Total Synthesis of Vancomycin—Part 3: Synthesis of the Aglycon

K. C. Nicolaou,* Alexandros E. Koumbis, Masaru Takayanagi, Swaminathan Natarajan, Nareshkumar F. Jain, Toshikazu Bando, Hui Li, and Robert Hughes[a]

Abstract: The total synthesis of the vancomycin aglycon (**2**, Figure 1) is described. Construction of the key intermediate, tricyclic triazene **3a** (Figure 2), was accomplished in the order C-O-D →AB/C-O-D →AB/C-O-D/D-O-E. The C-O-D ring system **18a** (Scheme 2) was formed by using the triazene ring-closure methodology from a precursor (**17**) already possessing the AB biaryl fragment **6**, synthesized by a Suzuki coupling reaction. At this point, a macrolactamization reaction furnished the AB ring system. Tripeptide **5** was incorporated in the main framework and the triazene ring-closure methodology was applied again to achieve the formation of D-O-E ring system, providing tricyclic triazene **3a** (Scheme 6). The latter was converted to the fully protected vancomycin aglycon **45a** by first introducing the phenolic moiety (derivative **43a**) and then oxidizing the AA-7 side chain (Scheme 12). Finally, global deprotection afforded vancomycin's aglycon (**2**). Atropisomerization was successfully performed for D-O-E ring systems.

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

Introduction

In the preceding two papers[1, 2] in this series, we described the development of basic methodology for the construction of vancomycin's key amino acid building blocks and the evaluation of a number of strategies towards the vancomycin skeleton. These studies helped to shape our final plan towards the total synthesis of vancomycin[3] (**1**, Figure 1) and its aglycon[4] (**2**, Figure 1). The subject of this article is the implementation of this strategy and the total synthesis of vancomycin aglycon (**2**).[5]

Results and Discussion

Retrosynthetic analysis and strategy

It was presumed that vancomycin (**1**, Figure 1) could be synthesized from its aglycon (**2**, Figure 1). Furthermore, it was

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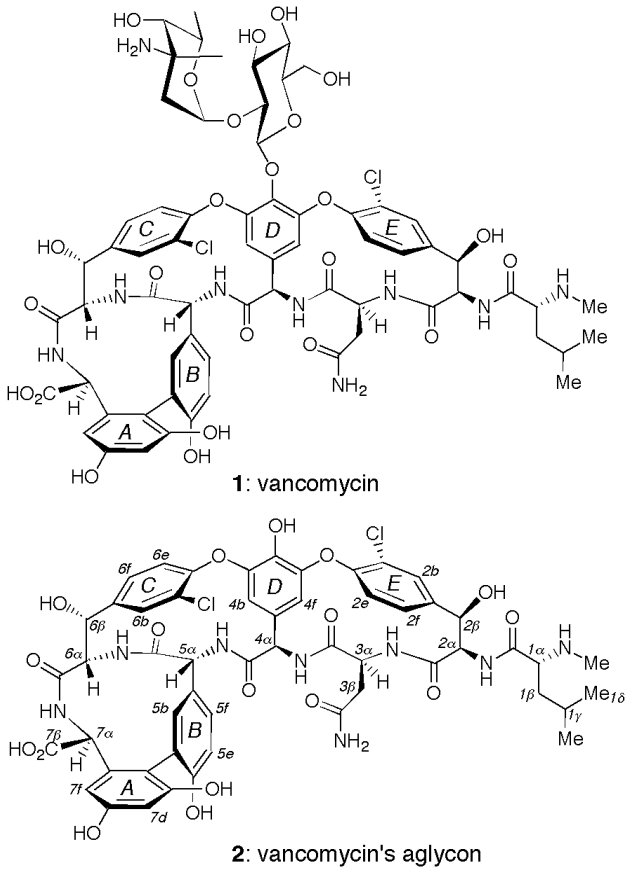

Figure 1. Molecular structures of vancomycin (**1**) and vancomycin aglycon (**2**).

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anticipated that **2** could be derived from the protected triazene **3a** (Figure 2), a structure containing the entire skeleton of the aglycon, plus functionality suitable for its potential conversion to **2**, and thence to **1**. This strategic analysis defined for us compound **3a** as the key advanced subtarget, whose retrosynthetic disassembly is shown in Figure 2. Thus, the four building blocks **4**–**7** emerged as the second generation of subtargets. Below, we describe the forward synthetic sequences that led to the construction and assembly of these intermediates to the desired targets and related systems. As a reminder from the preceding papers,[1, 2] the chosen path will entail construction of ring systems C-O-D, AB, and D-O-E, in that order.

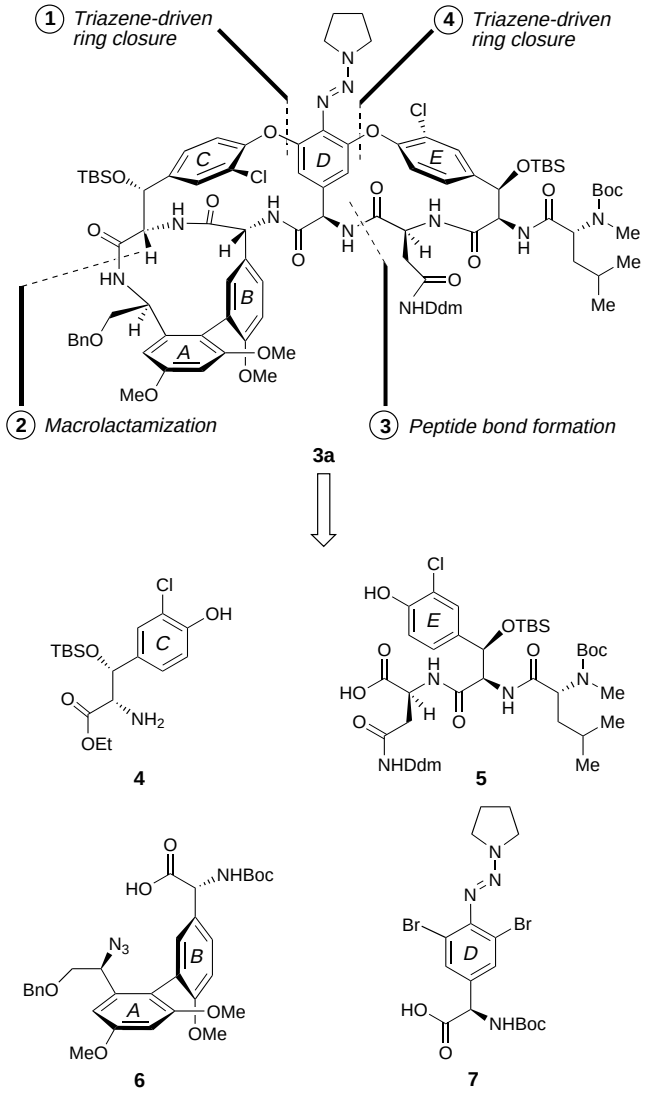


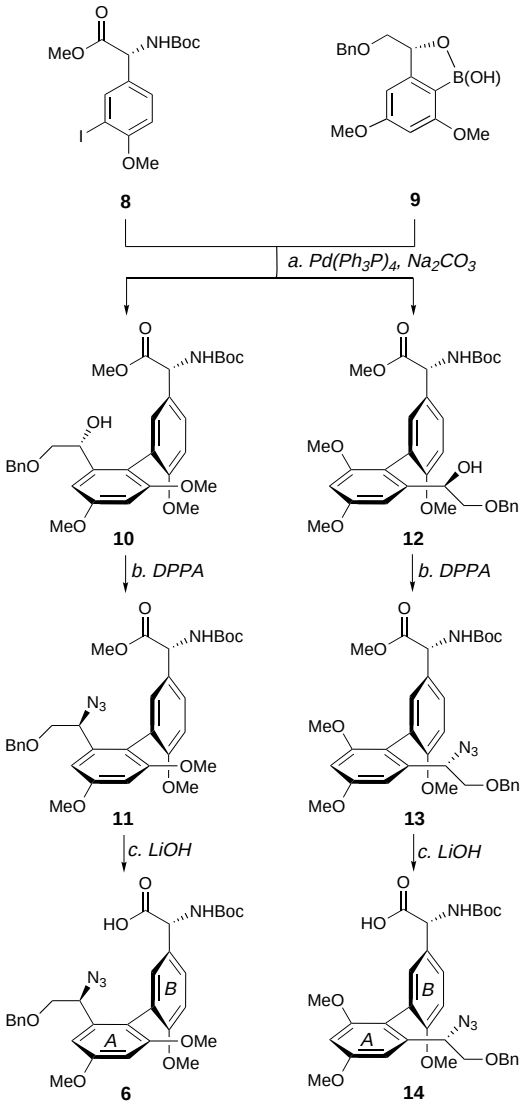
Figure 2. Retrosynthetic analysis of protected triazene **3a**. Bn = benzyl; Boc = *tert*-butoxycarbonyl; Ddm = 4,4′-dimethoxyldiphenylmethyl; TBS = *tert*-butyldimethylsilyl.

Abstract in Greek:

Σε αυτο το αρθρο περιγραφεται η ολικη συνθεση του αγλυκου της βανκομυκινης (**2**, Φιγουρα 1). Η συνθεση του σημαντικου ενδιαμεσου **3a** (τρικυκλικη τριαζινη, Φιγουρα 2) πραγματοποιηθηκε κατα τη σειρα C-O-D→AB/C-O-D→AB/C-O-D/D-O-E. Το C-O-D κυκλικο συστημα **18a** (Σχημα 2) παρασκευστηκε χρησιμοποιοντας τη μεθοδολογια κυκλοποιησης μεσω τριαζινης απο μια προδρομη ενωση (**17**) που ηδη εμπεριειχε το AB διαρυλικο συστημα **6**, το οποιο συντεθηκε μεσω μιας αντιδρασης συζευξης τυπου Suzuki. Σε αυτο το σημειο εφαρμοστηκε μια αντιδραση μακρολακτονοποιησης για τη συνθεση του AB δακτυλιου. Μετα την ενσωματωση του τριπεπτιδιου **5** στον κυριως σκελετο, εφαρμοστηκε ξανα η μεθοδολογια κυκλοποιησης μεσω τριαζινης για το σχηματισμο του D-O-E δακτυλιου και ετσι συντεθηκε η τρικυκλικη τριαζινη **3a** (Σχημα 6). Η τελευταια μετατραπηκε στο πληρως προστατευμενο αγλυκο της βανκομυκινης **45a** εισαγοντας αρχικα τη φαινολικη ομαδα (παραγωγο **43a**) και οξειδωνοντας την πλευρικη αλυσιδα του AA–7 (Σχημα 12). Το τελευταιο σταδιο για την παρασκευη του αγλυκου της βανκομυκινης (**2**) αφορα στην απομακρυνση ολων των ομαδων προστασιας. Η ατροποισομερειωση διεξηχθει επιτυχως σε ορισμενα D-O-E κυκλικα συστηματα.

Construction of biaryl systems

Scheme 1 depicts the construction of the key amino acid derivative **6** and its atropisomer (**14**) from building blocks **8** and **9**, whose synthesis has already been described in the



Scheme 1. Construction of biaryl system by Suzuki reaction. a) 0.2 equiv of $Pd(Ph_3P)_4$, 1.2 equiv of Na_2CO_3, PhMe/MeOH/H_2O (10:1:0.5), 90 °C, 4 h, **10**:**12** ca. 2:1 ratio of atropisomers, 84 % combined yield; b) 2.5 equiv of DPPA, 2.5 equiv of DEAD, 2.5 equiv of Ph_3P, THF, – 20 °C, 2 h, 95 % of **11**, 90 % of **13**; c) 1.5 equiv of LiOH, THF/H_2O (1:1), 0 °C, 2 h, 99 % of **6**, 99 % of **14**. DEAD = diethyl azodicarboxylate; DPPA = diphenylphosphoryl azide.

preceding paper.[2] Thus, aryl iodide **8** and boronic acid **9** entered smoothly into a Suzuki[6] coupling reaction [$Pd(Ph_3P)_4$, Na_2CO_3, 90 °C] to afford a 2:1 mixture of atropisomers **10** and **12** in 84% combined yield. Chromatographic separation of these two atropisomers allowed separate elaboration of each.[7] The desired atropisomer (**10**, major) was directly converted to azide **11** (95% yield) by the action of DPPA (for abbreviations of reagents see legends in Schemes) in the presence of DEAD and Ph_3P.[8] Similarly, azide **13** was obtained from alcohol **12** in 90% yield. Both **11** and **13** underwent clean saponification to carboxylic acids **6** and **14**, respectively, when treated with LiOH in THF/H_2O (1:1) at 0 °C (99% yield in each case).

Construction of AB/C-O-D systems

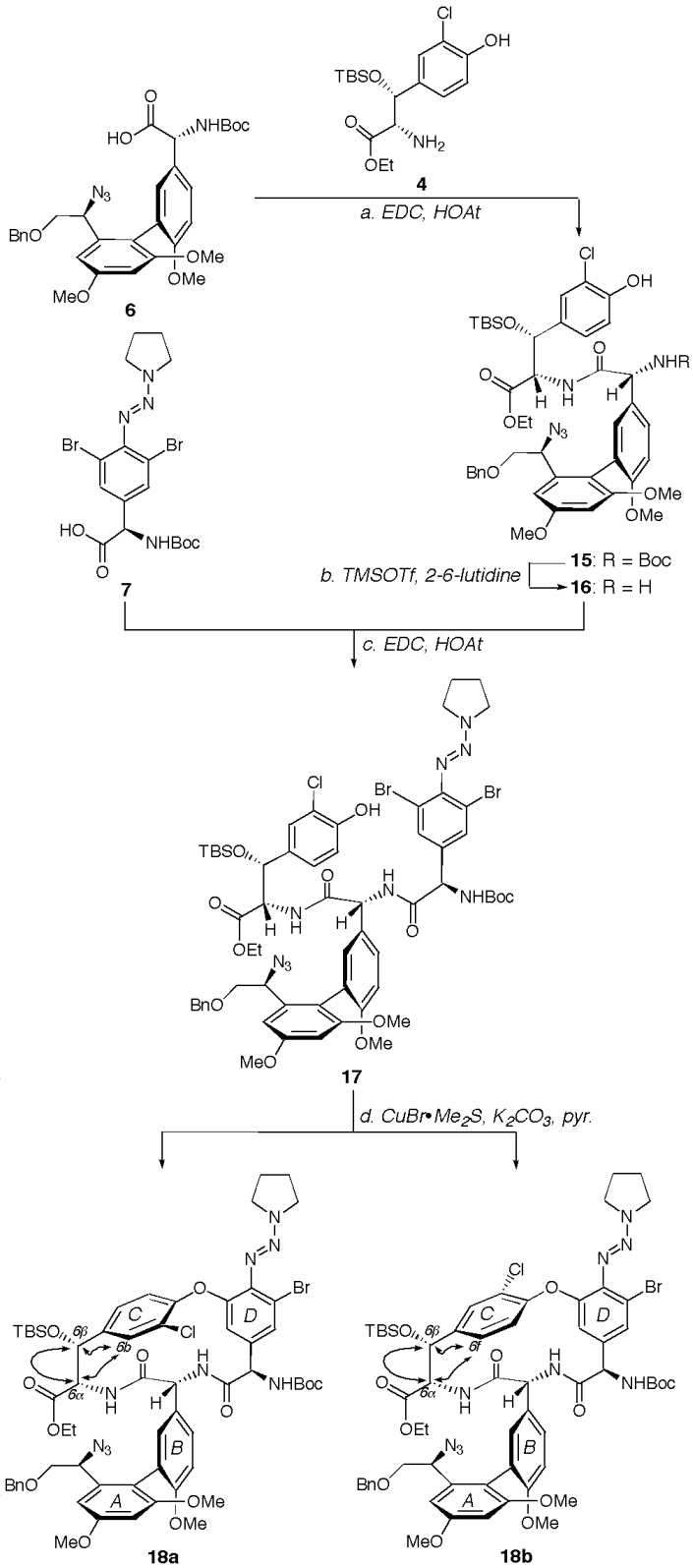
Scheme 2 presents the peptide coupling of key intermediates **4**, **6**, and **7** and ring closure of the resulting tripeptide (**17**) to C-O-D rings **18a** and **18b**. Thus, mixing **6** and **4** in the presence of EDC and HOAt[9] at low temperature (−30 → −10 °C) resulted in the formation of **15** (87% yield). Exposure of **15** to excess TMSOTf (3.3 equiv) and 2,6-lutidine (3.0 equiv) precipitated loss of the Boc group,[10] furnishing **16** (90% yield), whose coupling with amino acid fragment **7** to afford **17** was facilitated by the action of EDC and HOAt (85% yield). Ring closure of **17** was induced by $CuBr \cdot Me_2S$, K_2CO_3, and pyridine in refluxing MeCN[11] and afforded C-O-D ring products **18a** (natural atropisomer) and **18b** (unnatural atropisomer) in about 1:1 ratio and 67% combined yield. The structural assignment of these atropisomers was based on NOE studies which revealed the indicated crucial effects (see structures **18a** and **18b** and Table 1).

Table 1. Diagnostic NOEs for structural determination of selected atropisomers.[a]

Compound	Solvent	(^{1}H-^{1}H) NOE[b]
18a	$CDCl_3$	6α↔6β; 6α↔6b; 6β↔6b
18b	$CDCl_3$	6α↔6β; 6α↔6f; 6β↔6f
22a	CD_3COCD_3	6α↔6β; 6α↔6b; 6β↔6b 5α↔5b; 6α↔5α
22b	CD_3COCD_3	6α↔6β; 6α↔6f; 6β↔6f 5α↔5b; 6α↔5α
27a	CD_3COCD_3	6α↔6β; 6α↔6b; 6β↔6b
27b	CD_3COCD_3	6α↔6β; 6α↔6f; 6β↔6f
31a	CD_3COCD_3	6α↔6f; 6β↔6b; 5α↔5f
31b	CD_3COCD_3	6α↔6b; 6β↔6f; 5α↔5f

[a] COSY and ROESY, 600 MHz, 300 K. [b] For the atom labeling see structures in Schemes 2, 3, 4 and 5.

The unnatural atropisomer served as a model to scout the territory ahead and secure a safe sequence before the more precious natural atropisomer was committed. Scheme 3 shows the push forward of both **18a** and **18b** to the stage of the AB/C-O-D systems **23a** and **23b**. Thus, it was found experimentally that the correct sequence to prepare the required precursors, amino acids **21a** and **21b**, was the one involving: a) TBS removal (nBu_4NF, 95% for **19a**; 98% for **19b**);



Scheme 2. Formation of C-O-D ring systems **18a** and **18b** from natural biaryl atropisomer. a) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, −30 → −10 °C, 12 h, 87%; b) 3.3 equiv of TMSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 90%; c) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, −78 → 0 °C, 12 h, 85%; d) 2.0 equiv of $CuBr \cdot Me_2S$, 2.0 equiv of K_2CO_3, 1.9 equiv of pyr., MeCN, reflux, 1.5 h, **18a**:**18b** ca. 1:1 ratio of atropisomers, 67% combined yield. EDC = 1-ethyl-3-(3-dimethylamino)-propylcarbodiimide hydrochloride; HOAt = 1-hydroxy-7-azobenzotriazole; Tf = trifluoromethanesulfonyl; TMS = trimethylsilyl.

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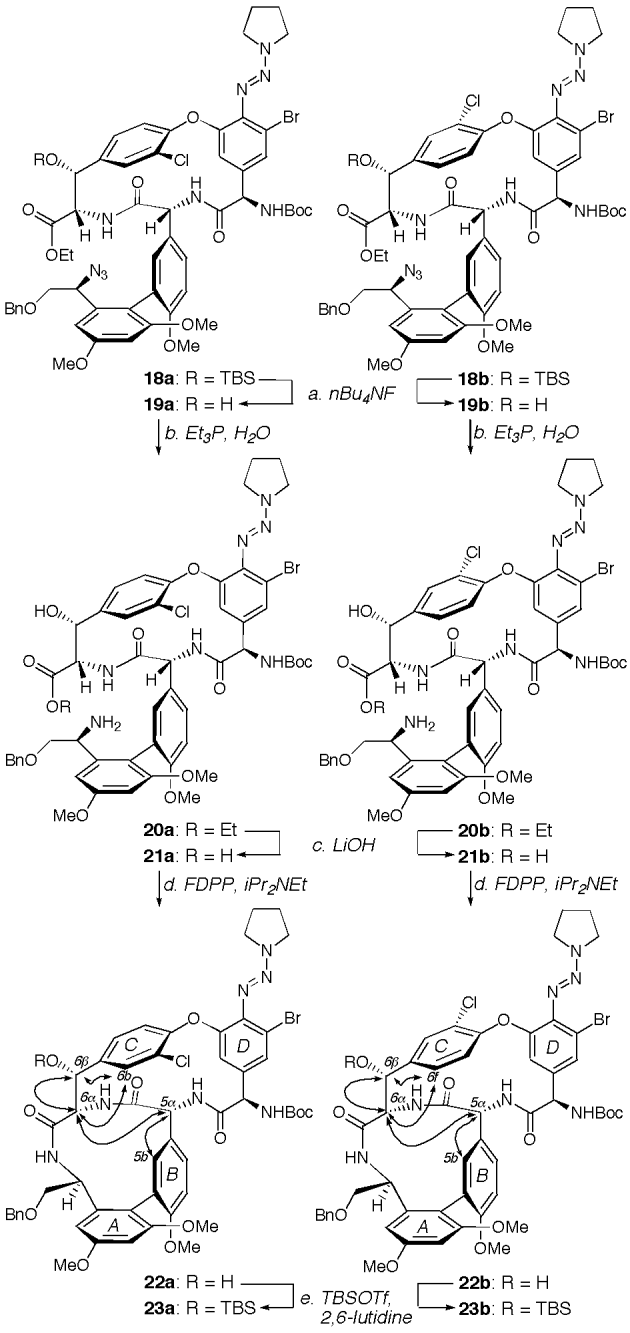


Scheme 3. Construction of AB/C-O-D bicyclic systems **23a** and **23b** from natural biaryl system. a) 1.1 equiv of nBu$_4$NF, THF, $-25 \rightarrow -15\,^{\circ}$C, 3 h, 95% of **19a**, 98% of **19b**; b) 2.0 equiv of Et$_3$P, MeCN/H$_2$O (4:1), 25 °C, 20 h, 78% of **20a**, 79% of **20b**; c) 5.0 equiv of LiOH, THF/H$_2$O (1:1), $-5 \rightarrow 0\,^{\circ}$C, 10 min, 92% of **21a**, 90% of **21b**, crude yields; d) 3.0 equiv of FDPP, 5.0 equiv of iPr$_2$NEt, DMF, $0 \rightarrow 25\,^{\circ}$C, 12 h, 86% of **22a**, 60% of **22b**; e) 5.0 equiv of TBSOTf, 15 equiv of 2,6-lutidine, CH$_2$Cl$_2$, $-20\,^{\circ}$C, 2 h, 85% of **23a**, 80% of **23b**. DMF = dimethylformamide; FDPP = pentafluorophenyl diphenylphosphinate.

b) reduction[12] of the azide (Et$_3$P-H$_2$O, 78% for **20a**; 79% for **20b**); and c) ester hydrolysis [LiOH, THF/H$_2$O (1:1), 92% for **21a**; 90% for **21b**, crude yields]. It should be noted that the ester moiety resisted hydrolysis under a variety of conditions in the presence of the bulky TBS group. The macrolactamization of **21a** and **21b** proceeded smoothly in DMF at ambient temperatures in the presence of FDPP[13] and iPr$_2$NEt, furnishing AB/C-O-D ring systems **22a** and **22b** in 86 and 60% yield respectively. The stereochemical assignment of the C-O-D atropisomers as well as the stereochemical arrangement of the AB biaryl system were based on NOE studies, and specifically on the effects indicated on the structures of **22a** and **22b** (see Scheme 3 and Table 1). Finally, the free hydroxy group in **22a** and **22b** was silylated (5.0 equiv of TBSOTf, 15 equiv of 2,6-lutidine, 85% for **23a**; 80% for **23b**) in preparation for the next act.

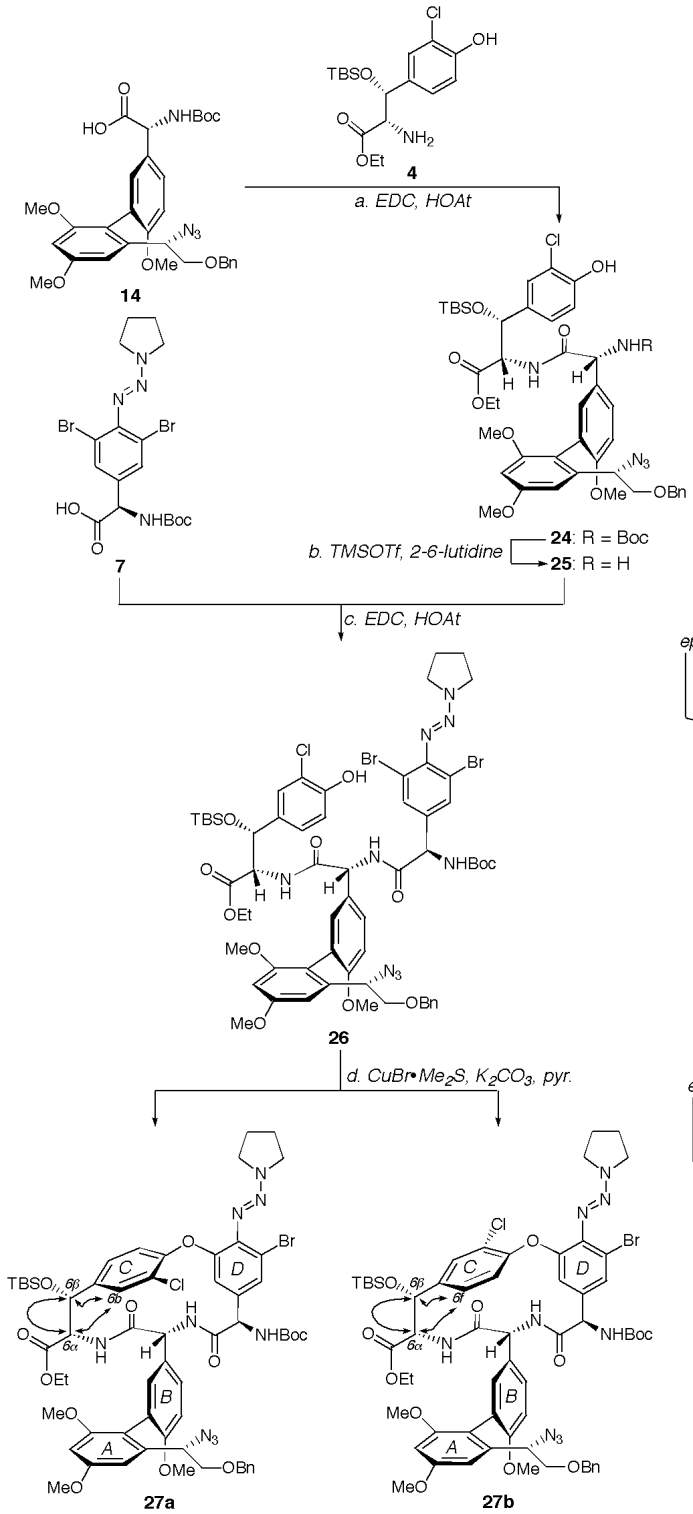
In order to investigate the atropisomerization of AB/C-O-D system on the C-O-D site, five intermediates of the sequence shown in Scheme 3 (**18a**, **19a**, **20a**, **22a** and **23a**) and their atropisomers were selected for thermal treatment. Unfortunately these intermediates failed to atropisomerize in various solvents and led either to decomposition upon heating at the conditions described by Boger et al.[14] or to recovery of starting material at lower temperatures.

At this stage it was decided to explore the elaboration of the unnatural atropisomer of the biaryl system, compound **14**, in the hope that atropisomerization at some future juncture could bring it back to the proper stereochemistry. Schemes 4 and 5 present our findings along these lines.

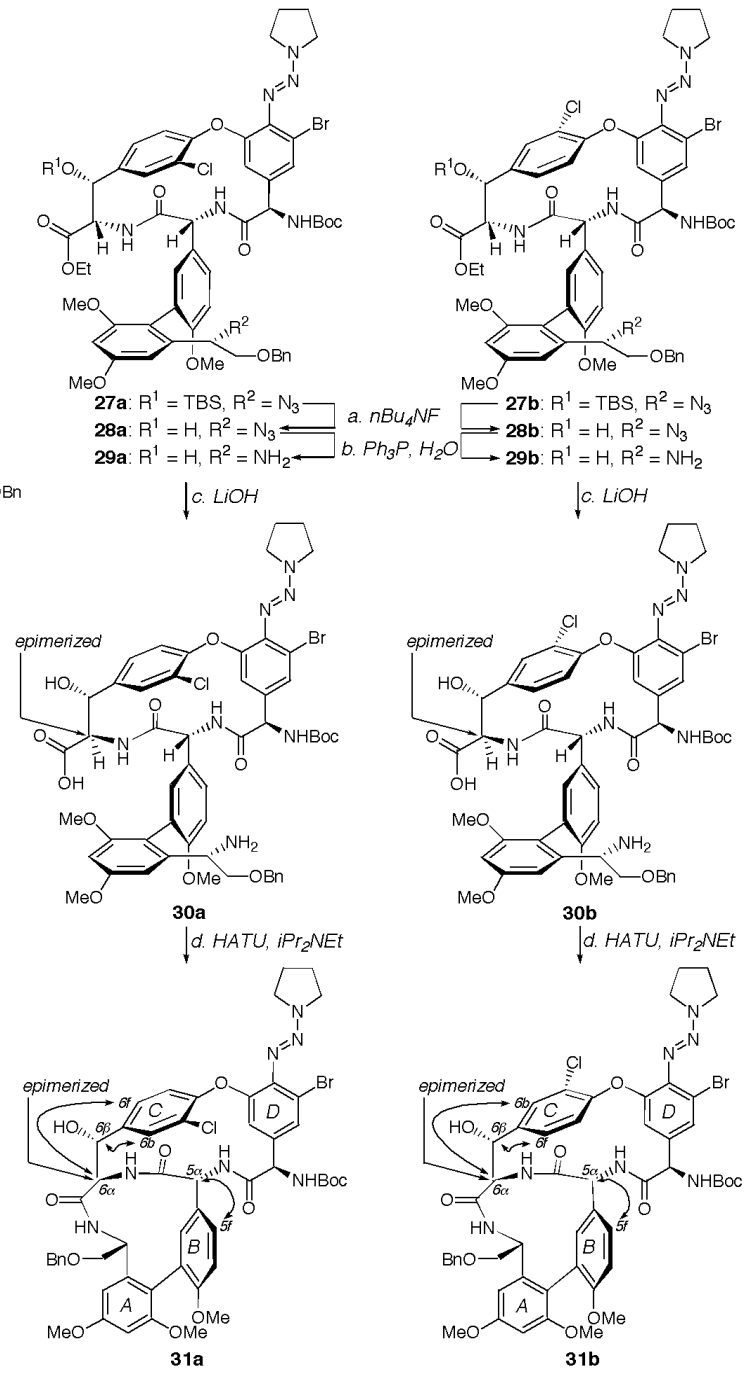
Amino acid derivatives **14** and **4** were joined together through the action of EDC and HOAt, leading to compound **24** in 83% yield (Scheme 4). The Boc group was then removed from the latter compound (**24**) by treatment with excess TMSOTf (3.4 equiv) and 2,6-lutidine (3.0 equiv), furnishing amino compound **25**. Coupling of **25** with central amino acid triazene derivative **7** (EDC, HOAt) led to tripeptide **26** in 70% yield, while cyclization of the latter by the usual protocol (CuBr·Me$_2$S, K$_2$CO$_3$, pyridine, MeCN, reflux)[11] gave C-O-D ring systems **27a** and **27b** (ca. 1:1 ratio) in 61% combined yield. NOE studies aided the stereochemical assignments of these atropisomers (see arrows on structures, Scheme 4 and Table 1).

The further elaboration of the atropisomeric C-O-D ring systems **27a** and **27b** (Scheme 5) revealed some interesting stereochemical effects. Thus, following the same sequence developed for the conversion of compounds **18a** and **18b** to their amino acid derivatives (see Scheme 3), the TBS group was first removed from **27a** (nBu$_4$NF, 90% yield) and **27b** (nBu$_4$NF, 92% yield) to afford **28a** and **28b**, respectively. The azido group was then reduced[15] (Ph$_3$P, H$_2$O, 60 °C) in each isomer, furnishing amines **29a** (82% yield) and **29b** (71% yield), respectively. Exposure of ethyl esters **29a** and **29b** to LiOH in MeOH/H$_2$O (10:1) at 0 °C resulted in saponification of the ethyl ester group, but with essentially complete epimerization at the adjacent center (indicated on the structure and based on NOE studies) leading to amino acids **30a** (92% yield) and **30b** (90% yield), respectively. Finally, macrolactamization of **30a** and **30b** was carried out in DMF at ambient temperature with HATU[16] and iPr$_2$NEt, furnishing AB/C-O-D ring systems **31a** (50% yield) and **31b** (51% yield), respectively. Stereochemical assignments were made based on NOE studies again, as indicated on structures **31a** and **31b** (see also Table 1).

It was quite apparent at this stage that with their drastic stereochemical differences from the natural systems, compounds **31a** and **31b** could not be brought into the main-



Scheme 4. Formation of C-O-D ring systems **27a** and **27b** from unnatural biaryl atropisomer. a) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, 0 °C, 10 h, 83 %; b) 3.4 equiv of TMSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 91 %; c) 3.0 equiv of EDC, 3.3 equiv of HOAt, THF, 0 °C, 10 h, 70 %; d) 3.0 equiv of CuBr · Me_2S, 3.0 equiv of K_2CO_3, 3.0 equiv of pyr., MeCN, reflux, 20 min, **27a**:**27b** ca. 1:1 ratio of atropisomers, 61 % combined yield.



