Practical Synthesis of Oligosaccharides. Partial Synthesis of Avermectin B_{1a}

K. C. Nicolaou,*† R. E. Dolle,‡ D. P. Papahatjis, and J. L. Randall

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received December 15, 1983. Revised Manuscript Received March 2, 1984*

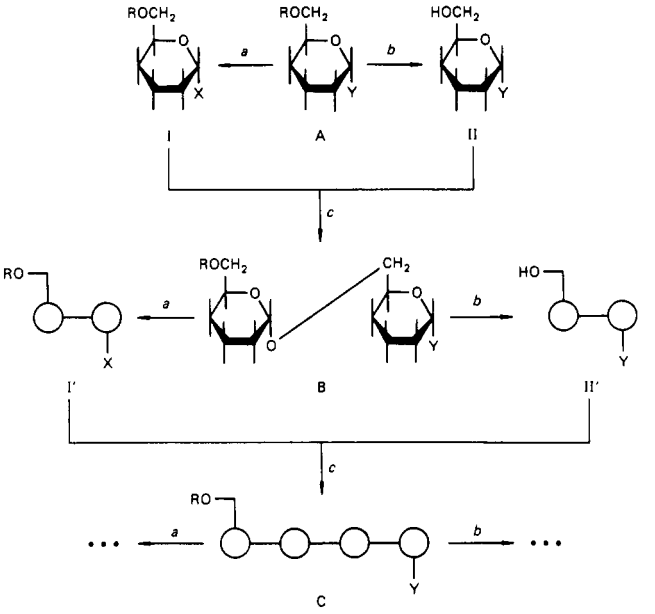
Abstract: A practical synthesis of oligosaccharides from phenylthio sugars via glycosyl fluorides is described. The new technology is applied to the synthesis of hexasaccharide **9** from a glucose derivative and avermectin B_{1a} (**11**) from an avermectin B_{1a} aglycon derivative.

The very high abundance and paramount biological importance of oligo- and polysaccharide-containing natural products needs little, if any, introduction.[1] Present synthetic methods for construction of such molecules, however, leave considerable margin for improvement in terms of efficiency, generality, and stereoselectivity.[2,3] A particularly serious complication arises during attempts to activate the terminal anomeric center, necessary for further coupling, under conditions that do not damage the existing construction including the O-glycosidic bonds.[4] In this paper we wish to report a general and practical sequence for the synthesis of oligosaccharides and their attachment onto aglycons and the first applications of this technology to the synthesis of a hexasaccharide and of a member of the avermectin family of antiparasitic agents, avermectin B_{1a}.

The general problem of oligosaccharide synthesis and a solution that allows for repetitive and block-based operations are presented in Scheme I, using a protected glucose derivative as the carbohydrate unit. For a practical and general synthesis of such complex and sensitive structures as the saccharides, the following strategy and requirements are crucial in the selection of groups R and Y: (1) groups R and Y must secure high chemical stability (long shelf life and chromatographic tolerance) for the starting monomer A and subsequent building blocks B, C,..., (2) activation of these central intermediates (A, B, C,...) should proceed under mild and highly selective conditions toward intermediates I and II in high yields, thus completing *stage-1 activation*, (3) both intermediates I and II must be active enough for glycosidic bond formation upon further activation (*stage-2 activation*) but yet sufficiently stable for chromatographic manipulation, a requirement that becomes crucial in multistep and small-scale operations, (4) coupling between 1 and II during stage-2 activation should proceed under mild conditions, preferably with stereochemical control, and (5) repetition of the process should not break preconstructed O-glycosidic bonds. In practice, R = Si-*t*-BuPh$_2$ (or Si-*t*-BuMe$_2$), Y = SPh, and X = F and (a), for Scheme I, NBS (1.1 equiv), DAST (1.2 equiv), CH_2Cl_2, −15–0°C, (b) *n*-Bu_4NF (1.2 equiv), THF, 0–25 °C, and (c) $SnCl_2$ (1.2 equiv), $AgClO_4$ (1.1 equiv), Et_2O, 4AMS −15 → 25 °C[5] proved to be an excellent combination of functional groups and reaction conditions establishing a simple and highly effective technology for oligosaccharide synthesis (Scheme I).

