JOC*Note*

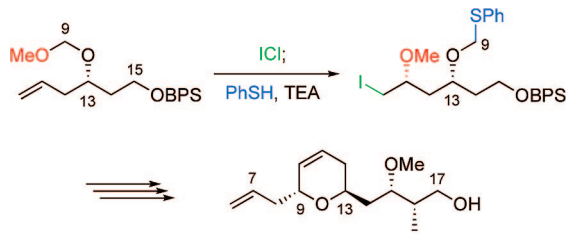
Electrophile-Induced Ether Transfer: Stereoselective Synthesis of 2,6-Disubstituted-3,4-Dihydropyrans

Rendy Kartika, Jeffrey D. Frein, and Richard E. Taylor*

Department of Chemistry and Biochemistry and the Walther Cancer Research Center, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, Indiana 46556

taylor.61@nd.edu

Received April 2, 2008

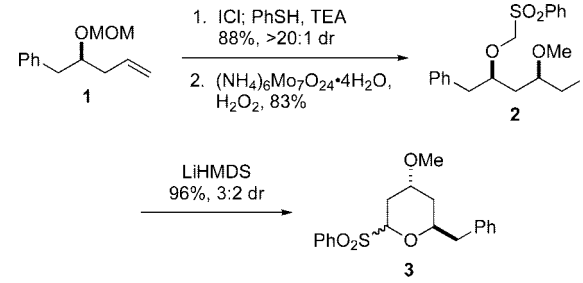


C7-C17 Fragment of Swinholide A

Stereoselective synthesis of *trans*-2,6-disubstituted-3,4-dihydropyrans has been achieved from a simple homoallylic alkoxyether via a three-step sequence: electrophile-induced ether transfer, cyclization, and functionalization, which is highlighted by a rare example of Ferrier rearrangement of allylic ether. This methodology was successfully implemented for the asymmetric synthesis of a C7−C17 fragment of swinholide A.

Heterocycles are the most common ring system found in polyketides. Their presence adds a significant degree of conformational rigidity and are thus likely to be critical to the pharmacophore of biologically active natural products. 2,6-Disubstituted pyrans with a variety of oxidation levels represent a particularly common motif. A 3,4-dihydro- varient appears in several biologically important polyketides, such as the swinholides,[1] scytophycins,[2] and misakinolides.[3] In line with our recent efforts in the development of synthetic methodology for the stereoselective production of polyketide synthetic fragments,[4,5] we present our approach to *trans*-2,6-disubstituted-3,4-dihydropyrans highlighted by our recently developed three-step sequence to oxygen heterocycles: electrophile-induced ether transfer, cyclization, and functionalization.

SCHEME 1. Efficient Production of Sulfonyl Pyran 3



In our recent communication, we described an efficient and robust production of stereochemically rich 2-sulfone tetrahydropyran **3** from a simple alkoxyether protected homoallylic alcohol **1**.[5a] Treatment of **1** with iodine monochloride followed by trapping the corresponding chloromethyl ether intermediate[4] with thiophenol and subsequent oxidation produced sulfonyl ether **2** in high yield with excellent *syn* stereocontrol. Treatment of **2** with LiHMDS led to efficient cyclization which produced anomeric sulfonyl pyran **3** as a mixture of diastereomers, Scheme 1.

With sulfonyl pyran **3** in hand, we envisioned a two-step functionalization to access key oxocarbonium ion intermediate **A** on a path to 2,6-*trans*-dihyropyrans **5**, Table 1. The elimination of the anomeric sulfone using a mixture of magnesium bromide and triethylamine assisted by ultrasound cleanly afforded glycal **4** in 95% yield as precedented by the previous work of Ley and co-workers.[6,7] As demonstrated by several examples in Table 1, the ionization of glycal **4** with TMSOTf in CH_2Cl_2 followed addition of various nuclophiles provided the Ferrier rearrangement products **5** in excellent yield and diastereoselectivity.[8] For example, when allylic silanes were used as nucleophiles, dihydropyrans **5a** and **5b** were produced in excellent yields and as a single diastereomer under both catalytic and stoichiometric amounts of TMSOTf (entries 1−3).[9] Other nucleophiles such as organozinc, organotin (entries 4−6), and enol silanes (entries 7 and 8) also provided products **5c**−**5g** in high yield and diastereoselectivity. Interestingly, slight erosion in diastereoselectivity was observed with a bulkier nucleophile (entry

(1) (a) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511. (b) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963. (c) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Yamashita, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2409. (d) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710. (e) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629. (f) Kobayashi, M.; Tanaka, J.; Katori, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2960. (g) Tsukamoto, S.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3185.

