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Synthesis of (−)-Centrolobine by Prins Cyclizations that Avoid Racemization

Shinji Marumoto, James J. Jaber, Justin P. Vitale, and Scott D. Rychnovsky*

Department of Chemistry, 516 Rowland Hall, University of California−Irvine, Irvine, California 92697-2025

srychnov@uci.edu

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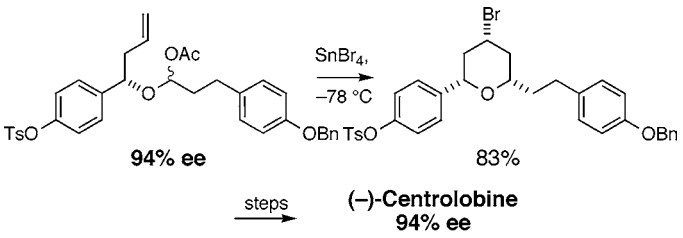
ABSTRACT



The segment-coupling Prins cyclization avoids two of the problems common to other Prins cyclization protocols: side-chain exchange and partial racemization by reversible 2-oxonia Cope rearrangement. Model studies demonstrate the stereochemical fidelity of Prins cyclizations using α-acetoxy ethers compared with direct aldehyde–alcohol Prins reactions. Furthermore, we propose a mechanism for the racemization observed in some intermolecular Prins cyclizations. Two straightforward syntheses of optically pure (−)-centrolobine highlight the utility of Prins cyclizations.

The Prins cyclization is a potentially powerful method for preparing tetrahydropyran rings.[1] A number of groups have been investigating Prins cyclization reactions and applying these reactions to natural product syntheses.[2] The segment-coupling Prins cyclization developed in our lab[3] is distinct from other methods in that the key cyclization precursor is an α-acetoxy ether, which is prepared by reductive acetylation of a homoallylic ester.[4] Prins cyclizations can be initiated from mixtures of aldehydes and homoallylic alcohols,[2] and though this procedure may be more direct than our segment-coupling route, a number of side reactions associated with this approach have recently come to light.[2e,g,6c] These side reactions include partial racemization and the exchange of aldehyde and alcohol side chains leading to mixtures of products. In this communication, we compare the segment-coupling Prins cyclization with direct alcohol−aldehyde cyclizations and show that these complications can

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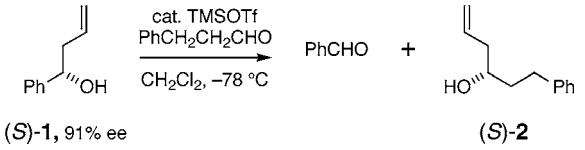
be avoided. Furthermore, our approaches to (−)-centrolobine demonstrate the utility of both alcohol−aldehyde and segment-coupling Prins reactions in natural product synthesis.

We became concerned with the problem of racemization while investigating an allyl transfer reaction[5] mediated by a 2-oxonia Cope rearrangement.[6] Table 1 shows some results

Table 1. Partial Racemization in a 2-Oxonia Cope Allyl Transfer Reaction



(*S*)-**1**, 91% ee (*S*)-**2**

entry[a]	equiv of (*S*)-**1**	equiv of aldehyde	% ee of (*S*)-**2**[b]
1	1.0	0.9	20
2	1.5	1.0	63
3	1.5	1.0	60[c]
4	3.0	1.0	68[c]

[a] Yields were not determined. All of the aldehyde was consumed within minutes. [b] The ees were determined by GC analysis on a Chiraldex γ-TA column. [c] In these reactions, 1.5 equiv of TMSOTf was used.

of this investigation. Optically active alcohol (*S*)-**1** did transfer the allyl group to an aliphatic aldehyde in the presence of a Lewis acid, but significant racemization accompanied the reaction. The racemization was reduced but not eliminated by using a larger excess of the allyl donor. A similar transfer using an α-acetoxy ether precursor showed no racemization.[6d]

