Total Synthesis of Vancomycin—Part 1: Design and Development of Methodology

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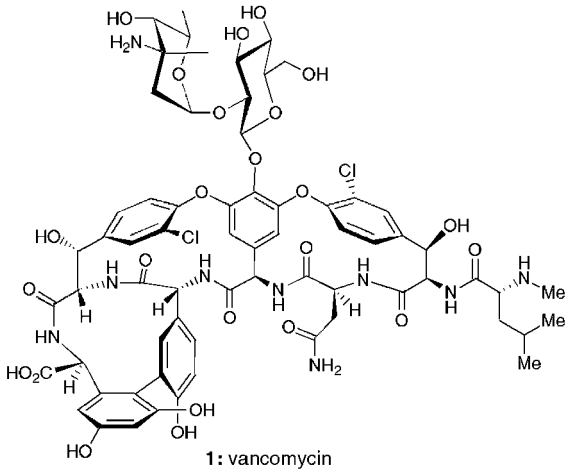
Abstract: *o*-Halosubstituted aromatic triazenes (e.g. **I**, Scheme 1) react with aryloxides (e.g. **II**, Scheme 1) in the presence of $CuBr \cdot Me_2S$, K_2CO_3 and pyridine in acetonitrile at reflux to afford biaryl ethers (e.g. **V**, Scheme 1). This general methodology (Tables 1 and 2) was applied to the construction of the C-O-D and D-O-E vancomycin model systems **37** (Scheme 2) and **50** (Scheme 3), demonstrating its potential in a projected total synthesis of vancomycin (**1**, Figure 1). For the construction of the vancomycin model AB biaryl ring system, a sequential strategy involving a Suzuki coupling of the C-O-D aryl iodide **74** (Scheme 7) and boronic acid **53** (Scheme 4), followed by macrolactamization was demonstrated, in which the preformed C-O-D ring framework served to preorganize the precursor for cyclization. The latter investigation led to Suzuki-coupling-based asymmetric synthesis of biaryl systems in which 2,2-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) was found to be the optimum ligand (Tables 3 and 4).

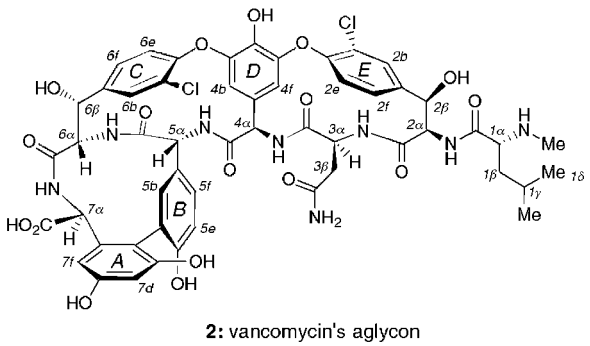
Keywords: amino acids · antibiotics · synthetic methods · total synthesis · vancomycin

Introduction

The discovery and development of penicillin[1] as a drug to fight infectious diseases followed by an avalanche of several other antibacterial agents meant a milestone victory of humankind over bacteria. While these agents saved millions of lives, they did not tame bacteria. On the contrary, this war led to the emergence of newer and more dangerous bacterial strains, which responded defiantly against the known antibacterial agents. Vancomycin (**1**, Figure 1), a prominent member of the glycopeptide class of antibiotics,[2] proved to be, for a number of decades now, the last line of defense against such bacteria. But even vancomycin (**1**) has elicited evolution of bacterial strains which are resistant to its action and which are beginning to threaten the very foundation of



1: vancomycin



2: vancomycin's aglycon

Figure 1. Molecular structures of vancomycin (**1**) and vancomycin's aglycon (**2**).

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our defenses against the bacterial kingdom.[3, 4] Because of the need for newer antibiotics effective against drug-resistant bacteria and in search of new basic knowledge that may facilitate the drug discovery process within the vancomycin field, we embarked on a program directed at the total synthesis of vancomycin (**1**). In this and the following three articles,[5–7] we lay out the details of our investigations that culminated in the development of a number of synthetic technologies and strategies[8] and the eventual total synthesis of both vancomycin (**1**)[9] and its aglycon (**2**).[10] Both the Evans[11] and the Boger[12] groups have achieved the total synthesis of the vancomycin aglycon. The novel and challenging molecular architecture of vancomycin (**1**) ensured an adventurous journey, rich in exciting discoveries and enabling technologies for biology and medicine. The present paper describes the design and development of suitable methodologies for potential application to the vancomycin problem.

Vancomycin (**1**) was discovered by scientists at Eli Lilly in 1956[13] from fermentation broths of *Streptomyces orientalis* (later renamed *Nocardia orientalis*, and finally reclassified as *Amycolatopsis orientalis*),[14] which was grown from a soil sample collected in the jungles of Borneo. Approved as an antibiotic by the FDA in 1958, vancomycin became increasingly popular, especially against methicillin-resistant *Staphylococcus aureus* (MRSA) and *coagulase negative Staphylococci* (CNS). Its mechanism of action involves binding to the D-Ala-D-Ala fragment of the peptidoglycan and inhibiting its biosynthesis. This binding is enhanced by spontaneous dimerization of the antibiotic.[15] Bacteria have learned, however, to evade vancomycin's targeting by evolving D-Ala-D-Ala to D-Ala-D-Lac, which suffers from the depletion of one hydrogen bond in the binding complex.[16] The observation of drug resistance towards vancomycin by *Staphylococcus aureus* (MRSA) in three geographically different locations in 1997,[4c] rung bells of alarm among scientists and clinicians, and the race is now on for the development of new antibiotics against vancomycin-resistant bacteria.

Vancomycin (**1**) possesses a unique molecular architecture.[17] It consists of a cyclic heptapeptide framework providing a highly rigid scaffold onto which is attached a disaccharide moiety consisting of a glucose unit and a vancosamine moiety. The cyclic core of vancomycin includes three macrocyclic systems, all of which are associated with atropisomerism. Thus, because of their substitution patterns and strained nature, the AB (12-membered) biaryl ring, the C-O-D (16-membered), and the D-O-E (16-membered) biaryl ether ring systems reside in the specific conformations shown in structure **1**. It is also noteworthy that one of the two amide bonds within the 12-membered ring exists in its cisoid form. Rotation around the appropriate C–C and C–O bonds could place the substituents of the aromatic rings (OH and Cl) in different spatial orientations, giving rise to other atropisomers. But the energy barriers for such processes are too high for them to occur at ambient temperatures, leading to the observed stability of the indicated atropisomers. These structural features amounted to a multifaceted synthetic challenge, including the need to discover and invent new synthetic technologies and strategies for the construction of the two biaryl ether macrocycles (C-O-D and D-O-E) and the AB biaryl system. Below we describe the design and development of such technologies and strategies.

Abstract in Greek:

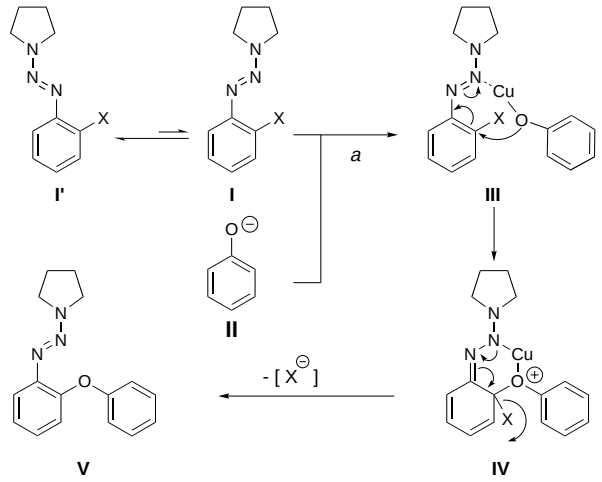
o–Αλογονουποκατεστημενες αρωματικες τριαζινες (π.χ. **I**, Σχημα 1) αντιδρουν με φαινοξειδια (π.χ. **II**, Σχημα 1) παρουσια $CuBr{\bullet}Me_2S$, K_2CO_3 και πυριδινης σε ξεον ακετονιτριλιο σχηματιζοντας διαρυλαιθερες (π.χ. **V**, Σχημα 1). Αυτη η γενικευμενη μεθοδολογια (Πινακες 1 και 2) εφαρμοστηκε για τη συνθεση των C-O-D και D-O-E μοντελων της βανκομυκινης **37** (Σχημα 2) και **50** (Σχημα 3), αποδεικνυοντας τη δυνατοτητα χρησης της σε μια σχεδιαζομενη ολικη συνθεση της βανκομυκινης (**1**, Φιγουρα 1). Για τη συνθεση των διαρυλο–κυκλικων μοντελων AB της βανκομυκινης περιγραφηκε μια στρατηγικη που περιλαμβανει αρχικα συζευξη τυπου Suzuki του C-O-D αρυλοιωδιδιου **74** (Σχημα 7) και του βορονικου οξεος **53** (Σχημα 4) και ακολουθως μακρολακτονοποιηση, στην οποια ο προσχηματισμενος C-O-D δακτυλιος οργανωνει τη διαμορφωση του προς κυκλοποιηση ενδιαμεσου. Η τελευταια μελετη οδηγησε στην ασυμμετρη συνθεση διαρυλο–συστηματων, μεσω συζευξης τυπου Suzuki, στην οποια βρεθηκε οτι το BINAP εδωσε τα καλυτερα αποτελεσματα (Πινακες 3 και 4).

Results and Discussion

The triazene-driven biaryl ether synthesis

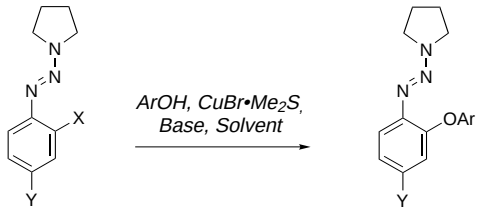
Due to the importance of the biaryl ether linkage, considerable efforts have been expanded towards the development of methods for its construction.[2] Amongst the most prominent reactions for the synthesis of biaryl ethers are those involving oxidative phenolic coupling,[18, 19] *o*-nitro-activated nucleophilic aromatic substitution,[20-25] metal-activated nucleophilic aromatic substitution,[26, 27] the classic Ullmann-type reactions,[28, 29] and boronic-acid-driven biaryl ether synthesis.[30] Despite the plethora of such reactions, however, the sensitivity and challenging structures of the vancomycin-type antibiotics dictated the search for new synthetic technologies and strategies for the formation of the biaryl ether linkages within the context of viable synthetic routes to these molecules.

Because of their ease of formation and also due to their susceptibility to chemical manipulations, aryl triazenes[31] were deemed attractive substrates for biaryl ether formation. The mechanistic rationale behind the design of the triazene-driven biaryl ether synthesis is shown in Scheme 1. Thus, it



Scheme 1. Strategy and presumed mechanistic rationale for the triazene-based synthesis of biaryl ethers. a) 5.0 equiv of PhOH, 5.0 equiv of $CuBr \cdot Me_2S$, 5.0 equiv of K_2CO_3, MeCN/pyr. (5:1, v/v, 0.005 M), 80 °C.

Table 1. Synthesis of monoaryl ethers by triazene-driven etherification.



Entry	X	Y	S	Base	Solvent	ArO	Temp (°C)	Time (h)	P	Yield (%)
1	Br	H	**3**	K_2CO_3	pyr.	PhO	115	16	**8**	53
2	Br	H	**3**	NaH	dioxane	PhO	100	4	**8**	71
3	Br	H	**3**	NaH	dioxane	*p*-Me-PhO	100	4	**9**	87
4	Br	H	**3**	NaH	dioxane	*o*-Cl-*p*-Me-PhO	100	4	**10**	58
5	Br	H	**3**	K_2CO_3	MeCN	PhO	80	16	**8**	NR
6	F	H	**4**	K_2CO_3	MeCN-pyr.	PhO	80	16	**8**	NR
7	Cl	H	**5**	K_2CO_3	MeCN-pyr.	PhO	80	16	**8**	NR
8	Br	H	**3**	K_2CO_3	MeCN-pyr.	PhO	80	16	**8**	65
9	I	H	**6**	K_2CO_3	MeCN-pyr.	PhO	80	16	**8**	78
10	Br	H	**3**	K_2CO_3	MeCN-pyr.	*o*-Cl-PhO	80	16	**11**	70
11	Br	H	**3**	K_2CO_3	MeCN-pyr.	*p*-Me-PhO	80	16	**9**	64
12	Br	H	**3**	K_2CO_3	MeCN-pyr.	*o*-Cl-*p*-Me-PhO	80	16	**10**	67
13	H	Br	**7**	K_2CO_3	MeCN-pyr.	PhO	80	16	**12**	NR

was reasoned that an *ortho*-substituted haloarene (**I**) could be encouraged to react with an aryloxide, such as **II**, through a copper bridge (or other complexing metal) as shown in **III**. Attack on the halogen-bearing carbon atom by the oxy-anion, followed by expulsion of halide, as shown in **IV**, to afford biaryl ether **V**, was considered a reasonable proposition. This expectation was rewarded with a mild method for the construction of biaryl ether bonds as demonstrated in Tables 1 (mono-biaryl) and 2 (bis-triaryl).

The requisite triazene compounds are usually crystalline and readily available from the corresponding anilines by diazotization followed by reaction with pyrrolidine. As seen in Tables 1 and 2, the triazene-based biaryl ether formation is highly efficient and quite general. Conditions were developed for the displacement of one or two iodides or bromides from the aromatic nucleus with one or two aryloxide units at relatively low temperatures in comparison to the classical Ullmann reaction. In all cases investigated, no reductive dehalogenation or biaryl coupling was observed. It was also established that the reactivities of halides were in the order of $I > Br \gg Cl, F$, which is in accord with the Ullmann reaction,[28] but opposite to that of the *o*-nitro-activated nucleophilic aromatic substitution, in which fluorides are the preferred substrates.[20] Furthermore, these studies established that only halides at the *ortho* position of triazenes enter the etherification reaction (entries 8 and 13, Table 1; entry 13, Table 2). Also, electron-deficient triazene halides reacted faster than electron-rich substrates (c.f. entries 10 and 14, Table 2). The same trend was also observed in the reaction of 2,6-dibromo-4-methyl triazene **13** with phenol. Thus, while the first substitution was complete within 1.5 h, the second one required a further 3.5 h for completion. In general, it was interesting to note that triazenes, with substitutions on both *ortho* positions, were found to be more reactive as compared with their mono-substituted counterparts (entry 8, Table 1 and entry 10, Table 2). All of these observations are in accord with the mechanistic rationale shown in Scheme 1. Thus, it was presumed that conformation **I′** (Scheme 1), which is not available in the *o*,*o*′-disubstituted triazenes, is detrimental to the desired substitution reaction. In support of this postulate, it was found that the substrate **15** with an *o*-methyl group in place of a bromine had a similar reaction rate to the *o*,*o*′-dibromotriazenes (entry 12, Table 2). This observation suggested that the effect of the second *ortho* substitution was more steric than electronic.

The effect of base and solvent were also investigated rather extensively. As seen from Tables 1 and 2, the most consistent results were obtained when $CuBr \cdot Me_2S$ was used in conjunction with K_2CO_3 and pyridine in MeCN as solvent. Interestingly, the presence of pyridine was essential in the cases of the milder base (K_2CO_3) (see entry 5, Table 1 and entry 9, Table 2) as opposed to the use of a stronger base (NaH), which did not require pyridine (entries 2–4, Table 1 and entries 2–4, 6 and 8, Table 2).

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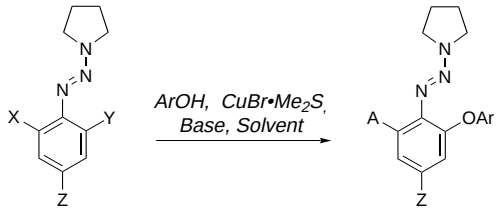
Table 2. Synthesis of biaryl ethers by triazene-driven etherification.

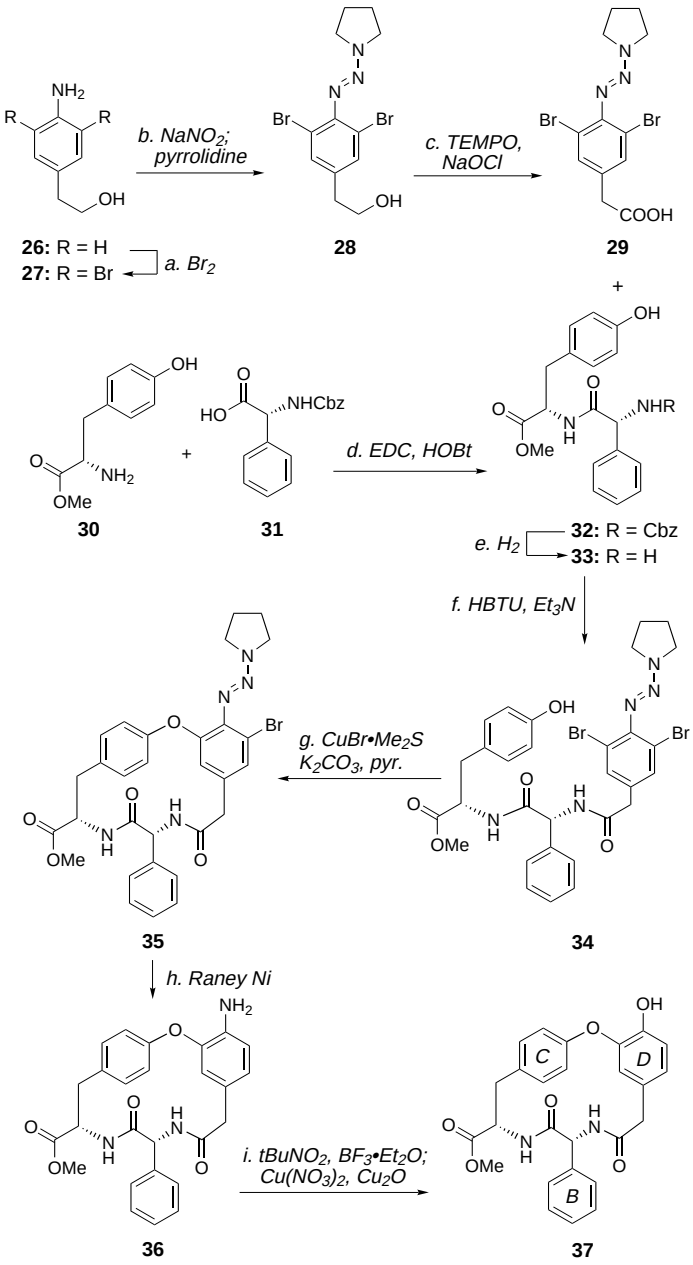


Entry	X	Y	Z	S	Base	Solvent	ArO	A	Temp (°C)	Time (h)	P	Yield (%)
1	Br	Br	Me	**13**	K_2CO_3	pyr.	PhO	PhO	115	4	**18**	84
2	Br	Br	Me	**13**	NaH	dioxane	PhO	PhO	100	1	**18**	79
3	Br	Br	Me	**13**	NaH	dioxane	*p*-Me-PhO	*p*-Me-PhO	100	1	**19**	82
4	Br	Br	Me	**13**	NaH	dioxane	*o*-Cl-PhO	*o*-Cl-PhO	100	1	**20**	50
5	Br	Br	Me	**13**	K_2CO_3	dioxane-pyr.	PhO	PhO	100	3.5	**18**	81
6	Br	Br	Me	**13**	NaH	THF	PhO	PhO	65	4	**18**	79
7	Br	Br	Me	**13**	K_2CO_3	THF-pyr.	PhO	PhO	65	20	**18**	77
8	Br	Br	Me	**13**	NaH	Et_2O	PhO	PhO	35	20	**18**	65
9	Br	Br	Me	**13**	K_2CO_3	MeCN	PhO	PhO	80	4	**18**	NR
10	Br	Br	Me	**13**	K_2CO_3	MeCN-pyr.	PhO	PhO	80	5	**18**	89
11	I	I	Me	**14**	K_2CO_3	MeCN-pyr.	PhO	PhO	80	4	**18**	83
12	Me	Br	Me	**15**	K_2CO_3	MeCN-pyr.	PhO	Me	80	5	**21**	56
13	Br	Br	Br	**16**	K_2CO_3	MeCN-pyr.	PhO	PhO	80	2	**22**	91
14	Br	Br	CO_2Me	**17**	K_2CO_3	MeCN-pyr.	PhO	PhO	80	2	**23**	82
15	Br	Br	Me	**13**	K_2CO_3	MeCN-pyr.	*o*-Cl-PhO	*o*-Cl-PhO	80	5	**20**	78
16	Br	Br	Me	**13**	K_2CO_3	MeCN-pyr.	*p*-Me-PhO	*p*-Me-PhO	80	5	**19**	70
17	Br	Br	Me	**13**	K_2CO_3	MeCN-pyr.	*o*-Cl-*p*-Me-PhO	*o*-Cl-*p*-Me-PhO	80	5	**24**	74
18	Br	Br	Me	**13**	K_2CO_3	MeCN-pyr.	PhS	PhS	80	4	**25**	84

