Total Synthesis of Vancomycin—Part 2: Retrosynthetic Analysis, Synthesis of Amino Acid Building Blocks and Strategy Evaluations

K. C. Nicolaou,* Christopher N. C. Boddy, Hui Li, Alexandros E. Koumbis, Robert Hughes, Swaminathan Natarajan, Nareshkumar F. Jain, Joshi M. Ramanjulu, Stefan Bräse, and Michael E. Solomon[a]

Abstract: Retrosynthetic analysis of vancomycin (**1**) defined vancomycin's aglycon (**2**) and protected triazene **3** (Figure 1) as advanced intermediates for an eventual total synthesis. Sequential assembly of **3** as shown in Figure 2 (strategy I) and Figure 3 (strategy II) led to amino acid building blocks **8**–**10** and **12**–**15**, respectively, representing vancomycin's amino acids AA-1 to AA-7. These amino acid fragments were constructed by stereoselective routes and the two synthetic strategies were tested for feasibility. Strategy I, postulating construction of the vancomycin main framework in the order of D-O-E →D-O-E/C-O-D →D-O-E/C-O-D/A-B, suffered from serious epimerization problems at the AA-4 stereocenter; while strategy II, involving the sequence C-O-D →C-O-D/AB →C-O-D/AB/D-O-E proved viable. These findings set the stage for the final drive towards vancomycin's aglycon (**2**) and vancomycin (**1**).

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

Introduction

In the preceding article, we described the design and development of methodologies which were considered suitable for application to the daunting challenge of the total synthesis of vancomycin (**1**, Figure 1).[1] Specifically, a triazene-driven mild cyclization method was developed, and its power was demonstrated in the construction of vancomycin model C-O-D and D-O-E biaryl ether ring systems.[1, 2] Furthermore, a strategy for the formation of the AB/C-O-D bicyclic framework of vancomycin based on sequential Suzuki coupling–macrolactamization approach was successfully tested.[1, 3] These technologies laid the foundation for the next phase of the program, namely, a focused retrosynthetic analysis, the preparation of the requisite amino acid building blocks,[4] and the evaluation of possible strategies towards the construction of the vancomycin main skeleton. In this paper, we describe our investigations along these lines and project forward to the next phase of the program.

[a] Prof. Dr. K. C. Nicolaou, C. N. C. Boddy, H. Li, Dr. A. E. Koumbis, R. Hughes, Dr. S. Natarajan, Dr. N. F. Jain, Dr. J. M. Ramanjulu, Dr. S. Bräse, Dr. M. E. Solomon
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093
Fax: (+1)858 784–2469
E-mail: kcn@scripps.edu

Results and Discussion

Retrosynthetic analysis

The structure of vancomycin[5] (**1**) comprises of a complex polycyclic framework carrying a colorful collection of appendages that includes amino, hydroxy, amido, carboxylic, phenolic, and chloride groups. The molecule can be divided into two segments, the vancomycin aglycon (**2**, Figure 1) and the disaccharide domain made of a vancosamine unit linked to a glucose unit through an α-glycoside bond. The disaccharide moiety is attached to the aglycon through a β-glycoside linkage at the phenolic group on ring-D. The admirable architecture of vancomycin presents an agonizing challenge to synthetic chemists.[6–11] Thus, in addition to the five aromatic rings of its heptapeptide framework, this diabolical core carries eight stereogenic centers (plus one on the appended *N*-methyl leucine). This structure is also cursed with three sites of atropisomerism which are associated with the macrocyclic systems AB, C-O-D, and D-O-E. The latter phenomenon has its origins in the substitution patterns of the aromatic rings involved (A, B, C and E) and the congested nature of the corresponding 12- and 16-membered macrocycles. Overall,

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the vancomycin framework is highly rigid and strained, providing synthetic chemists additional challenges with regard to its construction. Postponing the issue of transforming the triazene functionality to a phenolic group and attaching the sugar moieties onto a suitable acceptor enabled protected triazene **3** to be defined as the key subtarget for the synthesis (Figures 2 and 3). The indicated disconnections are discussed below.

The first retrosynthetic analysis of the basic framework of the vancomycin aglycon is shown in Figure 2 (Strategy I). Based on our model studies described in the preceding paper,[1] we chose the retrosynthetic disconnection at the indicated amide bond of the AB ring system, unraveling potential macrolactamization precursor **4**. The C-O-D macrocycle was then disconnected at the indicated aryl ether linkage, giving the precursor (**5**) for the triazene-driven biaryl ether formation reaction developed as part of this project. The cyclization substrate **5**, upon disconnection at the marked peptide bond, led to fragments **6** and **7** as the most logical precursors. Disassembly of intermediate **6** by a retro Suzuki coupling and a retro peptide bond formation as indicated, led to key building blocks **8**, **9** and **10**, respectively. Macrocyclic system **7** was sequentially disconnected by a retro triazene-driven cyclization, leading to potential precursor **11**, which was simply disassembled to its component amino acid fragments **12**–**15** by peptide bond disconnections as shown in Figure 2. The key question in this analysis was the sequence in which the macrocyclic rings were to be constructed. More specifically, while we were confident of the need to have the C-O-D ring in place in order to facilitate the construction of the AB ring system (requirement for preorganization), we had no basis to predict whether the construction of C-O-D should precede that of the of D-O-E (Figure 2) or vice versa.

An alternative (Strategy II) was, therefore, considered (Figure 3). Thus, the C-O-D ring would be constructed first by the triazene-driven cyclization of precursor **20**, which should be accessible from building blocks **10**, **12**, and **21** (derived from building blocks **8** and **9**). This C-O-D macrocycle should direct the construction of the C-O-D/AB system **18**, which upon coupling with tripeptide acid **17**, should lead to penultimate precursor **16**. Tripeptide **17** could easily be prepared from amino acid building blocks **13**–**15**. A final triazene-driven cyclization of compound **16** was then expected to allow entry into the desired skeleton **3**.

Abstract in Greek:

Η ρετροσυνθετικη αναλυση της βανκομυκινης (**1**) προσδιορισε το αγλυκο της (**2**) και την προστατευμενη τριαζινη **3** (Φιγουρα 1) ως τα προχωρημενα ενδιαμεσα για μια ενδεχομενη ολικη συνθεση της. Η διαδοχικη ρετροαναλυση της **3**, οπως φαινεται στη Φιγουρα 2 (Στρατηγικη I) και στη Φιγουρα 3 (Στρατηγικη II), οδηγησε στα ενδιαμεσα **8**–**10** και **12**–**15** αντιστοιχως, τα οποια αντιπροσωπευουν τα AA–1 εως AA–7 αμινοξεα της βανκομυκινης. Αυτα τα ενδιαμεσα παρασκευαστηκαν μεσω στερεοεκλεκτικων οδων και οι δυο συνθετικες στρατηγικες δοκιμαστηκαν ως προς την εφικτοτητα τους. Η Στρατηγικη I που περιλαμβανει τη συνθεση του κυριως σκελετου της βανβκομυκινης κατα τη σειρα D-O-E→D-O-E/C-O-D→D-O-E/C-O-D/AB μειονεκτει οσων αφορα στα σοβαρα προβληματα επιμερειωσης στο ασυμμετρο κεντρο του AA–4 αντιθετα η Στρατηγικη II που ακολουθει τη συνθετικη αλληλουχια C-O-D→C-O-D/AB→C-O-D/AB/D-O-E αποδεικτηκε βιωσιμη. Αυτα τα αποτελεσματα εθεσαν τις βασεις και ανοιξαν την οδο για τη συνθεση της βανκομυκινης (**1**) και του αγλυκου της (**2**).

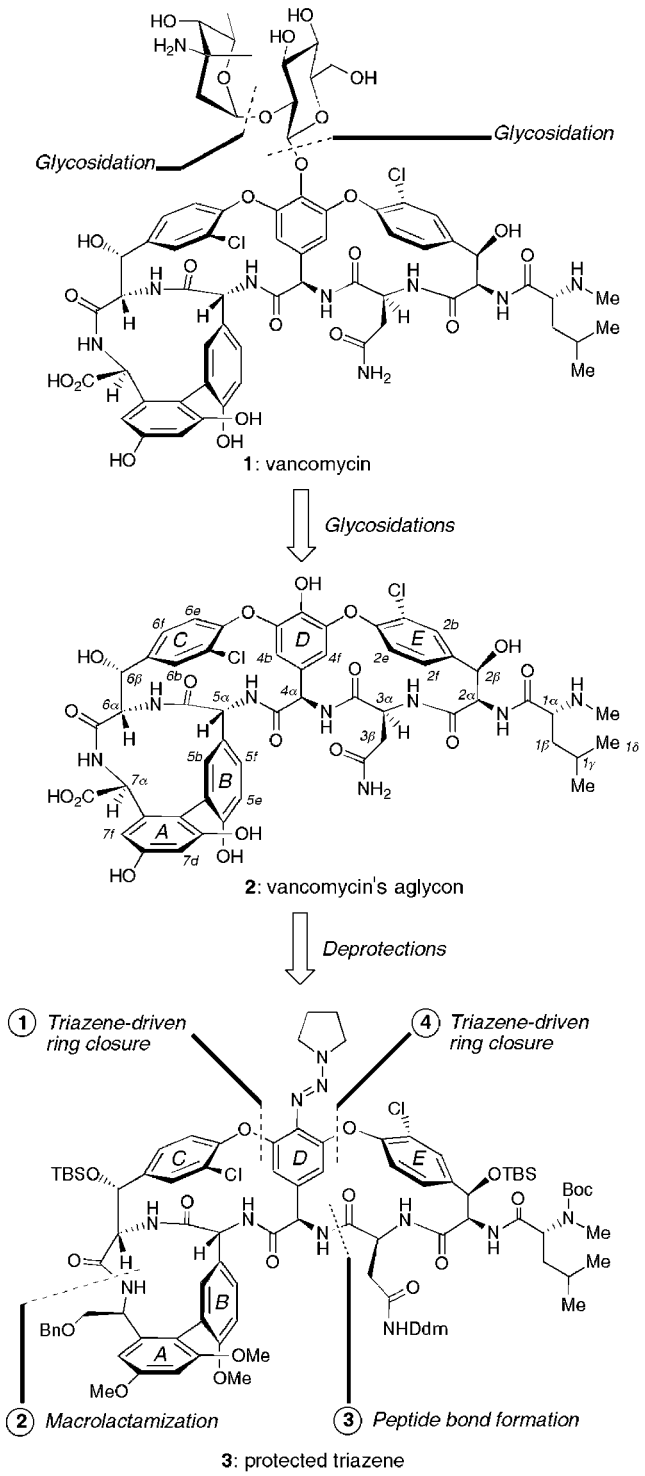

Figure 1. Structure and retrosynthetic analysis of vancomycin (**1**) and vancomycin's aglycon (**2**) (AA-1 to AA-7 represent the seven amino acids of vancomycin, see numbering on structure **2**).

Both strategies start from the same building blocks and are characterized by high degree of convergence. Both strategies leave the question of atropisomerism open and at the mercy of experimentation, even though possible solutions were contemplated. Such potential solutions included: a) thermal equilibration of the undesired atropisomers to the desired ones;[7d] b) temporary use of bulky substituents on the

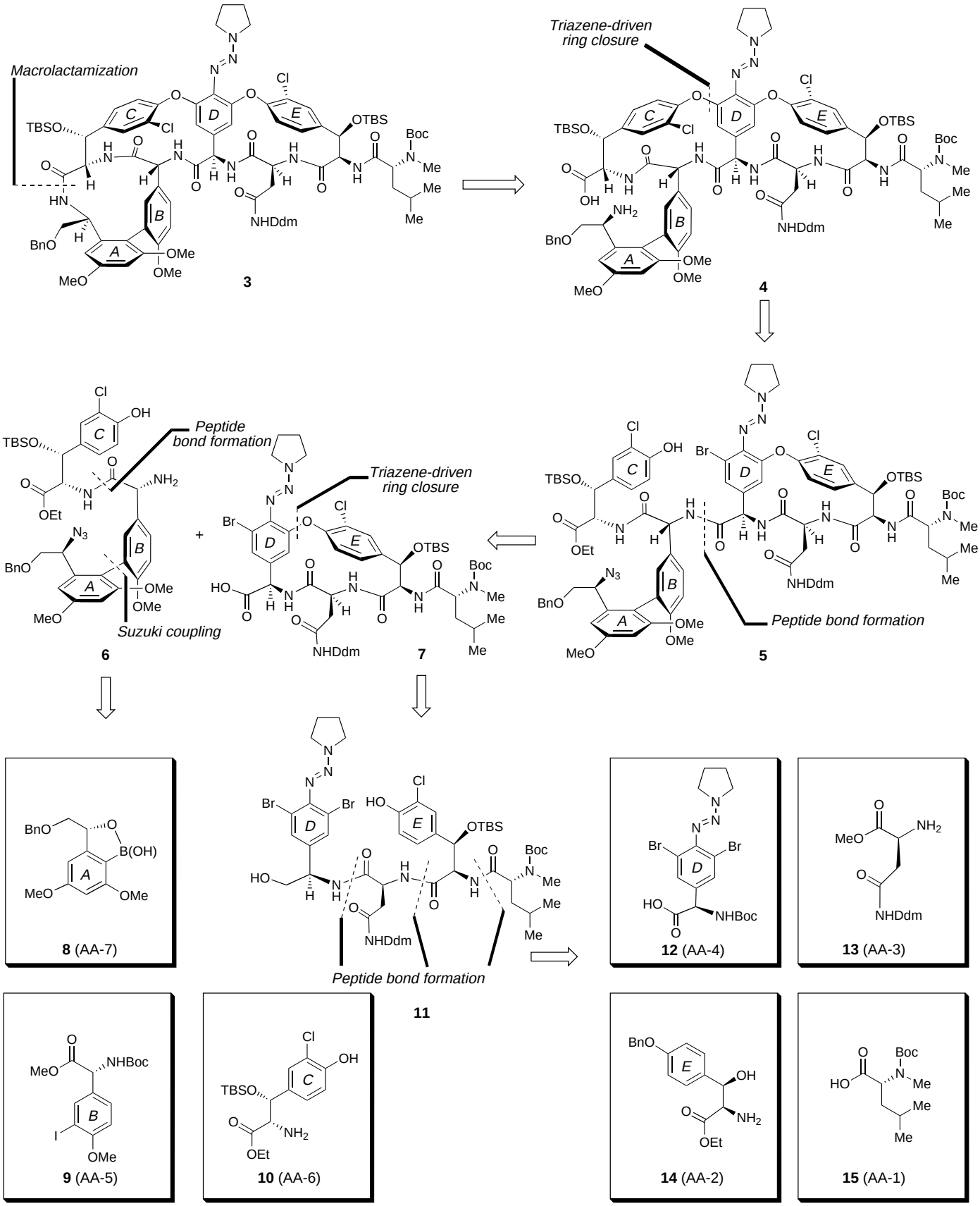

Figure 2. Retrosynthetic analysis of protected triazene **3**. Strategy I.

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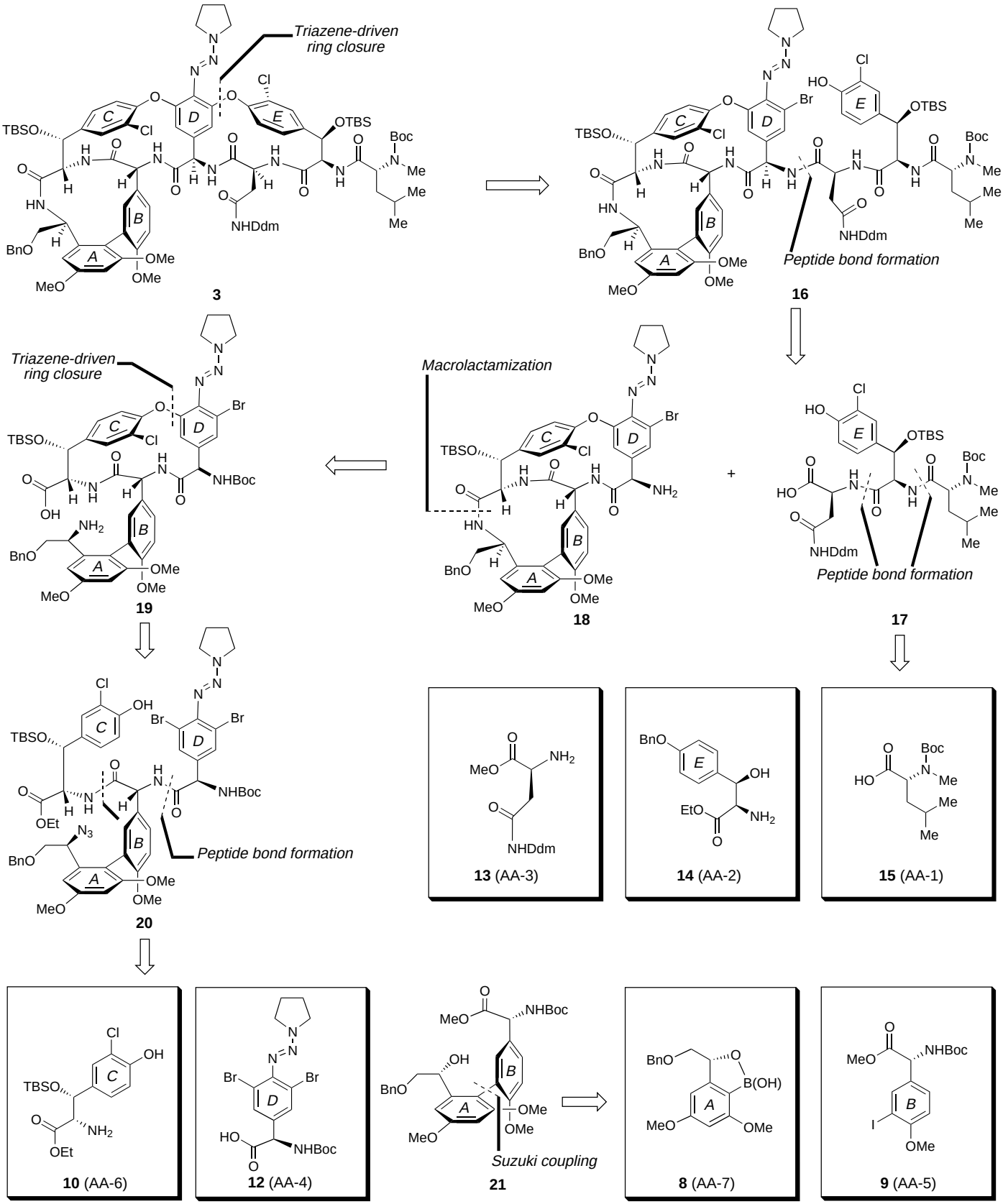


Figure 3. Retrosynthetic analysis of protected triazene **3**. Strategy II.

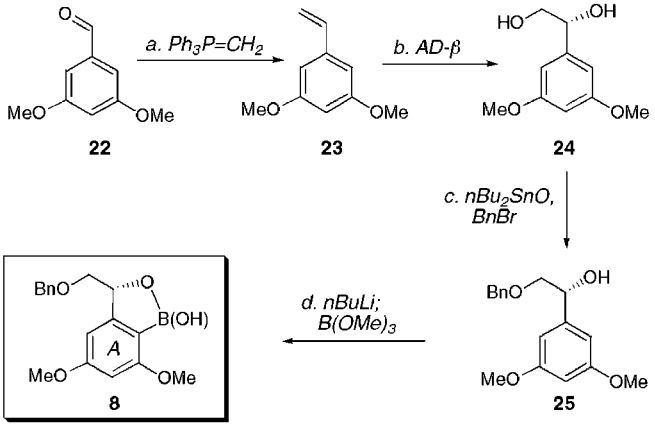
aromatic nuclei to direct the chlorines to their proper orientations during ring closure;[12] c) utilization of chiral side chains within the triazene moiety to direct the ring closures; and d) use of designed chiral copper ligands to exert influence on the stereoselectivity during the cyclization process.

In order to charter the final plan and to set the stage for the next phase of the synthesis, we proceeded to synthesize the required amino acid building blocks and evaluate the proposed strategies.

Synthesis of amino acid building blocks

Below, the synthesis of the required (according to Figures 2 and 3) vancomycin amino acid building blocks (**8**–**10** and **12**–**15**) will be discussed.

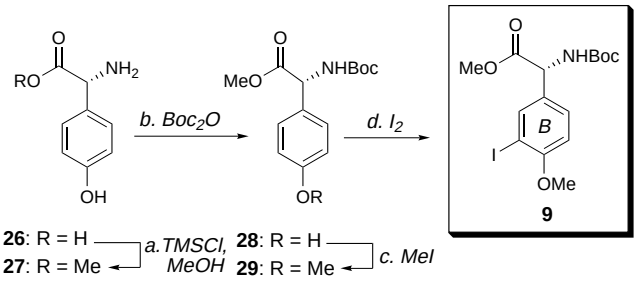
Amino acid building block 8 (AA-7):[13] Boronic acid derivative **8** required for the construction of the AA-7 amino acid building block was synthesized as summarized in Scheme 1.



Scheme 1. Synthesis of amino acid building block **8** (AA-7). a) 1.3 equiv of *n*BuLi, 1.5 equiv of $CH_3P^+Ph_3Br^-$, THF, −20 °C, 10 h, 91%; b) AD-β, 1.4 g mmol^{-1}, *t*BuOH/H_2O (1:1), 25 °C, 8 h, 96% ee, 92%; c) 1.0 equiv of nBu_2SnO, toluene, reflux, 1 h; then 1.5 equiv of BnBr, 0.5 equiv of nBu_4NI, 70 °C, 2 h, 89%; d) 2.2 equiv of *n*BuLi, benzene, 0→25 °C, 2 h; then 3.0 equiv of $B(OMe)_3$, THF, −78→25 °C, 6 h; 5% aq HCl, 55%. Bn = benzyl.

Thus, commercially available 3,5-dimethoxy benzaldehyde (**22**) was converted to terminal olefin **23** by a Wittig olefination reaction (91% yield) and the latter compound (**23**) was subjected to the Sharpless asymmetric dihydroxylation reaction[14] (AD-β) to furnish diol **24** in 96% *ee* and 92% yield of isolated product. Monobenzylation of **24** was achieved by the action of nBu_2SnO to afford a tin acetal derivative,[15] which upon reaction with BnBr in the presence of catalytic amount of nBu_4NI, led to selective protection of the terminal hydroxy group in **25**, (89% yield). Directed lithiation of **25** with 2.2 equivalents of *n*BuLi,[16] followed by quenching the intermediate dilithio derivative with freshly distilled $B(OMe)_3$ and aqueous acidic workup, led to the desired boronic acid **8** in 55% overall yield.

Amino acid building block 9 (AA-5):[17] The vancomycin AA-5 building block equivalent, compound **9**, was prepared from commercially available (D)-4-hydroxyphenylglycine **26**, as shown in Scheme 2. Thus, mild esterification of **26** in methanol



Scheme 2. Synthesis of amino acid building block **9** (AA-5). a) 2.1 equiv of TMSCl, MeOH, 25 °C, 15 h, 98%; b) 1.1 equiv of Boc_2O, 4.0 equiv of K_2CO_3, dioxane/H_2O (1:1), 25 °C, 4 h, 95%; c) 2.0 equiv of MeI, 4.0 equiv of K_2CO_3, DMF, 25 °C, 6 h, 93%; d) 1.2 equiv of I_2, 2.2 equiv of CF_3COOAg, $CHCl_3$, 25 °C, 12 h, 90%. TMS = trimethylsilyl; Boc = *tert*-butoxycarbonyl; DMF = dimethylformamide.

proceeded at ambient temperature under the influence of TMSCl[18] to afford methyl ester **27** in 98% yield. Protection of the amino group in **27** with Boc_2O in the presence of K_2CO_3 furnished derivative **28** (95% yield), which upon treatment with K_2CO_3 and MeI led to fully protected compound **29** in 93% yield. Finally, regioselective iodination of **29** was effected by I_2 in the presence of CF_3COOAg, furnishing the desired amino acid building block **9** in 90% yield.

Amino acid building block 10 (AA-6):[19] An expedient route to building block **10** (AA-6) took advantage of the recently disclosed Sharpless asymmetric aminohydroxylation reaction,[20] as shown in Scheme 3. The required starting material for this reaction, cinnamate **32**, was obtained from *p*-hydroxybenzaldehyde (**30**) by benzylation (K_2CO_3, BnBr, KI cat., 98% yield), followed by reaction with the anion derived from $(EtO)_2P(O)CH_2COOEt$ (KOH, 95% yield). Substrate **32** entered the Sharpless asymmetric aminohydroxylation reaction [NaOH, $BnOCONH_2$, *t*BuOCl, $(DHQD)_2AQN$, $K_2OsO_2(OH)_4$, *n*PrOH/H_2O (1:1)], affording directly amino alcohol **33** in its Cbz-protected form in 45% yield and 87% *ee*. The undesired enantiomer was removed later in the sequence upon formation of diastereomers (vide infra). The hydroxy group in **33** was then protected as its TBS ether (TBSOTf, 2,6-lutidine, 98% yield), leading to compound **34**, at which stage both the benzyl and benzyloxycarbonyl groups were removed by hydrogenolysis [H_2, 20% $Pd(OH)_2$/C, 97% yield] to afford amino phenol **35**. Finally, introduction of the chlorine atom *ortho* to the phenol group of **35** was smoothly accomplished through the use of SO_2Cl_2,[21] furnishing the desired amino acid building block **10** in 80% yield.

