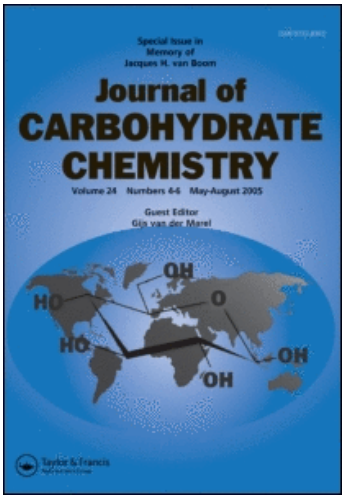


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Aglycon-Disaccharide Coupling in Mithramycin Analog Synthesis

Roger W. Binkley

To cite this Article Binkley, Roger W.(1990) 'Aglycon-Disaccharide Coupling in Mithramycin Analog Synthesis', Journal of Carbohydrate Chemistry, 9: 4, 507 — 511
To link to this Article: DOI: 10.1080/07328309008543850
URL: http://dx.doi.org/10.1080/07328309008543850

J. CARBOHYDRATE CHEMISTRY, 9(4), 507-511 (1990)

COMMUNICATION

AGLYCON-DISACCHARIDE COUPLING IN MITHRAMYCIN ANALOG SYNTHESIS

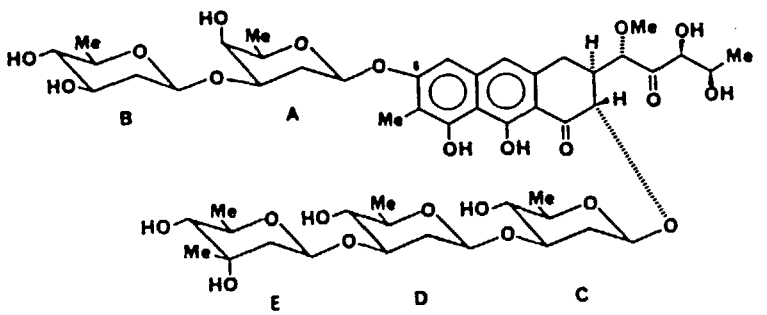
Roger W. Binkley

Department of Chemistry
Cleveland State University, Cleveland, Ohio 44115

Received December 18, 1989 - Final Form March 6, 1990

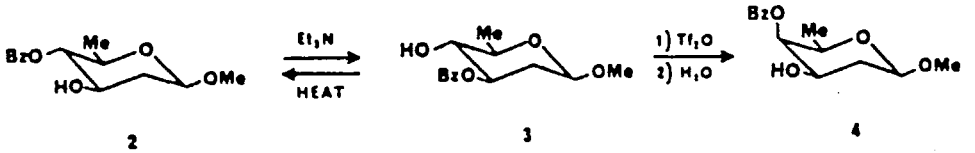
Mithramycin (1), chromomycin A_3, and olivomycin A are structurally related, antitumor agents which belong to the aureolic acid family of antibiotics.[1] Considerable research on the synthesis of both the aglycon[2-6] and carbohydrate[7-9] portions of these molecules naturally has led to interest in methods for joining carbohydrate and aglycon units together.[10] One type of coupling which is required for aureolic acid synthesis is that of the A-B disaccharide to the phenolic hydroxyl group at C-6.[11] In this communication such a process is described along with a flexible procedure for the formation of the protected A-B disaccharide used in the coupling process.