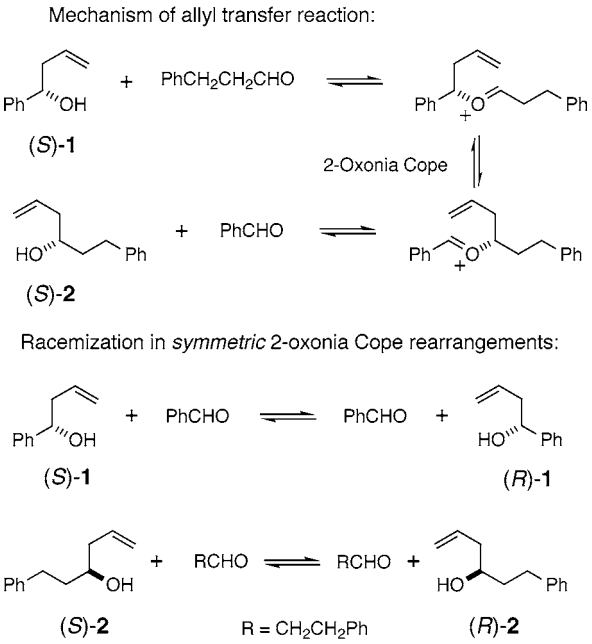


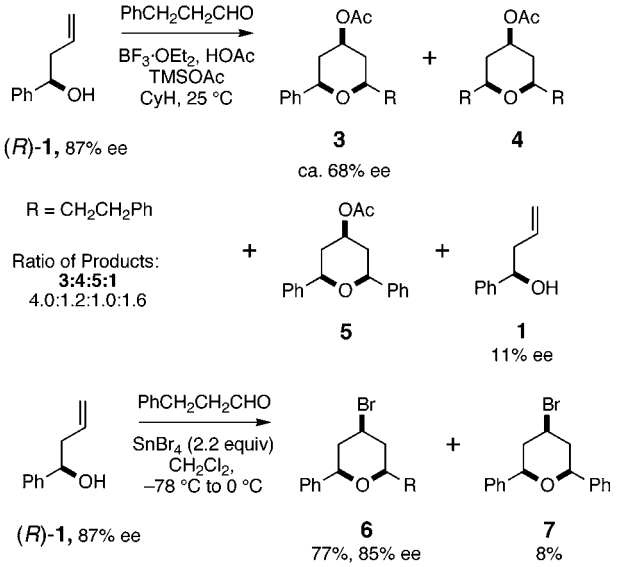
Figure 1. Mechanism of allyl transfer and racemization attributable to 2-oxonia Cope rearrangements.

The mechanism for the racemization is outlined in Figure 1. The allyl transfer reaction is mediated by a stereoselective 2-oxonia Cope rearrangement[6] of the asymmetric oxocarbenium ion. In this case, the rearrangement produces benzaldehyde and the homoallylic alcohol (*S*)-**2**. Racemization occurs when the benzaldehyde produced reacts with (*S*)-**1** to generate an oxocarbenium ion that undergoes a *symmetric* 2-oxonia Cope rearrangement to produce epimeric (*R*)-**1**. Similarly, product alcohol (*S*)-**2** can be racemized by the original aldehyde. Thus, allyl transfer in a *symmetric* 2-oxonia Cope rearrangement is the origin of the facile racemization in these experiments.

The combination of an aldehyde, a homoallylic alcohol, and a Lewis acid is a common protocol for carrying out Prins cyclizations, so we were not surprised when Willis reported partial racemization (from 94% ee to 79% ee) in a Prins cyclization catalyzed by $BF_3{\cdot}OEt_2$ and HOAc.[2g] We propose that this racemization is also mediated by allyl transfer in a *symmetric* 2-oxonia Cope rearrangement. Willis further reported the formation of symmetric tetrahydropyran side products, an observation that is consistent with the intervention of a 2-oxonia Cope reaction.[2g]

