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Addition of Allylstannanes to Glycal Epoxides. A Diastereoselective Approach to β-*C*-Glycosidation

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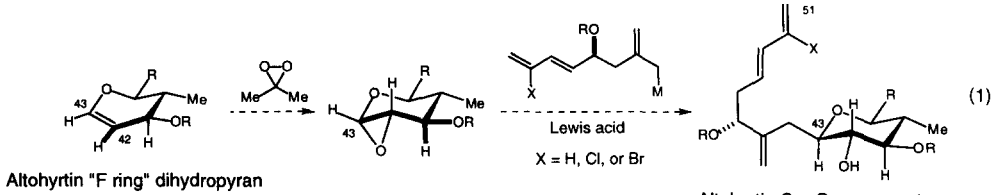
Abstract: A new method for the synthesis of β-*C*-allyl glycosides has been developed for use in the synthesis of the spongipyran macrolides. Functionalized dihydropyrans are transformed to *cis* tetrahydropyrans via a two step process: i) epoxidation using dimethyldioxirane and ii) Lewis acid mediated epoxide opening with allylstannanes as nucleophiles. This protocol, which can be successfully applied to complex systems, augments the limited body of methodology available for the preparation of β-configured *C*-glycosides.

The synthesis of *C*-glycosides has received considerable attention as a consequence of the importance of this structural motif in natural product synthesis and in the preparation of pharmaceutically useful carbohydrate analogs.[1] Among the methods for the preparation of *C*-glycosides, the addition of carbon nucleophiles to suitably activated anomeric electrophiles has been the most widely investigated. While α-stereoselective additions to anomeric electrophiles are well documented, the synthesis of β-*C*-glycosides in this manner remains a significant challenge.[2] In conjunction with our ongoing efforts directed toward the spongipyran macrolide altohyrtin C,[3] we have developed an effective method for the β-selective addition of allylstannanes to glycal epoxides. Our work finds precedent in chemistry developed by Danishefsky for the use of dihydropyrans as glycosyl donors.[4] We sought to develop an analogous epoxide opening process applicable to allylic carbon nucleophiles with possible applications to the construction of the altohyrtin C_{43}-C_{44} bond construction (eq. 1).

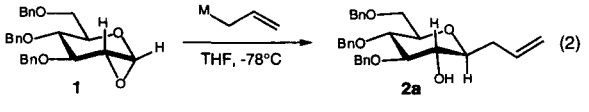


Altohyrtin "F ring" dihydropyran

Altohyrtin C_{39}-C_{51} segment

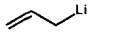
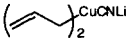
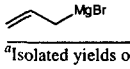
(1)

Initial allylation experiments[5] were performed on glucal epoxide **1**[4] (eq. 2; Table 1). While allylmagnesium bromide provided the desired β-*C*-glycoside (**2**) in 75% yield,[6,7] the corresponding allyllithium and allyl cuprate reagents were less effective. Diminished yields in these cases were attributed to metal-mediated epoxide rearrangements and oligosaccharide formation.



1 **2a** (2)

Table 1. Allylmetal Additions to Epoxide **1** (eq 2)

nucleophile	conditions	yield **2a**[a]
	THF, -78 °C	25%
	THF, -78 °C	43%
	THF, -78 °C	75%

[a]Isolated yields of β addition product are reported.

