Ether Transfer

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Electrophile-Induced Ether Transfer: Stereoselective Synthesis of 2,4,6-Trisubstituted Tetrahydropyrans**

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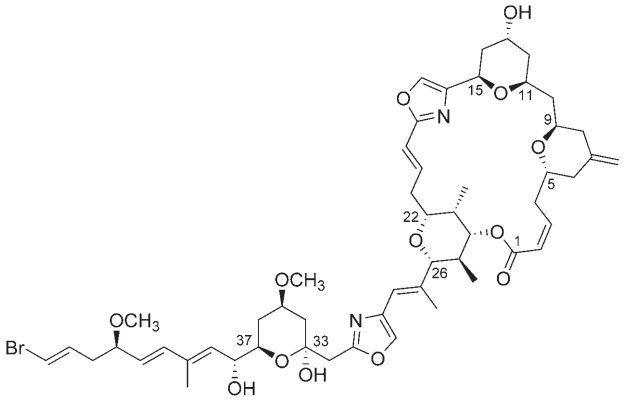
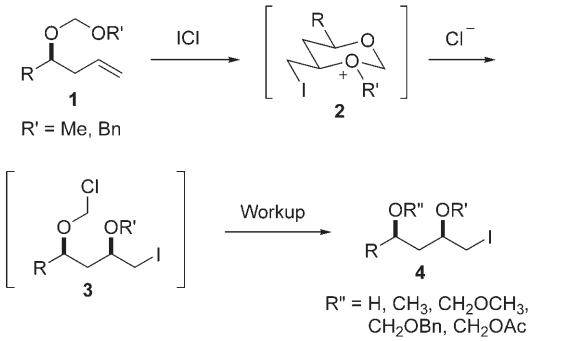
Polyketides represent an important class of natural products owing to their unique and diverse biological activities. The phorboxazoles,[1] a representative example, have become a popular target for synthetic chemists. Total syntheses of these complex structures have been accomplished by several groups.[2] Furthermore, the development of synthetic methods for the construction of their *bis*-tetrahydropyran C5–C15 region has been well documented.[3] Typically, different cyclization strategies were employed to install each of the stereocomplementary rings within this fragment.[4] Herein, we wish to report our approach to a stereoselective synthesis of both 4-substituted, 2,6-*cis*- and 2,6-*trans*-tetrahydropyran rings through a common strategy, which is highlighted by our newly developed methodology, electrophile-induced ether transfer. Moreover, application of this method to the synthesis of the C3–C17 *bis*-tetrahydropyran fragment of phorboxazole A is presented.



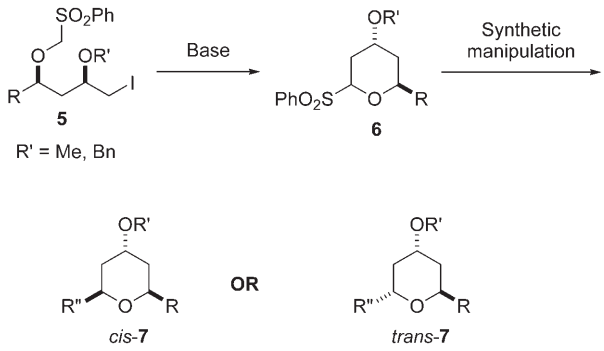
Phorboxazole A

We recently reported that *syn*-diol mono- or diethers **4**, could be prepared in high yield and excellent diastereoselectivity in a single step from a simple alkoxymethyl ether protected homoallylic alcohol **1** through activation with ICl (Scheme 1).[5] Mechanistically, we surmised that activation of **1** with electrophilic iodine monochloride produces chairlike oxonium ion **2**, leading to chloromethyl ether **3**, which could be quenched with a variety of nucleophiles depending upon workup conditions.



Scheme 1. Electrophile-induced ether transfer. Bn = benzyl.

We envisioned that this methodology could be utilized to access 2,4,6-trisubstituted tetrahydropyran rings with the following rationale (Scheme 2). Conversion of intermediate



Scheme 2. Synthetic approach to 2,6-*cis*- or *trans*-tetrahydropyrans.

