– 26.3, – 29.3, – 31.4 and – 34.8 (total of 14 B); ESI-MS: (*m/z*): 268.3 [({$B_{20}H_{16}(OH)NH_3$}+2 H)$^-$].

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[1] B. L. Chamberland, E. L. Muetterties, *Inorg. Chem.* **1964**, *3*, 1450 – 1456; M. F. Hawthorne, R. L. Pilling, P. F. Stokely, *J. Am. Chem. Soc.* **1965**, *87*, 1893 – 1899.
[2] M. F. Hawthorne, R. L. Pilling, *J. Am. Chem. Soc.* **1966**, *88*, 3873.
[3] D. A. Feakes, K. Shelly, C. B. Knobler, M. F. Hawthorne, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 3029 – 3033; K. Shelly, D. A. Feakes, M. F. Hawthorne, P. G. Schmidt, T. A. Krisch, W. F. Bauer, *ibid.* **1992**, *89*, 9039 – 9043.
[4] M. F. Hawthorne, R. L. Pilling, P. F. Stokely, *J. Am. Chem. Soc.* **1965**, *87*, 4740 – 4746.
[5] A. R. Pitochelli, W. N. Lipscomb, M. F. Hawthorne, *J. Am. Chem. Soc.* **1962**, *84*, 3026 – 3027; B. G. DeBoer, A. Zalkin, D. H. Templeton, *Inorg. Chem.* **1968**, *6*, 1085 – 1090.
[6] a) Crystal structure analysis of $[Me_4N]_2$[**7**]: colorless crystals from ethanol/acetonitrile: $C_8H_{42}B_{20}N_2$, $M_r = 382.7$; crystal dimensions $0.18 \times 0.38 \times 0.5$ mm^3; Syntex $P\bar{1}$ diffractometer, $Cu_{K\alpha}$ radiation, $\lambda = 1.5418$ Å, 298 K; $\theta - 2\theta$ scan mode to $2\theta_{max} = 120°$. The unit-cell parameters were determined from 25 accurately centered reflections ($18.9° < 2\theta < 26.6°$): orthorhombic, space group *Pnam* (no. 62), $a = 10.279(2)$, $b = 34.000(5)$, $c = 8.310(2)$ Å, $V = 2904$ Å^3, $Z = 4$, $\rho_{calcd} = 0.97$ g cm^{-3}, $\mu = 2.94$ cm^{-1}. Of the 2330 unique reflections measured ($+h$, $+k$, $+l$), 1680 were considered observed ($I > 2\sigma(I)$), and the structure was solved by direct methods; 239 refined parameters, maximum residual electron density 0.13 e Å^{-3}, least-square refinement against $|F^2|$; $R = 0.078$ for the observed reflections, $R_w = 0.113$. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101 302. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[7] R. L. Pilling, M. F. Hawthorne, E. A. Pier, *J. Am. Chem. Soc.* **1964**, *86*, 3568 – 3569; C. H. Schwalbe, W. N. Lipscomb, *Inorg. Chem.* **1971**, *10*, 151 – 160.
[8] Crystal structure analysis of $[Me_3NH]$[**9**]: colorless crystals from an aqueous solution, $C_3H_{30}B_{20}N_2$, $M_r = 310.5$, crystal dimensions $0.48 \times 0.05 \times 0.55$ mm^3, Syntex $P\bar{1}$ diffractometer, $Cu_{K\alpha}$ radiation, $\lambda = 1.5418$ Å, 298 K; $\theta - 2\theta$ scan mode to $2\theta_{max} = 115°$. The unit-cell parameters were determined from 41 accurately centered reflections ($19.7° < 2\theta < 40.1°$): orthorhombic, space group $P2_12_12_1$, $a = 10.334(7)$, $b = 10.873(8)$, $c = 17.523(12)$ Å, $V = 1969$ Å^3, $Z = 4$, $\rho_{calcd} = 1.05$ g cm^{-3}, $\mu = 2.79$ cm^{-1}. Of the 1519 unique reflections measured ($+h$, $+k$, $+l$), 1318 were considered observed ($I > 2\sigma(I)$), and the structure was solved by direct methods; 156 refined parameters, maximum residual electron density 0.1 e Å^{-3}, least-square refinement against $|F^2|$; $R = 0.064$ for the observed reflections, $R_w = 0.082$.[6b]
[9] E. M. Georgiev, K. Shelly, D. A. Feakes, J. Kuniyoshi, S. Romano, M. F. Hawthorne, *Inorg. Chem.* **1996**, *35*, 5412 – 5416.