(2) (a) Moore, R. E.; Patterson, G. M. L.; Mynderse, J. S.; Barchi, J.; Norton, T. R.; Furusawa, E.; Furusawa, S. *Pure Appl. Chem.* **1986**, *58*, 263. (b) Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C. F.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300.

(3) (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Sakai, R.; Higa, T.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 6225. (b) Tanaka, J.; Higa, T.; Kobayashi, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2967.

(4) Liu, K.; Taylor, R. E.; Kartika, R. *Org. Lett.* **2006**, *8*, 5393.

(5) (a) Kartika, R.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 6874. (b) Kartika, R.; Taylor, R. E. *Heterocycles* **2007**, *74*, 447.

(6) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293.

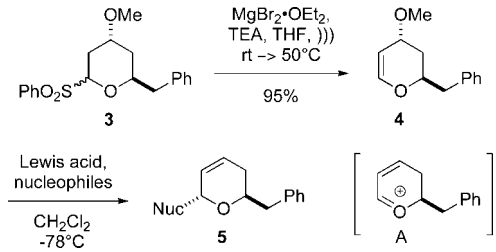
(7) Other established strategies for the preparation of glycals: (a) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380. (b) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082; also, see references 12–14.

(8) Recent reviews in Ferrier Rearrangement: Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153.

(9) The 2,6-*trans* stereoconfiguration of dihydropyran **5a** and **5h** were unambigously assigned based on ROESY experiment.

10.1021/jo800704d CCC: $40.75
Published on Web 06/21/2008

TABLE 1. Preparation of 2,6-*trans*-3,4-Dihydropyran 5



Entry	Lewis Acid	Nucleophile	Product	Yield[a] (d.r.)[b]
1	TMSOTf (2 eq)	TMS	**5a**	91% (>20:1)
2	TMSOTf (0.1 eq)	TMS	**5a**	90% (>20:1)
3	TMSOTf (2 eq)	TMS	**5b**	91% (>20:1)
4	TMSOTf (2 eq)	Et_2Zn	**5c**	89% (>20:1)
5	TMSOTf (2 eq)	$SnBu_3$	**5d**	96% (>20:1)
6	TMSOTf (3 eq)	$SnBu_3$	**5e**	78% (10:1)
7	TMSOTf (3 eq)	OTBS, Ph	**5f**	96% (>20:1)
8	TMSOTf (3 eq)	OTBS	**5g**	95% (>20:1)
9	TMSOTf (3 eq)	OTBS, MeO	**5h**	41%[c] (1:1)
10	BF_3•OEt_2 (3 eq)[d]	OTBS, MeO	**5h**	67%[e] (3.6:1)

[a] Yield was reported from the isolation of the major diastereomer. [b] Diasteromeric ratio was determined by ^{1}H NMR integration of the crude reaction mixture. [c] Minor 2,6-cis diastereomer was isolated in 40% yield. [d] Reaction was carried out in toluene. [e] Minor 2,6-cis diastereomer was isolated in 15% yield.

6). Furthermore, when a silyl ketene acetal was employed, dihydropyran **5h** was produced in a stereorandom fashion. Interestingly, the diastereoelectivity could be slightly improved to 3.6:1 if the activation was carried out with BF_3•OEt_2 in toluene, (entries 9 and 10). The exact origin of this unexpected stereoselectivity is unclear to us, but it appears the high reactivity of silyl ketene acetal clearly affects stereoselectivity. Similar observation has been reported by Paterson and co-workers.[10] It is also important to note that with enol silanes and ketene acetals, three equivalents of Lewis acid were required for the reaction to achieve completion (entries 7−10). We speculate that the stronger Lewis basicity of the newly generated carbonyl group compared to that of the starting ether readily competed for the Lewis acid.

In the typical Ferrier rearrangement process, an allylic acetate or tosylate is typically employed as the nucleofuge. In fact, to the best of our knowledge, the use of a secondary allylic ether for this purpose is not precedented most likely due to its poor leaving group ability and the fact that its relatively weak Lewis basicity may cause slow, inefficient ionization.[11] However, in our case, glycal **4** underwent rapid ionization. This reactivity is facilitated by the pseudoaxial orientation of the methoxy group,[12] a stereochemistry which is readily installed in our ether transfer reaction, where the σ^* antibonding orbital is oriented relatively parallel to the glycal π bond. The 2,6-*trans* stereochemistry was presumably assembled via subsequent axial delivery of nucleophiles to the newly generated oxocarbonium ion upon activation.[13] Since the observed diastereoselectivity eroded with bulkier nucleophiles, a contact-ion pair system might be involved in our system that could potentially hinder axial delivery.

