A Highly Stereoselective Synthesis of the AB Disaccharide Unit of Olivomycin A[1]

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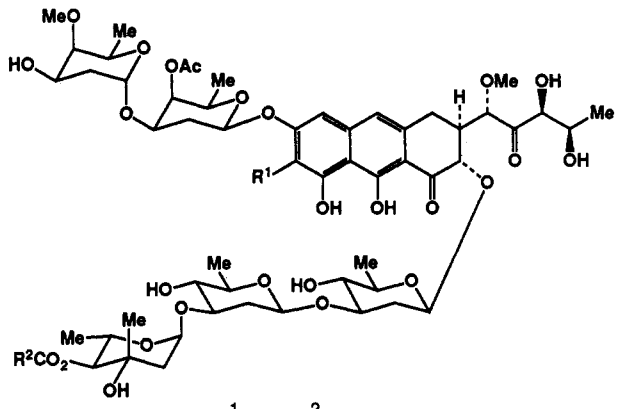
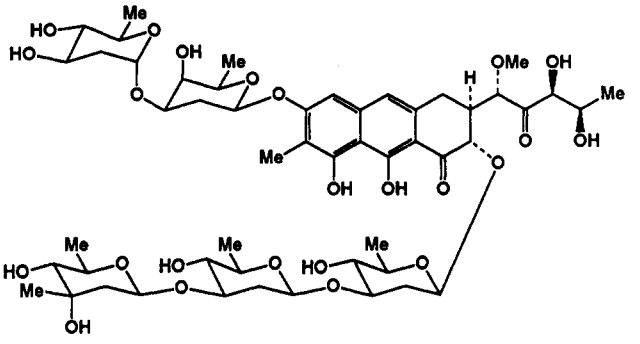
A highly stereoselective synthesis of the AB disaccharide (**4c**) of olivomycin A is described. The synthesis features the double asymmetric allylboration of α,β-dialkoxy aldehyde **8** using tartrate allylboronate (*S,S*)-**9**, which provides triol derivative **10** with the correct relative and absolute stereochemistry for utilization in syntheses of the A and B monosaccharides. The derived diol benzyl ether **11** was converted into 3-hydroxy-2-deoxy-*lyxo*-pyranoside **16** and thioglycoside **18** via the intermediacy of α-methyl 2-deoxy-*lyxo*-pyranoside **14α**, and then **16** and **18** were coupled in CH_2Cl_2 at 23 °C by using Nicolaou's NBS thioglycosidation procedure to give the α,α-disaccharide **4a** with >6:1 selectivity. Difficulties encountered in the hydrolysis or activation of the methyl glycoside function of **4a** prompted the synthesis to be revised by using intermediates containing more easily deprotected anomeric silyl (TBDMS) ethers. Diol **11** was thus selectively monosilylated to give **21**, which was smoothly converted via 2-deoxy-*lyxo*-pyranose **23** into thioglycoside **18** and 2-deoxypyranoside **27**, which possesses a TBMDS protecting group at the anomeric center. Intermediates **18** and **27** were coupled again by using the Nicolaou methodology in a CH_3CN–THF cosolvent mixture at −42 °C to give the AB disaccharide TBDMS acetal **4b** with ≥20:1 selectivity. Deprotection of the anomeric TBDMS acetal by using $Et_3NH^+F^-$ in CH_3CN then completed the synthesis of the olivomycin AB disaccharide unit **4c**.

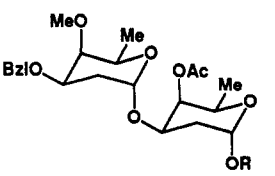
Olivomycin A (**1**), chromomycin A_3 (**2**), and mithramycin (**3**) are clinically active members of the aureolic acid family of anticancer agents.[2] These compounds are inhibitors of DNA-dependent RNA polymerase, and available structure–activity data indicate that the two oligosaccharide chains are essential for biological activity, influencing both the DNA binding profile as well as cellular uptake.[3,4] These factors, among others, have stimulated considerable interest in the total synthesis of these structurally complex antibiotics, the ultimate goal being the development of potentially less toxic analogues.[5] Several syntheses of the olivomycin aglycon, olivin, or its tri-*O*-methyl derivative, have been reported,[6] and Thiem has published a substantial body of work on the synthesis of the oligosaccharide fragments of 1–3, which also serve as a rigorous proof of the oligosaccharide stereostructures.[7,8] Other studies on the synthesis of the oligosaccharide units have also been reported.[9]



1, R^1 = H, R^2 = i-Pr, olivomycin A
2, R^1 = R^2 = Me, chromomycin A_3



3, mithramycin (aureolic acid)



4a, R = Me
4b, R = TBDMS
4c, R = H

(1) Portions of this research were performed at the Massachusetts Institute of Technology, Cambridge, MA, and are described in the Ph.D. Thesis of J. A. Straub (M.I.T., 1987). We gratefully acknowledge a grant from the National Cancer Institute (CA 29847) for support of the initial phase of these studies.

(2) (a) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience, New York, 1979; Chapter 3. (b) Skarbek, J. D.; Speedie, M. K. In *Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*; Aszalos, A., Ed; CRC Press: Boca Raton, FL, 1981; Chapter 5. (c) Pettit, G. R. *Biosynthetic Products for Cancer Chemotherapy*; Plenum Press, New York, 1977; Vol. 1, p 143.

(3) Chromomycin is reported to bind in the DNA minor groove as a 2:1 dimer: (a) Gao, Z.; Patel, D. *Biochemistry* **1989**, *28*, 751. (b) Banville, D. L.; Keniry, M. A.; Kam, M.; Shafer, R. H. *Ibid.* **1990**, *29*, 6521.

(4) Gupta, R. S. *J. Cell. Physiol.* **1982**, *113*, 11.

(5) For a review of synthetic efforts through 1987, see: Franck, R. W.; Weinreb, S. M. In *Studies in Natural Product Chemistry*; Rahman, A. U., Ed.; Elsevier: Amsterdam, 1989; pp 173–208.

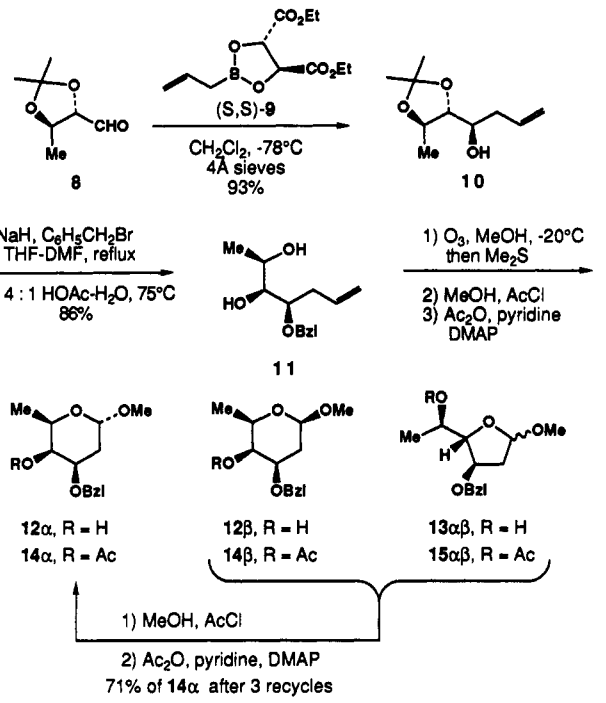
(6) (a) Racemic tri-*O*-methylolivin: Dodd, J. H.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811. (b) Optically active tri-*O*-methylolivin: Franck, R. W.; Bhat, V.; Subramaniam, C. S. *Ibid.* **1986**, *108*, 2455. (c) Olivin in the naturally occurring enantiomeric form: Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *Ibid.* **1987**, *109*, 7575. (d) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *Ibid.* **1989**, *111*, 2984.

(7) Oligosaccharide stereostructural assignments: (a) Thiem, J.; Meyer, B. *J. Chem. Soc., Perkin Trans.* **1979**, 1331. (b) Thiem, J.; Meyer, B. *Tetrahedron* **1981**, *37*, 551. (c) Thiem, J.; Schneider, G. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 58.

(8) Recent synthetic studies: (a) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954. (b) Thiem, J.; Schoettmer, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 555. (c) For a review, see: Theim, J. In *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds; ACS Symposium Series 386, 1989; Chapter 8.

