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The Activated Core Approach to Combinatorial Chemistry: A Selection of New Core Molecules

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Abstract: Four new activated core molecules suitable for use in solution-phase combinatorial organic chemistry have been prepared. These molecules represent an attempt to further explore shape-space and increase the structural diversity of prepared libraries, as well as to incorporate recognition elements in the cores to increase the chances for interaction with biological targets. Demonstrations of deconvolution strategies used to simplify complex libraries and build individual molecular species based on the cores are also provided.

A solution-phase approach to organic combinatorial chemistry has been developed in this research group. It avoids the use of multiple steps or protecting groups by creating the diversity in a one-pot procedure.[1-5] Like combinatorial methods involving synthesis on soluble polymer supports,[6] this method combines the numerical advantages of split synthesis on the solid support with the homogeneous reaction conditions of the solution phase. While some other solution-phase approaches[7] generate a relatively small number of compounds, this technique can easily be scaled to produce thousands of compounds. The activated core approach can be divided into three components: the core, the linker, and the building blocks. Each can be designed to give the desired level of diversity (numbers of compounds) and/or the desired physical property (solubility, shape space, chemical functionality).

The synthesis of new core molecules is often undertaken to provide different orientations of the attached building blocks, thereby increasing structural diversity. The properties of the core molecule have (in several assays) been critical to activity, as libraries made with the same building blocks and linkages have had very different activity levels.[1] Previous work in this group has demonstrated the use of 1,3,5,7-cubanetetracarboxylic acid chloride[3,8] and both 9,9-dimethyl-2,4,5,7-xanthenetetracarboxylic acid chloride[1-3] and -tetraisocyanate[4,5] as cores for combinatorial chemistry, and the methodology used to evaluate the reactivity of those cores was also used to evaluate the compounds of the present work, though these details are omitted for brevity. Four new core molecules (Figure 1) have been prepared to expand both the range of substituent geometries available for libraries and the chemical make-up of the cores themselves, and a concern with the ability to easily deconvolute large libraries manifests itself in their synthetic design.

In light of the criteria outlined above, it is not surprising that the four new core molecules have several traits in common. All four compounds—2,2',6,6'-biphenyl (**1**), 2,2',4,4'-biphenyl (**2**), *trans*-1,3,5-cyclohexane (**3**), and 2,2',6,6'-bipyridine (**4**)—have a low molecular weight and enough hydrophobicity to allow for

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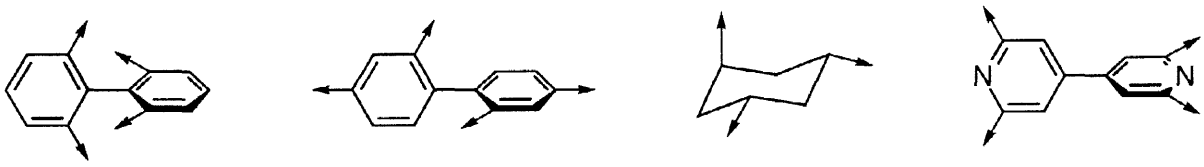


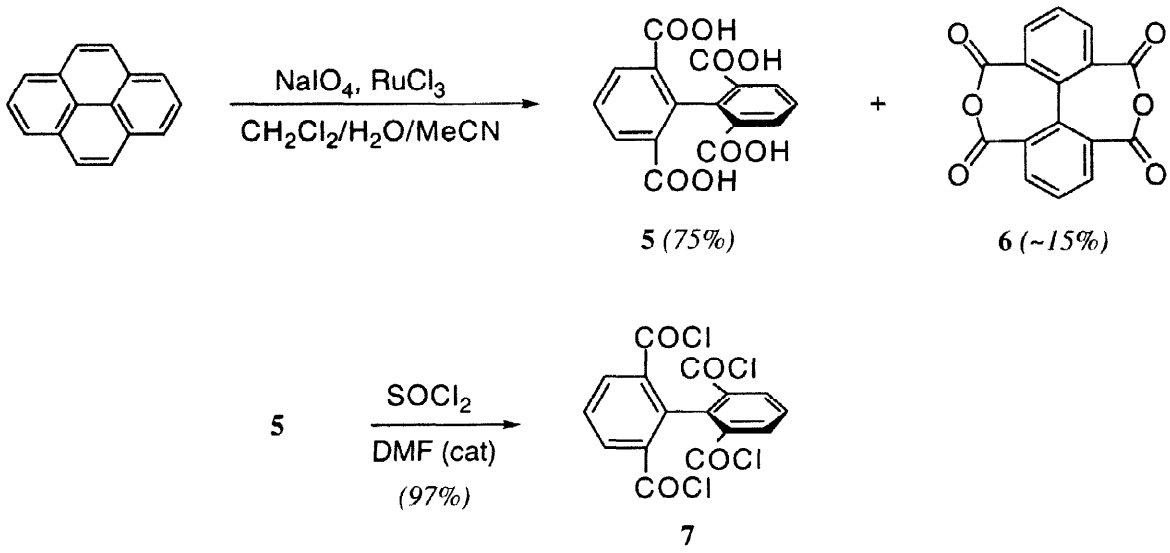
1 2 3 4

Figure 1

liquid-liquid extractions. No inherent toxicities of these cores are known. In fact, some derivatives of these molecules with different substitution patterns can be found in medicinal agents. Biphenyls are found in a number of pharmacologically active compounds, angiotension antagonists in particular.[9] Studies have indicated that the hydrophobicity inherent to these cores facilitates transport across membranes, increasing their bioavailability.[10]

The 2,2',6,6'-Tetrasubstituted Biphenyl Core

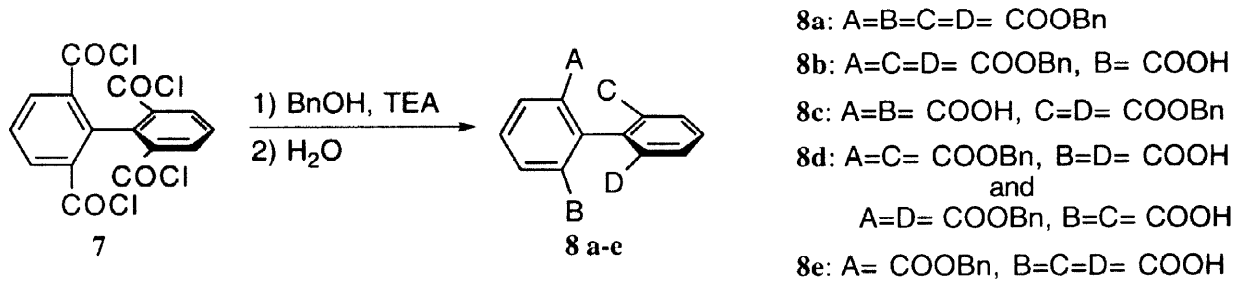
The all *ortho* isomer of biphenyl has a compact shape and a low (150 g/mol) molecular weight. These properties have not escaped the eye of medicinal and combinatorial chemists; several recent publications[9,11] have featured biphenyl-based molecules with a variety of substituents and substitution patterns. With this particular substitution pattern, hydrogen-bonding interactions are possible between adjacent groups, increasing the rigidity of the system and exemplifying one of its inherent advantages. Also, despite its high symmetry, the lack of rotation[12] about the biaryl bond allows a large number of compounds to be formed by the reaction with only a few building blocks.



Scheme 1. Synthesis of 2,2',6,6'-Bipyridinetetracarboxylic acid chloride.

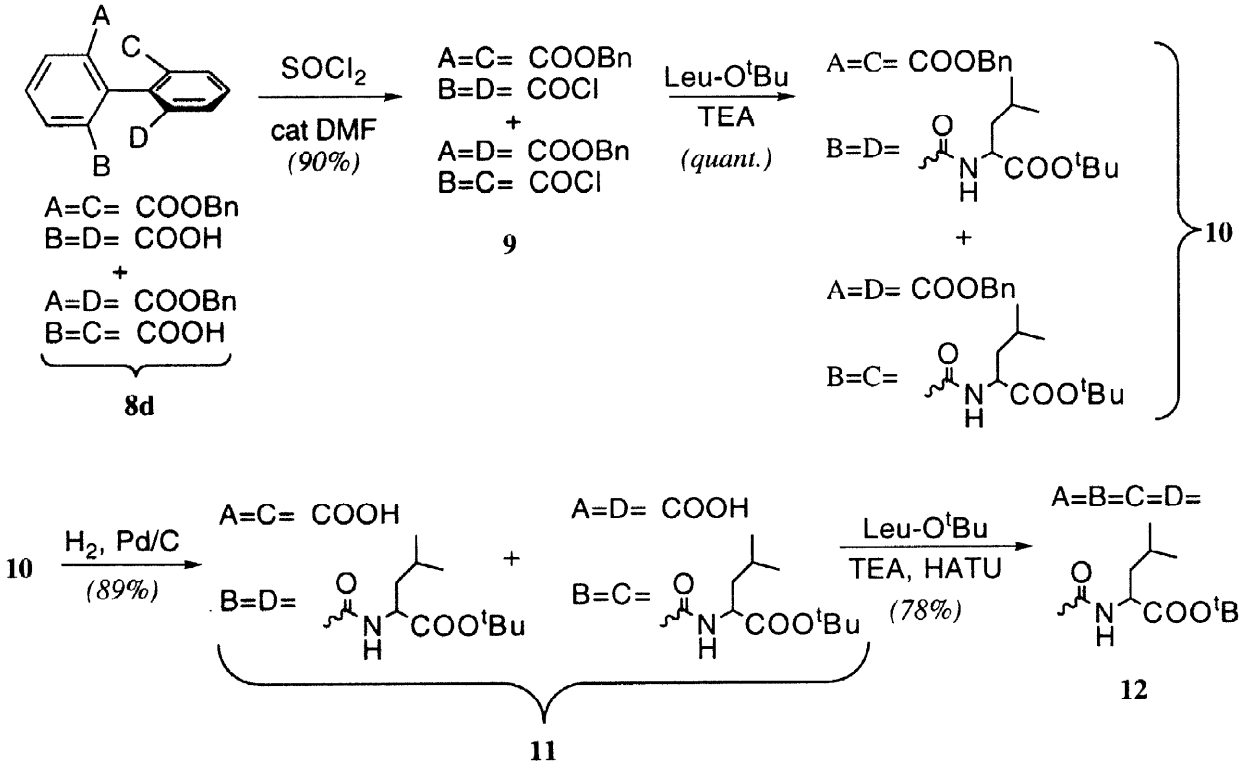
The existing tetraacid synthesis[13] gave erratic results in this laboratory. An alternative synthesis using a recent oxidation technique[14] employing $RuCl_3$ and $NaIO_4$ proceeded smoothly, upon optimization, to give the desired tetraacid (**5**) in 75% yield (Scheme 1), which could be removed from the more soluble dianhydride (**6**) byproduct by filtration. The corresponding tetraacid chloride was formed by reaction with excess thionyl

