[9] Abbreviations: Tfa: trifluoroacetyl; TFA: trifluoroacetic acid; DMSO: dimethyl sulfoxide; Boc: *tert*-butoxycarbonyl; NOE: nuclear Overhauser effect; Tf: trifluoromethanesulfonyl; Ms: methanesulfonyl; Ac:acetyl; Ddm: 4,4Ödimethoxydiphenylmethyl; Bn: benzyl; DCB: 3,4-dichlorobenzyl; Piv: pivaloyl.
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Total Synthesis of Vancomycin Aglycon—Part 1: Synthesis of Amino Acids 4 – 7 and Construction of the AB-COD Ring Skeleton

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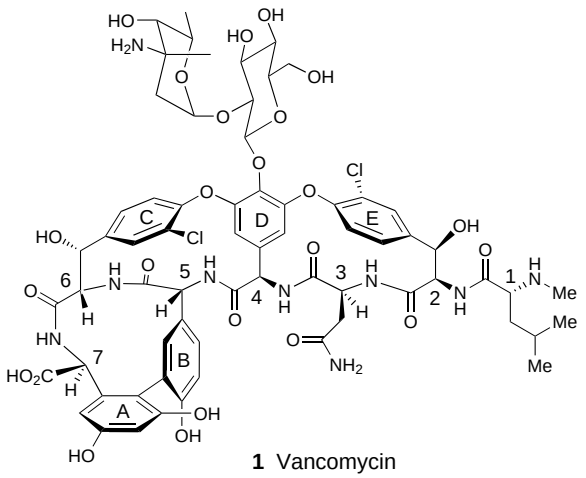
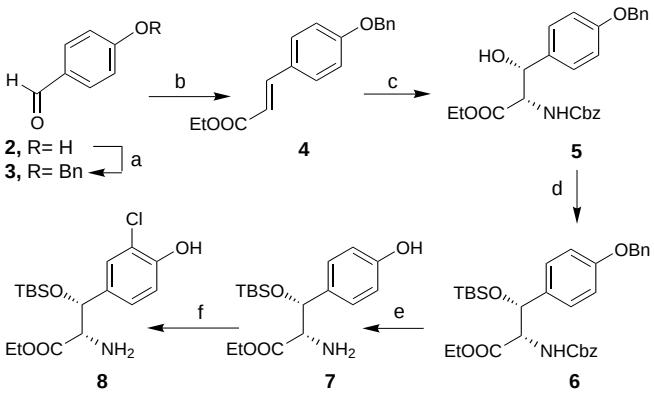
Vancomycin (**1**, Figure 1) is a clinically effective antibiotic used in cases of severe bacterial infections caused by several drug resistant pathogens.[1] Its medical importance and intriguing mode of action[2] coupled with its unusual molecular architecture[3] has fascinated synthetic chemists for some time.[4] Having established a number of new synthetic technologies and strategies aimed at this structural type,[5] we have recently focused our efforts on the total synthesis of **1**.[6] In this and the following communication,[7] we wish to report our progress and findings in the field, beginning with the stereoselective synthesis of amino acids 4 – 7 (compounds **8**, **22**, **27**, and **32**), the biaryl ring system (**35**), and the construction of the AB-COD skeleton (**46a**) of vancomycin.



1 Vancomycin

Figure 1. Molecular structure of vancomycin (**1**). The amino acids are labeled with numbers, and the aromatic rings with capital letters.

Scheme 1 outlines the synthesis of amino acid 6 in its protected form **8**. Thus, benzylation of 4-hydroxybenzaldehyde (**2**) with BnBr under basic conditions (98% yield),



Scheme 1. Reagents and conditions: a) K_2CO_3 (1.5 equiv), BnBr (1.0 equiv), KI (0.1 equiv), DMF, 25 °C, 12 h, 98%; b) $(EtO)_2(O)PCH_2COOEt$ (1.1 equiv), KOH (1.5 equiv), THF, 25 °C, 12 h, 95%; c) NaOH (3.0 equiv), $BnOCONH_2$ (3.1 equiv), *t*BuOCl (3.0 equiv), $(DHQD)_2AQN$ (0.05 equiv), $K_2[OsO_2(OH)_4]$ (0.04 equiv), *n*PrOH:H_2O (1:1), 25 °C, 12 h, 45% (87% *ee*); d) TBSOTf (1.1 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C, 0.5 h, 98%; e) H_2, $Pd(OH)_2$/C (0.01 equiv), MeOH, 0.5 h, 95%; f) SO_2Cl_2 (1.0 equiv), Et_2O (3.0 equiv), CH_2Cl_2, 0 °C, 1 h, 80%. Bn = benzyl; Cbz = benzyloxycarbonyl; TBS = *tert*-butyldimethylsilyl. TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate.

followed by olefination with the anion of $(EtO)_2(O)PCH_2COOEt$, furnished α,β-unsaturated ethyl ester **4** (95% yield) via compound **3**. Asymmetric aminohydroxylation (AA) according to the Sharpless protocol[8] gave directly the Cbz derivative (**5**) of the desired amino alcohol in 45% yield and

