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Chemistry of Epoxysulfones: Straightforward Synthesis of Versatile Chiral Building Blocks

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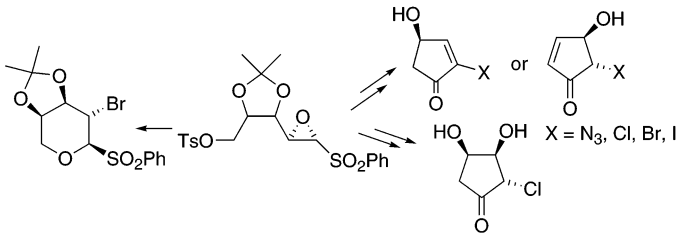
ABSTRACT



Several chiral building blocks have been obtained easily in large quantities from an epoxysulfone (9) that could be obtained in both enantiomeric forms from accessible starting materials.

Prostaglandins,[1] pentenomycin antibiotics,[2] ophiobolins,[3] and the antitumor antibiotic enediynes, such as the Neocarzinostatin Chromophore[4] and N1999A2,[5] are compounds of great interest due to their biological activities.[6]

Most syntheses of these compounds start with 4-hydroxycyclopent-2-en-1-one ((*S*)- or (*R*)-**1**), and in some cases the transformation into vinyl bromides or vinyl iodides is the first step. The double alkylation of 4-hydroxycyclopent-2-en-1-one ((*S*)- or (*R*)-**1**) and its protected forms is one of the most efficient routes to the E and F series of prostaglandins.[7] Caddick synthesized[8] the core of NCS-Chrom starting from cyclopentenone **2**. Levin,[9] starting from (*S*)-**1** protected as its TBDMS derivative, described an efficient route to prostanoid intermediates. Kishi[10] presented some years ago the synthesis of an ophiobolin analogue starting

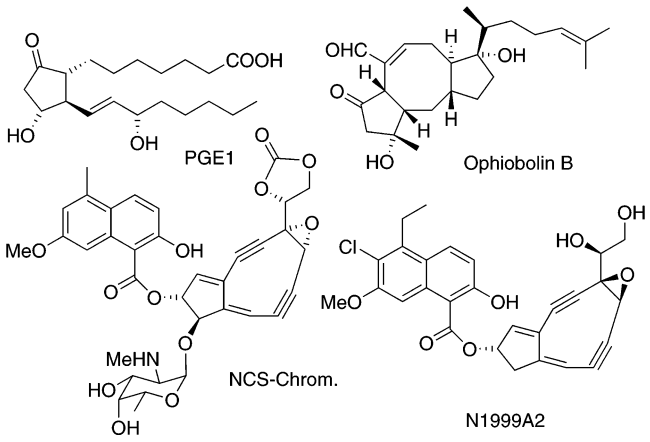


Figure 1.

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from (*R*)-**1** and transformed into **3** in the first step; and Johnson reported an easy synthesis of PGE_1 from a TBDMS-protected (*R*)-**1**, which was transformed into **4** in the first step.[11] Compound **1** has been obtained in both enantiomerically pure forms starting from L- or D-tartaric acid in six steps in a 22% yield,[12] or by a chemoenzymatic access starting from cyclopentane-1,3-dione to give a 30% yield of each enantiomer.[13] The corresponding vinyl halides were obtained by treatment of **1** in a bromination−dehydrobromination sequence[9] or in a one-step approach by treatment of **1** with I_2/pyridine in CCl_4.[14]

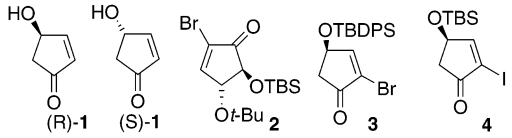
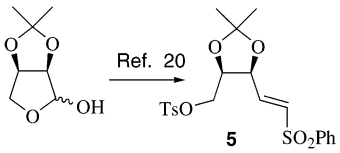


Figure 2.