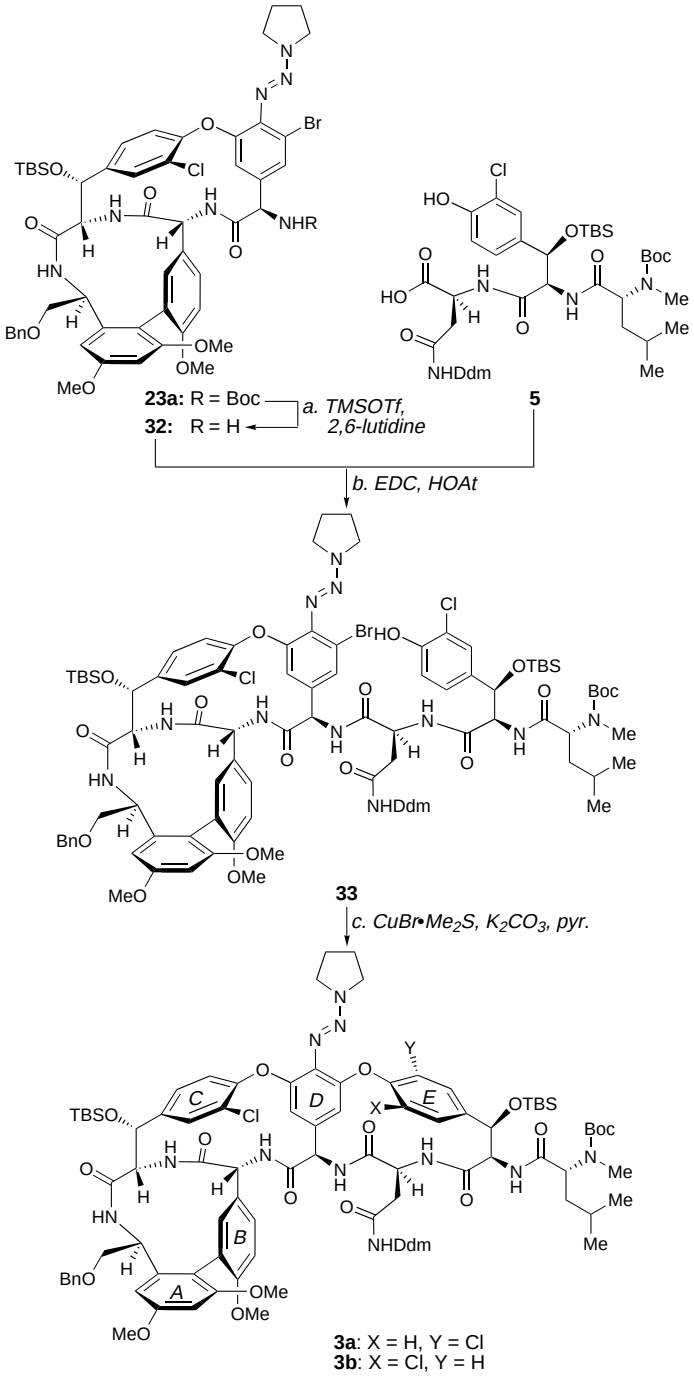
Scheme 5. Construction of AB/C-O-D bicyclic systems **31a** and **31b** from unnatural biaryl system. a) 1.5 equiv of nBu$_4$NF, THF, 0 °C, 2 h, 90 % of **28a**, 92 % of **28b**; b) 3.0 equiv of Ph_3P, 10.0 equiv of H_2O, THF, 60 °C, 3 h, 82 % of **29a**, 71 % of **29b**; c) 1.5 equiv of LiOH, MeOH/H_2O (10:1), 0 °C, 2 h, 92 % of **30a**, 90 % of **30b**; d) 1.5 equiv of HATU, 3.0 equiv of iPr$_2$NEt, DMF, 25 °C, 8 h, 50 % of **31a**, 51 % of **31b**. HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate.

stream chemistry of the program in a reasonable way. The saponification of esters **29a** and **29b** was also carried out in THF/H_2O mixtures, conditions which suppressed, to some extent, the epimerization. Interestingly, macrolactamization of the non-epimerized acids under the same conditions as for **30a** and **30b** proceeded less efficiently and gave the same epimerized products **31a** and **31b**. These results indicated that the AB/C-O-D frameworks with the unnatural AB atrop-structure prefer to reside in their epimeric form at $C_{6\alpha}$.

0947-6539/99/0509-2626 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 9

Construction of AB/C-O-D/D-O-E systems

We will now return to the main path of the chartered strategy towards the target, vancomycin aglycon (**2**). Scheme 6 depicts the processing of the natural atropisomer **23a** to the amino derivative **32**, setting the stage for the incorporation of tripeptide **5** whose synthesis has already been discussed in the preceding paper.[2] Thus, the Boc group was removed from the TBS ether **23a** by the action of excess TMSOTf (2.0 equiv) and 2,6-lutidine (3.0 equiv) to afford **32** in 96% yield. The anticipated union of **32** with tripeptide **5** was brought about in the presence of EDC and HOAt, furnishing the long-sought cyclization precursor **33** in 86% yield. The presence of the free phenolic group on ring E required the use of carefully controlled conditions for the success of this coupling. Finally, cyclization of **33** was effected by the use of $CuBr \cdot Me_2S$ in the presence of K_2CO_3 and pyridine in refluxing MeCN in the usual way, and the two formed atropisomers **3a** and **3b** (ca. 1:3 ratio, 74% combined yield) were chromatographically separated. The stereochemical assignments for the two atropisomers **3a** and **3b** were made on the basis of NOE studies, revealing the effects shown in Figure 3.



Scheme 6. Construction of AB/C-O-D/D-O-E tricyclic systems **3a** and **3b**. a) 2.0 equiv of TMSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, $-10\,^{\circ}C$, 0.5 h, 96%; b) 2.0 equiv of EDC, 10.0 equiv of HOAt, THF, $-15 \rightarrow 0\,^{\circ}C$, 12 h, 86%; c) 5.0 equiv of $CuBr \cdot Me_2S$, 5.0 equiv of K_2CO_3, 5.0 equiv of pyr., MeCN, reflux, 2 h, **3a**:**3b** ca. 1:3 ratio of atroipisomers, 74% combined yield.

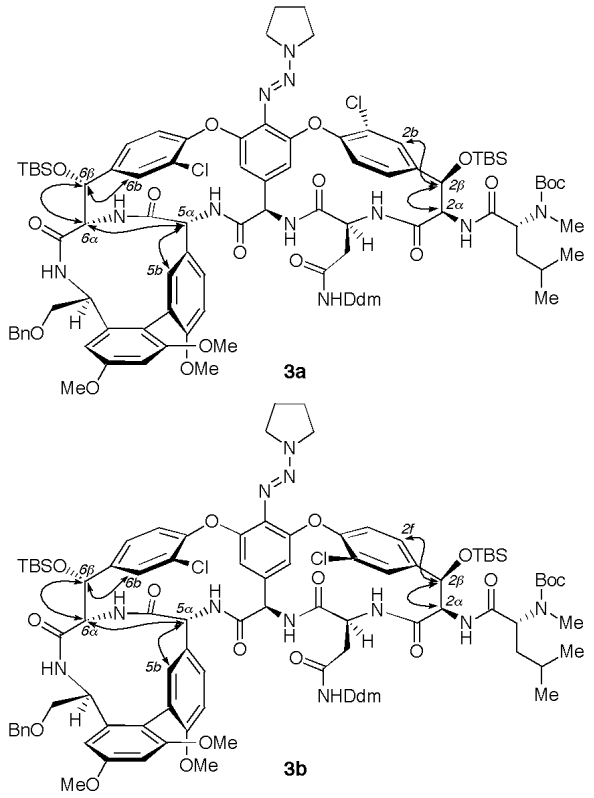
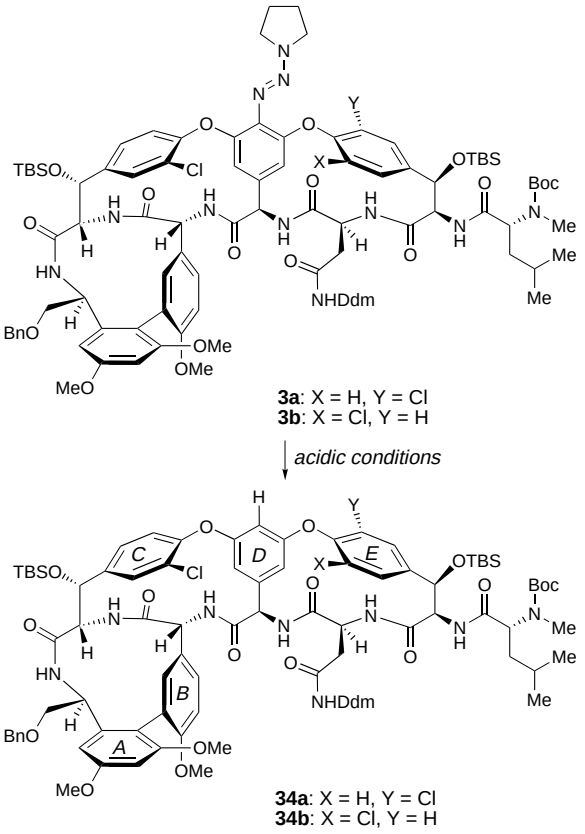


Figure 3. Stereochemical assignment of atropisomers **3a** and **3b** based on ^1H-^1H NOE measurements (COSY and ROESY, 600 MHz, CD_3OD, 323 K).

Removal of triazene functionality from AB/C-O-D/D-O-E ring systems

Having secured the triazene subtarget **3a**, the next task was to convert the triazene moiety to a phenolic group as required for vancomycin (**1**) and its aglycon (**2**). The chemical literature abounds with reports for this conversion and, indeed, our own model studies[11] were encouraging in this regard. Unfortunately, however, triazene **3a** proved stubbornly defiant to our attempts to transform it directly to the corresponding phenol. Various acidic conditions,[17, 18] including sequential $BF_3 \cdot Et_2O$, $Cu_3(NO_3)_2$ and Cu_2O treatment, or sulfonic acid resin, or aqueous H_2SO_4 in various solvents and at temperatures ranging from 0 to 80 °C, failed to produce significant amounts

of the desired phenol. Instead, reduced product **34a** and **34b** were obtained from **3a** and **3b**, respectively, in most cases where recovery of starting material or decomposition did not occur (Scheme 7 and Table 2). Indirect methods for the installment of the phenolic group on ring D were then sought.

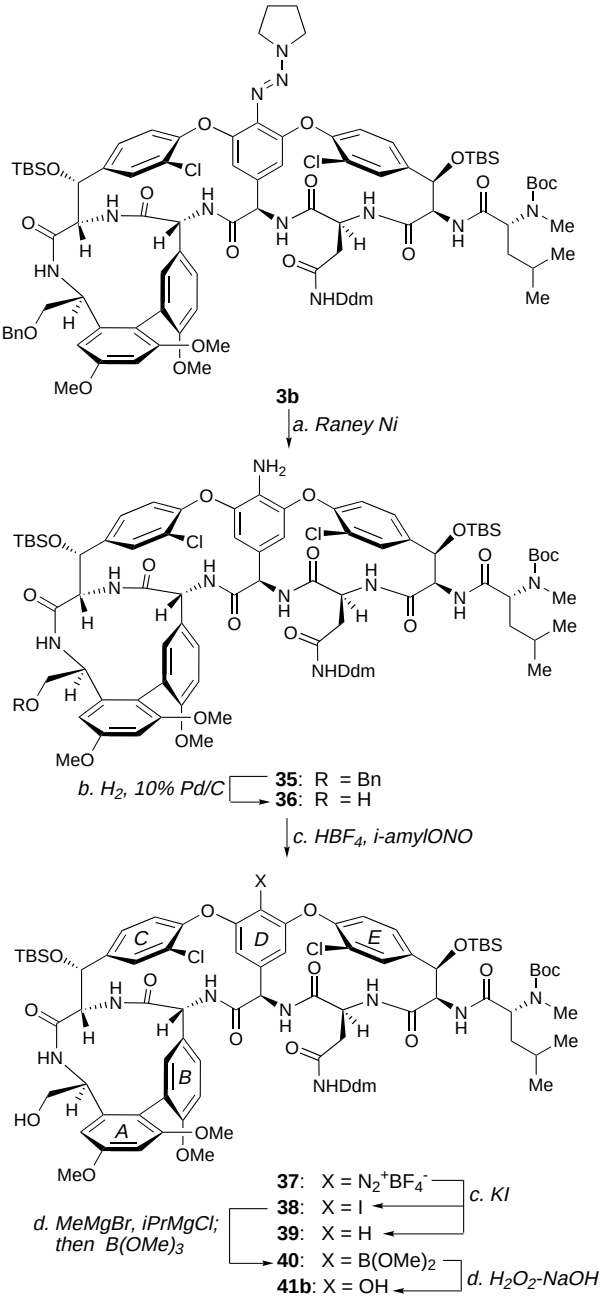


Scheme 7. Removal of triazene moiety from **3a** and **3b** under acidic conditions: reduction. For reagents and conditions see Table 2.

Table 2. Studies of removal of triazene moiety under acidic conditions.

Reagents	Solvent	Temp (°C)	Time (h)	Product/Yield (%)
H^+-resin[a]	MeCN/H_2O (1:1)	80	1	[b]
BF_3•Et_2O; then aq. $Cu(NO_3)_2$; Cu_2O	MeCN	0→25	0.5	**34a**/32
BF_3•Et_2O; then aq. $Cu(NO_3)_2$; Cu_2O	THF	0→25	0.5	**34a**/58
BF_3•Et_2O; then aq. $Cu(NO_3)_2$; Cu_2O	MeOH	0→25	0.5	**34a**/69
aq. 30% H_2SO_4	MeCN	0→50	3	**34a**/70
aq. 30% H_2SO_4	MeOH	0→50	1.5	[c]

[a] AG 50W-X12 (BIO-RAD). [b] 78% of **34a** from **3a**; 74% of **34b** from **3b**. [c] Decomposition.



Scheme 8. Reductive removal of the triazene moiety from unnatural atropisomer **3b**. a) Raney Ni, MeOH, 25 °C, 10 h; b) H_2, 10% Pd/C, MeOH, 25 °C, 4 h, 60% overall from **3b**; c) 20 equiv of HBF_4, 20 equiv of *i*-amylONO, MeCN, −20 °C, 0.5 h; then saturated aq. KI, −45 →25 °C, 2 h; d) 30 equiv of MeMgBr, THF, −50 → −20 °C, 1 h; 30 equiv of *i*PrMgCl, −60 → −40 °C, 2 h; 100 equiv of $B(OMe)_3$, −50 →0 °C, 1 h; 1:1 mixture of 30% aq. H_2O_2 and 10% aq. NaOH solution, −20 →0 °C, 20 min, 28% of **39** and 30% of **41b** overall from **36**.

As an alternative approach to the desired phenolic compound, we chose reduction of the triazene to the corresponding aniline, followed by diazotization, iodination, boronation, and oxidation. To explore this chemistry, the unnatural atropisomer **3b** was utilized first as shown in Scheme 8. Thus, Raney Ni[19] reduction of **3b** resulted in triazene cleavage, which was, however, accompanied by partial hydrogenolysis of the benzyl ether leading to **35** and **36** as an approximate 1:1 mixture. This mixture was then subjected to hydrogenation in the presence of 10% Pd/C to afford **36** in 60% overall yield from **3b**. The amino group in **36** was then diazotized by sequential treatment[18a, 20] with HBF_4 and *i*-amylONO, furnishing diazonium salt **37**, whose treatment with KI furnished a mixture of iodide **38** and reduced product **39**. This

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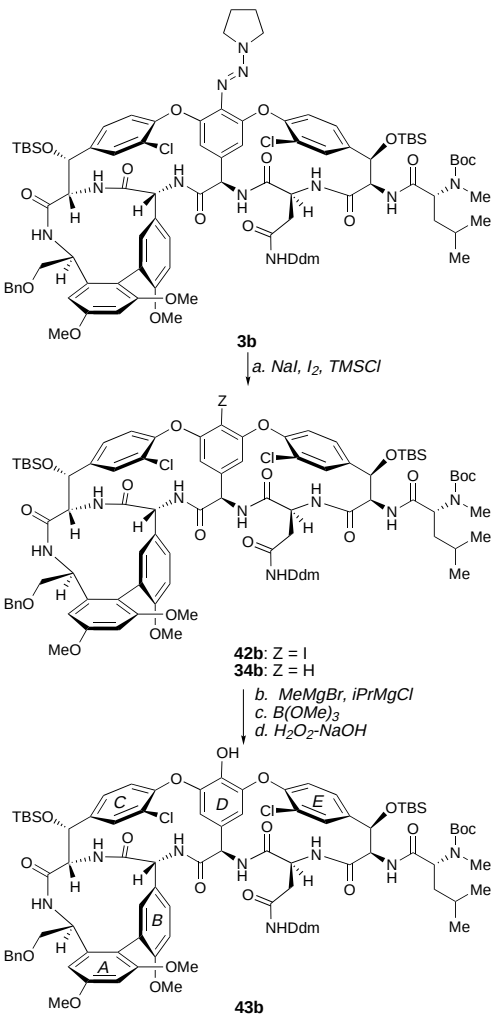
inseparable mixture (**38** + **39**) was taken through the following sequence and the desired product, phenol **41b**, was chromatographically separated from the unreacted, reduced compound **39**: a) deprotonation of all NH groups and iodine-metal exchange through the use of excess MeMgBr and *i*PrMgCl;[21] b) quenching of the so-formed aryl Grignard reagent with excess $B(OMe)_3$ to afford boronate **40**;[22] and, finally c) oxidation with H_2O_2 in the presence of aqueous NaOH, leading to phenol **41b**. This sequence afforded, after chromatographic separation, phenol **41b** in 30% overall yield from anilino compound **36**, and 28% reduced product **39**. These steps were carried out without observing any changes at the stereocenters or at the various functional groups of the molecule's framework.

Following the successful conversion of the unnatural atropisomer **3b** to the corresponding phenol (**41b**), we proceeded to apply the same chemistry to the natural isomer **3a**. Much to our surprise and disappointment, however, the reduction step with Raney Ni, and then Pd/C or $Pd(OH)_2$/C in the case of the natural atropisomer, led to inseparable mixtures of desired products and reduced compounds formed by rupture of the triazene and one aromatic chlorine bond, the latter most likely involving ring E. Furthermore, it was observed that the reduction process was significantly slower than in the case of the unnatural atropisomer **3b**. Apparently, the outside orientation of the chlorine on ring E in the natural atropisomer **3a** makes it vulnerable to hydrogenolysis, whereas in the case of **3b**, both C–Cl bonds are shielded inside the macrocyclic rings. Additionally, in the latter case (**3b**) the triazene functionality would be more accessible. Even though this sequence gave the desired products and eventually furnished phenol **41a** (see Scheme 12), its low efficiency and irreproducibility led us to explore a new approach to the desired aryl iodide of the natural atropisomer.

A direct method for the conversion of aryl triazenes to aryl iodides involves reaction with TMSI.[23] In order to test this methodology in our system, we initially performed experiments with the unnatural atropisomer **3b**, as shown in Scheme 9. Despite our expectations, however, treatment of **3b** with TMSCl-NaI in MeCN at ambient temperature led to the reduced product **34b** containing small amounts (ca. 5%) of the desired iodide **42b**. Assuming that the mechanism of this substitution reaction involved activation of the triazene moiety, followed by nucleophilic attack, we increased the amounts of iodide, but the result did not change significantly. To prove that the desired iodide was not the main product, some of the mixtures were subjected to the phenol formation sequence (as described above) and phenol **43b**, as well as reduced derivative **34b**, were isolated in a combined yield of 55–60% and ratios of ca. 1:20 (see Table 3). An experiment which involved heating of triazene **3b** in the presence of I_2 only in a sealed tube[24] afforded again the reduced derivative **34b** as the main product. The observation that changing concentration of reagents and temperature had no positive effect led to the hypothesis that a radical mechanism was involved in this substitution reaction. It was, therefore, reasoned that elemental iodine may serve as an effective trapping agent of the intermediate benzenoid radical, furnishing higher amounts of the desired halogenated product.



Scheme 9. Removal of triazene moiety from unnatural atropisomer **3b** with TMSI-I_2. a) 6.0 equiv of NaI, 6.0 equiv of I_2, 1.5 equiv of TMSCl, MeCN, 25 °C, 15 min; b) 30 equiv of MeMgBr, THF, $-50 \rightarrow -20$ °C, 1 h; 30 equiv of *i*PrMgCl, $-60 \rightarrow -40$ °C, 2 h; c) 100 equiv of $B(OMe)_3$, $-50 \rightarrow 0$ °C, 1 h; d) 1:1 mixture of 30% aq. H_2O_2 and 10% aq. NaOH solution, $-20 \rightarrow 0$ °C, 20 min, 29% of **34b** and 32% of **43b** overall from **3b**.

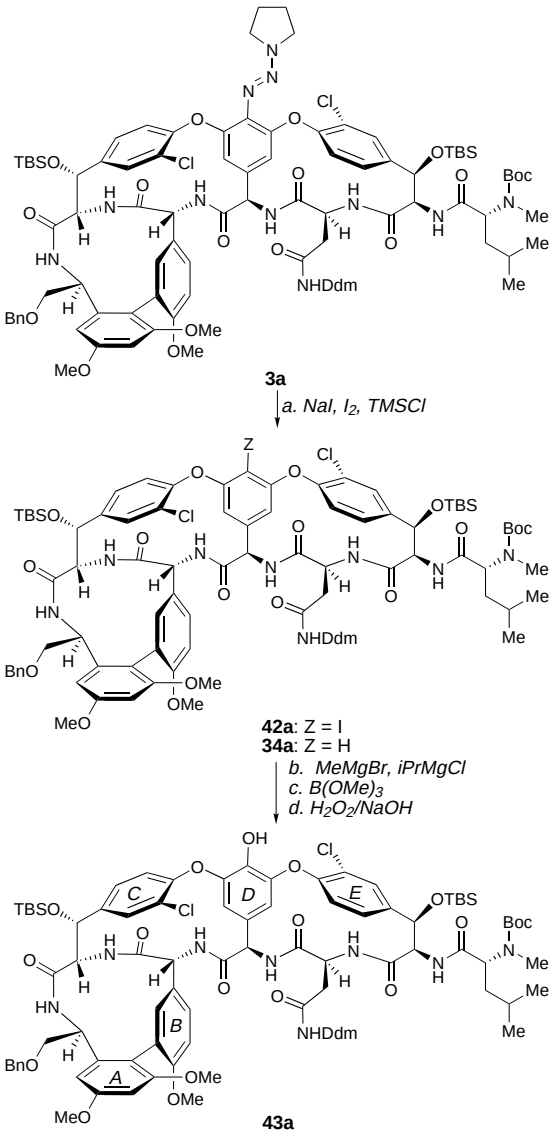
Table 3. Studies of conversion of triazene **3b** to iodide **42b** with TMSI.[a]

Entry	Temp. (°C)	NaI (equiv)	I_2 (equiv)	Conc.[c] (M)	Ratio[d] (**42b**:**34b**)	Ratio[e] (**43b**:**34b**)	Yield[f] (%) (**43b+34b**)
1	0	2	-	0.005	*ca.* 1:20	-	-
2	0	6	-	0.005	*ca.* 1:20	5:95	60
3	-30	6	-	0.005	*ca.* 1:20	-	-
4	25	6	-	0.005	*ca.* 1:20	8:92	58
5	25	6	-	0.001	*ca.* 1:20	-	-
6	60	6	-	0.005	*ca.* 1:20	-	-
7	60	6	-	0.001	*ca.* 1:20	-	-
8	25	60	-	0.005	*ca.* 1:20	5:95	55
9	0	6	2	0.005	1:2	39:6	57
10	25	6	2	0.005	1:2	41:59	61
11	25	6	6	0.005	1:1	52:48	61
12	0	6	6	0.005	1:1	50:50	58
13	25	6	10	0.005	[g]	-	-
14	80[b]	-	1.1	0.015	*ca.* 1:20	-	-

[a] All experiments were performed by using 1.5 equiv of TMSCl unless, otherwise stated. [b] Reaction was performed in a sealed tube without TMSCl. [c] Concentration in MeCN. [d] Ratio determined by mass spectrometry. [e] Ratio based on yields of isolated productts. [f] Combined yield of isolated products. [g] Formation of Boc-deprotected products was observed.

Indeed, experimentation with iodine as an additive established an optimum procedure for the formation of an inseparable mixture of the desired iodide **42b** and the reduced product **34b** (ca. 1:1) in 61% combined yield (see Scheme 9 and Table 3). It was interesting to observe that increasing the number of equivalents of iodine resulted in Boc removal.

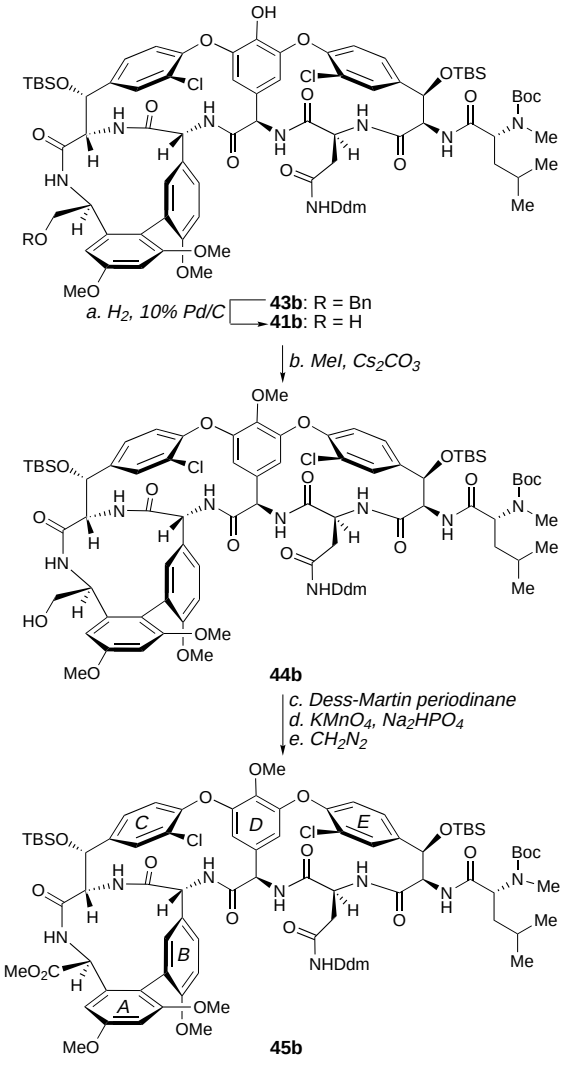
The application of the developed procedure for the installment of the iodide on ring D was then applied to the natural atropisomer, triazene **3a**, and, as shown in Scheme 10, it worked equally well. Thus, treatment of **3a** with TMSCl-NaI-I_2 in MeCN at room temperature, furnished an inseparable mixture of aryl iodide **42a** and reduced product **34a** which was subjected to the phenol forming protocol described above (iodine–magnesium exchange, boronation, and oxidation) to afford the desired phenol **43a** (34% overall yield form **3a**) and reduced product **34a** (34% yield). The two compounds (**43a** and **34a**) were separated by silica gel chromatography.



Scheme 10. Removal of triazene moiety from natural atropisomer **3a** with TMSI-I_2. a) 6.0 equiv of NaI, 6.0 equiv of I_2, 1.5 equiv of TMSCl, MeCN, 25 °C, 15 min; b) 30 equiv of MeMgBr, THF, −50 → −20 °C, 1 h; 30 equiv of *i*PrMgCl, −60 → −40 °C, 2 h; b) 100 equiv of $B(OMe)_3$, −50 → 0 °C, 1 h; c) 1:1 mixture of 30% aq. H_2O_2 and 10% aq. NaOH solution, −20 → 0 °C, 20 min, 34% of **34a** and 34% of **43a** overall from **3a**.

The final stages of the synthesis of the vancomycin aglycon

With the installment of the phenolic group on ring D, all that remained before the completion of the synthesis of the aglycon of vancomycin was the liberation and oxidation of the primary alcohol of AA-7 and global deprotection. Again, the unnatural atropisomer **43b** served as the substrate of choice for the first wave of experiments towards the aglycon (Scheme 11). Thus, hydrogenolysis of **43b** (H_2, 10% Pd/C) led smoothly to primary alcohol **41b** (94% yield). Methylation of the phenolic group of **41b** proceeded selectively with MeI in the presence of Cs_2CO_3 at 0 °C, furnishing **44b** in 94%



Scheme 11. Synthesis of fully protected unnatural vancomycin aglycon **45b**. a) H_2, 10% Pd/C, MeOH, 25 °C, 1.5 h, 94%; b) 10.0 equiv of Cs_2CO_3, 50 equiv of MeI, DMF, 0 °C, 2 h, 94%; c) 1.5 equiv of Dess–Martin periodinane, 2.0 equiv of $NaHCO_3$, CH_2Cl_2, 25 °C, 0.5 h; d) 10.0 equiv of $KMnO_4$ (1M aq. solution), *t*BuOH/5% aq. Na_2HPO_4 (3.5:1), 30 °C, 1.5 h; e) CH_2N_2, Et_2O, 25 °C, 12 h, 84% overall from **44b**.

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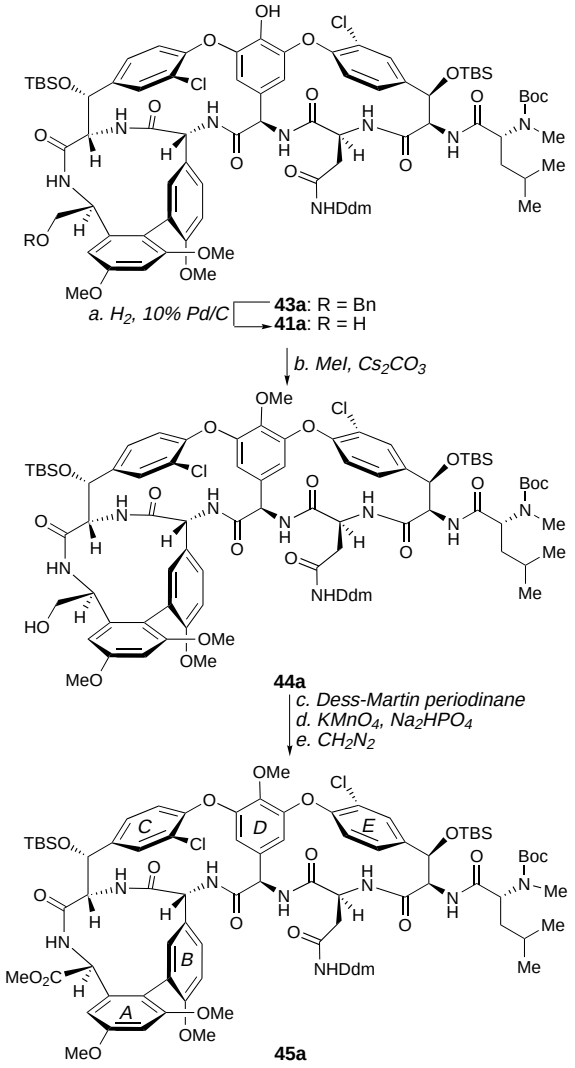
yield. Finally, oxidation of the primary alcohol with Dess–Martin periodinane,[25] followed by further oxidation[26] with aqueous $KMnO_4$ and exposure to diazomethane, gave the fully protected compound **45b** via the corresponding aldehyde and carboxylic acid, in 84% overall yield from **44b**.

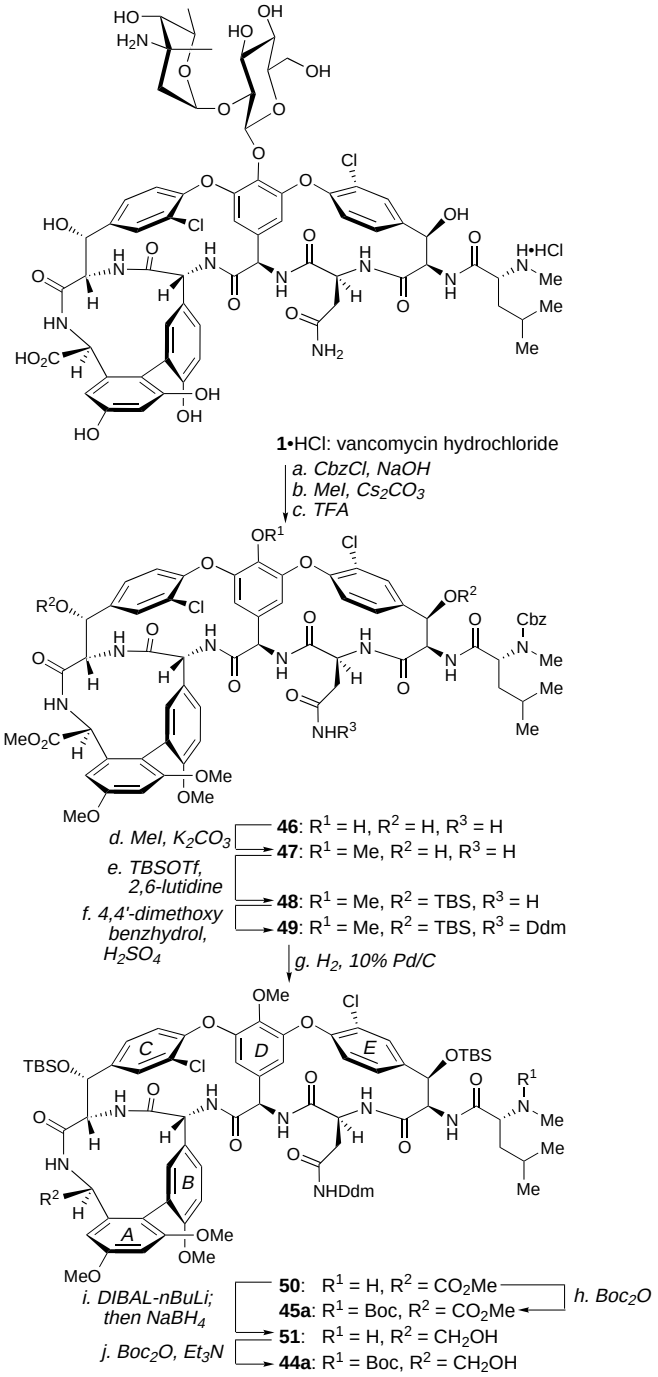
With the confidence gained from these results, we proceeded to apply the same sequence to the natural atropisomer **43a** (Scheme 12). Indeed, hydrogenolysis of **43a**, as before,



Scheme 12. Synthesis of fully protected natural vancomycin aglycon **45a**. a) H_2, 10% Pd/C, MeOH, 25 °C, 1.5 h, 87%; b) 10.0 equiv of Cs_2CO_3, 50 equiv of MeI, DMF, 0 °C, 2 h, 95%; c) 1.5 equiv of Dess–Martin periodinane, 2.0 equiv of $NaHCO_3$, CH_2Cl_2, 25 °C, 0.5 h; d) 10.0 equiv of $KMnO_4$ (1M aq. solution), *t*BuOH/5% aq. Na_2HPO_4 (3.5:1), 30 °C, 1.5 h; e) CH_2N_2, Et_2O, 25 °C, 12 h, 89% overall from **44a**.

led smoothly to **41a** (87% yield), which proved to be identical to a sample derived from vancomycin (**1**) by degradation (see Scheme 13 below for degradation studies). Furthermore, methylation of **41a** (Cs_2CO_3, MeI, 95%), followed by stepwise oxidation of the resulting derivative **44a** and methyl ester formation as described for **44b** (Scheme 11), furnished the fully protected vancomycin aglycon **45a** in 89% overall yield from **44a**. This compound was also found to be identical with an authentic sample derived from vancomycin (**1**).

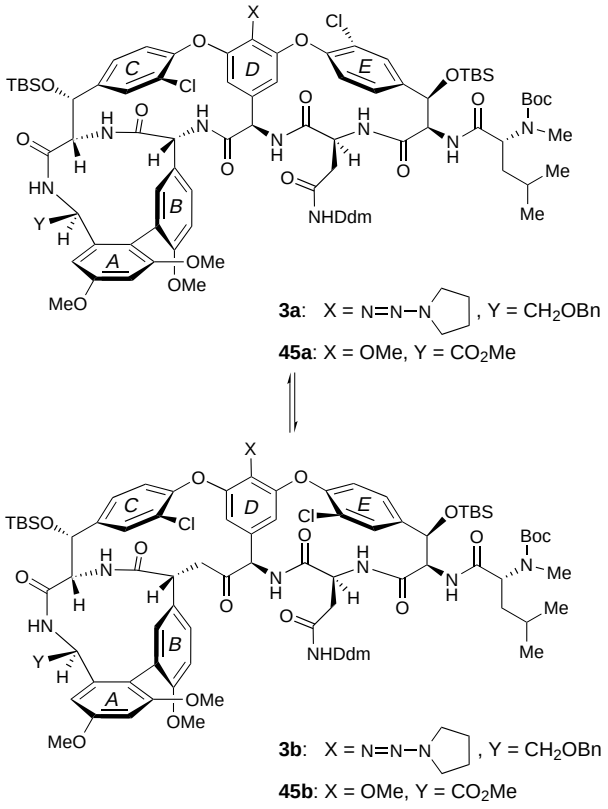
Compounds **44a** and **45a** were prepared by degradation from vancomycin hydrochloride (**1**·HCl), as described in Scheme 13. Vancomycin aglycon derivative **47** was prepared



Scheme 13. Degradation of vancomycin (**1**). a) 5.0 equiv of CbzCl, 15% aq. NaOH, MeOH, 25 °C, 0.5 h; b) 20 equiv of MeI, 8.0 equiv of Cs_2CO_3, DMF, 0 →25 °C, 20 h; c) TFA, CH_2Cl_2, 50 °C, 1 h, 39% overall from **1**·HCl; d) 10.0 equiv of MeI, 10.0 equiv of K_2CO_3, DMF, 0 →25 °C, 1 h, 98%; e) 11 equiv of TBSOTf, 11 equiv of 2,6-lutidine, −10 °C, 0.5 h, 80%; f) 100 equiv of 4,4′ -dimethoxy benzydrol, 1M H_2SO_4 in AcOH, AcOH, 0 →25 °C, 2 h, 76%; g) H_2, 10% Pd/C, MeOH/EtOAc (2:1), 25 °C, 2 h; h) 5.0 equiv of Boc_2O, dioxane/H_2O (10:1), 25 °C, 6 h, 90% overall from **49**; i) 12 equiv of DIBAL/*n*BuLi (1:1), THF, −10 °C, 0.5 h; 20 equiv of $NaBH_4$ in THF/H_2O (1:1), −10 →25 °C, 1 h, 65% overall from **49**; j) 7.0 equiv of Boc_2O, 7.0 equiv of Et_3N, MeOH/CH_2Cl_2 (1:1), 0 °C, 20 min, 93%. DIBAL = diisobutylaluminum hydride; Cbz = benzyloxycarbonyl; TFA = trifluoroacetic acid.

by sequential protection of the secondary amino group, carboxylic acid, and phenolic groups, following a known procedure.[14b, 27] TBS protection of the two benzylic hydroxy groups of **47** using excess of TBSOTf (11 equiv) and 2,6-lutidine (11 equiv) afforded compound **48** in 80% yield. Selective protection of the primary amide of **48** was achieved by using 4,4′-dimethoxy benzhydrol (100 equiv) in the presence of catalytic amount of H_2SO_4 in acetic acid and yielded **49** (76%). Then, the Cbz group was removed by mild hydrogenation conditions (10% Pd/C, MeOH/EtOAc 2:1) to provide **50**, the common synthetic intermediate for **44a** and **45a**. After extensive experimentation, DIBAL-ate (1:1 mixture of DIBAL and *n*BuLi) followed by $NaBH_4$ was found to be the most effective system for the reduction of the ester **50** in order to obtain alcohol **51** (65% yield overall from **49**). Finally, Boc protection of the secondary amine provided the *N*-Boc-alcohol **44a**. Additionally, the secondary amine of ester **50** was protected [Boc_2O (7.0 equiv), Et_3N (7.0 equiv), $MeOH/CH_2Cl_2$ (1:1)] to afford the *N*-Boc derivative **45a** in 93% yield overall from **49**.

