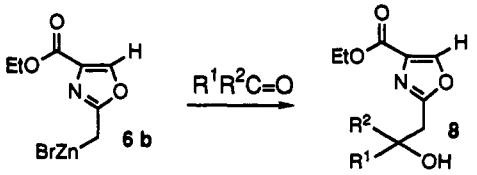
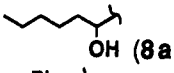
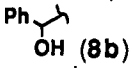
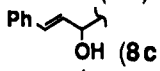
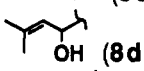
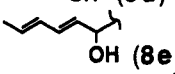
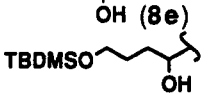
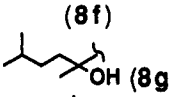
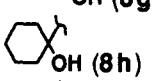
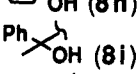
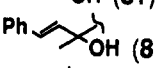
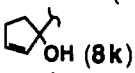
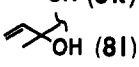
Table I. Addition of 6b to Aldehydes and Ketones



substrate	product	yield (%)
hexanal	 (8a)	92%
benzaldehyde	 (8b)	96%
PhCH=CHCHO	 (8c)	97%
$(Me)_2C$=CHCHO	 (8d)	62%
2,4-Hexadienal	 (8e)	40%
TBDMSO$(CH_2)_3$CHO	 (8f)	62%
$Me_2CH(CH_2)_2C(O)Me$	 (8g)	39%
cyclohexanone	 (8h)	49%
PhC(O)Me	 (8i)	47%
PhCH=CHC(O)Me	 (8j)	93%
cyclopentenone	 (8k)	90%
H_2C=CHC(O)Me	 (8l)	52%

6a can be considered as being heteroaromatic "benzylic". Knochel has published two examples of related "benzylic" halides[10e] (substituted furan and thiophene derivatives) which form organozinc derivatives which are then converted in situ into mixed Zn/Cu organometallics. The method presented here bypasses the need to form a mixed Zn/Cu derivative in reactions with aldehydes and ketones. Also, in Knochel's work with aldehydes as the electrophile,[10b] a Lewis acid (BF_3·OEt_2) was needed to activate the organometallic addition. However, our present route proceeds well without the need for added Lewis acids.

The range of different types of aldehydes and ketones which participate in this reaction[12] is seen in Table I. Aliphatic, aromatic, conjugated, and doubly conjugated aldehydes give fair to excellent yields of the corresponding secondary alcohols. Likewise, cyclic and acyclic (both aliphatic and conjugated) as well as aromatic ketones give the corresponding tertiary alcohols in fair to good yields. In reactions with α,β-unsaturated aldehydes and ketones, no products resulting from Michael additions are detected by ^1H NMR in the crude mixtures. Compound **8f** is particularly attractive as a possible intermediate for the synthesis of A15104 or 13-dehydroxy VM_1. The secondary alcohols **8a–8f** can be oxidized to ketones. For example, alcohol **8a** undergoes oxidation to the corresponding ketone using the Swern oxidation[13] (31% yield).

At present, acid chlorides do not react cleanly with **6b** when the organozinc is formed first and the acid chloride is added afterwards. However, the fact that a secondary alcohol β to the oxazole can be oxidized to a ketone bodes well for application of this methodology to the synthesis of streptogramin antibiotics.

In conclusion, a new heteroaromatic "benzylic" organozinc derivative has been generated and shown to react with a variety of aldehydes and ketones. Investigations are continuing using other types of electrophiles in reactions with **6b** and with other organometallic derivatives of the oxazole system. These results will be reported in due course.

Acknowledgment. We thank Dr. Tobias Rein and Nina Kann (Royal Institute, Stockholm) for many valuable discussions. A.R.G. acknowledges support received from a Fulbright Fellowship. We are also grateful for funding provided by the National Institutes of Health, the National Science Foundation (USA), and the Natural Science Research Council (Sweden).

Supplementary Material Available: Compound characterization data for **6a** and **8a–8l** (7 pages). This material is contained in many libraries on a microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) The simplicity of our procedure is demonstrated by the following representative example. Zinc dust (49 mg, 0.75 mmol) and THF (1 mL) under argon is cooled to 0 °C, and hexanal (55 mg, 0.55 mmol) is added, followed by the slow dropwise addition of **6a** (117 mg, 0.50 mmol) in THF (1 mL) from a 1000-μL syringe (1 drop every 10 s). The reaction is stirred at 0 °C for 2 h until TLC and GC show no **6a** remaining. The reaction is quenched with saturated aqueous NH_4Cl and extracted with ether. The organic phase is dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc in hexanes) gives 104 mg (92%) of **8a** as a white solid (mp 34–36 °C). Most reactions were run only once, and the yields are not optimized.

