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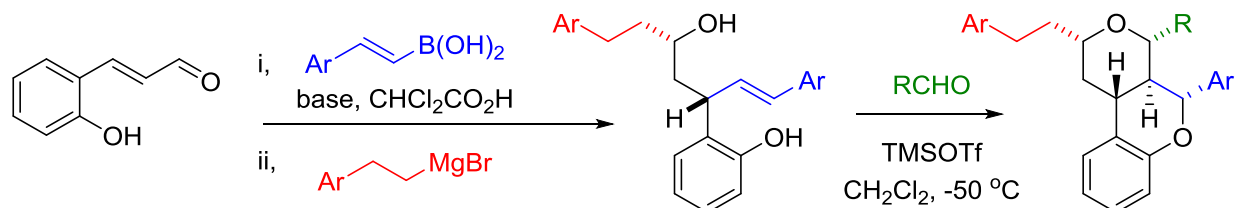
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Synthesis of Diarylheptanoid Scaffolds Inspired by Calyxins I and J

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Supporting Information Placeholder



ABSTRACT: γ,δ -Unsaturated alcohols are prepared efficiently in two steps from *o*-hydroxycinnamaldehyde. The TMSOTf-mediated reaction of the γ,δ -unsaturated alcohols with aldehydes creates 2 oxygen heterocycles and 3 new stereocentres in a single pot. The approach is versatile and by varying the boronic acid, Grignard reagent and aldehyde, different substituents may be introduced, whilst use of a chiral base in the conjugate addition gives enantioenriched products.

The development of strategies for the synthesis of fused heterocycles is an important goal as many such compounds display valuable biological properties. For example, a family of calyxins was isolated in small quantities from seeds of *Alpinia blepharocalyx* and their structures assigned originally by spectroscopic methods¹ and more recently confirmed by synthesis.² Three members of this family of diarylheptanoids, calyxins I, J and epicalyxin J, have not been synthesized but are of particular interest as they exhibit potent cytotoxic activity against human HT-1080 fibrosarcoma and murine colon 26-L5 carcinoma.³ They share a common tricyclic core in which the *trans*-fused oxygen heterocycles are further adorned by 3 equatorial side-chains (Figure 1). Our goal was to develop an efficient approach to the stereoselective synthesis of the dioxxygenated framework **1** which may be readily adapted for the preparation of analogues of these bioactive calyxins.

There are very few reported syntheses of the core tricyclic framework of calyxins I and J but one approach to racemic **2** ($\text{R} = \text{Ph}$, $\text{R}' = \text{H}$) uses a tandem Prins-Friedel-Crafts strategy.⁴ In addition Mead and co-workers have prepared **2** ($\text{R} = \text{R}' = p$ -methoxyphenyl) *via* the capture of two different benzylic cations in the stepwise generation of each oxygen heterocycle.⁵ They proposed that π -stacking of the two side-chains may play an important role in the stereochemical outcome of the second cyclization. Herein we describe our studies leading to an efficient one-pot cascade strategy for the enantioselective synthesis of **1** as well as a diastereomer with an axial substituent at C-3. The scope of the chemistry is explored demonstrating that it is readily adapted for the introduction of different side-chains.

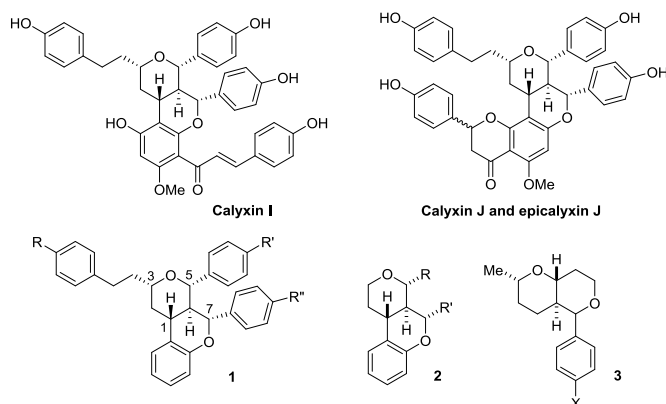
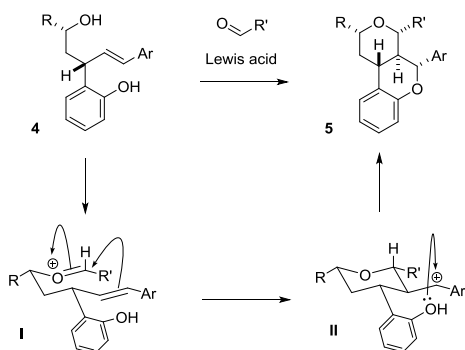


