

ence of NaH and [18]crown-6 (80% yield), to furnish compound **41** via alcohol **40**. Reaction of the highly sensitive olefinic orthoester **41** with NMO/OsO₄ in the presence of quinuclidine led to 1,2-diol **42** as the major product (70% yield, in an approximate 8:1 ratio with its diastereoisomer). The chromatographically purified diol **42** was then regioselectively converted into the monobenzoate **43** by treatment with *n*Bu₃SnO/BzCl (97% yield, in an approximate 5:1 ratio with its regioisomer).^[15] After chromatographic separation **43** was oxidized (Dess–Martin periodinane)^[16] and reduced with Li(*t*BuO)₃AlH to afford, via the corresponding ketone, the desired hydroxy compound **44** (80% overall yield for the last two steps). Having successfully installed the required α -hydroxy group at C2 of ring H, it was now time to remove the benzoate group from the C3 oxygen atom of ring H and to transform the resulting *trans*-1,2-diol system into the desired methylene acetal functionality. To accomplish this goal, benzoate **44** was treated with NaOH in MeOH and the resulting diol (**45**, 98% yield) was converted into methylene acetal **46**, in 90% yield, by slowly adding it to a mixture of aqueous NaOH, CH₂Br₂, and *n*Bu₄NBr at 65 °C.^[17] The remaining steps for the completion of the synthesis of the FGHA₂ fragment **2** involved the DDQ-induced removal of the PMB group from ring H of **46** to afford **47** (85% yield), esterification of the latter compound with acyl fluoride **4** in the presence of NaH in THF (96% yield), and removal of the TBS group from ring F of the obtained ester (*n*Bu₄NF, 90% yield; Scheme 6). The following communication^[18] describes the construction of the required DE fragment and the completion of the total synthesis of everninomicin 13,384-1 (**1**).^[19]

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Total Synthesis of Everninomicin 13,384-1— Part 3: Synthesis of the DE Fragment and Completion of the Total Synthesis**

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In the preceding communications,^[1, 2] we described the synthesis of the A₁B(A)C and FGHA₂ fragments of everninomicin 13,384-1 (**1**, Figure 1). Herein, we report the construction of the remaining DE fragment and the completion of the total synthesis of **1**. Figure 1 depicts the retrosynthetic excision of the DE fragment from **1** as the appropriately functionalized key intermediate **2**, and its further disconnection to building blocks **3** and **4**. The protecting groups on **2** were carefully defined so as to be compatible not only with its assembly, but also with its incorporation into the structure of the final target. The two main issues that had to be addressed for the synthesis of **2**

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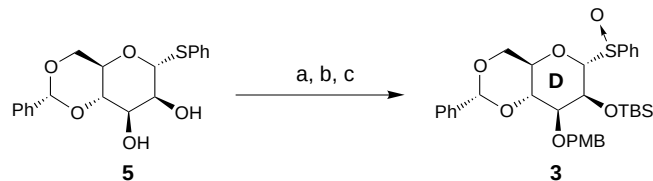


were the following: 1) construction of the β -mannoside linkage and 2) installment of the tertiary center on ring D. We chose the sulfoxide-based glycosidation reaction of Kahne et al.^[3] as the coupling procedure for **3** and **4** and designed the benzyldiene ring^[4] in **3** to ensure the stereocontrolled formation of the β -mannoside bond. The introduction of the methyl group at C3 of ring D was postponed until after the coupling to avoid unfavorable 1,3-diaxial interactions^[5] during the planned nucleophilic attack (see below).

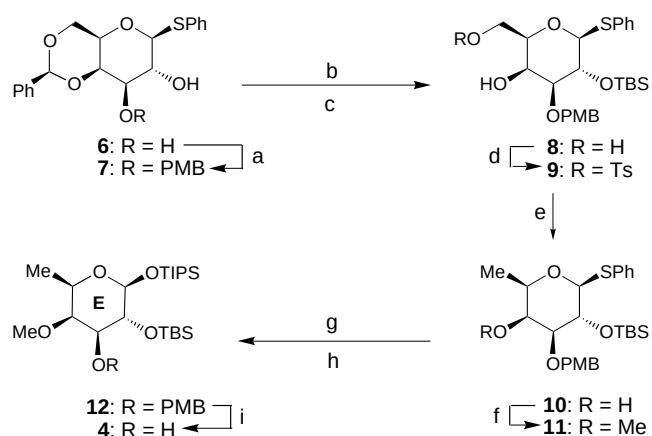
Chemical reaction scheme showing the conversion of compound **5** to compound **3** under conditions a, b, and c.

Compound **5** (left) is a bicyclic acetal derivative. It features a phenyl group (Ph), a hydroxyl group (OH), and a thioether group (SPh).

Compound **3** (right) is a bicyclic acetal derivative. It features a phenyl group (Ph), a thioether group (SPh), a tert-butyldimethylsilyl ether group (OTBS), and a p-methoxybenzyl group (OPMB).

