Pergamon

*Tetrahedron Letters*, Vol 35, No. 26, pp. 4501-4504, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00878-7

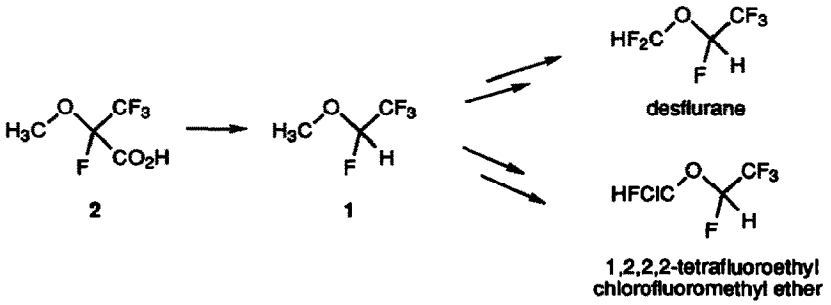
# Asymmetric Preparation of 1,2,2,2-Tetrafluoroethyl Methyl Ether, an Intermediate in the Synthesis of Volatile Anesthetics

**Leonid A. Rozov and Keith Ramig***

Ohmeda Inc., Pharmaceutical Products Division, 100 Mountain Ave., Murray Hill, NJ 07974

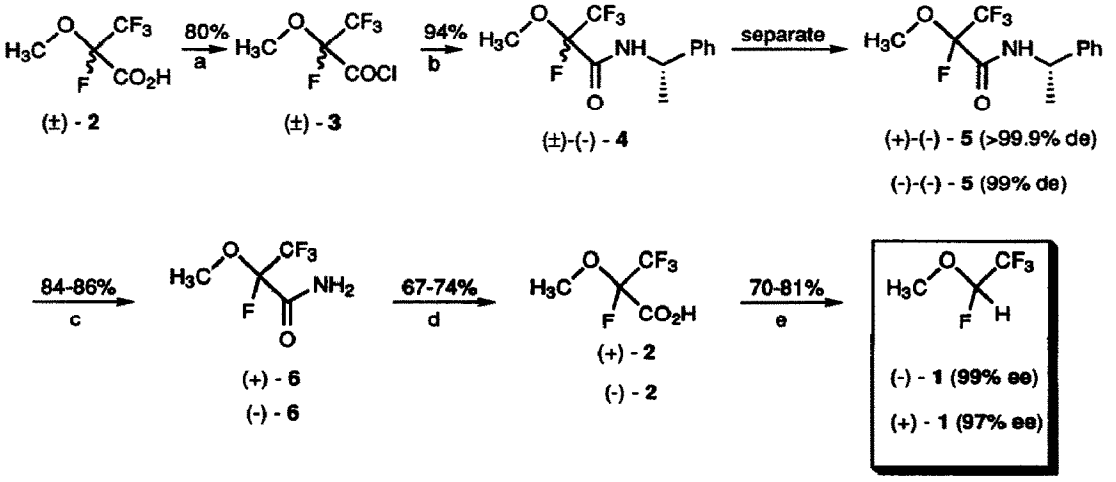
***Abstract:*** 1-Methoxytetrafluoropropionic acid (**2**) is resolved by diastereomeric amide formation with (*S*)-(-)-1-phenethylamine/chromatography/hydrolysis. Both enantiomers are obtained in ≥99% ee. Conversion of each enantiomeric acid to its potassium salt followed by thermolysis in triethylene glycol/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) gives the enantiomers of 1,2,2,2-tetrafluoroethyl methyl ether (**1**) with a very high degree of stereospecificity. The use of DMPU as co-solvent results in a significant yield improvement.

(±)-1,2,2,2-Tetrafluoroethyl methyl ether ((±)-**1**)[1] is an important intermediate in the synthesis[2] of the volatile anesthetics desflurane (Suprane®)[3] and 1,2,2,2-tetrafluoroethyl chlorofluoromethyl ether.[4] It is also an anesthetic itself.[1] It is most conveniently prepared from thermal decarboxylation[2,5] of the potassium salt of readily available 1-methoxytetrafluoropropionic acid (**2**).[6] We became interested in the stereochemistry of this process, in view of the recent realization that enantiomers of volatile anesthetics may have different or improved pharmacological properties compared to the racemate.[7] Individual enantiomers of volatile anesthetics have also been used to study the molecular mechanism of anesthesia.[8] It was anticipated that the thermolysis of



enantiomerically pure acid **2** would produce ether **1** with a high degree of retention or inversion, thus allowing the enantiomers of ether **1** to become useful intermediates in the asymmetric synthesis of volatile anesthetics.

