Synthetic Methods

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# Bicyclic Oxygen Heterocycles from γ,δ-Unsaturated Alcohols: Synthetic Targets Inspired by Blepharocalyxin D**

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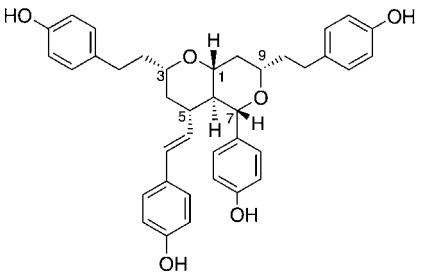
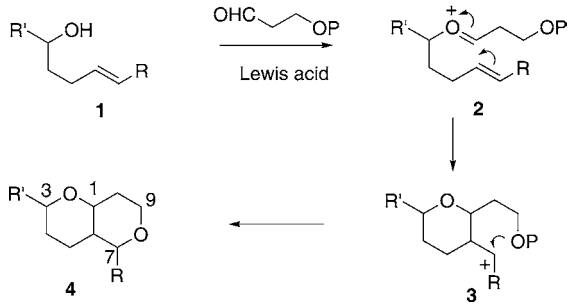
The development of strategies for the synthesis of fused heterocycles is an important goal as many such compounds display valuable properties. In this study we focus on the development of an efficient approach for the assembly of 2,8-dioxabicyclo[4.4.0]decanes. These scaffolds are present, for example, in the antiproliferative diarylheptanoid blepharocalyxin D (Scheme 1),[1] a rearrangement product of the



***Scheme 1.*** Structure of blepharocalyxin D.

antibiotic pseudomonic acid A,[2] and a series of pyranobenzopyrans[3] of interest as the core structures of liquid crystals.

The acid-promoted Prins cyclization of an oxocarbenium ion that is generated in situ, for example, from the reaction of a homoallylic alcohol with an aldehyde or from a homoallylic acetal or α-acetoxy ether, is a powerful synthetic method for the stereoselective synthesis of functionalized tetrahydropyrans.[4] Indeed, in their total synthesis of blepharocalyxin D, Lee and co-workers used two Prins cyclizations to generate the bicyclic skeleton.[1b,c] We proposed that this framework could be efficiently assembled in a single step from γ,δ-unsaturated alcohol **1**, in which the alkene is placed one position further away from the hydroxyl group than in substrates that are commonly used in Prins cyclizations (Scheme 2). By tethering the electrophile and nucleophile

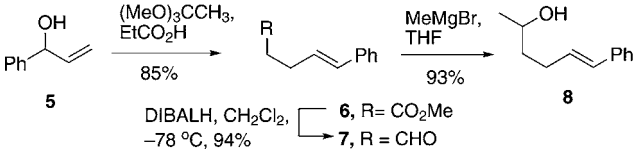


***Scheme 2.*** Proposed cyclization of γ,δ-unsaturated alcohol **1**. P = protecting group

into a single molecule, a cascade process would lead to the required bicyclic products **4** with concomitant generation of three new stereocenters.[5] This is an attractive strategy as competing oxonia-Cope rearrangements, which may occur in Prins cyclizations with homoallylic alcohols, are not an issue.[6] To be successful, it was anticipated that stabilization of the proposed carbocation **3** would be required. Mohr[7] as well as Kjellgren and Szabo[8] have shown that allylsilanes provide carbocation stabilization in the synthesis of 3-vinyltetrahydropyrans.[9]

We used a phenyl group to provide the necessary stabilization. The required substrate **8** was readily prepared in 76% overall yield from commercially available α-vinylbenzyl alcohol (**5**) by using a Johnson–Claisen rearrangement to establish the *E* configuration of the alkene. Reduction of methyl ester **6** with diisobutylaluminium hydride (DIBALH) and addition of MeMgBr to the resultant aldehyde **7** gave **8** (Scheme 3).

The initial electrophile for the key cyclization was protected 3-hydroxypropanal (Scheme 4). Various acid-mediated conditions for the coupling of alcohol **8** with 3-benzyloxypropanal (**9**) were investigated and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in $CH_2Cl_2$ was selected as the most promising for further study. At −10 °C *trans*-2,8-dioxabicyclo[4.4.0]decane (**10**) was the major product (77% yield) and was readily separated from the minor *cis*-isomer **11** (8% yield) by chromatography. At −50 °C, **10** was isolated in