Expeditious Routes to Evernitrose and Vancosamine Derivatives and Synthesis of a Model Vancomycin Aryl Glycoside**

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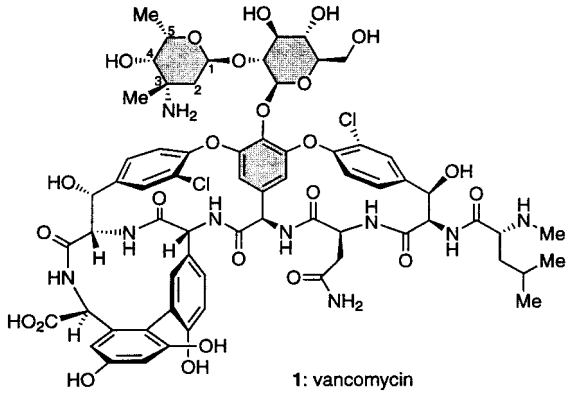
The antibiotics vancomycin[1] (**1**) and everninomicin 13,384-1[2] (for the structure, see following contribution)[3] include in their structures C3-branched 2,6-dideoxy-L-sugars containing



1: vancomycin

an amino[4] or a nitro group,[5] respectively. Our interest in the total synthesis of vancomycin[6] and everninomicin 13,384-1[7] dictated new synthetic routes to these unique sugars and methods for their attachment onto their respective target molecules. Here we report the successful attainment of both goals, culminating in the construction of key intermediates **11** and **16** (see Scheme 1) and the assembly of vancomycin disaccharide **22** (see Scheme 2). In the following communication[3] we describe the synthesis of an advanced everninomicin 13,384-1 segment incorporating the nitrosugar.

A key objective of our strategy toward the nitrogen-containing sugar units of these antibiotics was the construction of an intermediate (**7**), from which both compounds **11** and **16** could be generated (Scheme 1). Towards this goal, we envisioned a stereocontrolled *anti* addition[8] of an acyl anion equivalent to an aldehyde derived from L-lactic acid as a means to install the C4 stereocenter (the numbering is based on the final carbohydrate), where the functionality at C3 was projected to arise by nucleophilic chain extension of an

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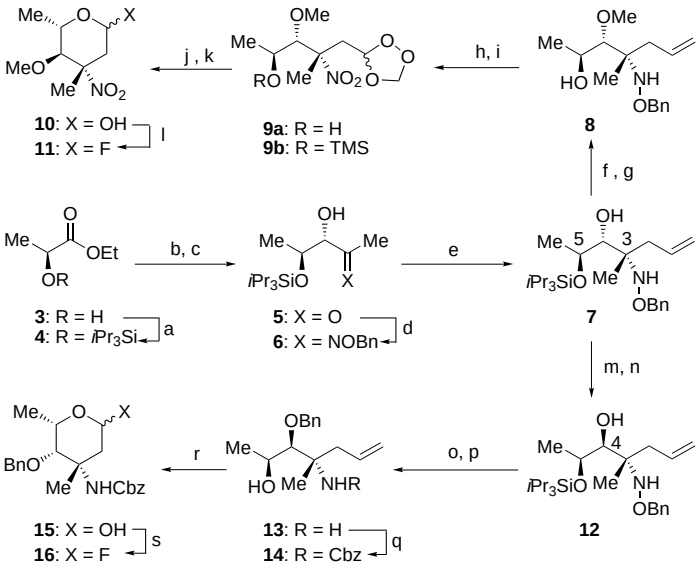


