

FACILE SYNTHESIS OF BOTH ENANTIOMERS OF 2, 3, 4, 5, 6-PENTAFLUORO- α -METHOXYBENZENEACETIC ACID IN HIGH OPTICAL PURITY¹

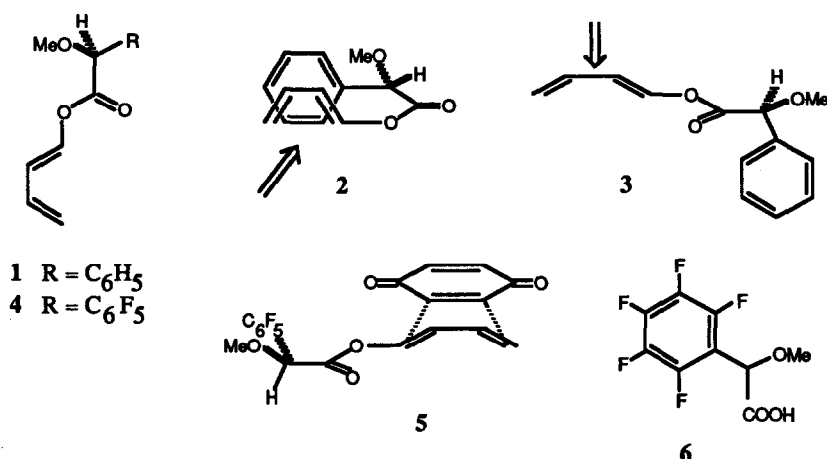
MICHAEL E. JUNG,* YOUNG H. JUNG,² and YASUYUKI MIYAZAWA

*Department of Chemistry and Biochemistry,
University of California, Los Angeles, California 90024, USA*

Abstract: Both the (*R*) and the (*S*) enantiomers of perfluorophenyl-*O*-methylmandelic acid, 6*R* and 6*S*, have been synthesized in high overall yield and optical purity by an application of the Sharpless asymmetric epoxidation scheme.

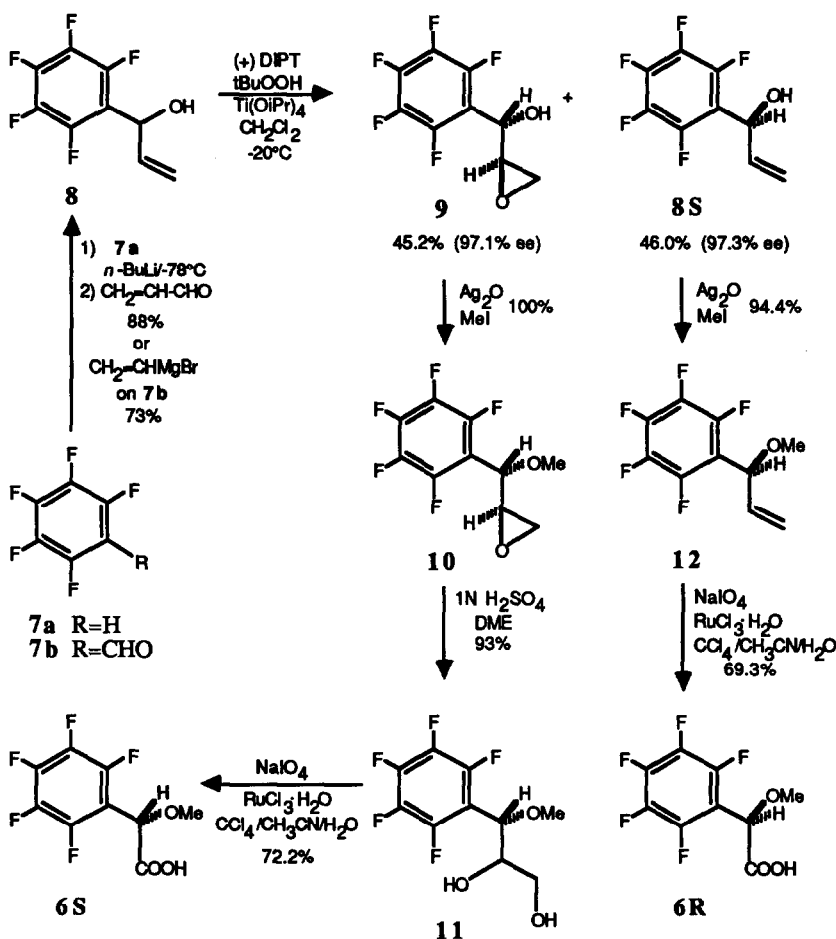
Ten years ago Trost and co-workers³ reported that high diastereoselectivity could be achieved in Diels-Alder cycloadditions of 1,3-butadien-1-yl *O*-methylmandelate **1** with activated dienophiles and mild Lewis acids and invoked a π -stacking model **2** to explain the results. More recently, Thornton and Siegel⁴ presented results which indicated that this π -stacking model was incorrect for Diels-Alder reactions of **1** and that the most likely transition structure had a completely different conformation, namely **3**, which predicted the observed stereoselectivity. Finally, recent computational studies by Tucker, Houk, and Trost⁵ have corroborated the conformational model of Thornton **3** as the most stable and therefore the most likely to control the stereoselectivity. In this paper⁵ Houk and co-workers also made the prediction that the perfluorophenyl analogue of **1**, namely **4**, would adopt a different transition state with dienophiles such as quinone, e.g., **5**, and should give the opposite stereoselectivity. In order to test this prediction, a facile synthesis of the required perfluorophenyl-*O*-methylmandelic acid **6** (2, 3, 4, 5, 6-pentafluoro- α -methoxybenzeneacetic acid) in high optical purity was needed. We now report the short, high-yielding synthesis of both enantiomers of this acid **6** in high optical purity from the same starting material using as the key step an application of the Sharpless kinetic resolution process. This synthesis is noteworthy in that both products of the kinetic resolution step, the epoxy alcohol and the allylic alcohol, are taken on to the separate enantiomers of the target molecule so that no material is wasted.