Amino acid building block 12 (AA-4):[22] The central amino acid building block **12** (AA-4) was synthesized from *p*-aminobenzoic acid (**36**), as summarized in Scheme 4. The sequence utilized the Sharpless asymmetric dihydroxylation

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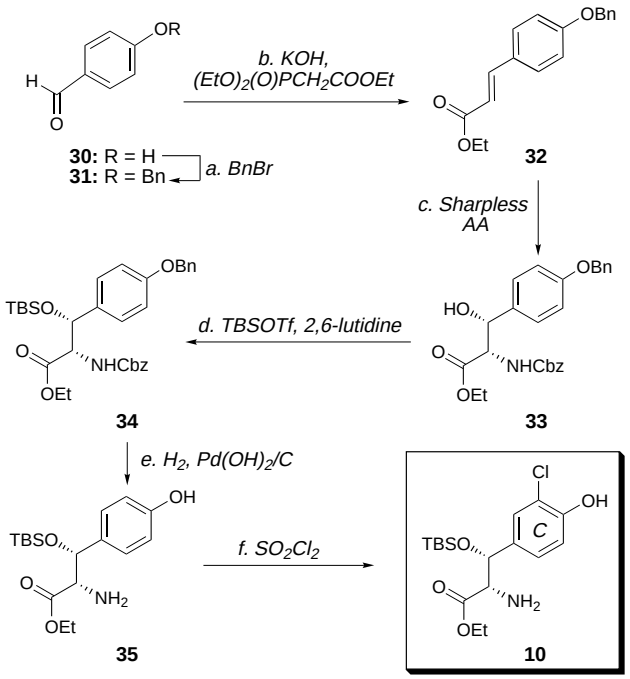
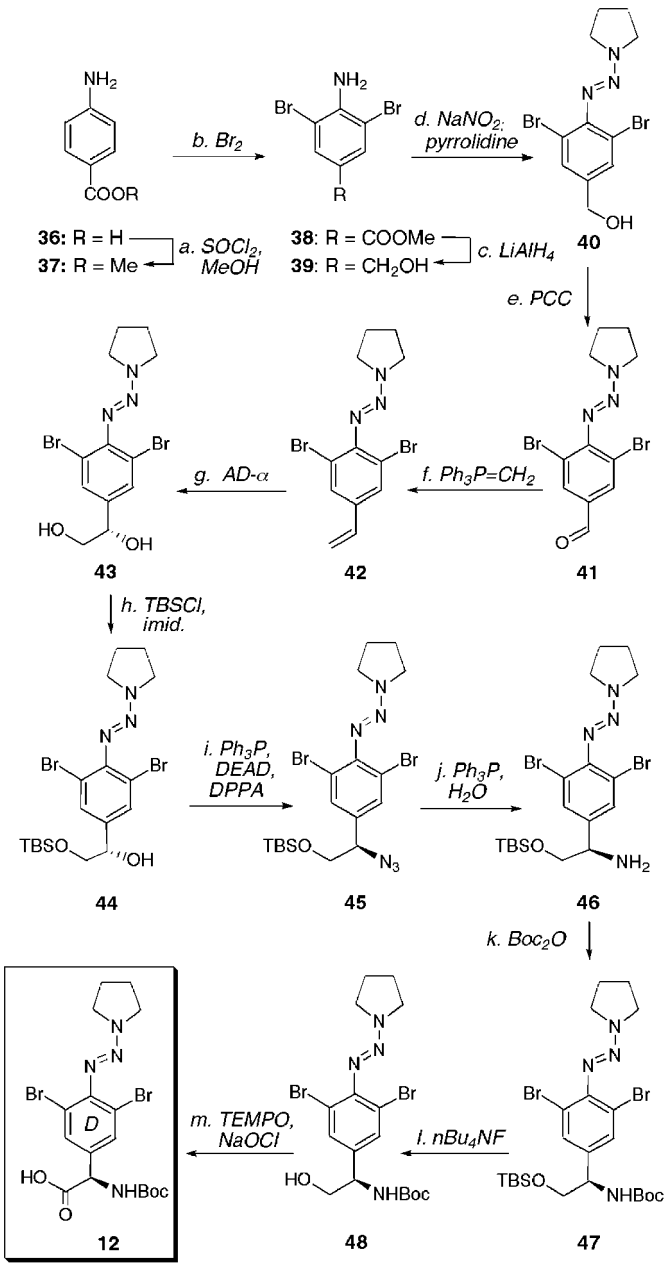


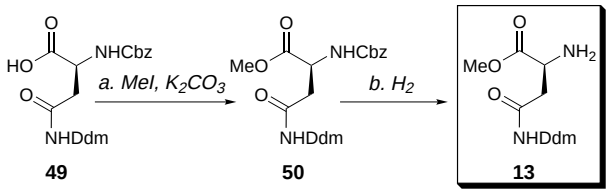
Scheme 3. Synthesis of amino acid building block **10** (AA-6). a) 1.5 equiv of K_2CO_3, 1.0 equiv of BnBr, 0.1 equiv of KI, DMF, 25 °C, 12 h, 98 %; b) 1.1 equiv of $(EtO)_2(O)PCH_2COOEt$, 1.5 equiv of KOH, THF, 25 °C, 12 h, 95 %; c) 3.0 equiv of NaOH, 3.1 equiv of $BnOCONH_2$, 3.0 equiv of *t*BuOCl, 0.05 equiv of $(DHQD)_2AQN$, 0.04 equiv of $K_2OsO_2(OH)_4$, *n*PrOH/H_2O (1:1), 25 °C, 12 h, 87 % *ee*, 45 %; d) 1.1 equiv of TBSOTf, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 98 %; e) H_2, 20 % $Pd(OH)_2$/C, MeOH, 25 °C, 0.5 h, 97 %; f) 1.0 equiv of SO_2Cl_2, Et_2O/CH_2Cl_2 (1:10), 0 °C, 1 h, 80 %. Cbz = benzyloxycarbonyl; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl. $(DHQD)_2AQN$ = 1,4-bis(dihydroquinidinyl)anthraquinone.



Scheme 4. Synthesis of amino acid building block **12** (AA-4). a) 1.0 equiv of $SOCl_2$, MeOH, reflux, 2 h, 100 %; b) 2.0 equiv of Br_2, AcOH, 25 °C, 0.5 h, 98 %; c) 1.5 equiv of $LiAlH_4$, THF, 0 °C, 2 h, 95 %; d) 5.0 equiv of 6 M aq HCl, 1.2 equiv of $NaNO_2$, AcOH/H_2O (1:1), 0 °C, 0.5 h; then 30 equiv of KOH, 1.5 equiv of pyrrolidine, 0 °C, 0.5 h, 75 %; e) 1.5 equiv of PCC, CH_2Cl_2, 25 °C, 2 h, 88 %; f) 1.4 equiv of *n*BuLi, 1.5 equiv of $CH_3P^+Ph_3Br^-$, THF, −20 °C, 2 h, 92 %; g) AD-α, 1.4 g mmol^{-1}, *t*BuOH/H_2O (1:1), 25 °C, 6 h, 95 % *ee*, 95 %; h) 1.1 equiv of TBSCl, 1.5 equiv of imidazole, DMF, 0 °C, 5 h, 88 %; i) 2.5 equiv of Ph_3P, 2.5 equiv of DEAD, 2.5 equiv of DPPA, THF, 0 °C, 2 h, 79 %; j) 3.0 equiv of Ph_3P, 10.0 equiv of H_2O, THF, 60 °C, 3 h, 78 %; k) 1.1 equiv of Boc_2O, 3.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 4 h, 95 %; l) 1.2 equiv of nBu_4NF, THF, 0 °C, 2 h, 93 %; m) 1.0 equiv of TEMPO, 3.0 equiv of 5 % aq NaOCl, 0.1 equiv of KBr, 5 % $NaHCO_3$/acetone (1:1), 0 °C, 1 h, 75 %. PCC = pyridinium chlorochromate; DEAD = diethyl azodicaboxylate; DPPA = diphenylphosphoryl azide; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

reaction to introduce the desired chirality, producing the targeted intermediate in its naturally occurring form and high overall yield. Thus, methylation of **36** ($SOCl_2$, MeOH) gave methyl ester **37** (100 % yield), which upon treatment with bromine in acetic acid provided dibromide **38** (98 % yield). Reduction of the ester functionality in **38** with $LiAlH_4$ (95 % yield), followed by diazotization (HCl, $NaNO_2$, AcOH/H_2O) and reaction of the resulting diazonium salt with pyrrolidine, furnished triazene **40** via amino alcohol **39** in 75 % overall yield. Oxidation of **40** (PCC, 88 % yield), followed by Wittig olefination of the resulting aldehyde **41**, furnished styrene derivative **42** (92 % yield). Asymmetric dihydroxylation of **42** with AD-α in *t*BuOH/H_2O (1:1) led to dihydroxy compound **43** in 95 % *ee* and 95 % yield. Selective protection of the primary hydroxy group in the latter compound (**43**) was accomplished with TBSCl in the presence of imidazole, furnishing **44** in 88 % yield. The secondary alcohol functionality in the resulting mono-TBS ether **44** was subjected to a Mitsunobu reaction with diphenylphosphoryl azide (DPPA) in the presence of Ph_3P and DEAD[23] to afford azide **45** in 79 % yield. Accompanied by complete inversion of configuration of the secondary alcohol, this reaction set the stage for the generation of the desired amino group. This task was accomplished by a mild reduction with Ph_3P/H_2O[24] at 60 °C, furnishing compound **46** (78 % yield), which was then protected with Boc_2O in the presence of Et_3N to give derivative **47** (95 % yield). Finally, fluoride-induced desilylation of **47** (nBu_4NF, 93 % yield) followed by oxidation with TEMPO and NaOCl led to the desired amino acid derivative **12** (AA-4) in 75 % yield.

Amino acid building block 13 (AA-3): Amino acid building block **13** was prepared from the known asparagine-derived compound **49**, as shown in Scheme 5. Thus, asparagine was converted to the corresponding *N*-Cbz compound and thence



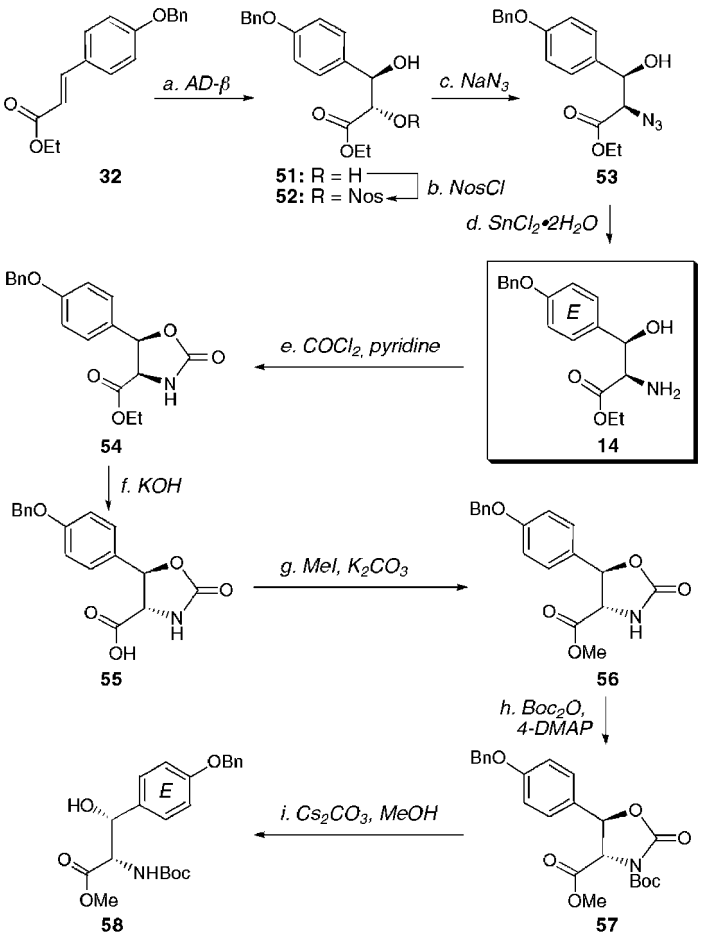
Scheme 5. Synthesis of amino acid building block **13** (AA-3). a) 2.0 equiv of MeI, 2.0 equiv of K_2CO_3, DMF, 25 °C, 12 h, 70 %; b) H_2, 20 % $Pd(OH)_2$/C, MeOH, 25 °C, 1 h, 99 %. Ddm = 4,4′-dimethoxydiphenylmethyl.

to the dimethoxydiphenyl methyl (Ddm) derivative **49** according to Koenig's procedure.[25] Methylation of **49** (K_2CO_3, MeI, 70 % yield), followed by removal of the Cbz protecting group by hydrogenolysis (H_2, 20 % $Pd(OH)_2$/C, 99 % yield), furnished the desired AA-3 building block **13**.

Amino acid building block 14 (AA-2):[26] The synthesis of amino acid building block **14** (Scheme 6) commenced with ethyl cinnamate **32** (see Scheme 3). The relatively low reactivity of the double bond of this substrate (**32**) required longer reaction time for the Sharpless asymmetric dihydroxylation procedure (AD-β) to give diol **51** in 92 % *ee* and 79 % yield. The latter compound (**51**) was then converted to mononosylate **52** (68 % yield) by the selective action of one equivalent of NosCl[10e] in the presence of Et_3N. This substrate underwent smooth S_N2 type displacement with NaN_3, furnishing azide **53** (90 % yield) with complete inversion of configuration. Finally, reduction of the azide group in **53**, accomplished by the action of $SnCl_2 \cdot 2H_2O$, resulted in the formation of the desired amino acid building block **14** (AA-2) in 90 % yield.

Intermediate **14** was further converted to AA-6 derivative **58** as shown in Scheme 6. Thus, exposure of **14** to phosgene allowed the formation of cyclic urethane **54** in 93 % yield, which underwent smooth epimerization exclusively at the α-center to the ester functionality in the presence of ethanolic KOH, leading to compound **56** after methylation (K_2CO_3, MeI, 87 % overall yield for two steps) of the resulting carboxylic acid **55**. Conversion of **56** to its Boc derivative **57** (Boc_2O, 4-DMAP, 53 % yield), followed by selective hydrolysis of the five-membered ring under basic conditions (Cs_2CO_3, MeOH, 80 % yield) led to compound **58**, demonstrating an alternative route to such structure from the one shown in Scheme 3.

Amino acid building block 15 (AA-1): Amino acid building block **15** (*N*-methyl leucine Boc derivative, see Scheme 7) is commercially available.



Scheme 6. Synthesis of amino acid building block **14** (AA-2) and precursor **58** (for AA-6). a) AD-β, 1.4 g mmol^{-1}, 1.0 equiv of $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 25 °C, 12 h, 92 % ee, 79 %; b) 1.0 equiv of NosCl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 5 h, 68 %; c) 1.5 equiv of NaN_3, DMF, 55 °C, 12 h, 90 %; d) 2.0 equiv of $SnCl_2 \cdot 2H_2O$, MeOH, 25 °C, 2 h, 90 %; e) 1.0 equiv of $COCl_2$, 2.0 equiv of pyr., CH_2Cl_2, −78 °C, 2 h, 93 %; f) 1.05 equiv of KOH, EtOH, reflux, 1 h; g) 1.5 equiv of MeI, 1.0 equiv of K_2CO_3, DMF, 25 °C, 12 h, 87 % from **54**; h) 1.1 equiv of Boc_2O, 0.15 equiv of 4-DMAP, THF, 25 °C, 2 h, 53 %; i) 0.4 equiv of Cs_2CO_3, MeOH, 25 °C, 2 h, 80 %. Nos = 4-nitrobenzene sulfonyl; 4-DMAP = 4-dimethylaminopyridine.

Evaluation of strategies

With the requisite amino acid building blocks (**8**–**10** and **12**–**15**) in hand, we were at the crossroads to make a decision as to which strategy to adopt for their assembly into the desired heptapeptide skeleton of vancomycin. As a prelude for the comparison between these two routes, the AA-1/AA-2/AA-3 tripeptide **17** required for both strategies I (Figure 2) and II (Figure 3) was first prepared from its residues as outlined in Scheme 7. Thus, coupling of amino alcohol **14** with Boc-protected *N*-methyl leucine **15**, facilitated by EDC/HOBt, resulted in the formation of dipeptide **59** (93 % yield), which was subsequently converted to its carboxylic acid **60**, without significant epimerization, by LiOH in THF/H_2O (1:1) at 0 °C (99 % yield). Attachment of the third amino acid building block, asparagine derivative **13**, was accomplished by EDC/HOAt induced coupling, leading to tripeptide **61** in 82 % yield. Protection of the hydroxy group in **61** (TBSOTf, 2,6-lutidine, 81 % yield) provided TBS ether **62**. Hydrogenolysis of the benzyl group from **62** [H_2, 20 % $Pd(OH)_2$/C, 99 % yield] liberated phenol **63**, which was subjected to chlorination at the *ortho* position (SO_2Cl_2) to afford chlorophenol methyl

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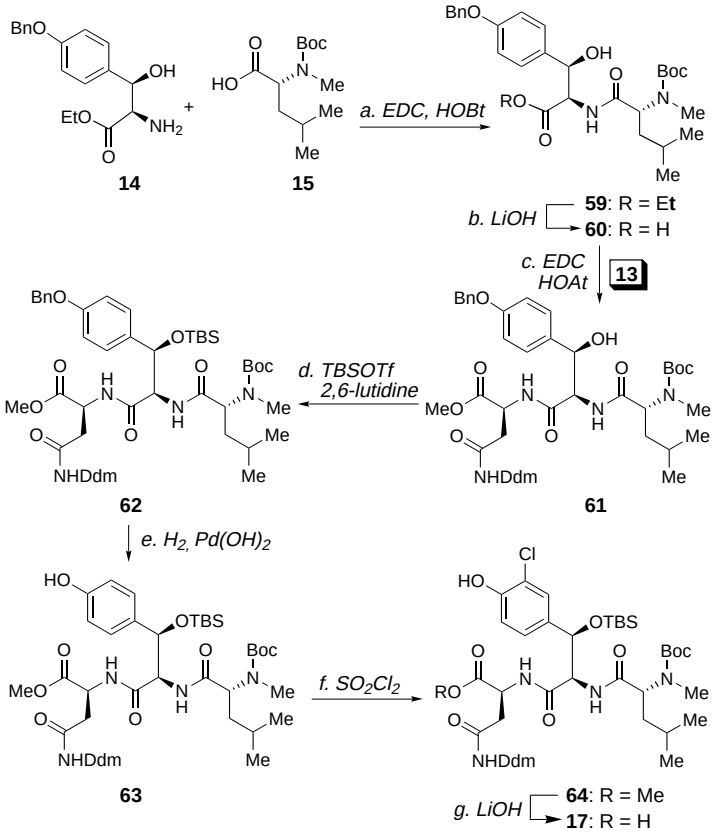
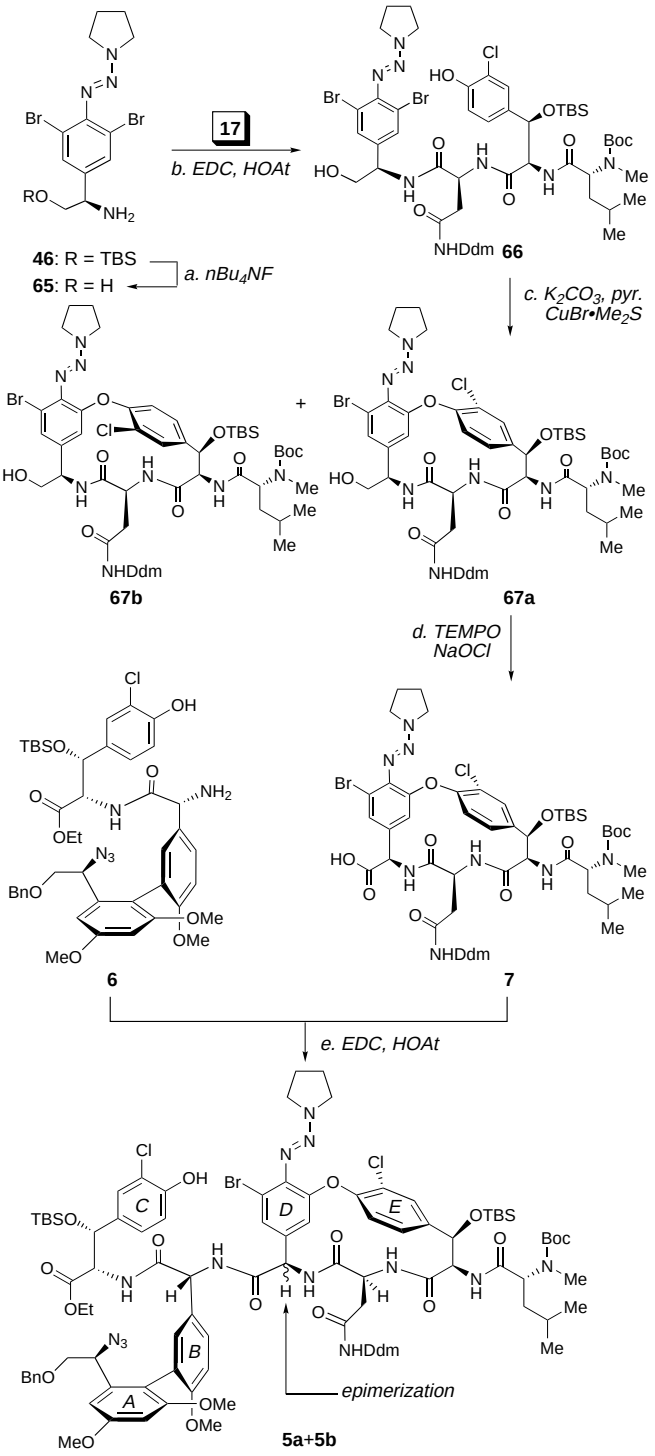


Scheme 7. Synthesis of tripeptide **17**. a) 3.0 equiv of EDC, 3.3 equiv of HOBt, THF, 0 °C, 12 h, 93 %; b) 2.0 equiv of LiOH, THF/H_2O (1:1), 0 °C, 1 h, 99 %; c) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, 0 °C, 12 h, 82 %; d) 1.3 equiv of TBSOTf, 2.2 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 81 %; e) H_2, 20 % $Pd(OH)_2$/C, MeOH, 25 °C, 1 h, 99 %; f) 1.1 equiv of SO_2Cl_2, Et_2O, 0 °C, 75 %; g) 4.0 equiv of LiOH, *t*BuOH/H_2O (2:1), 0 °C, 0.5 h, 95 %. HOAt = 1-hydroxy-7-azobenzotriazole; HOBt = 1-hydroxybenzotriazole; EDC = 1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride.

ester **64** in 75 % yield. Finally, LiOH-induced saponification of **64** in *t*BuOH/H_2O (2:1) at 0 °C furnished tripeptide acid **17** in 95 % yield without significant epimerization.

