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Tandem Prins Cyclization for the Stereoselective Synthesis of the 4,5-Diaryl-hexahydropyrano[3,4-*c*]chromene Skeleton of Calyxins I and J

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Dedicated to Dr. A. V. Rama Rao on the occasion of his 80th birthday

Keywords: Oxygen heterocycles / Cyclization / C–O bond formation / C–C bond formation / Lewis acids

A Prins bicyclization strategy for the stereoselective synthesis of *trans*-fused hexahydropyrano[3,4-*c*]chromene derivatives in good to excellent yields has been developed. The synthetic versatility of this approach has been demonstrated in the synthesis of calyxin I and J analogues. This is the first example of the synthesis of hexahydropyrano[3,4-*c*]chromene derivatives from (*E*)-3-[2-(benzyloxy)phenyl]-5-phenylpent-4-en-1-ol (**4b**) and aldehydes.

Introduction

Diarylheptanoids have been isolated from *Alpinia blepharocalyx* seeds and are used in Chinese traditional medicine for the treatment of stomach disorders.[1] They are known to display a broad spectrum of biological activities such as antioxidant, anti-inflammatory, antihepatotoxic, anticancer, and antiulcer behavior.[2,3]

The calyxins are a family of diarylheptanoids known to exhibit potent antiproliferative activity toward HT-1080 fibrosarcoma and colon 26-L5 carcinoma, with ED_{50} values of 1.71 and 0.89 μM, respectively.[4] Indeed, the pyranochromene ring is a common structural motif in various calyxins such as calyxin I, calyxin J, and epicalyxin I (Figure 1). As a result, there are some reports on the total synthesis of calyxins.[5,6] In addition, a tandem Prins/Friedel–Crafts cyclization sequence for the stereoselective synthesis of simple pyranochromene derivatives has been reported.[7] However, the formation of a diaryl-substituted pyranochromene ring system[8] for the synthesis of calyxin I and J analogues through a Prins cascade process has not yet been explored.

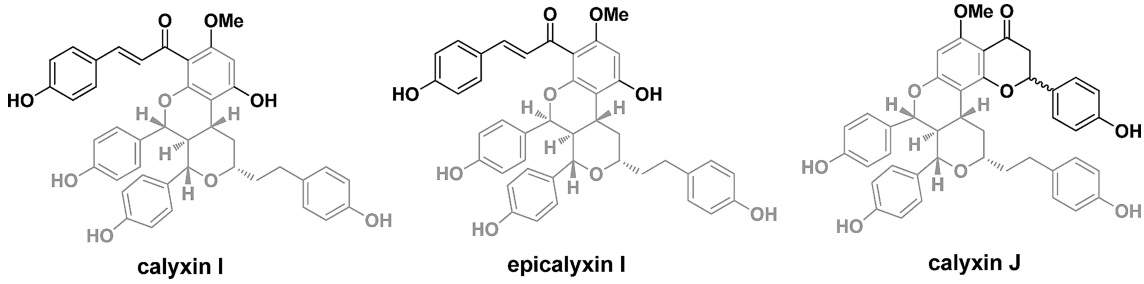

Figure 1. Biologically active natural products.

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Because of their potential application in cancer therapy, diarylheptanoids have emerged as highly attractive and im portant targets for chemical synthesis. "Prins cyclization" is a versatile method for the stereoselective construction of tetrahydropyran rings, which are core structures of many natural products.[9] In particular, intramolecular Prins cyclization is an attractive strategy for the stereoselective synthesis of fused or bridged tetrahydropyran derivatives.[10,11] Despite its potential application in natural products synthe-

