, 5H), 7.28−7.25 (m, 5H), 6.99 (t, J = 8 Hz, 1H), 6.64 (d, J = 8 Hz, 1H), 6.58 (d, J = 7 Hz, 1H), 5.05 (s, 4H), 4.17, 4.00 (ABq, J_{AB} = 15 Hz, 4H), 4.01 (s, 3H), 3.61 (broad s, 2H), 1.90 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.6, 166.4, 153.6, 145.6, 138.7, 135.4, 132.1, 131.6, 128.9, 128.8, 128.7, 126.9, 121.9, 120.9, 115.9, 111.0, 69.4, 67.0, 53.6, 30.0, 14.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{33}H_{30}NO_8Br_2$ 728.02395, found 728.02593.

*Dibenzyl 2,2′-((3,5-Dibromo-4-(methoxycarbonyl)-2′-methyl-3′-(methylamino)-[1,1′-biphenyl]-2,6-diyl)bis(oxy))diacetate (**20**).* 0.1 g (0.14 mmol) of **19** and 0.025 g (0.17 mmol) of **21** in THF (0.1 mL) were sonicated for 5 min to give a homogeneous solution. The mixture was then diluted with EtOH (0.16 mL) and stirred at room temperature for 12 h. Volatile components were removed under reduced pressure, and the reaction vial was cooled to 0 °C for 10 min. The residue was rinsed with chilled, dry DCM followed by hexanes to produce an off-white solid. The precipitate was isolated and taken up into DCM, dried over K_2CO_3, and filtered, and volatile components were removed under reduced pressure to give an off-white solid. The dry intermediate was dissolved in THF (0.3 mL), and 0.01 g (0.18 mmol) of $NaBH_4$ was added and stirred for 14 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ice, cold H_2O, and DCM; the organic layer was extracted, and the aqueous layer washed with additional DCM (2 × 4 mL). The combined organic layers were washed with additional H_2O (5 mL) and then brine (5 mL); the organic layer was dried over $MgSO_4$ and filtered, and volatile components were removed from the filtrate under reduced pressure to give a yellow foam. The foam was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, elution gradient 7:1/6:1) to yield 0.040 g (41%) of **20** as a white foam: R_f 0.38 (hexanes/ethyl acetate 2:1; IR (thin film, cm^{-1}) 3432, 3059, 2978, 2303, 2053, 1648, 1420, 1375, 1241, 1122, 892, 743; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (broad s, 5H), 7.26 (broad s, 5H), 7.12 (t, J = 8 Hz, 1H), 6.59 (d, J = 8 Hz, 1H), 6.53 (d, J = 8 Hz, 1H), 5.04 (s, 4H), 4.12, 4.00 (ABq, J = 15 Hz, 4H) 4.01 (s, 3H), 3.66 (broad s, 2H), 2.87 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.7, 166.4, 153.7, 147.9, 138.7, 135.5, 132.3, 131.1, 128.9, 128.8, 128.6, 127.2, 121.4, 119.2, 111.0, 109.9, 69.4, 67.0, 53.6, 31.2, 30.1, 28.7, 14.6, 14.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{34}H_{32}Br_2NO_8$ 742.0495, found 742.0496.

*(9H-Fluoren-9-yl)methyl (2-chloro-2-oxoethyl)carbamate (**22**).* To a solution of 0.030 g (0.1 mmol) of commercially available Fmoc-gly in DCM (0.5 mL) was added 0.07 mL (1.0 mmol) of thionyl chloride ($SOCl_2$), and the reaction mixture was refluxed for 30−45 min. The solution was cooled to room temperature, and the volatile components were removed under reduced pressure. The residue was dissolved in minimal DCM followed by hexanes to produce an off-white precipitate. The solid was filtered and dried in vacuo to afford 0.025 g (81%) of **22** as an off-white solid. Only IR spectra were obtained to confirm this highly reactive intermediate: (thin film, cm^{-1}) 3315, 3066, 2967, 2947, 1811, 1702, 1540, 1477, 1448, 1395, 1349, 1271, 1182, 1104, 1087, 1051, 991, 955, 919, 780, 758, 742.

