Total Synthesis of Everninomicin 13,384-1—Part 2: Synthesis of the $FGHA_2$ Fragment**

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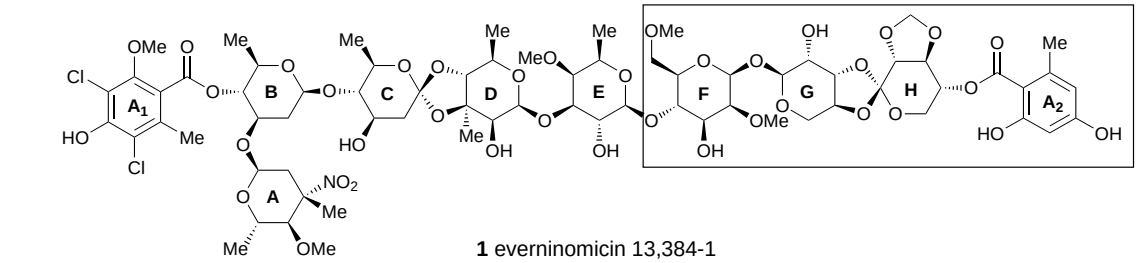
In the preceding paper,[1] we described the construction of the $A_1B(A)C$ fragment of everninomicin 13,384-1 (**1**). Herein we report the synthesis of the $FGHA_2$ fragment (**2**) of this target molecule (Figure 1). The novelty of this oligosaccharide fragment (**2**), which contains the challenging features of a 1→1′-disaccharide unit, a highly sensitive orthoester moiety, and a *trans*-methylene acetal, forced us into a somewhat linear, but nevertheless efficient, strategy.

Figure 1 outlines the retrosynthetic analysis upon which the successful strategy towards subtarget **2** was based. Thus, disconnection of the ester and orthoester bonds in **2** led to fragments **3** and **4**. Further disconnection of **3** at the indicated glycoside bond revealed diol **5** and 2-phenylselenoglycosyl



1 everninomicin 13,384-1

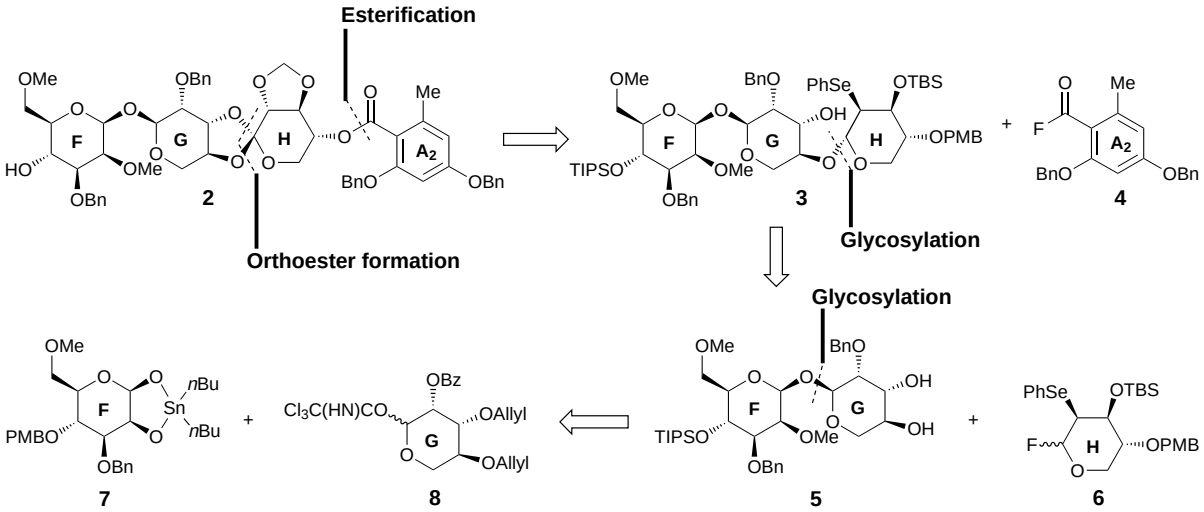


Figure 1. Retrosynthetic analysis of $FGHA_2$ fragment (**2**). Bn = benzyl; Bz = benzoyl; PMB = *p*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl.

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[**] We thank Dr. A. K. Ganguly for helpful discussions and a generous gift of everninomicin 13,384-1 and Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectroscopic, and X-ray crystallographic assistance, respectively. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, postdoctoral fellowships from M.E.C., Spain (R.M.R., Fulbright), the Japan Society for the Promotion of Science (H.S.), and the George Hewitt Foundation (K.C.F.), and grants from Schering Plough, Pfizer, Glaxo-Wellcome, Merck, Hoffmann-La Roche, DuPont, and Abbott Laboratories.

fluoride **6** as potential precursors. A selenium-assisted coupling of **5** with **6** was expected to furnish regio- and stereoselectively trisaccharide **3**, which would be poised for the formation of a Sinaÿ-type orthoester.[2] The success of this scheme depended on the stereoselectivity of this reaction (see Figures 2 and 3). Final disassembly of **5** led to tin acetal **7** and trichloroacetimidate **8** as starting building blocks for this disaccharide. The stereoselective construction of the 1→1′-disaccharide bridge of **5** from **7** and **8** was assured from our previous studies on model systems that culminated in an efficient new method[3] for accomplishing this task.