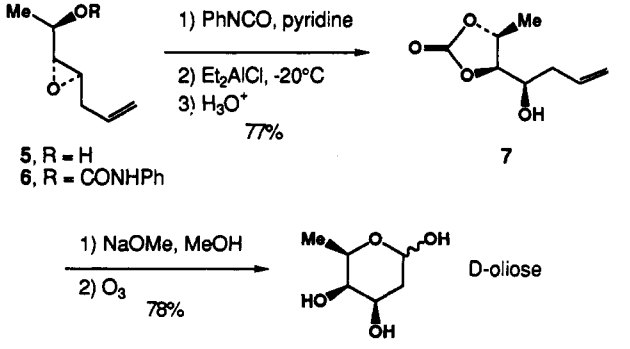
0022-3263/91/1956-1649$02.50/0

Scheme I



In continuation of our efforts to complete a total synthesis of **1**, we have developed an efficient and highly stereoselective synthesis of the AB disaccharide unit (**4**) of olivomycin A, the details of which are provided herein.[10]

Recognizing that disaccharide **4** consists of two differentially functionalized 2,6-dideoxy-D-*lyxo*-hexose ("D-oliose") units, we adopted a synthetic strategy that would permit both monosaccharides to be synthesized from a common precursor. Although we had already synthesized D-oliose precursor **7** by the Lewis acid mediated neighboring group promoted reaction of epoxy urethane **6**, this route was deemed unsuitable for the present purposes since the synthesis of the key intermediate **5** involves a Sharpless kinetic resolution–asymmetric epoxidation, and the yield of **5** was only 40% on the basis of the racemic allylic alcohol precursor.[11] We elected instead to utilize the asymmetric allylboration reaction to establish the stereochemistry of the carbohydrate backbone, anticipating that the synthetic efficiency would be much better if a resolution were avoided.[12-14]

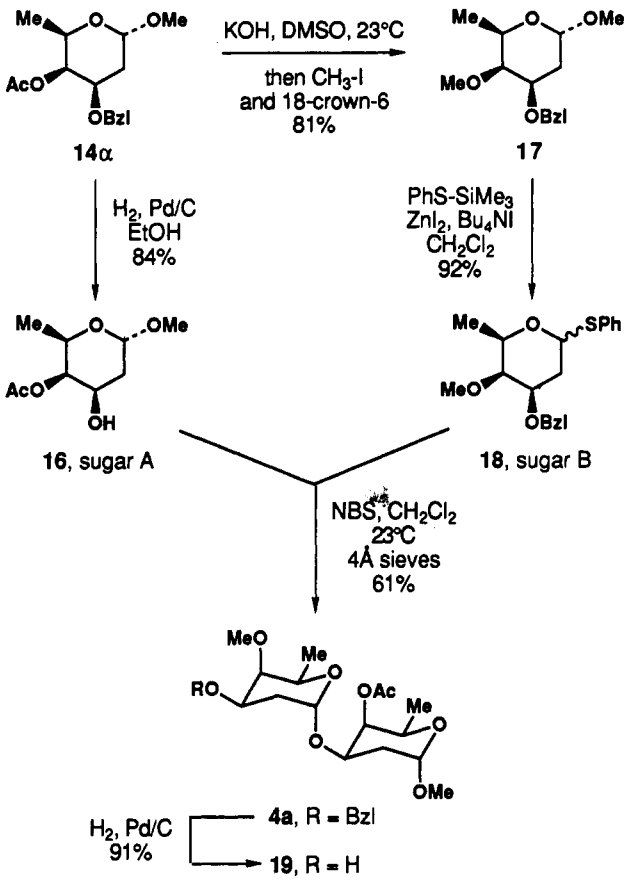


(9) For leading references to other studies on the synthesis of the aureolic acid oligosaccharides, see: (a) Ramesh, S.; Franck, R. W. *J. Chem. Soc., Chem. Commun.* **1989**, 960. (b) Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577. (c) Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *Ibid.* **1990**, *55*, 5 and literature cited therein. (d) Binkley, R. W. *J. Carbohydr. Chem.* **1990**, *9*, 507.

(10) A preliminary account of this work has appeared: Roush, W. R.; Straub, J. A. *Tetrrahedron Lett.* **1986**, *27*, 3349.

(11) (a) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1983**, *48*, 5093. (b) Roush, W. R.; Brown, R. J.; DiMare, M. *Ibid.* **1983**, *48*, 5083.

Scheme II



The synthesis of disaccharide **4a**, the initial target, began with the matched double asymmetric reaction of the readily available chiral aldehyde **8**[15] and diethyl tartrate allylboronate (*S,S*)-**9**.[13] This reaction provided the known homoallylic alcohol **10**,[16] typically with ≥98% stereoselectivity (Scheme I). Benzylation of **10** followed by hydrolysis of the acetonide gave diol **11** in 86% yield. Ozonolysis of **11** then provided 2,6-dideoxy-D-*lyxo*-hexose benzyl ether as a mixture of pyranose and furanose tautomers (72% yield). This mixture was converted to a mixture of methyl glycosides **12**α,β and **13**α,β (unseparable) that was directly acylated. Fortunately, α-pyranoside **14**α could be separated at this stage chromatographically (36% yield). The mixture of the β-pyranoside **14**β and the two furanose tautomers **15**α,β, obtained in 48% yield, was resubjected to the glycosidation conditions to regenerate a mixture of **12**α,β, and **13**α,β that was acylated and again

(12) For reviews of the reactions of allylmetal compounds and aldehydes, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, Vol. 2, in press.

(13) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Halterman, R. L. *Ibid.* **1986**, *108*, 294. (c) For fully optimized experimental conditions, see: Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. D. *J. Org. Chem.* **1990**, *55*, 4109. (d) For a detailed discussion of the stereoselectivity of the reactions of the tartrate allylboronates and alkoxy-substituted aldehydes, see: Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *Ibid.* **1990**, *55*, 4117. (e) For the reactions of the chiral crotylboronates and α-methyl chiral aldehydes, see: Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(14) For a stereochemically general synthesis of 2-deoxyhexoses based on the asymmetric allylboration of 2,3-epoxy aldehydes, see: Roush, W. R.; Straub, J. A.; VanNiewenhze, M. S. *J. Org. Chem.*, previous paper in this issue.

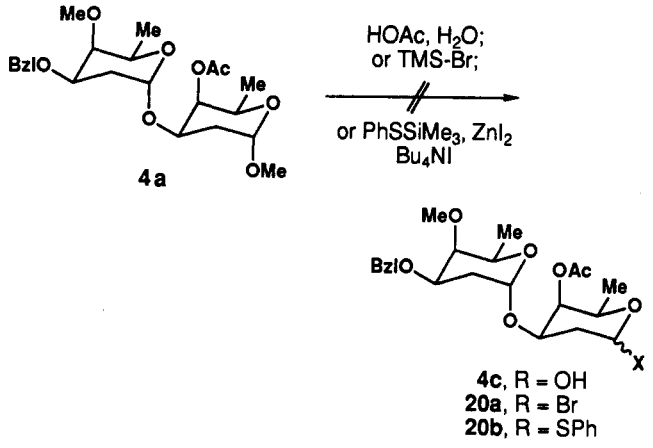
(15) (a) Servi, S. *J. Org. Chem.* **1985**, *50*, 5865. (b) See also Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227.

(16) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Tetrahedron Lett.* **1982**, *23*, 4143.

separated chromatographically. Recycling of the resulting 14β–15α,β mixture two additional times brought the overall yield of 14α to 71%.

