ORGANIC LETTERS

2003
Vol. 5, No. 11
1875−1878

Stereoselective Synthesis of Functionalized Precursors of the CDEF and CDE 2,6-Dideoxy-tetra- and Trisaccharide Units of Durhamycins A and B

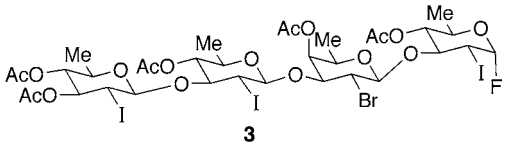
Timothy B. Durham and William R. Roush*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

roush@umich.edu

Received March 6, 2003

ABSTRACT



3

Highly stereoselective syntheses of functionalized precursors of the CDEF and CDE 2,6-dideoxy-tetra- and trisaccharide units of the anti-HIV aureolic acids durhamycins A and B using 2-deoxy-2-iodo- and 2-deoxy-2-bromopyranosyl donors are described.

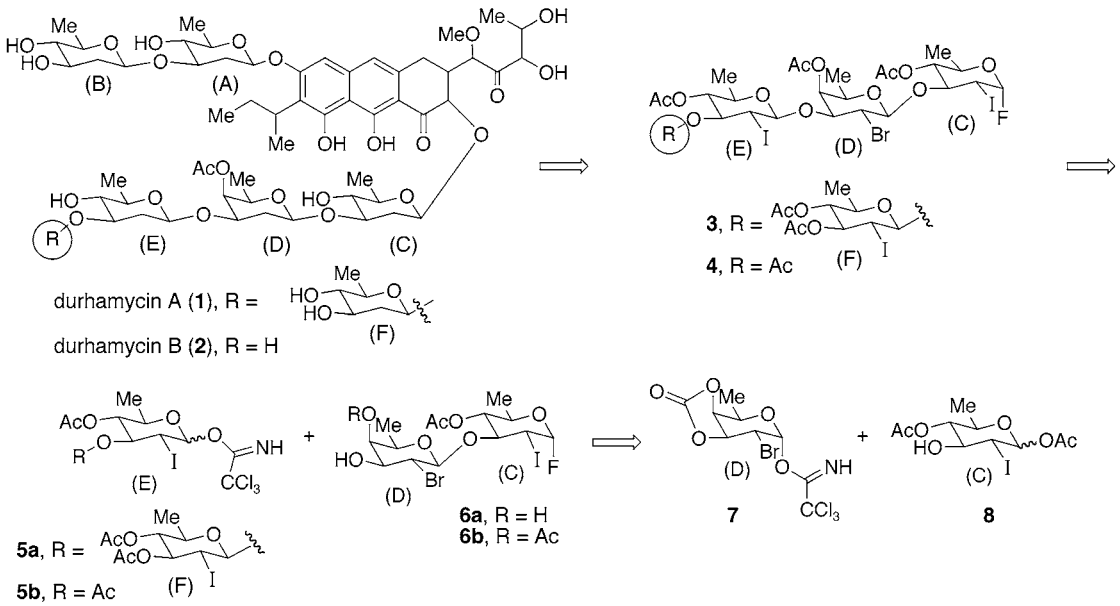
2-Deoxy and 2,6-dideoxy sugars are found in a plethora of biologically important natural products.[1] In general, the stereoselective construction of the glycosidic linkages in these systems is hampered by the absence of a directing group at C(2) of the parent 2-deoxy glycosyl donors.[2−4] This synthetic challenge has required the development of effective methods to control the stereochemical outcome of the glycosidation event. The synthesis of the exceedingly challenging 2-deoxy-β-glycosidic linkage has been addressed by installation of a directing group at C(2) which can be reductively removed after the glycosidation event.[2−6] A number of different directing groups have been utilized, including sulfur, selenium, nitrogen, oxygen, and halogen substituents.[2−4] In this context, our laboratory has used 2-deoxy-2-halo-glycosyl acetates,[7,8] trichloroacetimidates,[8−10] and fluorides[11] as highly stereoselective glycosyl donors and has reported applications of these technologies to the highly stereoselective synthesis of both 2-deoxy-β-gluco- and galactopyranosides. After the glycosidation reaction, the halogen directing groups are easily removed by reduction with Bu_3SnH to give the desired 2-deoxyglycosides. The utility of this technology has been demonstrated in our synthesis of the hexasaccharide unit of landomycin A.[12]