The construction of the individual building blocks are presented in Schemes 1–4. Building block F (**7**) was synthesized from the readily available phenylthioglycoside **9**[4] as follows (Scheme 1). Selective silylation of the primary hydroxyl group of **9** (TBSOTf/2,6-lutidine, 97%) gave silyl ether **10**, which was sequentially exposed to NaH/PMBCl/nBu_4NI (95% yield) and nBu_4NF (95% yield) to afford primary

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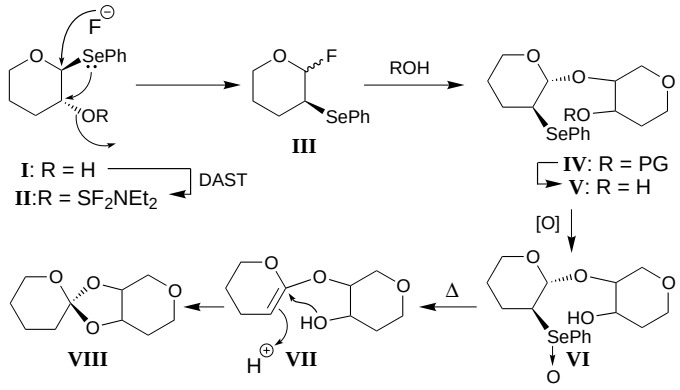
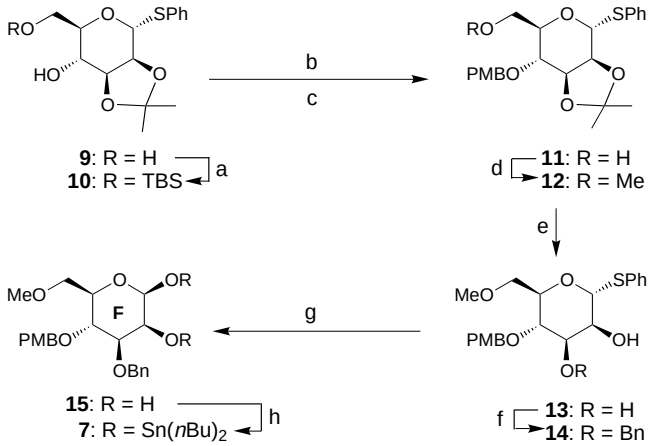


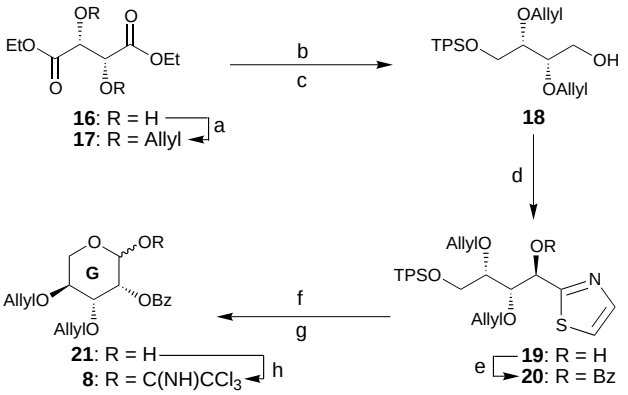
Figure 2. Orthoester formation via 1,2-migration of the phenylseleno group followed by glycosylation (**I**→**II**→**III**→**IV**)[10] and ring closure after *syn*-elimination (**V**→**VI**→**VII**→**VIII**).[2] DAST = diethylaminosulfur trifluoride; [O] = oxidant; PG = protecting group.



Scheme 1. Synthesis of carbohydrate building block F (**7**). a) 1.2 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2, 0→25 °C, 1 h, 97 %; b) 1.1 equiv NaH, 1.3 equiv PMBCl, 0.2 equiv nBu_4NI, DMF, 0→25 °C, 4 h, 95 %; c) 1.2 equiv nBu_4NF, THF, 25 °C, 1 h, 95 %; d) 1.1 equiv NaH, 1.3 equiv MeI, DMF, 0→25 °C, 1 h, 95 %; e) 0.2 equiv TsOH, 2.5 equiv $(CH_2OH)_2$, MeOH, 25 °C, 5 h, 85 %; f) 1.1 equiv nBu_2SnO, toluene, 110 °C, 3 h; 1.5 equiv BnBr, 0.2 equiv nBu_4NI, 25→110 °C, 5 h, 89 %; g) 1.5 equiv NBS, Me_2CO/H_2O (10/1), 0→25 °C, 2 h, 97 %; h) 1.1 equiv nBu_2SnO, MeOH, 90 °C, 3 h, 100 %. NBS = *N*-bromosuccinimide; Tf = trifluoromethanesulfonyl; Ts = *p*-toluenesulfonyl.

alcohol **11**. Methylation of **11** (NaH/MeI) then furnished methoxy compound **12** in 95 % yield. Acidic methanolysis (TsOH/MeOH) of the acetonide group from **12** led to diol **13** (85 % yield), which was selectively benzylated at C3 using the tin acetal technology[5] (nBu_2SnO/BnBr/nBu_4NI, 89 %) to afford **14**. Rupture of the thiophenyl group from **14** with NBS/H_2O furnished lactol **15** (97 % yield), which was converted into the desired tin acetal **7** by exposure to nBu_2SnO in refluxing MeOH (100 % yield).

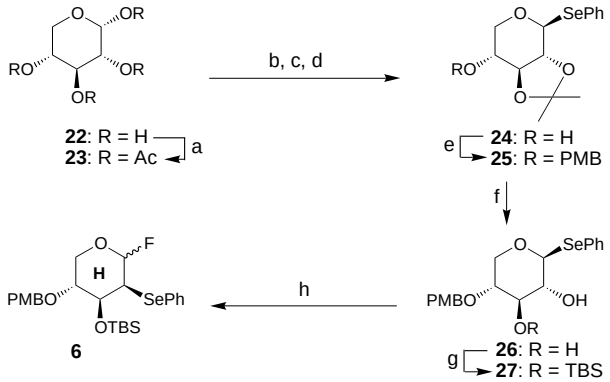
Scheme 2 summarizes the synthesis of the ring G trichloroacetimidate **8** starting from diethyl-L-tartrate (**16**). Thus, bisallylation of **16** was effected by treatment with NaH/allyl bromide to afford **17** (93 % yield). Reduction of both ester groups of **17** with LAH in refluxing diethyl ether (93 %) was followed by monosilylation (NaH/TPSCl) to furnish hydroxy silyl ether **18** in 90 % yield. Swern oxidation ($(COCl)_2$/DMSO/Et_3N)[6] of **18** led to the corresponding aldehyde, which was