Having prepared tripeptide carboxylic acid **17**, we proceeded to test the feasibility of Strategy I (Figure 2), in which construction of the D-O-E macrocycle was to precede that of the C-O-D ring system. As shown in Scheme 8, central amino acid derivative **46** (see Scheme 4 for its preparation) was desilylated with nBu$_4$NF, furnishing amino alcohol **65** (92 % yield), which upon coupling with tripeptide acid **17** in the presence of EDC and HOAt, afforded tetrapeptide **66** in 84 % yield. Cyclization of **66** under the influence of K_2CO_3, CuBr·Me_2S, and pyridine in MeCN at reflux led to a separable mixture of atropisomers **67a** and **67b** (**67a**:**67b**, ca. 3:1) in 87 % combined yield. NOE studies (Figure 4) revealed that the major product **67a** had the same chlorine orientation as in vancomycin. However, the benefit of this favorable atropselectivity did not compensate for the serious epimerization drawback which was soon to emerge along the sequence. Thus, the natural chlorine atropisomer (**67a**) was then subjected to TEMPO/NaOCl oxidation, affording the corresponding carboxylic acid (**7**) in 65 % yield. Attempted coupling of **7** with amine **6**[27] under the influence of EDC



Scheme 8. Synthesis of D-O-E ring system **7** and further elaboration. a) 1.1 equiv of nBu$_4$NF, THF, 0 °C, 2 h, 92 %; b) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, 0 °C, 10 h, 84 %; c) 3.0 equiv of CuBr·Me_2S, 3.0 equiv of K_2CO_3, 3.0 equiv of pyr., MeCN, reflux, 15 min, **67a**:**67b** ca. 3:1, 87 % combined yield; d) 1.1 equiv of TEMPO, 0.1 equiv of KBr, 5 % $NaHCO_3$/acetone (1:1), 3.0 equiv of 5 % aqueous NaOCl, 0 °C, 1 h, 65 %; e) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, −15 °C, 5 h, 72 %, **5a**:**5b** ca. 2:1 ratio.

and HOAt led to a mixture of two products in 72 % yield (ca. 2:1 ratio). These products were presumed to be the two epimers **5a** and **5b** at the indicated position (no assignment of stereochemistry was made). Screening of different coupling

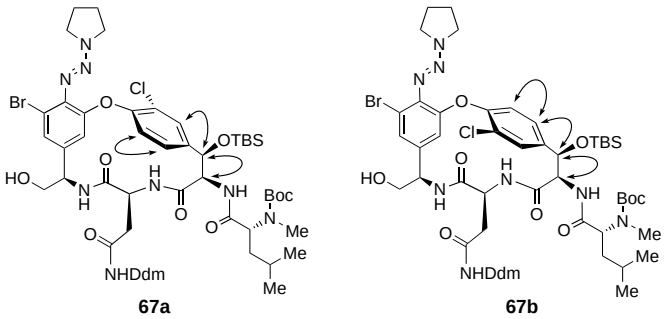
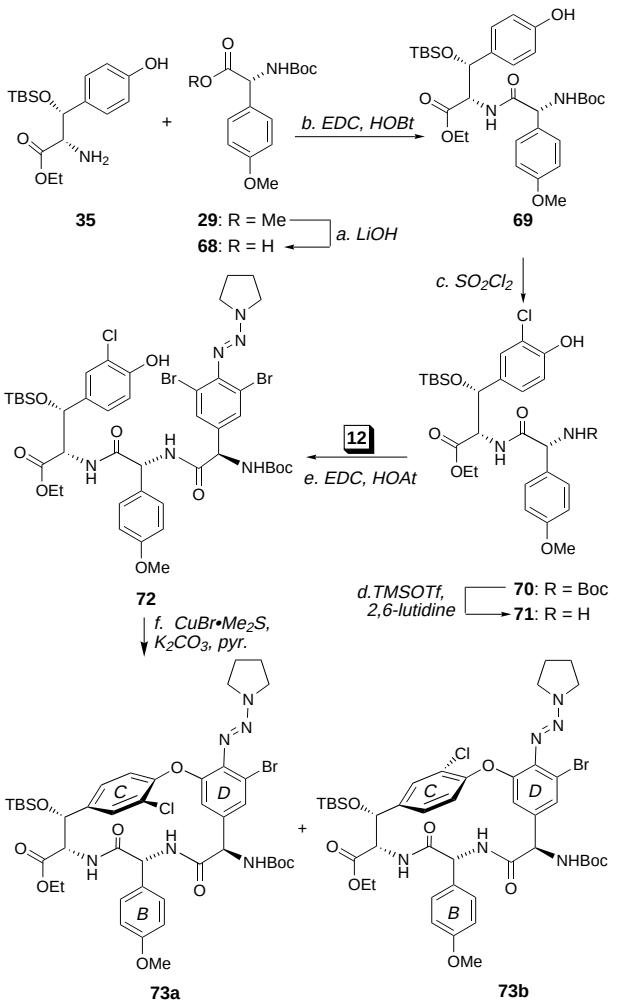


Figure 4. Assignment of stereochemistry of atropisomers **67a** and **67b** by ^{1}H-^{1}H NOE studies (COSY, ROSEY, 600 MHz, CD_3COCD_3).

reagents failed to solve this epimerization problem and only made the testing of strategy II (Figure 3) a more urgent priority.

To test strategy II (Figure 3), according to which formation of macrocycle C-O-D was to precede the construction of the D-O-E ring, the simpler *p*-methoxyphenylglycine derivative **68** (Scheme 9) was chosen in place of the AB biaryl amino acid building block. Thus, ester **29** (see Scheme 2) was hydrolyzed to carboxylic acid **68** (LiOH, 99% yield), which was then coupled with amine **35** (see Scheme 3) under the influence of EDC and HOBt to give dipeptide **69** in 81% yield (Scheme 9). The resulting phenol **69** was subjected to chlorination (SO_2Cl_2, 88% yield) to provide monochlorine derivative **70**, which upon exposure to excess TMSOTf (3.4 equiv) and 2,6-lutidine (3.0 equiv) followed by aqueous workup, furnished free amine **71** (75% yield). Incorporation of the triazene carboxylic acid **12** (see Scheme 4) into the growing peptide chain was then accomplished by the action of EDC and HOAt, leading to tripeptide **72** (79% yield). Ring closure of the latter compound (**72**) under the standard cylization conditions (K_2CO_3, CuBr · Me_2S, pyridine, MeCN, reflux) gave the desired C-O-D ring system **73a** together with its atropisomer **73b** (**73a**:**73b**, ca. 1:1, 52% combined yield). The two atropisomers were chromatographically separated and their stereo assignments were determined by NOE studies (see Figure 5).



Scheme 9. Synthesis of C-O-D model systems **73a** and **73b**. a) 1.5 equiv of LiOH, THF/H_2O (1:1), 0 °C, 0.5 h, 99%; b) 3.0 equiv of EDC, 3.3 equiv of HOBt, DMF, −20 → 0 °C, 12 h, 81%; c) 1.0 equiv of SO_2Cl_2, Et_2O/CH_2Cl_2 (5:1), −10 → 0 °C, 0.5 h, 88%; d) 3.4 equiv of 2,6-lutine, CH_2Cl_2, −10 °C, 1 h, 75%; e) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, −10 °C, 2 h, 79%; f) 3.0 equiv of CuBr · Me_2S, 3.0 equiv of K_2CO_3, 3.0 equiv of pyr., MeCN, reflux, 0.5 h, **73a**:**73b** ca. 1:1, 52% combined yield.

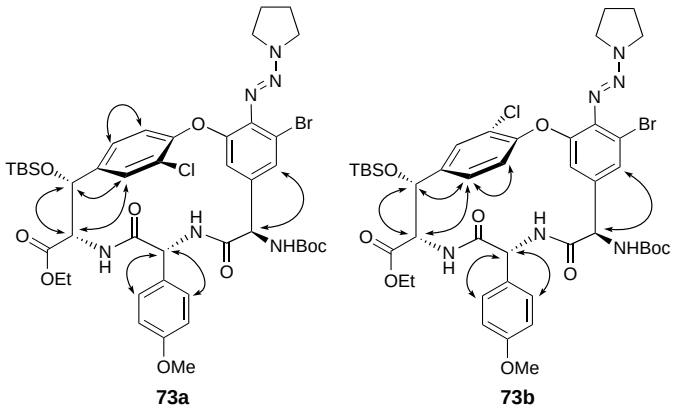


Figure 5. Assignment of stereochemistry of atropisomers **73a** and **73b** by ^{1}H-^{1}H NOE studies (COSY, ROESY, 600 MHz, CD_3COCD_3).

The preparation of the requisite dipeptide **80** is summarized in Scheme 10. Thus, compound **14** was protected as its *N*-Boc derivative **74** (Boc_2O, Et_3N, 93% yield), which was then hydrolyzed with LiOH at 0 °C to afford carboxylic acid **75** in 96% yield. Coupling of **75** with protected asparagine derivative **13** (EDC, HOBt) provided dipeptide **76** (65% yield), which upon treatment with TBSCl in the presence of imidazole gave fully protected compound **77** (75% yield). Deprotection of the benzyl group was accomplished by hydrogenolysis with 10% Pd/C to furnish phenol **78** (99% yield), which was then subjected to selective monochlorination to afford **79** in 91% yield. Final hydrolysis of the methyl ester functionality of **79** with LiOH provided carboxylic acid **80** (76% yield), which was further elaborated as shown in Scheme 11. Thus, treatment of **73a** with TMSOTf and 2,6-lutidine generated the free amine (**81**, 80% yield), which was coupled with dipeptide acid **80** by the action of EDC and HOAt, affording the cyclization precursor **82** in 81% yield. Finally, D-O-E cyclization of phenolic bromotriazene **82** in the presence of K_2CO_3, CuBr · Me_2S, and pyridine in MeCN at reflux, furnished the anticipated C-O-D/D-O-E framework **83** in 40% yield. However, the chlorine orientation within the

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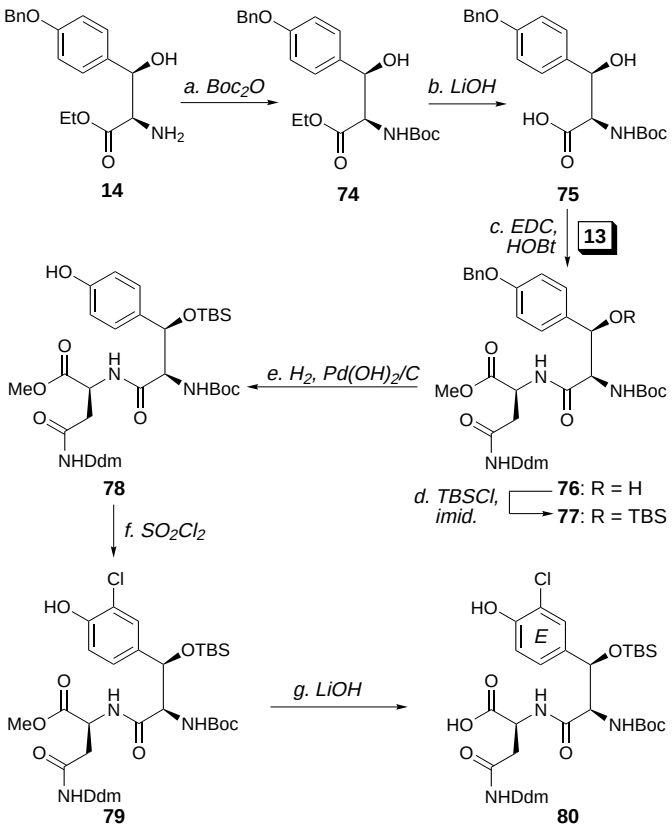
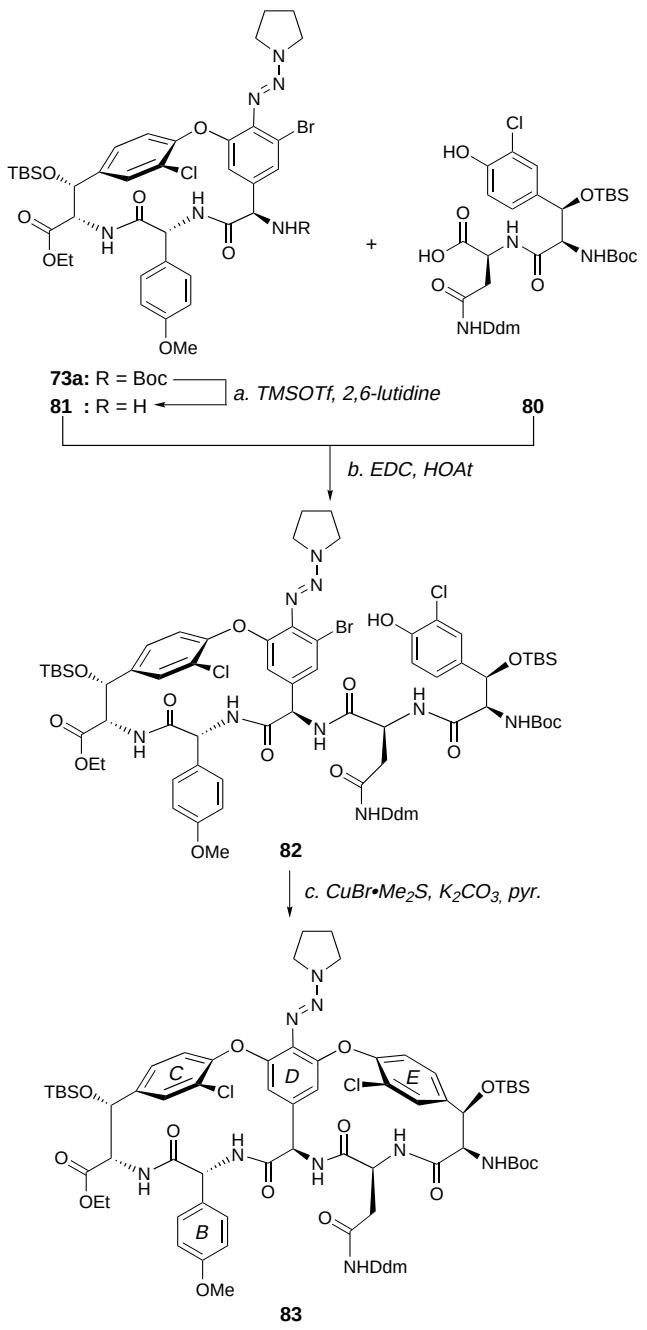


Scheme 10. Synthesis of dipeptide **80**. a) 1.1 equiv of Boc_2O, 1.2 equiv of Et_3N, CH_2Cl_2, 0 °C, 5 h, 93 %; b) 2.0 equiv of LiOH, THF/H_2O (1:1), 0 °C, 1 h, 96 %; c) 3.0 equiv of EDC, 3.5 equiv of HOBt, THF, −20 → 0 °C, 4 h, 65 %; d) 4.0 equiv of TBSCl, 8.0 equiv of imidazole, DMF, 25 °C, 24 h, 75 %; e) H_2, 10 % $Pd(OH)_2$/C, EtOH, 25 °C, 16 h, 99 %; f) 1.1 equiv of SO_2Cl_2, Et_2O/CH_2Cl_2 (5:1), 0 °C, 0.5 h, 91 %; g) 1.5 equiv LiOH, *t*BuOH/H_2O (4:1), 5 → 10 °C, 1 h, 76 %.



Scheme 11. Synthesis of C-O-D/D-O-E model system **83**. a) 10.0 equiv of TMSOTf, 16 equiv of 2,6-lutidine, CH_2Cl_2, −20 °C, 1 h, 80 %; b) 2.5 equiv of EDC, 11 equiv of HOAt, −15 → 0 °C, 2 h, 81 %; c) 5.5 equiv of CuBr·Me_2S, 5.5 equiv of K_2CO_3, 5.5 equiv of pyr., MeCN, reflux, 2 h, 40 %.

newly formed ring was of the unnatural configuration with regards to vancomycin (see Figure 6 for crucial NOEs). It appeared that strategy II might also be plagued with serious stereochemical problems of a different kind from those encountered in our explorations of strategy I. Of the two devilish problems, we chose to face the atropisomerism in the hope that the presence of the vancomycin's AB ring system would, perhaps, favor, at least to a satisfying degree, the natural configuration.

Conclusion

In this article, the structure of vancomycin (**1**) was analyzed retrosynthetically and two alternate strategies were devised (Strategies I and II). The required building blocks for implementation of these strategies were synthesized by efficient routes and two sequences were tested for their feasibility as viable routes to vancomycin (**1**).

These preliminary studies established strategy II, in which the sequence of formation of vancomycin's macrocycles followed C-O-D → C-O-D/AB → C-O-D/AB/D-O-E, as the least hazardous, but still risky approach to the target molecule. The road was now chosen for the final launch towards vancomycin (**1**). The third article in this series[28] describes our detailed journey to the aglycon of vancomycin (**2**), while the fourth paper in the series[29] provides a full account of the conversion of aglycon **2** to vancomycin (**1**) itself.

Experimental Section

General techniques: See paper 1 in this series.[1]

Diol 24: To a solution of olefin **23** (4.26 g, 26 mmol) in *t*BuOH/H_2O (1:1, 130 mL) at 25 °C was added AD-mix-β (36.4 g, 1.4 g mmol^{-1}) and the reaction mixture was stirred at that temperature for 8 h. The reaction was

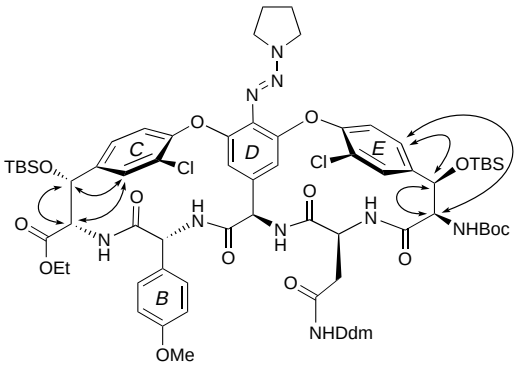


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Figure 6. Assignment of stereochemistry of atropisomers **83** by ^{1}H-^{1}H NOE studies (COSY, ROESY, 600 MHz, CD_3CN, 310 K).

quenched by the addition of sodium sulfite (39 g, 1.5 g mmol^{-1}) and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was subjected to flash column chromatography (silica gel, 30 → 50 % EtOAc in hexanes) to provide diol **24** (4.70 g, 96 % *ee*, 92 %). **24**: $R_f = 0.12$ (50 % EtOAc in hexanes); $[\alpha]_D^{22} = -25.7$ ($c = 0.91$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3384, 2939, 2839, 1605, 1459, 1429, 1345, 1295, 1204, 1156, 1064$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.51$ (d, $J = 2.0$ Hz, 2H, ArH), 6.38 (t, $J = 2.0$ Hz, 1H, ArH), 4.76-4.73 (m, 1H, H-7α), 3.78 (s, 6H, OCH_3), 3.74 (dd, $J = 11.5$, 3.5 Hz, 1H, H-7β), 3.64 (dd, $J = 11.5$, 8.5 Hz, 1H, H-7β), 2.50 (br. s, 2H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.9, 143.0, 103.9, 99.7, 74.7, 68.0, 55.4$; HRMS (FAB) calcd for $C_{10}H_{14}O_4Na$ [$M + Na^+$] 221.0790, found 221.0794.

Benzyl ether 25: A solution of diol **24** (517 mg, 2.6 mmol) in toluene (25 mL) was treated with nBu$_2$SnO (647 mg, 2.6 mmol). The resulting mixture was heated to reflux for 1 h with removal of H_2O with a Dean–Stark apparatus before it was cooled to 70 °C. To this solution were added BnBr (463 μL, 3.9 mmol) and nBu$_4$NI (480 mg, 1.3 mmol) sequentially and the reaction was stirred at 70 °C for 2 h before it was cooled to 25 °C. The organic phase was washed with H_2O (2 × 15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, 20 → 30 % EtOAc in hexanes, gradient elution) afforded **25** (666 mg, 89 %). **25**: $R_f = 0.47$ (silica gel, 50 % EtOAc in hexanes); $[\alpha]_D^{22} = -24.6$ ($c = 0.98$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3446, 2937, 2854, 1601, 1456, 1426, 1347, 1300, 1201, 1149, 1103, 1056$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.36$-7.34 (m, 5H, ArH), 6.55 (d, $J = 2.0$ Hz, 2H, ArH), 6.40 (t, $J = 2.0$ Hz, 1H, ArH), 4.68 (dd, $J = 8.5$, 3.5 Hz, 1H, H-7α), 4.60 (d, $J = 12.0$ Hz, 1H, OC*H*HPh), 4.56 (d, $J = 12.0$ Hz, 1H, OCH*H*Ph), 3.77 (s, 6H, OCH_3), 3.63 (dd, $J = 10.0$, 3.5 Hz, 1H, H-7β), 3.52 (dd, $J = 10.0$, 8.5 Hz, 1H, H-7β), 3.22 (br. s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.1, 142.4, 137.3, 128.5, 127.9, 127.8, 104.0, 99.8, 75.7, 73.4, 72.8, 55.3$; HRMS (FAB) calcd for $C_{17}H_{21}O_4$ [$M + H^+$] 289.1440, found 289.1448.

Boronic acid 8: A solution of alcohol **25** (950 mg, 3.3 mmol) in benzene (7 mL) was treated with nBuLi (1.6 M in hexanes, 4.5 mL, 7.2 mmol) at 0 °C dropwise and the resulting bright orange mixture was slowly warmed to 25 °C. After 2 h, the reaction was cooled to −78 °C and diluted with THF (15 mL). To this solution, freshly distilled B(OMe)$_3$ (1.12 mL, 9.9 mmol) was added and the resulting mixture was slowly warmed to 25 °C and stirred for 6 h. The reaction was quenched by the addition of 5 % HCl (20 mL) and the resulting mixture was extracted with EtOAc (3 × 25 mL), and the combined organic phases were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 20 → 30 % EtOAc in hexanes, gradient elution) afforded **8** (595 mg, 55 %). **8**: $R_f = 0.38$ (silica gel, 50 % EtOAc in hexanes); $[\alpha]_D^{22} = -15.1$ ($c = 0.85$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3405, 2933, 2841, 1605, 1585, 1462, 1421, 1400, 1328, 1201, 1149, 1077, 1075$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.35$–7.26 (m, 5H, ArH), 6.47 (s, 1H, ArH), 6.34 (s, 1H, ArH), 5.28 (dd, $J = 6.5$, 5.0 Hz, 1H, H-7α), 5.05 (s, 1H, BOH), 4.66 (d, $J = 12.5$ Hz, 1H, OC*H*HPh), 4.60 (d, $J = 12.5$ Hz, 1H, OCH*H*Ph), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.74 (dd, $J = 10.5$, 5.0 Hz, 1H, H-7β), 3.66 (dd, $J = 10.5$, 6.5 Hz, 1H, H-7β); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.1, 163.0, 158.5, 138.0, 129.3, 127.8, 127.7, 98.4, 97.6, 80.4, 76.7, 73.6, 73.5, 55.5, 55.3$; HRMS (FAB) calcd for $C_{17}H_{20}BO_5$ [$M + H^+$] 315.1404, found 315.1414.

Phenol 28: A solution of 4-hydroxyphenylglycine (**26**) (16.7 g, 100 mmol) in anhydrous MeOH (500 mL) at 25 °C was treated with chlorotrimethylsilane (26.6 mL, 210 mmol) dropwise. The resulting mixture was stirred at that temperature for 15 h before the solvent was removed in vacuo. The residue was dissolved in EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product **27** (17.7 g, 98 %) was taken into next step without further purification. To a solution of crude amino ester **27** (17.7 g) in dioxane/H_2O (1:1, 300 mL) at 25 °C was added K_2CO_3 (55.2 g, 400 mmol) and Boc_2O (24.0 g, 110 mmol). The resulting mixture was stirred for 4 h before it was diluted with EtOAc (600 mL). The organic layer was separated, washed with 1 % aqueous HCl (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10 → 20 % EtOAc in hexanes) to provide phenol **28** (26.2 g, 95 %). **28**: $R_f = 0.16$ (silica gel, 30 % EtOAc in hexanes); $[\alpha]_D^{22} = -109.1$ ($c = 1.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3366, 2978, 1766, 1684, 1514, 1443, 1367, 1255, 1226, 1154$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.4$ Hz, 2H, ArH), 6.80 (d, $J = 8.5$ Hz, 2H, ArH), 5.70 (d, $J = 6.8$ Hz, 1H, NH), 5.29 (d, $J = 7.1$ Hz, 1H, H-5α), 3.78 (s, 3H, OCH_3), 1.51 (s, 9H, tBuO); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.0, 156.4, 155.1, 128.4, 128.0, 115.8, 80.6, 57.0, 52.7, 28.3$; HRMS (FAB) calcd for $C_{14}H_{19}NO_5Na$ [$M + Na^+$] 304.1161, 304.1160.

Methyl ether 29: A solution of phenol **28** (28.1 g, 100 mmol) in anhydrous DMF (200 mL) was treated with K_2CO_3 (55.2 g, 400 mmol) and methyl iodide (12.5 mmol, 200 mmol). The resulting mixture was stirred at 25 °C for 6 h before it was diluted with EtOAc (800 mL). The organic layer was washed with 1 % aqueous HCl (300 mL), brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 5 → 15 % EtOAc in hexanes) to provide methyl ether **29** (27.4 g, 93 %). The product was identical as reported in literature.[30]

Iodide 9: A solution of methyl ester **29** (1.00 g, 3.4 mmol) in $CHCl_3$ (50 mL) at 25 °C was treated with CF_3COOAg (1.65 g, 7.5 mmol) and I_2 (1.04 g, 4.1 mmol) sequentially. The resulting mixture was stirred at 25 °C for 12 h before it was quenched by the addition of saturated aqueous Na_2SO_3 (20 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 20 mL) and the combined organic extracts were washed with H_2O (40 mL), brine (40 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10 → 20 % EtOAc in hexanes, gradient elution) afforded **9** (1.29 g, 90 %). **9**: $R_f = 0.22$ (silica gel, 20 % EtOAc in hexanes); $[\alpha]_D^{22} = -99.8$ ($c = 1.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3367, 2979, 1743, 1708, 1481, 1444, 1367, 1250, 1161, 1050, 1014$ cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): $\delta = 7.82$ (d, $J = 2.3$ Hz, 1H, ArH), 7.38 (dd, $J = 8.6$, 2.3 Hz, 1H, ArH), 6.89 (d, $J = 8.6$ Hz, 1H, ArH), 6.69 (d, $J = 7.9$ Hz, 1H, NH), 5.22 (d, $J = 7.9$ Hz, 1H, H-5α), 3.81 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 1.35 (s, 9H, tBuO); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta = 171.9, 158.7, 155.6, 138.9, 132.0, 129.8, 111.7, 86.1, 79.5, 57.1, 56.7, 52.7, 28.4$; HRMS (FAB) calcd for $C_{15}H_{21}INO_5$ [$M + H^+$] 422.0465, found 422.0450.

