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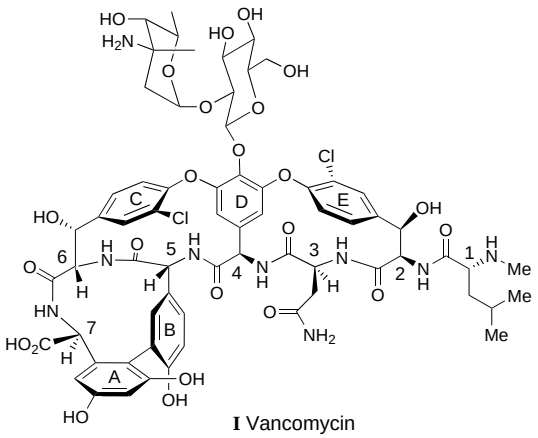
In the preceding communication,[1] we reported the synthesis of the AB-COD ring system of vancomycin (**I**, Figure 1). Herein, we describe conversion of this intermediate (**16**, see



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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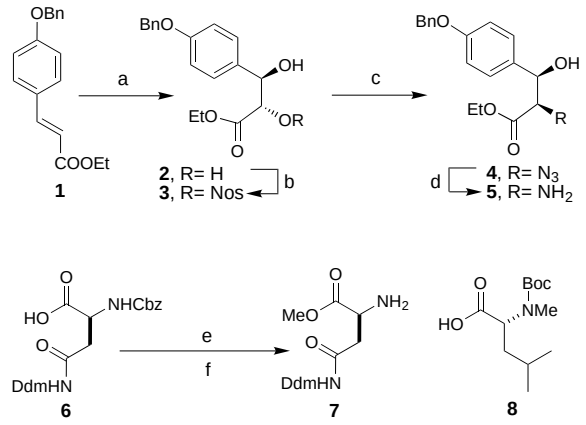
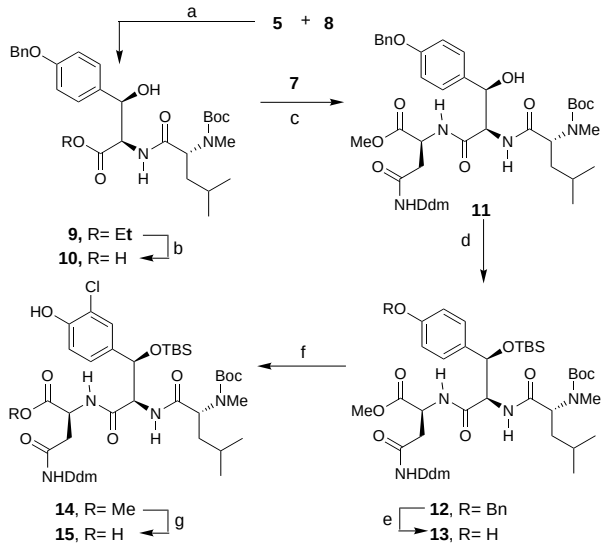


Scheme 1. Reagents and conditions: a) AD-β,[7] (1.4 g mmol^{-1}), Me-SO_2NH_2 (1.0 equiv), *t*BuOH/H_2O (1:1), 25 °C, 12 h, 79 % (92 % *ee*); b) NosCl (1.0 equiv), Et_3N (2.0 equiv), DMF, 0 °C, 5 h, 60 %; c) NaN_3 (1.5 equiv), DMF, 55 °C, 12 h, 90 %; d) $SnCl_2 \cdot H_2O$ (2.0 equiv), MeOH, 25 °C, 2 h, 90 %; e) MeI (2.0 equiv), K_2CO_3 (2.0 equiv), DMF, 25 °C, 12 h, 70 %; f) H_2, 20 wt % $Pd(OH)_2$/C, MeOH, 25 °C, 1 h, 99 %. Boc = *tert*-butoxycarbonyl; Bn = benzyl; Cbz = carbobenzyloxy; Ddm = 4,4′-dimethoxy diphenylmethyl; DMF = dimethylformamide; NosCl = 4-nitrobenzenesulfonyl chloride.