chloride in dichloromethane; the use of both oxalyl chloride and PCl_5 resulted in a product of much-reduced purity.



Scheme 2. Synthesis of biphenyl deconvolution compounds.

For compounds applicable to deconvolution we decided to explore benzyl ester/carboxylic acid combinations of the biphenyl compound. The tetraacid chloride (**7**) was reacted with 2.5 equivalents of benzyl alcohol in the presence of triethylamine (Scheme 2). The resulting mixture was then separated on a silica gel column and all of the compounds were isolated, although only a small amount of the monobenzyl ester (**8e**) was obtained.



Scheme 3. Stepwise synthesis of tetraamides.

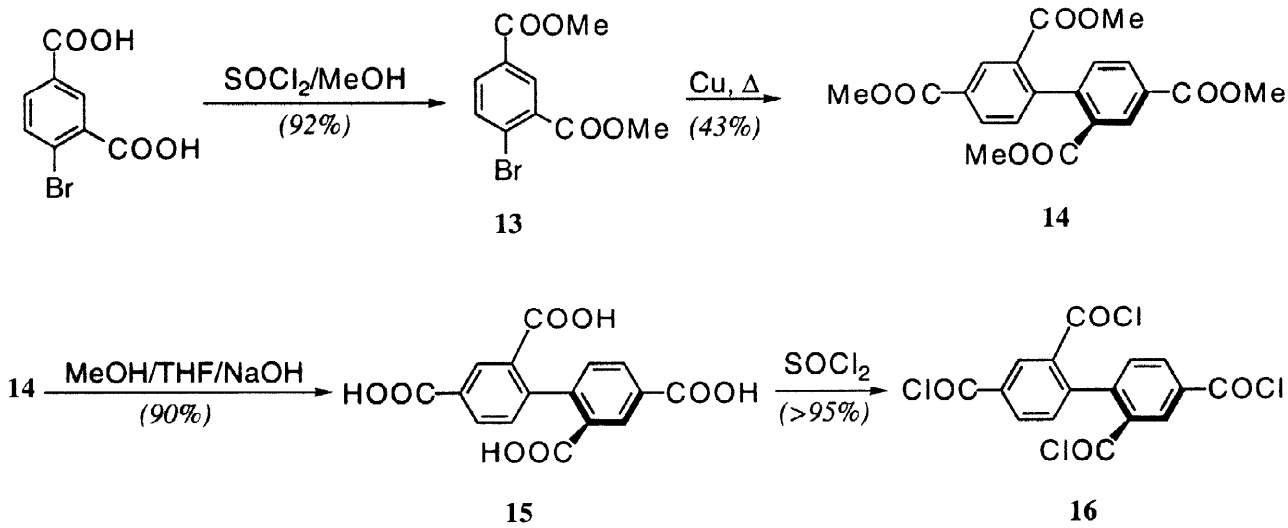
To test the validity of the deconvolution approach a trial synthesis was conducted (Scheme 3). The objective was to synthesize a known compound (the tetraleucine tetraamide **12**) using a stepwise approach, beginning with the dibenzyl ester/diacid (**8d**). After two leucines were attached, a diastereomeric mixture (**10**)

resulted (that could be partially resolved using preparative TLC). Hydrogenolysis afforded the diacid/dileucines **11** in high yield. The final step of the synthesis proved to be troublesome, however. With the more common coupling reagents (BOP-Cl, PyBOP[15]) the reaction failed to go to completion. Fortunately, the same reaction in the presence of the very reactive coupling reagent HATU[16] proceeded in acceptable yield. While this deconvolution scheme was used to synthesize a pure compound, different amines could easily be substituted, allowing for a range of isomers and enantiomers to be generated.

The 2,2',4,4'-Tetrasubstituted Biphenyl Core

The tetrasubstituted biphenyl **2** is advantageous for a number of reasons. The relatively low (C_2) symmetry, for example, allows for a number of compounds to be formed with only a few building blocks. Two of the building blocks (those at the 4 and 4' positions) diverge in opposite directions, while the other two (2 and 2') can assume a range of conformations, depending upon the torsion angle between the aryl moieties.[17]

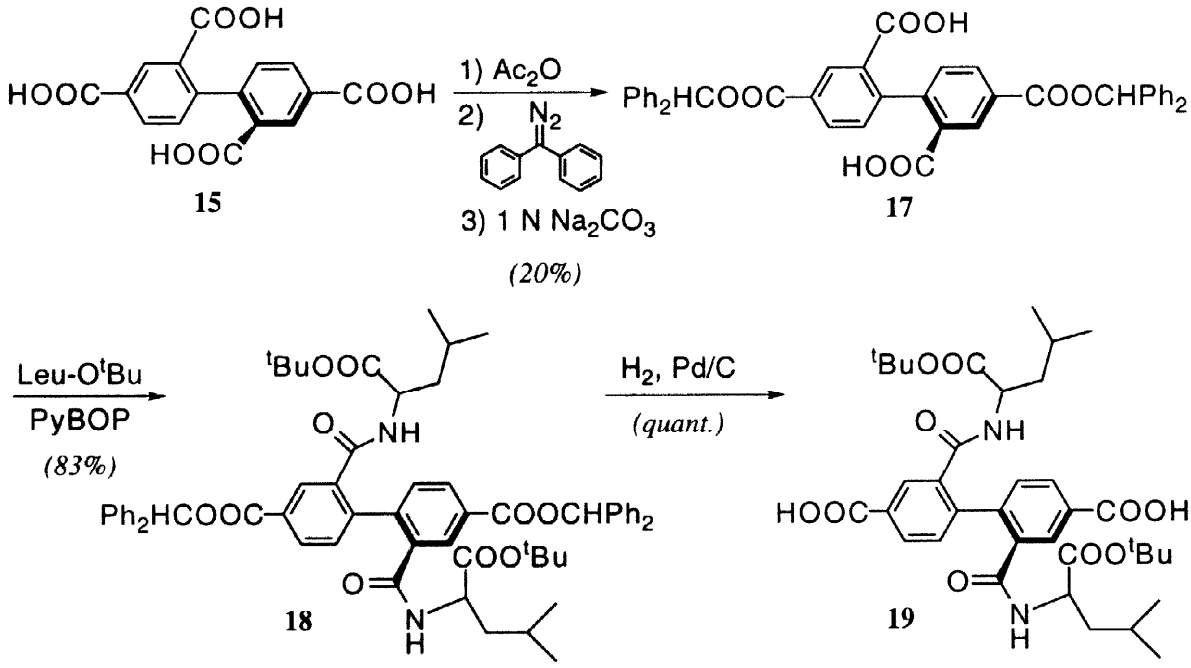
Several improvements to an earlier synthesis[18] of the biphenyl tetraacid have been made. The synthesis used to obtain such biphenyl derivatives is given in Scheme 4. The commercially available 4-bromoisophthalic acid was dissolved in methanol and esterified by slow addition of thionyl chloride[19] to give the dimethyl ester **13**. An Ullmann coupling[20] formed the biaryl bond to give **14**, and saponification of the methyl esters using standard procedures gave the tetraacid **15**. Activation with thionyl chloride and catalytic DMF gave the tetraacid chloride core (**16**) in pure form. Earlier procedures[21] used phosphorus pentachloride to activate the tetraacid **16**; however, in the case of the 2,2',6,6'-biphenyltetraacid chloride-based libraries residual phosphorus compounds could not be removed and resulted in library impurities. Activation with thionyl chloride was preferable because it was easier to handle and could be removed completely *in vacuo*.