***Scheme 3.*** Preparation of unsaturated alcohol **8**. THF = tetrahydofuran.

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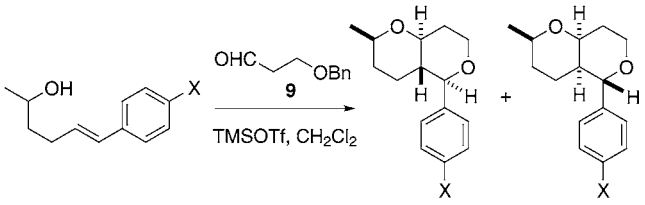



**8** X = H
**12** X = Cl
**15** X = Br
**17** X = OMe (Decomposition)
**18** X = $OSO_2Ph$
**20** X = $CF_3$

**10** X = H, 77%
**13** X = Cl, 75%
**16** X = Br , 78%

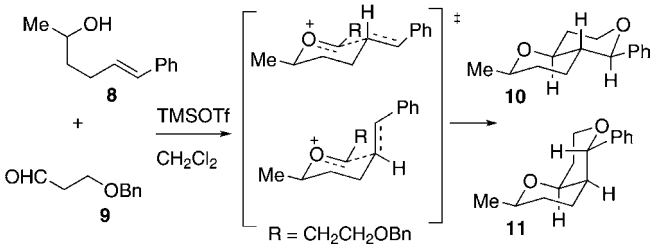
**11** X = H,
**14** X = Cl,

**19** X = $OSO_2Ph$, 83%
**21** X = $CF_3$, 73%

***Scheme 4.*** Reaction of alkenols with 3-benzyloxypropanal. Bn = benzyl

a similar yield with only a trace of **11**. The ratio of products was readily determined from the chemical shift of the H7 in the $^1H$ NMR spectrum of the crude mixture (the *trans*-fused product **10**, $\delta = 3.95$ ppm (d, $J = 10$ Hz); the *cis*-fused derivative **11** $\delta = 4.71$ ppm (d, $J = 11$ Hz)).[10]

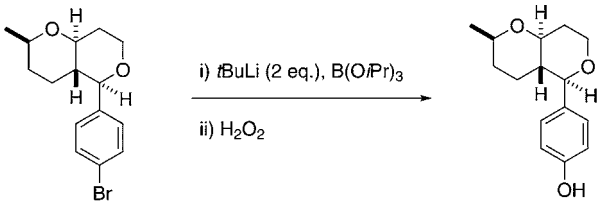
The conformational flexibility of the alkyl side-chain allows the alkene of **8** to achieve the required orbital overlap with the oxocarbenium ion in two orientations (Scheme 5). However the preference for the *trans*-product **10** can be rationalized by the Zimmerman–Traxler transition-state models.[11]




***Scheme 5.*** Formation of the two diastereomers **10** and **11**.

Having established that this cascade process was successful in generating both rings in **10** with the concomitant creation of three new stereogenic centers, we aimed to extend the synthetic utility of the reaction by using various functionalized aromatic groups. The acid-mediated reaction of (*E*)-6-(4-chlorophenyl)hex-5-en-2-ol (**12**) with 3-benzyloxypropanal gave the *trans*-fused product **13** in 75% isolated yield, and the reaction with the analogous bromide **15** gave **16** (Scheme 4). These halogenated products open the way for the synthesis a wide variety of derivatives. As many natural products, including blepharocalyxin D, contain *para*-hydroxylated phenyl groups, we focused on the conversion of bromide **16** to the analogous alcohol. Treatment of **16** with *t*BuLi and $B(OiPr)_3$ then subsequently with $H_2O_2$ under conditions modified from those reported by Lemieux, Snieckus, et al.,[12] gave phenol **22** in 76% yield (Scheme 6).

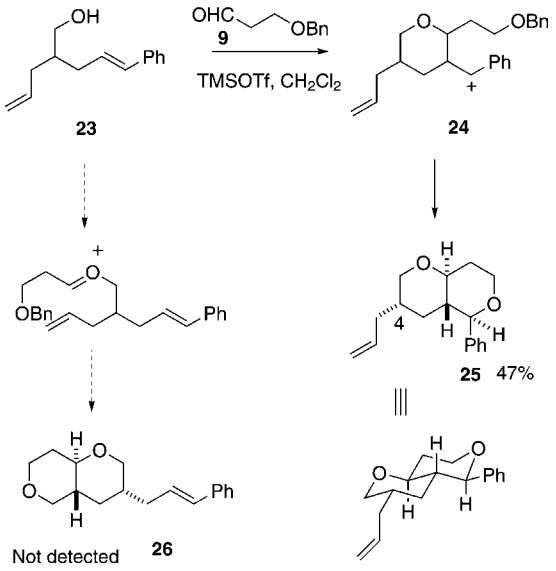
An alternative approach to 2,8-dioxabicycles with *p*-oxygenated phenyl groups at the C7 position is to start with the corresponding γ,δ-unsaturated alcohol. However, when alcohol **17**, which contains a *p*-methoxyphenyl sub-




