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Electrophile-Induced Ether Transfer: A New Approach to Polyketide Structural Units

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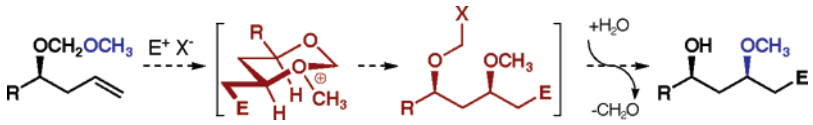
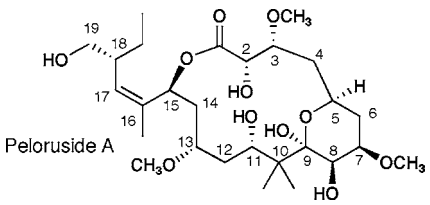
ABSTRACT



A strategically novel approach to the formation of *syn*-1,3-diol mono- and diethers through electrophilic activation of homoallylic alkoxymethyl ethers has been developed. The resulting polyketide-like synthetic fragments are generated in good yield and with excellent stereocontrol. A chairlike transition state is proposed to account for the high stereoselectivity. Varying the conditions of the reaction workup results in the efficient generation of mono- and diether containing structural units common to polyketide natural products.

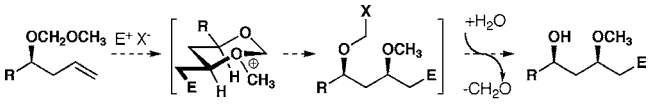
Polyketides represent an important class of natural products due to their diverse biological activity. Numerous polyketide natural products contain methyl ether functionality generated by either methoxymalonyl extender units or a selective *O*-methyl transferase associated with the PKS gene cluster. Peloruside A, a representative example that has received significant, recent, synthetic interest,[1,2] contains three such methyl ethers. Unfortunately, current synthetic methods for ether generation lack the selectivity of evolved proteins. Thus, discrete steps for generating a hydroxyl stereogenic center and subsequent methylation are typically bracketed by additional protecting-group manipulation steps.



A practical solution to this problem would utilize methanol as a coupling partner, but classic intermolecular iodoetherifications are unlikely to be stereo- and/or regioselective. However, the repeating pattern of 1,3-oxygenation, common to polyketides, offers the opportunity to exploit intramolecular delivery. Herein, we report a practical solution to the methyl ether problem associated with the synthesis of many polyketide natural products. Moreover, the new chemistry presented offers additional opportunities for the development of strategically novel approaches to the synthesis of structural units common to polyketide natural products.

The general approach is outlined in Scheme 1. A readily

Scheme 1. Electrophile-Induced Ether Transfer: General Strategy



available homoallylic alcohol, protected as a methoxymethyl ether (MOM), will be subjected to electrophilic activation conditions, E^+ (e.g., I_2, IBr, ICl, NIS, PhSeCl, etc.). On the basis of related cyclizations of homoallylic carbonates,[3] we expected formation of intermediate oxonium ion **2a**, through a chairlike transition state, leading to halomethyl ether **2b**.

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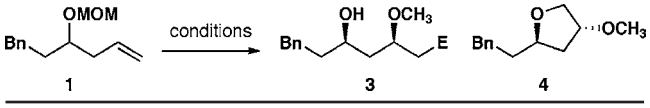
Hydrolysis would then provide a *syn*-1,3-diol monoether **3**. In contrast to current technology, the stereochemistry would be generated simultaneous to the ether functionality.[4,5]

The results of the initial exploration of the ether-transfer concept using a variety of electrophilic conditions are listed in Table 1. Methoxymethyl-protected homoallylic alcohol **1** was prepared in two steps in racemic form from commercially available materials. Toluene was shown to be the most suitable solvent. The choice of activation reagent was also critical in minimizing the formation of an alternative cyclization product, tetrahydrofuran **4**. Entry 8 demonstrated that methoxy transfer could be successfully accomplished in both high yield and high diastereoselectivity.[6]