Cinnamate 32: A solution of benzaldehyde **31** (2.30 g, 11.0 mmol) in THF (25 mL) was treated with potassium hydroxide (924 mg, 16.5 mmol), followed by dropwise addition of triethyl phosphonoacetate (2.4 mL, 12 mmol) over a period of 1 h. The reaction mixture was stirred vigorously for 12 h at 25 °C and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with H_2O (25 mL), saturated aqueous NH_4Cl (25 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue was recrystalized twice from MeOH to afford cinnamate **32** (2.90 g, 95 %). **32**: $R_f = 0.53$ (silica gel, 25 % EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2969, 2910, 2859, 1714, 1634, 1604, 1511, 1454, 1285, 1262, 1174, 1012, 983, 832, 816, 748, 697, 524$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 15.5$ Hz, 1H, C*H* = CHCO$_2$Et), 7.48-7.32 (m, 7H, ArH), 6.97 (d, $J = 8.8$ Hz, 2H, ArH), 6.31 (d, $J = 16.0$ Hz, 1H, CH = C*H*CO$_2$Et), 5.08 (s, 2H, OCH_2Ph), 4.25 (q, $J = 7.1$ Hz, 2H, CH_2CH$_3$), 1.24 (t, $J = 7.0$ Hz, 3H, CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.3, 160.5, 144.2, 136.5, 129.7, 128.6, 128.1, 127.4, 115.9, 115.2, 70.0, 60.3, 14.4$; HRMS (FAB) calcd for $C_{18}H_{18}O_3Na$ [$M + Na^+$] 283.1334, found 283.1326.

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Amino acid 33: Amino acid **33** was prepared from cinnamate **32** according to Sharpless AA protocol[20] (45% yield, 87% ee).

TBS ether 34: To a solution of alcohol **33** (500 mg, 1.11 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added 2,6-lutidine (194 μL, 1.67 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (284 μL, 1.22 mmol). The reaction was stirred at 0 °C for 0.5 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (silica gel, 0 →20% EtOAc in hexanes, gradient elution) to afford TBS ether **34** (613 mg, 98%). **34**: $R_f = 0.34$ (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{22} = -31.7$ ($c = 0.87$, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 2930, 1728, 1610, 1509, 1299, 1251, 1085, 836\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.45-7.21$ (m, 12H, ArH), 6.89 (d, $J = 8.6$ Hz, 2H, ArH), 5.50 (d, $J = 9.7$ Hz, 1H, NH), 5.24 (d, $J = 2.2$ Hz, 1H, H-6β), 5.02 (s, 2H, $NHCO_2CH_2$), 4.97 (s, 2H, OCH_2Ph), 4.41 (dd, $J = 9.7$, 2.2 Hz, 1H, H-6α), 4.23 (dq, $J = 10.8$, 7.3 Hz, 1H, $CHHCH_3$), 4.14 (dq, $J = 10.8$, 7.3 Hz, 1H, $CHHCH_3$), 1.28 (t, $J = 7.3$ Hz, 3H, CH_2CH_3), 0.84 (s, 9H, *t*BuSi), −0.04 (s, 3H, CH_3Si), −0.18 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.1$, 158.2, 155.9, 136.7, 136.2, 132.6, 128.3, 128.2, 127.8, 127.8, 127.7, 127.3, 127.2, 114.1, 74.1, 69.7, 66.5, 61.3, 61.0, 25.5, 17.8, 13.9, −4.8, −5.7; HRMS (FAB) calcd for $C_{32}H_{41}NO_6SiCs$ [$M + Cs^+$] 696.1757, found 696.1782.

Phenol 35: To a solution of protected amine **34** (430 mg, 0.76 mmol) in MeOH (8 mL) was added 20% $Pd(OH)_2/C$ (25 mg) at 25 °C. Hydrogen was bubbled through the solution for 0.5 h and the resulting suspension was filtered through a pad of celite. The celite was washed with MeOH (2 × 5 mL) and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to afford phenol **35** (250 mg, 97%). **35**: $R_f = 0.23$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -17.9$ ($c = 0.98$, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3362, 2936, 1738, 1614, 1515, 1255, 1080, 837\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD): $\delta = 7.16$ (d, $J = 8.6$ Hz, 2H, ArH), 6.76 (d, $J = 8.6$ Hz, 2H, ArH), 5.00 (d, $J = 4.0$ Hz, 1H, H-6β), 4.15 (dq, $J = 10.8$, 7.0 Hz, 1H, $CHHCH_3$), 4.06 (dq, $J = 10.8$, 7.0 Hz, 1H, $CHHCH_3$), 3.47 (d, $J = 4.0$ Hz, 1H, H-6α), 1.21 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 0.89 (s, 9H, *t*BuSi), 0.01 (s, 3H, CH_3Si), −0.18 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 173.5$, 158.4, 132.8, 128.8, 116.1, 77.1, 62.9, 62.3, 26.3, 19.0, 14.4, −4.3, −5.2; HRMS (FAB) calcd for $C_{17}H_{30}NO_4Si$ [$M + H^+$] 340.1944, found 340.1948.

Chloride 10: To a solution of amine **35** (1.63 g, 4.8 mmol) in CH_2Cl_2/ether (10:1, 5 mL) at 0 °C was added sulfuryl chloride (386 μL, 4.8 mmol) dropwise. The reaction mixture was stirred at that temperature for 1 h and then it was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was diluted with EtOAc (15 mL) and the organic layer was washed with H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (silica gel, 10 →20% EtOAc in hexanes, gradient elution) to afford chloride **10** (1.44 g, 80%). **10**: $R_f = 0.24$ (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -11.0$ ($c = 1.31$, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3366, 2943, 2849, 2555, 1737, 1602, 1502, 1467, 1290, 1255, 1079\ cm^{-1}$; ^1H NMR (400 MHz, CD_3OD): $\delta = 7.29$ (d, $J = 2.1$ Hz, 1H, H-6b), 7.09 (dd, $J = 8.4$, 2.1 Hz, 1H, H-6f), 6.88 (d, $J = 8.4$ Hz, 1H, H-6e), 4.99 (d, $J = 3.8$ Hz, 1H, H-6β), 4.16 (dq, $J = 10.8$, 7.2 Hz, 1H, $CHHCH_3$), 4.08 (dq, $J = 10.8$, 7.2 Hz, 1H, $CHHCH_3$), 3.47 (d, $J = 3.8$ Hz, 1H, H-6α), 1.22 (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 0.90 (s, 9H, *t*BuSi), 0.03 (s, 3H, CH_3Si), -0.15 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 173.8$, 154.1, 134.5, 129.3, 127.1, 121.5, 117.4, 76.6, 62.8, 62.3, 26.3, 19.0, 14.4, −4.4, −5.1; HRMS (FAB) calcd for $C_{17}H_{29}ClNO_4Si$ [$M + H^+$] 374.1554, found 374.1549.

Benzyl alcohol 39: A cooled suspension of $LiAlH_4$ (1.14 g, 30 mmol) at 0 °C in THF (40 mL) was treated dropwise with a solution of ester **38** [31] (6.18 g, 20 mmol) in THF (60 mL). The resulting mixture was stirred at 0 °C for 2 h before it was quenched by the slow addition of saturated aqueous NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 × 200 mL) and the combined organic extracts were washed with H_2O (150 mL), brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10 →20% EtOAc in hexanes, gradient elution) afforded **39** (5.34 g, 95%). **39**: $R_f = 0.28$ (silica gel, 30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3307, 1614, 1578, 1472, 1402, 1349, 1284, 1198, 1067, 1026\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.40$ (s, 2H, ArH), 4.53 (s, 2H, CH_2OH), 1.90–1.50 (br.s, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 141.4$, 132.3, 130.8, 108.7, 63.9; HRMS (FAB) calcd for $C_7H_7Br_2NO$ [M^+] 280.9464, found 280.9471.

Triazene alcohol 40: To a suspension of aniline **39** (10.0 g, 35.6 mmol) in acetic acid/H_2O (1:1, 80 mL) at 0 °C were added sequentially 6 M aqueous HCl (30 mL) and $NaNO_2$ (2.95 g, 42.7 mmol in 5 mL of H_2O). The resulting mixture was stirred at that temperature for 0.5 h before it was transferred dropwise to a flask charged with KOH (60 g, 1.07 mol) and pyrrolidine (4.4 mL, 53 mmol) in H_2O (250 mL) at 0 °C. The resulting precipitate was filtered and purified by flash column chromatography (silica gel, 10 →20% EtOAc in hexanes, gradient elution) to afford **40** (9.69 g, 75%). **40**: $R_f = 0.16$ (silica gel, 20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3331, 2872, 1537, 1408, 1343, 1308, 1214, 1190, 1049\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (s, 2H, ArH), 4.59 (s, 2H, CH_2OH), 3.96 (s, 2H, NCH_2), 3.72 (s, 2H, NCH_2), 2.11 (s, 2H, NCH_2CH_2), 2.06 (s, 2H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 146.6$, 140.2, 130.2, 117.8, 63.5, 51.3, 46.7, 23.9, 23.7; HRMS (FAB) calcd for $C_{11}H_{14}Br_2N_3O$ [$M + H^+$] 361.9504, found 361.9515.

Benzaldehyde 41: A solution of alcohol **40** (3.61 g, 10 mmol) in CH_2Cl_2 (50 mL) was treated with pyridium chlorochromate (PCC, 3.24 g, 15 mmol) at 25 °C. The suspension was stirred for 2 h before it was filtered through a pad of celite. The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (silica gel, 5 →10% EtOAc in hexanes, gradient elution) to afford **41** (3.18 g, 88%). **41**: $R_f = 0.32$ (silica gel, 10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2962, 1691, 1580, 1534, 1408, 1342, 1302, 1250, 1226, 1200\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.84$ (s, 1H, CHO), 8.04 (s, 2H, ArH), 3.99 (s, 2H, NCH_2), 3.74 (s, 2H, NCH_2), 2.14–2.09 (m, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 188.9$, 152.8, 134.1, 133.6, 118.5, 51.4, 46.9, 24.0, 23.5; HRMS (FAB) calcd for $C_{11}H_{12}Br_2N_3O$ [$M + H^+$] 361.9327, found 361.9336.

Styrene 42: A suspension of methyltriphenylphosphonium bromide (6.43 g, 18.0 mmol) in THF (30 mL) at −20 °C was treated with *n*BuLi (1.6 M solution in hexanes, 10.5 mL, 16.8 mmol) dropwise over 10 min and the resulting solution was stirred for 0.5 h. To this reaction mixture was added a solution of **41** (4.33 g, 12.0 mmol) in THF (25 mL) and the resulting orange suspension was stirred at that temperature for 2 h before it was quenched by the addition of H_2O (30 mL). The mixture was extracted with EtOAc (4 × 40 mL) and the combined organic phases were washed with H_2O (2 × 40 mL), brine (2 × 40 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 4 →8% ether in hexanes, gradient elution) afforded **42** (3.96 g, 92%). **42**: $R_f = 0.39$ (silica gel, 10% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2972, 2801, 1524, 1413, 1337, 1312, 1256, 1220\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$ (s, 2H, ArH), 6.54 (dd, $J = 17.5$, 10.8 Hz, 1H, ArCH), 5.69 (d, $J = 17.5$ Hz, 1H, ArCH=C*H*H), 5.26 (d, $J = 10.8$ Hz, 1H, ArCH=CH*H*), 3.95 (s, 2H, NCH_2), 3.70 (s, 2H, NCH_2), 2.06 (s, 4H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 147.2$, 136.4, 134.1, 130.0, 117.6, 115.2, 51.6, 46.9, 23.8, 23.4; HRMS (FAB) calcd for $C_{12}H_{14}Br_2N_3$ [$M + H^+$] 357.9554, found 357.9564.

Diol 43: To a stirred suspension of AD-α (14 g, 1.4 g mmol^{-1}) in *t*BuOH/H_2O (1:1, 100 mL) was added styrene **42** (3.59 g, 10 mmol) at 25 °C. The reaction mixture was stirred at ambient temperature for 6 h before sodium sulfite (15.0 g, 1.5 g mmol^{-1}) was added. The resulting mixture was stirred for 0.5 h and then it was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 40 →60% EtOAc in hexanes, gradient elution) afforded **43** (3.73 g, 95% *ee*, 95%). Chiral HPLC: chiralcell OD-H column (0.46 × 25 cm, 30% 2-propanol/hexane, 0.5 mL min^{-1}). Retention time = 10.22 (major enantiomer). Retention time = 9.23 (minor enantiomer). **43**: $R_f = 0.16$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = +79.4$ ($c = 1.21$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3354, 2954, 2862, 2349, 1415, 1308, 1215, 1067\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (s, 2H, ArH), 4.72 (dd, $J = 8.0$, 3.5 Hz, 1H, ArCH), 3.95 (s, 2H, NCH_2), 3.72 (s, 2H, NCH_2), 3.65 (dd, $J = 11.5$, 3.5 Hz, 1H, C*H*HOH), 3.55 (dd, $J = 11.5$, 8.0 Hz, 1H, CH*H*OH), 3.49 (br.s, 1H, OH), 2.12 (d, $J = 5.5$ Hz, 2H, NCH_2CH_2), 2.06 (d, $J = 5.5$ Hz, 2H, NCH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 146.8$, 140.2, 129.9, 118.0, 73.0, 67.8, 51.5, 46.8, 23.9, 23.7; HRMS (FAB) calcd for $C_{12}H_{16}Br_2N_3O_2$ [$M + H^+$] 391.9609, found 391.9623.

TBS ether 44: To a solution of diol **43** (3.36 g, 8.6 mmol) in DMF (40 mL) at 0 °C were added sequentially TBSCl (1.43 g, 9.5 mmol) and imidazole (8.77 g, 12.9 mmol). The resulting solution was stirred at that temperature for 5 h before H_2O (60 mL) was added. The reaction mixture was extracted

with EtOAc (4 × 50 mL) and the combined organic phases were washed with H_2O (80 mL), brine (80 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 5 → 10% EtOAc in hexanes, gradient elution) afforded compound **44** (3.84 g, 88%). **44**: R_f = 0.40 (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{22} = +22.8$ ($c = 1.43$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3384, 2954, 2928, 2856, 1419, 1358, 1316, 1256, 1113\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$ (s, 2H, ArH), 4.66 – 4.64 (m, 1H, ArCH), 3.95 (s, 2H, NCH_2), 3.74 – 3.70 (m, 3H, NCH_2 and C*H*HOSi), 3.49 (dd, $J = 10.0$, 8.5 Hz, 1H, CH*H*OSi), 3.06 (br. s, 1H, OH), 2.09 (s, 2H, NCH_2CH_2), 2.06 (s, 2H, NCH_2CH_2), 0.91 (s, 9H, *t*BuSi), 0.06 (s, 6H, CH_3Si); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 147.3, 139.4, 130.1, 117.6, 72.8, 68.4, 51.2, 46.6, 25.8, 24.0, 23.6, 18.3, -5.4$; HRMS (FAB) calcd for $C_{18}H_{30}Br_2N_3O_2Si$ $[M + H^+]$ 506.0475, found 506.0496.

Azide 45: To a solution of alcohol **44** (610 mg, 1.2 mmol) in THF (1.0 mL) at 0 °C were added sequentially triphenylphosphane (790 mg, 3.0 mmol), diethyl azodicarboxylate (DEAD, 470 μL, 3.0 mmol), and diphenylphosphoryl azide (DPPA, 650 μL, 3.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and then it was concentrated in vacuo. Flash column chromatography of the residue (silica gel, 5 → 10% ether in hexanes, gradient elution) afforded azide **45** (0.50 g, 79%). **45**: R_f = 0.39 (silica gel, 10% EtOAc in hexanes); $[\alpha]_D^{22} = -43.8$ ($c = 1.30$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2953, 2929, 2857, 2100, 1418, 1317, 1257, 1112\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$ (s, 2H, ArH), 4.50 (dd, $J = 7.6$, 4.4 Hz, 1H, ArCH), 3.96 (br. s, 2H, NCH_2), 3.79 (dd, $J = 10.2$, 4.4 Hz, 1H, C*H*HOSi), 3.74-3.69 (m, 3H, NCH_2 and CH*H*OSi), 2.06 (br. s, 4H, NCH_2CH_2), 0.90 (s, 9H, *t*BuSi), 0.07 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 147.9, 135.7, 131.0, 117.8, 67.8, 65.5, 51.2, 46.6, 25.8, 24.0, 23.6, 18.2, -5.5$; HRMS (FAB) calcd for $C_{18}H_{29}Br_2N_6OSi$ $[M + H^+]$ 531.0540, found 531.0562.

Amine 46: To a solution of azide **45** (1.17 g, 2.2 mmol) in THF was added triphenylphosphane (1.73 g, 6.6 mmol) and H_2O (400 μL, 22 mmol) at 25 °C. The resulting solution was heated to 60 °C for 3 h before it was cooled to 25 °C. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, 30 → 45% EtOAc in hexanes, gradient elution) to afford amine **46** (870 mg, 78%). **46**: R_f = 0.30 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -22.0$ ($c = 1.53$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2952, 2928, 2856, 1537, 1466, 1418, 1337, 1316, 1256, 1107\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.55$ (s, 2H, ArH), 3.98 (dd, $J = 7.5$, 4.0 Hz, 1H, ArCH), 3.94 (br. s, 2H, NCH_2), 3.71 (br. s, 2H, NCH_2), 3.66 (dd, $J = 9.5$, 4.0 Hz, 1H, C*H*HOSi), 3.46 (dd, $J = 9.5$, 7.5 Hz, 1H, CH*H*OSi), 2.08 (br. s, 2H, NCH_2CH_2), 2.04 (br. s, 2H, NCH_2CH_2), 0.88 (s, 9H, *t*BuSi), 0.02 (s, 6H, CH_3Si); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 147.0, 141.8, 130.8, 117.5, 68.9, 56.3, 51.1, 46.5, 25.8, 24.0, 23.6, 18.2, -5.4$; HRMS (FAB) calcd for $C_{18}H_{31}Br_2N_4OSi$ $[M + H^+]$ 505.0634, found 505.0649.

Boc-protected amine 47: To a solution of amine **46** (710 mg, 1.4 mmol) in CH_2Cl_2 (10 mL) at 25 °C were added Et_3N (585 μL, 4.2 mmol) and Boc_2O (336 mg, 1.5 mmol). The resulting solution was stirred for 4 h before it was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 15 → 25% EtOAc in hexanes, gradient elution) to afford Boc derivative **47** (810 mg, 95%). **47**: R_f = 0.50 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -40.2$ ($c = 1.70$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3449, 3332, 2953, 2930, 2858, 1715, 1490, 1418, 1365, 1336, 1256, 1188, 1116\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (s, 2H, ArH), 5.26 (br. s, 1H, NH), 4.61 (br. s, 1H, CHN), 3.94 (br. s, 2H, NCH_2), 3.84 (dd, $J = 10.0$, 4.0 Hz, 1H, C*H*HOSi), 3.72 – 3.62 (m, 3H, NCH_2 and CH*H*OSi), 2.09 (br. s, 2H, NCH_2CH_2), 2.07 (br. s, 2H, NCH_2CH_2), 1.42 (s, 9H, *t*BuO), 0.85 (s, 9H, *t*BuSi), −0.03 (s, 3H, CH_3Si), −0.05 (s, 3H, CH_3Si); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 155.1, 147.0, 146.7, 130.9, 117.5, 85.1, 66.0, 51.1, 46.5, 28.3, 27.4, 25.8, 24.0, 23.6, 18.2, -5.6, -5.7$; HRMS (FAB) calcd for $C_{23}H_{39}Br_2N_4O_3Si$ $[M + H^+]$ 605.1158, found 605.1135.

Alcohol 48: To a solution of compound **47** (665 mg, 1.1 mmol) in THF (12 mL) at 0 °C was added nBu$_4$NF (1.0 M solution in THF, 1.3 mL, 1.3 mmol). The resulting solution was stirred at that temperature for 2 h before it was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (4 × 15 mL), and the combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 30 → 40% EtOAc in hexanes, gradient elution) to afford alcohol **48** (500 mg, 93%). **48**: R_f = 0.36 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -48.9$ ($c = 1.28$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3419, 2976, 2875, 1695, 1536, 1502, 1417, 1365, 1314, 1256, 1165, 1056\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.46$ (s, 2H, ArH), 5.39 (br. s, 1H, NH), 4.59 (br. s, 1H, CHN), 3.93 (br. s, 2H, NCH_2), 3.75 – 3.69 (m, 4H, NCH_2 and CH_2O), 2.74 (br. s, 1H, OH), 2.08 (br. s, 2H, NCH_2CH_2), 2.04 (br. s, 2H, NCH_2CH_2), 1.42 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 155.7, 147.2, 138.9, 130.6, 117.9, 80.1, 65.8, 55.3, 51.2, 46.6, 28.3, 23.9, 23.6$; HRMS (FAB) calcd for $C_{17}H_{24}Br_2N_4O_3Cs$ $[M + Cs^+]$ 622.9269, found 622.9294.

Acid 12: To a solution of alcohol **48** (246 mg, 0.50 mmol) in acetone (2.5 mL) at 0 °C was added 5% aqueous $NaHCO_3$ (2.5 mL). The resulting suspension was stirred vigorously before the addition of KBr (1.2 mg, 0.05 mmol) and TEMPO (78 mg, 0.50 mmol). Sodium hypochlorite (5% aqueous solution, 2.0 mL) was added dropwise over 0.5 h and the resulting mixture was stirred at 0 °C for 1 h before the addition of H_2O (15 mL) and EtOAc (15 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 5 → 10% MeOH in $CHCl_3$, gradient elution) afforded acid **12** (386 mg, 75%). **12**: R_f = 0.18 (silica gel, 10% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -97.4$ ($c = 0.98$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3344, 2976, 2872, 1711, 1415, 1367, 1313, 1224, 1162, 1052, 1020\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.53$ (s, 2H, ArH), 4.89 (br. s, 1H, ArCH), 3.81 (br. s, 2H, NCH_2), 3.54 (br. s, 2H, NCH_2), 1.99 (br. s, 2H, NCH_2CH_2), 1.95 (br. s, 2H, NCH_2CH_2), 1.33 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 157.2, 148.7, 139.7, 132.2, 118.7, 112.0, 80.8, 52.3, 47.9, 28.7, 28.6, 24.9, 24.6$; HRMS (FAB) calcd for $C_{17}H_{22}Br_2N_4O_4Cs$ $[M + Cs^+]$ 636.9062, found 636.9087.

Amine 13: To a suspension of compound **50** (4.17 g, 8.25 mmol) in MeOH (120 mL) at 25 °C was added 20% $Pd(OH)_2$/C (100 mg). Hydrogen was bubbled through the reaction mixture for 1 h. The resulting mixture was filtered through a pad of celite and the celite was washed thoroughly with MeOH (2 × 30 mL). The combined filtrate was concentrated in vacuo to give crude amine **13** (3.06 g, 99%). **13**: R_f = 0.45 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -7.50$ ($c = 0.30$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3296, 2862, 1738, 1650, 1610, 1538, 1513, 1247, 1176, 1032\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 8.0$ Hz, 1H, NH), 7.13 – 7.10 (m, 4H, ArH), 6.81 (d, $J = 8.0$ Hz, 4H, ArH), 6.11 (d, $J = 8.0$ Hz, 1H, $CHAr_2$), 3.81 (d, $J = 2.5$ Hz, 1H, C*H*COOMe), 3.75 (s, 6H, OCH_3), 3.67 (s, 3H, OCH_3), 2.71 (dd, $J = 15.0$, 2.5 Hz, 1H, C*H*HCHCOOMe), 2.55 (dd, $J = 15.0$, 8.0 Hz, 1H, CH*H*CHCOOMe); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.4, 169.1, 158.6, 134.0, 128.3, 113.9, 55.6, 55.2, 52.4, 51.3, 39.3$; HRMS (FAB) calcd for $C_{20}H_{24}N_2O_5$ $[M + H^+]$ 373.1763, found 373.1770.