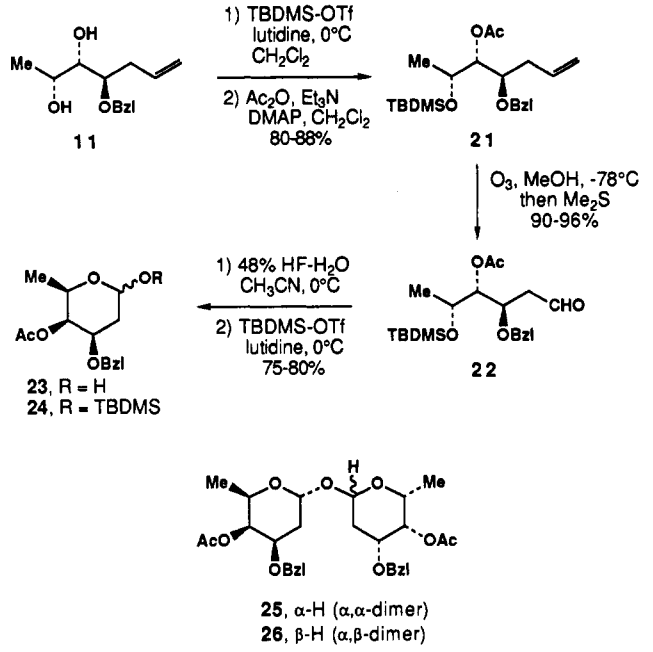
Hydrogenation of 14α over 10% Pd on C provided the A-ring monosaccharide **16** in 84% yield. Treatment of 14α with powdered KOH in Me_2SO followed by addition of MeI and 18-crown-6 provided methyl ether **17** in 81% yield (Scheme II), which was then converted into the thioglycoside **18**, an activated form of the B ring monosaccharide, in 92% yield by using Hanessian's procedure.[17] These intermediates were coupled by treatment of a mixture of **17** (1.1 equiv) and **18** (1.0 equiv) with NBS in CH_2Cl_2 at 23 °C in the presence of 4-Å molecular sieves.[18] Although a mixture of anomeric glycosides was anticipated at the outset,[18,19] we were delighted to find that this procedure provided α,α-disaccharide **4a** in 61% yield with ≥6:1 stereoselectivity. The stereochemistry of **4a** was verified by hydrogenolysis of the benzyl ether that provided the known disaccharide **19**.[20]

Although this synthesis of **4a** was highly stereoselective and was relatively efficient (10 steps, 17% yield from 8), the recycle of 14β and 15α,β notwithstanding, the problem of deprotection and activation of **4a** to provide a suitably activated disaccharide derivative for use in glycosidation reactions with the aglycon olivin remained to be solved. Unfortunately, attempts to hydrolyze **4a** to the free acetal **4c** by using aqueous HOAc,[21] or attempts to convert **4a** directly to the bromo or thiophenyl glycoside derivatives **20a,b** by using Me_3SiBr[20,22] or the Hanessian thioglycosidation protocol,[17] lead to competitive cleavage of the internal α-disaccharide linkage. It thus was clear that a different acetal protecting group was needed for the A-ring monosaccharide unit.



Since the main problem in the synthesis of 14α is the poor kinetic and thermodynamic selectivity for formation of the desired α-pyranoside from the dihydroxyaldehyde generated by ozonolysis of **11**,[23] we decided to differentiate the C(5) and C(6) hydroxyl groups of **11** prior to this step. Selective silylation of **11** was smoothly accomplished by using *tert*-butyldimethylsilyl triflate (TBDMS-OTf) and lutidine in CH_2Cl_2, providing the C(6)-monosilyl ether derivative in 82–90% yield along with a small amount (ca. 4%) of disilylated material (Scheme III). Acylation of the C(6)-monosilyl ether then provided **21** in 80–88% overall yield. Ozonolysis of **21** produced the fully protected aldehyde **22** in 90–96% yield that when treated with 48% aqueous HF in CH_3CN at 0 °C cyclized to the targeted hexose **23** (85–90% yield). Also obtained were small amounts of the structurally interesting α,α- and α,β-dimers **25** and **26**. It was not possible to suppress the formation of **25** and **26** by removing the TBDMS protecting group prior to the ozonolysis of **21** owing to the intervention of an extremely facile acyl migration reaction that produced a mixture of regioisomeric acetates. Silylation of **23** using TBDMS-OTf then provided **22** (as an anomeric mixture) in excellent yield.

Scheme III

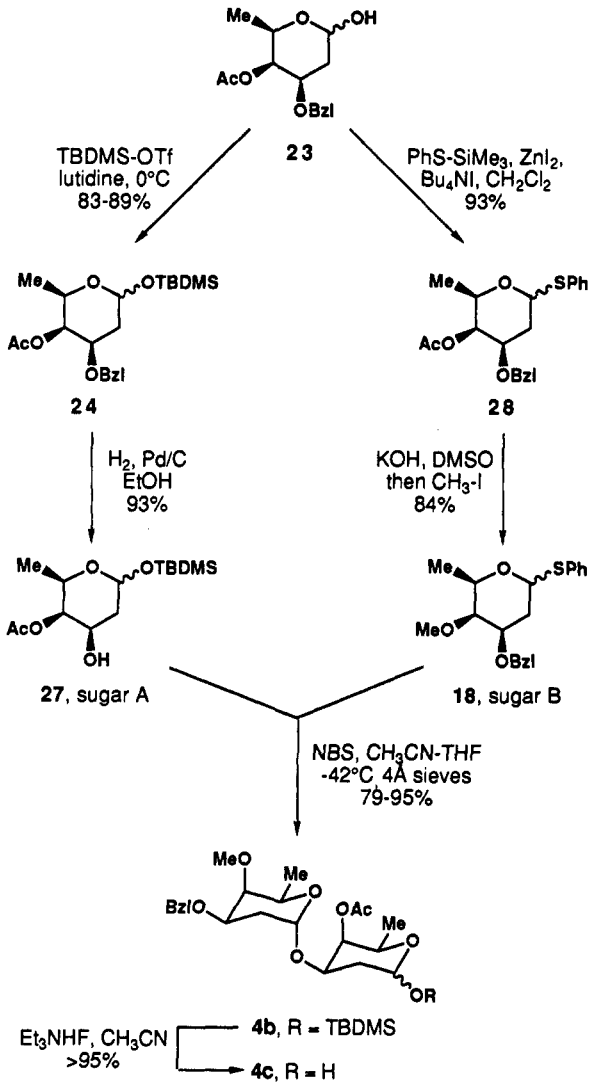


Recognizing that **22** and **24** are structural isomers, several attempts were made to convert **22** directly into **24** without the stoichiometric removal and reintroduction of the TBDMS group. Treatment of **22** with catalytic amounts of various Lewis acids including TBDMS-OTf or TBDMS-Cl in CH_3CN or THF at temperatures between −78 and −20 °C indeed accomplished the desired conversion. Unfortunately, however, significant amounts of dimers **25** and **26** were also produced. Consequently, the most efficient means of preparing **24** involves the two-step conversion proceeding via **23**.

With convenient and efficient syntheses of **23** and **24** in hand, we turned to the completion of the synthesis of the AB disaccharide **4c**. Thus, hydrogenation of **24** provided the desired A-ring monosaccharide **27** in 93% yield (Scheme IV). Thioglycoside **28** was prepared in 93% yield from **23** by using Hanessian's procedure.[17] Sequential treatment of **28** with KOH in DMSO to hydrolyze the

(17) Hanessian, S.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3.
(18) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430.
(19) For leading references to other thioglycosidation methods, see: (a) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275. (b) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13. Fügedi, P.; Garegg, P. J. *Ibid.* **1986**, *149*, C9. (c) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061. (d) Pozsgay, V.; Jennings, H. J. *J. Org. Chem.* **1987**, *52*, 4635. (e) Wuts, P. G. M.; Bigelow, S. S. *Ibid.* **1983**, *48*, 3489. (f) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3215. (g) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17. (h) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Ibid.* **1973**, *27*, 55.
(20) Thiem, J.; Meyer, B. *Chem. Ber.* **1980**, *113*, 3058.
(21) 2-Deoxy-α-glycosides are known to be labile to even to aqueous HOAc under mild conditions. See, for example: (a) Honda, S.; Kakehi, K.; Takai, H.; Takiura, K. *Carbohydr. Res.* **1973**, *29*, 477. (b) Miyamoto, M.; Kawamatsu, Y.; Shinohara, M.; Nakadaira, Y.; Nakanishi, K. *Tetrahedron* **1966**, *22*, 2785.
(22) Gillard, J. W.; Israel, M. *Tetrahedron Lett.* **1981**, *22*, 513.
(23) This problem is well known for sugars in the galactose series (as is 14α): Pater, R. H.; Coelho, R. A.; Mowery, D. F., Jr. *J. Org. Chem.* **1973**, *38*, 3272.

Scheme IV



acetyl group followed by addition of excess MeI then provided thiosugar **18** in 84% yield. The coupling of **27** and **18** was performed by using Nicolaou's NBS protocol as described for the synthesis of **4a**,[18] with the exception that it was performed in a 2:1 mixture of CH_3CN and THF at −42 °C. This reaction proved to be very fast and extremely selective; disaccharide **4b** was obtained in excellent yield (79–95%) with very high selectivity for the desired α-glycosidic linkage. The only instance in which a product with a β-glycosidic linkage was detected was one experiment in which the purified β-anomer of **27** was used as the glycosyl acceptor: this experiment provided 79% of **4b** along with 4% of a minor product that was identified as the β,β-isomer. Finally, the TBDMS group of **4b** was easily removed by treatment with $Et_3NH^+F^-$ in CH_3CN,[24] thus providing the targeted AB disaccharide unit **4c** in essentially quantitative yield.

