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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[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.

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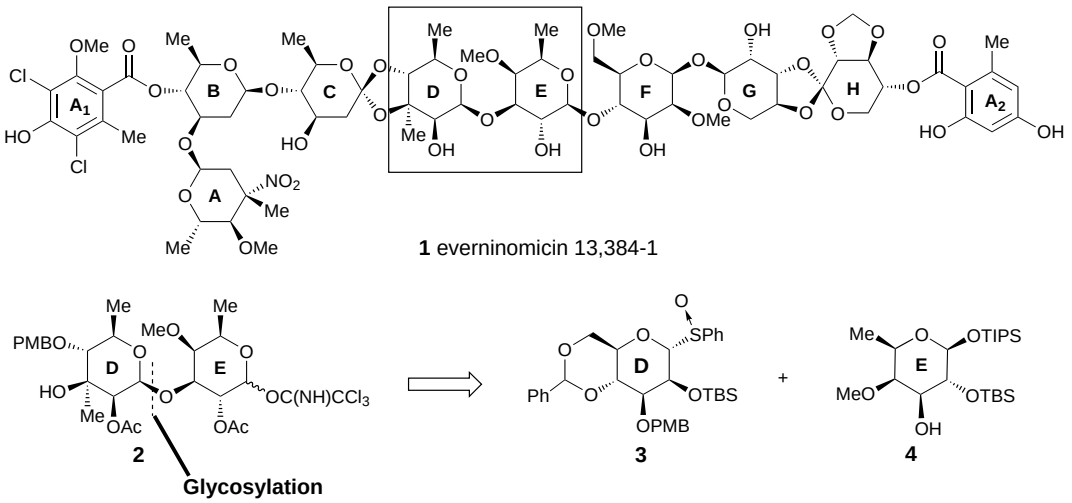
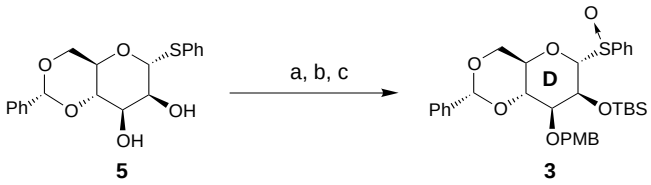


Figure 1. Retrosynthetic analysis of the DE fragment **2**. Ac = acetyl; PMB = *p*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl.

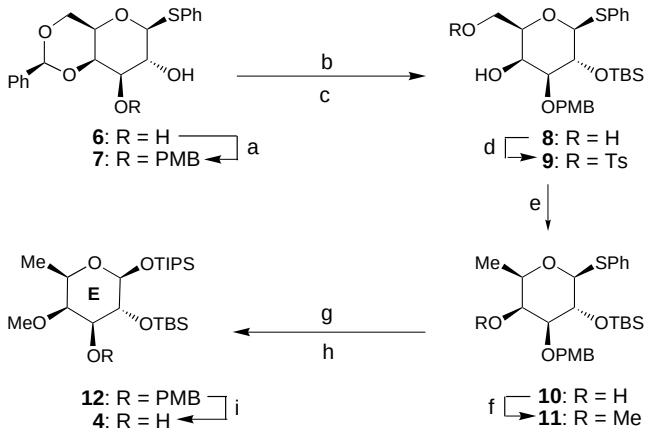
were the following: 1) construction of the β-mannoside linkage and 2) installment of the tertiary center on ring D. We chose the sulfoxide-based glycosidation reaction of Kahne et al.[3] as the coupling procedure for **3** and **4** and designed the benzylidene ring[4] in **3** to ensure the stereocontrolled 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).

Scheme 1 summarizes the construction of building block D (**3**), which proceeded smoothly from the known intermediate **5**.[6] Thus, the regioselective tin acetal mediated monoprotection of **5** as a PMB ether (nBu$_2$SnO-PMBCl/nBu$_4$NI, 83% yield) was followed by TBS introduction at the C2 hydroxyl group (TBSOTf/2,6-lutidine, 93% yield) and oxidation of the sulfur group with *m*CPBA (92% yield) to afford the desired sulfoxide **3** (approximate 4:1 mixture of separable diastereoisomers).