Scheme 4. Synthesis of the 2,2',4,4'-biphenyl tetraacid chloride activated core.

In order to deconvolute libraries based on this core molecule, a derivative protected at the 4- and 4'-sites was synthesized (Scheme 5). The 2,2'-dianhydride was formed in approximately 80% purity by the reaction of the tetraacid **15** with acetic anhydride in THF. The crude product was then directly reacted with diphenyldiazomethane[22] to give the 4,4'-(diphenylmethyl) diester, which was subsequently hydrolyzed with

aqueous Na_2CO_3 to give the diester diacid **17**. To demonstrate the feasibility of this deconvolution protocol **17** was coupled to the *t*-butyl ester of leucine using PyBOP to give the dileucine diester **18**. The diphenylmethyl protecting groups were then cleaved by hydrogenolysis to give the dileucine diamide diacid **19**, that could then be used to couple to additional amines to give the desired tetraamides.



Scheme 5. A route to differently functionalized 2,2'4,4'-biphenyl tetraamides.

The trans-1,3,5-Trisubstituted Cyclohexane Core

A core molecule that combines a low molecular weight with conformational flexibility is provided by *trans*-1,3,5-cyclohexane (**3**). In this case, the source of the conformational flexibility is derived from two possible chair conformations (Figure 2), which have been calculated (see experimental section) to be 2 kcal/mol different in energy. The use of only three sites for diversity is mitigated by the three prochiral tertiary carbons. This causes the two β carboxyl sites to be inequivalent upon substitution with a chiral building block (such as an amino acid) and increases the number of compounds formed during library synthesis. Although it is structurally similar to Kemp's triacid[23] (**21**, Figure 2), already used for creating molecular diversity,[24] the triacid derivative of **3** offers several distinct advantages. It has a lower molecular weight (42 g/mol less than **21**) and its reactive sites diverge enough to diminish steric biases and allow greater access to the functionalities of the building blocks.

The synthesis of the activated core molecule was straightforward (Scheme 6). The hydrogenation product of trimesic acid (a mixture of 85:15 *cis*:*trans*) was converted into its anhydride (not isolated, see Scheme 6) and was heated in the presence of NaOAc, which epimerized the α-carbon of the non-anhydride carboxyl position to the more thermodynamically stable *trans* isomer.[25] The anhydride was hydrolyzed in the same pot to give the *trans*-triacid **22**. Activation using standard conditions afforded the triacid chloride **23**, which was reacted with amines to form triamides (**24**, for example).

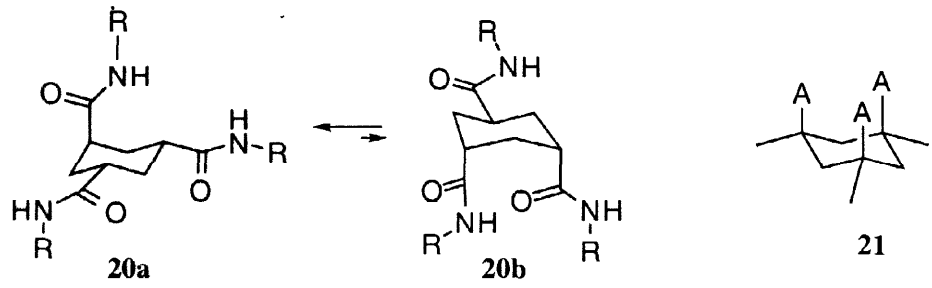
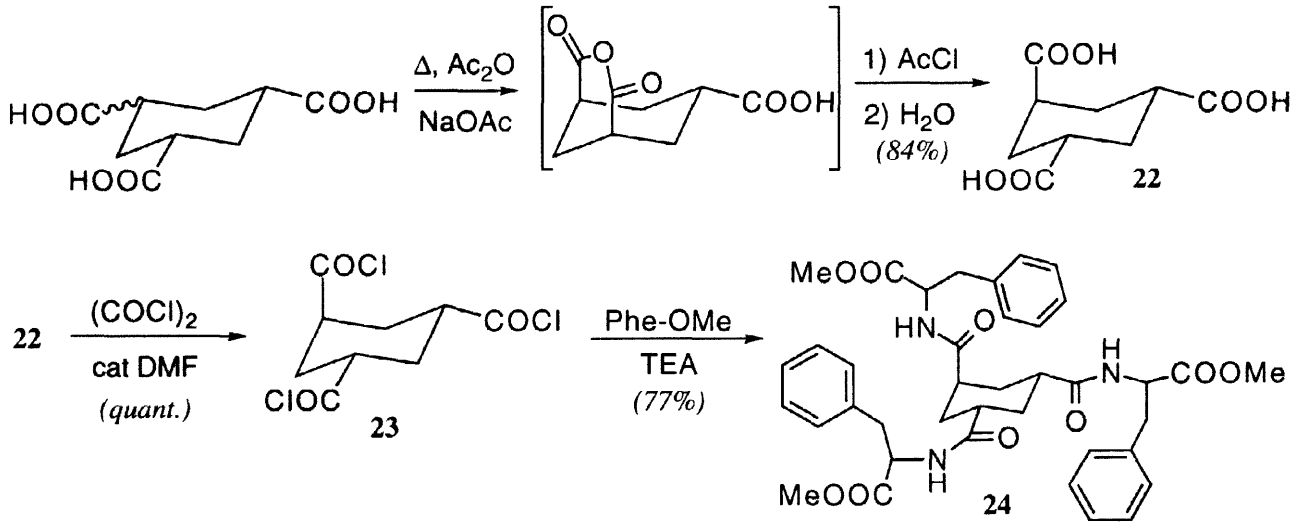


Figure 2. Molecular modeling (MM2*) indicates that the equatorial-equatorial conformation (**20a**) is 2 kcal/mol more stable (see experimental section) than the axial-axial conformation (**20b**), where R= benzyl. The structure of Kemp's triacid (**21**) (A= COOH) is given for comparison.

To date, a satisfactory method for deconvoluting the *trans*-1,3,5-cyclohexane core molecule has not been developed; however, a protocol involving the protection of the acid funtionality in the anhydride from Scheme 6 as a *t*-butyl ester, followed by attack of the anhydride by benzyl alcohol can be envisioned, and this should provide a racemic mixture of the two compounds containing one free acid and two different esters. Resolution of this mixture with an optically active base should provide the enantiomerically pure core with three distinct sites for reactivity.

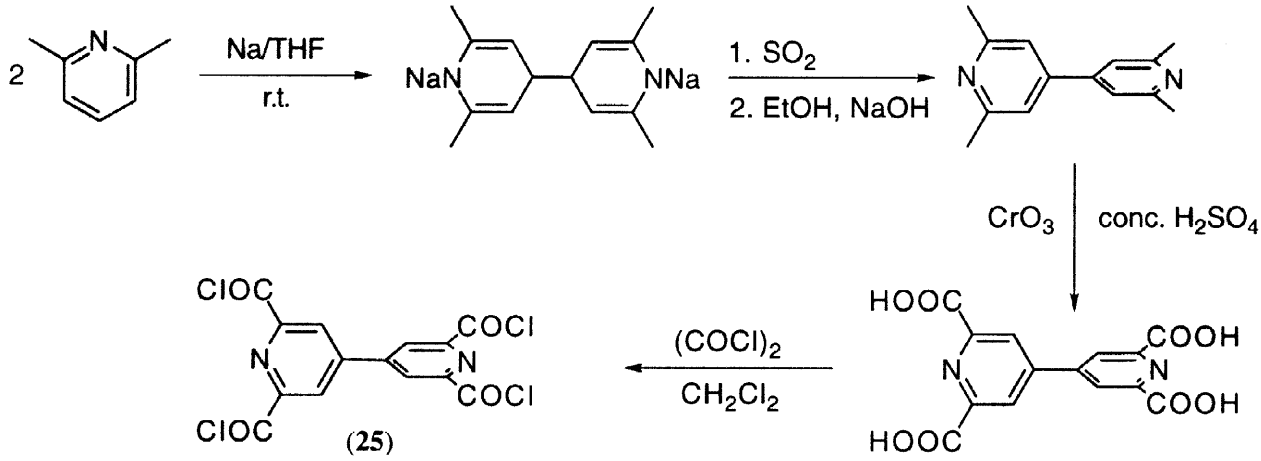


Scheme 6. Synthesis of the *trans*-1,3,5-cyclohexane triacid chloride activated core.