Ester 50: A solution of carboxylic acid **49** (24.6 g, 50 mmol) in anhydrous DMF (200 mL) at 25 °C was treated with K_2CO_3 (13.8 g, 100 mmol) and methyl iodide (6.23 mL, 100 mmol). The resulting mixture was stirred at that temperature for 12 h before it was diluted with EtOAc (800 mL). The mixture was washed with 1% aqueous HCl (400 mL), brine (400 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20 → 40% EtOAc in hexanes) to provide ester **50** (17.7 g, 70%). **50**: R_f = 0.23 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = +19.3$ ($c = 1.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3301, 1742, 1697, 1643, 1538, 1522, 1454, 1247, 1176, 1062\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.33 – 7.30$ (m, 5H, ArH), 7.08 – 7.00 (m, 4H, ArH), 6.83 – 6.79 (m, 4H, ArH), 6.19 (d, $J = 7.0$ Hz, 1H, C*H*NHCO), 6.06 (m, 2H, NH), 5.08 (s, 2H, OCH_2Ph), 4.57 – 4.55 (m, 1H, H-3α), 3.76 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.86 (dd, $J = 19.5$, 9.0 Hz, 1H, H-3β), 2.76 (dd, $J = 19.5$, 9.0 Hz, 1H, H-3β); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.7, 168.7, 158.8, 156.1, 136.2, 133.4, 128.5, 128.4, 128.3, 127.8, 66.8, 56.0, 55.2, 52.7, 50.8, 27.8$; HRMS (FAB) calcd for $C_{28}H_{30}N_2O_7Na$ $[M + Na^+]$ 529.1951, found 529.1941.

Diol 51: To a solution of cinnamate **32** (5.0 g, 28.3 mmol) in *t*BuOH/H_2O (1:1, 180 mL) at 25 °C were added AD-β (39.6 g, 1.4 g mmol^{-1}) and methanesulfonamide (2.69 g, 28.3 mmol). The reaction mixture was stirred for 12 h before sodium sulfite (42.5 g, 1.5 g mmol^{-1}) was added. The resulting mixture was stirred for 1 h and then it was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to give diol **51** (7.07 g, 79%, 92% *ee*). R_f = 0.52 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -31.3$ ($c = 1.15$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3318, 1870, 1715, 1616, 1515, 1383, 1301, 1249, 1177$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.41$ (d, $J = 7.5$ Hz, 2H, ArH), 7.39 – 7.36

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(m, 2H, ArH), 7.34–7.30 (m, 3H, ArH), 6.96 (d, $J = 8.5$ Hz, 2H, ArH), 5.05 (s, 2H, CH_2Ph), 4.92 (br.s, 1H, C*H*ArOH), 4.30 (br.s, 1H, C*H*COOEt), 4.23 (q, $J = 7.5$ Hz, 2H, OCH_2CH_3), 3.17 (br.s, 1H, OH), 2.77 (br.s, 1H, OH), 1.24 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 172.7, 158.5, 136.8, 132.3, 128.5, 127.9, 127.6, 127.4, 114.7, 74.6, 74.2, 69.9, 63.1, 14.1; HRMS (FAB) calcd for $C_{18}H_{20}O_5Na$ $[M + Na^+]$ 339.1208, found 339.1204.

Nosylate 52: To a solution of diol **51** (18.0 g, 57.0 mmol) in CH_2Cl_2 (285 mL) at 0 °C were added 4-nitrobenzene sulfonyl chloride (14.0 g, 56.9 mmol) and triethylamine (15.9 mL, 113.9 mmol). The reaction mixture was stirred for 5 h before it was quenched by the addition of saturated NH_4Cl (50 mL). The organic layer was washed with 1N HCl (100 mL), H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the resulting residue (silica gel, 20 → 30% EtOAc in hexanes, gradient elution) provided compound **52** (1.08 g, 68%). **52**: $R_f =$ 0.25 (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22} = +43.0$ ($c = 1.55$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3546$, 1761, 1609, 1531, 1511, 1374, 1349, 1187, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 9.0$ Hz, 2H, ArH), 7.83 (d, $J = 9.0$ Hz, 2H, ArH), 7.43–7.34 (m, 4H, ArH), 7.32 (t, $J = 7.0$ Hz, 1H, ArH), 7.12 (d, $J = 9.0$ Hz, 2H, ArH), 6.79 (d, $J = 9.0$ Hz, 2H, ArH), 5.13 (s, 1H, C*H*COOEt), 4.98 (s, 2H, CH_2Ph), 4.94 (d, $J = 4.0$ Hz, 1H, C*H*OH), 4.14 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 2.63 (d, $J = 4.0$ Hz, 1H, OH), 1.16 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.4$, 158.9, 150.4, 141.4, 136.4, 129.5, 129.1, 128.6, 128.1, 127.5, 127.4, 124.0, 114.7, 82.4, 73.1, 69.9, 62.5, 13.8; HRMS (FAB) calcd $C_{24}H_{23}NO_9SCs$ $[M + Cs^+]$ 634.0148, found 634.1035.

Azide 53: To a solution of nosylate **52** (14.0 g, 27.9 mmol) in DMF (110 mL) at 25 °C was added sodium azide (2.73 g, 41.9 mmol). The resulting mixture was then heated to 55 °C and stirred for 12 h. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with H_2O (250 mL), brine (250 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 5 → 15% EtOAc in hexanes, gradient elution) to give azide **53** (8.56 g, 90%). **53**: $R_f = 0.32$ (silica gel, 20% EtOAc in hexanes); $[\alpha]_D^{22} = +3.09$ ($c = 1.26$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3478$, 2111, 1736, 1610, 1512, 1244, 1174, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.42–7.37$ (m, 5H, ArH), 7.31 (d, $J = 9.0$ Hz, 2H, ArH), 6.97 (d, $J = 9.0$ Hz, 2H, ArH), 5.06 (s, 2H, CH_2Ph), 4.96 (d, $J =$ 7.0 Hz, 1H, C*H*OH), 4.24 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 4.08 (d, $J = 7.0$ Hz, 1H, C*H*COOEt), 2.78 (br.s, 1H, OH), 1.27 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.0$, 159.9, 137.0, 132.0, 128.6, 128.0, 127.9, 127.4, 114.9, 73.7, 70.0, 66.8, 62.2, 14.1; HRMS (FAB) calcd for $C_{18}H_{19}N_3O_4Na$ $[M + Na^+]$ 364.1273, found 364.1266.

Amine 14: To a solution of azide **53** (6.0 g, 17.6 mmol) in MeOH (88 mL) at 25 °C was added tin(II) chloride dihydrate (7.92 g, 35.2 mmol). The resulting mixture was stirred for 2 h before it was concentrated. The residue was taken up in EtOAc (50 mL) and washed with 3N aqueous NaOH (3 × 50 mL), H_2O (50 mL), brine (50 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (silica gel, 1 → 3% MeOH in $CHCl_3$) to give amine **14** (5.91 g, 90%). **14**: $R_f = 0.42$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -2.0$ ($c = 1.14$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3367$, 3048, 1731, 1610, 1592, 1511, 1454, 1241, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41–$ 7.35 (m, 4H, ArH), 7.31 (t, $J = 7.0$ Hz, 1H, ArH), 7.20 (d, $J = 9.0$ Hz, 2H, ArH), 6.92 (d, $J = 9.0$ Hz, 2H, ArH), 5.03 (s, 2H, CH_2Ph), 4.88 (d, $J =$ 5.5 Hz, 1H, H-2β), 4.14–4.08 (m, 2H, OCH_2CH_3), 3.74 (d, $J = 5.0$ Hz, 1H, C*H*COOEt), 2.30 (br.s, 1H, OH), 1.20 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.1$, 158.5, 136.8, 132.1, 128.5, 127.9, 127.6, 127.4, 114.7, 73.9, 69.9, 61.1, 59.9, 14.1; HRMS (FAB) calcd for $C_{18}H_{21}NO_4Na$ $[M + Na^+]$ 316.1549, found 316.1559.

Urethane 54: To a solution of hydroxy amine **14** (2.80 g, 8.8 mmol) in CH_2Cl_2 (90 mL) at −78 °C was added pyridine (1.43 mL, 17.7 mmol) and phosgene (1.93M in toluene, 4.6 mL, 8.8 mmol). The reaction mixture was stirred at that temperature for 2 h and then quenched by the slow addition of H_2O (40 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 30 → 50% EtOAc in hexanes, gradient elution) to give **54** (2.80 g, 93%). **54**: $R_f = 0.18$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -60.1$ ($c =$ 0.83, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3299$, 1773, 1751, 1731, 1515, 1255, 1204, 1022 cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): $\delta = 7.45$ (d, $J = 7.0$ Hz, 2H, ArH), 7.37 (t, $J = 7.2$ Hz, 2H, ArH), 7.31 (d, $J = 7.0$ Hz, 1H, ArH), 7.28 (d, $J = 9.0$ Hz, 2H, ArH), 7.02 (d, $J = 9.0$ Hz, 2H, ArH), 5.87 (d, $J = 9.0$ Hz, 1H, H-2β), 5.14 (s, 2H, CH_2Ph), 4.71 (d, $J = 9.0$ Hz, 1H, C*H*COOEt), 3.73-3.67 (m, 1H, $OCHHCH_3$), 3.58-3.51 (m, 1H, $OCHHCH_3$), 0.76 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta = 169.8$, 159.9, 158.7, 137.9, 129.0, 128.4, 128.3, 128.0, 128.0, 115.1, 79.0, 70.1, 61.3, 60.3, 13.6; HRMS (FAB) calcd for $C_{19}H_{19}NO_5Cs$ $[M + Cs^+]$ 474.0318, found 474.0311.

Methyl ester 56: To a solution of compound **54** (4.0 g, 11.7 mmol) in EtOH (13.8 mL) at 25 °C was added potassium hydroxide (689 mg, 12.2 mmol). The resulting mixture was heated to reflux for 1 h before it was cooled to 25 °C. The reaction mixture was acidified with 10% HCl (5 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude carboxylic acid **55** was dissolved in DMF (39 mL) at 25 °C. To this solution were added methyl iodide (1.1 mL, 17.6 mmol) and potassium carbonate (1.62 g, 11.7 mmol). The resulting mixture was stirred for 12 h before it was diluted with H_2O (40 mL). The reaction mixture was extracted with EtOAc (3 × 60 mL) and the combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 20 → 40% EtOAc in hexanes, gradient elution) of the residue gave pure methyl ester **56** (3.3 g, 87% overall yield for two steps). **56**: $R_f = 0.30$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = +40.6$ ($c = 0.60$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3285$, 1764, 1611, 1513, 1382, 1224, 1007 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.45-$ 7.35 (m, 5H, ArH), 7.33 (d, $J = 9.0$ Hz, 2H, ArH), 7.00 (d, $J = 9.0$ Hz, 2H, ArH), 5.79 (br.s, 1H, NH), 5.59 (d, $J = 5.0$ Hz, 1H, H-2β), 5.07 (s, 2H, CH_2Ph), 4.27 (d, $J = 5.0$ Hz, 1H, C*H*COOMe), 3.85 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.0$, 159.4, 136.5, 130.1, 128.6, 128.0, 127.4, 127.3, 127.0, 115.2, 79.3, 70.0, 61.2, 53.1; HRMS (FAB) calcd for $C_{18}H_{17}NO_5Na$ $[M + Na^+]$ 350.1004, found 350.1012.

***N*-Boc carbamate 57**: To a solution of ester **56** (3.0 g, 9.2 mmol) in THF (18.4 mL) at 25 °C was added di-*tert*-butyl dicarbonate (2.2 g, 10.1 mmol) and 4-dimethylaminopyridine (169 mg, 1.38 mmol). The resulting mixture was stirred at 25 °C for 2 h. The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (silica gel, 10 → 20% EtOAc in hexanes, gradient elution) to give compound **57** (2.1 g, 53%). **57**: $R_f = 0.30$ (silica gel, 25% EtOAc in hexanes); $[\alpha]_D^{22} = +58.0$ ($c =$ 1.66, $CHCl_3$) IR (thin film): $\tilde{\nu}_{max} = 1831$, 1739, 1727, 1612, 1514, 1324, 1249, 1077 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.42–7.36$ (m, 4H, ArH), 7.33 (d, $J = 7.0$ Hz, 1H, ArH), 7.28 (d, $J = 9.0$ Hz, 2H, ArH), 7.00 (d, $J = 9.0$ Hz, 2H, ArH), 5.30 (d, $J = 4.5$ Hz, 1H, H-2β), 5.06 (s, 2H, CH_2Ph), 4.62 (d, $J =$ 4.5 Hz, 1H, C*H*COOMe), 3.85 (s, 3H, $COOCH_3$), 1.49 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.0$, 159.6, 150.7, 148.4, 136.4, 129.0, 128.6, 128.1, 127.4, 126.7, 115.4, 84.8, 75.9, 70.1, 63.7, 53.2, 27.8; HRMS (FAB) calcd for $C_{23}H_{25}NO_7Na$ $[M + Na^+]$ 450.1529, found 450.1537.

Alcohol 58: To a solution of carbamate **57** (2.0 g, 4.7 mmol) in MeOH (70 mL) at 0 °C was added cesium carbonate (611 mg, 1.88 mmol). The reaction mixture was stirred at that temperature for 2 h and then concentrated under reduced pressure. The residue was taken up in EtOAc (50 mL) and washed with H_2O (30 mL), brine (30 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and flash column chromatography (silica gel, 20 → 40% EtOAc in hexanes) provided alcohol **58** (1.5 g, 80%). **58**: $R_f = 0.43$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -11.0$ ($c = 0.30$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3420$, 2941, 1717, 1616, 1511, 1367, 1243, 1172, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.41–7.31$ (m, 5H, ArH), 7.31 (d, $J = 9.0$ Hz, 2H, ArH), 6.94 (d, $J = 9.0$ Hz, 2H, ArH), 5.29 (d, $J = 7.0$ Hz, 1H, H-2β), 5.15 (br.s, 1H, NH), 5.04 (s, 2H, CH_2Ph), 4.48 (d, $J = 7.7$ Hz, 1H, C*H*COOMe), 3.73 (s, 3H, $COOCH_3$), 1.34 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.1$, 170.5, 158.6, 136.8, 132.0, 128.6, 127.9, 127.4, 127.2, 127.1, 73.6, 69.9, 59.3, 52.5, 29.6, 28.1; HRMS (FAB) calcd for $C_{22}H_{27}NO_6Na$ $[M + Na^+]$ 424.1736, found 424.1746.

Dipeptide 59: To a solution of amine **14** (615 mg, 2.1 mmol) and acid **15** (523 mg, 2.1 mmol) in THF (22 mL) at 0 °C were added HOBt (956 mg, 7.0 mmol) and EDC (1.22 g, 6.4 mmol). The reaction mixture was stirred at that temperature for 12 h before it was diluted with EtOAc (100 mL). The resulting mixture was washed with 5% aqueous HCl (3 × 30 mL), 5% aqueous $NaHCO_3$ (40 mL), H_2O (40 mL), brine (40 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 provide dipeptide **59** (1.08 g, 93%). **59**: $R_f = 0.14$ (silica

gel, 30% EtOAc in hexanes); $[\alpha]_D^{22} = +17.4$ ($c = 0.87$, $CHCl_3$); IR(thin film): $\tilde{\nu}_{max} = 3410, 2958, 1737, 1693, 1681, 1510, 1454, 1243, 1152, 1025\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 320 K): $\delta = 7.39$-7.29 (m, 5H, ArH), 7.12 (d, $J = 7.0$ Hz, 2H, ArH), 6.90 (d, $J = 8.5$ Hz, 2H, ArH), 5.26 (s, 1H), 5.14 (br.s, 1H), 5.02 (s, 2H, CH_2Ph), 4.87 (br.s, 1H, C*H*COOEt), 4.17 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 2.57 (s, 3H, NCH_3), 1.64 (br.s, 2H, $NCHCH_2$), 1.42 (s, 10H, *t*BuO, $CH(CH_3)_2$), 1.22 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 0.92 (d, $J = 7.0$ Hz, 3H, $CH(CH_3)_2$), 0.88 (d, $J = 7.0$ Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.6, 169.3, 158.5, 158.4, 156.4, 155.0, 136.8, 136.6, 131.1, 128.5, 128.4, 127.9, 127.3, 127.3, 114.7, 114.5, 80.9, 80.5, 74.6, 74.5, 69.8, 61.9, 59.0, 56.9, 56.1, 36.3, 29.8, 29.0, 28.2, 24.7, 23.2, 23.1, 21.6, 21.2, 14.0$; HRMS (FAB) calcd for $C_{30}H_{42}N_2O_7Cs$ $[M + Cs^+]$ 675.2046, found 675.2022.

Carboxylic acid 60: To a solution of ester **59** (390 mg, 0.72 mmol) in THF/H_2O (1:1, 7 mL) at 0 °C was added lithium hydroxide monohydrate (62 mg, 1.4 mmol) and the resulting mixture was stirred at that temperature for 1 h. The reaction mixture was carefully acidified with 5% aqueous HCl at 0 °C to pH 4 and then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with H_2O (25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo to give carboxylic acid **60** (370 mg, 99%). **60**: $R_f = 0.13$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +23.3$ ($c = 0.75$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3410, 1731, 1681, 1513, 1454, 1392, 1368, 1322, 1245, 1154, 1064, 1025, 909, 734\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 315 K): $\delta = 7.37$–7.32 (m, 5H, ArH), 7.20 (d, $J = 8.5$ Hz, 2H, ArH), 6.89 (d, $J = 8.1$ Hz, 2H, ArH), 5.08 (br.s, 1H, H-2β), 5.00 (s, 2H, CH_2Ph), 4.92-4.88 (m, 1H, C*H*COOH), 4.66 (br.s, 1H, COC*H*N) 2.51 (br.s, 3H, NCH_3), 1.56–1.52 (m, 2H, $NCHCH_2$), 1.45–1.40 (m, 10H, *t*BuO, $CH(CH_3)_2$), 0.91 (d, $J = 6.5$ Hz, 3H, $CH(CH_3)_2$), 0.87 (d, $J = 5.8$ Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.7, 158.5, 155.7, 136.7, 128.5, 127.4, 127.3, 114.5, 87.9, 81.3, 74.4, 74.2, 69.8, 58.6, 58.0, 57.7, 36.3, 29.5, 28.3, 24.5, 23.3, 23.0, 21.8, 21.1$; HRMS (FAB) calcd for $C_{28}H_{38}N_2O_7$ $[M + H^+]$ 515.2757, found 515.2770.

Tripeptide 61: To a solution of carboxylic acid **60** (2.66 g, 7.19 mmol) and amine **13** (3.69 g, 7.19 mmol) in THF (100 mL) at 0 °C was added HOAt (3.22 g, 23.7 mmol). The resulting mixture was stirred for 5 min before EDC (4.12 g, 21.6 mmol) was added. The reaction was allowed to warm to 25 °C and stirred for 12 h before it was diluted with EtOAc (400 mL). The reaction mixture was washed with aqueous 5% HCl (3 × 100 mL), 5% aqueous $NaHCO_3$(200 mL), H_2O (200 mL), brine (200 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. Flash column chromatography of the residue (silica gel, 50 → 70% EtOAc in hexanes, gradient elution) provided tripeptide **61** (4.50 g, 82%). $R_f = 0.28$ (silica gel, 70% EtOAc in hexanes); $[\alpha]_D^{22} = +35.4$ ($c = 0.94$, $CHCl_3$); IR(thin film): $\tilde{\nu}_{max} = 3312, 1742, 1650, 1610, 1511, 1453, 1387, 1247, 1175, 1148, 1033, 830, 732\ cm^{-1}$; ^1H NMR (500 MHz, CD_3SOCD_3, 315 K): $\delta = 8.61$ (d, $J = 7.0$ Hz, 1H, NH), 8.18 (d, $J = 6.5$ Hz, 1H, NH), 7.38–7.28 (m, 5H, ArH), 7.17 (d, $J = 7.0$ Hz, 2H, ArH), 7.11–7.09 (m, 5H, ArH), 6.85–6.82 (m, 5H, ArH), 5.96 (d, $J = 7.5$ Hz, 1H, $CHAr_2$), 5.32 (br.s, 1H, C*H*OH), 5.02 (s, 2H, CH_2Ph), 4.71 (d, $J = 6.5$ Hz, 1H, C*H*CONH), 4.66 (q, $J = 6.2$ Hz, 1H, C*H*CONH), 4.49 (t, $J = 7.0$ Hz, 1H, C*H*CONH), 3.68 (s, 6H, $ArOCH_3$), 3.49 (s, 3H, $COOCH_3$), 2.68 (dd, $J = 18.5$, 5.5 Hz, 1H, CHC*H*H), 2.60 (dd, $J = 18.5$, 5.5 Hz, 1H, CHCH*H*), 2.34 (br.s, 3H, NCH_3), 1.39 (br.s, 12H, *t*BuO, $CH(CH_3)_2$, CH_2CH), 0.83 (m, 6H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, CD_3SOCD_3): $\delta = 171.3, 170.9, 168.6, 158.8, 158.6, 136.9, 133.4, 128.6, 128.5, 128.4, 128.3, 127.9, 127.4, 114.8, 114.7, 114.6, 114.0, 80.9, 80.1, 76.8, 69.9, 57.8, 55.9, 55.2, 52.8, 49.5, 37.4, 36.1, 28.3, 24.5, 23.3, 21.6$; HRMS (FAB) calcd for $C_{48}H_{60}N_4O_{11}Cs$ $[M + Cs^+]$ 1001.3313, found 1001.3360.

TBS ether 62: To a solution of alcohol **61** (500 mg, 0.58 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added 2,6-lutidine (143 µL, 1.3 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (171 µL, 0.75 mmol). The reaction mixture was stirred at that temperature for 2 h and then it was quenched by the addition of 5% aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with saturated aqueous $CuSO_4$ (2 × 10 mL), brine (15 mL), dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue was subjected to flash column chromatography (silica gel, 10 → 30% EtOAc in hexanes, gradient elution) to yield compound **62** (462 mg, 81%). **62**: $R_f = 0.54$ (silica gel, 60% EtOAc in hexanes); $[\alpha]_D^{22} = +12.9$ ($c = 0.96$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2936, 1741, 1697, 1611, 1511, 1247, 1175, 1086, 1029\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 315 K): $\delta = 7.39$–7.22 (m, 5H, ArH), 7.12–7.07 (m, 6H, ArH), 6.89 (d, $J = 8.5$ Hz, 2H, ArH), 6.84–6.81 (m, 4H, ArH), 6.04 (br.s, 1H, $CHAr_2$), 5.10 (d, $J = 4.0$ Hz, 1H, CHOTBS), 5.01 (s, 2H, CH_2Ph), 4.82–4.78 (m, 1H, C*H*CONH), 4.65–4.62 (m, 2H, C*H*CONH), 3.77 (s, 6H, OCH_3), 3,59 (s, 3H, $COOCH_3$), 2.74 (br.d, 1H, $CHCH_2$), 2.65 (dd, $J = 18.0$, 4.0 Hz, 1H, $CHCH_2$), 2.52 (br.s, 3H, NCH_3), 1.43 (br.s, 12H, $OC(CH_3)_3$, $CH(CH_3)_2$, $CHCH_2$), 0.89 (m, 15H, *t*BuSi, $CH(CH_3)_2$), 0.02 (s, 3H, $SiCH_3$), −0.01 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.2, 171.0, 169.0, 168.8, 168.7, 158.8, 158.5, 136.9, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5, 114.7, 114.3, 114.0, 80.7, 80.6, 73.8, 69.9, 57.2, 55.9, 55.3, 55.2, 52.6, 48.9, 48.8, 37.4, 37.2, 36.3, 36.1, 29.6, 28.3, 28.2, 25.8, 25.7, 24.6, 24.3, 23.2, 23.1, 21.6, 21.7, 21.2, 18.1, 16.1, 8.2, 7.1, 1.0, −4.8, −5.1$; HRMS (FAB) calcd for $C_{54}H_{74}N_4O_{11}SiCs$ $[M + Cs^+]$ 1115.4178, found 1115.4116.

Phenol 63: To a solution of compound **62** (517 mg, 0.53 mmol) in MeOH (6 mL) was added 20% $Pd(OH)_2$/C (20 mg). Hydrogen was bubbled through the reaction mixture for 1 h. The solution was filtered through a pad of celite and the celite was washed thoroughly with MeOH (2 × 5 mL). The filtrate was concentrated in vacuo to give phenol **63** (480 mg, 99%). **63**: $R_f = 0.45$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = +15.7$ ($c = 0.73$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3328, 2955, 1743, 1661, 1612, 1512, 1465, 1249, 1175, 1086\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 315 K): $\delta = 7.16$ (d, $J = 9.0$ Hz, 2H, ArH), 7.14–7.08 (m, 4H, ArH), 6.85–6.81 (m, 4H, ArH), 6.71 (d, $J = 9.0$ Hz, 2H, ArH), 6.07 (d, $J = 10.6$ Hz, 1H, $CHAr_2$), 5.14 (d, $J = 4.5$ Hz, 1H, CHOTBS), 4.81–4.79 (m, 1H, C*H*CONH), 4.63–4.61 (m, 2H, C*H*CONH), 3.77 (s, 6H, OCH_3), 3.61 (s, 3H, $COOCH_3$), 2.85 (dd, $J = 18.0$, 6.5 Hz, 1H, CHC*H*H), 2.65 (dd, $J = 18.0$, 4.5 Hz, 1H, CHCH*H*), 2.56 (s, 3H, NCH_3), 1.50 (m, 3H, $CHCH_2$, $CH(CH_3)_2$), 1.40 (br.s, 9H, *t*BuO), 0.89–0.83 (m, 15H, *t*BuSi, $CH(CH_3)_2$), 0.01 (s, 3H, $SiCH_3$), −0.13 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.1, 169.1, 168.8, 158.9, 158.8, 156.3, 133.6, 128.8, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 115.5, 115.4, 115.2, 114.0, 113.9, 74.0, 59.9, 57.0, 55.9, 55.2, 52.6, 49.0, 40.3, 37.0, 36.2, 36.0, 29.7, 28.3, 25.8, 25.7, 24.6, 24.3, 23.3, 21.2, 18.1, 1.0, −4.8, −5.2$; HRMS (FAB) calcd for $C_{47}H_{68}N_4O_{11}SiCs$ $[M + Cs^+]$ 1025.3708, found 1025.3770.