The synthesis, properties, and direct utilization of phenyl thioglycosides (e.g., A, Scheme I) in the construction of O-glycosides have recently been reviewed.[2] *Their efficient conversion to glycosyl fluorides under conditions tolerated by most functions found in carbohydrates including groups and O-glycoside bonds was crucial to the present development.* Table I includes a number of glycosyl fluorides prepared from the indicated phenylthio glycosides by two different and new methods (methods A and B)[6] demonstrating the generality and efficiency of this transformation. The initial couplings of the activated carbohydrate units were carried out by further activation provided under conditions c

Scheme I. General Oligosaccharide Synthesis



a: NBS, DAST, CH_2Cl_2, 0° to 25° C; *b*: *n*-Bu_4NF, THF, 0° to 25° C; *c*: $SnCl_2$, $AgClO_4$, Et_2O, 4-Å MS, −15° to 25° C.

○: Glucose unit; 2,3,4-substituents omitted for clarity.

Scheme I (vide supra), a procedure found to be quite satisfactory for the operations reported here.

In an effort to demonstrate the repetitive and block-construction nature of this technology, we targeted the linear hexasaccharide

† Fellow of the A. P. Sloan Foundation, 1979–1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1985; J. S. Guggenheim Fellow, 1984.

‡ Dean's Fellow, University of Pennsylvania, 1983–1984.

(1) These include the (a) glycoproteins: Sharon, N.; Lis, H. *Chem. Eng. News* **1981**, *59* (13), 21. (b) Glycolipids: Anderson, L., Unger, F. M., Eds. *ACS Symp. Ser.* **1983**, 231. (c) Various antibiotics and anticancer agents: Berdy, J.; Aszalos, A.; Bostian, M.; McNitt, K. L. "CRC Handbook of antibiotic Compounds"; CRS Press: Boca Raton, FL, 1983; Vols. I–X. See also: (d) Kennedy, J. F.; White, C. A. "Bioactive Carbohydrates"; Wiley: New York, **1983**. (e) Tipson, R. S.; Horton, D., Eds. *Adv. Carbohyd. Chem. Biochem.* **1983**, *41* and references cited therein.

(2) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430 and references cited therein.

(3) For an excellent review, see: Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.

(4) For a typical example, see the recent and elegant synthesis of oligosaccharides with phytoalexin–elicitor activites in which the activation of a tetrasaccharide block proceeded in only 16% yield due to extensive degradation of the acid-sensitive glycosidic bonds: Ossowski, P.; Pilotti, A.; Garegg, P. J.; Lindberg, B. Angew. Chem., Int. Ed. Engl. **1983**, *22*, 793. For another recent and elegant example of an O-glycoprotein oligosaccharide synthesis by the trichloroacetimidate method, see: Schmidt, R. R.; Grundler, G. *Ibid.* **1983**, *22*, 776.

(5) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431; **1983**, 935.

(6) Previous methods for preparing glycosyl fluorides start with (a) Glycals: Korytnyk, W.; Valentekovic-Horuat. *Tetrahedron Lett.* **1980**, *21*, 1493. Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1970**, *24*, 240. Adamson, J.; Foster, A. B.; Hesse, R. H. *Chem. Commum.* **1969**, *309*. (b) Lactols: ref 5. (c) Glycosyl halides: Hall, L. D.; Steiner, P. R. *Can. J. Chem.* **1970**, *48*, 2439. (d) Glycosyl acetates: Brauns, D. H. *J. Am. Chem. Soc.* **1923**, *45*, 833.

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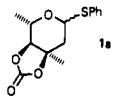
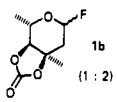
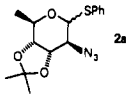
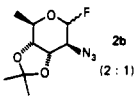
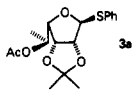
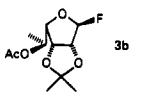
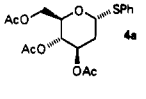
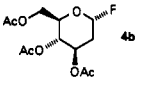
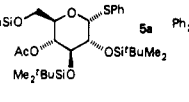
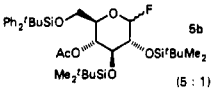
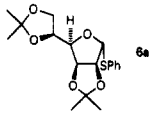
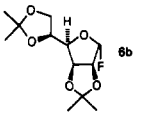
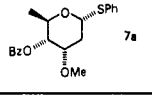
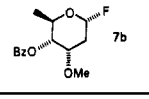
Table I. Formation of Glycosyl Fluorides from Phenyl Thioglycosides

