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A Bioinspired Strategy for the Enantioselective Synthesis of Bicyclic Oxygen Heterocycles

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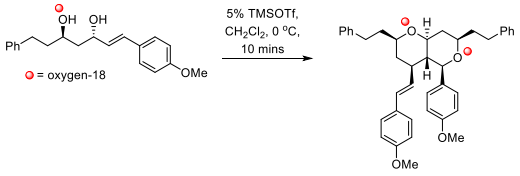


ABSTRACT: A new strategy is described for the direct conversion of unsaturated 3,5-dihydroxy-diarylheptanoids to dimeric products assembled on *trans*-2,8-dioxabicyclo[4.4.0]decane frameworks. The key atom-economical acid-mediated coupling creates 2 rings and 4 new stereocenters in a single-pot process. Oxygen-18 labelling studies are in accord with reactions proceeding via a cascade mechanism involving carbocationic intermediates. This approach enabled the concise total syntheses of analogues of the natural product blepharocalyxin D in 4 steps from simple starting materials.

Many compounds assembled on fused heterocycles display potent bioactivities, hence the development of efficient approaches for their synthesis is an important goal. Among them is a diverse family of diarylheptanoids which exhibit potent antiproliferative activities.[1] For example, Kadota and co-workers reported a series of related polyphenolic compounds from the seeds of *Alpinia blepharocalyx*,[2] a plant commonly used in Chinese traditional medicine. These natural products include linear diarylheptanoids (e.g. **1**, Figure 1), those assembled on a single tetrahydropyran/dihydropyran ring (e.g. **2** and calyxin L) as well as fused heterocyclic frameworks such as calyxin I.

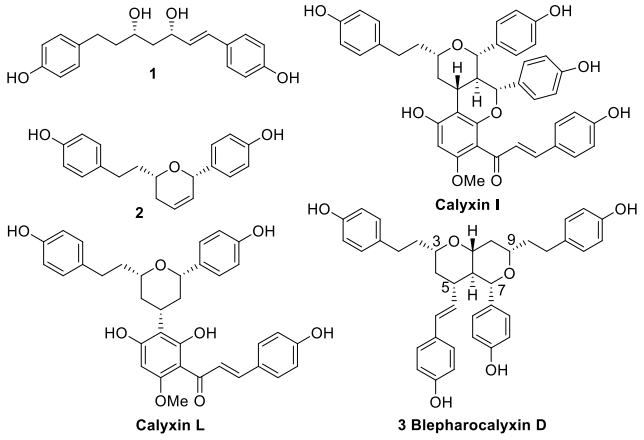


Figure 1. Examples of diarylheptanoids isolated from the seeds of *A. blepharocalyx*

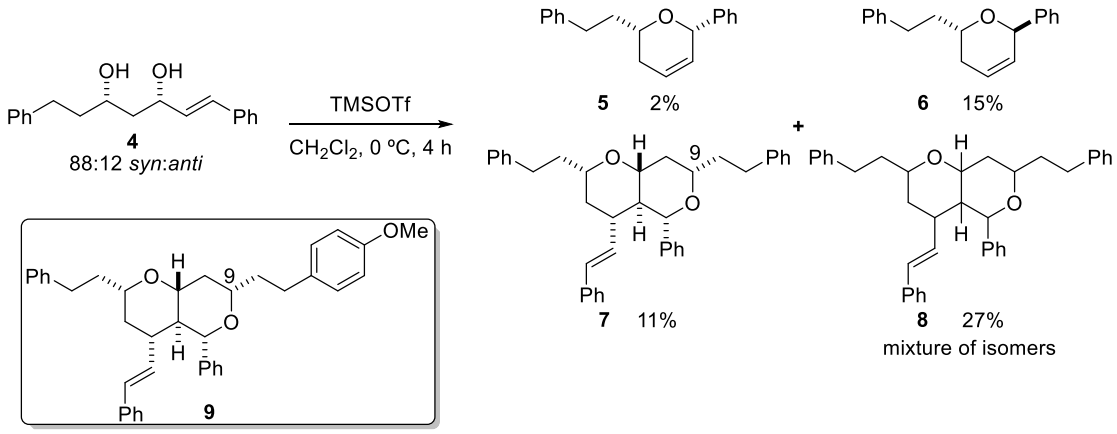
A diarylheptanoid of particular interest is blepharocalyxin D **3** isolated in small quantities (only 5 mg from 10 Kg of seeds of *A. blepharocalyx*) which exhibits potent antiproliferative activity against murine colon 26-L5 carcinoma and human HT 1080 fibrosarcoma cells.[2e] Structure activity studies on such compounds have been hampered by the paucity of available natural products and analogues.