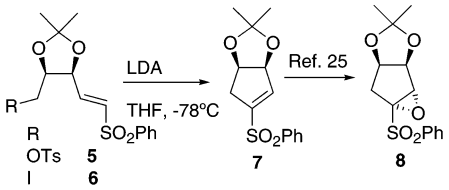
The versatility of vinyl sulfones in organic chemistry has been demonstrated by Backwall,[15] Fuchs,[16] Carretero,[17] and Padwa,[18] among others.[19] This paper describes a new contribution to extend the versatility of vinyl sulfone chemistry, in particular with compound **5**, easily obtained in two steps and in 76% yield from 2,3-*O*-isopropylidene-D-erythronolactol.[20] The enantiomer is also easily accessible, starting from L-arabinose.[21]

Scheme 1



Vinyl sulfones are known to react as Michael acceptors and to stabilize an anion in the α position.[22] Taking this reactivity into account, we started the transformation of the vinyl sulfone **5** or its iodide derivative **6** (obtained under the usual conditions) into cyclopentenone **7** by treatment with LDA in THF. The transformation gave low yields in both cases, 10% and 19%, respectively, with the majority of the starting material being recovered. Compound **7** has been obtained previously (although in racemic form) by Fuchs[23] and used in the synthesis of *dl*-cephalotaxine,[24] and has been epoxidized by Jackson to give epoxide **8** stereoselectively[25] (Scheme 2).

Scheme 2



The epoxidation of acyclic vinyl sulfones has been widely studied by Jackson,[26] and the reactivity of these species has been applied in the synthesis of natural products.[27] The stereoselectivity described by Jackson in systems similar to **5** depends on the oxidant used and on the protecting groups.[25] Having compound **5** in hand, we decided to study the epoxidation of this molecule to develop a route to the β-epoxide of the cyclized compound, which has not been previously described. When compound **5** was submitted to epoxidation conditions with *t*-BuOOLi or *t*-BuOOK, compounds **9** and **10** were obtained in an excellent yield in a ratio of 95:5 in both cases. The excellent stereoselectivity could be understood on the basis of less hindrance in transition state I than II (see Scheme 3). For a discussion see ref 25a. To study this further, the combined MCMM/Lowmode conformational search method in MacroModel[28] was used to locate low-energy conformers of **5**, using up to 2000 steps, the MMFF force field, TNCG minimization, and the GB/SA/CHCl3 model for solvation. The lowest energy conformers found corresponded directly to that required for transition state I. Geometry optimization of the lowest energy conformers of **5** of types I and II found in the MacroModel

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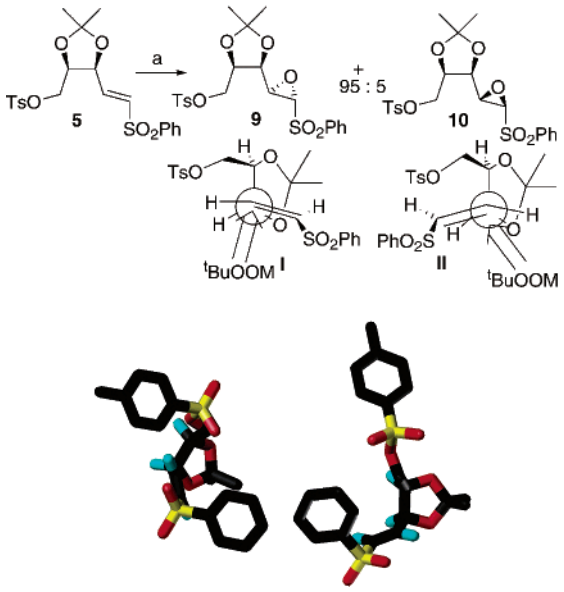
Scheme 3[a]

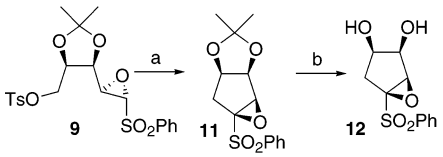


[a] Reagents and conditions: (a) *t*-BuOOLi, THF, −78 °C or *t*-BuOOK, THF, −78 °C, 95%.

search by using AM1 in MOPAC led to the conformations shown in color in Scheme 3, with the conformer corresponding to I being 4.7 kcal/mol lower in energy than that corresponding to II. Thus, the excellent diastereoselectivity shown may be due to a combination of a preponderance of the conformer of **5** in which the double bond is gauche to the C−O bond of the dioxolane, together with greater exposure of the π face of the double bond to attack by lithium *tert*-butylperoxide in these conformers than in the minor conformer in which the double bond is gauche to the C−H bond.