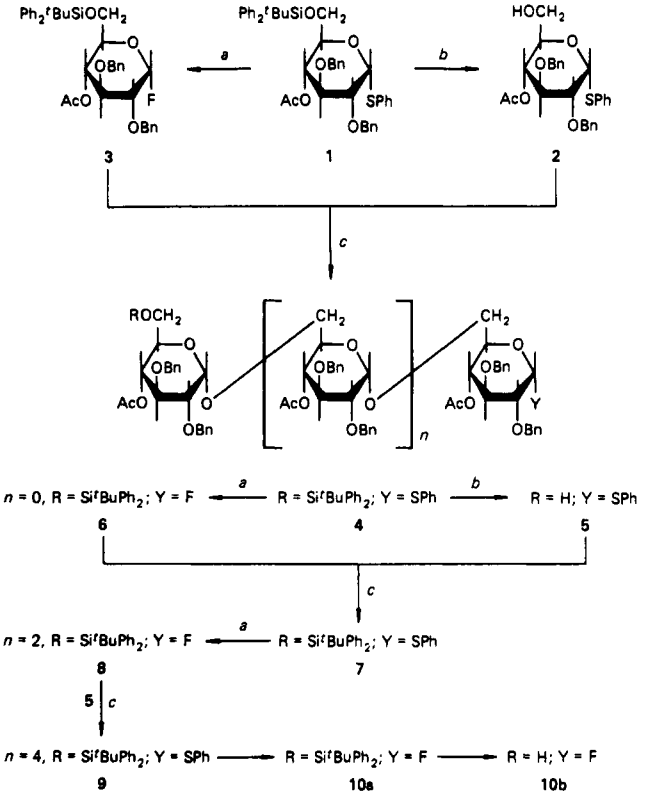
Entry	Phenylthioglycoside	Glycosyl fluoride (α : β ratio)	Yields (percent)	Method[a]
1	 1a	 1b (1 : 2)	75	B
2	 2a	 2b (2 : 1)	80 73	A B
3	 3a	 3b	71	B
4	 4a	 4b	70	A
5	 5a	 5b (5 : 1)	82 74	A B
6	 6a	 6b	91 80	A B
7	 7a	 7b	88	A

[a] Method A, DAST–NBS; method B, HF·pyr complex–NBS.

9 consisting of six glucose units linked in a 1→6 fashion (Scheme II). Thus, the glucose derivative **1**[7,8] was smoothly converted to the free hydroxy derivative **2** by conditions b (98% yield) and to glucosyl fluoride **3** (mixture of anomers 1:1)[9] by conditions a (90% yield). Coupling of **2** with **3** under conditions c resulted in the formation of disaccharide **4** (n = 0, 75% yield).[9] Pure tetrasaccharide **7** was similarly constructed (n = 2, 70% yield)[9] from pure **4** via the activated intermediates **5** (97% yield) and **6** (88% yield, anomeric mixture).[9] Finally, anomeric activation of **7** to fluoride **8** (conditions a, 89% yield, anomeric mixture)[9] followed by attachment of another disaccharide block **5** as described above, afforded the hexasaccharide **9** (n = 4, 66% yield).[9] It could also be demonstrated that further activation of both the anomeric center and the primary alkoxyl function, even within the same molecule in a sequential manner, could be achieved leading to compounds **10a** and **10b**, thus offering further opportunities.[10]

To demonstrate the usefulness of the present methodology to the synthesis of natural products, we include here an important application, from the avermectin area. Avermectin B_{1a} (**11**)[11] was

Scheme II. Synthesis of Hexasaccharide 9



For conditions *a*, *b* and *c* see Scheme 1.

constructed from its aglycon 5-*tert*-butyldimethylsily) ether **12**[12] and oleandrose derivative **13**[14] as follows (Scheme III). The

(7) The glucose derivative **1** was prepared from α-D-glucosepentaacetate in high overall yield by the following sequence: (a) 2.0 equiv of PhSH, 0.9 equiv of $SnCl_4$, benzene, 25 → 80 °C; (b) NaOMe–MeOH, 0 → 25 °C; (c) $PhCH(OMe)_2$–CSA catalyst, benzene, 25 °C; (d) $PhCH_2Br$–NaH, THF, 25 → 60 °C; (e) amberlyst 15–MeOH, reflux; (f) 1.1 equiv of *t*-$BuPh_2SiCl$–imid, DMF, 0 → 25 °C; (g) Ac_2O–DMAP, CH_2Cl_2, 0 → 25 °C.

