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STEREOSPECIFIC REARRANGEMENTS OF OPTICALLY ACTIVE 2-ARYL-3-ETHENYLOXIRANES TO GIVE OPTICALLY ACTIVE β–ETHENYLBENZENEETHANOLS: BENZYL VS. ALLYL CATIONS AND AN EFFICIENT SYNTHESIS OF (*S*)-IBUPROFEN[1]

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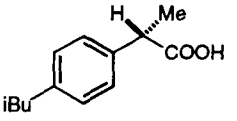
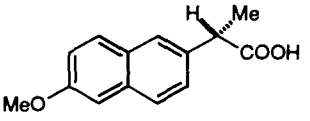
Summary: Rearrangements of aryl- and ethenyl-substituted oxiranes proceed well in the presence of triethylsilane and BF_3 to give optically active alcohols, which we have used for a synthesis of (*S*)-ibuprofen **1**. We have also shown that a vinyl group migrates to a benzylic cation faster than a phenyl group migrates to an allyl cation.

Over the last thirty years, optically active arylpropionic acids have found great use as antiinflammatory agents. Among the most widely used drugs are the compounds ibuprofen **1** and naproxen **2**. It has been shown that it is the (*S*) enantiomer of these compounds which has the beneficial antiinflammatory activity[4] and also is more ulcerogenic.[5] Recent studies have also shown that the (*R*)-enantiomer of these and other arylpropionic acids decreases the proliferation of colonic cells without ulceration.[6] Their high biological activity has led many chemists to develop syntheses of arylpropionic acids in optically active form.[7] We report herein an efficient synthesis of (*S*)-ibuprofen **1** in optically active form as well as the results of our investigation of epoxide rearrangements that allows for an estimation of the relative stability of benzylic and allylic cations.

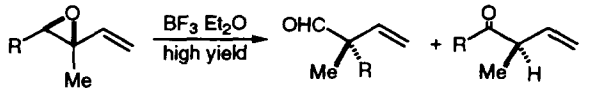


1



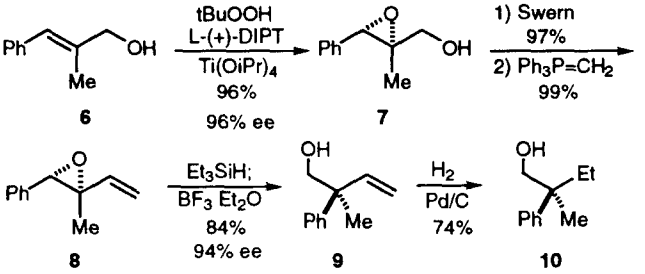
2

Recently we reported the stereospecific rearrangement of tertiary allylic epoxides **3** under very mild Lewis acid conditions.[8,9] When R was a good migrating group, e.g., benzylic or allylic, only the quaternary aldehydes **4** were obtained, while with poorer migrating groups, e.g., phenethyl or cyclohexylmethyl, a mixture of **4** and the ketones **5** was produced. We wanted to extend these studies to the rearrangement of other substituted epoxides, e.g., tertiary epoxides with aryl and vinyl substituents, as well secondary allylic and benzylic epoxides in order to

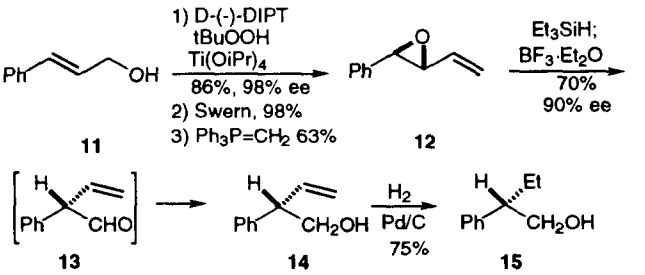


4 **5**

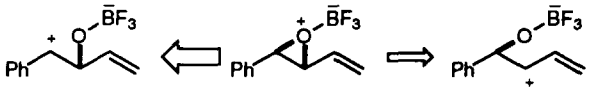
produce tertiary stereocenters in optically active form. Conversion of α-methylcinnamyl alcohol **6** into the first test substrate, the tertiary allylic epoxide **8**, was done by Sharpless epoxidation[10] to give the known epoxy alcohol **7**[10b] followed by Swern oxidation and Wittig olefination. The enantiomeric excess of all alcohols was measured by phosphorus NMR using the Alexakis reagent.[11] Treatment of the epoxide **8** with boron trifluoride etherate in the presence of the reducing agent triethylsilane afforded the product of phenyl migration to the tertiary carbocation, namely the alcohol **9**.[12] The sense of the chirality was proven by conversion of **9** into the known alcohol **10** which had an $[\alpha]_D^{25}$ = +6.88 (lit.[13] +6.8). Phenyl is therefore a good migrating group and a tertiary allylic carbocation is preferred to a benzylic cation.