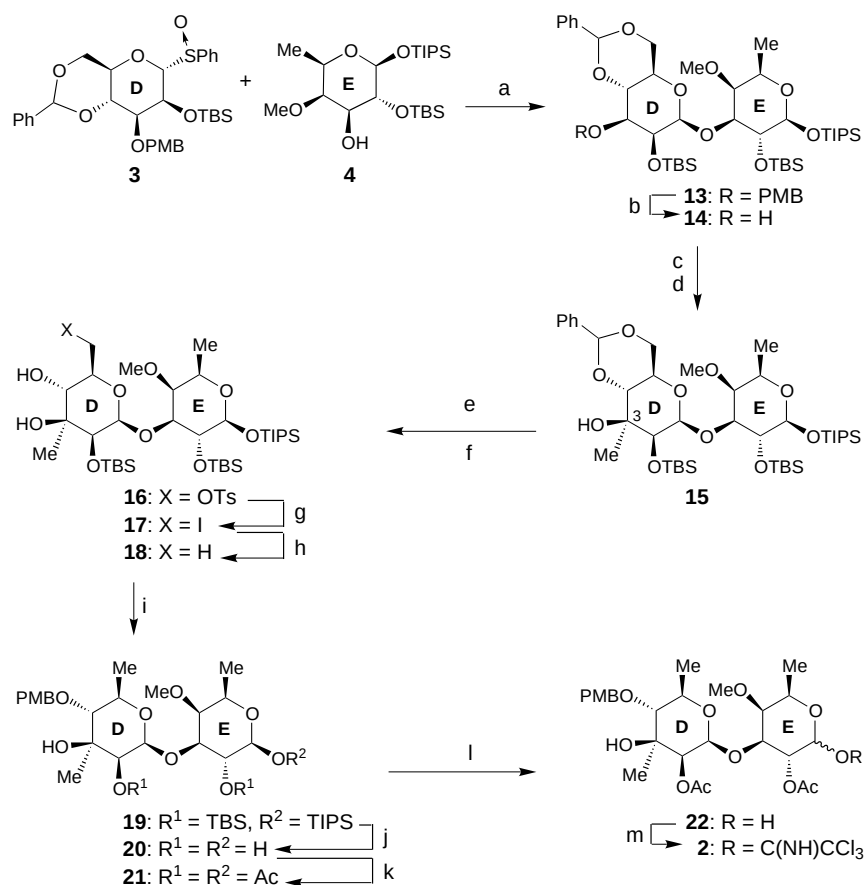


The synthesis of the other requisite fragment, ring E (**4**), is shown in Scheme 2. The tin acetal technology^[7] was again used to facilitate the PMB monoprotection of the starting material **6**^[8] (*n*Bu₂SnO/PMBCl/*n*Bu₄NI, 87% yield) and furnish the C3 protected intermediate **7**. TBS protection of the C2 hydroxyl group (TBSOTf/2,6-lutidine, 97% yield) followed by cleavage of the benzylidene group with Zn(OTf)₂/EtSH (77%) afforded diol **8**. Selective tosylation of the



primary hydroxyl group of **8** (TsCl/py, 97%) followed by LAH reduction led to derivative **10** (90%), which was methylated (NaH/MeI, 94% yield) at C4 to afford methoxy compound **11**. Finally, cleavage of the thiophenyl group from **11** with NBS/H₂O (95% yield) followed by silylation (TIPS-OTf/2,6-lutidine, 97%) afforded compound **12** (β : α ratio approximately 2:1), from which the PMB group was oxidatively removed (DDQ, 98% yield) to furnish the desired building block **4**.

The construction of key intermediate **2** from fragments **3** and **4** is summarized in Scheme 3. This assembly began with the stereoselective coupling of sulfoxide **3** with acceptor **4** in the presence of TiF_4 and di-*tert*-butyl-4-methyl pyridine (DTBMP) to afford the β -mannoside **13** (glycosidation with



Scheme 3. Assembly of DE fragment **2**. a) 1.3 equiv **3**, 1.3 equiv Tf₂O, 2.2 equiv DTBMP, CH₂Cl₂, -78 °C; 1.0 equiv **4**, -78 → 0 °C, 2 h, 71 %; b) 1.3 equiv DDQ, CH₂Cl₂/H₂O (10/1), 0 → 25 °C, 2 h, 95 %; c) 1.5 equiv NMO, 0.05 equiv TPAP, CH₂Cl₂, 25 °C, 2 h; d) 1.4 equiv MeLi, Et₂O, -78 °C, 1 h, 88 % over two steps; e) H₂, 0.2 equiv 10 % Pd/C (w/w), EtOAc, 25 °C, 2 h, 97 %; f) 1.2 equiv TsCl, py, 0 → 25 °C, 12 h, 87 %; g) 5.0 equiv LiI, DMF, 80 → 100 °C, 2 h, 86 %; h) 3.0 equiv *n*Bu₃SnH, 0.01 equiv AIBN, PhH, 80 °C, 0.5 h, 97 %; i) 1.1 equiv *n*Bu₂SnO, toluene, 110 °C, 10 h; 1.5 equiv PMBCl, 0.2 equiv *n*Bu₄NI, 25 → 110 °C, 8 h, 63 %; j) 4.0 equiv *n*Bu₄NF, THF, 25 °C, 6 h; k) 2.5 equiv Ac₂O, 4.0 equiv Et₃N, 0.2 equiv 4-DMAP, CH₂Cl₂, 0 → 25 °C, 1 h, 90 % over two steps; l) 1.3 equiv *n*BuNH₂, THF, 25 °C, 5 h, 86 %; m) 5.0 equiv CCl₃CN, 0.05 equiv DBU, CH₂Cl₂, 0 °C, 0.5 h, 89 % (α : β ca. 30:1). AIBN = 2,2'-azobisisobutyronitrile; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; 4-DMAP = 4-dimethylaminopyridine; DTBMP = di-*tert*-butyl-4-methylpyridine; NMO = *N*-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate.