3 to sulfone **5** would enable deprotonation of the acidic α proton and cyclization to **6**. Sulfonyl tetrahydropyran **6** could be then further functionalized, in a stereoselective manner, to either 2,6-*cis*- or 2,6-*trans*-tetrahydropyrans **7** by using chemistry that is analogous to that previously developed by Ley and co-workers.[6,9]

We began our exploration in the above-mentioned tetrahydropyran methodology by installing sulfone functionality directly in the ether-transfer reaction (Scheme 3). Treat-

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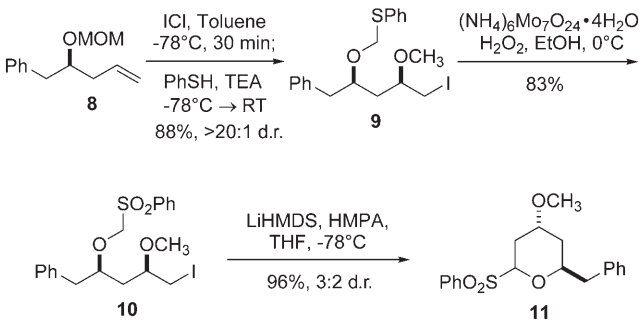
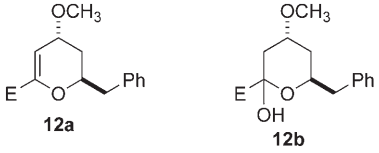


Scheme 3. Sulfone incorporation strategy and cyclization. HMPA = hexamethylphosphoramide.

ment of methoxymethyl (MOM)-protected homoallylic alcohol **8** with ICl in toluene at −78 °C, followed by quenching of the intermediate chloromethyl ether with a thiophenol/triethylamine (TEA) mixture afforded ether-transfer adduct **9** in 88 % yield as a single diastereomer. Subsequent sulfide oxidation by using an ammonium molybdate/H_2O_2 mixture provided sulfone **10**, which was then readily cyclized under lithium hexamethyldisilazide (LiHMDS) to sulfonyl pyran **11** as a 3:2 mixture of diastereomers; both steps proceeded in high yield. It is important to note that direct trapping of the chloromethyl ether intermediate with sodium benzenesulfinate did not produce sulfonyl ether **10**.

Sulfonyl pyran **11** was then transformed to 4-methoxy-2,6-*cis* tetrahydropyrans **14** through a two-step sequence: alkylation and reduction. After screening a variety of conditions, we found that deprotonation of **11** with excess sodium hexamethyldisilazide (NaHMDS) in toluene followed by the addition of electrophiles successfully yielded an alkylation product mixture of dihyropyran **12a** and tetrahydropyranol



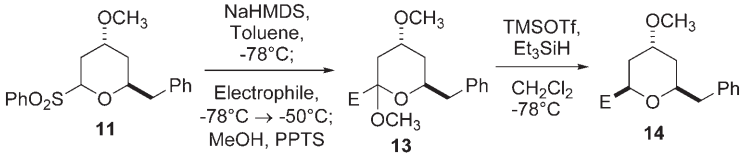
12b. This result was consistent with the finding reported by Ley et al.[6] in which the sulfone functionality was cleanly eliminated during the alkylation reaction. However, in these 4-alkoxy-substituted cases, hydration of **12a** readily occurred upon aqueous workup, and **12b** was found to be the major product.

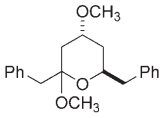
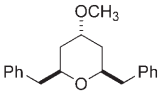
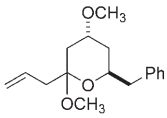
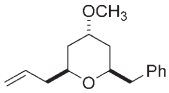
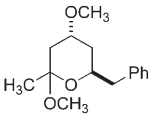
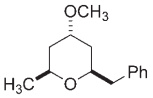
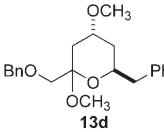
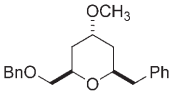
Both **12a** and **12b** were conveniently converted to methyl pyranoside **13** as a mixture of diastereomers upon standing in methanol with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). Exposure to a trimethylsilyl trifluoromethanesulfonate (TMSOTf) and Et_3SiH mixture reduced methyl pyranoside **13** to exclusively 2,6-*cis*-tetrahydropyran **14**.[7,8] The relative stereochemistry of the ring was unambiguously assigned by ^{1}H NMR coupling-constant analysis. Several electrophiles, including benzyl bromide, allyl bromide, methyl iodide, and benzyloxymethyl chloride (BOMCl) were screened, and the sequential alkylation–reduction sequence provided access to 4-alkoxy-2,6-*cis*-tetrahydropyrans in good yield with excellent diastereoselectivity (Table 1).

For the stereocomplementary 2,6-*trans*-tetrahydropyran, a direct ionization of **11** could be exploited. In fact, Ley and co-workers have previously demonstrated the ionization of benzenesulfonyl cyclic ethers by using aluminium chloride.[9] In these 4-alkoxy substrates, we found that treatment of sulfonyl pyran **11** with a slight excess of $AlCl_3$ and a variety of nucleophiles in toluene at −78 °C followed by warming up to −40 °C over one hour afforded tetrahydropyrans **15** in high yield and excellent diastereoselectivity (Table 2). The nucleophiles screened included allylsilanes, enolsilanes, and silyl ketene acetals. Once again, ^{1}H NMR coupling-constant determination of the relevant protons was utilized to deduce the relative stereochemistry of the ring.