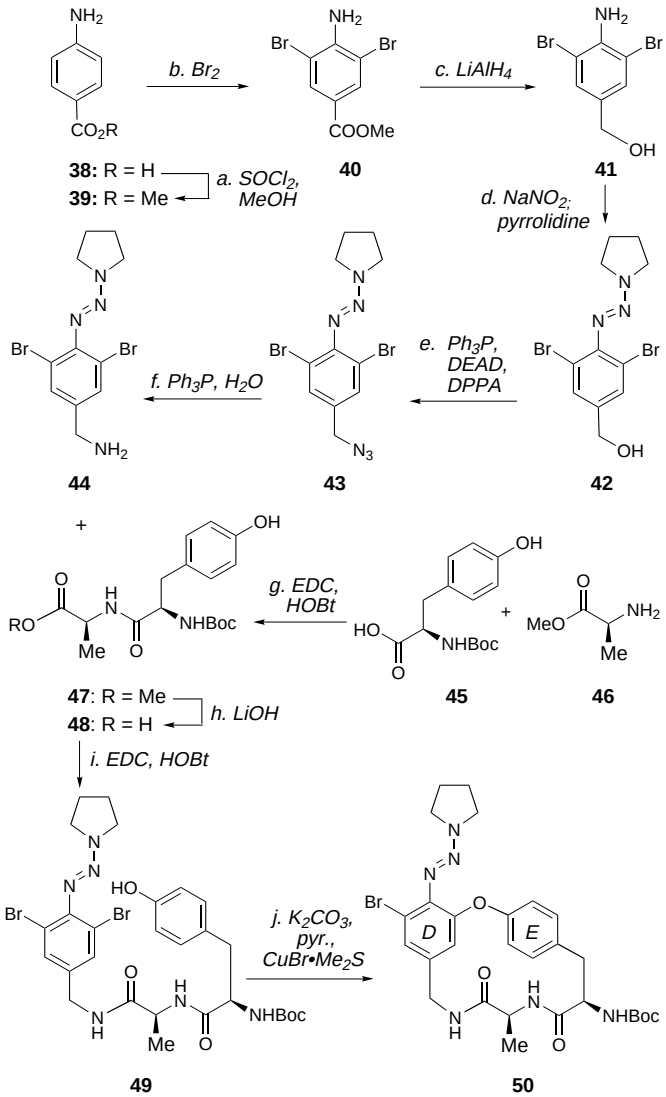
Vancomycin C-O-D and D-O-E model systems

Having developed the triazene-driven biaryl ether synthesis, and prior to embarking on the total synthesis of vancomycin, we proceeded to test its applicability to the construction of the C-O-D and D-O-E vancomycin model systems **37** and **50**. Scheme 2 summarizes the successful application of this reaction to the C-O-D model system **37**. Thus, (4-aminophenyl)ethyl alcohol (**26**) was sequentially dibrominated, diazotized, and treated with pyrrolidine to afford triazene **28** via intermediate **27** (83% overall yield). The latter compound (**28**) was then oxidized to carboxylic acid **29** (82% yield) by the action of TEMPO (for abbreviations of reagents, see legends in Schemes) and NaOCl. The dipeptide **33** [obtained by coupling of amino acid derivatives **30** and **31** (EDC, HOBt, 91% yield)[32] followed by deprotection (H_2, 10% Pd/C, 100%)] was coupled with acid **29** (HBTU, Et_3N, 63% yield)[33] to afford tripeptide **34**. The precursor **34** was then subjected to the ring closure procedure (2.5 equiv of K_2CO_3, 2.5 equiv of $CuBr \cdot Me_2S$, 3.0 equiv of pyridine, MeCN, 75 °C) to afford the C-O-D ring system **35** in 77% yield. The phenylglycine epimer of **34** was also prepared and subjected to the same cyclization conditions, leading to the corresponding epimer of **35**. NMR spectroscopic (500 MHz) studies on **35** and its epimer showed less than 5% epimerization at the phenylglycine center in each case, underscoring the mildness of this method. In order to demonstrate the chemical fertility of the triazene moiety, particularly in the context of a vancomycin total synthesis, compound **35** was subjected to Raney Ni reduction, resulting in the formation of aniline derivative **36** (71% yield). Subsequent diazotization of **36** (tBuNO$_2$-$BF_3 \cdot Et_2O$), followed by treatment of the resulting diazonium salt with $Cu(NO_3)_2$-Cu_2O, furnished phenol **37** in 60% overall yield.

The application of the triazene-driven cyclization reaction to the construction of the D-O-E vancomycin model system **50** is shown in Scheme 3. Thus, *p*-aminobenzoic acid (**38**) was first methylated ($SOCl_2$, MeOH, 98% yield) and then brominated (Br_2, AcOH, 99% yield) to afford dibromide **40** via compound **39**. Reduction of the methyl ester functionality in **40** with $LiAlH_4$ gave primary alcohol **41** (93% yield). The amino group of the latter compound (**41**) was diazotized ($NaNO_2$, aq HCl), and thence converted to triazene **42** by reaction of the resulting diazonium salt with pyrrolidine (73% overall yield). The primary hydroxyl group of **42** was then converted to an azide functionality[34] (DPPA, Ph_3P, DEAD,



Scheme 2. Synthesis of C-O-D model system **37**. a) 2.2 equiv of Br_2, AcOH, 25 °C, 0.5 h, 99 %; b) 1.3 equiv of $NaNO_2$, 5.0 equiv of 12 N aq HCl, THF/H_2O (10:1), 0 °C, 0.5 h; then 10.0 equiv of pyrrolidine, sat. aq K_2CO_3, 0 °C, 1 h, 84 %; c) 1.5 equiv of TEMPO, 3.0 equiv of 5 % aq NaOCl, 10 mol % of KBr, acetone/5 % $NaHCO_3$ (1:1), 0 °C, 2 h, 82 %; d) 1.5 equiv of EDC, 1.5 equiv of HOBt, DMF, 0 °C, 10 h, 91 %; e) H_2, 10 % Pd/C, MeOH, 25 °C, 1 h, 100 %; f) 1.5 equiv of HBTU, 2.0 equiv of **33**, 1.5 equiv of Et_3N, DMF, 0 °C, 18 h, 63 %; g) 2.5 equiv of K_2CO_3, 2.5 equiv of CuBr · Me_2S, 3.0 equiv of pyr., MeCN (0.01 M), 75 °C, 15 h, 77 %; h) Raney Ni, MeOH, reflux, 2 h, 71 %; i) 1.5 equiv of *t*$BuNO_2$, 3.0 equiv of $BF_3 \cdot Et_2O$, THF, −20 → 5 °C, 0.5 h; then sat. $Cu(NO_3)_2$, 5.0 equiv of Cu_2O, H_2O, 25 °C, 3 h, 60 %. DMF = dimethylformamide; EDC = 1-ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride; HOBt = 1-hydroxybenzotriazole; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; HBTU = 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; Cbz = benzyloxycarbonyl.



Scheme 3. Synthesis of D-O-E model system **50**. a) 1.1 equiv of $SOCl_2$, MeOH, reflux, 2 h, 98 %; b) 2.2 equiv of Br_2, AcOH, 25 °C, 0.5 h, 99 %; c) 3.0 equiv of $LiAlH_4$, THF, 0 °C, 4 h, 93 %; d) 1.3 equiv of $NaNO_2$, 5.0 equiv of 12 N aq HCl, THF/H_2O (10:1), 0 °C, 0.5 h; then 10.0 equiv of pyrrolidine, sat. aq K_2CO_3, 0 °C, 1 h, 73 %; e) 1.5 equiv of Ph_3P, 1.5 equiv of DEAD, 1.5 equiv of DPPA, THF, 25 °C, 2 h, 82 %; f) 2.0 equiv of Ph_3P, 10.0 equiv of H_2O, THF, 45 °C, 8 h, 80 %; g) 1.5 equiv of EDC, 1.5 equiv of HOBt, DMF, 0 °C, 8 h; h) 1.5 equiv of LiOH , MeOH/H_2O (1:1), 0 °C, 1 h, 85 % from **45**; i) 1.5 equiv of **48**, 3.0 equiv of EDC, 1.5 equiv of HOBt, DMF, 0 °C, 8 h, 45 %; j) 2.5 equiv of K_2CO_3, 2.5 equiv of CuBr · Me_2S, 3.0 equiv of pyr., MeCN (0.01 M), 75 °C, 6 h, 54 % (87 % conversion). DEAD = diethyl azodicarboxylate; DPPA = diphenylphosphoryl azide; Boc = *t*-butoxycarbonyl.

82 %) affording compound **43**, which was reduced to amine **44** by exposure to Ph_3P/H_2O (80 % yield). The other requisite coupling segment, dipeptide **48**, was obtained by joining amino acid derivatives **45** and **46** through the action of EDC/HOBt, followed by carefully controlled hydrolysis of the methyl ester (LiOH, MeOH/H_2O, 0 °C, 85 % yield for two steps). The coupling of **44** with **48** was facilitated by the action of EDC/HOBt, furnishing tripeptide **49** in 45 % yield and setting the stage for the ring-closure reaction. Exposure of precursor **49** to the developed cyclization protocol (K_2CO_3, CuBr · Me_2S, pyridine, MeCN, 75 °C) resulted in the formation of vancomycin D-O-E model system **50** (54 % yield based on 87 % conversion). No observable (NMR, 500 MHz) epimerization occurred in the formation of **50** from **49**.

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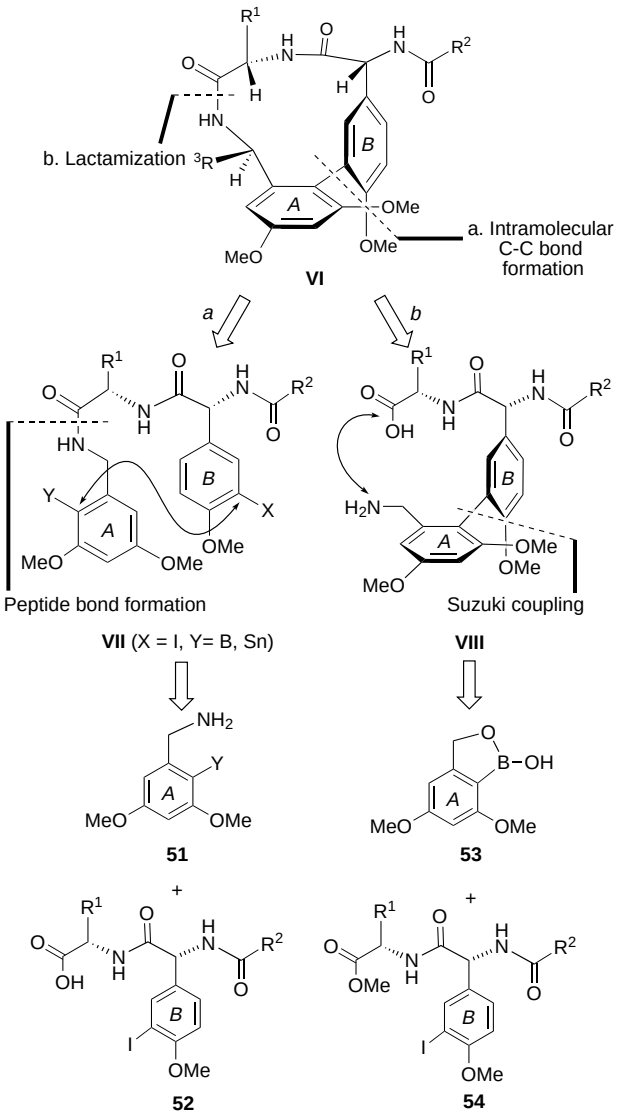
The successful construction of C-O-D (**37**) and D-O-E (**50**) model systems of vancomycin boded well for the application of the triazene-driven biaryl ether synthesis to a potential total synthesis of vancomycin. These expectations were realized as will be discussed later in this series of papers.[5–7]

Model study for the construction of the cyclic biaryl system (AB) of vancomycin

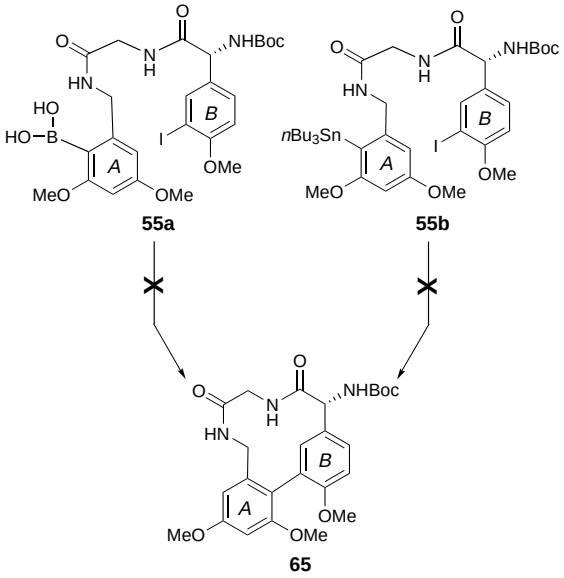
The 12-membered ring of vancomycin containing the biaryl system (AB) presents a serious synthetic challenge. Its daunting nature has its origins in the inherent strain associated with the medium ring size, its cisoid amide bond (AA-5/AA-6) and its highly substituted biaryl moiety. At the outset of our work on vancomycin, only one method existed for the construction of this strained system, that reported by the Evans group in 1993,[35] involving a vanadium-induced oxidative coupling reaction.

For the construction of this unusual structural moiety we considered two main strategies, as indicated retrosynthetically in Scheme 4. The first strategy (a) called for first assembling the peptide backbone and then closing the ring by a carbon–carbon bond forming reaction; whereas the second strategy (b) was to rely on forming the biaryl system early in the synthesis followed by a macrolactamization reaction to close the ring. These strategies required key building blocks **51**, **52** (for a), and **53**, **54** (for b) as starting materials, respectively. Attempted implementation of these strategies was revealing.

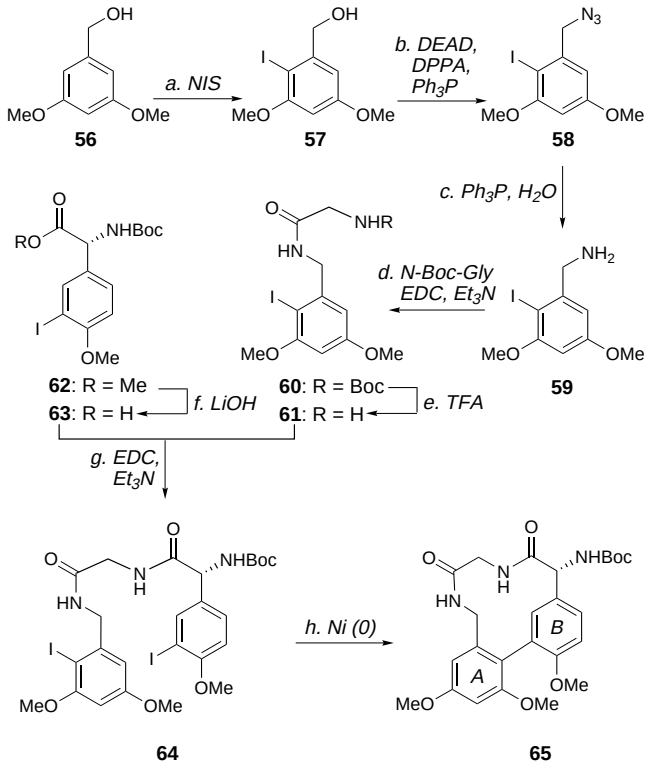
To test the first approach to the AB ring construction, substrates **55a** and **55b** (Scheme 5) were prepared by standard chemistry involving peptide couplings. However, neither the Suzuki coupling[36] (of **55a**) nor the Stille coupling[37] (of **55b**) was successful in delivering the desired 12-membered ring under a variety of conditions. It soon became evident that the strained nature of the targeted ring system did not allow these processes to proceed as desired. Faced with these negative results, we opted to test a nickel(0)-mediated strategy to form the required C–C bond between the two aromatic rings (A and B). Scheme 6 summarizes the model study exploring the nickel(0) technology. Thus 3,5-dimethoxybenzyl alcohol (**56**) was iodinated (NIS, 91% yield) to afford intermediate **57**, which upon Mitsunobu activation provided azide **58** in 82% yield. Reduction of azide **58** by Ph_3P/H_2O (80% yield), followed by coupling of the resulting amine (**59**) with *N*-Boc-glycine furnished dipeptide **60** (EDC, Et_3N, 81% yield). TFA-mediated Boc deprotection gave amine **61** in quantitative yield. Carboxylic acid **63** was generated from its readily available methyl ester (**62**) (LiOH, THF/H_2O, 99% yield) and coupled with amino compound **61** under the influence of EDC and Et_3N, leading to peptide **64** (92% yield). Exposure of precursor **64** to freshly prepared nickel(0) [generated from $(Ph_3P)_2NiCl_2$, Zn dust, and Ph_3P in DMF][38] at 55 °C resulted in the formation of the desired 12-membered ring **65** (26% yield as a mixture of two atropisomers, **65a** and **65b**, Figure 2). By-products in this reaction included reduced compounds, where one or both iodine atoms were replaced by hydrogen atoms, and dimeric materials. Despite the success in this model study, the low yield of the desired 12-membered



Scheme 4. Retrosynthetic analysis of model biaryl system **VI**: strategies a and b.



Scheme 5. Attempted intramolecular biaryl coupling reactions.



Scheme 6. Construction of model AB biaryl system **65** by nickel (**0**)-mediated coupling reaction. a) 1.5 equiv of NIS, DMF, 25 °C, 12 h, 91 %; b) 1.5 equiv of Ph_3P, 1.5 equiv of DEAD, 1.5 equiv of DPPA, THF, 0 °C, 2 h, 82 %; c) 3.0 equiv of Ph_3P, THF/H_2O (10:1), 45 °C, 4 h, 80 %; d) 1.0 equiv of *N*-Boc-Gly, 1.5 equiv of EDC, 2.5 equiv of Et_3N, DMF, 0 °C, 12 h, 81 %; e) TFA/CH_2Cl_2 (1:1), 0 →25 °C, 2 h, 100 %; f) 1.5 equiv of LiOH, THF/H_2O (1:1), 0 °C, 1 h, 99 %; g) 1.2 equiv of **63**, 1.3 equiv of EDC, 2.2 equiv of Et_3N, DMF, 0 °C, 12 h, 92 %; h) 1.8 equiv of $(Ph_3P)_2NiCl_2$, 1.8 equiv of Zn, 3.6 equiv of Ph_3P, DMF (0.002 M), 55 °C, 16 h, ca. 1:1 ratio of atropisomers, 26 % combined yield. NIS = *N*-iodosuccinimide; TFA = trifluoroacetic acid.

