ORGANIC LETTERS

2005
Vol. 7, No. 17
3621−3624

Synthesis of the Branched *C*-Glycoside Substructure of Altromycin B

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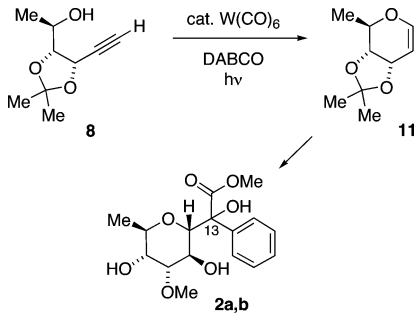
Received April 29, 2005

ABSTRACT



Tungsten-catalyzed cycloisomerization of alkynyl alcohols including 8 provides only the endocyclic enol ether (11) as a key intermediate for the branched *C*-glycoside substructure (2) of altromycin B. A sequence of Stille cross-coupling reaction and regio- and stereoselective functional group transformations affords each C13-diastereomer of the branched *C*-arylglycoside (2a and 2b).

Altromycin B (**1**, Figure 1), a member of the family of pluramycin antibiotics isolated from a South African bushveld soil, was first reported to have selective antibiotic activities against Gram-positive bacteria in the early 1990s and later reported to possess anticancer activity including in vivo activity against P388 leukemia, as well as colon, lung, and ovarian tumors.[1] The structure of altromycin B has been elucidated primarily by NMR spectroscopy, and thus the absolute stereochemistry of each of the widely separated chiral subunits has not been unambiguously assigned. Along with the studies on the biological activities, interactions between altromycin B with DNA[2] and its metal complex[3] have been reported. Despite the attractive biological activity of altromycin B and various congener natural products, none of the altromycin natural products have been prepared by total synthesis. Pasetto and Franck recently reported the synthesis of both possible C13 isomers (**2a**, **2b**) of the northwest quadrant of altromycin B, beginning with D-glucose.[4] However, their efforts to assign C13 stereochemistry on the basis of the NMR comparison of their synthetic compounds **2a** and **2b** with altromycin B (**1**) were unsuccessful because of the complexity of the natural product structure. In support of our ongoing studies directed at the total synthesis of altromycins, we report herein a different synthesis of substructures **2a** and **2b** arising from non-carbohydrate precursors.[5]

Our retrosynthetic analysis of **2a** and **2b** (Figure 1) envisioned a cross-coupling reaction[6] to form the C13 1,1-methylene linking the carbohydrate and aglycone sectors in **3**, with the carbohydrate coupling product **4** arising from the product of tungsten-catalyzed alkynol cycloisomerization of **5**.[7]

(1) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Hardy, D. J.; Swanson, S. J.; Barlow, G. J.; Tillis, P. M.; McAlpine, J. B. *J. Antibiot.* **1990**, 43, 223. (b) Brill, G. M.; McAlpine, J. B.; Whittern, D. N.; Buko, A. M. *J. Antibiot.* **1990**, *43*, 229.

(2) (a) Sun, D.; Hansen, M.; Clement, J. J.; Hurley, L. H. *Biochemistry* **1993**, *32*, 1068. (b) Hansen, M.; Hurley, L. *J. Am. Chem. Soc.* **1995**, *117*, 2421. (c) Hansen, M.; Yun, S.; Hurley, L. *Chem. Biol.* **1995**, *2*, 229. (d) Nakatani, K.; Okamoto, A.; Matsuno, T. Saito, I. *J. Am. Chem. Soc.* **1998**, *120*, 11219.

(3) (a) Menidiatis, C.; Methenitis, C.; Nikolis, N.; Peumatikakis, G. *J. Inorg. Biochem.* **2004**, *98*, 1795. (b) Nikolis, N.; Methenitis, C.; Pneumatikakis, G. *J. Inorg. Biochem*. **2003**, *95*, 177. (c) Nikolis, N.; Methenitis, C.; Pneumatikakis, G.; Fiallo, M. L. *J. Inorg. Biochem.* **2002**, *89*, 131.

(4) Pasetto, P.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 8042.

(5) For synthesis of the altromycin aglycone substructure, see the preceding communication: Fei, Z.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3617.