3) displacement with NaN_3 to afford **4** (90 % yield); and 4) reduction with $SnCl_2$ (90 % yield). The derivative of amino acid 3, **7**, was prepared from the known compound **6** simply by methylation to afford the corresponding methyl ester (70 % yield) followed by hydrogenolysis of the Cbz group (99 % yield).

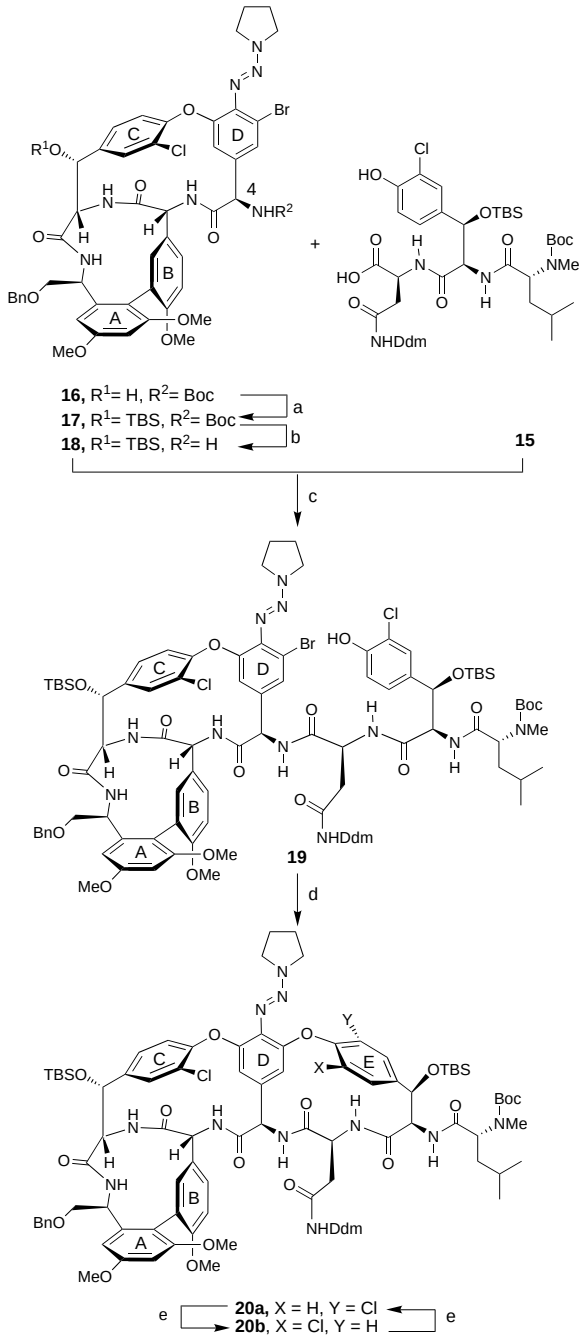
Tripeptide **15** was assembled as summarized in Scheme 2. Thus, coupling of fragments **5** and **8** proceeded smoothly under EDC/HOBt to give **9** (93 % yield), whereas attachment of fragment **7** onto the carboxylic acid group of dipeptide **10**, obtained from basic hydroylsis (LiOH, THF:H_2O, 99 % yield) of **9**, required the action of EDC/HOAt (82 % yield). Protection of the hydroxy group of **11** was then carried out



Scheme 2. Reagents and conditions: a) EDC (3.0 equiv), HOBt (3.3 equiv), THF, 0 °C, 12 h, 93 %; b) LiOH (2.0 equiv), THF/H_2O (1:1), 0 °C, 1 h, 99 %; c) EDC (3.0 equiv), HOAt (3.3 equiv), THF, 0 °C, 12 h, 82 %; d) TBSOTf (1.3 equiv), 2,6-lutidine (2.2 equiv), CH_2Cl_2, 0 °C, 2 h, 81 %; e) H_2, 20 wt % $Pd(OH)_2$/C, MeOH, 25 °C, 1 h, 99 %; f) SO_2Cl_2, Et_2O, 25 °C, 75 %; g) LiOH (4.0 equiv), *t*BuOH/H_2O (2:1), 0 °C, 0.5 h, 75 %. EDC = 1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride; HOAt = 1-hydroxy-7-azobenzotriazole; HOBt = 1-hydroxy-1*H*-benzotriazole; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonate.