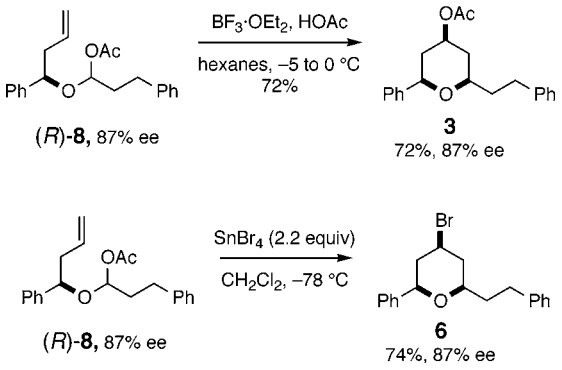
Our investigation of this racemization pathway is outlined in Schemes 1 and 2. The Prins cyclization between alcohol

Scheme 1. Partial Racemization with Aldehyde−Alcohol Prins Cyclization Reactions



1 and dihydrocinnamaldehyde was investigated under different Lewis acid conditions. Cyclization promoted by $BF_3{\cdot}OEt_2$ and HOAc led to partial racemization (from 87% ee to 68% ee) of the desired product **3** and formation of side chain exchange products **4** and **5**. This result is entirely consistent with Willis' observation.[2g] Presumably, the 2-oxonia Cope process mediates the exchange of the side chains and the partial racemization observed in the reaction. A similar cyclization also was promoted by $SnBr_4$. The reaction was more efficient and, much to our surprise, did not

Scheme 2. Prins Cyclizations with α-Acetoxy Ethers Prevent Racemization



racemize (from 87% ee to 85% ee) the major product **6**. Only 8% of the symmetric cyclization product **7** was isolated. Apparently the cyclization with $SnBr_4$ is much faster than that with $BF_3{\cdot}OEt_2$ and HOAc and suppresses the competing 2-oxonia Cope process. Thus, direct Prins cyclizations with aldehydes and alcohols led to partial racemization with $BF_3{\cdot}OEt_2$ but essentially no racemization with $SnBr_4$.

Segment-coupling Prins cyclizations leading to the same products are shown in Scheme 2. The α-acetoxy ether (*R*)-**8** was prepared by esterification and reductive acetylation of alcohol (*R*)-**1**. Cyclization with $BF_3{\cdot}OEt_2$ and HOAc generated tetrahydropyran **3** in 72% yield with no loss of optical purity. Cyclization with $SnBr_4$ produced tetrahydropyran **6** in 74% yield and also showed no loss of optical purity. The α-acetoxy ether substrates do not undergo the symmetric 2-oxonia Cope rearrangement leading to racemization or show any of the side chain exchange products. The direct aldehyde−alcohol cyclization with $SnBr_4$ works very well, and the segment coupling procedure offers no advantages for this substrate. The segment coupling procedure avoids racemization and side chain exchange found in the $BF_3{\cdot}OEt_2$-promoted cyclization and is to be preferred in the synthesis of 4-acetoxy tetrahydropyrans.

Two straightforward syntheses of optically pure (−)-centrolobine highlight the utility of Prins cyclizations. (−)-Centrolobine is an antibiotic isolated from the heartwood of *Centrolobium robustum*.[7] Its structure was elucidated in 1964 by total synthesis of the racemic methyl ether.[7] Solladie and co-workers recently reported the first enantioselective total synthesis of (−)-centrolobine, which also served to elucidate its absolute configuration.[8] The structure of (−)-centrolobine is presented in Figure 2.