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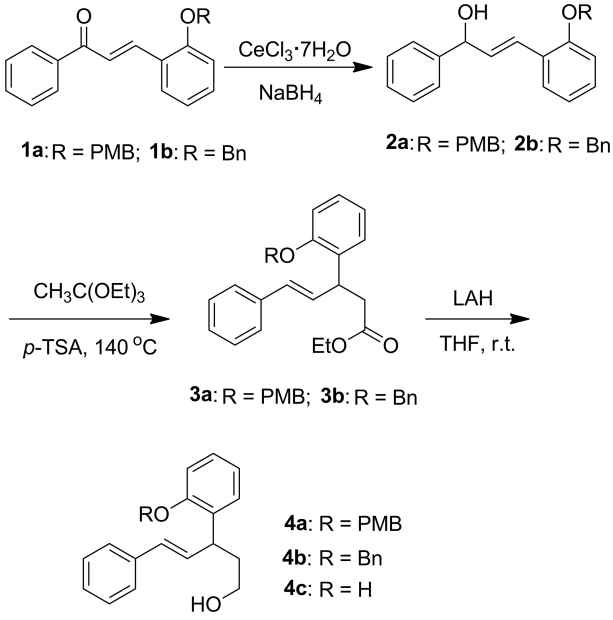
sis,[12,13] the scope of Prins bicyclization has not yet been explored for the synthesis of hexahydropyrano[3,4-*c*]-chromene derivatives from readily accessible γ,δ-unsaturated alcohols tethered with phenolic groups.

Results and Discussion

In the context of our interest in Prins-type cyclizations,[14] here we report a new approach to hexahydropyrano[3,4-*c*]chromene derivatives through Prins cyclization. The starting materials **4a**–**4c** were prepared through Johnson–Claisen rearrangement as shown in Scheme 1.



Scheme 1. Preparation of the starting materials **4a**–**4c**.

Accordingly, treatment of allylic alcohol **2** with triethyl orthoacetate in the presence of propionic acid in toluene at 140 °C over four days afforded the esters, but only in 35% yield. With use of *p*-TSA instead of propionic acid under solvent-free conditions, the corresponding esters were obtained with improved yields and enhanced reaction rates (reaction time < 48 h). Reduction of the esters with LAH gave the desired alcohols (Scheme 1).

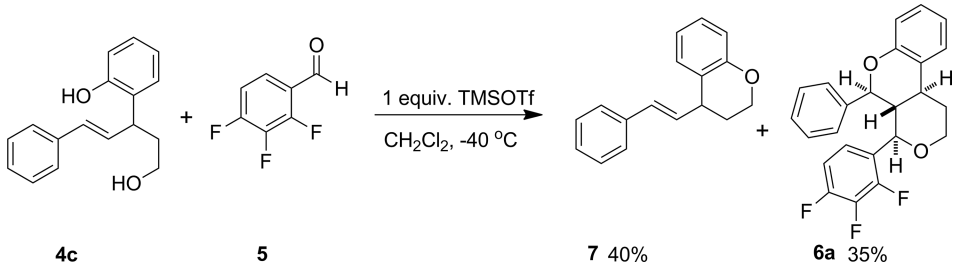
In a model reaction, we first attempted the coupling of (*E*)-2-(5-hydroxy-1-phenylpent-1-en-3-yl)phenol (**4c**) with 2,3,4-trifluorobenzaldehyde in the presence of TMSOTf. To our surprise, the expected product **6a** was obtained only in low yield along with undesired (*E*)-4-styrylchroman **7** as a major product (Scheme 2).

An attempt was made to improve the yield of **6a**. Accordingly, the reaction was performed with THP and TBS derivatives of **4c**. Surprisingly, these protecting groups also produced the undesired byproduct **7** as the major product along with the desired product **6a** (Scheme 2). Therefore, the reaction was further performed with PMB derivative **4a** ((*E*)-3-{2-[(4-methoxybenzyl)oxy]phenyl}-5-phenylpent-4-en-1-ol) and 2,3,4-trifluorobenzaldehyde in the presence of 1 equiv. of TMSOTf in dichloromethane. The corresponding *trans*-fused hexahydropyrano[3,4-*c*]-chromene was obtained in 90% yield as a mixture of **6a** and **8a** (structure of **8a**: Table 2, Entry a, below) in 3:7 ratio at 0 °C (Table 1, Entry 1). This undesired process is likely the result of the high reactivity of *p*-methoxybenzyl trimethylsilyl ether (PMBOTMS) after the Prins bicyclization, facilitating the formation of *p*-methoxybenzyl cation, a powerful benzylating agent, in the presence of a Lewis acid. In an attempt to improve the selectivity in favor of the desired **6a**, the reaction was performed at different temperatures. As shown in Table 1, when the reaction was performed at 0 °C the yield was better than that obtained at –78 °C, but the **6a**/**8a** ratio was considerably poorer (Table 1): at –78 °C the ratio of **6a** to **8a** was improved to 7:3, but the yield was decreased to 60%. Therefore, the yield and the ratio of **6a** to **8a** differ significantly with temperature.

