Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1417-1420, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Highly Enantioselective Synthesis of α-Fluoro Ketones *via* Allene Oxides

Marek M. Kabat#

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44,
01-224 Warszawa, Poland

(*Received in UK* 15 *March* 1993)

Abstract: *Optically active α-fluoroketones (96-97% ee) were obtained by the regioselective opening of chiral allene oxides with anhydrous tetrabutylammonium fluoride.*

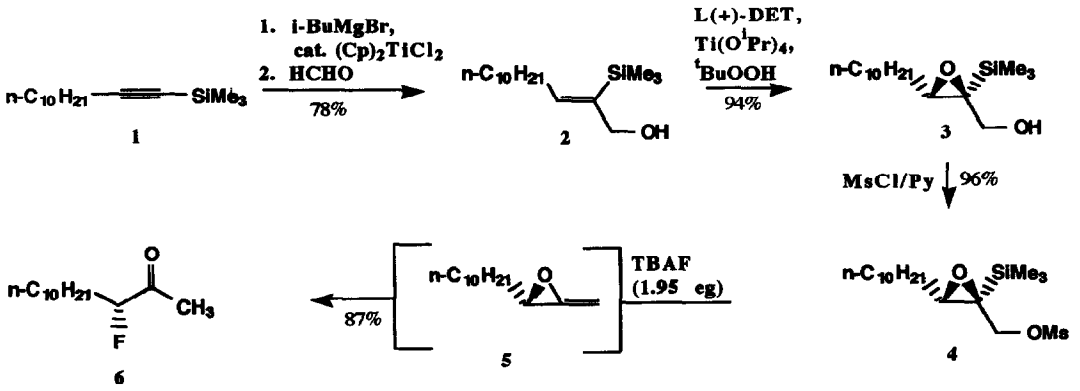
Interest in developing mild and selective methods for introducing fluorine into organic molecules has existed for a long time. The unique effect that the replacement of a specific hydrogen atom or a hydroxyl group by this element has on physical and chemical and biological properties of organic molecules[1] is of considerable significance for the preparation of biologically active substances[2], the construction of novel ferroelectric liquid crystalline polymers[3] and also as a test of synthetic strategy[4]. However, optically active fluorinated compounds where at least one of the asymmetric carbons bears a fluorine are difficult to prepare.[5] We report herein one effective solution to this problem, the highly enantioselective synthesis of α-fluoroketones (96-97% *ee*) which are obtained by the reaction of allene oxides with anhydrous tetrabutylammonium fluoride.

It is well established that the treatment of allene oxides with various nucleophiles leads to the formation of α-substituted ketones.[6] In this connection we have shown[7] recently that α-fluoromethyl ketones are formed by the treatment of allene oxides with anhydrous tetrabutylammonium fluoride. As a general methodology for the synthesis of optically active α-fluoro ketones, where the fluorine bonded carbon atom serves as a source of chirality for the molecule, we propose the incorporation of fluorine by the regioselective opening of chiral allene oxide. Scheme 1 outlines the pathway chosen to test the proposal that precursors leading to chiral allene oxides can be highly enantioselectively transformed into α-fluoroketones.

The model compound, 1-trimethylsilyl dodecyn-1 (**1**) was converted into the optically active silyl epoxide **3** in two steps: a) hydromagnesiation[8] followed by reaction with formaldehyde (2-bromomagnesium butane in the presence of 5% of titanocene dichloride then HCHO) to form (E)-allylic alcohol **2**, b) Sharpless asymmetric epoxidation[9] (^{t}BuOOH, L(+)-diethyl tartrate/titanium tetraisopropoxide, CH_2Cl_2, -23 °C, 4hrs) to give *(2R, 3S)*-epoxide **3**. The optical purity of **3** (*ee*=97%, $[\alpha]_D^{25}$=-22 , c 1.2, CH_2Cl_2) was established by its transformation into MTPA ester. Compound **3** was converted into the mesylate **4** which was then subjected to fluoride-promoted formation of allene oxide **5**. However, to obtain fluoroketone **6** directly from mesylate precursor **4**, *via* allene oxide **5**, 1.95 eq of anhydrous

tetrabutylammonium fluoride was applied as a source of nucleophilic fluoride. Treatment of THF solution of **4** with 1.95 eq of anhydrous TBAF at room temperature for 15 min led to the formation of *(R)*-3-fluoro-tridecan-2-one (**6**)[10] ($[\alpha]_D^{25}$=+50.7 , c 1.08, CH_2Cl_2) in 87% yield.