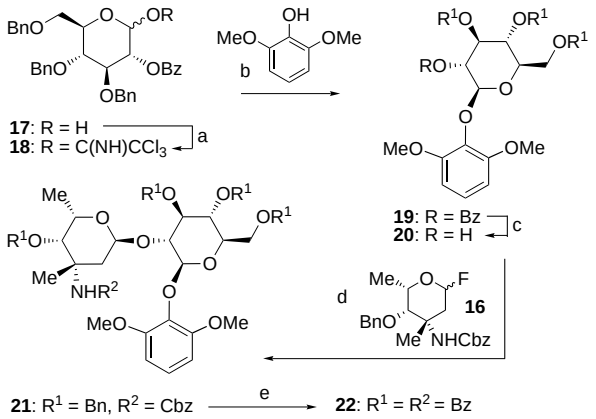
Scheme 1. Synthesis of carbohydrate donors **11** and **16**. a) iPr$_3$SiCl (1.1 equiv), imidazole (2.0 equiv), DMF, 10 h, 99%; b) DIBAL (1.3 equiv), CH_2Cl_2, $-78\,^\circ$C, 45 min; c) EVE-Li (1.3 equiv), THF, $-100\,^\circ$C; then 1N HCl (aq), THF/H_2O (80/20), 63% over three steps, $de = 85\%$; d) $BnONH_2 \cdot HCl$ (1.1 equiv), py, $0 \rightarrow 25\,^\circ$C, 97% ($E:Z \approx 4:1$); e) C_3H_5MgBr (2.5 equiv), Et_2O, $-35\,^\circ$C, 95% based on 50% conversion; f) NaH (1.1 equiv), MeI (1.3 equiv), DMF, $0 \rightarrow 25\,^\circ$C, 96%; g) nBu$_4$NF (1.1 equiv), THF, 92%; h) $(Me_3Si)_2NH$ (5.0 equiv), Me_3SiCl (0.05 equiv), CH_3CN; i) O_3, CCl_4/iC_8H_{18} (2/1), $-78 \rightarrow 25\,^\circ$C; j) TFA (2.0 equiv), 5 min; k) Ph_3P (2.0 equiv), 30 min, 82% over four steps; or i) O_3, CH_2Cl_2, $-78\,^\circ$C; k) Ph_3P (2.0 equiv), 30 min (**8** $\rightarrow$ **10**), 62% over two steps; l) DAST (1.3 equiv), CH_2Cl_2, $0\,^\circ$C, 30 min, 83%; m) $(COCl)_2$ (2.0 equiv), DMSO (2.5 equiv), Et_3N (4.0 equiv), $-78 \rightarrow 0\,^\circ$C, 91%; n) $NaBH_4$ (3.0 equiv), Et_2O/MeOH (5/1), $0\,^\circ$C, 2 h, 90%, $de = 92\%$; o) NaH (1.1 equiv), BnBr (1.2 equiv), nBu$_4$NI (0.2 equiv), DMF, $0 \rightarrow 25\,^\circ$C , 2 h, 96%; p) LAH (1.6 equiv), Et_2O, $25\,^\circ$C, 24 h; q) CbzCl (3.0 equiv), Na_2CO_3 (10.0 equiv), H_2O/THF (5/1), $0 \rightarrow 25\,^\circ$C, 30 min, 78% over two steps; r) 1. O_3, CH_2Cl_2, $-78\,^\circ$C, 1 h; 2. Ph_3P (2.0 equiv), $-78 \rightarrow 25\,^\circ$C, 3 h, 95%; s) DAST (1.4 equiv), CH_2Cl_2, 1 h, 85%. Bn = benzyl, Cbz = benzyloxycarbonyl, DAST = $Et_2N \cdot SF_3$, DIBAL = diisobutylaluminum hydride, EVE-Li = $CH_2C(OEt)Li$, LAH = lithium aluminum hydride, py = pyridine, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

oxime.[9] Thus, ethyl L-lactate (**3**, Scheme 1) was protected with the bulky iPr$_3$Si group to give **4** in high yield. Sequential reduction with DIBAL and addition of EVE-Li[10] at $-100\,^\circ$C followed by acidic workup afforded hydroxy ketone **5** as a mixture of diastereoisomers (85% *de*, 63% overall yield from **3**). After separation from its *syn* epimer by chromatography on silica gel, the *anti* isomer **5** was condensed with *O*-benzylhydroxylamine to afford the readily separable oxime ethers **6** (97%, $E:Z = 4:1$).[11] Gratifyingly, chain extension of the *E* isomer of **6** with allylmagnesium bromide at $-35\,^\circ$C afforded hydroxylamine **7** as the sole detectable diastereoisomer (95% based on 50% conversion).[12] Further elaboration of **7** to everninomicin carbohydrate **10** involved methylation of the free hydroxyl group (96%) followed by desilylation to afford **8** (92%). It was anticipated that exposure of **8** to ozone would generate simultaneously the required aldehyde and nitro groups.[13] However, ozonolysis of **8** (CH_2Cl_2, $-78\,^\circ$C) followed by workup with Me_2S and chromatography on silica gel afforded, instead of lactol **10**, the remarkably stable ozonide **9a** as a mixture of diastereoisomers (ca. 1:1). In contrast, workup with Ph_3P led smoothly to nitrosugar **10** (63% overall yield from **8**). The yield of the latter transformation was significantly improved by carrying out the ozonolysis in a 2:1 mixture of isooctane and CCl_4. Although the apolar nature of this solvent system dictated two additional steps (formation of the TMS ether prior to ozonolysis and removal of TMS prior to treatment with Ph_3P), the targeted nitrosugar **10** was obtained in 82% overall yield from **8**. Finally, exposure to DAST led to rapid conversion of **10** into a mixture of glycosyl fluorides **11** (83%).