Table 1. Effect of temperature on the formation of **6a**/**8a**.[a]

Entry	Promoter	Temp.	Time	Yield (%)[b]	Ratio[c] **6a**:**8a**
1	TMSOTf	0 °C	20 min	90	30:70
2	TMSOTf	–10 °C	20 min	88	45:55
3	TMSOTf	–20 °C	20 min	86	55:45
4	TMSOTf	–30 °C	20 min	85	60:40
5	TMSOTf	–40 °C	20 min	85	65:35
6	TMSOTf	–60 °C	40 min	75	65:35
7	TMSOTf	–78 °C	40 min	60	70:30

[a] The reaction was performed with 1 equiv. of TMSOTf on 0.5 mmol scale. [b] Isolated combined yields of products **6a**/**8a**. [c] Ratios of **6a** to **8a** were determined from the ^{1}H NMR spectroscopic data of the crude product mixtures.



Scheme 2. Prins cyclization of **4c** with 2,3,4-trifluorobenzaldehyde (**5**).

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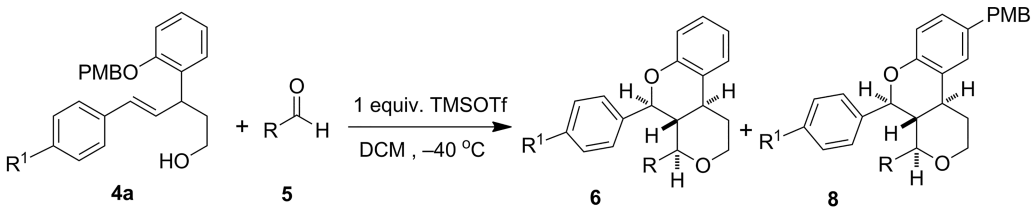
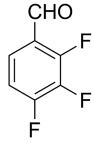
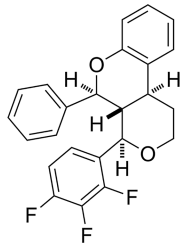
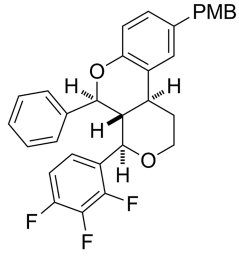
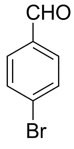
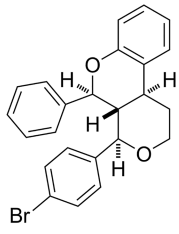
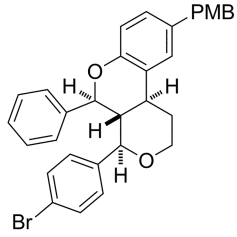
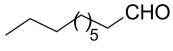
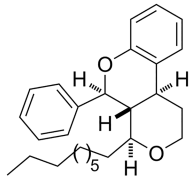
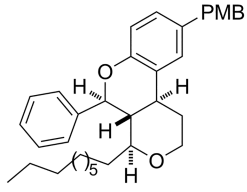
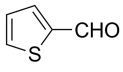
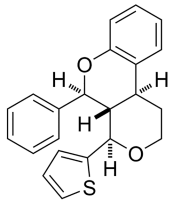
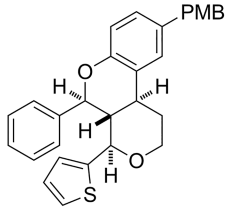
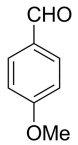
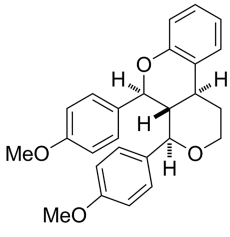
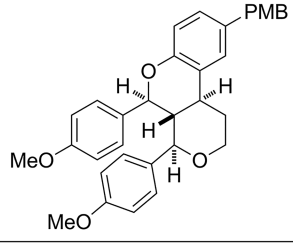
The best combination of yield and selectivity was achieved at –40 °C (Table 1, Entry 5). The products **6a** and **8a** were easily separated by column chromatography. The structures and configurations of **6a** and **8d** were confirmed by single-crystal X-ray crystallography (see the Supporting Information).[15]