The first challenge was resolution of acid **2**. The method of Kawa et al[9] was applied successfully (Scheme 1). Heating with subsequent distillation of the reaction mixture containing acid (±)-**2** and phthaloyl dichloride gave crude acid chloride (±)-**3**,[10] which was purified by fractional distillation. Amide formation with (*S*)-(-)-phenethylamine proceeded smoothly, affording amide (±)-(-)-**4**.[11] The crude mixture containing the diastereomers of secondary amide **4** could be separated on a 100 g scale by medium-pressure liquid chromatography on 230-400 mesh silica gel on elution with 10-50% EtOAc/hexane. After a final recrystallization from 9% EtOAc/hexane, the diastereomeric excess (de) of secondary amide (+)-(-)-**5** was >99.9% (HPLC analysis), while the de of secondary amide (-)-(-)-**5** was 99%. Debenzylation of secondary amides (+)-(-)-**5** and (-)-(-)-**5** with conc. $H_2SO_4$ furnished primary amides (+)-**6**[12] and (-)-**6**, respectively. Basic hydrolysis completed the resolution, yielding acids (+)-**2** and (-)-**2** after fractional distillation.




reagents: (a) phthaloyl dichloride, 200 °C, distillation; (b) (*S*)-(-)-phenethylamine/pyridine/$Et_2O$, reflux, 4 h; (c) conc. $H_2SO_4$, rt, 1 h; (d) 5 *M* NaOH, reflux, 2 h; (e) KOH/DMPU/TEG (1:4:1), ca. 205 °C, 2 h.

Scheme 1

Attention was then turned to the decarboxylation of acid (±)-**2**. The methyl ester of acid (±)-**2** has been converted to ether (±)-**1** in 50% yield by saponification with KOH followed by in situ thermolysis of the resulting potassium salt at 250 °C in triethylene glycol (TEG); these same conditions applied to acid (±)-**2** itself gave a yield of only 24%.[2] Dissatisfaction with these yields prompted us to find improved conditions. Use of CsOH or KOH/catalytic 18-crown-6 gave up to a 65% yield when applied to either acid (±)-**2** or its methyl ester. The best conditions employed 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as a co-solvent for the potassium salt. In this case, the yield was improved to an average of 75% while the temperature required for decarboxylation was lower by almost 50 °C. Both substitution of the larger $Cs^+$ for $K^+$ in the salt,

and use of strong metal cation complexing agents 18-crown-6 or DMPU would contribute to weakening of the metal-oxygen bond. This resulted in a much lower reaction temperature and presumably less unwanted decomposition.

A hint that this decarboxylation may be stereospecific is given by Vogl and Doyle,[13] who partially resolved and decarboxylated bromochlorofluoroacetic acid under similar conditions. The bromochlorofluoromethane produced maintained a high degree of optical activity. Also, Cram[14] has found varying levels of stereospecificity in the decarboxylation of a few acyclic carboxylic acids. We now demonstrate that acid **2** can be decarboxylated with a remarkably high degree of stereospecificity. Treatment of acid (+)-**2** with KOH/TEG/DMPU in a 1/1/4 molar ratio followed by thermolysis at ca. 205 °C for 2 h yielded ether (-)-**1**.[15] These same conditions when applied to acid (-)-**2** gave ether (+)-**1**. When the acid **2** used was derived from secondary amide **5** of ≥99.9% de, the ether **1** obtained had an ee of 99%. The ee of ether **1** was determined by chiral capillary GC.[16] At this point, it is not known whether the decarboxylation reaction proceeds with nearly exclusive retention or inversion of configuration. The determination of the absolute configurations of acid **2** and ether **1** will allow speculation about the mechanism of the transformation.

To conclude, we have prepared in good yield (+)- and (-)-1,2,2,2-tetrafluoroethyl methyl ether (**1**), the racemate of which is an intermediate in the synthesis of volatile anesthetics. Noteworthy is the highly stereospecific conversion of acid **2** to the title compound. When compared with other related stereospecific processes such as base-induced cleavage of tertiary alcohols[17] or the Haller-Bauer reaction,[18] this appears to be the most stereospecific cleavage of a C-C bond ever seen in an acyclic system. Experiments are in progress which will determine whether retention or inversion is the dominant outcome. As with many other pharmaceuticals containing stereogenic centers, it is becoming important to prepare and evaluate individual optical antipodes of volatile anesthetics. It is anticipated that this reaction will become a method to achieve that goal.

## ACKNOWLEDGMENTS

Much appreciated are Ms. Sarah Verbeke for performing the HPLC analyses, Mr. Martin Hackman for assistance with the chiral GC separations, and Dr. Hajimu Kawa (Exfluor, Austin, TX) for a helpful discussion. Dr. Gilbert Adelstein and Mr. Gerald Vernice are acknowledged for their encouragement of this work.

## REFERENCES AND NOTES

1. Siegemund, G.; Muschaweck, R. *US Patent 3 981 927*, **1976**.
2. Rozov, L. A.; Huang, C. G.; Vernice, G. G. *US Patent 5 205 914*, **1993**.
3. Terrell, R. C. *US Patent 4 762 856*, **1988**.
4. Siegemund, G.; Muschaweck, R. *Ger. Offen. 2 361 058*, **1975**.
5. LaZerte, J. D.; Hals, L. J.; Reid, T. S.; Smith, G. H. *J. Am. Chem. Soc.* **1953**, *75*, 4525. Hudlicky, T.; Fan, R.; Reed, J. W.; Carver, D. R.; Hudlicky, M. *J. Fluorine Chem.* **1992**, *59*, 9.
6. Synthesis in two steps from commercially available hexafluoropropylene oxide: Sianesi, D.; Pasetti, A.; Tarli, F. *J. Org. Chem.* **1966**, *31*, 2312.