Chloride 64: To a solution of phenol **63** (470 mg, 0.53 mmol) in ether (5 mL) at 0 °C under darkness was added thionyl chloride (50 µL, 0.64 mmol). The reaction mixture was stirred for 1 h and then it was quenched by the addition of 5% aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 10 → 30% EtOAc in hexanes, gradient elution) provided chloride **64** (360 mg, 75%). **64**: $R_f = 0.5$ (silica gel, 60% EtOAc in hexanes); $[\alpha]_D^{22} = +12.5$ ($c = 0.68$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3319, 1737, 1666, 1652, 1510, 1249, 1176\ cm^{-1}$; ^1H NMR (500 MHz, CD_3SOCD_3, 320 K): $\delta = 9.80$ (s, 1H, ArOH), 8.61 (d, $J = 7.3$ Hz, 1H, NH), 8.26 (d, $J = 5.0$ Hz, 1H, NH), 7.20 (s, 1H, ArH), 7.10 (d, $J = 7.1$ Hz, 4H, ArH), 6.99 (d, $J = 6.9$ Hz, 1H, ArH), 6.84–6.80 (m, 5H, ArH), 5.97 (d, $J = 7.1$ Hz, 1H, $CHAr_2$), 5.48 (d, $J = 6.3$ Hz, 1H, CHOTBS), 4.64 (d, $J = 4.7$ Hz, 1H, C*H*CONH), 4.51 (t, $J = 7.5$ Hz, 1H, C*H*CONH), 4.42 (br.s, 1H, C*H*CONH), 3.69 (s, 6H, OCH_3), 3.49 (s, 3H, $COOCH_3$), 2.67 (dd, $J = 19.5$, 6.5 Hz, 1H, CHC*H*H), 2.56 (dd, $J = 17.4$, 4.6 Hz, 1H, CHCH*H*), 2.40 (s, 3H, NCH_3), 1.40 (s, 12H, *t*BuO, $CH(CH_3)_2$, $CHCH_2$), 0.81–0.79 (m, 6H, $CH(CH_3)_2$), 0.70 (s, 9H, *t*BuSi), −0.08 (s, 3H, $SiCH_3$), −0.23 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, CD_3SOCD_3): $\delta = 171.2, 171.2, 170.8, 168.8, 168.5, 168.2, 158.8, 158.7, 151.4, 133.5, 133.5, 132.8, 132.5, 128.7, 128.4, 128.3, 128.2, 127.5, 126.6, 126.2, 120.0, 119.8, 116.4, 114.0, 113.8, 80.9, 80.2, 73.3, 60.4, 59.8, 55.9, 55.2, 52.6, 48.9, 37.2, 36.3, 29.9, 29.2, 28.2, 25.6, 24.6, 24.3, 23.3, 23.2, 21.6, 21.1, 21.0, 18.0, 14.1, −4.8, −5.1, −5.3$; HRMS (FAB) calcd for $C_{47}H_{67}ClN_4O_{11}SiCs$ $[M + Cs^+]$ 1059.3318, found 1059.3388.

Carboxylic acid 17: To a solution of tripeptide ester **64** (3.82 g, 4.1 mmol) in *t*BuOH (36 mL) at 0 °C was added H_2O (18 mL). The reaction mixture was further cooled to −5 °C for 15 min and then lithium hydroxide monohydrate (0.69 g, 16.4 mmol) was added. The resulting slurry was stirred vigorously at 0 °C for 0.5 h and then it was quenched by the addition of saturated aqueous NH_4Cl (50 mL). The mixture was diluted with CH_2Cl_2 (50 mL) and stirred at 0 °C for 0.5 h. The aqueous phase was acidified to pH 5 by dropwise addition of 5% aqueous HCl at 0 °C and then extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 0 → 100% EtOAc in hexanes, then 10% MeOH in EtOAc, gradient elution) to afford tripeptide carboxylic acid **17** (3.55 g, 95%). **17**: $R_f = 0.22$ (silica gel, 7.5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +5.29$ ($c = 2.61$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3306, 2958, 2931, 2857, 1650, 1508, 1251, 836\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta =$

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7.28 (d, $J = 2.0$ Hz, 1H, H-2b), 7.14 (d, $J = 2.6$ Hz, 2H, ArH (Ddm)), 7.13 (d, $J = 2.6$ Hz, 2H, ArH (Ddm)), 7.07 (dd, $J = 8.4$, 1.9 Hz, 1H, H-2f), 6.84 (d, $J = 1.7$ Hz, 2H, ArH (Ddm)), 6.84-6.83 (m, 1H, H-2e), 6.83 (d, $J = 1.5$ Hz, 2H, ArH (Ddm)), 6.08 (s, 1H, NHC*H* (Ddm)), 5.00 (d, $J = 7.0$ Hz, 1H, H-2β), 4.64 (d, $J = 7.0$ Hz, 1H, 2α), 4.58–4.44 (m, 2H, H-1α and H-3α), 3.75 (s, 3H, Ddm-OCH_3), 3.75 (s, 3H, Ddm-OCH_3), 2.84 (d, $J = 14.2$ Hz, 1H, H-3β_A), 2.77 (d, $J = 14.2$ Hz, 1H, H-3β_B), 2.51 (s, 3H, NCH_3), 1.51–1.35 (m, 3H, H-1β and H-1γ), 1.45 (s, 9H, *t*BuO), 0.87 (d, $J = 6.7$ Hz, 3H, H-1δ), 0.85 (d, $J = 6.5$ Hz, 3H, H-1δ'), 0.80 (s, 9H, *t*BuSi), 0.00 (s, 3H, CH_3Si), −0.16 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta = 173.6$, 173.3, 171.1, 161.0, 155.0, 136.7, 136.0, 130.8, 130.7, 130.4, 128.9, 122.2, 118.9, 115.9, 81.7, 75.8, 61.8, 58.9, 57.8, 56.8, 38.7, 29.9, 27.5, 26.6, 24.7, 23.2, 19.9, −3.3; HRMS (FAB) calcd for $C_{46}H_{64}ClN_4O_{11}SiCs_2$ [$M - H + 2Cs^+$] 1177.2138, found 1177.2088.

Amino alcohol 65: To a solution of TBS ether **46** (1.31 g, 2.6 mmol) in THF (25 mL) at 0 °C was added *n*Bu_4NF (1.0 M solution in THF, 2.9 mL, 2.9 mmol). The resulting solution was stirred at that temperature for 2 h and then it was quenched by the addition of saturated aqueous NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 × 40 mL) and the combined organic phases were washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 5 → 15% MeOH in $CHCl_3$, gradient elution) afforded **65** (938 mg, 92%). **65**: $R_f = 0.23$ (silica gel, 20% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -33.4$ ($c = 1.12$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3344$, 3292, 2971, 2866, 1415, 1338, 1309, 1223, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$ (s, 2H, ArH), 3.90 (br. s, 2H, NCH_2), 3.87 (dd, $J = 7.8$, 4.3 Hz, 1H, ArCH), 3.67 (br. s, 2H, NCH_2), 3.60 (dd, $J = 10.8$, 4.3 Hz, 1H, C*H*HOH), 3.42 (dd, $J = 10.8$, 7.8 Hz, 1H, CH*H*OH), 2.45 (br. s, 3H, OH and NH_2), 2.02 (br. s, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.0$, 141.6, 130.4, 117.7, 67.4, 56.1, 51.1, 46.5, 23.8, 23.5; HRMS (FAB) calcd for $C_{12}H_{17}Br_2N_4O$ [$M + H^+$] 392.9749, found 392.9747.

Tetrapeptide 66: A solution of hydroxy amine **65** (216 mg, 0.55 mmol), acid **17** (503 mg, 0.55 mmol) and HOAt (250 mg, 1.82 mmol) in THF (5 mL) at 0 °C was treated with EDC (315 mg, 1.65 mmol). The reaction mixture was stirred for 10 h and then quenched by the addition of saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with H_2O (15 mL), brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10 → 20% EtOAc in hexanes, gradient elution) afforded tetrapeptide **66** (594 mg, 84%). **66**: $R_f = 0.20$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22} = -47.5$ ($c = 1.14$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3314$, 2945, 1658, 1502, 1417, 1247, 1169, 1092, 1035 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3, 323 K): $\delta = 8.60$ (s, 1H, OH), 8.05 (d, $J = 8.1$ Hz, 1H, NH), 7.94 (d, $J = 7.7$ Hz, 1H, NH), 7.89 (d, $J = 8.1$ Hz, 1H, NH), 7.56 (s, 2H, ArH), 7.50 (s, 1H, ArH), 7.29 (d, $J = 8.3$ Hz, 1H, ArH), 7.18 (t, $J = 8.9$ Hz, 4H, ArH), 7.01 (d, $J = 8.3$ Hz, 1H, ArH), 6.88-6.84 (m, 4H, ArH), 6.72 (br. s, 1H, NH), 6.15 (d, $J = 8.2$ Hz, 1H, $CHAr_2$), 4.99 (d, $J = 8.0$ Hz, 1H), 4.90 (dd, $J = 13.1$, 5.9 Hz, 1H), 4.77–4.73 (m, 1H), 4.64 (br. s, 1H), 4.41 (dd, $J = 7.8$, 6.1 Hz, 1H), 3.97 (t, $J = 6.4$ Hz, 1H), 3.80 (br. s, 2H, NCH_2), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.75 (br. s, 2H, NCH_2), 3.07 (dd, $J = 15.7$, 3.8 Hz, 1H), 2.74–2.66 (m, 2H, H-3β), 2.44 (s, 3H, NCH_3), 2.06 (br. s, 4H, NCH_2CH_2), 1.53-1.49 (m, 1H), 1.42 (s, 9H, *t*BuO), 1.45–1.34 (m, 2H), 0.87-0.84 (m, 6H, $CH(CH_3)_2$), 0.83 (s, 9H, *t*BuSi), 0.02 (s, 3H, CH_3Si), −0.09 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, CD_3COCD_3, 323 K): $\delta = 173.1$, 171.3, 170.9, 170.4, 159.6, 159.6, 153.8, 147.7, 140.9, 135.5, 135.4, 134.2, 131.8, 129.4, 129.2, 127.9, 117.9, 117.5, 114.4, 80.4, 74.2, 65.8, 62.2, 56.3, 55.5, 55.5, 51.6, 51.0, 47.2, 36.9, 28.6, 28.5, 26.2, 26.1, 25.2, 24.5, 24.1, 23.6, 21.5, 18.5, −4.6, −4.8; HRMS (FAB) calcd for $C_{58}H_{79}Br_2ClN_8O_{11}SiCs$ [$M + Cs^+$] 1419.2734, found 1419.2734.

D-O-E cyclic system 67a and 67b: To a solution of tetrapeptide **66** (232 mg, 0.18 mmol) and $CuBr \cdot Me_2S$ (156 mg, 0.54 mmol) in degassed MeCN (18 mL) at 25 °C was added K_2CO_3 (75 mg, 0.54 mmol) and pyridine (44 μL, 0.54 mmol). The resulting mixture was refluxed and stirred for 15 min. The reaction mixture was cooled to 25 °C and filtered through a pad of celite. The celite was washed thoroughly with EtOAc (3 × 20 mL) and the combined organic layers were washed with H_2O (20 mL), brine (20 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and flash column chromatography of the residue (silica gel, 10 → 30% acetone in hexanes, gradient elution) afforded **67a** (141 mg, 65%) and **67b** (47 mg, 22%). **67a**: $R_f = 0.22$ (silica gel, 40% acetone in hexanes); $[\alpha]_D^{22} = +31.2$ ($c = 1.18$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3442$, 2954, 2493, 1673, 1647, 1502, 1416, 1324, 1245, 1166, 1107, 1028 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3, 323 K): $\delta = 7.99$ (d, $J = 8.2$ Hz, 1H, NH), 7.64–7.50 (br. s, 2H, NH and H-2f), 7.31 (d, $J = 1.9$ Hz, 1H, H-2b), 7.26 (d, $J = 8.3$ Hz, 1H, H-2e), 7.21 (d, $J = 1.5$ Hz, 1H, H-4b), 7.17–7.13 (m, 5H, NH and 4ArH), 6.88–6.85 (m, 5H, NH and 4ArH), 6.11 (d, $J = 8.4$ Hz, 1H, $CHAr_2$), 6.05 (br. s, 1H, H-4f), 5.54 (d, $J = 5.0$ Hz, 1H, H-2β), 4.90 (br. s, 1H, H-2α), 4.79 (br. s, 1H, H-4α), 4.66 (br. s, 1H, H-3α), 4.59 (br. s, 1H, H-1α), 3.82–3.72 (m, 6H), 3.77 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.86 (s, 3H, NCH_3), 2.85–2.66 (m, 2H, H-3β), 2.05 (br. s, 4H, NCH_2CH_2), 1.73–1.66 (m, 3H, H-1β and H-1γ), 1.50 (s, 9H, *t*BuO), 0.92 (s, 9H, *t*BuSi), 0.89–0.86 (m, 6H, $CH(CH_3)_2$), 0.14 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta = 173.1$, 171.4, 170.8, 170.7, 159.9, 159.9, 154.0, 148.0, 141.1, 135.7, 135.7, 134.4, 132.0, 129.8, 129.6, 129.5, 128.0, 118.0, 117.7, 114.7, 114.7, 80.6, 74.7, 66.0, 62.2, 56.6, 55.8, 55.7, 51.3, 37.5, 37.3, 28.7, 26.3, 25.5, 24.5 (br), 23.6, 22.1, 18.7, −4.4, −4.6; HRMS (FAB) calcd for $C_{58}H_{78}BrClN_8O_{11}Cs$ [$M + Cs^+$] calcd 1339.3477, found 1339.3543. **67b**: $R_f = 0.13$ (silica gel, 40% acetone in hexanes); $[\alpha]_D^{22} = +8.54$ ($c = 0.89$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3389$, 2941, 2862, 1673, 1509, 1410, 1318, 1245, 1166, 1100, 1034 cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3, 323 K): $\delta = 8.12$ (s, 1H, NH), 7.69–7.50 (m, 2H), 7.31 (s, 1H, NH), 7.21 (d, $J = 1.5$ Hz, 1H), 7.17–7.11 (m, 5H, ArH), 6.93–6.91 (m, 1H, ArH), 6.88-6.85 (m, 5H, ArH), 6.23–6.21 (m, 1H, H-4f), 6.09 (d, $J = 8.2$ Hz, 1H, $CHAr_2$), 5.53 (d, $J = 4.8$ Hz, 1H, H-2β), 4.90 (br. s, 1H, H-2α), 4.77 (br. s, 1H), 4.65 (br. s, 1H), 4.54 (br. s, 1H), 3.90 (br. s, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.80–3.73 (m, 1H), 3.65 (br. s, 2H, NCH_2), 3.49 (br. s, 1H), 2.87 (s, 3H, NCH_3), 2.60–2.55 (m, 2H, H-3β), 2.04 (br. s, 4H, NCH_2CH_2), 1.75–1.71 (m, 3H, H-1β and H-1γ), 1.53 (s, 9H, *t*BuO), 1.50–1.47 (m, 6H, $CH(CH_3)_2$), 0.91 (s, 9H, *t*BuSi), 0.13 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta = 172.7$, 171.3, 170.8, 168.6, 159.6, 158.0, 157.0, 153.8, 153.1, 139.8, 138.9, 138.6, 135.1, 129.4, 129.3, 128.7, 125.8, 125.4, 123.3, 122.8, 118.9, 118.8, 115.9, 115.4, 114.5, 80.6, 73.8, 73.6, 65.5, 60.9, 57.2, 56.7, 56.3, 55.5, 51.6, 51.1, 46.9, 39.2, 37.2, 28.6, 26.2, 25.4, 24.5, 24.1, 23.7, 22.1, 18.9, −4.8, −4.8; HRMS (FAB) calcd for $C_{58}H_{78}BrClN_8O_{11}Cs$ [$M + Cs^+$] calcd 1339.3477, found 1339.3544.

Carboxylic acid 7: To a solution of alcohol **67a** (500 mg, 0.414 mmol) in 5% aqueous $NaHCO_3$/acetone (1:1, 4 mL) at 0 °C were added TEMPO (71 mg, 0.46 mmol) and potassium bromide (5 mg, 0.04 mmol). Sodium hypochlorite (5% aqueous, 2 mL) was added dropwise and the resulting mixture was stirred for 1 h before it was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, 5 → 10% MeOH in $CHCl_3$) to afford carboxylic acid **7** (330 mg, 65%). **7**: ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.65$ (br. s, 1H), 7.54 (br. s, 1H), 7.35–7.32 (m, 1H), 7.23–7.20 (m, 1H), 7.08–7.05 (m, 4H), 6.86–6.82 (m, 4H), 6.08 (s, 1H), 5.89 (s, 1H), 5.51–5.48 (m, 1H), 5.16–5.10 (m, 1H), 5.04–4.80 (m, 2H), 4.66–4.59 (br. s, 1H), 3.90–3.75 (m, 4H), 3.77 (s, 3H), 3.76 (s, 3H), 2.84 (s, 3H), 2.65–2.60 (m, 2H), 2.08 (br. s, 4H), 1.60–1.50 (m, 12H), 0.87 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); HRMS (FAB) calcd for $C_{58}H_{76}BrClN_8O_{12}SiCs$ [$M + Cs^+$] 1353.3270, found 1353.3362.

Epimers 5a and 5b: A solution of acid **7** (140 mg, 0.11 mmol) and amine **6** (97 mg, 0.11 mmol) at −15 °C in THF (2.5 mL) was treated sequentially with HOAt (52 mg, 0.38 mmol) and EDC (66 mg, 0.33 mmol). The reaction mixture was stirred for 5 h before it was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20 → 40% EtOAc in hexanes) to afford **5a** (114 mg, 48%) and **5b** (57 mg, 24%). **5a**: $R_f = 0.08$ (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.55$–7.49 (m, 5H, ArH), 7.48–7.45 (m, 2H, ArH), 7.45–7.44 (m, 2H, ArH), 7.40 (d, $J = 2.4$ Hz, 1H, ArH), 7.38 (d, $J = 8.7$ Hz, 2H, ArH), 7.29 (d, $J = 8.7$ Hz, 2H, ArH), 7.24 (dd, $J = 8.7$, 2.5 Hz, 1H, ArH), 7.17 (dd, $J = 8.7$, 2.0 Hz, 1H, ArH), 7.12 (d, $J = 8.7$ Hz, 2H, ArH), 7.10 (d, $J = 8.7$ Hz, 2H, ArH), 7.12-7.10 (m, 2H, ArH), 7.02 (d, $J = 8.7$ Hz, 1H, ArH), 6.89 (d, $J = 2.4$ Hz, 1H, ArH), 6.78 (d, $J = 2.4$ Hz, 1H, ArH), 6.31 (s, 1H, ArH), 6.20 (s, 1H, $CHAr_2$), 5.88 (s, 1H), 5.76 (s, 1H), 5.67 (m, 1H), 5.42 (d, $J = 3.2$ Hz, 1H), 5.15 (m, 1H), 5.03 (d, $J = 4.8$ Hz, 1H), 4.99 (d, $J = 3.4$ Hz, 1H), 4.85–4.82 (m, 2H), 4.72–4.67 (m, 2H), 4.42–4.35 (m, 2H), 4.10–4.09 (m, 4H), 4.08 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 3.90–3.88 (m, 2H), 3.87 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.12 (s, 3H, NCH_3), 2.86–2.81 (m, 1H), 2.77–

2.73 (m, 1H), 2.04 (br. s, 2H), 1.94 (br. s, 2H), 1.56 (s, 9H, *t*BuO), 1.48 (t, $J=7.2$ Hz, 3H), 1.23–1.18 (m, 9H), 1.17 (s, 9H, *t*BuSi), 1.09 (s, 9H, *t*BuSi), 0.38 (s, 3H, CH_3Si), 0.34 (s, 3H, CH_3Si), 0.25 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); electrospray MS calcd for $C_{101}H_{128}BrCl_2N_{13}O_{20}Si_2Na$ $[M+Na^+]$ 2073, found 2073. **5b**: $R_f=0.12$ (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta=7.23-7.15$ (m, 5H, ArH), 7.12 (d, $J=8.3$ Hz, 1H, ArH), 7.10 (d, $J=1.8$ Hz, 1H, ArH), 7.04–7.00 (m, 4H), 6.91 (d, $J=8.6$ Hz, 2H, ArH), 6.83 (dd, $J=8.5$, 2.0 Hz, 1H, ArH), 6.79–6.74 (m, 6H, ArH), 6.69–6.65 (m, 2H, ArH), 6.51 (d, $J=2.3$ Hz, 1H, ArH), 6.41 (d, $J=2.3$ Hz, 1H, ArH), 5.94 (s, 1H, ArH), 5.79 (br. s, 1H), 5.54 (s, 1H), 5.42 (s, 1H), 5.35–5.30 (m, 2H), 5.11–5.10 (m, 1H), 4.80–4.70 (m, 3H), 4.67 (d, $J=3.3$ Hz, 1H), 4.52–4.50 (m, 2H), 4.38–4.32 (m, 2H), 4.04 (br. s, 2H), 3.86 (br. s, 2H), 3.73 (s, 3H, OCH_3), 3.70 (s, 6H, OCH_3), 3.72–3.68 (m, 2H), 3.51 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 2.42–2.39 (m, 2H), 1.98 (br. s, 4H), 1.41 (s, 9H, *t*BuO), 1.18–1.14 (m, 3H), 0.89–0.82 (m, 9H), 0.80 (s, 9H, *t*BuSi), 0.76 (s, 9H, *t*BuSi), 0.02 (s, 3H, CH_3Si), −0.02 (s, 3H, CH_3Si), −0.10 (s, 3H, CH_3Si), −0.24 (s, 3H, CH_3Si); electrospray MS calcd for $C_{101}H_{128}BrCl_2N_{13}O_{20}Si_2Na$ $[M+Na^+]$ 2073, found 2073.

Carboxylic acid 68: To a solution of amino acid **29** (8.80 g, 0.030 mol) in THF/H_2O (1:1, 150 mL) at 0 °C was added anhydrous LiOH (1.08 g, 0.045 mol). The resulting mixture was stirred at 0 °C for 0.5 h before it was quenched by the addition of saturated aqueous citric acid (150 mL). The aqueous phase was extracted with EtOAc (3 × 200 mL) and the combined organic extracts were washed with H_2O (50 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to afford crude carboxylic acid **68** (8.45 g, 99%), which was used in the next step without further purification.

Phenol 69: A solution of carboxylic acid **68** (911 mg, 3.23 mmol) and amine **35** (1.0 g, 2.95 mmol) in DMF (30 mL) at −20 °C was sequentially treated with HOBt (1.49 g, 9.73 mmol) and EDC (3.0 mg, 8.85 mmol). The resulting mixture was stirred at 0 °C for 12 h before it was quenched by the addition of saturated aqueous citric acid (60 mL). The aqueous phase was extracted with EtOAc (3 × 75 mL) and the combined organic extracts were washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 0→50% EtOAc in hexanes, gradient elution) afforded phenol **69** (1.44 g, 81%). **69**: $R_f=0.15$ (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22}=-49.6$ ($c=1.2$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3343$, 2931, 1694, 1514, 1252, 1169, 1082, 1039 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3): $\delta=8.28$ (s, 1H, OH), 7.33 (d, $J=8.5$ Hz, 1H, NH), 7.26 (d, $J=8.5$ Hz, 2H, H-5b), 6.98 (d, $J=8.0$ Hz, 2H, H-6b), 6.88 (d, $J=8.0$ Hz, 2H, H-5c), 6.64 (d, $J=8.0$ Hz, 2H, H-6c), 6.41 (br. s, 1H, NH), 5.27–5.21 (m, 2H, H-5α and H-6β), 4.53 (dd, $J=11.0$, 2.0 Hz, 1H, H-6α), 4.21–4.10 (m, 2H, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 1.39 (s, 9H, *t*BuO), 1.27 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 0.08 (s, 9H, *t*BuSi), −0.03 (s, 3H, CH_3Si), −0.23 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3): $\delta=170.7$, 160.2, 157.7, 132.4, 129.7, 129.5, 128.9, 128.5, 128.5, 115.6, 114.6, 75.0, 61.9, 60.1, 58.3, 55.5, 28.5, 26.1, 18.6, 14.4, −4.5, −5.3; HRMS (FAB) calcd for $C_{31}H_{46}N_2O_8SiCs$ $[M+Cs^+]$ 735.2078, found 735.2063.