Scheme 1. Synthesis of carbohydrate building block D (**3**). a) 1.1 equiv nBu$_2$SnO, toluene, 110 °C, 3 h; 1.5 equiv PMBCl, 0.2 equiv nBu$_4$NI, 25 → 110 °C, 83%; b) 1.2 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2, 0 → 25 °C, 0.5 h, 93%; c) 1.1 equiv *m*CPBA, CH_2Cl_2, −20 → 0 °C, 2 h, 92% (ca. 4:1 mixture of diastereoisomers). *m*CPBA = *m*-chloroperoxybenzoic acid; Tf = trifluoromethanesulfonyl.

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] (nBu$_2$SnO/PMBCl/nBu$_4$NI, 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



Scheme 2. Synthesis of carbohydrate building block E (**4**). a) 1.1 equiv nBu$_2$SnO, toluene, 110 °C, 3 h; 1.5 equiv PMBCl, 0.2 equiv nBu$_4$NI, 25 → 110 °C, 2 h, 87%; b) 1.2 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2, 0 → 25 °C, 1 h, 97%; c) 2.5 equiv Zn(OTf)$_2$, 20 equiv EtSH, CH_2Cl_2, 0 °C, 2 h, 77%; d) 1.1 equiv TsCl, py, 0 → 25 °C, 12 h, 97%; e) 1.6 equiv LAH, THF, 45 °C, 3 h, 90%; f) 1.1 equiv NaH, 1.3 equiv MeI, DMF, 0 → 25 °C, 1 h, 94%; g) 1.5 equiv NBS, Me_2CO/H_2O (10/1), 0 → 25 °C, 2 h, 95%; h) 1.2 equiv TIPSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2, 0 → 25 °C, 6 h, 97% (α:β ca. 1:2); i) 1.5 equiv DDQ, CH_2Cl_2/H_2O (10/1), 0 → 25 °C, 1 h, 98%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMF = dimethylformamide; LAH = lithium aluminum hydride; NBS = *N*-bromosuccinimide; py = pyridine; THF = tetrahydrofuran; Ts = *p*-toluenesulfonyl.

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/H_2O (95% yield) followed by silylation (TIPSOTf/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 Tf_2O and di-*tert*-butyl-4-methyl pyridine (DTBMP) to afford the β-mannoside **13** (glycosidation with

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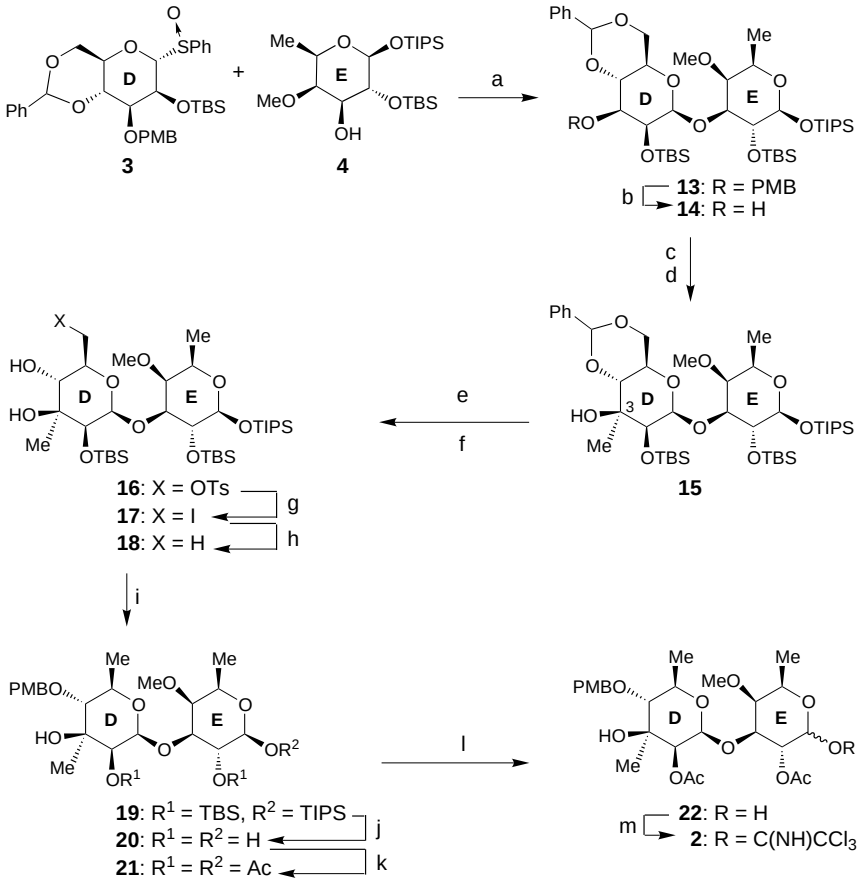