Blepharocalyxin D **3** is assembled on a *trans*-2,8-dioxabicyclo[4.4.4]decane with 4 equatorial side-chains. Its structure was determined using spectroscopic methods[2a] and later confirmed by total synthesis. In the first reported synthesis, Lee and co-workers used two separate Prins cyclizations to construct each oxane ring giving the natural product in 17 steps and 0.9% overall yield.[3] Later we developed a new approach *via* reaction of methyl 3,3-dimethoxypropionate with γ,δ-unsaturated alcohols to give the *trans*-fused bicyclic framework with creation of 2 rings and 4 stereocentres in a single pot. Further elaboration to introduce the C-9 side-chain gave blepharocalyxin D in 15 steps and 8% overall yield.[4]

To date no biosynthetic studies have been reported for these dimeric diarylheptanoids from *A. blepharocalyx*. However, Kadota and co-workers speculated on their possible biogenesis based on co-metabolites including diol **1** and dihydropyran **2** which may serve as biosynthetic building blocks to the more complex fused heterocyclic frameworks.[2e] This biosynthetic speculation gave inspiration for our development of a concise approach for the total synthesis of a series of related dimeric diarylheptanoids including (+)-blepharocalyxin D which are now reported alongside mechanistic studies.

To begin, racemic diol **4** was prepared using the approach of Cossy *et al*.[5] giving a mixture of diastereomers in favour of the *syn*-isomer. Treatment of diol **4** with TMSOTf in dry dichloromethane at 0 °C gave a mixture of products which were separated by column chromatography giving dihydropyrans **5** and **6** in 2% and 15% yield respectively (Scheme 1). In addition, several dimeric diarylheptanoids were formed including the desoxy-analogue **7** of blepharocalyxin D. The structure of **7** with the *trans* ring junction and 4 equatorial side-chains was determined by extensive NMR studies and confirmed by comparison with data for a similar product **9** (with a 9-*p*-methoxyphenethyl side-chain) for which the X-ray structure has been reported.[4]

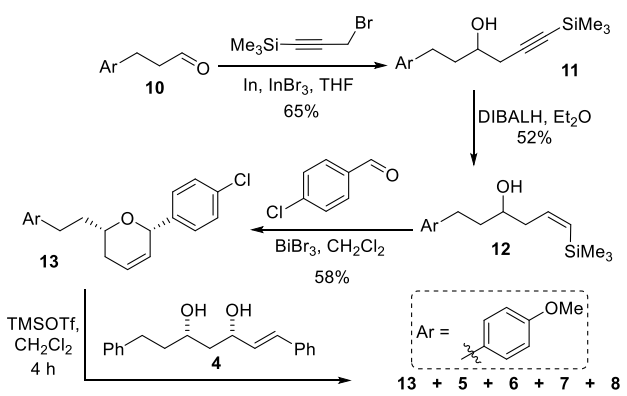
Scheme 1. Synthesis of dimeric diarylheptanoids from racemic diol 4.