Table 2. Preparation of hexahydropyrano[3,4-*c*]chromene derivatives.[a]



Entry	Aldehyde (**5**)	Product[b] **6**	Product[b] **8**	Time (min)	Yield (%)[c] **6**	Yield (%)[c] **8**
a				20	55	30
b				15	55	30
c				20	45	25
d				15	50	30
e				20	45	40

[a] Reactions were performed on 0.5 mmol scale. [b] All the products were characterized by ^{1}H and ^{13}C NMR and IR spectroscopy and by MS. [c] Yield refers to pure products after column chromatography.

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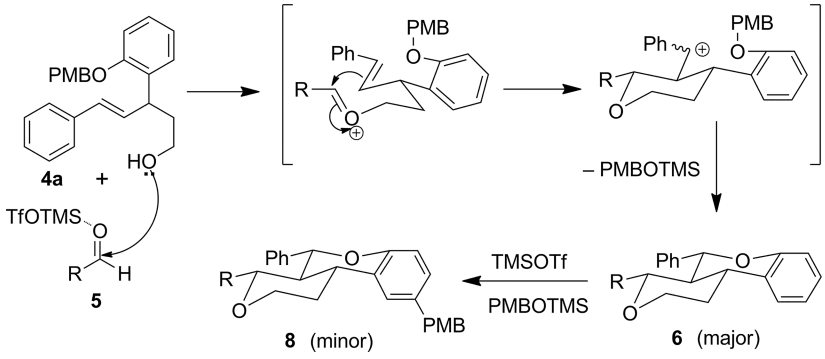


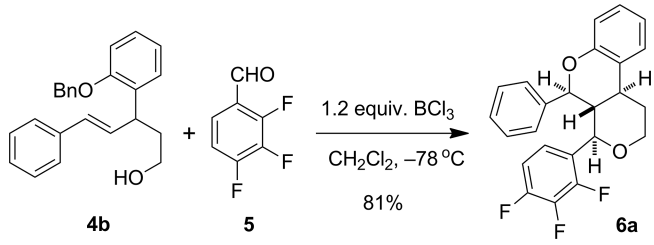
Scheme 3. A possible reaction pathway.

Inspired by the above result, we extended this method to other aldehydes such as 4-bromobenzaldehyde, *n*-decanal, anisaldehyde, and thiophene-2-carbaldehyde. In all cases the corresponding pyranochromene derivatives were obtained in good to excellent yields (Entries b, c, d, and e, Table 2). The efficiencies of Brønsted acids such as triflic acid (TfOH) and camphorsulfonic acid (CSA) and of Lewis acids such as $In(OTf)_3$, $Yb(OTf)_3$, and $Sc(OTf)_3$ in this conversion were tested. Of these, TMSOTf was found to be the superior promoter in terms of conversion. The acidity of the catalyst plays a crucial role in this reaction because the promoter needs to facilitate both Prins cyclization and PMB removal in a single step. Furthermore, we also examined the effect of other Lewis acids such as $InCl_3$, $InBr_3$, and $BF_3{\cdot}OEt_2$. The desired products were not obtained when the reactions were performed with these reagents. Next, we examined the effect of solvents such as dichloromethane, acetonitrile, tetrahydrofuran, and dichloroethane. Of these, dichloromethane gave the best results in terms of conversion.