Scheme 3. Assembly of DE fragment **2**. a) 1.3 equiv **3**, 1.3 equiv Tf_2O, 2.2 equiv DTBMP, CH_2Cl_2, $-78\,^{\circ}C$; 1.0 equiv **4**, $-78 \rightarrow 0\,^{\circ}C$, 2 h, 71%; b) 1.3 equiv DDQ, CH_2Cl_2/H_2O (10/1), $0 \rightarrow 25\,^{\circ}C$, 2 h, 95%; c) 1.5 equiv NMO, 0.05 equiv TPAP, CH_2Cl_2, $25\,^{\circ}C$, 2 h; d) 1.4 equiv MeLi, Et_2O, $-78\,^{\circ}C$, 1 h, 88% over two steps; e) H_2, 0.2 equiv 10% Pd/C (w/w), EtOAc, $25\,^{\circ}C$, 2 h, 97%; f) 1.2 equiv TsCl, py, $0 \rightarrow 25\,^{\circ}C$, 12 h, 87%; g) 5.0 equiv LiI, DMF, $80 \rightarrow 100\,^{\circ}C$, 2 h, 86%; h) 3.0 equiv nBu$_3$SnH, 0.01 equiv AIBN, PhH, $80\,^{\circ}C$, 0.5 h, 97%; i) 1.1 equiv nBu$_2$SnO, toluene, $110\,^{\circ}C$, 10 h; 1.5 equiv PMBCl, 0.2 equiv nBu$_4$NI, $25 \rightarrow 110\,^{\circ}C$, 8 h, 63%; j) 4.0 equiv nBu$_4$NF, THF, $25\,^{\circ}C$, 6 h; k) 2.5 equiv Ac_2O, 4.0 equiv Et_3N, 0.2 equiv 4-DMAP, CH_2Cl_2, $0 \rightarrow 25\,^{\circ}C$,1 h, 90% over two steps; l) 1.3 equiv nBuNH$_2$, THF, $25\,^{\circ}C$, 5 h, 86%; m) 5.0 equiv CCl_3CN, 0.05 equiv DBU, CH_2Cl_2, $0\,^{\circ}C$, 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 Et_2O at $-78\,^{\circ}C$. 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 conformation 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 (H_2/10% 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 nBuSnH/AIBN to afford the desired compound **18** in 97% yield. Protection at C4 of ring D was effected with nBu$_2$SnO/PMBCl/nBu$_4$NI leading to **19** (63% yield), which was completely desilylated (nBu$_4$NF) and tris-acetylated (Ac_2O/Et_3N/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 nBuNH$_2$ in THF to give lactol **22**, whose conversion into trichloroacetimidate **2** was accomplished by exposure to CCl_3CN and DBU (89%, α:β ratio approximately 30:1).

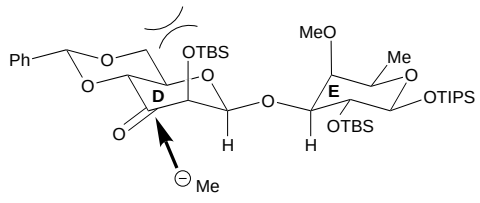

Figure 2. Illustration of the preferenial α-attack of MeLi on the C3 carbonyl group of ring D during the formation of compound **15**.