with TBSOTf in the presence of 2,6-lutidine to afford silyl ether **12**, from which the benzyl group was cleaved by hydrogenolysis (H_2, 20 % $Pd(OH)_2$/C, 99 %). Finally, chlorination of **13** (SO_2Cl_2, 75 % yield), followed by mild saponification (LiOH, *t*BuOH/H_2O, 75 % yield), furnished the desired tripeptide fragment **15**.

With the two segments **15** and **16** in hand, the task of joining them together and effecting the final ring closure came within reach (Scheme 3). In preparation for this union, the free



Scheme 3. Reagents and conditions: a) TBSOTf (10.0 equiv), 2,6-lutidine (20.0 equiv), CH_2Cl_2, −10 °C, 3.5 h, 83 % ; b) TMSOTf (3.0 equiv), 2,6-lutidine (1.2 equiv) , CH_2Cl_2, 0 °C, 2 h, 84 %; c) EDC (3.0 equiv), HOAt (10.0 equiv), −5 °C, 12 h, 81 %; d) $CuBr \cdot SMe_2$ (3.0 equiv), K_2CO_3 (3.0 equiv), pyridine (3.0 equiv), MeCN, reflux, 2 h, 72 %, **20a: 20b** about 1:3; e) 1,2-dichlorobenzene, 140 °C, 4 h, > 90 %, **20a:20b** about 1:1. TMS = trimethylsilyl.

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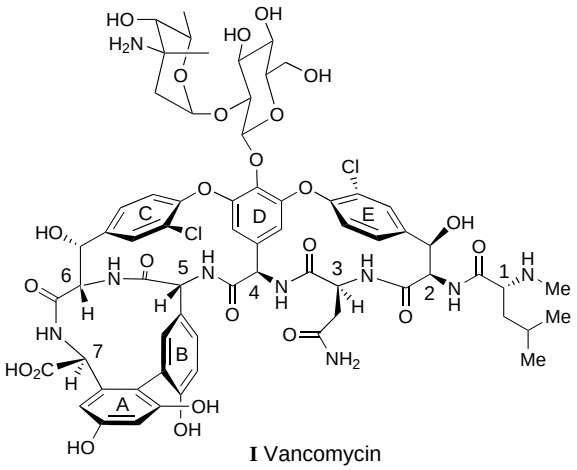
hydroxyl group of **16** was silylated with TBSOTf/2,6-lutidine to afford the corresponding silyl ether (**17**, 83 % yield), and the free amine at C-4 was released by removing the Boc group (TMSOTf, 2,6-lutidine, 84 % yield) to furnish compound **18**. The coupling of **18** and **15** was carried out smoothly in the presence of EDC/HOAt (81 % yield) leading to the cyclization precursor **19**. Ring closure of **19** was then achieved by subjecting it to the previously developed conditions ($CuBr \cdot SMe_2$, K_2CO_3, pyr. CH_3CN, $\triangle$),[3] furnishing the targeted polycyclic intermediate[4] in 72 % yield as a mixture of the two atropisomers **20a** and **20b** (ca. 1:3 ratio). COSY and ROESY NMR experiments facilitated the stereochemical assignment of the two atropisomers **20a** and **20b** (Figure 2). Selected



I Vancomycin

Figure 2. Stereochemical assignments of atropisomers **20a** and **20b** based on NOE measurements (COSY and ROESY, 600 MHz, CD_3OD, 323 K).

physical data for **20a**, **20b**, and their precursor compound **19** are listed in Table 1. Chromatographic separation followed by heating either atropisomer in 1,2-dichlorobenzene[5] at 140 °C for 4 h resulted in the formation of a mixture of the two atropisomers **20a** and **20b**, in a ratio of approximately 1:1 (> 90 % recovered yield).[6]

Culminating in the construction of a highly functionalized vancomycin scaffold, the chemistry described herein brings the total synthesis of this antibiotic and its aglycon within striking distance. The attainment of the latter goal is described in the following communication.[8]

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Table 1. Selected physical properties of compounds **19**, **20a** and **20b**.