The 2,2',6,6'-(4,4'-Bipyridine) Core

While the substituents attached to the core molecule are intended to be the main sources of binding interactions, the incorporation of additional binding groups on the core molecule itself should increase the maximal activity of strongly-binding library components. One way this can be accomplished is to use core molecules that contain basic nitrogens that can be protonated or act as good hydrogen-bond acceptors in a complex with macromolecular targets. A review of relevant literature reveals that Hünig and co-workers synthesized a molecule, 2,2',6,6'-(4,4'-bipyridine)tetraacid chloride (**25**),[26] that meets this criterion; it was

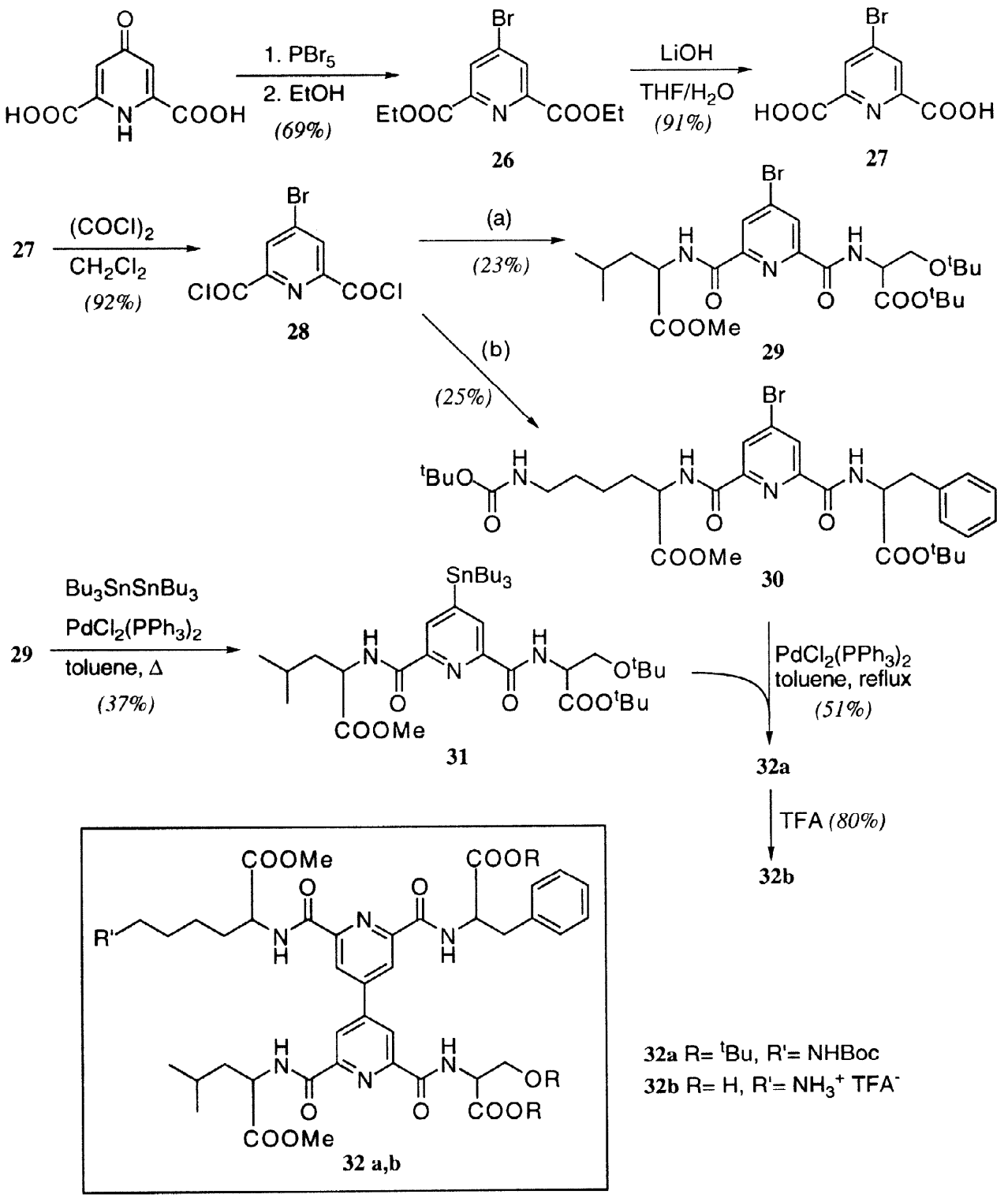
synthesized in this laboratory by similar procedures (Scheme 7). The ring nitrogens provide two more sites that can potentially increase the affinity of library members for binding partners.



Scheme 7. Synthesis of 2,2',6,6'-(4,4'-bipyridine)tetraacid chloride.

The route used to deconvolute libraries made with this core differs from those developed for the other core molecules described above in that rather than building the entire core with different protecting groups and attaching building blocks in a linear synthesis, a convergent synthesis is used that makes use of a Stille coupling[27] to create the bipyridyl bond once all substituents are already attached (see Scheme 8). In order to demonstrate the method's general utility, a synthesis of the hypothetical target molecue **32b** was undertaken. Compound **32b** was chosen because it contains a wide variety of amino acid substituents, including both free acids and methyl esters, and aliphatic, aromatic, heteroatomic, and charged side chains. By using one common intermediate, 4-bromo-2,6-bipyridinedicarboxylic acid chloride (**28**), various heterosubstituted 4-bromo-2,6-pyridinediamides (such as **29** and **30**) can be synthesized and purified (by silica gel column chromatography) from the two homodisubstituted compounds produced in the reaction. Then, by using a palladium-catalyzed stannyllation reaction[28] with bis(tributyltin) (which is tolerant of the amide functionality, unlike the transmetallation reactions involving an aryllithium or aryl Grignard and a trialkyltin halide more commonly used for stannyllation) a pyridylstannane (**31**) is produced. The subsequent Stille coupling and deprotection of the tetraamide proceed smoothly.

The four core molecules presented herein all were demonstrated to form amides from the reaction of a mixture of amines with activated carboxylic acid functionalities. In principle, any high-yielding and clean reaction could be applied to these cores and other linkers could be exploited. By expanding the variety of the geometries and chemical make-up of the core molecules used in the activated core molecule approach to combinatorial organic chemistry, an ever-widening range of libraries can be accessed.



Scheme 8. Deconvolution protocol for the 2,2',6,6'-(4,4'-bipyridine)tetraamide libraries. (a) L-leucine methyl ester hydrochloride, *O*-*t*-butyl-L-serine *t*-butyl ester hydrochloride, Et_3N, CH_2Cl_2. (b) N-Boc-L-lysine methyl ester hydrochloride, L-phenylalanine *t*-butyl ester hydrochloride, Et_3N, CH_2Cl_2.

EXPERIMENTAL SECTION

General. All reagents were purchased from Aldrich Chemical Company and were used without further purification except as noted. Amino acid esters, PyBOP, and HATU were acquired from Novabiochem (San Diego, CA). Deuterated solvents were obtained from Cambridge Isotopes Laboratories and deuterated chloroform was dried over 4 Å molecular sieves. Citric acid and HCl refer to 1 N stock solutions. NMR spectra were recorded on either a Bruker AC-250, a Bruker AM-300, or a Bruker DRX-600; TMS was used as a reference in some chloroform-*d* spectra, otherwise residual solvent was used as a reference. Either a Finnegan Mat 8200 (for HRMS/EI) or a VG ZAB-VSE (for HRMS/FAB) mass spectrometer was used to ascertain exact masses. FT-IR spectra were obtained on a Perkin Elmer Paragon 1000 PC FT-IR Spectrometer. Silica gel chromatography was performed with Silica Gel 60 (EM Science or Bodman, 230–400 mesh). TLC analysis was performed using glass-bound Silica Gel 60 (F254) plates.

Molecular Modeling. Molecular modeling was performed using Macromodel *v*5.5[29] and the MM2* force field, without solvent parameters. For the calculation of the energy difference between the two chair conformations (Figure 2) of *trans*-1,3,5-cyclohexane tribenzylamide, the two conformers were minimized independently and their total energy values subtracted to give 2.1 kcal/mol. This is roughly equivalent to the energy cost of placing two ethyl esters in a 1,3-diaxial relationship (2.2 kcal/mol), as computed by tabulated A values.[30] It is worth noting that molecular modeling did not recognize a hydrogen bond between the carbonyl oxygen of one building block and the amide -NH of the other building block when the 3,5-amides were both in axial positions. The presence of such a hydrogen bond would lower the energy of the diaxial conformer and increase its population relative to the diequatorial conformer.

Biphenyl 2,2',6,6'-tetracarboxylicacid (**5**). To pyrene (6.00 g, 29.7 mmol) in CH_2Cl_2 (120 mL) was added MeCN (120 mL) and water (180 mL). To the resulting biphasic solution was added $NaIO_4$ (60 g, 280 mmol) followed by Ru(III)Cl_3 (240 mg, 1.16 mmol). The solution warmed somewhat as the reaction began but was not vigorous. The reaction was run overnight (~16 h) with stirring and was filtered to give a yellow solid. The mixed solid (tetraacid/$NaIO_4$) was extracted with acetone (750 mL) and the acetone was refiltered to yield a yellow solution. Upon evaporation the product was identified as a mixture of the desired tetraacid and the corresponding dianhydride. The crude product was ground to a fine powder and was refluxed for 1 h in CH_2Cl_2 before being filtered hot. The tetraacid was collected as a white powder (7.4 g, 75% yield). m. p. >300° C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.4 (br s, 4 H), 7.96 (d, *J*= 7.6 Hz, 4 H), 7.45 (t, *J*= 7.8 Hz, 2 H). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 167.49, 142.07, 132.33, 131.82, 126.49. HRMS (FAB in NBA/NaI) calculated for $C_{16}H_{10}O_8Na$ $[M + Na]^+$ 353.0273, found 353.0264.