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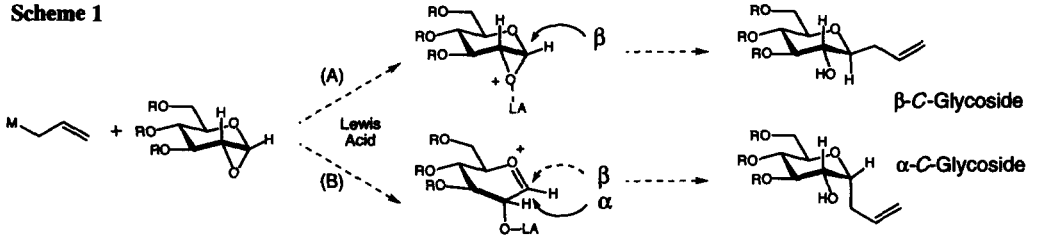
Given the difficulty of preparing allylic Grignard reagents in good yields,[8] we did not consider Grignard addition compatible with our desire to use this reaction in complex fragment coupling applications. Synthetically accessible and isolable allylsilanes or allylstannanes were instead identified as ideal candidates for development. Since these nucleophiles did not undergo spontaneous addition to epoxide **1**,[9] the use of Lewis acids as promoters for the reaction was investigated. The potential impact of Lewis acid promotion on anomeric selectivity is illustrated in Scheme 1. In the desired case (path A), a weakly activating Lewis acid labilizes the anomeric C-O bond and promotes displacement with inversion. Stronger Lewis acids, however, are expected to promote oxonium formation (path B), which will be followed by α addition.[10]

Scheme 1



Our results support this interpretation (eq. 3; Table 2). Methallyl- and allyl-tributylstannane were found to be viable nucleophiles in the presence of several Lewis acids. While stronger acids ($TiCl_4$, $SnCl_4$) afforded higher proportions of α products and low yields, use of silyl triflates provided the desired *C*-glycoside in moderate yields and reasonable β selectivities; the less reactive TESOTf gave a higher β ratio than TMSOTf. Use of the slightly weaker Lewis acid tributylstannyl triflate further improved the reaction, delivering essentially complete β stereoselectivity.

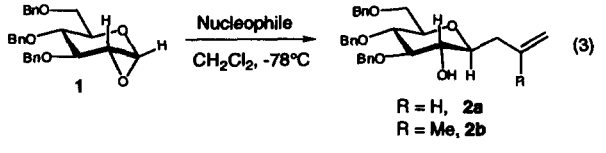
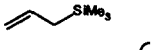
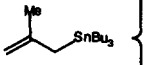
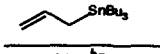


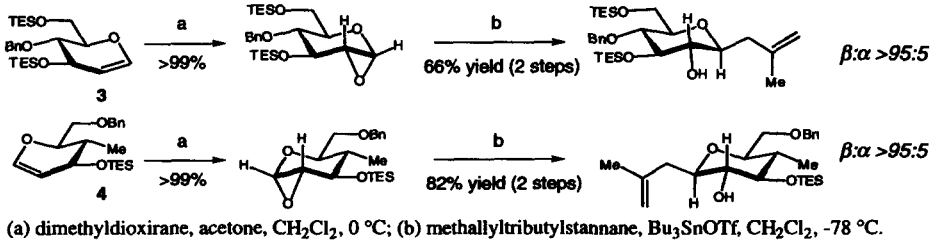
Table 2. Lewis acid-Mediated Allylstannane additions (eq 3)

nucleophile	Lewis Acid	β:α	yield[a]
	TMSOTf	--	0%
	TMSOTf	3.5:1[b]	51%[d]
	TESOTf	6.7:1[c]	56%[d]
	Bu_3SnOTf	**>95:5[b]**	**63%**
	$TiCl_4$	--	0%
	$SnCl_4$	1.4:1[c]	3%
	**Bu_3SnOTf**	**>95:5[b]**	**57%**

[a]Isolated yields. [b]Ratio determined by ^1H NMR. [c]Ratio determined by HPLC. [d]Isolated yield after acidic deprotection of O-silyl adduct.

Variation of the coupling partners serves to illustrate the generality of the tributylstannyl triflate mediated epoxide opening. Dihydropyrans **3** and **4** (corresponding to the altohyrtin F ring) underwent dimethyldioxirane[11]-mediated epoxidation and methallylstannane addition with high β selectivity in good yield (Scheme 2). No evidence of secondary or primary TES ether cleavage was observed.

Scheme 2



Conditions: (a) dimethyldioxirane, acetone, CH_2Cl_2, 0 °C; (b) methallyltributylstannane, Bu_3SnOTf, CH_2Cl_2, -78 °C.

