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The Prins Reaction Using Ketones: Rationalization and Application toward the Synthesis of the Portentol Skeleton

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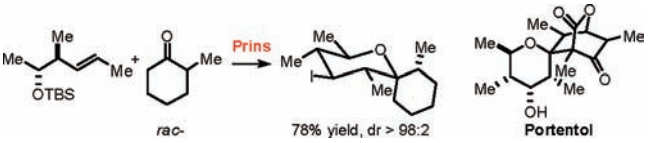
ABSTRACT



We report a TMSI-promoted Prins cyclization reaction with ketones as carbonyl partners to prepare polysubstituted chiral spirotetrahydropyrans. In the presence of racemic 2-methylcyclohexanone a dynamic kinetic resolution occurred affording one stereoisomer. The observed enantiospecificity has been rationalized by DFT calculation.

Lichens are among the most fascinating organisms, characterized by a symbiotic association between a fungus and a green algae or a cyanobacterium producing many biologically active metabolites. Recent studies have reported that many lichens contain a stable consortium of other microorganisms on the surface offering a wide molecular diversity.[1] Among the numerous lichenic derivatives, portentol **1** (Figure 1), a polypropionate isolated from *Roccella portentosa*, possesses a fascinating structure for which no synthesis (or synthetic approach) has been reported to date.[2] Despite the numerous major achievements in total synthesis that have been reported over the past half-century,[3] the portentol structure presents a unique challenge.

Retrosynthetic simplification of **1** can, in principle, be rather straightforward and, in our hands, yielded the spiroether **2** as a model substrate. Prins cyclization[4] involving an alkene appeared here to be the method of choice for preparing a polyfunctionalized tetrahydropyran of this sort, but despite significant advances in the Prins reaction field,[4] only a few examples that combine homoallylic alcohols and ketones are reported in the literature.[5] Based on this statement, we were intrigued by the possibility of constructing the portentol spirotetrahydropyran skeleton via a Prins cyclization. Thus polysubstituted chiral homoallylic alcohol **3** and cyclohexanone **4**, in the presence of a catalyst or promoter, could potentially undergo a Prins cyclization reaction to give **2** (Figure 1).

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(1) (a) Boustie, J.; Grube, M. *Plant Genetic Resources* **2003**, *3*, 273–287. (b) Podterob, A. P. *Pharm. Chem. J.* **2008**, *42*, 582–588. (c) Grube, M.; Berg, G. *Fung. Biol. Rev.* **2009**, *23*, 72–85.

(2) (a) Aberhart, D. J.; Overton, K. H. *Chem. Commun.* **1969**, 162–163. (b) Aberhart, D. J.; Overton, K. H. *Chem. Commun.* **1970**, 664–665. (c) Aberhart, D. J.; Overton, K. H.; Huneck, C. *J. Chem. Soc. (C)* **1970**, 1612–1623. (d) Ferguson, G.; Mackray, I. R. *Chem. Commun.* **1970**, 665–666. (e) Quilhot, W.; Garbarino, J. A.; Gambaro, V. *J. Nat. Prod.* **1983**, *46*, 594–595. (f) Pettit, G. R.; Zhang, Q.; Pinilla, V.; Herald, D. L.; Doubek, D. L.; Duke, J. A. *J. Nat. Prod.* **2004**, *67*, 983–985.

(3) (a) Nicolaou, K. C.; Sorensen, E. *Classics in Total Synthesis*; Wiley-VCH: 1996. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: 2003. (c) Nicolaou, K. C.; Chen, J. S. *Classics in Total Synthesis III*; Wiley-VCH: 2011.

(4) For a recent review, see: Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445.

(5) For significant examples, see: (a) Nishizawa, M.; Shigarahi, T.; Takao, H.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett.* **1999**, *40*, 1153–1156. (b) Sabitha, G.; Reddy, K. B.; Bhikshapathi, M.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 2807–2810. (c) Yadav, J. S.; Reddy, B. V. S.; Krishna, V. H.; Swamy, T.; Kumar, G. G. K. S. N. *Can. J. Chem.* **2007**, *85*, 412–417. (d) Castaldi, M. P.; Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 3362–3365.