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 $BF_3 \cdot Et_2O$ in CH_2Cl_2 at $-20\,^{\circ}C$ 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 $A_1B(A)C$ fragment as well as for the overall strategy towards the final target molecule prompted a number of protecting group exchanges

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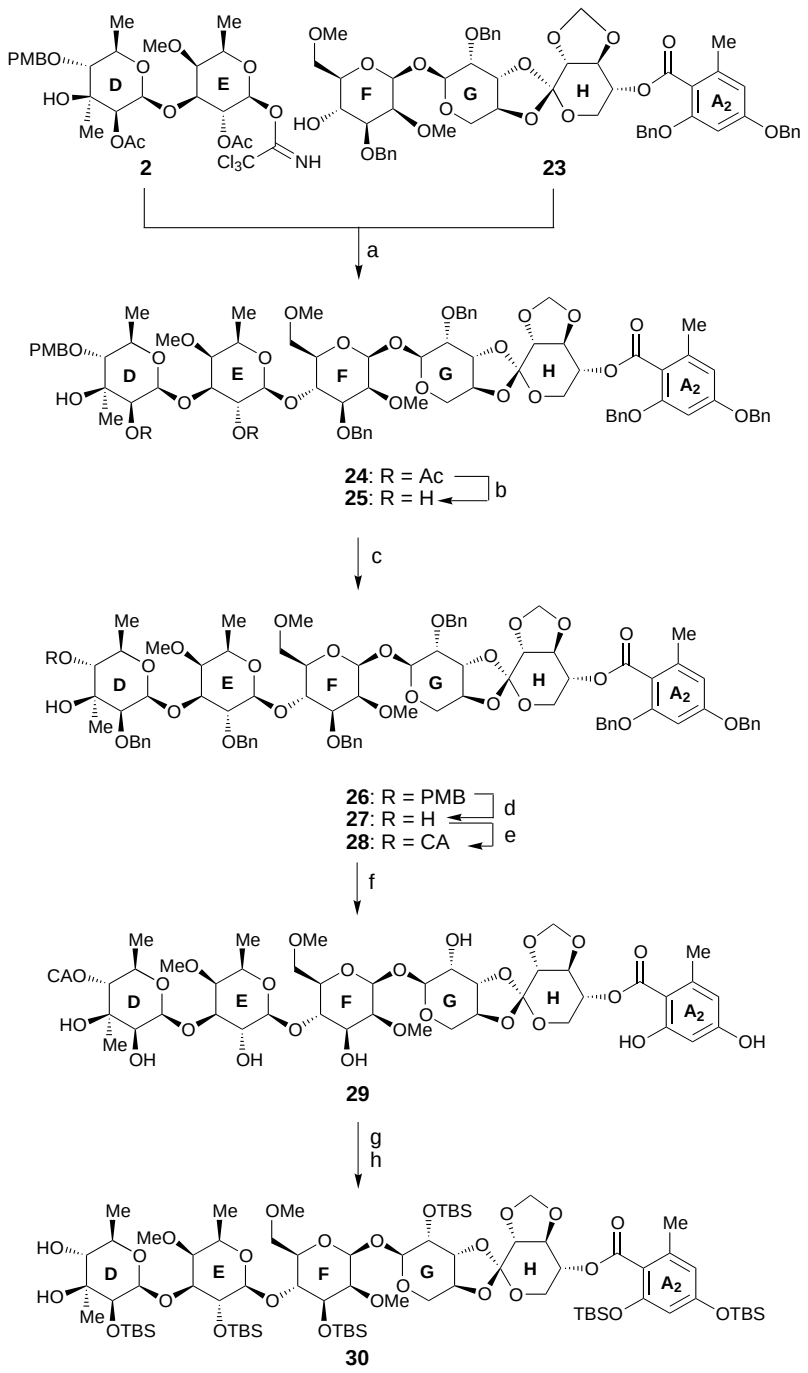

Scheme 4. Completion of the synthesis of the DEFGHA$_2$ fragment (**30**). a) 1.6 equiv **2**, 0.5 equiv $BF_3 \cdot Et_2O$, CH_2Cl_2, $-20\,^\circ C$; 2 h, 55% yield of desired β-anomer, 18% of unknown compound (β-anomer) and 5% yield of α-anomer (α:β ca. 1:9); b) 0.5 equiv K_2CO_3, MeOH, 25 °C, 2 h, 85%; c) 2.5 equiv NaH, 3.0 equiv BnBr, THF, 0 → 25 °C, 2 h, 95%; d) 1.3 equiv DDQ, CH_2Cl_2/H_2O (10/1), 0 → 25 °C, 2 h, 95%; e) 1.5 equiv $(CA)_2O$, 3.0 equiv Et_3N, 0.2 equiv 4-DMAP, CH_2Cl_2, 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, CH_2Cl_2, 0 → 25 °C, 8 h, 65%; h) 0.2 equiv K_2CO_3, MeOH, 25 °C, 15 min, 85%. CA = chloroacetyl.

