# Application of Glycosyltetrazoles in Oligosaccharide Synthesis: Assembly of the C3 Trisaccharide Component of the Antibiotic PI-080

Aditya Sobti, Kyungjin Kim, and Gary A. Sulikowski*

*Department of Chemistry, Texas A&M University, College Station, Texas 77843*

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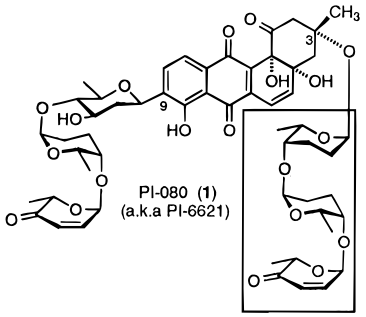
The antibiotic PI-080 (**1**) is a member of the angucycline family of antibiotics and identical in structure to PI-6621.[1,2] This microbial metabolite was isolated from cultured broths of *Streptomyces matensis* and found to strongly inhibit blood coagulation induced by adenosine diphosphate, arachadonic acid, and heparin. The anticoagulant activity appears to be associated with the oligosaccharide rather than the aglycon portion of **1**. The oligosaccharide region of **1** is composed of two trisaccharide components terminating in the unsaturated sugar L-aculose. One trisaccharide is attached to the aglycon at the C9 position through a nonhydrolyzable *β-C*-aryl glycoside bond while the second is conjugated to the aglycon at the C3 position through a labile α-*O*-glycosidic linkage with two L-rhodinose sugars insulating the aglycon and L-aculose sugar. From a synthetic perspective, a notable feature of the latter trisaccharide is that its installation would require the glycosylation of the C3 *tertiary* alcohol.[3]




Considerable attention has been devoted to the stereocontrolled assembly of 2,6-dideoxyoligosaccharides in connection with the synthesis of various antibiotics including the anthracyclines, aureolic acid, and enediyne antibiotics.[4] In contrast, the synthesis of 2,3,6-trideoxyoligosaccharides has received scant attention.[5] The synthesis of PI-080 (**1**), as well as other bioactive angucycline antibiotics, provides an opportunity for investigating the synthesis of trideoxyoligosaccharides as well as the glycosylation of sterically hindered tertiary alcohols. We report herein stereoselective syntheses of the PI-080 trisaccharide **10** and the glycoconjugate **17** by the application of the α-glycosylation method using glycosyl tetrazoles as glycosyl donors.[6,7]

Glycosyl tetrazoles are prepared in high yield by the condensation of 2-deoxy sugars with an excess of 1*H*-tetrazole using di-*tert*-butyl *N,N*-diethylphosphoramidite as a condensing agent. Upon activation with either $ZnCl_2$ or an alkylating agent such as $(CH_3)_3OBF_4$, these donors serve to glycosylate various alcohols providing selectively α-glycosides. In the present example, we started with known aryl glycoside **2a**.[8] Oxidative removal of the C1 *p*-methoxyphenyl group followed by condensation with 1*H*-tetrazole afforded **2c** in 90% overall yield.[9a,10] Treatment of a −78 °C solution of **2c** and **3** (1 equiv) in propionitrile with $(CH_3)_3OBF_4$ (2 equiv) followed by slowly warming the mixture to 15 °C provided disaccharide **4** in 60% yield (4:1; α:*β* anomers), along with 28% recovered **3**.[10] After oxidation with CAN and condensation with 1*H*-tetrazole, glycosyltetrazole **6**[9b,10] was obtained in 59% yield. Coupling of **6** with **3** [1 equiv of **3**, $CH_2Cl_2$, −78 → 15 °C, 4 Å MS, 2 equiv of $(CH_3)_3OBF_4$, 4 h] proceeded to give trisaccharide **7**[10] as a >95:5 mixture of α and *β* anomers in 40% yield, along with 46% recovered **3**. Following completion of the trisaccharide framework, we turned our attention to the conversion of the C4‴ acetate to a keto group. To this end, removal of the C4‴ acetyl group followed by Dess−Martin periodinane oxidation afforded ketone **9**[10] as a white solid (91%).[11] Finally, removal of the *p*-methoxyphenyl group [2 equiv of CAN, $CH_3CN$ (aq)] provided PI-080 trisaccharide (**10**). The $^{13}C$ and $^1H$ NMR spectral data of

(1) For an excellent review of angucycline antibiotics, see: Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103−137.