It is expected that the reactions would proceed through the formation of an oxocarbenium ion from the hemiacetal formed in situ from the aldehyde and γ,δ-unsaturated alcohol **4a**, likely after activation with TMSOTf. Subsequently, the *E*-oxocarbenium ion is attacked by the internal olefin, resulting in the formation of a benzylic carbocation,[12b] which is simultaneously trapped with formation of a benzyl ether, leading to the formation of pyranochromenes **6** and **8** as depicted in Scheme 3.

To improve the selectivity, we further carried out the reaction with a benzyl ether protecting group (compound **4b**) instead of the *p*-methoxybenzyl ether moiety (compound **4a**). However, no cleavage of the benzyl ether was observed during the cyclization when 1 equiv. of TMSOTf was used. Therefore, we performed the cyclization of (*E*)-3-[2-(benzyloxy)phenyl]-5-phenylpent-4-en-1-ol (**4b**) with 2,3,4-trifluorobenzaldehyde in the presence of a stronger Lewis acid: BCl_3 in dichloromethane at –78 °C. Interestingly, the corresponding *trans*-fused hexahydropyrano[3,4-*c*]-chromene **6a** was obtained as a single product in 81% yield (Scheme 4).

Remarkably, no formation of the side product corresponding to **8a** was observed under the above conditions, due to the low reactivity of the benzyl chloride, which is



Scheme 4. Prins cascade reaction between **4c** and 2,3,4-trifluorobenzaldehyde (**5**).

formed in situ from benzyl ether **4b** and a stoichiometric amount of BCl_3 at –78 °C. The scope of this method was further evaluated with respect to various aromatic aldehydes such as benzaldehyde, 3-bromo-4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 2-chlorobenzaldehyde, 4-nitrobenzaldehyde, piperonal, and 2,4,5-trifluorobenzaldehyde. In case of 2,4,5-trifluoro derivative **6r**, the presence of three fluorine atoms was confirmed by ^{19}F NMR spectroscopy. The relative stereochemistry of compound **6r** was determined by detailed 1D and 2D NMR experiments. The large scalar coupling constants, $^3J_{H4\text{-}H9}$ = 11.5, $^3J_{H9\text{-}H10}$ = 10.1, $^3J_{H4\text{-}H5(ax)}$ = 11.5, $^3J_{H5(ax)\text{-}H6(ax)}$ = 12.5 Hz, along with the observation of nOe cross peaks of H4/H6(ax), H6(ax)/H8, H8/H10, H4/H10, H5(ax)/H9, H4/H8 confirm the proposed stereochemistry (Figure S2 in the Supporting Information). The presence of three fluorine atoms was characterized by ^{19}F-^{13}C scalar couplings, which are presented in the Supporting Information.

In all cases, the corresponding pyranochromene derivatives were obtained in good to excellent yields (Table 3). This method works not only with aromatic aldehydes but also with aliphatic aldehydes.

In the cases of aliphatic aldehydes, the corresponding alkyl-substituted pyranochromene derivatives were obtained in slightly lower yields than in the cases of their aromatic counterparts. This method is effective even with acid-sensitive cinnamaldehyde, affording the corresponding *trans*-fused hexahydropyrano[3,4-*c*]chromene in good yield. The efficacy of this approach was also tested by performing the reaction with heteroaromatic aldehydes such as furan-2-carbaldehyde.

In order to show the synthetic utility of this methodology, we attempted the synthesis of analogues of

