# Total Synthesis of Vancomycin Aglycon—Part 3: Final Stages

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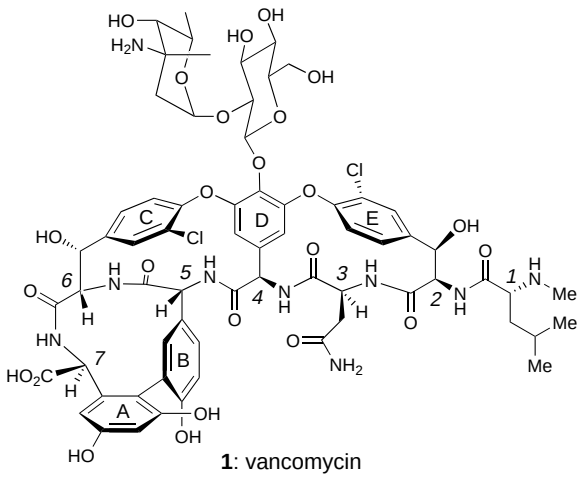
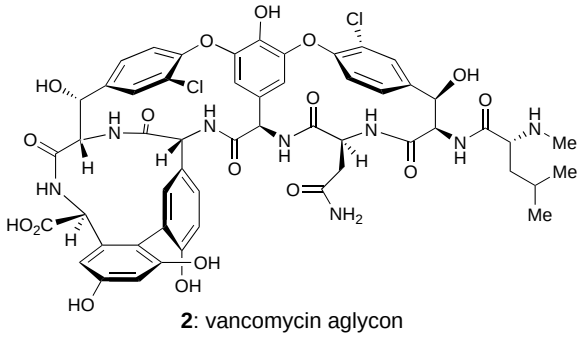
In the two preceding communications,[1, 2] we described the construction of the vancomycin (**1**) key amino acid building blocks and their assembly to the skeletal framework (**3**) of this naturally occurring antibiotic. For completion of the total synthesis of the vancomycin aglycon (**2**), the following tasks remained: a) conversion of the triazene moiety into a phenol group; b) oxidation of the homobenzylic alcohol to a carboxyl group; and c) removal of all the protecting groups. Herein we report the accomplishments of these tasks which culminated in the total synthesis of the aglycon (**2**) of vancomycin (**1**).

The substitution of the triazene moiety with a hydroxyl group in the advanced vancomycin precursor **3**[2] (Scheme 1) proved more challenging than anticipated. Thus, initial attempts to effect this transformation by using standard methods (for example, aqueous acidic conditions,[3] diazotization followed by treatment with $Cu_2O/Cu_3(NO_3)_2 \cdot 2.5\,H_2O$[4]) failed to produce significant amounts of the desired phenolic compound, leading instead to the corresponding reduction product **8**. It was after considerable experimentation that the following sequence was devised and proved successful in delivering the targeted vancomycin aglycon (**2**). Thus, the triazene functionality in **3** was reduced with Raney Ni[5] in an efficient reaction that also caused partial debenzylation, producing a mixture of aniline derivatives **4** and **5** (ca. 1:1 ratio). Further hydrogenolysis of this mixture ($H_2$, 10% $Pd(OH)_2$/C) resulted in clean formation of the aniline derivative **5** (85% yield from **3**). Diazotization of the amino group in compound **5** by the action of $HBF_4$ and isoamyl nitrite at $-20\,^{\circ}C$ furnished diazonium salt **6** which was treated in situ with saturated aqueous potassium iodide solution to afford iodide **7**. The latter compound (**7**) was found to be contaminated with the corresponding reduced product **8** (ca. 6:4 ratio in favor of **7**, inseparable mixture). This mixture was converted into the desired phenol (**10**) via its boronate (**9**), at which stage the reduced product was easily removed by silica gel chromatography. Thus, deprotonation of all the NH groups in **7** and halogen–metal exchange at $-40\,^{\circ}C$ with excess MeMgBr and *i*PrMgBr,[6] followed by quenching of the resulting aryl Grignard species with excess $B(OMe)_3$, resulted in the formation of the aryl boronate[7, 8] derivative **9**. This compound (**9**) was then oxidized in situ with basic $H_2O_2$, leading to a mixture of phenol **10** and reduced product **8**. Preparative layer silica gel chromatography gave pure **10** in 50% overall yield (from **5**). It is worth noting that no significant stereochemical changes were observed during these transformations. Prior to oxidation of the primary hydroxyl group to the desired carboxylic acid moiety, it was considered prudent to protect the phenolic group. This objective was achieved by exposure of **10** to excess of MeI in the presence of $Cs_2CO_3$, leading to methoxy derivative **11** in 95% yield.