(13) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Synthesis of C–D–E Trisaccharide Precursors of Olivomycin A

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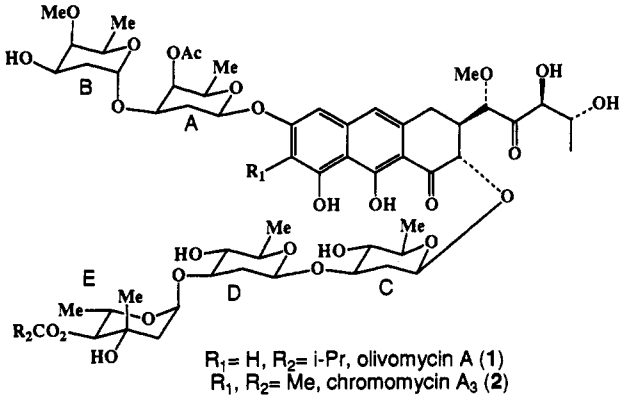
Summary: Syntheses of functionalized C–D–E trisaccharide precursors (**16**, **5**) of olivomycin A are reported. A stereoselective C–D β-glycosidation was accomplished by employing 2-deoxy-2-(phenylthio)-α-glucotrichloroacetimidate **8**. The α-D–E glycosidic linkage was introduced by using 2-deoxy-2-iodo-α-glycosyl acetate donor **14** as the glycosyl transfer agent.

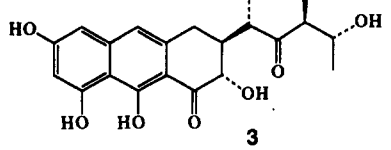
Olivomycin A (**1**) is a member of the aureolic acid family of antitumor antibiotics which also includes mithramycin

0022-3263/92/1957-4799$03.00/0

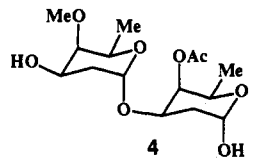
and chromomycin (2).[1-3] These compounds, which have been used as chemotherapeutic agents, are inhibitors of DNA-dependent RNA polymerase. In the presence of divalent metal ions, these agents form dimers which bind DNA duplexes in the minor groove, showing selectivities for GC rich sequences.[2] We have previously described a synthesis of the aglycon (olivin, 3),[3,4a] an enantioselective synthesis of the A–B disaccharide (4),[4b] and have developed a method for the synthesis of β-aryl-2-deoxyglycosides (as occurs in the linkage between the A–B disaccharide and the aglycone) via the Mitsunobu reaction.[5] Thiem has synthesized the chromomycin C–D–E trisaccharide by utilizing a 2,6-dideoxy-2-bromoglucosyl bromide as the C and D residue precursor and an olivomycal derivative as the E-ring donor.[6] We report here the stereoselective syntheses of two C–D–E trisaccharide precursors **16** and **5**, of which **5** is suitably functionalized for elaboration and eventual coupling with the aglycon.



R_1= H, R_2= i-Pr, olivomycin A (1)
R_1, R_2= Me, chromomycin A_3 (2)



3



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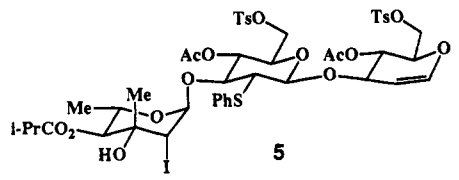
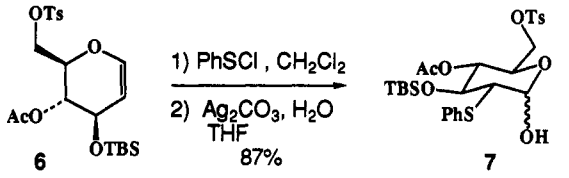
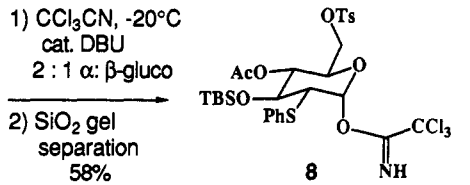