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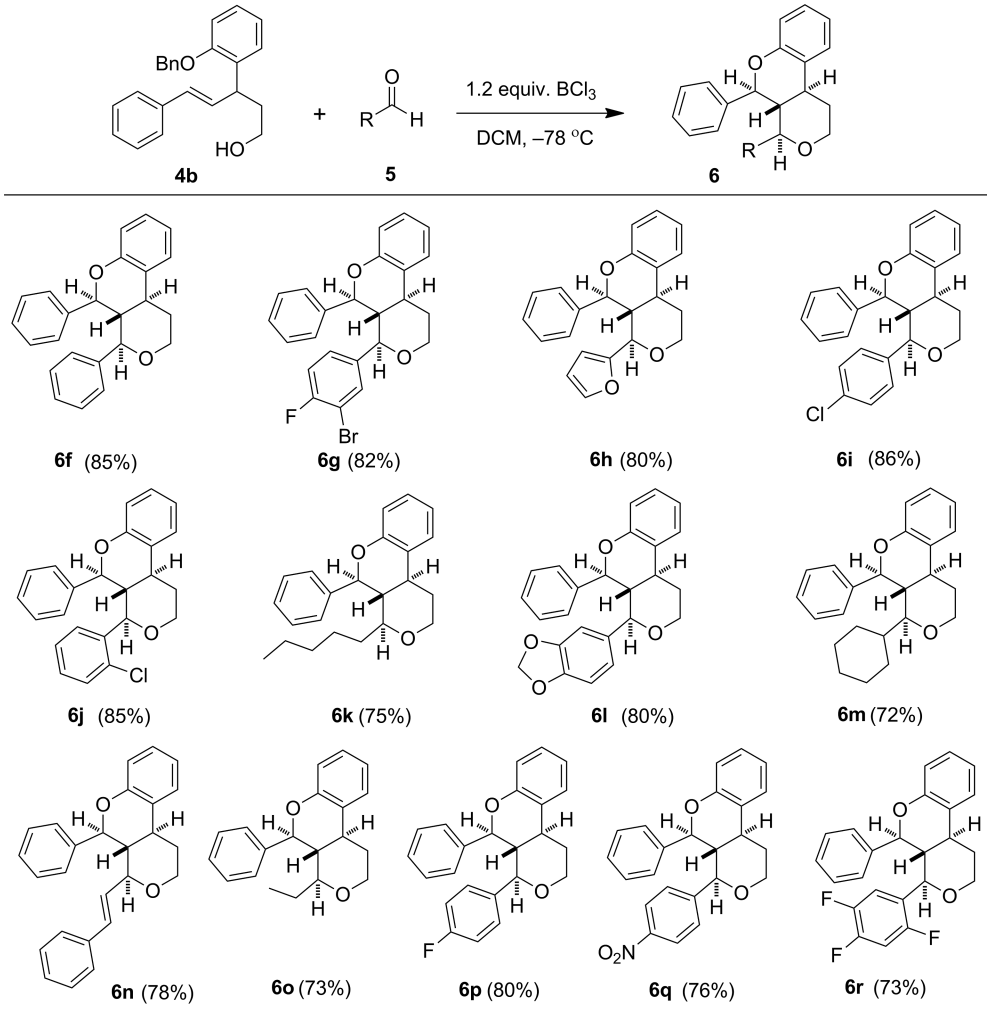
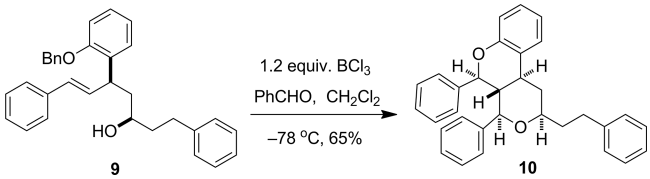
Table 3. Preparation of hexahydropyrano[3,4-*c*]chromene derivatives.[a,b]



[a] The reactions were performed on 0.5 mmol scale. [b] Yields refer to pure products after column chromatography.

calyxin I and J (Scheme 5). These compounds have fascinating structures and biological profiles, and calyxin I can be used as a lead compound for producing new anticancer drugs. Accordingly, the starting material, γ,δ-unsaturated alcohol **9**, was prepared in two steps from the alcohol **4b** through a sequential oxidation followed by a Grignard reaction. Treatment of γ,δ-unsaturated alcohol **9** with benzaldehyde in the presence of 1.2 equiv. BCl_3 at –78 °C gave compound **10**, the core structure of calyxins I and J, in 65% yield (Scheme 5). This protocol is simple and convenient and provides the desired products in good yields and with high stereoselectivity.



