Pergamon

Tetrahedron Letters, Vol. 35, No. 22, pp. 3661-3664, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0658-K

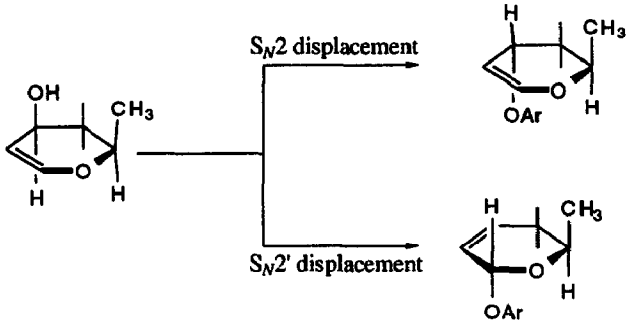
Mitsunobu Reactions of Glycals with Phenoxide Nucleophiles are S_N2'-Selective

Aditya Sobti and Gary A. Sulikowski*

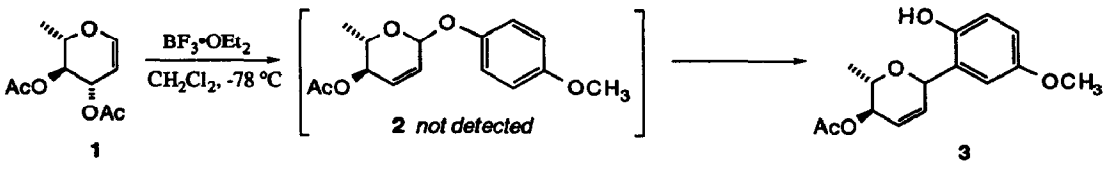
Department of Chemistry, Texas A&M University, College Station, Texas 77843

Abstract: The C^3-hydroxyl group of L-rhamnal (**4**) and D-glucal **7** underwent S_N2'-selective Mitsunobu displacements with substituted phenoxide nucleophiles. These reactions provide access to the corresponding α-arylglycoside.

We required a method for the preparation of α-*O*-aryl glycoside of 2,3,6-trideoxy sugars in connection with planned syntheses of angucycline antibiotics.[1] A direct preparation starts with a substituted glycal and requires an allylic displacement of the C^3-hydroxyl in preference to direct nucleophilic attack. This transformation would serve to eliminate the C^3 substituent and simultaneously introduce an oxidatively removable group at C^1 (i.e. p-methoxyphenyl).

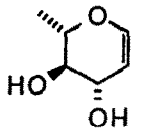
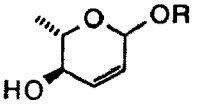
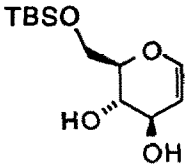
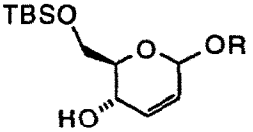
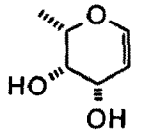
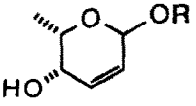


The first approach attempted in this work involved a Ferrier reaction of 3,4-di-*O*-acetylrhamnal **1**.[2] Unfortunately, the only observable product from this reaction was C-arylglycosides **3**; none of the desired *O*-arylglycoside **2** was detected. Apparently, the desired product **2** suffered *O*-to-*C* glycoside rearrangement under the acid conditions of the Ferrier transformation. Similar rearrangements have been reported by other groups.[3] Later, we found that the Ferrier rearrangement was viable using 15 equivalents of 4-methoxyphenol at elevated temperatures in the absence of a Lewis acid.[4] However, a mixture of stereoisomers was formed and isolation of the product was experimentally difficult.



Mitsunobu displacements of allylic hydroxyl groups are generally considered to proceed with high S_N2 regioselectivity.[5] This has been elegantly demonstrated by using an optically active allylic alcohol for which S_N2 and S_N2'-allylic displacements would yield enantiomeric products.[6] Nevertheless, we felt that the natural bias of glycals to undergo allylic substitution in nucleophilic displacements reactions could override the intrinsic preference for direct displacement in Mitsunobu reactions.[7] As illustrated by the results shown in the Table below this reasoning proved to be well founded.