Figure 1. Diarylheptanoids from *A. blepharocalyx* and synthetic fragments

For synthesis of our target pyranochromene derivative **1** it was envisaged that a γ,δ -unsaturated alcohol could be used as the substrate if a phenol is present in the substrate to serve as the nucleophile (Scheme 1). We proposed that an acid-mediated reaction of γ,δ -unsaturated alcohol **4** with an aldehyde would generate oxycarbenium ion **I** and, following cyclization to stabilized carbocation **II**, trapping by the phenol would give the required tetrahydropyranochromene **5**. In accord with this proposal we have shown previously that the acid-mediated condensation of (*E*)-6-arylhex-5-en-2-ols with an electrophile possessing a tethered nucleophile (e.g. 3-benzyloxypropanal) gives 2,8-dioxabicyclo[4.4.0]decanes **3** in good yields (75-83%).^{6,7}

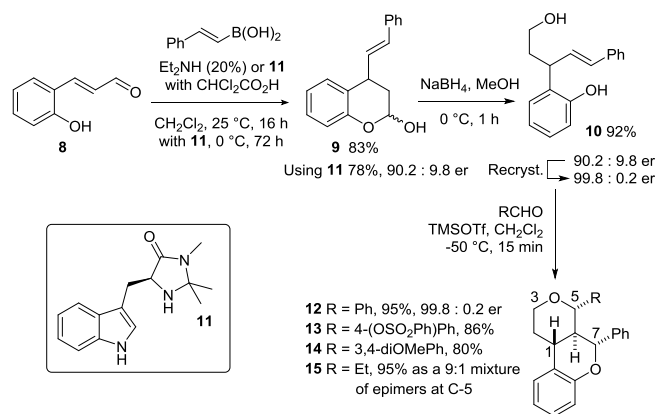
Scheme 1. Proposed cascade reaction for the synthesis of **5**



To begin, an efficient and versatile approach for the synthesis of a series of γ,δ -unsaturated alcohols was required. Primary alcohol **10** was prepared in 2 steps and 76 % overall yield from the known⁸ *o*-hydroxycinnamaldehyde **8**. A 1,4-addition of phenylvinylboronic acid to **8** in the presence of Et₂NH gave lactol **9** which was reduced with NaBH₄ (Scheme 2).

The key cyclization of γ,δ -unsaturated alcohol **10** with benzaldehyde was investigated and, following optimization, it was found that use of TMSOTf, in CH₂Cl₂ at -50 °C gave the required product **12** in 95% yield as a single diastereomer while generating 2 rings and 3 new stereocentres in one-pot (Scheme 2). NMR studies (500 MHz, CDCl₃) revealed that **12** has the required *trans* ring junction (1-H: δ 3.09, td, *J* 11.5, 4.0 Hz; 6-H: δ 2.48, dt, *J* 11.5, 9.5 Hz) with both side-chains equatorial (5-H: δ 4.27, d, *J* 9.5 Hz; 7-H: δ 4.90, *J* 9.5 Hz). Various electrophiles could be used in the cyclization including benzaldehydes with electron-deficient or electron-rich aromatic rings; the 4-phenylsulfonyl and 3,4-dimethoxy derivatives **13** and **14** were isolated in 86% and 80% yield respectively. When propanal was used as the electrophile, a 9:1 mixture of epimers **15** at C-5 was formed in 95% yield. Reddy and co-workers have very recently published their investigations on a similar cyclization.⁹ However they reported that reaction of either **10** with 2,3,4-trifluorobenzaldehyde or the corresponding PMB protected phenol with a series of aldehydes in the presence of TMSOTf at -40 °C which gave a mixture of products in varying yields.⁹

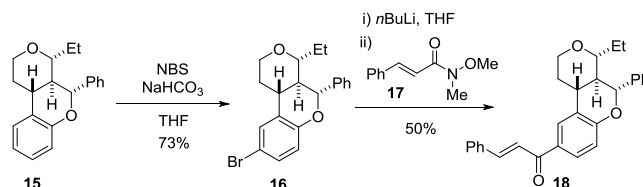
Scheme 2. Synthesis and cyclization of γ,δ -unsaturated alcohol **10**



Our strategy has the added benefit that an enantioselective conjugate addition may be achieved using a chiral base.¹⁰ Indeed we found that using imidazolidinone **11** and CHCl₂CO₂H in place of Et₂NH in the 1,4-addition step, the resultant lactol **9** was isolated with 90:10 er (established by chiral SFC) thus enabling the enantioselective synthesis of our targets. The enantiopurity of primary alcohol **10** was improved to 99.8:0.2 er following recrystallization from chloroform/pentane. Following conversion of **10** to the pyranochromene derivative **12** it was confirmed that there was no loss of stereochemical integrity during the cascade reaction.