A thorough search of the literature confirmed that the desired α -methoxy acid **6** was unknown although other similar derivatives, e.g., the α -hydroxy compound and the α -methoxy- α -methyl compounds, had been prepared.⁶ However, the routes developed for the preparation of these compounds did not seem favorable for the production of **6**



in high optical purity, without recourse to a classical resolution sequence.^{6ab} In order to avoid this resolution process, we decided to investigate the use of the very efficient Sharpless kinetic resolution epoxidation technique for the preparation of **6** in both enantiomeric forms. In particular we wanted to develop a method whereby both of the products of the kinetic resolution could be independently converted into the two enantiomers of **6** so that no material would be lost. With this goal in mind, the synthesis shown in Scheme 1 was carried out.

The desired substrate for the Sharpless reaction, namely the racemic allylic alcohol **8**, could be prepared by either of two routes from commercially available pentafluorophenyl derivatives. Reaction of pentafluorobenzene **7a** with *n*-BuLi at -78°C followed by addition of freshly distilled acrolein afforded **8** in 88% yield.⁷ Alternatively, addition of vinylmagnesium bromide to pentafluorobenzaldehyde **7b** furnished the same compound **8** in 73% yield. Reaction of **8** with various (+) dialkyl tartrates, *t*-butyl hydroperoxide, and titanium tetrakisopropoxide produced the optically active epoxy alcohol **9** and the kinetically resolved allylic alcohol **8S** in varying yields and optical purities. While the optical purity of one or the other product could be increased by the use of more or less peroxide, we wished to find conditions which maximized the yield and purity of both. After much experimentation, we found that treatment of a solution of 1 eq of the allylic alcohol **8** (8.09 g), 0.1 eq of Ti(OiPr)₄, and 0.16 eq of (+)-diisopropyl tartrate containing 21 g of 4 Å molecular sieves with 0.68 eq of a solution of *t*-butyl hydroperoxide (nominally 3M in 2,2,4-trimethylpentane) in methylene chloride at -21 °C for 27 days followed by normal workup and careful column chromatography (10% ethyl acetate in hexane) afforded 45.2% (3.919 g) of the epoxy alcohol **9** in 97.1% ee and 46% (3.723 g) of the kinetic resolved allylic alcohol **8S** in 97.3% ee. The enantiomer excess (ee) of each compound was determined by integration of the respective peaks in the ¹H NMR spectrum of each sample in CDCl₃ with a small amount of Eu(hfc)₃ (usually about 0.3 - 0.4 eq) at 200 MHz. The racemic materials were prepared so that the positions of the peaks due to the



Scheme 1

diastereomeric complexes could be determined, as we have described before in similar compounds.⁸ Thus both products of the Sharpless epoxidation of **8** are available in excellent yield and very high optical purity.