To investigate if a dihydropyran is involved in the coupling process, dihydropyran **13** was synthesized with *p*-methoxy phenyl and *p*-chlorophenyl groups required to determine the origin of the aromatic rings in the dimeric products (Scheme 2). An indium-mediated propargylation of aldehyde **10**[6] and subsequent DIBALH reduction of alkyne **11** gave *Z*-vinylsilane **12**. Prins cyclisation of **12** with *p*-chlorobenzaldehyde in the presence of $BiBr_3$[7] gave dihydropyran **13** in 58% yield as a single diastereomer; the *syn* configuration was determined by ^{1}H NMR spectroscopy and comparison with reported analogues.[8] Treatment of a mixture of dihydropyran **13** and diol **4** with TMSOTf returned unchanged dihydropyran **13** and products (**5**-**8**) isolated previously from the starting diol **4**. Hence a dihydropyran is not involved in the synthesis of the dimeric diarylheptanoids. Optimization of the reaction conditions by varying the temperature and acid showed no improvement on the original conditions of 5% TMSOTf in CH_2Cl_2 at 0 °C. Whilst both *syn* and *anti* diols gave dimeric products under the optimised conditions, a slightly higher yield of the blepharocalyxin analogue was general observed in the case of the anti-diols (e.g *syn*-diol **4** and *anti*-diol **18** gave **7** in 11% and 20% yield respectively)

Racemic diols **17**-**19** with variously *para*-substituted aromatic rings were prepared *via* an aldol reaction of 4-phenylbutan-2-one and aldehydes **14**-**16** with MgI_2 and DIPEA,[9] followed by reduction under Evans' conditions[10] (Scheme 3). This reaction sequence was simple to perform on a multigram scale.

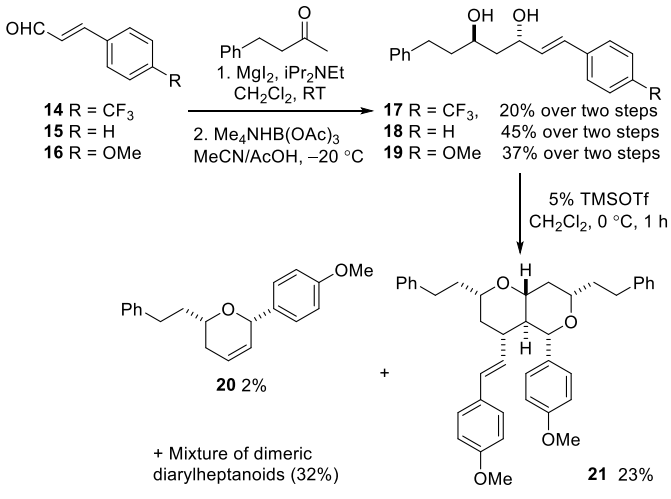
Scheme 2. Synthesis of dihydropyran 13 and reaction with diol 4



Diols **17**, **18** and **19** were reacted separately under the same conditions (5% TMSOTf in CH_2Cl_2) at 0 °C. After 1 hour, diol **17** with the electron-withdrawing *p*-trifluoromethylphenyl group simply returned starting material. In the case of diol **18** cyclic products were observed but ca. 50 % of starting material was also recovered. In contrast, diol **19** with the *p*-methoxyphenyl group gave blepharocalyxin D analogue **21** in 23% yield along with a further 32% of mixed dimeric products. No starting material **19** was detected. These results are in accord with the proposal that the reaction proceeds *via* carbocationic intermediates stabilised by the presence of the electron-rich *p*-methoxyphenyl ring.