Scheme 2. Synthesis of carbohydrate building block G (**8**). a) 2.1 equiv NaH, 2.1 equiv allylBr, 0.1 equiv nBu_4NI, 0.1 equiv [18]crown-6, THF, 0→25 °C, 4 h, 93 %; b) 2.6 equiv LAH, Et_2O, 25→35 °C; 93 %; c) 1.0 equiv NaH, 1.1 equiv TPSCl, 0.1 equiv nBu_4NI, THF, 0→25 °C, 4 h, 90 %; d) 1. 2.0 equiv $(COCl)_2$, 2.5 equiv DMSO, −78 °C, 2 h; 2. 4.0 equiv Et_3N, −78→−40 °C, 2 h; 3. TMS/thiazole, −40→0 °C; 4. 1.5 equiv PPTS, MeOH, 0→25 °C, 91 % (1:1 mixture of diastereoisomers); e) 1.1 equiv BzCl, 1.5 equiv Et_3N, 0.2 equiv 4-DMAP, CH_2Cl_2, 0→25 °C, 2 h, 98 %; f) 1. 1.2 equiv MeOTf, MeCN, 25 °C, 0.5 h; 2. 2.4 equiv $NaBH_4$, MeOH, 0→25 °C, 0.5 h; 3. 1.2 equiv $CuCl_2$, 8.0 equiv CuO, MeCN/H_2O (5/1), 25 °C, 2 h; g) 1.5 equiv nBu_4NF, THF, 25 °C, 2 h, 81 % over four steps; h) 5.0 equiv CCl_3CN, 0.05 equiv DBU, CH_2Cl_2, 0→25 °C, 0.5 h, 85 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; 4-DMAP = 4-(dimethylamino)pyridine; DMSO = dimethylsulfoxide; LAH = lithium aluminum hydride; PPTS = pyridinium *p*-toluene sulfonate; TMS = trimethylsilyl; TPS = *tert*-butyldiphenylsilyl.

exposed to TMS/thiazole according to the method of Dondoni et al.[7] to afford, after acidic workup (PPTS/MeOH), the homologated chain **19** (91 % yield, approximate 1:1 ratio of epimeric alcohols). It is interesting to note here that when we used the acetonide counterpart of the bis-allyl aldehyde derived from **18** we observed a ratio of more than 10:1 of the desired:undesired alcohols in the Dondoni reaction. However, subsequent difficulties with protecting group manipulation led to the adoption of the less selective sequence described above, whose efficiency was improved by recycling the wrong isomer (oxidation/reduction). Benzoylation of the chromatographically pure alcohol **19** (BzCl/Et_3N/4-DMAP, 98 %), followed by thiazole rupture (MeOTf; $NaBH_4$; CuO; one-pot reaction)[7] and desilylation (nBu_4NF) led to lactol **21** (81 % overall yield) via benzoate **20**. Finally, formation of the trichloroacetimidate **8**[8] was easily accomplished by exposure to CCl_3CN in the presence of DBU (85 % yield).

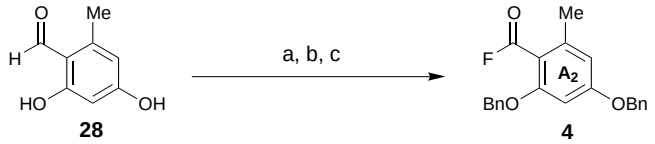
Scheme 3 presents the synthesis of ring H as the 2-phenylselenoglycosyl fluoride **6** from D-xylose (**22**). Peracetylation of **22** (Ac_2O/Et_3N/4-DMAP, 98 % yield) followed by treatment with $PhSeH/BF_3 \cdot Et_2O$[9] led to a mixture of α- and β-glycosides (α:β approximately 1:5, 93 % yield). The desired β-glycoside was subjected to basic methanolysis (K_2CO_3/MeOH) and the resulting triol was exposed to $CH_3(CH_3O)C{=}CH_2$/TFA to afford predominantly the 2,3-acetonide **24** (74 % yield over two steps). The remaining hydroxyl group in **24** was then protected as a PMB ether (NaH/PMBCl/nBu_4NI, 95 % yield) and the acetonide was removed under acidic conditions (PPTS/MeOH) to furnish diol **26** (96 % yield). The next task was to protect the C3 hydroxyl group of **26**, an objective that was achieved by exposure of the latter compound to TBSOTf/2,6-lutidine in



Scheme 3. Synthesis of carbohydrate building block H (**6**). a) 5.0 equiv Ac_2O, 8.0 equiv Et_3N, 0.2 equiv 4-DMAP, CH_2Cl_2, 0→25 °C, 2 h, 98 %; b) ca. 2.0 equiv PhSeH, 0.2 equiv $BF_3 \cdot Et_2O$, CH_2Cl_2, 0→25 °C, 4 h, 93 % (α:β ca. 1:5); c) 0.3 equiv K_2CO_3, MeOH, 25 °C, 5 h; d) 1.5 equiv $CH_3(CH_3O)C{=}CH_2$, 0.2 equiv TFA, DMF, 45 °C, 3 h, 74 % over two steps; e) 1.1 equiv NaH, 1.3 equiv PMBCl, 0.2 equiv nBu_4NI, DMF, 0→25 °C, 2 h, 95 %; f) 0.2 equiv PPTS, MeOH, 0→25 °C, 2 h, 96 %; g) 1.1 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2, 0→25 °C, 0.5 h, 91 %; h) 1.5 equiv DAST, CH_2Cl_2, 0 °C, 20 min, 100 %. DMF = dimethylformamide; TFA = trifluoroacetic acid.