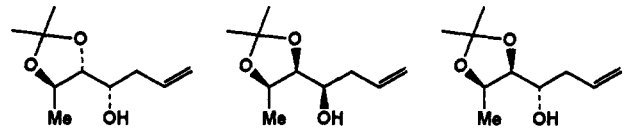
In summary, we have developed a highly stereoselective synthesis of **4c** that corresponds to the AB disaccharide units of olivomycin A (**1**) as well as chromomycin A_3 (**2**). Efforts to complete a total synthesis of **1** are ongoing and additional progress will be reported in due course.

Experimental Section

General. All reactions were conducted in oven-dried (125 °C) glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, tetrahydrofuran (THF), and toluene were distilled from sodium benzophenone ketyl; CH_2Cl_2 and acetonitrile were distilled from CaH_2, methanol from Mg turnings. Removal of solvents was performed by using a rotary evaporator at reduced pressure.

Analytical thin layer chromatography (TLC) was performed by using Kieselgel 60 F_{254} glass plates precoated with a 0.25-mm thickness of silica gel. Column chromatography was peformed on kieselgel 60 (230–400 mesh) silica gel according to the method of Still.[25] Preparative TLC was performed on kieselgel 60 F_{254} glass plates precoated with a 0.50-mm thickness of silica gel. Unless noted otherwise, all compounds isolated by chromatography were sufficiently pure (>95% according to ^1H NMR analysis) for use directly in subsequent preparative reactions.

***lyxo*-Hept-1-ene-4,5,6-triol 5,6-Acetonide (10).** A solution of aldehyde **8** (1.25 g, 8.70 mmol)[15] in CH_2Cl_2 (7 mL) was added dropwise to a −78 °C solution of (*S,S*)-diethyl tartrate allylboronate **9** (2.88 g, 11.3 mmol)[13b,14] and 4-Å molecular sieves (200 mg) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at −78 °C overnight and then was allowed to warm to 23 °C. Aqueous NaOH (1 N, 10 mL) was added, and the mixture was stirred for 45 min. The aqueous phase was extracted with ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Analysis of the crude product by GC (10-ft Chromosorb G on Carbowax column; 80°/2 min, then 10°/min ramp to 190 °C) indicated that the ratio of **10** (t_R 11.5 min) and its hydroxyl epimer **29** (t_R 10.5 min) was 98:2. Also present were



small amounts (1–5% total, variable from run to run) of epimers **30** (t_R 10.9 min) and **31** (t_R 11.9 min) that derive from the C-(2)-epimer of **8**. The crude product was chromatographed (20% EtOAc/hexanes) to give 1.51 g (93%) of **10** as a colorless liquid: R_f 0.32 (20% EtOAc/hexanes); $[\alpha]^{22}_D$ −2.6° (*c* = 0.89, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.87–5.78 (m, 1 H), 5.18–5.12 (m, 2 H), 4.09 (dq, *J* = 7.8, 6.1 Hz, 1 H), 3.72 (tdd, *J* = 5.5, 5.5, 3.8 Hz, 1 H), 3.48 (dd, *J* = 7.8, 5.5 Hz, 1 H), 2.39–2.34 (m, 1 H), 2.22–2.15 (m, 1 H), 2.18 (d, *J* = 3.8 Hz, 1 H, OH), 1.38 (s, 3 H) 1.36 (s, 3 H), 1.32 (d, *J* = 6.1 Hz, 3 H); IR (neat) 3460, 3060, 1645 cm^{-1}; MS *m/z* 186 (M^+). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.20; H, 9.81.

***lyxo*-4-*O*-Benzylhept-1-ene-4,5,6-triol (11).** A solution of alcohol **10** (7.87 g, 42.2 mmol) in dry THF (50 mL) was added dropwise via syringe over 10 min to a 0 °C suspension of NaH (2.33 g, 57% in oil, 55.3 mmol) in THF (50 mL). The cooling bath was removed and the mixture stirred at 23 °C for 1 h. The mixture was then cooled to 0 °C and neat benzyl bromide (15.3 mL, 129 mmol) was added. The mixture was then stirred at 23 °C for 24 h. The reaction was quenched by the slow addition of water (ca. 20 mL) and diluted with ether (100 mL). The organic layer was washed with water (2 × 100 mL) and brine (2 × 100 mL). The combined aqueous layers were extracted with ether (2 × 150 mL). The combined organic extracts were dried over $MgSO_4$ and then filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (hexane to elute excess benzyl bromide, followed by 6% EtOAc–hexane to elute the product), giving 0.3 g of recovered **10** (4%) and 10.2 g (88%) of the product benzyl ether as a pale yellow liquid: R_f 0.48 (10% EtOAc/hexane; $[\alpha]^{22}_D$ −33.1° (*c* = 0.51, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 5.97–5.87 (m, 1 H), 5.18–5.09 (m, 2 H), 4.66 and 4.58 (AB dd, *J* = 11.4 Hz, 2 H), 4.06 (dq, *J* = 7.6, 6.1 Hz, 1 H), 3.63 (dd, *J* = 7.6, 6.1 Hz, 1 H), 3.58 (dt, *J* = 6.1, 4.5 Hz, 1 H), 2.50–2.38 (m, 2 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 1.33 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 134.3, 128.3, 127.8, 127.6, 108.0, 82.9, 79.2, 75.0, 72.3, 35.6, 27.3, 26.9, 19.4; IR (neat) 2970, 1645, 1605, 1450, 1375 cm^{-1}; MS *m/z*

(24) Hünig, S.; Wehner, G. *Synthesis* **1975**, 180.

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

261 ($M^+ - CH_3$). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.51; H, 8.51.

A solution of the above benzyl ether (2.08 g, 7.52 mmol) in 80% aqueous HOAc (15 mL) was heated to 75 °C for 4 h. Most of the solvent was removed in vacuo and the residual HOAc was removed by coevaporation with heptane. The residue was purified by flash column chromatography (45% EtOAc/hexanes) to give 98 mg of recovered benzyl ether (5%) and 1.55 g of **11** (87% yield) as a pale yellow liquid: R_f 0.34 (45% EtOAc/hexanes); $[\alpha]^{22}_D$ -19.8° (c = 0.33, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5 H), 5.92–5.82 (m, 1 H), 5.21–5.08 (m, 2 H), 4.68 and 4.54 (AB dd, J = 11.3 Hz, 2 H), 4.08 (qdd, J = 6.4, 2.9, 2.4 Hz, 1 H), 3.68 (td, J = 6.1, 4.4 Hz, 1 H), 3.41–3.37 (m, 1 H), 2.66 (d, J = 2.9 Hz, 1 H for OH), 2.50 (d, J = 7.9 Hz, 1 H for OH), 2.52–2.46 (m, 1 H), 2.39–2.33 (m, 1 H), 1.20 (d, J = 6.4 Hz, 3 H); IR (neat) 3550, 3000, 2940, 1635, 1480, 1450, 1200, 1080 cm^{-1}; MS m/z 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.79. Found: C, 71.03; H, 8.79.

***lyxo*-5-Acetoxy-4-(benzyloxy)-6-(*tert*-butyldimethylsilyoxy)hept-1-ene (21).** To a 0 °C solution of diol **11** (1.55 g, 6.6 mmol) in CH_2Cl_2 (20 mL) were added 2,4-lutidine (2.3 mL, 19.9 mmol) and TBDMS-OTf (1.57 mL, 6.7 mmol) dropwise via syringe. The mixture was stirred at 0 °C for 30 min and then was quenched with brine (50 mL) and diluted with ether (100 mL). The aqueous layer was extracted with 100 mL of ether. The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (7% EtOAc/hexanes) to give 112 mg of the disilylated product (3.6%; R_f 0.8) and 2.03 g (88%) of the desired C(6)-mono-TBDMS ether as a colorless liquid: R_f = 0.50 (10% EtOAc/hexanes); $[\alpha]^{22}_D$ -47.0° (c = 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5 H), 5.99–5.92 (m, 1 H), 5.20–5.10 (m, 2 H), 4.67 and 4.42 (AB dd, J = 11.1 Hz, 2 H), 4.18 (qd, J = 6.3, 1.9 Hz, 1 H), 3.46–3.41 (m, 1 H), 3.29 (ddd, J = 9.0, 8.3, 1.9 Hz, 1 H), 2.66–2.58 (m, 1 H), 2.54–2.48 (m, 1 H), 2.42 (d, J = 9.0 Hz, 1 H for OH), 1.22 (d, J = 6.3 Hz, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.071 (s, 3 H); IR (neat) 3540, 1635 cm^{-1}; MS (CI) m/z 351 (M^+ + 1).