The stereochemistry of compound **9** was established by X-ray crystallography (Figure 3). As would be expected from the stabilization of anions in the α-position of epoxysulfones,[29] treatment of **9** with LiHMDS gives an 87% yield of the cyclized compound **11**, which was deprotected under the usual acid conditions to diol **12** (Scheme 4). To the best of

Scheme 4[a]



[a] Reagents and conditions: (a) LiHMDS, THF, −78 °C, 87%; (b) TsOH, MeOH, 95%.

our knowledge this is the first time that compound **11** has been synthesized.

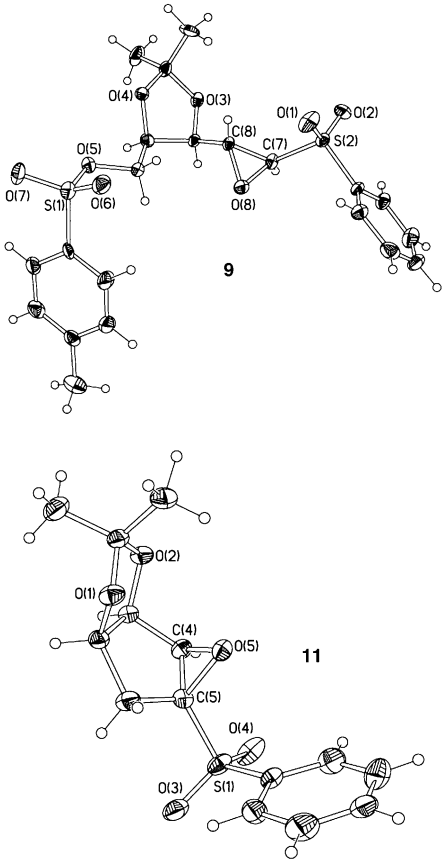


Figure 3. Single-crystal X-ray structures of **9** and **11**. Selected bond lengths for **9** (Å): O(8)−C(7) 1.393(9), O(8)−C(8) 1.414 (8), C(7)−C(8) 1.429 (7). Selected bond lengths for **11** (Å): O(5)−C(4) 1.494(13), O(5)−C(5) 1.393 (12), C(4)−C(5) 1.47 (2).

Compound **11** was crystallized from Et_2O and the X-ray data were obtained.

Sulfonyloxiranes show asymmetry of the two C−O bonds, the bond adjacent to the sulfonyl group being the shorter, as can be seen for compounds **9** and **11**. What is most striking is the dramatic difference between the bond lengths C(4)−O(5) and C(5)−O(5) (for crystallographic numbering for **11** see Figure 3) in comparison with compound **8** (O(5)−C(4) 1.449, O(5)−C(5) 1.436 and C(4)−C(5) 1.475[25]). This could be due to an interaction between the lone pairs of the epoxide and of the acetonide for **11**.

With compound **9** thus available to us in gram quantities, we decided to study the cyclization reaction and the reactivity of the cyclic compound. Compounds **11** and **12** seemed to us to be excellent precursors for the synthesis of cyclopentanones, based upon the reported reactivity of this kind of compound.[30] However, on treatment with various reagents, only in one case was the expected cyclopentanone obtained (entry 6 of Table 1). The reactivity of compounds **11** and **12** is described in Table 1.