Atropisomerization of vancomycin-like skeletons was investigated by using tricyclic triazene **3a** and methyl ester **45a**, and their D-O-E atropisomers **3b** and **45b** (Scheme 14).



Scheme 14. Atropisomerization studies of tricyclic systems. For conditions and equilibrium ratios see Table 4.

Alcohols **44a** (Scheme 12) and **44b** (Scheme 11) were found to be unsuitable substrates for this study, since they were not chromatographically separable. While heating either **3a** or **3b** in polar solvents (DMF or DMSO) failed to give atropisomerization, heating these derivatives in 1,2-dichlorobenzene at 140 °C for 4 h led to a mixture of starting material and the corresponding atropisomer in a ratio of about 6:4 and 80-84% combined yields (Table 4). Tricyclic methyl esters **45a** and **45b** were also heated in 1,2-dichlorobenzene for 8 h and furnished separable mixtures of starting material and the corresponding atropisomer in a ratio of about 1:1 and 82–87% combined yields (see Scheme 14 and Table 4). Significantly, all the successful experiments proved that heating at about 130–140 °C in 1,2-dichlorobenzene allows atropisomerization only within the D-O-E ring system, leaving the stereochemistry of the AB and C-O-D ring systems intact, as reported by Boger's group for similar vancomycin-derived systems.[14]

Table 4. Atropisomerization studies of tricyclic systems **3a,b** and **45a,b**.

Compound	Solvent	Temp (°C)	Time (h)	Ratio (**a**:**b**)	Yield (% **a**+**b**)
3a	1,2-dichlorobenzene	140	4	62:38	84
3b	1,2-dichlorobenzene	140	4	41:59	80
45a	1,2-dichlorobenzene	130	8	54:46	87
45b	1,2-dichlorobenzene	130	8	43:57	82

The atropisomerization of unnatural atropisomers **3b** and **45b** served to enrich the supplies of the desired atropisomers **3a** and **45a** needed for the final drive towards the vancomycin aglycon (**2**).

The final task remaining for the total synthesis of vancomycin's aglycon (**2**) was the removal of all the residing protecting groups from **45a**. These included two TBS groups, a Boc group, a Ddm protecting group, and five methyl groups—one on the carboxylic acid and four on the phenolic moieties. Our initial attempt to accomplish this goal involved one step and called upon the synergistic action of $AlBr_3$ and EtSH[28] (Scheme 15). Pleasantly, this combination of reagents in CH_2Cl_2 and at ambient temperatures resulted in the desired global deprotection of **45a** in 30–50% yield, furnishing the vancomycin's aglycon (**2**). A stepwise deprotection involving nBu_4NF/HOAc to remove the silyl ethers, giving diol **52**, followed by exposure to $AlBr_3$/EtSH, as above, resulted in a 43% overall yield of the aglycon. Finally, a second, stepwise procedure employing HF · pyr./pyr. in THF[29] at 0 →25 °C and $AlBr_3$/EtSH improved the overall yield of vancomycin aglycon (**2**) from **45a**, via **52**, to 62%.

Synthetic vancomycin's aglycon **2** exhibited identical properties (HPLC, IR, $[\alpha]_D^{22}$, ^1H NMR and mixed ^1H NMR) with those of an authentic sample derived from vancomycin (**1**) by degradation.[30]

Conclusion

In this article we described the chemistry leading from the essential amino acid building blocks to the vancomycin aglycon (**2**). The assembly proceeded smoothly, not withstanding the atropisomerism problem, from rings C-O-D to AB/C-O-D to AB/C-O-D/D-O-E, furnishing a triazene derivative, whose conversion to the required phenolic func-

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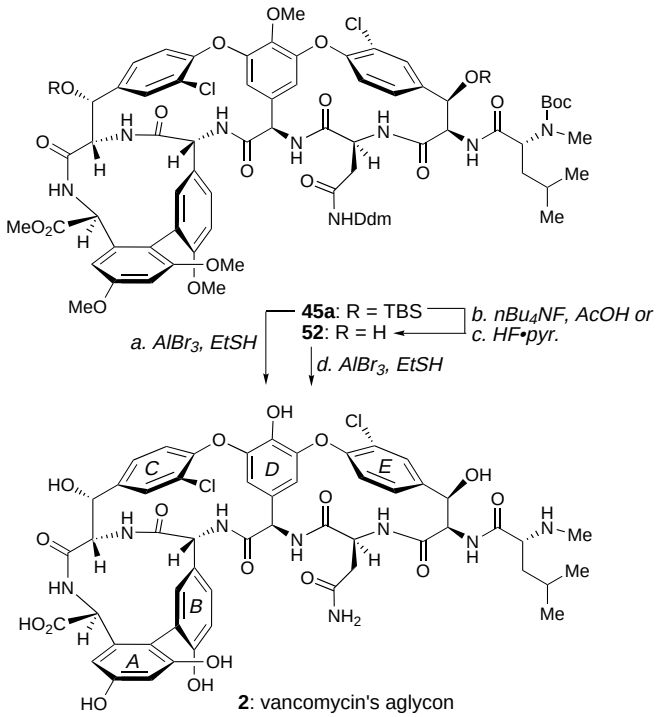

Scheme 15. Synthesis of vancomycin aglycon (**2**). a) 40 equiv of $AlBr_3$, $EtSH/CH_2Cl_2$ (1:1), 25 °C, 4 h, 30–50 %; b) 50 equiv of nBu_4NF, 50 equiv of AcOH, THF, 25 °C, 48 h; c) HF · pyr./pyr.,THF, 0 →25 °C, 12 h; d) 40 equiv of $AlBr_3$, $EtSH/CH_2Cl_2$ (1:1), 25 °C, 4 h, [43 % of **2** overall from **45a** through b); 62 % of **2** overall from **45a** through c)].

tionality was accomplished by iodination, boronation and oxidation. Final oxidation of the AA-7 side chain to the desired carboxylic acid group, followed by global deprotection gave vancomycin aglycon (**2**). Atropisomerization studies failed to convert the unnatural atropisomers at the C-O-D or AB/C-O-D stages, but proved successful in equilibrating the atropisomeric D-O-E domains within the final AB/C-O-D/D-O-E framework, starting from either one. In the following paper[31] we describe the conversion of the vancomycin aglycon (**2**) to vancomycin itself (**1**).

Experimental Section

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

Natural biaryl 10 and unnatural biaryl 12: To a solution of aryl iodide **8** [1.08 g, 2.8 mmol, in toluene (25 mL)] were added sequentially boronic acid **9** [1.32 g, 4.2 mmol, dissolved in MeOH (2.5 mL)], Na_2CO_3 [0.36 g, 3.4 mmol, dissolved in H_2O (1.3 mL)], and tetrakistriphenylphosphanepalladium(**0**) [$Pd(Ph_3P)_4$, 0.65 g, 0.6 mmol]. The resulting mixture was heated to 90 °C for 4 h. The reaction mixture was cooled to 25 °C and diluted with EtOAc (25 mL). The organic phase was washed with H_2O (25 mL), brine (25 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 20 →40 % EtOAc in hexanes, gradient elution) to afford atropisomers **10** (1.04 g, 56 % yield) and **12** (0.52 g, 28 % yield). **10**: R_f = 0.30 (silica gel, 50 % EtOAc in hexanes); $[\alpha]_D^{22} = -79.1$ (c = 0.78, EtOAc); IR (thin film): $\tilde{\nu}_{max}$ = 3447, 2936, 1741, 1717, 1604, 1489, 1458, 1325, 1262, 1201, 1158, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 6H, ArH), 7.01 (d, J = 1.9 Hz, 1H, H-5b), 6.92 (d, J = 8.6 Hz, 1H, H-5e), 6.76 (d, J = 2.4 Hz, 1H, H-7f), 6.46 (d, J = 2.4 Hz, 1H, H-7d), 5.41 (d, J = 6.8 Hz, 1H, NH), 5.25 (d, J = 6.8 Hz, 1H, H-5α), 4.59 (dd, J = 8.4, 3.5 Hz, 1H, H-7α), 4.39 (d, J = 11.9 Hz, 1H, OCH_AHPh), 4.35 (d, J = 11.9 Hz, 1H, OCH_BPh), 3.83 (s, 3H, 7e-OCH_3), 3.70 (s, 3H, CO_2CH_3), 3.65 (s, 3H, 5d-OCH_3), 3.63 (s, 3H, 7c-OCH_3), 3.45 (dd, J = 10.3, 8.4 Hz, 1H, H-7β_A), 3.40 (dd, J = 10.3, 3.5 Hz, 1H, H-7β_B), 2.10 (br.s, 1H, OH), 1.41 (s, 9H, tBuO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 160.4, 157.8, 156.8, 154.9, 141.2, 137.9, 131.9, 129.0, 128.4, 128.2, 127.7, 127.6, 125.2, 117.8, 111.4, 101.8, 98.5, 80.1, 74.8, 73.1, 70.0, 56.9, 55.7, 55.3, 52.5, 28.3; HRMS (FAB) calcd for $C_{32}H_{39}NO_9Cs$ [$M + Cs^+$] 714.1679, found 714.1654. **12**: R_f = 0.20 (silica gel, 40 % EtOAc in hexanes); $[\alpha]_D^{22} = -48.9$ (c = 2.3, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3436, 2943, 2837, 1737, 1708, 1602, 1496, 1449, 1320, 1255, 1155, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 4H, ArH), 7.24–7.19 (m, 2H, ArH), 7.11 (d, J = 2.4 Hz, 1H, ArH), 6.83–6.80 (m, 2H, ArH), 6.46 (d, J = 2.4 Hz, 1H, ArH), 5.47 (d, J = 7.4 Hz, 1H, NH), 5.28 (d, J = 7.4 Hz, 1H, H-5α), 4.70-4.65 (m, 1H, H-7α), 4.40 (d, J = 12.2 Hz, 1H, OCH_AHPh), 4.33 (d, J = 12.2 Hz, 1H, OCH_BPh), 3.85 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.34–3.32 (m, 2H, H-7β), 1.43 (s, 9H, tBuO); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9, 160.3, 157.9, 157.6, 154.8, 140.5, 137.8, 130.4, 128.5, 128.3, 128.2, 127.6, 127.4, 125.4, 118.1, 111.0, 101.8, 98.2, 79.9, 74.4, 72.5, 69.5, 56.9, 55.7, 55.2, 55.1, 52.5, 28.2; HRMS (FAB) calcd for $C_{32}H_{39}NO_9Cs$ [$M + Cs^+$] 714.1679, found 714.1654.

Natural biaryl azide 11: A solution of natural biaryl alcohol **10** (2.56 g, 4.4 mmol) in THF (40 mL) was cooled to −20 °C, and treated sequentially with triphenylphosphane (2.88 g, 11 mmol), diphenylphosphorylazide (DPPA, 2.4 mL, 11 mmol), and diethyl azodicarboxylate (DEAD, 1.7 mL, 11 mmol). The reaction mixture was stirred at −20 °C for 2 h, then concentrated, and the residue was purified by flash column chromatography (silica gel, 20 →30 % EtOAc in hexanes, gradient elution) to afford natural biaryl azide **11** (2.52 g, 95 % yield). **11**: R_f = 0.72 (silica gel, 50 % EtOAc in hexanes); $[\alpha]_D^{22} = -97.4$ (c = 0.98, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3376, 2936, 2098, 1746, 1714, 1605, 1488, 1455, 1342, 1261, 1202, 1160, 1059, 1030, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 6H, ArH), 7.09 (d, J = 2.2 Hz, 1H, H-5b), 6.85 (d, J = 8.6 Hz, 1H, H-5e), 6.56 (d, J = 2.4 Hz, 1H, H-7f), 6.46 (d, J = 2.4 Hz, 1H, H-7d), 5.54 (d, J = 7.3 Hz, 1H, NH), 5.29 (d, J = 7.3 Hz, 1H, H-5α), 4.50 (dd, J = 8.8, 3.4 Hz, 1H, H-7α), 4.45 (d, J = 12.2 Hz, 1H, OCH_AHPh), 4.35 (d, J = 12.2 Hz, 1H, CH_BPh), 3.82 (s, 3H, 7e-OCH_3), 3.69 (s, 3H, CO_2CH_3), 3.63 (s, 3H, 5d-OCH_3), 3.56-3.46 (m, 2H, H-7β), 3.50 (s, 3H, 7c-OCH_3), 1.42 (s, 9H, tBuO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 160.3, 158.0, 157.3, 154.7, 137.6, 136.9, 130.9, 128.7, 128.2, 128.1, 127.5, 127.4, 124.6, 118.8, 111.0, 102.3, 98.5, 79.9, 73.2, 72.7, 62.0, 56.7, 55.6, 55.2, 55.1, 52.5, 28.1; HRMS (FAB) calcd for $C_{32}H_{38}N_4O_8Cs$ [$M + Cs^+$] 739.1744, found 739.1766.

Unnatural biaryl azide 13: A solution of unnatural biaryl alcohol **12** (1.28 g, 2.2 mmol) in THF (20 mL) was cooled to −20 °C and treated sequentially with triphenylphosphane (1.44 g, 5.5 mmol), diphenylphosphorylazide (DPPA, 1.19 mL, 5.5 mmol), and diethyl azodicarboxylate (DEAD, 870 µL, 5.5 mmol). The reaction mixture was stirred at -20 °C for 2 h, then concentrated, and the residue was purified by flash column chromatography (silica gel, 20 →30 % EtOAc in hexanes, gradient elution) to afford unnatural biaryl azide **13** (1.20 g, 90 % yield). **13**: R_f = 0.17 (silica gel, 30 % EtOAc in hexanes); $[\alpha]_D^{22} = -16.1$ (c = 1.22, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3354, 2978, 2097, 1737, 1596, 1484, 1249, 1155, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36-7.20 (m, 6H, ArH), 7.04 (d, J = 2.0 Hz, 1H, ArH), 6.96 (d, J = 8.5 Hz, 1H, ArH), 6.61 (d, J = 2.5 Hz, 1H, ArH), 6.50 (d, J = 2.5 Hz, 1H, ArH), 5.45 (d, J = 7.5 Hz, 1H, NH), 5.27 (d, J = 7.5 Hz, 1H, H-5α), 4.47 (dd, J = 9.0, 3.5 Hz, 1H, H-7α), 4.37 (d, J = 12.0 Hz, 1H, OCH_AHPh), 4.32 (d, J = 12.0 Hz, 1H, OCH_BPh), 3.84 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.44 (dd, J = 10.5, 9.0 Hz, 1H, H-7β_A), 3.33 (dd, J = 10.5, 3.5 Hz, 1H, H-7β_B), 1.42 (s, 9H, tBuO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 160.4, 157.9, 156.4, 154.8, 137.9, 131.3, 128.4, 128.3, 128.0, 127.5, 127.4, 127.4, 124.5, 118.4, 111.1, 102.5, 98.7, 80.0, 73.6, 73.0, 62.6, 56.9, 55.7, 55.4, 55.3, 52.4, 28.2; HRMS (FAB) calcd for $C_{32}H_{38}N_4O_8Cs$ [$M + Cs^+$] 739.1744, found 739.1766.

Natural biaryl carboxylic acid 6: A solution of natural biaryl carboxylic ester **11** (1.0 g, 1.6 mmol) in THF/H_2O (1:1) (16 mL) was cooled to 0 °C and lithium hydroxide monohydrate (101 mg, 2.4 mmol) was added. After 2 h, CH_2Cl_2 (100 mL) was added, and the reaction mixture was quenched by the dropwise addition of 0.1 % aqueous HCl at 0 °C, until pH 5 was reached. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 2 →5 % MeOH in CH_2Cl_2, gradient elution) to afford natural biaryl carboxylic acid **6** (0.94 g, 99 %). **6**: R_f = 0.20 (silica gel, 5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -32.4$ (c = 3.5,

MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3350, 2938, 2099, 1716, 1605, 1488, 1456, 1259, 1158, 1060, 838 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 330 K): δ = 7.39 (dd, J = 8.5, 2.3 Hz, 1H, H-5f), 7.29 – 7.15 (m, 5H, ArH), 7.09 (d, J = 2.3 Hz, 1H, H-5b), 6.94 (d, J = 8.5 Hz, 1H, H-5e), 6.63 (d, J = 2.4 Hz, 1H, H-7f), 6.55 (d, J = 2.4 Hz, 1H, H-7d), 5.15 (br.s, 1H, H-5α), 4.54 (dd, J = 7.8, 4.3 Hz, 1H, H-7α), 4.33 (br.s, 2H, OCH_2Ph), 3.81 (s, 3H, 7e-OCH$_3$), 3.61 (s, 3H, 5d-OCH$_3$), 3.55 (s, 3H, 7c-OCH$_3$), 3.56 – 3.50 (m, 2H, H-7β), 1.40 (s, 9H, tBuO); ^{13}C NMR (100 MHz, CD_3OD, 330 K): δ = 174.7, 161.9, 159.7, 158.9, 157.3, 139.2, 138.1, 131.8, 131.0, 129.4, 129.2, 128.6, 128.5, 126.1, 120.4, 112.2, 103.9, 99.2, 80.7, 74.5, 73.4, 63.2, 58.7, 56.1, 55.8, 55.8, 28.7; HRMS (FAB) calcd for $C_{31}H_{36}N_4O_8Cs$ [M + Cs$^+$] 725.1587, found 725.1611.

Unnatural biaryl carboxylic acid 14: A solution of unnatural biaryl carboxylic ester **13** (1.0 g, 1.6 mmol) in THF/H_2O (1:1, 15 mL) was cooled to 0 °C, and anhydrous lithium hydroxide (58 mg, 2.4 mmol) was added. The resulting mixture was stirred at 0 °C for 2 h, and then it was quenched by the dropwise addition of saturated aqueous citric acid (1 mL). The reaction mixture was extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 2 → 5 % MeOH in $CHCl_3$, gradient elution) to afford unnatural biaryl carboxylic acid **14** (0.94 g, 99 % yield). **14**: R_f = 0.25 (silica gel, 10 % MeOH in $CHCl_3$); $[\alpha]_D^{22}$ = – 13.8 (c = 2.0, MeOH); IR (KBr): $\tilde{\nu}_{max}$ = 3440, 2953, 2096, 1716, 1685, 1606, 1507, 1257, 1158, 1059, 1019 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.38 (dd, J = 8.6, 2.4 Hz, 1H, ArH), 7.25 – 7.12 (m, 5H, ArH), 7.00 – 6.98 (m, 2H, ArH), 6.55 (d, J = 2.4 Hz, 1H, ArH), 6.52 (d, J = 2.4 Hz, 1H, ArH), 5.11 (s, 1H, H-5α), 4.37 (dd, J = 8.5, 3.8 Hz, 1H, H-7α), 4.24 (d, J = 9.5 Hz, 1H, OCH_AHPh), 4.17 (d, J = 9.5 Hz, 1H, OCHH_BPh), 3.75 (s, 3H, OCH$_3$), 3.64 (s, 3H, OCH$_3$), 3.58 (s, 3H, OCH$_3$), 3.45 – 3.33 (m, 2H, H-7β), 1.38 (s, 9H, tBuO); ^{13}C NMR (100 MHz, CD_3OD): δ = 174.5, 162.0, 159.5, 158.0, 157.5, 139.4, 138.9, 133.1, 130.3, 129.4, 129.3, 128.7, 128.6, 126.0, 120.2, 112.4, 104.0, 99.5, 79.5, 74.7, 74.0, 63.9, 58.6, 56.2, 56.0, 55.8, 28.7; HRMS (FAB) calcd for $C_{31}H_{36}N_4O_8Cs$ [M + Cs$^+$] 725.1587, found 725.1601.

AB/C dipeptide 15: A solution of natural biaryl carboxylic acid **6** (30.5 g, 51.5 mmol) and amine **4** (21.1 g, 56.4 mmol) in THF (600 mL) was cooled to – 30 °C. HOAt (23.1 g, 170 mmol) and EDC (29.6 g, 154.4 mmol) were added and the resulting mixture was left under vigorous stirring for 12 h, while the temperature was raised slowly to – 10 °C. H_2O (1 L) and EtOAc (2 L) were added, and the aqueous phase was extracted with EtOAc (2 × 500 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 25 % EtOAc in hexanes) to afford AB/C dipeptide **15** (42.5 g, 87 %). **15**: R_f = 0.53 (silica gel, 50 % EtOAc in hexanes); $[\alpha]_D^{22}$ = – 13.0 (c = 3.4, EtOAc); IR (thin film): $\tilde{\nu}_{max}$ = 3421, 2931, 2874, 2099, 1734, 1684, 1606, 1505, 1258, 1202, 1161, 1091, 836 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 330 K): δ = 7.30 – 7.17 (m, 7H, ArH), 7.06 (d, J = 2.4 Hz, 1H, H-5b), 6.94 (dd, J = 8.4, 2.2 Hz, 1H, H-6f), 6.92 (d, J = 8.4 Hz, 1H, H-5e), 6.77 (d, J = 8.4 Hz, 1H, H-6e), 6.64 (d, J = 2.4 Hz, 1H, H-7f), 6.54 (d, J = 2.4 Hz, 1H, H-7d), 5.22 (s, 1H, H-5α), 5.18 (d, J = 2.7 Hz, 1H, H-6β), 4.63 (d, J = 2.7 Hz, 1H, H-6α), 4.54 (dd, J = 7.3, 4.6 Hz, 1H, H-7α), 4.37 (s, 2H, OCH_2Ph), 4.17 (dq, J = 10.8, 7.1 Hz, 1H, OCH_AHCH$_3$), 4.11 (dq, J = 10.8, 7.1 Hz, 1H, OCHH_BCH$_3$), 3.82 (s, 3H, 7e-OCH$_3$), 3.59 (s, 3H, 7c-OCH$_3$), 3.57 (s, 3H, 5d-OCH$_3$), 3.57-3.52 (m, 2H, H-7β), 1.43 (s, 9H, tBuO), 1.22 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 0.87 (s, 9H, tBuSi), 0.01 (s, 3H, CH$_3$Si), -0.14 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CD_3OD, 330 K): δ = 173.0, 171.2, 162.1, 160.1, 159.2, 157.3, 154.0, 139.5, 138.5, 134.2, 132.1, 131.4, 129.7, 129.3, 129.1, 128.7, 128.6, 127.2, 126.8, 121.7, 121.2, 117.7, 112.7, 104.8, 100.1, 81.3, 75.1, 74.4, 73.9, 63.4, 62.9, 60.8, 59.7, 56.5, 56.1, 56.1, 28.8, 26.4, 19.0, 14.4, – 4.4, – 5.0; HRMS (FAB) calcd for $C_{48}H_{62}ClN_5O_{11}SiCs$ [M + Cs$^+$] 1080.2958, found 1080.2926.

AB/C amine 16: A solution of AB/C dipeptide **15** (5.20 g, 5.5 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C. Freshly distilled 2,6-lutidine (1.9 mL, 16.5 mmol) was added, followed by the dropwise addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf, 3.3 mL, 18.2 mmol). The reaction mixture was kept at 0 °C for 3 h, and then it was allowed to warm to 25 °C. After 2 h, it was recooled to 0 °C and CH_2Cl_2 (250 mL) was added, followed by saturated aqueous $NaHCO_3$ (250 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 35 → 80 % EtOAc in hexanes, gradient elution) to afford AB/C amine **16** (4.2 g, 90 %). **16**: R_f = 0.29 (silica gel, 5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = + 8.9 (c = 2.0, EtOAc); IR (thin film): $\tilde{\nu}_{max}$ = 3419, 2933, 2874, 2099, 1734, 1654, 1604, 1508, 1458, 1342, 1260, 1201, 1157, 1091, 1030, 837 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.31 – 7.18 (m, 7H, ArH), 7.11 (d, J = 2.4 Hz, 1H, H-5b), 7.03 (dd, J = 8.5, 2.0 Hz, 1H, H-6f), 6.90 (d, J = 8.6 Hz, 1H, H-5e), 6.80 (d, J = 8.5 Hz, 1H, H-6e), 6.60 (d, J = 2.4 Hz, 1H, H-7f), 6.52 (d, J = 2.4 Hz, 1H, H-7d), 5.27 (d, J = 2.4 Hz, 1H, H-6β), 4.60 (dd, J = 8.4, 3.8 Hz, 1H, H-7α), 4.58 (d, J = 2.4 Hz, 1H, H-6α), 4.47 (s, 1H, H-5α), 4.34 (br.s, 2H, OCH_2Ph), 4.13 (dq, J = 10.8, 7.2 Hz, 1H, OCH_AHCH$_3$), 4.05 (dq, J = 10.8, 7.2 Hz, 1H, OCHH_BCH$_3$), 3.81 (s, 3H, 7e-OCH$_3$), 3.57 (s, 3H, 7c-OCH$_3$), 3.54 (s, 3H, 5d-OCH$_3$), 3.59 – 3.47 (m, 2H, H-7β), 1.16 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3), 0.89 (s, 9H, tBuSi), 0.01 (s, 3H, CH$_3$Si), – 0.15 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CD_3OD): δ = 176.0, 171.1, 161.9, 159.8, 158.8, 154.2, 139.3, 138.3, 134.2, 133.9, 131.8, 129.4, 129.2, 129.0, 128.7, 128.6, 126.9, 126.3, 121.4, 120.6, 117.4, 112.3, 103.9, 99.2, 74.9, 74.6, 73.7, 63.3, 62.8, 60.6, 59.6, 56.1, 55.9, 55.8, 26.2, 19.0, 14.4, – 4.4, – 5.2; HRMS (FAB) calcd for $C_{43}H_{54}ClN_5O_9SiCs$ [M + Cs$^+$] 980.2434, found 980.2464.

AB/C/D tripeptide 17: A solution of carboxylic acid **7** (91 mg, 0.18 mmol) and AB/C amine **16** (150 mg, 0.18 mmol) in THF (2 mL) was cooled to – 78 °C. HOAt (80 mg, 0.59 mmol) and EDC (104 mg, 0.54 mmol) were added, and the resulting mixture was left under vigorous stirring for 12 h, while the temperature was raised to 0 °C. H_2O (5 mL) and EtOAc (10 mL) were added, and after 10 min, the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 10 → 30 % EtOAc in hexanes, gradient elution) to afford AB/C/D tripeptide **17** (205 mg, 85 %). **17**: R_f = 0.48 (silica gel, 50 % EtOAc in hexanes); $[\alpha]_D^{22}$ = – 23.0 (c = 2.7, EtOAc); IR (thin film): $\tilde{\nu}_{max}$ = 3328, 2932, 2858, 2100, 1676, 1606, 1508, 1419, 1341, 1260, 1202, 1159, 1094, 837, 735 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, 330 K): δ = 7.58 (s, 2H, H-4b), 7.30 – 7.18 (m, 5H, ArH), 7.20 (d, J = 1.9 Hz, 1H, H-6b), 7.11 (d, J = 2.4 Hz, 1H, H-5b), 7.03 (dd, J = 8.5, 2.4 Hz, 1H, H-5f), 6.91 (dd, J = 8.1, 1.9 Hz, 1H, H-6f), 6.90 (d, J = 8.5 Hz, 1H, H-5e), 6.75 (d, J = 8.1 Hz, 1H, H-6e), 6.63 (d, J = 2.4 Hz, 1H, H-7f), 6.54 (d, J = 2.4 Hz, 1H, H-7d), 5.55 (s, 1H, H-5α), 5.18 (s, 1H, H-4α), 5.16 (d, J = 3.2 Hz, 1H, H-6β), 4.64 (d, J = 3.2 Hz, 1H, H-6α), 4.51 (dd, J = 6.5, 5.4 Hz, 1H, H-7α), 4.42 (d, J = 12.2 Hz, 1H, OCH_AHPh), 4.39 (d, J = 12.2 Hz, 1H, OCHH_BPh), 4.12 (dq, J = 10.8, 7.1 Hz, 1H, OCH_AHCH$_3$), 4.07 (dq, J = 10.8, 7.1 Hz, 1H, OCHH_BCH$_3$), 3.80 (s, 3H, 7e-OCH$_3$), 3.76 (br.s, 4H, NCH_2CH$_2$), 3.61 (s, 3H, 5d-OCH$_3$), 3.60-3.55 (m, 2H, H-7β), 3.55 (s, 3H, 7c-OCH$_3$), 2.03 (br.s, 4H, NCH$_2$CH_2), 1.37 (s, 9H, tBuO), 1.17 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 0.84 (s, 9H, tBuSi), – 0.02 (s, 3H, CH$_3$Si), – 0.15 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CD_3OD, 330 K): δ = 171.8, 171.0, 171.0, 162.1, 160.0, 159.2, 156.9, 153.8, 149.2, 139.5, 138.6, 138.5, 134.3, 132.5, 132.5, 130.3, 129.3, 129.3, 129.2, 128.7, 128.6, 127.1, 126.7, 121.6, 121.3, 118.8, 117.6, 112.8, 104.9, 100.2, 81.5, 75.0, 74.3, 74.1, 63.3, 62.8, 61.1, 58.6, 58.2, 56.6, 56.1, 56.1, 28.7, 26.3, 24.7, 19.0, 14.4, – 4.4, – 5.0; HRMS (FAB) calcd for $C_{60}H_{74}Br_2ClN_9O_{12}SiCs$ [M + Cs$^+$] 1468.2323, found 1468.2403.

Natural AB/C-O-D azide 18a and unnatural AB/C-O-D azide 18b: In a flame-dried flask containing AB/C/D tripeptide **17** (150 mg, 0.11 mmol) were added anhydrous K_2CO_3 (31 mg, 0.22 mmol) and CuBr · Me_2S (46 mg, 0.22 mmol) followed by the addition of freshly distilled MeCN (2.2 mL). This mixture was warmed to 70 °C, freshly distilled pyridine (17 µL, 0.21 mmol) was added, and the mixture was stirred at reflux for 1.5 h. After the reaction mixture had cooled, EtOAc (5 mL) and saturated aqueous NH_4Cl (5 mL) were added and it was vigorously stirred for 10 min. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 0 → 15 % EtOAc in benzene, gradient elution) to afford faster moving natural AB/C-O-D azide **18a** (47 mg, 34 %), and slower moving unnatural AB/C-O-D azide **18b** (46 mg, 33 %). **18a**: R_f = 0.69 (silica gel, 30 % EtOAc in benzene); $[\alpha]_D^{22}$ = + 136.7 (c = 1.4, EtOAc); IR (thin film): $\tilde{\nu}_{max}$ = 3362, 2934, 2099, 1732, 1674, 1605, 1505, 1416, 1338, 1259, 1201, 1158, 1098, 835 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.42 (dd, J = 8.3, 2.4 Hz, 1H, H-5f), 7.40 (d, J = 2.2 Hz, 1H, H-6b), 7.37 (d, J = 1.8 Hz, 1H, H-4f), 7.29 – 7.18 (m, 5H, ArH), 7.03 (d, J = 8.3 Hz, 1H, H-5e), 6.91 (dd, J = 8.6, 2.2 Hz, 1H, H-6f), 6.76 (d, J = 1.8 Hz, 1H, H-4b), 6.67 (d, J = 2.6 Hz, 1H, H-7f), 6.66 (d, J = 8.6 Hz, 1H, H-6e), 6.48 (d, J = 2.6 Hz, 1H, H-7d), 6.43 (br.s, 1H, H-5b), 5.41 (d, J = 2.2 Hz, 1H, H-6β), 5.23 (s, 1H, H-5α), 4.95 (s, 1H, H-4α), 4.71 (d, J = 2.2 Hz, 1H, H-6α), 4.62 (dd, J = 8.1, 3.3 Hz, 1H, H-7α), 4.38

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(d, $J = 12.3$ Hz, 1H, OCH_AHPh), 4.30 (dq, $J = 10.9$, 7.2 Hz, 1H, OCH-H_ACH$_3$), 4.17 (d, $J = 12.3$ Hz, 1H, OCHH_BPh), 4.12 (dq, $J = 10.9$, 7.2 Hz, 1H, OCHH_BCH$_3$), 3.84 (s, 3H, 7e-OCH$_3$), 3.79 (br.s, 4H, NCH_2CH$_2$), 3.61 (s, 3H, 7c-OCH$_3$), 3.59 (s, 3H, 5d-OCH$_3$), 3.40 (dd, $J = 11.0$, 3.3 Hz, 1H, H-7β_A), 3.36 (dd, $J = 11.0$, 8.1 Hz, 1H, H-7β_B), 2.06 (br.s, 4H, NCH$_2$CH_2), 1.42 (s, 9H, *t*BuO), 1.32 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH_3), 0.81 (s, 9H, *t*BuSi), 0.00 (s, 3H, CH$_3$Si), -0.15 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CD$_3$OD, 330 K): $\delta = 170.7$, 170.4, 170.1, 162.0, 159.8, 159.6, 157.7, 155.0, 153.4, 142.6, 139.8, 138.9, 138.8, 136.3, 133.4, 129.5, 129.4, 129.2, 129.1, 128.7, 128.4, 128.1, 127.6, 127.4, 127.2, 124.0, 120.3, 119.9, 117.8, 113.0, 105.0, 100.0, 81.5, 74.9, 74.7, 73.6, 63.2, 62.4, 61.4, 61.2, 58.9, 56.6, 56.0, 28.7, 26.5, 24.7, 18.9, 14.3, −4.1, −5.3; HRMS (FAB) calcd for $C_{60}H_{73}BrClN_9O_{12}SiCs$ [$M + Cs^+$] 1386.3074, found 1386.3010. **18b**: $R_f = 0.42$ (silica gel, 30% EtOAc in benzene); $[\alpha]_D^{22} = -32.9$ ($c = 2.0$, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3363$, 2634, 2099, 1718, 1670, 1605, 1489, 1420, 1339, 1253, 1201, 1159, 1093, 837 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$OD, 330 K): $\delta = 7.52$ (d, $J = 1.8$ Hz, 1H, H-6b), 7.45 (dd, $J = 8.8$, 2.4 Hz, 1H, H-5f), 7.32–7.31 (m, 2H, H-6f and H-5b), 7.29–7.21 (m, 5H, ArH), 7.18 (d, $J = 8.3$ Hz, 1H, H-6e), 7.13 (d, $J = 8.8$ Hz, 1H, H-5e), 7.08 (d, $J = 2.6$ Hz, 1H, H-4f), 6.78 (d, $J = 0.8$ Hz, 1H, H-4b), 6.69 (d, $J = 2.2$ Hz, 1H, H-7f), 6.56 (d, $J = 2.2$ Hz, 1H, H-7d), 5.44 (d, $J = 2.6$ Hz, 1H, H-6β), 5.39 (s, 1H, H-4α), 5.34 (s, 1H, H-5α), 4.62 (d, $J = 2.6$ Hz, 1H, H-6α), 4.61 (dd, $J = 7.7$, 3.3 Hz, 1H, H-7α), 4.43 (br.s, 2H, OCH_2Ph), 4.27 (dq, $J = 10.8$, 7.1 Hz, 1H, OCH_AHCH$_3$), 4.09 (dq, $J = 10.8$, 7.1 Hz, 1H, OCHH_BCH$_3$), 3.82 (s, 3H, 7e-OCH$_3$), 3.81 (br.s, 4H, NCH_2CH$_2$), 3.65 (s, 3H, 5d-OCH$_3$), 3.62 (s, 3H, 7c-OCH$_3$), 3.61-3.56 (m, 2H, H-7β), 2.07 (br.s, 4H, NCH$_2$CH_2), 1.42 (s, 9H, *t*BuO), 1.27 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3), 0.83 (s, 9H, *t*BuSi), −0.02 (s, 3H, CH$_3$Si), −0.08 (s, 3H, CH$_3$Si); ^{13}C NMR (100 MHz, CD$_3$OD, 330 K): $\delta = 171.2$, 170.3, 169.9, 162.1, 160.0, 157.7, 153.2, 153.1, 141.0, 140.4, 139.6, 138.8, 137.3, 134.3, 130.2, 129.7, 129.3, 128.7, 128.6, 128.1, 127.5, 127.3, 125.5, 120.7, 119.9, 115.0, 113.4, 105.4, 100.2, 81.3, 75.0, 74.3, 74.1, 63.2, 63.1, 61.1, 59.3, 58.6, 56.7, 56.2, 56.1, 28.7, 26.5, 24.7, 18.9, 14.4, −4.3, −5.1; HRMS (FAB) calcd for $C_{60}H_{73}BrClN_9O_{12}SiCs$ [$M + Cs^+$] 1388.3066, found 1388.3155.