S_N2 inversion)^[3,4] in 71 % yield. The PMB group was then removed from ring D (DDQ, 95 % yield), the resulting alcohol was oxidized to the corresponding ketone with the aid of TPAP/NMO, and the latter compound was treated with MeLi in Et₂O at -78 °C. To our delight, the latter reaction produced the desired tertiary alcohol **15** in 88 % overall yield (from **14**) and as a single stereoisomer (determined by NOE/NMR experiments). Figure 2 depicts the presumed confor-

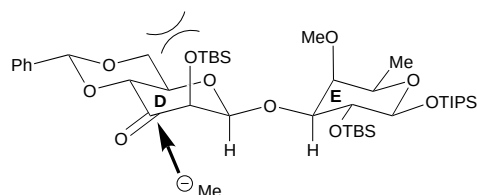
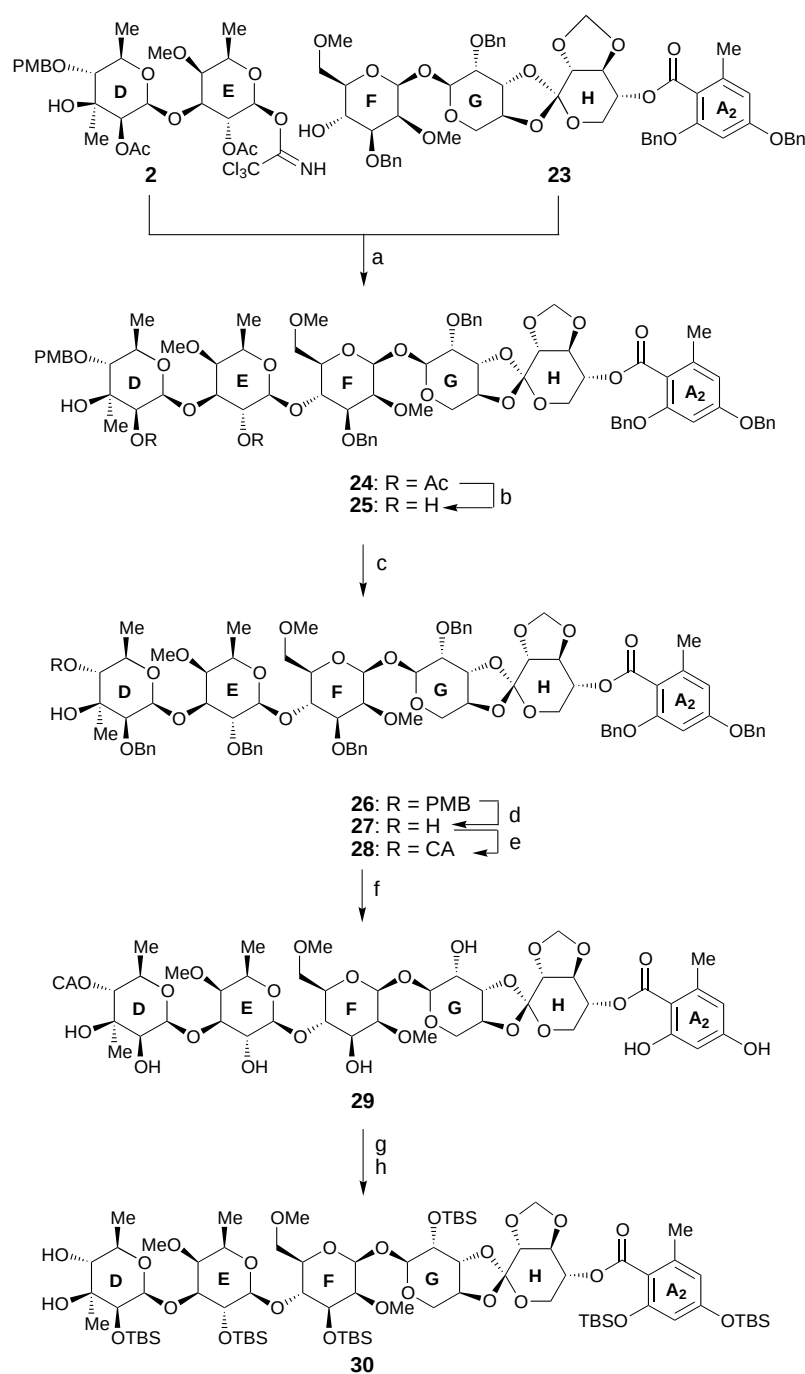