Table 1. Electrophile-Induced Methoxy Transfer: Initial Exploration



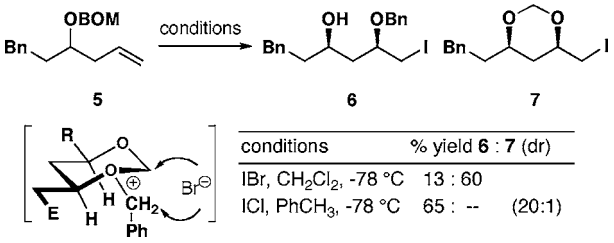
1 3 4

entry	conditions; workup	E	yield **3** (dr)[a]	yield **4**[b]
1	PhSeCl, $PhCH_3$, −78 °C	PhSe	not observed	not observed
2	$I(coll)_2PF_6$, CH_2Cl_2, rt	I	trace	not observed
3	IBr, $PhCH_3$, −78 °C; Na_2SO_3, H_2O	I	54% (25:1)	26%
4	ICl, CH_2Cl_2, −78 °C; Na_2SO_3, H_2O	I	65% (8:1)	21%
5	ICl, $PhCH_3$, −78 °C; Na_2SO_3, H_2O	I	59% (15:1)	not observed
6	ICl, $PhCH_3$, −78 °C; $NaHSO_3$, H_2O	I	76% (15:1)	not observed
7	ICl, $PhCH_3$, −78 °C; NH_4OH	I	73% (14:1)	not observed
8	ICl, $PhCH_3$, −78 °C; DIPA, H_2O	I	87% (12:1)	not observed

[a] Diastereomeric ratio was determined by ^1H and ^{13}C NMR.[6a] [b] The stereochemistry of **4** was confirmed by independent synthesis from **3** (see Supporting Information).

Presumably, related ethers would transfer efficiently as long as steric or electronic differences compared to the methyl substrate were insignificant. In fact, the benzyloxymethyl substrate **5**, readily prepared from commercially available BOMCl, underwent efficient benzyl ether transfer (Scheme 2).[6b,c] This process significantly expands the scope of the reaction because, in contrast to methyl ethers, benzyl groups can be easily removed by hydrogenolysis. Thus, the ether transfer method provides access to orthogonally protected *syn*-1,3-diol units. Surprisingly, no products related to tetrahydrofuran **4** were observed with the corresponding benzyloxymethyl substrate **5**. However, under IBr/CH_2Cl_2 conditions, competitive benzyl cleavage was observed and acetal **7** was isolated as the major product.[7] Activation with ICl in toluene provided exclusively the ether transfer product **6**.

Scheme 2. Electrophile-Induced Benzyl Transfer: Competitive Cleavage



5 6 7

conditions	% yield **6** : **7** (dr)
IBr, CH_2Cl_2, -78 °C	13 : 60
ICl, $PhCH_3$, -78 °C	65 : -- (20:1)

The intermediacy of chloromethyl ether **2b** was supported by NMR observation in toluene-d_8 (see Supporting Information). Thus, we speculated that a methanolic workup would regenerate the methoxylmethyl group and provide access to orthogonally protected diethers. Successful demonstration of this idea as well as the overall scope of the ether transfer are highlighted in Table 2. Reaction workup with either MeOTMS or basic methanol solutions provided diethers in good yield and excellent diastereoselectivity (entries 1 and 2). Moreover, benzyl alcohol workup generated a BOM-ether and provided **13**. Propionate substrates **16** and **18** demonstrated a strong preference for 1,3-syn products regardless of the stereochemistry of allylic substitution (entries 5 and 6). For evaluation of the scope of this chemistry, entry 7 was an important test. Appropriate protecting group selection[8]

(1) For the total syntheses of peloruside A, see: (a) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648−1652. (b) Jin, M.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303−1305.

(2) For additional synthetic efforts towards peloruside A, see: (a) Paterson, I.; Di Francesco, M. E.; Kühn, T. *Org. Lett.* **2003**, *5*, 599. (b) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967. (c) Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959. (d) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 7659. (e) Gurjar, M. K.; Pedduri, Y.; Ramana, P. C. V.; Puranik, V. G.; Gonnade, R. G. *Tetrahedron Lett.* **2003**, *45*, 387. (f) Liu, B.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 71. (g) Engers, D. W.; Bassindale, M. J.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 663. (h) Roulland, E.; Ermolenko, M. S. *Org. Lett.* **2005**, *7*, 2225. (i) Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941. (j) Hoye, T. R.; Ryba, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 8256.

(3) (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013−4018. (b) Duan, J. J.-W.; Smith, A. B., III *J. Org. Chem.* **1993**, *58*, 3703−3711.

(4) A related delivery of an ether has been applied to the stereocontrolled synthesis of glycosides: (a) Cumpstey, I.; Chayajarus, K.; Fairbanks, A. J.; Redgrave, A. J.; Seward, C. M. P. *Tetrahedron: Asymmetry* **2004**, *15*, 3207. (b) This chemistry is in a class of reactions defined by temporary tethers: Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289.

(5) For additional examples of acetals participating in electrophilic cyclization reactions, see: (a) Molas, P.; Matheu, M. I.; Castillíon, S. *Tetrahedron Lett.* **2004**, *45*, 3721. (b) Fujioka, H.; Ohba, Y.; Hirose, H.; Murai, K.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 734. (c) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 2489.

