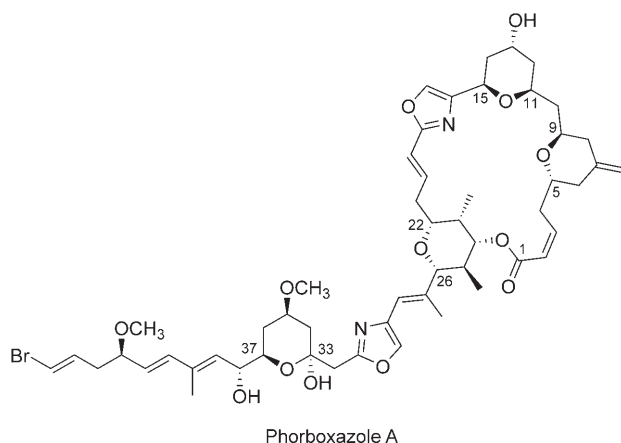


Electrophile-Induced Ether Transfer: Stereoselective Synthesis of 2,4,6-Trisubstituted Tetrahydropyrans**

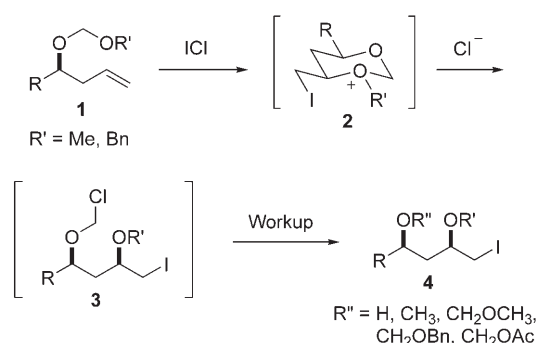
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Polyketides represent an important class of natural products owing to their unique and diverse biological activities. The phorboxazoles,^[1] a representative example, have become a popular target for synthetic chemists. Total syntheses of these complex 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.



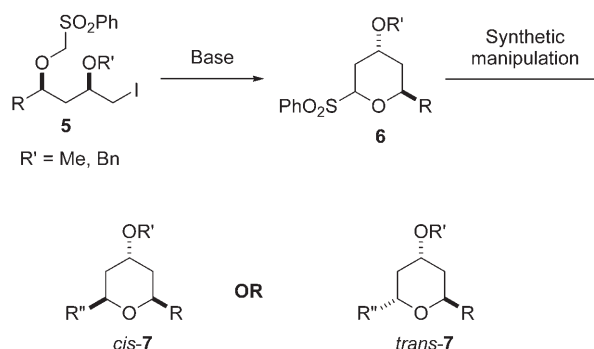
We recently reported that *syn*-diol mono- or diethers **4**, could be prepared in high yield and excellent diastereoselectivity in a single step from a simple alkoxyethyl ether

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.

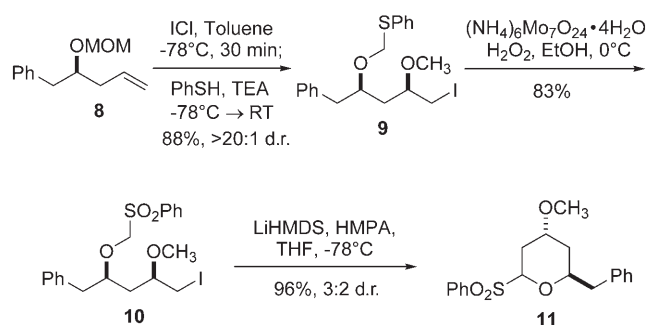
3 to sulfone **5** would enable deprotonation of the acidic α proton and cyclization to **6**. Sulfonyl tetrahydropyran **6** could be then further functionalized, in a stereoselective manner, to either 2,6-*cis*- or 2,6-*trans*-tetrahydropyrans **7** by using chemistry that is analogous to that previously 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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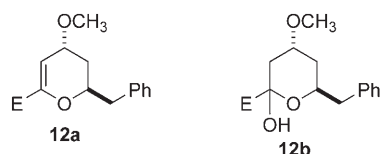
Supporting information (including the experimental details) for this article is available on the WWW under <http://www.angewandte.org> or from the author.