Table 1. Mitsunobu reaction of glycals with substituted phenols.

entry	substrate	reaction conditions	product	yield % (α:β)
1	 **4**	a	 **5** R=*p*-$CH_3OC_6H_4$	80% (α only)
		b	**6** R=*p*-$NO_2C_6H_4$	78% (α only)
2	 **7**	a	 **8** R=*p*-$CH_3OC_6H_4$	55% (α only)
		b	**9** R=*p*-$NO_2C_6H_4$	68% (α only)
3	 **10**	a	 **11**	50% (1:2)

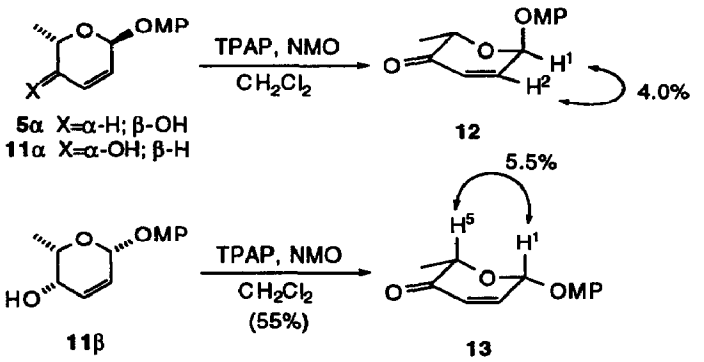
a) *p*-$CH_3OC_6H_4OH$ (1.2 equiv); DEAD (1.6 equiv); Ph_3P (1.1 equiv); CH_2Cl_2, 0 °C

b) *p*-$NO_2C_6H_4OH$ (1.2 equiv); DEAD (1.6 equiv); Ph_3P (1.1 equiv); CH_2Cl_2, 0 °C

The Mitsunobu reaction has found considerable application in the synthesis of aryl- and acylglycosides.[3,8] Two significant observations have been made while employing the Mitsunobu reaction in glycosidic bond formation. First, the displacement of the anomeric hydroxyl group proceeds with inversion of configuration.[8d,f] Secondly, selective displacement of the anomeric hydroxyl group over other hydroxyl groups is possible, thus eliminating the need for protecting group manipulation.[8d] Based upon the second observation we examined the condensation between p-methoxyphenol and L-rhamnal (**4**) without protection of the C^4 hydroxyl group. Dropwise addition of diethyl azodicarboxylate (DEAD) to a solution of p-methoxyphenol and L-rhamnal (**4**) in dichloromethane at 0 °C resulted in full consumption of the starting glycal within 1 h. Following concentration and purification by flash chromatography arylglycoside **5α** was

obtained in 80% yield, no other isomers were isolated.[9,10] In a similar fashion p-nitrophenol was coupled with L-rhamnal (**4**) to provide **9α**.[9] The displacement reaction was then extended to 6-O-t-butyldimethysilyl ether of D-glucal (**7**). While the chemical yield of the displacement eroded in this case, the stereochemical integrity of the reaction remained high providing exclusively the corresponding α-aryl glycosides **8α** and **9α**.[9] In contrast to L-rhamnal (**4**) and silyl protected D-glucal **7**, the condensation of p-methoxyphenol with L-fucal (**10**) produced a 1:2 mixture of **11α** and **11β**.

The stereochemical assignment of the products were determined in the following manner. Tetrapropylperruthenate oxidation of allylic alcohol **5α** provided ketone **12** (61%).[11] Oxidation of the minor isomer from the Mitsunobu coupling of L-fucal (**10**) with p-methoxyphenol also provided **12** (45%).[9,10] On the other hand, oxidation of **11β** provided isomeric ketone **13** (55%).[10,11] The structures of **12** and **13** were assigned based on NMR analysis. In particular, irradiation of the H^1 proton of ketone **12** resulted in a 4.0% nuclear Overhauser enhancement of H^2. While similar irradiation of the H^1 proton in **13** produced a 5.5% nuclear Overhauser enhancement of H^5. Ketones **12** and **13** were therefore assigned α- and β-configurations respectively.



Preparation of methoxy-substituted phenyl glycosides is of particular value since this facilitates subsequent oxidative removal of the aryl substituent if necessary.[12] On the other hand, nitrophenyl glycosides are useful since they are frequently used as synthetic substrates for certain glycosidases and glycosyl transferases.[13] Of particular concern to us, these studies provide a paradigm for synthesis of the trisaccharide fragment of the angucycline antiobiotic PI-080.[1]

Acknowledgments

This work was supported in part by the donors of The Petroleum Research Fund, administered by the American Chemical Society, and the Robert A. Welch Foundation (A-1230). G. A. S. thanks the American Cancer Society for a Junior Faculty Research Award.

References and Notes

1. (a) Kawashima, A.; Kishimura, Y.; Tamai, M.; Hanada, K. *Chem. Pharm. Bull.* **1989**, 37, 3429. (b) Review: Rohr, J; Thiericke, R. *Natural Product Reports* **1992**, *9*, 103.