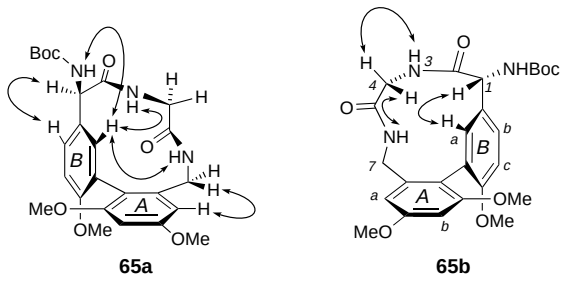


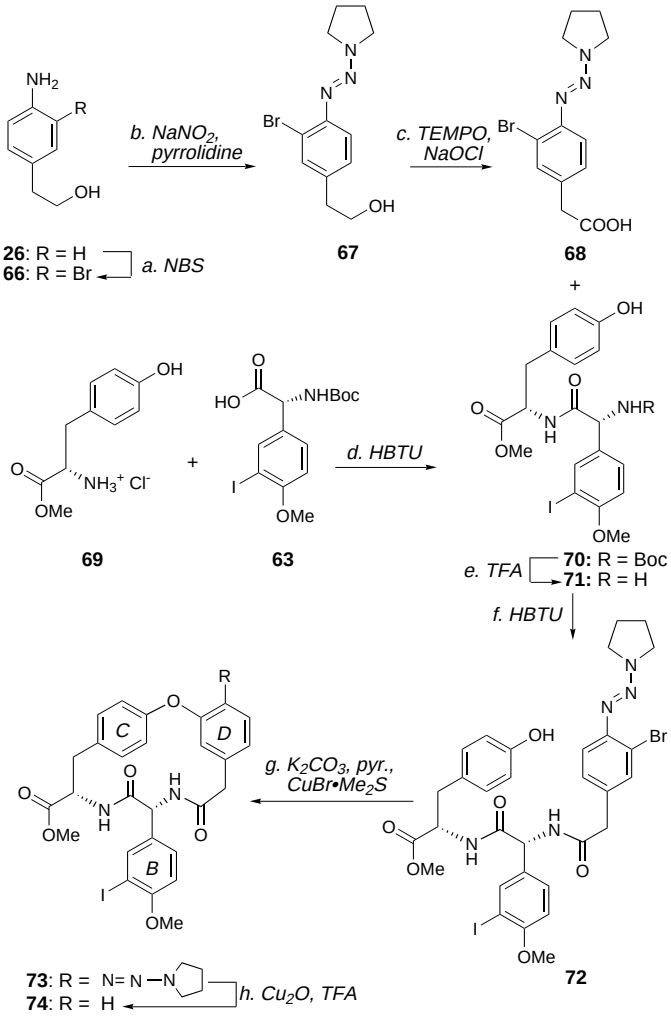
Figure 2. Assignments of stereochemistry of atropisomers **65a** and **65b** by ^1H-^1H NOE studies (COSY, NOESY, $CDCl_3$, 600 MHz).

ring steered us away from this strategy and into a new direction involving a Suzuki coupling – macrolactamization sequence to form the desired AB ring system. Furthermore, it was decided at this juncture to implement the well-known preorganization strategy to assist the pending ring closure process.

The Suzuki coupling – macrolactamization strategy towards the AB/C-O-D bicyclic system of vancomycin

Having failed to develop an efficient method for the ring closure of vancomycin's AB ring system by formation of the central C–C bond of the biaryl system, we turned our attention to strategy b (Scheme 4). According to this approach, the central C–C bond of the biaryl system was envisioned to be formed at the early stages of the sequence by a Suzuki coupling; while the 12-membered ring would be constructed subsequently, by a macrolactamization process. However, in view of previous findings by Brown et al.,[39] who failed to cyclize such a system, and by Evans et al.,[35] who succeeded in such an endeavor by preassembling the C-O-D ring of vancomycin, we opted to test the preorganization strategy summarized in Schemes 7 and 8. Thus, it was anticipated that the preformed C-O-D macrocycle would impose enough rigidity into the precursor chain for the AB ring system so as to organize it into a favorable conformational state for cyclization.

To this end, the C-O-D model system **74** was first constructed as shown in Scheme 7. Thus, the required building



Scheme 7. Construction of model C-O-D template **74**. a) 1.2 equiv of NBS, DMF, 25 °C, 12 h, 62 %; b) 1.2 equiv of conc. aq HCl, 1.0 equiv of $NaNO_2$, 0 °C, 0.5 h; then sat. aq K_2CO_3, 10.0 equiv of pyrrolidine, 0 °C, 1 h, 83 %; c) 1.0 equiv of TEMPO, 0.1 equiv of KBr, 1.3 equiv of NaOCl, acetone:5 % $NaHCO_3$ (1:1), 0 °C, 1.5 h, 86 %; d) 1.2 equiv of HBTU, 3.0 equiv of Et_3N, DMF, 0 →25 °C, 3 h, 90 %; e) TFA:CH_2Cl_2 (1:1), 0 °C, 1 h, 100 %; f) 1.2 equiv of HBTU, 3.0 equiv of Et_3N, DMF, 0 →25 °C, 3 h, 90 %; g) 2.9 equiv of CuBr·Me_2S, 2.4 equiv of K_2CO_3, 3.0 equiv of pyr., MeCN, reflux, 36 h, 67 % (10 % recovered **72** and 6 % arylglycine epimer of **73**); h) 2.2 equiv of TFA, 5.0 equiv of Cu_2O, THF, reflux, 1 h, 90 %. NBS = *N*-bromosuccinimide.

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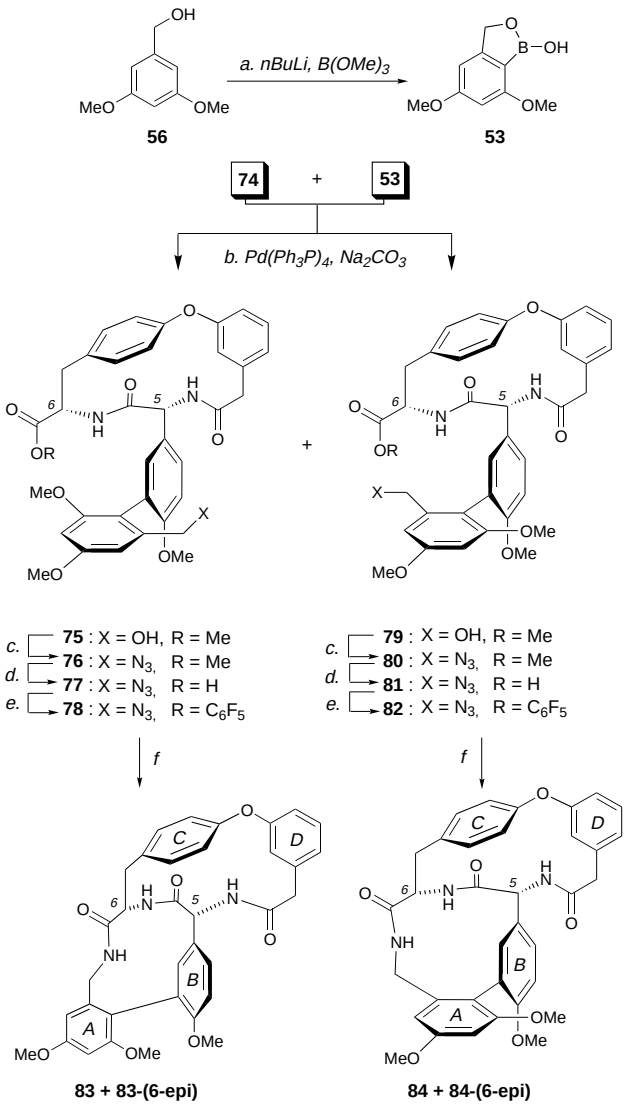
block **68** was synthesized from aniline derivative **26** by NBS bromination to afford bromide **66** (62% yield), diazotization ($NaNO_2$, aq HCl) followed by reaction of the resulting diazonium salt with pyrrolidine, leading to triazene **67** (83% overall yield), and TEMPO/NaOCl oxidation (86% yield). The tripeptide precursor **72** was finally assembled by first coupling (*S*)-tyrosine methyl ester derivative **69** with (*R*)-4-methoxyl-3-iodophenylglycine derivative **63** (HBTU/Et_3N) to afford dipeptide **70** (90% yield), deprotecting the latter (TFA) leading to amine **71** (100% yield), and attaching triazene carboxylic acid **68** by HBTU/Et_3N facilitated coupling (90% yield). Ring closure of **72** was effected by refluxing in MeCN in the presence of K_2CO_3, $CuBr \cdot Me_2S$ and pyridine, furnishing C-O-D model system **73** in 67% yield, along with 10% recovered starting material and 6% of the arylglycine epimer of **73**. Reductive removal of the triazene group from **73** with TFA and Cu_2O in refluxing THF led to the desired intermediate **74** (90% yield).

The further elaboration of compound **74** towards the targeted AB/C-O-D ring system required the Suzuki partner **53**, whose construction and incorporation into the molecule are shown in Scheme 8. Thus, 3,5-dimethoxylbenzyl alcohol (**56**) was directly converted to boronic acid derivative **53** by treatment with 2.2 equivalents of *n*BuLi, followed by quenching the derived dianion with $B(OMe)_3$ and workup with aqueous HCl (46% overall yield). The Suzuki coupling of iodide **74** with boronic acid derivative **53** proceeded smoothly in the presence of $Pd(Ph_3P)_4$ catalyst and Na_2CO_3 in toluene/MeOH/H_2O at 90 °C to afford a mixture of atropisomers **75** and **79** (ca. 1:1 ratio, 80% combined yield). The two isomers were chromatographically separated, but their stereochemical assignments had to await cyclization to the AB/C-O-D framework before being revealed by NMR spectroscopy (vide infra). While the biaryl system obtained from coupling of **74** with the parent boronic acid corresponding to **53** (lacking the methoxyl groups) proved to be a single compound (by TLC and NMR spectroscopy), due to free rotation around the central C–C biaryl bond; atropisomers **75** and **79** did not undergo isomerization even at 60 °C. Furthermore, no epimerization at C5 and C6 was observed. Each atropisomer was elaborated individually as follows. Thus, the less polar isomer (**75**, $R_f = 0.28$, silica gel, EtOAc) was treated with HN_3, DEAD, and Ph_3P leading to the corresponding azide compound **76** in 69% yield. The latter intermediate (**76**) was then saponified by treatment with LiOH in THF/H_2O (1:1) at 0 °C, furnishing carboxylic acid **77** in quantitative yield. Conversion of this acid (**77**) to its pentafluorophenyl ester (**78**), followed by slow addition of a solution (dioxane-cyclohexene) of crude **78** to 10% Pd/C and pyrrolidinopyridine stirred in dioxane/EtOH at 90 °C, led to the formation of **83**, plus its 6-epimer, compound **83-(6-epi)**, in 30% combined yield from **77** [**83**:**83-(6-epi)** ca. 1:2]. The more polar isomer (**79**, $R_f = 0.23$, silica gel, EtOAc) was taken through the same sequence, leading to compounds **84** and **84-(6-epi)** in similar yields. The stereochemical assignment of compounds **83**, **83-(6-epi)**, **84**, and **84-(6-epi)** were based on ^1H-^1H NOESY experiments. Figure 3 indicates the crucial NOE values which were used to define the stereostructure of **83** and **84** (both of the natural stereochemistry at C6 and both containing cisoid amide bonds).



Scheme 8. Construction of AB/C-O-D model bicyclic systems **83** and **84** by the Suzuki–macrolactamization strategy. a) 2.2 equiv of *n*BuLi, benzene, 0 °C, 2 h; then 3.0 equiv of $B(OMe)_3$, THF, −78 →25 °C, 6 h, 5% aq HCl, 46%; b) 10 mol% of $Pd(PPh_3)_4$, 1.0 equiv of Na_2CO_3, toluene/MeOH/H_2O (80:18:2), 90 °C, 2 h, **75**:**79** ca. 1:1, 80% combined yield; c) 5.0 equiv of HN_3, 5.0 equiv of DEAD, 5.0 equiv of Ph_3P, THF, 0 →25 °C, 1 h, 69%; d) 1.5 equiv of LiOH, THF/H_2O (1:1), 0 °C, 0.5 h, 100%; e) 2.0 equiv of C_6F_5OH, 1.2 equiv of DCC, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 1 h; f) 3.0 equiv of 4-pyrrolidinopyridine, 0.3 equiv of 10% Pd/C, dioxane/ethanol/cyclohexene (90:8:2), 0.001M, 90 °C, 5 h, 30% from **77** and **81**. C_6F_5OH = pentafluorophenol; DCC = *N*,*N*′-dicyclohexylcarbodiimide; 4-DMAP = 4-dimethylaminopyridine.

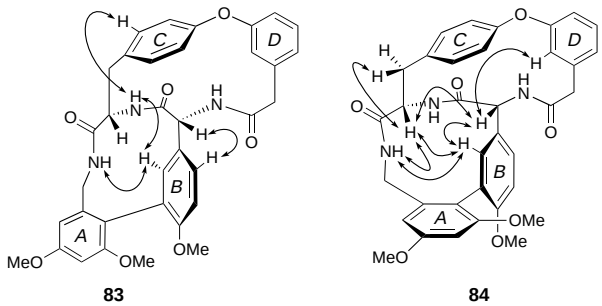


Figure 3. Assignments of stereochemistry of bicyclic systems **83** and **84** by ^1H-^1H NOE studies (COSY, NOESY, 600 MHz, $CDCl_3$, 323 K).

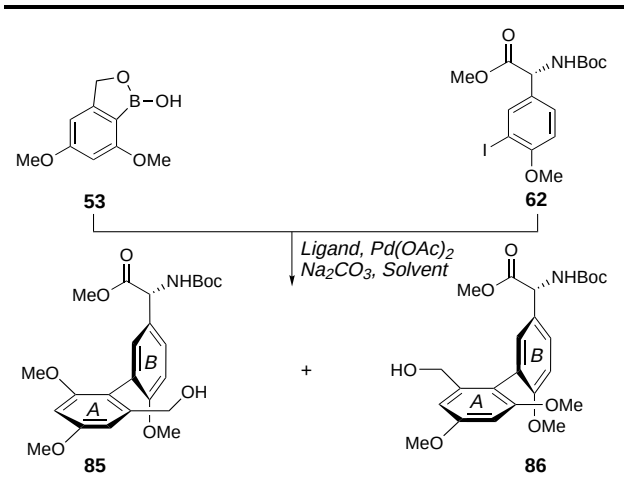
Despite the observed epimerization at C-6, which is presumed to occur after ring closure, these results were encouraging and boded well for application to vancomycin. For one, we learned that we could potentially rely on the Suzuki–macrolactamization strategy to construct the notorious AB macrocycle. Secondly, we could optimistically speculate that epimerization at C-6 may not necessarily surface in the real case where the proper substitutions and additional rings may change the thermodynamics of the system.

Catalytic asymmetric synthesis of biaryl systems by Suzuki coupling

Substituted biaryl systems are common structural moieties in natural products. Their synthesis, especially in enantiomerically pure form, is, therefore, deemed important.[40] The Suzuki coupling reaction has proven quite valuable in assembling such structures in racemic form. Despite the obvious potential for an asymmetric version of the Suzuki biaryl coupling, there have been no reports for the asymmetric version of this process. The only claim for an asymmetric synthesis of a biaryl system is that by Hayashi et al.,[41] who reported a modest asymmetric induction in the coupling of a chromium tricarbonyl complex. As part of our program directed towards the total synthesis of vancomycin, we investigated the possibility of asymmetric induction in the Suzuki coupling synthesis of biaryl systems already mentioned above. Specifically, it was observed that the Suzuki coupling of iodoarene-containing C-O-D model system **74** with boronic acid derivative **53** in the presence of Ph_3P proceeded with no diastereoselectivity. This observation, coupled with our desire to control the atrop-selectivity during our synthesis, gave us the impetus to develop an asymmetric version of this reaction.

Table 3 summarizes our findings so far, which clearly suggest that it may be possible to control the atrop-selectivity of the Suzuki biaryl synthesis. As expected, achiral ligands, such as Ph_3P and DPPP, led to no selectivity. Screening of a number of readily available chiral ligands revealed that BINAP[42] was the best in inducing diastereoselectivity in the coupling of compound **62** and **53**. Moreover, in the BINAP case, the observed diastereoselectivity was reversed upon switching the chirality of the ligand. The solvent effect was also studied, leading to the observation that THF at 60 °C provided the highest diastereoselectivity (ca. 3.5:1 ratio for **85** and **86**, 75% combined yield, entries 14 and 15, Table 3). (*S*,*S*)-(+)-DIOP,[43] (*R*,*R*)-(−)-Me-DuPHOS,[44] (−)-PPFA,[45] and (*S*)-(−)-BINAPAs[46] catalysts gave lower selectivities in this reaction. The relatively high temperatures required for the Suzuki coupling reactions led to the suspicion that atropisomerization during the reaction may have been responsible for the loss of partial asymmetric induction. Heating of a 3:1 mixture of atropisomers **85** and **86** in toluene at 90 °C for 3 h led to complete scrambling, furnishing a 1:1 mixture of **85** and **86**, thus, confirming the atropisomerization hypothesis. On the other hand, when the same 3:1 mixture of **85** and **86** was heated in THF at 60 °C for 3 h, no isomerization was detected, leading to the conclusion that entries 14 and 15 (Table 3) represent true asymmetric induction. It is also clear that in toluene, the diastereoselectivity of this reaction must be higher than the one observed, and that the 3:1 ratio is a result of slow deterioration of the kinetic ratio via atropisomerization.

Table 3. Catalytic asymmetric synthesis of biaryl systems by Suzuki coupling: acyclic model system.