Natural AB/C-O-D alcohol 19a: A solution of natural protected AB/C-O-D alcohol **18a** (7.9 g, 6.3 mmol) in THF (65 mL) was cooled to −25 °C and tetra-*n*-butylammonium fluoride (TBAF, 1.0 M solution in THF, 6.9 mL, 6.9 mmol) was added dropwise. The reaction mixture was allowed to stir at −15 °C for 3 h, and then quenched by the addition of saturated aqueous NH$_4$Cl (300 mL). EtOAc (300 mL) was added, and the aqueous phase was extracted with EtOAc (100 mL). The combined organic layers were dried (Na$_2$SO$_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 25 →40% EtOAc in hexanes, gradient elution) to afford natural AB/C-O-D alcohol **19a** (6.83 g, 95%). **19a**: $R_f = 0.39$ (silica gel, 40% EtOAc in benzene); $[\alpha]_D^{22} = +124.2$ ($c = 0.90$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3413$, 3357, 2972, 2936, 2869, 2836, 2100, 1695, 1667, 1605, 1502, 1462, 1413, 1338, 1263, 1201, 1158, 1057, 735, 699 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$OD, 330 K): $\delta = 7.41$ (dd, $J = 8.7$, 2.5 Hz, 1H, H-5f), 7.38 (d, $J = 1.8$ Hz, 1H, H-6b), 7.33 (dd, $J = 8.4$, 1.7, 1H, H-6f), 7.32 (d, $J = 1.8$ Hz, 1H, H-4f), 7.28-7.17 (m, 5H, ArH), 6.97 (d, $J = 8.5$ Hz, 1H, H-5e), 6.75 (d, $J = 8.4$ Hz, 1H, H-6e), 6.71 (d, $J = 1.9$ Hz, 1H, H-4b), 6.62 (d, $J = 2.4$ Hz, 1H, H-7f), 6.50 (d, $J = 2.4$ Hz, 1H, H-7d), 6.41 (d, $J = 1.7$ Hz, 1H, H-5b), 5.37 (d, $J = 3.6$ Hz, 1H, H-6β), 5.34 (s, 1H, H-5α), 5.04 (s, 1H, H-4α), 4.82 (d, $J = 3.7$ Hz, 1H, H-6α), 4.56 (dd, $J = 8.0$, 4.0 Hz, 1H, H-7α), 4.36 (d, $J = 12.3$ Hz, 1H, OCH_AHPh), 4.22 (d, $J = 12.2$ Hz, 1H, OCHH_BPh), 4.21 (q, $J = 7.1$ Hz, 2H, OCH_2CH$_3$), 3.82 (s, 3H, 7e-OCH$_3$), 3.82-3.78 (br.s, 4H, NCH_2CH$_2$), 3.62 (s, 3H, 7c-OCH$_3$), 3.54 (s, 3H, 5d-OCH$_3$), 3.45 (dd, $J = 11.1$, 4.0 Hz, 1H, H-7β_A), 3.42 (dd, $J = 11.1$, 8.0 Hz, 1H, H-7β_B), 2.05 (br.s, 4H, NCH$_2$CH_2), 1.41 (s , 9H, *t*BuO), 1.25 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (600 MHz, CD$_3$OD, 330 K): $\delta = 171.5$, 171.1, 170.4, 162.2, 159.8, 159.6, 157.8, 155.0, 153.4, 141.9, 140.5, 139.8, 138.8, 136.4, 132.3, 129.9, 129.7, 129.4, 128.8, 128.6, 128.6, 128.0, 127.8, 127.3, 126.9, 124.8, 120.3, 120.3, 116.0, 112.8, 104.3, 99.6, 81.6, 74.9, 73.4, 72.9, 63.0, 62.7, 61.0, 60.5, 58.7, 56.5, 56.1, 56.1, 28.8, 24.9, 14.6; HRMS (FAB) calcd for $C_{54}H_{59}BrClN_9O_{12}Cs$ [$M + Cs^+$] 1274.2189, found 1274.2244.

Unnatural AB/C-O-D alcohol 19b: A solution of unnatural protected AB/C-O-D alcohol **18b** (1.26 g, 1.0 mmol) in THF (1.5 mL) was cooled to −25 °C and tetra-*n*-butylammonium fluoride (TBAF, 1.0 M solution in THF, 1.1 mL, 1.1 mmol) was added dropwise. The reaction mixture was allowed to stir at −15 °C for 3 h, and then quenched by the addition of saturated aqueous NH$_4$Cl (50 mL). EtOAc (50 mL) was added, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic layers were dried (Na$_2$SO$_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 25 →40% EtOAc in hexanes, gradient elution) to afford unnatural AB/C-O-D alcohol **19b** (1.12 g, 98%). **19b**: $R_f = 0.32$ (silica gel, 40% EtOAc in benzene); $[\alpha]_D^{22} = -43.1$ ($c = 1.1$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3414$, 3318, 2974, 2934, 2872, 2099, 1694, 1667, 1605, 1504, 1488, 1416, 1338, 1261, 1159, 1063, 736, 699 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$OD, 330 K): $\delta = 7.66$ (d, $J = 1.3$ Hz, 1H, H-6b), 7.44 (dd, $J = 8.6$, 2.4 Hz, 1H, H-5f), 7.30-7.20 (m, 7H, ArH), 7.09 (d, $J = 8.6$ Hz, 1H, H-5e), 7.08 (d, $J = 2.8$ Hz, 1H, H-4f), 7.00 (d, $J = 8.8$ Hz, 1H, H-6e), 6.62 (d, $J = 2.3$ Hz, 1H, H-7f), 6.55 (d, $J = 2.3$ Hz, 1H, H-7d), 6.32 (s, 1H, H-4b), 5.47 (s, 1H, H-4α), 5.42 (d, $J = 3.9$ Hz, 1H, H-6β), 5.25 (s, 1H, H-5α), 4.82 (d, $J = 3.9$ Hz, 1H, H-6α), 4.58 (t, $J = 6.0$ Hz, 1H, H-7α), 4.38 (d, $J = 12.4$ Hz, 1H, OCH_AHPh), 4.33 (d, $J = 12.4$ Hz, 1H, OCHH_BPh), 4.21 (q, $J = 7.1$ Hz, 2H, OCH_2CH$_3$), 3.85-3.81 (m, 4H, NCH_2CH$_2$), 3.82 (s, 3H, 7e-OCH$_3$), 3.64 (s, 3H, 5d-OCH$_3$), 3.54 (s, 3H, 7c-OCH$_3$), 3.53 (br.d, $J = 6.0$ Hz, 2H, H-7β), 2.06 (br.s, 4H, NCH$_2$CH_2), 1.41 (s, 9H, *t*BuO), 1.23 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (150 MHz, CD$_3$OD, 330 K): $\delta = 171.6$, 171.5, 170.3, 162.2, 160.1, 159.6, 155.7, 153.7, 152.6, 141.5, 140.9, 139.7, 138.7, 137.1, 132.1, 130.0, 129.8, 129.5, 129.3, 128.8, 128.7, 128.5, 128.1, 127.1, 126.0, 125.1, 120.8, 120.1, 114.4, 112.9, 104.6, 99.8, 81.4, 74.6, 73.7, 72.7, 63.3, 63.0, 61.1, 58.7, 58.5, 56.6, 56.1, 56.1, 28.8, 24.9, 14.6; HRMS (FAB) calcd for $C_{54}H_{59}BrClN_9O_{12}Cs$ [$M + Cs^+$] 1272.2209, found 1272.2150.

Natural AB/C-O-D amine 20a: A solution of natural AB/C-O-D azide **19a** (390 mg, 0.34 mmol) in MeCN/H$_2$O (4:1) (11.5 mL) was treated with triethylphosphane (100 µL, 0.68 mmol) for 20 h at 25 °C. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 1 →3% MeOH in CH$_2$Cl$_2$, gradient elution) to afford the natural AB/C-O-D amine **20a** (296 mg, 78%). **20a**: $R_f = 0.29$ (silica gel, 5% MeOH in CH$_2$Cl$_2$); $[\alpha]_D^{22} = +50.5$ ($c = 0.40$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3326$, 2971, 2931, 2871, 1713, 1694, 1682, 1667, 1659, 1604, 1556, 1503, 1415, 1316, 1245, 1157, 1058, 735, 699 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$OD, 330 K): $\delta = 7.41$ (d, $J = 2.2$ Hz, 1H, H-6b), 7.36 (dd, $J = 8.7$, 2.6 Hz, 1H, H-5f), 7.35 (dd, $J = 8.8$, 2.2, 1H, H-6f), 7.31 (d, $J = 2.2$ Hz, 1H, H-4f), 7.29-7.17 (m, 5H, ArH), 6.97 (d, $J = 8.8$ Hz, 1H, H-5e), 6.80 (br.s, 1H, H-4b), 6.77 (d, $J = 8.5$ Hz, 1H, H-6e), 6.76 (d, $J = 2.6$ Hz, 1H, H-7f), 6.50 (d, $J = 2.6$ Hz, 1H, H-7d), 6.48 (d, $J = 1.3$ Hz, 1H, H-5b), 5.38 (d, $J = 3.5$ Hz, 1H, H-6β), 5.36 (s, 1H, H-5α), 5.10 (s, 1H, H-4α), 4.82 (d, $J = 3.5$ Hz, 1H, H-6α), 4.32 (d, $J = 12.7$ Hz, 1H, OCH_AHPh), 4.27 (d, $J = 12.5$ Hz, 1H, OCHH_BPh), 4.21 (dq, $J = 7.0$, 1.7 Hz, 2H, OCH_2CH$_3$), 3.86 (dd, $J = 8.3$, 3.5 Hz, 1H, H-7α), 3.83 (s, 3H, 7e-OCH$_3$), 3.83–3.78 (br.s, 4H, NCH_2CH$_2$), 3.63 (s, 3H, 7c-OCH$_3$), 3.53 (s, 3H, 5d-OCH$_3$), 3.35 (dd, $J = 10.1$, 3.5 Hz, 1H, H-7β_A), 3.30 (dd, $J = 10.1$, 8.3 Hz, 1H, H-7β_B), 2.08 (br.s, 4H, NCH$_2$CH_2), 1.43 (s, 9H, *t*BuO), 1.27 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH_3); ^{13}C (150 MHz, CD$_3$OD, 330 K): $\delta = 171.5$, 171.3, 170.6, 162.23, 159.7, 159.7, 157.7, 154.0, 153.4, 143.4, 141.9, 140.7, 140.1, 136.9, 132.3, 129.8, 129.7, 129.5, 128.8, 128.6, 128.2, 127.9, 127.9, 127.3, 124.7, 120.7, 120.1, 116.0, 112.7, 104.0, 99.0, 81.6, 76.1, 73.5, 72.9, 63.0, 61.0, 58.8, 56.5, 56.1, 56.1, 52.5, 28.8, 24.9, 14.6; HRMS (FAB) calcd for $C_{54}H_{61}BrClN_7O_{12}Cs$ [$M + Cs^+$] 1246.2304, found 1246.2358.

Unnatural AB/C-O-D amine 20b: A solution of unnatural AB/C-O-D azide **19b** (570 mg, 0.5 mmol) in MeCN/H$_2$O (4:1) (16.8 mL) was treated with triethylphosphane (145 µL, 1.0 mmol) for 20 h at 25 °C. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 1 →3% MeOH in CH$_2$Cl$_2$, gradient elution) to afford the unnatural AB/C-O-D amine **20b** (440 mg, 79%). **20b**: $R_f = 0.19$ (silica gel, 5% MeOH in CH$_2$Cl$_2$); $[\alpha]_D^{22}$ ($c = 1.9$, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3293$, 2973, 2933, 2836, 1741, 166, 1608, 1556, 1490, 1416, 1262, 1158, 1057, 736 cm^{-1}; ^{1}H NMR (600 MHz, CD$_3$OD, 330 K): $\delta = 7.62$ (d, $J = 1.2$ Hz, 1H, H-6b), 7.36 (dd, $J = 8.6$, 2.4 Hz, 1H, H-5f), 7.30-7.20 (m, 7H, ArH), 7.11 (d, $J = 8.3$ Hz, 1H, H-5e), 7.09 (s, 1H, H-4f), 7.00 (d, $J = 8.5$ Hz, 1H, H-6e), 6.74 (d, $J = 2.4$ Hz, 1H, H-7f), 6.51 (d, $J = 2.3$ Hz, 1H, H-7d), 6.35 (d, $J = 1.5$ Hz, 1H, H-4b), 5.43 (s, 1H, H-4α), 5.41 (d, $J = 3.8$ Hz, 1H, H-6β), 5.25 (s, 1H, H-5α), 4.81 (d, $J = 3.8$ Hz, 1H, H-6α), 4.34 (br.d, $J = 2.9$ Hz, 2H, OCH_2Ph), 4.18 (dq, $J = 7.2$, 1.6 Hz, 2H, OCH_2CH$_3$), 3.93 (dd, $J = 8.5$, 3.9 Hz, 1H, H-7α), 3.82 (s, 3H, 7e-OCH$_3$), 3.82 (br.s, 4H, NCH_2CH$_2$), 3.64 (s, 3H, 5d-OCH$_3$), 3.52 (s, 3H, 7c-OCH$_3$), 3.42 (dd, $J = 10.0$, 4.0 Hz, 1H, H-7β_A), 3.39 (dd, $J = 10.0$, 8.6 Hz, 1H, H-7β_B), 2.06 (br.s, 4H, NCH$_2$CH_2), 1.41 (s, 9H, *t*BuO), 1.24 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (150 MHz, CD$_3$OD, 330 K): $\delta = 171.5$, 171.4, 170.5, 162.2, 159.8, 159.5, 157.6, 153.5, 152.4, 143.1, 141.4, 140.9, 139.9, 137.1, 132.2, 129.9, 129.5, 129.4, 128.8, 128.6, 128.4, 128.1, 127.9, 126.0, 125.2, 120.8, 120.0, 114.3, 112.6, 104.2,

99.2, 81.4, 76.0, 73.7, 72.6, 63.0, 61.0, 58.6, 56.6, 56.1, 56.1, 52.7, 28.9, 24.8, 14.6; HRMS (FAB) calcd for $C_{54}H_{61}BrClN_7O_{12}Cs$ $[M+Cs^+]$ 1246.2304, found 1246.2252.

Natural AB/C-O-D carboxylic acid 21a: A solution of natural AB/C-O-D carboxylic ester **20a** (112 mg, 0.1 mmol) in THF/H_2O (1:1) (5 mL) was cooled at $-5\,^\circ$C, and lithium hydroxide monohydrate (21 mg, 0.5 mmol) was added. After vigorous stirring at $0\,^\circ$C for 10 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). CH_2Cl_2 (5 mL) was added, and the pH of the mixture was adjusted to 5 by adding dropwise a cooled 1% aqueous HCl. The aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), concentrated, and the residue, crude carboxylic acid **21a** (100 mg, 92%), was used in the macrolactamization reaction without further purification.

Unnatural AB/C-O-D carboxylic acid 21b: A solution of unnatural AB/C-O-D carboxylic ester **20b** (89 mg, 80 μmol) in THF/H_2O (1:1) (4 mL) was cooled at $-5\,^\circ$C, and lithium hydroxide monohydrate (17 mg, 0.4 mmol) was added. After vigorous stirring at $0\,^\circ$C for 10 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl (4 mL). CH_2Cl_2 (4 mL) was added, and the pH of the mixture was adjusted to 5 by adding dropwise a cooled 1% aqueous HCl. The aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), concentrated, and the residue, crude carboxylic acid **21b** (78 mg, 90%), was used in the macrolactamization reaction without further purification.

Natural AB/C-O-D bicyclic triazene 22a: A solution of crude natural AB/C-O-D amino acid **21a** (100 mg, 0.092 mmol) in freshly distilled DMF (20 mL) was cooled to $0\,^\circ$C. Freshly distilled *i*Pr_2NEt (80 μL, 0.46 mmol) and pentafluorophenyl diphenylphosphinate (FDPP, 108 mg, 0.28 mmol) were added, and the mixture was allowed to warm slowly to $25\,^\circ$C. After stirring for 12 h, EtOAc (100 mL) was added, and the reaction mixture was washed with brine (3×50 mL). The combined aqueous phases were extracted with EtOAc (50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 0.5 →1.5% MeOH in CH_2Cl_2, gradient elution) to afford natural AB/C-O-D bicyclic triazene **22a** (85 mg, 86%). **22a**: $R_f=0.24$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=-46.6$ ($c=1.1$, EtOAc); IR (thin film): $\tilde{\nu}_{max}=3317, 2970, 2929, 2873, 1693, 1681, 1667, 1659, 1605, 1555, 1504, 1485, 1415, 1320, 1248, 1158, 1058, 734, 700\ cm^{-1}$; ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta=7.62$ (d, $J=2.2$ Hz, 1H, H-6b), 7.46 (dd, $J=8.3, 2.2$ Hz, 1H, H-6f), 7.38–7.25 (m, 6H, ArH), 7.14 (dd, $J=8.8, 2.2$ Hz, 1H, H-5f), 7.07 (d, $J=2.2$ Hz, 1H, H-5b), 7.06 (d, $J=8.1$ Hz, 1H, H-6e), 6.97 (d, $J=8.8$ Hz, 1H, H-5e), 6.91 (d, $J=2.2$ Hz, 1H, H-7f), 6.64 (d, $J=2.2$ Hz, 1H, H-7d), 5.84 (s, 1H, H-4b), 5.48 (br.s, 1H, H-4α), 5.21 (s, 1H, H-6β), 4.71 (s, 1H, H-5α), 4.62 (d, $J=11.8$ Hz, 1H, OCH_AHPh), 4.58 (d, $J=11.8$ Hz, 1H, OCHH_BPh), 4.42 (dd, $J=7.7$, 4.2 Hz, 1H, H-7α), 4.06 (d, $J=1.3$ Hz, 1H, H-6α), 3.98 (dd, $J=10.1$, 7.9 Hz, 1H, H-7β_A), 3.90 (dd, $J=10.1$, 4.4 Hz, 1H, H-7β_B), 3.84 (s, 3H, 7e-OCH_3), 3.81 (br.s, 4H, NCH_2CH_2), 3.69 (s, 3H, 7c-OCH_3), 3.65 (s, 3H, 5d-OCH_3), 2.06 (br.s, 4H, NCH_2CH_2), 1.42 (s, 9H, *t*BuO); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta=171.0$, 171.0, 168.5, 161.3, 159.9, 158.5, 156.3, 153.1, 152.6, 142.3, 141.0, 140.0, 139.9, 139.0, 136.4, 129.4, 129.3, 128.9, 128.8, 128.5, 128.3, 128.3, 127.6, 127.5, 125.5, 124.5, 122.9, 119.7, 114.9, 113.9, 106.8, 99.0, 80.0, 73.9, 73.3, 70.7, 64.3, 57.0, 56.4, 56.0, 55.3, 53.1, 28.6, 24.5; HRMS (FAB) calcd for $C_{52}H_{55}BrClN_7O_{11}Cs$ $[M+Cs^+]$ 1202.1875, found 1202.1933.

Unnatural AB/C-O-D bicyclic triazene 22b: A solution of crude unnatural AB/C-O-D aminoacid **21b** (109 mg, 0.1 mmol) in freshly distilled DMF (20 mL) was cooled to $0\,^\circ$C. Freshly distilled *i*Pr_2NEt (87 μL, 0.50 mmol) and pentafluorophenyl diphenylphosphinate (FDPP, 115 mg, 0.30 mmol) were added, and the mixture was allowed to warm slowly to $25\,^\circ$C. After stirring for 12 h, EtOAc (100 mL) was added, and the mixture was washed with brine (3×60 mL). The combined aqueous phases were extracted with EtOAc (50 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 1.0 →1.5% MeOH in CH_2Cl_2, gradient elution) to afford unnatural bicyclic triazene **22b** (64 mg, 60%). **22b**: $R_f=0.17$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=-14.7$ ($c=1.6$, EtOAc); IR (thin film): $\tilde{\nu}_{max}=3415, 3274, 2973, 2934, 2871, 2837, 1659, 1485, 1416, 1318, 1264, 1158, 1056\ cm^{-1}$; ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta=7.63$ (d, $J=2.0$ Hz, 1H, H-6b), 7.38 (dd, $J=8.5, 2.0$ Hz, 1H, H-6f), 7.37-7.21 (m, 5H, ArH), 7.28–7.25 (m, 1H, ArH), 7.15 (dd, $J=8.6, 2.3$ Hz, 1H, H-5f), 7.08 (d, $J=8.3$ Hz, 1H, H-6e), 7.04 (d, $J=2.3$ Hz, 1H, H-4f), 6.97 (d, $J=8.7$ Hz, 1H, H-5e), 6.90 (d, $J=2.3$ Hz, 1H, H-7f), 6.62 (d, $J=2.3$ Hz, 1H, H-7d), 5.88 (d, $J=1.4$ Hz, 1H, H-4b), 5.50 (br.s, 1H, H-4α), 5.24 (s, 1H, H-6β), 4.73 (s, 1H, H-5α), 4.61 (d, $J=11.9$ Hz, 1H, OCH_AHPh), 4.58 (d, $J=11.8$ Hz, 1H, OCHH_BPh), 4.40 (dd, $J=7.6, 4.2$ Hz, 1H, H-7α), 4.06 (d, $J=1.6$ Hz, 1H, H-6α), 3.98 (dd, $J=10.2, 7.6$ Hz, 1H, H-7β_A), 3.90 (dd, $J=10.2, 4.3$ Hz, 1H, H-7β_B), 3.82 (s, 3H, 7e-OCH_3), 3.82 (br.s, 4H, NCH_2CH_2),3.68 (s, 3H, 5d-OCH_3), 3.63 (s, 3H, 7c-OCH_3), 2.05 (br.s, 4H, NCH_2CH_2), 1.42 (s, 9H, *t*BuO); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta=171.0$, 168.3, 161.2, 159.7, 158.4, 156.0, 152.4, 152.2, 142.2, 140.8, 139.8, 139.8, 138.7, 136.3, 130.6, 129.4, 129.2, 129.1, 128.6, 128.3, 127.6, 127.4, 126.5, 126.1, 125.5, 125.4, 122.8, 119.6, 113.8, 113.7, 106.7, 98.9, 79.9, 73.8, 72.9, 70.6, 64.2, 64.1, 56.3, 55.8, 55.1, 53.1, 53.0, 28.6, 24.4; HRMS (FAB) calcd for $C_{52}H_{55}BrClN_7O_{11}Cs$ $[M+Cs^+]$ 1202.1865, found 1202.1799.

Natural AB/C-O-D silyl alcohol 23a: A solution of natural AB/C-O-D alcohol **22a** (790 mg, 0.74 mmol) in CH_2Cl_2 (40 mL) was cooled to $-20\,^\circ$C. Freshly distilled 2,6-lutidine (1.3 mL, 11 mmol) was added dropwise, followed by the dropwise addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.85 mL, 3.7 mmol). The reaction mixture was stirred at $-15\,^\circ$C for 2 h, quenched by the addition of saturated aqueous $NaHCO_3$ (40 mL), and then left under vigorous stirring at $25\,^\circ$C for 2 h. The aqueous phase was extracted with EtOAc (100 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 0 →50% EtOAc in hexanes, gradient elution) to afford natural AB/C-O-D silyl alcohol **23a** (744 mg, 85%). **23a**: $R_f=0.56$ (silica gel, 40% EtOAc in benzene); $[\alpha]_D^{22}=+38.0$ ($c=0.70$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3308, 2953, 2928, 2857, 1680, 1655, 1486, 1262, 1158, 1104, 838, 782, 700\ cm^{-1}$; ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta=7.61$ (d, $J=2.0$ Hz, 1H, H-6b), 7.40 (dd, $J=8.3$, 1.7 Hz, 1H, H-6f), 7.38-7.25 (m, 6H, ArH), 7.11 (bd, $J=8.3$ Hz, 1H, H-5f), 7.07 (d, $J=8.5$ Hz, 1H, H-6e), 7.03 (d, $J=2.2$ Hz, 1H, H-5b), 6.95 (d, $J=8.1$ Hz, 1H, H-5e), 6.95 (s, 1H, H-7f), 6.62 (d, $J=2.2$ Hz, 1H, H-7d), 5.82 (s, 1H, H-4b), 5.48 (br.s, 1H, H-4α), 5.26 (s, 1H, H-6β), 4.67 (s, 1H, H-5α), 4.58 (d, $J=11.4$ Hz, 1H, OCH_AHPh), 4.55 (d, $J=11.8$ Hz, 1H, OCHH_BPh), 4.42-4.39 (m, 1H, H-7α), 4.04 (br.s, 1H, H-6α), 3.92 (t, $J=11.4$ Hz, 1H, H-7β_A), 3.84 (dd, $J=11.6$, 3.5 Hz, 1H, H-7β_B), 3.82 (s, 3H, 7e-OCH_3), 3.82–3.78 (br.s, 4H, NCH_2CH_2), 3.67 (s, 3H, 7c-OCH_3), 3.62 (s, 3H, 5d-OCH_3), 2.04 (br.s, 4H, NCH_2CH_2), 1.40 (s, 9H, *t*BuO), 0.86 (s, 9H, *t*BuSi), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3OD, 330 K): $\delta=173.0$, 172.1, 169.2, 162.0, 160.2, 159.0, 157.6, 153.4, 153.1, 142.1, 141.2, 139.9, 139.5, 137.1, 129.6, 129.5, 129.4, 129.4, 129.3, 129.0, 128.3, 128.2, 127.5, 126.2, 126.1, 124.9, 123.1, 120.3, 114.7, 114.3, 106.9, 99.7, 81.4, 75.0, 74.5, 71.0, 65.3, 56.6, 56.6, 56.3, 55.9, 53.3, 28.8, 26.4, 24.9, 19.3, −4.6, −4.7; HRMS (FAB) calcd for $C_{58}H_{69}BrClN_7O_{11}SiCs$ $[M+Cs^+]$ 1316.2742, found 1316.2684.

Unnatural AB/C-O-D silyl alcohol 23b: A solution of unnatural AB/C-O-D alcohol **22b** (1.07 g, 1.0 mmol) in CH_2Cl_2 (50 mL) was cooled to $-20\,^\circ$C. Freshly distilled 2,6-lutidine (1.7 mL, 15 mmol) was added dropwise, followed by the dropwise addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1.15 mL, 5.0 mmol). The reaction mixture was stirred at $-15\,^\circ$C for 2 h, quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL), and then left under vigorous stirring at $25\,^\circ$C for 2 h. The aqueous phase was extracted with EtOAc (120 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 →50% EtOAc in hexanes, gradient elution) to afford unnatural silyl alcohol **23b** (945 mg, 80%). **23b**: $R_f=0.29$ (silica gel, 30% EtOAc in benzene); $[\alpha]_D^{22}=-43.7$ ($c=1.1$, MeOH); IR (thin film): $\tilde{\nu}_{max}=3406, 3283, 2951, 2928, 2855, 1692, 1681, 1658, 1504, 1486, 1416, 1324, 1256, 1201, 1157, 1098, 838, 781, 699\ cm^{-1}$; ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta=7.56$ (d, $J=1.8$ Hz, 1H, H-6b), 7.40-7.32 (m, 6H, ArH), 7.30–7.27 (m, 1H, ArH), 7.15 (dd, $J=8.3$, 1.8 Hz, 1H, H-6f), 7.12 (d, $J=8.3$ Hz, 1H, H-6e), 7.02 (d, $J=2.6$ Hz, 1H, H-4f), 6.97 (d, $J=8.3$ Hz, 1H, H-5e), 6.96 (d, $J=2.2$ Hz, 1H, H-7f), 6.62 (d, $J=2.2$ Hz, 1H, H-7d), 5.87 (d, $J=1.3$ Hz, 1H, H-4b), 5.52 (br.s, 1H, H-4α), 5.32 (s, 1H, H-6β), 4.71 (s, 1H, H-5α), 4.59 (d, $J=11.8$ Hz, 1H, OCH_AHPh), 4.56 (d, $J=11.8$ Hz, 1H, OCHH_BPh), 4.41 (s, 1H, H-7α), 4.06 (d, $J=1.8$ Hz, 1H, H-6α), 3.92 (br.t, $J=9.0$ Hz, 1H, H-7β_A), 3.86 (dd, $J=9.7$, 3.5 Hz, 1H, H-7β_B), 3.83 (s, 3H, 7e-OCH_3), 3.83-3.79 (m, 4H, NCH_2CH_2), 3.68 (s, 3H, 5d-OCH_3), 3.63 (s, 3H, 7c-OCH_3), 2.06 (br.s, 4H, NCH_2CH_2), 1.43 (s, 9H, *t*BuO), 0.89 (s, 9H, *t*BuSi), 0.04 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3OD, 330 K):

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δ = 173.1, 172.1, 169.2, 161.9, 160.2, 159.0, 157.6, 153.1, 152.9, 142.1, 141.2, 140.0, 139.5, 137.0, 131.3, 129.6, 129.4, 129.0, 128.6, 128.6, 128.1, 126.8, 126.2, 126.1, 125.9, 123.1, 120.4, 114.3, 113.9, 107.0, 99.7, 81.4, 74.8, 74.5, 71.0, 65.2, 56.6, 56.5, 56.3, 55.9, 53.4, 28.8, 26.4, 24.9, 19.3, −4.6, −4.7; HRMS (FAB) calcd for $C_{58}H_{69}BrClN_7O_{11}SiCs$ $[M+Cs^+]$ 1314.2751, found 1314.2680.

AB/C dipeptide 24: A solution of amine **4** (1.68 g, 4.5 mmol) and unnatural biaryl carboxylic acid **14** (2.67 g, 4.5 mmol) in THF (50 mL) was cooled to 0 °C. HOAt (2.02 g, 14.9 mmol) and EDC (2.59 g, 13.5 mmol) were added, and the reaction mixture was stirred at 0 °C for 10 h. The reaction was quenched by the addition of saturated aqueous citric acid (10 mL) and the resulting mixture was extracted with EtOAc (4 × 60 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 20 →30 % EtOAc in hexanes, gradient elution) to afford AB/C dipeptide **24** (3.54 g, 83 % yield). **24**: R_f = 0.09 (silica gel, 30 % EtOAc in hexanes); $[\alpha]_D^{22} = -24.5$ (c = 1.6, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3425, 2943, 2861, 2097, 1696, 1602, 1496, 1349, 1255, 1202, 1155, 1091, 1026 cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 8.67 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.37 (s, 1H), 7.32-7.22 (m, 5H), 7.14 (dd, J = 8.5, 2.0 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.46 (d, J = 7.5 Hz, 1H), 5.31 – 5.29 (m, 2H), 4.62 (dd, J = 9.0, 2.5 Hz, 1H), 4.41 (dd, J = 9.0, 4.0 Hz, 1H), 4.29 (d, J = 12.0 Hz, 1H, OCH_AHPh), 4.26 (d, J = 12.0 Hz, 1H, OCHH_BPh), 4.20-4.17 (m, 1H, OCH_AHCH$_3$), 4.12 – 4.09 (m, 1H, OCHH_BCH$_3$), 3.83 (s, 3H, OCH$_3$), 3.73 (s, 3H, OCH$_3$), 3.65 (s, 3H, OCH$_3$), 3.49 (dd, J = 10.8, 9.0 Hz, 1H, H-7β_A), 3.41 (dd, J = 10.8, 3.7 Hz, 1H, H-7β_B), 1.38 (s, 9H, tBuO), 1.25 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 0.87 (s, 9H, tBuSi), 0.02 (s, 3H, CH$_3$Si), −0.15 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 171.5, 170.4, 161.2, 159.1, 157.2, 155.7, 153.1, 139.5, 138.5, 134.0, 132.5, 131.7, 130.4, 128.9, 128.6, 128.2, 128.0, 127.0, 125.1, 120.5, 120.0, 117.2, 111.7, 103.9, 99.0, 79.4, 74.4, 74.3, 73.1, 63.1, 62.0, 60.0, 58.1, 56.0, 55.7, 55.6, 28.5, 26.1, 18.6, 14.4, −4.4, −5.3; HRMS (FAB) calcd for $C_{48}H_{62}ClN_5O_{11}SiCs$ $[M+Cs^+]$ 1080.2958, found 1080.2997.

AB/C amine 25: A solution of AB/C dipeptide **24** (1.61 g, 1.7 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.04 mL, 5.8 mmol) and 2,6-lutidine (594 μL, 5.1 mmol) were added, and the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 30 →50 % EtOAc in hexanes, gradient elution) to afford AB/C amine **25** (1.31 g, 91 % yield). **25**: R_f = 0.15 (silica gel, 50 % EtOAc in hexanes); $[\alpha]_D^{22} = -28.1$ (c = 1.6, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3448, 2097, 1713, 1696, 1646, 1608, 1508, 1490, 1261, 1155, 1061, 1020 cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 8.92 (br. s, 1H), 8.55 (d, J = 10.0 Hz, 1H), 7.44 (dd, J = 8.5, 2.0 Hz, 1H), 7.35 (s, 1H), 7.30 – 7.27 (m, 2H), 7.23 – 7.22 (m, 3H), 7.15-7.13 (m, 2H), 6.99 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 5.37 (s, 1H), 4.78 (s, 1H), 4.63 (dd, J = 10.0, 1.9 Hz, 1H), 4.47 (dd, J = 9.0, 3.5 Hz, 1H), 4.27 (d, J = 12.0 Hz, 1H, OCH_AHPh), 4.21 (d, J = 12.0 Hz, 1H, OCHH_BPh), 4.16-4.12 (m, 1H, OCH_AHCH$_3$), 4.06-4.02 (m, 1H, OCHH_BCH$_3$), 3.83 (s, 3H, OCH$_3$), 3.69 (s, 3H, OCH$_3$), 3.64 (s, 3H, OCH$_3$), 3.53 (dd, J = 11.0, 9.0 Hz, 1H, H-7β_A), 3.43 (dd, J = 11.0, 3.5 Hz, 1H, H-7β_B), 1.19-1.16 (m, 3H, OCH$_2$CH_3), 0.95 (s, 9H, tBuSi), 0.05 (s, 3H, CH$_3$Si), −0.15 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 171.9, 170.5, 169.8, 161.3, 159.1, 156.8, 153.3, 139.4, 138.5, 134.2, 132.9, 132.8, 129.2, 128.9, 128.8, 128.0, 126.7, 124.9, 120.5, 119.9, 117.0, 111.7, 103.8, 99.0, 74.7, 74.6, 73.1, 67.9, 63.5, 62.0, 58.4, 56.0, 55.7, 55.6, 26.0, 18.6, 14.3, −4.4, −5.4; HRMS (FAB) calcd for $C_{43}H_{54}ClN_5O_9SiCs$ $[M+Cs^+]$ 980.2434, found 980.2404.