Biphenyl 2,2',6,6'-tetracarboxylicacid chloride (**7**). The tetraacid **5** (25 mg, 0.075 mmol) was suspended in CH_2Cl_2 (1.5 mL) and cooled prior to the addition of thionyl chloride (1 mL, excess) and DMF (2 μL, catalytic). The suspension was allowed to warm to room temperature under a $CaCl_2$ drying tube. After 1 h the suspension was warmed to reflux until a homogenous solution developed (about 4 h). After another hour at reflux the orange solution was concentrated to dryness, dry toluene was added, and the solution was concentrated again to

yield a yellow solid. After evacuation on a high vacuum for 1 h the compound (29 mg, 97%) appeared pure by NMR. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.57 (d, *J*= 8.1 Hz, 4 H), 7.81 (t, *J*= 8.1 Hz, 2 H).

Synthesis and isolation of benzylation products (**8a-e**). To a solution of the tetraacid chloride **7** (3.0 g, 7.5 mmol) in CH_2Cl_2 (250 mL) was added anhydrous benzyl alcohol (2.5 equiv, 2 mL, 20 mmol) followed by Et_3N (2.6 mL, 19 mmol). After stirring 12 h water (2 mL) was added and the solution was stirred vigorously for 2 h. After washing with HCl, the organic layer was evaporated to an orange oil. A similar procedure was carried out using 2 equiv of benzyl alcohol and the two samples of orange oil were pooled for separation (**8**). Silica-gel column chromatography using an acetic acid/hexane/EtOAc gradient provided good separation of most of the expected products. The compounds are presented in order of elution.

Biphenyl 2,2',6,6'-tetrabenzyl ester (**8a**). Large silver flakes (220 mg, 0.32 mmol). m.p. 101–105° C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.94 (d, *J*= 7.8 Hz, 4 H), 7.41 (t, *J*= 7.8 Hz, 2 H), 7.27 (m, 6 H), 7.12 (m, 4 H), 4.90 (s, 8 H). HRMS (FAB in NBA/CsI) calcd for $C_{44}H_{34}O_8Cs$ $[M + Cs]^+$ 823.1308, found 823.1323.

Biphenyl 2,2',6-tribenzyl ester-6'-carboxylic acid (**8b**). Gummy orange solid (1.40 g, 2.33 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, *J*= 7.9 Hz, 2 H), 8.05 (dd, *J*= 7.8, 1.4 Hz, 1 H), 8.02 (dd, *J*= 7.8, 1.5 Hz, 1 H), 7.42 (t, *J*= 7.9 Hz, 1 H), 7.32 (m, 13 H), 7.18 (m, 8 H), 5.00 (br s, 4 H), 4.98 (s, 2 H). HRMS (FAB in NBA/CsI) calcd for $C_{37}H_{28}O_8Cs$ $[M + Cs]^+$ 733.0839, found 733.0816.

Biphenyl 2,6-dibenzyl ester-2',6'-dicarboxylic acid (**8c**). Faint yellow powder (140 mg, 0.27 mmol). ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.11 (d, *J*= 7.9 Hz, 2 H), 8.03 (d, *J*= 7.7 Hz, 2 H), 7.51 (t, *J*= 7.7 Hz, 1 H), 7.37 (t, *J*= 7.9 Hz, 1 H), 7.27 (m, 6 H), 7.19 (m, 4 H), 4.96 (s, 4 H). HRMS (FAB in NBA/CsI) calcd for $C_{30}H_{22}O_8Cs$ $[M + Cs]^+$ 643.0369, found 643.0390.

Biphenyl 2,2'-dibenzyl ester-6,6'-dicarboxylic acid (**8d**). White powder (603 mg, 1.18 mmol). ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.09 (dd, *J*= 7.7, 1.6 Hz, 2 H), 8.04 (dd, *J*= 8.0, 1.5 Hz, 2 H), 7.44 (t, *J*= 7.8 Hz, 2 H), 7.3-7.25 (m, 6 H), 7.20-7.16 (m, 4 H), 4.97 (d, *J*= 12.5 Hz, 2 H), 4.91 (d, *J*= 12.3 Hz, 2 H). ^{13}C NMR (75.4 MHz, acetone-d_6) δ 167.18, 166.33, 149.36, 143.02, 136.58, 133.73, 133.41, 131.87, 128.84, 128.67, 128.47, 127.31, 66.66. HRMS (FAB in NBA/CsI) calcd for $C_{30}H_{22}O_8Cs$ $[M + Cs]^+$ 643.0369, found 643.0381.

Biphenyl 2-benzyl ester-2',6,6'-tricarboxylic acid (**8e**). The mono benzyl product was contaminated by residual dibenzyl ester **8d** which could not be removed.

Biphenyl 2,2'-dibenzyl ester-6,6'-diacid chloride (**9**). To a solution of **8d** (50 mg, 0.10 mmol) in CH_2Cl_2 (25 mL) was added a slight excess of thionyl chloride (35 μL, 0.30 mmol) at rt. Catalytic DMF (0.25 μL) was added and the solution was refluxed for 2 h under nitrogen. After drying under reduced pressure the product acid chloride **9** was recovered as a light yellow solid (50 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, *J*= 7.7 Hz, 2 H), 8.18 (d, *J*= 7.6 Hz, 2 H), 7.47 (t, *J*= 7.9 Hz, 2 H), 7.31 (m, 6 H), 7.14 (m, 4 H), 4.98 (s, 4 H).

Biphenyl 2,2'-dibenzyl ester-6,6'-dileucine-OtBu diamide (**10**). The diacid chloride **9** (50 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (20 mL) and a small excess of Leu-O*t*Bu·HCl (48 mg, 0.22 mmol) was added followed by an excess of Et_3N (22 mL, 0.30 mmol). The reaction mixture was stirred at rt for 1 h, at which time the reaction did not appear complete by TLC (4:1 hexane:EtOAc). An additional equivalent of leucine and triethylamine were added, immediately following which the TLC showed one major product. After washing with 0.5 N HCl and 0.5 N KOH the product diamide was recovered as a yellow semisolid. The mixture of diastereomers was isolated as a light yellow solid (75 mg). ^1H and ^{13}C NMR of the diastereomeric pair were consistent with the proposed structures. The diastereomers were partially separated by preparative TLC (4:1 hexane:EtOAc) to allow peak assignment. The ^1H NMR of the lower R_f product appears as follows and the spectra of the isomer may be extrapolated based on comparison to the crude mixture. Integrations are approximate due to overlap with the residual diastereomer. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.38 (d, *J*= 9 Hz, 2 H), 7.99 (dd, *J*= 8, 1 Hz, 1 H), 7.49 (dd, *J*= 7.7, 1 Hz, 1 H), 7.33 (t, *J*= 7.6 Hz, 1 H), 7.29-7.19 (m, 13 H), 5.03 (s, 4 H), 4.30 (m, 2 H), 1.31 (s, 18 H), 1.21 (m, 6 H), 0.79 (d, *J*= 8.0 Hz, 6 H), 0.75 (d, *J*= 8.0 Hz, 6 H). LRMS of diastereomeric mixture (FAB in NBA/CsI) calcd for $C_{50}H_{61}O_{10}N_2$ $[M + H]^+$ 849.4, found 849.

Biphenyl 2,2'-diacid-6,6'-dileucine-OtBu diamide (**11**). To the dileucine diester **10** (70 mg, 0.084 mmol) in 4:1 EtOAc:EtOH (10 mL) was added 5% Pd/C (25 mg, cat) and the suspension was stirred at rt under a hydrogen atmosphere for 2 h. The (3:2 ratio of) diastereomeric diacid products was then filtered through Celite to remove the Pd/C and dried to a fine white powder (50 mg, 89%). ^1H NMR of the diastereomeric mixture was consistent with the proposed structures. The amide protons had very different shifts due to differences in hydrogen-bonding microenvironments (δ 8.94 versus δ 8.04). HRMS of the mixture (FAB in NBA/CsI) calcd for $C_{36}H_{48}O_{10}N_2Cs$ $[M + Cs]^+$ 801.2363, found 801.2341.

Biphenyl 2,2',6,6'-tetraleucine-OtBu tetraamide (**12**). To a solution of **11** in dry DMF (5 mL) was added leucine-O*t*Bu·HCl (26 mg, 0.12 mmol, 2.2 equiv) and Et_3N (23 μL, 0.16 mmol, 3.0 equiv). The solution was chilled to 0° and treated with HATU (44 mg, 0.12 mmol, 2.2 equiv) to give a bright yellow solution. After stirring at 0° the yellow color had faded and the reaction appeared incomplete by TLC (4:1 hexane:EtOAc). An excess of Et_3N was added to drive the reaction to completion and after 1 h at rt only one major product was observed. The reaction mixture was diluted with EtOAc (25 mL), washed (2x HCl, 2x sat $NaHCO_3$), dried with Na_2SO_4, and evaporated to provide the pure tetraleucine tetraamide as a white powder (95 mg, 78%). This compound was identical to the tetraleucine synthesized using 4.4 equiv of leucine and 1 equiv of biphenyl tetraacid chloride. HPLC analysis: >90% pure (λ= 254 nm). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.67 (d, *J*= 8 Hz, 4 H), 7.47 (d, *J*= 8 Hz, 4 H), 7.30 (t, *J*= 8 Hz, 2 H), 4.30 (m, 4 H), 1.31 (s, 36 H), 1.29 (m, 12 H), 0.79 (d, *J*= 6 Hz, 24 H). HRMS (FAB in NBA/CsI) calcd for $C_{56}H_{87}O_{12}N_4$ $[M + H]^+$ 1007.6320, found 1007.6349.