Entry	Ligand	Solvent	Temp(°C)	Time(h)	Yield (%)	Ratio[a]
1	Ph_3P	PhMe	90	2	83	1:1
2	DPPP[b]	PhMe	90	5	77	1:1
3	(*S*,*S*)-DIOP[c]	PhMe	90	7	70	1.5:1
4	(*R*,*R*)-Me-DuPHOS[d]	PhMe	90	2	68	1:1.5
5	(*R*)-BINAP[e]	PhMe	90	10	80	3:1
6	(*S*)-BINAP[e]	PhMe	90	10	80	1:3
7	(*S*)-PPFA[f]	PhMe	90	12	53	1:1.2
8	(*S*)-BINAPAs[g]	PhMe	90	14	51	1:1.2
9	(*R*)-BINAP[e]	PhH	80	15	40	2:1
10	(*R*)-BINAP[e]	DMSO	90	3	42	1.2:1
11	(*S*)-BINAP[e]	DMF	80	2.5	52	1:2
12	(*R*)-BINAP[e]	DMPU	80	3.5	45	1.2:1
13	(*S*)-BINAP[e]	dioxane	90	10	70	1:1.2
14	(*R*)-BINAP[e]	THF	60	2	75	3.5:1
15	(*S*)-BINAP[e]	THF	60	2	75	1:3.5

[a] Absolute configuration not determined, ratio measured by ^1H NMR integration of signals at $\delta = 3.66$ and 3.67. [b] DPPP: 1,3-bis(diphenylphosphino)propane. [c] (*S*,*S*)-DIOP: (4*S*,5*S*)-(+)-*o*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. [d] (*R*,*R*)-Me-DuPHOS: (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethyl-phospholano]benzene. [e] BINAP: 2,2(-bis(diphenylphosphino)-1,1′-binaphthyl. [f] PPFA: (*R*)-1-[(*S*)-2(diphenylphosphino)-ferrocenyl]ethyldimethylamine. [g] BINAPAs: 2,3′-bis(diphenylarsino)-1,1′-binaphthyl. DMSO = dimethyl sulfoxide; DMF = dimethylformamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

In order to explore the possibility of obtaining even higher diastereoselectivities in the Suzuki coupling reaction, we decided to attempt the incorporation of the boronic acid aryl system **53** into the main frame after the construction of the C-O-D macrocycle. Having studied the properties of the expected products **75** and **79** (Table 4) previously, we were cognizant of the fact that they do not suffer atropisomerization at 90 °C. Palladium(0)-induced coupling of **74** and **53** in the presence of Ph_3P led smoothly and in 80% yield to a 1:1 mixture of atropisomers **75** and **79**, indicating that the chirality of the macrocyclic ring had no influence on the diastereoselectivity. The same reaction with (*R*)- or (*S*)-BINAP in toluene

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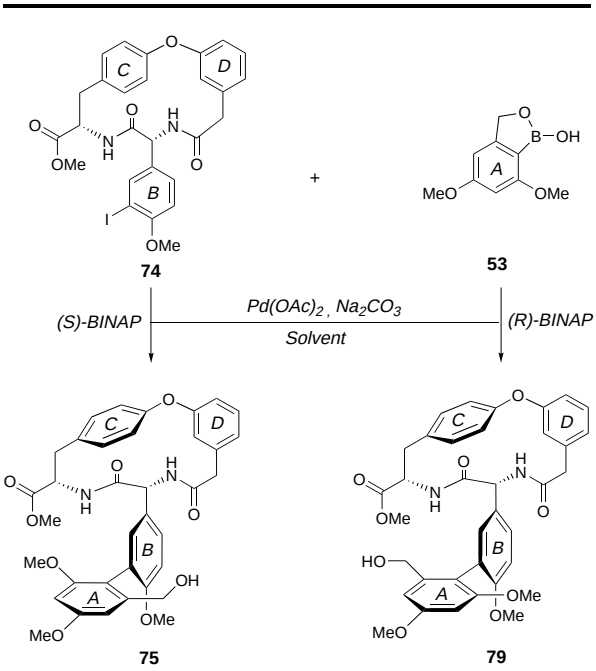
Table 4. Catalytic asymmetric synthesis of biaryl systems by Suzuki coupling: cyclic model system.



Entry	Ligand	Solvent	Temp (°C)	Time (h)	Yield (%)	Ratio (**75**:**79**)
1	Ph_3P	PhMe	90	2	80	1:1
2	BINAP	PhMe	90	12	trace	-
3	BINAP	THF	65	12	trace	-
4	(*S*)-BINAP	DMF	80	8	60	2.3:1
5	(*S*)-BINAP	PhMe:THF(1:1)	70	5	40(70[a])	>95:5[b]
6	(*R*)-BINAP	PhMe:THF(1:1)	70	5	40(70[a])	<5:95[b]

[a] Conversion based on recovered starting material. [b] The other atropisomer was not detectable by ^{1}H NMR spectroscopy (500 MHz). BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

at 90 °C failed to produce significant amount of product (entry 2, Table 4), presumably due to the insolubility of the ligand-substrate complex in this solvent. Similarly disappointing results were obtained in THF. Using DMF as solvent improved the yield of the products to 60%, but the diastereoselectivity was only ca. 2.3:1 (**75**:**79**) (entry 4, Table 4). However, when a mixture of PhMe/THF (1:1) was used as solvent, BINAP led to the exclusive formation of one of the two isomers, depending on the chirality of the ligand (entries 5 and 6, Table 4). Unfortunately, the reaction in PhMe/THF was rather sluggish, producing **75** or **79** only in 40% yield based on 70% conversion (entries 5 and 6, Table 4). It is expected that new ligands capable of effecting higher asymmetric induction and at lower temperature could improve even further the state of affairs in this important area of synthesis.

Conclusion

In this article, we laid out the challenge of vancomycin (**1**) and described the rational design and development of methodology for its total synthesis. The triazene-driven synthesis of biaryl ethers which was ultimately applied successfully to the total synthesis of vancomycin (**1**) relies on the ability of the triazene moiety to complex copper ions, thus bringing together the two components for facile interaction. This methodology was sequentially demonstrated in open-chain systems, as well as C-O-D, D-O-E, and AB/C-O-D model systems of the target's main framework. For the AB biaryl system of vancomycin, the failure of the attempts involving intramolecular Suzuki or Stille coupling processes to form the strained, 12-membered ring, led us to a nickel(0)-mediated cyclization reaction, which, however, was overshadowed by a more reliable process involving sequential intermolecular Suzuki coupling and macrolactamization. The development of the latter protocol was accompanied by an asymmetric Suzuki coupling synthesis of substituted biaryl systems employing BINAP as a chiral ligand. With these methodologies well established, we were then ready to address the retrosynthetic analysis and strategy for a total synthesis of vancomycin and to embark on the construction of the required amino acid building blocks as well as to explore preliminary plans for their assembly to the desired framework. The articles[5–7] that follow deal with these issues.

Experimental Section

General techniques: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene, and diethyl ether (ether) were distilled from sodium benzophenone; methylene chloride (CH_2Cl_2) was freshly distilled from calcium hydride. Anhydrous solvents were also obtained by passing them through activated commercially available alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution, and heat as developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on Bruker DRX-600, AMX-500, or AMX-400 instruments and calibrated by using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br. = broad, br. s = broad singlet. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix or IONSPEC FTMS spectrometer (MALDI) with DHB as matrix. Melting points (m.p.) are uncorrected, and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus.

General procedure (A) for reactions between *o*-haloaryl triazenes and phenols (Table 1): A flame-dried flask was charged with triazene (1.0 equiv), $CuBr \cdot Me_2S$ (5.0 equiv), phenol (1.2 equiv), and the specified base (5.0 equiv). The mixture was diluted with solvent to yield a solution approximately 0.1 M in triazene halide, and pyridine (Table 1, entries 6–13, 20 vol% of solvent) was added. The reaction mixture was heated at the indicated temperature (Table 1) for the specified time before it was allowed to cool to 25 °C. The resulting slurry was filtered through a pad of celite and the celite was washed thoroughly with ether. The product was isolated by

flash column chromatography. The example below illustrates further the procedure.

(2-Phenoxy-phenyl)-pyrrolidin-1-yl-diazene (8) (Table 1, entry 8): General procedure (A). To a flame-dried flask charged with a mixture of [(2-bromophenyl)azo]pyrrolidine (**3**) (254 mg, 1.0 mmol), phenol (113 mg, 1.2 mmol), $CuBr \cdot Me_2S$ (1.03 g, 5.0 mmol), and K_2CO_3 (690 mg, 5.0 mmol) was added acetonitrile (10 mL), followed by pyridine (2 mL). The reaction mixture was heated to 80 °C and maintained at that temperature for 16 h before it was allowed to cool to 25 °C. The mixture was filtered through a pad of celite and the celite was washed thoroughly with ether (3 × 20 mL). The combined organic phases were washed with 5% aqueous NH_4Cl (20 mL), H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the product was purified by flash column chromatography (silica gel, 3→5% ether in petroleum ether, gradient elution), furnishing **8** (174 mg, 65%). **8**: m.p. 84–85 °C (petroleum ether); $R_f = 0.52$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2966$, 2868, 1581, 1483, 1409, 1371, 1342, 1237, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47-7.45$ (m, 1H, ArH), 7.26–7.22 (m, 2H, ArH), 7.15–7.12 (m, 2H, ArH), 7.09–7.06 (m, 1H, ArH), 6.98–6.91 (m, 3H, ArH), 3.95–3.75 (br.s, 2H, NCH_2), 3.46–3.24 (br.s, 2H, NCH_2), 1.92–1.88 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 159.6, 147.0, 142.7, 129.1, 125.9, 124.8, 122.0, 121.4, 118.9, 116.9, 50.8, 46.2, 23.7; HRMS (FAB) calcd for $C_{16}H_{18}N_3O$ $[M+H^+]$ 268.1450, found 268.1455.

Pyrrolidin-1-yl-(2-*p*-tolyloxy-phenyl)-diazene (9) (Table 1, entry 11): This compound was prepared according to general procedure (A) in 64% yield. **9**: $R_f = 0.50$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} =$ 2970, 2861, 1583, 1502, 1482, 1407, 1346, 1319, 1238, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.45–7.43 (m, 1H, ArH), 7.11–7.08 (m, 2H, ArH), 7.04 (d, $J = 8.5$ Hz, 2H, ArH), 7.02–7.01 (m, 1H, ArH), 6.83 (d, $J = 8.5$ Hz, 2H, ArH), 3.95–3.60 (br.s, 2H, NCH_2), 3.60–3.25 (br.s, 2H, NCH_2), 2.28 (s, 3H, CH_3), 1.93–1.88 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 156.9, 149.5, 143.4, 130.9, 129.6, 125.8, 124.4, 121.5, 118.9, 117.2, 50.8, 46.4, 23.7, 20.6; HRMS (FAB) calcd for $C_{17}H_{20}N_3O$ $[M+H^+]$ 282.1606, found 282.1601.

[2-(2-Chloro-4-methyl-phenoxy)-phenyl]-pyrrolidin-1-yl-diazene (10) (Table 1, entry 12): This compound was prepared according to general procedure (A) in 67% yield. **10**: $R_f = 0.54$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2956$, 2875, 1482, 1407, 1339, 1312, 1252, 1102, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.47 (dd, $J = 7.5$, 2.5 Hz, 1H, ArH), 7.20 (d, $J = 1.5$ Hz, 1H, ArH), 7.14–7.08 (m, 2H, ArH), 7.06–7.04 (m, 1H, ArH), 6.85 (dd, $J = 8.0$, 2.0 Hz, 1H, ArH), 6.62 (d, $J = 8.0$ Hz, 1H, ArH), 3.91–3.74 (br.s, 2H, NCH_2), 3.45–3.25 (br.s, 2H, NCH_2), 2.26 (s, 3H, CH_3), 1.93–1.88 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 152.7, 149.0, 142.8, 132.1, 130.3, 127.9, 125.7, 124.9, 121.5, 118.8, 117.7, 50.8, 46.1, 24.2, 20.3; HRMS (FAB) calcd for $C_{17}H_{19}ClN_3O$ $[M+H^+]$ 316.1217, found 316.1209.

[2-(2-Chloro-phenoxy)-phenyl]-pyrrolidin-1-yl-diazene (11) (Table 1, entry 10): This compound was prepared according to general procedure (A) in 70% yield. **11**: $R_f = 0.56$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2966$, 2868, 1575, 1477, 1409, 1342, 1317, 1268, 1237, 1099, 1058, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.49 (dd, $J = 6.5$, 1.5 Hz, 1H, ArH), 7.38 (dd, $J = 8.0$, 1.5 Hz, 1H, ArH), 7.17–7.12 (m, 3H, ArH), 7.06–7.03 (m, 1H, ArH), 6.91–6.87 (m, 1H, ArH), 6.69 (dd, $J = 6.5$, 1.5 Hz, 1H, ArH), 3.91–3.81 (br.s, 2H, NCH_2), 3.38–3.17 (br.s, 2H, NCH_2), 1.91–1.86 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 155.2, 148.5, 142.8, 129.9, 127.3, 125.8, 125.3, 123.0, 122.1, 118.8, 117.5, 50.4, 46.1, 23.7; HRMS (FAB) calcd for $C_{16}H_{17}ClN_3O$ $[M+H^+]$ 302.1060, found 302.1069.

General procedure (B) for reactions between 2,6-dihalo triazenes and phenols (Table 2): A flame-dried flask was charged with 2,6-dihalo triazene (1.0 equiv), $CuBr \cdot Me_2S$ (10.0 equiv), phenol (2.4 equiv), and the specified base (10.0 equiv). To this mixture was added acetonitrile, furnishing a solution approximately 0.1M in triazene, and pyridine (Table 2, entries 10–18, 20 vol% of solvent) was introduced. The reaction mixture was heated at the indicated temperature (Table 2) for the specified time before it was cooled to 25 °C. The resulting slurry was filtered through a pad of celite, and the celite was washed thoroughly with ether. The product was isolated by flash column chromatography. The following example further illustrates this procedure.

(4-Methyl-2,6-bis-phenoxy-phenyl)-pyrrolidin-1-yl-diazene (18) (Table 2, entry 10). General procedure (B): A mixture of [(2,6-dibromophenyl)-azo]pyrrolidine (**13**) (173 mg, 0.5 mmol), phenol (113 mg, 1.2 mmol), $CuBr \cdot Me_2S$ (1.03 g, 5.0 mmol), and K_2CO_3 (690 mg, 5.0 mmol) in acetonitrile (5 mL) in a flame-dried flask was treated with pyridine (1 mL). The reaction mixture was heated to 80 °C and stirred at that temperature for 5 h before it was cooled to 25 °C. The mixture was filtered through a pad of celite, and the celite was washed thoroughly with ether (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (15 mL), H_2O (15 mL), brine (15 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 3→6% ether in petroleum ether, gradient elution), furnishing compound **18** (166 mg, 89%). **18**: m.p. 84–85 °C (EtOAc in petroleum ether); $R_f = 0.36$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2966$, 2868, 1593, 1563, 1483, 1452, 1421, 1329, 1213, 1164, 1041, 857, 753, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.28–7.22 (m, 4H, ArH), 6.97 (dd, $J = 9.0$, 8.0 Hz, 2H, ArH), 6.91 (d, $J = 8.0$ Hz, 4H, ArH), 6.73 (s, 2H, ArH), 3.55 (br.s, 2H, NCH_2), 3.15 (br.s, 2H, NCH_2), 2.28 (s, 3H, CH_3), 1.76 (br.s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 158.4, 148.7, 135.4, 134.3, 129.0, 121.6, 118.3, 117.0, 51.1, 46.5, 23.4, 23.3, 20.9; HRMS (FAB) calcd for $C_{23}H_{24}N_3O_2$ $[M+H^+]$ 374.1869, found 374.1862.

(4-Methyl-2,6-bis-*p*-tolyloxy-phenyl)-pyrrolidin-1-yl-diazene (19) (Table 2, entry 16): This compound was prepared according to general procedure (B) in 70% yield. **19**: $R_f = 0.36$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2969$, 2858, 2367, 1606, 1569, 1501, 1421, 1329, 1219, 1164, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.04 (d, $J = 8.5$ Hz, 4H, ArH), 6.82 (d, $J = 8.5$ Hz, 4H, ArH), 6.63 (s, 2H, ArH), 3.59 (br.s, 2H, NCH_2), 3.25 (br.s, 2H, NCH_2), 2.29 (s, 6H, CH_3), 2.23 (s, 3H, CH_3), 1.81-1.76 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 156.0, 149.4, 135.3, 131.1, 129.5, 117.4, 117.3, 50.9, 45.8, 23.5, 21.0, 20.5; HRMS (FAB) calcd for $C_{25}H_{28}N_3O_2$ $[M+H^+]$ 402.2182, found 402.2170.

[2,6-Bis-(2-chloro-phenoxy)-4-methyl-phenyl]-pyrrolidin-1-yl-diazene (20) (Table 2, entry 15): This compound was prepared according to general procedure (B) in 78% yield. **20**: $R_f = 0.46$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2953$, 2874, 1589, 1479, 1447, 1408, 1328, 1265, 1233, 1059, 1035, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.35 (dd, $J = 7.5$, 1.5 Hz, 2H, ArH), 7.09–7.07 (m, 2H, ArH), 6.93–6.90 (m, 2H, ArH), 6.79 (s, 2H, ArH), 6.76 (dd, $J = 8.5$, 1.5 Hz, 2H, ArH), 3.56 (br.s, 2H, NCH_2), 3.02 (br.s, 2H, NCH_2), 2.31 (s, 3H, CH_3), 1.75 (br.s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 154.1, 148.1, 135.4, 133.5, 129.8, 127.3, 122.8, 122.4, 119.1, 117.5, 50.4, 45.1, 23.4, 23.4; HRMS (FAB) calcd for $C_{23}H_{22}N_3O_2Cl_2$ $[M+H^+]$ 442.1089, found 442.1073.

(2,4-Dimethyl-6-phenoxy-phenyl)-pyrrolidin-1-yl-diazene (21) (Table 2, entry 12): This compound was prepared according to general procedure (B) in 56% yield. **21**: m.p. 76–77 °C (EtOAc in petroleum ether); $R_f = 0.54$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2956$, 2874, 1590, 1560, 1490, 1423, 1323, 1216, 1163, 1043, 857, 757, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.24–7.21 (m, 2H, ArH), 6.96–6.93 (m, 1H, ArH), 6.87–6.84 (m, 3H, ArH), 6.96–6.93 (m, 1H, ArH), 3.70 (br.s, 2H, NCH_2), 3.40 (br.s, 2H, NCH_2), 2.28 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.92–1.88 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 158.1, 146.9, 140.5, 134.8, 132.8, 129.0, 127.4, 121.2, 120.2, 116.8, 48.0 (very br.), 23.7, 20.9, 18.1; HRMS (FAB) calcd for $C_{18}H_{21}N_3OCs$ $[M+Cs^+]$ 428.0739, found 428.0749.

(4-Bromo-2,6-bis-phenoxy-phenyl)-pyrrolidin-1-yl-diazene (22) (Table 2, entry 13): This compound was prepared according to general procedure (B) in 91% yield. **22**: $R_f = 0.41$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 3051$, 2970, 2861, 1563, 1489, 1400, 1339, 1312, 1211, 1156, 1075, 1034, 750, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.29 (t, $J =$ 9.0 Hz, 4H, ArH), 7.04 (t, $J = 9.0$ Hz, 2H, ArH), 7.00 (s, 2H, ArH), 6.95 (d, $J = 9.0$ Hz, 4H, ArH), 3.62 (br.s, 2H, NCH_2), 3.15 (br.s, 2H, NCH_2), 1.80 (s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 157.6, 150.1, 135.7, 129.2, 122.5, 120.1, 117.6, 116.7, 50.8, 45.5, 23.6, 23.3; HRMS (FAB) calcd for $C_{22}H_{21}BrN_3O_2$ $[M+H^+]$ 438.0817, found 438.0804.

3,5-Diphenoxy-4-(pyrrolidin-1-yl-azo)-benzoic acid methyl ester (23) (Table 2, entry 14): Compound **23** was prepared according to general procedure (B) in 82% yield. **23**: $R_f = 0.16$ (silica gel, 10% EtOAc in hexanes); IR (KBr): $\tilde{\nu}_{max} = 2917$, 2856, 1718, 1566, 1490, 1413, 1312, 1211, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.57 (s, 2H, ArH), 7.27–7.24 (m, 4H, ArH), 7.00 (t, $J = 7.5$ Hz, 2H, ArH), 6.90 (d, $J = 7.5$ Hz, 4H, ArH), 3.83 (s, 3H, OCH_3), 3.60 (br.s, 2H, NCH_2), 3.14 (br.s, 2H, NCH_2), 1.78 (br.s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 166.0, 158.1,

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149.3, 141.0, 129.3, 126.8, 122.3, 118.9, 117.4, 52.2, 51.0, 45.7, 23.7, 23.3; HRMS (FAB) calcd for $C_{24}H_{24}N_3O_4$ $[M+H^+]$ 418.1767, found 418.1775.