10.1021/ol050975u CCC: $30.25 © 2005 American Chemical Society
Published on Web 07/20/2005

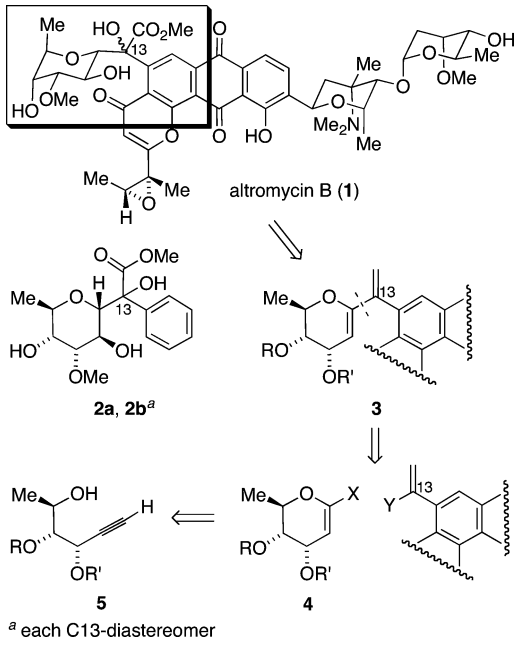
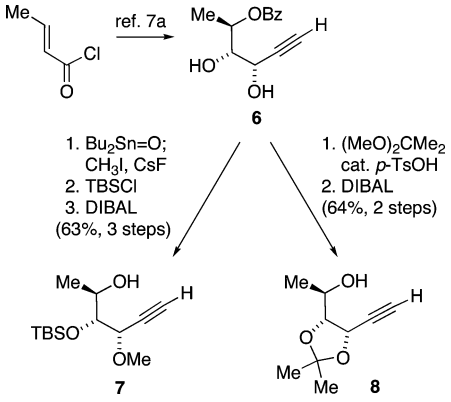


Figure 1. Retrosynthetic analysis.

Our synthesis began with the known diol **6** (Scheme 1).[7a] We observed regioselective formation of the methyl ether from the propargylic alcohol using cyclic stannylene activation of the diol, followed by silylation of the remaining alcohol and removal of the benzoate protective group with DIBAL reduction to afford alkynyl alcohol **7**. Alternatively,

Scheme 1. Preparation of Alkynyl Alcohols **7** and **8**

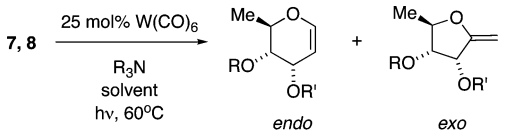


protection of diol **6** with 2,2-dimethoxypropane in the presence of catalytic *p*-TsOH, followed by DIBAL reduction of the benzoate ester provided the cyclic acetonide-protected alkynol **8**.

(6) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.

(7) (a) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304. (b) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653. (c) Alcázar, E.; Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 3877.

Table 1. Cycloisomerizations of Alkynyl Alcohols **7** and **8**



9 R = TBS, R' = Me **10**
11 R, R' = Me_2C **12**

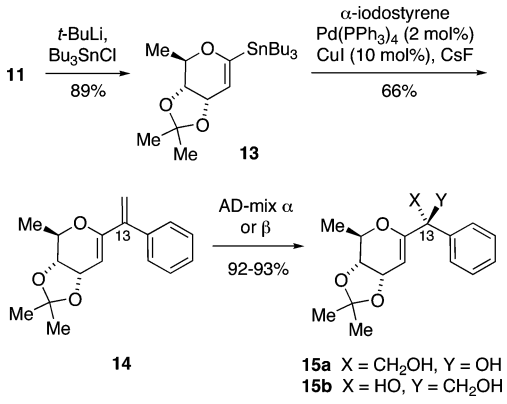
substrate	R_3N	solvent	products (ratio)[a]	combined yield (%)
7	DABCO	THF	**9, 10** (4:1)	33
8	Et_3N	THF	**11, 12** (7:1)	52
8	DABCO	THF	**11, 12** (10:1)	68
8	Et_3N	toluene	**11, 12** (8:1)	64
8	DABCO	toluene	**11** (*endo* only)	72[b]

[a] Determined by ^{1}H NMR (400 MHz). [b] Isolated yield with 10 mol % $W(CO)_6$.

The tungsten-catalyzed cycloisomerization was initially conducted with substrate **7** (Table 1). In contrast to other alkynol substrates explored in our laboratory, the preparation of six-membered glycal **9** could be optimized to provide only 33% yield. The crude ^{1}H NMR spectrum of the product mixture suggested the formation of a minor amount of the exocyclic methylene regioisomer **10**, but this byproduct could not be isolated.[8] However, cycloisomerization of the acetonide-protected substrate **8** gave better results. After optimization of the tertiary amine base and choice of solvent,[9] we obtained glycal **11** as the only regioisomeric product in good isolated yield.