1,3-Dimethyl-4-bromobenzene dicarboxylate (**13**). To a suspension of 4-bromoisophthalic acid (10.0 g, 0.0410 mol) in MeOH (150 mL) at 0° was added thionyl chloride (10.0 mL, 0.140 mol) dropwise. The reaction was allowed to stir for 24 h before it was filtered and concentrated. The resulting oil was taken up in CH_2Cl_2 (250 mL) and was rinsed with saturated $NaHCO_3$ (2x 35 mL). Upon concentration and standing, a white, oily solid formed. Trituration with hexanes gave a white powder (10.1 g, 90%). m. p. 59–60° C. ^1H NMR ($CDCl_3$, 300

MHz): δ 8.43 (d, *J*= 2.0 Hz, 1 H), 7.94 (dd, *J*= 8.3, 2.1 Hz, 1 H), 7.75 (d, *J*= 8.2 Hz, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H). HRMS (FAB in NBA/NaI) calcd for $C_{10}H_{10}O_4Br$ $[M + H]^+$ 272.9762, found 272.9772.

2,2',4,4'-Biphenyl tetramethyl ester (**14**). The dimethyl ester **13** (6.00 g, 22.0 mmol) was pulverized with Cu powder (4.2 g, 66 mmol) and the mixture was added to a 100 mL pressure tube sealed with a teflon cap. This was heated to 200° C for 4 h, cooled to rt, and the brown solid was extracted (4x 100 mL 5% MeOH in $CHCl_3$, with sonication). Filtration and concentration gave a solid that was preloaded onto silica gel with neat CH_2Cl_2. Elution (CH_2Cl_2→10:1 CH_2Cl_2:MeOH), followed by concentration of the pure fractions resulted in a white powder (2.49 g, 44%). R_f= 0.3 (20:1 CH_2Cl_2:MeOH). m. p. 185–186° C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.70 (d, *J*= 1.9 Hz, 2 H), 8.20 (dd, *J*= 8.0 Hz, 1.9 Hz, 2 H), 7.26 (d, *J*= 7.8 Hz, 2 H), 3.95 (s, 6 H), 3.66 (s, 6 H). HRMS (FAB in NBA/NaI) calcd for $C_{20}H_{19}O_8$ $[M + H]^+$ 387.1080, found 387.1089.

2,2',4,4'-Biphenyl tetraacid (**15**). The tetraester **14** (1.39 g, 3.59 mmol) was suspended in a solution of THF (75 mL), methanol (7.5 mL), and 2 N NaOH (28 mL). After 2 h at rt the solution was warmed to reflux for 3 h. The solvents were evaporated and water (50 mL) was added. Acidification to pH 1 with conc HCl produced a precipitate, which was filtered (after standing overnight at 0°C) to afford a white solid (1.09 g, 92%). m. p. >300° C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 13.1 (br s, 4 H), 8.45 (d, *J*= 1.4 Hz, 2 H), 8.09 (dd, *J*= 8.0, 1.7 Hz, 2 H), 7.31 (d, *J*= 8.0 Hz, 2 H). ^{13}C (DMSO-d_6, 75.4 MHz) δ 166.89, 166.68, 146.98, 131.96, 130.65, 130.34, 129.95. HRMS (FAB in NBA/NaI) calcd for $C_{16}H_{10}O_8Na$ $[M + Na]^+$ 353.0273, found 353.0257.

2,2',4,4'-Biphenyl tetraacid chloride (**16**). To the biphenyl tetraacid **15** (250 mg, 0.75 mmol) suspended in $CHCl_3$ (15 mL) was added $SOCl_2$ (10 mL, excess), followed by DMF (5 μL, cat). After stirring for 30 min at rt the suspension was warmed to reflux for 2.5 h, at which point the solution became clear. Concentration of the solution gave a white solid, toluene was added, and the suspension was again evaporated to give a white solid (296 mg, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.03 (d, *J*= 2.0 Hz, 2 H), 8.42 (dd, *J*= 8.5, 2.1 Hz, 2 H), 7.25 (d, *J*= 8.4 Hz, 2 H).

4,4'-Bis(Diphenylmethyl) biphenyl dicarboxylate-2,2'-dicarboxylic acid (**17**). Acetic anhydride (0.15 mL, 1.6 mmol) was added to the biphenyl tetraacid **16** (0.40 g, 1.2 mmol) in THF (8 mL). The turbid solution was warmed to reflux under a drying tube for 8 h, more Ac_2O (0.05 mL, 0.5 mmol) was added, and the solution was stirred for 12 h at rt. Concentration afforded a white solid that appeared by ^{1}H NMR to be 80% desired product. The crude anhydride was suspended in acetone (10 mL) and diphenyldiazomethane (0.65 g in 10 mL acetone, 3.35 mmol) was added dropwise. The flask was protected from light and was stirred under nitrogen for 48 h, during which time the red suspension was observed to almost completely decolorize. To hydrolyze the anhydride, Na_2CO_3 (1 N, 30 mL) was added and the suspension was stirred for 1 h. Acidification to pH 2 using 2 N HCl and subsequent extraction (3x 30 mL $CHCl_3$) and drying over $MgSO_4$ produced a viscous oil. Silica gel chromatography (20:1→4:1 CH_2Cl_2:MeOH) was used to isolate a polar compound (R_f= 0.2, 10:1 CH_2Cl_2:MeOH). Partial concentration, followed by cooling of the product fractions, gave white, fluffy crystals (160 mg, 20%). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.01 (br s, 2 H), 7.90 (d, *J*= 6.9 Hz, 2 H), 7.50 (d, *J*= 7.5 Hz, 8 H), 7.38 (t, *J*= 7.7 Hz, 8 H), 7.30 (t, *J*= 7.4 Hz, 4 H), 7.11 (d, *J*= 7.6 Hz, 2 H), 7.07 (s, 2 H). LRMS

(ESI +) calcd for $C_{42}H_{30}O_8Na$ $[M + Na]^+$ 685, found 685. LRMS (ESI –) calcd for $C_{42}H_{29}O_8$ $[M - H]^-$ 661, found 661.

Biphenyl 2,2'-dileucine diamide-4,4'-diphenylmethyl dicarboxylate (**18**). PyBOP (42 mg, 0.080 mmol) and **17** (20 mg, 0.030 mmol) were dissolved in DMF (2 mL). After 5 min DIEA (0.028 mL, 0.16 mmol) and Leu-OtBu·HCl (18 mg, 0.080 mmol) in DMF (1 mL) were added to the biphenyl-PyBOP flask under a drying tube. After 12 h, water (10 mL) and CH_2Cl_2 (25 mL) were added; the organic layer was rinsed (1x 10 mL water, 1x 10 mL citric acid) and dried over $MgSO_4$. Concentration gave an oil which was preloaded onto SiO_2 and chromatographed (5:1 hexanes:EtOAc, R_f= 0.9) to give a white solid (25 mg, 83%). ^1H NMR (acetone-d_6, 300 MHz): δ 8.42 (d, *J*= 8.0 Hz, 2 H), 8.30 (s, 2 H), 8.22 (dd, *J*= 8.0, 1.6 Hz, 2 H), 7.55 (d, *J*= 7.7 Hz, 8 H), 7.41 (t, *J*= 8.0 Hz, 8 H), 7.33 (t, *J*= 7.6 Hz, 4 H), 7.16 (s, 2 H), 4.26 (q, *J*= 7.3 Hz, 2 H), 1.43-1.3 (m, 24 H), 0.74 (m, 12 H). HRMS (FAB in NBA/CsI) calcd for $C_{62}H_{68}N_2O_{10}Cs$ $[M + Cs]^+$ 1133.3928, found 1133.3923.

Biphenyl 2,2'-dileucine diamide-4,4'-dicarboxylic acid (**19**). A solvent mixture of 4:1 EtOAc:EtOH (5 mL) was used to dissolve **18** (20 mg, 0.020 mmol). To this was added 10% Pd/C (5 mg, cat) and the flask was evacuated and back-filled three times with H_2 (atm). Stirring for 3 h, filtration through Celite, and concentration gave an oily white solid. Trituration with hexanes gave the product as a white solid in quantitative yield. ^1H NMR (acetone-d^6, 300 MHz,): δ 11.5 (br s, 2 H), 8.39 (d, *J*= 8.2 Hz, 2 H), 8.22 (d, *J*= 1.1 Hz, 2 H), 7.29 (d, *J*= 7.9 Hz, 2 H), 4.29 (q, *J*= 7.4 Hz, 2 H), 1.5-1.1 (m, 24 H), 1.16 (m, 2 H), 0.79 (m, 12 H). HRMS (FAB in NBA/CsI) calcd for $C_{36}H_{47}O_{10}N_2Cs_2$ $[M - H^+ + 2Cs^+]^+$ 933.1339, found 933.1301.