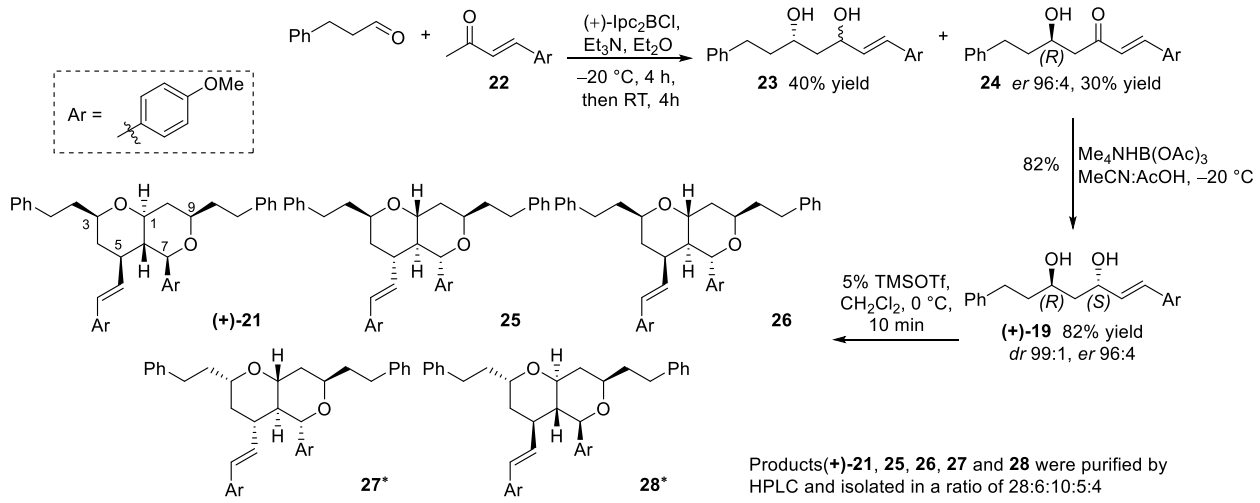
To prepare enantiomerically enriched diol **(+)-19**, dihydrocinnamaldehyde was coupled with ketone **22** in the presence of (+)-Ipc_2BCl and triethylamine[11] at –20 °C for 4 h, giving hydroxyketone **24** with 75:25 *er* in 81% yield. To improve the *er*, the reaction mixture was then warmed to room temperature and monitored by chiral HPLC until one of the enantiomers had been almost fully consumed. Following column chromatography, (*R*)-hydroxyketone **24** was isolated with 96:4 *er* and diol **23** in 40% yield. Directed reduction of hydroxyketone **24** gave the required *anti*-diol **(+)-19** in 82% yield with 99:1 *dr*.

Scheme 3. Two step synthesis of racemic *anti*-diols and reaction with TMSOTf



Treatment of diol **(+)-19** with 5% TMSOTf for just 10 minutes at 0 °C gave the novel analogue **(+)-21** of the natural product blepharocalyxin D with the *trans*-2,8-dioxabicyclo[4.4.0]decane framework and 4 equatorial side-chains (Scheme 4). Further dimeric diarylheptanoids **25**-**28** were purified by HPLC and their structures determined by extensive NMR studies. It was evident that all four products were assembled on a *trans*-2,8-dioxabicyclodecane framework (coupling of 1-H to 6-H, *J* 10-11 Hz) with the 7-methoxyphenyl group equatorial in each case (coupling 6-H to 7-H, *J* 10-11 Hz). The structures of the isomers varied by having one or more axial side-chains as confirmed from analysis of coupling constants combined with nOe studies (supporting information).

Scheme 4. Enantioselective synthesis of *anti*-diol (+)-19 and reaction with TMSOTf (*or the enantiomers)



Furthermore compounds **25**-**27**, each with a C-9 axial side-chain, showed a characteristic downfield shift of the signal assigned to 9-H(eq) to δ 4.2 ppm from δ 3.5 (9-Hax) in blepharocalyxin analogue **21** and isomer **28**.The major products **21**, **25** and **26** each arise from coupling two molecules of the major enantiomer (3*S*, 5*R*) of starting diol **19**. In contrast, the remaining 2 products **27** and **28** were isolated in very low yields, 3% and 1% respectively, and originate from coupling the enantiomers of the starting material.