A solution of the above mono-TBDMS ether (1.99 g, 5.67 mmol) in CH_2Cl_2 (20 mL) at 0 °C was treated with Et_3N (7.9 mL, 56.7 mmol), Ac_2O (2.68 mL, 28.4 mmol), and a catalytic amount of DMAP. The mixture was stirred at 23 °C overnight and then diluted with Et_2O (200 mL) and brine (100 mL). The aqueous layer was separated and extracted with Et_2O (2 × 150 mL). The combined organic extracts were washed with brine (100 mL) and saturated $CuSO_4$ solution (2 × 150 mL) and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue purified by chromatography on silica gel (8% EtOAc/hexane), giving 2.22 g of **21** (88% from **11**) as a clear colorless liquid: R_f 0.50 (10% EtOAc/hexane); $[\alpha]^{23}_D$ +36.7° (c = 0.95, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5 H), 5.91–5.82 (m, 1 H), 5.12–5.07 (m, 2 H), 5.09 (dd, J = 5.9, 4.3 Hz, 1 H), 4.64 and 4.49 (AB dd, J = 11.2 Hz, 2 H), 4.02 (qd, J = 6.3, 5.9 Hz, 1 H), 3.63 (ddd, J = 6.5, 4.3, 2.6 Hz, 1 H), 2.41–2.34 (m, 1 H), 2.33–2.27 (m, 1 H), 2.09 (s, 3 H), 1.13 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.071 (s, 3 H), 0.055 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 138.1, 135.0, 128.3, 127.9, 127.6, 116.8, 77.2, 76.5, 71.3, 67.3, 34.4, 25.7, 21.1, 20.4, 17.9, -4.3, -4.7; IR (neat) 2960, 1745, 1645, 1235, 1080 cm^{-1}; MS (CI) m/z 393 (M^+ + 1). Anal. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.29; H, 9.19.

4-*O*-Acetyl-3-*O*-benzyl-2,6-dideoxy-D-*lyxo*-pyranose (23). A -78 °C solution of **21** (1.20 g, 3.05 mmol) in MeOH (20 mL) was treated with a stream of O_3 in O_2 for 8 min. The reaction was carefully monitored by TLC analysis. Excess O_3 was removed by continued flashing with N_2, and then excess Me_2S (3 mL) was added. This mixture was stirred overnight at 23 °C and then concentrated in vacuo. Purification of the crude product by flash column chromatography on silica gel (15% EtOAc/hexanes) gave 1.16 g of aldehyde **22** (96%) as a colorless viscous oil: R_f 0.40 (20% EtOAc/hexane); $[\alpha]^{22}_D$ +53.4° (c = 1.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (dd, J = 2.4, 1.6 Hz, 1 H), 7.35–7.24 (m, 5 H), 5.21 (dd, J = 6.0, 3.4 Hz, 1 H), 4.69 and 4.48 (AB dd, J = 11.0 Hz, 1 H), 4.15 (ddd, J = 8.3, 3.6, 3.4 Hz, 1 H), 3.92 (qd, J = 6.4, 6.0 Hz, 1 H), 2.77 (ddd, J = 16.9, 8.3, 2.4 Hz, 1 H), 2.54 (ddd, J = 16.9, 3.6, 1.6 Hz, 1 H), 2.09 (s, 3 H), 1.14 (d, J = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.071 (s, 3 H), 0.054 (s, 3 H); IR (neat) 2960, 2860, 2710, 1745, 1725 cm^{-1}; HRMS for $C_{15}H_{19}O_5$ (M + TBDMS), calcd 279.1232, found 279.1242.

A 0 °C solution of aldehyde **22** (173 mg, 0.44 mmol) in CH_3CN (2 mL) was treated with 10 drops of 48% HF in H_2O (ca. 0.89 mmol). The mixture was stirred at 0 °C for 3 h and then was diluted with water (20 mL) and extracted with $CHCl_3$ (2 × 25 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash column chromatography on silica gel (35% EtOAc/hexanes) gave 110 mg (90%) of viscous **23** as an anomeric mixture (ca. 2:1 ratio in favor of α-OH anomer), 7.4 mg (6%) of α,α-dimer **25**, and 5 mg (4%) of impure α,β-dimer **26**.

Data for **23**: R_f (0.35 in 35% EtOAc–hexane); ^1H NMR (500 MHz, $CDCl_3$); α-OH anomer δ 7.38–7.26 (m, 5 H), 5.44 (br s, 1 H), 5.35 (d, J = 2.7 Hz, 1 H), 4.70 and 4.44 (AB dd, J = 11.4 Hz, 1 H), 4.22 (q, J = 6.6 Hz, 1 H), 3.99 (ddd, J = 11.8, 5.3, 2.7 Hz, 1 H), 2.68 (dd, J = 2.4, 2.4 Hz, 1 H for OH), 2.17 (s, 3 H), 2.00 (dddd, J = 13.0, 11.8, 3.4, 2.4 Hz, 1 H), 1.94 (dd, J = 13.0, 5.3 Hz, 1 H), 1.16 (d, J = 6.6 Hz, 3 H); β-OH anomer δ 7.38–7.26 (m, 5 H), 5.25 (d, J = 2.9 Hz, 1 H), 4.76 (ddd, J = 9.4, 7.1, 2.2 Hz, 1 H), 4.69 and 4.46 (AB dd, J = 11.8 Hz, 1 H), 3.61 (q, J = 6.5 Hz, 1 H), 3.58 (ddd, J = 12.2, 4.6, 2.9 Hz, 1 H), 3.30 (d, J = 7.1 Hz, 1 H for OH), 2.18 (s, 3 H), 2.10 (ddd, J = 12.6, 4.6, 2.2 Hz, 1 H), 1.80 (ddd, J = 12.6, 12.2, 9.4 Hz, 1 H), 1.23 (d, J = 6.5 Hz, 3 H); IR (neat, for the mixture) 3400, 1725 cm^{-1}; HRMS (CI) for $C_{15}H_{21}O_5$ (M^+ + 1) for the mixture, calcd 281.1389, found 281.1409. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.99; H, 7.03.

Data for α,α-dimer **25**: mp 114–116 °C; $[\alpha]^{23}_D$ +218° (c = 1.54, $CHCl_3$); R_f 0.23 (30% EtOAc–hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5 H), 5.35 (br d, J = 3.7 Hz, 1 H), 5.24 (d, J = 3.0 Hz, 1 H), 4.72 and 4.43 (AB dd, J = 11.3 Hz, 2 H), 3.92 (q, J = 6.5 Hz, 1 H), 3.88 (ddd, J = 12.1, 4.8, 3.0 Hz, 1 H), 2.17 (s, 3 H), 2.07 (ddd, J = 12.9, 12.1, 3.7 Hz, 1 H), 1.79 (ddd, J = 12.9, 4.8, 1.1 Hz, 1 H), 1.16 (d, J = 6.5 Hz, 3 H); IR (neat) 1735 cm^{-1}; HRMS for $C_{21}H_{27}O_7$ (M - C_7H_7 - HOAc), calcd 391.1756, found 391.2844.

Partial data for α,β-dimer **26**: R_f 0.32 (30% EtOAc–hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 10 H), 5.34 (br d, J = 3.0 Hz, 1 H), 5.24 (d, J = 3.3 Hz, 1 H), 5.18 (br s, 1 H), 4.69 and 4.42 (A'B' dd, J = 11.3 Hz, 2 H), 4.68 and 4.45 (A''B'' dd, J = 12.0 Hz, 1 H), 4.60 (dd, J = 9.8, 2.4 Hz, 1 H), 4.30 (q, J = 6.6 Hz, 1 H), 4.01 (ddd, J = 10.9, 6.3, 3.0 Hz, 1 H), 3.59 (qd, J = 6.4, 1.0 Hz, 1 H), 3.55 (ddd, J = 12.1, 4.9, 3.3 Hz, 1 H), 2.18 (s, 3 H), 2.16 (s, 3 H), 2.02–1.85 (m, 4 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.11 (d, J = 6.6 Hz, 3 H); IR (neat) 1735 cm^{-1}.