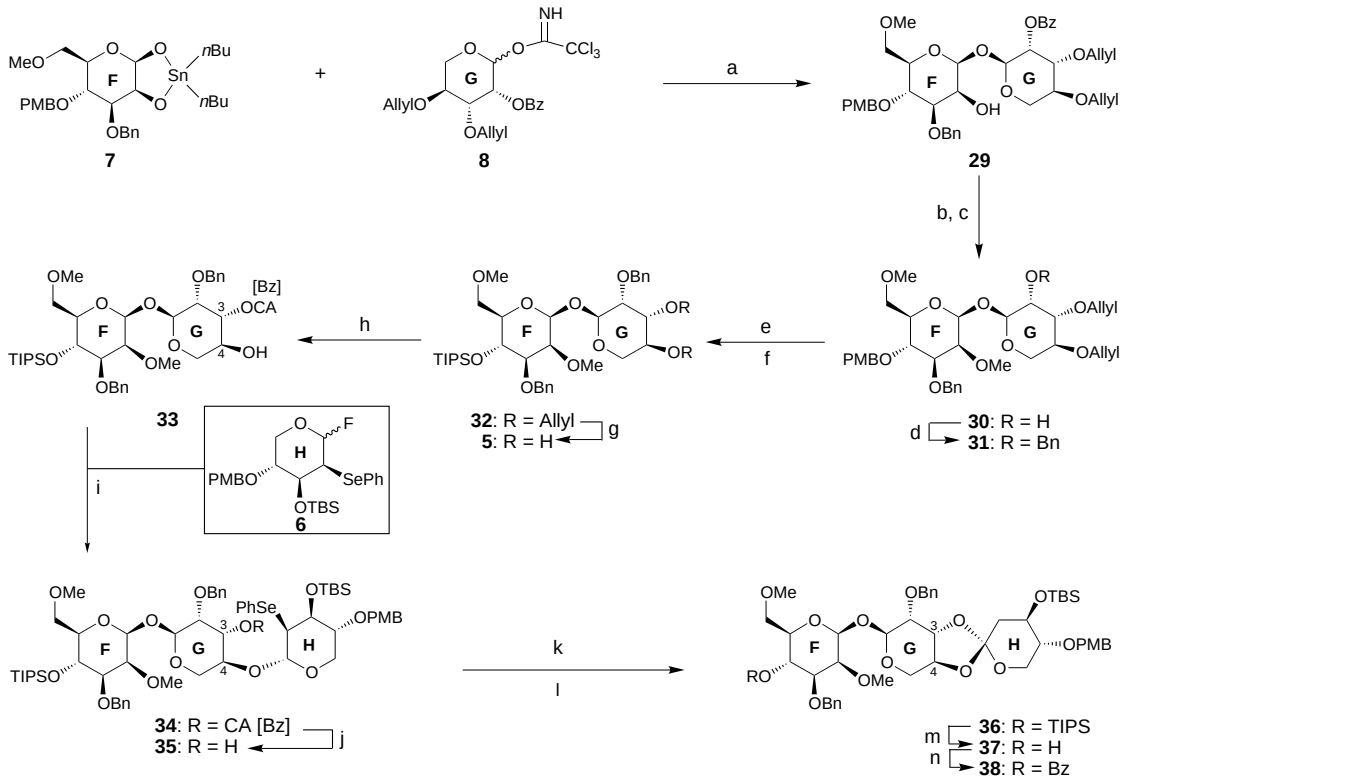
THF at −78 °C to give **27** in 91 % yield. Parenthetically, and interestingly, treatment of **26** with the same silylating reagent in CH_2Cl_2, instead of THF, led to the C2 derivative (96 %), an observation that has to await an explanation. Having set the stage for the 1,2-migration,[10] the targeted 2-phenylselenoglycosyl fluoride **6** was then formed by simple treatment of **27** with DAST (100 % yield). This maneuver represents a new reaction[11] in carbohydrate chemistry and played a crucial role in the success of this total synthesis.

The construction of the aromatic fragment A_2 (**4**) is depicted in Scheme 4. Thus, benzylation of **28**[1] (K_2CO_3/BnBr, 92 %) followed by oxidation ($NaClO_2$, 80 % yield) and fluorination of the resulting carboxylic acid ($(Me_2N)_2CF^+PF_6^-$, 80 % yield)[12] furnished the desired acyl fluoride **4** in high overall yield.



Scheme 4. Synthesis of aromatic ring A_2 (**4**). a) 2.5 equiv BnBr, 4.0 equiv K_2CO_3, Me_2CO, 70 °C, 92 %; b) 2.4 equiv $NaClO_2$, 2.5 equiv NaH_2PO_4, DMSO, 0 °C, 12 h, 80 %; c) 1.5 equiv $(Me_2N)_2CF^+PF_6^-$, 2.0 equiv iPr_2NEt, CH_2Cl_2, 0→25 °C, 2 h, 80 %.

The assembly of building blocks **4**–**8** to form the targeted intermediate **2** is presented in Schemes 5 and 6. The first task was to construct stereoselectively the 1→1′-trehalose-type



Scheme 5. Assembly of FGH fragment **38**. a) 1. 0.3 equiv TMSOTf, CH_2Cl_2, 0→25 °C, 8 h; 2. 0.3 equiv PPTS, MeOH, 25 °C, 1 h, 74 % over two steps; b) 1.1 equiv NaH, 1.3 equiv MeI, DMF, 0→25 °C, 1 h, 87 %; c) 0.3 equiv NaOH, MeOH, 25 °C, 1 h, 95 %; d) 1.1 equiv NaH, 1.3 equiv BnBr, 0.2 equiv nBu_4NI, DMF, 0→25 °C, 4 h, 90 %; e) 1.5 equiv DDQ, CH_2Cl_2/H_2O (10/1), 0→25 °C, 1 h, 91 %; f) 1.2 equiv TIPSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2, 0→25 °C, 1 h, 97 %; g) 1. 2.5 equiv DABCO, 0.1 equiv $[(Ph_3P)_3RhCl]$, EtOH/H_2O (10/1), 90 °C, 2 h; 2. 2.2 equiv NMO, 0.05 equiv OsO_4, Me_2CO/H_2O (10/1), 25 °C, 8 h, 81 %; h) 1.1 equiv nBu_2SnO, toluene, 110 °C, 3 h; 1.5 equiv CACl, 0→25 °C, 1 h, 97 % (1:1 mixture of regioisomers); i) 2.0 equiv **6**, 1.8 equiv $SnCl_2$, 0→25 °C, Et_2O, 3 h, 92 %; j) 0.2 equiv K_2CO_3, MeOH, 25 °C, 1 h, 98 %; k) 10.0 equiv $NaIO_4$, 8.0 equiv $NaHCO_3$, MeOH/CH_2Cl_2/H_2O (3/2/1), 25 °C, 2 h; l) vinyl acetate/toluene/diisopropylamine (2/2/1), sealed tube, 140 °C, 16 h, 81 %; m) 1.1 equiv nBu_4NF, THF, 0 °C, 2 h, 95 %; n) 1.2 equiv BzCl, 1.8 equiv Et_3N, 0.2 equiv 4-DMAP, CH_2Cl_2, 0→25 °C, 2 h, 97 %. CA = chloroacetyl; DABCO = 1,4-diazabicyclo[2.2.2]octane; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; NMO = *N*-methylmorpholine *N*-oxide.