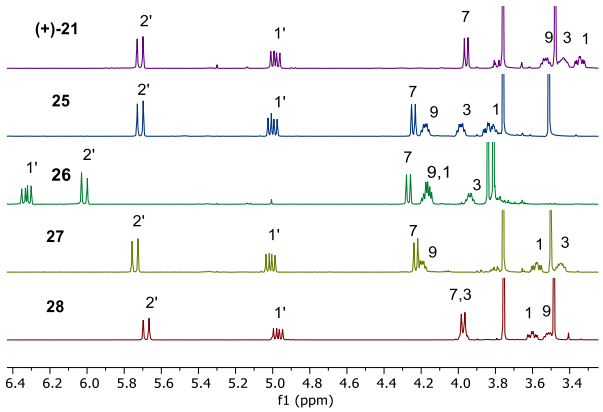
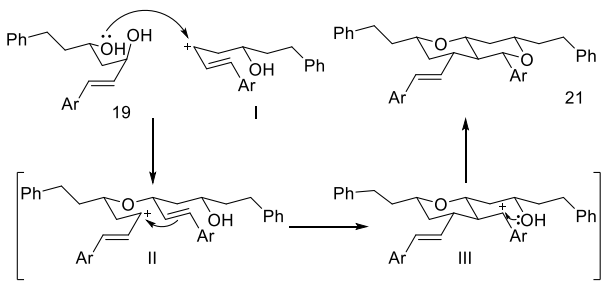


Figure 2. Comparison of the ^{1}H NMR spectra of compounds **21, 25-28.**

Results from the studies described herein using substrates with the electron-rich and electron-deficient aromatic rings (Scheme 3), combined with the array of products formed (Scheme 4) are in accord with the proposed mechanism for the formation of the dimeric diarylheptanoids illustrated in Scheme 5 for the major diastereomer **21**. Loss of the allylic hydroxyl group from diol **19** gives carbocation **I** stabilised by the aromatic ring (Ar). Coupling of diol **19** with **I** and loss of the second allylic alcohol generates a further intermediate **II**. Intramolecular cyclization leads to formation of the new carbon-carbon bond and secondary carbocation **III** again stabilized by the aromatic ring. Finally, cyclization delivers the bicyclic product **21**. Whilst the *trans*-fused rings with all equatorial side-chains is preferred, other diastereomers may arise by non-stereoselective attack on the carbocationic intermediates.

An interesting feature of the proposed mechanism is that the allylic alcohols must be lost selectively from the diols in the coupling process, thus both oxygens in the heterocycles will originate from the 5-hydroxyl group of starting diol **19**. This proposal was verified using an oxygen-18 labelling experiment. [^{18}O] Diol **29** was prepared *via* the approach shown in Scheme 4 starting from [^{18}O] dihydrocinnamaldehyde (50% incorporation, prepared by exchange with $H_2{}^{18}O$) and (*E*)-4-phenylbut-3-en-2-one. The incorporation of label was confirmed by the presence of two signals assigned to C-5 in the ^{13}C-NMR spectrum arising from the characteristic upfield shift (ca δ 0.02 ppm) of ^{13}C-^{18}O compared with ^{13}C-^{16}O (Figure 3).

Scheme 5. Proposed mechanism for formation of dimeric diarylheptanoids



[^{18}O]-Diol **29** was treated under the standard TMSOTf-mediated reaction conditions and the major dimeric product **7**

isolated by column chromatography. The ^{13}C NMR spectrum clearly showed that the signals assigned to all four oxygenated carbons in the rings, C-1 (δ 79.13), C-3 (δ 75.77), C-7 (δ 83.39), and C-9 (δ 75.02), included an isotopically labelled upfield signal with retention of all the oxygen-18 label from the starting diol **29**, consistent with the proposed cascade mechanism (Scheme 5).