The aureolic acid antibiotics consist of a large family of structurally similar antitumor agents, including olivomycin, mithramycin, and UCH9.[13−18] A high degree of structural homogeneity exists with the aglycon units of these com-

(1) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1−84.
(2) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385−8417.
(3) Veyrières, A. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 368−405.
(4) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.
(5) Thiem, J.; Gerken, M. *J. Carbohydr. Chem.* **1983**, *1*, 229−249.
(6) Thiem, J.; Gerken, M.; Bock, K. *Liebigs Ann. Chem.* **1983**, 462−470.
(7) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541−3542.
(8) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871−1874.
(9) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891−893.
(10) Chong, P. Y.; Roush, W. R. *Org. Lett.* **2002**, *4*, 4523−4526.
(11) Blanchard, N.; Roush, W. R. *Org. Lett.* **2003**, *5*, 81−84.
(12) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124−6125.
(13) Remers, W. A. In *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1979; pp 133−175.
(14) Skarbek, J. D.; Speedie, M. K. In *Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*; Aszalos, A., Ed.; CRC Press: Boca Raton, FL, 1981; Vol. 1, pp 191−235.

10.1021/ol034395d CCC: $25.00 © 2003 American Chemical Society
Published on Web 04/29/2003

Scheme 1



pounds. The most significant structural differences between members of this family occur in the 2,6-dideoxy oligosaccharide units. Indeed, the biological properties of the aureolic acid antibiotics (originating from the binding of 2:1 complexes of the aureolic acids and Mg^{2+} to the minor groove of DNA)[19−22] appear to be dependent upon the nature of the carbohydrate chains.[23−25] Therefore, the ability to construct a variety of different 2,6-dideoxy oligosaccharides and attach these units to the aglycons in a highly stereocontrolled manner is the key synthetic challenge impeding the development of novel aureolic acid analogues.

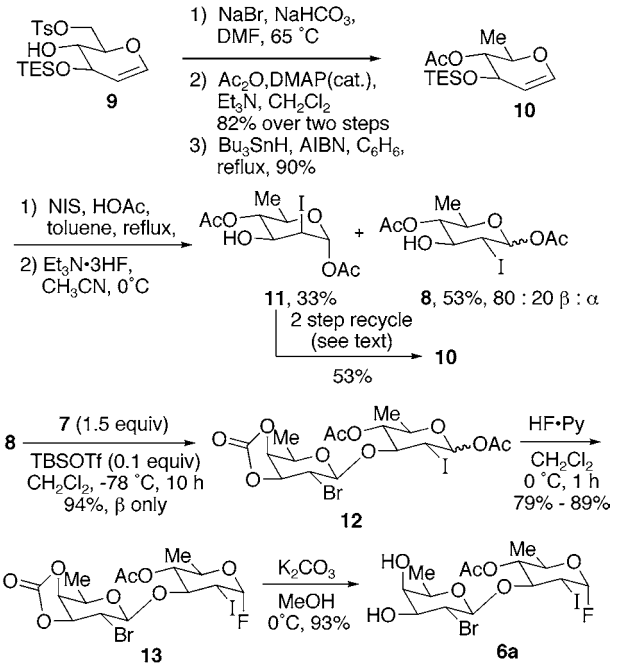
In connection with our continuing efforts toward the synthesis of aureolic acids and their analogues,[26−28] we became interested in durhamycins A (**1**) and B (**2**), which were recently isolated from *Actinoplanes durhamensis* (Scheme 1).[29] Durhamycin A is a potent inhibitor of HIV Tat transactivation (IC_{50} = 4.8 nM)[29] and contains both disaccharide and tetrasaccharide components in which all of the glycosidic linkages are of the β-configuration. Durhamycin B (**2**) is also active against HIV Tat (IC_{50} = 48 nM).[29] From a synthetic perspective, the β-D-galactosyl-(1→3)-β-D-glucoside (CD) unit is of considerable interest, as it is a common structural unit found in other aureolic acid antibiotics, including UCH9[17] and mithramycin.[16] Significantly, the efficient construction of 2-deoxy-β-galactopyranosides has proven to be a challenging problem.[8] However, we envisioned that use of 2-halo-gluco- and galactopyranosyl donors could allow efficient, stereocontrolled construction of the CDEF and CDE 2,6-dideoxy-β-tetra- and trisaccharide units of durhamycins A (**1**) and B (**2**). We report herein the successful realization of this goal.