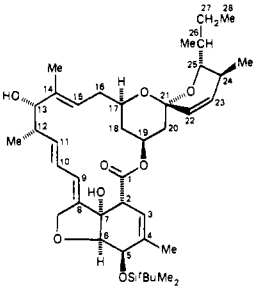
(8) All new compounds were characterized by spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

(9) Although the reactivity of the two anomeric fluorides was observed to be different, they both enter the glycosidation reaction leading predominantly to the α-glycoside. The minor amounts (5%) of the β-isomer in the glycosidation reaction was removed chromatographically.

(10) Further results will be reported in due course.

(11) (a) Albers-Schonberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. (b) Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K., *Ibid.* **1981**, *103*, 4221. (c) Campbell, W. C.; Fisher, M. H.; Stapley, E. O.; Albers-Schonberg, G.; Jacob, T. A. *Science (Washington, D. C)* **1983**, *221*, 823.

(12) The aglycon derivative **12** was prepared from avermectin B_{1a} by acid

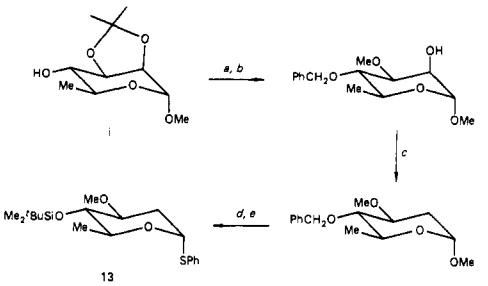


12

hydrolysis (H_2SO_4–THF–H_2O, 25 °C)[13] followed by selective monosilylation (1.1 equiv of *t*-$BuMe_2SiC$–imid, DMF, 0 → 25 °C) in ca 50% overall yield.

(13) Mrozik, H.; Eskola, P.; Arison, B. H.; Albers-Schonberg, G.; Fisher, M. H. *J. Org. Chem.* **1982**, *47*, 489.

(14) The oleandrose derivative **13** was synthesized from the readily



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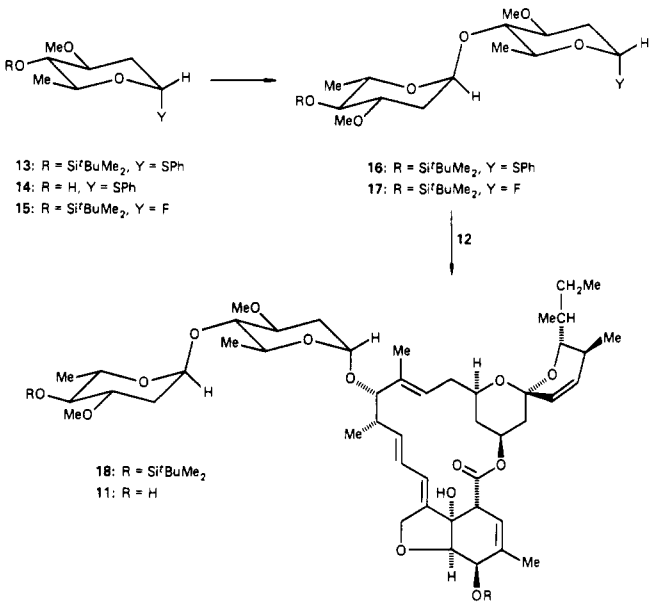
available L-rhamnose derivative i[15] by the following sequence: (a) $PhCH_2Br$–KH, THF, 25 °C then AcOH–H_2O (3:1), 60 °C (98%); (b) *n*-Bu_2SnO–MeOH, 70 °C then MeI–DMF, 60 °C[2] (78%); (c) PhOC(S)Cl–pyr, 25 °C then *n*-Bu_3SnH–AIBN, toluene, 80 °C (90%), (d) $Pd(OH)_2$–H_2, MeOH–EtOAc (3:1), 25 °C then *t*-BuMe SiCl–imid, DMF, 25 °C (95%); (e) Me_3SiSPh–ZnI_2–*n*-Bu_4NI, 60 °C[216] (82%, α:β anomers 3:1 ratio).