19: $R_f = 0.29$ [silica gel, 1:2:7 acetone: ethyl acetate: benzene]; $[\alpha]_D^{25} = +21.3$ ($c = 0.52$, CH_3OH); IR (film): $\tilde{\nu}_{max}$ 3334, 2944, 2924, 2847, 2360, 1659, 1606, 1508, 1484, 1464, 1250, 1202, 1172, 1148, 1109, 1031 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone): $\delta = 8.18$ (br s, 2H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.68 (d, $J = 1.9$ Hz, 1H), 7.58 (d, $J = 7.3$ Hz, 1H), 7.49 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.40 – 7.33 (m, 6H), 7.28 (m, 1H), 7.16 – 7.07 (m, 6H), 7.04 (m, 1H), 6.95 (d, $J = 2.1$ Hz, 1H), 6.89 (d, $J = 9.1$ Hz, 1H), 6.87 – 6.81 (m, 5H), 6.89(d, $J = 5.4$ Hz, 1H), 6.62 (d, $J = 2.0$ Hz, 1H), 6.19 (br s, 1H), 6.11 (d, $J = 8.2$ Hz, 1H), 5.95 (br s, 2H), 5.48 (s, 1H), 5.10(d, $J = 5.8$ Hz, 1H), 4.83 (m, 1H), 4.73 (d, $J = 6.3$ Hz, 1H), 4.68 (dd, $J = 8.1$, 5.8 Hz, 1H), 4.61 – 4.58 (br, 1H), 4.58 (s, 2H), 4.44 (br s, 1H), 4.35 (d, $J = 11.9$ Hz, 1H), 3.96 (m, 1H), 3.89 (dd, $J = 9.9$, 3.5 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.85 – 3.60 (m, 5H), 3.74 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 2.86 (dd, $J = 15.5$, 4.7 Hz, 1H), 2.71 (m, 1H), 2.56 (s, 3H), 2.03 (m, 4H), 1.71 – 1.32 (m, 12H), 0.90 (s, 9H), 0.82 (s, 9H), 0.88 – 0.84 (m, 6H), 0.084 (s, 3H), 0.044 (s, 3H), 0.020 (s, 3H), – 0.13 (s, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone): $\delta = 171.5$, 171.0, 170.1, 169.9, 169.8, 169.6, 167.8, 161.1, 159.7, 159.6, 158.2, 153.3, 153.1, 152.3, 147.0, 141.6, 140.8, 139.8, 139.4, 138.0, 136.1, 135.5, 134.1, 131.5, 130.2, 129.6, 129.4, 129.3, 129.0, 128.9, 128.7, 128.3, 128.1, 127.9, 127.6, 127.3, 126.1, 125.3, 124.3, 122.5, 121.0, 119.7, 117.5, 114.6, 114.6, 113.6, 98.8, 98.3, 93.8, 93.7, 92.0, 80.1, 74.7, 74.4, 73.7, 70.6, 70.5, 64.2, 60.5, 60.4, 56.4, 56.2, 56.0, 55.7, 55.6, 55.5, 55.4, 52.7, 51.0, 38.8, 37.5, 37.4, 28.6, 26.2, 26.1, 25.4, 24.2, 23.5, 22.0, 18.8, 18.6, 14.4, – 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: 2110.6354.