  1433-7851/99/3822-3342 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1999**, *38*, No. 22

linkage between rings F and G, a challenge that was solved by applying our recently developed methodology for 1→1′-disaccharide construction. Thus, the coupling of tin acetal **7** with trichloroacetimidate **8** (Scheme 5) proceeded smoothly under the catalytic influence of TMSOTf in CH_2Cl_2 leading, after PPTS-induced cleavage of the intermediate TMS ether, to disaccharide **29** in 74% overall yield. As expected from our previous findings[3] the 1→1′-disaccharide linkage was formed in a completely stereocontrolled fashion, furnishing **29** as a single isomer. The free hydroxyl group in **29** was methylated (NaH/MeI, 87% yield) and the benzoyl group at C2 of ring G, which played a crucial role in directing the stereochemical outcome of the glycoslylation reaction, was removed by treatment with NaOH in MeOH to afford alcohol **30** (95% yield). For strategic reasons, a benzyl group was installed on the hydroxyl group of **30** (NaH/BnBr/nBu$_4$NI, 90% yield) to afford **31**, and the PMB group of ring F was replaced with a TIPS group (DDQ, 91% yield; TIPSOTf/2,6-lutidine, 97% yield) to furnish compound **32**. Removal of the allyl protecting groups from **32** required initial treatment with Wilkinson's catalyst and DABCO, followed by cleavage of the resulting enol ethers with OsO_4/NMO, to furnish **5** in 81% overall yield. Despite the nonselective differentiation of the two hydroxyl groups of **5**—even with the tin acetal technology,[5] which led to hydroxychloroacetate **33** (nBu$_2$SnO/CACl, 97% yield) and its regioisomer (approximately 1:1 ratio)—an efficient pathway to the next stage was secured. Thus, while the indicated regioisomer (**33**) was used directly as a carbohydrate acceptor in a glycosidation reaction with glycosyl fluoride **6** ($SnCl_2$, Et_2O) to give trisaccharide **34** (92% yield) stereoselectively, its regioisomer required further manipulation prior to being used in the forward sequence. Specifically, the C4 regioisomer of **33**, was benzoylated (BzCl/Et_3N/4-DMAP, 94%) and the chloroacetate group was removed (Et_3N/MeOH (1/3), 90% yield) leading to the C3 benzoate counterpart of **33**. This compound was then subjected to the same coupling procedure with **6** to afford the benzoate analogue of trisaccharide **34** (90% yield). Cleavage of the ester group from **34** (or its benzoate analogue) with K_2CO_3 in MeOH led to alcohol **35** in 98% yield (Table 1), which was now poised for a Sinaÿ orthoester formation.[2] Thus, having assisted in the construction of the glycoside bond linking rings G and H, the 2-phenylseleno group was now utilized to prepare the ground for the formation of the second C–O bond between these two rings. To ensure the stereochemistry of the expected orthoester bond between rings G and H, we had to rely on the anomeric effect,[13] which is maximized in the sequence adopted for the formation of the two C–O bonds (see Figure 3). Extensive model studies demonstrated that the correct orthoester stereochemistry could only be obtained by first attaching the H ring to the C4 oxygen atom of ring G and then constructing the second oxygen bridge (C3), rather than the other way around (which leads to the opposite orthoester stereochemistry, see Figure 3). Thus, oxidation of the phenylseleno group with $NaIO_4$ followed by heating the crude selenoxide in a mixture of vinyl acetate/toluene/diisopropylamine (2/2/1) in a sealed tube at 140 °C effected sequential *syn*-elimination at the anomeric position and ring closure[2] to furnish orthoester **36** in 81% yield and with a diastereoselectivity of approximately 8:1. The stereochemistry of the orthoester linkage in this series of compounds was determined by NMR spectroscopic techniques and correlation with a structure of one such isomer determined unambiguously by X-ray crystallographic analysis

Table 1. Selected physical and spectroscopic data of compounds **35**, **44**, and **2**.