Glycal **11** with the acetonide protective group also proved ideal for conversion into the stannylated glycal **13** (Scheme 2), due to the tolerance of the acetonide upon reaction with

Scheme 2. Synthesis of Diols **15a** and **15b**



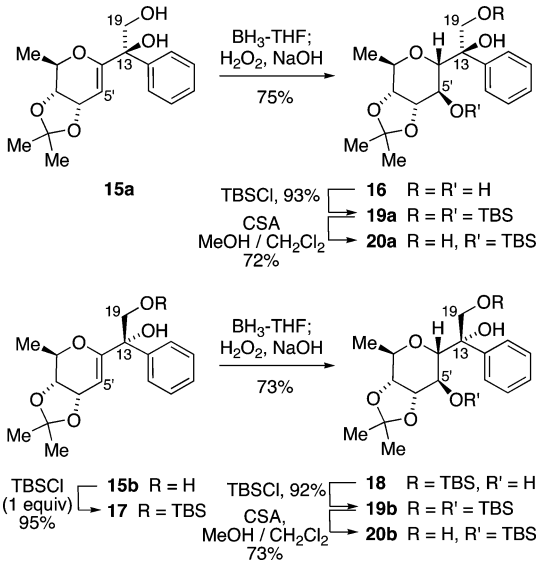
tert-butyllithium as well as solubility for subsequent transformations, relative to silyl ether protected glycals including

(8) Wipf and Graham have also noted substituent effects on regioselectivity of this transformation: Wipf, P.; Graham, T. H. *J. Org. Chem.* **2003**, *68*, 8798.

(9) Iwasawa has observed dramatic solvent effects on the regioselectivity of mechanistically related tungsten carbonyl-promoted carbacyclizations: (a) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871. (b) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, *4*, 2569. (c) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928.

9. Although the Stille cross coupling reaction between **13** and α-iodostyrene was initially irreproducible under the usual conditions recommended for stannyl glycal partners,[10] especially on millimole scales, the synergistic effect of copper(I) salts and fluoride ion[11] [$Pd(PPh_3)_4$ (2 mol %), CuI (10 mol %), CsF (2 equiv), DMF, 45 °C] provided a robust solution for this important transformation in our synthesis, affording C13-disubstituted diene **14** in 66% yield.[12] Dihydroxylation[13] of **14** using AD-mix α or *β* regioselectively occurred at the less-substituted alkene and produced a separable mixture of diastereomers **15a** and **15b** (**15a**:**15b** = 0.9:1 with AD-mix α; 3.6:1 with AD-mix *β*).

Scheme 3. Synthesis of Diols **20a** and **20b**



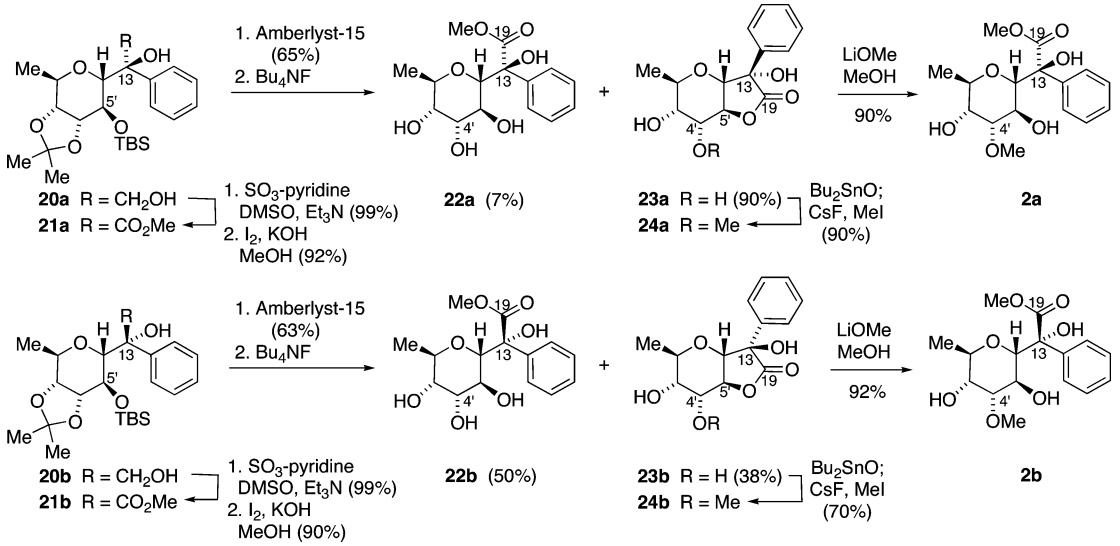
Treatment of diol **15a** with borane·THF followed by $NaOH/H_2O_2$ oxidation provided triol **16** in 75% yield (Scheme 3), with stereochemistry of **16** consistent with sterically controlled addition of borane to the convex face of the acetonide-protected glycal **15a**. However, the other diastereomer **15b** produced a hydroxyl group *syn* to the adjacent acetonide protected group as the major product under the same reaction conditions. We postulate that the primary C19-alcohol may be directing the stereochemistry of hydroboration,[14] since the mono-TBS ether **17** provided the expected stereoisomer **18** consistent with sterically controlled addition.