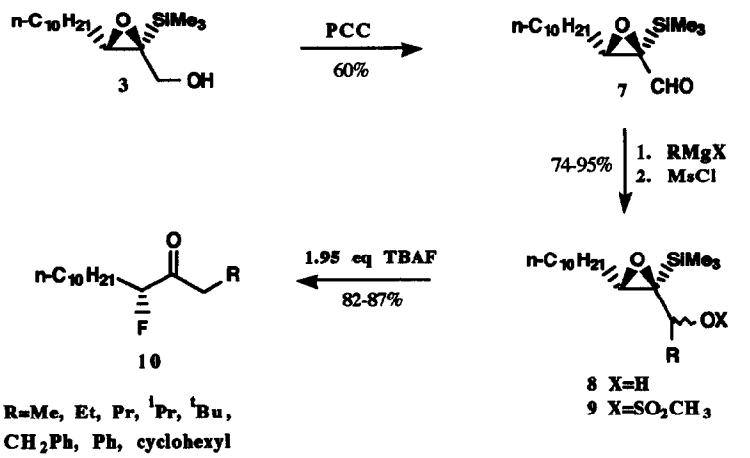
SCHEME 1



The optical purity of fluoroketone **6** (*97% ee*) was determined using ^1H nmr and comparison of the spectra of the separately prepared respective racemate[11] of **6** with that obtained by asymmetric synthesis as shown above. Both spectra were measured in the presence of the shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III). It is worth mentioning that fluoroketeone **6** did not racemise when 1.95-2.0 eq of TBAF *per* 1 eq of mesylate **4** was used. However, the presence of even a small excess of TBAF promoted racemization.

In order to determine the scope and limitations of the method presented above, various fluoroketones were obtained from optically active silylepoxide **3** (Scheme 2). Oxidation[13] of the hydroxyl group in **3** with pyridinium chlorochromate (CH_2Cl_2, rt, 1h) afforded aldehyde **7** in 60 % yield. Reaction of **7** with different Grignard reagents (1 eq of RMgX in Et_2O, 0 °C, R=Me, Et, Pr, ^iPr, ^tBu, CH_2Ph, Ph, cyclohexyl) gave a mixture of diastereomeric alcohols **8**. The ratio of diastereomers in **8**, which was dependent on the Grignard reagent used, had no influence on the synthesis of target molecules because the newly created asymmetric center was discarded in the later stage. Mesylation of the hydroxyl function in **8** afforded diastereomeric mesylates **9**. Finally, a THF solution of **9** was treated with 1.95 eq of anhydrous tetrabutylammonium fluoride at room temperature for 15 min-1h to afford[14] the desired fluoroketone **10** as the sole product. The optical purity of **10** was established with shift reagent by ^1H nmr as 96-97% *ee* . This reflects the *ee* of the epoxide **3** obtained *via* Sharpless asymmetric epoxidation of allylic alcohol **2**.

SCHEME 2



In summary, we have presented a highly enantioselective (96-97% *ee*), very mild method for the synthesis of optically active α-fluoro ketones *via* allene oxides. It is worth mentioning that with the growing interest in developing Positron-Emitting Transaxial Tomography (P.E.T.T.)[15] applying ^{18}F isotope in the presented methodology should lead to introduction of the isotope into biologically interesting molecules.

REFERENCES AND NOTES

Present address: Hafslund Nycomed Drug Research, Nycomed Bioreg AS, Gaustadalleen 21, N-0371 Oslo, Norway.

1) For a review on fluorinated natural products, see: M. Meyer and D. O'Hagan, *Chem. in Britain*, **September 1992**, 785;

2) J. T. Welch and S. Eswarakrishnan in *"Fluorine in Bioorganic Chemistry"*. John Willey and Sons; New York, Chichester, Brisbane, Toronto, Singapore, 1991;

3) a) T. Kitazume, T. Ohnogi, and K. Ito, *J. Am. Chem. Soc.*, **112**, 6608 (1990); b) D. M. Walba, H. A. Razavi, N. A. Clark, and D. S. Parmar, *J. Am. Chem. Soc.*, **110**, 8686 (1988);

4) S. Rosen and R. Filler, *Tetrahedron*, **41**, 1111 (1985);

5) For a recent asymmetric preparation of monofluorocarbonyl compound see: a) E. Fritz-Langhals and G. Schutz, *Tetrahedron Lett.*, **34**, 293 (1993); b) M. Ihara, N. Tanigouchi, T. Kai, K. Sataoh, and K. Fukumoto, *J. Chem. Soc. Perkin Trans I.*, 221 **1992**; c) T. Iwaoka, T. Murohashi, M. Sato, and Ch. Kaneko, *Tetrahedron Asymm.*, **3**, 1025, (1992); d) F. A. Davies and W. Han, *Tetrahedron Lett.*, **33**, 1153 (1992); e) M. Saburi, L. Shao, T. Sakurai, and Y. Uchida, *Tetrahedron Lett.*, **33**, 7877 (1992); f) T. Yamazaki, J. T.