Synthesis of methyl 4-*O*-benzoyl-2,6-dideoxy-β-D-*lyxo*-hexopyranoside (4) from methyl 4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-hexopyranoside (2)[12] was accomplished by migration of the benzoyl group from O-4



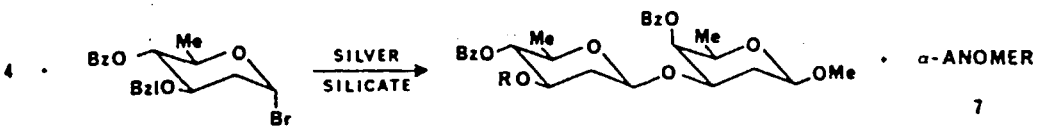
1

Scheme I



2 3 4

to O-3 (to give 3) followed by a triflate rearrangement which included an inversion of configuration at C-4 and a reverse migration of the benzoyl group in a highly stereo- and regioselective reaction.[12] The glycosyl acceptor 4 then was coupled with 4-*O*-benzoyl-3-*O*-benzyl-2,6-dideoxy-α-D-*arabino*-hexopyranosyl bromide (5),[9f] using the silver-silicate method developed by Paulsen,[13] to give the β-disaccharide 6 in 72% yield along with a 13% yield of the α-anomer 7 (β/α = 5.4/1). Light-initiated debenzylation of 6 (NBS, $CaCO_3$, and water) gave an 88% yield of 8,[9c] a compound which then was benzoylated to produce the disaccharide 9 containing the mithramycin A-B ring system fully protected by groups which could be removed under mildly basic conditions. These deprotection conditions were significant since the aureolic acids are hydrolyzed under weakly acidic conditions (acetic acid in water), are unstable in the presence of strong bases, but are de-esterified under mildly basic conditions (potassium carbonate in methanol).[14]



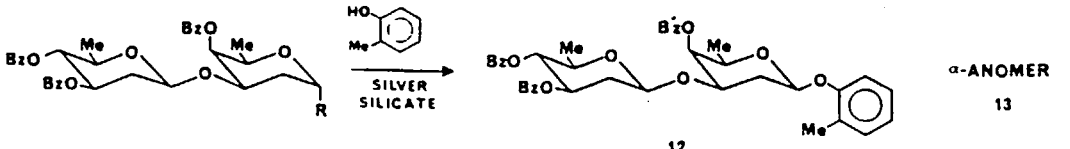
5 6 R = Bzl 7

8 R = H

9 R = Bz

Hydrolysis of 9 in acetic acid - water (2/1) at 100 °C for 3 h gave an 80% yield of 10, which was converted into the corresponding glycosyl bromide (11) in quantitative yield using bromotrimethylsilane in benzene at room temperature, and then reacted with o-methylphenol in the presence of silver silicate in toluene at 25 °C to give the β-glycoside 12[15] in 65% yield along with a 21% yield of the α-anomer 13 (β/α = 3/1).

Since reaction occurs without difficulty between the phenolic hydroxyl group in the model aglycon (*o*-cresol) and the glycosyl bromide 11, effective conditions now have been established for the essential aglycon-disaccharide coupling step in mithramycin synthesis.



10 R = OH

11 R = Br

12

ACKNOWLEDGMENT

The author appreciates financial support for this work from the Research Challenge Program.

REFERENCES, AND FOOTNOTES

1. (a) M. Slavik and S. K. Carter, *Adv. Pharmacol. Chemother.*, *12*, 1 (1975); (b) W. A. Remers, *The Chemistry of Antitumor Antibiotics*, Wiley: New York, 1979, Vol. 1, Ch. 3; (c) J. D. Sharbeck and M. K. Speedie in *Antitumor Compounds of Natural Origin*, A. Aszalos, Ed.; CRC Press: New York, 1981, Ch. 5; (d) W. A. Remers, *Antineoplastic Agents*, Wiley-Interscience: New York, NY, 1984, p 197; (e) R. W. Franck and S. M. Weinreb in *Studies in Natural Product Chemistry*, A. Rahman, Ed.; Elsevier: Amsterdam, 1989, 175.

2. (a) R. W. Franck and T. V. John, *J. Org. Chem.*, **45**, 1170 (1980) and **48**, 3269 (1983); (b) S. C. Datta, R. W. Franck, and P. D. Noire, *J. Org. Chem.*, **49**, 2785 (1984); (c) R. W. Franck, C. S. Subramaniam, T. V. John, and J. F. Blount, *Tetrahedron Lett.*, 25, 2439 (1984); (d) R. W. Franck, V. Bhat, and C. S. Subramanian, *J. Am. Chem. Soc.* 108, 2455 (1986).