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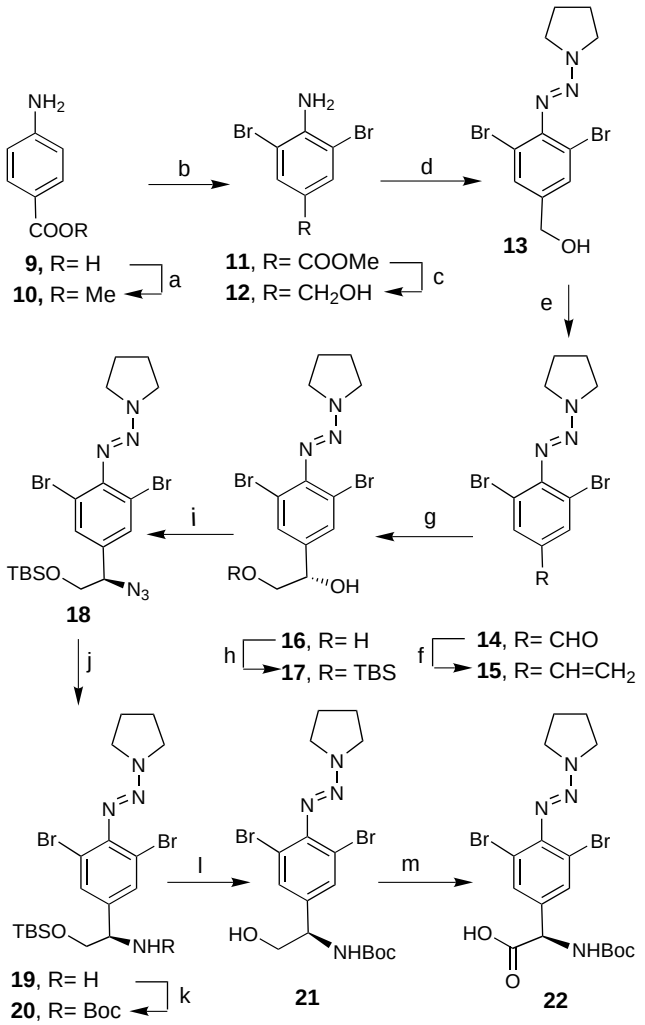
87% *ee*. The hydroxy group in **5** was then protected by exposure to TBSOTf and 2,6-lutidine (98% yield), and the resulting compound **6** was subjected to hydrogenolysis (H_2, 10% $Pd(OH)_2/C$), which caused cleavage of both the benzyl and Cbz groups, affording phenol **7** (95% yield). Finally, chlorination of **7** with SO_2Cl_2[9] resulted in the formation of the targeted intermediate **8** in 80% yield. This enantiomerically enriched fragment was coupled with pure fragment **35** and the diastereoisomers were separated (see Scheme 4).

The synthesis of the central amino acid (amino acid 4) equivalent **22** was carried out as shown in Scheme 2. Thus, 4-aminobenzoic acid (**9**) was methylated and thence brominated to afford dibromide **11** (98% overall yield) via methyl ester **10**. The ester group in **11** was reduced with $LiAlH_4$ to afford alcohol **12** (95% yield) and the amino group of the latter was diazotized ($NaNO_2$/HCl). The formed diazonium salt was then intercepted with pyrrolidine to afford triazene **13** in 75% overall yield. Oxidation of the hydroxy group in **13** with PCC led to the corresponding aldehyde (**14**, 88% yield), which was converted by Wittig reaction into terminal olefin **15** (92% yield). Asymmetric dihydroxylation (AD) with AD-α according to the Sharpless procedure[10] then furnished diol **16** (95% yield, 95% *ee*) which was selectively silylated with TBSCl/imidazole to afford monosilylated compound **17** (88% yield). Reaction of **17** with DPPA in the presence of Ph_3P and DEAD afforded, with inversion of configuration,[11] azide **18** in 79% yield, while reduction of the latter with Ph_3P and H_2O at 65 °C led to the desired amine **19** (78% yield). Finally, formation of the Boc derivative **20** ($(Boc)_2O$, Et_3N, 95% yield) followed by desilylation (TBAF, 93% yield) and oxidation with TEMPO/NaOCl (75% yield) led to triazene carboxylic acid **22** via compound **21**.

