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1,3-Transposition of Primary Allylic Alcohols: Synthesis of Optically Active Secondary and Tertiary Allylic Alcohols

Rosa L. Dorta,[a] María S. Rodríguez,[a] José A. Salazar,* Ernesto Suárez

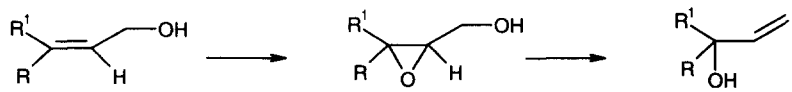
Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 3, 38206-La Laguna, Tenerife, Spain. [a]Departamento de Química Orgánica, Universidad de La Laguna, Tenerife, Spain.

Abstract: The reduction of optically active 2,3-epoxy alcohols, suitably prepared by the Sharpless asymmetric epoxidation of primary allylic alcohols, with the system triphenylphosphine/ iodine/imidazole/2,6-lutidine/water, leads in a single step to optically active secondary and tertiary allylic alcohols. © 1997 Elsevier Science Ltd.

Optically active allylic alcohols have been frequently used in organic synthesis as chiral building blocks for the preparation of natural products.[1] There are several methods for the synthesis of optically active allylic alcohols, the most widely used being the Sharpless kinetic resolution of racemic allylic alcohols.[2] However, the maximum yield is limited to 50% and tertiary allylic alcohols are unsuitable substrates for kinetic resolution.

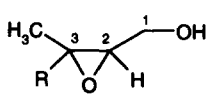
To overcome this problem, several methods for the synthesis of chiral allylic alcohols have been reported, most of them involving the reductive rearrangement of 2,3-epoxy alcohols by metals[3] or halides,[4] or tellurium-based chemistry.[5] However, such procedures require the prior preparation and isolation of suitable derivatives of the alcohol such as sulfonates and halides. To our knowledge, the titanium(III)-induced regioselective deoxygenation of 2,3-epoxy alcohols is the only reported procedure that directly undergoes the rearrangement to secondary allylic alcohols.[6]

Scheme 1

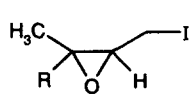


We report here on an additional and convenient method to accomplish the one-step rearrangement of chiral 2,3-epoxy alcohols to optically active secondary and tertiary allylic alcohols using the system triphenylphosphine, iodine, imidazole, 2,6-lutidine and water. The overall reaction (Scheme 1) involves a stereospecific 1,3-allylic transposition of the hydroxy group and the double bond.

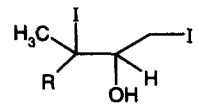
The results obtained are shown in Table 1. Entries 1 and 2 summarize the initial attempts at rearrangement of 2,3-epoxygeraniol **1**. The reactions were carried out under anhydrous conditions, the 1-iodo



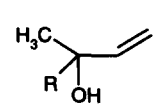
1 (2*S*, 3*S*)
2 (2*R*, 3*R*)
3 (2*S*, 3*R*)



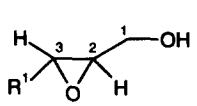
4 (2*S*, 3*S*)



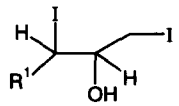
5 (2*S*, 3*R*)



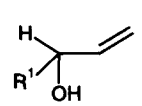
6 (3*S*)
7 (3*R*)



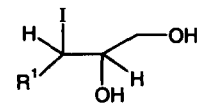
8 (2*S*, 3*S*)



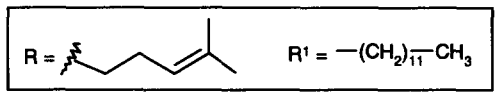
9 (2*R*, 3*S*)



10 (3*S*)



11 (2*R*, 3*S*)



derivative **4** being the main product obtained. The structure of the diiodohydrin **5** was established by COSY and HMQC experiments, assuming an S_N2 opening of the epoxide ring.[7] All attempts to increase the yields of linalool **6** by changing the reaction conditions were unsuccessful. As shown in entry 3, the course of the reaction underwent a surprising change with the addition of 1 mmol of H_2O per mmol of substrate, the rearranged allylic alcohol **6** being obtained in 47% yield (see the proposed reaction mechanism). The low yield of **6** is probably due to the long reaction time required as a consequence of the low solubility of the reagents in benzene. Thus, the use of 1,2-dichloroethane as cosolvent (entry 4) allows the formation of (3*S*)-(+)-linalool in 77% yield and >95% ee after 2h at 75-80 °C.[8]