Intermediate **7** also served as a convenient precursor of the vancomycin derivative **16**. Alcohol **7** carries the correct configurations at C3 and C5 and is readily converted into its C4 epimer **12** by Swern oxidation followed by chelation-controlled $NaBH_4$ reduction (90% yield, 92% *de*; Scheme 1). After purification of **12**, benzylation (96%) and exposure to LAH resulted in the formation of amino alcohol **13** by removal of both the benzyloxy and silyl groups.[14] The latter compound was converted into its Cbz-protected derivative **14** under standard conditions (78% over two steps). Finally, cleavage of the terminal olefin by ozonolysis followed by treatment with Ph_3P afforded a approximately 1:1 mixture of lactols **15** in 95% yield. As in the case of **11**, conversion of **15** into the glycosyl donor **16** was smoothly effected with DAST (85%).

With multigram quantities of L-vancosamine and L-evernitrose donors **16** and **11** at hand, strategies for attachment to their respective natural products were investigated. The stereoselective construction of a vancomycin disaccharide model system is shown in Scheme 2, whereas the introduction of evernitrose into its everninomicin segment is reported in the following communication.[3]

From the reported techniques for forming β-linked aryl glycosides,[15-17] the trichloroacetimidate method[18] was found to be the most suitable for our purpose. Thus, conversion of glucose derivative **17** into its trichloroacetimidate **18** followed by coupling with 2,6-dimethoxyphenol in the presence of



Scheme 2. Synthesis of the vancomycin model disaccharide. a) Cl_3CCN (5.0 equiv), DBU (cat.), CH_2Cl_2, $0\,^\circ$C, 15 min, 100%; b) $BF_3 \cdot Et_2O$ (0.6 equiv), CH_2Cl_2, 4-Å molecular sieves, $-30 \rightarrow 25\,^\circ$C, 24 h, 95%, $\beta:\alpha \approx 13:1$; c) 1% aq NaOH, MeOH, $25\,^\circ$C, 3 h, 90%; d) **16** (1.6 equiv), $BF_3 \cdot Et_2O$ (0.3 equiv), Me_3SiOTf (0.3 equiv), CH_2Cl_2, 4-Å molecular sieves, $-30 \rightarrow 25\,^\circ$C, 72 h, 89% based on 90% conversion, $\alpha:\beta \approx 10:1$; e) 1. H_2, Pd/C, EtOAc; 2. BzCl (7.0 equiv), py, 85% over two steps. Bz = benzoyl, DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene, Tf = trifluoromethylsulfonyl.

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$BF_3 \cdot Et_2O$ afforded the desired aryl glycoside **19** in excellent yield (95%) and with high stereoselectivity ($\beta:\alpha \approx 13:1$). Debenzoylation gave direct access to glycosyl acceptor **20**, setting the stage for coupling with glycosyl fluoride **16**. A combination of $BF_3 \cdot Et_2O$ and Me_3SiOTf was found to be highly effective for activation of **16**, furnishing, upon coupling with **20**, the desired α-glycoside **21** in 89% yield (based on 90% conversion) and with a stereoselectivity of about 10:1 (Table 1). Finally, hydrogenation and benzoylation of **21** gave the protected disaccharide **22** (85% over two steps). The configuration of the newly formed glycosidic bond was confirmed by NMR spectroscopy on **21** ($J_{1,2ax} = 4.5$ Hz)[16, 19] and **22**. The latter compound was also synthesized through glucal chemistry by Danishefsky and co-workers.[16]

In summary, we have synthesized vancosamine derivative **15** (11 steps from **3**, ca. 25% overall yield) and evernitrose (**10**, 9 steps from **3**, ca. 30% overall yield) from a common chiral intermediate derived from L-lactic acid. The described chemistry also provides a plausible scenario for the incorporation of the carbohydrate domain of vancomycin into its parent compound.[20]

Table 1. Selected physical properties of compounds **10**, **15**, and **21**.

