(neighbor conformations) was calculated. The structure with the highest number of neighbors was taken as the center of a cluster, and formed together with all its neighbors a (first) cluster. The structures of this cluster were thereafter eliminated from the pool of structures. The process was repeated until the pool of structures was empty. In this way, a series of nonoverlapping clusters of structures was obtained.

Free energies of folding were calculated as $\Delta G_{\text{folding}} = -k_B T \ln(p_{\text{folded}}/p_{\text{unfolded}})$, where k_B is the Boltzmann constant, T is the temperature, and p_{folded} and p_{unfolded} are the relative probabilities of the folded and unfolded conformations; p_{folded} and p_{unfolded} are approximated by the number of folded and unfolded conformations sampled in the simulations.

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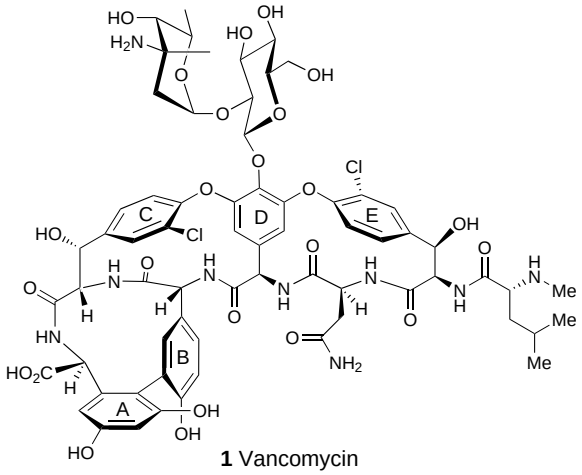
Total Synthesis of Vancomycin**

K. C. Nicolaou,* Helen J. Mitchell, Nareshkumar F. Jain, Nicolas Winssinger, Robert Hughes, and Toshikazu Bando

Within the class of the glycopeptide antibiotics[1] vancomycin (**1**)[2] occupies a commanding position as a highly effective and widely used clinical agent for combating severe bacterial infections caused by drug resistant pathogens.[1–3] This novel



1 Vancomycin

antibiotic, isolated from actinomycetes *Streptomyces orientalis* (later renamed *Nocardia orientalis* and finally reclassified as *Amycolatopsis orientalis*[2c]), has recently[3] moved to center stage by virture of its increasing importance in chemistry, biology, and medicine. The total synthesis of this antibiotic has long been considered as a formidable challenge to synthetic organic chemistry.[4] Intense research efforts in recent times have culminated in the total synthesis of the vancomycin aglycon **2** (see Scheme 1), recently accomplished by the research group of Evans[5] and our own.[6] Herein we wish to report the total synthesis of vancomycin (**1**) itself. This synthesis involves sequential glycosidations of a suitably protected derivative of the previously synthesized vancomycin aglycon **2**[6] and delivers the target molecule in a highly efficient and stereoselective manner.