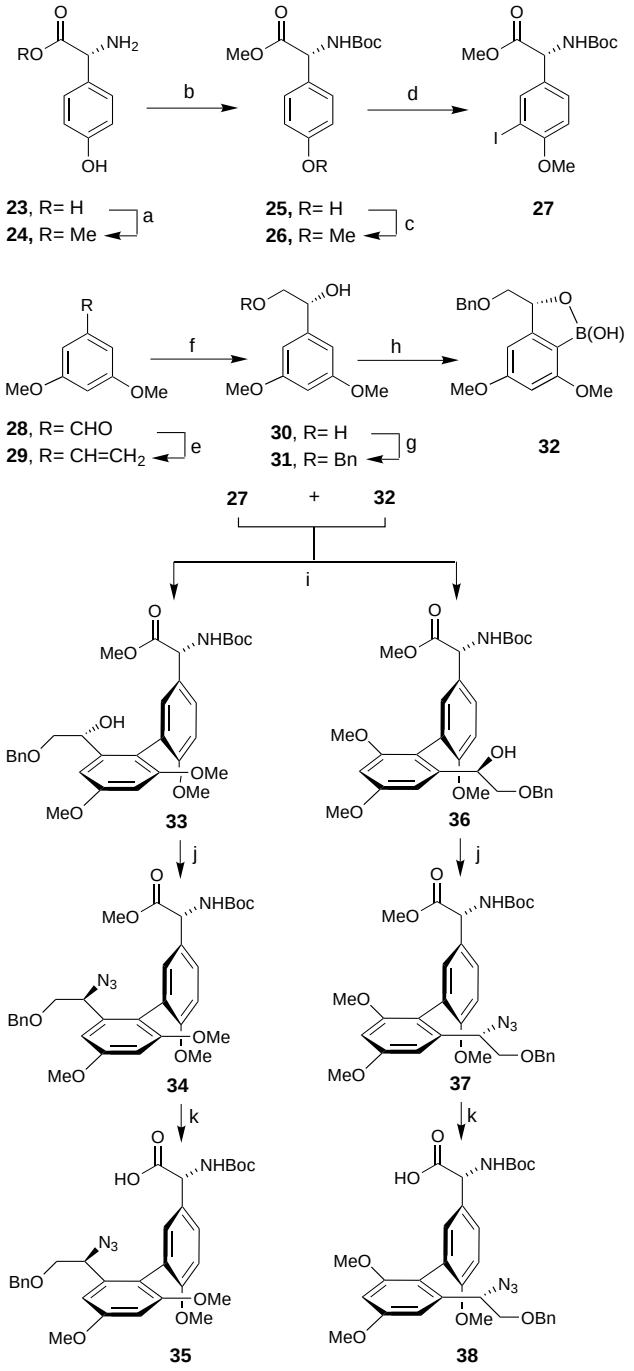


Scheme 2. Reagents and conditions: a) $SOCl_2$ (1.0 equiv), MeOH, reflux, 2 h, 100%; b) Br_2 (2.0 equiv), AcOH, 25 °C, 0.5 h, 98%; c) $LiAlH_4$ (1.5 equiv), THF, 0 °C, 2 h, 95%; d) 6 M HCl (5.0 equiv), $NaNO_2$ (1.2 equiv), AcOH:H_2O (1:2), 0 °C, 0.5 h, then KOH (8.0 equiv), pyrrolidine (1.5 equiv), 0 °C, 0.5 h, 75%; e) PCC (1.5 equiv), CH_2Cl_2, 25 °C, 2 h, 88%; f) *n*BuLi (1.4 equiv), CH_3PPh_3Br (1.5 equiv), THF, −20 °C, 2 h, 92%; g) AD-α (1.4 g mmol^{-1}), *t*BuOH/H_2O (1:1), 6 h, 95%, (95% *ee*); h) TBSCl (1.1 equiv), imidazole (1.5 equiv), DMF, 0 °C, 5 h, 88%; i) Ph_3P (2.5 equiv), DEAD (2.5 equiv), DPPA (2.5 equiv), THF, 0 °C, 2 h, 79%; j) Ph_3P (3.0 equiv), H_2O (10.0 equiv), THF, 60 °C, 3 h, 78%; k) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 4 h, 95%; l) TBAF (1.2 equiv), THF, 0 °C, 2 h, 93%; m) TEMPO (1.0 equiv), 5% aq. NaOCl (3.0 equiv), 5% $NaHCO_3$, KBr (0.05 equiv), Me_2CO, 0 °C, 1 h, 75%. Boc = *tert*-butoxycarbonyl; DEAD = diethyl azodicaboxylate; DPPA = diphenylphosphoryl azide; PCC = pyridinium chlorochromate; TBAF = tetra-*n*-butylammonium fluoride; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

The more challenging AB biaryl system of vancomycin,[4a, 5b,c] which contains the amino acids 5 and 7, was constructed in the form of its azide equivalent **35** from its components **27** and **32**, as summarized in Scheme 3. Fragment **27** was synthesized in a straightforward manner from 4-hydroxyphenylglycine (**23**) by esterification (**23** → **24**, 98%), Boc derivative formation (**24** → **25**, 95%), methylation (**25** → **26**, 93%), and iodination (**26** → **27**, 90%). The boronic acid derivative **32** corresponding to amino acid 7 was constructed from 3,5-dimethoxybenzaldehyde (**28**) by a sequence requiring Wittig olefination (**28** → **29**, 91%), Sharpless asymmetric dihydroxylation (**29** → **30**, AD-β, 92% yield, 96% *ee*), selective monobenzylation with $n(Bu_2SnO)$/BnBr (**30** → **31**, 89%),[12] and boronation (**31** → **32**, 55%). The latter operation was effected by the action of *n*BuLi (2.2 equiv) on benzylic alcohol **31**,[13] followed by quenching with $B(OMe)_3$ and acidic hydrolysis.

Coupling of fragments **27** and **32** proceeded smoothly under Suzuki conditions[14] ($[Pd(Ph_3P)_4]$ cat., Na_2CO_3) furnishing the two atropisomers **33** and **36** in 84% yield and about 2:1 ratio. The major compound was proven to be the desired natural atropisomer **33** by incorporating it into the AB-COD ring system of vancomycin (see compound **46a** in Scheme 5) and establishing its stereochemistry by NOE studies (Table 2). Both atropisomers **33** and **36** were taken through the sequence shown in Scheme 3 to the desired biaryl fragments **35** and **38**, respectively. Thus, introduction of an azido group (DPPA, Ph_3P, DEAD)[11] accompanied by inversion of stereochemistry (**33** → **34**, 95% and **36** → **37**, 90%) was followed by ester hydrolysis with LiOH in aqueous THF (**34** → **35**, 99% and **37** → **38**, 99%).

Having constructed these appropriate functionalized fragments, we were in a position to address their assembly into more advanced systems. Below, we describe the coupling of these intermediates and the assembly of the AB-COD framework of vancomycin with the correct stereochemistry and functionality for further elaboration, as well as work on related isomers.[4a, b] These studies also allowed the identification of the proper atropisomer of the AB biaryl system and



Scheme 3. Reagents and conditions: a) TMSCl (2.1 equiv), MeOH, 25 °C, 15 h, 98 %; b) $(Boc)_2O$ (1.1 equiv), K_2CO_3 (4.0 equiv), dioxane:H_2O (1:1), 25 °C, 4 h, 95 %; c) MeI (2.0 equiv), K_2CO_3 (4.0 equiv), DMF, 25 °C, 6 h, 93 %; d) I_2 (1.2 equiv), CF_3COOAg (2.2 equiv), $CHCl_3$, 25 °C, 12 h, 90 %; e) *n*BuLi (1.3 equiv), CH_3PPh_3Br (1.5 equiv), THF, −20 °C, 10 h, 91 %; f) AD-β (1.4 g mmol^{-1}), *t*BuOH/H_2O (1:1), 25 °C, 8 h, 92 % (96 % *ee*); g) nBu_2SnO (1.0 equiv), toluene, reflux, 1 h, then BnBr (1.5 equiv), nBu_4NI (0.5 equiv), 70 °C, 2 h, 89 %; h) *n*BuLi (2.2 equiv), benzene, 0 → 25 °C, 2 h, then $B(OMe)_3$, THF, −78 °C → 25 °C, 6 h, dilute HCl, 55 %, i) $[Pd(Ph_3P)_4]$ (0.2 equiv), Na_2CO_3 (1.2 equiv), $PhCH_3$/MeOH/H_2O (10:1:0.5), 90 °C, 4 h, about 2:1 (**33**:**36**) ratio of atropisomers, 84 % combined yield; j) DPPA (2.5 equiv), DEAD (2.5 equiv), Ph_3P (2.5 equiv), THF, −20 °C, 2 h, 95 % of **34**, 90 % of **37**; k) LiOH (1.5 equiv), THF/H_2O (1:1), 0 °C, 0.5 h, 99 % of **35**, 99 % of **38**. TMS = trimethylsilyl.

of the COD ring framework through NMR spectroscopic techniques (see structures **46a** and **46b** and Tables 1 and 2).

Table 1. Selected physical properties of compounds **8**, **22, 34**, **42a**, and **46a**.

8: $R_f = 0.24$ [silica gel, 5 % methanol in chloroform]; $[\alpha]_D^{25} = -11.5$ ($c = 0.85$ $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3366, 2943, 2849, 2555, 1737, 1602, 1502, 1467, 1290, 1255, 1079\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.19$ (d, $J = 2.0$ Hz, 1H), 6.99 (dd, $J = 8.5$, 2.0 Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 4.89 (d, $J = 3.5$ Hz, 1H), 4.06 (m, 1H), 3.98 (m, 1H), 3.37 (bs, 1H), 1.12 (t, J = 5.0 Hz, 3H), 0.80 (s, 9H), −0.08 (s, 3H), −0.26 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 173.8, 154.1, 134.5, 129.3, 127.1, 121.5, 117.3, 76.7, 62.8, 62.3, 26.2, 19.0, 14.4, -4.4, -5.1$; HRMS (FAB): calcd for $C_{17}H_{29}ClNO_4Si$ [M+H$^+$]: 374.1554; found: 374.1549.