Scheme III. Partial Synthesis of Avermectin B_{1a} (11)



phenylthio glycoside **13** was converted to the hydroxy component **14** (100% yield) and to the glycosyl fluoride **15** (80% yield) and the two units coupled to afford the disaccharide **16** (65% yield, α-anomer exclusively) as described above. Activation of the disaccharide **16** at the anomeric center as the fluoride **17** (85% yield) followed by coupling to the aglycon **12** furnished the avermectin B_{1a} derivative **18** (62% yield, α-anomer exclusively) from which avermectin B_{1a} (**11**) was generated by exposure to excess n-Bu_4NF in THF (0 °C, 89% yield) thus completing a partial synthesis of this important antiparasitic agent.[17]

Furthermore, we found glycosyl fluorides to be excellent substrates for C- and N-glycosylation reactions leading to highly desirable intermediates for the synthesis of various C-glycosides, N-glycosids, and glycopeptides.[18]

The potential of the disclosed technology to the construction of oligo- and polysaccharides and other carbohydrate-containing natural products of biological importance is obvious and considerable. Future applications may include extrapolations to solid-phase procedures, total and partial syntheses of naturally occurring molecules, analogues of medicinally important compounds for structure–activity studies, and other predesigned targets of theoretical and biological interest.

Experimental Section

General. ^1H NMR spectra were recorded on a Bruker WH-250 MHz spectrometer in $CDCl_3$ and are reportd in δ from Me_4Si. IR spectra were recorded on Perkin-Elmer Model 281B or 781 infrared spectrophotometer and the IR figures reported are ν_{max} in cm^{-1}.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light and 7% phosphomolybdic acid in ethanol–heat as developing agent. Preparative layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere using dry freshly distilled solvents under anhydrous conditions unless otherwise noted. Ethereal solvents were dried and distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. Amines were distilled under argon from calcium hydride. Reaction temperatures were externally measured. NMR multiplicites are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broad; J = coupling constant (Hz). Only the strongest and/or structurally most important peaks are reported for the IR. All yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials.

Preparation of Tetrasaccharide Fluoride 8. The carefully dried thioglycoside **7** (570 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (3 mL) under argon and cooled to −15 °C. The stirred solution was then treated with DAST (60 μL, 0.45 mmol) and allowed to stir for 2 min before NBS (70 mg, 0.39 mmol) was added. After 25 min, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and poured into an ice-saturated $NaHCO_3$ solution (3 mL). The organic phase was separated and washed with saturated $NaHCO_3$ solution (3 mL) and brine (3 mL), before drying ($MgSO_4$) and evaporation. The oily product so obtained was subjected to flash column chromatography (silica, ether–petroleum ether mixtures) to afford pure fluoride **8** (463 mg, 85%): R_f 0.26 (60% ether in petroleum ether); $[\alpha]^{25}_D$ + 63.94° (c 0.011, CH_2Cl_2); IR (neat) ν_{max} 3035, 2930, 2860, 1748 ($COCH_3$), 1500, 1454, 1430, 1368, 1231, 1156, 1100, 1041, 731, 695 cm^{-1}; ^1H NMR δ 7.72–7.62 (m, 4 H, $SiPh_2$), 7.38–7.04 (m, 46 H), 5.62 (d, J = 3.4 Hz, 1 H, anomeric), 5.53 (dd, J = 53.1, 2.3 Hz, 0.55 H, CHF, α-anomer), 5.39 (d, J = 3.8 Hz, 1 H, anomeric), 5.41 (dd, J = 53.7, 5.8 Hz, 0.45 H, CHF, β-anomer) 5.35 (d, J = 3.7 Hz, 1 H, anomeric), 5.22 (t, J = 9.6 Hz, 1 H C*H*OAc), 5.01–3.41 (m, 39 H), 2.11 (s, 1.4 H, OAc), 2.08 (s, 1.6 H, OAc), 2.05, 1.88, 1.82 (all s, 3 H each, OAc), 1.03 (s, 9 H, t-Bu). Anal. ($C_{104}H_{115}O_{24}SiF$) C, H.

