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

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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



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 nitrogencontaining 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) iPr₃SiCl (1.1 equiv), imidazole (2.0 equiv), DMF, 10 h, 99 %; b) DIBAL (1.3 equiv), CH₂Cl₂, -78 °C, 45 min; c) EVE-Li (1.3 equiv), THF, -100 °C; then 1N HCl (aq), THF/H₂O (80/20), 63% over three steps, de = 85%; d) BnONH₂·HCl (1.1 equiv), py, $0 \rightarrow 25$ °C, 97 % $(E:Z\approx 4:1);$ e) C_3H_5MgBr (2.5 equiv), Et_2O_2 , $-35^{\circ}C_2$, 95% based on 50% conversion; f) NaH (1.1 equiv), MeI (1.3 equiv), DMF, $0 \rightarrow 25$ °C, 96%; g) nBu_4NF (1.1 equiv), THF, 92%; h) (Me₃Si)₂NH (5.0 equiv), Me₃SiCl (0.05 equiv), CH₃CN; i) O₃, CCl₄/*i*C₈H₁₈ (2/1), $-78 \rightarrow 25 \degree$ C; j) TFA (2.0 equiv), 5 min; k) Ph₃P (2.0 equiv), 30 min, 82 % over four steps; or i) O₃, CH₂Cl₂, -78 °C; k) Ph₃P (2.0 equiv), 30 min ($8 \rightarrow 10$), 62% over two steps; 1) DAST (1.3 equiv), CH₂Cl₂, 0°C, 30 min, 83 %; m) (COCl)₂ (2.0 equiv), DMSO (2.5 equiv), Et₃N (4.0 equiv), $-78 \rightarrow 0^{\circ}$ C, 91%; n) NaBH₄ (3.0 equiv), Et₂O/MeOH (5/1), 0°C, 2 h, 90%, de = 92%; o) NaH (1.1 equiv), BnBr (1.2 equiv), nBu_4NI (0.2 equiv), DMF, $0 \rightarrow 25^{\circ}C$, 2 h, 96%; p) LAH (1.6 equiv), Et₂O, 25 °C, 24 h; q) CbzCl (3.0 equiv), Na₂CO₃ (10.0 equiv), H₂O/THF (5/1), $0 \rightarrow 25$ °C, 30 min, 78% over two steps; r) 1. O₃, CH₂Cl₂, -78° C, 1 h; 2. Ph₃P (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 =CH2C(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 *i*Pr₃Si group to give 4 in high yield. Sequential reduction with DIBAL and addition of EVE-Li^{[10]} at -100 °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 Obenzylhydroxylamine to afford the readily separable oxime ethers 6 (97%, E:Z=4:1).^[11] Gratifyingly, chain extension of the E isomer of 6 with ally lmagnesium bromide at -35 °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 (CH₂Cl₂, -78° C) followed by workup with Me₂S and chromatography on silica gel afforded, instead of lactol 10, the remarkably stable ozonide 9a as a mixture of diastereoisom-

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ers (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 CCl₄. 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 NaBH₄ 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 Ph₃P 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) Cl₃CCN (5.0 equiv), DBU (cat.), CH₂Cl₂, 0°C, 15 min, 100%; b) BF₃·Et₂O (0.6 equiv), CH₂Cl₂, 4-Å molecular sieves, $-30 \rightarrow 25$ °C, 24 h, 95%, $\beta:\alpha \approx 13:1$; c) 1% aq NaOH, MeOH, 25°C, 3 h, 90%; d) **16** (1.6 equiv), BF₃·Et₂O (0.3 equiv), Me₃SiOTf (0.3 equiv), CH₂Cl₂, 4-Å molecular sieves, $-30 \rightarrow 25$ °C, 72 h, 89% based on 90% conversion, $\alpha:\beta \approx 10:1$; e) 1. H₂, 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.

BF₃·Et₂O afforded the desired aryl glycoside **19** in excellent yield (95%) and with high stereoselectivity (β : $\alpha \approx 13:1$). Debenzoylation gave direct access to glycosyl acceptor **20**, setting the stage for coupling with glycosyl fluoride **16**. A combination of BF₃·Et₂O and Me₃SiOTf 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