***Scheme 6.*** Conversion of bromide **16** to alcohol **22**.

stituent, was subjected to the standard cyclization reaction, decomposition occurred (Scheme 4). The styrene portion of **17** is highly activated by the electron-rich aromatic ring and such styrenes are known to be susceptible to polymerization.[13] Indeed, treatment of **17** alone with TMSOTf in $CH_2Cl_2$ led to rapid decomposition. In contrast, when the key cyclization was conducted on the γ,δ-unsaturated alcohol **18**, which contains the electron-deficient aromatic ring with a *p*-phenylsulfonyl group, dioxabicycle **19** was isolated in 83% yield as a single diastereomer. Hydrolysis of the sulfonyl ester with potassium carbonate in methanol at reflux gave alcohol **22** in 79% yield. Many biologically important compounds contain fluorine, and pleasingly the electron-deficient aromatic system **20** with the *p*-trifluoromethyl group also cyclized cleanly to give the *trans*-2,8-dioxabicycle **21** in a 73% yield of isolated product.

With an efficient strategy for the assembly of 2,8-dioxabicycles in hand, the requirement for stabilization of the C7 carbocation was confirmed by using hydroxydiene **23**, which was prepared by allylation of ester **6** and subsequent reduction to the primary alcohol with $LiAlH_4$. Reaction of **23** with aldehyde **9** under the standard conditions gave no trace of product **26** from cyclization through the terminal double bond (Scheme 7). The sole product that was isolated from this reaction was the 4-propenyl derivative **25**, in accordance with the reaction proceeding via the stabilized carbocation **24**. This



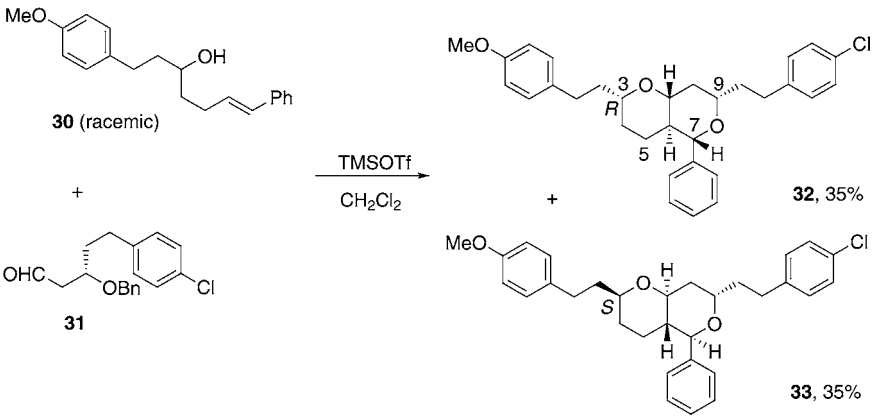

***Scheme 7.*** Cyclization of dienol **23**.

enabled the stereoselective introduction of an allyl group at the C4 position with the potential for further manipulation to a diverse range of functional groups.

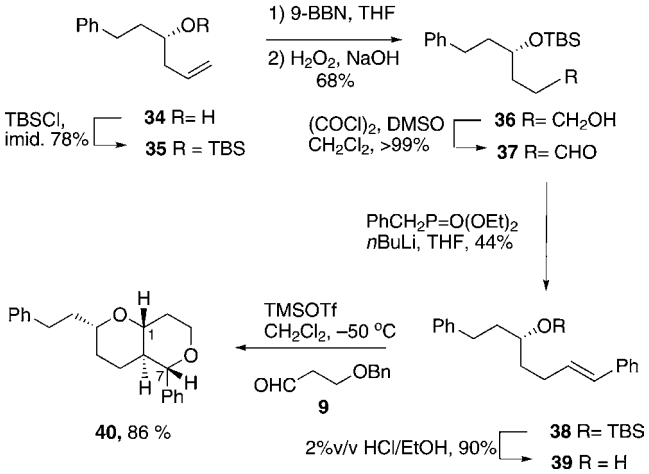
Blepharocalyxin D is assembled on a *trans*-2,8-dioxabicyclo[4.4.0]decane scaffold that has equatorial side-chains at the C3, C5, C7, and C9 positions (Scheme 1).[1] Having established that this bicyclic framework with equatorial groups at the C3 and C7 positions may be assembled efficiently from γ,δ-unsaturated alcohols, we turned our attention to the incorporation of a further substituent at the C9 position to give analogues of blepharocalyxin D. The acid-mediated reaction of racemic unsaturated alcohol **8** with (*R*)-3-benzyloxybutanal (**27**) gave two bicyclic products **28** and **29** from the reaction of the enantiopure aldehyde with each enantiomer of alcohol **8** (Scheme 8). The reactions are likely to proceed via tetrahydropyrans **I** and **II**, which each have three equatorial substituents that are generated from the cyclization of the initially formed oxocarbenium ions. In the case of (3*R*)-diastereomer **I**, the second ring closure leads to an equatorial group at the C9 position to give **28**, whereas the (3*S*)-isomer **II** gave the bicyclic product **29**, which has an axial methyl group (H9 in **28**, $\delta = 3.75$ (dqd, $J = 11$, 6, and 2 Hz); H9 in **29** $\delta = 4.5$ (apparent quin, $J = 7$ Hz)). The two products were readily separated by chromatography and the structures were confirmed by extensive NMR spectroscopic studies.