A synthesis of centrolobine by Prins cyclization needs to address the problem of the electron-rich aromatic ring. Willis has shown and we have also found[9] that homoallylic alcohols

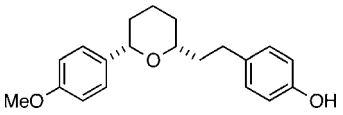
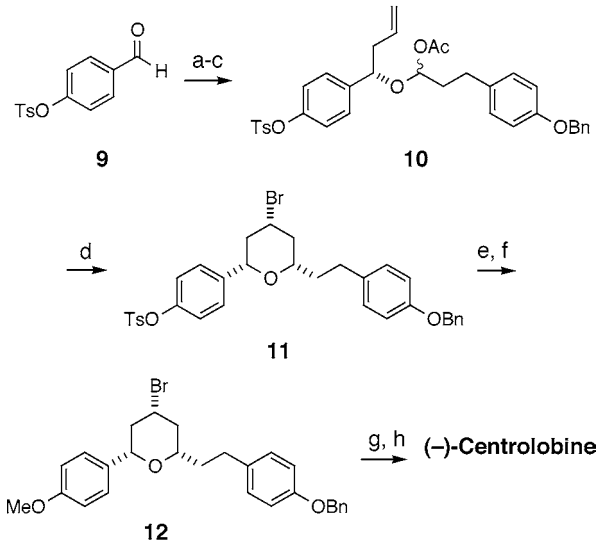


Figure 2. Structure and absolute configuration of (−)-centrolobine.

in which the alcohol is adjacent to an electron-rich aromatic ring do not undergo normal Prins cyclization but rather suffer solvolysis of the alcohol, complete racemization, and the production of a number of side products.[2g,i] This solvolysis reaction is an alternative mechanism for the racemization observed in some Prins reactions.[2g,i] Thus, the *p*-methoxy group must be masked or introduced indirectly. The first route explored the use of a tosylate to deactivate the phenol and is presented in Scheme 3.

Scheme 3. Synthesis of (−)-Centrolobine Using a Tosylate Protecting Group[a]



[a] Reagents and conditions: (a) (*S*)-BINOL, $Ti(O\text{-}iPr)_4$, allyl-$SnBu_3$, 79%, 94% ee. (b) DCC, DMAP, 4-(BnO)$C_6H_4CH_2CH_2CO_2H$, 94%. (c) (i) DIBAL-H, −78 °C; (ii) Ac_2O, DMAP, pyridine 93%. (d) $SnBr_4$, CH_2Cl_2, −78 °C, 84%. (e) K_2CO_3, MeOH, reflux. (f) MeI, K_2CO_3, acetone, 85% from **11**. (g) Bu_3SnH, AIBN (cat.) $PhCH_3$, reflux, 86%. (h) H_2, 10% Pd/C, 72%.

The synthesis of (−)-centrolobine commenced with a Keck enantioselective allylation of aldehyde **9** to give the homoallylic alcohol in 94% ee, Scheme 3.[10] Esterification and reductive acetylation led to the α-acetoxy ether **10**. Cyclization promoted by $SnBr_4$ generated the all-equatorial tetra-

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(9) Jaber, J. J. Ph.D. Thesis, University of California−Irvine, Irvine, California, 2002. Compound **10** (Scheme 3) with a Bn in place of the Ts group led to fragmentation rather than Prins cyclization upon treatment with $BF_3{\cdot}OEt_2$ at 0 °C.

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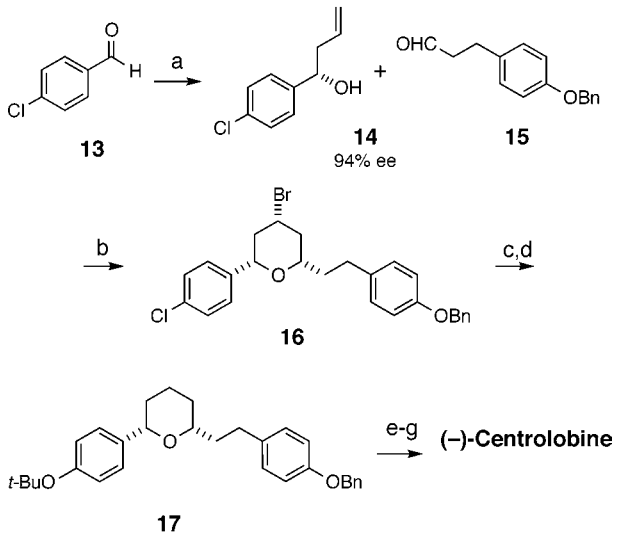
hydropyran **11** in 84% yield without any side chain exchange reactions. The tosylate protecting group was replaced with a methyl ether by basic hydrolysis and alkylation. The synthesis was completed by radical reduction to remove the bromide and hydrogenation to remove the benzyl group. Synthetic (−)-centrolobine was identical to the natural product by ^{1}H NMR, ^{13}C NMR, and IR analysis. The optical rotation of the synthetic material ($[\alpha]^{25}_D$ −93.1 (*c* 0.16, $CHCl_3$)) was essentially equal to that reported by Solladie ($[\alpha]^{25}_D$ −93 (*c* 1.0 $CHCl_3$))[8] and demonstrates that the Prins cyclization proceeds without racemization. The synthesis proceeds in eight steps from aldehyde **9** with an overall yield of 30.5%.