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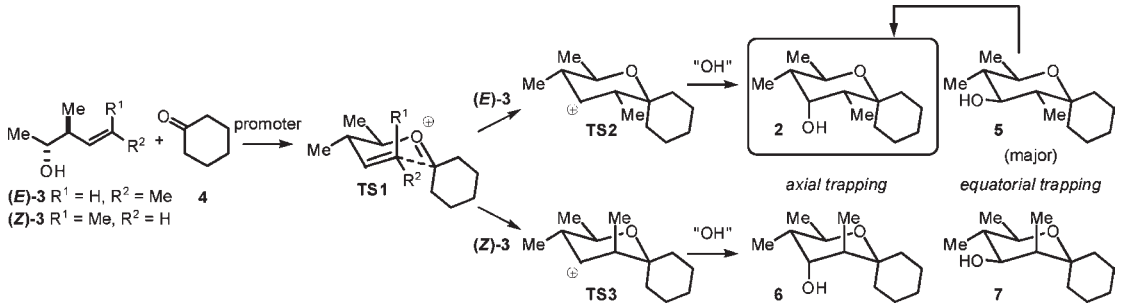
Scheme 1. Plausible Mechanism, ChairLike Transition State and Stereochemical Outcome



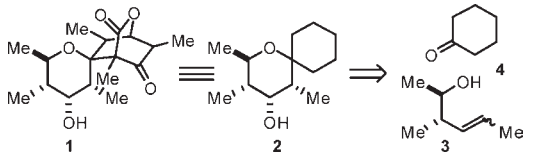


Figure 1. Structure of portentol **1** and retrosynthetic approach.

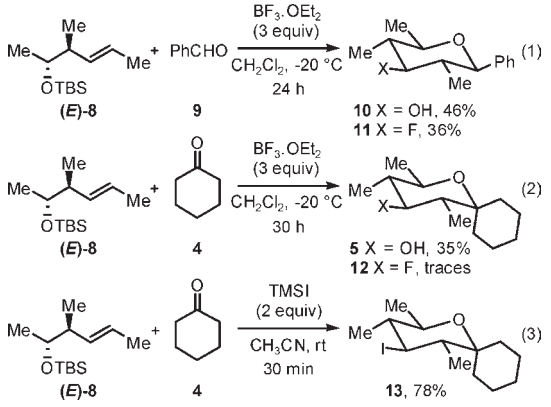
The stereochemical outcome of the Prins cyclization reaction can be anticipated relying on the accepted general mechanism and by invoking the chairlike transition state (Scheme 1). The oxocarbenium ion intermediate **TS1** would undergo a 6-*endo* cyclization to give selectively the carbocation **TS2** or **TS3** (respectively formed from **(*E*)-3** or **(*Z*)-3**) that could then be trapped by various nucleophiles.

According to the Alder's model,[6] a preferential equatorial trapping of the nucleophile will usually occur. Therefore, it would be necessary to carry out the Prins cyclization reaction with the homoallylic alcohol **(*E*)-3** leading probably to **5** as the major product which could lead to the desired spiroether **2** after an inversion of the absolute configuration of the alcohol function. Detailed studies on the Prins cyclization reaction involving polysubstituted homoallylic alcohols and ketones are reported herein.

In our initial investigation, the search for optimal reaction conditions was conducted using the enantiopure homoallylic silylether **(*E*)-8**[7] and benzaldehyde **9** by varying the promoter, solvent, and temperature.[8] Boron trifluoride etherate was proven to be an effective promoter for the reaction process (Scheme 2, eq 1). Because water was produced during the formation of the oxocarbenium ion intermediate, the hydroxy product **10** was obtained along with the fluoride compound **11**.[9] It is also noteworthy that the optically active tetrahydropyrans **10** and **11** were formed with excellent diastereoselectivities (> 98:2) after careful examination of the crude reaction mixture by NMR.