Preparation of Hexasaccharide 9. To a magnetically stirred, cold (−15 °C) suspension of $AgClO_4$ (95 mg, 0.46 mmol), $SnCl_2$ (87 mg, 0.46 mmol), and 4-Å molecular sieves (1.5 g, crushed and flamed) in dry ether (7 mL) under argon was added the dry alcohol **5** (224 mg, 0.25 mmol) in dry ether (3.5 mL). After 2 min, the fluoride **8** (224 mg, 0.25 mmol) in dry ether (3.5 mL) was added, and the reaction was allowed to stir at −15 °C for 2 h and then at room temperature for 10 h. The reaction mixture was diluted with ether (50 mL) and filtered through Celite. Washing the filtrate with saturated $NaHCO_3$ solution (2 mL) and brine (2 mL) followed by drying ($MgSO_4$) and evaporation afforded an oily product, which was subjected to flash column chromatography (silica, ethyl acetate–benzene mixtures) to afford hexasaccharide **9** (442 mg, 66%): R_f 0.29 (15% ethyl acetate in benzene); $[\alpha]^{25}_D$ 66.50° (c 1.9, CH_2Cl_2); IR (neat) ν_{max} 3035, 2925, 1745 ($COOCH_3$), 1500, 1482, 1455, 1368, 1232, 1160, 1100, 1030, 735, 695, 679 cm^{-1}; ^1H NMR δ 7.69–7.62 (m, 4 H, $SiPh_2$), 7.59–7.49 (m, 2 H, SPh), 7.47–7.01 (m, 69 H, Ar), 5.58 (d, J = 3.6 Hz, 1 H, anomeric), 5.44 (d, J = 3.6 Hz, 1 H, anomeric), 5.40 (d, J = 3.9Hz, 1 H, anomeric), 5.39 (d, J = 4.1 Hz, 1 H, anomeric), 5.30 (d, J = 3.6 Hz, 1 H, anomeric), 5.23 (t, J = 9.5Hz, 1 H, C*H*OAc, on ring F), 4.95–3.40 (m, 60 H), 2.11, 2.10, 2.07, 2.04, 1.88, 1.82 (all s, 3 H each, OAc), 1.03 (s, 9 H, t-Bu). Anal. ($C_{154}H_{168}O_{36}SiS$) C, H.

Preparation of Phenylthio Disaccharide 16. To a suspension of $AgClO_4$ (50 mg, 0.24 mmol), $SnCl_2$ (46 mg, 0.24 mmol), and crushed 4-Å molecular sieves (200 mg, dried) in dry ether (3.5 mL) under argon at −15 °C was added alcohol **14** (61 mg, 0.24 mol) in ether (1.5 mL). The fluoride **15** (68 mg, 0.24 mmol) in ether (1.5 mL) was added in one portion and the reaction mixture brought to room temperature over a 30-min period. The reaction mixture was diluted with ether (30 mL) and filtered through Celite and the filtrate washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL) and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave a yellow syrup, which, was upon flash column chromatography (silica, ether–petroleum ether mixtures), provided **16** (80 mg, 65%): R_f 0.24 (30% ether in petroleum ether); $[\alpha]^{25}_D$ −28.39° (c 1.9, CH_2Cl_2); IR (neat) ν_{max} 3045, 2950, 2920, 2880, 2860, 1580, 1380, 1240, 1190, 1095, 915, 885, 830, 770 cm^{-1}; ^1H NMR δ 7.45 (m, 2 H, SPh), 7.28 (m, 3 H, SPh), 5.58 (d, J = 5.0 Hz, H-1), 5.31 (d, J = 2.0 Hz, 1 H, H-1′), 4.17 (m, 1 H, H-5), 3.70 (m, 1 H, H-5′), 3.58 and 3.35 (multiplets, 1 H each, H-3, H-3′), 3.39 and 3.33 (two s, 3 H each, OCH_3), 3.26 and 3.14 (dd, J = 9.0, 9.0 Hz, 1 H each, H-4, H-4′), 2.45 and 2.30 (dd, J = 15.0, 3.5 Hz, 1 H each, H-2$_e$, H-2′$_e$, 1.95 and 1.50 (ddd, J = 14.0, 10.0, 5.0 Hz, 1 H each, H-2a, H-2′a), 1.28 and 1.21 (two d, J = 6.0 Hz, 3 H each, H-6, H-6′), 0.90 (s, 9 H, t-Bu), 0.90 and 0.07 (two s, 3 H each, $SiMe_2$); HRMS calcd for $C_{24}H_{44}O_6SiS$ (M^+) 512.7983,

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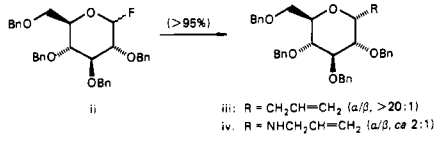
(18) For example, 1-fluorotetra-O-benzylglucose (ii) reacted withh $Me_3SiCH_2Ch—CH_2/BF_3{\cdot}Et_2O$ (CH_2Cl_2, 0 °C) or $Me_2AlNHCH_2CH═CH_2$ (CH_2Cl_2, 0 °C) to afford, in essentially quantitative yield, 1-allyl-O-tetrabenzylglucose (iii) or 1-(aminoallyl)tetra-O-benzylglucose (iv). These and



other reactions of glycosyl fluorides will be reported in due course.

found 512.7988.