3. (a) R. P. Hatch, J. Shringapure, and S. M. Weinreb, *J. Org. Chem.* **43**, 4172 (1978); (b) J. H. Dodd, S. M. Weinreb, *Tetrahedron Lett.* 3593 (1979); (c) J. H. Dodd, R. S. Garigipate, and S. M. Weinreb, *J. Org. Chem.*, 47, 4045 (1982); (d) J. H. Dodd, J. E. Sarrett, Jr. and S. M. Weinreb, *J. Am. Chem. Soc.* **106**, 1811 (1984).

4. (a) W. R. Roush, M. R. Michaelides, D. F. Tai, and W. K. M. Chong, *J. Am. Chem. Soc.* 109, 7575 (1987); (b) W. R. Roush, M. R. Michaelides, D. F. Tai, B. M. Lesur, W. K. M. Chong, and D. J. Harris, *J. Am. Chem. Soc.* 111, 2984 (1989); (c) W. R. Roush in *Trends in Synthetic Carbohydrate Chemistry,* D. Horton, L. D. Hawkins, and G. J. McGarvey, Eds.; American Chemical Society: Washington, DC, 1989, p 242.

5. G. A. Kraus and M. D. Hagen, *J. Org. Chem,.* 48, 3265 (1983).

6. A. V. Rama Rao, T. G. M. Dhar, M. K. Gujar, J. S. Yadav, *Indian J. Chem.* 35B, 999 (1986).

7. (a) W. R. Roush, D. J. Harris, and B. M. Lesur, *Tetrahedron Lett.* 24, 2227 (1983); (b) W. R. Roush, and B. M. Lesur, *Tetrahedron Lett.* 24, 2231 (1983); (c) W. R. Roush and J. A. Straub, *Tetrahedron Lett.,* 27, 3349 (1986).

8. (a) J. Thiem and H. Karl, *Chem. Ber.,* 113, 3039 (1980); (b) J. Thiem and J. Elvers, *Chem. Ber.,* 113, 3049 (1980); (c) J. Thiem and B. Meyer, *Chem. Ber.* 113, 3058, 3067, and 3075 (1980); (d) J. Thiem and B. Meyer, *Tetrahedron* 37, 554 (1981); (e) J. Thiem and H. P. Wessel, *Liebigs Ann. Chem.,* 2216 (1981); (f) J. Thiem, M. Gerken, and K. Bock, *Liebigs Ann. Chem.,* 462 (1983); (g) J. Thiem, M. Gerken, and G. Snatzke, *Liebigs Ann. Chem.,* 448 (1983); (h) J. Thiem and S. Kopper, *J. Carbohydr. Chem.* 2, 75 (1983); (i) J. Thiem and M. Gerken, *J. Carbohydr. Chem.* 1, 229 (1982); (j) J. Thiem and G. Schneider, *Angew. Chem. Int. Ed. Engl.* 22, 58 (1983); (k) J. Thiem and M. Gerken, *J. Org. Chem.* 50, 954 (1985); (l) J. Thiem, G. Schneider, and V. Sinnwell, *Liebigs Ann. Chem.,* 814 (1986); (m) J. Thiem and B. Schottmer, *Angew. Chem. Int. Ed. Engl.* 26, 555 (1987); (n) J. Thiem, M. Gerken, B. Schottmer, and J. Weigand, *Carbohydr. Res.* 164, 327 (1987).