2. (a) Ferrier, R. *J. Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199-266. (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570. (c) Grynkiewicz, G.; Preibe, W.; Zamojski, Q. *Carbohydr. Res.* **1979**, *68*, 33.
3. (a) Booma, C.; Balasubramanian, K.K. *Tetrahedron Lett.* **1993**, *34*, 6757. (b) Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005.
4. Brakata, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890.
5. Mitsunobu, O. *Synthesis* **1981**, 1.
6. Trost, B. M.; Kondo, Y. *Tetrahedron Lett.* **1991**, *32*, 1613.
7. Examples of S_N2' Mitsunobu Reactions: (a) Farina, V. *Tetrahedron Lett.* **1989**, *30*, 6645. (b) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891. (c) Lumin, S.; Yadagiri, P.; Falck, J. R. *Tetrahedron Lett.* **1988**, *29*, 4237. (d) Charette, A. B.; Cote, B. *Tetrahedron Lett.* **1993**, *34*, 6833.
8. (a) Grynkiewicz, G. *Carbohydr. Res.* **1977**, *53*, C11. (b) Szarek, W. A.; Jarrell, H. C.; Jones, J. K. N. *Carbohydr. Res.* **1977**, *57*, C13. (c) Garegg, P. J.; Iversen, T.; Norberg, T. *Carbohydr. Res.* **1979**, *73*, 313. (d) Smith, A. B., III; Hale, K. J.; Rivero, R. Z. *Tetrahedron Lett.* **1986**, *27*, 5813. (e) Nicolaou, K. C.; Groneberg, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4085. (f) Roush, W. R.; Lin, X-F. *J. Org. Chem.* **1991**, *56*, 5740.
9. The structure assigned to each new compound was in accord with its ^1H and ^{13}C NMR (200 and 50 MHz respectively) spectra, as well as elemental composition data [HRMS (parent ion identification) and/or combustion analysis (± 0.4%)].
10. **5α**: $[\alpha]^D_{20}$ -132.12° (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 3500, 1598 cm^{-1}; ^1H-NMR (200 MHz,$CDCl_3$) δ 7.02 (d, *J* = 9.1 Hz ,2H), 6.87 (d, *J* = 9.2 Hz, 2H), 6.04 (d, *J* = 10.0 Hz, 1H), 5.93 (m,1H), 5.51 (d, *J* = 2.6 Hz, 1H), 3.90 (m, 2H), 3.79 (s, 3H), 2.06 (s, OH, 1H), 1.35 (d, *J* = 5.9 Hz, 3H). ^{13}C-NMR (50 MHz,$CDCl_3$) δ 155.3, 151.8, 134.7, 126.4, 118.8, 114.9, 94.4, 69.8, 69.2, 56.1, 32.0, 18.4, 14.5.
12: $[\alpha]^D_{20}$ -105.74° (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) 1714 cm^{-1}; ^1H-NMR (200 MHz,$CDCl_3$) δ 7.06 (d, *J* = 9.02 Hz, 2H) 6.97 (dd *J* = 3.7, 10.2 Hz, 1H), 6.89 (d, *J* = 9.1 Hz, 2H), 6.23 (d, *J* = 10.1 Hz ,1H), 5.78 (d, *J* = 3.5 Hz, 1H), 4.74 (q, *J* = 6.7 Hz, 1H), 3.80 (s ,3H), 1.43 (d , *J* = 6.8 Hz, 3H). ^{13}C-NMR (50 MHz,$CDCl_3$) δ 196.5, 155.2, 150.9, 142.3, 127.6, 118.0, 114.5, 92.6, 70.9, 55.5, 15.1.
13: $[\alpha]^D_{20}$ +84.13° (*c* 23, $CHCl_3$); IR ($CHCl_3$) 1702 cm^{-1}; ^1H-NMR (200 MHz,$CDCl_3$) δ 7.02 (d, *J* = 8.9 Hz, 2H), 6.97 (m, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.22 (d, *J* = 10.3 Hz ,1H), 5.85 (s, 1H), 4.34 (q, *J* = 7.0 Hz ,1H), 3.76 (s, 3H), 1.50 (d, *J* = 6.96 Hz, 3H). ^{13}C-NMR (50 MHz,$CDCl_3$) δ 196.3, 155.1, 150.5, 144.7, 127.8, 117.9, 114.3, 93.9, 75.3, 55.4, 17.8.
11. Griffith, W. P.; Ley, S. V.; Whicombe, G. P.; White, A. D. *JCS Chem. Commun.* **1987**, 1625.
12. Slaghek, T. M.; Hypponen, T. K.; Ogawa, T.; Kamerling, J. P.; Vliegenthart, J. F. G. *Tetrahedron Lett.* **1993**, *49*, 7939.
13. Nilson, K. G. I. In *Opportunities in Biotransformations*; Copping, L. G.; Martin, R. E.; Pickett, Z. A.; Bucke, C.; Bunch, A. W., Eds.; Elsvier: Amsterdam, **1990**, pp 131-139.

(*Received in USA* 15 *February* 1994; *revised* 25 *March* 1994; *accepted* 31 *March* 1994)