35: $R_f = 0.18$ (silica gel, 50% EtOAc in hexanes); $\alpha_D^{22} = -22.7$ ($c = 2.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3451, 3051, 2930, 2863, 1612, 1582, 1513, 1463, 1383, 1357, 1304, 1251, 1110, 1031, 942, 885, 883\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 7.1$, 2H, ArH), 7.39–7.25 (m, 12H, ArH), 7.15 (t, $J = 7.8$ Hz, 2H, ArH), 7.06 (t, $J = 7.3$ Hz, 1H, ArH), 6.86 (d, $J = 8.6$, 2H, ArH (PMB)), 5.16 (d, $J = 1.7$, 1H, G-1), 4.87 and 4.69 (AB, $J = 12.2$ Hz, 2H, CH_2Ar), 4.80 (d, $J = 9.1$, 1H, H-1), 4.69 and 4.40 (AB, $J = 11.1$ Hz, 2H, CH_2Ar), 4.66 (s, 1H, F-1), 4.61 and 4.47 (AB, $J = 12.1$ Hz, 2H, CH_2Ar), 4.30 (br s, 1H, H-3), 4.01–3.92 (m, 5H, G-4, F-4, H-5, H-5, G-2), 3.83–3.79 (m, 1H, G-3), 3.80 (s, 3H, OMe (PMB)), 3.71–3.68 (m, 2H, G-5, F-6), 3.61 (dd, $J = 9.1$, 2.7 Hz, 1H, H-2), 3.56 (dd, $J = 10.5$, 6.1 Hz, 1H, F-6), 3.51 (d, $J = 2.6$ Hz, 1H, F-2), 3.47 (s, 3H, OMe (F-2)), 3.33–3.31 (m, 2H, F-3, F-5), 3.32 (s, 3H, OMe (F-6)), 3.22 (br s, 1H, H-4), 3.15 (t, $J = 10.9$ Hz, 1H, G-5), 1.02–0.96 (m, 21H, (iPr)$_3$Si), 0.90 (s, 9H, tBuSi), 0.14 (s, 3H, MeSi), −0.07 (s, 3H, MeSi); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 159.4, 138.4, 138.0, 131.6, 131.6, 129.6, 129.4, 128.5, 128.4, 128.2, 128.1, 127.6, 127.5, 127.4, 127.4, 127.2, 126.0, 113.9, 102.8, 95.6, 95.2, 82.2, 78.9, 77.4, 76.8, 76.3, 74.4, 73.6, 72.9, 71.9, 70.8, 70.5, 70.1, 68.0, 63.4, 61.5, 60.3, 59.0, 55.2, 48.4, 25.7, 18.2, 18.0, 18.0, 18.0, 13.2, 13.0, −4.4, −4.8$; HR-MS (FAB), calcd for $C_{61}H_{90}O_{14}SeSi_2Cs$ [M + Cs]: 1315.4089, found: 1315.4022

44: $R_f = 0.34$ (silica gel, 50% EtOAc in hexanes); $\alpha_D^{22} = -19.2$ ($c = 0.12$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3448, 2943, 2861, 1725, 1614, 1514, 1455, 1372, 1308, 1255, 1108, 1079, 1032, 843, 779\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.04$ (d, $J = 7.1$, 2H, ArH), 7.61 (t, $J = 7.4$ Hz, 1H, ArH), 7.47 (t, $J = 7.9$ Hz, 2H, ArH), 7.37–7.29 (m, 10H, ArH), 7.12 (d, $J = 8.6$, 2H, PMB), 6.75 (d, $J = 8.6$, 2H, PMB), 5.42 (t, $J = 9.2$ Hz, 1H, H-3), 5.34 (s, 1H, G-1), 4.87 and 4.66 (AB, $J = 11.6$ Hz, 2H, CH_2Ar), 4.67 (s, 1H, F-1), 4.63 and 4.56 (AB, $J = 11.5$ Hz, 2H, CH_2Ar), 4.53 and 4.50 (AB, $J = 11.0$ Hz, 2H, CH_2Ar), 4.48 (ddd, $J = 10.5$, 10.5, 4.5 Hz, 1H, G-4), 4.33 (br s, 1H, G-2), 4.11 (dd, $J = 9.6$, 4.5 Hz, 1H, G-5), 4.00 (dd, $J = 10.2$, 2.3 Hz, 1H, G-3), 3.90 (dd, $J = 11.4$, 5.4 Hz, 1H, H-5), 3.87 (t, $J = 9.0$ Hz, 1H, F-4), 3.82–3.76 (m, 3H, H-2, H-4, G-5), 3.76 (s, 3H, OMe (PMB)), 3.69 (t, $J = 10.7$ Hz, 1H, H-5), 3.62 (dd, $J = 10.4$, 1.8 Hz, 1H, F-6), 3.55 (dd, $J = 10.8$, 5.3 Hz, 1H, F-6), 3.52 (s, 3H, OMe (F-2)), 3.49 (br s, 1H, F-2), 3.33 (s, 3H, OMe (F-6)), 3.29–3.27 (m, 2H, F-3, F-5), 2.49 (d, $J = 8.3$ Hz, 1H, OH), 0.86 (s, 9H, tBuSi), 0.04 (s, 3H, MeSi), 0.03 (s, 3H, MeSi); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 167.1, 159.4, 137.9, 137.8, 133.4, 129.9, 129.5, 129.5, 128.4, 128.3, 128.3, 127.8, 127.7, 127.7, 127.6, 119.3, 113.8, 95.7, 82.0, 81.7, 77.1, 76.7, 75.8, 73.6, 73.4, 72.7, 71.9, 71.4, 71.4, 69.7, 67.5, 63.3, 62.5, 61.8, 59.0, 55.2, 29.7, 25.9, 18.1, −3.7, −5.1$; HR-MS (FAB), calcd for $C_{53}H_{68}O_{16}SiNa$ [$M + Na^+$]: 1011.4174, found: 1011.4205