We envision that tetrasaccharide **3** and trisaccharide **4** can serve as activated precursors of the CDEF and CDE oligosaccharide segments of **1** and **2**, respectively (Scheme 1). According to our analysis, the CD fragments **6a** and/or **6b** would serve as substrates for glycosidation reactions with glycosyl imidates **5a** and **5b** en route to **3** and **4**. Finally, we anticipated that CD disaccharides **6a**,**b** could be prepared from donors **7** and **8**, by exploiting their different anomeric reactivities.[7−9]

We focused our initial efforts on the synthesis of the common CD fragment **6**. Toward this end, tosylate **9** was heated with NaBr in dry DMF,[30] and then the C(4)−OH was acylated with acetic anhydride to furnish the 6-bromo glycal in 82% overall yield (Scheme 2). The C(6) bromide was then reduced with Bu_3SnH to provide 6-deoxy glucal **10**. Glucal **10** was then functionalized by treatment with NIS and AcOH

(15) Remers, W. A.; Iyengar, B. S. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, 1995; pp 577−679.
(16) Wohlert, S. E.; Künzel, E.; Machinek, R.; Méndez, C.; Salas, J. A.; Rohr, J. *J. Nat. Prod.* **1999**, *62*, 119−121.
(17) Katahira, R.; Uosaki, Y.; Ogawa, H.; Yamashita, Y.; Nakano, H.; Yoshida, M. *J. Antibiot.* **1998**, *51*, 267−274.
(18) Ogawa, H.; Yamashita, Y.; Katahira, R.; Chiba, S.; Iwasaki, T.; Ashizawa, T.; Nakano, H. *J. Antibiot.* **1998**, *51*, 261−266.
(19) Gao, X.; Mirau, P.; Patel, D. J. *J. Mol. Biol.* **1992**, *223*, 259.
(20) Sastry, M.; Patel, D. J. *Biochemistry* **1993**, *32*, 6588−6604.
(21) Aich, P.; Dasgupta, D. *Biochemistry* **1995**, *34*, 1376−1385.
(22) Katahira, R.; Katahira, M.; Yamashita, Y.; Ogawa, H.; Kyogoku, Y.; Yoshida, M. *Nucleic Acids Res.* **1998**, *26*, 744−755.
(23) Remsing, L. L.; Garcia-Bernardo, J.; Gonzalez, A.; Künzel, E.; Rix, U.; Braña, A. F.; Bearden, D. W.; Méndez, C.; Salas, J. A.; Rohr, J. *J. Am. Chem. Soc.* **2002**, *124*, 1606−1614.
(24) Silva, D. J.; Kahne, D. E. *J. Am. Chem. Soc.* **1993**, *115*, 7962−7970.
(25) Silva, D. J.; Goodnow, R., Jr.; Kahne, D. *Biochemistry* **1993**, *32*, 463−471.
(26) Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990−1991.
(27) Roush, W. R.; Powell, N. A.; James, R. A. *Aust. J. Chem.* **2002**, *55*, 113−121.
(28) Roush, W. R.; James, R. A. *Aust. J. Chem.* **2002**, *55*, 141−146.
(29) Jayasuriya, H.; Lingham, R. B.; Graham, P.; Quamina, D.; Herranz, L.; Genilloud, O.; Gagliardi, M.; Danzeisen, R.; Tomassini, J. E.; Zink, D. L.; Guan, Z.; Singh, S. B. *J. Nat. Prod.* **2002**, *65*, 1091−1095.
(30) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825−8836.