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

10: $R_{\rm f}$ =0.25 (silica gel, 70% Et₂O in hexanes); $[\alpha]_{\rm D}^{22}$ = -31.5 (*c*=1.0 in CHCl₃); IR (thin film): $\bar{\nu}_{\rm max}$ =3381,2987,2942,2842,1548,1455,1393,1354, 1285, 1183, 1155, 1102, 1046, 988, 942, 913, 876, 857 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 5.32 (bd, *J*=4.0 Hz, 1 H, α -H1), 4.88 (dd, *J*=8.0, 4.0 Hz, 1 H, β -H1), 3.91 (dq, *J*=10.0, 6.0 Hz, 1 H, α -H5), 3.84 (bs, 1 H, OH), 3.76 (d, *J*=10.0 Hz, 1 H, α -H4), 3.74 (d, *J*=10.0 Hz, 1 H, β -H4), 3.46 (dq, *J*=10.0, 6.0 Hz, 1 H, β -H5), 3.41 (s, 3H, α -OCH₃), 3.39 (s, 3H, β -OCH₃), 3.15, (bs, 1 H, OH), 2.41 (dd, *J*=13.5, 4.5 Hz, 1 H, α -H2_{eq}), 2.23 (m, 2 H, β -H2_{eq,ax}), 2.17 (dd, *J*=6.5 Hz, 3 H, α -H6), 1.31 (d, *J*=6.0 Hz, 3 H, β -H3); ¹³C NMR (125 MHz, CDCl₃) δ = 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 C₈H₁₅O₅NNa [*M*+Na⁺]: 228.0848, found: 228.0848.

15: $R_{\rm f} = 0.12$ (silica gel, 60% Et₂O in hexanes); $[\alpha]_{\rm D}^{22} = -56.8$ (c = 0.5 in CHCl₃); 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, CDCl₃, 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, CH₂Ar), 4.92 (bs, 1H, NH), 4.87 (m, 2.5 H, β -H1, NH, CH₂Ar), 4.64 and 4.54 (AB, J = 11.0 Hz, 0.8 H, CH₂Ar), 4.62 and 4.50 (AB, J = 11.0 Hz, 1.2 H, CH₂Ar), 4.29 (bq, J = 6.5 Hz, 0.4 H, α -H5), 3.82 (bq, M = 6.5 Hz, 0.4 H, α -H5), 3.82 (bq, M = 6.5 Hz, 0.4 H, α -H5), 3.82 (bq, M = 6.5 Hz, 0.4 H, α -H5), 3.82 (bq, M = 6.5 Hz, 0.4 H, α -H5), 3.82 (bq, M = 6.5 Hz, 0.4 H, α -H5), 3.82 (bq, M = 6.5 Hz, 0.4 H, α -H5), 3.82 (bq, M = 6.5 Hz, 0.4 Hz 6.5 Hz, 0.6 H, β -H5), 3.56 (bs, 0.4 H, α -H4), 3.52 (bs, 0.6 H, β -H4), 3.15 (d, J = 8.0 Hz, 0.6 H, β -OH), 2.61 (dd, J = 8.0, 1.5 Hz, 0.4 H, β -H2_{ax}), 1.96 (dd, $J\,{=}\,13.0,~4.5~{\rm Hz},~0.6~{\rm H},~\alpha{-}{\rm H2}_{\rm eq}),~1.81~({\rm bd},~J\,{=}\,11.0~{\rm Hz},~0.4~{\rm H},~\beta{-}{\rm H2}_{\rm ax}),~1.78$ (bd, J = 13.5 Hz, 0.6 H, α -H2_{ax}); 1.73 (s, 1.2 H, α -H3), 1.55 (s, 1.8 H, β -H3), 1.30 (d, J = 6.5 Hz, 0.8 H, α -H6), 1.30 (d, J = 6.5 Hz, 1.2 H, β -H6); ¹³C NMR $(125 \text{ MHz}, \text{CDCl}_3): \delta = 154.8, 154.8, 137.9, 136.6, 136.4, 128.5, 128.4, 128.2,$ 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 C₂₂H₂₇O₅NNa [*M* + Na⁺]: 408.1787, found: 408.1780.