10: $R_f = 0.25$ (silica gel, 70% Et_2O in hexanes); $[\alpha]_D^{22} = -31.5$ ($c = 1.0$ in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3381, 2987, 2942, 2842, 1548, 1455, 1393, 1354, 1285, 1183, 1155, 1102, 1046, 988, 942, 913, 876, 857\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.32$ (bd, $J = 4.0$ Hz, 1H, α-H1), 4.88 (dd, $J = 8.0$, 4.0 Hz, 1H, β-H1), 3.91 (dq, $J = 10.0$, 6.0 Hz, 1H, α-H5), 3.84 (bs, 1H, OH), 3.76 (d, $J = 10.0$ Hz, 1H , α-H4), 3.74 (d, $J = 10.0$ Hz, 1H, β-H4), 3.46 (dq, $J = 10.0$, 6.0 Hz, 1H, β-H5), 3.41 (s, 3H, α-OCH_3), 3.39 (s, 3H, β-OCH_3), 3.15, (bs, 1H, OH), 2.41 (dd, $J = 13.5$, 4.5 Hz, 1H, α-$H2_{eq}$), 2.23 (m, 2H, β-$H2_{eq,ax}$), 2.17 (dd, $J = 13.5$, 1.5 Hz, 1H, α-$H2_{ax}$), 1.81 (s, 3H, α-H3), 1.66 (s, 3H, β-H3), 1.36 (d, $J = 6.5$ Hz, 3H, α-H6), 1.31 (d, $J = 6.0$ Hz, 3H, β-H3); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 92.4$, 90.6, 90.1, 89.6, 84.5, 84.2, 71.2, 66.1, 66.0, 66.0, 60.8, 60.8, 44.2, 40.8, 18.5, 18.4, 18.3, 16.6; HR-MS (FAB) calcd for $C_8H_{15}O_5NNa$ [$M + Na^+$]: 228.0848, found: 228.0848.

15: $R_f = 0.12$ (silica gel, 60% Et_2O in hexanes); $[\alpha]_D^{22} = -56.8$ ($c = 0.5$ in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3410, 3064, 3032, 2930, 1713, 1517, 1453, 1380, 1350, 1280, 1240, 1208, 1160, 1068, 962, 885, 821, 753, 699, 585, 552, 486\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, mixture of anomers, ca. 1.8:1): $\delta =$ 7.32–7.27 (m, 10H, ArH), 5.34 (bs, 0.4H, α-H1), 5.03 and 4.99 (AB, $J =$ 12.5 Hz, 2H, CH_2Ar), 4.92 (bs, 1H, NH), 4.87 (m, 2.5H, β-H1, NH, CH_2Ar), 4.64 and 4.54 (AB, $J = 11.0$ Hz, 0.8H, CH_2Ar), 4.62 and 4.50 (AB, $J = 11.0$ Hz, 1.2H, CH_2Ar), 4.29 (bq, $J = 6.5$ Hz, 0.4H, α-H5), 3.82 (bq, $J =$ 6.5 Hz, 0.6H, β-H5), 3.56 (bs, 0.4H, α-H4), 3.52 (bs, 0.6H, β-H4), 3.15 (d, $J = 8.0$ Hz, 0.6H, β-OH), 2.61 (dd, $J = 8.0$, 1.5 Hz, 0.4H, β-$H2_{ax}$), 1.96 (dd, $J = 13.0$, 4.5 Hz, 0.6H, α-$H2_{eq}$), 1.81 (bd, $J = 11.0$ Hz, 0.4H, β-$H2_{ax}$), 1.78 (bd, $J = 13.5$ Hz, 0.6H, α-$H2_{ax}$); 1.73 (s, 1.2H, α-H3), 1.55 (s, 1.8H, β-H3), 1.30 (d, $J = 6.5$ Hz, 0.8H, α-H6), 1.30 (d, $J = 6.5$ Hz, 1.2H, β-H6); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 154.8$, 154.8, 137.9, 136.6, 136.4, 128.5, 128.4, 128.2, 128.2, 128.1, 128.1, 127.8, 92.7, 91.4, 80.1, 78.8, 75.8, 75.6, 70.1, 66.3, 66.2, 64.8, 55.3, 53.6, 40.5, 36.3, 29.7, 24.0, 22.0, 17.7, 17.5; HR-MS (FAB) calcd for $C_{22}H_{27}O_5NNa$ [$M + Na^+$]: 408.1787, found: 408.1780.