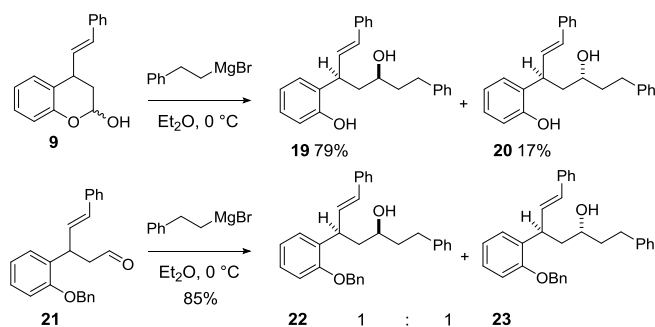
To prepare analogues more closely related to calyxin J and epicalyxin J further functionality was required on the fused aromatic ring. This could be achieved either by starting with a more complex phenol in γ,δ -unsaturated alcohol **10** or by selectively manipulating the cyclization product. The latter approach was investigated using **15** as the substrate (Scheme 3). Treatment of **15** with *N*-bromosuccinimide and NaHCO₃ gave bromide **16** in 73% yield; the regiochemical outcome of the reaction was confirmed by nOe studies. Bromide **16** was converted to cinnamoyl derivative **18** via lithiation with *n*BuLi followed by reaction with Weinreb amide **17**.

Scheme 3. Introduction of the cinnamoyl side-chain



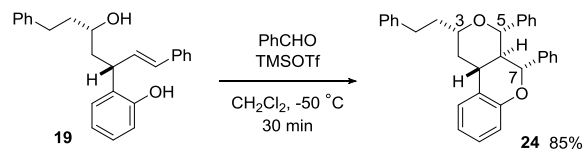
With optimized conditions in hand for the key cyclization to generate the tricyclic framework with 2 equatorial substituents, the next challenge was stereoselective synthesis of the secondary alcohol **4** required for cyclization to **5** (Scheme 1). Thus lactol **9** was reacted with phenethylmagnesium bromide to give ca 5:1 mixture of diastereomers **19** and **20** in 96% yield, which were separated by column chromatography. The major alcohol **19** was recrystallized from ethyl acetate/hexane and X-ray crystallography confirmed that the hydroxyl group and styryl side-chain were *syn* (see Supporting Information). The selectivity in this addition was unexpected, and we propose that it may arise through chelation of the phenol-OH to the Grignard reagent. Indeed following selective protection of phenol of **10** as a benzyl ether, using benzyl bromide and K₂CO₃, a sequential oxidation to aldehyde **21** and reaction with phenethylmagnesium bromide gave a 1:1 mixture of diastereomers **22** and **23** in 85% yield, these co-eluted on column chromatography. Each secondary alcohol **19** and **20** was separately converted to their corresponding benzyl ether **22** and **23** and comparison of the spectral data confirmed the results from the Grignard reaction.¹¹

Scheme 4. Synthesis of cyclization substrates **19** and **20**



The TMSOTf-mediated reaction of diastereomer **19** with benzaldehyde gave cyclized product **24** as a single diastereomer in 85% yield (Scheme 5). ¹H-NMR coupling constants combined with nOe studies established the structure **24** with the *trans* ring junction and all 3 side-chains equatorial. In this case both the phenol and phenethyl side-chains can occupy pseudo-equatorial positions in the oxycarbenium transition state, thus generating the 3 new stereocentres via the cascade process proposed in Scheme 1.

Scheme 5. Reaction of diastereomer **19** with benzaldehyde



Reaction of the diastereomeric alcohol **20** with benzaldehyde and TMSOTf also proceeded to form a single diastereomer **25** in good yield (75%) (Scheme 6). The product was recrystallized from chloroform/pentane and X-ray crystallography confirmed that **25** had the expected *trans* ring junction but with an axial substituent at C-3 (Figure 2). In this case if the reaction proceeds through an oxycarbenium ion **I** in a chair-like transition state, then the phenethyl side chain occupies a pseudo-axial position and, following cyclization to generate the first heterocycle, the resultant stabilized carbocation **II** is captured by the equatorial phenol (Scheme 6).