2: $R_f = 0.21$ (silica gel, 60% EtOAc in hexanes); $\alpha_D^{22} = -5.7$ ($c = 0.14$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3448, 2955, 2919, 2872, 1725, 1602, 1449, 1378, 1255, 1155, 1108, 1049, 932, 738\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta =$ 7.39–7.23 (m, 20H, ArH), 6.43 (s, 2H, ArH (A_2)), 5.44 (ddd, $J = 9.7$, 9.7, 5.5 Hz, 1H, H-4), 5.33 (d, $J = 0.8$ Hz, 1H, G-1), 5.18 (s, 1H, OCH_2O), 5.05 (s, 1H, OCH_2O), 5.02 (s, 2H, CH_2Ar (A_2)), 5.00 (s, 2H, CH_2Ar (A_2)), 4.77 and 4.61 (AB, $J = 11.7$ Hz, 2H, CH_2Ar), 4.75 and 4.66 (AB, $J = 11.9$ Hz, 2H, CH_2Ar), 4.69 (s, 1H, F-1), 4.54 (ddd, $J = 10.5$, 10.5, 4.5 Hz, 1H, G-4), 4.29 (br s, 1H, G-2), 4.18 (dd, $J = 9.7$, 4.6 Hz, 1H, G-5), 4.12 (dd, $J = 11.3$, 5.4 Hz, 1H, H-5), 4.05 (dd, $J = 10.2$, 2.4 Hz, 1H, G-3), 3.94 (t, $J = 9.8$ Hz, 1H, H-3), 3.88 (t, $J = 9.5$ Hz, 1H, F-4), 3.82 (dd, $J = 10.6$, 10.6 Hz, 1H, G-5), 3.70 (dd, $J = 10.5$, 3.7 Hz, 1H, F-6), 3.63 (dd, $J = 10.5$, 5.1 Hz, 1H, F-6), 3.61–3.59 (m, 2H, F-2, H-2), 3.60 (s, 3H, OMe (F-2)), 3.56 (dd, $J = 11.3$, 9.7 Hz, 1H, H-5), 3.37 (s, 3H, OMe (F-6)), 3.36–3.34 (m, 2H, F-3, F-5), 2.72 (br s, 1H, OH), 2.32 (s, 3H, Me (A_2)); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 166.8, 160.6, 157.3, 138.7, 137.7, 137.5, 136.3, 136.3, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.5, 127.4, 127.0, 119.1, 115.8, 108.1, 98.2, 96.7, 96.0, 96.0, 81.3, 81.0, 77.4, 75.6, 74.9, 73.2, 72.4, 71.8, 70.3, 70.1, 70.1, 69.6, 67.8, 63.4, 63.4, 61.8, 59.3, 53.8, 29.6, 29.6, 27.7, 20.0, 14.1, 14.0$; HR-MS (FAB), calcd for $C_{55}H_{60}O_{17}Cs$ [$M + Na^+$]: 1015.3728, found: 1015.3735

  1433-7851/99/3822-3343 $ 17.50+.50/0

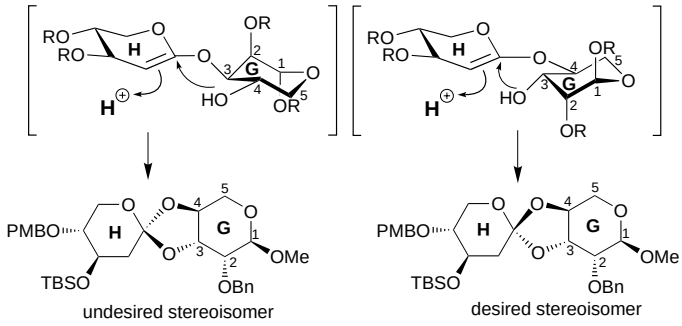


Figure 3. Transition states illustrating the stereoselective formation of the GH orthoester. The joining of rings G and H through the C4 oxygen atom followed by ring closure was crucial for the formation of the desired orthoester stereoisomer. A C3 linked disaccharide leads predominantly to the undesired orthoester stereoisomer.

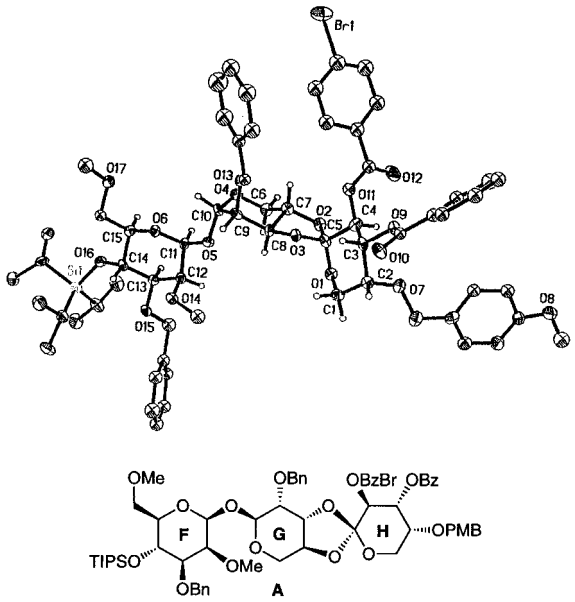
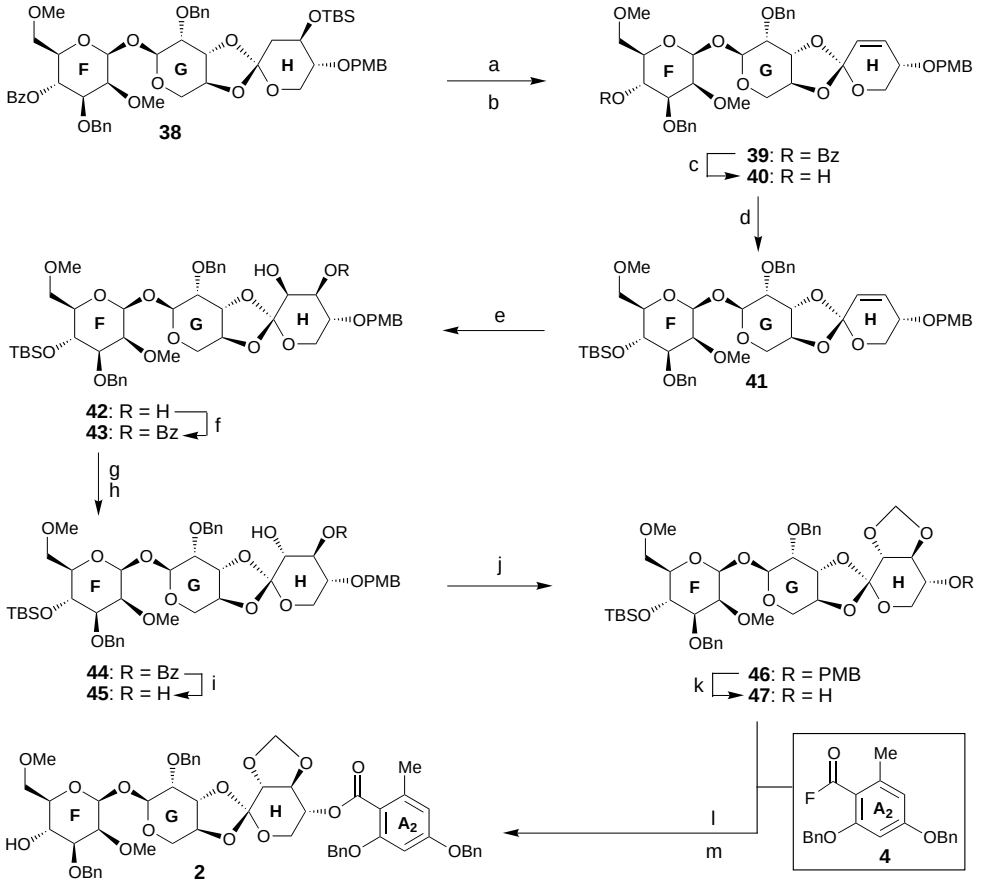