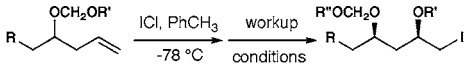
(6) (a) The syn stereochemistry was determined by NMR spectroscopic analysis: Hoffman, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3980. (b) The syn-1,3-relative stereochemistry was determined by hydrogenolysis of the benzyl ether and ^{13}C NMR spectroscopic analysis of the corresponding acetonide. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (c) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

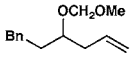
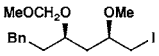
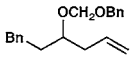
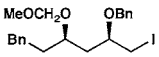
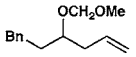
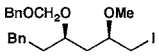
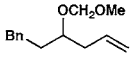
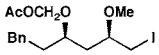
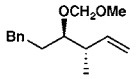
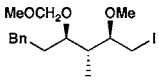
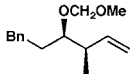
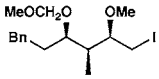
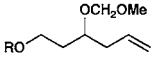
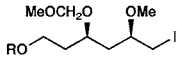
(7) Deprotection of benzyl ethers involved in iodoetherification reactions is well established: Rychnovsky, S. D.; Barlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(8) For a discussion of the lowered basicity of silyl ethers relative to alkyl ethers, see: Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.

(9) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 1201.

Table 2. Electrophile-Induced Methoxy Transfer: Reaction Scope



entry	substrate		product		workup		yield (dr)
1		**8**		**9**	a b		76% (13:1) 75% (13:1)
2		**10**		**11**	a b		67% (25:1) 56% (25:1)
3		**12**		**13**	c		80% (13:1)
4		**14**		**15**	d		88% (13:1)
5		**16**		**17**	a		56% (10:1)
6		**18**		**19**	a		89% (>25:1)
7		**20** R = TBDPS, **21** R = Bz		**22** **23**	a a		73% (>25:1) 62% (15:1)
			22 R = TBDPS, **23** R = Bz				

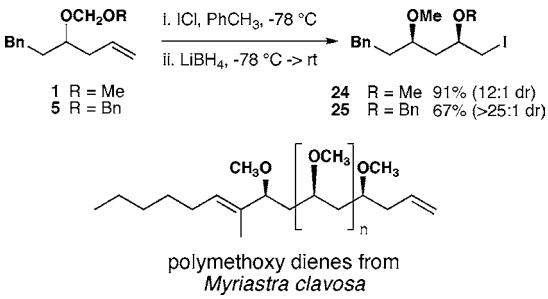
[a] $TMSOCH_3$. [b] CH_3OH, *i*Pr_2NEt. [c] BnOH, *i*Pr_2NEt. [d] AcOH, *i*Pr_2NEt; −78 °C → rt.

enabled exclusive ether transfer, and alternative cyclization events were not observed. These results augur well for application of this methodology to the synthesis of more complicated polyketide-like structures.

The in situ generated chloromethyl ether **2b** is a versatile intermediate with the ability to react with a variety of nucleophiles and provide unique structures applicable to natural product synthesis. An additional example, complementary to the ether transfer, is shown in Scheme 3. Electrophilic activation followed by a reductive workup provided access to methyl ethers through selective hydride addition. Coupled with a lithium borohydride quench, the MOM-protected substrate **1** provided the bismethyl ether **24** in 91% yield.

The reaction shown in Scheme 3 is ideally suited for application to the synthesis of the isotactic polymethoxydiene

Scheme 3. Electrophile-Induced Ether Transfer: Reduction Quench



class of marine polyketides.[9] Similarly, the BOM-protected substrate **5** provided the orthogonally protected diether substrate **25**, a stereocomplementary fragment to diether **9**.

Methods for the asymmetric synthesis of polyketide structural units have evolved such that even gram-scale syntheses of complex natural products are obtainable given the proper rationale.[10] We have developed a fundamentally new tactic capable of significantly simplifying the creation of functionality common to polyketide natural products by controlling the generation of a stereogenic center simultaneous with ether incorporation. Moreover, the demonstrated ability to trap the intermediate with a variety of nucleophiles offers additional opportunities for synthetic creativity. Application of these methods to our second-generation synthesis of peloruside A as well as other natural products is currently underway in our laboratories and will be reported in due course.

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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.

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(10) Mickel, S. J. *Curr. Opin. Drug Dev.* **2004**, *7*, 869. Smith, A. B., III *J. Org. Chem.* **1993**, *58*, 3703−3711.