***tert*-Butyldimethylsilyl 4-*O*-Acetyl-3-*O*-benzyl-2,6-dideoxy-D-*lyxo*-pyranoside (24).** To a 0 °C solution of lactol **23** (283 mg, 1.01 mmol) in CH_2Cl_2 (20 mL) were added 2,4-lutidine (0.35 mL, 3.03 mmol) and TBDMS-OTf (0.28 mL, 1.21 mmol). The mixture was stirred for 50 min at 0 °C and then was diluted with CH_2Cl_2 (150 mL) and H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Filtration, concentration of the filtrate in vacuo, and chromatography of the residue on silica gel (10% EtOAc/hexanes) gave 354 mg of **24** (89%) as a mixture of anomers. Samples of the two isomers were separated by careful multiple elution preparative TLC for spectroscopic characterization, but on a routine basis this mixture was used in the next transformation without separation.

Data for α-pyranoside **24α**: R_f 0.57 (10% EtOAc/hexane, three elutions); $[\alpha]^{26}_D$ +116° (c = 0.74, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5 H), 5.35 (dd, J = 3.0, 1.3 Hz, 1 H), 5.33 (dd, J = 3.1, 1.3 Hz, 1 H), 4.71 and 4.44 (AB dd, J = 11.4 Hz, 1 H), 4.09 (qd, J = 6.6, 1.3 Hz, 1 H), 3.96 (ddd, J = 12.3, 4.8, 3.1 Hz, 1 H), 2.16 (s, 3 H), 2.00 (ddd, J = 12.3, 12.3, 3.0 Hz, 1 H), 1.79 (ddt, J = 12.3, 4.8, 1.3 Hz, 1 H), 1.13 (d, J = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.083 (s, 3 H), 0.076 (s, 3 H); IR (neat) 2950, 1740 cm^{-1}; HRMS for $C_{17}H_{25}O_5Si$ (M^+ - C_4H_9), calcd 337.1471, found 337.1466. Anal. Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.68. Found: C, 64.30; H, 8.46.

Data for β-pyranoside **24β**: R_f 0.66 (10% EtOAc/hexane three elutions); $[\alpha]^{26}_D$ +45.9° (c = 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5 H), 5.22 (ddd, J = 3.1, 1.2, 0.9 Hz, 1 H), 4.73 (dd, J = 9.4, 3.0 Hz, 1 H), 4.68 and 4.44 (AB dd, J = 11.8 Hz, 1 H), 3.57–3.52 (m, 2 H), 2.17 (s, 3 H), 1.95 (dddd, J = 12.3,

4.7, 3.0, 0.9 Hz, 1 H), 1.86 (ddd, J = 12.3, 12.3, 9.4 Hz, 1 H), 1.21 (d, J = 6.3 Hz, 3 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H); IR (neat) 2950, 2850, 1735 cm^{-1}; HRMS for $C_{17}H_{25}O_5Si$ ($M^+ - C_4H_9$), calcd 337.1471, found 337.1467.

***tert*-Butyldimethylsilyl 4-*O*-Acetyl-2,6-dideoxy-D-*lyxo*-pyranoside (27).** A solution of benzyl ether **24** (304 mg, 0.77 mmol; an anomeric mixture) in EtOH (3 mL) containing ca. 20 mg of 10% Pd–C was stirred under H_2 (1 atm) for 2 days at 23 °C. The solution was filtered and concentrated in vacuo. Chromatography of the residue on silica gel (25% EtOAc/hexanes) gave 62 mg of recovered **24** (20%) and 179 mg of **27** (76% yield; 93% based on consumed **24**).

The hydrogenolysis reaction has been performed by using purified samples of the α- and β-anomers of **24**, or on mixtures of them as described here, and similar results were obtained in all cases. The two anomers can be partially separated by silica gel chromatography, but mixtures were routinely used in the coupling reaction with thioglycoside **18**.

Data for α-pyranoside **27α**: R_f 0.36 (30% EtOAc/hexane); mp 83–85 °C (solidified on standing); $[\alpha]^{23}_D$ +99.1° (c = 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (br s, 1 H), 5.04 (d, J = 2.7 Hz, 1 H), 4.32–4.26 (m, 1 H), 4.13 (q, J = 6.6 Hz, 1 H), 2.19 (d, J = 4.9 Hz, 1 H for OH), 2.17 (s, 3 H), 1.89–1.80 (m, 2 H), 1.13 (d, J = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.095 (s, 3 H), 0.083 (s, 3 H); IR (neat) 3440, 1730 cm^{-1}; HRMS for $C_{14}H_{27}O_5Si$ ($M^+ - 1$), calcd 303.1628, found 303.1632. Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27. Found: C, 55.60; H, 8.89.

Data for β-pyranoside **27β**: R_f 0.35 (30% EtOAc/hexane); $[\alpha]^{23}_D$ −3.0° (c = 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.94 (br d, J = 3.3 Hz, 1 H), 4.74 (dd, J = 9.4, 2.1 Hz, 1 H), 3.93–3.87 (m, 1 H), 3.59 (qd, J = 6.5, 1.1 Hz, 1 H), 2.17 (s, 3 H), 2.01 (d, J = 5.2 Hz, 1 H for OH), 1.97 (dddd, J = 12.2, 4.7, 2.1, 0.9 Hz, 1 H), 1.72 (d, J = 12.5, 12.2, 9.4 Hz, 1 H), 1.21 (d, J = 6.5 Hz, 3 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); IR (neat) 3450 (br), 1730 cm^{-1}; HRMS for $C_{14}H_{27}O_5Si$ ($M^+ - 1$), calcd 303.1628, found 303.1643. Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27. Found: C, 55.05; H, 9.27.

Synthesis of Thioglycoside 18 from 23. To a solution of lactol **23** (270 mg, 0.96 mmol) in CH_2Cl_2 (6 mL) was added TMS-SPh (912 mL, 4.8 mmol), Bu_4NI (0.43 g, 1.16 mmol) and ZnI_2 (0.92 g, 2.89 mmol). The mixture was stirred at 23 °C for 3 h, diluted with CH_2Cl_2 (50 mL), and poured into H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (80% CH_2Cl_2/hexanes, followed by 20% EtOAc/hexanes) gave 333 mg (93%) of thioglycoside **28** as ca. 3:1 mixture in favor of the α-anomer. The anomers were separated by preparative TLC for spectroscopic characterization, but mixtures were routinely used in the following reaction.

Data for α-D-pyranoside **28α**: R_f 0.37 (15% EtOAc/hexanes); $[\alpha]^{24}_D$ +310° (c = 1.98, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2 H), 7.38–7.24 (m, 8 H), 5.74 (dd, J = 5.7, 0.9 Hz, 1 H), 5.39 (dd, J = 3.0, 1.0 Hz, 1 H), 4.72 and 4.48 (AB dd, J = 11.4 Hz, 2 H), 4.46 (q, J = 6.5 Hz, 1 H), 3.92 (ddd, J = 12.4, 4.7, 3.0 Hz, 1 H), 2.42 (ddd, J = 13.4, 12.4, 5.7 Hz, 1 H), 2.17 (s, 3 H), 2.11 (dddd, J = 13.4, 4.7, 1.0, 0.9 Hz, 1 H), 1.18 (d, J = 6.5 Hz, 3 H); IR (neat) 1735, 1560 cm^{-1}; MS (CI) m/z 373 (M^+).

Data for the β-D-pyranoside **28β**: R_f 0.29 (15% EtOAc/hexanes); $[\alpha]^{22}_D$ +12.8° (c = 0.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2 H), 7.37–7.24 (m, 8 H), 5.28 (br d, J = 3.0 Hz, 1 H), 4.75 (dd, J = 11.2, 2.9 Hz, 1 H), 4.67 and 4.46 (AB dd, J = 11.9 Hz, 2 H), 3.62 (qd, J = 6.4, 1.1 Hz, 1 H), 3.60 (ddd, J = 10.9, 5.6, 3.0 Hz, 1 H), 2.17 (s, 3 H), 2.12–2.02 (m, 2 H), 1.26 (d, J = 6.4 Hz, 3 H); IR (neat) 1735, 1560 cm^{-1}; HRMS for $C_{15}H_{19}O_4$ (M^+ − SPh), calcd 263.1283, found 263.1272.