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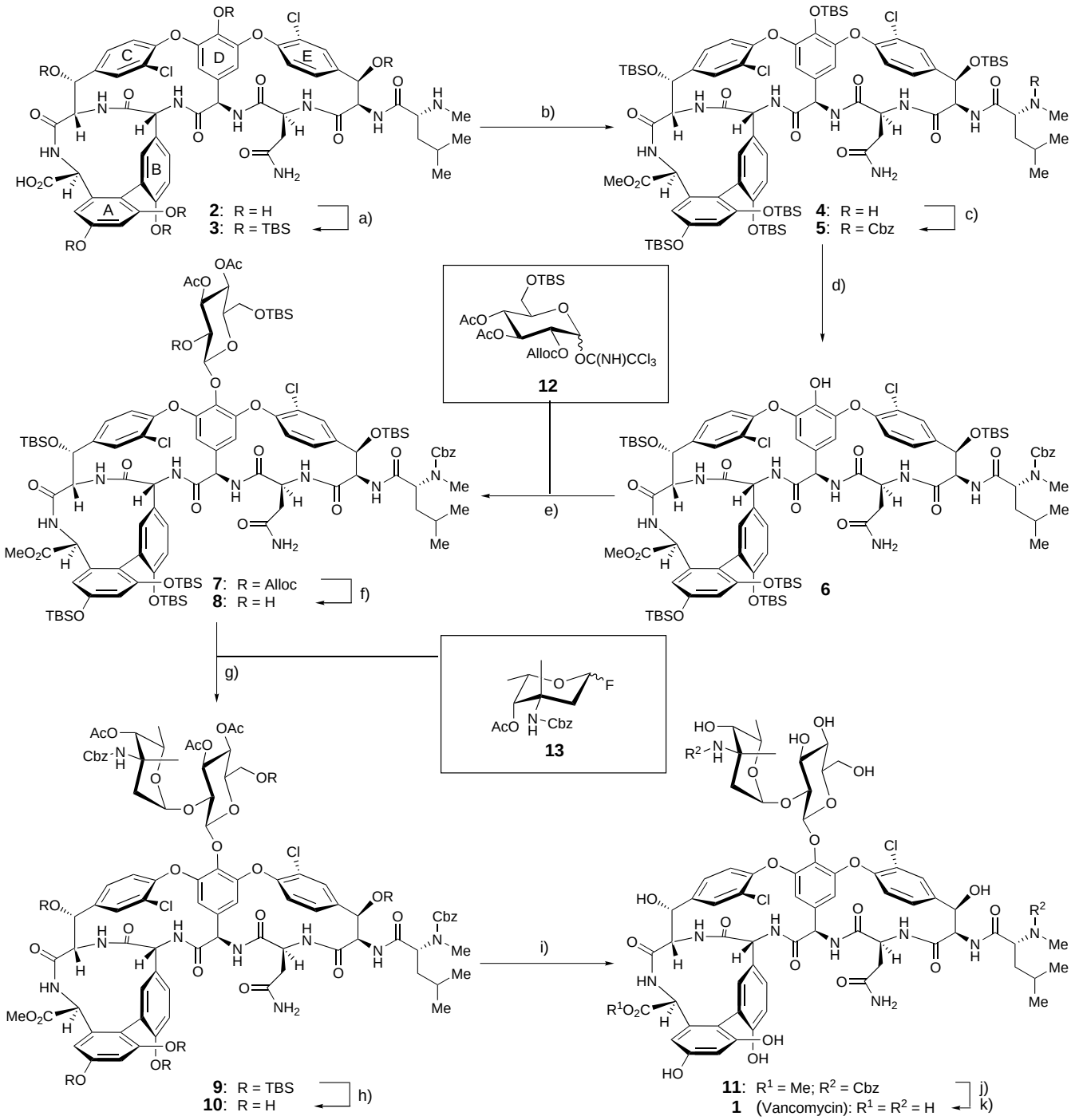
Before the challenging task of attaching the carbohydrate moieties onto the aglycon of vancomycin at the phenolic group of ring D could be attempted a suitably protected derivative had to be constructed. To this end, **2** was persilylated with TBSOTf in the presence of 2,6-lutidine to afford, after aqueous workup, the hexa(TBS) derivative **3** in 72% yield. Exposure of **3** to excess CH_2N_2 in diethyl ether gave methylester **4** (91% yield), which led to the Cbz-protected derivative **5** (92% yield) upon treatment with CbzCl and an aqueous solution of $NaHCO_3$. The key removal of the TBS group on ring D of **5** was effected selectively by exposure to $KF \cdot Al_2O_3$,[7] which furnished the desired vancomycin glycoside acceptor **6** in 60% yield (Scheme 1; Table 1).