[2,6-Bis-(2-chloro-4-methyl-phenoxy)-4-methyl-phenyl]-pyrrolidin-1-yl-diazene (24) (Table 2, entry 17): This compound was prepared according to general procedure (B) in 74% yield. **24**: $R_f = 0.48$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 2966, 2866, 1759, 1605, 1569, 1489, 1415, 1323, 1244, 1207, 1059, 1035, 992, 808\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.17 (d, $J = 2.0$ Hz, 2H, ArH), 6.89 (dd, $J = 8.5$, 2.0 Hz, 2H, ArH), 6.69 (d, $J = 8.5$ Hz, 2H, ArH), 6.68 (s, 2H, ArH), 3.55 (br.s, 2H, NCH_2), 3.15 (br.s, 2H, NCH_2), 2.26 (s, 9H, CH_3), 1.81-1.77 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 151.9, 148.9, 135.4, 132.6, 130.3, 128.0, 122.9, 118.1, 118.0, 51.1, 46.5, 23.7, 21.2, 20.4; HRMS (FAB) calcd for $C_{25}H_{26}Cl_2N_3O_2$ $[M+H^+]$ 470.1402, found 470.1424.

(4-Methyl-2,6-bis-phenylsulfanyl-phenyl)-pyrrolidin-1-yl-diazene (25) (Table 2, entry 18): This compound was prepared from thiophenol according to general procedure (B) in 84% yield. **25**: $R_f = 0.52$ (silica gel, 10% ether in petroleum ether); IR (KBr): $\tilde{\nu}_{max} = 3052, 2966, 2866, 1575, 1538, 1477, 1415, 1317, 1256, 1213, 1158, 1023, 851, 783, 740, 685\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.43-7.41 (m, 4H, ArH), 7.33-7.26 (m, 6H, ArH), 6.62 (s, 2H, ArH), 3.85 (br.s, 2H, NCH_2), 3.55 (br.s, 2H, NCH_2), 2.02 (s, 3H, CH_3), 1.97 (br.s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 145.0, 135.5, 134.5, 132.9, 130.6, 129.0, 128.2, 127.3, 51.1, 46.9, 23.8, 20.6; HRMS (FAB) calcd for $C_{23}H_{24}N_3S_2$ $[M+H^+]$ 406.1412, found 406.1424.

Triazene alcohol 28: A solution of amino alcohol **26** (1.64 g, 12 mmol) in glacial acetic acid (100 mL) at 25 °C was treated dropwise with Br_2 (1.4 mL, 26.4 mmol). The resulting mixture was stirred for 0.5 h before it was poured into ice-water (250 mL). The precipitate was filtered and washed with H_2O (3×30 mL). The product was taken into the next step without further purification. A solution of alcohol **27** (2.95 g, 10 mmol) in THF/H_2O (10:1, 100 mL) was treated with concentrated HCl (4.2 mL) at 0 °C, and then aqueous $NaNO_2$ (0.90 g, 13 mmol in 5 mL of H_2O) was added dropwise over 0.5 h. The resulting solution was slowly transferred to a flask charged with pyrrolidine (8.4 mL, 100 mmol) and K_2CO_3 (8.28 g, 60 mmol) in H_2O (200 mL) at 0 °C and stirred for 1 h. The aqueous phase was extracted with EtOAc (3×200 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl (200 mL), brine (200 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 20 →30% EtOAc in hexanes, gradient elution) to furnish triazene **28** (3.17 g, 84%). **28**: m.p. 66–67 °C (MeOH); $R_f = 0.30$ (silica gel, 40% EtOAc in hexanes); IR (KBr): $\tilde{\nu}_{max} =$ 3383, 2947, 2872, 1589, 1535, 1416, 1338, 1314, 1223, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$ (s, 2H, ArH), 3.95 (br.s, 2H, NCH_2), 3.80 (br.s, 2H, NCH_2), 3.71 (br.s, 2H, CH_2O), 2.77 (t, $J = 6.5$ Hz, 2H, CH_2Ar), 2.09 (br.s, 4H, NCH_2CH_2), 1.65 (br.s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 146.4, 137.6, 132.7, 117.6, 63.1, 51.1, 46.5, 37.8, 24.1, 22.5; HRMS (FAB) calcd for $C_{12}H_{16}Br_2N_3O$ $[M+H^+]$ 378.0670, found 378.0856.

Carboxylic acid 29: A solution of **28** (50 mg, 0.13 mmol) in acetone (400 µL) at 0 °C was added to a 5% aqueous $NaHCO_3$ solution (400 µL). The mixture was treated sequentially with KBr (1.6 mg, 0.013 mmol) and TEMPO (31 mg, 0.20 mmol). Sodium hypochlorite (aqueous 4–6%, 400 µL) was added dropwise over 20 min, and the mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the resulting mixture was extracted with EtOAc (2×10 mL). The combined organic phases were washed with H_2O (15 mL), brine (15 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 5 →10% MeOH in CH_2Cl_2, gradient elution) to afford carboxylic acid **29** (42 mg, 82%). **29**: m.p. 80–85 °C (decomp); $R_f = 0.40$ (silica gel, 15% MeOH in CH_2Cl_2); IR (KBr): $\tilde{\nu}_{max} = 3441, 2972, 2873, 1711, 1632, 1589, 1537, 1416\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.51$ (s, 2 H, ArH), 3.91 (br.s, 2H, NCH_2), 3.64 (br.s, 2H, NCH_2), 3.54 (br.s, 2H, CH_2CO_2), 2.07 (br.s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 175.9, 148.0, 136.2, 134.4, 118.6, 52.5, 47.5, 41.0, 24.7, 22.9; HRMS (FAB) calcd for $C_{12}H_{14}Br_2N_3O_2$ $[M+H^+]$ 389.9453, found 389.9440.

Dipeptide 32: A solution of amine **30** (150 mg, 0.77 mmol), acid **31** (438 mg, 1.5 mmol) and HOBt (135 mg, 1.0 mmol) in DMF (6 mL) was treated with EDC (177 mg, 0.92 mmol) at 0 °C for 10 h. The reaction mixture was diluted with EtOAc (25 mL) and washed with 5% aqueous citric acid (10 mL), 5% aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10 →30% EtOAc in hexanes, gradient elution) afforded dipeptide **32** (324 mg, 91%). **32**: m.p. 132 °C (EtOAc in hexanes); $R_f =$ 0.50 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -1.27$ ($c = 1.0$, MeOH); IR (KBr): $\tilde{\nu}_{max} = 3065, 3032, 2956, 1734, 1687, 1651, 1616, 1541, 1515, 1452, 1384, 1232, 1113, 1053\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta =$ 7.34–7.26 (m, 10H, ArH), 6.73 (d, $J = 7.5$ Hz, 2H, ArH), 6.53 (d, $J = 7.5$ Hz, 2H, ArH), 5.26 (s, 1H, CHCON), 4.60–4.50 (m, 1H, CH_2CHCO), 3.69 (s, 2H, CH_2O), 3.30 (s, 3H, OCH_3), 2.97–2.85 (m, 2H, CH_2CH); ^{13}C NMR (125 MHz, CD_3OD): $\delta =$ 181.1, 173.2, 172.0, 157.3, 138.6, 131.2, 129.8, 129.7, 129.5, 129.3, 129.1, 128.9, 128.5, 128.1, 116.3, 68.1, 60.5, 55.3, 52.8, 52.3, 37.6; HRMS (FAB) calcd for $C_{26}H_{27}N_2O_6$ $[M+H^+]$ 463.1869, found 463.1879.

Tripeptide 34: A solution of dipeptide **32** (85 mg, 0.18 mmol) in MeOH (2 mL) was stirred with 10% $Pd(OH)_2/C$ (8 mg) under H_2 at ambient temperature for 1 h. Filtration through a pad of celite, followed by removal of solvent under reduced pressure afforded crude amine **33** (82 mg, 100%), which was used in the next step without further purification. A solution of acid **29** (77 mg, 0.20 mmol) and amine **33** (183 mg, 0.40 mmol) in DMF (2 mL) was treated with HBTU (114 mg, 0.30 mmol) and Et_3N (42 µL, 0.30 mmol) at 0 °C. The reaction mixture was stirred at that temperature for 18 h before the addition of saturated aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash column chromatography (silica gel, 1 →3% MeOH in CH_2Cl_2, gradient elution) to afford pure tripeptide **34** (88 mg, 63%). **34**: m.p. 202 °C (EtOAc in hexanes); $R_f = 0.35$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -2.72$ ($c =$ 0.52, MeOH); IR (KBr): $\tilde{\nu}_{max} = 3296, 2953, 2923, 2873, 1745, 1643, 1537, 1515, 1416, 1360, 1222\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta =$ 7.51 (s, 2H, ArH), 7.32–7.21 (m, 5H, ArH), 6.73 (d, $J = 8.5$ Hz, 2H, ArH), 6.52 (d, $J =$ 8.5 Hz, 2H, ArH), 5.50 (s, 1H, CHCON), 4.63 (d, $J = 9.0$, 5.0 Hz, 1H, CH_2CHCO), 3.88 (br.s, 2H, NCH_2), 3.67 (s, 3H, OCH_3), 3.64 (br.s, 2H, NCH_2), 3.52 (br.s, 2H, CH_2CO), 2.97 (dd, $J = 14.0$, 5.0 Hz, 1H, CH_2CH), 2.78 (dd, $J = 14.0$, 9.0 Hz, 1H, CH_2CH), 2.02 (br.s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, CD_3OD): $\delta =$ 173.2, 172.0, 172.0, 157.3, 148.2, 138.6, 136.1, 131.2, 129.9, 129.9, 128.6, 128.3, 122.6, 118.7, 116.3, 58.5, 55.4, 52.8, 52.3, 48.5, 41.7, 37.5, 24.9, 24.9; HRMS (FAB) calcd for $C_{30}H_{31}Br_2N_5O_5Cs$ $[M+Cs^+]$ 831.9746, found 831.9723.

C-O-D ring system 35: A solution of tripeptide **34** (70 mg, 0.10 mmol) and $CuBr \cdot Me_2S$ (72 mg, 0.25 mmol) in degassed acetonitrile (10 mL) was treated with K_2CO_3 (35 mg, 0.25 mmol) and pyridine (25 µL, 0.30 mmol). The resulting mixture was heated to 75 °C and stirred at that temperature for 15 h. The reaction mixture was cooled to 25 °C and filtered through a pad of celite with thorough washing with EtOAc (3×20 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 2 →4% MeOH in $CHCl_3$, gradient elution) to afford product **35** (48 mg, 77%). **35**: $R_f =$ 0.27 (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = +16.4$ ($c = 0.53$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3062, 2955, 2873, 1743, 1643, 1596, 1504, 1412, 1331, 1317, 1267, 1211, 1120, 1105, 1032\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD): $\delta =$ 7.42 (dd, $J = 8.2$, 2.5 Hz, 1H, ArH), 7.36–7.27 (m, 5H, ArH), 7.17 (dd, $J = 8.2$, 2.1 Hz, 1H, ArH), 7.09 (d, $J = 1.5$ Hz, 1H, ArH), 6.95 (dd, $J = 8.5$, 2.5 Hz, 1H, ArH), 6.80 (dd, $J = 8.5$, 2.5 Hz, 1H, ArH), 6.15 (d, $J = 1.5$ Hz, 1H, ArH), 5.48 (s, 1H, CHCON), 4.65-4.62 (m, 1H, CH_2CHCO), 3.90 (br.s, 2H, NCH_2), 3.67 (s, 3H, OCH_3), 3.67 (br.s, 2H, NCH_2), 3.52 (d, $J = 14.4$ Hz, 1H, CH_2CO), 3.43 (dd, $J = 14.0$, 5.0 Hz, 1H, CH_2CH), 3.30 (d, $J = 14.0$ Hz, 1H, CH_2CO), 3.05 (dd, $J = 14.0$, 9.0 Hz, 1H, CH_2CH), 2.06 (br.s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, CD_3OD): $\delta =$ 171.2, 170.9, 169.3, 155.3, 154.1, 138.4, 137.7, 133.8, 133.3, 132.0, 131.2, 128.0, 127.6, 127.0, 126.0, 121.5, 121.2, 117.9, 114.9, 56.2, 52.9, 52.8, 51.1, 48.0, 41.2, 34.8, 23.3, 23.3; HRMS (FAB) calcd for $C_{30}H_{30}BrN_5O_5Cs$ $[M+Cs^+]$ 752.0485, found 752.0466.

Amine 36: A solution of triazene **35** (62 mg, 0.10 mmol) in MeOH (1 mL) was treated with excess of Raney Ni (W2). The resulting mixture was heated to reflux for 2 h and then cooled to 25 °C. The reaction mixture was filtered through a pad of celite and the celite was washed with EtOAc ($3 \times$ 5 mL). The filtrate was concentrated and flash column chromatography of the resulting residue (silica gel, 50 →70% EtOAc in hexanes, gradient elution) afforded product **36** (37 mg, 71%). **36**: $R_f = 0.16$ (silica gel, 70% EtOAc in hexanes); $[\alpha]_D^{22} = +10.1$ ($c = 0.22$, CH_2Cl_2); IR (KBr): $\tilde{\nu}_{max} =$ 3038, 1743, 1632, 1510, 1440, 1345, 1282, 1218 cm^{-1}; ^1H NMR (600 MHz, $CD_3OD/CDCl_3$, 1:1): $\delta = 7.41-7.37$ (m, 3H, ArH), 7.35 (br.d, $J = 8.0$ Hz,

1H, ArH), 7.21 (br. d, $J = 8.0$ Hz, 1H, ArH), 6.99 (d, $J = 7.1$ Hz, 2H, ArH), 6.82 (d, $J = 8.2$ Hz, 1H, ArH), 6.75 (br. d, $J = 8.3$ Hz, 2H, ArH), 6.59 (br. s, 1H, ArH), 6.18 (d, $J = 6.7$ Hz, 1H, NH), 6.06 (d, $J = 8.2$ Hz, 1H, ArH), 5.75 (d, $J = 8.4$ Hz, 1H, NH), 5.46 (br. s, 1H, CHCON), 4.74 – 4.69 (m, 1H, CH_2CHCO), 3.76 (s, 3H, OCH_3), 3.57 (d, $J = 16.4$ Hz, 1H, CH_2CO), 3.33 (d, $J = 16.4$ Hz, 1H, CH_2CO), 3.25 (dd, $J = 13.3$, 4.0 Hz, 1H, CH_2CH), 2.45 (dd, $J = 13.3$, 11.3 Hz, 1H, CH_2CH); ^{13}C NMR (125 MHz, CD_3OD): $\delta =$ 172.3, 171.6, 169.2, 159.4, 154.1, 136.6, 133.0, 132.9, 132.2, 130.2, 129.7, 128.3, 125.8, 123.3, 121.3, 120.3, 117.1, 58.3, 54.3, 43.5, 39.7; HRMS (FAB) calcd for $C_{26}H_{25}N_3O_5$ [M^+] 460.1872, found 460.1886.

Phenol 37: Amine **36** (55 mg, 0.12 mmol) dissolved in THF (1 mL) was added dropwise to a chilled ($-20\,^\circ$C) solution of $BF_3 \cdot Et_2O$ (59 μL, 0.48 mmol) in THF (200 μL). To this solution was added tBuNO$_2$ (50 μL, 0.42 mmol) dissolved in THF (200 μL) over 0.5 h. The reaction mixture was stirred at $-20\,^\circ$C for 10 min, and was then allowed to reach $-5\,^\circ$C. Cold (0 °C) Et_2O (2 mL) was added and the resulting precipitate was collected by filtration and dried under vacuum. To this precipitate was added saturated aqueous $Cu(NO_3)_2$ (12 mL), followed by Cu_2O (86 mg, 0.60 mmol) and the reaction mixture was stirred at 25 °C for 3 h before it was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 30 →50 % EtOAc in hexanes, gradient elution), furnishing phenol **37** (33 mg, 60 %). **37**: $R_f = 0.22$ (silica gel, 70 % EtOAc in hexanes); $[\alpha]^{22}_D = +10.2$ ($c = 0.25$, CH_2Cl_2); IR (KBr): $\tilde{\nu}_{max} = 3318$, 3038, 2945, 2910, 1737, 1644, 1592, 1510, 1434, 1347, 1277, 1218 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.44 - 7.38$ (m, 6H, ArH), 7.22 (dd, $J = 7.1$, 2.4 Hz, 1H, ArH), 7.10 (d, $J = 6.8$ Hz, 1H, ArH), 6.96 (d, $J = 8.2$ Hz, 1H, ArH), 6.82 (dd, $J =$ 8.2, 2.4 Hz, 1H, ArH), 6.78 (dd, $J = 8.2$, 1.7 Hz, 1H, ArH), 6.70 (br. s, 1H, ArH), 6.67 (d, $J = 1.8$ Hz, 1H, ArH), 6.11 (d, $J = 7.9$ Hz, 1H, NH), 6.00 (s, 1H, OH), 5.73 (d, $J = 8.8$ Hz, 1H, NH), 5.45 (d, $J = 8.0$ Hz, 1H, $COCHNH$), 4.72 (ddd, $J = 10.8$, 8.8, 4.4 Hz, 1H, CH_2CHCO), 3.77 (s, 3H, OCH_3), 3.60 (d, $J = 16.9$ Hz, 1H, CH_2CO), 3.39 (d, $J = 16.9$ Hz, 1H, CH_2CO), 3.24 (dd, $J = 13.3$, 4.4 Hz, 1H, CH_2CH), 2.47 (dd, $J = 13.5$, 10.8 Hz, 1H, CH_2CH); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 172.2$, 171.3, 169.3, 158.6, 149.4, 146.7, 136.4, 133.7, 133.2, 132.5, 130.2, 129.8, 128.4, 127.9, 126.1, 123.5, 121.4, 119.9, 117.0, 58.4, 54.4, 43.6, 39.7; HRMS (FAB) calcd for $C_{26}H_{24}N_2O_6Cs$ [$M + Cs^+$] 593.0669, found 593.0656.

Amino alcohol 41: A solution of amino ester **40** (1.38 g, 4.47 mmol) in THF (30 mL) at 0 °C was treated with $LiAlH_4$ (510 mg, 13.4 mmol) portionwise. The resulting mixture was stirred at 0 °C for 4 h and then it was quenched by slow addition of H_2O (1 mL). The reaction mixture was extracted with EtOAc (3 × 40 mL) and the combined organic phases were washed with 5 % aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the solid product obtained was recrystallized from EtOH to afford pure amino alcohol **41** (1.22 g, 93 %). **41**: $R_f = 0.28$ (silica gel, 30 % EtOAc in hexanes); IR (KBr): $\tilde{\nu}_{max} = 3307$, 1614, 1578, 1472, 1402, 1349, 1284, 1198, 1067, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.40 (s, 2H, ArH), 4.53 (s, 2H, CH_2), 1.90 – 1.50 (br. s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 141.4, 132.3, 130.7, 108.7, 63.9; HRMS (FAB) calcd for $C_7H_7Br_2NO$ [M^+] 278.8894, found 278.8886.