Figure 2. Illustration of the preferential α -attack of MeLi on the C3 carbonyl group of ring D during the formation of compound **15**.

mation of ring D of **14** and the trajectory of the reagent leading to the desired product. Thus, in contrast to a monosaccharide unit D carrying a 1- α substituent in which the reagent would have encountered repulsive 1,2- or 1,3-interactions, the β -mannoside disaccharide system containing the bulky and axially orientated TBS group at C2 proved ideal for setting the tertiary stereocenter on ring D. Difficulties with protecting the highly hindered tertiary alcohol in **15** led us to the conviction that we could leave it free for the rest of the sequence without much interference—a prediction that turned out both correct and fortunate. The next task was to deoxygenate the C6 position of ring D, suitably protect the C4 hydroxyl group of ring D, and activate the C1 carbon atom of ring E. To this end, the benzylidene group of **15** was removed by hydrogenolysis (H₂/10 % Pd/C, 97 % yield) and the primary hydroxyl group so generated was tosylated selectively over the secondary hydroxyl group (TsCl/py, 87 % yield) to afford **16**. Difficulties with the direct reduction of this tosylate forced us to proceed through iodide **17** (LiI, 86 % yield), which was smoothly reduced with *n*Bu₃SnH/AIBN to afford the desired compound **18** in 97 % yield. Protection at C4 of ring D was effected with *n*Bu₂SnO/*n*Bu₄NI leading to **19** (63 % yield), which was completely desilylated (*n*Bu₄NF) and tris-acetylated (Ac₂O/Et₃N/4-DMAP) to afford triacetate **21** in 90 % overall yield (ratio of α - and β -anomers approximately 1:1) via the tetraol **20**. Finally, the anomeric acetate was selectively removed from the latter compound (**22**) by the mild action of *n*BuNH₂ in THF to give lactol **22**, whose conversion into trichloroacetimidate **2** was accomplished by

exposure to CCl₃CN and DBU (89 %, α : β ratio approximately 30:1).

The coupling of the key intermediates **2** and **23** and the elaboration of the resulting fragment to the next advanced key intermediate, **30** is shown in Scheme 4. Thus, reaction of the trichloroacetimidate **2** with hydroxy fragment **23** in the presence of BF₃·Et₂O in CH₂Cl₂ at -20 °C furnished oligosaccharide **24** with the desired β -glycoside linkage (between rings E and F) and in 55 % yield. In addition to **24**, this reaction also produced a small amount of the corresponding α -glycoside (5 % yield) and an as of yet unidentified isomer of **24** (β -glycosidic linkage between rings E and F, 18 % yield). The sensitivity of these advanced intermediates and our intention to prepare them in a suitable form for their pending union with the A₁B(A)C fragment as well as for the overall strategy towards the final target molecule prompted a number of protecting group exchanges



Scheme 4. Completion of the synthesis of the DEFGHA₂ fragment (**30**). a) 1.6 equiv **2**, 0.5 equiv BF₃·Et₂O, CH₂Cl₂, −20 °C, 2 h, 55% yield of desired β-anomer, 18% of unknown compound (β-anomer) and 5% yield of α-anomer (α:β ca. 1:9); b) 0.5 equiv K₂CO₃, MeOH, 25 °C, 2 h, 85%; c) 2.5 equiv NaH, 3.0 equiv BnBr, THF, 0→25 °C, 2 h, 95%; d) 1.3 equiv DDQ, CH₂Cl₂/H₂O (10/1), 0→25 °C, 2 h, 95%; e) 1.5 equiv (CA)₂O, 3.0 equiv Et₃N, 0.2 equiv 4-DMAP, CH₂Cl₂, 0→25 °C, 1 h, 98%; f) 0.5 equiv 10% Pd/C (w/w), EtOAc, 25 °C, 4 h, 85%; g) 8.0 equiv TBSOTf, 20 equiv 2,6-di-*tert*-butylpyridine, CH₂Cl₂, 0→25 °C, 8 h, 65%; h) 0.2 equiv K₂CO₃, MeOH, 25 °C, 15 min, 85%. CA = chloroacetyl.

at this stage. Three sets of protecting groups on fragment DEFGHA₂ were tested before a final forward path was found.

We initially targeted the hexabenzylated diol **27** (Scheme 4) as a potential partner in the projected final coupling reaction with the A₁B(A)C fragment. With this objective in mind,