Scheme 1. Total synthesis of vancomycin (**1**). a) TBSOTf (20 equiv); 2,6-lutidine (60 equiv), CH_2Cl_2/DMF (10/1), 0 → 23 °C, 7 h, 72%; b) CH_2N_2 (excess), Et_2O, 0 °C, 30 min, 91%; c) Cbz-Cl (5.0 equiv), $NaHCO_3$ (10.0 equiv), 1,4-dioxane/H_2O (10/1), 0 °C, 30 min, 92%; d) $KF \cdot Al_2O_3$ (ca. 1 equiv), CH_3CN, 0 °C, 2 h, 60%; e) **12** (5.0 equiv), $BF_3 \cdot Et_2O$ (10.0 equiv), CH_2Cl_2, −78 °C, 6 h, 82%; f) *n*Bu_3SnH (4.0 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), CH_2Cl_2, 23 °C, 30 min, 85%; g) **13** (4.0 equiv), $BF_3 \cdot Et_2O$ (3.0 equiv), CH_2Cl_2, −30 °C, 2 h, 84%; h) $HF \cdot$ pyr./pyr. (1:1, excess), THF, 0 → 23 °C, 12 h, 80%; i) K_2CO_3 (5.0 equiv), MeOH, 23 °C, 4 h, 95%; j) Raney nickel, *n*PrOH/H_2O (2/1), 23 °C, 45 min; k) LiOH (solid, 5.0 equiv), THF/H_2O (1/1), 0 °C, 20 min, 85% (from **11**). Alloc = allyloxycarbonyl, Cbz = benzyloxycarbonyl, DMF = dimethylformamide, TBS = *tert*-butyldimethylsilyl, TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate.

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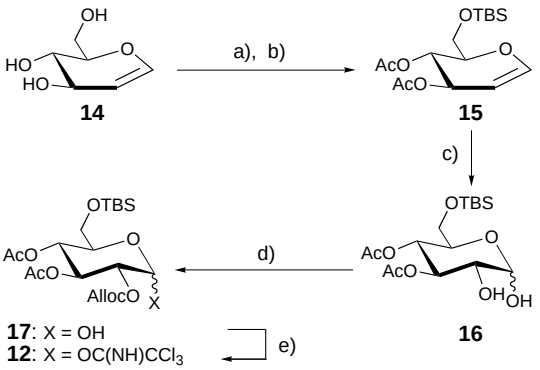
Table 1. Selected physical and spectroscopic data for **6**, **7**, and **9**.

6: $R_f = 0.31$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} = -14.0$ ($c = 1.12$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3403, 2995, 2857, 1751, 1676, 1670, 1658, 1508, 1472, 781\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.71$ (s, 1H), 7.47 (dd, $J = 1.0, 8.5$ Hz, 1H), 7.37–7.22 (m, 8H), 7.04 (d, $J = 8.0$ Hz, 1H), 7.01 (dd, $J = 2.0, 8.5$ Hz, 1H), 6.75 (d, $J = 8.5$, 1H), 6.40 (d, $J = 2.0$ Hz, 1H), 6.32 (d, $J = 2.0$ Hz, 1H), 5.86 (br s, 2H), 5.69 (s, 1H), 5.46 (d, $J = 10.0$ Hz, 1H), 5.34 (s, 1H), 5.33 (s, 1H), 5.14 (m, 2H), 4.96 (m, 1H), 4.91 (s, 1H), 4.85 (m, 1H), 4.70 (m, 1H), 4.08 (s, 1H), 3.74 (s, 3H), 2.95 (s, 3H), 2.38 (m, 2H), 1.80 (m, 1H), 1.48 (m, 2H), 1.00 (s, 9H), 0.93 (m, 6H), 0.90 (s, 9H), 0.84 (s, 9H), 0.63 (s, 9H), 0.21 (s, 6H), 0.16 (s, 3H), 0.10 (s, 3H), 0.08 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), −0.8 (s, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone, 315 K): $\delta = 175.6, 173.4, 172.8, 171.1, 168.0, 156.3, 155.8, 155.8, 153.9, 152.1, 150.1, 149.1, 148.3, 148.2, 137.2, 136.4, 133.5, 133.4, 133.0, 129.5, 129.1, 128.2, 128.2, 127.6, 127.4, 126.9, 126.4, 124.7, 120.4, 113.4, 113.1, 111.6, 105.0, 99.1, 74.6, 74.5, 70.3, 66.9, 64.1, 64.1, 64.0, 58.1, 55.3, 55.3, 49.1, 42.5, 41.3, 37.5, 36.4, 36.3, 35.1, 26.3, 26.2, 26.1, 25.7, 25.6, 25.5, 25.3, 25.2, 25.1, 23.6, 22.6, 22.3, 19.4, 19.3, 19.1, 19.0, 18.9, 18.7, 18.6, 18.6, 18.4, 18.3, −3.7, −3.7, −3.8, −3.9, −4.1, −4.1, −4.2, −4.3, −4.5, −4.6$; HR-MS (FAB): calcd for $C_{92}H_{130}Cl_2N_8O_{19}Si_5Cs$ [M+Cs$^+$]: 1993.6730; found: 1993.6606.