Preparation of Disaccharide Fluoride 17. To a solution of phenyl thioglycoside **16** (56 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at −15 °C was added DAST (21 L, 0.16 mmol) under argon followed by NBS (25 mg, 0.14 mmol). After 15 min at −15 °C, the reaction mixture was poured onto saturated $NaHCO_3$ (5 mL) and extracted with ether (3 × 10 mL). The ether extracts were combined, washed with brine (5 mL), and dried ($MgSO_4$). Evaporation of the solvent followed by flash column chromatography (silica, ether–petroleum ether mixtures) furnished the glycosyl fluoride **17**, (40 mg, 85%) with an anomeric ratio of ca. 5:1 (α:β): R_f 0.24 (30% ether in petroleum ether); IR (neat ν_{max} 2940, 2920, 2880, 2860, 1380, 1240, 1100, 965, 820, 765 cm^{-1}; ^1H NMR (α:β ca. 5:1) δ 5.68 (d, $J_{1,F}$ = 50 Hz, 0.8 H, H-1), 5.34 (d, $J_{1,F}$ = 50 Hz, 0.2 H, H-1), 5.33 (d, $J_{1',2'}$ = 5.0 Hz, 0.8 H, H-1'), 5.29 (d, $J_{1',2'}$ = 5.0 Hz, 0.2 H, H-1'), 3.90 (m, 1 H, H-5), 3.70 (m, 1 H, H-5'), 3.55 (m, 1 H, H-3), 3.45 (m, 1 H, H-3'), 3.38 and 3.34 (two s, 2.4 H each, OCH_3), 3.37 and 3.32 (two s, 0.6 H each, OCH_3), 3.30 and3.14 (dd, J = 9.0, 9.0 Hz, 1 H each, H-4 and H-4'), 2.45 (m, 1 H, H-2_{eq}), 2.30 (dd, J = 15.0, 3.5 Hz, 1 H, H-$2'_{eq}$), 1.60 (m, 1 H, H-2_{ax}), 1.50 (m, 1 H, H-$2'_{ax}$), 1.40 (d, J = 5.0 Hz, 0.6 H, H-6), 1.32 (d, J = 7.5 Hz, 2.4 H, H-6), 1.22 (d, J = 6.0 Hz, 3 H, H-6'), 0.90 (s, 9 H, *-Bu), 0.12 and 0.10 (two s, 3 H each, (Me_2Si); HRMS calcd for $C_{18}H_{39}O_6SiF$ (M^+) 398.6018, found 398.6020.

Preparation of Avermectin B_{1a} Bis(silyl ether) 18. To a suspension of $AgClO_4$ (12 mg, 0.06 mmol), $SnCl_2$ (11 mg, 0.06 mmol), crushed 4-Å molecular sieves (100 mg, dried) in dry ether (1 mL) under argon at −15 °C was added alcohol **12** (52 mg, 0.074 mmol) in ether (1 mL). Addition of fluoride **17** (24 mg, 0.057 mmol), stirring at 0 °C for 16 h, and standard workup as in the preparation of **16**, afforded **18** (38 mg, 62% yield) after flash column chromatography (silica, ether–petroleum ether mixtures): R_f 0.22 (30% ether in petroleum ether); $[\alpha]^{25}_D$ +29.35° (*c* 0.51, CH_2Cl_2); IR (thin film) ν_{max} 3500, 3020, 2970, 2940, 2860, 1710, 1470, 1390, 1260, 1140, 1105, 990, 840 cm^{-1}; ^1H NMR δ 5.86 and 5.75 (two m, 1 H and 3 H, respectively, H-9, H-10, H-11, H-22), 5.55 (dd, J = 10.0, 2.0 Hz, 1 H, H-23), 5.41 (m, 3 H, H-3, H-19, H-1''), 5.00 (m, 1 H, H-15), 4.78 (1 H, H-1'), 4.70 and 4.59 (two d, J = 15.0 Hz, 1 H each, C-8-CH_2O), 4.45 (m, 1 H, H-5), 4.12 (s, 1 H, OH), 3.95 (brs, 1 H, H-13), 3.86 (m, 2 H, H-5' or H-5'', H-17), 3.84 (d, J = 5.5 Hz, 1 H, H-6), 3.65 (m, 3 H, H-5'' or H-5', H-3', H-3''), 3.48 (d, J = 10.0 Hz, 1 H, H-25), 3.45 and 3.35 (two s, 3 H each, OCH_3), 3.40 (brs, 1 H, H-2), 3.21 (dd, J = 8.0, 8.0 Hz, 1H, H-4'), 3.12 (dd, J = 8.0, 8.0 Hz, 1 H, H-4''), 2.51 (m, 1 H, H-12), 2.30 (m, 5 H, H-16, H-24, H -2'$_e$, H -2''$_e$), 2.05 (dd, J = 5.0, 12.0 Hz, 1 H, H-18e), 1.80 (s, 3 H, C-4-CH_3) 1.76 (m, 1 H, H-2'$_a$ or H-2''$_a$), 1.55 (m, 5 H, H-20, H-26, H-27), 1.52 (s, 3 H, C-14-CH_3), 1.25 (d, J = 8.0Hz, 3H, H-6'' or H-6'), 1.22 (d, J = 5.0 Hz, 3 H, H-6'' or H-6'), 1.17 (d, J = 7.5 Hz 3 H, C-12-CH_3), 0.95–0.80 (m, 11 H, H-18a, H-2'$_a$ or H-2''$_a$, H-28, C-24-CH_3, C-26-CH_3), 0.94 and 0.90 (two s, 9 H each, *t*-Bu), 0.15 (s, 6 H, Me_2Si), 0.1 and 0.09 (two s, 3 H each, Me_2Si). Anal. ($C_{60}H_{100}O_{14}Si_2$) C, H.