Welch, J. S. Plummer, and R. H. Gimi, *Tetrahedron Lett.*, **34**, 4267 (1991); g) A. Focella, F. Bizarro, and C. Exon, *Synthetic Comm.*, **21**, 2165 (1991); h) P. Bravo and G. Resnati, *Tetrahedron Asymm.*, **1**, 661 (1990); i) P. Bravo, E. Piovosi, G. Resnati, and G. Fronza, *J. Org. Chem.*, **54**, 5171 (1989); j) J. T. Welch and K. W. Seper, *J. Org. Chem.*, **53**, 2991 (1988); k) T. Kitazume, T. Kobayashi, T. Yamamoto, and T. Yamazaki, *J. Org. Chem.*, **52**, 3218 (1987);

6) T. H. Chang and B. S. Ong, *Tetrahedron*, **36**, 2269 (1980);

7) M. M. Kabat, *J. Fluorine Chem.*, **42**, 435 (1989);

8) F. Sato, H. Ishikawa, and M. Sato, *Tetrahedron Lett.*, **22**, 85 (1981);

9) a) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980); b) Y. Gao, R. M. Hansen, J. M. Klunder, S. Y. Ko, H, Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987);

10) $[\alpha]_D^{25}$=50.7 (c 1.08, CH_2Cl_2). ^1H nmr ($CDCl_3$), δ: 0.88 (t, J=6.6 Hz, 3H, $\mathbf{CH_3}$-CH_2), 1.2-1.5 (m, 16H, CH_2), 1.7-1.9 (m, 2H, CH_2), 2.25 (d, $J_{(HF)}$=4.8 Hz, 3H, CH_3CO-), 4.71 (ddd, $J_{1(HF)}$=50.5 Hz, J_2=4.6 Hz, J_3=7.8 Hz, 1H, **CH**F). ^{13}C nmr ($CDCl_3$), δ: 14.31 (CH_3), 22.86 (CH_2), 24.68 (CH_2), 26.00 (CH_3), 29.36 (CH_2), 29.50 (2xCH_2), 29.72 (CH_2), 31.83 (CH_2), 32.11 (CH_2), 32.24 (CH_2), 96.20 (d, J_{CF}=182.7 Hz, CFH) 208.63 (d, J_{CF}=24.6 Hz, C=O). ^{19}F nmr ($CDCl_3$), δ: -190.1 (dddq, J_1=50.8 Hz, J_2=28 Hz, J_3=24 Hz, J_4=4.8 Hz). IR ($CHCl_3$): 1720 (C=O) cm^{-1}. MS-LR (m/e, %): 216 (M^+, 8), 145 (9), 140 (30), 131 (14), 111 (12), 97 (18), 89 (16), 85 (22), 76 (22), 43 (100). MS-HR: for $C_{13}H_{25}OF$ calculated 216.1889; found 216.1906. Elemental analysis: $C_{13}H_{25}FO$ requires C, 72.18%; H, 11.65%; found C, 72.30%, H, 11.57%.

11) Prepared in analogous way to presented for asymmetric synthesis of **6** but for epoxidation of **2** vanadium acetylacetonate/^{t}BuOOH system[12] was applied.

12) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973);

13) Y. Takeda, T. Matsumoto, and F. Sato, *J. Org. Chem.*, **51**, 4728 (1986);

14) Typical experimental procedure. Synthesis of *(R)*-4-fluoro-tetradeca-3-one (**10**, R=Me) from **9** (R=Me). A stirred solution of mesylate **9** (R=Me) (227mg, 0.60 mM) in dry THF (4ml) was treated with an anhydrous tetrabutylammonium fluoride (1.14 ml of 1M solution in THF, 1.14 mM) at room temperature for 15 minutes. Then solution was taken into pentane (20 ml) and was washed with water (3x20 ml) whereupon it was dried. After evaporation of solvent the crude product was purified by passing it through a short path of silica gel (4 g) using hexane:Et_2O (99:1) as eluate to give **10** (R=Me) (114 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$=+50.8 (c 1.14, CH_2Cl_2). ^1H nmr ($CDCl_3$), δ: 0.88 (t, J=6.7 Hz, 3H, CH_3), 1.07 (t, J=7.2 Hz, CH_3), 1.2-1.35 (m, 14H, CH_2), 1.35-1.5 (m, 2H, CH_2), 1.7-1.9 (m, 2H, CH_2), 2.5-2.7 (m, 2H, CH_2-O-), 4.74 (ddd, $J_{1(HF)}$=51 Hz, J_2=8.4 Hz, J_3=4.6 Hz, CHF). ^{19}F nmr ($CDCl_3$) δ: -192.9 (dddt, J_1=50.4 Hz, J_2=29 Hz, J_3=23 Hz, J_4=3 Hz). ^{13}C nmr ($CDCl_3$), δ: 6.73 (CH_3), 14.10 (CH_3), 22.70 (CH_2), 24.51 (CH_2), 29.19 (2xCH_2), 29.34 (2xCH_2), 29.56 (2xCH_2), 31.34 (CH_2), 31.90 (CH_2), 32.60 (CH_2), 96.13 (d, J_{CF}=183.1 Hz, CHF), 208.60 (d, J_{CF}=24.4 Hz, C=O). IR ($CHCl_3$): 1721 (C=O) cm^{-1}. MS-LR (m/e, %): 231 (M+H, 40), 183 (14), 132 (17), 90 (87), 57 (100). MS-HR: for $C_{14}H_{27}FO$ calculated 230.2046; found 230.2053. Elemental analysis: $C_{14}H_{27}OF$ requires C, 72.99%; H, 11.81%; found C, 72.90%; H, 12.03%.

15) R. Dagani, *Chem. Eng. News*, **Nov 9**, 1981, p. 30;