Scheme 6: Reaction of diastereomer **20** with benzaldehyde

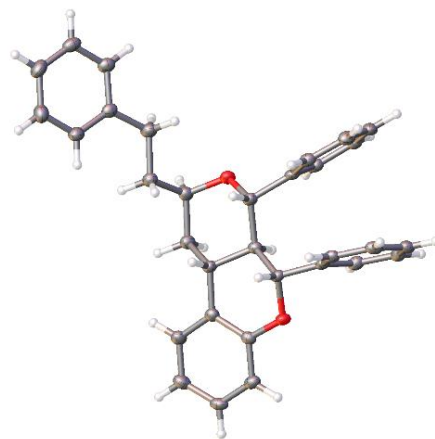
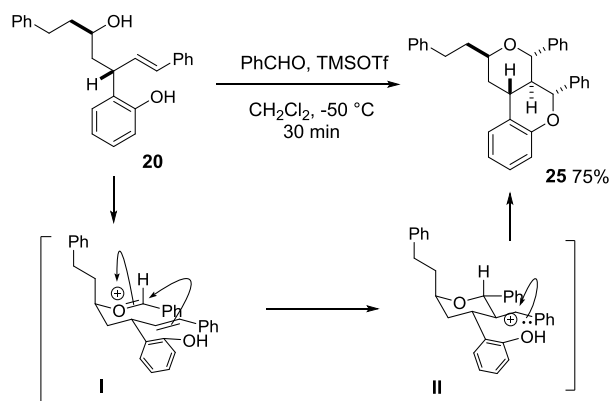
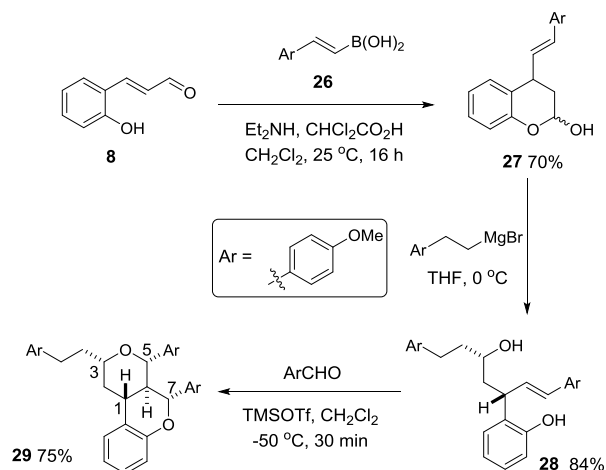


Figure 2. X-ray crystal structure of **25** with C-3 side-chain axial. Ellipsoids depicted at 50% probability level

To further explore the scope of this chemistry and to access further analogues of calyxins I and J, γ,δ -unsaturated alcohol **28** possessing electron-rich *p*-methoxyphenyl groups was prepared in 2 steps. Conjugate addition of boronic acid **26** to *o*-hydroxycinnamaldehyde **8** followed by addition of *p*-methoxyphenethylmagnesium bromide to the resultant lactol **27** giving secondary alcohol **28** with excellent stereocontrol. Reaction of **28** with anisaldehyde gave the crystalline product **29** in 75% isolated yield (Scheme 7). X-ray crystallography confirmed that the 3 side-chains were equatorial and also revealed that the aromatic substituents at C-5 and C-7 were parallel with potential for π -stacking interactions as proposed by Mead⁵ in his calculations. It was particularly pleasing to note the good yield of **29** from **28**, as the styrene portion is activated by the electron-rich aromatic ring and such styrenes are known to be susceptible to polymerization.¹² Indeed we have shown previously⁶ that this is a problem in the synthesis of *trans* 2,8-dioxabicyclo[4.4.0]decanes **3** via reaction of (*E*)-6-arylhex-4-en-2-ol with 3-benzyloxpropanal and TMSOTf. Degradation occurred with the *p*-methoxyphenyl substrate whereas with a series of substrates with less activated rings, for example a phenyl group, cyclization proceeded cleanly to give **3** (X = H, 77% yield).

Scheme 7. Synthesis *p*-methoxyphenyl analogue **29**



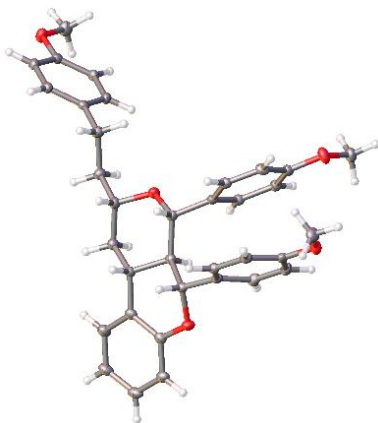


Figure 3. X-ray crystal structure of all-equatorial product **29**. Ellipsoids depicted at 50% probability level

In conclusion, an efficient approach is reported for the rapid stereocontrolled assembly of pyranochromene derivatives **1** from γ,δ -unsaturated alcohols. The substrates for the key cyclization are readily prepared in 2 steps from *o*-hydroxycinnamaldehyde **8** via 1,4-addition of a boronic acid followed by a stereoselective Grignard reaction. The TMSOTf-mediated cascade reaction of γ,δ -unsaturated alcohols and aldehydes creates 2 oxygen heterocycles and 3 new stereocentres in a single pot. The approach is versatile and by varying the boronic acid, Grignard reagent or aldehyde different substituents may be introduced, whilst use of a chiral base in the conjugate addition gives enantioenriched products.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. X-ray crystallographic data (CIF file) of **19**, **25** and **29**. This material is available free of charge via the Internet at <http://pubs.acs.org>

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Notes

The authors declare no competing financial interest.

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