AB/C tripeptide 26: A solution of AB/C amine **25** (1.27 g, 1.5 mmol) and carboxylic acid **7** (756 mg, 1.5 mmol) in THF (15 mL) was cooled to 0 °C. HOAt (673 mg, 5.0 mmol) and EDC (867 mg, 4.5 mmol) were added, and the reaction mixture was stirred at 0 °C for 10 h. The reaction was quenched by the addition of saturated NH_4Cl (5 mL) and the resulting mixture was extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 15 →35 % EtOAc in hexanes, gradient elution) afforded AB/C tripeptide **26** (1.40 g, 70 % yield). **26**: R_f = 0.25 (silica gel, 40 % EtOAc in hexanes); $[\alpha]_D^{22} = -35.5$ (c = 1.5, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3410, 2932, 2100, 1675, 1606, 1499, 1418, 1342, 1259, 1201, 1158, 1094 cm^{-1}; ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 8.67 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.67 (s, 2H), 7.33 – 7.24 (m, 5H), 7.16 (d, J = 2.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 6.56 – 6.55 (m, 1H), 5.60 (d, J = 8.0 Hz, 1H), 5.36 (d, J = 7.5 Hz, 1H), 5.22 (d, J = 2.3 Hz, 1H), 4.57 (dd, J = 9.0, 2.3 Hz, 1H), 4.40 (dd, J = 8.0, 4.0 Hz, 1H), 4.35 (d, J = 12.5 Hz, 1H, OCHH$_B$Ph), 4.32 (d, J = 12.5 Hz, 1H, OCHH_BPh), 4.15 – 4.12 (m, 1H, OCH_AHCH$_3$), 4.08 – 4.04 (m, 1H, OCHH_BCH$_3$), 3.91 – 3.88 (m, 2H, NCH_2CH$_2$), 3.83 (s, 3H, OCH$_3$), 3.75 (s, 3H, OCH$_3$), 3.66 (s, 3H, OCH$_3$), 3.63 – 3.60 (m, 2H, NCH_2CH$_2$), 3.49 – 3.44 (m, 2H, H-7β), 2.04 (br. s, 4H, NCH$_2$CH_2), 1.31 (s, 9H, tBuO), 1.19 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 0.83 (s, 9H, tBuSi), −0.02 (s, 3H, CH$_3$Si), −0.18 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 170.8, 170.1, 169.2, 161.2, 159.1, 157.2, 155.4, 153.0, 148.5, 139.6, 138.9, 138.6, 133.9, 132.7, 132.2, 131.1, 129.0, 128.6, 128.2, 128.0, 127.9, 127.0, 124.9, 120.4, 120.1, 118.0, 117.2, 111.7, 104.0, 99.1, 79.7, 74.3, 74.2, 73.2, 63.3, 61.9, 60.1, 57.4, 56.7, 56.1, 55.7, 55.6, 51.7, 47.3, 28.4, 26.0, 24.6, 24.1, 18.6, 14.4, −4.5, −5.3; HRMS (FAB) calcd for $C_{60}H_{74}Br_2ClN_9O_{12}SiCs$ $[M+Cs^+]$ 1468.2315, found 1468.2410.

AB/C-O-D azide 27a and AB/C-O-D azide 27b: To a solution of AB/C tripeptide **26** (1.60 g, 1.2 mmol) in degassed acetonitrile (150 mL) were added sequentially $CuBr \cdot Me_2S$ (1.04 g, 3.6 mmol), K_2CO_3 (497 mg, 3.6 mmol), and pyridine (300 μL, 3.6 mmol). The reaction mixture was heated at reflux for 20 min and then it was cooled to 25 °C. The reaction mixture was diluted with EtOAc (400 mL) and the organic layers were washed with 5 % aqueous NH_4Cl (200 mL), H_2O (200 mL), brine (200 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 10 →30 % EtOAc in hexanes, gradient elution) to afford AB/C-O-D azide **27a** (452 mg, 30 % yield) and AB/C-O-D azide **27b** (467 mg, 31 % yield). **27a**: R_f = 0.53 (silica gel, 40 % acetone in hexanes); $[\alpha]_D^{22} = +41.9$ (c = 1.1, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3411, 2944, 2844, 2099, 1707, 1602, 1488, 1463, 1414, 1334, 1255, 1155, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.31 – 7.23 (m, 5H), 7.19 (d, J = 7.0 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 1.5 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.86 – 6.84 (m, 1H), 6.61 (d, J = 2.2 Hz, 1H), 6.52 (d, J = 2.2 Hz, 1H), 5.78 (d, J = 9.0 Hz, 1H), 5.63 (d, J = 8.0 Hz, 1H), 5.51 (d, J = 6.0 Hz, 1H), 5.31-5.28 (m, 2H), 5.12 (br. s, 1H), 4.61 (dd, J = 7.7, 1.5 Hz, 1H), 4.49 (dd, J = 8.5, 4.0 Hz, 1H), 4.41-4.36 (m, 2H, OCH_2Ph), 4.31-4.28 (m, 1H, OCH_AHCH$_3$), 4.09 – 4.05 (m, 1H, OCHH_BCH$_3$), 3.98 (br. s, 2H, NCH_2CH$_2$), 3.85 (s, 3H, OCH$_3$), 3.77 (br. s, 2H, NCH_2CH$_2$), 3.76 (s, 3H, OCH$_3$), 3.72 (s, 3H, OCH$_3$), 3.41 (dd, J = 10.0, 9.0 Hz, 1H, H-7β_A), 3.32 (dd, J = 10.0, 4.0 Hz, 1H, H-7β_B), 2.04 (br. s, 4H, NCH$_2$CH_2), 1.40 (s, 9H, tBuO), 1.32 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 0.70 (s, 9H, tBuSi), −0.10 (s, 3H, CH$_3$Si), −0.20 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 168.4, 167.8, 160.5, 158.0, 156.7, 155.1, 153.0, 138.3, 137.9, 137.7, 137.1, 135.9, 134.8, 130.3, 128.5, 128.4, 128.2, 127.6, 127.5, 127.4, 127.0, 126.5, 126.0, 125.8, 125.1, 121.6, 119.1, 117.6, 111.8, 102.3, 98.7, 79.9, 73.6, 73.4, 73.1, 62.7, 61.8, 60.0, 57.8, 55.6, 55.5, 55.4, 51.2, 46.4, 29.7, 28.3, 25.4, 23.9, 23.6, 17.7, 14.1, −4.6, −5.8; HRMS (FAB) calcd for $C_{60}H_{73}BrClN_9O_{12}SiCs$ $[M+Cs^+]$ 1388.3066, found 1388.3138. **27b**: R_f = 0.41 (silica gel, 40 % acetone in hexanes); $[\alpha]_D^{22} = -25.9$ (c = 0.58, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3411, 3341, 2934, 2854, 2357, 2099, 1707, 1672, 1602, 1488, 1463, 1414, 1339, 1255, 1160, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.29 – 7.26 (m, 5H), 7.18 (m, 1H), 7.17 (d, J = 7.0 Hz, 1H), 7.09 – 7.07 (m, 2H), 7.04 (s, 1H), 6.98 (s, 1H), 6.63 (d, J = 2.5 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 5.79-5.77 (m, 2H), 5.38 – 5.34 (m, 2H), 5.29 (d, J = 7.5 Hz, 1H), 5.21 (br. s, 1H), 4.67 (d, J = 8.5 Hz, 1H), 4.51 (dd, J = 8.5, 4.0 Hz, 1H), 4.39 – 4.36 (m, 2H, OCH_2Ph), 4.32 – 4.29 (m, 1H, OCH_AHCH$_3$), 4.11 – 4.06 (m, 1H, OCHH_BCH$_3$), 3.99 (br. s, 2H, NCH_2CH$_2$), 3.85 (s, 3H, OCH$_3$), 3.78 (s, 3H, OCH$_3$), 3.77 (br. s, 2H, NCH_2CH$_2$), 3.73 (s, 3H, OCH$_3$), 3.40 (dd, J = 10.5, 8.5 Hz, 1H, H-7β_A), 3.30 (dd, J = 10.5, 4.0 Hz, 1H, H-7β_B), 2.09 (br. s, 4H, CH$_2$CH_2), 1.41 (s, 9H, tBuO), 1.33 (t, J = 7.5 Hz, 3H, OCH$_2$CH_3), 0.73 (s, 9H, tBuSi), −0.06 (s, 3H, CH$_3$Si), −0.17 (s, 3H, CH$_3$Si); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 168.3, 168.2, 160.5, 158.0, 156.8, 152.5, 151.9, 140.7, 138.7, 138.0, 137.8, 135.3, 134.6, 133.9, 129.6, 128.9, 128.3, 127.6, 127.4, 127.3, 126.9, 126.8, 125.7, 125.6, 125.0, 124.9, 117.7, 115.0, 111.8, 102.3, 98.8, 80.0, 73.5, 73.3, 73.0, 62.7, 61.8, 60.0, 59.0, 58.1, 55.6, 55.5, 55.4, 51.1, 46.5, 28.2, 25.4, 23.9, 23.6, 17.7, 14.1, −4.5, −5.8; HRMS (FAB) calcd for $C_{60}H_{73}BrClN_9O_{12}SiCs$ $[M+Cs^+]$ 1388.3066, found 1388.2990.

AB/C-O-D alcohol 28a: A solution of AB/C-O-D TBS-ether **27a** (1.13 g, 0.9 mmol) in THF (10 mL) was cooled to 0 °C. Tetra-*n*-butylammonium fluoride (TBAF, 1.0 M solution in THF, 1.4 mL, 1.4 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and the resulting mixture was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with 5% aqueous NH_4Cl (20 mL), H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 20 →40% EtOAc in hexanes, gradient elution) to afford AB/C-O-D alcohol **28a** (925 mg, 90% yield). **28a**: $R_f = 0.26$ (silica gel, 40% acetone in hexanes); $[\alpha]_D^{22} = +52.2$ ($c = 1.86$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3316, 2965, 2097, 1698, 1659, 1605, 1488, 1415, 1337, 1317, 1244, 1181, 1064, 1025\ cm^{-1}$; ^1H NMR (400 MHz, CD_3COCD_3): $\delta = 7.90$ (d, $J = 8.4$ Hz, 1H), 7.68 (d, $J = 7.1$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.54 (d, $J = 1.5$ Hz, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 7.32 – 7.21 (m, 5H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 7.06 (d, $J = 8.7$ Hz, 1H), 6.65 (d, $J = 2.4$ Hz, 1H), 6.58 (d, $J = 2.4$ Hz, 1H), 6.37 (d, $J = 1.5$ Hz, 1H), 6.36-6.34 (m, 1H), 5.79 (d, $J = 9.2$ Hz, 1H), 5.59 (d, $J = 8.5$ Hz, 1H), 5.48 (dd, $J = 9.0$, 4.1 Hz, 1H), 5.36 (d, $J = 8.6$ Hz, 1H), 4.92 (dd, $J = 7.3$, 4.3 Hz, 1H), 4.51 (t, $J = 6.1$ Hz, 1H), 4.36 (d, $J = 12.3$ Hz, 1H, OCH_AHPh), 4.30 (d, $J = 12.3$ Hz, 1H, $OCHH_BPh$), 4.15 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.90 (br.s, 2H, NCH_2CH_2), 3.83 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.65 (br.s, 2H, NCH_2CH_2), 3.64 (s, 3H, OCH_3), 3.55 (d, $J = 6.2$ Hz, 2H, H-7β), 2.06 (br.s, 4H, NCH_2CH_2), 1.35 (s, 9H, *t*BuO), 1.22 (t, $J = 4.1$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): $\delta = 170.8$, 169.6, 169.3, 161.3, 159.1, 157.4, 152.9, 151.9, 140.7, 140.6, 139.5, 138.5, 137.1, 132.8, 129.8, 129.3, 129.1, 128.9, 128.1, 128.1, 128.0, 127.1, 126.8, 125.4, 125.3, 124.6, 119.7, 119.3, 114.7, 111.8, 103.9, 99.0, 79.7, 74.4, 73.1, 71.7, 63.5, 61.9, 61.3, 57.6, 57.0, 56.0, 55.7, 55.6, 51.6, 47.0, 28.4, 24.5, 24.1, 14.4; HRMS (FAB) calcd for $C_{54}H_{59}BrClN_9O_{12}Cs$ [$M + Cs^+$] 1272.2209, found 1272.2275.

AB/C-O-D alcohol 28b: A solution of AB/C-O-D TBS-ether **27b** (1.13 g, 0.9 mmol) in THF (10 mL) was cooled to 0 °C. Tetra-*n*-butylammonium fluoride (TBAF, 1.0 M solution in THF, 1.4 mL, 1.4 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and the resulting mixture was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with 5% aqueous NH_4Cl (20 mL), H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 20 →40% EtOAc in hexanes, gradient elution) to afford AB/C-O-D alcohol **28b** (945 mg, 92% yield). **28b**: $R_f = 0.22$ (silica gel, 40% acetone in hexanes); $[\alpha]_D^{22} = -27.8$ ($c = 1.5$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3405, 3321, 2973, 2926, 2353, 2100, 1702, 1660, 1599, 1486, 1416, 1341, 1317, 1256, 1195, 1153, 1064, 1026\ cm^{-1}$; ^1H NMR (500 MHz, CD_3COCD_3): $\delta = 8.09$ (d, $J = 8.0$ Hz, 1H), 7.71 (s, 1H), 7.68 (br.s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.35 – 7.32 (m, 1H), 7.31 – 7.24 (m, 5H), 7.18 (d, $J = 2.5$ Hz, 1H), 7.07 (d, $J = 8.5$ Hz, 1H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.64 (d, $J = 2.5$ Hz, 1H), 6.57 (d, $J = 2.5$ Hz, 1H), 6.36 (d, $J = 7.5$ Hz, 1H), 6.26 (s, 1H), 5.84 (d, $J = 9.5$ Hz, 1H), 5.55 (d, $J = 8.5$ Hz, 1H), 5.48 (dd, $J = 8.5$, 5.0 Hz, 1H), 5.38 (d, $J = 9.5$ Hz, 1H), 4.97 (dd, $J = 7.5$, 4.5 Hz, 1H), 4.50 (t, $J = 6.0$ Hz, 1H), 4.36 (d, $J = 12.5$ Hz, 1H, OCH_AHPh), 4.30 (d, $J = 12.5$ Hz, 1H, $OCHH_BPh$), 4.15 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 3.92-3.88 (m, 2H, NCH_2CH_2), 3.83 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.66 – 3.65 (m, 2H, NCH_2CH_2), 3.64 (s, 3H, OCH_3), 3.53 (d, $J = 6.5$ Hz, 2H, H-7β), 2.08 – 2.06 (m, 2H, NCH_2CH_2), 2.03 – 2.01 (m, 2H, NCH_2CH_2), 1.34 (s, 9H, *t*BuO), 1.20 (t, $J = 6.5$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta = 171.0$, 169.7, 169.4, 161.3, 159.1, 157.4, 155.0, 152.8, 151.7, 141.1, 140.2, 139.6, 138.6, 137.0, 132.6, 130.2, 129.3, 129.0, 128.9, 128.1, 128.0, 127.9, 127.7, 125.4, 124.5, 124.4, 119.6, 119.3, 113.9, 111.8, 103.9, 99.0, 79.7, 74.4, 73.2, 71.5, 63.5, 61.9, 60.9, 57.9, 57.3, 56.1, 55.8, 55.7, 51.6, 47.0, 28.4, 24.2, 24.1, 14.5; HRMS (FAB) calcd for $C_{54}H_{59}BrClN_9O_{12}Cs$ [$M + Cs^+$] 1272.2209, found 1272.2289.

AB/C-O-D amine 29a: To a solution of AB/C-O-D azide **28a** (870 mg, 0.8 mmol) in THF (8 mL) were added triphenylphosphane (629 mg, 2.4 mmol) and H_2O (144 μL, 8.0 mmol). The reaction mixture was heated to 60 °C for 3 h. The reaction mixture was cooled to 25 °C and diluted with EtOAc (40 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (20 mL), H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 1 →4% MeOH in $CHCl_3$, gradient elution) to afford AB/C-O-D amine **29a** (732 mg, 82% yield). **29a**: $R_f = 0.17$ (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = +51.9$ ($c = 1.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3306, 2965, 2926, 1698, 1654, 1600, 1488, 1415, 1317, 1259, 1200, 1157, 1059, 1030\ cm^{-1}$; ^1H NMR (500 MHz, CD_3COCD_3): $\delta = 7.92$ (d, $J = 8.3$ Hz, 1H), 7.64 (br.s, 1H), 7.58 (d, $J = 8.5$ Hz, 1H), 7.53 (d, $J = 1.5$ Hz, 1H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.30 (s, 1H), 7.27 – 7.24 (m, 4H), 7.19 – 7.16 (m, 4H), 7.03 (d, $J = 9.0$ Hz, 1H), 6.90 (d, $J = 2.5$ Hz, 1H), 6.47 (d, $J = 2.5$ Hz, 1H), 6.39 (s, 1H), 6.31 (d, $J = 7.5$ Hz, 1H), 5.60 (d, $J = 8.5$ Hz, 1H), 5.47 – 5.44 (m, 1H), 5.35 (d, $J = 8.5$ Hz, 1H), 4.91-4.88 (m, 1H), 4.55 (t, $J = 6.0$ Hz, 1H), 4.25 (d, $J = 12.5$ Hz, 1H, OCH_AHPh), 4.18 (d, $J = 12.5$ Hz, 1H, $OCHH_BPh$), 4.17 – 4.11 (m, 2H, OCH_2CH_3), 3.89 (br.s, 2H, NCH_2CH_2), 3.79 (s, 3H, OCH_3), 3.66 (br.s, 2H, NCH_2CH_2), 3.65 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.57 (br.d, $J = 6.0$ Hz, 2H, H-7β), 2.05 – 2.03 (m, 4H, NCH_2CH_2), 1.36 (s, 9H, *t*BuO), 1.19 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta = 170.8$, 169.6, 169.3, 160.9, 158.9, 157.8, 156.1, 152.9, 152.0, 143.0, 140.7, 140.6, 140.3, 137.2, 133.0, 129.6, 129.3, 128.9, 128.4, 127.9, 127.7, 127.1, 126.7, 126.6, 125.5, 124.7, 119.7, 119.2, 114.8, 111.5, 105.4, 97.7, 79.7, 76.3, 72.8, 71.9, 61.9, 61.4, 61.3, 57.6, 57.1, 56.1, 55.6, 55.4, 51.6, 47.0, 28.5, 24.5, 24.1, 14.4; HRMS (FAB) calcd for $C_{54}H_{62}BrClN_7O_{12}$ [$M + H^+$] 1114.3328, found 1114.3355.

AB/C-O-D amine 29b: To a solution of AB/C-O-D azide **28b** (870 mg, 0.8 mmol) in THF (8 mL) were added triphenylphosphane (629 mg, 2.4 mmol) and H_2O (144 μL, 8.0 mmol). The reaction mixture was heated to 60 °C for 3 h. The reaction mixture was cooled to 25 °C and diluted with EtOAc (40 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (20 mL), H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 1 →4% MeOH in $CHCl_3$, gradient elution) to afford AB/C-O-D amine **29b** (635 mg, 71% yield). **29b**: $R_f = 0.11$ (silica gel, 5% MeOH in $CHCl_3$); $[\alpha]_D^{22} = -24.6$ ($c = 1.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ 3307, 2948, 2858, 1699, 1660, 1604, 1486, 1413, 1312, 1261, 1200, 1155, 1059 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): $\delta = 8.12$ (d, $J = 8.5$ Hz, 1H), 7.73 (s, 1H), 7.68 (br.s, 1H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.38 – 7.35 (m, 1H), 7.29 – 7.17 (m, 7H), 7.10 (d, $J = 8.5$ Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.92 (d, $J = 2.0$ Hz, 1H), 6.47 (d, $J = 2.5$ Hz, 1H), 6.31 (d, $J = 8.0$ Hz, 1H), 6.26 (s, 1H), 5.84 (d, $J = 8.0$ Hz, 1H), 5.54 (d, $J = 8.4$ Hz, 1H), 5.48 (d, $J = 4.1$ Hz, 1H), 5.37 (d, $J = 8.5$ Hz, 1H), 4.98 (dd, $J = 7.5$, 5.0 Hz, 1H), 4.56 – 4.53 (m, 1H), 4.25 (d, $J = 12.5$ Hz, 1H, OCH_AHPh), 4.18 (d, $J = 12.5$ Hz, 1H, $OCHH_BPh$), 4.14 – 4.10 (m, 2H, OCH_2CH_3), 3.90 (br.s, 2H, NCH_2CH_2), 3.79 (s, 3H, OCH_3), 3.67 – 3.65 (m, 2H, NCH_2CH_2), 3.65 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.58 – 3.55 (m, 2H, H-7β), 2.06 – 2.00 (m, 4H, NCH_2CH_2), 1.36 (s, 9H, *t*BuO), 1.20 – 1.14 (m, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta = 171.0$, 169.8, 169.4, 160.9, 158.9, 157.7, 155.9, 152.8, 151.6, 143.0, 141.1, 140.4, 140.2, 137.1, 132.9, 129.9, 129.3, 128.9, 128.2, 128.0, 128.0, 127.7, 127.6, 126.5, 124.5, 124.3, 119.7, 119.3, 113.9, 111.4, 105.4, 97.7, 79.7, 76.3, 72.7, 71.5, 61.9, 61.3, 60.8, 57.8, 57.3, 56.0, 55.6, 55.4, 51.6, 47.0, 28.4, 24.5, 24.1, 14.5; HRMS (FAB) calcd for $C_{54}H_{61}BrClN_7O_{12}Cs$ [$M + Cs^+$] 1248.2294, found 1248.2347.

AB/C-O-D carboxylic acid 30a: To a solution of AB/C-O-D amino ester **29a** (1.23 g, 1.1 mmol) in MeOH/H_2O (10:1, 11 mL) at 0 °C was added anhydrous Lithium hydroxide (39 mg, 1.7 mmol) and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl (3 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL), brine (15 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 5 →12% MeOH in $CHCl_3$, gradient elution) to afford AB/C-O-D carboxylic acid **30a** (1.10 g, 92% yield). **30a**: $R_f = 0.25$ (silica gel, 15% MeOH in $CHCl_3$); $[\alpha]_D^{22} = +28.6$ ($c = 0.83$, MeOH); IR (thin film): $\tilde{\nu}_{max} =$ 3371, 2975, 1658, 1606, 1491, 1408, 1246, 1199, 1158, 1059 cm^{-1}; ^1H NMR (600 MHz, CD_3SOCD_3): $\delta = 8.91$ (d, $J = 8.3$ Hz, 1H), 8.77 (d, $J = 9.9$ Hz, 1H), 8.56 (br.s, 2H), 7.51 (dd, $J = 8.6$, 1.6 Hz, 1H), 7.44 (s, 1H), 7.33 – 7.25 (m, 7H), 7.18 (d, $J = 8.4$ Hz, 1H), 7.11 (s, 1H), 7.01 – 6.98 (m, 3H), 6.64 (s, 1H), 6.08 (s, 1H), 5.51 (d, $J = 8.9$ Hz, 1H), 5.35 (d, $J = 8.3$ Hz, 1H), 4.66 (d, $J = 10.3$ Hz, 1H), 4.58 – 4.51 (m, 1H), 4.38 – 4.28 (m, 2H, OCH_2Ph), 3.87 (br.s, 2H, NCH_2CH_2), 3.82 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.60 (br.s, 2H, NCH_2CH_2), 3.59 (s, 3H, OCH_3), 3.45 – 3.35 (2H, obscured by solvent, H-7β), 2.02 (br.s, 2H, NCH_2CH_2), 1.97 (br.s, 2H, NCH_2CH_2), 1.30 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, CD_3SOCD_3): $\delta = 171.8$, 168.3, 168.1, 160.1, 158.0, 155.6, 155.2, 150.7, 150.0, 149.4, 140.9, 138.2, 137.8, 136.6, 135.1, 131.1, 130.9, 130.7, 130.4, 128.1, 127.7, 127.3, 124.6, 124.4, 124.0, 123.1, 118.7, 117.9, 112.4, 111.0, 103.4, 98.9, 78.3, 73.1, 72.2, 71.0, 57.2, 55.8, 55.6, 55.6, 55.5, 54.3, 51.3, 50.8, 46.5, 28.0, 23.5, 23.0; HRMS (FAB) calcd for $C_{52}H_{57}BrClN_7O_{12}Cs$ [$M + Cs^+$] 1220.1980, found 1220.2052.

0947-6539/99/0509-2638 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 9

AB/C-O-D carboxylic acid 30b: To a solution of AB/C-O-D amino ester **29b** (1.23 g, 1.1 mmol) in MeOH/H_2O (10:1, 11 mL) at 0 °C was added anhydrous Lithium hydroxide (39 mg, 1.7 mmol) and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl (3 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL), brine (15 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 5→12% MeOH in $CHCl_3$, gradient elution) to afford AB/C-O-D carboxylic acid **30b** (1.08 g, 90% yield). **30b**: $R_f = 0.19$ (silica gel, 15% MeOH in $CHCl_3$); $[\alpha]_D^{22} = +6.3$ ($c = 0.68$, MeOH); IR (thin film): $\tilde{\nu}_{max} =$ 3319, 2966, 1661, 1602, 1490, 1414, 1361, 1314, 1261, 1202, 1155, 1067, 1026 cm^{-1}; ^1H NMR (400 MHz, CD_3SOCD_3): $\delta = 9.10$ (d, $J = 9.1$ Hz, 1H), 8.25 (br.s, 1H), 7.64–7.61 (m, 2H), 7.43 (d, $J = 9.4$ Hz, 1H), 7.39 (d, $J =$ 8.6 Hz, 1H), 7.34–7.24 (m, 6H), 7.10 (s, 1H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.84 (s, 1H), 6.54 (s, 1H), 6.37 (d, $J = 8.0$ Hz, 1H), 6.01 (s, 1H), 5.55 (d, $J =$ 9.3 Hz, 1H), 5.44 (br.s, 1H), 5.20 (d, $J = 8.9$ Hz, 1H), 5.03–5.00 (m, 1H), 4.27 (br.s, 2H, OCH_2Ph), 3.91 (br.s, 2H, NCH_2CH_2), 3.81 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.66-3.63 (br.s, 2H, NCH_2CH_2), 3.61 (s, 3H, OCH_3), 3.33–3.30 (m, 2H, H-7β), 2.04–2.00 (br.s, 4H, NCH_2CH_2), 1.35 (s, 9H, *t*BuO); ^{13}C NMR (100 MHz, CD_3SOCD_3): $\delta = 170.0$, 169.0, 168.9, 159.7, 157.7, 156.3, 155.3, 151.8, 149.5, 140.2, 138.6, 138.5, 135.9, 130.9, 129.8, 128.3, 128.2, 127.4, 127.4, 127.3, 127.2, 126.5, 125.4, 124.8, 124.5, 123.0, 118.5, 118.1, 112.5, 110.9, 103.3, 97.5, 78.6, 74.7, 71.8, 69.8, 59.8, 59.5, 56.6, 55.6, 55.5, 55.2, 51.3, 50.8, 46.5, 28.1, 23.6, 23.1; HRMS (FAB) calcd for $C_{52}H_{57}BrClN_7O_{12}Cs$ [$M + Cs^+$] 1218.1991, found 1218.1919.

AB/C-O-D bicycle 31a: To a solution of AB/C-O-D amino acid **30a** (109 mg, 0.1 mmol) and *i*Pr_2NEt (52 μL, 0.3 mmol) in DMF (4 mL) at 25 °C was added HATU (57 mg, 0.15 mmol) and the reaction mixture was stirred for 8 h at 25 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1 mL), and the resulting mixture was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with 5% aqueous NH_4Cl (10 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 10→20% acetone in hexanes, gradient elution) to afford AB/C-O-D bicycle **31a** (54 mg, 50% yield). **31a**: $R_f = 0.35$ (silica gel, 40% acetone in hexanes); $[\alpha]_D^{22} = +17.5$ ($c = 0.86$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ 3399, 2917, 2847, 1658, 1403, 1318, 1282, 1162, 1085, 1028 cm^{-1}; ^1H NMR (600 MHz, CD_3COCD_3): $\delta = 8.14$ (d, $J = 8.5$ Hz, 1H, NH), 7.64 (d, $J =$ 7.6 Hz, 1H, H-6f), 7.52 (d, $J = 7.4$ Hz, 1H, H-5f), 7.38 (s, 1H, H-4f), 7.33–7.31 (m, 2H), 7.28-7.24 (m, 3H), 7.21 (d, $J = 2.1$ Hz, 1H, H-6b), 7.14 (d, $J =$ 8.2 Hz, 1H, H-6e), 7.11 (d, $J = 8.2$ Hz, 1H, H-5e), 6.88 (d, $J = 9.8$ Hz, 1H, NH), 6.75 (s, 1H, H-5b), 6.61 (d, $J = 2.1$ Hz, 1H, H-7f), 6.57 (d, $J = 3.0$ Hz, 1H, H-7d), 6.34 (d, $J = 9.2$ Hz, 1H, NH), 6.18 (s, 1H, H-4b), 5.62–5.58 (m, 2H, H-4α and H-5α), 5.34–5.33 (m, 1H), 5.15–5.14 (m, 1H, H-7α), 4.75 (d, $J = 9.8$ Hz, 1H, H-6β), 4.50 (d, $J = 11.7$ Hz, 1H, OCH_AHPh), 4.47 (d, $J =$ 9.8 Hz, 1H, H-6α), 4.33 (d, $J = 11.7$ Hz, 1H, OCHH_BPh), 3.90–3.89 (m, 2H, NCH_2CH_2), 3.84 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.66-3.63 (br.s, 2H, NCH_2CH_2), 3.63 (s, 3H, OCH_3), 3.27–3.24 (m, 1H, H-7β_A), 3.07–3.03 (m, 1H, H-7β_B), 2.04 (m, 4H, NCH_2CH_2), 1.19 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta = 171.4$, 170.7, 170.2, 161.0, 159.9, 158.8, 152.7, 145.0, 141.0, 140.3, 139.0, 138.7, 137.9, 133.0, 132.7, 130.7, 130.2, 128.8, 128.2, 128.1, 128.0, 126.7, 126.6, 125.6, 125.4, 124.9, 119.1, 119.0, 114.7, 112.5, 108.7, 98.4, 79.3, 74.4, 74.3, 72.6, 72.4, 57.1, 57.0, 56.6, 55.8, 55.7, 55.4, 51.3, 46.8, 28.2, 24.2, 23.8; HRMS (FAB) calcd for $C_{52}H_{55}BrClN_7O_{11}Cs$ [$M + Cs^+$] 1202.3142, found 1202.3197.

AB/C-O-D bicycle 31b: To a solution of AB/C-O-D amino acid **30b** (109 mg, 0.1 mmol) and *i*Pr_2NEt (52 μL, 0.3 mmol) in DMF (4 mL) at 25 °C was added HATU (57 mg, 0.15 mmol). The reaction mixture was stirred for 8 h at 25 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1 mL) and the resulting mixture was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with 5% aqueous NH_4Cl (10 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 10→20% acetone in hexanes, gradient elution) to afford AB/C-O-D bicycle **31b** (55 mg, 51% yield). **31b**: $R_f = 0.23$ (silica gel, 40% acetone in hexanes); $[\alpha]_D^{22} = +2.64$ ($c = 0.83$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 3401, 3295, 2931, 1661, 1602, 1496, 1414, 1361, 1314, 1255, 1155, 1085 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): $\delta = 8.31$ (d, $J = 7.5$ Hz, 1H, NH), 7.79 (d, $J = 1.5$ Hz, 1H, H-6b), 7.62 (d, $J = 10.5$ Hz, 1H, NH), 7.52 (dd, $J = 8.2$, 2.2 Hz, 1H, H-5f), 7.40 (s, 1H, H-4f), 7.32–7.23 (m, 5H), 7.10 (d, $J = 8.5$ Hz, 1H, H-5e), 7.01 (dd, $J = 8.5$, 2.0 Hz, 1H, H-6f), 6.93 (d, $J = 10.0$ Hz, 1H, NH), 6.83 (d, $J = 2.5$ Hz, 1H, H-6e), 6.76 (d, $J = 1.5$ Hz, 1H, H-5b), 6.61 (d, $J = 2.5$ Hz, 1H, H-7f), 6.58 (d, $J = 2.5$ Hz, 1H, H-7d), 6.44 (d, $J = 1.9$ Hz, 1H, H-4b), 6.35 (d, $J = 9.0$ Hz, 1H, NH), 5.68–5.66 (m, 2H, H-4α and OH), 5.46 (d, $J = 8.0$ Hz, 1H, H-5α), 5.16-5.11 (m, 1H, H-7α), 4.76 (d, $J = 9.5$ Hz, 1H, H-6β), 4.49 (d, $J = 12.0$ Hz, 1H, OCH_AHPh), 4.39 (t, $J = 10.5$ Hz, 1H, H-6α), 4.32 (d, $J = 12.0$ Hz, 1H, OCHH_BPh), 3.85 (s, 3H, OCH_3), 3.84–3.80 (m, 2H, NCH_2CH_2), 3.69 (s, 3H, OCH_3), 3.68–3.61 (m, 2H, NCH_2CH_2), 3.63 (s, 3H, OCH_3), 3.24 (dd, $J = 10.5$, 5.5 Hz, 1H, H-7β_A), 3.06 (dd, $J =$ 10.5, 9.0 Hz, 1H, H-7β_B), 2.06–1.96 (m, 4H, NCH_2CH_2), 1.43 (s, 9H, *t*BuO); ^{13}C NMR (125 MHz, CD_3COCD_3): $\delta = 171.4$, 170.9, 170.5, 161.0, 159.9, 158.8, 155.6, 153.1, 152.0, 141.5, 139.5, 139.0, 138.7, 137.9, 133.0, 133.0, 130.4, 129.6, 128.8, 128.7, 128.2, 128.0, 126.9, 126.6, 124.9, 121.4, 119.2, 118.9, 114.8, 112.5, 108.7, 98.4, 79.4, 74.2, 72.5, 72.4, 57.4, 56.5, 55.9, 55.8, 55.7, 55.7, 55.4, 51.3, 46.7, 28.2, 24.2, 23.8; HRMS (FAB) calcd for $C_{52}H_{55}BrClN_7O_{11}Cs$ [$M + Cs^+$] 1202.3142, found 1202.3206.