**1**: vancomycin



**2**: vancomycin aglycon

The oxidation of the primary hydroxyl group in **11** was smoothly effected by sequential treatment with Dess–Martin reagent[9] and potassium permanganate,[10] furnishing, after treatment with diazomethane, methyl ester **12** via the corresponding aldehyde and carboxylic acid (90% overall yield). Finally, all protecting groups were removed from **12** by exposure to $AlBr_3$ and EtSH,[11] furnishing vancomycin aglycon (**2**) in 50% yield. Synthetic aglycon **2**[12, 13] and derivative **12**[14] revealed identical physical properties (HPLC, $^{13}C$ NMR, IR, $[\alpha]_D^{25}$, MS) to those exhibited by samples derived from natural vancomycin (**1**)[15] (see Table 1 for selected physical data).

The chemistry described in this series of papers paves the way for the total synthesis of vancomycin (**1**) itself and other

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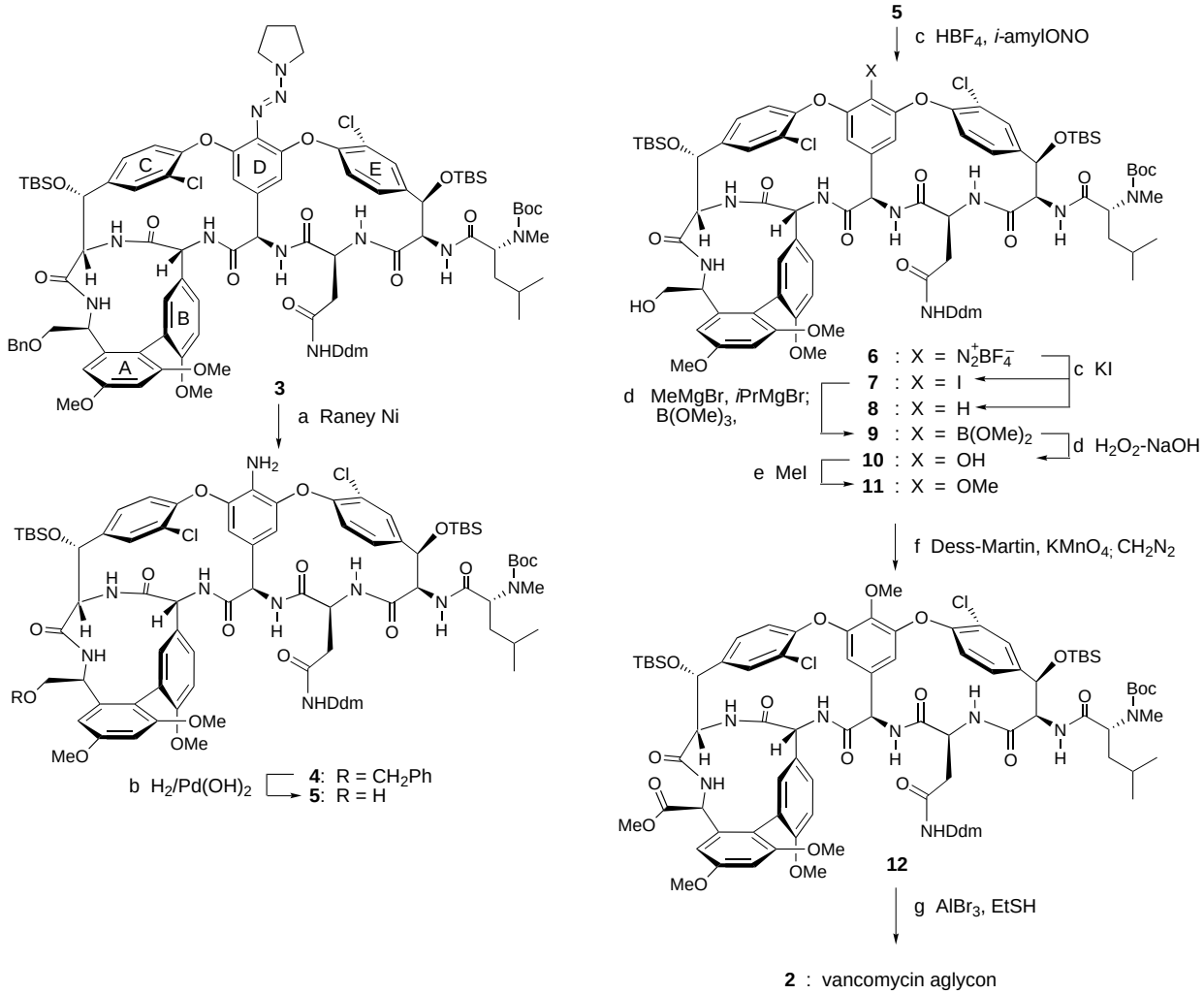
[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for assistance with the NMR spectroscopy and mass spectrometry, respectively. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, postdoctoral fellowships from the National Institutes of Health USA (to J.M.R.) and the George E. Hewitt Foundation, and grants from Pfizer, Schering Plough, Hoffmann La Roche, and Dupont Merck.