21: $R_f = 0.18$ (silica gel, 50% Et_2O in hexanes); $[\alpha]_D^{22} = -43.8$ ($c = 0.24$ in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3409, 3031, 2931, 1723, 1599, 1497, 1478, 1455, 1363, 1297, 1256, 1215, 1111, 1062, 735, 699\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.31-7.18$ (m, 25H, ArH), 7.02 (t, $J = 8.5$ Hz, 2H, phenol-H), 6.57 (d, $J = 8.5$ Hz, 2H, phenol-H), 5.32 (bd, $J = 4.5$ Hz, 1H, H1′), 5.08 (d, $J = 7.5$ Hz, 1H, H1), 4.98 (AB, $J = 11.0$ Hz, 2H, CH_2Ar), 4.90 (s, 1H, NH), 4.83 (AB, $J = 11.0$ Hz, 2H, CH_2Ar), 4.68 (AB, $J = 11.0$ Hz, 2H, CH_2Ar), 4.55 (AB, $J = 11.5$ Hz, 2H, CH_2Ar), 4.50 (m, 1H, H5′), 4.45 (AB, $J =$ 12.0 Hz, 2H, CH_2Ar), 3.94 (t, $J = 8.0$ Hz, 1H, H3), 3.77 (s, 6H, OCH_3), 3.72–3.65 (m, 3H, H2, H4, H6a), 3.61 (dd, $J = 12.0$, 5.5 Hz, 1H, H6b), 3.41 (s, 1H, H4′), 3.37 (m, 1H, H5), 1.84 (s, 3H, H3′), 1.83 (d, $J = 13.0$ Hz, 1H, $H2'_{eq}$), 1.78 (dd, $J = 13.0$, 4.5 Hz, 1H, $H2'_{ax}$), 1.09 (d, $J = 6.5$ Hz, 3H, H6′); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 154.9$, 153.9, 138.6, 138.4, 138.1, 136.6, 134.0, 130.0, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 124.0, 105.5, 100.7, 97.7, 86.0, 80.9, 78.2, 75.8, 75.8, 75.7, 75.3, 74.7, 73.6, 68.8, 66.0, 64.3, 56.1, 53.7, 36.6, 29.7, 23.4, 17.4; HRMS (FAB) calcd for $C_{57}H_{63}O_{12}NCs$ [$M + Cs^+$]: 1086.3405, found: 1086.3450.

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[1] a) M. H. McCormick, W. M. Stark, G. F. Pittenger, R. C. Pittenger, G. M. McGuire, *Antibiot. Annu.* **1956**, *1955–1956*, 606–611; b) D. H. Williams, V. Rajananda, M. P. Williamson, G. Bojesen in *Topics in Antibiotic Chemistry*, *Vol. 5* (Ed.: P. G. Sammes), Ellis Horwood, Chichester, **1980**, pp. 119–158.

[2] A. K. Ganguly, B. Pramanih, T. M. Chan, O. Sarre, Y.-T. Liu, J. Morton, V. M. Girijavallabhan, *Heterocycles* **1989**, *28*, 83–88.

[3] K. C. Nicolaou, R. M. Rodríguez, H. J. Mitchell, F. L. van Delft, *Angew. Chem.* **1998**, *110*, 1975–1977; *Angew. Chem. Int. Ed.* **1998**, *37*, 1874–1876.

[4] a) T. T. Thang, F. Winternitz, *J. Chem. Soc. Chem. Commun*. **1979**, 153–154; b) I. Dyong, H. Friege, *Chem. Ber*. **1979**, *112*, 3273–3281; c) T. T. Thang, F. Winternitz, *Tetrahedron Lett*. **1980**, *21*, 4495–4498; d) H. I. Ahmad, J. S. Brimacombe, A. S. Mengech, L. C. N. Tucker, *Carbohydr. Res.* **1981**, *93*, 288–293; e) I. Dyong, H. Friege, H. Luftmann, H. Merten, *Chem. Ber*. **1981**, *114*, 2669–2680; f) G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, *Tetrahedron Lett*. **1981**, *22*, 5073–5076; g) J. S. Brimacombe, A. S. Mengech, K. M. M. Rahman, L. C. N. Tucker, *Carbohydr. Res.* **1982**, *110*, 207–215; h) G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, *J. Carbohydr. Chem*. **1983**, *2*, 225–248; i) Y. Hamada, A. Kawai, T. Shioiri, *Tetrahedron Lett*. **1984**, *25*, 5413–5414; j) F. M. Hauser, S. R. Ellenberger, *J. Org. Chem*. **1986**, *51*, 50–57; k) I. Dyong, J. Weigand, J. Thiem, *Liebigs Ann. Chem*. **1986**, 577–599; l) A. Klemer, H. Wilbers, *Liebigs Ann. Chem*. **1987**, 815–823; m) Y. Hamada, A. Kawai, T. Matsui, O. Hara, T. Shioiri, *Tetrahedron* **1990**, *46*, 4823–4846; n) R. Greven, P. Jütten, H.-D. Scharf, *Carbohydr. Res.* **1995**, *275*, 83–93.

[5] a) J. Yoshimura, M. Matsuzawa, K. Sato, M. Funabashi, *Chem. Lett.* **1977**, 1403–1406; b) J. Yoshimura, M. Matsuzawa, M. Funabashi, *Bull. Chem. Soc. Jpn*. **1978**, *51*, 2064–2067; c) J. S. Brimacombe, A. S. Mengech, M. S. Saeed, *Carbohydr. Res.* **1979**, *75*, C5–C7; d) J. Yoshimura, M. Matsuzawa, K. Sato, Y. Nagasawa, *Carbohydr. Res.* **1979**, *76*, 67–78; e) J. S. Brimacombe, A. S. Mengech, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2054–2060; f) J. S. Brimacombe, M. S. Saeed, T. J. R. Weakley, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2061–2064; g) P. Jütten, H.-D. Scharf, *Carbohydr. Res.* **1991**, *212*, 93–108.