7. Harris, B.; Moody, E.; Skolnick, P. *European J. Pharmacol.* **1992**, *217*, 215. Pearson, D. L. Ph.D. Dissertation, Cornell University, **1990**; *Diss. Abstr. Int. B* **1992**, *52*, 6400. Lysko, G.; Robinson, J.; Ferrone, R. Submitted to *European J. Pharmacol.*
8. Franks, N. P.; Lieb, W. R. *Nature* **1994**, *367*, 607; Franks, N. P.; Lieb, W. R. *Science* **1991**, *254*, 427.
9. Kawa, H.; Yamaguchi, F.; Ishikawa, N. *Chem. Lett.* **1982**, 745.
10. Muffler, H.; Siegemund, G.; Schwertfeger, W. *J. Fluorine Chem.* **1982**, *21*, 107.
11. All new compounds gave satisfactory spectroscopic and elemental analyses. Other data: Secondary amide (+)-(-)-**5** - $R_f$ in 20% EtOAc/hexane = 0.41; mp = 63-4 °C; $[\alpha]_D^{25}$ = -83° (c = 1, $CHCl_3$). Secondary amide (-)-(-)-**5** - $R_f$ in 20% EtOAc/hexane = 0.29; mp = 71-2 °C; $[\alpha]_D^{25}$ = -112° (c = 1, $CHCl_3$). Primary amide (+)-**6** - mp = 114 °C; $[\alpha]_D^{25}$ = +33° (c = 1, MeOH). Primary amide (-)-**6** - mp = 114 °C; $[\alpha]_D^{25}$ = -30° (c = 1, MeOH). Acid (+)-**2** - $[\alpha]_D^{25}$ = +24° (c = 1, $CHCl_3$). Acid (-)-**2** - $[\alpha]_D^{25}$ = -21° (c = 1, $CHCl_3$). Ether (-)-**1** - $[\alpha]_D^{25}$ = -66° (c = 1, $CHCl_3$). Ether (+)-**1** - $[\alpha]_D^{25}$ = +59° (c = 1, $CHCl_3$).
12. Racemate: Pasetti, A.; Tarli, F.; Sianesi, D. *Gazz. Chim. Ital.* **1968**, *98*, 277.
13. Doyle, T. R.; Vogl, O. *J. Am. Chem. Soc.* **1989**, *111*, 8510.
14. Cram, D. J.; Wingrove, A. S. *J. Am. Chem. Soc.* **1963**, *85*, 1100. Cram, D. J.; Haberfield, P. *J. Am. Chem. Soc.* **1961**, *83*, 2363. Cram, D. J.; Haberfield, P. *J. Am. Chem. Soc.* **1961**, *83*, 2354.
15. Typical experimental procedure: A mixture of 19.2 g (0.11 mol) of acid (+)-**2**, 16 mL of TEG, 55 mL of DMPU, and 7.0 g (88%, 0.11 mol) of KOH pellets was heated in a 250 mL reaction flask equipped with a distillation head attached to an oil bubbler. After the water produced in the reaction was distilled off and discarded, a cold finger cooled by dry ice/acetone was put between the distillation head and the bubbler. The evolution of $CO_2$ started at 155 °C; at 180-190 °C the product started to condense in the distillation receiver and the cold finger. The reaction mixture was held at 200 °C for 1 h, and at 210 °C for 1 h. The product which collected in the cold finger was warmed to room temperature under a dry ice condenser until the evolution of low boiling materials stopped, and then was combined with the product which collected in the distillation receiver. Washing with cold water and drying over $CaCl_2$ gave 10.1 g (70%) of ether (-)-**1**, bp 38-39 °C (lit.[1] for racemate, bp 36-38 °C). The chemical purity of this material was >98% (GC area %), and the ee was 99%.
16. The gas chromatograph was fitted with a 40 m G-TA glass capillary column (Advanced Separation Technologies (ASTEC), Whippany, New Jersey, USA) at 35 °C, flow rate 1 mL/min. Retention times: (+)-**1** - 4.0 min, (-)-**1** - 5.6 min.
17. Hoffmann, T. D.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 1009 and earlier papers in this series. D. J. Cram *Fundamentals of Carbanion Chemistry* Academic Press: New York, 1965, chapter IV.
18. Gilday, J. P.; Paquette, L. A. *Org. Prep. Proc. Int.* **1990**, *22*, 169 and references therein.


(*Received in USA* 31 *March* 1994; *revised* 25 *April* 1994; *accepted* 4 *May* 1994)