*Dibenzyl 2, 2′-((3′-(2-((((9H-Fluoren-9-yl)methoxy)carbonyl)-amino)-N-methylacetamido)-3,5-dibromo-4-(methoxycarbonyl)-2;-methyl-[1,1′-biphenyl]-2,6-diyl)bis(oxy))diacetate (**23**).* To 0.050 g (0.07 mmol) of **20** in 0.62 mL of $CHCl_3$ was added 0.03 g (0.09 mmol) of Fmoc-gly acid chloride **22** (generated according to above procedure and used immediately thereafter) in 0.37 mL of $CHCl_3$ followed by 0.62 mL of saturated $NaHCO_3$ solution, and the reaction mixture was stirred at room temperature for 20 min. The solution was diluted with DCM (10 mL) and saturated $NaHCO_3$ solution (10 mL), the organic layer was extracted, and the aqueous layer was washed with DCM (3 × 10 mL). The organics were dried over $MgSO_4$ and filtered, and the volatile components were removed from the filtrate under reduced pressure to give a light brown crude oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate, elution gradient 5:1/3:1/2:1) to give 0.046 g (67%) of **23** as a white foam: R_f 0.31 (hexanes/ethyl acetate, 1:1); IR (thin film, cm^{-1}) 3392, 2926, 2855, 1751, 1722, 1660, 1581, 1421, 1369, 1329, 1299, 1234, 1193, 1134, 1028, 998, 864, 845, 806, 735; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7 Hz, 2H), 7.48 (d, J = 7 Hz, 2H), 7.32−7.25 (m, 5H), 7.22−7.18 (m, 5H), 7.14−7.06 (m, 7H), 5.49 (broad s, 1H), 4.94 (s, 4H), 4.23−4.14 (m, 4H), 4.10−4.01 (m, 4H), 3.94 (s, 3H), 3.88 (d, J = 15 Hz, 2H), 3.65, 3.32 (qd, J = 4, 17 Hz, 2H), 3.08 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.6, 166.8, 165.8, 156.1, 153.1, 144.0, 143.9, 141.3, 141.3, 139.3, 136.2, 135.1, 135.0, 133.6, 131.0, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.4, 127.1, 125.2, 120.0, 111.3, 111.0, 69.2, 69.1, 67.0, 66.8, 53.4, 47.1, 43.2, 36.3, 15.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{51}H_{45}N_2O_{11}Br_2$ 1019.13846, found 1019.13665.

*2,2′-((3′-(2-Acetamido-N-methylacetamido)-3,5-dibromo-4-(methoxycarbonyl)-2′-methyl-[1,1′-biphenyl]-2,6-diyl)bis(oxy))-diacetic Acid (**24**).* To a nitrogen charged flask, 0.007 g (0.008 mmol)

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of **4** and 0.001 g (0.003 mmol) of PtO_2 were added and dried under reduced pressure for 5 min and backfilled with nitrogen twice. Under a hydrogen atmosphere, ethyl acetate (0.2 mL) was added and stirred for 13 h. The reaction mixture was passed through a Celite plug and washed with ethyl acetate (2 mL). Volatile components were removed from the filtrate under reduced pressure to obtain 0.005 g (91%) of **24** as a glass-like foam. R_f 0.1 (9:1 ethyl acetate/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 8 Hz, 1H) 7.22 (d, J = 8 Hz, 1H), 7.11 (d, J = 8 Hz, 1H), 6.89 (broad s, 2H), 4.33, 4.03 (ABq, J = 16, 15 Hz, 2H), 4.17−3.97 (m, 2H), 3.68, 3.58 (ABq, J = 18, 4 Hz, 2H), 3.74 (s, 3H), 3.16 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.2, 169.8, 169.4, 168.7, 168.0, 166.0, 154.3, 153.4, 141.0, 139.7 135.9, 134.2, 132.3, 131.8, 129.2, 128.3, 112.1, 111.4, 70.5, 69.3, 53.8, 47.9, 43.1, 43.0, 36.6, 32.3, 30.0, 29.7, 26.7, 25.8, 24.7, 23.2, 23.0, 21.5, 15.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}Br_2N_2O_{10}$ 656.97140, found 656.97329.

*Di-tert-butyl 2,2′-((3′-(2-Acetamido-N-methylacetamido)-4-methyoxycarbonyl)-2′-methyl-[1,1′-biphenyl]-2,6-dilyl)bis(oxy))-diacetate (**26**).* To 0.020 g (0.028 mmol) of carboxylate **25** in a vial was added a 0.11 mL of a 20% piperidine/DMF solution, and the reaction mixture was stirred at room temperature for 30 min. Then 0.35 mL (4.06 mmol) of acetic anhydride and 1.16 mL (15.4 mmol) of pyridine were added, and the solution was stirred at room temperature for 30 min. The volatile components were removed from the filtrate under reduced pressure to give a crude brown oil. The oil was purified by flash chromatography (SiO_2, hexanes/ethyl acetate/methanol elution gradient 1:5/1:20) to give 0.015 g (90%) of **26** as a white foam: R_f 0.22 (100% ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.27 (m, 2H), 7.19−7.12 (m, 3H), 6.47 (broad s, 1H), four protons of conformers [4.64, 4.53 (ABq, J_{AB} = 16 Hz), 4.55, 4.50 (ABq J_{AB} = 15 Hz)], 3.91 (s, 3H)], 3.70 (qd, J = 18, 4 Hz, 2H), 3.29 (s, 3H), 2.03, (s, 3H), 1.98 (s, 3H), 1.45 (s, 18H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.7, 168.9, 167.7. 166.3, 155.9, 155.7, 140.1, 135.8, 135.7, 131.3, 130.7, 127.0, 126.8, 123.1, 106.1, 105.98, 82.5, 82.2 65.9. 65.6, 52.3, 42.2, 36.3, 28.0, 23.1, 14.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{32}H_{42}N_2O_{10}Na$ 637.2737, found 637.2761.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02307.

Copies of ^{1}H, ^{13}C, and 2D ROESY/EXSY NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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