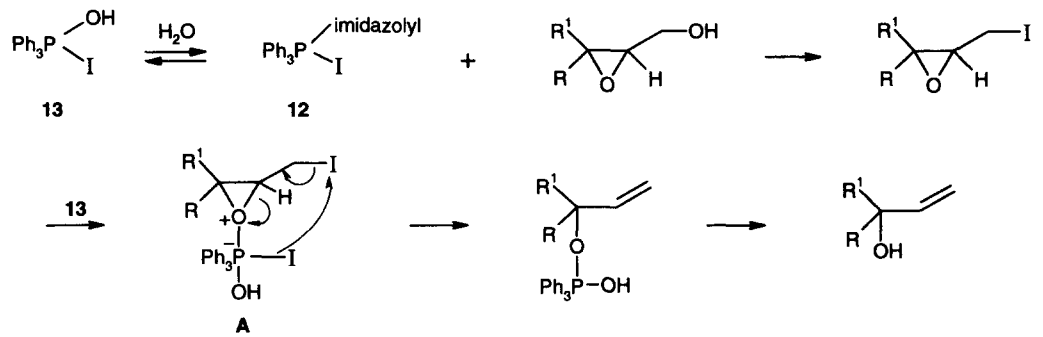
The addition of an excess of H_2O clearly decreased the yield of **6**; thus, as shown in Table 1 (entry 5), the addition of 3 mmol of H_2O per mmol of substrate led to a complex mixture of unstable products (linalool was not observed), the major one being the corresponding primary allylic iodide which quickly decomposed upon handling.[9] As expected, similar treatment of the epoxides of geraniol and nerol, **2** and **3**, obtained by using (-)-DET and (+)-DET, respectively, gave (3*R*)-(-)-linalool **7** in good enantiomeric excess (entries 6 and 7). Under slightly modified conditions (entry 8), the 2,3-disubstituted epoxide **8** [(+)-DET was employed][10] gave the rearranged secondary allylic alcohol **10.** In this case, the corresponding iodohydrin **9** was formed in large amounts (24%).[11] With the aim of improving the yield of **10** several reaction conditions were tested without any success.

The proposed reaction mechanism is depicted in Scheme 2. The phosphine derivative **12** transformed the primary alcohol into the iodide but did not produce its rearrangement (see entries 1 and 2 of the Table 1). The phosphine hydroxyiodide **13** is the reagent that caused the rearrangement of the epoxyiodide, possibly through the intermediate **A**, to give the allylic alcohol.

Table 1. Rearrangement of 2,3-Epoxy Alcohols.

Entry	Epoxide	Conditions[a]	Compounds (yield %)	ee (%)[b]
1	**1**	A	**4** (61), **5** (5), **6** (5)	-
2	**1**	B	**4** (16), **5** (5)	-
3	**1**	C	**5** (3), **6** (47)	-
4	**1**	D	**6** (77)	>95
5	**1**	E	complex mixture	-
6	**2**	D	**7** (68)	90
7	**3**	D	**7** (66)	90
8	**8**	F	**9** (24), **10** (56)	85[c]
9	**4**	G	**5** (40), **6** (55)	-

[a] Solvents and reagents were carefully dried. Work-up procedure: the reaction mixture was quenched with cold aqueous solutions of $Na_2S_2O_3$, $NaCO_3H$ and Et_2O. **A**: epoxide (1 mmol), benzene (40 ml), imidazole (4 mmol), Ph_3P (4 mmol), I_2 (3 mmol), 75-80 °C, 4 h. **B**: the same as **A** but using 1,2-dichloroethane as solvent. **C**: epoxide (1 mmol), benzene (40 ml), imidazole (1 mmol), 2,6-lutidine (3 mmol), Ph_3P (4 mmol), I_2 (3 mmol), H_2O (1 mmol), 75-80 °C, 5 h. **D**: epoxide (1 mmol), benzene/1,2-dichloroethane 3/1 (40 ml), imidazole (1 mmol), 2,6-lutidine (3 mmol), Ph_3P (4 mmol), I_2 (3 mmol), H_2O (1 mmol), 75-80 °C, 2 h. **E**: the same as **D** but adding 3 mmol of H_2O. **F**: epoxide (1 mmol), benzene/1,2-dichloroethane 3/1 (40 ml), imidazole (1 mmol), 2,6-lutidine (2 mmol), Ph_3P (4 mmol), I_2 (1.5 mmol), H_2O (1 mmol), 65 °C, 1.5 h. **G**: iodoepoxide (1 mmol), benzene/1,2-dichloroethane 3/1 (40 ml), $Ph_3P(OH)I$ (1 mmol), 70-80 °C, 1 h. [b] The enantiomeric excess of the chiral allylic alcohols was measured by ^1H NMR analysis with $Eu(hfc)_3$. [c] The enantiomeric excess corresponds to the acetyl derivative of **10**.