With the methodology to access the stereocomplementary 4-alkoxy-2,6-*cis*- and 2,6-*trans*-tetrahydropyrans in hand, phorboxazole A, particularly its C5–C15 *bis*-tetrahydropyran region, caught our interest. This natural product is an ideal target which would demonstrate the applicability of our method in complex-molecule synthesis. Our retrosynthetic analysis indicated that the C5–C15 *bis*-tetrahydropyran of phorboxazole A could be assembled through two successive ether-transfer, cyclization, and functionalization reactions to

Table 1: 2,6-*cis*-Pyran **14** from the alkylation–reduction sequence.



Electrophile	Alkylation product **13**[a]	Yield[b] [%]	Reduction product **14**[c]	Yield[d] [%]
benzyl bromide	 **13a**	79	 **14a**	91
allyl bromide	 **13b**	85	 **14b**	82
methyl iodide	 **13c**	97	 **14c**	72
BOMCl	 **13d**	82	 **14d**	66

[a] Typical alkylation conditions: NaHMDS (3 equiv) and alkylating agent (4 equiv). [b] Isolated as a mixture of diastereomers. [c] Typical reduction conditions: TMSOTf (3 equiv) and Et_3SiH (2 equiv). [d] Isolated as a single diastereomer. ^{1}H NMR analysis of the crude mixture in all cases indicated a greater than 20:1 d.r. [e] PPTS was not added during methanolysis. [f] Reaction was warmed up to −40 °C.

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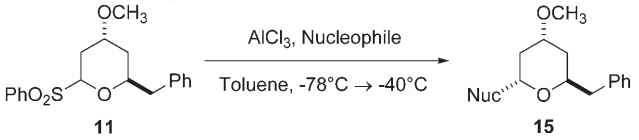
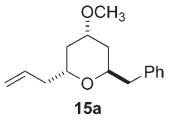
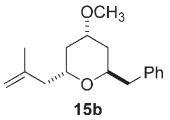
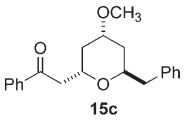
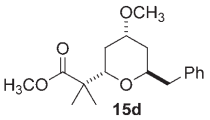
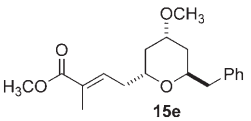
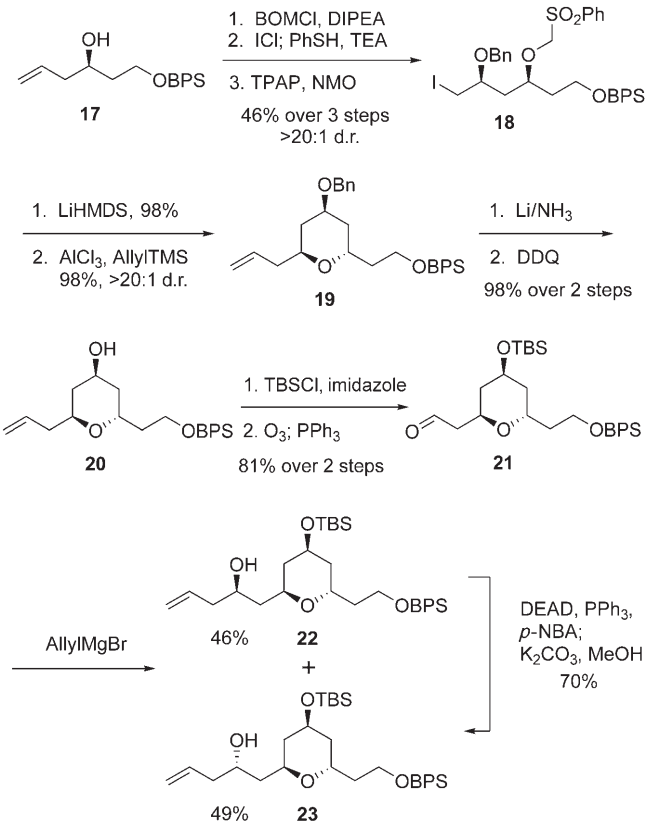
Table 2: 2,6-*trans*-Pyran **15** from the substitution reaction.[a]



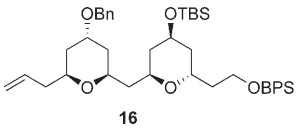
Nucleophile	Substitution product **15**	Yield[b] [%]
TMS	 **15a**	80
TMS	 **15b**	86
OTBS, Ph	 **15c**	82
OTBS, OCH_3	 **15d**	80
OTBS, OCH_3	 **15e**	70

[a] Typical reaction conditions: $AlCl_3$ (1.5 equiv) and nucleophiles (3 equiv). [b] Isolated as a single diastereomer. ^1H NMR analysis of the crude mixture in all cases indicated a greater than 20:1 d.r.