The complex allylstannanes **6** corresponding to the altohyrtin C sidechain were also found to be compatible with the reaction conditions (eq. 4; Table 3). A dependence on the allylstannane's hydroxyl protecting group was noted in these cases. All variations provided high β:α selectivities, but the isolated yields differed significantly. More sterically demanding alcohol protecting groups generally afforded lower yields (entries A-C),[12] while the electronically deactivating acetate protecting group also gave poor results (entry D). Use of higher concentrations of allylstannane also improved the reaction efficiency (entry E vs. entry C), supporting the interpretation that the rate of stannane addition must compete with the rate of nonproductive decomposition of the epoxide. Since the unreacted allylstannanes could be quantitatively recovered after flash chromatography, the use of multiple equivalents of stannane was regularly employed; the optimal protocol entailed treatment of **5** with tributylstannyl triflate and 16 equivalents of TMS protected allylstannane **6c**.[13]

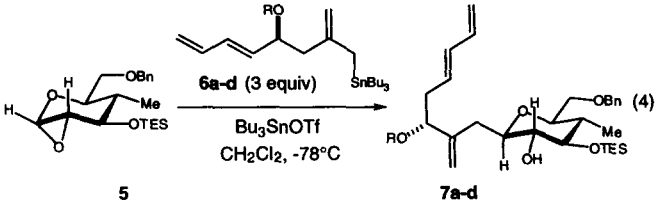


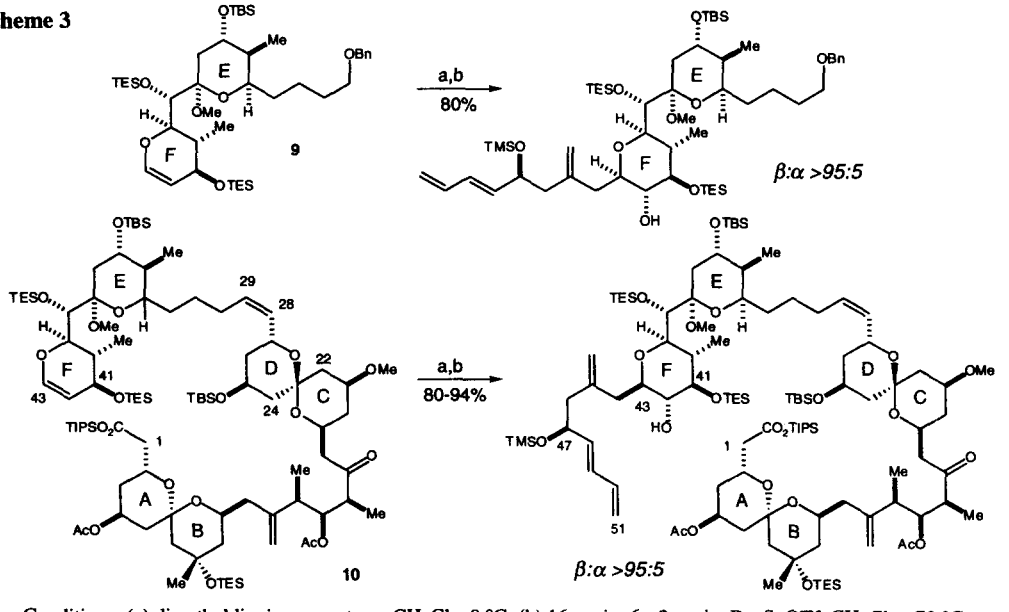
Table 3. Allylstannane structure vs. Reaction Efficiency (eq 4)

entry	R	β:α	yield[a]
A	TES (**7a**)	>95:5	35%
B	MOP (**7b**)	>95:5	48%
C	TMS (**7c**)	>95:5	65%
D	Ac (**7d**)	>95:5	25%
E	TMS[b] (**7c**)	>95:5	75%

[a] Isolated yields are reported. [b] 16 equivalents of allylstannane were used.