(2) PI-080: (a) Kawashima, A.; Kishimura, Y.; Tamai, M.; Hanada, K. *Chem. Pharm. Bull.* **1989**, *37*, 3429−3431. PI-6621: (b) Kawashima, A.; Yoshimura, Y.; Kamigori, K.; Yagishi, M.; Mizutani, T. *Chem. Abstr.* **1989**, *114*, 22464d.

(3) For recent examples of a glycosylation of a tertiary alcohol, see: (a) Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871−8872. (b) Hatakeyama, S.; Kawamura, M.; Takano, S. *J. Am. Chem. Soc.* **1994**, *116*. 4081−4082. (c) Yan, L.; Kahne, D. *Synlett* **1995**, 523−524.

(4) Anthracycline antibiotics: (a) 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; Chapter 8. (b) Monneret, C.; Martin, A.; Pais, M. *J. Carbohydr. Chem.* **1988**, *7*, 417−434. (c) Suzuki, K.; Sulikowski, G. A.; Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 8895−8902. (d) Kolar, C.; Kneissl, G. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 809−811. (e) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580−1581. Aureolic acid antibiotics: (f) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954−958. (g) Thiem, J.; Gerkeno, M.; Schottmer, B.; Weigand, *J. Carbohydr. Res.* **1987**, *164*, 327−341. (h) Thiem, J.; Meyer, B. *Tetrahedron* **1981**, *37*, 551−558. (i) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236−2250 and references cited within. (j) Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717−3727 and references cited within. (k) Ramesh, S.; Franck, R. W. *J. Chem. Soc., Chem. Commun.* **1989**, 960−962. (l) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1461−1463. Enediyne antibiotics: (m) Halcomb, R. L.; Wittman, M. D.; Olson, S. H.; Danishefsky, S. J.; Golik, J.; Wong, H.; Vyas, D. *J. Am. Chem. Soc.* **1991**, *113*, 5080−5082. (n) Nicolaou, K. C.; Groneberg, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4085−4086. (o) Nicolaou, K. C.; Groneberg, R. D.; Miyazaki, T.; Sylianides, N. A.; Schuze, T. J.; Stahl, W. *J. Am. Chem. Soc.* **1990**, *112*, 8193−8195. (p) Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766−1775 and references cited within. (q) Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720−5749 and references cited within.

(5) For an example of a glycosylation using a 2,3,6-trideoxyglycosyl bromide, see: Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513.

(6) For an excellent recent review of *O*-glycosylation methods, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(7) (a) Falahatpisheh, N.; Sulikowski, G. A. *Synlett* **1994**, 672−674. (b) Watanabe, Y.; Nakamoto, C.; Yamamoto, Y.; Ozaki, S. *Tetrahedron* **1994**, *50*, 6523−6536.

(8) (a) Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett.* **1994**, *35*, 3661−3664. (b) Noshita, T.; Sugiyama, T.; Kitazumi, Y.; Oritani, T. *Tetrahedron Lett.* **1994**, *35*, 8259−8262.

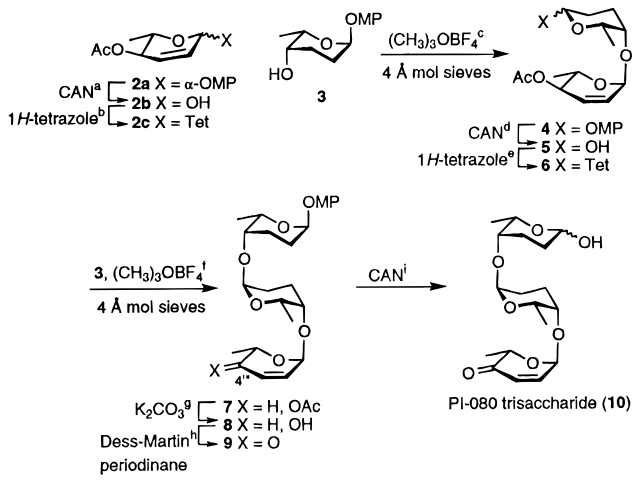
(9) (a) Glycosyltetrazoles **2c** and **11b** are produced as a mixture of N-2 and N-1 isomers. The isomers are separated by column chromatography and glycosylate alcohols with comparable efficiency using $(CH_3)_3OBF_4$ as an activating agent. See ref 7a. (b) Glycosyl tetrazole **6** is obtained exclusively as the N-2 isomer.

(10) The structure assigned to each new compound was in accord with its infrared, 400-MHz $^1H$ NMR, and 50 MHz $^{13}C$ NMR spectra, as well as appropriate parent ion identificaton by high-resolution mass spectrometry.