To a solution of **28** (328 mg, 0.88 mmol; a mixture of anomers) in Me_2SO (3 mL) was added powdered KOH (0.28 g, 5.0 mmol). The mixture (yellow) was stirred at 23 °C for 1 h. Methyl iodide (0.33 mL, 5.3 mmol) was then added and the solution again turned clear. The reaction was stirred overnight, then was diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with H_2O (2 × 50 mL), dried ($MgSO_4$) filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (13% EtOAc/hexanes) provided 255 mg (84%) of the thioglycoside **18** (anomeric mixture) as a yellow liquid. This material was indistinguishable from samples of **18** prepared from **17** (see supplementary material). The following data are for a 25:75 mixture of α- and β-anomers: R_f = 0.55 in 20% EtOAc/hexanes; $[\alpha]^{22}_D$ +157° (c = 0.40, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) α-D-pyranoside δ 7.52–7.20 (m, 10 H), 5.73 (dd, J = 5.5, 1.1 Hz, 1 H), 4.65 and 4.64 (AB dd, J = 11.9 Hz, 2 H), 4.27 (q, J = 6.5 Hz, 1 H), 3.86 (ddd, J = 12.2, 4.5, 2.5 Hz, 1 H), 3.63 (s, 3 H), 3.40 (dd, J = 2.5, 1.3 Hz, 1 H), 2.49 (ddd, J = 13.1, 12.2, 5.5 Hz, 1 H), 2.11 (dddd, J = 13.1, 4.5, 1.3, 1.1 Hz, 1 H), 1.26 (d, J = 6.5 Hz, 3 H); β-D-pyranoside δ 7.52–7.20 (m, 10 H), 4.70–4.67 (m, 1 H), 4.64 and 4.60 (AB dd, J = 12.2 Hz, 2 H), 3.62 (s, 3 H), 3.56–3.52 (m, 1 H), 3.44 (qd, J = 6.4, 0.8 Hz, 1 H), 3.30 (br d, J = 2.5 Hz, 1 H), 2.18–2.12 (m, 2 H), 1.33 (d, J = 6.4 Hz, 3 H); IR (neat for the mixture) 3020, 2920, 1560, 1475, 1365, 1200, 1080, 720 cm^{-1}; MS m/z 344 (M^+). Anal. Calcd for $C_{20}H_{24}O_3S$ (for the mixture): C, 69.74; H, 7.02. Found: C, 69.48; H, 6.74.

***tert*-Butyldimethylsilyl 4-*O*-Acetyl-3-(3-*O*-benzyl-2,6-dideoxy-4-*O*-methyl-α-D-*lyxo*-pyranosyl)-2,6-dideoxy-D-*lyxo*-pyranoside (4b).** A mixture of thioglycoside **18** (16 mg, 0.046 mmol), purified alcohol **27α** (15 mg, 0.049 mmol), and 4-Å molecular sieves (ca. 20 mg) in CH_3CN–THF (3 mL, 2:1) was cooled to −42 °C. Recrystallized NBS (12 mg, 0.070 mmol) was then added. The mixture was stirred at −42 °C for 50 min and 23 °C for 10 min and then was diluted with saturated aqueous $NaHCO_3$ solution (13 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$ solution (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by preparative TLC (0.5-mm plate 15% EtOAc/hexanes, four elutions) gave 23 mg of α,α-disaccharide **4b** (92%).

This reaction has been run by using purified samples of **27α**, **27β**, or mixtures of them, and similar results were obtained in all cases. In one experiment with **27β**, a small amount (4%, but still contaminated with some other minor impurities) of an isomer that was identified as the β,β-isomer of **4b**. Stereochemical assignments and the following ^1H and ^{13}C NMR assignments are based on 2D NMR ^1H–^1H correlation experiments, ^1H–^{13}C correlation experiments, and ^1H decoupling experiments.

Data for α,α-isomer of **4b**: R_f 0.60 (30% EtOAc–hexane); $[\alpha]^{27}_D$ +156° (c = 0.96, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5 H), 5.34 (br s, 1 H, H_1), 5.15 (br s, 2 H, H_4, $H_{1'}$), 4.59 and 4.58 (AB, J = 11.9 Hz, 2 H), 4.24 (ddd, J = 12.2, 4.7, 3.0 Hz, 1 H, H_3), 4.10 (q, J = 6.6 Hz, 1 H, H_5), 3.80 (ddd, J = 12.0, 4.6, 2.6 Hz, 1 H, $H_{3'}$), 3.74 (q, J = 6.5 Hz, 1 H, $H_{5'}$), 3.60 (s, 3 H), 3.33 (br s, 1 H, $H_{4'}$), 2.12 (s, 3 H), 2.04 (ddd, J = 12.8, 12.0, 3.8 Hz, 1 H, $H_{2'ax}$), 1.95 (ddd, J = 12.3, 12.2, 3.1 Hz, 1 H, H_{2ax}), 1.77 (dd, J = 12.8, 4.6 Hz, 1 H, $H_{2'eq}$), 1.60 (dd, J = 12.3, 4.7 Hz, 1 H, H_{2eq}), 1.22 (d, J = 6.5 Hz, 3 H, $H_{6'}$), 1.10 (d, J = 6.6 Hz, 3 H, H_6), 0.89 (s, 9 H), 0.094 (s, 3 H), 0.085 (s, 3 H): ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 138.7, 128.3, 127.4, 127.2, 94.6 ($C_{1'}$), 92.5 (C_1), 78.6 ($C_{4'}$), 74.7 ($C_{3'}$), 70.1, 69.0 (C_4), 66.8 ($C_{5'}$), 66.6 (C_3), 64.7 (C_5), 61.4 ($C_{7'}$), 33.8 (C_2), 30.1 ($C_{2'}$), 25.6, 20.8, 17.9, 16.8 ($C_{6'}$), 16.7 (C_6), -4.6, -5.9; IR (neat) 2950, 2860, 1740 cm^{-1}; HRMS for $C_{24}H_{37}O_8Si$ (M^+ − C_4H_9), calcd 481.2258, found 481.2243.

Data for α,β-isomer of **4b**: R_f 0.43 (30% EtOAc–hexane); $[\alpha]^{24}_D$ +86.6° (c = 1.55, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 5.09 (br d, J = 3.7 Hz, 1 H, $H_{1'}$), 5.03 (dd, J = 3.2, 1.1 Hz, 1 H, H_4), 4.75 (ddd, J = 8.1, 3.5, 1.0 [from decoupling] Hz, 1 H, H_1), 4.59 and 4.57 (AB dd, J = 12.0 Hz, 2 H), 3.83–3.76 (m, 3 H, H_3, $H_{3'}$ $H_{5'}$), 3.61 (s, 3 H), 3.55 (qd, J = 6.4, 1.1 Hz, 1 H, H_5), 3.32 (br s, 1 H, $H_{4'}$), 2.10 (s, 3 H), 2.03 (ddd, J = 12.4, 12.4, 3.7 Hz, 1 H, $H_{2'ax}$), 1.78 (ddd, J = 12.3, 12.3, 8.1 Hz, 1 H, H_{2ax}), 1.77–1.74 (m, 2 H, H_{2eq}, $H_{2'eq}$), 1.24 (d, J = 6.6 Hz, 3 H, $H_{6'}$), 1.18 (d, J = 6.4 Hz, 3 H, H_6), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 138.6, 128.3, 127.5, 127.2, 95.7 ($C_{1'}$), 95.0 (C_1), 78.6 ($C_{4'}$), 74.5, 70.7, 70.1, 69.2 (C_5), 67.7 (C_4), 67.0, 61.4, 36.1 (C_2), 30.1 ($C_{2'}$), 25.8, 20.9, 18.1, 17.0 ($C_{6'}$), 16.7 (C_6), −4.1, −5.0; IR ($CHCl_3$) 3020, 2915, 2850, 1730 cm^{-1}; HRMS for $C_{28}H_{45}O_8Si$ ($M^+ - 1$), calcd 537.2884, found 537.2888.

Partial data for β,β-isomer of **4b**: R_f 0.27 (30% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5 H), 5.04 (d, J = 3.3 Hz, 1 H), 4.71 (dd, J = 9.5, 2.2 Hz, 1 H, H_1), 4.60 and 4.57 (AB dd, J = 12.2 Hz, 1 H), 4.46 (dd, J = 8.8, 3.1 Hz, 1 H, $H_{1'}$), 3.95 (ddd, J = 12.3, 4.5, 3.3 Hz, 1 H), 3.59 (s, 3 H), 3.52 (q, J = 6.4 Hz, 1 H), 3.47–3.43 (m, 1 H), 3.34 (q, J = 6.5 Hz, 1 H), 3.21 (br s, 1 H), 2.09 (s, 3 H), 1.97–1.92 (m, 1 H), 1.92–1.85 (m, 2 H),

1.74 (ddd, J = 12.3, 12.3, 9.5 Hz, 1 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.13 (d, J = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.086 (s, 3 H).