All of the studies described above involve racemic (*E*)-2-hydroxy-6-arylhex-5-en-2-ols as substrates, which lead to 2,8-dioxabicycles with an equatorial methyl group at the C3 position. In contrast, blepharocalyxin D has a 2-arylethyl group at the C3 position. Hence, for the synthesis of further analogues of blepharocalyxin D, racemic alcohol **30**, which has a *p*-methoxyarylethyl group (Scheme 9), was prepared by the addition of the requisite Grignard reagent to aldehyde **7**. The reaction of **30** with (*S*)-3-benzyloxyaldehyde **31** under the standard conditions gave (−)-2,8-dioxabicycle **32** in 35% yield (from cyclization with the *R* enantiomer of **30**) and diastereomer **33** in 35% yield (from cyclization with the *S* enantiomer of **30**).

To extend the utility of this method, a route for the enantioselective synthesis of (+)-γ,δ-unsaturated alcohol **39** was developed (Scheme 10). The known[14] (*S*)-allylic alcohol



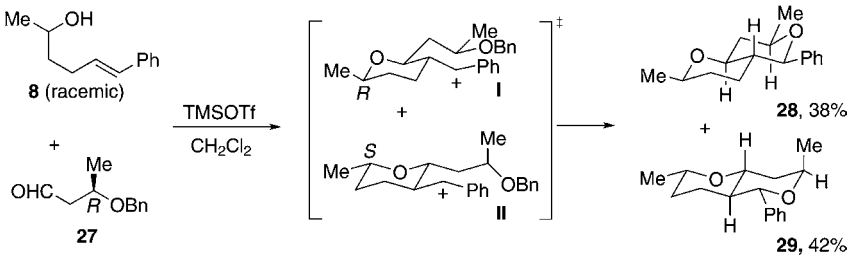

***Scheme 9.*** Preparation of trisubstituted 2,8-dioxabicyclodecanes.




***Scheme 10.*** Enantioselective synthesis of **40**. DMSO = dimethylsulfoxide; TBS = *tert*-butyldimethylsilyl.

**34** was prepared by a Keck allylation of dihydrocinnamaldehyde,[15] and was then protected as silyl ether **35**. After hydroboration of the alkene with 9-borabicyclo[3.3.1]nonane (9-BBN)/$H_2O_2$, the resultant primary alcohol **36** was oxidized under Swern conditions to give aldehyde **37** in 68% yield over the 2 steps. Treatment of **37** with diethyl benzylphosphonate in the presence of *n*BuLi gave **38** with the required *E* geometry at the double bond. Subsequent deprotection of the silyl ether of **38** gave alcohol **39**.[16] Treatment of **39** with 3-benzyoxylpropanal in the presence of TMSOTf gave (−)-2,8-dioxa[4.4.0]bicyclodecane (**40**) in 86% yield.

In conclusion, an efficient approach for the rapid stereocontrolled assembly of 2,8-dioxa[4.4.0]bicyclodecanes from γ,δ-unsaturated alcohols has been reported. The substrates for the key cyclizations are readily prepared in high yield by using either a Johnson–Claisen rearrangement or Horner–Wadsworth–Emmons reaction to establish the *E* configuration at the double bond. The cascade process generates the two heterocyclic rings and creates up to three new stereogenic centers in




***Scheme 8.*** Preparation of trisubstituted 2,8-dioxabicyclodecanes.

a single pot. This approach is versatile and enables substituents to be introduced at the C3, C4, C7, and C9 positions of the bicyclic framework with excellent stereocontrol.

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