Scheme 2

The reagent **13**, obtained in an alternative way by the reaction of triphenylphosphine oxide with hydriodic acid,[12] transformed the epoxyiodide **4** into the rearranged allylic alcohol **6** in 1 h at 75-80 °C (entry 9). However, **13** did not convert alcohols into iodides. Thus, for example, the reaction of **13** with the epoxy alcohol **8** (2 equiv, 2 h, rt) gave the iodohydrin **11** in 66% yield besides starting material (30% yield). All the above explains the failure of the rearrangement when an excess of water was present (entry 5).

To explore the scope of this reaction, several secondary alcohols bearing a 2,3-epoxide function were tested. However, their rearrangement to allylic alcohols did not take place, the sole reaction observed being the formation of the iodohydrin by nucleophilic opening of the epoxide.[13]

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7. As a consequence of the electronic effect of the C-1 hydroxy group all the iodohydrins obtained have the iodine atom located at the C-3 position, independently of their degree of substitution. Compound **5**: IR ($CHCl_3$) 3540 cm^{-1}; ^1H NMR ($CDCl_3$) 5.13 (1H, m, H-C_6), 3.76 (1H, m, H-C_2), 3.30 (2H, m, 2H-C_1), 1.96 (3H, s), 1.70 (3H, s), 1.65 (3H, s). ^{13}C NMR ($CDCl_3$) 132.99, 62.01 (C), 122.55, 79.74 (CH), 44.47, 26.42, 11.70 (CH_2), 30.43, 25.65, 17.01 (CH_3). MS m/z 408 (M^+, 1%).
8. Interestingly, this solvent mixture allows the transformation of primary and secondary alcohols into their corresponding iodides at room temperature and with short reaction times. For example, dihydrocholesterol gives the corresponding 3α-iodide derivative in quantitative yield after 3 h at room temperature. The above compares advantageously with the related reported transformation using toluene alone, for which high temperatures (120 °C for secondary alcohols) and longer reaction times are required: Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
9. This primary allylic iodide arises presumably by triphenylphosphine-promoted reduction of the iodohydrin, which is preferably formed as a consequence of the high concentration of $Ph_3P(OH)I$ under the reaction conditions (see mechanism): Sonnet, P. E. *Synthesis* **1980**, 828.
10. Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803.
11. Compound **9:** IR ($CHCl_3$) 3538 cm^{-1}; ^1H NMR ($CDCl_3$) 4.20 (1H, m, H-C_3), 3.53 (2H, m, 2H-C_1), 3.50 (1H, m, H-C_2), 0.88 (3H, t, *J* 6.5 Hz). ^{13}C NMR ($CDCl_3$) 74.43, 42.51 (CH), 35.10, 31.90, 29.62(x3), 29.54(x2), 29.39, 29.35, 28.74, 22.68, 14.00 (CH_2), 14.14 (CH_3). MS *m/z* 480 (M^+, 7%). Compound **10**: $[\alpha]_D$ + 4.4 ($CHCl_3$); IR (CCl_4) 3619 cm^{-1}; ^1H NMR ($CDCl_3$) 5.96-5.79 (1H, H-C_2), 5.27-5.07 (2H, 2H-C_1), 4.10 (1H, m, H-C_3), 0.88 (3H, t, *J* 6.6 Hz). ^{13}C NMR ($CDCl_3$) 141.33, 73.22 (CH), 114.42, 37.01, 31.89, 29.63(x3), 29.56(x3), 29.33, 25.31, 22.65 (CH_2), 14.07 (CH_3). MS m/z 226 (M^+, 1%).
12. Ph_3PO (2 mmol), HI (57%, 1 mmol), benzene/1,2-dichloroethane 7/3 (10 ml), 0 °C, 5 min.
13. Iodohydrins are quickly formed (15 to 30 min at 70 °C) and decompose over longer reaction times.

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