22: $R_f = 0.18$ [silica gel, 10 % methanol in chloroform]; $[\alpha]_D^{25} = -97.4$ ($c =$ 0.98 MeOH); IR (film): $\tilde{\nu}_{max} = 3344, 2976, 2872, 1711, 1415, 1367, 1313, 1223, 1162, 1052, 1020\ cm^{-1}$; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.53$ (s, 2H), 4.89 (bs, 1H), 3.81 (bs, 2H), 3.54 (bs, 2H), 1.99 (bs, 2H), 1.95 (bs, 2H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 157.2, 148.7, 139.7, 132.2, 118.7, 112.0, 80.8, 52.3, 47.9, 28.7, 28.6, 24.9, 24.6$; HRMS (FAB): calcd for $C_{17}H_{22}Br_2N_4O_4Cs$ [M+Cs$^+$]: 636.9062; found: 636.9087.

34: $R_f = 0.22$ [silica gel, 30 % ethyl acetate in hexanes]; $[\alpha]_D^{25} = -18.1$($c =$ 0.25 $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3359, 2936, 2838, 2092, 1744, 1713, 1603, 1488, 1459, 1343, 1255, 1201, 1159, 1056\ cm^{-1}$; ^1H NMR (500 MHz, [D_6]acetone): $\delta = 7.43$ (dd, $J = 8.5$, 2.0 Hz, 1H), 7.32 – 7.21 (m, 5H), 7.16 (d, $J = 2.0$ Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.67 (d, $J = 6.0$ Hz, 1H), 6.63 (d, $J = 2.5$ Hz, 1H), 6.58 (d, $J = 2.5$ Hz, 1H), 5.29 (d, $J = 8.0$ Hz, 1H), 4.62 (dd, $J = 9.2$, 3.0 Hz, 1H), 4.35 (s, 2H), 3.84 (s, 3H), 3.65 (s, 3H), 3.65 (s, 3H), 3.59 (s, 3H), 3.60 – 3.56 (m, 1H), 3.50 – 3.49 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 172.5, 161.4, 161.2, 160.8, 159.3, 158.6, 154.9, 131.8, 129.9, 129.1, 128.9, 128.2, 128.2, 125.8, 119.8, 112.0, 103.8, 98.9, 79.1, 74.4, 73.0, 62.9, 58.0, 56.1, 55.6, 55.6, 52.5, 28.5$; HRMS (FAB): calcd for $C_{32}H_{38}N_4O_8Cs$ [M+Cs$^+$]: 739.1744; found: 739.1718.

42a: $R_f = 0.58$ [silica gel, 50 % acetone in hexanes]; $[\alpha]_D^{25} = +85.8$ ($c = 1.94$ $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3418, 3365, 2955, 2932, 2859, 2099, 1720, 1675, 1605, 1503, 1409, 1341, 1259, 1201, 1158, 1098, 1027\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47$ (br s, 1H), 7.30 (d, $J = 2.0$ Hz, 1H), 7.28 – 7.17 (m, 10H), 6.83 (d, $J = 8.5$ Hz, 1H), 6.71 (m, 2H), 6.66 (d, $J = 2.0$ Hz, 1H), 6.39 (d, $J = 2.0$ Hz, 1H), 6.10 (d, $J = 8.5$ Hz, 1H), 5.18 (m, 1H), 4.91 (m, 1H), 4.72 (d, $J = 9.0$ Hz, 1H), 4.57 (dd, $J = 8.5$, 3.0 Hz, 1H), 4.46 – 4.38 (m, 2H), 4.32 – 4.26 (m, 1H), 4.16 (m, 1H), 4.09 (m, 1H), 3.96 (br s, 2H), 3.86 (s, 3H), 3.71 (br s, 2H), 3.60 (s, 3H), 3.51 (s, 3H), 3.39 (dd, $J = 11.0$, 9.0 Hz, 1H), 3.30 (m, 1H), 2.06 (m, 4H), 1.40 (s, 9H), 1.32 (dd, $J = 7.5$, 7.0 Hz, 3H), 0.75 (s, 9H), −0.06 (s, 3H), −0.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.5, 168.4, 168.2, 160.2, 157.8, 157.5, 154.5, 152.1, 141.9, 138.3, 137.5, 136.5, 134.2, 132.2, 129.3, 128.3, 128.1, 127.7, 127.6, 127.5, 127.2, 126.7, 126.6, 125.5, 125.2, 122.5, 119.6, 117.6, 117.5, 111.1, 102.5, 98.6, 80.3, 73.6, 73.3, 71.9, 62.0, 60.3, 59.8, 57.5, 55.6, 55.3, 55.1, 53.3, 51.0, 46.2, 28.2, 25.6, 24.0, 23.6, 17.8, 14.1, -4.4, -5.8$; HRMS (FAB): calcd for $C_{60}H_{73}BrClN_9O_{12}SiCs$ [M+Cs$^+$]: 1386.3074; found: 1386.3160.

46a: $R_f = 0.11$ [silica gel, 50 % acetone in hexanes]; $[\alpha]_D^{25} = -20.8$ ($c = 0.48$ $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3273, 2930, 1651, 1488, 1416, 1318, 1249, 1159, 1097, 1058, 1029\ cm^{-1}$; ^1H NMR (600 MHz, [D_6]acetone): $\delta = 8.14$ (s, 1H), 7.64 (d, $J = 1.9$ Hz, 1H), 7.49 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.37 – 7.32 (m, 6H), 7.26 (m, 1H), 7.14 (d, $J = 2.3$ Hz, 1H), 7.06 (m, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 6.93 (d, $J = 8.6$ Hz, 1H), 6.88 (d, $J = 2.1$ Hz, 1H), 6.62 (d, $J = 2.1$ Hz, 1H), 6.22 (d, $J = 10.9$ Hz, 1H), 6.06 (d, $J = 8.5$ Hz, 1H), 5.90 (s, 1H), 5.63 (d, $J = 8.5$ Hz, 1H), 5.41 (d, $J = 3.8$ Hz, 1H), 5.18 (d, $J = 4.5$ Hz, 1H), 4.75 (d, $J = 5.8$ Hz, 1H), 4.57 (m, 2H), 4.40 – 4.37 (m, 2H), 3.96 – 3.93 (m, 1H), 3.89 (br s, 2H), 3.83 (s, 3H), 3.82 – 3.79 (m, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 3.69 – 3.62 (br s, 2H), 2.06 (m, 4H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 170.8, 170.6, 168.4, 162.7, 161.0, 159.5, 158.1, 156.0, 152.5, 152.2, 142.2, 140.5, 139.5, 139.5, 138.7, 136.1, 129.1, 128.7, 128.6, 128.3, 128.0, 127.9, 127.4, 127.0, 125.0, 124.2, 122.3, 119.4, 114.4, 113.2, 106.1, 98.4, 79.6, 73.6, 72.9, 70.2, 63.9, 56.6, 56.0, 55.6, 55.0, 52.7, 51.6, 47.0, 36.1, 28.5, 24.5, 24.1$; HRMS (FAB): calcd for $C_{52}H_{55}BrClN_7O_{11}Cs$ [M+Cs$^+$]: 1200.1886; found: 1200.1965.