Scheme 5. Synthesis of an analogue of calyxins I and J.

Conclusions

In conclusion, a new Prins bicyclization strategy for the synthesis of hexahydropyrano[3,4-*c*]chromene derivatives has been developed. In the case of *p*-methoxybenzyl ether **4a**, two product types were formed (**6** and **8**), whereas the single products **6** were obtained from benzyl ether **4b**. However, in both cases the *trans*-fused product type was formed exclusively. The scope of this process is demonstrated in the stereoselective synthesis of the core structure of calyxins I and J, which are reported antioxidant, anti-inflammatory, anticancer, and antiulcer agents. This approach generates two heterocyclic rings with four new stereogenic centers in a one-pot operation.

Experimental Section

General: All the solvents were dried by standard procedures. Reactions were performed in oven-dried round-bottomed flasks fitted with rubber septa, and the reactions were conducted under nitro-

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gen. Glass syringes were used to transfer the solvents. Crude products were purified by column chromatography on silica gel (60–120 or 100–200 mesh). TLC plates were viewed by exposure to ultraviolet light and/or iodine vapors and/or an acidic methanolic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (≈250 °C). Organic solutions were concentrated with a rotary evaporator at 35–40 °C. IR spectra were recorded with a FTIR spectrometer. ^{1}H NMR and ^{13}C NMR (proton-decoupled) spectra were recorded with 200, 300, 400, or 500 MHz NMR spectrometers in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded with a mass spectrometer by electron ionization (EI and ESI) or atmospheric pressure chemical ionization (APCI) techniques.

Typical Procedure for Prins Cascade Cyclization: TMSOTf (1 equiv.) or BCl_3 (1.2 equiv.) was added to a stirred solution of a γ,δ-unsaturated alcohol (**4a**, **4b,** or **9**, 0.5 mmol) and an aldehyde (0.6 mmol) in dry dichloromethane (5 mL). The resulting mixture was stirred at –78 °C under nitrogen for the specified time. After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (1.0 mL) and extracted with dichloromethane (2–5 mL). The organic layers were combined, washed with brine (3–5 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) with ethyl acetate/hexane as eluent to afford the pure product.

Supporting Information (see footnote on the first page of this article): Spectral data for **6a**–**r**, **8a**–**e**, **4c**, **9**, **2a**, **3a**, **4b**, and **7**, copies of ^{1}H and ^{13}C NMR spectra of products **6a**–**r**, **8a**–**e**, **10**, **7**, **4a**, and **4b**, and X-ray data for compounds **6a** and **8d**.

Acknowledgments

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[15] CCDC-943365 (for **6a**) and -954068 (for **8d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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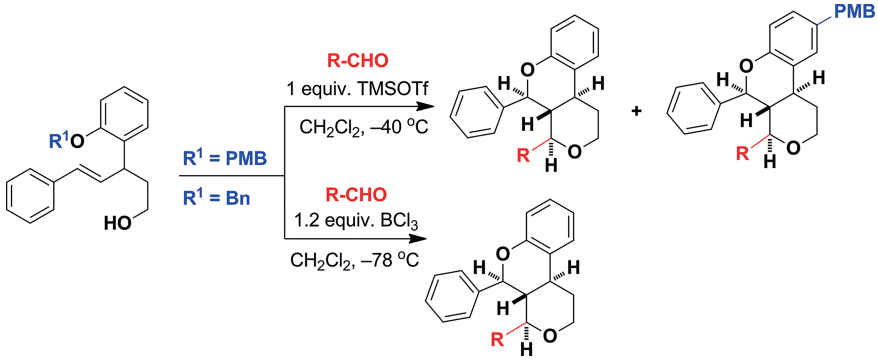

A Prins-type bicyclization strategy for the stereoselective synthesis of *trans*-fused hexahydropyrano[3,4-*c*]chromene derivatives in good to excellent yields is reported.

Keywords: Oxygen heterocycles / Cyclization / C–O bond formation / C–C bond formation / Lewis acids

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