5

After evaluating a number of potential C or D residue glycosyl donors,[7,8] 2-deoxy-2-(phenylthio)-α-1-(trichloroacetimido)glucopyranose 8 was determined to be suitable.[9]



6 7 7 to 1 α- : β-gluco



8

Highly selective addition of PhSCl to the known glycal 6[10] (1.3 equiv of PhSCl, CH_2Cl_2, 23 °C), followed by Ag_2CO_3-promoted hydrolysis of the intermediate glycosyl chloride (5% aqueous THF, 4 equiv of Ag_2CO_3) provided lactol 7 in 87% yield in a one-pot operation.[11] Conversion of 7 to imidate 8 required the use of catalytic DBU and trichloroacetonitrile as solvent to avoid epimerization at C(2).[12] Other more standard methods (CCl_3CN, THF, NaH, or CCl_3CN, CH_2Cl_2, cat. DBU) led to considerable epimerization at C(2).[13] Interestingly, under conditions (0.2 M 7 in CH_2Cl_2, 10 equiv of CCl_3CN, cat. DBU) leading to 40–50% of C(2) epimerization in the conversion of lactol 7 to imidate 8, 3,4,6-tri-*O*-benzyl-2-deoxy-2-(phenylthio)-glucopyranose and 3,4-di-*O*-benzyl-2,6-dideoxy-2-(phe-

(1) (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. (b) U.S.A.–U.S.S.R. Monograph Methods for Development of New Anticancer Drugs. NCI Monograph 45, DHEW Publication No. (NIH) 76-1037, 1977.

(2) Aureolic acid-DNA complex NMR studies: (a) Gao, X.; Patel, D. J. *Biochemistry* **1989**, *28*, 751. (b) Gao, X.; Patel, D. J. *Ibid.* **1990**, *29*, 10940. (c) Banville, D. L.; Keniry, M. A.; Kam, M.; Shafer, R. H. *Ibid.* **1990**, *29*, 6521. (d) Banville, D. L.; Keniry, M. A.; Shafer, R. H. *Ibid.* **1990**, *29*, 9294. Aureolic acid–DNA footprinting studies: (e) Van Dyke, M. W.; Dervan, P. B. *Ibid.* **1983**, *22*, 2373. (f) Fox, K. R.; Howarth, N. R. *Nuc. Acids Res.* **1985**, *13*, 8695. (g) Cons, B. M. G.; Fox, K. R. *Ibid.* **1989**, *17*, 5447. (h) Cons, B. M. G.; Fox, K. R. *Biochemistry* **1991**, *30*, 6314.

(3) For synthetic efforts through 1987, see: Franck, R. W.; Weinreb, S. M. In *Studies in Natural Products Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; pp 173–208.

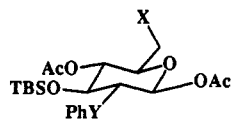
(4) (a) Synthesis of olivin: Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (b) Synthesis of A–B disaccharide: Roush, W. R.; Lin, X.-F.; Straub, J. A. *J. Org. Chem.* **1991**, *56*, 1649.

(5) Roush, W. R.; Lin, X.-F. *J. Org. Chem.* **1991**, *56*, 5740.

(6) (a) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954. See also: Thiem, J. In *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; ACS Symposium Series 386; American Chemical Society: Washington, DC, 1989; p 131. (b) For other recent work on the synthesis of the aureolic acid oligosaccharides: Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577. Binkley, R. W. *J. Carbohydr. Chem.* **1990**, *9*, 507.

(7) (a) For a comprehensive list of leading references for methods of 2-deoxy-β-glycoside synthesis, see: Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5–7. (b) See also: Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084–2092.

(8) The preparation and glycosylation reactions of **Ia–d** will be discussed in a future publication.



I
a. X=OTs, Y=S
b. X=H, Y=S
c. X=H, Y=Se
d. X=Br, Y=Se

(9) (a) For the use of 3,4,6-tri-*O*-benzyl-2-deoxy-2-(phenylthio)trichloroacetimidoglucopyranose as a donor in β-selective glycosylations, see: Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694–697. (b) For the first application of a 2-phenylthio substituent to control the stereochemistry of glycoside formation: Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466.

(10) Crich, D.; Ritchie, T. J. *Carbohydr. Res.* **1990**, *197*, 324.