Table 1. Selected physical and spectroscopic data of compounds **2** and **12**.

**2** (trifluoroacetate salt): $[\alpha]_D^{25} = +80.63$ ($c = 0.4$, $CH_3OH$); IR (KBr): $\tilde{\nu}_{max} =$ 3398, 3010, 2918, 2846, 1717, 1671, 1589, 1513, 1431, 1262, 1206, 1175, 1139, 1057, 1032 $cm^{-1}$; $^1H$ NMR (600 MHz, $CD_3OD$, 330 K): $\delta = 7.73$ (br. d, $J =$ 7.8 Hz, 1H), 7.68 (bs, 1H), 7.64 (d, $J = 2$ Hz, 1H), 7.54 (dd, $J = 8.3$, 1.6 Hz, 1H), 7.5 (br. d, $J = 7.9$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.06 (d, $J = 2$ Hz, 1H), 6.95 (m, 2H), 6.45 (d, $J = 2.2$ Hz, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 5.95 (br. s, 1H), 5.91 (br. s, 1H), 5.78 (br. s, 1H), 5.34 (br. s, 2H), 5.26 (d, $J =$ 3.6 Hz, 1H), 4.79 (s, 1H), 4.75 (s, 1H), 4.68 (d, $J = 5.7$ Hz, 1H), 4.24 (br. d, $J = 8.3$ Hz, 1H), 4.16 (s, 1H), 3.99 (dd, $J = 7.2$, 7.0 Hz, 1H), 2.96 (br. d, 1H), 2.75 (s, 3H), 2.0–1.8 (m, 2H), 1.75–1.57 (m, 2H), 0.89 (d, $J = 6.4$ Hz, 3H), 0.88 (d, $J = 6.3$ Hz, 3H); for signal assignments see ref. [18]; $^{13}C$ NMR (150 MHz, $CD_3OD$, 330 K): $\delta = 175.5$, 172.5, 171.8, 170.4, 170.1, 169.4, 168.9, 159.3, 158.0, 156.6, 153.5, 151.7, 149.9, 148.5, 142.4, 141.0, 137.6, 136.1, 131.8, 130.2, 129.2, 128.8, 128.5, 128.1, 127.3, 126.5, 125.3, 122.3, 119.0, 118.6, 110.3, 108.2, 106.7, 104.3, 74.3, 73.4, 64.1, 62.2, 59.8, 58.8, 57.5, 56.6, 55.3, 52.9, 40.3, 36.5, 33.1, 25.6, 23.0, 22.8, 17.2; MALDI MS: calcd for $C_{52}H_{53}Cl_2N_8O_{17}$ [$M+H^+$]: 1143, found 1143.