trans-1,3,5-Cyclohexane tricarboxylic acid (**22**).[25] To a mixture of *cis* and *trans*-1,3,5-cyclohexane tricarboxylic acid (10.9 g, 50.3 mmol) was added NaOAc (1.00 g, 12.2 mmol) and Ac_2O (20 mL, 210 mmol). After refluxing for 4 h under a drying tube the solution was cooled to rt and acetyl chloride (10.0 mL 141 mmol) was added. The light green solution was refluxed for 2 h. Upon cooling a white precipitate formed and the mixture was filtered. The solid was discarded and the filtrate was poured into water (100 mL) and stirred for 16 h at rt. Concentration of the resulting solution to one-tenth of its original volume gave a fluffy white solid, which was filtered and recrystallized from water to give a white solid (9.14 g, 84%). m. p. 208–211° C. ^1H NMR (DMSO-d_6, 600 MHz): δ 12.28 (s, 3 H), 2.81 (t, *J*= 2.2 Hz, 1H), 2.35 (tt, *J*= 12.4, 3.3 Hz, 2 H), 2.16 (d, *J*= 13 Hz, 2 H), 2.04 (d, *J*= 13 Hz, 1 H), 1.41 (td, *J*= 13.2, 5 Hz, 2 H), 1.33 (q, *J*= 12.7 Hz, 1 H). LRMS (ESI –) calcd for $C_9H_{11}O_6$ $[M - H]^-$ 215, found 215.

trans-1,3,5-Cyclohexane tricarboxylic acid chloride (**23**). The cyclohexane tricarboxylic acid **22** (0.50 g, 2.8 mmol) was suspended in CH_2Cl_2 (50 mL), and oxalyl chloride (1.5 mL, 17 mmol) was added, followed by DMF (2 μL, cat). After stirring for 1 h at rt the system was heated to reflux for 3 h to give a clear solution. Evaporation of the solvent gave a slightly yellow oil in quantitative yield. ^1H NMR (acetone-d_6, 300 MHz): δ 2.85 (m, 1 H), 2.47 (tt, *J*= 12.5, 3.5, 2 H), 2.25 (d, *J*= 13.5 Hz, 2 H), 2.14 (d, *J*= 13.1 Hz, 1 H), 1.47 (td, *J*= 13.1, 5.0 Hz, 2 H), 1.38 (q, *J*= 12.7 Hz, 1 H).

trans-1,3,5-Cyclohexane triphenylalanine-OMe triamide (**24**). To the cyclohexane tricarboxylic acid chloride **23** (50 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) was added Phe-OMe·HCl (136 mg, 0.627 mmol) and Et_3N (180 μL, 1.3 mmol) in CH_2Cl_2 (6 mL). After 2 h at rt the mixture was transferred to a separatory funnel with CH_2Cl_2 (20 mL); the solution was rinsed with citric acid, dried over $MgSO_4$, filtered, and concentrated to a white foam (102 mg, 77%). HPLC analysis (λ= 258 nm) indicated this compound to be ≥87% pure. ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.72-7.67 (m, 2 H), 7.61 (d, *J*= 7.7 Hz, 1 H), 6.73-6.55 (m, 15 H), 3.89-3.81 (m, 3 H), 3.03 (s, 3 H), 3.02 (s, 3 H), 3.01 (s, 3 H), 2.85 (m, 1 H), 2.50-2.30 (m, 6 H), 2.07 (d, *J*= 12 Hz, 2 H), 1.92 (d, *J*= 12 Hz, 1 H), 1.15 (d, *J*= 12 Hz, 1 H), 0.95 (appar t, *J*= 12 Hz, 1 H), 0.83-0.75 (m, 2 H), 0.56 (q, *J*= 12 Hz, 1 H). HRMS (FAB in NBA/CsI) calcd for $C_{39}H_{45}N_3O_9Cs$ $[M + Cs]^+$ 832.2210, found 832.2231.

2,2',6,6'-(4,4'-Bipyridine)tetracarboxylic acid chloride (**25**).[26] All intermediates were prepared according to Ref. 26. A modification of the synthesis of **25** was used as follows. A CH_2Cl_2 (70 mL) suspension of 2,2',6,6'-(4,4'-bipyridine)tetracarboxylic acid (1.00 g, 3.01 mmol), oxalyl chloride (2.1 mL, 24 mmol) and six drops of a 4% solution of DMF in CH_2Cl_2 was refluxed under nitrogen for 17 h. The solution was filtered through Celite and concentrated to yellow solids, which were recrystallized from hot toluene to yield a white powder (0.796 g, 65%).

Diethyl 4-bromo-2,6-pyridinedicarboxylate (**26**).[31] Procedure adapted from Ref. 31. Chelidamic acid monohydrate (6.32 g, 31.4 mmol) and phosphorus pentabromide (63 g, 150 mmol) were heated to 90° C, whereupon the solids formed a melt. This was stirred at 90° C for 1 h 45 min. After the solution cooled, 45 mL chloroform was added and the solution was filtered. The filtrate was chilled in an ice bath as 250 mL ethanol was slowly added to the solution. All solvent was removed by rotary evaporation, as well as a high boiling, oily, clear liquid, yielding dirty crystals. Recrystallization from ethanol yielded pale yellow crystals (6.56 g, 69%).

4-Bromo-2,6-pyridinedicarboxylic acid (**27**). To a solution of **26** (8.6 g, 28 mmol) in 200 mL THF was added a solution of lithium hydroxide monohydrate (2.9 g, 69 mmol) in 40 mL water. This was stirred together for 2 h 45 min, then the solution was acidified to pH 0-1 with concentrated hydrochloric acid. The acidified solution solidified upon standing; with the addition of more water and sonication the solids broke up and were filtered, then dried on a steam bath, yielding a white powder (7.07 g, 91%). m.p. 205–209° C (dec.). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 8.35 (s, 2H). ^{13}C NMR (DMSO-d_6, 151 MHz): δ 164.89, 150.18, 134.45, 130.37. FT-IR (KBr pellet, cm^{-1}): 684, 719, 805, 897, 1174, 1207, 1314, 1400, 1477, 1573, 1732, 3093, 3385, 3489. HRMS (FAB in NBA/NaI) calcd for $C_7H_4BrNO_4$ $[M]^+$ 245.9402, found 245.9404.

4-Bromo-2,6-pyridinedicarboxylic acid chloride (**28**). To a suspension of **27** (7.06 g, 25.8 mmol) in 290 mL CH_2Cl_2 was added oxalyl chloride (8.6 mL, 13 g, 99 mmol) and catalytic DMF (6 drops 4% solution in CH_2Cl_2). The stirred suspension was refluxed for 20 h. The cooled solution was filtered through Celite to remove hazy undissolved material and the solution was concentrated. The residue was dissolved in toluene and again the solvent was removed by rotary evaporation, yielding salmon-colored micro crystals (7.41 g, 92%). m. p. 105–108° C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.49 (s, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 168.90, 150.10, 136.35, 132.21. FT-IR (NaCl disc, cm^{-1}): 3077.4, 1759.8, 1554.3, 1427.9, 1251.8, 987.9, 937.7, 926.8, 908.0, 710.9. LRMS (ESI +) calcd for $C_7H_3BrCl_2NO_2$ $[M + H]^+$ 274/276, found 274/276.

4-Bromo-2-(leucine methyl ester)-6-(O-t-butylserine t-butyl ester)pyridine (**29**). To a chilled (0°C) solution of leucine methyl ester hydrochloride (1.26 g, 6.93 mmol) and *O-t*-butylserine *t*-butyl ester hydrochloride (1.76 g, 6.93 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (3 mL) and a solution of **28** (1.96 g, 6.30 mmol) in CH_2Cl_2 (25 mL). This was stirred under nitrogen for 13 h, warming to rt. The solution was diluted to 100 mL with CH_2Cl_2 and was washed with HCl, saturated $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to off-white solids. Compound **29** was separated from the other two diamides formed by silica gel column chromatography (8:1 Hexane:EtOAC) and was isolated as a pale yellow oil (0.843 g, 23%). ^1H NMR ($CDCl_3$, 600 MHz): δ 8.52 (d, *J*= 1.4 Hz, 1 H [low intensity]), 8.50 (d, *J*= 1.5 Hz, 1 H [low intensity]), 8.44 (d, *J*= 8.5 Hz, 1 H), 8.10 (d, *J*= 8.3 Hz, 1 H), 4.84–4.81 (m, 1 H), 4.79 (dt, *J*= 8.4 Hz, 3.0 Hz, 1 H), 3.95 (dd, *J*= 2.7 Hz, 9.0 Hz, 1 H), 3.78 (s, 3 H), 3.71 (dd, *J*= 3.1 Hz, 9.0 Hz, 1 H), 1.83–1.74 (m, 3 H), 1.50 (s, 9 H), 1.20 (s, 9 H), 1.01 (d, *J*= 4.5 Hz, 3 H), 1.00 (d, *J*= 4.5Hz, 3 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 173.10, 169.32, 162.44, 162.28, 149.96, 149.61, 136.39, 128.93, 128.81, 82.29, 73.45, 62.24, 53.64, 52.49, 51.18, 41.56, 28.06, 27.40, 24.96, 22.90, 21.89. HRMS (FAB in NBA/NaI) calcd for $C_{25}H_{38}BrN_3O_7Na$ $[M + Na]^+$ 594.1791, found 594.1766.

