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Prins Cyclizations: Labeling Studies and Application to Natural Product Synthesis

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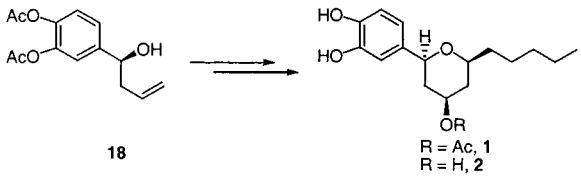
ABSTRACT



The first syntheses of two natural products, catechols 1 and 2, isolated from *Plectranthus sylvestris* (*labiatae*), are reported. Oxygen-18 labeling studies support the proposed intermediacy of a stabilized benzylic cation in the acid-promoted cyclization of an aldehyde and benzylic homoallylic alcohol possessing an electron-rich aromatic ring. In contrast, with an electron-deficient aromatic ring the pathway via a benzylic cation is only minor.

Tetrahydropyrans **1** and **2** are among a series of catechols isolated from extracts of *Plectranthus sylvestris (labiatae)*, a plant found in the woody hills around Kilimandscharo in East Africa.[1] These compounds are potent antioxidants and possess anti-inflammatory properties. The structures of **1** and **2** were elucidated by a combination of spectroscopic studies, and the absolute stereochemistry was deduced by application of Mosher's method. (*R*)-MTPA and (*S*)-MTPA ester derivatives of alcohol **2** were prepared, and their ^{1}H NMR spectra were compared, indicating that the natural products possess the *R* configuration at C-4.

To confirm the structure and absolute stereochemistry of natural products **1** and **2**, we envisaged that the tetrahydropyran could be readily prepared via reaction of hexanal, acetic acid, and the homoallylic alcohol **3**, in an acid-mediated Prins-type cyclization. Similar cyclizations have been widely used for the stereocontrolled synthesis of 2,4,6-trisubstituted tetrahydropyrans.[2] These reactions are believed to proceed via formation of an oxycarbenium ion (generated in situ either from reaction of a homoallylic alcohol with an aldehyde or from a homoallylic acetal), which undergoes an intramolecular cyclization, giving the tetrahydropyran with all three substituents located in an equatorial position.

It has been suggested that cationic oxonia-Cope rearrangements may participate in Prins cyclizations and related reactions.[3]

In our retrosynthetic analysis of the catechols **1** and **2** (Scheme 1), protection of the phenolic hydroxyl groups in homoallylic alcohol **3** was deemed necessary to avoid

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(1) Juch, M.; Ruedi, P. *Helv. Chim. Acta* **1997**, *80*, 436.

(2) For example: (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. (b) Yang, J.; Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **1999**, *40*, 1627. (c) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. (d) Markó, I. E.; Chellé, F. *Tetrahedron Lett.* **1997**, *38*, 2895.

(3) Examples of such rearrangements include: (a) Rychnovsky, S. D.; Maramoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. (b) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. (c) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (d) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron.* **1994**, *50*, 7129. (e) Gasparski, C. M.; Herrinton, P. M.; Overman, L. E.; Wolfe, J. P. *Tetrahedron Lett.* **2000**, *41*, 9431. (f) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (g) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5365.

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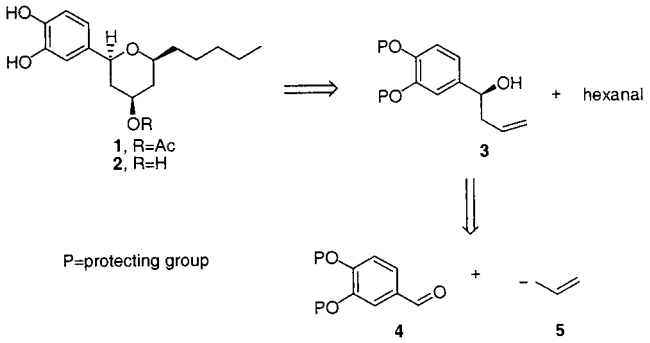
Scheme 1. Retrosynthetic Analysis of Catechols **1** and **2**