Triazene alcohol 42: A solution of amine **41** (2.81 g, 10 mmol) in THF/H_2O (10:1, 100 mL) was treated with concentrated HCl (4.2 mL) at 0 °C. A chilled aqueous solution (0 °C) of $NaNO_2$ (0.90 g, 13 mmol in 5 mL H_2O) was added dropwise over 0.5 h. The resulting solution was slowly transferred to a flask charged with pyrrolidine (8.4 mL, 100 mmol) and K_2CO_3 (8.28 g, 60 mmol) in H_2O (200 mL) at 0 °C and stirred for 1 h. The aqueous phase was extracted with EtOAc (3 × 150 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl (200 mL), brine (200 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, 20 →30 % EtOAc in hexanes, gradient elution) to afford triazene **42** (2.64 g, 73 %). **42**: m.p. 69 °C (MeOH); $R_f = 0.40$ (silica gel, 40 % EtOAc in hexanes); IR (KBr): $\tilde{\nu}_{max} = 3436$, 1618, 1548, 1468, 1432, 1403, 1345, 1283, 1201, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.41 (s, 2H, ArH), 4.52 (d, $J = 4.5$ Hz, 2H, CH_2O), 3.81 (br. s, 4H, NCH_2), 3.13 (br. s, 1H, OH), 2.05 (br. s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 145.8, 140.8, 129.8, 117.6, 62.9, 51.1, 46.7, 23.8, 23.6; HRMS (FAB) calcd for $C_{11}H_{13}Br_2N_3ONa$ [$M + Na^+$] 383.9323, found 383.9337.

Triazene azide 43: A solution of triazene alcohol **42** (542 mg, 1.5 mmol) in THF (15 mL) at 25 °C was treated sequentially with triphenylphosphane (590 mg, 2.25 mmol), DEAD (360 μL, 2.25 mmol) and DPPA (485 μL, 2.25 mmol). The resulting solution was stirred at 25 °C for 2 h. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 20 →30 % EtOAc in hexanes, gradient elution) to afford triazene azide **43** (475 mg, 82 %). **43**: $R_f = 0.39$ (silica gel, 10 % EtOAc in hexanes); IR (KBr): $\tilde{\nu}_{max} = 3381$, 2970, 2871, 2351, 1416, 1336, 1313, 1223, 1119, 1069, 1027, 902, 738, 541 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.52 (s, 2H, ArH), 3.94 (br. s, 2H, NCH_2), 3.81 (br. s, 2H, CH_2N_3), 3.71 (br. s, 2H, NCH_2), 2.30 (br. s, 2H, CH_2), 2.09 (br. s, 2H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 147.9, 133.9, 131.8, 118.0, 53.0, 51.1, 46.5, 23.9, 23.5; HRMS (FAB) calcd for $C_{11}H_{12}Br_2N_6Na$ [$M +$ Na^+] 408.9389, found 408.9393.

Amine 44: A solution of azide **43** (463 mg, 1.2 mmol) in THF (12 mL) was treated with triphenylphosphane (629 mg, 2.4 mmol) and H_2O (220 μL, 12 mmol). The resulting solution was heated to 45 °C and stirred at that temperature for 8 h. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 20 →30 % EtOAc in hexanes, gradient elution) to afford amine **44** (346 mg, 80 %). **44**: $R_f = 0.23$ (silica gel, 40 % EtOAc in hexanes); IR (KBr): $\tilde{\nu}_{max} = 3400$, 3060, 2978, 2860, 1637, 1584, 1531, 1408, 1261, 1161, 1114 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.48 (s, 2H, ArH), 3.94 (br. s, 2H, NCH_2), 3.81 (br. s, 2H, CH_2NH_2), 3.71 (br. s, 2H, NCH_2), 2.30 (br. s, 2H, NCH_2CH_2), 2.09 (br. s, 2H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 146.7, 132.8, 131.1, 117.7, 51.0, 46.4, 44.7, 23.9, 23.5; HRMS (FAB) calcd for $C_{11}H_{14}Br_2N_4Na$ [$M +$ Na^+] 382.9471, found 382.9483.

Dipeptide 47: A solution of amine **46** (557 mg, 5.4 mmol), acid **45** (1.52 g, 5.4 mmol), and HOBt (948 mg, 7.0 mmol) in DMF (25 mL) was treated with EDC (1.24 g, 6.5 mmol) at 0 °C for 8 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous citric acid (2 × 30 mL), 5 % aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 2 →4 % MeOH in $CHCl_3$, gradient elution) afforded dipeptide **47** (1.62 g, 85 %). **47**: $R_f = 0.30$ (silica gel, 5 % MeOH in $CHCl_3$); $[\alpha]^{22}_D = -0.85$ ($c = 1.0$, MeOH); IR (KBr): $\tilde{\nu}_{max} = 2931$, 1759, 1640, 1543 cm^{-1}; ^{1}H NMR (500 MHz, CD_3SOCD_3): $\delta = 7.73$ (d, $J = 8.5$ Hz, 2 H, ArH), 7.34 (d, $J = 8.5$ Hz, 2H, ArH), 4.93 – 4.84 (m, 2H, $CHCH_2$, $CHCH_3$), 4.87 – 4.84 (m, 1H, $CHCH_2O$), 4.40 (br. t, $J = 7.0$ Hz, 1H, $CHCH_2N$), 3.53 – 3.30 (m, 2H, $NCHCH_2$), 2.02 (s, 9H, tBuO), 1.92 (d, $J = 7.0$ Hz, 3H, $CHCH_3$); ^{13}C NMR (125 MHz, CD_3SOCD_3): $\delta =$ 174.0, 171.4, 155.8, 155.1, 130.3, 130.2, 128.1, 114.8, 78.0, 55.8, 47.5, 37.1, 28.2, 17.5; HRMS (FAB) calcd for $C_{17}H_{25}N_2O_6$ [$M + H^+$] 353.1713, found 353.1716.

D-O-E cyclization precursor 49: A solution of dipeptide ester **47** (915 mg, 2.6 mmol) in MeOH/H_2O (1:1, 25 mL) at 0 °C was treated with anhydrous LiOH (94 mg, 3.9 mmol). The resulting solution was stirred at 0 °C for 1 h before 5 % aqueous citric acid (5 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give crude carboxylic acid **48** (880 mg, 100 %), which was used in the next step without further purification. A solution of amine **44** (936 mg, 2.6 mmol), acid **48** (1.32 g, 3.9 mmol) and HOBt (527 mg, 3.9 mmol) in DMF (25 mL) was treated with EDC (1.50 g, 7.8 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 8 h and then was diluted with EtOAc (100 mL). The organic layer was washed with saturated aqueous NH_4Cl (30 mL), 5 % aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography of the resulting residue (silica gel, 2 →5 % MeOH in $CHCl_3$, gradient elution) afforded product **49** (812 mg, 45 %). **49**: $R_f = 0.15$ (silica gel, 5 % MeOH in $CHCl_3$); $[\alpha]^{22}_D = -2.13$ ($c = 1.7$, MeOH); IR (KBr): $\tilde{\nu}_{max} = 3306$, 2978, 2931, 1666, 1594, 1515, 1454, 1416, 1366, 1314, 1249, 1165, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.62 (s, 1H, NH), 7.42 (s, 2H, ArH), 6.91 (d, $J = 8.5$ Hz, 2H, ArH), 6.78 (br. s, 1H, NH), 6.65 (d, $J = 8.5$ Hz, 2H, ArH), 5.55 (br. s, 1H, NH), 4.45-4.42 (m, 1H, $CHCH_2Ar$), 4.39-4.21 (m, 3H, NCH_2Ar, $CHCH_3$), 3.92 (br. s, 2H, NCH_2), 3.69 (br. s, 2H, NCH_2), 2.93 (dd, $J = 13.5$, 6.5 Hz, 1H, $NCHCH_2$), 2.88 (dd, $J = 13.5$, 7.5 Hz, 1H, $NCHCH_2$), 2.26 (s, 1H, OH), 2.07 (br. s, 2H, CH_2), 2.04 (br. s, 2H, NCH_2CH_2), 1.37 (s, 9H, tBuO), 1.20 (d, $J = 6.5$ Hz, 3H, $CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 172.3, 171.9, 171.3, 155.4, 146.9, 137.1, 135.6, 131.4, 130.4, 128.2, 127.1, 117.9, 115.5, 80.4, 56.4, 51.1, 48.8, 46.6, 41.8, 37.3, 28.3, 23.8, 23.3, 17.5;

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HRMS (FAB) calcd for $C_{28}H_{36}Br_2N_6O_5Cs$ [$M+Cs^+$] 827.0168, found 827.0195.

D-O-E ring system 50: A solution of tripeptide **49** (76 mg, 0.11 mmol) and $CuBr\cdot Me_2S$ (80 mg, 0.28 mmol) in degassed acetonitrile (11 mL) was treated with K_2CO_3 (38 mg, 0.28 mmol) and pyridine (27 μL, 0.33 mmol). The resulting mixture was heated to 75 °C, stirred at that temperature for 6 h, and then cooled to 25 °C. The reaction mixture was filtered through a pad of celite and the celite was washed thoroughly with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 2 →4 % MeOH in $CHCl_3$, gradient elution) to afford model system **50** (36 mg, 54 %) and recovered tripeptide **49** (10 mg, 13 %). **50**: $R_f = 0.23$ (silica gel, 5 % MeOH in $CHCl_3$); $[\alpha]_D^{22} = +10.6$ ($c = 0.91$, MeOH); IR (KBr): $\tilde{\nu}_{max} = 3401, 3306, 3072, 2976, 2936, 2873, 1714, 1651, 1599, 1563, 1504, 1412, 1366, 1335, 1250, 1203, 1163\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD, 323 K): $\delta =$ 7.47 (dd, $J = 8.5$, 2.5 Hz, 1 H, ArH), 7.09 (s, 1 H, ArH), 7.07 (dd, $J = 8.5$, 2.5 Hz, 1 H, ArH), 7.00 (dd, $J = 8.5$, 2.5 Hz, 1 H, ArH), 6.80 (dd, $J =$ 8.5, 2.5 Hz, 1 H, ArH), 6.02 (br. s, 1 H, ArH), 4.69 (d, $J = 16.0$ Hz, 1 H, $ArCH_2N$), 4.30-4.29 (m, 1 H, $CHCH_2Ar$), 4.36 (q, $J = 7.0$ Hz, 1 H, $CHCH_3$), 3.90 (br. s, 4 H, NCH_2), 3.72 (d, $J = 16.0$ Hz, 1 H, $ArCH_2N$), 3.25 (dd, $J =$ 14.0, 5.5 Hz, 1 H, $CHCH_2Ar$), 2.94 (dd, $J = 14.0$, 2.7 Hz, 1 H, $CHCH_2Ar$), 2.01 (br. s, 4 H, NCH_2CH_2), 1.48 (s, 9 H, *t*BuO), 1.20 (d, $J = 7.0$ Hz, 3 H, $CHCH_3$); ^{13}C NMR (125 MHz, CD_3OD, 323 K): $\delta =$ 174.6, 171.9, 156.6, 155.1, 139.8, 138.0, 134.3, 132.9, 131.9, 124.7, 123.5, 123.1, 119.3, 114.5, 82.0, 58.3, 53.0, 49.8, 49.5, 48.4, 42.1, 37.2, 28.6, 23.7, 23.7, 20.0; HRMS (FAB) calcd for $C_{28}H_{35}BrN_6O_5Cs$ [$M+Cs^+$] 747.0907, found 747.0888.

Iodide alcohol 57: A solution of alcohol **56** (437 mg, 2.6 mmol) in DMF (10 mL) at 25 °C was treated with *N*-iodosuccinimide (878 mg, 3.9 mmol). The resulting solution was stirred at that temperature for 12 h, and then it was quenched by the addition of aqueous saturated Na_2SO_3 (10 mL). The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with 5 % aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, 20 →40 % EtOAc in hexanes, gradient elution) to give product **57** (696 mg, 91 %). **57**: $R_f = 0.17$ (silica gel, 40 % EtOAc in hexanes); IR (thin film) $\tilde{\nu}_{max} = 3366, 2931, 1578, 1449, 1420, 1314, 1196, 1155, 1038, 1008\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 6.67 (d, $J = 2.5$ Hz, 1 H, ArH), 6.32 (d, $J = 2.5$ Hz, 1 H, ArH), 4.60 (s, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 2.72 (br. s, 1 H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 161.1, 158.3, 144.6, 105.0, 97.8, 77.5, 69.3, 56.3, 55.5; HRMS (FAB) calcd for $C_9H_{11}IO_3$ [M^+] 293.9753, found 293.9755.

Azide 58: A solution of alcohol **57** (588 mg, 2.0 mmol) in THF (15 mL) at 0 °C was treated sequentially with DEAD (470 μL, 3.0 mmol), triphenylphosphane (786 mg, 3.0 mmol), and DPPA (650 μL, 3.0 mmol). The resulting solution was stirred at 0 °C for 2 h, and then concentrated in vacuo to afford an oil, which was purified by flash column chromatography (silica gel, 10 →30 % ether in hexanes, gradient elution), furnishing azide **58** (523 mg, 82 %). **58**: $R_f = 0.35$ (silica gel, 20 % EtOAc in hexanes); IR (thin film) $\tilde{\nu}_{max} = 2942, 2355, 2098, 1578, 1450, 1425, 1340, 1315, 1205, 1156, 1083\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.62$ (d, $J = 2.6$ Hz, 1 H, ArH), 6.40 (d, $J = 2.6$ Hz, 1 H, ArH), 4.48 (s, 2 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 161.2, 159.1, 140.0, 106.2, 98.4, 79.8, 59.4, 56.5, 55.5; HRMS (FAB) calcd for $C_9H_{11}IN_3O_2$ [$M+H^+$] 319.9896, found 319.9892.

Amine 59: To a solution of azide **58** (510 mg, 1.6 mmol) in THF/H_2O (10:1, 10 mL) was added triphenylphosphane (1.26 g, 4.8 mmol) and the resulting solution was heated to 45 °C for 4 h with stirring. The solution was cooled to 25 °C and the solvent was removed in vacuo. The residue was subjected to flash column chromatography (silica gel, 1 →5 % MeOH in $CHCl_3$, gradient elution) to afford amine **59** (375 mg, 80 %). **59**: $R_f = 0.37$ (silica gel, 10 % MeOH in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3366, 2931, 1578, 1449, 1420, 1320, 1202, 1155, 1067, 1002\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 6.62 (d, $J = 2.5$ Hz, 1 H, ArH), 6.34 (d, $J = 2.5$ Hz, 1 H, ArH), 3.86 (s, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 1.74 (s, 2 H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.3, 158.8, 147.2, 105.6, 97.3, 79.6, 56.4, 55.5, 51.7$; HRMS (FAB) calcd for $C_9H_{13}INO_2$ [$M+H^+$] 293.9991, found 293.9994.

Dipeptide 60: A solution of amine **59** (162 mg, 0.55 mmol), *N*-Boc-Gly (97 mg, 0.55 mmol), and Et_3N (190 μL, 1.38 mmol) in DMF (3 mL) was treated with EDC (158 mg, 0.83 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 12 h, and then the reaction was quenched by the addition of saturated NH_4Cl solution (3 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with 5 % aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 20 →40 % EtOAc in hexanes, gradient elution) to give dipeptide **60** (200 mg, 81 %). **60**: $R_f = 0.13$ (silica gel, 40 % EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3314, 2924, 1675, 1650, 1583, 1504, 1449, 1314, 1156, 1064\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 6.60 (d, $J = 2.5$ Hz, 1 H, ArH), 6.36 (d, $J = 2.5$ Hz, 1 H, ArH), 6.62 (br. s, 1 H, NH), 5.11 (br. s, 1 H, NH), 4.51 (d, $J = 6.5$ Hz, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.82 (br. s, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 1.43 (s, 9 H, *t*BuO); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 169.2, 161.3, 158.9, 156.0, 142.1, 106.6, 98.2, 80.4, 79.9, 56.5, 55.6, 48.3, 44.5, 28.3; HRMS (FAB) calcd for $C_{16}H_{24}IN_2O_5$ [$M+H^+$] 451.0730, found 451.0722.

Carboxylic acid 63: A solution of ester **62** (809 mg, 2.1 mmol) in THF/H_2O (1:1, 15 mL) was treated with anhydrous LiOH (76 mg, 3.2 mmol) at 0 °C for 1 h. The reaction was quenched by the addition of saturated NH_4Cl solution (10 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), and dried (Na_2SO_4). The solvent was removed in vacuo to afford crude **63** (778 mg, 99 %), which was taken into next step without further purification.

Tripeptide 64: A solution of dipeptide **60** (300 mg, 0.67 mmol) in CH_2Cl_2 (1 mL) at 0 °C was treated with TFA (1 mL). The solution was allowed to reach ambient temperature and stirred for 2 h before it was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with 5 % aqueous $NaHCO_3$ (2 × 10 mL), H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting crude dipeptide amine **61** (233 mg, 100 %) was taken into the next step without further purification. To a solution of amine **61** (70 mg, 0.2 mmol), acid **63** (97 mg, 0.24 mmol), and Et_3N (61 μL, 0.44 mmol) in DMF (2 mL) was added EDC (50 mg, 0.26 mmol) at 0 °C, and the resulting solution was stirred at that temperature for 12 h. The reaction was quenched by the addition of saturated NH_4Cl (5 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 5 % $NaHCO_3$ (15 mL), brine (15 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 20 →40 % EtOAc in hexanes, gradient elution) to afford tripeptide **64** (136 mg, 92 %). **64**: $R_f = 0.14$ (silica gel, 40 % EtOAc in hexanes); $[\alpha]_D^{22} = -42.6$ ($c = 0.39$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3333, 2966, 2355, 1743, 1670, 1590, 1486, 1456, 1364, 1248, 1162\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.77 (d, $J = 2.0$ Hz, 1 H, ArH), 7.37 (br. s, 1 H, NH), 7.28 (dd, $J = 8.5$, 2.0 Hz, 1 H, ArH), 7.00 (br. s, 1 H, NH), 7.67 (d, $J = 8.5$ Hz, 1 H, ArH), 6.48 (d, $J = 2.5$ Hz, 1 H, ArH), 6.30 (d, $J = 2.5$ Hz, 1 H, ArH), 5.83 (d, $J = 6.5$ Hz, 1 H, CH), 5.15 (br. s, 1 H, NH), 4.38 (d, $J =$ 6.0 Hz, 2 H, CH_2), 3.98-3.85 (m, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 1.34 (s, 9 H, *t*BuO); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 170.9, 168.5, 161.1, 158.7, 158.0, 155.2, 141.7, 137.9, 131.4, 128.5, 110.9, 106.1, 97.8, 86.3, 80.3, 79.4, 57.4, 56.4, 56.3, 55.5, 48.5, 43.3, 28.2; HRMS (FAB) calcd for $C_{25}H_{31}I_2N_3O_7Cs$ [$M+Cs^+$] 871.9306, found: 871.9329.