AB/C-O-D bicyclic amine 32: A solution of natural AB/C-O-D Boc-protected amine **23a** (59 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was cooled to −15 °C. Trimethylsilyl trifluoromethanesulfonate (TMSOTf, 18 μL, 0.1 mmol) was added dropwise. After stirring at −10 °C for 1 h, freshly distilled 2,6-lutidine (18 μL, 0.15 mmol) was added dropwise, and the mixture was stirred at −10 °C for 0.5 h. Then, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL), and left for 0.5 h at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 0→20% EtOAc in hexanes, gradient elution, and then 20→40% EtOAc in CH_2Cl_2, gradient elution) to afford AB/C-O-D bicyclic amine **32** (52 mg, 96%). **32**: $R_f = 0.14$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +29.5$ ($c = 1.2$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3363$, 2939, 2857, 1672, 1486, 1416, 1321, 1263, 1105, 837 cm^{-1}; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.61$ (d, $J = 2.0$ Hz, 1H, H-6b), 7.39 (dd, $J = 8.4$, 2.0 Hz, 1H, H-6f), 7.51 (s, 1H, H-4f), 7.37–7.26 (m, 5H, ArH), 7.11 (dd, $J = 8.6$, 2.3 Hz, 1H, H-5f), 7.07 (d, $J = 8.4$ Hz, 1H, H-6e), 7.04 (d, $J = 2.3$ Hz, 1H, H-5b), 6.95 (d, $J = 1.7$ Hz, 1H, H-7f), 6.94 (d, $J = 8.2$ Hz, 1H, H-5e), 6.62 (d, $J = 2.2$ Hz, 1H, H-7d), 5.80 (d, $J = 1.1$ Hz, 1H, H-4b), 5.26 (s, 1H, H-6β), 4.69 (s, 1H, H-5α), 4.58 (s, 1H, H-4α), 4.57 (d, $J = 11.8$ Hz, 1H, OCH_AHPh), 4.55 (d, $J = 11.8$ Hz, 1H, OCHH_BPh), 4.41–4.39 (m, 1H, H-7α), 4.04 (s, 1H, H-6α), 3.90 (t, $J = 10.0$ Hz, 1H, H-7β_A), 3.84 (dd, $J =$ 10.0, 3.4 Hz, 1H, H-7β_B), 3.82 (s, 3H, 7e-OCH_3), 3.82–3.79 (m, 4H, NCH_2CH_2), 3.67 (s, 3H, 7c-OCH_3), 3.61 (s, 3H, 5d-OCH_3), 2.04 (br.s, 4H, NCH_2CH_2), 0.86 (s, 9H, *t*BuSi), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3OD, 330 K): $\delta = 175.8$, 173.1, 172.2, 162.0, 160.2, 159.0, 153.6, 153.0, 142.0, 141.0, 140.9, 139.9, 139.5, 137.1, 129.6, 129.4, 129.1, 129.0, 128.7, 128.3, 128.1, 127.4, 126.1, 124.9, 123.1, 120.3, 114.4, 114.3, 106.9, 99.7, 75.0, 74.5, 71.0, 65.2, 58.4, 56.6, 56.6, 56.3, 55.7, 53.3, 26.4, 24.8, 19.3, −4.6, −4.7; HRMS (MALDI-FTMS) calcd for $C_{53}H_{61}BrClN_7O_9Na$ [$M + Na^+$] 1104.3070, found 1104.3135.

AB/C-O-D/E heptapeptide 33: A solution of AB/C-O-D bicyclic amine **32** (438 mg, 0.4 mmol) and tripeptide carboxylic acid **5** (812 mg, 0.89 mmol) in THF (8 mL) was cooled to −15 °C. HOAt (544 mg, 4 mmol) was added, and the mixture was stirred vigorously for 10 min. EDC (153 mg, 0.8 mmol) was then added, and the resulting mixture was stirred for 12 h while the temperature was raised slowly to 0 °C. H_2O (10 mL) and EtOAc (10 mL) were added, and after 10 min the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 0→50% EtOAc in hexanes, gradient elution) to afford AB/C-O-D/E heptapeptide **33** (680 mg, 86%). **33**: $R_f = 0.25$ [silica gel, acetone/EtOAc/benzene (1:2:7)]; $[\alpha]_D^{22} = +21.9$ ($c = 2.6$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3307$, 2954, 2930, 2856, 1655, 1508, 1418, 1322, 1249, 1106, 837 cm^{-1}; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.59$ (d, $J = 1.8$ Hz, 1H, H-6b), 7.39 (dd, $J = 8.4$, 1.8 Hz, 1H, H-6f), 7.37–7.26 (m, 7H, ArH), 7.09–7.01 (m, 9H, ArH), 6.94 (d, $J = 1.9$ Hz, 1H, H-4f), 6.87 (d, $J = 8.7$ Hz, 1H, H-5e), 6.84–6.78 (m, 4H, ArH), 6.60 (d, $J = 2.2$ Hz, 1H, H-7d), 6.03 (br.s, 1H, H-4b), 5.83 (br.s, 1H, NHCH (Ddm)), 5.26 (br.s, 1H, H-6β), 4.86-4.84 (m, 2H, H-2β and H-5α), 4.64 (br.s, 1H, H-2α), 4.57 (d, $J = 11.7$ Hz, 1H, OCH_AHPh), 4.54 (d, $J = 11.7$ Hz, 1H, OCHH_BPh), 4.39 (br.s, 1H, H-4α), 4.02 (br.s, 1H, H-6α), 3.90 (dd, $J = 10.0$, 7.6 Hz, 1H, H-7α), 3.84–3.76 (m, 6H, H-7β and NCH_2CH_2), 3.81 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 2.75 (dd, $J = 15.6$,

5.1 Hz, 1H, H-3β_A), 2.73 (dd, J = 15.6, 7.2 Hz, 1H, H-3β_B), 2.44 (s, 3H, NCH_3), 2.03 (br. s, 4H, NCH_2CH_2), 1.43-1.33 (m, 3H, H-1β and H-1γ), 1.38 (br. s, 9H, *t*BuO), 0.86 (s, 9H, *t*BuSi), 0.85 (d, J = 6.2 Hz, 3H, H-1δ), 0.82 (d, J = 6.0 Hz, 3H, H-1δ') 0.75 (s, 9H, *t*BuSi), 0.02 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si), -0.05 (s, 3H, CH_3Si), −0.22 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 171.4, 171.0, 170.7, 170.1, 169.9, 169.8, 167.8, 161.1, 159.7, 159.7, 159.6, 158.2, 153.3, 153.0, 152.3, 141.6, 140.7, 139.8, 139.4, 138.0, 136.1, 135.5, 135.5, 134.1, 129.6, 129.3, 129.0, 128.7, 128.3, 128.1, 127.9, 127.5, 127.3, 126.0, 125.3, 124.4, 122.5, 121.0, 119.7, 117.6, 114.6, 114.6, 113.6, 106.4, 98.8, 80.2, 74.8, 74.5, 73.7, 70.6, 66.0, 64.2, 57.2, 56.4, 56.2, 55.7, 55.5, 55.2, 52.7, 51.0, 38.8, 37.5, 30.7, 28.7, 26.2, 26.1, 25.4, 24.3, 23.5, 22.0, 18.9, 18.7, −4.6, −4.7, −4.8, −4.9; HRMS (FAB) calcd for $C_{99}H_{124}BrCl_2N_{11}O_{19}Si_2Cs$ [M + Cs^+] 2110.6208, found 2110.6068.

Natural tricyclic triazene 3a and unnatural tricyclic triazene 3b: In a flame-dried flask containing AB/C-O-D/E heptapeptide **33** (33 mg, 0.017 mmol) were added anhydrous K_2CO_3 (12 mg, 0.083 mmol) and $CuBr \cdot Me_2S$ (17 mg, 0.083 mmol), followed by the addition of anhydrous MeCN (0.85 mL). After 5 min at 25 °C, freshly distilled pyridine (6.7 μL, 0.083 mmol) was added and the mixture was stirred at reflux for 2 h. After it was cooled to 0 °C, EtOAc (5 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was stirred vigorously for 0.5 h at 0 °C. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered through a pad of silica gel, concentrated, and the residue was purified by flash column chromatography (silica gel, 0 → 25 % EtOAc in CH_2Cl_2, gradient elution) to afford faster moving natural tricyclic triazene **3a** (6.0 mg, 19 %), and slower moving unnatural tricyclic triazene **3b** (17.5 mg, 55 %). **3a**: R_f = 0.40 (silica gel, 60 % EtOAc in benzene); $[\alpha]_D^{22}$ = +33.8 (c = 2.4, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3000, 2953, 2930, 2855, 1668, 1648, 1509, 1486, 1244, 1106, 834, 778, 700 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.60 (br. s, 1H, H-2b), 7.55 (d, J = 1.7 Hz, 1H, H-6b), 7.47 (dd, J = 8.3, 1.7 Hz, 1H, H-6f), 7.36 – 7.25 (m, 7H, H-2f, H-6e and ArH (Bn)), 7.04 – 7.01 (m, 2H, H-2e and H-5b), 6.98 (d, J = 8.3 Hz, 2H, ArH (Ddm)), 6.92 (br. s, 1H, H-5f), 6.91 – 6.88 (m, 3H, H-7f and ArH (Ddm)), 6.83 (br. d, J = 8.8 Hz, 3H, H-5e and ArH (Ddm)), 6.71 (d, J = 8.3 Hz, 2H, ArH (Ddm)), 6.56 (d, J = 2.2 Hz, 1H, H-7d), 5.88 (br. s, 1H, NHC*H* (Ddm)), 5.86 (br. s, 1H, H-4b), 5.80 (br. s, 1H, H-4f), 5.49 (d, J = 4.9 Hz, 1H, H-2β), 5.45 (br. s, 1H, H-4α), 5.29 (br. s, 1H, H-6β), 4.94 – 4.92 (m, 1H, H-2α), 4.90 – 4.87 (m, 1H, H-3α), 4.78 – 4.76 (m, 1H, H-1α), 4.62 (br. s, 1H, H-5α), 4.58 – 4.53 (m, 2H, OCH_2Ph), 4.48 – 4.37 (m, 1H, H-7α), 4.04 (br. s, 1H, H-6α), 3.92 – 3.89 (m, 1H, H-7β_A), 3.86 – 3.84 (m, 5H, H-7β_B and NCH_2CH_2), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 2.65 – 2.59 (m, 1H, H-3β_A), 2.57 (dd, J = 16.2, 6.1 Hz, 1H, H-3β_B), 2.06 (br. s, 4H, NCH_2CH_2), 1.75 – 1.71 (m, 1H, H-1γ), 1.48 (br. s, 9H, *t*BuO), 1.39 – 1.37 (m, 2H, H-1β), 0.90 (s, 9H, *t*BuSi), 0.89 (s, 9H, *t*BuSi), 0.84 (d, J = 6.6 Hz, 3H, H-1δ), 0.80 (d, J = 6.2 Hz, 3H, H-1δ'), 0.11 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.1, 171.7, 171.3, 167.9, 161.3, 159.9, 159.9, 159.8, 158.4, 153.7, 153.4, 152.0, 142.0, 140.2, 139.9, 139.7, 136.3, 135.7, 131.9, 130.1, 129.7, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.6, 128.4, 128.1, 127.8, 125.7, 125.5, 125.1, 122.8, 114.9, 114.8, 114.1, 106.7, 106.5, 99.1, 80.7, 74.8, 74.4, 73.9, 70.9, 64.6, 60.3, 56.7, 56.6, 56.4, 56.3, 56.0, 55.9, 55.7, 55.6, 37.6, 30.7, 28.9, 26.6, 26.5, 25.8, 24.6, 23.9, 22.5, 19.2, 19.2, −4.2, −4.4, −4.6; HRMS (FAB) calcd for $C_{99}H_{123}Cl_2N_{11}O_{19}Si_2Cs$ [M + Cs^+] 2028.6967, found 2028.6849. **3b**: R_f = 0.30 (silica gel, 60 % EtOAc in benzene); $[\alpha]_D^{22}$ = −20.3 (c = 1.8, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3307, 2954, 2928, 2859, 1667, 1651, 1510, 1488, 1251, 1103, 835, 780, 698 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.68 (br. s, 1H, H-2b), 7.57 (d, J = 1.9 Hz, 1H, H-6b), 7.46 (dd, J = 8.3, 2.0, 1H, H-6f), 7.35 – 7.27 (m, 6H, H-2e and ArH (Bn)), 7.19 – 7.12 (m, 2H, H-2f and H-6e), 7.07 – 6.98 (m, 4H, H-5b, H-5f and ArH (Ddm)), 6.94 – 6.92 (m, 3H, H-7f and ArH (Ddm)), 6.87 – 6.85 (m, 1H, H-5e), 6.82 (d, J = 8.2 Hz, 2H, ArH (Ddm)), 6.72 (d, J = 7.1 Hz, 2H, ArH (Ddm)), 6.57 (d, J = 2.3 Hz, 1H, H-7d), 5.88 (br. s, 1H, H-4b), 5.87 (br. s, 1H, NHC*H* (Ddm)), 5.79 (br. s, 1H, H-4f), 5.50 (d, J = 4.6 Hz, 1H, H-2β), 5.45 (br. s, 1H, H-4α), 5.29 (br. s, 1H, H-6β), 4.87 – 4.85 (m, 2H, H-2α and H-3α), 4.81 – 4.79 (m, 1H, H-1α), 4.65 (br. s, 1H, H-5α), 4.57 (d, J = 11.6 Hz, 1H, OCH_AHPh), 4.54 (d, J = 11.5 Hz, 1H, OCH_BHPh), 4.05 (br. s, 1H, H-6α), 3.90 – 3.87 (m, 1H, H-7α), 3.84 – 3.81 (m, 6H, H-7β and NCH_2CH_2), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 2.77 (s, 3H, NCH_3), 2.75 – 2.50 (m, 2H, H-3β), 2.05 (br. s, 4H, NCH_2CH_2), 1.70 – 1.68 (m, 1H, H-1γ), 1.50 (s, 9H, *t*BuO), 1.38 – 1.34 (m, 2H, H-1β), 0.89 (s, 9H, *t*BuSi), 0.88 (s, 9H, *t*BuSi), 0.87 (d, J = 6.5 Hz, 3H, H-1δ), 0.86 (d, J = 6.6 Hz, 3H, H-1δ'), 0.11 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.4, 171.8, 171.3, 170.6, 167.9, 161.3, 159.9, 159.9. 158.3, 153.5, 153.3, 153.0, 152.0, 142.0, 140.2, 139.7, 136.4, 135.8, 129.7, 129.6, 129.5, 129.3, 129.0, 128.9, 128.6, 128.5, 128.1, 127.8, 126.8, 125.5, 125.2, 122.8, 114.9, 114.8, 114.0, 108.1, 106.7, 106.2, 99.1, 80.7, 74.9, 74.4, 73.9, 70.9, 64.6, 60.3, 56.7, 56.7, 56.4, 56.4, 56.0, 55.7, 55.7, 53.0, 52.8, 37.8, 30.7, 29.0, 26.6, 26.5, 25.8, 24.6, 23.9, 22.5, 19.3, 19.2, −4.4, −4.5, −4.6, −4.7; HRMS (FAB) calcd for $C_{99}H_{123}Cl_2N_{11}O_{19}Si_2Cs$ [M + Cs^+] 2028.6967, found 2028.7090.

Treatment of natural tricyclic triazene 3a with H$^+$-resin: H$^+$-resin (AG 50W-X12, BIO-RAD) (200 mg) was suspended in H_2O (1 mL) and heated to 80 °C. A solution of natural tricyclic triazene **3a** (9.0 mg, 0.005 mmol) in MeCN (1 mL) was added dropwise over a period of 45 min, while the temperature was kept at 80 °C. After 10 min, the mixture was cooled to 25 °C. EtOAc (3 mL), H_2O (3 mL) and solid $NaHCO_3$ (100 mg) were added, and the mixture was stirred vigorously for 0.5 h. The aqueous phase was extracted with EtOAc (2 × 2 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 5 % MeOH in CH_2Cl_2) to afford natural tricyclic reduced compound **34a** (7.0 mg, 78 %). **34a**: R_f = 0.26 (silica gel, 5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = +16.2 (c = 1.2, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3304, 2955, 2931, 2856, 1681, 1659, 1650, 1513, 1505, 1486, 1249, 1110, 837, 781 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.60 (br. s, 1H, H-2b), 7.48 – 7.46 (m, 2H, H-6b and H-6f), 7.36 – 7.23 (m, 7H, H-2f, H-6e and ArH (Bn)), 7.08 (br. d, J = 8.8 Hz, 1H, H-2e), 7.02 (br. s, 2H, H-4d and H-5b), 6.98 (d, J = 8.8 Hz, 2H, ArH (Ddm)), 6.96 (d, J = 8.8 Hz, 1H, H-5f), 6.92 (br. s, 1H, H-7f), 6.86 (bd, J = 8.3 Hz, 3H, H-5e and ArH (Ddm)), 6.82 (d, J = 8.8 Hz, 2H, ArH (Ddm)), 6.68 (d, J = 7.4 Hz, 2H, ArH (Ddm)), 6.56 (d, J = 2.1 Hz, 1H, H-7d), 6.21 (br. s, 1H, NHC*H* (Ddm)), 5.85 (br. s, 1H, H-4b), 5.72 (br. s, 1H, H-4f), 5.53 (d, J = 4.8 Hz, 1H, H-2β), 5.42 (br. s, 1H, H-4α), 5.31 (br. s, 1H, H-6β), 4.98 – 4.93 (m, 2H, H-2α and H-3α), 4.74 – 4.71 (m, 1H, H-1α), 4.62 (br. s, 1H, H-5α), 4.58 – 4.53 (m, 2H, OCH_2Ph), 4.00 (br. s, 1H, H-6α), 3.92 – 3.89 (m, 1H, H-7α), 3.86 – 3.78 (m, 2H, H-7β), 3.79 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 2.77 (s, 3H, NCH_3), 2.66 – 2.63 (m, 1H, H-3β_A), 2.61 (dd, J = 16.3, 5.7 Hz, 1H, H-3β_B), 1.73 – 1.70 (m, 1H, H-1γ), 1.48 (br. s, 9H, *t*BuO), 1.38 – 1.34 (m, 2H, H-1β), 0.92 (s, 9H, *t*BuSi), 0.89 (s, 9H, *t*BuSi), 0.82 (d, J = 6.1 Hz, 3H, H-1δ), 0.78 (d, J = 6.1 Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.1, 171.7, 171.6, 171.0, 169.1, 162.0, 161.3, 161.0, 160.0, 159.8, 159.8, 158.3, 152.1, 151.4, 142.2, 140.4, 140.3, 139.7, 136.6, 135.8, 130.5, 129.8, 129.5, 129.5, 129.3, 129.3, 129.0, 129.0, 129.0, 128.6, 128.3, 127.9, 125.6, 125.5, 124.9, 122.8, 114.9, 114.8, 114.2, 106.7, 106.5, 106.2, 105.6, 99.1, 80.7, 75.0, 74.3, 73.8, 70.9, 64.8, 60.3, 56.8, 56.4, 56.3, 56.0, 55.9, 55.7, 55.7, 52.7, 51.5, 39.9, 37.5, 30.5, 28.9, 26.6, 26.6, 25.8, 23.8, 22.6, 19.3, 19.3, −4.1, −4.3, −4.5, −4.6; HRMS (FAB) calcd for $C_{95}H_{116}Cl_2N_8O_{19}Si_2Cs$ [M + Cs^+] 1933.6343, found 1933.6456.

Treatment of unnatural tricyclic triazene 3b with H$^+$-resin: H$^+$-resin (AG 50W-X12, BIO-RAD) (275 mg) was suspended in H_2O (1.2 mL) and heated to 80 °C. A solution of unnatural tricyclic triazene **3b** (12.0 mg, 0.0063 mmol) in MeCN (1 mL) was added dropwise over a period of 45 min, while the temperature was kept at 80 °C. After 10 min, the mixture was cooled to 25 °C. EtOAc (3 mL), H_2O (3 mL), and solid $NaHCO_3$ (120 mg) were added, and the mixture was stirred vigorously for 0.5 h. The aqueous phase was extracted with EtOAc (2 × 2.5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 5 % MeOH in CH_2Cl_2) to afford unnatural tricyclic reduced compound **34b** (8.4 mg, 74 %). **34b**: R_f = 0.26 (silica gel, 5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = −6.7 (c = 1.5, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3306, 2954, 2930, 2856, 1682, 1667, 1660, 1650, 1609, 1513, 1504, 1486, 1251, 1109, 837, 781 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 323 K): δ = 7.72 (br. s, 1H, H-2b), 7.54 (br. s, 1H, H-6b), 7.45 (bd, J = 8.2 Hz, 1H, H-6f), 7.36 – 7.35 (m, 2H, ArH (Bn)), 7.32-7.30 (m, 2H, ArH (Bn)), 7.28 – 7.23 (m, 3H, H-2e, H-6e and ArH (Bn)), 7.18 (bd, J = 7.9 Hz, 1H, H-2f), 7.03-6.98 (m, 5H, H-5b, H-5f, H-4d and ArH (Ddm)), 6.92 – 6.88 (m, 4H, H-5e and H-7f ArH (Ddm)), 6.82 (d, J = 8.5 Hz, 2H, ArH (Ddm)), 6.71 (d, J = 8.7 Hz, 2H, ArH (Ddm)), 6.56 (d, J = 2.2 Hz, 1H, H-7d), 5.96 (br. s, 1H, H-4b), 5.87 (br. s, 1H, NHC*H* (Ddm)), 5.80 (br. s, 1H, H-4f), 5.53 (d, J = 4.7 Hz, 1H, H-2β), 5.38 (br. s, 1H, H-4α), 5.29 (br. s, 1H, H-6β), 4.85 – 4.84

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(m, 2H, H-2α and H-3α), 4.78 (br. d, J = 9.0 Hz, 1H, H-1α), 4.61 (br. s, 1H, H-5α), 4.57 (d, J = 11.7 Hz, 1H, OCH_AHPh), 4.54 (d, J = 11.7 Hz, 1H, OCHH_BPh), 4.02 (br. s, 1H, H-6α), 3.90 (t, J = 8.5 Hz, 1H, H-7α), 3.84–3.80 (m, 2H, H-7β), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 2.76 (s, 3H, NCH_3), 2.62–2.58 (m, 1H, H-3β_A), 2.53 (dd, J = 15.0, 6.6 Hz, 1H, H-3β_B), 1.71–1.69 (m, 1H, H-1γ), 1.49 (s, 9H, *t*BuO), 1.42–1.40 (m, 2H, H-1β), 0.89 (s, 18H, *t*BuSi), 0.84 (d, J = 6.3 Hz, 3H, H-1δ), 0.81 (d, J = 5.7 Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.4, 171.8, 171.3, 170.5, 169.0, 167.7, 161.6, 161.3, 159.9, 159.9, 159.8, 158.4, 152.0, 151.2, 142.5, 140.5, 140.2, 139.7, 136.5, 135.8, 129.7, 129.6, 129.4, 129.3, 129.0, 128.5, 128.0, 127.8, 126.6, 125.6, 124.8, 122.7, 115.0, 114.9, 114.0, 107.0, 106.7, 106.5, 105.5, 99.1, 80.7, 74.9, 74.3, 73.9, 70.9, 64.6, 60.4, 56.8, 56.7, 56.6, 56.4, 56.3, 56.0, 55.7, 52.7, 39.8, 37.7, 30.5, 29.0, 26.6, 26.5, 25.8, 23.8, 22.6, 19.3, 19.2, −4.3, −4.4, −4.6; HRMS (FAB) calcd for $C_{95}H_{116}Cl_2N_8O_{19}Si_2Cs$ [M + Cs^+] 1931.6327, found 1931.6151.

Treatment of natural tricyclic triazene 3a with $BF_3 \cdot Et_2O$ and Cu^{2+}/Cu^+ in MeCN: A solution of natural tricyclic triazene **3a** (4 mg, 0.002 mmol) in MeCN (0.5 mL) was cooled to 0 °C. $BF_3 \cdot Et_2O$ (10 μL, 0.008 mmol) was added, and the reaction mixture was stirred for 15 min at 0 °C. Then, saturated aqueous $Cu(NO_3)_2$ (100 μL) and Cu_2O (1 mg) were added, and the reaction mixture was warmed to 25 °C and stirred for 0.5 h. EtOAc (30 mL) was added, and the aqueous phase was extracted with EtOAc (30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 60% EtOAc in hexanes) to afford natural tricyclic reduced compound **34a** (1.2 mg, 32%).

Treatment of natural tricyclic triazene 3a with $BF_3 \cdot Et_2O$ and Cu^{2+}/Cu^+ in THF: A solution of natural tricyclic triazene **3a** (4 mg, 0.002 mmol) in THF (0.5 mL) was cooled to 0 °C. $BF_3 \cdot Et_2O$ (10 μL, 0.008 mmol) was added, and the reaction mixture was stirred for 15 min at 0 °C. Then, saturated aqueous $Cu(NO_3)_2$ (100 μL) and Cu_2O (1 mg) were added, and the reaction mixture was warmed to 25 °C and stirred for 0.5 h. EtOAc (30 mL) was added, and the aqueous phase was extracted with EtOAc (30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 60% EtOAc in hexanes) to afford natural tricyclic reduced compound **34a** (2.2 mg, 58%).

Treatment of natural tricyclic triazene 3a with $BF_3 \cdot Et_2O$ and Cu^{2+}/Cu^+ in MeOH: A solution of natural tricyclic triazene **3a** (4 mg, 0.002 mmol) in MeOH (0.5 mL) was cooled to 0 °C. $BF_3 \cdot Et_2O$ (10 μL, 0.008 mmol) was added, and the reaction mixture was stirred for 15 min at 0 °C. Then, saturated aqueous $Cu(NO_3)_2$ (100 μL) and Cu_2O (1 mg) were added, and the reaction mixture was warmed to 25 °C and stirred for 0.5 h. EtOAc (30 mL) was added, and the aqueous phase was extracted with EtOAc (30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 60% EtOAc in hexanes) to afford natural tricyclic reduced compound **34a** (2.6 mg, 69%).

Treatment of natural tricyclic triazene 3a with H_2SO_4 in MeCN: A solution of natural tricyclic triazene **3a** (12 mg, 0.0063 mmol) in MeCN (1.5 mL) was cooled to 0 °C. 30% aqueous H_2SO_4 (1.5 mL) was added, and the reaction mixture was warmed to 50 °C and stirred for 3 h. EtOAc (5 mL) and H_2O (2 mL) were added and the aqueous phase was extracted with EtOAc (10 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 60% EtOAc in hexanes) to afford natural tricyclic reduced compound **34a** (8 mg, 70%).

Treatment of natural tricyclic triazene 3a with H_2SO_4 in MeOH: A solution of natural tricyclic triazene **3a** (12 mg, 0.0063 mmol) in MeOH (1.5 mL) was cooled to 0 °C. 30% Aqueous H_2SO_4 (1.5 mL) was added, the reaction mixture was warmed to 50 °C and stirred for 1.5 h. TLC indicated formation of a complicated mixture.

Unnatural tricyclic aniline 36: Raney Ni (30 mg) was added to a solution of unnatural tricyclic triazene **3b** (30 mg, 0.0158 mmol) in MeOH (5 mL). The reaction mixture was stirred at 25 °C for 10 h, filtered through celite, concentrated, and the residue was checked with ^{1}H NMR spectroscopy and proved to be a mixture of **35** and **36** (ca. 1:1). This mixture was subjected to debenzylation by addition of 10% Pd/C (15 mg) to a solution of the residue in MeOH (5 mL). H_2 was bubbled through the mixture for 4 h. The reaction mixture was filtered through celite, concentrated, and the residue was purified by preparative TLC (silica gel, 7% MeOH in CH_2Cl_2) to afford unnatural tricyclic aniline **36** (16.4 mg, 60% overall from **3b**). **36**: R_f = 0.24 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = −5.8 (c = 0.83, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3311, 2956, 1685, 1654, 1560, 1508, 1458, 1252, 840 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.73 (br. s, 1H, H-2b), 7.56 (d, J = 2.0 Hz, 1H, H-6b), 7.48 (dd, J = 8.3, 2.0 Hz, 1H, H-6f), 7.30 (d, J = 8.2 Hz, 1H, H-2e), 7.19 (br. d, J = 7.0 Hz, 1H, H-2f), 7.07 (d, J = 8.3 Hz, H-6e), 7.02–6.98 (m, 4H, H-5b, H-5f and ArH (Ddm)), 6.92–6.90 (m, 3H, H-7f and ArH (Ddm)), 6.87 (d, J = 8.1 Hz, 1H, H-5e), 6.73 (d, J = 8.7 Hz, 2H, ArH (Ddm)), 6.59 (d, J = 2.3 Hz, 1H, H-7d), 6.29 (d, J = 8.7 Hz, 2H, ArH (Ddm)), 5.86 (br. s, 1H, H-4b), 5.78 (br. s, 1H, NHC*H* (Ddm)), 5.77 (br. s, 1H, H-4f), 5.54 (d, J = 4.8 Hz, 1H, H-2β), 5.34 (br. s, 1H, H-4α), 5.31 (br. s, 1H, H-6β), 4.89–4.87 (m, 2H, H-2α and H-3α), 4.80–4.79 (m, 1H, H-1α), 4.63 (br. s, 1H, H-5α), 4.21–4.19 (m, 1H, H-7α), 4.07 (br. s, 1H, H-6α), 4.00 (dd, J = 10.9, 8.2 Hz, 1H, H-7β_A), 3.92 (dd, J = 10.8, 4.9 Hz, 1H, H-7β_B), 3.88 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.77 (s, 3H, NCH_3), 2.57–2.53 (m, 2H, H-3β), 1.70–1.69 (m, 1H, H-1γ), 1.50 (s, 9H, *t*BuO), 1.39–1.38 (m, 2H, H-1β), 0.92 (s, 9H, *t*BuSi), 0.89 (s, 9H, *t*BuSi), 0.83 (d, J = 6.3 Hz, 3H, H-1δ), 0.80 (d, J = 5.1 Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.2, 171.3, 171.2, 170.7, 169.4, 161.2, 159.6, 158.1, 157.0, 151.5, 147.8, 147.6, 147.4, 141.7, 139.9, 139.7, 136.0, 135.5, 129.5, 129.3, 128.7, 128.3, 128.2, 127.8, 127.5, 127.2, 126.6, 125.2, 124.9, 122.5, 114.6, 114.5, 113.7, 107.3, 106.3, 105.4, 98.7, 80.5, 74.5, 74.1, 64.2, 64.0, 60.1, 57.0, 56.4, 56.1, 55.9, 55.7, 55.5, 55.3, 52.4, 39.8, 37.4, 30.4, 28.7, 26.3, 26.2, 25.5, 23.6, 22.3, 19.0, 18.9, −4.7, −4.7, −4.9; HRMS (FAB) calcd for $C_{88}H_{111}Cl_2N_9O_{19}Si_2Cs$ [M + Cs^+] 1856.5966, found 1856.6084.

Sandmeyer reaction of aniline 36: A solution of unnatural tricyclic aniline **36** (22.7 mg, 0.0132 mmol) in MeCN (2 mL) was cooled to −20 °C. 48% Aqueous HBF_4 (34.5 μL, 0.264 mmol) and *i*-amylONO (35.5 μL, 0.264 mmol) were added, and the reaction mixture was vigorously stirred at −20 °C. After 0.5 h, the reaction mixture was cooled to −45 °C, and a saturated solution of KI (1 mL) was added in one shot. The reaction mixture was vigorously stirred for 2 h, while the temperature was raised slowly to 25 °C. EtOAc (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous Na_2SO_3 (5 mL) were added sequentially, and the mixture was allowed to stir for 15 min. The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 50% EtOAc in CH_2Cl_2) to afford an inseparable mixture of unnatural tricyclic iodide **38** and unnatural tricyclic reduced compound **39** (18.6 mg, ca. 6:4 from ^{1}H NMR). This mixture was used directly in the next reaction.

Unnatural tricyclic phenol 41b: A solution in anhydrous THF (12 mL) of a ca. 6:4 mixture of iodide **38** and reduced compound **39** (18.6 mg), prepared as described above, was cooled to −50 °C. MeMgBr (1.4 M solution in THF, 0.28 mL, 0.396 mmol) was added dropwise and the mixture was allowed to warm to −20 °C. After stirring for 1 h, the reaction mixture was recooled to −60 °C, and *i*PrMgCl (2.0 M solution in THF, 0.20 mL, 0.4 mmol) was added dropwise. The mixture was kept at −40 °C for 2 h, and then cooled to −50 °C before the addition of freshly distilled trimethyl borate (0.15 mL, 1.32 mmol). After vigorously stirring for 1 h at 0 °C, the reaction mixture was recooled to −20 °C. A mixture of 30% aqueous H_2O_2 and 10% aqueous NaOH (1:1, 1 mL) was added, and vigorous stirring was applied for 20 min at 0 °C. Without allowing the temperature to raise, EtOAc (4 mL) and saturated aqueous $Na_2S_2O_3 \cdot 5H_2O$ (1 mL) were added. The reaction mixture was stirred for 5 min, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 5% MeOH in CH_2Cl_2) to afford faster moving unnatural tricyclic reduced compound **39** (6.3 mg, 28% overall from **36**), and slower moving unnatural tricyclic phenol **41b** (6.8 mg, 30% overall from **36**). **39**: R_f = 0.24 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ = −23.4 (c = 1.1, EtOAc); IR (thin film): $\tilde{\nu}_{max}$ = 3300, 2955, 1672, 1609, 1512, 1253, 1107, 837 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.75 (br. s, 1H, H-2b), 7.56 (d, J = 1.9 Hz, 1H, H-6b), 7.46 (dd, J = 8.4, 2.0 Hz, 1H, H-6f), 7.25 (d, J = 8.2 Hz, 1H, H-2e), 7.18 (br. d, J = 8.6 Hz, 1H, H-2f), 7.04–7.00 (m, 5H, H-5b, H-5f, H-6e and ArH (Ddm)), 6.92–6.88 (m, 5H, H-4d, H-5e, H-7f and ArH (Ddm)), 6.82 (d, J = 8.7 Hz, 2H, ArH (Ddm)), 6.72 (d, J = 8.7 Hz, 2H, ArH (Ddm)), 6.58 (d, J = 2.2 Hz, 1H, H-7d), 5.91 (br. s, 1H, H-4b), 5.87 (br. s, 1H, NHC*H* (Ddm)), 5.81 (br. s, 1H, H-4f), 5.53 (d, J = 4.7 Hz, 1H, H-2β), 5.39 (br. s, 1H, H-4α), 5.31 (br. s, 1H, H-6β), 4.87–4.84 (m, 2H, H-2α and

H-3α), 4.78–4.77 (m, 1H, H-1α), 4.63 (br.s, 1H, H-5α), 4.20 (dd, J = 7.6, 4.9 Hz, 1H, H-7α), 4.06 (br.s, 1H, H-6α), 4.00 (dd, J = 10.2, 8.2 Hz, 1H, H-7β_A), 3.93 (dd, J = 10.0, 4.9 Hz, 1H, H-7β_B), 3.87 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.77 (s, 3H, NCH_3), 2.62–2.60 (m, 1H, H-3β_A), 2.52 (dd, J = 16.1, 6.8 Hz, 1H, H-3β_B), 1.70-1.68 (m, 1H, H-1γ), 1.50 (s, 9H, *t*BuO), 1.39–1.37 (m, 2H, H-1β), 0.92 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.84 (d, J = 6.3 Hz, 3H, H-1δ), 0.81 (d, J = 4.0 Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.3, 171.6, 171.2, 170.4, 170.3, 168.8, 161.3, 161.1, 159.6, 158.1, 151.8, 151.0, 142.5, 142.4, 142.1, 140.2, 139.7, 136.1, 135.5, 129.5, 129.4, 129.3, 129.2, 128.7, 128.3, 127.8, 127.4, 126.3, 125.3, 124.6, 122.5, 114.6, 114.5, 113.7, 106.8, 106.3, 105.3, 98.7, 80.5, 74.6, 74.1, 64.3, 63.7, 60.2, 57.2, 56.5, 56.5, 56.3, 56.1, 55.7, 55.5, 55.4, 52.4, 39.6, 37.4, 30.5, 28.7, 26.3, 26.2, 25.5, 23.6, 19.0, 18.9, −4.7, −4.9; HRMS (FAB) calcd for $C_{88}H_{110}Cl_2N_8O_{19}Si_2Cs$ [$M + Cs^+$] 1841.5857, found 1841.5712. **41b**: R_f = 0.32 (silica gel, 7.5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -23.3$ (c = 2.80, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3306, 2954, 2930, 2857, 1660, 1510, 1250, 1107, 837, 780 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.74 (br.s, 1H, H-2b), 7.57 (br.s, 1H, H-6b), 7.48 (dd, J = 8.3, 1.7 Hz, 1H, H-6f), 7.28 (d, J = 8.3 Hz, 1H, H-2e), 7.19 (br.d, J = 7.0 Hz, 1H, H-2f), 7.07 (d, J = 8.2 Hz, H-6e), 7.01–6.99 (m, 4H, H-5b, H-5f and ArH (Ddm)), 6.92–6.90 (m, 3H, H-7f and ArH (Ddm)), 6.87 (d, J = 9.5 Hz, 1H, H-5e), 6.82 (d, J = 8.6 Hz, 2H, ArH (Ddm)), 6.73 (d, J = 8.6 Hz, 2H, ArH (Ddm)), 6.59 (d, J = 2.0 Hz, 1H, H-7d), 5.86 (br.s, 1H, H-4b), 5.82 (br.s, 1H, NHC*H* (Ddm)), 5.79 (br.s, 1H, H-4f), 5.53 (d, J = 4.8 Hz, 1H, H-2β), 5.40 (br.s, 1H, H-4α), 5.32 (br.s, 1H, H-6β), 4.90–4.87 (m, 2H, H-2α and H-3α), 4.81–4.79 (m, 1H, H-1α), 4.63 (br.s, 1H, H-5α), 4.20 (t, J = 5.0 Hz, 1H, H-7α), 4.07 (br.s, 1H, H-6α), 4.00 (t, J = 10.8 Hz, 1H, H-7β_A), 3.93 (dd, J = 10.8, 4.9 Hz, 1H, H-7β_B), 3.87 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.77 (s, 3H, NCH_3), 2.62–2.59 (m, 1H, H-3β_A), 2.52 (dd, J = 15.3, 5.8 Hz, 1H, H-3β_B), 1.70–1.68 (m, 1H, H-1γ), 1.50 (s, 9H, *t*BuO), 1.39–1.38 (m, 1H, H-1β_A), 1.29–1.28 (m, 1H, H-1β_B), 0.91 (s, 9H, *t*BuSi), 0.89 (s, 9H, *t*BuSi), 0.83 (d, J = 4.4 Hz, 3H, H-1δ), 0.81 (d, J = 4.9 Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.2, 171.5, 171.2, 170.5, 168.9, 161.2, 159.6, 158.1, 152.3, 151.4, 148.7, 148.6, 141.8, 140.1, 139.7, 136.0, 135.6, 135.5, 129.9, 129.8, 129.7, 129.5, 129.3, 128.8, 128.5, 128.3, 128.0, 127.8, 127.5, 126.4, 125.3, 124.8, 122.5, 114.6, 114.5, 113.7, 107.8, 106.3, 106.0, 98.7, 80.5, 74.6, 74.1, 64.2, 63.8, 60.0, 57.2, 56.4, 56.1, 55.7, 55.5, 55.5, 55.3, 52.4, 39.7, 37.4, 30.5, 28.7, 26.3, 26.2, 25.5, 23.6, 22.3, 19.0, 18.9, −4.6, −4.7, −4.9; HRMS (FAB) calcd for $C_{88}H_{110}Cl_2N_8O_{20}Si_2Cs$ [$M + Cs^+$] 1857.5806, found 1857.5693.