To demonstrate the applicability of our method to complex molecule syntheses, we became interested in targeting the marine polyketide, swinholide A, particularly the C7−C17 dihydropyran region represented as synthetic fragment **6**.[14–16]

Our approach to fragment **6** would begin with readily accessible, enantiomerically pure homoallylic alcohol **7**,[17] Figure 1.

(10) (a) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261. (b) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413.

(11) Ley and co-workers have demonstrated similar Ferrier rearrangement using a tertiary allylic ether for the construction of the spiroketal moiety in okadaic acid: Ley, S. V.; Humphries, A. C.; Eick, H.; Downham, R.; Ross, A. R.; Boyce, R. J.; Pavey, J. B. J.; Pietruszka, J. *J. Chem. Soc., Perkin Trans.1* **1998**, 3907.

(12) The conformation of dihydropyran **4** was deduced by ^{1}H NMR coupling-constant analysis.

(13) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383.

(14) Nicolaou's total synthesis of swinholide A: (a) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1147. (b) Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Patron, A. P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1151. (c) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**, *118*, 3059. (d) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem.−Eur. J.* **1996**, *2*, 847.

(15) Paterson's total synthesis of swinholide A: (a) Paterson, I.; Cumming, J. *Tetrahedron Lett.* **1992**, *33*, 2847. (b) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261. (c) Paterson, I.; Yeung, K. *Tetrahedron Lett.* **1993**, *34*, 5347. (d) Paterson, I.; Smith, J. D. *Tetrahedron Lett.* **1993**, *34*, 5354. (e) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 3405. (f) Paterson, I.; Smith, J. D.; Ward, R. A.; Cumming, J. G. *J. Am. Chem. Soc.* **1994**, *116*, 2615. (g) Paterson, I.; Yeung, K.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (h) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (i) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (j) Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K. *Tetrahedron* **1995**, *51*, 9437. (k) Paterson, I.; Yeung, K.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9467.

(16) Nakata's synthetic approach to preswinholide A: (a) Nakata, T.; Komatsu, T.; Nagasawa, K. *Chem. Rev. Bull.* **1994**, *42*, 2403. (b) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 8225. (c) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6881. (d) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6885.

(17) Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6567.

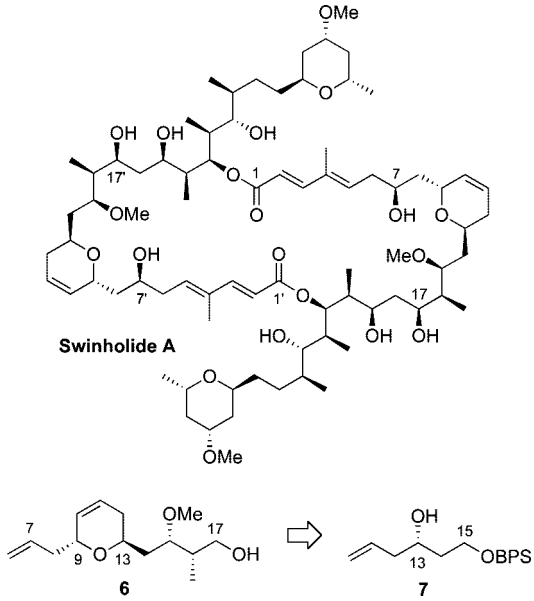


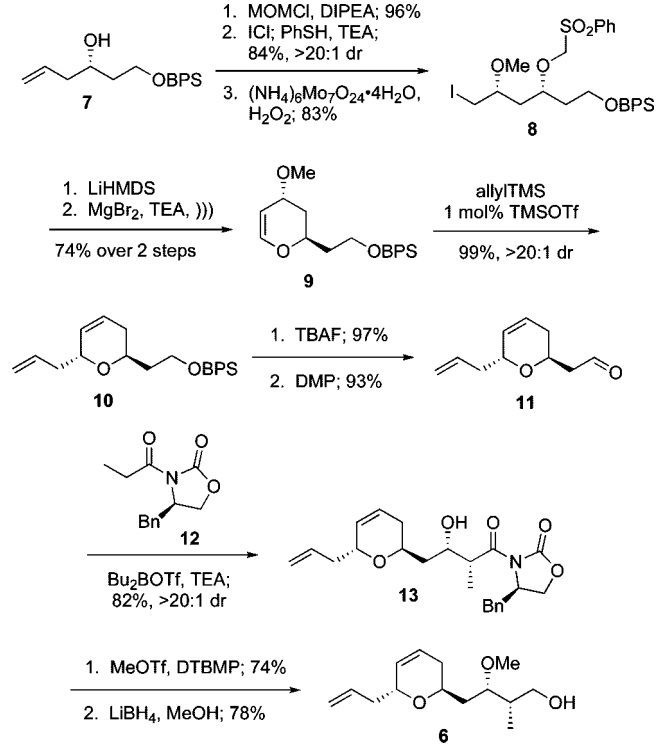
FIGURE 1. C1−C17 fragment of swinholide A.