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/H₂O₂ 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 benzenesulfonate 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 dihydropyran **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 Et₃SiH mixture reduced methyl pyranoside **13** to exclusively 2,6-*cis*-tetrahydropyran **14**.^[7,8] The relative stereochemistry of the ring was unambiguously assigned by ¹H 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

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

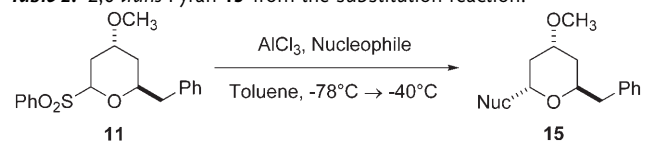
Electrophile	Alkylation product 13 ^[a]	Yield ^[b] [%]
	Reduction product 14 ^[c]	Yield ^[d] [%]
benzyl bromide		79
		91
allyl bromide		85
		82
methyl iodide		97
		72
BOMCl		82
		66

[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 Et₃SiH (2 equiv). [d] Isolated as a single diastereomer. ¹H 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.

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 AlCl₃ 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, ¹H NMR coupling-constant determination of the relevant protons was utilized to deduce the relative stereochemistry of the ring.

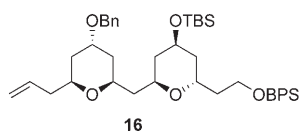
With the methodology to access the stereocomplementary 4-alkoxy-2,6-*cis*- and 2,6-*trans*-tetrahydropyrans in hand, phorbaxazole **A**, particularly its C5–C15 *bis*-tetrahydropyran region, caught our interest. This natural product is an ideal target which would demonstrate the applicability of our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

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

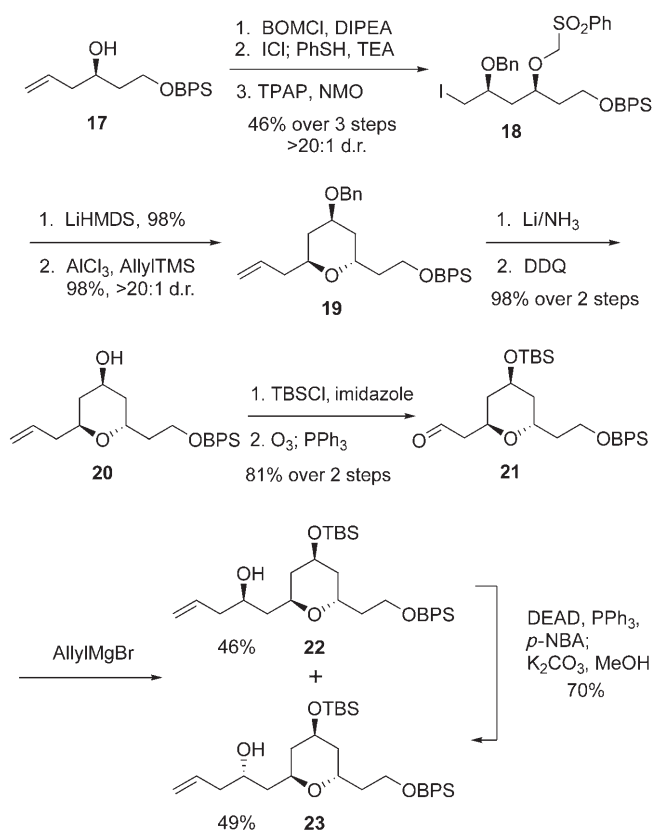
		
Nucleophile	Substitution product 15	Yield ^[b] [%]
		80
		86
		82
		80
		70

[a] Typical reaction conditions: AlCl₃ (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.

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



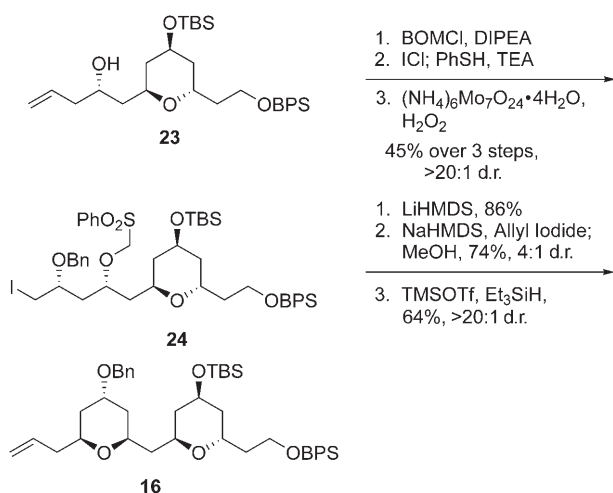
We began our synthesis to *bis*-tetrahydropyran **16** with enantiomerically enriched homoallylic alcohol **17** (Scheme 4).^[10] BOM protection of **17** followed by ether-transfer and subsequent sulfide-oxidation reactions provided **18** in 46 % yield over three steps and as a single diastereomer. 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/H₂O₂ 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/NH₃ mixture. Under these conditions, the



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

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,



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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