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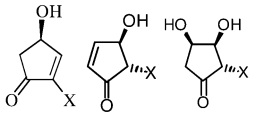
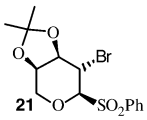
Table 1. Reaction of Compounds **9**, **11**, and **12**[e]

	S.M.	Rgn[a]	X			
1	**11**	$MgBr_2$[b]	Br	**13**, 43%	**14**,19%	
2	**11**	$MgBr_2$[c]	Br	**13**, 60%	**14**,26%	
3	**12**	$MgBr_2$[c]	Br	**13**, 26%	**14**,66%	
4	**11**	LiCl[d]	Cl	**15**, 43%	**16**,19%	
5	**11**	LiCl[b]	Cl	**15**, 80%		
			SO_2Ph	**17**, 6%		
6	**12**	LiCl[b]	Cl	**15**, 5%	**16**,5%	**18**,75%
			SO_2Ph	**17**, 8%		
7	**11**	LiI[d]		-	-	
8	**11**	LiI[b]	H	R-**1**,81%		
9	**12**	LiI[b]	I	**19**, 72%		
10	**11**	NaN_3[b]	N_3	**20**, 70%		
11	**12**	NaN_3[b]	N_3	**20**, 95%		
12	**9**	$MgBr_2$[b]		70%		

[a] All reactions were done with 3 equiv of reagent with the exception of $MgBr_2$, which was done with 2 equiv. Reaction temperature was 60 °C or reflux except for entry 3, which was done at rt. [b] Solvent: THF. [c] Solvent: Et_2O/THF. [d] Solvent: acetone. [e] S.M. stands fro starting material.

When both compounds were subjected to treatment with different nucleophiles under the usual conditions, cyclopentenones were obtained. All products in the table can be rationalized by the well-known nucleophilic attack at the unhindered position of the epoxide, with concomitant sulfinic acid loss to initially generate an α-cyclopentanone-acetonide of general structure **18** (X varied). α- or α′-enolization and *β*-elimination from this intermediate secure the products of Table 1. To test this hypothesis, compound **18** was treated with acetone−*p*-TsOH, but instead of the corresponding acetonide, a 1:1 mixture of compounds **15** and **16** was obtained. Thus, it is likely that initial formation of the cyclopentanone is followed by a rapid elimination, unexpected on the basis of precedent with open-chain analogues,[26b] to give the corresponding cyclopentenealcohols.

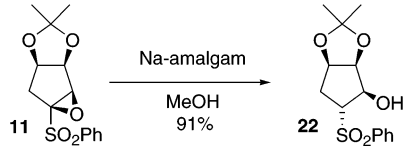
From Table 1 it is clear that by using $MgBr_2$ (entries 2 and 3) the same products are obtained but in inverse ratio, depending on whether the starting material was **11** or **12**, while use of LiCl (entries 5 and 6) gave rise to **15** from **11** in excellent yield, or **18** (the only compound that shows no elimination) from **12**. The use of LiI in acetone did not give any opening, the starting material being recovered (entry 7). When the solvent was changed to tetrahydrofuran (entries 8 and 9), use of LiI led to the synthesis of compound (*R*)-**1** or the vinyl iodide **19**, both in good yield, depending upon whether the starting material was **11** or **12**. Vinyl azide **20** (entries 10 and 11) was obtained from either starting material in good yield.

When compound **9** was treated with $MgBr_2$ under the usual conditions, the THP−sulfone **21** was obtained in good yield. These kinds of compounds have been used widely by Ley et al. in natural product synthesis.[31]

The structure and stereochemistry of all compounds were determined by extensive NMR studies.

Finally, to explore other kinds of reactivity for compound **11**, it was subjected to desulfonylation under the usual conditions with sodium amalgam,[32] giving as sole product and in high yield the hydroxy sulfone **22**, whose stereochemistry was established by NOE experiments (Scheme 5).

Scheme 5



Analogous compounds have been used as central intermediates for the synthesis of tricyclo-DNA.[33]

Thus, this is an excellent procedure for obtaining vinyl bromides, chlorides, iodides, azides, or halogenated cyclopentenones such as **14**, as well as cyclopentanones such as **18** or **22** and THP−sulfones such as **21**, in excellent yield. The method is easy to scale up, and it is worth bearing in mind that the starting materials could be obtained in both enantiomerically pure forms. Some of these compounds have not been described to date and are useful starting materials for the synthesis of biologically important targets, generating new ideas for the synthesis of prostaglandin analogues and other interesting compounds such as the enediynes. Further studies on the scope and applications of this methodology are actively under way in these laboratories.

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Supporting Information Available: Experimental procedures and complete characterization for all new compounds, as well as the X-ray crystalographic analysis data for **9** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035701Q

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