Treatment of unnatural tricyclic triazene 3b with TMSI (Table 3, entries 1–8): NaI (1.5–4.5 mg, 0.01–0.30 mmol) was added to a solution of unnatural tricyclic triazene **3b** (9 mg, 0.005 mmol) in MeCN (1–5 mL). After 5 min, trimethylsilyl chloride (1 μL, 0.0075 mmol) was added dropwise, and the mixture was allowed to stir at the temperatures shown in Table 3, for 15 min. Then, 5% aqueous $NaHCO_3$ (0.5 mL) was added, and the mixture was stirred vigorously for 10 min. The aqueous phase was extracted with ether (3 × 1 mL). The combined organic layers were dried (Na_2SO_4), filtered through a pad of silica gel, and concentrated. In all cases, desired unnatural tricyclic iodide **42b** was detected only as a trace (< 5%) by mass spectrometry. For entries 2, 4, and 8, the crude mixture was subjected to the next reaction (phenol formation protocol, see unnatural tricyclic phenol **43b**). Faster moving unnatural tricyclic reduced compound **34b** and slower moving unnatural tricyclic phenol **43b** were isolated in the yields given in Table 3.

Treatment of unnatural tricyclic triazene 3b with TMSI-I_2 (Table 3, entries 9–13): NaI (4.5 mg, 0.03 mmol) and I_2 (2.5–12.7 mg, 0.01–0.05 mmol) were added to a solution of unnatural tricyclic triazene **3b** (9 mg, 0.005 mmol) in MeCN (1 mL). After 5 min, trimethylsilyl chloride (1.0 μL, 0.0075 mmol) was added dropwise, and the mixture was allowed to stir at the temperatures shown in Table 3, for 15 min. Then, 5% aqueous $NaHCO_3$ (0.5 mL) was added, followed by the addition of 5% aqueous $Na_2S_2O_3 \cdot 5H_2O$ (0.5 mL). After 10 min, the aqueous phase was extracted with ether (3 × 1 mL). The combined organic layers were dried (Na_2SO_4), filtered through a pad of silica gel, and concentrated. The ratio of inseparable unnatural tricyclic iodide **42b** and unnatural tricyclic reduced compound **34b** was determined by mass spectrometry (see Table 3). In one case (entry 13), excess I_2 caused removal of the Boc group, and a complicated mixture was formed. The crude mixture of iodide **42b** and reduced compound **34b** was used in the next reaction (phenol formation protocol, see unnatural tricyclic phenol **43b**). Faster moving unnatural tricyclic reduced compound **34b** and slower moving unnatural tricyclic phenol **43b** were isolated in the yields given in Table 3.

Treatment of unnatural tricyclic triazene 3b with I_2 in a sealed tube (Table 3, entry 14): I_2 (1.4 mg, 0.0055 mmol) was added to a solution of unnatural tricyclic triazene **3b** (9 mg, 0.005 mmol) in freshly distilled and well degassed (with Ar) MeCN (0.35 mL) in a sealed tube. This mixture was heated at 80 °C for 1 h and then cooled to 25 °C. 5% aqueous $Na_2S_2O_3 \cdot 5H_2O$ (0.5 mL) was added, and the reaction mixture was vigorously stirred for 10 min. The aqueous phase was extracted with ether (3 × 1 mL). The combined organic layers were dried (Na_2SO_4), filtered through a pad of silica gel, and concentrated. The desired unnatural tricyclic iodide **42b** was detected as a trace (> 5%) by mass spectrometry.

Natural tricyclic iodide 42a: NaI (36 mg, 0.24 mmol) and I_2 (61 mg, 0.24 mmol) were added to a solution of natural tricyclic triazene **3a** (76 mg, 0.04 mmol) in MeCN (8 mL). After 5 min, trimethylsilyl chloride (7.6 μL, 0.06 mmol) was added dropwise, and the mixture was allowed to stir at 25 °C for 15 min. Then, 5% aqueous $NaHCO_3$ (3.5 mL) was added, followed by the addition of 5% aqueous $Na_2S_2O_3 \cdot 5H_2O$ (3.5 mL). After 10 min, the aqueous phase was extracted with ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered through a pad of silica gel, and concentrated. The inseparable mixture of natural tricyclic iodide **42a** and natural tricyclic reduced compound **34a** (ca. 1:1 by mass spectrometry) was used in the next reaction without further purification.

Natural tricyclic phenol 43a: An approximate 1:1 mixture of natural tricyclic iodide **42a** and natural tricyclic reduced compound **34a** (prepared as described above) in THF (12 mL) was cooled to −50 °C. MeMgBr (1.4 M solution in THF, 0.86 mL, 1.2 mmol) was added dropwise, and the mixture was allowed to warm to −20 °C. After stirring for 1 h, the mixture was recooled to −60 °C, and *i*PrMgCl (2.0 M solution in THF, 0.6 mL, 1.2 mmol) was added dropwise. The mixture was kept at −40 °C for 2 h, and then cooled to −50 °C before the addition of freshly distilled trimethyl borate (0.45 mL, 4 mmol). The reaction mixture was vigorously stirred for 1 h at 0 °C and then recooled to −20 °C. A mixture of 30% aqueous H_2O_2 and 10% aqueous NaOH (1:1, 3 mL) was added, and vigorous stirring at 0 °C was applied for 20 min. Without allowing the temperature to raise, EtOAc (10 mL) and saturated aqueous $Na_2S_2O_3 \cdot 5H_2O$ (2 mL) were added. The mixture was stirred for 5 min, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 5% MeOH in CH_2Cl_2) to afford faster moving natural tricyclic reduced compound **34a** (24.3 mg, 34% overall from **3a**), and slower moving natural tricyclic phenol **43a** (24.5 mg, 34% overall from **3a**). **43a**: R_f = 0.23 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +8.8$ (c = 1.2, MeOH); IR (thin film): $\tilde{\nu}_{max}$ = 3304, 2955, 2930, 2857, 1667, 1659, 1652, 1511, 1487, 1247, 838, 780 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): δ = 7.60 (br.s, 1H, H-2b), 7.49–7.46 (m, 2H, H-6b and H-6f), 7.35–7.25 (m, 7H, H-2f, H-6e and ArH (Bn)), 7.08 (br.d, J = 7.4 Hz, 1H, H-2e), 7.02 (br.s, 1H, H-5b), 6.98 (d, J = 8.8 Hz, 2H, ArH (Ddm)), 6.95 (d, J = 8.8 Hz, 1H, H-5f), 6.91 (br.s, 1H, H-7f), 6.86 (br.d, J = 8.3 Hz, 3H, H-5e and ArH (Ddm)), 6.82 (d, J = 8.8 Hz, 2H, ArH (Ddm)), 6.69 (br.d, J = 7.5 Hz, 2H, ArH (Ddm)), 6.56 (d, J = 2.2 Hz, 1H, H-7d), 6.18 (br.s, 1H, NHC*H* (Ddm)), 5.84 (br.s, 1H, H-4b), 5.74 (br.s, 1H, H-4f), 5.54 (d, J = 4.4 Hz, 1H, H-2β), 5.44 (br.s, 1H, H-4α), 5.29 (br.s, 1H, H-6β), 5.00–4.94 (m, 2H, H-2α and H-3α), 4.76–4.74 (m, 1H, H-1α), 4.61 (br.s, 1H, H-5α), 4.57 (d, J = 15.4 Hz, 1H, OCH_AHPh), 4.53 (d, J = 15.5 Hz, 1H, $OCHH_BPh$), 4.42–4.39 (m, 1H, H-7α), 4.00 (br.s, 1H, H-6α), 3.92–3.88 (m, 1H, H-7β_A), 3.82–3.80 (m, 1H, H-7β_B), 3.79 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 2.70–2.65 (m, 2H, H-3β), 1.72–1.69 (m, 1H, H-1γ), 1.48 (br.s, 9H, *t*BuO), 1.40–1.36 (m, 2H, H-1β), 0.92 (s, 9H, *t*BuSi), 0.89 (s, 9H, *t*BuSi), 0.82 (d, J = 6.1 Hz, 3H, H-1δ), 0.78 (d, J = 6.1 Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): δ = 172.1, 171.6, 171.0, 169.2, 161.3, 159.9, 159.8, 159.8, 158.3, 152.6, 151.8, 149.5, 148.4, 142.0, 140.3, 140.1, 139.7, 136.5, 136.2, 135.8, 130.5, 129.8, 129.6, 129.5, 129.3, 129.1, 129.0, 128.5, 128.3, 127.9, 127.7, 127.6, 125.7, 125.5, 125.1, 122.8, 114.9, 114.8, 114.1, 107.4, 106.7, 106.2, 99.1, 80.7, 74.9, 74.3, 73.8, 70.9, 65.0, 64.8, 60.3, 56.8, 56.4, 56.3, 55.9, 55.7, 52.7, 55.7, 52.6, 37.5, 30.5, 28.9, 26.6, 26.6, 25.8, 23.8, 22.5, 19.3, −4.1, −4.3, −4.5, −4.6;

0947-6539/99/0509-2642 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 9

HRMS (FAB) calcd for $C_{95}H_{116}Cl_2N_8O_{20}Si_2Cs$ $[M+Cs^+]$ 1949.6292, found 1949.6134.

Unnatural tricyclic iodide 42b: NaI (27 mg, 0.18 mmol) and I_2 (46 mg, 0.18 mmol) were added to a solution of unnatural tricyclic triazene **3b** (57 mg, 0.03 mmol) in MeCN (6 mL). After 5 min, trimethylsilyl chloride (5.7 μL, 0.045 mmol) was added dropwise, and the mixture allowed to stir at 25 °C for 15 min. Then, 5% aqueous $NaHCO_3$ (2.5 mL) was added, followed by the addition of 5% aqueous $Na_2S_2O_3\cdot 5H_2O$ (2.5 mL). After 10 min, the aqueous phase was extracted with ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered through a pad of silica gel, and concentrated. The inseparable mixture of unnatural tricyclic iodide **42b** and unnatural tricyclic reduced compound **34b** (ca. 1:1 by mass spectrometry) was used in the next reaction without further purification.

Unnatural tricyclic phenol 43b: An approximate 1:1 mixture of unnatural tricyclic iodide **42b** and unnatural tricyclic reduced compound **34b** (prepared as described above) in THF (10 mL) was cooled to −50 °C. MeMgBr (1.4 M solution in THF, 0.65 mL, 0.9 mmol) was added dropwise, and the mixture was allowed to warm to −20 °C. After stirring for 1 h, the mixture was recooled to −60 °C, and *i*PrMgCl (2.0 M solution in THF, 0.45 mL, 0.9 mmol) was added dropwise. The mixture was kept at −40 °C for 2 h, and then cooled to −50 °C, before the addition of freshly distilled trimethyl borate (0.34 mL, 3 mmol). The reaction mixture was vigorously stirred for 1 h at 0 °C and then recooled to −20 °C. A mixture of 30% aqueous H_2O_2 and 10% aqueous NaOH (1:1, 2.5 mL) was added and vigorous stirring at 0 °C was applied for 20 min. Without allowing the temperature to raise, EtOAc (10 mL), and saturated aqueous $Na_2S_2O_3\cdot 5H_2O$ (2 mL) were added. The mixture was stirred for 5 min, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was purified by preparative TLC (silica gel, 5% MeOH in CH_2Cl_2) to afford faster moving unnatural tricyclic reduced compound **34b** (15.7 mg, 29% overall from **3b**), and slower moving unnatural tricyclic phenol **43b** (17.4 mg, 32% overall from **3b**). **43b**: $R_f = 0.21$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -5.6$ ($c = 3.6$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3304$, 2955, 2931, 2856, 1668, 1612, 1513, 1486, 1251, 1107, 838 cm^{-1}; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.75$ (br. s, 1H, H-2b), 7.54 (br. s, 1H, H-6b), 7.45 (br. d, $J = 8.3$, Hz, 1H, H-6f), 7.37 (d, $J = 5.8$ Hz, 2H, ArH (Bn)), 7.31 (t, $J = 7.4$ Hz, 2H, ArH (Bn)), 7.28–7.23 (m, 2H, H-2e and ArH (Bn)), 7.19–7.18 (m, 1H, H-2f), 7.00–6.98 (m, 4H, H-6e, H-7f and ArH (Ddm)), 6.92–6.90 (m, 4H, H-5b, H-5f and ArH (Ddm)), 6.87 (d, $J = 9.3$ Hz, 1H, H-5e), 6.82 (d, $J = 8.6$ Hz, 2H, ArH (Ddm)), 6.72 (d, $J = 8.6$ Hz, 2H, ArH (Ddm)), 6.57 (br. s, 1H, H-7d), 5.95 (br. s, 1H, H-4b), 5.87 (br. s, 1H, NHC*H* (Ddm)), 5.77 (br. s, 1H, H-4f), 5.54 (d, $J = 4.8$ Hz, 1H, H-2β), 5.40 (br. s, 1H, H-4α), 5.29 (br. s, 1H, H-6β), 4.92–4.90 (m, 2H, H-2α and H-3α), 4.81–4.80 (m, 1H, H-1α), 4.61 (br. s, 1H, H-5α), 4.54 (2H, obscured by solvent, OCH_2Ph), 4.20–4.19 (m, 1H, H-7α), 4.03 (br. s, 1H, H-6α), 3.90–3.89 (m, 1H, H-7β_A), 3.82 (dd, $J = 10.6$, 3.7 Hz, 1H, H-7β_B), 3.79 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 2.77 (s, 3H, NCH_3), 2.63–2.61 (m, 1H, H-3β_A), 2.52 (dd, $J = 15.6$, 6.3 Hz, 1H, H-3β_B), 1.70–1.69 (m, 1H, H-1γ), 1.49 (s, 9H, *t*BuO), 1.42–1.40 (m, 2H, H-1β), 0.89 (s, 18H, *t*BuSi), 0.84 (d, $J = 10.6$ Hz, 3H, H-1δ), 0.82 (d, $J = 7.5$ Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta = 172.2$, 171.5, 171.2, 170.7, 170.4, 168.9, 167.6, 161.0, 159.6, 159.5, 158.1, 157.0, 152.4, 151.4, 148.8, 148.6, 141.9, 139.9, 139.4, 136.2, 135.5, 135.5, 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.7, 128.5, 128.3, 128.2, 127.6, 127.5, 127.3, 126.3, 125.2, 124.8, 122.5, 114.6, 114.5, 113.7, 107.7, 106.5, 106.0, 98.8, 80.5, 74.7, 74.1, 73.6, 70.6, 64.4, 57.1, 56.4, 56.1, 55.9, 55.7, 55.5, 52.6, 52.4, 39.8, 37.5, 30.2, 28.7, 26.3, 26.2, 25.5, 23.6, 22.3, 19.0, 19.0, −4.6, −4.8; HRMS (FAB) calcd for $C_{95}H_{116}Cl_2N_8O_{20}Si_2Cs$ $[M+Cs^+]$ 1947.6276, found 1947.6470.

Natural tricyclic alcohol 41a: 10% Pd/C (20 mg) was added to a solution of natural tricyclic phenol **43a** (21 mg, 0.0116 mmol) in MeOH (2 mL), and H_2 was bubbled through the solution for 1.5 h at 25 °C. The reaction mixture was filtered through celite, concentrated, and the residue was purified by preparative TLC (silica gel, 5% MeOH in CH_2Cl_2) to afford natural tricyclic alcohol **41a** (17.4 mg, 87%). **41a**: $R_f = 0.22$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +3.5$ ($c = 0.40$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3306$, 2953, 2932, 2857, 1680, 1666, 1659, 1651, 1514, 1505, 1487, 1248, 837, 780 cm^{-1}; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.62$ (br. s, 1H, H-2b), 7.50–7.47 (m, 2H, H-6b and H-6f), 7.32 (br. s, 1H, H-2f), 7.28 (d, $J = 8.3$ Hz, 1H, H-6e), 7.10 (br. d, $J = 7.9$ Hz, 1H, H-2e), 7.03 (br. d, $J = 0.6$ Hz, 1H, H-5b), 6.99 (d, $J = 8.3$ Hz, 2H, ArH (Ddm)), 6.95 (d, $J = 9.2$ Hz, 1H, H-5f), 6.91 (br. d, $J = 0.5$ Hz, 1H, H-7f), 6.88 (br. d, $J = 8.8$ Hz, 3H, H-5e and ArH (Ddm)), 6.83 (d, $J = 8.3$ Hz, 2H, ArH (Ddm)), 6.71 (br. d, $J = 7.9$ Hz, 2H, ArH (Ddm)), 6.59 (br. s, 1H, H-7d), 6.13 (br. s, 1H, NHC*H* (Ddm)), 5.86 (br. s, 1H, H-4b), 5.75 (br. s, 1H, H-4f), 5.55 (d, $J = 4.4$ Hz, 1H, H-2β), 5.46 (br. s, 1H, H-4α), 5.33 (br. s, 1H, H-6β), 5.00–4.94 (m, 2H, H-2α and H-3α), 4.79–4.75 (m, 1H, H-1α), 4.66 (br. s, 1H, H-5α), 4.24–4.21 (m, 1H, H-7α), 4.06 (br. s, 1H, H-6α), 4.03–4.00 (m, 1H, H-7β_A), 3.93 (dd, $J = 10.5$, 4.4 Hz, 1H, H-7β_B), 3.88 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 2.79 (s, 3H, NCH_3), 2.70–2.60 (m, 2H, H-3β), 1.75–1.72 (m, 1H, H-1γ), 1.49 (br. s, 9H, *t*BuO), 1.40–1.37 (m, 2H, H-1β), 0.95 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.83 (d, $J = 6.2$ Hz, 3H, H-1δ), 0.80 (d, $J = 6.2$ Hz, 3H, H-1δ'), 0.13 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta = 172.2$, 171.6, 171.6, 171.2, 171.0, 161.4, 159.9, 159.9, 158.3, 152.7, 151.9, 149.5, 148.4, 142.0, 140.2, 140.1, 136.4, 136.2, 135.8, 130.5, 129.8, 129.7, 129.5, 129.2, 128.3, 127.8, 125.7, 125.6, 125.1, 122.8, 114.9, 114.8, 114.1, 106.5, 106.2, 99.0, 80.8, 74.9, 74.4, 64.7, 64.0, 60.3, 56.8, 56.4, 56.3, 56.0, 55.7, 55.7, 52.7, 37.5, 29.0, 26.6, 25.8, 23.8, 22.7, 19.3, 19.2, −4.3, −4.5, −4.7; HRMS (FAB) calcd for $C_{88}H_{110}Cl_2N_8O_{20}Si_2Cs$ $[M+Cs^+]$ 1857.5806, found 1857.5919.

Unnatural tricyclic alcohol 41b: 10% Pd/C (30 mg) was added to a solution of unnatural tricyclic phenol **43b** (36.3 mg, 0.02 mmol) in MeOH (3 mL), and H_2 was bubbled through the solution for 1.5 h at 25 °C. The reaction mixture was filtered through celite, concentrated, and the residue was purified by preparative TLC (silica gel, 5% MeOH in CH_2Cl_2) to afford unnatural tricyclic alcohol **41b** (32.5 mg, 94%).

Natural tricyclic methylated phenol 44a: Cs_2CO_3 (32.3 mg, 0.1 mmol) was added to a solution of natural tricyclic alcohol **41a** (17.1 mg, 0.01 mmol) in DMF (1 mL), and the mixture was cooled to 0 °C. Then, MeI (31 μL, 0.5 mmol) was added dropwise. After 2 h at 0 °C, saturated aqueous NH_4Cl (1 mL) and EtOAc (1 mL) were added. The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL), dried (Na_2SO_4), and the residue was purified by flash column chromatography (silica gel, 50 → 80% EtOAc in hexanes, gradient elution) to afford natural tricyclic methylated phenol **44a** (16.4 mg, 95%). **44a**: $R_f = 0.35$ (silica gel, 7.5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -7.5$ ($c = 0.44$, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3301$, 2954, 2930, 2856, 1681, 1667, 1659, 1651, 1513, 1504, 1487, 1246, 838, 780 cm^{-1}; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.62$ (br. s, 1H, H-2b), 7.54 (br. s, 1H, H-6b), 7.50 (br. d, $J = 8.6$ Hz, 1H, H-6f), 7.36–7.33 (m, 1H, H-2f), 7.26 (d, $J = 8.4$ Hz, 1H, H-2e), 7.07 (br. d, $J = 8.7$ Hz, 1H, H-6e), 7.02 (d, $J = 2.2$ Hz, 1H, H-5b), 6.96 (d, $J = 6.8$ Hz, 2H, ArH (Ddm)), 6.94 (d, $J = 8.7$ Hz, 1H, H-5f), 6.91 (d, $J = 2.1$ Hz, 1H, H-7f), 6.88 (br. d, $J = 8.4$ Hz, 3H, H-5e and ArH (Ddm)), 6.83 (d, $J = 8.7$ Hz, 2H, ArH (Ddm)), 6.72-6.70 (m, 2H, ArH (Ddm)), 6.58 (d, $J = 2.1$ Hz, 1H, H-7d), 5.96 (br. s, 1H, NHC*H* (Ddm)), 5.85 (br. s, 1H, H-4b), 5.73 (br. s, 1H, H-4f), 5.52 (d, $J = 4.7$ Hz, 1H, H-2β), 5.45 (br. s, 1H, H-4α), 5.32 (br. s, 1H, H-6β), 4.93–4.90 (m, 2H, H-2α and H-3α), 4.75-4.73 (m, 1H, H-1α), 4.63 (br. s, 1H, H-5α), 4.23-4.19 (m, 1H, H-7α), 4.17 (s, 3H, OCH_3), 4.06 (br. s, 1H, H-6α), 4.00 (t, $J = 10.0$ Hz, 1H, H-7β_A), 3.92 (dd, $J = 10.9$, 4.9 Hz, 1H, H-7β_B), 3.87 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 2.64–2.61 (m, 1H, H-3β_A), 2.58 (dd, $J = 16.4$, 6.0 Hz, 1H, H-3β_B), 1.72–1.70 (m, 1H, H-1γ), 1.51 (br. s, 9H, *t*BuO), 1.38–1.34 (m, 2H, H-1β), 0.94 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.83 (d, $J = 6.5$ Hz, 3H, H-1δ), 0.79 (d, $J = 6.2$ Hz, 3H, H-1δ'), 0.13 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3CN, 335 K): $\delta = 172.8$, 172.2, 171.8, 170.8, 169.5, 168.9, 161.5, 160.1, 159.7, 158.6, 154.8, 153.6, 152.0, 151.7, 141.9, 140.4, 139.6, 138.7, 136.0, 135.5, 130.3, 129.7, 129.6, 129.5, 129.3, 129.2, 128.6, 128.3, 127.4, 127.0, 125.9, 125.4, 124.9, 122.5, 115.1, 115.0, 114.7, 107.1, 106.8, 106.4, 99.1, 81.0, 74.5, 74.2, 65.2, 63.8, 62.1, 60.5, 57.1, 56.9, 56.8, 56.4, 56.1, 55.9, 55.8, 55.5, 52.4, 37.7, 30.6, 29.0, 26.6, 26.5, 25.7, 23.8, 22.3, 19.2, 19.2, −4.0, −4.3, −4.4, −4.6; HRMS (FAB) calcd for $C_{89}H_{112}Cl_2N_8O_{20}Si_2Cs$ $[M+Cs^+]$ 1871.5963, found 1871.5844.

Unnatural tricyclic methylated phenol 44b: Cs_2CO_3 (49 mg, 0.15 mmol) was added to a solution of alcohol **41b** (26 mg, 0.015 mmol) in DMF (1 mL), and the mixture was cooled to 0 °C. Then, MeI (47 μL, 0.75 mmol) was added dropwise. After 2 h at 0 °C, saturated aqueous NH_4Cl (1.5 mL) and EtOAc (1.5 mL) were added. The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine

(3×8 mL), dried (Na_2SO_4), and the residue was purified by flash column chromatography (silica gel, 50 →80 % EtOAc in hexanes, gradient elution) to afford unnatural tricyclic methylated phenol **44b** (24.5 mg, 94 %). **44b**: $R_f = 0.35$ (silica gel, 7.5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -16.5$ ($c = 0.98$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3306, 2953, 2929, 2856, 1681, 1667, 1660, 1651, 1513, 1504, 1486, 1250, 837, 781\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.77$ (br. s, 1H, H-2b), 7.56 (d, $J = 1.8$ Hz, 1H, H-6b), 7.48 (dd, $J = 8.3$, 1.8 Hz, 1H, H-6f), 7.24 – 7.17 (m, 2H, H-2e and H-2f), 7.12 (br. d, $J = 8.7$ Hz, 1H, H-6e), 7.02 – 6.98 (m, 4H, H-5b, H-5f and ArH (Ddm)), 6.94 – 6.88 (m, 3H, H-7f and ArH (Ddm)), 6.84 – 6.81 (m, 3H, H-5e and ArH (Ddm)), 6.73 (d, $J = 8.5$ Hz, 2H, ArH (Ddm)), 6.59 (d, $J = 2.2$ Hz, 1H, H-7d), 5.97 (br. s, 1H, H-4b), 5.86 (br. s, 1H, NHC*H* (Ddm)), 5.80 (br. s, 1H, H-4f), 5.40 (d, $J = 4.8$ Hz, 1H, H-2β), 5.44 (br. s, 1H, H-4α), 5.32 (br. s, 1H, H-6β), 4.92-4.90 (m, 2H, H-2α and H-3α), 4.80-4.78 (m, 1H, H-1α), 4.63 (br. s, 1H, H-5α), 4.20 (br. s, 4H, H-7α and 4d-OCH_3), 4.08 (br. s, 1H, H-6α), 4.00 (t, $J = 8.1$ Hz, 1H, H-7β_A), 3.92 (dd, $J = 10.9$, 5.0 Hz, 1H, H-7β_B), 3.87 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.77 (s, 3H, NCH_3), 2.63 – 2.61 (m, 1H, H-3β_A), 2.53 (dd, $J =$ 15.8, 6.2 Hz, 1H, H-3β_B), 1.72 – 1.71 (m, 1H, H-1γ), 1.50 (s, 9H, *t*BuO), 1.43 – 1.40 (m, 2H, H-1β), 0.93 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.84 (d, $J = 6.4$ Hz, 3H, H-1δ), 0.82 (d, $J = 4.4$ Hz, 3H, H-1δ'), 0.13 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta = 172.2, 171.6, 171.4, 170.7, 170.4, 170.3, 168.8, 161.2, 159.6, 158.1, 154.0, 153.8, 151.7, 151.0, 142.0, 140.3, 139.7, 138.2, 136.1, 135.6, 135.5, 135.1, 129.5, 129.3, 129.0, 128.5, 128.3, 127.8, 127.7, 127.5, 126.4, 125.3, 125.1, 124.6, 122.5, 114.6, 114.5, 113.8, 107.2, 106.3, 106.0, 98.8, 80.5, 74.7, 74.1, 64.3, 63.8, 61.2, 60.1, 57.2, 56.5, 56.1, 56.1, 56.0, 55.7, 55.5, 55.4, 52.5, 39.7, 37.4, 30.5, 28.7, 26.3, 26.2, 25.5, 23.6, 22.3, 19.0, -4.6, -4.9$; HRMS (FAB) calcd for $C_{89}H_{112}Cl_2N_8O_{20}Si_2Cs$ $[M + Cs^+]$ 1871.5963, found 1871.5840.

Natural tricyclic methyl ester 45a: $NaHCO_3$ (1.3 mg, 0.015 mmol) and Dess – Martin periodinane reagent (4.8 mg, 0.011 mmol) were added to a solution of natural tricyclic alcohol **44a** (13 mg, 0.0075 mmol) in CH_2Cl_2 (2.5 mL). After 0.5 h at 25 °C, EtOAc (4 mL) and saturated aqueous $NaHCO_3$ (containing 300 mg of $Na_2S_2O_3 \cdot 5H_2O$) (4 mL), were added. The reaction mixture was allowed to stir vigorously for 0.5 h and then EtOAc (4 mL) was added. The organic layer was washed sequentially with saturated aqueous $NaHCO_3$ (1.5 mL) and H_2O (1.5 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in *t*BuOH (2.5 mL), and warmed to 30 °C. 5 % Aqueous NaH_2PO_4 (0.7 mL) and 1M aqueous $KMnO_4$ (1 mL) were added, and the reaction mixture was stirred vigorously at 30 °C for 1.5 h. EtOAc (20 mL) was added and the reaction mixture was cooled to 0 °C. Saturated aqueous Na_2SO_3 was added dropwise under vigorous stirring in order to reduce excess of $KMnO_4$ to MnO_2 (purple color to brown). Then, a cooled 4 % aqueous solution of HCl was added to adjust the pH to 3, at 0 °C. The aqueous phase was extracted with EtOAc ($3 \times$ 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was treated with a solution of CH_2N_2 for 12 h at 25 °C. The reaction mixture was concentrated, and the residue was purified by preparative TLC (silica gel, 5 % MeOH in CH_2Cl_2) to afford natural tricyclic methylester **45a** (11.8 mg, 89 %). **45a**: $R_f = 0.40$ (silica gel, 5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +5.8$ ($c = 0.12$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 3405, 2954, 2856, 1671, 1583, 1508, 1488, 1420, 1391, 1365, 1323, 1247, 1203, 1176, 1157, 1111, 1061, 1024, 838, 781 cm^{-1}; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.60 - 7.57$ (m, 1H, H-2b), 7.57 (br. s, 1H, H-6b), 7.52 (dd, $J = 8.3$, 1.3 Hz, 1H, H-6f), 7.34 (br. s, 1H, H-2f), 7.25 (d, $J = 8.3$ Hz, 1H, H-6e), 7.08 (br. d, $J = 7.0$ Hz, 1H, H-2e), 7.01 (d, $J = 2.2$ Hz, 1H, H-5b), 6.98 (d, $J =$ 8.8 Hz, 2H, ArH (Ddm)), 6.96 (br. d, $J = 8.5$ Hz, 1H, H-5f), 6.88 (br. d, $J =$ 8.3 Hz, 3H, H-5e and ArH (Ddm)), 6.82 (d, $J = 8.8$ Hz, 2H, ArH (Ddm)), 6.71 (br. d, $J = 8.8$ Hz, 2H, ArH (Ddm)), 6.63 (d, $J = 2.2$ Hz, 1H, H-7d), 6.36 (d, $J = 2.2$ Hz, 1H, H-7f), 5.84 (br. s, 2H, H-4b and NHC*H* (Ddm)), 5.72 (br. s, 1H, H-4f), 5.52 (d, $J = 4.9$ Hz, 1H, H-2β), 5.43 (br. s, 1H, H-4α), 5.36 (br. s, 1H, H-6β), 4.92 – 4.88 (m, 2H, H-2α and H-3α), 4.82 (br. s, 1H, H-7a), 4.76 – 4.73 (m, 1H, H-1α), 4.54 (br. s, 1H, H-5α), 4.16 (s, 3H, OCH_3), 4.06 (br. s, 1H, H-6α), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 2.64-2.60 (m, 1H, H-3β_A), 2.57 (dd, $J = 15.8$, 5.7 Hz, 1H, H-3β_B), 1.75 – 1.70 (m, 1H, H-1γ), 1.47 (br. s, 9H, *t*BuO), 1.38 – 1.34 (m, 2H, H-1β), 0.91 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.84 (d, $J = 6.1$ Hz, 3H, H-1δ), 0.79 (d, $J = 6.1$ Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.08 (s, 6H, CH_3Si), 0.07 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3CN, 335 K): $\delta =$ 172.9, 172.1, 171.9, 171.6, 171.1, 169.6, 168.3, 161.8, 160.3, 160.1, 158.8, 154.9, 153.7, 152.0, 151.8, 141.9, 140.4, 138.8, 137.0, 136.2, 135.8, 135.6, 135.6, 130.5, 129.8, 129.7, 129.3, 128.5, 128.1, 126.9, 125.4, 124.9, 122.5, 115.3, 115.2, 115.0, 107.0, 106.4, 106.3, 100.2, 81.1, 74.7, 74.3, 64.9, 62.2, 61.1, 60.6, 58.1, 57.2, 57.0, 56.9, 56.6, 56.2, 56.0, 55.8, 53.1, 52.5, 39.9, 37.8, 30.7, 29.2, 26.8, 26.7, 25.8, 23.8, 22.4, 19.3, 19.2, -4.1, -4.2, -4.4, -4.5; HRMS (MALDI-FTMS) calcd for $C_{90}H_{112}Cl_2N_8O_{21}Si_2Na$ $[M + Na^+]$ 1789.6755, found 1789.6784.