In retrospect, we now know that the major atropisomer of the biaryl system described above possesses the correct stereochemical arrangement (**35**, Scheme 3) for the vancomycin molecule. The coupling of this biaryl fragment with

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Table 2. Diagnostic NOEs for structural determination of selected atropisomers.[a]

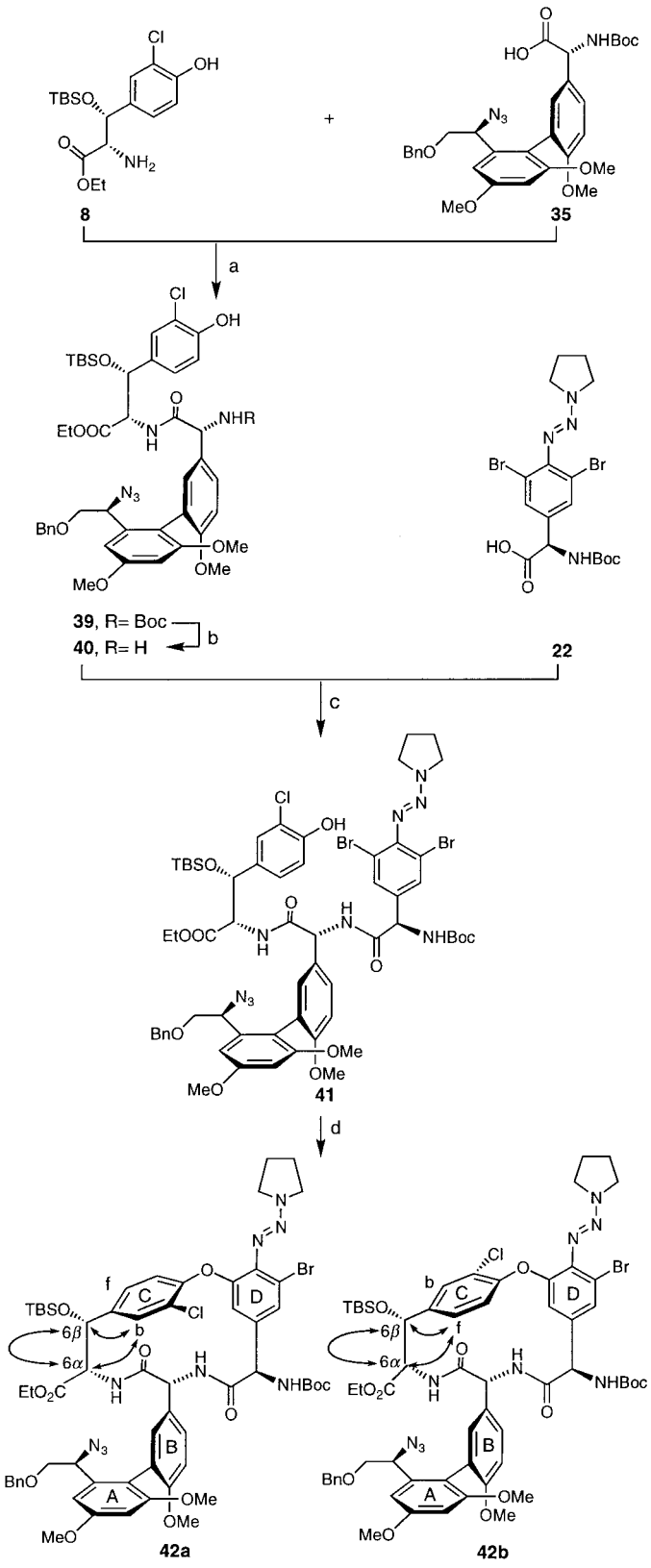
Compound	Solvent	(^{1}H – ^{1}H) NOE[b]
42a	$CDCl_3$	$6\alpha \leftrightarrow 6\beta$; $6\alpha \leftrightarrow$ Cb; $6\beta \leftrightarrow$ Cb
42b	$CDCl_3$	$6\alpha \leftrightarrow 6\beta$; $6\alpha \leftrightarrow$ Cf; $6\beta \leftrightarrow$ Cf
46a	[D_6]acetone	$6\alpha \leftrightarrow 6\beta$; $6\alpha \leftrightarrow$ Cb; $6\beta \leftrightarrow$ Cb; $5\alpha \leftrightarrow$ Bb; $6\alpha \leftrightarrow 5\alpha$
46b	[D_6]acetone	$6\alpha \leftrightarrow 6\beta$; $6\alpha \leftrightarrow$ Cf; $6\beta \leftrightarrow$ Cf; $5\alpha \leftrightarrow$ Bb; $6\alpha \leftrightarrow 5\alpha$
50a	[D_6]acetone	$6\alpha \leftrightarrow 6\beta$; $6\alpha \leftrightarrow$ Cb; $6\beta \leftrightarrow$ Cb
50b	[D_6]acetone	$6\alpha \leftrightarrow 6\beta$; $6\alpha \leftrightarrow$ Cf; $6\beta \leftrightarrow$ Cf
54a	[D_6]acetone	$6\alpha \leftrightarrow$ Cf; $6\beta \leftrightarrow$ Cb; $5\alpha \leftrightarrow$ Bf
54b	[D_6]acetone	$6\alpha \leftrightarrow$ Cb; $6\beta \leftrightarrow$ Cf; $5\alpha \leftrightarrow$ Bf