Scheme 2



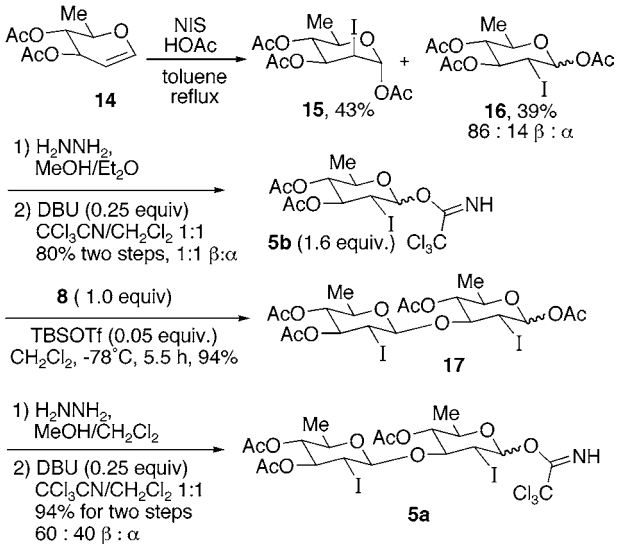
in refluxing toluene.[7] The resulting 39:45:16 mixture of α-manno:*β*-gluco:α-gluco iodoacetates was inseparable by flash chromatography or HPLC. Treatment of this mixture with $Et_3N{\cdot}(HF)_3$ provided free alcohols **11** and **8**,[31] which were easily separated by flash chromatography. The *manno* acetate **11** was then recycled back to glucal **10** by silylation with TESCl and treatment with LiI (THF, 23 °C).[7]

Glycosidation of acetate **8**[32] with galactopyranosyl trichloroacetimidate **7**[8] was effected by treatment with catalytic TBSOTf at −78 °C, which gave *β*-disaccharide **12** in 94% yield (Scheme 2).[33,34] Disaccharide **12** was then converted to α-glycosyl fluoride **13** by treatment with HF·pyridine.[35]

To transform fluoride **13** into a suitable acceptor for elaboration to **3** and **4**, it was necessary to unmask the carbonate-protected diol. We hoped that diol **6a** could be used as the acceptor in selective glycosidation reactions leading to oligosaccharides **3** and **4**. Toward this end, treatment of carbonate **13** with K_2CO_3 in methanol at 0 °C provided diol **6a** in 93% yield (Scheme 2).

With diol **6a** in hand, we focused on the preparation of E and EF donors **5a** and **5b**. Thus, 6-deoxy glucal **14**[36] was halo-acetoxylated to yield both manno and gluco acetates **15** and **16** (Scheme 3).[37] Selective deprotection of **16** by

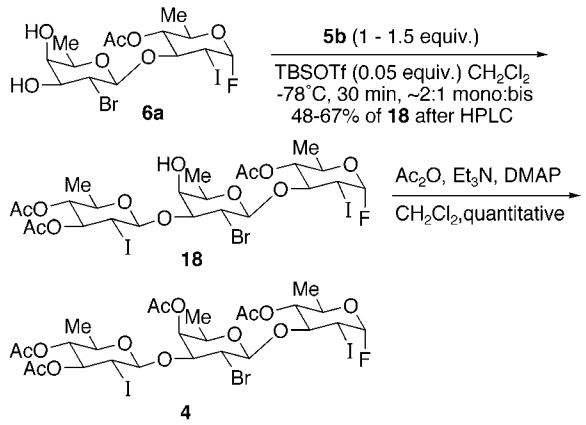
Scheme 3



treatment with hydrazine[38] followed by exposure to DBU in Cl_3CCN/CH_2Cl_2 [39,40] provided donor **5b**. To access EF donor **5a**, acetate **8** was glycosylated with imidate **5b** to provide *β*-disaccharide **17**.[34] Disaccharide **17** was then transformed to imidate **5a** by using a reaction sequence analogous to that employed for conversion of **16** to **5b**.

We first targeted trisaccharide **4** in order to investigate the selectivity of glycosidation reactions using diol **6a** (Scheme 4). Thus, treatment of a mixture of imidate **5b** and

Scheme 4



diol **6a** with catalytic TBSOTf in CH_2Cl_2 at −78 °C provided the desired disaccharide **18** along with the bis-glycosidation

(31) Mixture of gluco anomers could be enriched in the *β*-diastereomer by careful recrystallization from Et_2O/hexanes (from 80:20 up to 98:2 *β*: α).

(32) We originally hoped to convert acetate **8** to the corresponding glycosyl fluoride for use in construction of the CD unit **6a**. However, the α-fluoride produced by treatment of **8** with HF·pyridine was highly unstable and decomposed so readily that its use as an acceptor in such a glycosidation reaction was impractical.

(33) All reported ratios were determined by ^1H NMR analysis of the crude reaction mixtures. Stereochemical assignments of all isolated products were made using ^1H, ^{13}C, and COSY NMR analyses.