4-Bromo-2-(N-Boc-lysine methyl ester)-6-(phenylalanine t-butyl ester)pyridine (**30**). To a chilled (0°C) solution of *N*-Boc-lysine methyl ester hydrochloride (1.06 g, 3.57 mmol) and phenylalanine *t*-butyl ester hydrochloride (0.92 g, 3.6 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (3 mL) and **28** (1.01 g, 3.25 mmol). The solution was stirred for 17 h loosely capped, warming to rt. The solution was diluted to 50 mL with CH_2Cl_2 and was washed with HCl, saturated $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to a yellow oil. Compound **30** was separated from the other two diamides formed by silica gel column chromatography (4:1 Hexane:EtOAC) and was isolated as a white solid (0.565 g, 25%). m.p. 50–54° C. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.50 (d, *J*= 2.0 Hz, 1 H), 8.48 (d, *J*= 1.9 Hz, 1H), 8.13 (d, *J*= 7.9 Hz, 1 H), 8.03 (d, *J*= 8.1 Hz, 1 H), 7.31–7.29 (m, 2 H), 7.25–7.22 (m, 3 H), 4.95–4.92 (m, 1 H), 4.78–4.74 (m, 1 H), 4.65 (br. t, 1 H), 3.80 (s, 3 H), 3.24 (d, *J*= 6.0 Hz, 2 H), 3.14–3.04 (m, 2 H), 2.04–1.97 (m, 1 H), 1.85–1.79 (m, 1 H), 1.54–1.47 (m, 2 H), 1.43–1.36 (m, 20 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 172.54, 170.61, 162.43, 162.00, 156.30, 149.83, 149.67, 136.64, 136.31, 129.85, 128.98, 128.84, 127.42, 82.92, 54.09, 52.74, 52.54, 40.33, 38.34, 32.23, 29.55, 28.51, 28.10, 22.76. FT-IR (NaCl disc, cm^{-1}): 3341.7, 2976.2, 2932.1, 1736.3, 1676.7, 1523.0, 1454.7, 1365.8, 1249.2, 1155.2, 912.4, 842.6, 730.2. HRMS (FAB in NBA/CsI) calcd for $C_{32}H_{43}BrN_4O_8Cs$ $[M + Cs]^+$ 823.1319 / 825, found 823.1344 / 825.

4-(tri-n-Butylstannyl)-2-(leucine methyl ester)-6-(O-t-butylserine t-butyl ester)pyridine (**31**). A solution of **29** (0.843 g, 1.47 mmol), bis(tributyltin) (2.3 mL, 4.5 mmol), and dichlorobis(triphenylphosphine) palladium (II) (11.4 mg, 0.0162 mmol) in toluene (10 mL) was stirred and heated to 80°C. A brown color developed as the reaction progressed. The solution was heated for 2 h 40 min, then after cooling it was concentrated to a dark brown oil. Column chromatography (8:1 hexane:EtOAc), after elution of excess bis(tributyltin), yielded a clear oil (0.430 g, 37%). ^1H NMR ($CDCl_3$, 600 MHz): δ 8.55 (br. t, *J*= 7.8 Hz, 1 H), 8.45[32](d, *J*= 5.4 Hz, 2 H), 8.22 (br. t, *J*= 8.3 Hz, 1 H), 4.84–4.80 (m, 2H), 3.95 (dd, *J*= 2.7, 8.7 Hz, 1 H), 3.77 (s, 3 H), 3.70 (dd, *J*= 2.8, 8.7 Hz, 1 H), 1.82–1.77 (m, 3 H), 1.53–1.46 (m, 15 H), 1.38–1.35 (m, 6 H), 1.20 (s, 12 H), 1.18–1.10 (m, 6 H), 1.02–1.00 (m, 6 H), 0.87 (t, *J*= 7.3 Hz, 9 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 173.66, 169.81, 164.90, 164.64, 158.42, 146.18, 146.13, 133.33, 133.25, 82.40, 73.78, 53.50, 52.38, 50.41, 40.98, 28.91,

27.99, 27.30, 27.25, 24.92, 22.89, 21.71, 13.55, 9.76. HRMS (FAB in NBA/CsI) calcd for $C_{37}H_{65}N_3O_7SnCs$ [M + Cs]$^+$ 915.5332, found 915.5368.

2-(leucine methyl ester)-6-(O-t-butylserine t-butyl ester)-2'-(N-Boc-lysine methyl ester)-6'-(phenylalanine t-butyl ester)-4,4'-bipyridine (**32a**). A toluene (5 mL) solution of **30** (0.389 g, 0.562 mmol), **31** (0.420 g, 0.537 mmol), and dichlorobis(triphenylphosphine) palladium (II) (18.9 mg, 0.0269 mmol) was refluxed for 17 h, turning from yellow to brown in color over this period. The solution was concentrated to brown solids and column chromatography (4:1→3:1 hexane:EtOAc gradient) yielded a thick, clear oil (0.305 g, 51%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.75–8.73 (m, 4H), 8.57 (d, *J*= 8.5 Hz, 1 H), 8.26 (d, *J*= 8.1 Hz, 1 H), 8.23 (d, *J*= 8.2 Hz, 1 H), 7.32–7.24 (m, 5 H), 5.01 (dt, *J*= 2.7, 8.9 Hz, 1 H), 4.91–4.81 (m, 3 H), 4.68 (br. t, 1 H), 3.97 (dd, *J*= 2.7, 8.9 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.75 (dd, *J*= 2.8, 8.9 Hz, 1 H), 3.28 (d, *J*= 6.0 Hz, 2 H), 3.29–3.05 (m, 2 H), 2.03–2.00 (m, 1 H), 1.86–1.81 (m, 4 H), 1.55–1.52 (m, 11 H), 1.45 (br. s, 11 H), 1.40 (s, 9 H), 1.22 (s, 9 H), 1.03 (d, *J*= 5.7 Hz, 3 H), 1.02 (d, *J*= 5.7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 173.34, 172.68, 170.78, 169.55, 163.11, 163.00, 162.91, 162.57, 156.28, 150.44, 150.27, 150.17, 150.13, 147.92, 147.66, 136.36, 129.87, 128.79, 127.37, 123.25 (3 overlapping peaks), 123.18, 82.83, 82.34, 79.16, 73.57, 62.50, 54.03, 53.65, 52.66, 52.50 (2 overlapping peaks), 51.20, 41.61, 40.30, 38.41, 32.20, 29.60, 28.46, 28.11, 28.07, 27.45, 25.02, 22.98, 22.76, 21.93. FT-IR (NaCl disc, cm^{-1}): 3335.5, 2974.7, 2933.7, 2249.6, 1741.0, 1677.5, 1522.3, 1456.1, 1366.6, 1248.9, 1158.1, 903.5, 847.2, 733.0. HRMS (FAB in NBA/CsI) calcd for $C_{57}H_{81}N_7O_{15}Cs$ [M + Cs]$^+$ 1236.4845, found 1236.4913.

2-(leucine methyl ester)-6-serine-2'-(lysine methyl ester, trifluoroacetate salt)-6'-(phenylalanine)-4,4'-bipyridine (**32b**). Compound **32a** (0.208 g, 0.230 mmol) was stirred at rt in TFA for 19 h. The TFA was removed by rotary evaporation, and the resulting oil was precipitated by sonication with 1:1 Et_2O/hexane. Filtration yielded a white powder (0.143 g, 80%). m.p. 153–158° C (dec.). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 13.0 (br. s), 9.53 (d, *J*= 7.9 Hz, 1 H), 9.51 (d, *J*= 8.1 Hz, 1 H), 9.43 (d, *J*= 7.8 Hz, 1 H), 9.32 (d, *J*= 8.1 Hz, 1 H), 8.58–8.52 (m, 4 H), 7.72 (br. s, 3 H), 7.38 (d, *J*= 7.4 Hz, 2 H), 7.25 (t, *J*= 7.5 Hz, 2 H), 7.17 (t, *J*= 7.4 Hz, 1 H), 5.11 (br. s, 1 H), 4.68–4.57 (m, 4 H), 3.93 (d, *J*= 5.3 Hz, 2 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 3.33 (dd, *J*= 4.3, 13.8 Hz, 1 H), 3.24 (dd, *J*= 10.8, 13.5 Hz, 1 H), 2.82–2.78 (m, 2 H), 2.03–1.91 (m, 3 H), 1.77–1.60 (m, 4 H), 1.48–1.42 (m, 2 H), 0.95 (d, *J*= 6.3 Hz, 3 H), 0.92 (d, *J*= 6.3 Hz, 3 H). ^{13}C NMR (DMSO-d_6, 151 MHz): δ 172.67, 172.51, 171.93, 171.46, 163.20, 163.04, 162.88, 162.84, 149.83, 149.60 (2 overlapping peaks), 149.42, 137.97, 129.17, 128.22, 126.43, 122.65, 122.60, 122.52 (2 overlapping peaks), 60.80, 55.44, 54.42, 52.26, 52.11, 52.07, 50.96, 39.28, 38.64, 36.11, 30.05, 26.59, 24.56, 22.77, 22.52, 21.41. FT-IR (KBr pellet, cm^{-1}): 3351.1, 2959.9, 1734.2, 1653.3, 1534.0, 1200.0, 900.1, 651.1. HRMS (FAB in NBA/CsI) calcd for $C_{40}H_{49}N_7O_{13}Cs$ [M + Cs]$^+$ 968.2443, found 968.2410.

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