7: $R_f = 0.33$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} = +7.9$ ($c = 0.3$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3550, 2956, 2929, 2874, 2857, 1760, 1691, 1667, 1644, 1599, 1504, 1471, 1416, 1362, 1307, 1234, 1172, 1111, 1062, 948, 923, 837, 781\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.52$ (s, 1H), 7.51 (s, 1H), 7.45 (m, 2H), 7.42–7.30 (m, 10H), 7.27 (s, 1H), 7.07 (d, $J = 2.0$ Hz, 1H), 7.01 (dd, $J = 2.0, 8.5$ Hz, 1H), 6.77 (d, $J = 8.5$ Hz, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 6.35 (d, $J = 2.0$ Hz, 1H), 5.80–5.75 (m, 3H), 5.56–5.15 (m, 6H), 5.05–4.85 (m, 6H), 4.64 (m, 2H), 4.30 (dd, $J = 4.5, 11.0$ Hz, 1H), 4.11 (s, 1H), 3.85–3.80 (m, 1H), 3.82 (dd, $J = 3.0, 9.0$ Hz, 1H), 3.75 (s, 3H), 2.94 (s, 3H), 2.50–2.39 (m, 2H), 2.03 (s, 3H), 2.00 (s, 3H), 1.84 (m, 1H), 1.60–1.45 (m, 2H), 1.02 (s, 9H), 0.95 (s, 9H), 0.92–0.91 (m, 6H), 0.87 (s, 9H), 0.78 (s, 9H), 0.75 (s, 9H), 0.65 (s, 9H), 0.23 (s, 6H), 0.21 (s, 3H), 0.12 (s, 6H), 0.11 (s, 3H), 0.09 (s, 6H), 0.02 (s, 3H), −0.07 (s, 3H), −0.08 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (150 MHz, [D$_6$]acetone, 315 K): $\delta = 181.5, 171.8, 171.1, 170.5, 170.1, 170.1, 169.8, 169.0, 167.9, 167.9, 156.4, 155.8, 154.7, 154.0, 152.9, 151.8, 151.7, 141.4, 139.6, 138.0, 137.3, 137.2, 136.1, 132.7, 131.9, 130.5, 129.5, 129.5, 129.4, 129.4, 129.3, 129.3, 129.3, 129.0, 128.9, 128.8, 128.5, 128.0, 127.6, 127.3, 126.9, 126.4, 126.0, 124.9, 120.6, 120.5, 1118.2, 113.2, 111.6, 106.9, 104.5, 76.9, 76.8, 74.7, 74.2, 74.1, 74.0, 70.3, 69.0, 68.0, 64.2, 63.6, 60.1, 60.1, 57.7, 57.6, 55.6, 55.3, 54.8, 54.0, 52.8, 52.7, 52.2, 49.2, 39.7, 38.7, 38.7, 37.3, 36.6, 30.0, 26.4, 26.2, 26.2, 26.0, 25.7, 25.6, 25.5, 23.6, 23.5, 23.4, 22.8, 22.8, 20.9, 20.6, 19.0, 18.8, 18.3, 18.3, 14.2, 11.7, −3.9, −3.9, −4.2, −4.2, −4.3, −4.5, −4.6, −4.7, −4.8, −4.9, −5.3, −5.4$; HR-MS (FAB): calcd for $C_{112}H_{162}Cl_2N_8O_{28}Si_6Cs$ [M+Cs$^+$]: 2440.8874; found: 2440.8738.