Avermectin B_{1a} (11). The bis(silyl ether) **18** (22 mg, 0.02 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. *n*-Bu_4NF (1 M in THF, 44 μL, 0.044 mmol) was added and the reaction mixture kept at 0 °C for 16 h. The reaction mixture was flash chromatographed directly (silica, ether–petroleum ether mixture) to afford avermectin B_{1a} (**11**) (15 mg, 89%) identical with an authentic sample by IR, ^1H NMR, MS, TLC, and $[\alpha]^{25}_D$.

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Supplementary Material Available: Listing of ^1H NMR data of **3b**, **4b**, **6b**, **7b**, **3**, **4**, **12**, and **15**, (3 pages). Ordering information is given on any current masthead page.

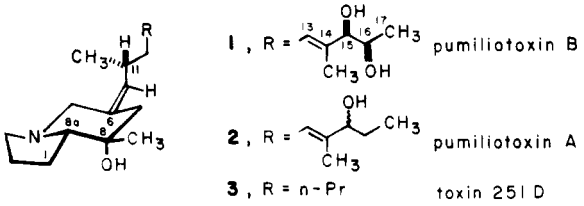
Enantioselective Total Syntheses of Pumiliotoxin B and Pumiliotoxin 251D. A General Entry to the Pumiliotoxin A Alkaloids via Stereospecific Iminium Ion–Vinylsilane Cyclizations

Larry E. Overman,* Kenneth L. Bell, and Fumitaka Ito

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received July 22, 1983. Revised Manuscript Received February 20, 1984*

Abstract: Enantioselective total syntheses of pumiliotoxin B (**1**) and pumiliotoxin 251D (**3**) are reported. The synthesis of pumiliotoxin B unambiguously establishes, for the first time, the complete stereostructure of this potentially important cardiac agent. The key synthetic tactic is the use of an iminium ion–vinylsilane cyclization (**6** → **4**, eq 1) to both form the indolizidine ring system and establish the *Z* stereochemistry of the alkylidene side chain.

Pumiliotoxins A (**2**) and B (**1**) were first isolated from the Panamanian poison frog *Dendrobates pumilio* in 1967.[1,2] Originally believed to be steroidal alkaloids, the structure of these toxins remained obscure until 1980 when a simpler alkaloid, pumiliotoxin 251D (**3**), was found as a major component of the basic skin extracts of the Ecuadorian poison frog, *Dendrobates Tricolor*.[3] X-ray analysis of the crystalline hydrochloride of 251D



established the structure and absolute configuration of this toxin[3] and provided the key for partial structure elucidation of the pumiliotoxin A class of dendrobatid alkaloids.[2] These alkaloids, of which pumiliotoxin B is one of the most complex members, have in common the unusual (*Z*)-6-alkylideneindolizidine (1-azabicyclo[4.3.0]nonane) ring system. The stereostructure of the side-

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