Scheme 4. Synthesis of the C3–C13 region of phorboxazole A. DEAD = diethylazodicarboxylate, DIPEA = *N*,*N*-diisopropylethylamine, *p*-NBA = *para*-nitrobenzoic acid.

provide the advanced intermediate **16** (BPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl). Our successfully implemented strategy is described below.



We began our synthesis to *bis*-tetrahydropyran **16** with enantiomerically enriched homoallylic alcohol **17** (Scheme 4).[10] BOM protection of **17** followed by ether-transfer and subsequent sulfide-oxidation reactions provided **18** in 46% yield over three steps and as a single diastereomer. Tetra-*n*-propylammonium perruthenate and *N*-methylmorpholine-*N*-oxide (TPAP, NMO) was a more-suitable oxidant[11] in this particular substrate as sulfide oxidation with ammonium molybdate/H_2O_2 was low yielding, presumably owing to the limited solubility of starting material in the reaction medium. LiHMDS-mediated cyclization of **18** followed by cationic allylation of the resulting sulfonyl pyran set up the first tetrahydropyran ring **19** in excellent yield and diastereoselection. This ring represents the 2,6-*trans*-stereochemistry of the C5–C9 region. The benzyl group was then removed with a Li/NH_3 mixture. Under these conditions, the phenyl groups within the BPS ether were converted to cyclohexadienes. Exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided **20** in an essentially quantitative yield for the two steps. After silylation, oxidative cleavage of the terminal olefin gave aldehyde **21** in good yield. An addition of allylmagnesium bromide to this aldehyde afforded a diastereomeric mixture of homoallylic alcohols **22** and **23** in a near-quantitative yield, which were easily separated by column chromatography. The stereochemistry of alcohol **22** was then converted by Mitsunobu inversion to the desired alcohol **23**,[12] and its absolute stereochemistry was determined by Mosher's ester analysis.[13] Attempts to control the aldehyde-addition facial selectivity with a reagent-controlled allylation were unsuccessful.

Homologation of the second tetrahydropyran fragment was then accomplished on homoallylic alcohol **23**. BOM-protection, ether-transfer, and oxidation reactions gave the sulfonyl ether **24** in satisfactory yield as a single diastereomer (Scheme 5). The strength of the methodology is now clearly demonstrated by its applicability to complex substrates. Furthermore, the ether-transfer reaction proceeded very smoothly and remarkably, no decomposition was detected despite the reactive nature of iodine monochloride. Cyclization of **24** afforded the corresponding sulfonyl pyran, which was then subjected to the alkylation–reduction sequence. In this complex substrate, alkylation of the intermediate sulfone anion proved slow under our initial conditions. However,

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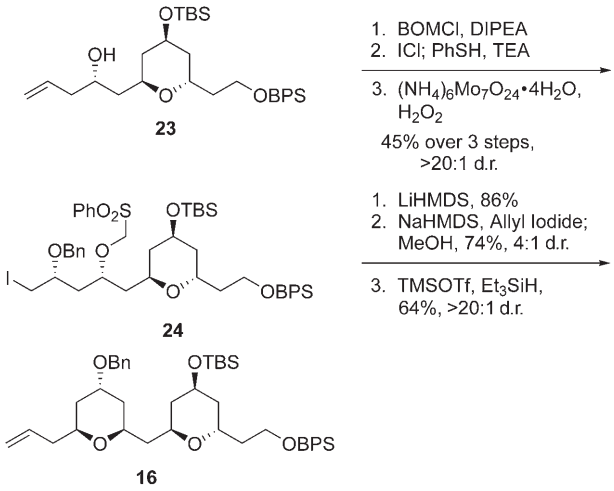

Scheme 5. Completion of *bis*-tetrahydropyran fragment **16**.

after optimization, the alkylation product was isolated in 74% yield as a mixture of diastereomers. The completion of the synthesis of *bis*-tetrahydropyran fragment **16** was accomplished by a stereoselective reduction by using TMSOTf and Et_3SiH.

In conclusion, we have developed a new methodology for the production of 2,4,6-trisubstituted tetrahydropyrans that are common to biologically active polyketides. Stereocomplementary tetrahydropyran fragments are accessed from a common intermediate that is readily obtained through electrophile-induced ether transfer that was previously reported by our laboratory. The successful application of the chemistry to the stereoselective synthesis of the C5–C15 *bis*-tetrahydropyran region of phorboxazole A supports the method's broad scope and scalability. Further applications of this methodology are currently ongoing in our laboratory and will be reported in due course.

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Keywords: ether transfer · oxocarbonium ions · oxygen heterocycles · phorboxazoles · polyketides

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