

Synthesis of Diarylheptanoid Scaffolds Inspired by Calyxins I and J

Thomas D. Ackrill, Hazel A. Sparkes, and Christine L. Willis*

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

Supporting Information

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 two oxygen heterocycles and three new stereocenters in a single pot. The approach is versatile, and by



varying the boronic acid, Grignard reagent, and aldehyde, different substituents may be introduced, while 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 were 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 three equatorial side chains (Figure 1). Our goal



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

was to develop an efficient approach to the stereoselective synthesis of the dioxygenated 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 (R = Ph, R' = H) uses a tandem Prins–Friedel–Crafts strategy.⁴ 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.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.

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)

Received: June 30, 2015

gives 2,8-dioxabicyclo[4.4.0]decanes 3 in good yields (75–83%).^{6,7}

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 two 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 CH_2Cl_2 at -50 °C, gave the required product 12 in 95% yield as a single diastereomer while generating two rings and three new stereocenters 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 the 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, gave a mixture of products in varying vields.9

Our strategy has the added benefit that an enantioselective conjugate addition may be achieved using a chiral base.¹⁰ Indeed we found that, by using imidazolidinone **11** and $CHCl_2CO_2H$ in place of Et_2NH 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

Scheme 3. Introduction of the Cinnamoyl Side Chain



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.

With optimized conditions in hand for the key cyclization to generate the tricyclic framework with two 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 a 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_2CO_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 coeluted 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.





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 three side chains as equatorial. In this case both the phenol and phenethyl side chains can occupy pseudoequatorial positions in the oxycarbenium transition state, thus generating the three new stereocenters via the cascade process proposed in Scheme 1.

Organic Letters

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 recrystal-

Scheme 6. Reaction of Diastereomer 20 with Benzaldehyde



lized 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



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

reaction proceeds through an oxycarbenium ion I in a chairlike transition state, then the phenethyl side chain occupies a pseudoaxial position and, following cyclization to generate the first heterocycle, the resultant stabilized carbocation II is captured by the equatorial phenol (Scheme 6).

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 two steps. Conjugate addition of boronic acid **26** to *o*hydroxycinnamaldehyde **8** followed by addition of *p*-methoxyphenethylmagnesium bromide to the resultant lactol **27** gave 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 three 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 (Figure 3). It was particularly pleasing to note



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

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* 2,8dioxabicyclo[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).

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 two steps from *o*-hydroxy-cinnamaldehyde 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 two oxygen heterocycles and three new stereocenters in a single pot. The approach is versatile, and by varying the

Organic Letters

boronic acid, Grignard reagent, or aldehyde, different substituents may be introduced, while 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**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01848.

AUTHOR INFORMATION

Corresponding Author

*E-mail: chris.willis@bristol.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to James Smith and Giacomo Crisenza (School of Chemistry, University of Bristol) for their assistance with chiral SFC and HPLC, respectively, and to Professors Varinder Aggarwal and Tom Simpson for valuable discussions. We thank Drs. Craig Butts and Paul Gates for NMR and MS, respectively, and the University of Bristol for support.

REFERENCES

(1) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. J. Nat. Prod. **2001**, *64*, 208.

(2) (a) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. J. Org. Chem. 2006, 71, 3176. (b) Tian, X.; Rychnovsky, S. D. Org. Lett. 2007, 9, 4955.

(3) (a) Gewali, M. B.; Tezuka, Y.; Banskota, A. H.; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733. (b) Ali, M. S.; Banskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull.* **2001**, *24*, 525.

(4) Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C. J. Synlett 2005, 1912.
(5) Cakir, S. P.; Stokes, S.; Sygula, A.; Mead, K. T. J. Org. Chem. 2009, 74, 7529.

(6) Bunt, A. J.; Bailey, C. D.; Cons, B. D.; Edwards, S. J.; Elsworth, J. D.; Pheko, T.; Willis, C. L. Angew. Chem., Int. Ed. **2012**, *51*, 3901.

(7) Recent examples of intramolecular capture of carbocations generated from homoallylic alcohols in Prins cyclizations include:
(a) Elsworth, J. D.; Willis, C. L. Chem. Commun. 2008, 1587.
(b) Subba Reddy, B. V.; Medaboina, D.; Sridhar, B. J. Org. Chem. 2015, 80, 653.
(c) Subba Reddy, B. V.; Jalal, S.; Borkar, P.; Yadav, J. S.; Reddy, P. P.; Kunwar, A. C.; Sridhar, B. Org. Biomol. Chem. 2012, 10, 6562.
(d) Indukuri, K.; Unnava, R.; Deka, M. J.; Saikia, A. K. J. Org. Chem. 2013, 78, 10629.

(8) Zu, L.; Zhang, S.; Xie, H.; Wang, W. Org. Lett. **2009**, *11*, 1627. (9) To achieve the synthesis of racemic **2** (R = Ph, R' = various groups), Reddy and co-workers used a benzyl protected phenol in the presence of BCl₃ at -78 °C: Reddy, B. V. S.; Reddy, M. R.; Reddy, S. G.; Sridhar, B.; Kumar, S. K. Eur. J. Org. Chem. **2015**, 2015, 3103.

(10) (a) Lelais, G.; MacMillan, D. W. C. Aldrichimica Acta **2006**, *39*, 79. (b) Choi, K.-S.; Kim, S.-G. Tetrahedron Lett. **2010**, *51*, 5203.

(11) This result is in contrast to that of Reddy and co-workers 9 who imply that the same reaction gave a single diastereomer.

(12) (a) Satoh, K.; Kamigaito, M.; Sawamoto, M. Macromolecules **2000**, 33, 5830. (b) Duan, Z.; Xuan, X.; Wu, Y. Tetrahedron Lett. **2007**, 48, 5157.