After protecting alcohol **7** as a MOM ether, the ether-transfer reaction with thiophenol−triethylamine workup, and subsequent oxidation afforded sulfonylether **8** in good yield with high stereocontrol. LiHMDS mediated cyclization followed by elimination of the anomeric sulfone under $MgBr_2$ and TEA afforded 2,3-dihydropyran **9** in 74% yield over two steps. Exposure of **9** to the Ferrier reaction conditions with allyltrimethylsilane and very low catalyst loading of TMSOTf produced 3,4-dihydropyran **10** in nearly quantitative yield and as a single diastereomer. Removal of the BPS ether with TBAF unmasked the primary alcohol which was then oxidized with Dess-Martin periodinane[18] to aldehyde **11**. Both steps proceeded in high yields. Aldehyde **11** was then subjected to a *syn*-aldol reaction with oxazolidinone **12** under Evans' protocol[19] to afford aldol adduct **13** in 82% yield. Subsequent *O*-methylation[20] followed by reductive removal of the auxiliary completed our synthetic route to dihydropyran **6**. The spectroscopic analyses of fragment **6** were in a complete agreement to those reported by Nicolaou and coworkers.[14d]

In contrast to traditional methods, our ether transfer chemistry provides direct access to orthogonally protected *syn*-1,3-diol structural units. The method has now been applied to both acyclic as well as pyran fragments common to polyketides. The current strategy is highlighted by electrophile-induced ether transfer reaction which subsequently installs the functionality with the requisite stereochemistry for the rare examples of allylic ether Ferrier rearrangement to provide 2,6-disubstituted-3,4-dihydropyrans. The broad scope of the method and scalability is demonstrated by its successful application to the construction of C7−C17 fragment of swinholide A. Further applications and extensions of the methodology are currently ongoing in our laboratory and will be reported in due course.

(18) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(19) Gage, J. R.; Evans, D. A. *Org. Syn.* **1990**, *68*, 83.
(20) Mitchell, I. S.; Pattenden, G.; Stonehouse, J. *Org. Biomol. Chem.* **2005**, *3*, 4412.

SCHEME 2. Asymmetric Synthesis to Fragment 6



Experimental Section

Representative Procedures for the Ferrier Rearrangement of Glycal 4 with Allyltrimethylsilane. Dihydropyran **4** (100 mg, 0.489 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to −78 °C. After addition of allyltrimethylsilane (0.23 mL, 1.47 mmol), a freshly prepared 1 M solution of TMSOTf buffered with oven-dried solid $NaHCO_3$ (0.98 mL, 0.98 mmol) was then added dropwise. The reaction mixture was stirred for 5 min and then quenched with phosphate buffer (pH 7.00, 20 mL). After separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were then combined, dried over $MgSO_4$, and concentrated under vacuum. ^{1}H NMR of the crude reaction mixture indicated >20:1 diastereomeric ratio. The crude material was purified with silica gel column using 95:5 hexanes: EtOAc solvent system to give the Ferrier rearrangement product **5a** as clear oil in 91% yield (95.0 mg, 0.443 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.31 − 7.28 (2H, m), 7.25 − 7.20 (3H, m), 5.82 (1H, m), 5.78 − 5.70 (2H, m), 5.01 (1H, m), 4.98 (1H, m), 4.25 (1H, m), 3.95 (1H, dddd, J = 6.5, 6.5, 6.0, 6.0 Hz), 2.92 (1H, dd, J = 13.5, 7.0 Hz), 2.75 (1H, dd, J = 13.5, 6.0 Hz), 2.36 (1H, m), 2.23 (1H, m), 2.02 − 1.98 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 138.7, 134.8, 129.3, 129.2, 128.2, 126.1, 124.1, 116.7, 72.5, 69.1, 41.8, 38.8, 30.0. IR (cm^{-1}): f = 3064, 3030, 2924, 1496, 1455, 1075, 914, 700. HRMS-FAB $(M - H)^+$ = 213.1279 calculated for $C_{15}H_{17}O$, experimental = 213.1279.

Acknowledgment. R.K. thanks the University of Notre Dame for the financial support through the Reilly Fellowship award. J.D.F. is a Walther Cancer Research Center postdoctoral fellow.

Supporting Information Available: Full experimental and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800704D