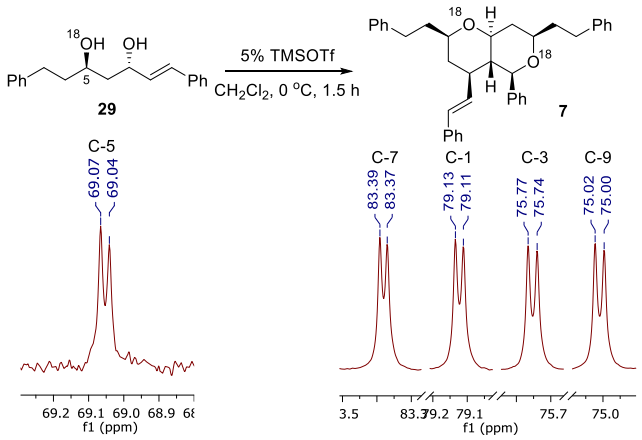
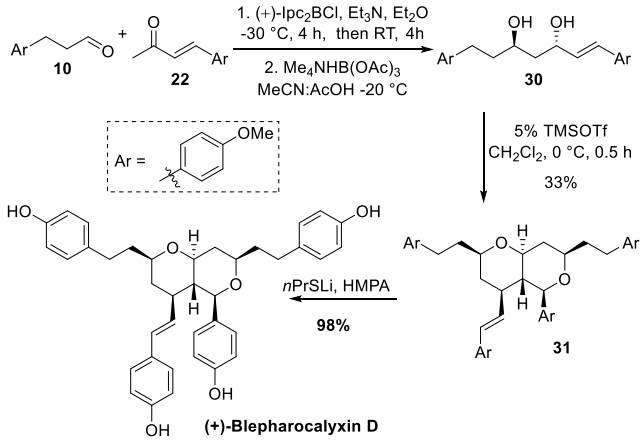


Figure 3. Diagnostic signals in the ^{13}C NMR spectra of oxygen-18 labelled **29** and **7**

Finally, this new acid-mediated procedure was used in the total synthesis of the enantiomer of the natural product, blepharocalyxin D. The required substrate **30** for the key dimerisation was prepared in 2 steps *via* an aldol reaction of aldehyde **10** and ketone **22** followed by directed reduction of the resultant β-hydroxyketone as shown in Scheme 6. Treatment of **30** with TMSOTf gave bicyclic product **31** which was deprotected using LiSPr/HMPA to give (+)-blepharocalyxin D in 4 steps from simple starting materials. The synthetic sample of (+)-blepharocalyxin D gave an optical rotation of $[\alpha]_D$ +80.3 (*c*. 0.7 MeOH), in accord for it being the enantiomer of the natural product.[3a,4]

Scheme 6. Total synthesis of (+)-blepharocalyxin D



In conclusion, we have developed a bioinspired approach for the efficient synthesis of bicyclic heterocycles assembled on a *trans*-2,8-dioxabicyclo[4.4.0]decane decorated with 4 side-chains. A series of unsaturated 3,5-dihydroxydiarylheptanoids were prepared using aldol chemistry followed by a directed reduction of the resultant β-hydroxyketones. The key atom economic step involves an acid mediated (5% TMSOTf) coupling of these linear dihydroxy-diarylheptanoid to produce 2 oxane rings and 4 new stereocentres in one pot. Oxygen-18 labelling studies were in accord with the proposed cascade mechanism of dimerisation. Several analogues of blepharocalyxin D have been prepared including the total synthesis of the enantiomer of the natural product which was achieved in 4 steps and 13% overall yield from simple starting materials, aldehyde **10** and enone **22**. In comparison with previous total syntheses of blepharocalyxin D[3a,4] this concise approach significantly reduces the number of steps to such targets and will give access to a library of dimeric diarylheptanoids for further biological assessment.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectroscopic data and ^1H and ^{13}C NMR spectra of all purified compounds (PDF)

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Notes

The authors declare no competing financial interest

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