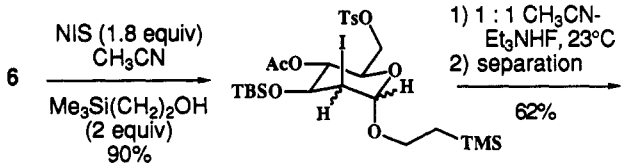
(11) All new compounds were fully characterized (^{1}H NMR, IR, optical rotation, CH analysis and/or high-resolution mass spectrum).

(12) Zimmermann, P.; Greilich, U.; Schmidt, R. R. *Tetrahedron Lett.* **1990**, *31*, 1849.

(13) It has been reported that Cs_2CO_3–CCl_3CN is superior to NaH- or DBU-promoted glycosyl imidate formation (Urban, F. J.; Moore, B. S.; Breitenbach, R. *Tetrahedron Lett.* **1990**, *31*, 4421). However, these conditions led to C.2 epimerization in the conversion of all 2-deoxy-2-phenylthio lactols we studied, including benzylated substrates.

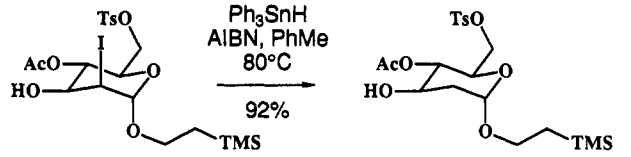
nylthio)glucopyranose could be activated as trichloroacetimidates without appreciable epimerization. In any event, treatment of a −20 °C, 0.2 M solution of lactol **7** in CCl_3CN with 3–5 mol % of DBU afforded a 2:1 mixture of α- and β-gluco imidates, contaminated by only 5–7% (by ^1H NMR analysis) of the C(2) epimeric product. Separation of this mixture by silica gel flash chromatography afforded α-imidate **8** in 58% yield. The more reactive β-imidate anomer hydrolyzes on the chromatography column, and up to 25% of lactol **7** has been recovered.

An initial C-ring acceptor (**11**) was prepared by treatment of glycal **6** with 2-(trimethylsilyl)ethanol (2 equiv) and NIS (1.8 equiv) in CH_3CN, which gave a 5.4:1 mixture of α-manno- and β-gluco-2-deoxy-2-iodoglycosides **9** in 90% combined yield.[14] Desilylation of the mixture (1:1 Et_3NHF-CH_3CN, 23 °C, 24–48 h) and then separation of the isomers provided isomerically pure **10** in 62% yield.[15] Reductive removal of the C(2) iodo group (Ph_3SnH, PhMe, AIBN, 80 °C) gave **11** in 92% yield.



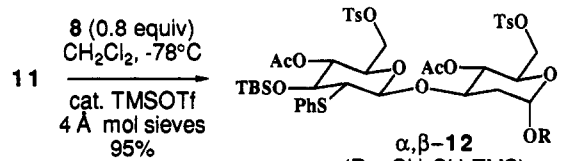
9

5.4 : 1 α-manno : β-gluco

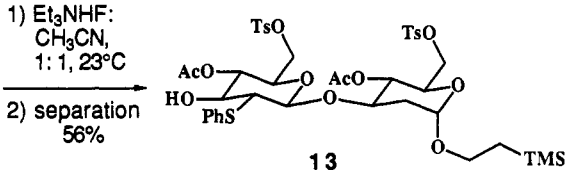


10 **11**

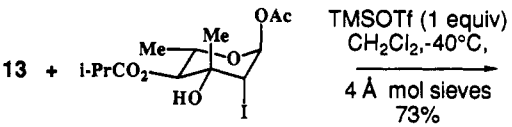
Glycosylation of **11** by imidate **8** (0.8 equiv of **8**, CH_2Cl_2, −78 °C, 4-Å molecular sieves, 0.2–0.5 equiv of TMSOTf, 5 min) proceeded with good efficiency and good β-selectivity, providing C–D disaccharide α,β-**12** as a mixture of anomers (8:1; β:α) in 95% combined yield. Desilylation of the mixture (Et_3NHF, CH_3CN) enabled chromatographic separation of the anomers and provided **13** as a single diastereomer. Attempts at direct acid-promoted glycosylations of model acceptors with glycal **18**[16] were thwarted by the tendency of **18** to undergo Ferrier rearrangement, even under conditions recently reported to disfavor this process for glycals unbranched at C.3 (e.g., Ph_3P·HBr or LiBr–Dowex H^+ resin).[17,18] However, the synthesis of C–D–E trisaccharide **16** was completed by the stereoselective α-glycosylation of **13** with E-residue donor