4-*O*-Acetyl-3-*O*-(3-*O*-benzyl-2,6-dideoxy-4-*O*-methyl-α-D-*lyxo*-pyranosyl)-2,6-dideoxy-D-*lyxo*-pyranose (4c). A solution of **4b** (40 mg, 0.075 mmol) and $Et_3NH^+F^-$ (8 equiv) in CH_3CN (2 mL) was heated to 70 °C for 2.5 h. Saturated $NaHCO_3$ solution (0.5 mL) was added and the mixture was stirred at 23 °C for 10 min. The solution was diluted with additional aqueous $NaHCO_3$ (10 mL) and was extracted with EtOAc (4 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$ solution (20 mL) and brine (2 × 20 mL) and dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified with preparative TLC (0.5-mm plate, 50% EtOAc/hexanes, two elutions), giving 32 mg (100%) of disaccharide **4c** as ca. 2:1 mixture in favor of α-OH anomer.

This reaction has been run with the purified α,α- and α,β-anomers of **4b**, or on mixtures of them; the yields have always been quantitative. It was noticed that the β-TBDMS anomer of **4b** was desilylated faster when a mixture was used. The following ^1H and ^{13}C NMR assignments are based on 2D NMR ^1H–^1H correlation, ^1H–^{13}C correlation, and ^1H decoupling experiments.

Data for **4c**: R_f 0.20 (50% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$) data for α-OH anomer δ 7.40–7.25 (m, 5 H), 5.40 (d, J = 3.5 Hz [after D_2O exchange], 1 H, H_1), 5.14 (d, J = 2.6 Hz, 1 H, H_4), 5.12 (d, J = 3.8 Hz, 1 H, $H_{1'}$), 4.56 (s, 2 H), 4.23–4.17 (m, 2 H, H_3, H_5), 3.80–3.75 (m, 1 H, $H_{3'}$, overlapping with $H_{3'}$ and $H_{5'}$ of the β-anomer), 3.76 (q, J = 6.5 Hz, 1 H, $H_{5'}$), 3.58 (s, 3 H), 3.31 (br s, 1 H, $H_{4'}$), 2.85 (br s, 1 H, OH), 2.10 (s, 3 H), 2.02 (ddd, J = 12.5, 12.5, 3.8 Hz, 1 H, $H_{2'ax}$), 1.89 (ddd, J = 12.6, 12.6, 3.5 Hz, 1 H, H_{2ax}), 1.73 (br dd, J = 12.6, 4.9 Hz, 2 H, H_{2eq}, $H_{2'eq}$, almost superimposed), 1.22 (d, J = 6.5 Hz, 3 H, $H_{6'}$), 1.10 (d, J = 6.5 Hz, 3 H, H_6); data for β-OH anomer δ 7.40–7.25 (m 5 H), 5.08 (d, J = 3.6 Hz, 1 H, $H_{1'}$), 5.05 (d, J = 3.2 Hz, 1 H, H_4), 4.78 (ddd, J = 9.6, 6.6, 1.9 Hz, 1 H, H_1), 4.56 (s, 2 H), 4.25–4.17 (m, 1 H, H_5), 3.38 (ddd, J = 12.3, 4.8, 3.2 Hz, 1 H, H_3), 3.80–3.73 (m, 2 H, $H_{3'}$, $H_{5'}$), 3.58 (s, 3 H), 3.54 (d, J = 6.6 Hz, 1 H, OH), 3.31 (br s, 1 H, $H_{4'}$), 2.09 (s, 3 H), 2.05–1.68 (m, 4 H, H_{2ax}, $H_{2'ax}$, H_{2eq}, and $H_{2'eq}$), 1.22 (d, J = 6.5 Hz, 3 H, $H_{6'}$), 1.18 (d, J = 6.4 Hz, 3 H, H_6); ^{13}C NMR (125 MHz, $CDCl_3$) (for the mixture) δ 170.75 (carbonyl, for both anomers), 138.59, 138.49, 128.34, 128.32, 127.50, 127.45, 127.23, 127.21, 95.62, 94.99, 94.36, 92.37, 78.64, 78.54, 74.57, 74.40, 70.34, 70.11, 70.08, 69.42, 68.89, 67.50, 67.12, 66.98, 66.70, 64.72, 61.38, 61.36, 34.89, 31.42, 30.17, 30.06, 20.82, 20.77, 16.97 ($C_{6'}$ for both anomers), 16.78, 16.66; IR (neat) 3420, 3090, 3070, 2860, 2815, 1740 cm^{-1}; HRMS for $C_{22}H_{30}O_7$ ($M^+ - H_2O$), calcd 406.1991, found 406.1974. Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 61.96; H, 7.64.

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Registry No. 1, 6988-58-5; 2, 7059-24-7; 4a, 106023-24-9; α,α-4b, 131013-38-2; α,β-4b, 131013-40-6; β,β-4b, 131013-41-7; α-4c, 131041-37-7; β-4c, 131013-42-8; 8, 99603-55-1; 9, 127851-95-0; 10, 106062-13-9; 10 benzyl ether, 106062-14-0; 11, 106062-15-1; 11 TBDMS derivative, 131013-39-3; α-12, 107908-97-4; β-12, 131013-43-9; α-13, 131013-31-5; β-13, 131013-44-0; α-14, 4833-12-9; β-14, 106023-19-2; α-15, 106023-20-5; β-15, 106023-21-6; 16, 4092-40-4; 17, 3868-01-7; α-18, 106023-22-7; β-18, 106023-23-8; 19, 75810-18-3; 21, 131013-32-6; 22, 131013-33-7; α-23, 131013-34-8; β-23, 131013-45-1; α-24, 131013-35-9; β-24, 131013-46-2; 25, 131013-36-0; 26, 131100-33-9; α-27, 131041-38-8; β-27, 131013-47-3; α-28, 131013-37-1; β-28, 131013-48-4; 29, 85273-19-4; 30, 131100-34-0; 31, 131100-35-1.

Supplementary Material Available: Experimental procedures for the syntheses of 14α–19 and ^1H NMR spectra of 24 (α,β mixture), 25, 26, α,α-4b, β,α-4b, and β,β-4b (10 pages). Ordering information is given on any current masthead page.

Notes

Mechanistic Details for SET-Promoted Photoadditions of Amines to Conjugated Enones Arising from Studies of Aniline–Cyclohexenone Photoreactions

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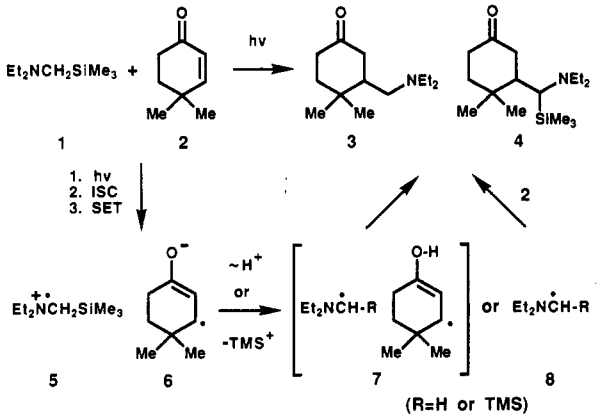
Introduction

Previous studies exploring photoaddition reactions of α-silyl amines and α,β-unsaturated ketones have led to a number of interesting proposals concerning the mechanistic features of these single electron transfer (SET) promoted processes[1,2] and have suggested potential synthetic applications.[3] In mechanistic studies of the *N*-[(trimethylsilyl)methyl]-*N*,*N*-diethylamine (1) addition to 4,4-dimethylcyclohex-2-en-1-one (2), we observed that the relative yields of the non-TMS (3) and TMS adducts (4)

Scheme I



were dependent upon the nature of the solvent, metal cation additives, and amine concentration. These results were interpreted in terms of a mechanism (Scheme I) in which the relative rates of intermediate amine cation radical 5 deprotonation and desilylation are governed by the basicity of the enone anion radical 6, which itself is controlled by hydrogen bonding and metal cation coordination. Furthermore, we suggested that in cases where the enone anion radical is rendered nonbasic by hydrogen bonding in polar protic solvents, amine cation radical 5

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