[a] ^{1}H-^{1}H NOESY, 600 MHz, 300 K. [b] For the atom labeling in **42a** and **42b** see formula of compounds **46a** and **46b** in Scheme 5.

amino acid 6 in the form of derivative **8** (EDC/HOAt, 85% yield, de ca. 13:1), and the elaboration of the resulting dipeptide **39** (chromatographically separated from the minor diastereoisomer) to the desired COD ring system **42a** and its atropisomer **42b** is shown in Scheme 4. Thus, cleavage of the Boc group from **39** by the action of TMSOTf and 2,6-lutidine (90% yield), followed by EDC/HOAt induced coupling of the resulting amine **40** with the derivative of the central amino acid, **22**, furnished tripeptide **41** in 76% yield. Exposure of **41** to $CuBr \cdot SMe_2$, K_2CO_3, and pyridine in CH_3CN at reflux[5a] resulted in the formation of the two atropisomers of the COD ring **42a** and **42b** in 60% combined yield (ca. 1:1 ratio). NMR (e.g. COSY and NOESY) analysis of **42a** and **42b** established the identity of these two atropisomers by revealing the expected NOE data for each compound (see Scheme 4 and Tables 1 and 2).

The elaboration of both atropisomers **42a** and **42b** to the respective AB-COD ring frameworks (**46a** and **46b**) is shown in Scheme 5. It was indeed pleasing to observe that the second ring closure could be effected smoothly by a lactamization protocol as we demonstrated recently in model systems.[5c] Thus, the correct atropisomer **42a** was desilylated with TBAF, furnishing hydroxy ester **43a** (80% yield). This deprotection was necessary to facilitate, in a subsequent step, the basic hydrolysis of the ethyl ester which proved, otherwise, robust. The azido group in **43a** was then reduced to an amino group by the action of Et_3P in the presence of H_2O at 25 °C, furnishing amino ester **44a** (71% yield), which was hydrolyzed easily with LiOH in THF/H_2O (1:1) at 0 °C to afford amino acid **45a** (68% yield). Finally, exposure of **45a** to FDPP[15] in the presence of iPr$_2$NEt in DMF at 25 °C resulted in the formation of the AB-COD ring framework **46a** in 71% yield. A similar sequence allowed the preparation of **46b** from **42b** via intermediates **43b** – **45b**. Again NMR spectroscopy (COSY and NOESY) proved instrumental in establishing the stereochemical arrangement within these unusual frameworks and the arrangement of the AB ring system. Thus, the observed NOEs (see Scheme 5 and Table 2) for **46a** and **46b** were consistent with those observed for **42a** and **42b** with regards to the COD ring stereochemistry and also established the stereochemical identity of the original biaryl system **35** as being natural.

In order to learn more about the properties of the various atropisomers of the AB-COD ring systems, we undertook the



Scheme 4. Reagents and conditions: a) EDC (3.0 equiv), HOBt (3.3 equiv), THF, 0 °C, 12 h, 85%; b) TMSOTf (3.4 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C, 3 h, 90%; c) EDC (3.0 equiv), HOAt (3.3 equiv), THF, −5 °C, 12 h, 76%; d) $CuBr \cdot SMe_2$ (3.0 equiv), K_2CO_3 (3.0 equiv), pyridine (3.0 equiv), MeCN, reflux, 20 min, ca. 1:1 ratio of atropisomers, 60% combined yield. EDC = 1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride; HOAt = 1-hydroxy-7-azabenzotriazole; HOBt = 1-hydroxybenzotriazole.