As mentioned above, we wanted to see whether secondary allylic and benzylic epoxides would rearrange to give tertiary aldehydes in optically active form. Since both phenyl and vinyl groups are good migrating groups, we realized that we could test the cation-stabilizing ability of a benzylic group vs. an allylic group by the following simple experiment, namely rearrangement of the optically active epoxide **12**. Making the assumption that phenyl and vinyl are comparable in their migratory aptitudes, the product ratio would then be determined by which cation is preferentially formed, the benzylic or the allylic cation. The substrate **12** was prepared by Sharpless epoxidation of cinnamyl alcohol **11**[10b] (86%, 96% ee) followed by Swern oxidation and Wittig olefination (62% overall). Treatment of **12** with 1.3 eq of triethylsilane followed by addition of 1.3 eq boron trifluoride etherate in dichloromethane at -78 °C afforded a 70% yield of the alcohol **14** which had an enantiomeric excess of 90% (from ^{31}P NMR integration).[14] The sense of chirality was assigned as (*S*) by comparison of the optical rotation of the reduction

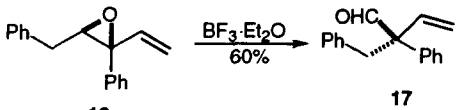


product β-ethyl-benzeneethanol **15** ($[\alpha]_D^{25}$ = +14.5) with that in the literature.[15] Thus the initially formed complex **A** rearranges predominately via migration of the vinyl group to the benzylic cation in **B** (rather than via migration of the phenyl group to the allylic cation in **C**) to form the aldehyde **13** which is then reduced in situ by the silane.[16] If the assumption of similar migratory abilities of the two groups is correct, then this result implies that a benzylic cation is more stable than an allylic one.

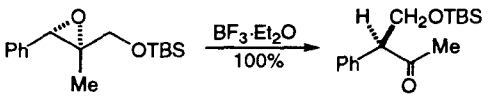


B **A** **C**

Several other rearrangements have also been carried out, e.g., epoxide **16** to give the aldehyde **17**[17] and the migration of a silyloxymethyl group to a benzylic center, **18** → **19**.[18]

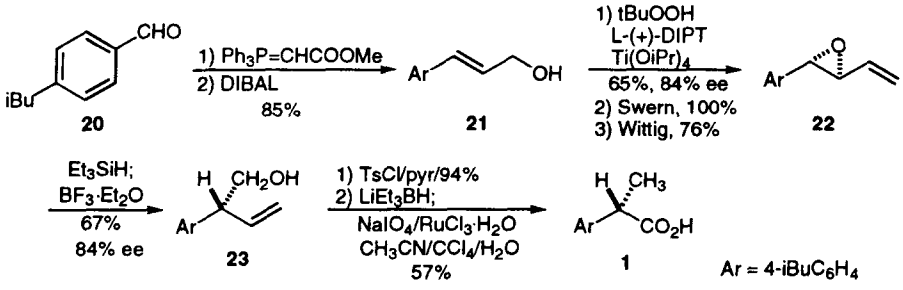


16 **17**



18 **19**

We have applied these rearrangements to the synthesis of ibuprofen in its active (*S*) enantiomeric form. Wittig olefination and reduction of the known aldehyde **20**[19] (prepared from isobutylbenzene by acetylation, oxidation, and conversion of acid to aldehyde) gave the cinnamyl alcohol **21** (Ar = 4-iBuC$_6$H$_4$). Sharpless epoxidation using L-(+)-DIPT followed by Swern oxidation and methylenation gave the key substrate **22**. Rearrangement as before using triethylsilane afforded the desired alcohol **23** in 67% yield and with no loss of enantiomeric purity. Tosylation, reduction with Super-Hydride®, and oxidative cleavage of the alkene with $RuCl_3$ and periodate gave (*S*)-ibuprofen **1** in 54% overall yield from **23**.



20 **21** **22** **23** **1**

We are currently studying the use of analogous rearrangements of systems similar to these in synthesis.

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