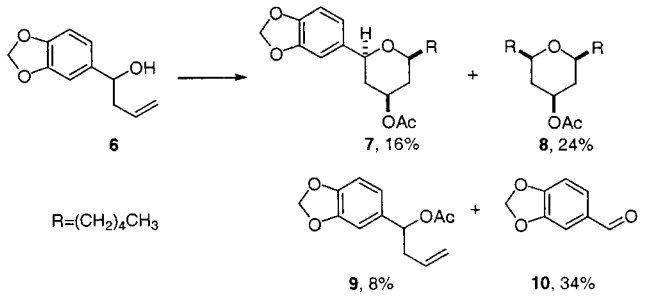


unwanted side reactions. The homoallylic alcohol may be prepared via a stereoselective addition of the synthon **5** to the benzaldehyde derivative **4**.

This approach was validated using racemic alcohol **6**, which was readily prepared in 92% yield from commercially available piperonal and allylmagnesium chloride. Several methods have been reported for the introduction of oxygenated substituents at C-4 of tetrahydropyrans in Prins cyclizations with varying success.[4] In recent studies into the stereocontrolled synthesis of 4-hydroxy-2,5-disubstituted tetrahydropyrans, we have shown that hydrolysis of the esters formed from reaction of homoallylic acetals with either trifluoroacetic acid or $BF_3{\cdot}OEt_2$, in the presence of AcOH as the nucleophile and TMSOAc to act as a fluoride trap, gave yields of between 50% and 70%.[5]

Thus, cyclization of homoallylic alcohol **6** with hexanal was investigated using $BF_3{\cdot}OEt_2$ in the presence of AcOH and TMSOAc at room temperature, giving the required tetrahydropyran **7** as a single diastereomer but in a disappointing 16% yield (Scheme 2). Another tetrahydropyran,

Scheme 2. Reaction of Homoallylic Alcohol **6** with Hexanal, $BF_3{\cdot}OEt_2$ (2 equiv), AcOH (5 equiv),and TMSOAc (4 equiv) in C_6H_{12} at Room Temperature



8, was isolated as the major heterocycle (24% yield), the plane of symmetry being clearly revealed in the ^{13}C NMR spectrum, which contained only 10 signals. In addition, the acetate **9** (8% yield) and parent aldehyde **10** (34% yield) were also isolated from the reaction.

A proposed mechanism to account for the formation of these products is shown in Figure 1.[6] In the presence of

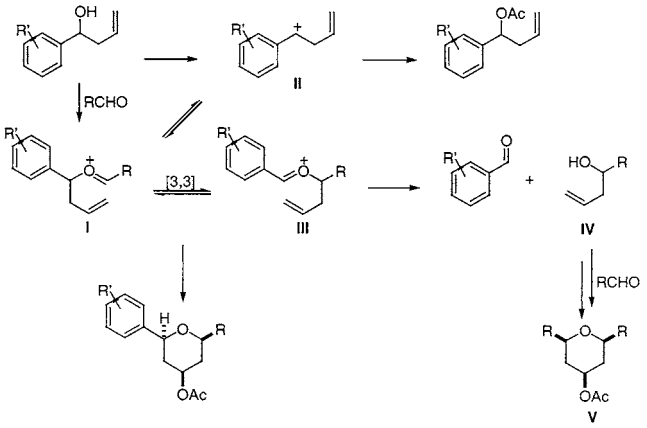


Figure 1. Proposed mechanism for the reaction of a benzylic homoallylic alcohol with RCHO, TMSOAc, AcOH, and $BF_3{\cdot}OEt_2$.