(34) We were not able to detect any α-glycosidation products.

(35) Jünneman, J.; Lundt, I.; Thiem, J. *Acta Chem. Scand.* **1991**, *45*, 494−498.

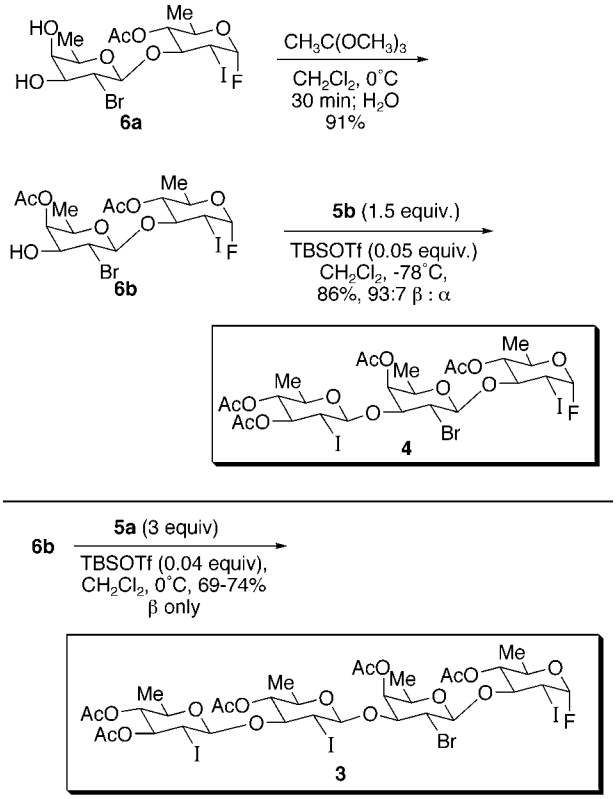
(36) Tulshian, D. B.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474−475.

(37) While acetate **16** is a potential donor for glycosidation of **6a**, attempts to effect the TBSOTF-promoted glycosidation reaction of **6a** and **16** resulted in decomposition.

(38) Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368−373.

(39) Schmidt, R. R. *Adv. Carbohydr. Chem. Biochem.* **1994**, *33*, 21−123.

Scheme 5



product (not shown) in a ~2:1 ratio (Scheme 4).[34] Acylation of alcohol **18** then provided fully functionalized and activated trisaccharide **4** in quantitative yield.

To circumvent the "over-glycosidation" encountered using diol **6a**, we opted to reverse the order of the final steps of our sequence. Thus, treatment of diol **6a** with trimethyl orthoacetate and catalytic $TsOH{\cdot}H_2O$ in CH_2Cl_2 at 0 °C followed by addition of water provided C(4) acetate **6b** in 91% yield (Scheme 5).[41] To our delight, exposure of acetate **6b** and imidate **5b** to catalytic TBSOTf (CH_2Cl_2, −78 °C) provided trisaccharide **4** in 86% yield with 93:7 β:α selectivity. Satisfyingly, tetrasaccharide **3** was also prepared in 74% yield by glycosidation of acetate **6b** with imidate **5a**.[34,42]

In summary, we have completed highly stereoselective syntheses of fully functionalized and activated precursors of the CDEF and CDE 2,6-dideoxy-β-tetra- and trisaccharide units of the anti-HIV aureolic acids durhamycin A (**1**) and B (**2**). Key features of these syntheses include the exploitation of the differential reactivity profiles of donors **5b**, **7**, and **8** and the exceptionally high stereoselectivity of all glycosidation reactions (≥93:7). This work serves to further demonstrate the potential of 2-deoxy-2-halo glycosyl donors for the rapid and highly stereoselective construction of precursors of 2-deoxy-β-oligosaccharides. Further efforts toward the synthesis of the durhamycins and other natural products containing 2-deoxy glycoside units will be reported in due course.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM38907) for support of this research.

Supporting Information Available: Experimental protocols and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034395D

(40) Schmidt, R. R.; Jung, K.-H. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 5−59.

(41) Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, *61*, 4469−4471.

(42) Imidate **5a** was very poorly soluble in dichloromethane at temperatures below 0 °C and completely insoluble in diethyl ether and propionitrile. Use of less than 3 equiv of imidate **5a** resulted in a decrease in the overall yield.