Compounds **16** and **18** were separately treated with TBSCl and imidazole to afford bis-TBS-protected compounds **19a** and **19b**, for which the primary alcohols were then selectively deprotected with catalytic CSA to provide **20a** and **20b**.[15]

The synthesis of the altromycin branched glycoside substructure **2a** was completed from diol **20a**, beginning with Parikh−Doering oxidation followed by I_2/KOH oxidation of the intermediate aldehyde to the methyl ester **21a** (Scheme 4).[16] Sequential removal of acetonide and silyl ether protective groups resulted in only trace formation of the tetraol-methyl ester **22a** but rather the bicyclic lactone **23a** as the major product. The rigidity of the fused bicyclic structure differentiated the remaining secondary alcohols of **23a** so that the C4′ equatorial alcohol was regioselectively converted into the methyl ether **24a** via the cyclic stannylene intermediate.[17] Opening of the lactone to the methyl ester of target compound **2a** was initially accomplished by acidic methanolysis (Amberlyst-15, MeOH), but better yields were consistently obtained under basic conditions.[18] An identical series of transformations was conducted from the diastereomeric diol **20b** to provide **2b**.

The C13 hydroxyl stereochemistry was confirmed by X-ray crystallography of intermediate **23b**, and NOE studies with diastereomer **23a** allowed unambiguous stereochemical assignments for all synthetic products.[19] The ^1H NMR spectra for our synthetic compounds **2a** and **2b** matched the data published by Pasetto and Franck for these two compounds.[4]

Scheme 4. Conversion of Diols **20a** and **20b** to the Corresponding Altromycin Branched Glycoside Substructures **2a** and **2b**



In combination with concurrent research into the synthesis of the altromycin aglycone,[5] further studies directed toward the total synthesis of the altromycin natural products are in progress.

Acknowledgment. We thank the National Institutes of Health (CA 59703) for support of this research. We also acknowledge use of shared instrumentation provided by grants from the National Institutes of Health, National Science Foundation, and the Georgia Research Alliance (NMR spectroscopy, mass spectrometry, X-ray diffractometry) as well as the University Research Committee of Emory University (polarimeter). We also appreciate the work of Dr. Kenneth I. Hardcastle and Mr. Xikui Fang for crystal structure determinations of **23b** and **24b**.

Supporting Information Available: Experimental procedures and characterization data for new compounds, including data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Mee, P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132. For effect of Cu(I) in the Stille cross-coupling reaction, see: (b) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (c) Kapadia, V. F. S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *12*, 1047. (d) Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305. (e) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(12) In all cases formation of the undesired homodimerization byproduct from glycal **13** could not be completely suppressed (ca. 20% yield). The attempted Stille cross coupling reaction with the bis-TBS-protected stannyl glycal corresponding to **13** was unsuccessful, perhaps as a result of the poor solubility of this stannylated glycal in DMF.

(13) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Stereochemical assignments for **15a** and **15b** are based on conversions to bicyclic lactones **23a** and **23b**, respectively.

(14) Transition metal catalyzed hydroborations: (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (b) Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1991**, *113*, 4042. An unsuccessful attempt to achieve hydroxyl-directed hydroboration has been reported: (c) Smith, A. B., III; Yokoyama, Y.; Huryn, D. M.; Dunlap, N. K. *Tetrahedron Lett.* **1987**, *28*, 3659.

(15) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

(16) (a) Parikh, J.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505. (b) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329. Chromium(VI) oxidations resulted in oxidative cleavage of the C13−C19 bond.

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(19) See Supporting Information for NOE studies on **23a**, as well as crystallographic information for **23b** and **24b**.