Chloride 70: A solution of phenol **69** (1.48 g, 2.46 mmol) in Et_2O/CH_2Cl_2 (5:1, 30 mL) at −10 °C was treated with SO_2Cl_2 (0.25 mL, 2.50 mmol). The resulting reaction mixture was stirred at 0 °C for 0.5 h and then quenched with saturated aqueous $NaHCO_3$ (60 mL). The mixture was then extracted with EtOAc (3 × 60 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 30% EtOAc in hexanes) afforded chloride **70** (1.38 g, 88%). **70**: $R_f=0.15$ (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22}=-51.6$ ($c=0.68$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3417$, 2930, 1682, 1513, 1252, 1167, 1090, 1030 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3): $\delta=8.66$ (s, 1H, OH), 7.34 (s, 1H, H-6b), 7.28–7.22 (m, 3H, H-5b and H-6f), 6.91 (s, 1H, NH), 6.88 (d, $J=8.0$ Hz, 2H, H-5c), 6.80 (d, $J=7.0$ Hz, 1H, H-6e), 6.35 (br. s, 1H, NH), 5.27 (s, 1H, H-5α), 5.25 (d, $J=7.0$ Hz, 1H, H-6β), 4.59 (dd, $J=9.0$, 2.0 Hz, 1H, H-6α), 4.25–4.12 (m, 2H, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 1.39 (s, 9H, *t*BuO), 1.29 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 0.85 (s, 9H, *t*BuSi), 0.00 (s, 3H, CH_3Si), −0.19 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3): $\delta=171.2$, 170.4, 160.2, 154.3, 153.1, 143.4, 134.2, 129.3, 128.6, 126.8, 120.5, 117.1, 114.7, 79.3, 74.3, 62.0, 59.9, 58.2, 55.5, 28.5, 26.0, 18.6, 14.4, −4.5, −5.3; HRMS (FAB) calcd for $C_{31}H_{53}N_2O_8SiCl$ $[M+H^+]$ 637.2712, found 637.2736.

Amine 71: Chloride **70** (583 mg, 0.915 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to −10 °C. Trimethylsilyl trifluoromethanesulfonate (550 µL, 3.04 mmol) was added dropwise over 5 min. The reaction mixture was stirred at −10 °C for 0.5 h at which time 2,6-lutidine (320 µL, 2.75 mmol) was added. After stirring for 0.5 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (60 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 10% MeOH in CH_2Cl_2) afforded amine **71** (384 mg, 75%). **71**: $R_f=0.21$ (silica gel, 80% EtOAc in hexanes); $[\alpha]_D^{22}=-27.4$ ($c=1.6$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3347$, 2957, 1733, 1661, 1514, 1552, 1091, 1030 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.47$ (d, $J=9.5$ Hz, 1H, NH), 7.30 (d, $J=8.5$ Hz, 2H, H-5b), 7.17 (d, $J=2.0$ Hz, 1H, H-6b), 6.97 (dd, $J=8.5$, 2.0 Hz, 1H, H-6f), 6.89 (d, $J=8.5$ Hz, 2H, H-5c), 6.84 (d, $J=8.5$ Hz, 1H, H-6e), 5.23 (d, $J=2.0$ Hz, 1H, H-6β), 4.59 (dd, $J=9.5$, 2.0 Hz, 1H, H-6α), 4.42 (s, 1H, H-5α), 4.22–4.18 (m, 1H, OC*H*HCH$_3$), 4.14–4.10 (m, 1H, OCH*H*CH$_3$), 3.80 (s, 3H, OCH_3), 1.26 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 0.86 (s, 9H, *t*BuSi), −0.03 (s, 3H, CH_3Si), −0.20 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=174.0$, 170.7, 160.3, 151.8, 134.8, 133.7, 129.3, 127.5, 126.7, 120.4, 116.9, 115.2, 74.2, 62.5, 60.1, 59.8, 56.1, 26.4, 18.8, 14.9, −3.8, −4.8; HRMS (FAB) calcd for $C_{26}H_{37}N_2O_6SiClCs$ $[M+Cs^+]$ 669.1164, found 669.1148.

Tripeptide 72: A solution of carboxylic acid **12** (320 mg, 0.630 mmol) and amine **71** (368 mg, 0.686 mmol) in THF (25 mL) at −10 °C was sequentially treated with HOAt (284 mg, 2.08 mmol) and EDC (363 mg, 1.89 mmol). The resulting mixture was stirred at −10 °C for 2 h before it was quenched by the addition of H_2O (40 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with saturated aqueous NH_4Cl (40 mL), saturated aqueous $NaHCO_3$ (40 mL), brine (40 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 70% acetone in hexanes) afforded tripeptide **72** (512 mg, 79%). **72**: $R_f=0.43$ (silica gel, 30% EtOAc in benzene); $[\alpha]_D^{22}=-43.2$ ($c=0.63$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3321$, 2930, 1668, 1514, 1417, 1253, 1094, 1029 cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): $\delta=8.72$ (s, 1H, OH), 8.05 (br. s, 1H, NH), 7.70 (s, 2H, H-4b), 7.46 (d, $J=9.5$ Hz, 1H, NH), 7.25 (s, 1H, H-6b), 7.21 (d, $J=9.0$ Hz, 2H, H-5b), 6.89–6.82 (m, 3H, H-5c and H-6f), 6.75 (d, $J=8.5$ Hz, 1H, H-6e), 6.63 (br. s, 1H, NH), 5.56 (d, $J=8.0$ Hz, 1H, H-5α), 5.37 (br. s, 1H, H-4α), 5.24 (d, $J=3.0$ Hz, 1H, H-6β), 4.55 (dd, $J=9.5$, 3.0 Hz, 1H, H-6α), 4.18–4.05 (m, 2H, OCH_2CH_3), 3.91–3.86 (br. s, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 3.63–3.58 (br. s, 2H, NCH_2), 2.13–2.02 (br. d, 4H, NCH_2CH_2), 1.36 (s, 9H, *t*BuO), 1.21 (t, $J=7.5$ Hz, 3H, OCH_2CH_3), 0.83 (s, 9H, *t*BuSi), −0.03 (s, 3H, CH_3Si), −0.21 (s, 3H, CH_3Si); ^{13}C NMR (125 MHz, CD_3CN): $\delta=170.3$, 170.1, 169.3, 160.1, 155.6, 152.3, 148.5, 138.0, 134.1, 132.0, 130.7, 129.0, 128.8, 128.2, 126.5, 120.1, 116.8, 114.8, 80.2, 73.7, 62.3, 59.8, 57.3, 56.8, 55.7, 51.8, 47.2, 28.2, 25.7, 24.4, 23.9, 18.3, 14.2, −4.8, −5.5; HRMS (FAB) calcd for $C_{43}H_{59}N_6O_9ClSiBr_2Cs$ $[M+Cs^+]$ 1157.1049, found 1157.1103.

C-O-D Ring System 73a and 73b: To a solution of tripeptide **72** (540 mg, 0.527 mmol), $CuBr\cdot Me_2S$ (294 mg, 1.43 mmol) and K_2CO_3 (192 mg, 1.39 mmol) in degassed MeCN (20 mL) at 25 °C was added pyridine (106 µL, 1.31 mmol). The resulting mixture was refluxed for 0.5 h and then it was cooled to 25 °C, diluted with EtOAc (40 mL) and quenched with saturated aqueous NH_4Cl (40 mL). The reaction mixture was stirred for 0.5 h and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (40 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and flash column chromatography of the residue (silica gel, 10→30% acetone in hexanes, gradient elution) afforded C-O-D ring system **73a** (122 mg, 25%) and **73b** (136 mg, 27%). **73a**: $R_f=0.12$ (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22}=+19.5$ ($c=0.98$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3307$, 2928, 1714, 1514, 1416, 1337, 1252, 1178, 1097, 1030 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3): $\delta=7.53$ (d, $J=2.0$ Hz, 1H, H-6b), 7.44–7.39 (m, 3H, H-4f and H-5b), 7.28–7.18 (m, 2H, NH, H-6f), 7.14 (d, $J=8.5$ Hz, 1H, H-6e), 7.12 (s, 1H, H-4b), 7.02 (d, $J=9.0$ Hz, 2H, H-5c), 6.38 (br. s, 1H, NH), 5.80 (d, $J=9.0$ Hz, 1H, NH), 5.46 (d, $J=8.0$ Hz, 1H, H-4α), 5.44 (d, $J=2.0$ Hz, 1H, H-6β), 5.31–5.23 (br. s, 1H, H-5α), 4.46 (d, $J=8.5$ Hz, 1H, H-6α), 4.25-4.17 (m, 1H, OC*H*HCH$_3$), 4.12–4.04 (m, 1H, OCH*H*CH$_3$), 3.96–3.85 (br. s, 2H, NCH_2), 3.82 (s, 3H, OCH_3), 3.69–3.61 (br. s, 2H, NCH_2), 2.14–2.03 (br. d, 4H, NCH_2CH_2), 1.37 (s, 9H, *t*BuO), 1.27 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 0.77 (s, 9H, *t*BuSi), −0.03 (s, 3H, CH_3Si), −0.14 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3): $\delta=$ 169.4, 168.7, 168.5, 160.9, 154.2, 152.5, 138.8, 132.3, 130.7, 129.5, 128.6, 128.0, 126.8, 126.7, 123.0, 119.0, 118.4, 115.3, 114.7, 114.5, 79.5, 74.4, 62.4, 61.0, 58.2, 57.7, 55.6, 51.6, 47.0, 28.5, 26.0, 24.5, 24.1, 18.4, 14.3, −4.3, −5.6; HRMS

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(FAB) calcd for $C_{43}H_{56}N_6O_9SiClBrCs$ $[M+Cs^+]$ 1077.1790, found 1077.1759. **73b**: $R_f=0.21$ (silica gel, 30% acetone in hexanes); $[\alpha]_D^{22}=-11.5$ ($c=0.46$, CH_3OH); IR (thin film): $\tilde{\nu}_{max}=3417$, 2929, 1714, 1514, 1416, 1336, 1253, 1164, 1093, 1031 cm^{-1}; ^1H NMR (600 MHz, CD_3CN): $\delta=$ 7.37 (dd, $J=8.5$, 2.0 Hz, 1H, H-6f), 7.34 (dd, $J=2.0$, 1.0 Hz, 1H, H-6b), 7.26 (d, $J=8.5$ Hz, 1H, H-6e), 7.22 (s, 1H, H-4f), 7.14 (br.s, 2H, H-5b), 7.01 (d, $J=8.5$ Hz, 2H, H-5c), 6.83 (s, 1H, H-4b), 6.77 (d, $J=4.5$ Hz, 1H, NH), 5.92 (s, 1H, NH), 5.68 (d, $J=9.0$ Hz, 1H, NH), 5.42 (d, $J=2.0$ Hz, 1H, H-6β), 5.12 (d, $J=4.5$ Hz, 1H, H-5α), 5.00 (s, 1H, H-4α), 4.67 (s, 1H, H-6α), 4.22–4.17 (m, 1H, OC*H*HCH$_3$), 4.08-4.04 (m, 1H, OCH*H*CH$_3$), 3.97–3.90 (br.s, 2H, NCH$_2$), 3.80 (s, 3H, OCH$_3$), 3.72–3.62 (br.s, 2H, NCH$_2$), 2.12–2.06 (br.s, 2H, NCH$_2$C*H*$_2$), 2.05–1.98 (br.s, 2H, NCH$_2$C*H*$_2$), 1.39 (s, 9H, *t*BuO), 1.26, (t, $J=7.0$ Hz, 3H, OCH$_2$C*H*$_3$), 0.75 (s, 9H, *t*BuSi), −0.05 (s, 3H, CH$_3$Si), −0.18 (s, 3H, CH$_3$Si); ^{13}C NMR (150 MHz, CD_3CN): $\delta=$169.8, 169.4, 168.9, 161.0, 158.4, 152.3, 151.8, 140.3, 130.3, 129.8, 128.2, 128.0, 127.1, 126.5, 125.2, 119.7, 119.1, 117.2, 115.2, 114.8, 74.9, 73.8, 62.7, 60.5, 59.1, 58.6, 55.9, 51.8, 47.1, 28.3, 25.8, 25.6, 24.1, 18.3, 14.1, −4.9, −5.3; HRMS (FAB) calcd for $C_{43}H_{56}N_6O_9SiClBrCs$ $[M+Cs^+]$ 1077.3030, found 1077.3067.

Alcohol 74: To a solution of amine **14** (230 mg, 0.73 mmol) in CH_2Cl_2 (7.3 mL) at 0 °C was added triethylamine (0.13 mL, 0.95 mmol) and Boc_2O (183 mg, 0.84 mmol). The reaction mixture was stirred for 5 h and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 30% EtOAc in hexanes) afforded alcohol **74** (300 mg, 93%). **74**: $R_f=$ 0.33 (silica gel, 30% EtOAc in hexanes); $[\alpha]_D^{22}=-62.4$ ($c=1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}=3347$, 1733, 1667, 1513, 1257, 1091, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.35$-7.24 (m, 4H, ArH), 7.32-7.30 (m, 1H, ArH), 7.18 (d, $J=8.5$ Hz, 2H, H-2b), 6.92 (d, $J=8.0$ Hz, 2H, H-2c), 5.28 (bd, $J=$ 7.5 Hz, 1H, H-2β), 5.13 (br.s, 1H, NH), 5.04 (s, 2H, CH$_2$Ph), 4.65–4.63 (m, 1H, H-2α), 4.14 (q, $J=7.0$ Hz, 2H, OC*H*$_2$CH$_3$), 3.94 (br.s, 1H, OH), 1.42 (s, 9H, *t*BuO), 1.19 (t, $J=7.5$ Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=169.8$, 158.7, 156.3, 136.8, 131.6, 128.6, 128.5, 127.4, 127.3, 114.5, 80.5, 74.7, 69.9, 61.6, 59.6, 28.2, 14.0; HRMS (FAB) calcd for $C_{23}H_{29}NO_5Na$ $[M+Na^+]$ 438.1897, found 438.1904.

Carboxylic acid 75: A solution of alcohol **74** (3.34 g, 8.03 mmol) in THF/H_2O (1:1, 50 mL) at 0 °C was treated with anhydrous LiOH (385 mg, 16.2 mmol). The resulting mixture was stirred for 1 h before it was acidified to pH 3 by the addition of saturated aqueous $KHSO_4$. The aqueous phase was extracted with EtOAc (3 × 150 mL) and the combined organic extracts were washed with brine (75 mL), dried (Na_2SO_4) and concentrated in vacuo to afford crude carboxylic acid **75** (3.00 g, 96%), which was taken into the next step without further purification.

Dipeptide 76: A solution of acid **75** (1.90 g, 5.14 mmol) and amine **13** (1.60 g, 4.28 mmol) in THF (45 mL) at −20 °C was sequentially treated with HOBt (1.91 g, 14.1 mmol) and EDC (2.44 mg, 12.8 mmol). The resulting mixture was stirred at 0 °C for 4 h before it was quenched by the addition of saturated aqueous NH_4Cl (90 mL). The aqueous phase was extracted with EtOAc (3 × 125 mL) and the combined organic extracts were washed with H_2O (75 mL), brine (75 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 20 → 70% EtOAc in hexanes, gradient elution) afforded dipeptide **76** (2.03 g, 65%). **76**: $R_f=$ 0.25 (silica gel, 70% EtOAc in hexanes); $[\alpha]_D^{22}=-3.98$ ($c=0.93$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3323$, 2953, 1737, 1657, 1511, 1247, 1175, 1033 cm^{-1}; ^1H NMR (600 MHz, CD_3SOCD_3): $\delta=8.77$ (d, $J=8.5$ Hz, 1H, NH), 8.28 (d, $J=8.0$ Hz, 1H, NH), 7.40–7.27 (m, 5H, ArH), 7.23 (d, $J=8.5$ Hz, 2H, ArH), 7.12 (d, $J=7.5$ Hz, 4H, ArH), 6.89 (d, $J=8.5$ Hz, 2H, ArH), 6.85 (d, $J=8.5$ Hz, 4H, ArH), 6.57 (d, $J=9.5$ Hz, 1H, NH), 5.96 (d, $J=8.5$ Hz, 1H, CHAr$_2$), 5.43 (d, $J=5.0$ Hz, 1H, H-2β), 5.04 (s, 2H, CH$_2$Ph), 4.69–4.64 (m, 1H, OH), 4.59 (dd, $J=8.5$, 5.0 Hz, 1H, H-2α), 4.09–4.02 (m, 1H, H-3α), 3.69 (s, 6H, OCH$_3$), 3.53 (s, 3H, COOCH$_3$), 2.70 (dd, $J=15.5$, 7.0 Hz, 1H, H-3β), 2.58 (dd, $J=15.5$, 5.0 Hz, 1H, H-3β), 1.20 (s, 9H, *t*BuO); ^{13}C NMR (150 MHz, CD_3SOCD_3): $\delta=172.9$, 171.7, 169.4, 159.4, 159.4, 158.8, 156.0, 138.5, 136.0, 135.9, 129.7, 129.6, 129.5, 129.0, 128.6, 115.2, 115.0, 114.9, 79.2, 73.5, 70.4, 60.9, 56.4, 56.0, 53.2, 50.1, 38.4, 29.3; HRMS (FAB) calcd for $C_{41}H_{47}N_3O_{10}Cs$ $[M+Cs^+]$ 874.2316, found 874.2345.

TBS ether 77: A solution of dipeptide **76** (263 mg, 0.361 mmol) in DMF (5 mL) was treated with TBSCl (200 mg, 1.33 mmol) and imidazole (200mg, 2.94 mmol) at 25 °C. The resulting mixture was stirred for 24 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (40 mL) and the resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 30% EtOAc in hexanes) afforded TBS ether **77** (227 mg, 75%). **77**: $R_f=0.24$ (silica gel, 45% EtOAc in hexanes); $[\alpha]_D^{22}=-23.6$ ($c=1.0$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3306$, 2931, 1738, 1714, 1514, 1455, 1372, 1250, 1176, 1091, 1037 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): $\delta=7.96$ (d, $J=8.5$ Hz, 1H, NH), 7.55 (d, $J=8.0$ Hz, 1H, NH), 7.47 (d, $J=7.5$ Hz, 2H, H-2b), 7.39–7.29 (m, 5H, ArH), 7.20–7.10 (m, 4H, ArH), 6.95 (d, $J=$ 8.5 Hz, 2H, H-2c), 6.86 (d, $J=9.0$ Hz, 4H, ArH), 6.11 (d, $J=8.5$ Hz, 1H, CHAr$_2$), 5.59 (d, $J=8.5$ Hz, 1H, H-2β), 5.15 (d, $J=6.0$ Hz, 1H, NH), 5.06 (s, 2H, CH$_2$Ph), 4.82–4.74 (m, 1H, H-3α), 4.38–4.29 (m, 1H, H-2α), 3.76 (s, 6H, OCH$_3$), 3.54 (s, 3H, COOCH$_3$), 2.90–2.82 (m, 1H, H-3β), 2.73 (dd, $J=16.0$, 5.5 Hz, 1H, H-3β), 1.33 (s, 9H, *t*BuO), 0.87 (s, 9H, *t*BuSi), 0.06 (s, 3H, CH$_3$Si), −0.11 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta=$ 171.7, 169.6, 169.1, 159.4, 159.3, 159.1, 155.5, 138.1, 135.3, 135.2, 133.5, 129.2, 129.0, 129.0, 128.9, 128.7, 128.3, 128.2, 114.8, 114.3, 114.2, 79.1, 74.8, 70.2, 61.8, 56.0, 55.3, 52.1, 49.5, 37.6, 28.2, 26.0, 18.4, −4.9, −5.1; HRMS (FAB) calcd for $C_{47}H_{61}N_3O_{10}SiCs$ $[M+Cs^+]$ 988.3157, found 988.3181.

Phenol 78: To a solution of TBS ether **77** (219 mg, 0.256 mmol) in ethanol (5 mL) was added 10% $Pd(OH)_2/C$ (20 mg). The suspension was placed under a H_2 atmosphere. After stirring for 16 h, the reaction mixture was filtered through celite and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 50% EtOAc in hexanes) afforded phenol **78** (195 mg, 99%). **78**: $R_f=0.40$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}=-23.2$ ($c=1.2$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3310$, 1650, 1513, 1248, 1093 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): $\delta=8.29$ (s, 1H, OH), 7.94 (d, $J=7.5$ Hz, 1H, NH), 7.54 (d, $J=7.5$ Hz, 1H, NH), 7.23 (d, $J=8.0$ Hz, 2H, ArH), 7.20–7.14 (m, 4H, ArH), 6.87 (d, $J=8.5$ Hz, 4H, ArH), 6.78 (d, $J=$ 8.5 Hz, 2H, ArH), 6.10 (d, $J=8.5$ Hz, 1H, CHAr$_2$), 5.54 (d, $J=9.0$ Hz, 1H, H-2β), 5.11 (d, $J=5.5$ Hz, 1H, NH), 4.82–4.76 (m, 1H, H-2α), 4.33–4.27 (m, 1H, H-3α), 3.76 (s, 6H, OCH$_3$), 3.57 (s, 3H, COOCH$_3$), 2.88 (dd, $J=$ 14.5, 3.0 Hz, 1H, H-3β), 2.73 (dd, $J=14.5$, 5.5 Hz, 1H, H-3β), 1.32 (s, 9H, *t*BuO), 0.84 (s, 9H, *t*BuSi), 0.04 (s, 3H, CH$_3$Si), −0.12 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta=171.7$, 169.7, 169.0, 159.4, 159.3, 157.5, 155.5, 135.3, 135.2, 131.9, 129.2, 129.0, 128.3, 115.4, 114.2, 114.2, 79.1, 74.6, 61.9, 56.0, 55.2, 49.4, 37.6, 28.2, 25.9, 19.2, −4.9, −5.2; HRMS (FAB) calcd for $C_{40}H_{55}N_3O_{10}SiCs$ $[M+Cs^+]$ 898.2711, found 898.2732.

Chloride 79: A solution of phenol **78** (244 mg, 0.318 mmol) in Et_2O/CH_2Cl_2 (5:1, 6 mL) at 0 °C was treated dropwise with SO_2Cl_2 (40 μL, 0.400 mmol). The resulting solution was stirred for 0.5 h before it was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 2% MeOH in CH_2Cl_2) afforded chloride **79** (232 mg, 91%). **79**: $R_f=0.42$ (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}=-26.4$ ($c=0.89$, MeOH); IR (thin film): $\tilde{\nu}_{max}=$ 3316, 2930, 1742, 1667, 1514, 1250, 1176, 1092, 1036 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): $\delta=8.72$ (s, 1H, OH), 7.96 (d, $J=8.0$ Hz, 1H, NH), 7.66 (d, $J=8.0$ Hz, 1H, NH), 7.39 (s, 1H, H-2b), 7.21–7.14 (m, 5H, ArH), 6.95 (d, $J=8.5$ Hz, 1H, H-2e), 6.87 (d, $J=8.5$ Hz, 4H, ArH), 6.11 (d, $J=8.0$ Hz, 1H, CHAr$_2$), 5.72 (d, $J=8.5$ Hz, 1H, H-2β), 5.06 (d, $J=5.5$ Hz, 1H, NH), 4.83–4.78 (m, 1H, H-2α), 4.34–4.29 (m, 1H, H-3α), 3.76 (s, 6H, OCH$_3$), 3.57 (s, 3H, COOCH$_3$), 2.93-2.89 (m, 1H, H-3β), 2.75 (dd, $J=15.5$, 5.5 Hz, 1H, H-3β), 1.31 (s, 9H, *t*BuO), 0.85 (s, 9H, *t*BuSi), 0.04 (s, 3H, CH$_3$Si), −0.11 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta=$ 172.1, 170.1, 169.4, 159.8, 159.7, 155.9, 153.4, 135.7, 134.3, 129.6, 129.4, 127.7, 120.7, 114.6, 79.5, 74.8, 62.0, 56,4, 55,6, 52.5, 49.9, 38.0, 28.5, 26.3, 18.8, −4.5, −4.7; HRMS (FAB) calcd for $C_{40}H_{54}N_3O_{10}SiClCs$ $[M+Cs^+]$ 932.2321, found 932.2344.