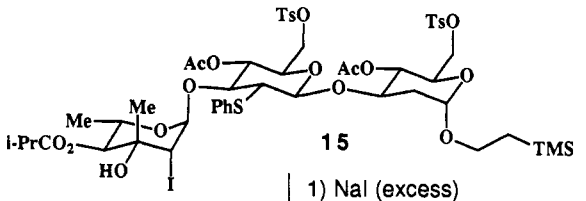
α,β-**12**
(R = CH_2CH_2TMS)
8 to 1 β- : α- gluco



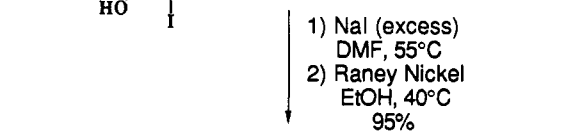
13

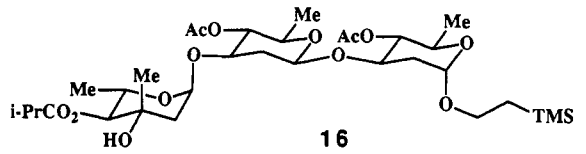


14 (1.0 equiv)



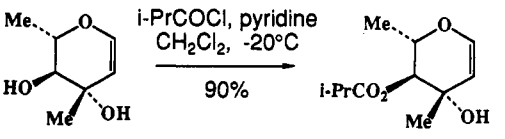
15



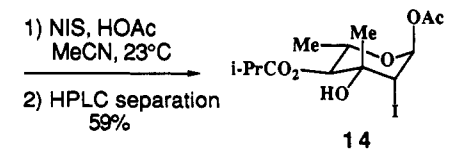


16

14, prepared by treatment of **18** with NIS in the presence of HOAc (2 equiv of HOAc, 1.8 equiv of NIS, CH_3CN).[19] Treatment of a −40 °C solution of **13** and **14** (1.0 equiv) in CH_2Cl_2 with TMSOTf (1 equiv) provided trisaccharide **15** in 73% yield, along with 13% of recovered **13**. Iodide displacement (large excess of NaI, DMF, 55 °C; 95%) followed by reduction (W-2 Raney Nickel, EtOH, 23 °C) gave the olivomycin C–D–E trisaccharide **16** in 95% yield.



17 **18**



14

In the interest of preparing a functionalized C–D–E trisaccharide (e.g., **5**) suitable for coupling to a protected

(14) Horton, D.; Priebe, W.; Sznaidman, M. *Carbohydr. Res.* **1990**, *205*, 71.

(15) All desilylations in the present study were conducted in 1:1 Et_3NHF–CH_3CN at room temperature (24–48 h) to avoid intramolecular tosylate displacement by C(3)-OH, a complication that resulted when reaction mixtures were heated by as little as 20 °C above ambient.

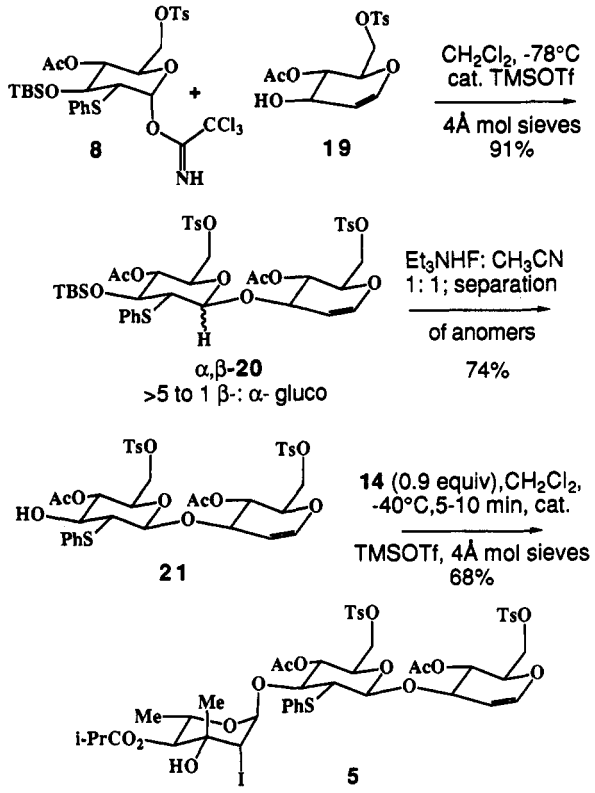
(16) Olivomycal (**17**) was prepared according to a published procedure: Jung, G.; Klemer, A. *Chem. Ber.* **1981**, *114*, 740.