9: $R_f = 0.36$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} = -9.0$ ($c = 0.3$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3550, 2928, 2876, 2856, 1755, 1718, 1682, 1654, 1504, 1470, 1458, 1416, 1298, 1252, 1062, 837\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD, 333 K): $\delta = 7.60–7.41$ (m, 3H), 7.40–7.18 (m, 10H), 7.09 (s, 2H), 7.03 (m, 2H), 6.79 (s, 1H), 6.78 (s, 1H), 6.44 (d, $J = 2$ Hz, 1H), 6.32 (s, 1H), 5.80 (s, 2H), 5.66–5.30 (m, 6H), 5.29–4.80 (m, 8H), 5.01 and 4.88 (AB, $J = 12.5$ Hz, 2H), 4.66 (m, 2H), 4.18–4.07 (m, 2H), 3.85–3.80 (m, 2H), 3.77 (s, 3H), 3.64 (m, 1H), 2.94 (s, 3H), 2.50 (m, 2H), 2.05 (s, 3H), 2.05–2.00 (m, 2H), 2.03 (s, 3H), 1.96 (s, 3H), 1.55 (m, 3H), 1.29 (s, 3H), 1.09 (d, $J = 5.5$ Hz, 3H), 1.03 (s, 9H), 0.96 (s, 9H), 0.93 (m, 6H), 0.88 (s, 9H), 0.82 (s, 9H), 0.76 (s, 9H), 0.66 (s, 9H), 0.24 (s, 6H), 0.19 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 12H), 0.04 (s, 3H), -0.06 (s, 6H); ^{13}C NMR (150 MHz, [D$_6$]acetone, 315 K): $\delta = 175.6, 173.4, 172.8, 171.2, 169.0, 169.0, 168.8, 168.1, 168.1, 168.0, 167.9, 167.9, 167.9, 157.5, 157.5, 156.4, 156.4, 156.4, 155.8, 155.3, 155.3, 155.0, 138.6, 138.5, 138.4, 138.4, 138.4, 137.3, 137.3, 137.3, 130.0, 130.0, 129.4, 129.4, 129.4, 129.0, 128.9, 128.9, 128.7, 128.7, 128.5, 128.5, 128.5, 120.8, 120.6, 120.6, 113.4, 112.0, 111.6, 98.6, 98.4, 95.2, 64.0, 60.2, 60.2, 60.1, 60.1, 60.1, 59.8, 59.8, 59.8, 59.8, 55.4, 55.4, 55.4, 55.4, 55.3, 55.3, 55.3, 55.2, 54.6, 53.4, 52.7, 52.1, 39.4, 39.3, 37.4, 37.3, 37.3, 36.4, 36.4, 36.4, 26.5, 26.4, 26.4, 26.2, 26.2, 26.2, 26.1, 25.7, 25.7, 24.2, 23.7, 23.7, 20.7, 20.7, 20.7, 20.6, 20.6, 20.6, 19.1, 19.1, 19.1, 18.8, 18.3, 18.3, 18.3, 17.9, 17.8, 17.6, −3.8, −3.8, −4.2, −4.2, −4.2, −4.2, −4.4, −4.4, −4.6, −4.7, −4.8, −4.8$; HR-MS (FAB): calcd for $C_{125}H_{179}Cl_2N_9O_{31}Si_6Cs$ [M+Cs$^+$]: 2676.1712; found: 2676.1552.

The final reaction scheme for the successful attachment of the disaccharide unit onto substrate **6** required considerable experimentation and fine-tuning of the protecting groups and glycosidation reaction. For example, initial successes of glycosidation with fully O-benzylated and N-Cbz protected carbohydrate donors[8] were countered by failure to remove the benzyl groups without reductive cleavage of the chloride on ring E. Similarly, attempts at glycosidation with persilylated or peracetylated carbohydrate donors were thwarted by steric hindrance, lability under the glycosidation conditions used, and/or low reactivity. A rewarding compromise was obtained when the glucose-derived donor was loaded with a trichloroacetimidate[9] at C1, an allyloxycarbonyl group at C2, acetate groups at C3 and C4, and a TBS group at C6 (→**12**, Schemes 1 and 2) and the vancosamine-derived donor included a fluoride[10] activating group at C1, a Cbz group on the nitrogen atom and an acetate group at C4 (→**13**, Schemes 1 and 3). The two carbohydrate donors **12** and **13** were prepared from readily available starting materials as summarized in Schemes 2 and 3, respectively.