21: $R_{\rm f} = 0.18$ (silica gel, 50% Et₂O in hexanes); $[\alpha]_{\rm D}^{22} = -43.8$ (c = 0.24 in CHCl₃); 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, CDCl₃): $\delta = 7.31 - 7.18$ (m, 25 H, ArH), 7.02 (t, J = 8.5 Hz, 2 H, 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, 1 H, H1), 4.98 (AB, J = 11.0 Hz, 2 H, CH₂Ar), 4.90 (s, 1 H, NH), 4.83 (AB, J=11.0 Hz, 2H, CH₂Ar), 4.68 (AB, J=11.0 Hz, 2H, CH₂Ar), 4.55 (AB, J = 11.5 Hz, 2H, CH₂Ar), 4.50 (m, 1H, H5'), 4.45 (AB, J = 10.5 CH₂Ar), 4.50 (m, 1H, H5'), 4.45 (AB, J = 10.5 CH₂Ar) 12.0 Hz, 2H, CH₂Ar), 3.94 (t, J = 8.0 Hz, 1H, H3), 3.77 (s, 6H, OCH₃), 3.72 - 3.65 (m, 3H, H2, H4, H6a), 3.61 (dd, J = 12.0, 5.5 Hz, 1H, H6b), 3.41 (s, 1 H, H4'), 3.37 (m, 1 H, H5), 1.84 (s, 3 H, H3'), 1.83 (d, J = 13.0 Hz, 1 H, $H2'_{eq}$, 1.78 (dd, J = 13.0, 4.5 Hz, 1H, $H2'_{ax}$), 1.09 (d, J = 6.5 Hz, 3H, H6'); ¹³C NMR (125 MHz, CDCl₃): $\delta = 154.9$, 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 C₅₇H₆₃O₁₂NCs $[M + Cs^+]$: 1086.3405, found: 1086.3450.

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]

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Scheme 1. Synthesis of **8**. a) L-(+)-diisopropyl tartrate (0.09 equiv), Ti(O*i*Pr)₄ (0.072 equiv), *t*BuOOH (2.0 equiv), CH₂Cl₂, -15° C, 9 d; b) TBSCl (1.2 equiv), imidazole (1.5 equiv), CH₂Cl₂, $0 \rightarrow 25^{\circ}$ C, 85% over two steps; c) LiEt₃BH (1.0 m in THF, 1.1 equiv), CH₂Cl₂, -40° C, 1 h, 91%; d) CH₂=CHC(O)Cl (1.1 equiv), Et₃N (1.2 equiv), CH₂Cl₂, $0 \rightarrow 25^{\circ}$ C, 1 h, 90%; e) (PCy₃)₂Ru(=CHPh)Cl₂ (0.15 equiv), CH₂Cl₂, 40° C, 72 h, 90%; f) DIBAL (2.2 equiv), CH₂Cl₂, -78° C, 1 h, 98%; g) OsO₄ (0.03 equiv), NMO (1.5 equiv), acetone/H₂O (20/1), 25^{\circ}C, 24 h, 97%; h) Ac₂O (4.0 equiv), Et₃N (6.0 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, $0 \rightarrow 25^{\circ}$ C, 2 h, 98%; i) PhSH (1.3 equiv), Me₃SiOTf (0.03 equiv), CH₂Cl₂, $0 \rightarrow 25^{\circ}$ C, 3 h, 69%; j) K₂CO₃ (0.2 equiv), MeOH, 25°C, 3 h, 100%. Cy = cyclohexyl, DIBAL = diisobutylaluminum hydride, 4-DMAP =4-dimethylaminopyridine, NMO =4-methylmorpholine *N*-oxide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl.

among these are the formation of $A_1B(A)$ and A_1BC systems

by Scharf et al.^[2h, k-m] and approaches to 2-deoxy-β-glycosides

Stereocontrolled Synthesis of the Everninomicin A₁B(A)C Ring Framework**

K. C. Nicolaou,* Rosa M. Rodríguez, Helen J. Mitchell, and Floris L. van Delft

Everninomicin^[1] (13,384-1, 1), a highly effective antibiotic against drug-resistant bacterial strains, is a member of the



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 **A**₁ as well as their assembly to the **A**₁**B**(**A**)**C** ring system (**28**, see Scheme 5) of everninomicin (**1**). The reported chemistry features a number of interesting strategies including a) an ap-

orthosomycin family of compounds. Its novel and challenging structure encompasses, among other structural elements, the nitrosugar A and the fully substituted aromatic ring A_1 , and has stimulated a number of synthetic studies.^[2] Notable

[**] This work was financially supported by the National Institutes of Health (USA) and the Skaggs Institute for Chemical Biology. We also thank the M. E. C., Spain (R.M.R., Fullbright), and the Netherlands Organization for Scientific Research (NWO; (F.L.v.D.) for fellowships. proach 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 **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 LiEt₃BH ("super hydride") followed by esterification with acryloyl chloride under basic conditions (Et₃N) provided diolefin **4** (90%). Ring-closing metathesis induced by (PCy₃)₂Ru(=CHPh)Cl₂ 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 OsO₄-catalyzed dihydroxylation of the resulting

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