compound **24** was deacetylated (K₂CO₃/MeOH) to furnish triol **25** (85% yield), which was then cleanly dibenzylated with NaH/BnBr in THF (90% yield) to give hexabenzyl ether **26**^[9] in which the tertiary alcohol on ring D remained free. The removal of the PMB group from **26** with DDQ proceeded in 95% yield to furnish the desired diol **27**. This compound, however, proved unsuitable for further elaboration. Problems associated with **27** included low glycosidation yields with the A₁B(A)C fragment and rupture of the highly sensitive C-D orthoester moiety upon attempted debenzylation. We then opted for the hexaacetylated counterpart of **27** (details will be reported in a later paper), but again we encountered poor coupling yields with the same A₁B(A)C partner. Our third generation strategy involved the adoption of the hexa-TBS derivative **30** (Scheme 4) as the DEFGHA₂ coupling partner, and this time we were successful. To reach **30** we proceeded from **27** as follows: Selective formation of the secondary chloroacetate on ring D (CA₂O/Et₃N/4-DMAP, 98% yield) led to **28**, which was subjected to hydrogenolysis (H₂/10% Pd/C) to afford heptaol **29** (85% yield). Six TBS groups were then installed on **29** through exposure to excess TBSOTf in the presence of 2,6-di-*tert*-butylpyridine to afford a hexa-TBS derivative (with a free tertiary OH group on ring D, 65% yield), from which the chloroacetate group was removed with K₂CO₃ in MeOH to give the targeted intermediate **30** (85% yield; Table 1).

The final assembly of the everninomicin 13,384-1 (**1**) skeleton and the final stages of the total synthesis are shown in Scheme 5. Thus, coupling of the A₁B(A)C glycosyl fluoride donor **31**^[1] with the DEFGHA₂ hexa-TBS diol acceptor **30** in the presence of SnCl₄ in Et₂O proceeded smoothly, and with complete stereocontrol,^[10] to afford the 2-phenylseleno glycoside **32** (70% yield). Formation of the remaining orthoester site was then accomplished with equal facility under the Sinaï conditions^[11] (NaIO₄ oxidation to the selenoxide in MeOH/CH₂Cl₂/H₂O (3/2/1) followed by heating in a sealed tube at 140 °C in toluene/vinyl acetate/diisopropylamine (2/2/1)) to afford the fully protected everninomicin 13,384-1 derivative **33** in 65%

yield and as a single stereoisomer. Generation of everninomicin 13,384-1 (**1**) from **33** entailed the following two steps: a) hydrogenolysis (H₂/10% Pd/C, NaHCO₃, *t*BuOMe) to remove the two benzyl ethers and b) desilylation (*n*Bu₄NF/THF) to cleave all six TBS groups (75% overall yield). Synthetic everninomicin 13,384-1 (**1**) was identical by the

Table 1. Selected physical and spectroscopic data of compounds **2**, **30**, and **33**.

2: R_f = 0.60 (silica, 80% EtOAc in hexanes); IR (thin film): $\bar{\nu}_{\max}$ = 3495, 3331, 2928, 2951, 2884, 1743, 1678, 1614, 1508, 1455, 1373, 1243, 1091, 1049, 844, 791 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 8.54 (s, 1H, NH), 7.27 (d, J = 8.5 Hz, 2H, PMB), 6.87 (d, J = 8.5 Hz, 2H, PMB), 6.47 (d, J = 3.7 Hz, 1H, E-1), 5.28 (dd, J = 10.6, 3.7 Hz, 1H, E-2), 4.99 (s, 1H, D-2), 4.81 (s, 1H, D1), 4.81 and 4.56 (AB, J = 11.0 Hz, 2H, CH_2Ar), 4.16–4.12 (m, 2H, E-3, E-5), 3.79 (s, 3H, OMe (PMB)), 3.59 (s, 3H, OMe (E-4)), 3.57 (brs, 1H, E-4), 3.42 (dq, J = 9.6, 5.9 Hz, 1H, D-5), 3.32 (d, J = 9.6 Hz, 1H, D-4), 2.14 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.37 (s, 3H, Me (D-3)), 1.35 (d, J = 6.0 Hz, 3H, D-6), 1.26 (d, J = 6.6 Hz, 3H, E-6); ^{13}C NMR (125 MHz, CDCl_3): δ = 170.1, 170.0, 161.1, 159.0, 130.5, 129.8, 114.4, 98.5, 94.3, 91.6, 82.5, 81.7, 76.1, 75.0, 74.3, 71.0, 69.4, 65.5, 61.5, 55.5, 30.2, 21.2, 21.0, 20.3, 18.2, 16.3