**12:** $R_f = 0.40$ (silica gel, 5% MeOH in $CH_2Cl_2$); IR (KBr): $\tilde{\nu}_{max} = 2930$, 2855, 2338, 1741, 1675, 1647, 1610, 1577, 1506, 1487, 1664, 1417, 1318, 1238, 1173, 1107, 1022, 830 $cm^{-1}$; $^1H$ NMR (600 MHz, $CD_3OD$, 330 K): $\delta = 7.62$ (m, 2H), 7.55 (dd, $J = 1.84$ Hz, 1H), 7.35 (br. s, 1H), 7.21 (d, $J = 12.6$ Hz, 1H), 7.07 (m, 1H), 6.98 (m, 3H), 6.91 (d, $J = 9$ Hz, 1H), 6.87 (d, $J = 9.6$ Hz, 1H), 6.80 (d, $J = 11.4$ Hz, 2H), 6.72 (m, 2H), 6.63 (d, $J = 2.7$ Hz, 1H), 6.35 (d, $J =$ 2.28 Hz, 1H), 5.85 (s, 1H), 5.71 ( m, 1H), 5.70 (s, 1H), 5.51 (d, $J = 4.8$ Hz, 1H), 5.41 (s, 1H), 4.91 (m, 1H), 4.85 (m, 1H), 4.75 (m, 1H), 4.19 (br. s, 1H), 4.14 (s, 3H), 4.07 (br. s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.71 (s, 3H), 3.44 (s, 3H), 2.78 ( s, 3H), 2.54 (m, 2H), 2.31 (m, 1H), 2.21 (m, 1H), 1.41 (br. s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.84 (d, $J = 6.24$ Hz, 3H), 0.79 (d, $J = 6.24$ Hz, 3H), 0.13 (s, 3H), 0.1 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}C$ NMR (150 MHz, $CD_3OD$, 330 K): $\delta = 175.6$, 174.4, 173.5, 172.4, 172.1, 171.3, 169.6, 168.6, 161.3, 160.1, 160.0, 159.9, 159.7, 159.6, 158.6, 158.3, 154.1, 152.4, 151.3, 141.5, 139.4, 138.3, 136.5, 136.3, 135.0, 134.6, 130.7, 129.7, 129.5, 129.0, 128.9, 128.7, 128.0, 127.8, 125.0, 124.6, 124.5, 122.8, 114.6, 114.4, 113.0, 107.1, 106.1, 105.8, 99.1, 74.2, 73.5, 64.3, 61.6, 60.9, 60.5, 57.5, 56.5, 56.1, 55.7, 55.6, 55.4, 52.2, 36.4, 30.0, 28.4, 27.3, 24.9, 24.2, 23.1, 20.3, 18.7, 13.9, -5.0, -5.1, -5.4; FAB HRMS: calcd for $C_{90}H_{112}Cl_2N_8O_{21}Si_2Cs$ [$M+Cs^+$]: 1899.5912, found 1899.6060.




Scheme 1. Reagents and conditions: a) Raney Ni, MeOH, 25 °C, 10 h; b) $H_2$, $Pd(OH)_2$/C, 25 °C, 1 h, 85% overall from **3**; c) $HBF_4$ (20 equiv), isoamyl nitrite (20 equiv), MeCN, −20 °C, 0.5 h; then saturated aqueous KI, −20 → 25 °C, 2 h; d) MeMgBr (30 equiv), −40 → −20 °C, 1 h; then *i*PrMgBr (30 equiv), −40 °C, 2 h; $B(OMe)_3$ (100 equiv), −40 → 0 °C, 1 h; 1:1 mixture of 30% aqueous $H_2O_2$ and 10% aqueous NaOH solution, −20 → 0 °C, 0.5 h, overall 50% **10** and 40% **8** from **5**; e) $Cs_2CO_3$ (5 equiv), MeI (10 equiv), DMF (0.01 M), 0 °C, 1 h, 95%; f) Dess–Martin periodinane (3.0 equiv), $CH_2Cl_2$, 0.5 h; $KMnO_4$ (1 M aqueous solution, 10 equiv), *t*BuOH/5% aqueous $Na_2HPO_4$, 0.5 h; $CH_2N_2$, $Et_2O$, 25 °C, 5 min, 90%; g) $AlBr_3$ (20 equiv), EtSH:$CH_2Cl_2$ (1:1), 25 °C, 2.5 h, 50%. Boc = *tert*-butoxycarbonyl; Bn = benzyl; Ddm = 4,4-dimethoxydiphenylmethyl; DMF = dimethylformamide; TBS = *tert*-butyldimethylsilyl.