electron-donating substituents on the aromatic ring, oxycarbenium ion **I** may be formed either directly from the homoallylic alcohol or via the benzylic cation **II** (which is the direct precursor of the homoallylic acetate). An oxonia-Cope rearrangement of **I** to **III** is favored, leading to **IV** via an allyl transfer, and hence the symmetrical tetrahydropyran **V** is formed as the major product. In support of this mechanism, we have shown that, on reaction of an enantioenriched homoallylic alcohol with propanal in the presence of $BF_3{\cdot}OEt_2$, AcOH, and TMSOAc, the resultant tetrahydropyran had low ee (<5%) in the presence of electron-donating groups on the aromatic ring. In contrast, under the same conditions, a homoallylic alcohol that possesses an electron-withdrawing group, which would not favor the formation of the benzylic cation **II** or the oxonia-Cope rearrangement to **III**, gave the unsymmetrical tetrahydropyran as the sole product, with little loss in enantiopurity.[6]

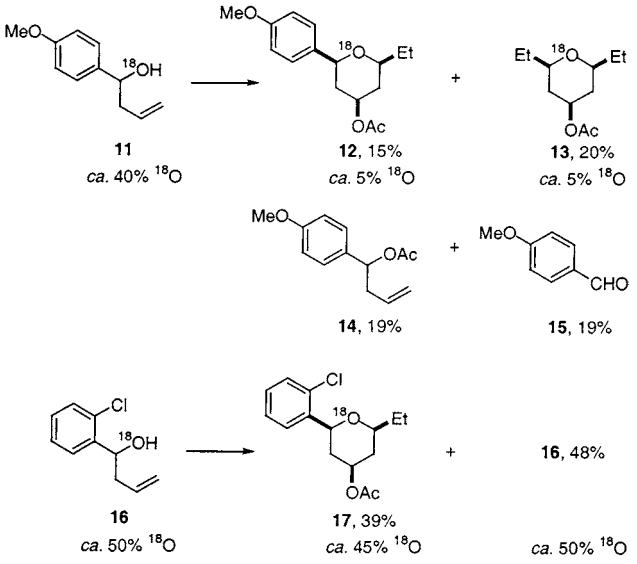
To further verify the mechanisms illustrated in Figure 1 we undertook isotopic labeling experiments (Scheme 3). It would be expected that the percentage incorporation of an oxygen-18 label in the hydroxyl group of the starting homoallylic alcohol **11** with an electron-rich aromatic ring would be significantly reduced in both tetrahydropyrans **12** and **13**, if the pathway involving the stabilized benzylic cation **II** is favored. In contrast, the label should be retained in the tetrahydropyran **17**, derived from the homoallylic alcohol **16** containing an electron-deficient aromatic ring, where the benzylic cation is less stabilized. The required substrates **11** and **16** were prepared by labeling the corresponding ben-

(4) (a) Nishizawa, M.; Shigaraki, T.; Takao, H.; Imagawa, H.; T. *Tetrahedron Lett*. **1999**, *40*, 1153. (b) Zhang, W.-C.; Viswanathan, G. S.; Li, C.-J. *Chem. Commun*. **1999**, 291. (c) Zhang, W.-C.; Li, C.-J.; Sugihara *Tetrahedron* **2000**, *56*, 2403. (d) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett*. **1996**, *37*, 8679. (e) Viswanathan, G. S.; Yang, J.; Li, C.-J. *Org. Lett.* **1999**, *1*, 993. (f) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022.

(5) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun*. **2001**, 835.

(6) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577.

Scheme 3. Reaction of Homoallylic Alcohols **11** and **16** with $BF_3.OEt_2$ (2 equiv), AcOH (5 equiv), TMSOAc (4 equiv) in C_6H_{12} at Room Temperature



zaldehydes[7] using $^{18}OH_2$ and then treating them with allylmagnesium chloride in THF.

The incorporation of oxygen-18 was readily determined by ^{13}C NMR spectroscopy, in which a small upfield shift (ca. δ 0.02 ppm) of the signal assigned to C-1 was apparent in each case as a result of the α-isotope effect.