9. (a) R. W. Binkley, *J. Carbohydr. Chem.* 4, 227 (1985); (b) R. W. Binkley, *J. Org. Chem.* 50, 5646 (1985); (c) R. W. Binkley and M. A. Abdulaziz, *J. Org. Chem.,* 52, 4713 (1987); (d) R. W. Binkley and D. J. Koholic, *J. Carbohydr. Chem.* 7, 487 (1988); (e) R. W. Binkley and J. S. Schneider, *J. Carbohydr. Chem.* 7, 157 (1988); (f) R. W. Binkley and D. J. Koholic, *J. Org. Chem.* 54, 3577 (1989) (The procedure described in this paper was used for preparation of 6); (f) R. W. Binkley and D. G. Hehemann, *J. Org. Chem.,* 55, 378 (1990).

10. S. Ramesh and R. W. Franck, *Chem. Commun.,* 960 (1989).

11. (a) D. Crich and T. J. Ritchie, *Chem. Commun.,* 1461 (1988) and *Carbohydr. Res.,* 190, C3 (1989); (b) S. Ramesh, N. Kaila, G. Grewal, and R. W. Franck, *J. Org. Chem.,* 55, 5 (1990).

12. (a) R. W. Binkley and M. R. Sivik, *J. Org. Chem.* 51, 2619 (1986); (b) R. W. Binkley and M. R. Sivik, *J. Carbohydr. Chem.* 6, 647 (1986). The procedure for conducting triflate rearrangement and the mechanism for this process are described in these papers.

13. H. Paulsen, W. Kutschker, and O. Lockhoff, *Chem. Ber.* 114, 3233 (1981); (b) H. Paulsen and O. Lockhoff, *Chem. Ber.*, 114, 3102 (1981).

14. (a) M. Miyamoto, Y. Kawamatsu, K. Kawashima, M. Shinohara, K. Tanaka, S. Tatsuoka, and K. Nakanishi, *Tetrahedron*, 23, 421 (1967). (b) M. Kam, R. H. Shafer, and E. Berman, *Biochemistry*, 27, 3581 (1988). Potassium carbonate in methanol is sufficiently basic to catalyze an internal cyclization reaction in chromomycin A_3[14a]; thus, even milder deprotection conditions may be needed.

15. Characterizing data for compound 12: R_f = 0.38 (50/1 toluene-ethyl acetate); ^{13}C NMR: δ 16.33 ($ArCH_3$), 1697 (C_6), 17.67 ($C_{6'}$), 32.40 (C_2), 36.63 ($C_{2'}$), 70.34, 70.47, 70.60 (C_4, C_5, $C_{5'}$), 71.38 ($C_{3'}$), 72.88 C_3), 74.28 ($C_{4'}$), 96.76 ($C_{1'}$), 98.38 (C_1), 114.58, 122.25, 126,80, 127.68, 128.32, 129.46, 129.98, 132.95 (aromatic carbons), 165.68, 166.10 (C=O); ^1H NMR: δ 1.30 ($H_{6'}$, $J_{5',6'}$ = 6.4 Hz), 1.32 (H_6, $J_{5,6}$ = 6.6 Hz), 1.83 ($H_{2a'}$, $J_{1',2a'}$ = 9.9 Hz, $J_{2a',2e'}$ = 11.7 Hz, $J_{2a',3'}$ = 11.4 Hz), 2.32-2.39 (H_{2a}, H_{2e}), 3.68 ($H_{5'}$, $J_{4',5'}$ = 9.2 Hz), 3.90 ($H_{4,5}$ <1 Hz), 4.21 (H_3, $J_{3,4}$ = 3.2 Hz), 4.87 ($H_{1'}$), 5.16 (H_1, $J_{1,2e}$ = 5.0 Hz, $J_{1,2a}$ = 10 Hz), 5.17 ($H_{4'}$, $J_{3',4'}$ = 9.7 Hz, 5.29 ($H_{3'}$), 5.51 (H_4), 6.90-7.62, 7.83-8.16 (aromatic protons). Anal. Calcd for $C_{40}H_{40}O_{10}$: C, 70.57; H, 5.92. Found: C, 70.79; H, 5.80.