AB model system 65: To a stirred solution of $(Ph_3P)_2NiCl_2$ (59 mg, 0.09 mmol) and triphenylphosphane (48 mg, 0.18 mmol) in degassed DMF (10 mL) at 55 °C was added zinc dust (5.9 mg, 0.09 mmol). After stirring for 0.5 h, a solution of tripeptide **64** (37 mg, 0.05 mmol) in DMF (15 mL) was slowly transferred to the reaction mixture by cannula. The resulting solution was stirred at 55 °C for 16 h, and then it was quenched by the addition of saturated NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with H_2O (30 mL), brine (30 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 0 →2 % MeOH in $CHCl_3$, gradient elution) to afford **65a** (3.2 mg, 13 %) and **65b** (3.2 mg, 13 %). **65a**: $R_f = 0.20$ (silica gel, 2.5 % MeOH in $CHCl_3$); $[\alpha]_D^{22} = -45.7$ ($c = 0.37$, CH_2Cl_2); IR (KBr): $\tilde{\nu}_{max} = 3320, 2924, 1673, 1611, 1585, 1501, 1366, 1324, 1256, 1157, 1110, 1063\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$) (see Figure 2 for numbering): $\delta =$ 7.82 (t, $J =$ 6.6 Hz, 1 H, N_3H), 7.40 (br. s, 1 H, N_6H), 7.30 (dd, $J = 8.3$, 2.1 Hz, 1 H, Ar_AH_b), 7.08 (br. s, 1 H, Ar_AH_a), 6.95 (d, $J = 8.3$ Hz, 1 H, Ar_AH_c), 6.85 (br. s, 1 H, NHBoc), 6.58 (d, $J = 2.2$ Hz, 1 H, Ar_BH_b), 6.56 (d, $J = 2.2$ Hz, 1 H,

Ar_BH_a), 4.81 (br. s, 1H, H_1), 3.86–3.84 (m, 1H, H_7), 3.76–3.74 (m, 1H, H_4), 3.72 (s, 3H, OCH_3), 3.66–3.64 (m, 1H, H_4), 3.63 (s, 6H, OCH_3), 3.30-3.28 (m, 1H, H_7), 1.34 (s, 9H, *t*BuO); ^{13}C NMR (150 MHz, CD_3SOCD_3): $\delta =$ 172.1, 170.4, 167.5, 159.5, 158.1, 156.7, 137.4, 132.9, 129.9, 127.7, 124.1, 120.8, 110.8, 107.9, 97.9, 78.3, 59.7, 55.7, 55.5, 55.3, 43.7, 43.3, 28.1; HRMS (FAB) calcd for $C_{25}H_{31}N_3O_7Na$ $[M+Na^+]$ 508.2060, found 508.2067. **65b**: $R_f = 0.25$ (silica gel, 2.5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -18.1$ ($c = 0.63$, CH_2Cl_2); IR (KBr): $\tilde{\nu}_{max} = 3314$, 2924, 2853, 1677, 1581, 1504, 1459, 1366, 1320, 1262, 1160, 1110 cm^{-1}; ^{1}H NMR (600 MHz, CD_3SOCD_3): $\delta =$ 8.57 (br. s, 1H, N_3H), 8.29 (br. s, 1H, N_6H), 7.38–7.36 (m, 2H, NHBoc, Ar_AH_b), 7.18 (s, 1H, Ar_AH_a), 6.98 (d, $J = 8.6$ Hz, 1H, Ar_AH_c), 6.50 (s, 2H, $Ar_BH_{a,b}$), 5.13–5.12 (m, 1H, H_1), 4.24–4.13 (m, 2H, H_7), 3.81 (s, 3H, OCH_3), 3.86–3.82 (m, 1H, H_4), 3.74 (s, 3H, OCH_3), 3.70–3.68 (m, 1H, H_4), 3.67 (s, 3H, OCH_3), 1.32 (s, 9H, *t*BuO); ^{13}C NMR (150 MHz, CD_3SOCD_3): $\delta =$ 171.1, 168.9, 160.8, 158.4, 156.4, 155.3, 142.3, 130.2, 130.1, 129.8, 128.2, 127.8, 110.0, 105.4, 97.4, 78.7, 57.6, 56.5, 55.5, 55.1, 47.8, 42.4, 28.1; HRMS (FAB) calcd for $C_{25}H_{31}N_3O_7Na$ $[M+Na^+]$ 508.2060, found 508.2069.

Amine 66: A solution of **26** (343 mg, 2.5 mmol) in DMF (20 mL) was treated with *N*-bromosuccinimide (534 mg, 2.0 mmol) at 25 °C for 12 h. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 solution (20 mL) and the resulting mixture was extracted with EtOAc (3×30 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 10 → 40% EtOAc in hexanes, gradient elution) to give amine **66** (333 mg, 62%). **66**: $R_f = 0.26$ (silica gel, 50% EtOAc in hexanes); IR (thin film) $\tilde{\nu}_{max} = 3281$, 1616, 1495, 1051, 1018, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$ (s, 1H, ArH), 6.93 (d, $J = 8.0$ Hz, 1H, ArH), 6.68 (d, $J = 7.5$ Hz, 1H, ArH), 3.73 (t, $J = 6.50$ Hz, 2H, CH_2OH), 3.60-3.30 (br. s, 2H, NH_2), 2.68 (t, $J = 7.0$ Hz, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 142.4, 132.7, 129.7, 128.9, 115.8, 109.3, 63.5, 37.8; HRMS (FAB) calcd for $C_8H_{11}BrNO$ $[M+H^+]$ 216.0024, found 216.0029.

Triazene alcohol 67: A solution of amine **66** (1.67 g, 5.6 mmol) in 0.1N aqueous HCl (6.7 mL) at 0 °C was treated with aqueous $NaNO_2$ (386 mg in 1 mL H_2O, 5.6 mmol). The resulting solution was stirred for 0.5 h before it was transferred slowly to a flask charged with pyrrolidine (4.7 mL, 56 mmol) in saturated aqueous K_2CO_3 (100 mL) at 0 °C. The mixture was stirred for 1 h and then it was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with H_2O (50 mL), brine (50 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, 10 → 30% EtOAc in hexanes, gradient elution) to afford triazene alcohol **67** (1.38 g, 83%). **67**: $R_f = 0.34$ (silica gel, 50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3366$, 2950, 2862, 1477, 1417, 1395, 1340, 1313, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.37$ (s, 1H, ArH), 7.27 (d, $J = 8.0$ Hz, 1H, ArH), 7.02 (dd, $J =$ 8.0, 1.0 Hz, 1H, ArH), 3.84 (br. s, 2H, NCH_2), 3.69 (t, $J = 6.5$ Hz, 2H, CH_2O), 3.65 (br. s, 2H, NCH_2), 2.70 (t, $J = 7.0$ Hz, 2H, CH_2), 2.48 (br. s, 1H, OH), 1.95 (br. s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 146.9, 136.7, 133.0, 128.3, 118.9, 118.3, 63.1, 50.8, 46.5, 38.0, 23.5, 23.5; HRMS (FAB) calcd for $C_{12}H_{17}BrN_3O$ $[M+H^+]$ 298.0555, found 298.0550.

Carboxylic acid 68: A solution of alcohol **67** (300 mg, 1.0 mmol) in acetone (3.1 mL) at 0 °C was added to a 5% aqueous $NaHCO_3$ solution (3.1 mL), and the resulting mixture was treated sequentially with KBr (12 mg, 0.1 mmol) and TEMPO (155 mg, 1.0 mmol). Sodium hypochlorite (5% in H_2O, 4 mL) was added dropwise over 20 min, and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the resulting mixture was extracted with EtOAc (2×20 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 20 → 40% EtOAc in hexanes, gradient elution) to give carboxylic acid **68** (267 mg, 86%). **68**: $R_f = 0.22$ (silica gel, 50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3460$, 2920, 2861, 1760, 1713, 1461, 1261, 1096 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.47$ (s, 1H, ArH), 7.30–7.29 (m, 1H, ArH), 7.14–7.11 (m, 1H, ArH), 3.81 (br. s, 2H, NCH_2), 3.60 (br. s, 2H, NCH_2), 3.48 (s, 2H, CH_2CO), 1.94 (br. s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, CD_3OD): $\delta =$ 177.6, 148.4, 134.9, 134.5, 129.8, 119.9, 119.2, 67.4, 51.6, 48.4, 24.6, 24.6; HRMS (FAB) calcd for $C_{12}H_{15}BrN_3O_2$ $[M+H^+]$ 312.0348, found 312.0340.

Dipeptide 70: To a stirred solution of tyrosine methyl ester **69** (478 mg, 1.4 mmol), acid **63** (570 mg, 1.4 mmol), and Et_3N (580 μL, 4.2 mmol) in DMF (15 mL) was added HBTU (637 mg, 1.7 mmol) at 0 °C. The reaction mixture was slowly warmed to 25 °C, stirred for 3 h, and then diluted with EtOAc (60 mL). The organic phase was washed with 5% aqueous HCl (2×20 mL), 5% aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed in vacuo, and flash column chromatography (silica gel, 20 → 40% EtOAc in hexanes, gradient elution) of the residue afforded product **70** (736 mg, 90%). **70**: $R_f = 0.28$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = +1.23$ ($c = 2.6$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 3344, 1740, 1663, 1510, 1488, 1439, 1368, 1252, 1165, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.69 (d, $J = 2.5$ Hz, 1H, ArH), 7.24 (s, 1H, OH), 7.20 (dd, $J = 8.5$, 1.5 Hz, 1H, ArH), 6.87 (d, $J = 8.5$ Hz, 1H, ArH), 6.73-6.65 (m, 2H, ArH), 6.54 (s, 2H, ArH), 6.15 (br. s, 1H, NH), 5.79 (br. s, 1H, NH), 5.00 (br. s, 1H, CH), 4.77 (dd, $J = 5.5$, 5.5 Hz, 1H, $CHCH_2$), 3.86 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.89 (d, $J = 6.0$ Hz, 2H, CH_2), 1.38 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 171.7, 169.9, 169.6, 158.0, 155.2, 154.8, 137.9, 132.2, 130.2, 128.5, 126.2, 121.6, 115.5, 111.0, 86.4, 80.3, 57.0, 56.3, 53.1, 52.5, 36.6, 28.2; HRMS (FAB) calcd for $C_{24}H_{29}IN_2O_7Cs$ $[M+Cs^+]$ 717.0074, found 717.0098.

Tripeptide 72: To a solution of dipeptide **70** (1.2 g, 2.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TFA (10 mL). The resulting solution was stirred for 1 h before it was concentrated under reduced pressure. The crude product (**71**, 970 mg) was taken into next step without further purification. A solution of acid **68** (499 mg, 1.6 mmol), amine **71** (726 mg, 1.6 mmol), and Et_3N (670 μL, 4.8 mmol) in DMF (15 mL) was treated with HBTU (728 mg, 1.92 mmol) at 0 °C. The resulting solution was allowed to reach ambient temperature and stirred for 3 h. The reaction was diluted with EtOAc (60 mL) and the organic phase was washed with saturated aqueous NH_4Cl (30 mL), 5% aqueous $NaHCO_3$ (30 mL), brine (30 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, 30 → 60% EtOAc in hexanes, gradient elution) to afford tripeptide **72** (1.12 g, 90%). **72**: $R_f =$ 0.47 (silica gel, 80% EtOAc in hexanes); $[\alpha]_D^{22} = +21.7$ ($c = 0.49$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3289$, 2950, 1740, 1642, 1510, 1389, 1252 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.18$ (s, 1H, OH), 8.76-8.72 (m, 2H, NH), 7.74 (d, $J = 2.0$ Hz, 1H, ArH), 7.48 (s, 1H, ArH), 7.24 (d, $J = 8.0$ Hz, 1H, ArH), 7.16–7.14 (m, 2H, ArH), 6.84 (d, $J = 9.0$ Hz, 1H, ArH), 6.79 (d, $J = 8.5$ Hz, 2H, ArH), 6.53 (d, $J = 8.7$ Hz, 2H, ArH), 5.47 (d, $J = 8.0$ Hz, 1H, CH), 4.35–4.25 (m, 1H, $CHCH_2$), 3.88 (br. s, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2CO), 3.55 (br. s, 2H, NCH_2), 3.31 (s, 3H, OCH_3), 2.93–2.79 (m, 2H, $CHCH_2$), 2.02 (br. s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 172.0, 170.0, 169.0, 157.1, 155.2, 144.0, 138.3, 133.7, 132.0, 131.7, 130.3, 130.0, 128.8, 128.5, 126.0, 121.1, 120.0, 118.9, 118.0, 115.7, 111.1, 56.4, 55.8, 53.2, 52.5, 51.0, 47.0, 42.3, 38.5, 24.0, 23.5; HRMS (FAB) calcd for $C_{31}H_{33}BrIN_5O_6Cs$ $[M+Cs^+]$ 909.9713, found 909.9743.

C-O-D ring system 73: To a solution of tripeptide **72** (78 mg, 0.10 mmol) and $CuBr \cdot Me_2S$ (84 mg, 0.29 mmol) in degassed acetonitrile (10 mL) were added K_2CO_3 (33 mg, 0.24 mmol) and pyridine (25 μL, 0.30 mmol). The resulting mixture was heated to reflux and stirred for 36 h. The reaction mixture was cooled to 25 °C and filtered through celite. The celite was washed thoroughly with EtOAc (3×20 mL) and the combined filtrate was washed with H_2O (20 mL), brine (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 30 → 60% EtOAc in hexanes, gradient elution) to afford compound **73** (47 mg, 67%), **73** epimer (4 mg, 6%), and recovered tripeptide **72** (8 mg, 10%). **73**: $R_f = 0.28$ (silica gel, 80% EtOAc in hexanes); $[\alpha]_D^{22} = -46.2$ ($c = 1.0$, THF); IR (thin film): $\tilde{\nu}_{max} = 3285$, 2948, 2874, 1744, 1644, 1506, 1487, 1212 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.42 (d, $J = 2.7$ Hz, 1H), 7.37 (d, $J = 10.2$ Hz, 1H), 7.31 (dd, $J = 10.5$, 2.6 Hz, 1H, ArH), 7.22 (dd, $J = 10.4$, 3.1 Hz, 1H, ArH), 7.13 (dd, $J = 10.5$, 2.7 Hz, 1H, ArH), 6.99 (dd, $J = 10.3$, 2.1 Hz, 1H, ArH), 6.84 (dd, $J = 12.7$, 2.7 Hz, 1H, ArH), 6.79 (dd, $J = 7.8$, 2.3 Hz, 1H, ArH), 6.78 (d, $J = 10.5$ Hz, 1H, ArH), 6.64 (d, $J = 2.2$ Hz, 1H, ArH), 6.15 (d, $J = 8.6$ Hz, 1H, ArH), 5.68 (d, $J = 11.3$ Hz, 1H), 5.24 (d, $J = 8.7$ Hz, 1H), 4.79–4.68 (m, 1H), 3.90-3.70 (m, 4H, NCH_2), 3.87 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.56 (d, $J =$ 18.3 Hz, 1H), 3.38 (d, $J = 18.3$ Hz, 1H), 3.24 (dd, $J = 16.9$, 5.9 Hz, 1H), 2.53 (dd, $J = 16.8$, 13.3 Hz, 1H), 2.03 (br. s, 4H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 172.9, 172.7, 170.5, 167.4, 159.5, 156.7, 155.5, 140.7, 139.3, 134.5, 133.6, 132.6, 130.2, 129.8, 123.8, 123.2, 122.8, 119.6, 116.4, 116.2, 111.9, 71.6, 69.8, 56.2, 55.8, 54.4, 52.8, 43.0, 36.3, 24.8, 19.3; HRMS (FAB) calcd for $C_{31}H_{32}IN_5O_6Cs$ $[M+Cs^+]$ 830.0452, found 830.0438.

C-O-D template 74: A solution of compound **73** (80 mg, 0.11 mmol) in THF (1 mL) was treated with TFA (20 μL, 0.25 mmol) at 25 °C. After

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stirring for 15 min, Cu_2O (83 mg, 0.55 mmol) was added and the resulting mixture was heated at reflux for 1 h. After cooling to 25 °C, the reaction mixture was filtered through a pad of celite with thorough washing (EtOAc). The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, 20→40% EtOAc in hexanes, gradient elution) to give product **74** (59 mg, 90%). **74**: $R_f = 0.55$ (silica gel, 70% EtOAc in hexanes); $[\alpha]_D^{22} = -55.8$ ($c = 2.8$, THF); IR (thin film) $\tilde{\nu}_{max} = 3331, 3060, 1741, 1649, 1591, 1504, 1440, 1231, 1169, 1030, 755\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.41 (d, $J = 2.0$ Hz, 1H, ArH), 7.32–7.27 (m, 2H, ArH), 7.19–7.16 (m, 1H, ArH), 7.12 (dd, $J = 8.0, 2.0$ Hz, 1H, ArH), 7.01–6.95 (m, 2H, ArH), 6.84 (d, $J = 7.5$ Hz, 1H, ArH), 6.78 (d, $J = 8.0$ Hz, 1H, ArH), 5.88 (d, $J = 8.5$ Hz, 1H, ArH), 6.56 (s, 1H), 6.20 (d, $J = 6.5$ Hz, 1H, NH), 5.88 (d, $J = 8.5$ Hz, 1H, NH), 5.27 (d, $J = 7.0$ Hz, 1H, CH), 4.72–4.70 (m, 1H, CH), 3.89 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.60 (d, $J =$ 12.0 Hz, CH*H*, 1H), 3.41 (d, $J = 12.0$ Hz, CH*H*, 1H), 3.23 (dd, $J = 13.0$, 10.0 Hz, CH*H*, 1H), 2.68 (dd, $J = 13.0$, 11.5 Hz, CH*H*, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 170.8, 169.2, 168.6, 160.6, 157.4, 154.6, 137.3, 136.1, 132.3, 131.4, 130.7, 128.9, 128.3, 127.8, 121.8, 121.2, 121.0, 115.0, 114.8, 113.2, 110.0, 55.2, 54.0, 52.5, 51.1, 41.7, 34.6; HRMS (FAB) calcd for $C_{27}H_{25}INO_6Cs$ [$M + Cs^+$] 732.9812, found 732.9831.

Boronic acid 53: A stirred solution of alcohol **56** (370 mg, 2.2 mmol) in benzene (4 mL) at 0 °C was treated with *n*BuLi (1.6 M in hexanes, 3.0 mL, 4.8 mmol). The resulting solution was stirred for 2 h, and then it was cooled to −78 °C. THF (8.0 mL) was added, followed by freshly distilled $B(OMe)_3$ (1.3 mL, 11.0 mmol). The reaction mixture was slowly warmed to 25 °C and stirred at that temperature for 6 h. The reaction was quenched by the addition of 5% aqueous HCl (5 mL) and the resulting mixture was diluted with EtOAc (25 mL). The organic phase was washed with H_2O (2 × 15 mL), brine (15 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 10→40% EtOAc in hexanes, gradient elution) to afford boronic acid derivative **53** (172 mg, 46%). **53**: $R_f = 0.27$ (silica gel, 50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3388, 2927, 1765, 1693, 1555, 1149, 1108, 1087\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.31$ (d, $J = 0.7$ Hz, 1H, ArH), 6.23 (d, $J = 0.7$ Hz, 1H, ArH), 4.87 (s, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 164.4, 164.2, 162.5, 157.4, 104.3, 96.9, 70.5, 55.1, 54.9; HRMS (FAB) calcd for $C_9H_{11}BO_4Na$ [$M + Na^+$] 193.0787, found 193.0791.

