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Synthesis of Diarylheptanoid Scaffolds Inspired by Calyxins I and J

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ABSTRACT: \(\gamma,\delta\)-Unsaturated alcohols are prepared efficiently in two steps from \(o\)-hydroxycinnamaldehyde. The TMSOTf-mediated reaction of the \(\gamma,\delta\)-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 methods and more recently confirmed by synthesis. 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. 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 dioxygenated framework 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 (R = Ph, R’ = H) uses a tandem Prins-Friedel-Crafts strategy. In addition Mead and co-workers have prepared 2 (R = R’ = p-methoxyphenyl) via the capture of two different benzylic cations in the stepwise generation of each oxygen heterocycle. They proposed that \(\pi\)-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](image-url)
Our strategy has the added benefit that an enantioselective conjugate addition may be achieved using a chiral base.\textsuperscript{10} Indeed we found that using imidazolidinone 11 and CHCl$_3$CO$_2$H in place of Et$_3$NH 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 $\gamma,\delta$-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 NaHCO$_3$ gave bromide 16 in 73% yield; the regiochemical outcome of the reaction was confirmed by nOe studies. Bromide 16 was converted to cinnamyl derivative 18 via lithiation with nBuLi 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 K$_2$CO$_3$, 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.\textsuperscript{11}
The TMSOTf-mediated reaction of diastereomer 19 with benzaldehyde gave cyclized product 24 as a single diastereomer in 85% yield (Scheme 5). $^1$H-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**

To further explore the scope of this chemistry and to access further analogues of calyxins I and J, $\gamma,\delta$-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 $\pi$-stacking interactions as proposed by Mead 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. Indeed we have shown previously 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-benzoxipropanol 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 2. X-ray crystal structure of 25 with C-3 side-chain axial. Ellipsoids depicted at 50% probability level.

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

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

11. This result is in contrast to that of Reddy and co-workers9 who imply that the same reaction gave a single diastereomer.