(17) Ph_3P·HBr: Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.

(18) Dowex H^+ resin/LiBr: Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468.

(19) The reaction of **18**, NIS, and HOAc provides a 2.2:1 mixture of **14** and the β-gluco diastereomer in 93% combined yield. Isomerically pure **14** was obtained in 59% yield from **18** by preparative HPLC.[20] Efforts are currently underway to improve the selectivity of this reaction. **Note Added in Proof.** A co-worker (Dr. K. Briner) has found recently that the reaction of **18**, NIS, and HOAc in propionitrile at −65 °C provides **14** with 9:1 selectivity.

(20) HPLC purifications were performed on the following system: Rheodyne 7125 injector, Water 6000A pump and a Waters R401 RI detector using either a Rheodyne Dynamax 60A or Whatman Partisil M9 silica gel column.



olivin derivative, glycal **19**[21] was glycosylated with **8** (0.8 equiv of **8**, CH_2Cl_2, -78 °C, 4-Å molecular sieves, 0.2 equiv of TMSOTf, 5 min) to give glycal disaccharide **α,β-20** as a mixture of anomers (>5:1; β:α) in 91% combined yield.[22] The mixture was desilylated (Et_3NHF–CH_3CN, 23 °C) and, after separation of the α-anomer by flash silica gel chromatography, C–D disaccharide **21** was obtained as a single diastereomer in 74% yield. Glycosylation of **21** with **14** as before (0.9 equiv of **14**, 0.3 equiv of TMSOTf, -40 °C, CH_2Cl_2, 4-Å molecular sieves, 5 min) gave C–D–E trisaccharide **5** in 68% yield, along with 16% of recovered **21**.

Further elaborations of trisaccharide **5** and studies on the glycosidation of the aglycon are currently under investigation. Progress along these lines will be reported in due course.

Acknowledgment. We gratefully acknowledge support provided by a grant from the National Institute of General Medical Sciences (GM 38907).

Supplementary Material Available: Experimental procedures, tabulated spectral data, and ^1H and ^{13}C NMR spectra for **8**, **11**, **16**, and **19** and ^1H NMR spectra for the β-gluco isomer of **10**, **α,β-12**, the α-gluco isomer of **13**, **α,β-20**, and the α-gluco isomer of **21** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) Glycal **19** was prepared from **6** by treatment with Et_3NHF–CH_3CN (1:1), 23 °C (75%).

(22) To the best of our knowledge, Danishefsky was the first to employ glycal alcohols as acceptors in glycosidation reactions: (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (b) Halcomb, R. L.; Danishefsky, S. J. *Ibid.* **1989**, *111*, 6661.

Articles

Radical Routes to Indolizidines. Synthesis of (-)-Slaframine

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The synthesis of (-)-slaframine (**5**) was executed in 11 steps and 25% overall yield from resolved 3(*S*)-hydroxy-4-pentenamide (**22**). Two cyclization reactions were used to form the indolizidine skeleton and also to provide the necessary stereocontrol at C-8a and C-6 of the natural product. "Iodolactamization" of **22** gave selectively the *cis*-pyrrolidinone **21**. Later in the synthesis, a silane-mediated radical cyclization of the phenylseleno lactam **33** gave selectively the 6α-hydroxyindolizidinone **35a**, an event predictable from model studies such as **14c** → **15c**. Replacement of hydroxy with azido and reduction of the lactam carbonyl gave "slaframine azide", **38**, a stable and easily convertible immediate precursor to **5**.

Iodolactams can be made by iodocyclization of unsaturated amides, as for **1** → **2**.[1-3] Although N-substituted amides do not give high yields in this cyclization reaction, N-substituted lactams can be made by alkylation of **2**, or better, the derived phenylselenolactam **3**, as previously reported.[4] Such N-alkylated lactams are useful as substrates for free-radical-initiated cyclization,[4] and several indolizidine derivatives **4** have been prepared in this way. These examples feature some novel radical acceptor groups: bromoalkene, chloroalkene, and (ethoxymethoxy)alkene. The cyclizations are also notable for the predominance of six-membered rig formation, in contrast

(1) Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803.
(2) Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.
(3) Knapp, S.; Gibson, F. S. *Org. Synth.* **1991**, *70*, 101.
(4) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *38*, 5397.

0022-3263/92/1957-4802$03.00/0