Figure 4. ORTEP drawing of orthoester **A** derived from an X-ray crystallographic analysis.[20]

(Figure 4). Subsequent findings dictated a need for an exchange of protecting group at this stage for the C4 hydroxyl group of ring F. Thus, exposure of **36** to nBu$_4$NF in THF led exclusively to alcohol **37** (95% yield). It is worth noting here that whereas treatment of **35** with nBu$_4$NF removed the TBS group selectively, the same reagent proved selective for the removal of the TIPS group from **36**, presumably as a consequence of a conformational change and/or the absence of the free OH group in going from **35** to **36**. A benzoate group was then installed on the free hydroxyl group of ring F of **37** (BzCl/Et$_3$N/4-DMAP) to furnish **38** (97% yield).

The next task was the installment of an α-hydroxyl group at the C2 position of ring H. To this end, the TBS group of **38** (Scheme 6) was removed from ring H (nBu$_4$NF/AcOH/THF, 95% yield) and the resulting alcohol was dehydrated by treatment with Martin sulfurane[14] in the presence of catalytic amounts of Et$_3$N to give olefin **39** (85% yield), thus setting the stage for a dihydroxylation reaction. Before that operation, however, it was found necessary to exchange the benzoate group on ring F for a TBS group to ensure the success of subsequent steps. Thus, compound **39** was debenzoylated with K$_2$CO$_3$/MeOH (90% yield) and the resulting alcohol was exposed to TBSCl in the pres-



Scheme 6. Completion of the synthesis of the FGHA$_2$ fragment **2**. a) 1.5 equiv nBu$_4$NF, 0.2 equiv AcOH, THF, 25 °C, 1 h, 95%; b) 4.0 equiv Martin sulfurane, 0.05 equiv Et$_3$N, CHCl$_3$, 50 °C, 2 h, 85%; c) 0.5 equiv K$_2$CO$_3$, MeOH, 25 °C, 6 h, 90%; d) 6.0 equiv of NaH, 12 equiv TBSCl, 1.0 equiv [18]crown-6, THF, 0 →25 °C, 4 h, 80%; e) 2.2 equiv NMO, 0.5 equiv OsO$_4$, 1.0 equiv quinuclidine, Me$_2$CO/H$_2$O (10/1), 25 °C, 36 h, 70% (8:1 mixture of diastereoisomers); f) 1.1 equiv nBu$_2$SnO, MeOH, reflux, 3 h; 1.5 equiv BzCl, 1,4-dioxane, 15 °C, 0.5 h, 97% (5:1 mixture of regioisomers); g) 4.0 equiv Dess–Martin periodinane, 20 equiv NaHCO$_3$, CH$_2$Cl$_2$, 25 °C,1 h; h) 1.1 equiv Li(tBuO)$_3$AlH, Et$_2$O, −10 °C, 1 h, 80% over two steps; i) 0.2 equiv NaOH, MeOH, 25 °C, 1 h, 98%; j) 3.0 equiv nBu$_4$NBr, CH$_2$Br$_2$/50% aqueous NaOH (1/1), 65 °C, 2 h, 90%; k) 1.5 equiv DDQ, CH$_2$Cl$_2$/H$_2$O (10/1), 0 →25 °C, 1 h, 85%; l) 1.0 equiv NaH, THF, 0 →25 °C; then 1.5 equiv **4**, 2 h, 96%; m) 1.2 equiv nBu$_4$NF, THF, 25 °C, 1 h, 90%.

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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/OsO_4 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 nBu$_2$SnO/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(tBuO)$_3$AlH 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, CH_2Br_2, and nBu$_4$NBr at 65 °C.[17] The remaining steps for the completion of the synthesis of the FGHA$_2$ 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 (nBu$_4$NF, 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]

Received: August 6, 1999 [Z13842IE]
German version: *Angew. Chem.* **1999**, *111*, 3529–3534

Keywords: antibiotics · carbohydrates · everninomicin · glycosylations · total synthesis

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[19] All new compounds exhibited satisfactory spectral and exact mass data.
[20] Further details will be reported in a full account of this total synthesis. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134793. 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).

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

K. C. Nicolaou,* Helen J. Mitchell, Rosa María Rodríguez, Konstantina C. Fylaktakidou, and Hideo Suzuki

In the preceding communications,[1, 2] we described the synthesis of the A$_1$B(A)C and FGHA$_2$ 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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[**] We thank Dr. A. K. Ganguly for helpful discussions and a generous gift of everninomicin 13,384-1 and Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectroscopic, and X-ray crystallographic assistance, respectively. This work was financially supported by the National Institutes of Health (USA), the Skaggs Institute for Chemical Biology, postdoctoral fellowships from M.E.C., Spain (R.M.R., Fulbright), the Japan Society for the Promotion of Science (H.S.), and the George Hewitt Foundation (K.C.F.), and grants from Schering Plough, Pfizer, Glaxo, Merck, Hoffmann-La Roche, DuPont, and Abbott Laboratories.