Encouraged by this result we next investigated the reaction with cyclohexanone **4** (Scheme 2, eq 2). Despite numerous attempts to optimize the reaction, the conversion remained low and the expected product **5** was isolated as the sole diastereoisomer in moderate yield and only traces of the fluoride derivative **12** were observed. Sabitha et al.[5b] described an efficient synthesis of spiroethers from various ketones and homoallylic alcohols in acetonitrile using TMSI (generated in situ) as the promoter and nucleophile source. With these reaction conditions in mind, we decided to apply them to our substrates (Scheme 2, eq 3). We were delighted to observe a complete conversion after a few minutes of stirring. An exclusive equatorial attack of the iodide on the carbocation species occurred; the iodospirotetrahydropyran **13** was obtained as the major diastereoisomer (> 98:2) as established by NMR analysis of the crude reaction mixture. It was isolated in good yield (78%).

Scheme 2. Initial Investigations



With appropiate Prins cyclization reaction conditions in hand, we focused on the scope of this transformation (Table 1). As noted with the cyclohexanone **4**, a single

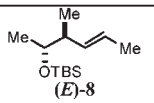
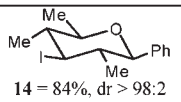
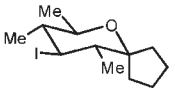
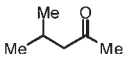
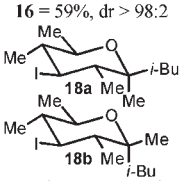
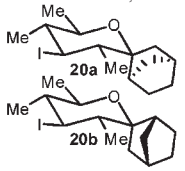
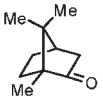
(6) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961.

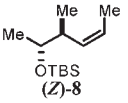
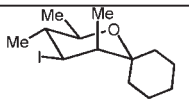
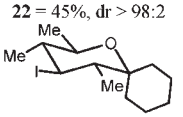
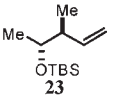
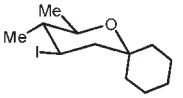
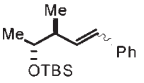
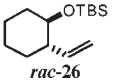
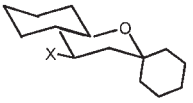
(7) The isolation of the homoallylic alcohol **3** gave nonreproducible yields. Moreover, whatever the reaction conditions used for the Prins cyclization reaction, the homoallylic alcohol **3** decomposes quickly in the reaction mixture leading to the expected product in very low yield. Fortunately, the reaction works well using its silylether form.

(8) The most significant results are summarized in Supporting Information.

(9) (a) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471–2483. (b) Launey, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010**, *6*, 41.

Table 1. Scope of the Prins Cyclization Reaction with TMSI

Entry			Product
1	 **(*E*)-8**	PhCHO **9**	 **14** = 84%, dr > 98:2
2	**(*E*)-8**	 **15**	 **16** = 59%, dr > 98:2
3	**(*E*)-8**	 **17**	 **18a** / **18b** = 1:1, 59%
4	**(*E*)-8**	 **19**	 **20a** / **20b** = 6:4, 56%
5	**(*E*)-8**	 **21**	no Prins product

Entry			Product
6	 **(*Z*)-8**	 **4**	 **22** = 45%, dr > 98:2  **13** = 19%, dr > 98:2
7	 **23**	**4**	 **24** = 61%, dr > 98:2
8	 **(*E*) or (*Z*)-25**	**4**	no Prins product
9	 ***rac*-26**	**4**	 X = I, ***rac*-27** X = NHAc, ***rac*-28** ***rac*-27** = 46%, ***rac*-28** = 32%, in CH_3CN ***rac*-27**, 90% in CH_2Cl_2