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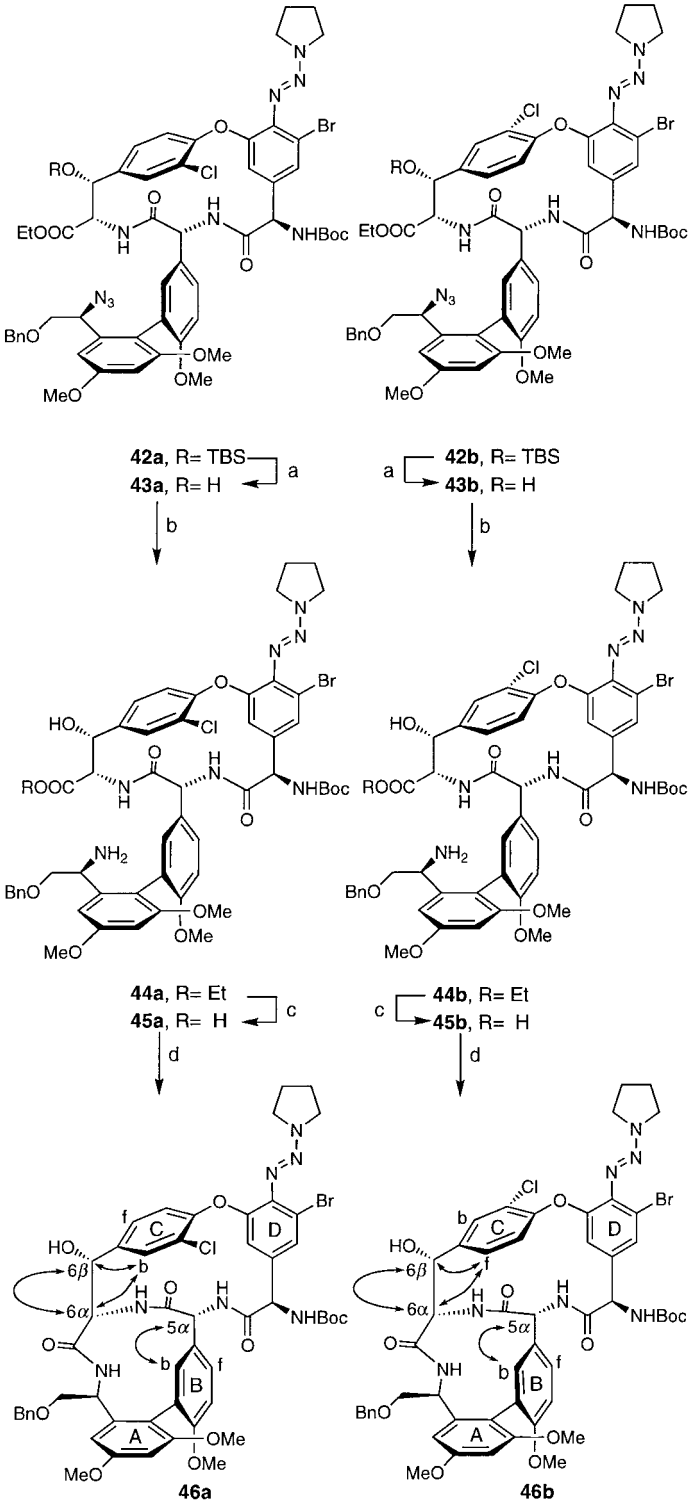
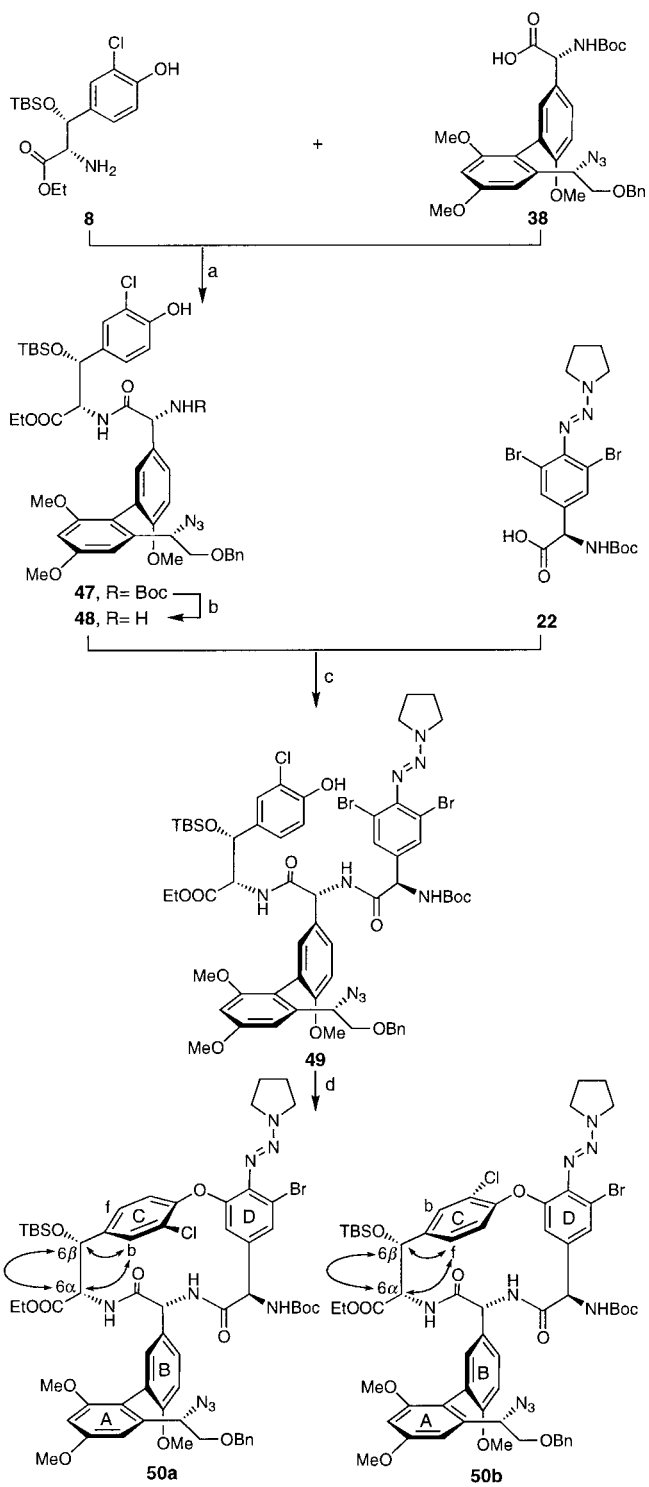


Scheme 5. Reagents and conditions: a) TBAF (1.5 equiv), THF, 0 °C, 2 h, 80% of **43a**, 100% of **43b**; b) Et_3P (2.0 equiv), H_2O (10.0 equiv), CH_3CN, 25 °C, 12 h, 71% of **44a**, 79% of **44b**; c) LiOH (5.0 equiv), THF/H_2O (1:1), 0 °C, 20 min, 68% of **45a**, 62% of **45b**; d) FDPP (3.0 equiv), iPr_2NEt (5.0 equiv), DMF, 25 °C, 12 h, 71% of **46a**, 52% of **46b**. FDPP = pentafluorophenyl diphenylphosphinate.



Scheme 6. Reagents and conditions: a) EDC (3.0 equiv), HOAt (3.3 equiv), THF, 0 °C, 10 h, 83%; b) TMSOTf (3.4 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C, 3 h, 91%; c) EDC (3.0 equiv), HOAt (3.3 equiv), THF, 0 °C, 10 h, 70%; d) $CuBr \cdot SMe_2$ (3.0 equiv), K_2CO_3 (3.0 equiv), pyridine (3.0 equiv), MeCN, reflux, 20 min, about 1:1 ratio of atropisomers, 60% combined yield.

incorporation of the atropisomer of the biaryl system **35**, compound **38**, into the AB-COD framework. As outlined in Scheme 6, the coupling of **38** with fragments **8** and **22** and the further elaboration proceeded in a similar fashion as for its isomer **35**, furnishing the two atropisomers **50a** and **50b** via intermediates **47**–**49**. However, it was interesting to observe facile epimerization at the indicated positions (see structures **53** and **54**, Scheme 7) on attempted elaboration of **50a** and