The homoallylic alcohols **11** and **16** were treated separately under the standard cyclization conditions with propanal, AcOH, TMSOAc, and $BF_3{\cdot}OEt_2$ at room temperature, and following workup the products were purified by flash chromatography and analyzed by ^1H and ^{13}C NMR spectroscopy and MS (Scheme 3). On reacting the 4-methoxy derivative **11** (ca. 40% ^{18}O), no isotopic label was apparent in either the 4-methoxybenzaldehyde **15** (as would be expected as any label would be readily exchanged on workup) or homoallylic acetate **14**. The percentage incorporation of oxygen-18 into the tetrahydropyrans **12** and **13** was significantly reduced to ca. 5% as apparent from the ^{13}C NMR spectrum, which showed upfield shifts (ca. δ 0.02 ppm in each case) of the signals assigned to C-2 and C-6 (δ 76.71 and 76.82, respectively) (Figure 2).

In contrast, the 2-chloro derivative **16** (ca. 50% ^{18}O) yielded tetrahydropyran **17** with ca. 45% oxygen-18 located solely in the heterocycle as apparent from the ^{13}C NMR spectrum, which showed upfield shifts (ca. δ 0.02 ppm in each case) of the signals assigned to C-2 and C-6 (δ 74.06 and 77.06, respectively) (Figure 3).

These results are in accord with the proposal that the reaction may proceed via a benzylic cation, the formation of which is favored in the cases where the aromatic ring possesses an electron-donating substituent (Figure 1).

Having demonstrated that Prins cyclizations are more efficient for the enantioselective synthesis of 2,4,6-trisubstituted tetrahydropyrans from benzylic alcohols that possess an electron-deficient rather than electron-rich aromatic ring, we returned to the synthesis of natural products **1** and **2** and selected 3,4-diacetoxybenzaldehyde as the starting material. Treatment of the aldehyde with (−)-DIPCl and allylmagnesium chloride at −78 °C, followed by oxidation and hydrolysis of the resultant borane at room temperature with NaOH and H_2O_2 (rather than under reflux as described by Brown and co-workers[8] to avoid hydrolysis of the acetate groups) gave the required homoallylic alcohol **18** in 76% yield and 90% ee (as determined from the Mosher ester). Reaction of **18** with hexanal, $BF_3{\cdot}OEt_2$, AcOH, and TMSOAc gave the desired 2,4,6-trisubstituted tetrahydropyran **19**, $[\alpha]_D$ +4.2 (*c* 1.3, $CHCl_3$), in 72% isolated yield (80% ee by chiral HPLC); no symmetrical tetrahydropyran was isolated (Scheme 4).

To complete the synthesis of acetate **1**, it was necessary to selectively hydrolyze the triacetate **19**. Treatment of **19** with the K_2CO_3 (0.45 equiv) in MeOH for 5 min gave, after purification by flash chromatography, the required acetate **1** as a white solid in 91% yield. The spectral data of **1** were identical to those of the natural product and the synthetic acetate had an optical rotation $[\alpha]_D$ +2.4 (*c* 0.8, $CHCl_3$), whereas for the natural product $[\alpha]_D$ +2.6 (*c* 1.7, $CHCl_3$) was reported.[1]

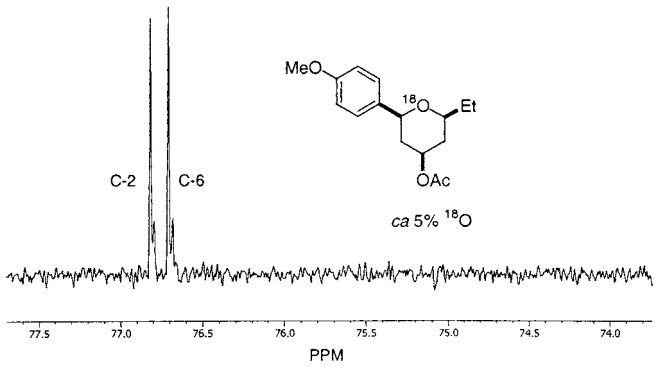


Figure 2. ^{13}C NMR spectrum showing C-2 and C-6 of **12** recorded in C_6D_6.