diastereoisomer was obtained for the reactions involving **(*E*)-8** and benzaldehyde **9** or cyclopentanone **15**. The structure of these was confirmed by NMR analysis (Table 1, entries 1 and 2). The formation of product occurs by a chairlike transition state with equatorial trapping of the halogen. A mixture of two diastereoisomers **18a** and **18b** in a ratio of 1:1 was isolated after reaction with the isobutyl methyl ketone (Table 1, entry 3). Use of the bicyclic norcamphor **19** led to a mixture of two diastereoisomers **20a** and **20b** in a ratio of 6:4 (Table 1, entry 4). A more hindered ketone like camphor **21** did not lead to any cyclized product, with no reaction occurring under the TMSI-promoted Prins reaction conditions. We also examined the effect of the olefin nature on the Prins cyclization reaction using cyclohexanone **4** as the ketone partner. Thus use of **(*Z*)-8** afforded a mixture of two diastereoisomers **22** and **13** (Table 1, entry 6). The formation of the latter is probably due to a rapid *cis*/*trans* isomerization of the double bond under the reaction conditions. A monosubstituted alkene works well as demonstrated by the reaction between **23** and **4** which provided **24** in good yield (Table 1, entry 7). By way of contrast, no Prins cyclization product was formed with a bulky substituent like a phenyl group on the terminal olefin. We only observed loss of the silyl protecting group from the starting material (Table 1, entry 8). While we had never seen the formation of a product resulting from the trapping of acetonitrile before (Prins–Ritter reaction),[10] the addition of ***rac*-26** to **4** in acetonitrile produced a mixture of the iodo derivative ***rac*-27** and the acetamide ***rac*-28** in a 1:1 ratio (Table 1, entry 9). Changing acetonitrile for methylene chloride as the solvent allowed us to isolate ***rac*-27** as a single diastereoisomer in high yield (90%).

We then turned our attention to the Prins cyclization reaction involving 2-substituted ketones (Scheme 3). Addition of 1 equiv of the racemic 2-methylcyclohexanone ***rac*-29** to 1 equiv of the enantiopure alkene **(*E*)-8** in the presence of TMSI (generated in situ) in acetonitrile or methylene chloride furnished **30** as essentially a single diastereoisomer (checked as usual by careful examination of the crude reaction mixture by NMR) in good yield (eq 1).[11] To our knowledge, it is the first example of a Prins cyclization reaction with dynamic kinetic resolution (DKR) of one partner of the reaction.[12]

This remarkable phenomenon has been confirmed. Starting from both the **(*S*)-29** or **(*R*)-29**, the same product **30** was formed in good yield. It is likely that the slow-reacting (*S*) enantiomer undergoes a very fast isomerization through enolization into the fast-reacting enantiomer (*R*) to lead finally to **30** solely. Moreover, the enantiomer ***ent*-30** was obtained in similar yield by the reaction between ***ent*-(*E*)-8** and ***rac*-29**.[13] The same process occurred

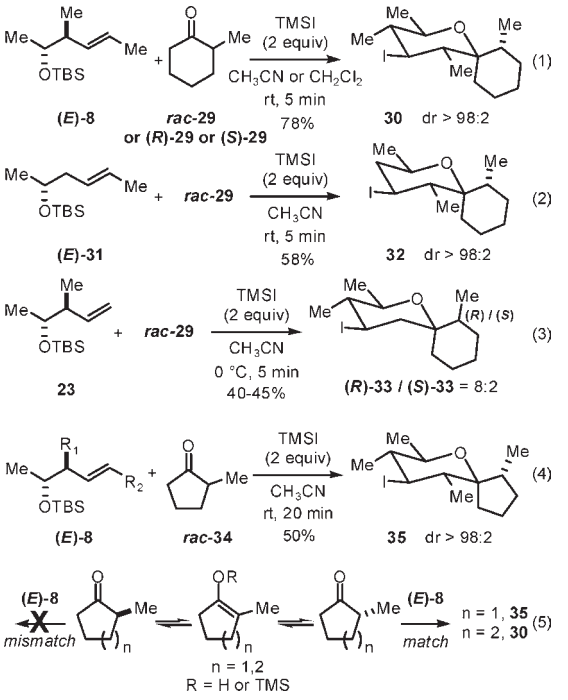
(10) For representative examples of Prins–Ritter reactions, see: (a) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128–4130. (b) Yadav, J. S.; Reddy, S. B. V.; Aravind, S.; Kumar, G. G. K. S. N.; Reddy, G. M. *Tetrahedron* **2008**, *64*, 3025–3031.