Unnatural tricyclic methyl ester 45b: $NaHCO_3$ (1.7 mg, 0.02 mmol) and Dess – Martin periodinane reagent (6.4 mg, 0.015 mmol) were added to a solution of alcohol **44b** (17.4 mg, 0.01 mmol) in CH_2Cl_2 (2.5 mL). After 0.5 h at 25 °C, EtOAc (5 mL) and saturated aqueous $NaHCO_3$ (containing 380 mg of $Na_2S_2O_3 \cdot 5H_2O$) (5 mL) were added. The reaction mixture was allowed to stir vigorously for 0.5 h and then EtOAc (5 mL) was added. The organic layer was washed sequentially with saturated aqueous $NaHCO_3$ (2 mL) and H_2O (2 mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in *t*BuOH (3.5 mL) and warmed to 30 °C. 5 % Aqueous NaH_2PO_4 (0.9 mL) and 1M aqueous $KMnO_4$ (1.3 mL) were added, and the reaction mixture was stirred vigorously at 30 °C for 1.5 h. EtOAc (25 mL) was added, and the reaction mixture was cooled to 0 °C. Saturated aqueous Na_2SO_3 was added dropwise under vigorous stirring in order to reduce excess of $KMnO_4$ to MnO_2 (purple color to brown). Then, a cooled 4 % aqueous solution of HCl was added to adjust the pH to 3, at 0 °C. The aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the residue was treated with a solution of CH_2N_2 in ether for 12 h at 25 °C. The reaction mixture was concentrated, and the residue was purified with preparative TLC (silica gel, 5 % MeOH in CH_2Cl_2) to afford unnatural tricyclic methyl ester **45b** (14.8 mg, 84 %). **45b**: $R_f = 0.36$ (silica gel, 5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -7.0$ ($c = 0.43$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3300, 2953, 2930, 2857, 1681, 1667, 1660, 1651, 1512, 1505, 1486, 1250, 838, 780\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.77 - 7.75$ (m, 1H, H-2b), 7.58 (d, $J =$ 1.9 Hz, 1H, H-6b), 7.48 (dd, $J = 8.3$, 1.8 Hz, 1H, H-6f), 7.23 (d, $J = 8.3$ Hz, 1H, H-2e), 7.20 (br. d, $J = 8.2$ Hz, 1H, H-2f), 7.03 (d, $J = 8.0$ Hz, 1H, H-6e), 7.00 – 6.98 (m, 4H, H-5b, H-5f and ArH (Ddm)), 6.91-6.90 (m, 3H, H-5e and ArH (Ddm)), 6.82 (d, $J = 8.5$ Hz, 2H, ArH (Ddm)), 6.72 (d, $J = 8.7$ Hz, 2H, ArH (Ddm)), 6.40 (d, $J = 2.2$ Hz, 1H, H-7d), 6.35 (d, $J = 2.2$ Hz, 1H, H-7f), 5.95 (br. s, 1H, H-4b), 5.85 (br. s, 1H, NHC*H* (Ddm)), 5.80 (br. s, 1H, H-4f), 5.54 (d, $J = 4.8$ Hz, 1H, H-2β), 5.42 (br. s, 1H, H-4α), 5.36 (br. s, 1H, H-6β), 4.88 – 4.86 (m, 2H, H-2α and H-3α), 4.81 (s, 1H, H-7α), 4.81 – 4.77 (m, 1H, H-1α), 4.58 (br. s, 1H, H-5α), 4.20 (s, 3H, 4d-OCH_3), 4.05 (br. s, 1H, H-6α), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.78 (s, 3H, NCH_3), 2.63 – 2.60 (m, 1H, H-3β_A), 2.51 (dd, $J = 15.0$, 5.5 Hz, 1H, H-3β_B), 1.70 – 1.69 (m, 1H, H-1γ), 1.50 (s, 9H, *t*BuO), 1.39 – 1.38 (m, 1H, H-1β_A), 1.29 – 1.27 (m, 1H, H-1β_B), 0.91 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.84 (d, $J = 6.3$ Hz, 3H, H-1δ), 0.81 (d, $J = 6.1$ Hz, 3H, H-1δ'), 0.12 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si); ^{13}C NMR (150 MHz, CD_3COCD_3, 323 K): $\delta = 172.2, 171.8, 171.6, 170.7, 170.4, 168.7, 161.2, 160.1, 159.6, 158.2, 153.9, 153.7, 151.6, 151.0, 142.0, 140.3, 138.1, 137.7, 137.1, 136.2, 135.4, 135.1, 129.5, 129.5, 129.1, 129.0, 128.5, 128.2, 128.0, 127.5, 126.4, 124.6, 124.3, 122.3, 114.6, 114.5, 113.8, 107.3, 106.1, 105.9, 99.3, 80.5, 74.5, 74.1, 69.4, 64.0, 61.1, 60.1, 57.6, 56.5, 56.2, 56.1, 55.8, 55.5, 52.5, 52.2, 39.6, 37.4, 30.4, 28.7, 26.3, 26.2, 25.5, 23.6, 22.3, 19.0, 18.9, -4.7, -4.8, -4.9$; HRMS (MALDI-FTMS) calcd for $C_{90}H_{112}Cl_2N_8O_{21}Si_2Na$ $[M + Na^+]$ 1791.6726, found 1791.6737.

Trimethylated *N*-Cbz-vancomycin aglycon methyl ester 46: Vancomycin hydrochloride, **1** · HCl, (0.50 g, 0.35 mmol) in MeOH (10 mL) was treated with CbzCl (0.25 mL, 1.75 mmol) at 25 °C for 0.5 h. Then, 15 % aqueous NaOH was slowly added to the reaction mixture to adjust the pH to 7. The reaction mixture was stirred for 0.5 h, filtered through a pad of silica gel, and concentrated. The residue was triturated with CH_2Cl_2, and dried in vacuo to afford *N*-Cbz-vancomycin as a crude residue. A solution of the crude *N*-Cbz-vancomycin in DMF (1 mL) was treated sequentially with Cs_2CO_3 (0.91 g, 2.8 mmol) and MeI (0.43 mL, 6.90 mmol) at 0 °C. The reaction mixture was slowly warmed to 25 °C and stirred for 20 h. The reaction mixture was dried in vacuo to afford trimethylated *N*-Cbz-vancomycin methyl ester as a crude residue. A solution of the crude trimethylated *N*-Cbz-vancomycin methyl ester in CH_2Cl_2 (5 mL) was treated with trifluoroacetic acid (5 mL) and the resulting solution was stirred at 50 °C for 1 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 0 →5 % MeOH in CH_2Cl_2, gradient elution) to afford trimethylated *N*-Cbz-

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vancomycin aglycon methyl ester **46** (180 mg, 39% overall from **1**·HCl). **46**: $R_f = 0.32$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +40.0$ ($c = 0.28$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3397, 2956, 1735, 1670, 1508, 1490, 1437, 1400, 1322, 1233, 1177, 1159, 1081, 1060, 1009\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 323 K): $\delta = 7.62$ (d, $J = 2.0$ Hz, 1H), 7.58 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.43 (br.s, 1H), 7.38–7.30 (m, 6H), 7.23 (d, $J = 8.5$ Hz, 1H), 7.17–7.12 (m, 2H), 7.05 (d, $J = 2.5$ Hz, 1H), 6.97 (d, $J = 9.0$ Hz, 1H), 6.70 (d, $J = 2.0$ Hz, 1H), 6.38 (d, $J = 2.0$ Hz, 1H), 5.72 (s, 1H), 5.71 (d, $J = 2.0$ Hz, 1H), 5.40 (s, 1H), 5.37 (br.s, 1H), 5.32 (s, 1H), 5.20 (br.s, 3H), 4.93 (br.d, $J = 4.5$ Hz, 1H), 4.85 (br.s, 1H), 4.80 (s, 1H), 4.64 (s, 1H), 4.13 (br.s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 2.96 (s, 3H), 2.62 (br.s, 1H), 2.37 (dd, $J =$ 15.5, 7.0 Hz, 1H), 1.78–1.76 (m, 1H), 1.64–1.63 (m, 1H), 1.52 (br.s, 1H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.93-0.88 (m, 3H); ^{13}C NMR (150 MHz, CD_3COCD_3, 315 K): $\delta = 172.1$, 171.9, 171.3, 170.1, 168.8, 161.2, 160.1, 158.2, 158.0, 151.9, 151.0, 148.7, 142.2, 138.0, 136.7, 136.6, 135.9, 135.4, 129.5, 129.3, 129.2, 128.9, 128.7, 128.4, 128.0, 127.6, 127.2, 125.7, 125.4, 124.9, 124.1, 122.3, 113.8, 108.1, 105.9, 105.7, 99.3, 73.2, 72.5, 68.2, 68.0, 63.7, 59.7, 58.2, 57.8, 56.3, 56.2, 56.1, 55.8, 55.2, 52.5, 37.3, 31.0, 25.5, 25.4, 23.6, 22.2; HRMS (FAB) calcd for $C_{65}H_{66}Cl_2N_8O_{19}Cs$ $[M + Cs^+]$ 1465.2876, found 1465.2962.

Tetramethylated *N*-Cbz-vancomycin aglycon methyl ester 47: A solution of trimethylated *N*-Cbz-vancomycin aglycon methyl ester **46** (80 mg, 0.06 mmol) in DMF (0.4 mL) was treated sequentially with K_2CO_3 (83 mg, 0.60 mmol) and MeI (37 μL, 0.60 mmol) at 0 °C. The reaction mixture was slowly warmed to 25 °C and stirred for 1 h. The reaction mixture was dried in vacuo, and the residue was purified by flash column chromatography (silica gel, 2 → 5% MeOH in CH_2Cl_2, gradient elution) to afford tetramethylated *N*-Cbz-vancomycin aglycon methyl ester **47** (79 mg, 98%). **47**: $R_f = 0.34$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +27.7$ ($c =$ 1.1, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3387, 2952, 1668, 1505, 1412, 1320, 1233, 1060, 1022\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.58$ (s, 1H), 7.58 (br.d, $J = 8.5$ Hz, 1H), 7.44 (br.s, 1H), 7.35–7.26 (m, 6H), 7.13 (br.s, 1H), 7.07 (br.d, $J = 8.5$ Hz, 1H), 7.02 (d, $J = 2.0$ Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.95 (d, $J = 8.5$ Hz, 1H), 6.67 (d, $J = 2.0$ Hz, 1H), 6.35 (d, $J = 2.0$ Hz, 1H), 5.85 (s, 1H), 5.70 (s, 1H), 5.40 (s, 1H), 5.33 (br.s, 1H), 5.29 (s, 1H), 5.17 (br.s, 3H), 4.93 (br.d, $J = 4.0$ Hz, 1H), 4.82 (br.s, 1H), 4.76 (s, 1H), 4.61 (s, 1H), 4.15 (s, 3H), 4.11 (br.s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 2.93 (s, 3H), 2.65 (br.s, 1H), 2.35 (dd, $J = 15.5$, 7.0 Hz, 1H), 1.77–1.74 (m, 1H), 1.64–1.62 (m, 1H), 1.49 (br.s, 1H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.88 (br.s, 3H); ^{13}C NMR (150 MHz, CD_3OD, 330 K): $\delta = 173.3$, 172.9, 171.7, 171.1, 170.9, 169.5, 161.4, 160.0, 158.4, 153.6, 153.5, 152.3, 150.8, 142.1, 138.0, 137.4, 136.3, 136.2, 134.4, 129.7, 129.5, 129.0, 128.3, 128.1, 128.0, 127.7, 127.6, 125.0, 124.4, 124.3, 122.1, 113.6, 107.9, 105.9, 99.1, 93.9, 72.4, 71.9, 68.4, 64.1, 61.4, 60.1, 58.3, 57.7, 56.0, 55.9, 55.6, 55.2, 52.4, 52.3, 37.0, 30.4, 25.4, 23.0, 21.4; HRMS (FAB) calcd for $C_{66}H_{68}Cl_2N_8O_{19}Cs$ $[M + Cs^+]$ 1479.3032, found 1479.3110.

Tetramethylated *N*-Cbz-di-TBS-vancomycin aglycon methyl ester 48: A solution of tetramethylated *N*-Cbz-vancomycin aglycon methyl ester **47** (104 mg, 0.077 mmol) in CH_2Cl_2 (2 mL) was treated sequentially with 2,6-lutidine (0.2 mL, 0.87 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.1 mL, 0.86 mmol) at −10 °C. The resulting mixture was stirred at −10 °C for 0.5 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 30 → 80% EtOAc in hexanes; then 5% MeOH in CH_2Cl_2, gradient elution) to afford tetramethylated *N*-Cbz-di-TBS-vancomycin aglycon methyl ester **48** (98 mg, 80%). **48**: $R_f = 0.29$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = +11.9$ ($c = 0.32$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3398, 2929, 2855, 1750, 1654, 1609, 1583, 1508, 1489, 1420, 1323, 1234, 1203, 1159, 1111, 1062, 1025, 839, 782\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.65$ (br.s, 1H), 7.54 (s, 1H), 7.49 (br.d, $J = 8.5$ Hz, 1H), 7.34–7.28 (m, 7H), 7.11 (d, $J = 2.0$ Hz, 1H), 7.00–6.97 (m, 2H), 6.67 (d, $J =$ 2.0 Hz, 1H), 6.54 (br.s, 1H), 6.38 (d, $J = 2.0$ Hz, 1H), 6.08 (br.s, 1H), 5.75 (s, 1H), 5.52 (d, $J = 4.5$ Hz, 1H), 5.43 (s, 1H), 5.36 (s, 1H), 5.21 (br.s, 3H), 4.98 (d, $J = 4.5$ Hz, 1H), 4.83–4.81 (m, 1H), 4.82 (s, 1H), 4.59 (s, 1H), 4.21 (s, 3H), 4.07 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 2.95 (s, 3H), 2.49 (br.s, 1H), 2.36 (dd, $J = 15.5$, 5.5 Hz, 1H), 1.82–1.80 (m, 1H), 1.53–1.50 (m, 2H), 0.93 (s, 9H), 0.90 (d, $J = 6.0$ Hz, 3H), 0.87 (s, 18H), 0.13 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR [150 MHz, $CD_3OD/CDCl_3$ (10:1), 330 K] $\delta = 174.6$, 173.6, 172.6, 171.9, 171.6, 171.4, 169.9, 169.0, 161.8, 160.2, 158.8, 154.7, 153.7, 152.9, 151.8, 141.8, 139.8, 139.0, 137.6, 136.8, 136.6, 134.9, 130.4, 130.2, 129.5, 128.9, 128.3, 128.2, 128.0, 127.4, 125.6, 124.9, 124.8, 122.4, 114.1, 108.1, 107.3, 106.5, 106.3, 99.6, 74.6, 73.6, 68.8, 64.9, 62.2, 60.5, 58.1, 57.9, 56.5, 56.4, 56.1, 55.8, 55.7, 52.7, 52.3, 37.7, 30.6, 26.5, 26.3, 25.7, 23.7, 21.8, 19.2, 18.9, −4.5, −4.7, −4.8, −4.9; HRMS (FAB) calcd for $C_{78}H_{96}Cl_2N_8O_{19}Si_2Cs$ $[M + Cs^+]$ 1707.4762, found 1707.4844.

Tetramethylated *N*-Cbz-*N*-Ddm-di-TBS-vancomycin aglycon methyl ester 49: A solution of tetramethylated *N*-Cbz-di-TBS-vancomycin aglycon methyl ester **48** (33 mg, 0.021 mmol) in AcOH (2.1 mL) was treated sequentially with 4,4′-dimethoxy benzhydrol (0.5 g, 2.0 mmol) and H_2SO_4 (1.0 M solution in AcOH, 0.1 mL, 0.1 mmol) at 0 °C. The reaction mixture was slowly warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with EtOAc (10 mL), washed with H_2O (10 mL × 3), and neutralized by the addition of saturated aqueous $NaHCO_3$ (10 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 5 → 80% EtOAc in hexanes, gradient elution) to afford tetramethylated *N*-Cbz-*N*-Ddm-di-TBS-vancomycin aglycon methyl ester **49** (29 mg, 76%). **49**: $R_f = 0.34$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -2.3$ ($c =$ 0.52, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3405, 2954, 2856, 1670, 1506, 1490, 1247, 1176, 1111, 1061, 1025, 838\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN, 340 K): $\delta =$ 9.03 (br.s, 1H), 7.54 (br.s, 1H), 7.48 (s, 1H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.37–7.07 (m, 10H), 7.03 (d, $J = 8.5$ Hz, 2H), 6.89–6.82 (m, 1H), 6.87 (d, $J =$ 8.5 Hz, 2H), 6.83 (d, $J = 8.5$ Hz, 2H), 6.70 (d, $J = 2.0$ Hz, 1H), 6.59 (br.s, 1H), 6.40 (d, $J = 2.0$ Hz, 1H), 6.30–6.10 (m, 2H), 5.88 (d, $J = 7.5$ Hz, 1H), 5.77 (s, 1H), 5.51 (d, $J = 4.5$ Hz, 1H), 5.48 (s, 1H), 5.34 (s, 1H), 5.17 (br.s, 2H), 4.94–4.91 (m, 1H), 4.91 (br.s, 1H), 4.84–4.81 (m, 1H), 4.76 (d, $J =$ 6.5 Hz, 1H), 4.56 (d, $J = 5.0$ Hz, 1H), 4.21 (s, 3H), 3.94 (d, $J = 12.0$ Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.62 (s, 3H), 2.95 (s, 3H), 2.55–2.51 (m, 1H), 2.47–2.44 (m, 1H), 1.78–1.71 (m, 1H), 1.55–1.49 (m, 2H), 0.94 (s, 9H), 0.92 (s, 9H), 0.89 (d, $J = 5.5$ Hz, 3H), 0.83 (br.s, 3H), 0.12 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN, 340 K): $\delta = 172.6$, 172.1, 171.9, 171.5, 171.1, 169.5, 168.3, 161.9, 160.4, 160.2, 158.8, 154.9, 153.7, 152.1, 151.8, 142.0, 140.4, 138.8, 138.5, 137.1, 136.3, 135.7, 135.6, 130.5, 129.7, 129.7, 129.6, 129.4, 129.3, 129.1, 128.6, 128.3, 128.2, 127.0, 125.5, 125.0, 122.5, 115.3, 115.2, 115.0, 107.2, 106.4, 100.2, 74.7, 74.2, 68.4, 64.9, 62.2, 60.7, 58.1, 57.2, 57.1, 56.9, 56.6, 56.2, 56.1, 55.9, 53.1, 52.5, 39.9, 37.9, 31.4, 30.5, 26.6, 26.5, 25.9, 23.7, 22.4, 19.3, 19.2, −4.2, −4.3, −4.5; HRMS (FAB) calcd for $C_{93}H_{110}Cl_2N_8O_{21}Si_2Cs$ $[M + Cs^+]$ 1935.5771, found 1935.5665.

Tetramethylated *N*-Ddm-di-TBS-vancomycin aglycon methyl ester 50: A solution of tetramethylated *N*-Cbz-*N*-Ddm-di-TBS-vancomycin aglycon methyl ester **49** (45 mg, 0.025 mmol) in MeOH/EtOAc (2:1) (3 mL) was treated with 10% Pd-C (5 mg) at 25 °C under H_2. The reaction mixture was stirred for 2 h. Then it was filtered through celite, concentrated, and dried in vacuo to afford tetramethylated *N*-Ddm-di-TBS-vancomycin aglycon methyl ester **50** (41 mg) as a crude residue.

Tetramethylated *N*-Ddm-di-TBS-vancomycin aglycon alcohol 51: A solution of crude tetramethylated *N*-Ddm-di-TBS-vancomycin aglycon methyl ester **50** (41 mg) in THF (1.5 mL) was treated with DIBAL/*n*BuLi (1:1) ate complex (1.5 M solution in THF, 0.2 mL, 0.3 mmol) at −10 °C. The reaction mixture was stirred for 0.5 h. A solution of $NaBH_4$ (19 mg, 0.50 mmol) in THF/H_2O (1:1, 2.3 mL) was added and the reaction mixture was slowly warmed at 25 °C and stirred for 1 h. The reaction mixture was diluted with EtOAc (60 mL), filtered through celite, dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 20–80% EtOAc in hexanes, gradient elution) to afford tetramethylated *N*-Ddm-di-TBS-vancomycin aglycon alcohol **51** (28 mg, 65%). **51**: $R_f = 0.66$ (silica gel, EtOAc); $[\alpha]_D^{22} = -38.3$ ($c = 0.23$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3402, 2954, 2856, 1670, 1609, 1584, 1509, 1246, 1176, 1108, 1061, 1028, 838\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN, 330 K): $\delta = 8.70$ (br.s, 1H), 8.06 (br.s, 1H), 7.57 (s, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.26 (d, $J =$ 8.0 Hz, 1H), 7.18-7.05 (m, 7H), 6.96 (s, 1H), 6.86 (d, $J = 8.5$ Hz, 2H), 6.81 (d, $J = 8.5$ Hz, 2H), 6.62 (s, 1H), 6.57 (br.s, 1H), 6.48 (br.s, 1H), 5.94–5.91 (m, 2H), 5.81 (s, 1H), 5.57–5.53 (m, 1H), 5.47 (s, 1H), 5.21 (br.s, 1H), 4.92–4.68 (m, 3H), 4.40 (br.s, 2H), 4.14 (s, 3H), 4.11-4.10 (m, 3H), 3.89 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 2.91–2.88 (m, 1H), 2.79 (br.s, 1H), 2.30 (s, 3H), 1.75–1.73 (m, 1H), 1.51–1.41 (m, 2H), 0.98 (s, 9H), 0.96 (s, 9H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 6.5$ Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz,

CD_3CN, 330 K): $\delta = 175.4$, 172.2, 171.0, 168.8, 168.6, 161.0, 159.8, 159.2, 158.1, 153.7, 151.2, 150.9, 142.0, 140.8, 139.3, 137.9, 135.3, 135.1, 134.9, 130.0, 129.2, 129.1, 128.9, 128.7, 128.1, 127.6, 126.5, 125.8, 125.0, 121.9, 114.8, 114.8, 114.0, 105.8, 98.5, 73.6, 65.6, 61.6, 56.8, 56.6, 56.5, 56.2, 56.0, 55.8, 55.8, 54.6, 52.6, 43.4, 38.5, 35.9, 30.1, 26.2, 25.7, 23.6, 23.1, 21.7, 18.8, −4.3, −4.5, −4.8, −5.1; HRMS (FAB) calcd for $C_{84}H_{104}Cl_2N_8O_{18}Si_2Cs$ $[M + Cs^+]$ 1771.5439, found 1771.5310.

Tetramethylated *N*-Boc-*N*-Ddm-di-TBS-vancomycin aglycon alcohol 44a (from degradation): A solution of tetramethylated *N*-Ddm-di-TBS-vancomycin aglycon alcohol **51** (28 mg, 0.0165 mmol) in MeOH/CH_2Cl_2 (1:1, 1.9 mL) was treated sequentially with Boc_2O (25 mg, 0.116 mmol) and triethylamine (42.5 μL, 0.116 mmol) at 0 °C, and the reaction mixture was stirred for 20 min. Then, it was diluted with CH_2Cl_2 (20 mL), and washed with H_2O (50 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 5 → 60 % EtOAc in hexanes, gradient elution) to afford tetramethylated *N*-Boc-*N*-Ddm-di-TBS-vancomycin aglycon alcohol **44a** (26.7 mg, 93 %).

Tetramethylated *N*-Boc-*N*-Ddm-di-TBS-vancomycin aglycon methyl ester 45a (from degradation): A solution of crude tetramethylated *N*-Ddm-di-TBS-vancomycin aglycon methyl ester **50** (41 mg) in dioxane/H_2O (10:1) (1 mL) was treated with Boc_2O (27 mg, 0.125 mmol) at 25 °C. The reaction mixture was stirred for 6 h, cooled at 0 °C, and then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 5 → 80 % EtOAc in hexanes, gradient elution) to afford tetramethylated *N*-Boc-*N*-Ddm-di-TBS-vancomycin aglycon methyl ester **45a** (40 mg, 90 %).

Atropisomerization of unnatural tricyclic triazene 3b to natural tricyclic triazene 3a and vice versa: A solution of unnatural tricyclic triazene **3b** or natural tricyclic triazene **3a** (10 mg, 0.005 mmol) in freshly distilled and thoroughly degassed 1,2-dichlorobenzene (2.5 mL) was heated under Ar at 140 °C for 4 h. The reaction mixture was concentrated, and the residue was purified by preparative TLC (silica gel, 5 % MeOH in CH_2Cl_2). By using unnatural atropisomer **3b** as starting material, natural atropisomer **3a** (3.3 mg, 33 %) and recovered unnatural atropisomer **3b** (4.7 mg, 47 %) were isolated in a ratio of 41:59. Using natural atropisomer **3a** as starting material, unnatural atropisomer **3b** (3.2 mg, 32 %) and recovered natural atropisomer **45a** (5.2 mg, 52 %) were isolated in a ratio of 38:62.

Atropisomerization of unnatural methyl ester 45b to natural methyl ester 45a and vice versa: A solution of unnatural methyl ester **45b** or natural methyl ester **45a** (10 mg, 0.0057 mmol) in freshly distilled and thoroughly degassed 1,2-dichlorobenzene (2.5 mL) was heated under Ar at 130 °C for 8 h. The reaction mixture was concentrated and the residue was purified by preparative TLC (silica gel, 3 % MeOH in CH_2Cl_2). By using unnatural atropisomer **45b** as starting material, natural atropisomer **45a** (3.5 mg, 35 %) and recovered unnatural atropisomer **45b** (4.7 mg, 47 %) were isolated in a ratio of 43:57. By using natural atropisomer **45a** as starting material, unnatural atropisomer **45b** (4 mg, 40 %) and recovered natural atropisomer **45a** (4.7 mg, 47 %) were isolated in a ratio of 46:54.

Vancomycin aglycon 2 (one-step deprotection): Aluminium tribromide (31 mg, 0.118 mmol) was added to 1,2-dibromoethane (0.1 mL) and the resulting mixture was stirred for 10 min at 25 °C. Ethanethiol (0.2 mL) was added, and the mixture was vigorously stirred for 10 min at 25 °C. Then, a solution of fully protected vancomycin aglycon **45a** (5.2 mg, 0.00294 mmol) in CH_2Cl_2 (0.2 mL) was added, and the mixture was stirred for 4 h at 25 °C. EtOAc (10 mL) was added, and the reaction was quenched by the addition of MeOH (1 mL). After 0.5 h of vigorous stirring at 25 °C, the reaction mixture was dried (Na_2SO_4), concentrated at 25 °C, and the residue was purified by preparative HPLC [rt = 28.9 min, gradient: 0 – 20 min, MeCN/H_2O (+0.1 % TFA) (5:95 → 30:70); 20 – 30 min, MeCN/H_2O (+0.1 % TFA) (30:70 → 60:40), RP C18, 9 mL min^{-1}] to afford vancomycin aglycon **2** (1.0 mg, 30 %).

Vancomycin aglycon 2 (two-step deprotection, with *n*Bu$_4$NF): A solution of fully protected vancomycin aglycon **45a** (4.8 mg, 0.00271mmol) in THF (0.25 mL) was treated with tetra-*n*-butylammonium fluoride (TBAF, 1.0 M solution in THF, 0.14 mL, 0.14 mmol) and AcOH (80 μL, 0.14 mmol) for 48 h at 25 °C. Then, the reaction mixture was cooled to 0 °C, quenched by the addition of H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to afford crude diol **52**. Aluminum tribromide (29 mg, 0.108 mmol) was added to 1,2-dibromoethane (0.1 mL), and the resulting mixture was stirred for 10 min at 25 °C. Ethanethiol (0.2 mL) was added, and the mixture was vigorously stirred for 10 min at 25 °C. Then, a solution of crude diol **52** in CH_2Cl_2 (0.2 mL) was added, and the mixture was stirred for 4 h at 25 °C. EtOAc (10 mL) was added, and the reaction was quenched by the addition of MeOH (1 mL). After 0.5 h of vigorous stirring at 25 °C, the reaction mixture was dried (Na_2SO_4), concentrated at 25 °C, and the residue was purified by HPLC [rt = 28.9 min, gradient: 0 – 20 min, MeCN/H_2O (+0.1 % TFA) (5:95 → 30:70); 20 – 30 min, MeCN/H_2O (+0.1 % TFA) (30:70 → 60:40), RP C18, 9 mL min^{-1}] to afford vancomycin aglycon **2** (1.3 mg, 43 % overall from **45a**).

Vancomycin aglycon 2 (two-step deprotection, with HF · pyr.): A solution of fully protected vancomycin aglycon **45a** (5.0 mg, 0.00283 mmol) in THF (0.2 mL) in a polyethylene vial was cooled to 0 °C. Then, pyridine (0.1 mL) and HF · pyridine (0.1 mL) were added, and the reaction mixture was stirred for 12 h while the temperature was raised slowly to 25 °C. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL) and extracted with EtOAc (5 mL). The organic phase was washed with brine (1 mL), dried (Na_2SO_4), and concentrated to afford crude diol **52**. Aluminum tribromide (30 mg, 0.113 mmol) was added to 1,2-dibromoethane (0.1 mL) and the resulting mixture was stirred for 10 min at 25 °C. Ethanethiol (0.2 mL) was added, and the mixture was vigorously stirred for 10 min at 25 °C. Then, a solution of crude diol **52** in CH_2Cl_2 (0.2 mL) was added, and the mixture was left for 4 h at 25 °C. EtOAc (10 mL) was added, and the reaction was quenched by the addition of MeOH (1 mL). After 0.5 h of vigorous stirring at 25 °C, the reaction mixture was dried (Na_2SO_4), concentrated at 25 °C, and the residue was purified by HPLC [rt = 28.9 min, gradient: 0 – 20 min, MeCN/H_2O (+0.1 % TFA) (5:95 → 30:70); 20-30 min, MeCN/H_2O (+0.1 % TFA) (30:70 → 60:40), RP C18, 9 mL min^{-1}] to afford vancomycin aglycon **2** (2.0 mg, 62 % overall from **45a**). **2**: HPLC rt = 20.4 min [gradient: 0-20 min, MeCN/H_2O (+0.1 % TFA) (5:95 → 30:70); 20-24 min, MeCN/H_2O (+0.1 % TFA) (30:70), RP C18, 1 mL/min]; $[\alpha]_D^{22} = +65.4$ ($c = 0.22$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3304$, 2957, 2924, 1667, 1644, 1514, 1488, 1429, 1224, 1201, 1139, 1060, 1011, 839, 800, 718 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.75$ (d, $J = 8.8$ Hz, 1 H, H-6f), 7.70 (s, 1 H, H-2b), 7.63 (d, $J = 1.8$ Hz, 1 H, H-6b), 7.55 (d, $J = 7.9$ Hz, 1 H, H-6e), 7.51 – 7.48 (m, 1 H, H-2f), 7.16 (d, $J = 8.8$ Hz, 1 H, H-2e), 7.07 (d, $J = 1.8$ Hz, 1 H, H-5b), 6.70 – 6.67 (m, 2 H, H-5e and H-5f), 6.45 (d, $J = 2.2$ Hz, 1 H, H-7f), 6.43 (d, $J = 2.2$ Hz, 1 H, H-7d), 6.00 (s, 1 H, H-4α), 5.94 (br. s, 1 H, H-4f), 5.35 (br. s, 2 H, H-4b and H-6β), 5.26 (d, $J = 3.5$ Hz, 1 H, H-2β), 4.74 (s, 1 H, H-5α), 4.71 (s, 1 H, H-7α), 4.28 (d, $J = 7.9$ Hz, 1 H, H-3α), 4.16 (s, 1 H, H-6α), 3.98 (t, $J = 6.8$ Hz, 1 H, H-1α), 2.96 (br. d, $J = 15.8$ Hz, 1 H, H-3β_A), 2.77 (s, 3 H, NCH_3), 2.05 (dd, $J = 16.2$, 9.2 Hz, 1 H, H-3β_B), 1.85 – 1.83 (m, 1 H, H-1β_A), 1.70 – 1.63 (m, 2 H, H-1β_B and H-1γ), 0.92 (d, $J = 5.7$ Hz, 3 H, H-1δ), 0.91 (d, $J = 5.3$ Hz, 3 H, H-1δ'); ^{13}C NMR (150 MHz, CD_3OD, 323 K): $\delta = 175.1$, 174.2, 171.9, 171.3, 169.6, 168.8, 168.3, 158.7, 157.5, 156.0, 152.9, 151.1, 149.4, 147.9, 141.9, 140.4, 137.0, 136.7, 135.6, 129.7, 128.6, 128.2, 127.9, 127.4, 126.8, 125.0, 124.7, 121.7, 118.3, 118.0, 107.5, 106.1, 103.7, 73.7, 72.8, 63.5, 61.6, 59.3, 58.1, 56.0, 54.8, 52.3, 39.8, 35.9, 32.5, 25.0, 22.5, 22.2; HRMS (MALDI-FTMS) calcd for $C_{53}H_{53}Cl_2N_8O_{17}$ $[M + H^+]$ 1143.2906, found 1143.2911. **2** (from degradation): HPLC rt = 20.4 min [gradient: 0 – 20 min, MeCN/H_2O (+0.1 % TFA) (5:95 → 30:70); 20 – 24 min, MeCN/H_2O (+0.1 % TFA) (30:70), RP C18, 1 mL min^{-1}]; $[\alpha]_D^{22} = +70.0$ ($c = 0.22$, MeOH); IR (thin film): $\tilde{\nu}_{max} = 3294$, 3041, 2963, 2925, 1669, 1643, 1513, 1490, 1427, 1229, 1201, 1181, 1137, 1061, 1011, 840, 800, 720 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta = 8.85$ (d, $J = 6.5$ Hz, 1 H, NH partially exchanged), 8.60 (d, $J = 6.2$ Hz, 1 H, NH partially exchanged), 7.75 (d, $J = 8.8$ Hz, 1 H, H-6f), 7.70 (s, 1 H, H-2b), 7.64 (br. s, 1 H, H-6b), 7.55 (d, $J = 8.3$ Hz, 1 H, H-6e), 7.51 – 7.48 (m, 1 H, H-2f), 7.16 (d, $J = 8.3$ Hz, 1 H, H-2e), 7.07 (d, $J = 2.2$ Hz, 1 H, H-5b), 6.71-6.65 (m, 2 H, H-5e and H-5f), 6.45 (d, $J = 2.2$ Hz, 1 H, H-7f), 6.43 (d, $J = 2.2$ Hz, 1 H, H-7d), 6.00 (s, 1 H, H-4α), 5.94 (br. s, 1 H, H-4f), 5.35 (br. s, 2 H, H-4b and H-6β), 5.26 (d, $J = 3.5$ Hz, 1 H, H-2β), 4.74 (br. d, $J = 6.1$ Hz, 1 H, H-5α), 4.71 (br. s, 1 H, H-7α), 4.28 (d, $J = 7.4$ Hz, 1 H, H-3α), 4.16 (br. s, 1 H, H-6α), 3.98 (t, $J = 7.0$ Hz, 1 H, H-1α), 2.96 (br. d, $J = 14.0$ Hz, 1 H, H-3β_A), 2.77 (s, 3 H, NCH_3), 2.05 (dd, $J = 15.4$, 9.7 Hz, 1 H, H-3β_B), 1.86-1.83 (m, 1 H, H-1β_A), 1.70-1.63 (m, 2 H, H-1β_B and H-1γ), 0.92 (d, $J = 5.2$ Hz, 3 H, H-1δ), 0.91 (d, $J = 5.7$ Hz, 3 H, H-1δ'); HRMS (MALDI-FTMS) calcd for $C_{53}H_{53}Cl_2N_8O_{17}$ $[M + H^+]$ 1143.2906, found 1143.2940.

0947-6539/99/0509-2646 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 9

Acknowledgments

We thank Dr. D. H. Huang and Dr. G. Suizdak for NMR spectroscopic and mass spectrometric assistance, respectively. This work was financially supported by the National Institutes of Health, USA (AI38893), The Skaggs Institute for Chemical Biology, and grants from Pfizer, Schering Plough, Hoffmann La Roche, Merck, Boehringer Ingelheim, Abbott Laboratories and Glaxo.

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Received: March 29, 1999 [F 1707]