20a: $R_f = 0.45$ [silica gel, 60 % ethyl acetate in benzene]; $[\alpha]_D^{25} = +20.0$ ($c = 0.11$, CH_3OH); IR (film): $\tilde{\nu}_{max}$ 3353, 2925, 2857, 2341, 2340, 1966, 1878, 1654, 1640, 1606, 1586, 1566, 1503, 1484, 1401, 1387, 1323, 1245, 1202, 1109, 1065, 1031 cm^{-1}; ^1H NMR (600 MHz, CD_3OD, 323 K): $\delta = 7.59$ (br s, 1H), 7.48 (d, $J = 6.7$ Hz, 1H), 7.36 – 7.26 (m, 8H), 7.21 (bd, $J = 8.0$ Hz, 1H), 7.16 (m, 1H), 7.08 – 6.97 (m, 9H), 6.72 (d, $J = 8.2$ Hz, 2H), 6.56 (d, $J = 2.5$ Hz, 1H), 5.86 (s, 1H), 5.78 (s, 1H), 5.72 (s, 1H), 5.48 (d, $J = 4.5$ Hz, 1H), 5.43 (br s, 1H), 5.29 (s, 1H), 4.90 (br s, 1H), 4.85 (br s, 1H), 4.77 (br s, 1H), 5.56 (m, 2H), 4.38 (br s, 1H), 4.09 (br s, 1H), 3.85 – 3.60 (m, 7H), 3.80 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.42 (s, 3H), 2.78 (br s, 3H), 2.64 – 2.55 (m, 2H), 2.07 (m, 4H), 1.80 – 1.30 (m, 12H), 1.11 – 0.7 (m, 24H), 0.1 (s, 3H), 0.65 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); HRMS (FAB): calcd for $C_{99}H_{123}Cl_2N_{11}O_{19}Si_2Cs$ [M+Cs$^+$]: 2028.6967; found: 2028.6820.

20b: $R_f = 0.29$ [silica gel, 60 % ethyl acetate in benzene]; $[\alpha]_D^{25} = -7.27$ ($c = 0.11$, CH_3OH); IR (film): $\tilde{\nu}_{max}$ 2358, 2337, 2062, 2015, 1868, 1844, 1828, 1791, 1770, 1681, 1667, 1652, 1607, 1578, 1509, 1458, 1464, 1417, 1391, 1362, 1322, 1251 cm^{-1}; ^1H NMR (600 MHz, [D$_6$]acetone, 323 K): $\delta = 8.27$ (br s, 1H), 7.68 – 7.54 (m, 5H),7.43 – 7.41 (m, 3H), 7.38 – 7.35 (m, 3H), 7.31 – 7.29 (m, 4H), 7.26 – 7.22 (m, 3H), 7.14 – 7.11 (m, 6H), 7.00 – 6.98 (m, 2H), 6.98 (d, $J = 2.1$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 6.86 – 6.82 (m, 5H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.62 (d, $J = 2.3$ Hz, 1H), 6.31 (d, $J = 8.3$ Hz, 1H), 6.01 (d, $J = 8.1$ Hz, 1H), 5.90(s, 1H), 5.84 (br s, 1H), 5.48 (s, 1H), 5.50 (d, $J = 3.3$ Hz, 2H), 5.09 (br s, 1H), 4.70 (m, 2H), 4.46 (br s, 1H), 4.39 (d, $J = 12.0$ Hz, 1H), 3.99 (t, $J = 9.9$, 9.6 Hz, 1H), 3.92 (dd, $J = 9.9$, 3.4 Hz, 1H), 3.85 (s, 3H), 3.84 – 3.79 (m, 4H), 3.78 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 3.55 (s, 3H), 2.84 (s, 3H), 2.09 – 2.05 (m, 4H), 1.71 (br s, 1H), 1.62 – 1.60 (m, 1H), 1.52 (s, 9H), 0.95 (s, 9H), 0.93 (s, 9H), 0.93 – 0.90 (m, 6H), 0.16 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); HRMS (FAB): calcd for $C_{99}H_{123}Cl_2N_{11}O_{19}Si_2Cs$ (M+Cs$^+$): 2028.6967; found: 2028.6832.

[1] Preceding communication: K. C. Nicolaou, S. Natarajan, H. Li, N. F. Jain, R. Hughes, M. Solomon, J. Ramanjulu, C. N. C. Boddy, M. Takayanagi, *Angew. Chem.* **1998**, *109*, 2872 – 2878; *Angew. Chem. Int. Ed.* **1998**, *37*, 2708 – 2714.

[2] For a similar procedure, see: A. V. R. Rao, T. K. Chakraborty, K. L. Reddy, A. S. Rao, *Tetrahedron Lett.* **1994**, *35*, 5043 – 5046.

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