  1433-7851/98/3719-2718 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 19

naturally occurring glycopeptide antibiotics and sets the stage for the design and synthesis of combinatorial libraries of these important structures for chemical biology studies. Particularly rewarding in this venture were the development and utilization of the triazene-based synthetic technology for the construction of complex biaryl ethers[16] and the adoption of the Suzuki coupling reaction in the strategy[1] for the synthesis of the AB ring system of the target molecule.[17,19]

Received: August 21, 1998 [Z12317IE]
German version: *Angew. Chem.* **1998**, *110*, 2881 – 2883
**Keywords:** amino acids · antibiotics · natural products · total synthesis · vancomycin

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[13] HPLC conditions for vancomycin aglycon (**2**): C18 reverse-phase column (Vydac), gradient solvent system containing 0.05 % TFA ($H_2O$:$CH_3CN$, 95:5 → 70:30, 0 → 20 min), flow rate 1.0 mL min$^{-1}$, 25 °C, retention time 17.2 min.
[14] Authentic compound **12** was obtained from natural vancomycin hydrochloride by the following sequence: 1) introduction of the benzyloxycarbonyl (Cbz) group at the N atom (Cbz-Cl, NaOH, MeOH/$H_2O$); 2) methylation of the three phenolic hydroxy groups and the carboxyl moiety ($Cs_2CO_3$, MeI, DMF); 3) sugar hydrolysis (TFA, $CH_2Cl_2$[12]); 4) methylation of the newly liberated phenolic hydroxy group ($Cs_2CO_3$, MeI, DMF); 5) silylation of the benzylic hydroxy group (TBSOTf, 2,6-lutidine); 6) protection of the primary amide with a Ddm groups (Ddm-OH, AcOH, $H_2SO_4$ cat.); and 7) Cbz → Boc exchange ($H_2$, 10 % $Pd(OH)_2$/C; then $Boc_2O$, $Et_3N$). (TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate).
[15] We thank Dr. L. Homer Pearce of Lilly Research Laboratories for a generous gift of naturally occurring vancomycin.
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[19] Note added in proof (Sept. 3, 1998): Direct conversion of triazene **3** into the corresponding aryl iodide was achieved by treatment with TMSCl)NaI in acetonitrile at 0 °C: H. Ku, J. R. Barrio, *J. Org. Chem.* **1981**, *46*, 5239 – 5241.

# Site-Directed Surface Derivatization of MCM-41: Use of High-Resolution Transmission Electron Microscopy and Molecular Recognition for Determining the Position of Functionality within Mesoporous Materials**

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*Dedicated to Professor Sir John M. Thomas on the occasion of his 65th birthday*

There is considerable commercial interest in the immobilization of catalysts on solid oxide supports, since the active materials thus prepared are considerably easier to handle, retrieve, and recycle than their homogeneous counterparts.[1] They may also exhibit improved activities and selectivities over those found for the homogeneous analogues. An approach used frequently in the heterogenization of homogeneous catalysts onto siliceous materials is the covalent linking of the active moiety to the surface through a surface-bound tether containing a functional group (for example $(MeO)_3Si$-$CH_2CH_2CH_2NH_2$).[2, 3] This methodology has been employed successfully in the functionalization of various traditional types of silica support, and with the advent of mesoporous silicas, in particular MCM-41,[4] it has been utilized extensively in the development of the surface chemistry of these materials.

The two key features of mesoporous silicas are their highly regular structure composed of channels in a hexagonal arrangement with diameters of 20 to 100 Å and their large surface areas ($\geq 750\ m^2 g^{-1}$). The large pore sizes offer the possibility to tether sizeable and complex catalytically active sites within the silica framework. The topological restraints produced by the confinement of solvent, substrate, and reactant may be expected to give a greater efficiency and selectivity in the catalytic process (Figure 1 a).

MCM-41 is composed of particles that usually range in size from 0.5 to 5 μm. Both the internal and external surfaces terminate in a layer of silanol groups (Si – OH), which are the reactive handle by which any derivatization/anchoring of catalytic centers may take place. Hence, derivatization of the surface of freshly calcined MCM-41 with an appropriately functionalized tether for anchoring a given catalyst will take

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[**] This work was supported by a Smithson Research Fellowship (The Royal Society/Peterhouse) to D.S.S, an EPSRC post-doctoral research award to B.F.G.J and an EU Fellowship (TMR) to T.M.