[6] a) K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T. Y. Yue, H. Li, S. Bräse, J. M. Ramanjulu, *J. Am. Chem. Soc*. **1997**, *119*, 3421–3422; b) K. C. Nicolaou, X. J. Chu, J. M. Ramanjulu, S. Natarajan, S. Bräse, F. Rübsam, C. N. C. Boddy, *Angew. Chem.* **1997**, *109*, 1518–1519; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1539–1540; c) K. C. Nicolaou, J. M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C. N. C. Boddy, F. Rübsam, *Chem. Commun.* **1997**, 1899–1900.

[7] K. C. Nicolaou, F. L. van Delft, S. C. Conley, H. J. Mitchell, J. Jin, R. M. Rodríguez, *J. Am. Chem. Soc.* **1997**, *119*, 9057–9058.

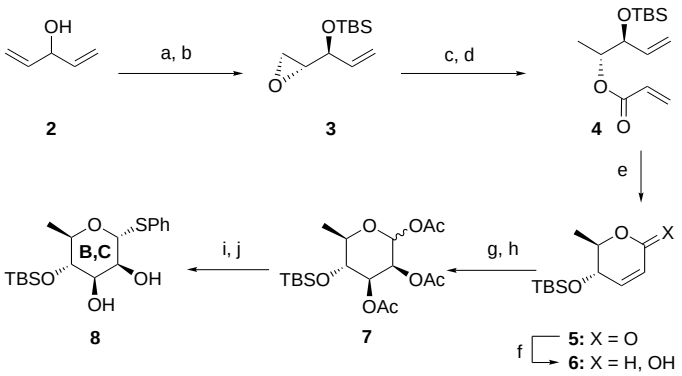
[8] M. Hirama, I. Nishizaki, T. Shigemoto, S. Itô, *J. Chem. Soc. Chem. Commun.* **1986**, 393–394.

[9] J. A. Marco, M. Cards, J. Murga, F. González, E. Falomir, *Tetrahedron Lett*. **1997**, *38*, 1841–1844.

[10] a) J. E. Baldwin, G. A. Höfle, O. W. Lever, Jr., *J. Am. Chem. Soc*. **1974**, *96*, 7125–7127; b) R. K. Boeckman, Jr., K. J. Bruza, *J. Org. Chem*. **1979**, *44*, 4781–4788.

[11] The minor *Z* isomer of **6** was unreactive under these conditions, whereas prolonged reaction time or higher temperatures led to desilylation. Regeneration of the *E* isomer was effected by equilibration of the *Z*-oxime (*t*BuOOH, CCl_4, 77 °C, 70% yield, ca. 4:1): N. B. Barhate, A. S. Gajare, R. D. Wakharkar, A. Sudalai, *Tetrahedron Lett.* **1997**, *38*, 653–656.

[12] For unclear reasons, condensation fails to go to completion, even upon use of a large excess of Grignard reagent, at increased dilution or temperature, or by reverse addition.
[13] P. S. Bailey, J. E. Keller, *J. Org. Chem.* **1968**, *33*, 2680 – 2684.
[14] E. F. J. de Vries, J. Brussee, A. van der Gen, *J. Org. Chem.* **1994**, *59*, 7133 – 7137.
[15] D. Kahne, S. Walker, Y. Cheng, D. V. Engen, *J. Am. Chem. Soc.* **1989**, *111*, 6881 – 6882.
[16] R. G. Dushin, S. J. Danishefsky, *J. Am. Chem. Soc.* **1992**, *114*, 3471 – 3475.
[17] B. A. Garcia, J. L. Poole, D. Y. Gin, *J. Am. Chem. Soc.* **1997**, *119*, 7597 – 7598.
[18] R. R. Schmidt, J. Michel, *Angew. Chem.* **1980**, *92*, 763 – 764; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731 – 732.
[19] A. W. Johnson, R. M. Smith, R. D. Guthrie, *J. Chem. Soc. Perkin Trans. 1* **1972**, 2153 – 2159.
[20] All new compounds exhibited satisfactory spectral and exact mass data.