(11) The structure of **30** was established with the help of 2D NMR and confirmed by X-ray analysis after its conversion into a 4-amide. See Supporting Information.

(12) Noyori et al. reported a similar observation in the course of the reduction of 2-isopropylcyclohexanone in the presence of an enantiopure ruthenium catalyst; see: Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872–4873.

(13) Absolute configuration of **(*E*)-8**: 2*R*,3*S*; ***ent*-(*E*)-8**: 2*S*,3*R*. Optical rotation of **30**: [α] = +18.0 (*c* 1.7, $CHCl_3$); ***ent*-30**: [α] = −16.0 (*c* 1.3, $CHCl_3$).

Scheme 3. Case of 2-Methyl Cyclic Ketones



with the olefin **(*E*)-31** to give **32** as a single isomer. In the absence of a substituent on the terminal position of the olefin, the DKR does not seem to take place and a mixture of two diastereoisomers was obtained in a moderate yield (eq 3). Finally, the same process occurred with a five-membered ring with a lower yield (as observed previously).

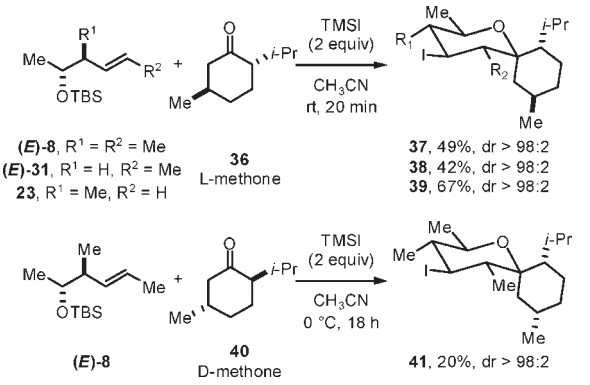
While the Prins cyclization between the L-menthone **36** and **(*E*)-8** led to the single diastereoisomer **37** after 20 min at rt in good yield, the reaction was less facile and much slower with the D-menthone **40** (Scheme 4). After the reaction stirred overnight at 0 °C, only the spiroether **41** was formed and isolated in low yield.[14] This product is the result of a slow epimerization of the chiral center at the α-position of the ketone function. These results support our previous observations; a matched pair of reagents affords the product in good yield whereas a mismatched pair induces the epimerization of the α-chiral center of the ketone before reaction (Scheme 3, eq 5).

DFT calculations have been used to study the Prins cyclization reaction between **(*E*)-8** and ***rac*-29**.[15] The calculated reaction path shows that the chairlike transition state **TS1-(*R*)** and **TS2-(*R*)** are more stable than **TS1-(*S*)** and **TS2-(*S*)** by 3.5 kcal/mol, confirming the preferential formation of **30**. This important energy difference surely

(14) Only a part of **40** has been recovered; no trace of the olefin **(*E*)-8** has been found in the crude reaction mixture.

(15) DFT calculations are detailed in the Supporting Information.

Scheme 4. Case of Menthone



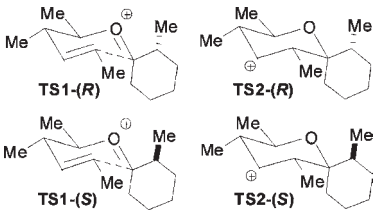


Figure 2. Chairlike transition state calculated by DFT.

led to the differentiation observed for both enantiomers of ***rac*-29** during the reaction (Figure 2).

In conclusion we have described a TMSI-promoted Prins cyclization reaction between substituted silyl ether of homoallylic alcohol and ketones to afford polysubstituted spirotetrahydropyrans. In the case of 2-substituted cyclic ketones, a DKR process has been observed. Additionally, DFT calculations of the Prins cyclization reaction have been undertaken. Extension of this reaction to polyfunctionalized ketones and application to the synthesis of portentol are in progress and will be reported in due course.

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Supporting Information Available. Full details of the preparation of starting materials and experimental procedures including ^{1}H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.