Scheme 2. Synthesis of glucose donor **12**. a) TBS-Cl (1.0 equiv); imidazole (1.5 equiv), DMF, 0→23 °C, 1 h, 82%; b) Ac_2O (3.0 equiv), Et_3N (5.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 2 h, 97%; c) OsO_4 (0.05 equiv), NMO (1.2 equiv), acetone/H_2O (9/1), 23 °C, 12 h, 84%; d) Alloc-Cl (1.0 equiv), Et_3N (1.5 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 10 min, 35%; e) Cl_3CCN (10.0 equiv), DBU (0.05 equiv), CH_2Cl_2, 0 °C, 89%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, 4-DMAP = 4-dimethylaminopyridine, NMO = 4-methylmorpholine *N*-oxide

Glycosidation of **6** with excess trichloroacetimidate **12** proceeded smoothly at −78 °C in dichloromethane and in the presence of $BF_3 \cdot Et_2O$ to afford monosaccharide **7** in 82% yield.[11] The desired β stereochemistry was assumed at this stage, based on model studies, and was later confirmed by the successful conversion of this intermediate into vancomycin (**1**). The C2 hydroxyl group of the glucose ring was then liberated selectively and in high yield (85%) by treatment with nBu$_3$SnH/Pd[12] to afford the new glycoside acceptor **8** onto which vancosamine had to be installed. The latter goal was achieved by reaction of **8** with excess vancosamine donor **13** in dichloromethane and in the presence of $BF_3 \cdot Et_2O$ at −30 °C, to furnish the vancomycin derivative **9** in a yield of 84%. The required α stereochemistry of the newly formed glycoside bond, presumably enhanced by participation of the C4 acetoxy group as observed from model studies, was finally confirmed by the completion of the total synthesis of

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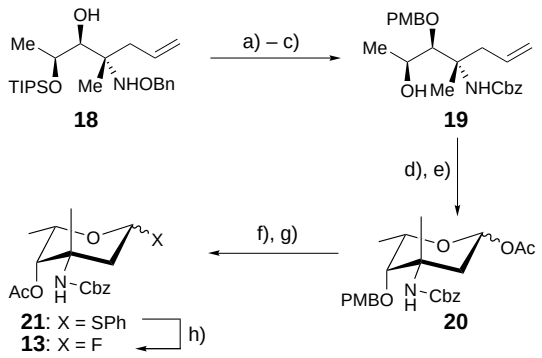

Scheme 3. Synthesis of vancosamine donor **13**. a) NaH (1.1 equiv), PMB-Cl (1.3 equiv), THF, 0 → 23 °C, 3 h, 93 %; b) $LiAlH_4$ (4.0 equiv), Et_2O, reflux, 18 h; c) Cbz-Cl (1.5 equiv), $NaHCO_3$ (2.0 equiv), 1,4-dioxane/H_2O (4/1), 23 °C, 2 h, 81 % (over two steps); d) O_3 (excess), CH_2Cl_2, −78 °C, 10 min; Me_2S −78 → 23 °C, 6 h, 92 %; e) Ac_2O (2.0 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 2 h, 96 %; f) PhSH (4.0 equiv); $BF_3 \cdot Et_2O$ (4.0 equiv), CH_2Cl_2, −20 °C, 1 h, 91 %; g) Ac_2O (2.0 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 2 h, 97 %; h) 1. NBS (1.5 equiv), acetone/H_2O (9/1), 0 °C, 30 min, 94 %; 2. DAST (1.2 equiv), CH_2Cl_2, 0 °C, 30 min, 100 %. DAST = diethylaminosulfur trifluoride, NBS = *N*-bromosuccinimide, PMB = *para*-methoxybenzyl, TIPS = triisopropylsilyl.

vancomycin (**1**) by sequential removal of the protecting groups from **9** (→**10** →**11** →**1**; see Scheme 1). Synthetic **11** was found to be spectroscopically (NMR) and chromatographically[13] identical with a sample prepared from natural vancomycin (**1**)[14] as indicated in Scheme 4. Synthetic vancomycin (**1**) was identical with an authentic sample (mixed NMR, HPLC[13]).

We also developed a synthesis of the acceptor **6** from vancomycin (**1**, Scheme 4) to facilitate semisynthetic studies and in order to pave the way for the practical construction of vancomycin libraries. Thus, vancomycin (**1**) was persilylated by exposure to excess TBSOTf and 2,6-lutidine in solution (dichloromethane/DMF) to give, after aqueous work-up, the nona(TBS) derivative **22** in 65 % yield. Treatment of **22** with excess CH_2N_2 in diethyl ether furnished methylester **23**, which was converted into the bis(Cbz) derivative **24** by exposure to excess Cbz-Cl and $NaHCO_3$ (80 % over two steps). Finally, reaction of the latter compound (**24**) with TFA/Me_2S/CH_2Cl_2 (1/1/1) at ambient temperature and under carefully controlled conditions furnished the desired vancomycin acceptor **6** in a yield of 60 %.