Scheme 1. Synthesis of **8**. a) L-(+)-diisopropyl tartrate (0.09 equiv), $Ti(OiPr)_4$ (0.072 equiv), *t*BuOOH (2.0 equiv), CH_2Cl_2, $-15\,^\circ C$, 9 d; b) TBSCl (1.2 equiv), imidazole (1.5 equiv), CH_2Cl_2, $0 \rightarrow 25\,^\circ C$, 85% over two steps; c) $LiEt_3BH$ (1.0 M in THF, 1.1 equiv), CH_2Cl_2, $-40\,^\circ C$, 1 h, 91%; d) $CH_2{=}CHC(O)Cl$ (1.1 equiv), Et_3N (1.2 equiv), CH_2Cl_2, $0 \rightarrow 25\,^\circ C$, 1 h, 90%; e) $(PCy_3)_2Ru(=CHPh)Cl_2$ (0.15 equiv), CH_2Cl_2, $40\,^\circ C$, 72 h, 90%; f) DIBAL (2.2 equiv), CH_2Cl_2, $-78\,^\circ C$, 1 h, 98%; g) OsO_4 (0.03 equiv), NMO (1.5 equiv), acetone/H_2O (20/1), $25\,^\circ C$, 24 h, 97%; h) Ac_2O (4.0 equiv), Et_3N (6.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, $0 \rightarrow 25\,^\circ C$, 2 h, 98%; i) PhSH (1.3 equiv), Me_3SiOTf (0.03 equiv), CH_2Cl_2, $0 \rightarrow 25\,^\circ C$, 3 h, 69%; j) K_2CO_3 (0.2 equiv), MeOH, $25\,^\circ C$, 3 h, 100%. Cy = cyclohexyl, DIBAL = diisobutylaluminum hydride, 4-DMAP = 4-dimethylaminopyridine, NMO = 4-methylmorpholine *N*-oxide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl.

Stereocontrolled Synthesis of the Everninomicin $A_1B(A)C$ Ring Framework**

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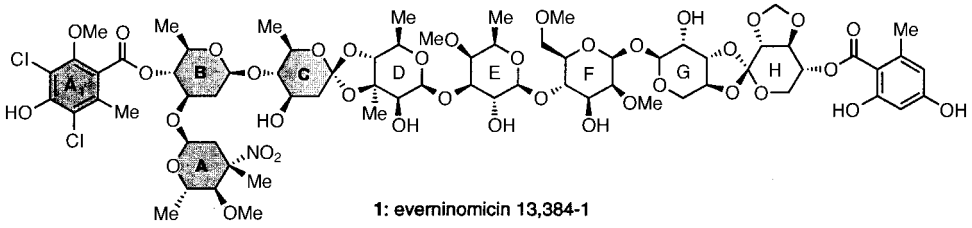
Everninomicin[1] (13,384-1, **1**), a highly effective antibiotic against drug-resistant bacterial strains, is a member of the orthosomycin family of compounds. Its novel and challenging structure encompasses, among other structural elements, the nitrosugar **A** and the fully substituted aromatic ring $\mathbf{A_1}$, and has stimulated a number of synthetic studies.[2] Notable among these are the formation of $\mathbf{A_1B(A)}$ and $\mathbf{A_1BC}$ systems by Scharf et al.[2h, k–m] and approaches to 2-deoxy-β-glycosides by Sinay et al.[2i–j] In the preceding contribution[3] we described a stereoselective synthesis of evernitrose (ring **A**) in its activated form (**26**, see Scheme 5). Here we report efficient constructions of rings **B**, **C**, and $\mathbf{A_1}$ as well as their assembly to the $\mathbf{A_1B(A)C}$ ring system (**28**, see Scheme 5) of everninomicin (**1**). The reported chemistry features a number of interesting strategies including a) an approach based on ring-closing olefin metathesis[4] to the common precursor **8** for carbohydrate systems **B** and **C** (see Scheme 1), b) control of the stereochemistry of the 2-deoxy-β-anomeric by a 1,2-migration and a sulfur-directed glycosidation,[5] and c) use of an acyl fluoride to effect formation of the sterically demanding ester bond between rings $\mathbf{A_1}$ and **B**.



An asymmetric synthesis of the common precursor to rings **B** and **C** is shown in Scheme 1. Sharpless epoxidation of prochiral divinylmethanol (**2**)[6] followed by silylation (TBSCl, imidazole, 85% over two steps)[7] furnished epoxide **3**. Regioselective ring opening of **3** with $LiEt_3BH$ ("super hydride") followed by esterification with acryloyl chloride under basic conditions (Et_3N) provided diolefin **4** (90%). Ring-closing metathesis induced by $(PCy_3)_2Ru(=CHPh)Cl_2$ as catalyst afforded lactone **5** (90%).[8] Contrary to expectations, dihydroxylation of **5** under a variety of conditions led to the wrong diastereomer, with the oxygen atoms *cis* to the bulky TBS group. Fortunately, reduction of lactone **5** with DIBAL, followed by OsO_4-catalyzed dihydroxylation of the resulting

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