(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

0022-3263/96/1961-0006$12.00/0 

**Scheme 1**[a]

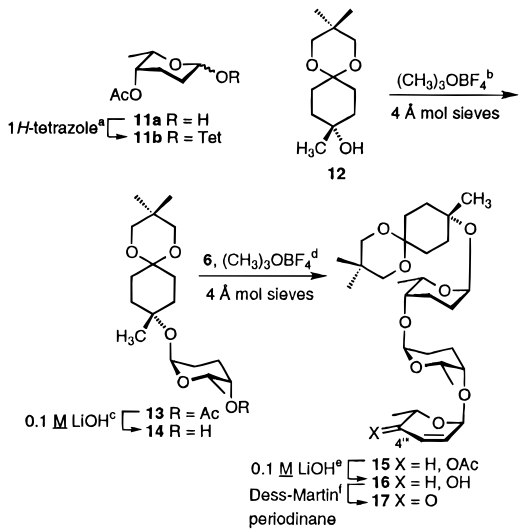



[a] Key: (a) $CH_3CN$ (aq), 20 °C, 92%; (b) $(t\text{-}C_4H_9O)_2PN(Et)_2$, THF, 20 °C, 93%; (c) $CH_3CH_2CN$, −78 to 15 °C, 60%; (d) $CH_3CN$ (aq), 20 °C, 95%; (e) $(t\text{-}C_4H_9O)_2PN(Et)_2$, THF, 20 °C, 62%; (f) $CH_2Cl_2$, −78 to 15 °C, 40%; (g) $CH_3OH$, 20 °C, 91%; (h) $CH_2Cl_2$, 20 °C, 100%; (i) $CH_3CN$ (aq), 20 °C, 84%.

synthetic **10** and a sample obtained by acid hydrolysis of PI-080 (**1**) were identical in all respects.[2a,12]

Outlined in Scheme 2 is the assembly of a model system for the merging of the PI-080 aglycon and trisaccharide **10**. In this study, we elected to use tertiary alcohol **12** as a model for the PI-080 aglycon. We have recently described the synthesis of 4-*O*-acetyl-L-rhodinose (**11a**)[13] which is condensed with 1*H*-tetrazole to afford donor **11b** (58%).[9a,10] Glycosylation of **12** by tetrazole **11b** (1.2 equiv of **12**, $CH_2Cl_2$, 0 °C, 4 Å molecular sieves, 2 equiv $(CH_3)_3OBF_4$, 2.5 h) proceeded in modest yield (47%) to provide **13**[10] as a mixture of anomers (>98:2; α:*β*), along with 45% recovered **12**.[3] Following deacetylation, **14** was glycosylated with previously described tetrazole **6**. In the event, coupling of **14** and **6** proceeded with modest efficiency to provide trisaccharide **15**[10] (18−23%).

**Scheme 2**[a]




[a] Key: (a) $(t\text{-}C_4H_9O)_2PN(Et)_2$, THF, 20 °C, 58%; (b) $CH_2Cl_2$, −78 to 20 °C, 47%; (c) EtOH, 20 °C, 82%; (d) $CH_2Cl_2$, −78 to 15 °C, 18−23%; (e) EtOH, 20 °C, 81%; (f) $CH_2Cl_2$, 20 °C, 94%.

Removal of the C4‴ acetyl group followed by oxidation yielded ketone **17**[10] in good overall yield.

In summary, we have described the first synthesis of the trisaccharide **10** common to the antibiotic PI-080 (**1**). Correlation of synthetic **10** with material obtained by degradation of **1** serves to corroborate the assigned structure of the C3 trisaccharide of PI-080 (**1**). In a second study, we outlined the synthesis of trisaccharide **17** which served as a model for the formal merging of **10** and the aglycon sector of PI-080 (**1**) in a projected total synthesis of **1**. Progress toward the total synthesis of **1** as well as other complex angucycline antibiotics will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectral data for all compounds (12 pages).

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(12) Trisaccharide **10** has been isolated as a product of fermentation from *Streptomyces* SGN-366 and reported to inhibit induced blood platelet aggregation in vitro. See: Kawamata, M; Ojima, N.; Nakamura, T.; Izure, Y.; Konno, K.; Yasuda, H.*Chem. Abstr.* **1987**, *106*, 100840z.

(13) (a) Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett* **1995**, *36*, 4193−4196. (b) For other syntheses of L-rhodinose, see: (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *Tetrahedron* **1989**, *45*, 5141−5150. (c) Boeckman, R. K., Jr.; Potenza, J. C.; Enholm, E. J. *J. Org. Chem.* **1987**, *52*, 469−472. (d) Servi, S. *J. Org. Chem.* **1985**, *50*, 5865−5867.