30: R_f = 0.27 (silica, 40% Et₂O in hexanes); α_D^{25} = –29.1 (c = 0.10, CHCl_3); IR (thin film): $\bar{\nu}_{\max}$ = 3495, 2955, 2919, 2861, 1737, 1602, 1467, 1361, 1255, 1073, 838, 779 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 6.29 (d, J = 1.7 Hz, 1H, ArH (A_2)), 6.16 (d, J = 1.8 Hz, 1H, ArH (A_2)), 5.33 (dt, J = 10.1, 10.1, 5.6 Hz, 1H, H-4), 5.18 (s, 1H, OCH_2O), 5.06 (s, 1H, OCH_2O), 5.05 (brs, 1H, F-1), 5.01 (s, 1H, G-1), 4.68 (s, 1H, D-1), 4.39 (dt, J = 10.3, 10.3, 2.5 Hz, 1H, G-4), 4.24 (brs, 1H, G-2), 4.17 (dd, J = 11.1, 5.4 Hz, 1H, H-5), 4.12 (brs, 1H, F-3), 4.08 (d, J = 7.4 Hz, 1H, E-1), 4.05 (dd, J = 9.4, 4.8 Hz, 1H, G-5), 4.00 (dd, J = 10.1, 2.2 Hz, 1H, G-3), 3.96 (dd, J = 9.4, 9.4 Hz, 1H, G-5), 3.95 (t, J = 9.4 Hz, 1H, H-3), 3.89 (dd, J = 8.3 Hz, 1H), 3.84 (brs, 1H), 3.78–3.76 (m, 1H), 3.77 (s, 1H, D-2), 3.64 (dd, J = 8.0, 8.0 Hz, 1H, E-2), 3.59 (dd, J = 10.0, 10.0 Hz, 1H, H-5), 3.58 (d, J = 9.5 Hz, 1H, H-2), 3.53 (s, 3H, OMe (E-4)), 3.52–3.51 (m, 1H, D-5 or E-5), 3.49–3.37 (m, 4H, F-2), 3.40 (s, 3H, OMe (F-2)), 3.33–3.29 (m, 2H, D-5 or E-5), 3.30 (s, 3H, OMe (F-6)), 2.44 (s, 1H, OH), 2.24 (s, 3H, Me (A_2)), 1.93 (brs, 1H, OH), 1.29 (d, J = 5.9 Hz, 3H, D-6 or E-6), 1.27 (d, J = 6.5 Hz, 3H, D-6 or E-6), 1.16 (s, 3H, Me (D-3)), 0.96 (s, 9H, $t\text{BuSi}$), 0.95 (s, 9H, $t\text{BuSi}$), 0.92 (s, 9H, $t\text{BuSi}$), 0.90 (s, 9H, $t\text{BuSi}$), 0.90 (s, 9H, $t\text{BuSi}$), 0.89 (s, 9H, $t\text{BuSi}$), 0.28 (s, 3H, MeSi), 0.21 (s, 3H, MeSi), 0.18 (s, 3H, MeSi), 0.18 (s, 3H, MeSi), 0.14 (s, 3H, MeSi), 0.10 (s, 3H, MeSi), 0.10 (s, 3H, MeSi), 0.10 (s, 3H, MeSi), 0.09 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.06 (s, 3H, MeSi); ^{13}C NMR (125 MHz, CDCl_3): δ = 167.4, 157.3, 153.9, 137.9, 119.0, 118.9, 114.9, 108.4, 103.5, 101.6, 97.2, 96.4, 84.8, 82.4, 81.1, 77.3, 76.7, 76.4, 75.1, 73.9, 72.7, 71.3, 70.6, 70.5, 70.0, 69.5, 65.8, 63.3, 63.0, 62.4, 58.4, 29.3, 28.0, 25.8, 25.6, 19.8, 18.4, 18.2, 18.1, 18.0, 17.1, 16.3, 15.3, –3.4, –3.7, –3.9, –4.2, –4.3, –4.4, –4.6, –4.9, –4.9, –5.0, –5.2; HR-MS (FAB): calcd for $\text{C}_{77}\text{H}_{144}\text{O}_{25}\text{Si}_6\text{Na}$ [$M + \text{Na}^+$]: 1659.8509, found: 1659.8452