Carboxylic acid 80: A solution of chloride **79** (132 mg, 0.165 mmol) in *t*BuOH/H_2O (4:1, 10 mL) was cooled to 5 °C and the resulting slurry was treated with a solution of LiOH monohydrate (9 mg, 0.214 mmol) in H_2O (1 mL). The mixture was warmed to 10 °C and stirred for 1 h. The reaction was quenched with 1% aqueous HCl (1 mL), diluted with H_2O (10 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. Flash column chromatography of the residue (silica gel, 10% MeOH in CH_2Cl_2) afforded carboxylic acid **80** (98 mg, 76%). **80**: $R_f=$ 0.08 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=-21.7$ ($c=1.2$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3362$, 2930, 1660, 1513, 1249, 1176, 1093 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): $\delta=7.30$ (s, 1H, H-2b), 7.13 (d, $J=6.0$ Hz, 4H, ArH), 7.10 (d, $J=8.0$ Hz, 1H, H-2f), 6.87–6.81 (m, 5H, ArH), 6.41 (d, $J=9.5$ Hz, 1H, CHAr$_2$), 6.05 (br.s, 1H, H-2β), 4.92 (d, $J=6.0$ Hz, 1H, NH), 4.62 (br.s,

1H, H-2α), 4.23 – 4.19 (m, 1H, H-3α), 3.75 (s, 6H, OCH_3), 2.82 – 2.71 (br.s, 2H, H-3β), 1.31 (s, 9H, *t*BuO), 0.82 (s, 9H, *t*BuSi), 0.02 (s, 3H, CH_3Si), – 0.15 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3OD): $\delta = 171.0$, 160.0, 159.7, 159.7, 156.6, 156.1, 153.6, 135.0, 134.9, 133.6, 129.3, 129.2, 127.3, 120.7, 116.6, 114.2, 80.0, 75.0, 62.0, 56.5, 55.1, 49.3, 39.0, 28.1, 25.8, 18.5, – 5.1, – 5.3; HRMS (FAB) calcd for $C_{39}H_{52}N_3O_{10}SiClCs$ $[M + Cs^+]$ 918.2165, found 918.2143.

Amine 81: To a solution of compound **73a** (12.8 mg, 0.0136 mmol) in CH_2Cl_2 (4 mL) at – 20 °C was added trimethylsilyl trifluoromethanesulfonate (25 µL, 0.138 mmol). The reaction mixture was stirred at – 20 °C for 1 h. 2,6-Lutidine (25 µL, 0.215 mmol) was then added and the reaction mixture was stirred for an additional 20 min. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (silica gel, EtOAc) to afford amine **81** (9.1 mg, 80 %). **81**: $R_f = 0.36$ (silica gel, EtOAc); $[\alpha]_D^{22} = +36.9$ ($c = 0.55$, MeCN); IR (thin film): $\tilde{\nu}_{max} = 3418$, 2926, 1770, 1668, 1514, 1417, 1336, 1250, 1099 cm^{-1}; ^1H NMR (600 MHz, CD_3CN): $\delta = 7.69$ (br.s, 1H, NH), 7.47 (d, $J = 2.0$ Hz, 1H, H-6b), 7.34 (d, $J = 2.0$ Hz, 1H, H-4f), 7.01 (d, $J = 8.5$ Hz, 1H, H-6f), 6.91 (d, $J = 9.0$ Hz, 2H, H-5b), 6.87 – 6.84 (m, 3H, H-5c and H-6e), 6.82 (d, $J = 2.0$ Hz, 1H, H-4b), 5.72 (d, $J = 10.0$ Hz, 1H, NH), 5.37 (d, $J = 2.0$ Hz, 1H, H-6β), 4.96 (d, $J = 3.0$ Hz, 1H, H-5α), 4.77 (dd, $J = 10.0$, 2.0 Hz, 1H, H-6α), 4.25 (s, 1H, H-4α), 4.25 – 4.18 (m, 1H, OC*H*HCH_3), 4.09-4.04 (m, 1H, OCH*H*CH_3), 3.94 – 3.84 (br.s, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 3.69 – 3.62 (br.s, 2H, NCH_2), 2.10 – 1.96 (br.d, 4H, NCH_2CH_2), 1.27, (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 0.71 (s, 9H, *t*BuSi), – 0.06 (s, 3H, CH_3Si), – 0.25 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 176.7$, 170.0, 169.4, 160.8, 154.3, 153.9, 138.6, 134.2, 130.0, 128.8, 128.5, 128.4, 126.9, 123.8, 119.4, 118.7, 117.5, 114.7, 110.1, 73.6, 62.6, 61.5, 60.1, 58.6, 55.7, 47.2, 40.7, 30.1, 29.8, 25.7, 18.2, 14.1, – 4.5, – 5.7; HRMS (FAB) calcd for $C_{38}H_{48}N_6O_7SiClBrCs$ $[M + Cs^+]$ 975.1280, found 975.1256.

Pentapeptide 82: A solution of amine **81** (7.0 mg, 0.0083 mmol) and carboxylic acid **80** (5.0 mg, 0.0064 mmol) in THF (0.3 mL) at – 15 °C was stirred for 15 min before the addition of HOAt (9.8 mg, 0.071 mmol). After 5 min EDC (3.0 mg, 0.016 mmol) was added and stirring was continued for an additional 2 h while the temperature was raised to 0 °C. The reaction was quenched by the addition of H_2O (5 mL) and diluted with EtOAc (5 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The resulting residue was purified by flash column chromatography (silica gel, 40 % EtOAc in benzene) to afford pentapeptide **82** (8.3 mg, 81 %). **82**: $R_f = 0.21$ (silica gel, 5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +5.54$ ($c = 0.83$, MeCN); IR (thin film): $\tilde{\nu}_{max} = 3318$, 2928, 1663, 1513, 1415, 1250, 1177, 1098, 1032 cm^{-1}; ^1H NMR (600 MHz, CD_3CN): $\delta = 7.49$ (s, 1H, NH), 7.47-7.44 (br.s, 1H, NH), 7.41 (dd, $J = 1.5$, 0.5 Hz, 1H, H-6b), 7.37 (br.s, 1H, OH), 7.31 (d, $J = 2.0$ Hz, 1H, H-4f), 7.24 (d, $J = 8.5$ Hz, 2H, H-5b), 7.20 – 7.16 (m, 3H, H-2b, H-6f and NH), 7.09 – 7.05 (m, 5H, H-6e and ArH), 7.02 – 6.98 (m, 3H, H-4b and H-5c), 6.96 (d, $J = 8.0$ Hz, 1H, H-2f), 6.83 (d, $J = 12.0$ Hz, 2H, ArH), 6.80 – 6.75 (m, 3H, H-2e and ArH), 6.67 (d, $J = 7.5$ Hz, 1H, NH), 5.94 (d, $J = 8.0$ Hz, 1H, $CHAr_2$), 5.76 (d, $J = 9.0$ Hz, 1H, NH), 5.42 (d, $J = 7.5$ Hz, 1H, H-5α), 5.37 (d, $J = 1.5$ Hz, 1H, H-6β), 5.28 (d, $J = 7.0$ Hz, 1H, H-4α), 5.21 (br.s, 1H, H-2β), 4.96 (br.s, 1H, NH), 4.67 – 4.61 (m, 1H, H-3α), 4.51 (d, $J = 9.5$ Hz, 1H, H-6α), 4.21 – 4.16 (m, 2H, H-2α and OC*H*HCH_3), 4.09 – 4.02 (m, 1H, OCH*H*CH_3), 3.95 – 3.87 (br.s, 2H, NCH_2), 3.80 (s, 3H, 5-OCH_3), 3.74 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.67 – 3.61 (br.s, 2H, NCH_2), 2.75 – 2.69 (m, 1H, H-3β), 2.58 – 2.53 (m, 1H, H-3β), 2.17 – 2.09 (bd, 4H, NCH_2CH_2), 1.23 (s, 9H, *t*BuO), 1.20 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 0.82 (s, 9H, *t*BuSi), 0.76 (s, 9H, *t*BuSi), 0.00 (s, 3H, CH_3Si), -0.05 (s, 3H, CH_3Si), – 0.15 (s, 3H, CH_3Si), – 0.17 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 171.3$, 170.8, 170.1, 169.3, 169.1, 168.1, 161.0, 159.6, 159.5, 157.5, 153.6, 152.9, 152.5, 141.6, 139.1, 137.1, 135.2, 135.2, 134.2, 130.9, 129.8, 129.2, 129.2, 129.1, 127.1, 127.0, 126.6, 123.1, 120.7, 119.6, 119.3, 119.0, 117.7, 117.6, 115.4, 114.6, 113.1, 112.1, 80.0, 74.3, 74.2, 62.7, 61.1, 60.8, 58.3, 56.5, 56.1, 55.9, 55.7, 55.6, 51.9, 51.1, 47.2, 37.5, 28.3, 25.9, 25.8, 24.5, 24.1, 18.6, 18.3, 14.4, – 4.4, – 4.8, – 5.0, – 5.7; HRMS (FAB) calcd for $C_{77}H_{98}N_9O_{16}SiCl_2BrCs$ $[M + Cs^+]$ 1742.4285, found 1742.4194.

C-O-D/D-O-E System 83: To a solution of pentapeptide **82** (8.0 mg, 0.005 mmol), $CuBr \cdot Me_2S$ (5.7 mg, 0.028 mmol) and K_2CO_3 (4.0 mg, 0.29 mmol) in degassed MeCN (0.6 mL) at 25 °C was added pyridine (2 µL, 0.026 mmol). The resulting mixture was refluxed for 2 h. The reaction mixture was cooled to 25 °C, diluted with EtOAc (10 mL) and quenched with saturated aqueous NH_4Cl (5 mL). The mixture was stirred for 0.5 h and then the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and filtered through a pad of silica gel. The solvent was removed in vacuo and the residue was purified by preparative TLC (silica gel, 40 % acetone in hexanes) to afforded C-O-D/D-O-E system **83** (3.0 mg, 40 %). **83**: $R_f = 0.40$ (silica gel, 40 % acetone in hexanes); $[\alpha]_D^{22} = -43.2$ ($c = 0.25$, MeCN); IR (thin film): $\tilde{\nu}_{max} = 3402$, 2926, 1668, 1513, 1350, 1251, 1097 cm^{-1}; ^1H NMR (600 MHz, CD_3CN, 310 K): $\delta = 7.54$ (s, 1H, H-2b), 7.48 (s, 1H, H-6b), 7.39 – 7.36 (m, 1H, NH), 7.33 – 7.28 (m, 3H, NH and H-5b), 7.17 (s, 2H, H-2f and H-4f), 7.08 – 7.03 (m, 6H, H-6f, ArH and NH), 6.99 (d, $J = 8.5$ Hz, 2H, H-5c), 6.89 (d, $J = 8.0$ Hz, 1H, NH), 6.85 (d, $J = 8.5$ Hz, 1H, H-6e), 6.82 – 6.77 (m, 5H, H-2e and ArH), 6.61 (s, 1H, H-4b), 5.88 (d, $J = 7.5$ Hz, 1H, $CHAr_2$), 5.75 (d, $J = 8.5$ Hz, 1H, NH), 5.71 (s, 1H, H-2β), 5.42 (s, 1H, H-6β), 5.40 (d, $J = 8.5$ Hz, 1H, H-4α), 5.30 (d, $J = 8.0$ Hz, 1H, H-5α), 4.63 – 4.59 (m, 2H, H-2α and H-3α), 4.54 (d, $J = 7.0$ Hz, 1H, H-6α), 4.20 – 4.13 (m, 1H, OC*H*HCH_3), 4.07 – 4.01 (m, 1H, OCH*H*CH_3), 3.81 (s, 3H, 5-OCH_3), 3.80 – 3.74 (br.s, 4H, NCH_2), 3.73 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.67 – 2.63 (m, 1H, H-3β), 2.42 (dd, $J = 16.0$, 6.0 Hz, 1H, H-3β), 2.08-2.05 (br.s, 4H, NCH_2CH_2), 1.39 (s, 9H, *t*BuO), 1.23 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 0.91 (s, 9H, *t*BuSi), 0.83 (s, 9H, *t*BuSi), 0.13 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si), – 0.02 (s, 3H, CH_3Si), – 0.09 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 174.6$, 171.5, 170.0, 169.5, 169.3, 168.6, 160.9, 159.6, 159.5, 157.7, 152.5, 152.2, 151.5, 151.3, 140.1, 135.2, 135.1, 134.5, 131.6, 130.6, 130.5, 129.9, 129.3, 129.0, 128.5, 127.8, 127.4, 125.9, 125.6, 120.3, 119.6, 116.9, 115.5, 114.6, 114.5, 108.5, 79.7, 74.0, 73.4, 62.6, 62.0, 60.9, 60.9, 57.8, 56.9, 55.9, 55.7, 54.0, 51.6, 38.3, 28.5, 26.0, 25.9, 24.2, 18.7, 18.4, 14.1, – 4.3, – 4.9, – 5.1, – 5.7; HRMS (FAB) calcd for $C_{77}H_{97}N_9O_{16}Si_2Cl_2Cs$ $[M + Cs^+]$ 1662.5023, found 1662.5108.

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[1] K. C. Nicolaou, H. Li, C. N. C. Boddy, J. M. Ramanjulu, T.-Y. Yue, S. Natarajan, X.-J. Chu, S. Bräse, *Chem. Eur. J.* **1999**, *5*, 2584 – 2601.
[2] K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T.-Y. Yue, H. Li, S. Bräse, J. M. Ramanjulu, *J. Am. Chem. Soc.* **1997**, *119*, 3421 – 3422.
[3] K. C. Nicolaou, J. M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C. N. C. Boddy, F. Rübsam, *Chem. Commun.* **1997**, 1899 – 1900.
[4] For preliminary communications on the synthesis of vancomycin amino acid building blocks, see: a) K. C. Nicolaou, S. Natarajan, H. Li, N. F. Jain, R. Hughes, M. E. Solomon, J. M. Ramanjulu, C. N. C. Boddy, M. Takayanagi, *Angew. Chem.* **1998**, *110*, 2872 – 2879; *Angew. Chem. Int. Ed.* **1998**, *37*, 2708 – 2714; b) K. C. Nicolaou, N. F. Jain, S. Natarajan, R. Hughes, M. E. Solomon, H. Li, J. M. Ramanjulu, M. Takayanagi, A. E. Koumbis, T. Bando, *Angew. Chem.* **1998**, *110*, 2879 – 2881; *Angew. Chem. Int. Ed.* **1998**, *37*, 2714 – 2717.
[5] For key papers and reviews, see: reference [1].
[6] a) D. A. Evans, J. A. Ellman, K. M. DeVries, *J. Am. Chem. Soc.* **1989**, *111*, 8912 – 8914; b) D. A. Evans, D. A. Evrard, S. D. Rychnovsky, T. Fruh, W. G. Whittingham, K. M. DeVries, *Tetrahedron Lett.* **1992**, *33*, 1189 – 1192; c) D. A. Evans, C. J. Dinsmore, *Tetrahedron Lett.* **1993**, *34*, 6029 – 6032; d) D. A. Evans, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, *J. Am. Chem. Soc.* **1993**, *115*, 6426 – 6427; e) D. A. Evans, P. S. Watson, *Tetrahedron Lett.* **1996**, *37*, 3251 – 3254; f) D. A. Evans,

  0947-6539/99/0509-2620 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 9

C. J. Dinsmore, A. M. Ratz, D. A. Evrard, J. C. Barrow, *J. Am. Chem. Soc.* **1997**, *119*, 3417–3418; g) D. A. Evans, J. C. Barrow, P. S. Watson, A. M. Ratz, C. J. Dinsmore, D. A. Evrard, K. M. D eVries, J. A. Ellman, S. D. Rychnovsky, J. Lacour, *J. Am. Chem. Soc.* **1997**, *119*, 3419–3420; h) D. A. Evans, C. J. Dinsmore, A. M. Ratz, *Tetrahedron Lett.* **1997**, *38*, 3189–3192; i) D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. L. Katz, *Angew. Chem.* **1998**, *110*, 2864–2868; *Angew. Chem. Int. Ed.* **1998**, *37*, 2700–2704; j) D. A. Evans, C. J. Dinsmore, P. S. Watson, M. R. Wood, T. I. Richardson, B. W. Trotter, J. L. Katz, *Angew. Chem.* **1998**, *110*, 2868–2872; *Angew. Chem. Int. Ed.* **1998**, *37*, 2704–2708.

[7] a) D. L. Boger, Y. Nomoto, B. R. Teegarden, *J. Org. Chem.* **1993**, *58*, 1425–1433; b) D. L. Boger, R. M. Borzilleri, S. Nukui, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3091–3096; c) D. L. Boger, R. M. Borzilleri, S. Nukui, *J. Org. Chem.* **1996**, *61*, 3561–3565; d) D. L. Boger, O. Loiseleur, S. L. Castle, R. T. Beresis, J. H. Wu, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3199–3202; e) D. L. Boger, R. M. Borzilleri, S. Nukui, R. T. Beresis, *J. Org. Chem.* **1997**, *62*, 4721–4736; f) D. L. Boger, R. T. Beresis, O. Loiseleur, J. H. Wu, S. L. Castle, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 721–724; g) D. L. Boger, S. Miyazaki, L. Olivier, R. T. Beresis, S. L. Castle, J. H. Wu, Q. Jin, *J. Am. Chem. Soc.* **1998**, *120*, 8920–8926; h) D. L. Boger, S. L. Castle, S. Miyazaki, J. H. Wu, R. T. Beresis, O. Loiseleur, *J. Org. Chem.* **1999**, *64*, 70–80.

[8] a) R. Beugelmans, G. P. Singh, M. Bois-Choussy, J. Chastanet, J. Zhu, *J. Org. Chem.* **1994**, *59*, 5535–5542; b) R. Beugelmans, J. Zhu, N. Husson, M. Bois-Choussy, G. P. Singh, *J. Chem. Soc. Chem. Commun.* **1994**, 439–440; c) R. Beugelmans, S. Bourdet, J. Zhu, *Tetrahedron Lett.* **1995**, *36*, 1279–1282; d) J. Zhu, R. Beugelmans, S. Bourdet, J. Chastanet, G. Roussi, *J. Org. Chem.* **1995**, *60*, 6389–6396; e) M. Bois-Choussy, R. Beugelmans, J.-P. Bouillon, J. Zhu, *Tetrahedron Lett.* **1995**, *36*, 4781–4784; f) J. Zhu, J.-P. Bouillon, G. P. Singh, J. Chastanet, R. Beugelmans, *Tetrahedron Lett.* **1995**, *36*, 7081–7084; g) R. Beugelmans, L. Neuville, M. Bois-Choussy, J. Zhu, *Tetrahedron Lett.* **1995**, *36*, 8787–8790; h) R. Beugelmans, M. Bois-Choussy, C. Vergne, J.-P. Bouillon, J. Zhu, *Chem. Commun.* **1996**, 1029–1030; i) M. Bois-Choussy, L. Neuville, R. Beugelmans, J. Zhu, *J. Org. Chem*. **1996**, *61*, 9309–9322; j) C. Vergne, M. Bois-Choussy, R. Beugelmans, J. Zhu, *Tetrahedron Lett.* **1997**, *38*, 1403–1406; k) C. Vergne, J.-P. Bouillon, J. Chastanet, M. Bois-Choussy, J. Zhu, *Tetrahedron: Asymmetry* **1998**, *9*, 3095–3103; l) C. Vergne, M. Bois-Choussy, J. Zhu, *Synlett* **1998**, 1159–1160.

[9] a) A. J. Pearson, J. G. Park, *J. Org. Chem*. **1992**, *57*, 1744–1752; b) A. J. Pearson, J. G. Park, P. Y. Zhu, *J. Org. Chem*. **1992**, *57*, 3583–3589; c) A. J. Pearson, H. Shin *Tetrahedron* **1992**, *48*, 7527–7538; d) A. J. Pearson, K. Lee, *J. Org. Chem.* **1994**, *59*, 2304–2313; e) A. J. Pearson, H. Shin, *J. Org. Chem.* **1994**, *59*, 2314–2323; f) A. J. Pearson, K. Lee, *J. Org. Chem*. **1995**, *60*, 7153–7160; g) A. J. Pearson, G. Bignan, *Tetrahedron Lett*. **1996**, *37*, 735–738; h) A. J. Pearson, G. Bignan, P. Zhang, M. Chelliah, *J. Org. Chem.* **1996**, *61*, 3940–3941; i) A. J. Pearson, P. Zhang, G. Bignan, *J. Org. Chem.* **1997**, *62*, 4536–4538; j) A. J. Pearson, V. C. Mariappan, G. C. Bignan, *Synthesis* **1997**, 536–540.

[10] a) A. V. R. Rao, T. K. Chakraborty, S. P. Joshi, *Tetrahedron Lett.* **1992**, *33*, 4045–4048; b) A. V. R. Rao, T. K. Chakraborty, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1992**, *33*, 4799–4802; c) A. V. R. Rao, M. K. Gurjar, V. Kaiwar, V. B. Khare, *Tetrahedron Lett.* **1993**, *34*, 1661–1664; d) A. V. R. Rao, K. L. Reddy, M. M. Reddy, *Tetrahedron Lett.* **1994**, *35*, 5039–5042; e) A. V. R. Rao, T. K. Chakraborty, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, *35*, 5043–5046; f) A. V. R. Rao, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, *35*, 5047–5050; g) A. V. R. Rao, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, *35*, 8465–8468; h) A. V. R. Rao, K. L. Reddy, A. S. Rao, T. V. S. K. Vittal, M. M. Reddy, P. L. Pathi, *Tetrahedron Lett.* **1996**, *37*, 3023–3026; i) A. V. R. Rao, M. K. Gurjar, P. Lakshmipathi, M. M. Reddy, M. Nagarajan, S. Pal, B. V. N. B. S. Sarma, N. K. Tripathy, *Tetrahedron Lett*. **1997**, *38*, 7433–7426; j) A. V. R. Rao, *Pure Appl. Chem.* **1998**, *70*, 391–396.

[11] a) N. Pant, A. D. Hamilton, *J. Am. Chem. Soc.* **1988**, *110*, 2002–2003; b) M. J. Stone, M. S. Van Dyk, P. M. Booth, D. H. Williams, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1629–1635; c) A. G. Brown, M. J. Crimmin, P. D. Edwards, *J. Chem. Soc.*, *Perkin Trans. 1* **1992**, 123–130; d) R. B. Lamont, D. G. Allen, I. R. Clemens, C. E. Newall, M. V. J. Ramsay, M. Rose, S. Fortt, T. Gallagher, *J. Chem. Soc. Chem. Commun*. **1992**, 1693–1695; e) K. Nakamura, S. Nishiyama, S. Yamamura, *Tetrahedron Lett.* **1996**, *37*, 191–192; f) H. Konishi, T. Okuno, S. Nishiyama, S. Yamamura, K. Koyasu, Y. Terada, *Tetrahedron Lett.* **1996**, *37*, 8791–8794.

[12] K. C. Nicolaou, S. Natarajan, C. N. C. Boddy, unpublished results, **1998**.

[13] For an alternative preparation of AA-7 building block, see: reference [6b].

[14] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2484–2547.

[15] S. David, S. Hanessian, *Tetrahedron* **1985**, *41*, 643–663.

[16] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.

[17] For an alternative preparation of AA-5 building block, see: reference [7e].

[18] M. A. Brook, T. H. Chan, *Synthesis* **1983**, 201–203.

[19] For alternative preparations of AA-6 building blocks, see: references [6i, 7b, and 8f].

[20] B. Tao, G. Schlingloff, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 2507–2509.

[21] D. Masilamani, M. M. Rogic, *J. Org. Chem.* **1981**, *46*, 4486–4489.

[22] For alternative preparations of AA-4 building blocks, see: a) F. A. Davis, D. L. Fanelli, *J. Org. Chem.* **1998**, *63*, 1981–1985; b) T. K. Chakraborty, K. A. Hussain, G. V. Reddy, *Tetrahedron* **1995**, *51*, 9179–9190; c) T. K. Chakraborty, G. V. Reddy, G. V. Hussain, *Tetrahedron Lett.* **1991**, *32*, 7597–7600; d) references [7c, 8f, 8h, and 8k].

[23] B. Lal, B. N. Pramanik, M. S. Manhas, A. K. Bose, *Tetrahedron Lett.* **1977**, 1977–1980.

[24] Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, *48*, 1353–1406.

[25] W. Koenig, R. Geiger, *Chem. Ber.* **1970**, *103*, 2041–2051.

[26] For alternative preparations of AA-2 building blocks, see: a) A. Girard, C. Greek, D. Ferroud, J. P. Genet, *Tetrahedron Lett.* **1996**, *37*, 7967–7970; b) A. Solladie-Cavallo, T. Nsenda, *Tetrahedron Lett.* **1998**, *39*, 2191–2194; c) references [6e, 7b, 7e and 10e].

[27] For preparation of amine **6**, see: reference [28].

[28] K. C. Nicolaou, A. E. Koumbis, M. Takayanagi, S. Natarajan, N. F. Jain, T. Bando, H. Li, R. Hughes, *Chem. Eur. J.* **1999**, *5*, 2622–2647.

[29] K. C. Nicolaou, H. J. Mitchell, N. F. Jain, T. Bando, R. Hughes, N. Winssinger, S. Natarajan, A. E. Koumbis, *Chem. Eur. J.* **1999**, *5*, 2648–2667.

[30] D. Marcovici-Mizrahi, H. E. Gottlieb, V. Marks, A. Nudelman, *J. Org. Chem.* **1996**, *61*, 8402–8406.

[31] B. R. De Costa, A. Lewin, J. A. Schoenheimer, P. Skolnick, K. C. Rice, *Heterocycles* **1991**, *32*, 2343–2355.

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