Biaryl atropisomers 75 and 79: Iodide **74** (1.98 g, 3.3 mmol) was dissolved in toluene (30 mL). To the resulting solution were added sequentially $Pd(Ph_3P)_4$ (381 mg, 0.33 mmol), boronic acid **53** (1.28 g, 6.6 mmol) dissolved in MeOH (3 mL), and aqueous Na_2CO_3 (350 mg, 3.3 mmol) at 25 °C. The reaction mixture was stirred vigorously for 5 min and then it was heated at 90 °C for 2 h. The reaction mixture was diluted with EtOAc (60 mL) and washed with H_2O (30 mL), brine (30 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 40→80% EtOAc in hexanes, gradient elution) to afford two atropisomers **75** (845 mg, 40%) and **79** (845 mg, 40%). **75**: $R_f = 0.28$ (silica gel, EtOAc); $[\alpha]_D^{22} = +29.1$ ($c = 0.26$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3324, 2944, 1734, 1652, 1601, 1508, 1437, 1237, 1149\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.31 (dd, $J = 6.2, 2.1$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.14–7.06 (m, 3H), 6.95 (d, $J = 8.5$ Hz, 1H), 6.89 (d, $J = 2.3$ Hz, 1H), 6.81 (d, $J = 7.5$ Hz, 1H), 6.78 (dd, $J = 6.1, 2.1$ Hz, 1H), 6.70 (d, $J = 2.3$ Hz, 1H), 6.59 (dd, $J = 5.7, 2.5$ Hz, 1H), 6.52 (s, 1H), 6.47 (d, $J =$ 2.4 Hz, 1H), 6.14 (d, $J = 6.9$ Hz, 1H), 5.87 (d, $J = 8.9$ Hz, 1H), 5.30 (d, $J =$ 6.9 Hz, 1H, CH), 4.80-4.76 (m, 1H, C*H*CH_2), 4.31 (d, $J = 12.1$ Hz, 1H), 4.25 (d, $J = 12.1$ Hz, 1H), 3.85 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.58 (d, $J = 16.5$ Hz, 1H), 3.38 (d, $J = 16.5$ Hz, 1H), 3.55 (s, 3H, OCH_3), 3.22 (dd, $J = 13.5$, 4.8 Hz, 1H), 2.59 (dd, $J = 13.5$, 10.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 171.4, 169.5, 169.0, 161.2, 160.4, 157.8, 157.1, 157.0, 141.1, 136.3, 132.5, 132.3, 132.1, 131.3, 129.9, 128.3, 127.3, 125.6, 123.8, 122.7, 121.0, 117.7, 117.4, 117.3, 111.6, 104.4, 98.3, 63.6, 57.3, 55.7, 55.6, 55.3, 53.3, 52.5, 43.4, 38.4; HRMS (FAB) calcd for $C_{36}H_{36}N_2O_9Cs$ [$M + Cs^+$] 773.1475, found 773.1447. **79**: $R_f = 0.23$ (silica gel, EtOAc); $[\alpha]_D^{22} = +48.5$ ($c = 0.40$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3332, 1738, 1646, 1603, 1501, 1436, 1237, 1145\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3/CD_3OD$, 1:1): $\delta =$ 7.41 (s, 1H), 7.21–7.18 (m, 2H, ArH), 7.12–7.11 (m, 1H, ArH), 7.00–6.97 (m, 2H, ArH), 6.93–6.90 (m, 2H, ArH), 6.78 (d, $J = 7.7$ Hz, 1H, ArH), 6.68 (d, $J = 2.3$ Hz, 1H, ArH), 6.62–6.61 (m, 1H, ArH), 6.46–6.41 (m, 2H, ArH), 6.27 (s, 1H, ArH), 5.27 (d, $J = 6.5$ Hz, 1H, CH), 4.67–4.63 (m, 1H, C*H*CH_2), 4.05 (d, $J = 13.2$ Hz, 1H), 3.86 (d, $J = 13.2$ Hz, 1H), 3.82 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.43 (d, $J = 14.9$ Hz, 1H), 3.36 (d, $J = 14.9$ Hz, 1H), 3.30–3.26 (m, 1H), 3.17 (dd, $J = 13.8$, 5.5 Hz, 1H), 2.89–2.85 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3/CD_3OD$, 1:1): $\delta =$ 172.4, 171.6, 170.5, 162.0, 161.5, 158.4, 158.3, 157.1, 142.4, 137.0, 133.4, 133.1, 131.8, 131.7, 130.7, 129.3, 128.3, 126.4, 124.1, 123.3, 122.4, 118.5, 117.6, 116.8, 112.0, 104.8, 98.4, 62.8, 58.0, 56.5, 56.4, 56.0, 54.2, 54.1, 53.1, 44.1; HRMS (FAB) calcd for $C_{36}H_{36}N_2O_9Cs$ [$M + Cs^+$] 773.1475, found 773.1495.

Azide 76: To a solution of alcohol **75** (367 mg, 0.55 mmol) dissolved in THF (5 mL) at 0 °C were sequentially added triphenylphosphane (721 mg, 2.75 mmol), DEAD (435 μL, 2.75 mmol), and hydrazoic acid (HN_3) (118 mg in 0.5 mL of toluene, 2.75 mmol) [**Caution**: hydrazoic acid is toxic and explosive!]. The reaction was allowed to reach 25 °C and stirred for 1 h. The solution was diluted with brine (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to flash column chromatography (silica gel, 20→50% EtOAc in hexanes, gradient elution) to give azide **76** (252 mg, 69%). **76**: $R_f = 0.60$ (silica gel, EtOAc); $[\alpha]_D^{22} = +23.2$ ($c = 0.31$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3334, 2938, 2099, 1738, 1651, 1601, 1505, 1442, 1237, 1154, 1038\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.31 (dd, $J = 8.5, 2.2$ Hz, 1H, ArH), 7.26–7.22 (m, 1H, ArH), 7.14–7.07 (m, 3H, ArH), 6.95 (d, $J =$ 8.5 Hz, 1H, ArH), 6.89 (d, $J = 7.8$ Hz, 1H, ArH), 6.82 (d, $J = 7.5$ Hz, 1H, ArH), 6.79 (dd, $J = 8.2, 2.2$ Hz, 1H, ArH), 6.61–6.56 (m, 3H), 6.49 (d, $J =$ 2.4 Hz, 1H, ArH), 6.05 (d, $J = 7.3$ Hz, 1H), 5.85 (d, $J = 8.9$ Hz, 1H), 5.35 (d, $J = 7.3$ Hz, 1H, CH), 4.82-4.75 (m, 1H, C*H*CH_2), 4.11 (d, $J = 13.8$ Hz, 1H), 4.07 (d, $J = 13.8$ Hz, 1H), 3.85 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.62 (d, $J = 16.8$ Hz, 1H), 3.41 (d, $J = 16.8$ Hz, 1H), 3.53 (s, 3H, OCH_3), 3.25 (dd, $J = 13.5$, 4.7 Hz, 1H, CHCH_2), 2.55 (dd, $J = 13.5$, 10.5 Hz, 1H, CHCH_2); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 172.1, 170.5, 169.8, 162.2, 161.2, 159.0, 158.1, 157.8, 137.3, 137.2, 133.3, 133.2, 133.1, 132.3, 130.8, 129.6, 128.2, 125.9, 124.8, 123.7, 121.7, 119.1, 118.7, 118.3, 112.3, 105.5, 99.5, 58.1, 56.5, 56.4, 56.2, 54.3, 53.9, 53.4, 44.2, 39.5; HRMS (FAB) calcd for $C_{36}H_{35}N_5O_8Cs$ [$M + Cs^+$] 798.1540, found 798.1562.

Azide 80: Azide **80** was similarly prepared from **79** according to the above procedure in 69% yield. **80**: $R_f = 0.46$ (silica gel, EtOAc); $[\alpha]_D^{22} = +51.3$ ($c = 0.24$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3328, 2929, 2100, 1741, 1648, 1601, 1505, 1444, 1343\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.35 (dd, $J = 8.3, 2.0$ Hz, 1H, ArH), 7.22 (d, $J = 6.1$ Hz, 1H), 7.19–7.16 (m, 2H), 7.06 (dd, $J =$ 8.1, 2.1 Hz, 1H), 6.96 (d, $J = 7.5$ Hz, 1H), 6.83 (d, $J = 7.5$ Hz, 1H), 6.70 (dd, $J = 8.2$, 2.2 Hz, 1H), 6.60 (s, 1H), 6.54 (d, $J = 2.3$ Hz, 2H), 6.51 (d, $J =$ 2.3 Hz, 1H), 6.30 (dd, $J = 8.2, 2.5$ Hz, 1H), 6.16 (d, $J = 6.3$ Hz, 1H), 5.79 (d, $J = 9.4$ Hz, 1H), 5.28 (d, $J = 6.3$ Hz, 1H, CH), 4.88–4.83 (m, 1H, C*H*CH_2), 3.86 (s, 3H, OCH_3), 3.85 (d, $J = 14.0$ Hz, 1H), 3.66 (d, $J = 14.0$ Hz, 1H), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.62 (d, $J = 16.7$ Hz, 1H), 3.39 (d, $J = 16.7$ Hz, 1H), 3.29 (dd, $J = 13.3$, 4.4 Hz, 1H, CHCH_2), 3.40 (dd, $J = 13.3$, 11.8 Hz, 1H, CHCH_2); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 172.4, 170.3, 169.9, 162.0, 161.2, 158.9, 158.5, 158.3, 137.3, 137.2, 133.6, 133.0, 131.9, 131.8, 130.9, 129.8, 127.3, 126.3, 124.9, 123.6, 121.9, 119.5, 119.0, 118.5, 112.2, 105.7, 99.2, 58.4, 56.6, 56.5, 56.3, 54.2, 53.5, 53.3, 44.6, 39.8; HRMS (FAB) calcd for $C_{36}H_{35}N_5O_8Cs$ [$M + Cs^+$] 798.1540, found 798.1566.

AB/C-O-D bicyclic system 83: To a solution of ester **76** (520 mg, 0.75 mmol) in THF/H_2O (1:1, 7.5 mL) at 0 °C was added anhydrous LiOH (27 mg, 1.13 mmol), and the resulting mixture was stirred at that temperature for 0.5 h. The reaction mixture was diluted with H_2O (10 mL) and acidified with citric acid to pH 4 at 0 °C. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with H_2O (15 mL), brine (15 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product **77** was taken into the next step without further purification. To a stirred solution of acid **77** (39 mg, 0.06 mmol) in CH_2Cl_2 (0.6 mL) at 25 °C were sequentially added DCC (15 mg, 0.072 mmol), 4-DMAP (1.5 mg, 0.012 mmol), and pentafluorophenol (22 mg, 0.12 mmol). After stirring for 1 h at 25 °C, the reaction mixture was filtered through a pad of celite, concentrated, and the crude product was taken directly to the next step. To a stirred mixture of freshly distilled dioxane (30 mL) containing 10% Pd/C (5 mg), absolute EtOH (1.5 mL), and 4-pyrrolidinopyridine (27 mg, 0.18 mmol) at 90 °C was added, over a period of 1.5 h, a solution of the crude pentafluorophenol ester in cyclohexene (4 mL) and dioxane (10 mL). After the addition was completed, the reaction mixture was allowed to stir at 90 °C for an additional 5 h, after which time it was cooled to 25 °C and filtered through a pad of celite. The celite was washed thoroughly with EtOAc (2 × 15 mL),

the combined filtrate was concentrated under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 0→5% MeOH in $CHCl_3$, gradient elution) to give compounds **83** (46 mg, 10%) and **83-(6-epi)** (91 mg, 20%). **83**: $R_f = 0.16$ (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = +8.20$ ($c = 0.30$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3349, 2916, 1661, 1650, 1603, 1582, 1487, 1455, 1255, 1022\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$, 323 K): $\delta =$ 7.90 (d, $J = 7.2$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.23–7.21 (m, 1H), 7.11–7.08 (m, 3H), 7.03–6.99 (m, 4H), 6.79 (d, $J = 6.4$ Hz, 1H), 6.75 (s, 1H), 6.52 (s, 1H), 6.49 (s, 1H), 5.79 (br.s, 1H), 5.51 (br.s, 1H), 5.45 (d, $J = 11.7$ Hz, 1H), 4.84 (d, $J = 4.8$ Hz, 1H), 4.09–4.05 (m, 1H), 3.95–3.93 (m, 1H), 3.84 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.52–3.42 (m, 3H), 2.52–2.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 172.8, 172.5, 168.1, 160.6, 160.0, 158.3, 156.8, 155.0, 136.8, 136.3, 134.1, 132.9, 132.4, 130.8, 129.5, 129.3, 128.7, 126.2, 124.3, 122.4, 122.3, 119.7, 115.5, 112.8, 112.4, 107.6, 98.2, 55.8, 55.7, 55.2, 54.1, 45.4, 42.2, 35.2, 29.4; HRMS (FAB) calcd for $C_{35}H_{33}N_3O_7Cs$ $[M + Cs^+]$ 740.1373, found 740.1401. **83-(6-epi)**: $R_f = 0.21$ (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -53.0$ ($c = 0.37$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3263, 2923, 1724, 1644, 1501, 1459, 1268, 1119, 1066, 1019\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$, 323 K): $\delta =$ 7.46 (dd, $J = 8.4, 6.1$ Hz, 1H, ArH), 7.19-7.16 (m, 1H, ArH), 7.11 (dd, $J = 8.3, 1.9$ Hz, 1H, ArH), 7.01 (dd, $J = 8.1, 2.1$ Hz, 1H, ArH), 6.98 (dd, $J = 6.5, 3.9$ Hz, 1H, ArH), 6.98–6.97 (br.s, 1H, NH), 6.93 (dd, $J = 8.3, 2.1$ Hz, 1H, ArH), 6.88 (d, $J = 8.4$ Hz, 1H, ArH), 6.82 (dd, $J = 8.2, 2.1$ Hz, 1H, ArH), 6.77 (d, $J = 2.4$ Hz, 1H, ArH), 6.66 (d, $J = 7.5$ Hz, 1H, ArH), 6.57 (d, $J = 2.3$ Hz, 1H, ArH), 6.54 (d, $J = 2.3$ Hz, 1H, ArH), 6.04 (s, 1H, ArH), 5.65 (br.s, 1H, NH), 5.50 (d, $J = 8.6$ Hz, 1H, CH), 5.39 (d, $J = 9.3$ Hz, 1H, NH), 4.35-4.31 (m, 1H, C*H*CH_2), 3.97 (dd, $J = 12.9, 5.1$ Hz, 1H, CH_2N), 3.87 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.46 (dd, $J = 12.9, 2.3$ Hz, 1H, CH_2N), 3.35 (d, $J = 14.6$ Hz, 1H), 3.31 (d, $J = 14.6$ Hz, 1H), 2.98 (dd, $J = 13.4, 4.3$ Hz, 1H, CHC*H*$_2$), 2.75–2.71 (m, 1H, CHC*H*$_2$); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 173.3, 171.6, 170.2, 161.2, 160.0, 158.6, 155.3, 139.6, 138.1, 137.0, 134.4, 133.1, 132.9, 132.2, 131.7, 130.4, 128.3, 125.9, 124.0, 122.9, 122.0, 121.8, 117.4, 113.4, 112.1, 108.6, 99.4, 56.9, 56.6, 56.3, 55.5, 46.4, 43.8, 35.2, 30.5; HRMS (FAB) calcd for $C_{35}H_{34}N_3O_7$ $[M + H^+]$ 608.2397, found 608.2416.

Bicyclic systems 84 and 84-(6-epi): Compounds **84** and **84-(6-epi)** were similarly prepared from compound **80** according to the above procedure in 10% and 20% yield, respectively. **84**: $R_f = 0.31$ (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -31.5$ ($c = 0.20$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2919, 2848, 1725, 1640, 1605, 1504, 1459, 1228, 1152, 1092\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$, 323 K): $\delta =$ 7.29 (dd, $J = 8.1, 2.0$ Hz, 1H, ArH), 7.22 (d, $J = 6.3$ Hz, 1H, ArH), 7.20 (dd, $J = 8.8, 2.3$ Hz, 1H, ArH), 7.08 (d, $J = 8.1$ Hz, 1H, ArH), 7.05-7.03 (m, 3H, ArH), 6.81 (dd, $J = 8.1, 2.4$ Hz, 1H, ArH), 6.94 (d, $J = 8.7$ Hz, 1H, ArH), 6.78 (d, $J = 7.2$ Hz, 1H, ArH), 6.57 (d, $J = 2.0$ Hz, 1H, ArH), 6.48 (d, $J = 2.0$ Hz, 1H, ArH), 6.32 (br.s, 1H, ArH), 5.78 (br.s, 1H, ArH), 5.65–5.62 (m, 1H, NH), 5.12 (m, 1H, NH), 5.04 (d, $J = 5.8$ Hz, 1H, CH), 4.30–4.20 (m, 1H, CH_2), 4.16 (ddd, $J = 13.2, 11.4, 2.7$ Hz, 1H, CH), 3.74 (dd, $J = 14.9, 5.9$ Hz, 1H, CH_2), 3.72 (dd, $J = 12.0, 2.7$ Hz, 1H, CH_2), 3.81 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.57 (d, $J = 15.0$ Hz, 1H, CH_2CO), 3.45 (d, $J = 15.0$ Hz, 1H, CH_2CO), 3.47 (s, 3H, OCH_3), 2.47 (dd, $J = 13.2, 12.0$ Hz, 1H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$, 323 K): $\delta =$ 171.3, 170.7, 169.1, 160.9, 160.0, 158.1, 156.9, 154.1, 137.7, 136.6, 135.5, 134.4, 132.9, 130.5, 130.0, 129.1, 125.6, 123.4, 122.1, 121.1, 119.7, 116.9, 114.1, 112.4, 111.9, 108.2, 99.2, 56.8, 56.6, 56.1, 55.1, 49.2, 43.6, 43.4, 35.0; HRMS (FAB) calcd for $C_{35}H_{33}N_3O_7Cs$ $[M + Cs^+]$ 740.1373, found 740.1398. **84-(6-epi)**: $R_f = 0.35$ (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -11.1$ ($c = 0.27$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3318, 2919, 2849, 1650, 1544, 1503, 1450, 1233, 1151\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$, 323 K): $\delta =$ 7.23-7.20 (m, 2H, ArH), 7.17 (dd, $J = 8.6, 2.4$ Hz, 1H, ArH), 7.12 (d, $J = 2.4$ Hz, 1H, ArH), 7.03 (dd, $J = 10.5, 2.2$ Hz, 1H, ArH), 7.00 (d, $J = 8.6$ Hz, 1H, NH), 7.00–6.96 (m, 1H, ArH), 6.88 (d, $J = 8.6$ Hz, 1H, ArH), 6.83 (d, $J = 7.5$ Hz, 1H, ArH), 6.62-6.57 (m, 3H, 1 NH, 2 ArH), 6.50 (d, $J = 2.3$ Hz, 1H, ArH), 6.42 (d, $J = 2.3$ Hz, 1H, ArH), 6.01 (s, 1H, ArH), 5.72 (d, $J = 8.6$ Hz, 1H, CH), 5.60 (d, $J = 9.7$ Hz, 1H, NH), 4.52 (dd, $J = 14.8, 10.3$ Hz, 1H, CH_2N), 4.41-4.36 (m, 1H, C*H*CH_2), 3.78 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.65 (d, $J = 14.5$ Hz, 1H), 3.52 (d, $J = 14.5$ Hz, 1H), 3.55 (dd, $J = 14.8, 2.5$ Hz, 1H, CH_2N), 3.45 (s, 3H, OCH_3), 3.46-3.43 (m, 1H, CHC*H*$_2$), 2.50–2.48 (m, 1H, CHC*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 171.2, 170.7, 169.1, 160.8, 160.0, 158.5, 157.1, 156.9, 154.1, 137.7, 136.6, 134.3, 132.6, 132.4, 130.0, 129.1, 125.6, 124.8, 123.1, 122.1, 121.0, 119.6, 116.9, 112.4, 111.9, 106.6, 98.3, 55.8, 55.6, 55.3, 54.2, 49.2, 43.6, 43.3, 35.0; HRMS (FAB) calcd for $C_{35}H_{33}N_3O_7Cs$ $[M + Cs^+]$ 740.1373, found 740.1396.

General procedure for the asymmetric Suzuki coupling (Table 3): To a stirred solution of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) in toluene at ambient temperature was added the specified ligand (0.03 mmol), and the resulting solution was heated at 50 °C for 1 h. Iodide **62** (19 mg, 0.05 mmol) in toluene (1 mL), boronic acid **53** (19 mg, 0.1 mmol) in MeOH (300 μL), and Na_2CO_3 (7.4 mg, 0.07 mmol) in H_2O (70 μL) were added sequentially. The reaction mixture was heated at the indicated temperature for specified period of time and then it was cooled to 25 °C and diluted with EtOAc (3 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (3 mL), brine (3 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the products were isolated by preparative thin-layer chromatography (PTLC) as a mixture of atropisomers **85** and **86** in the indicated yields.

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