The mild nature of this transformation is further emphasized by the complex fragment couplings shown in Scheme 3. Altohyrtin intermediate **9**[3] was an excellent substrate for the glycosidation protocol despite a documented propensity toward elimination of the E-ring lactol methyl ether. The fully functionalized altohyrtin precursor **10**[3] likewise underwent epoxidation and sidechain addition without competing oxidation of the C_{28}-C_{29} olefin or epimerization of the Lewis acid-sensitive C_{23} spiroketal center. These results indicate that the protocol reported here should be applicable in a variety of multifunctional settings.

Scheme 3



Conditions: (a) dimethyldioxirane, acetone, CH_2Cl_2, 0 °C; (b) 16 equiv. **6c**, 2 equiv. Bu_3SnOTf, CH_2Cl_2, -78 °C.

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References and Footnotes

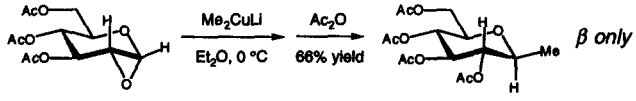
1) Recent reviews on *C*-glycosides: (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545-8599; (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Oxford, 1995.

2) A few examples have been reported; β-*C*-glycosides from anomeric acetates: (a) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *39*, 6815-6818; via episulfonium ions: (b) Smolyakova, I. P.; Smit, W. A.; Zal'chenko, E. A.; Chizhov, O. S.; Shashkov, A. S. *Tetrahedron Lett.* **1993**, *34*, 3047-3050; (c) Kawakami, H.; Ebata, T.; Koseki, K.; Okano, K.; Matsumoto, K.; Matsushita, H. *Heterocycles* **1993**, *36*, 2765-2776; via (putative) intermediate glycal epoxides: (d) Shulman, M. L.; Shiyan, S. D.; Khorlin, A. Y. *Carbohydrate Research* **1974**, *33*, 229-235; (e) Hanessian, S.; Liak, T. J.; Dixit, D. M. *Carbohydrate Research* **1981**, *88*, C14-C19.

3) (a) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angewandte Chem. Int. Ed. Engl.* **1997**, *36*, 2744-2748; (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Phar. Bull.* **1993**, *41*, 989-991.

4) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.

5) These experiments are precedented by a single example of β-selective cuprate addition to Brigl's anhydride: Bellosta, V.; Czernecki, S. *J. Chem. Soc. Chem. Comm.* **1989**, 199-200.



6) This result has recently been reported independently: Best, W. M.; Ferro, V.; Harle, J.; Stick, R. V.; Tilbrook, D. M., G. *Aust. J. Chem.* **1997**, *50*, 463-472.

7) The assignment of β stereochemistry for all adducts was based on difference NOE data and analysis of ^{1}H NMR coupling constants.

8) Oppolzer, W.; Kundig, E. P.; Bishop, P. M.; Perret, C. *Tetrahedron Lett.* **1982**, *23*, 3901-3904; Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* **1984**, *25*, 3305-3308.

9) Methallyl tributylstannane and epoxide **1** do not react in DMF at room temperature.

10) Lewis, M. D.; Cha, K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976-4978.

11) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847-2853.

12) We speculate that steric congestion around the reacting center lowers the nucleophilicity of the allylstannane. The consequent failure of the allylstannane addition to compete with nonproductive epoxide decomposition is presumed to be responsible for the lower yields observed for larger allylstannane protecting groups. Results in a similar system (epoxide **1**) indicated that TBS (21% yield) and TBDPS (0% yield) protecting groups followed this trend.