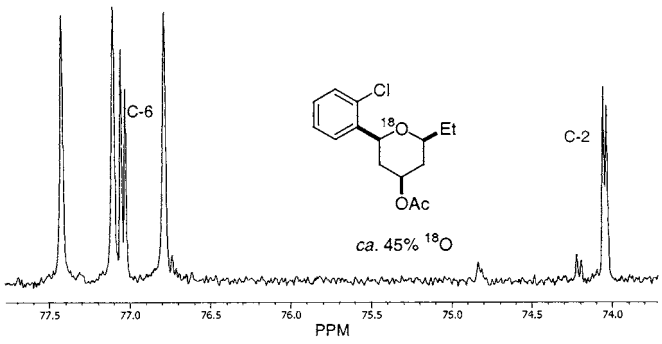
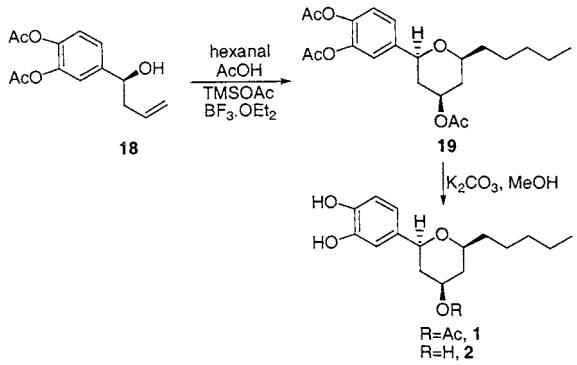


Figure 3. ^{13}C NMR spectrum showing C-2 and C-6 of **17** recorded in $CDCl_3$.

(7) Piotr, G.; Stec, W. J. *Tetrahedron Lett.* **1983**, *24*, 3899.

Scheme 4. Completion of the Natural Product Synthesis



To prepare the triol **2**, triacetate **19** was treated with K_2CO_3 (1.5 equiv) in MeOH for 90 min. It was found that better yields of the required product were obtained when the reaction was carried out in the dark. Following chromatography, the required catechol **2** was isolated in 68% yield. All spectral data of **2** were identical to those reported for the natural product, and the synthetic material had an optical rotation $[\alpha]_D$ −27.4 (*c* 2.1, MeOH), which is in accord with that expected from the published rotation of the natural product, $[\alpha]_D$ −37.5 (*c* 1.2, MeOH), considering that our material had been prepared in 80% ee.[1]

(8) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319.

In conclusion, we have shown that the outcome of the reaction of aldehydes with benzylic homoallylic alcohols under acidic conditions is dependent upon the substituents on the aromatic ring of the alcohol. Results from oxygen-18 labeling studies are in accord with the proposal that an electron-rich aromatic ring leads to the formation of oxycarbenium ion **I** mainly via a benzylic cation intermediate **II** and then favors an oxonia-Cope rearrangement of **I** leading to the formation of a symmetrical tetrahydropyran via a side-chain exchange process (Figure 1). In contrast, with electron-deficient rings, the formation of the benzylic cation **II** and the oxonia-Cope rearrangement are less favored and the Prins cyclization proceeds to give the expected 2,4,6-trisubstituted tetrahydropyran in which the majority of the oxygen-18 label in the starting homoallylic alcohol is retained in the product. These mechanistic studies have facilitated the first stereocontrolled synthesis of the catechol tetrahydropyrans **1** and **2**, two natural products from *Plectranthus sylvestris (labiatae)*, confirming their structures and absolute configurations.

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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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