The second synthesis of (−)-centrolobine used a *p*-chloro substituent to introduce the *p*-methoxy group and is outlined in Scheme 4. The unexpected success of the alcohol−aldehyde Prins cyclization with $SnBr_4$ prompted us to incorporate it into this route. Alcohol **14** (1.1 equiv) and aldehyde **15** (1.0 equiv) were treated with $SnBr_4$ to produce Prins cyclization product **16** in 73% yield without significant racemization.[11] Selective removal of the bromide by radical reduction proceeded uneventfully. Replacement of the chloride with a *tert*-butoxy group using Buchwald's Pd-catalyzed process gave the desired product in 82% yield.[12] Cleavage of the *tert*-butyl group with TFA and etherification introduced the required methyl ether, and hydrogenolysis completed the synthesis. The spectral data for synthetic (−)-centrolobine matched that reported in the literature and the data for our previously prepared sample. The optical rotation of the synthetic material ($[\alpha]^{25}_D$ −92.3 (*c* 0.07, $CHCl_3$)) is essentially identical to that of the previously prepared synthetic sample and to the literature value. The synthesis of (−)-centrolobine was accomplished in seven steps and 30% overall yield. The use of a chloride surrogate and the alcohol−aldehyde Prins cyclization reduced the number of steps and produced a similar overall yield as the previous route.

Scheme 4. Synthesis of (−)-Centrolobine Using a Chloride Surrogate for the Methoxy Group[a]



[a] Reagents and conditions: (a) (*S*)-BINOL, Ti(O-*i*Pr)$_4$, allyl-$SnBu_3$, 99%, 94% ee; (b) $SnBr_4$, CH_2Cl_2, from −78 to −30 °C, 73%; (c) Bu_3SnH, AIBN (cat.) $PhCH_3$, reflux, 86%; (d) $Pd_2(dba)_3$, 2-(di-*tert*-butylphosphino)biphenyl, NaO*t*-Bu, 82%; (e) TFA, CH_2Cl_2; (f) MeI, K_2CO_3, acetone; (g) H_2, 10% Pd/C, 57% from **16**.

The segment-coupling Prins cyclization is an efficient reaction that avoids the side-chain exchange and the partial racemization found with some of the direct alcohol−aldehyde cyclization protocols. We propose that the racemization takes place through a *symmetric* 2-oxonia Cope rearrangement that is not observed with α-acetoxy ether precursors. The utility of the segment-coupling and direct Prins cyclization for natural product synthesis was demonstrated in two enantioselective syntheses of (−)-centrolobine. The syntheses differ in the selection of a protecting group for the electron-rich aromatic ring, but both routes proceed without racemization. The Prins cyclization is a powerful method for the synthesis of tetrahydropyran-containing natural products.

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Supporting Information Available: Preparation and characterization of the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Rotation of **16** prepared in Scheme 4: $[\alpha]^{25}_D$ −44.9 (*c* 1.77, CH_2Cl_2). An α-acetoxy ether route to **16** gave material with a nearly identical optical rotation: $[\alpha]^{25}_D$ −44.4 (*c* 1.70, CH_2Cl_2).

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