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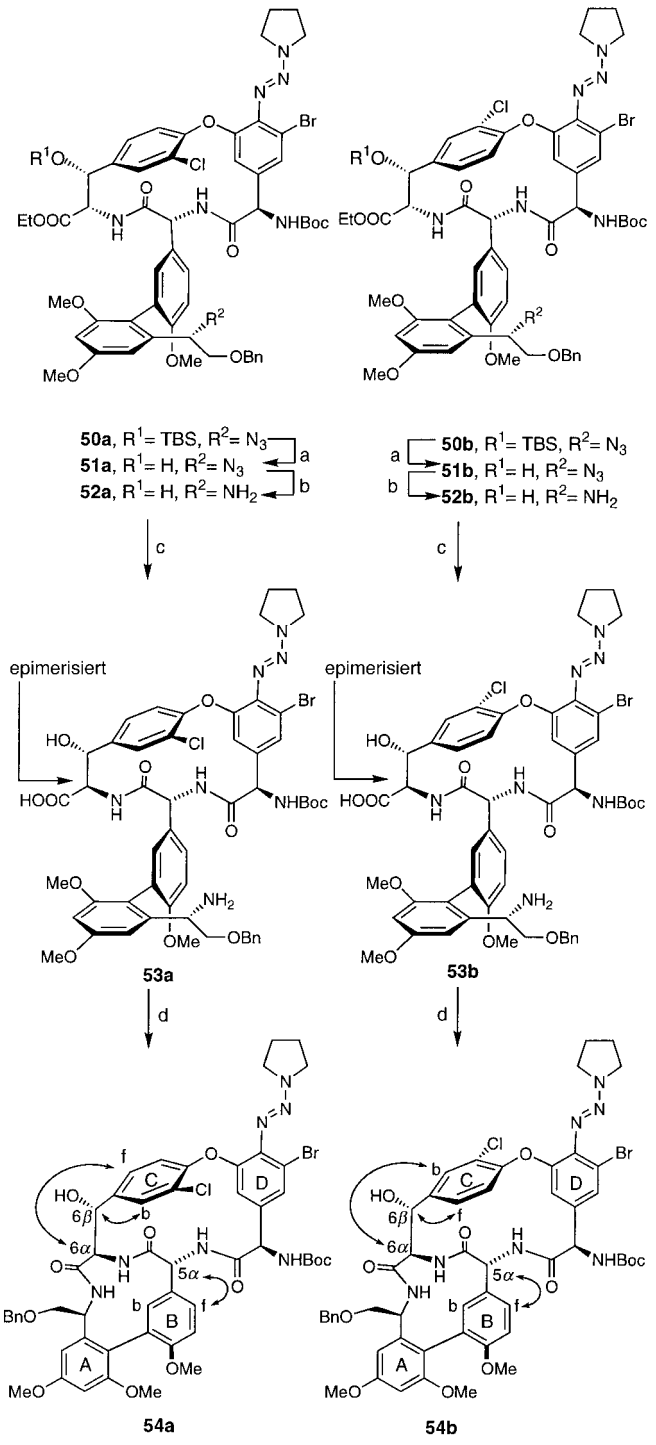

Scheme 7. Reagents and conditions: a) TBAF (1.5 equiv), THF, 0 °C, 2 h, 90% of **51a**, 95% of **51b**; b) Ph_3P (3.0 equiv), THF, H_2O (10.0 equiv), 60 °C, 3 h, 82% of **52a**, 71% of **52b**; c) LiOH (1.5 equiv), MeOH:H_2O (10:1), 0 °C, 2 h, 92% of **53a**, 90% of **53b**; d) HATU (1.5 equiv), iPr$_2$NEt (3.0 equiv), DMF, 25 °C, 8 h, 50% of **54a**, 51% of **54b**. HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate.

50b to the corresponding AB-COD ring frameworks. Thus, while desilylation of **50a** and **50b** and subsequent reduction of the azido group proceeded smoothly to afford amino esters **52a** and **52b** via **51a** and **51b**, respectively, attempted LiOH saponification of the ethyl ester in aqueous MeOH/H_2O (10:1) at 0 °C resulted in essentially complete epimerization of the adjacent stereocenters to furnish **53a** and **53b**. Lactamization of the amino acids **53a** and **53b** in the presence of HATU[16] and iPr$_2$NEt resulted in the formation of the respective AB-COD ring frameworks **54a** and **54b**. The stereochemical assignments were based on experiments with both sets of compounds **53a**/**53b** and **54a**/**54b** which revealed the appropriate coupling constants ($J_{6\alpha,6\beta} = 9.8$ Hz for **54a** and **54b**) and NOEs (see structures **54a** and **54b**, Scheme 7 and Table 2). While it was possible to arrest the epimerization process during the saponification of **52a** and **52b** by changing the hydrolysis conditions (THF/H_2O, 1:1), the ring-closure reactions with the non-epimerized amino acids proceeded with lower yields and, most significantly, with epimerization at the indicated positions,[4e] leading to the same products **54a** and **54b** as before. Thus, it appears that, with the unnatural AB atropisomers in place, the AB-COD ring frameworks prefer to reside in the epimeric form shown, irrespective of the atropisomeric position of the chlorine atom.

Further elaboration of the natural AB-COD framework (**46a**) to the vancomycin AB-COD-DOE tricyclic framework and its conversion into the aglycon of vancomycin are reported in the following communications.[7]

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Total Synthesis of Vancomycin Aglycon—Part 2: Synthesis of Amino Acids 1 – 3 and Construction of the AB-COD-DOE Ring Skeleton

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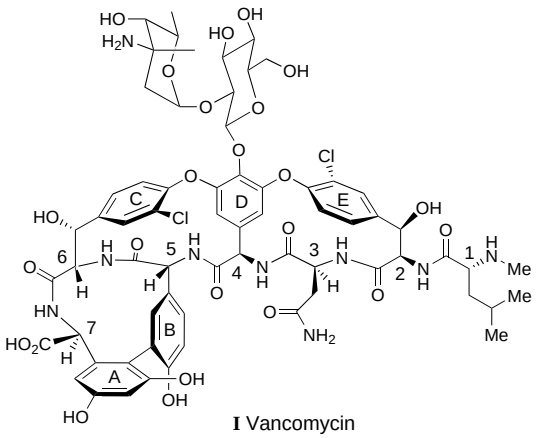
In the preceding communication,[1] we reported the synthesis of the AB-COD ring system of vancomycin (**I**, Figure 1). Herein, we describe conversion of this intermediate (**16**, see



I Vancomycin

Figure 1. Molecular structure of vancomycin **I**.

Scheme 3) into the AB-COD-DOE framework (**20a**, see Scheme 3) of vancomycin (**I**) by assembling and attaching the required tripeptide **15**, followed by triazene-driven ring closure.

Scheme 1 presents the three amino acid derivatives [compounds **8** (amino acid 1), **5** (amino acid 2), and **7** (amino acid 3)] required for the completion of the AB-COD-DOE ring framework, and their construction from readily available substrates. Thus, the derivative of amino acid 2, **5,** was reached from aryl ester **1** by the following four-step sequence:[2] 1) Sharpless asymmetric dihyroxylation (AD) to give **2** (79% yield, 92% *ee*); 2) regioselective nosylation (nosyl = Nos = 4-nitrobenzenesulfonyl), to give **3** (60% yield);

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