33: R_f = 0.32 (silica, 60% Et₂O in hexanes); α_D^{25} = –19.5 (c = 0.20, CHCl_3); IR (thin film): $\bar{\nu}_{\max}$ = 2955, 2919, 2861, 1737, 1602, 1543, 1455, 1384, 1255, 1108, 1067, 1038, 838, 779 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 7.57 (d, J = 7.1 Hz, 2H, ArH), 7.43–7.31 (m, 8H, ArH), 6.29 (d, J = 1.8 Hz, ArH (A_2)), 6.16 (d, J = 1.8 Hz, ArH (A_2)), 5.35 (dt, J = 9.9, 9.9, 5.5 Hz, 1H, H-4), 5.18 (s, 1H, OCH_2O), 5.07 (brs, 1H, F-1), 5.06 (s, 1H, OCH_2O), 5.05 and 5.02 (AB, J = 10.2 Hz, 2H, CH_2Ar), 5.00 (s, 1H, G-1), 4.95 (dd, J = 4.6, 1.4 Hz, 1H, A-1), 4.88 (t, J = 9.4 Hz, 1H, B-4), 4.86 (s, 1H, D-1), 4.75 (brd, J = 9.8 Hz, 1H, B-1), 4.68 and 4.57 (AB, J = 11.0 Hz, 2H, CH_2Ar), 4.39 (dt, J = 10.5, 10.5, 4.8 Hz, 1H, G-4), 4.23 (brs, 1H, G-2), 4.17 (dd, J = 11.4, 5.7 Hz, 1H, H-5), 4.14 (brs, 1H, F-3), 4.09 (s, 1H, D-2), 4.07 (d, J = 7.4 Hz, 1H, E-1), 4.04 (dd, J = 9.2, 4.4 Hz, 1H, G-5), 4.01 (dd, J = 10.1, 2.6 Hz, 1H, G-3), 3.97 (dd, J = 10.1, 9.2 Hz, 1H, G-5), 3.93 (t, J = 9.6 Hz, 1H, H-3), 3.89 (brt, J = 8.3 Hz, 1H), 3.86–3.80 (m, 5H, B-3, C-3, D-4, E-5, F-4), 3.82 (s, 3H, OMe (A_1)), 3.72 (dq, J = 6.2, 4.0 Hz, 1H, D-5), 3.65 (dd, J = 9.2, 9.2 Hz, 1H, E-2), 3.64 (d, J = 9.7 Hz, 1H, A-4), 3.59 (t, J = 11.0 Hz, 1H, H-5), 3.59 (d, J = 9.2 Hz, 1H, H-2), 3.56 (s, 3H, OMe (E-4)), 3.53–3.50 (m, 4H, C-5), 3.48–3.46 (m, 1H, A-5), 3.47 (dd, J = 9.2, 3.1 Hz, 1H, E-3), 3.43 (t, J = 3.5 Hz, 1H, F-2), 3.39 (s, 3H, OMe (F-2)), 3.35 (s, 3H, OMe (A-4)), 3.34–3.33 (m, 2H, B-5, F-5), 3.30 (s, 3H, OMe), 2.51 (dd, J = 12.5, 8.5 Hz, 1H, C-2), 2.45 (dd, J = 13.7, 4.9 Hz, 1H, A-2), 2.38 (s, 3H, Me (A_1)), 2.29 (brdd, J = 12.4, 8.6 Hz, 1H, B-2), 2.26 (s, 3H, Me (A_2)), 2.01 (dd, J = 13.7, 1.6 Hz, 1H, A-2), 1.90 (t, J = 12.1 Hz, 1H, C-2), 1.70–1.66 (m, 1H, B-2), 1.68 (s, 3H, Me, A-3), 1.34 (s, 3H, Me, D-3), 1.32 (d, J = 6.4 Hz, 3H, B-6), 1.31 (d, J = 6.2 Hz, 3H, D-6), 1.28 (d, J = 6.6 Hz, 3H, E-6), 1.26 (d, J = 6.8 Hz, 3H, C-6), 0.96 (s, 9H, $t\text{BuSi}$), 0.95 (s, 9H, $t\text{BuSi}$), 0.94 (s, 9H, $t\text{BuSi}$), 0.90 (s, 9H, $t\text{BuSi}$), 0.89 (s, 18H, $t\text{BuSi}$), 0.83 (d, J = 6.2 Hz, 3H, Me (A-6)), 0.21 (s, 6H, MeSi), 0.19 (s, 3H, MeSi), 0.18 (s, 6H, MeSi), 0.14 (s, 3H, MeSi), 0.10 (s, 6H, MeSi), 0.10 (s, 3H, MeSi), 0.09 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.07 (s, 3H, MeSi), 0.06 (s, 3H, MeSi); ^{13}C NMR (125 MHz, CDCl_3): δ = 167.1, 165.6, 157.3, 153.9, 152.3, 153.2, 138.7, 137.9, 135.9, 134.8, 128.6, 128.6, 128.5, 127.5, 126.4, 126.0, 121.7, 120.1, 119.0, 119.0, 114.9, 108.5, 103.5, 102.3, 100.2, 97.2, 96.4, 92.6, 89.9, 84.3, 82.8, 82.4, 81.5, 81.1, 79.0, 77.3, 76.1, 75.1, 74.9, 74.1, 73.5, 72.8, 72.4, 71.8, 71.6, 71.1, 70.5, 70.4, 70.0, 69.1, 68.3, 66.2, 63.3, 63.0, 62.5, 62.0, 60.8, 58.4, 46.2, 40.1, 38.8, 36.4, 29.7, 26.2, 26.0, 25.8, 25.6, 25.6, 19.8, 19.3, 19.2, 18.4, 18.3, 18.3, 18.1, 18.1, 18.0, 18.0, 17.6, 16.2, 11.6, –3.7, –3.8, –3.9, –4.2, –4.3, –4.4, –4.4, –4.5, –4.5, –4.9, –5.0, –5.2; MS (electrospray ionization): calcd for $\text{C}_{120}\text{H}_{195}\text{O}_{38}\text{Cs}$ [$M + \text{Cs}^+$]: 2496/2497, found: 2498/2499

usual criteria (TLC, ^1H NMR, ^{13}C NMR, IR, MS, α_D^{25}) with an authentic sample.^[12]