at this stage. Three sets of protecting groups on fragment DEFGHA$_2$ 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 A$_1$B(A)C fragment. With this objective in mind, compound **24** was deacetylated (K_2CO_3/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 A$_1$B(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 A$_1$B(A)C partner. Our third generation strategy involved the adoption of the hexa-TBS derivative **30** (Scheme 4) as the DEFGHA$_2$ 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 (CA_2O/Et_3N/4-DMAP, 98% yield) led to **28**, which was subjected to hydrogenolysis (H_2/10% 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 K_2CO_3 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 A$_1$B(A)C glycosyl fluoride donor **31**[1] with the DEFGHA$_2$ hexa-TBS diol acceptor **30** in the presence of $SnCl_2$ in Et_2O 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 Sinaÿ conditions[11] ($NaIO_4$ oxidation to the selenoxide in MeOH/CH_2Cl_2/H_2O (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 (H_2/ 10% Pd/C, $NaHCO_3$, *t*BuOMe) to remove the two benzyl ethers and b) desilylation (nBu$_4$NF/THF) to cleave all six TBS groups (75% overall yield). Synthetic everninomicin 13,384-1 (**1**) was identical by the

  1433-7851/99/3822-3348 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1999**, *38*, No. 22

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): $\tilde{\nu}_{max} = 3495$, 3331, 2928, 2951, 2884, 1743, 1678, 1614, 1508, 1455, 1373, 1243, 1091, 1049, 844, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.54$ (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 (br s, 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, $CDCl_3$): $\delta =$ 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% Et_2O in hexanes); $\alpha_D^{22} = -29.1$ ($c = 0.10$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3495$, 2955, 2919, 2861, 1737, 1602, 1467, 1361, 1255, 1073, 838, 779 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.29$ (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 (br s, 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 (br s, 1H, G-2), 4.17 (dd, $J = 11.1$, 5.4 Hz, 1H, H-5), 4.12 (br s, 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 (br s, 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 (br s, 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*BuSi), 0.95 (s, 9H, *t*BuSi), 0.92 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.89 (s, 9H, *t*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); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.4$, 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 $C_{77}H_{144}O_{25}Si_6Na$ [$M + Na^+$]: 1659.8509, found: 1659.8452

33: $R_f = 0.32$ (silica, 60% Et_2O in hexanes); $\alpha_D^{22} = -19.5$ ($c = 0.20$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2955$, 2919, 2861, 1737, 1602, 1543, 1455, 1384, 1255, 1108, 1067, 1038, 838, 779 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.57$ (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 (br s, 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 (br d, $J = 9.8$ 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 (br s, 1H, G-2), 4.17 (dd, $J = 11.4$, 5.7 Hz, 1H, H-5), 4.14 (br s, 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 (br t, $J = 8.3$ 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 (br dd, $J = 12.4$, 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*BuSi), 0.95 (s, 9H, *t*BuSi), 0.94 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.89 (s, 18H, *t*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), 0.06 (s, 3H, MeSi); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.1$, 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 $C_{120}H_{193}O_{38}Cs$ [$M + Cs^+$]: 2496/2497, found: 2498/2499

usual criteria (TLC, ^1H NMR, ^{13}C NMR, IR, MS, α_D^{22}) 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 Sinaÿ orthoester protocol formation;[11] the sulfoxide-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]

Received: August 6, 1999 [Z13843IE]
German version: *Angew. Chem.* **1999**, *111*, 3535–3540