13) Representative experimental procedure: A solution of 4.2 mg (0.012 mmol) dihydropyran **4** in 2 mL CH_2Cl_2 was cooled to 0 °C. A solution of dimethyldioxirane in acetone (reference 11) was added portionwise via cannula until TLC analysis indicated complete consumption of the dihydropyran. The reaction was then concentrated under a steady stream of nitrogen. To the concentrated epoxide was added allylstannane **6c** (97.6 mg, 0.196 mmol, 16.2 equiv) in 0.600 mL CH_2Cl_2. The resulting solution was cooled to -78 °C, and a room temperature solution of Bu_3SnOTf (10.6 mg, 0.024 mmol, 2 equiv) in 0.400 mL CH_2Cl_2 was added rapidly via cannula (0.200 mL CH_2Cl_2 rinse). The reaction was stirred for 20 min at -78 °C, then quenched by the addition of 0.250 mL triethylamine. The reaction was diluted with saturated aqueous $NaHCO_3$ and Et_2O and warmed to room temperature. The organic layer was separated and washed with saturated aqueous sodium chloride, then dried over sodium sulfate, filtered, and concentrated. Flash chromatography (silica gel, 1.5 x 10 cm, linear gradient, 5-10% ethyl acetate/hexanes) provided adduct **7c** (5.2 mg, 75%) and recovered allylstannane **6c** (89.7 mg, 0.179 mmol, 15 equiv). Data for **7c**: $[\alpha]^{23}_D$ +9.9 (*c* 0.27, CH_2Cl_2); IR (neat) 3490, 2954, 2876, 1604, 1453, 1414, 1367, 1250, 1074, 1005, 951, 900, 842, 741, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H, Ar*H*); 6.29 (ddd, *J* = 16.9, 10.3, 10.3 Hz, 1H, =CH-C*H*=CH$_2$); 6.15 (dd, *J* = 15.2, 10.6 Hz, 1H, =C*H*-CH=CH$_2$); 5.69 (dd, *J* = 15.2, 6.2 Hz, 1H, C*H*=CH-CH=CH$_2$); 5.15 (d, *J* = 16.8 Hz, one of CH=C*H*$_2$); 5.04 (d, *J* = 10.0 Hz, one of CH=C*H*$_2$); 4.97 (s, 1H, one of -C(=C*H*$_2$)-R); 4.87 (s, 1H, one of -C(=C*H*$_2$)-R); 4.59 (d, *J* = 12.2 Hz, 1H, one of C*H*$_2$Ph); 4.52 (d, *J* = 12.2 Hz, 1H, one of C*H*$_2$Ph); 4.32 (dd, *J* = 12.6, 6.3 Hz, 1H, C*H*OTMS); 3.64 (dd, *J* = 11.0, 1.9 Hz, one of C*H*$_2$OBn); 3.52 (dd, *J* = 11.0, 4.9 Hz, one of C*H*$_2$OBn); 3.31 (dt, *J* = 8.4, 3.1 Hz, 1H, -C*H*CH$_2$C(=CH$_2$)CH$_2$CHOTMS-); 3.24-3.16 (m, 3H, C*H*OH, C*H*OTES, C*H*CH$_2$OBn); 2.58 (dd, *J* = 14.7, 2.8 Hz, 1H, one of C*H*$_2$C(=CH$_2$)CH$_2$CHOTMS-); 2.36-2.29 (m, 2H, C(=CH$_2$)C*H*$_2$CHOTMS-); 2.26 (dd, *J* = 14.7, 8.1 Hz, 1H, one of C*H*$_2$C(=CH$_2$)-CH$_2$CHOTMS-); 2.03 (d, *J* = 2.4 Hz, 1H, CHO*H*); 1.74-1.66 (m, 1H, C*H*CH$_3$); 0.98 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$); 0.91 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$); 0.67 (q, *J* = 7.9 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$); 0.10 (s, 9H, Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 138.5, 136.9, 136.6, 129.9, 128.3, 127.6, 127.5, 116.7, 114.6, 80.8, 80.5, 78.5, 76.1, 73.4, 71.7, 71.0, 45.2, 39.5, 39.2, 13.3, 7.0, 5.5, 0.3; Exact mass calcd. for $C_{32}H_{54}O_5Si_2Na$: 597.3408; found: 597.3433 (FAB, *m*-nitrobenzyl alcohol, NaI added).