The conversion of **9** and **8S** into the desired optically active acids **6S** and **6R**, respectively, followed straightforward chemistry. Alkylation of the free alcohol of **9** with silver oxide and methyl iodide gave a quantitative yield of the methyl ether **10**. Direct oxidation of **10** to give **6S** could be accomplished but not in satisfactory yield. Therefore we resorted to a simple two-step alternative. Acid-catalyzed hydrolysis of the epoxide gave a 93% yield of a mixture of two diols **11**, which could be separated by column chromatography into a major and a minor diastereomer. However, this was unnecessary since the crude mixture of diols **11** could be readily oxidized using sodium metaperiodate with catalytic ruthenium trichloride⁹ to give the desired (*S*) acid **6S** in 72.2% yield. Thus this acid is available in three steps and 67.1% overall yield from the epoxy alcohol **9**. The conversion of **8S** into the (*R*) acid **6R**

followed an analogous route. Methylation of the alcohol as before gave the olefinic methyl ether **12** in 94.4% yield. Analogous oxidation of **12** using periodate and catalytic ruthenium trichloride furnished the desired (*R*) acid **6R** in 69.3% yield, thus making it available from **8S** in two steps and 65.4% overall yield. The purities of the final products, the acids **6R** and **6S**, was determined to be greater than 98% ee by integration of the singlets due to the methyl esters protons in the 200 MHz ^1H NMR spectra of the corresponding methyl esters (prepared by treatment of **6** with thionyl chloride and then dry methanol) taken in CDCl_3 with a small amount (approximately 0.5 eq) of the chiral shift reagent $\text{Eu}(\text{hfc})_3$.

It is important to point out that these sequences can be done on a relatively large scale so that gram quantities of the final acids can be readily produced. We are currently investigating the use of these acids to prepare the required 1,3-butadien-1-yl perfluorophenyl-*O*-methylmandelates **4** in order to test the predictions of reversed stereoselectivity.

In summary, then, the allylic alcohol **8** can be converted into both the (*S*) and (*R*) perfluorophenyl-*O*-methylmandelic acids, **6S** and **6R**, in overall yields of 30.3% and 30.1% respectively.

Acknowledgement: We thank Drs. Houk and Tucker for alerting us to this problem and the National Institutes of Health (GM-41592) for generous financial support.

REFERENCES AND NOTES

1. Presented at the 6th European Symposium on Organic Chemistry, Belgrade, Sept. 1989.
2. Current address: Dong Duck University, College of Pharmacy, Sung Buk-Gu, Wol kog-Dong, Seoul, Korea.
3. Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.
4. Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225. For a very recent study of the effects of a methyl substituent α to the phenyl ring on the selectivity, see: Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.*, **1990**, *112*, 6743.
5. Tucker, J. A.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1990**, *112*, 5465.
6. a) Valente, E. J.; Pohl, L. R.; Trager, W. F. *J. Org. Chem.* **1980**, *45*, 543. b) Pohl, L. R.; Trager, W. F. *J. Med. Chem.* **1973**, *16*, 475. c) Barbour, A. K.; Buxton, M. W.; Coe, P. L.; Stephens, R.; Tatlow, J. C. *J. Chem. Soc.* **1961**, 808. d) Chambers, R. D.; Clark, M.; Spring, D. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2464. e) Shadrina, L. P.; Dormidontov, Yu. P. *J. Org. Chem. USSR*, **1981**, *17*, 1251 [*Zh. Org. Khim.* **1981**, *17*, 1408]. f) Hegeman, G. D.; Root, R. T. *Arch. Microbiol.*, **1976**, *110*, 19.
7. a) Harper, R. J., Jr.; Soloski, E. J.; Tamborski, C. *J. Org. Chem.* **1964**, *29*, 2385. b) Chambers, R. D.; Clark, M.; Spring, D. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2464.
8. Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637.
9. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.