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

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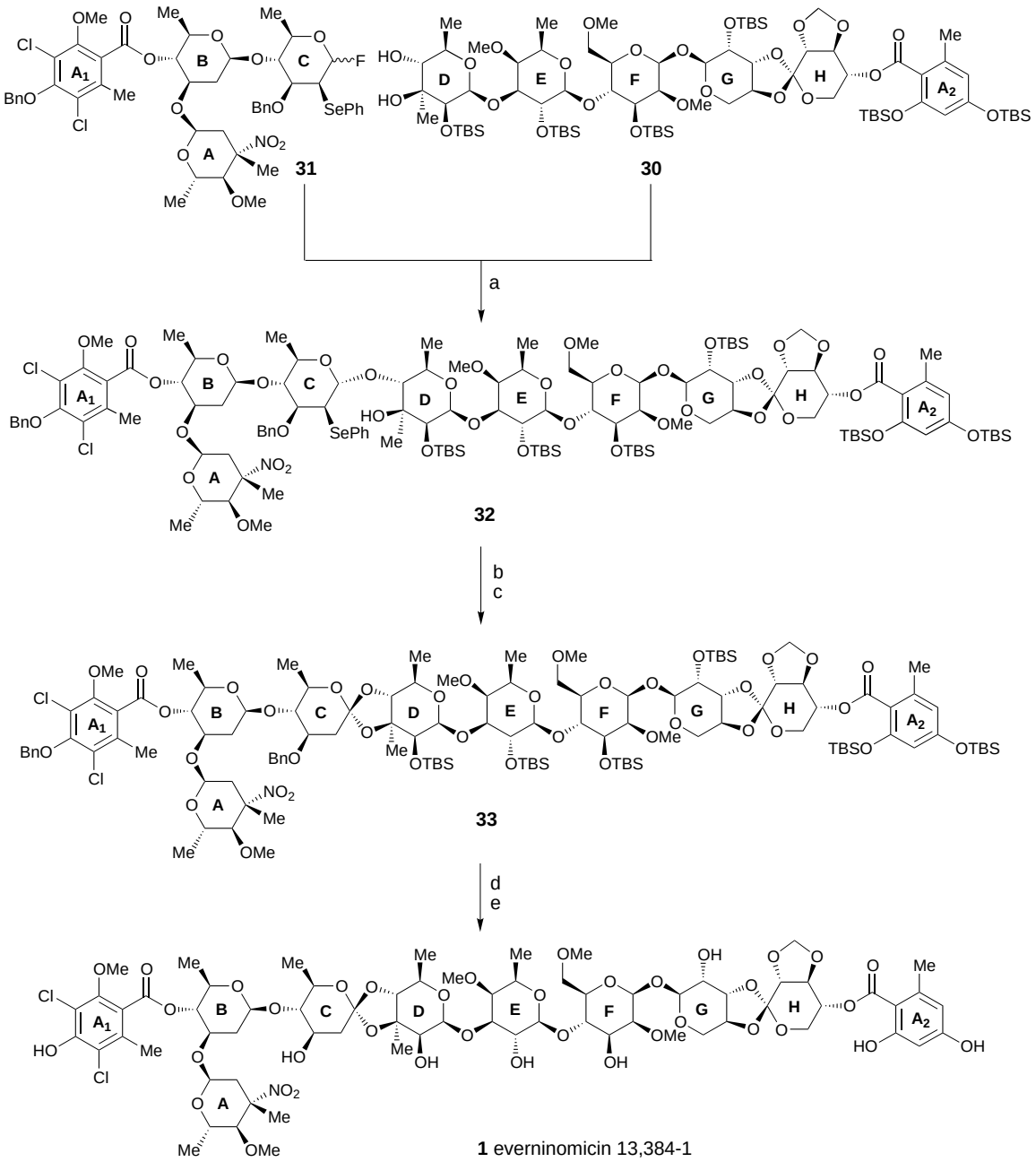

Scheme 5. Completion of the total synthesis of everninomicin 13,384-1 (**1**). a) 2.0 equiv **31**, 1.8 equiv $SnCl_2$, Et_2O, 0 → 25 °C, 6 h, 70 %; b) 10 equiv $NaIO_4$, 8.0 equiv $NaHCO_3$, MeOH/CH_2Cl_2/H_2O (3/2/1), 25 °C, 4 h; c) vinyl acetate/toluene/diisopropylamine (2/2/1), sealed tube, 140 °C, 16 h, 65 % over two steps; d) H_2, 0.1 equiv 10 % Pd/C (w/w), 4.0 equiv $NaHCO_3$, *t*BuOMe, 25 °C, 1 h; e) 10.0 equiv *n*Bu_4NF, THF, 25 °C, 10 h, 75 % over two steps.

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