The work described here completes the total synthesis of vancomycin (**1**) from simple chemical building blocks and opens the way for the design and synthesis of vancomycin libraries for biological studies. Ahead lies the particularly attractive semisynthesis of analogues[15] with molecular diversity around the carbohydrate region of the molecule in which solid-phase and/or combinatorial chemistry may play an important role. Furthermore, with the conquest of vancomycin (**1**) the fall of other members of the group of the glycopeptide antibiotics should be considered as a matter of time.

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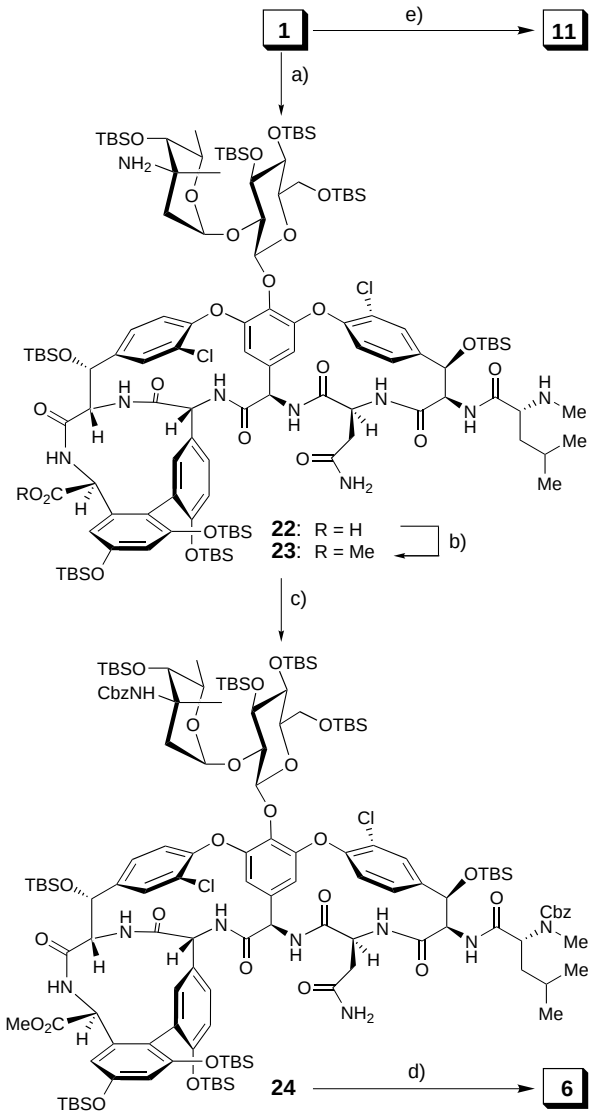

Scheme 4. Degradation of vancomycin (**1**). a) TBSOTf (excess); 2,6-lutidine (excess), CH_2Cl_2/DMF (10/1), 0 → 23 °C, 18 h; aq. $NaHCO_3$, 23 °C, 60 h, 65 %; b) CH_2N_2 (excess), Et_2O, 0 °C, 30 min; c) Cbz-Cl (5.0 equiv), $NaHCO_3$ (excess), 1,4-dioxane/H_2O (10/1), 0 °C, 30 min, 80 % (over two steps); d) TFA/Me_2S/CH_2Cl_2 (1/1/1; 0.01 M), 23 °C, 3 h, 60 %; e) 1. Cbz-Cl (3.0 equiv), $NaHCO_3$ (7.0 equiv), 1,4-dioxane/H_2O (5/1), 0 °C, 30 min; 2. MeI (20 equiv), $NaHCO_3$ (10.0 equiv), DMF, 0 °C, 30 min. TFA = trifluoroacetic acid.

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[14] We thank Dr. Homer Pearce of Lilly Research Laboratories for a generous gift of natural vancomycin (**1**).

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