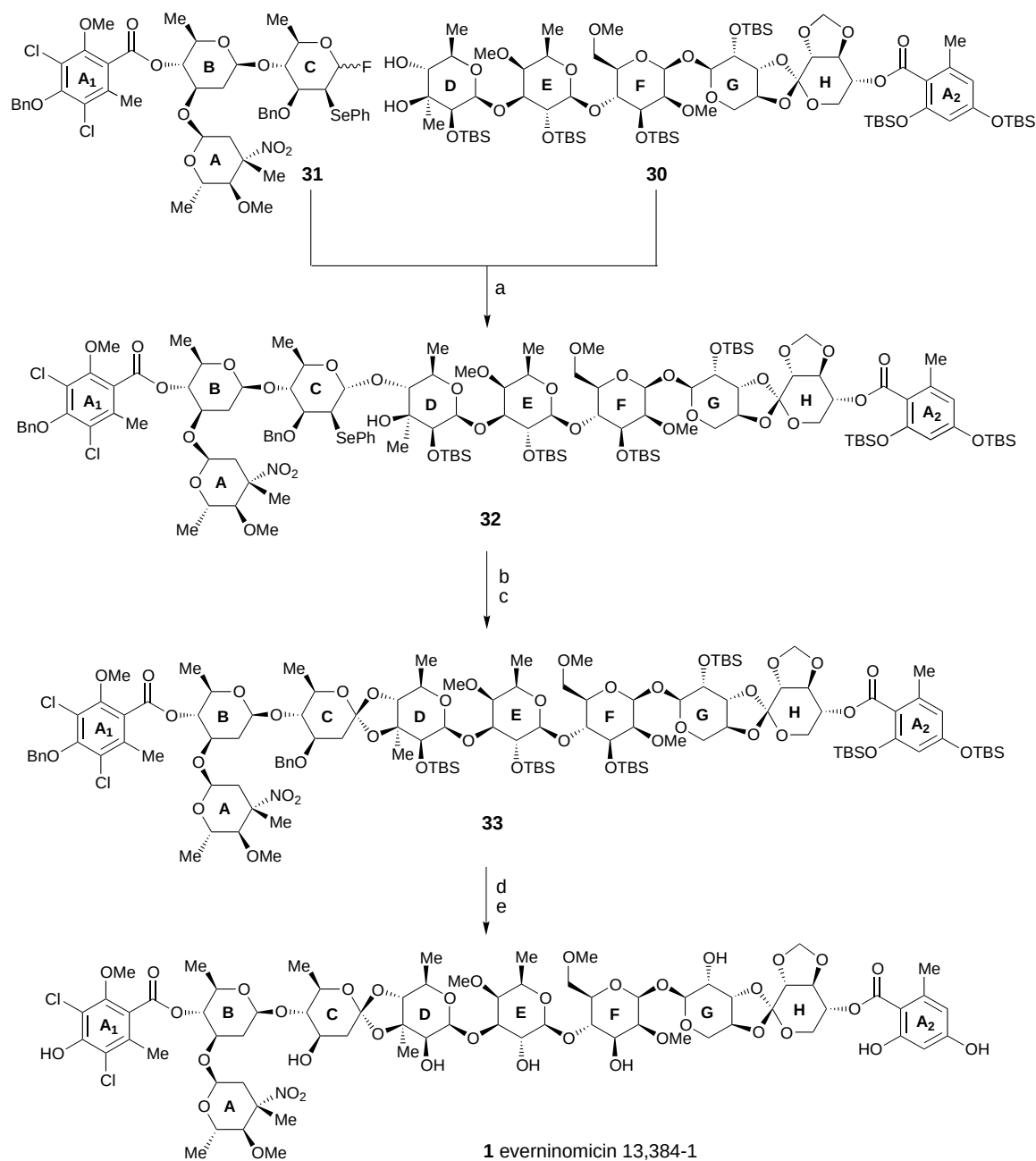
The reported total synthesis of everninomicin 13,384-1 (**1**) constituted an adventurous journey during which we have demonstrated the power of novel synthetic reactions both from our own and other laboratories. Most notable of these methods are the 1,2-phenylthio^[10] and the 1,2-phenylseleno migrations on carbohydrate templates and their use in stereocontrolled glycosidation reactions; the tin acetal based stereocontrolled construction of 1→1'-disaccharides;^[13] the use of acyl fluorides for the formation of sterically hindered esters; the Sinaï orthoester protocol formation;^[11] the sulf-oxide-based β -mannoside forming glycosidation by Kahne et al.;^[3,4] the trichloroacetimidate glycosidation method of Schmidt and Michel;^[14] the glycosyl fluoride methodology of Mukaiyama et al.;^[15] and the tin acetal technology^[7] for differentiating 1,2-diols. Furthermore, a great deal of knowledge regarding selectivity in manipulating protective groups was gathered and considerable light was shed on conformational effects on selective functionalization of carbohydrate templates. Most importantly and as a result of this synthesis, the stage is now set for further advances in the antibiotics field, including semisynthesis of designed analogues, solid-

phase synthesis, combinatorial chemistry, and chemical biology studies.^[16]

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Scheme 5. Completion of the total synthesis of everninomicin 13,384-1 (**1**). a) 2.0 equiv **31**, 1.8 equiv SnCl₂, Et₂O, 0 → 25 °C, 6 h, 70%; b) 10 equiv NaIO₄, 8.0 equiv NaHCO₃, MeOH/CH₂Cl₂/H₂O (3/2/1), 25 °C, 4 h; c) vinyl acetate/toluene/diisopropylamine (2/2/1), sealed tube, 140 °C, 16 h, 65% over two steps; d) H₂, 0.1 equiv 10% Pd/C (w/w), 4.0 equiv NaHCO₃, *t*BuOMe, 25 °C, 1 h; e) 10.0 equiv *n*Bu₄NF, THF, 25 °C, 10 h, 75% over two steps.

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