Enzymatic Racemic Resolution of a Fluorinated Substrate and Syntheses of E and Z Alkenes as Precursors for Some Biologically Active Fluoro-hexoses

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Fluorinated Substrate, Enzymatic Racemic Resolution, Alkenes

A fluorinated substrate 6 was prepared and then the enantiomers (6a and 7a) were separated by an enzyme in presence of an acetylating agent. The optical purity of 6a and 7a were determined by derivatising them into their MTPA-esters and then by taking their 19F NMR spectra. It was observed that, PL 266 (enzyme), benzene (solvent), 24 h (time), 40 °C (temp.) and vinyl acetate (acetylating agent) were the ideal conditions for racemic resolution. The optical purity was further improved by changing the solvent (hexane), amount of enzyme (PL 266; 3000 units), reaction time (12 h) and amount of acetylating agent (vinyl acetate; two molar). The optically pure species was used for the preparation of E and Z alkenes.

Introduction

Fluorinated compounds have been of great interest to synthetic and medicinal chemists for a considerable time due to the unique physical and biological properties imparted by fluorine [1–2]. A number of reviews have been published on this topic [3]. Incorporation of fluorine atom(s) into the organic molecules may bring about drastic changes in the nature of the parent materials. The fluorinated compounds have been broadly applied in the development of novel pharmaceutically active compounds [4–6] and optical devices [7–9]. Monofluoroacetic acid is well known to show very high toxicity, which is considered to be due to the inhibitory block effect of metabolic pathway of TCA cycle [10].

Over the last thirty five years the biochemical derivatisation of organic compounds by enzymes, bacteria and fungi has assumed considerable importance as a method which often compliments chemical transformation [11–13]. The functional groups can be introduced into the molecule in a regio- and stereospecific manner under the conditions that are quite mild [14]. These methods are also applicable to resolve the racemic mixtures.

Results and Discussion

Preparation of fluorinated substrate

The mono-ether 1 was prepared by treating propane-diol with sodium hydride in DMF and then with benzyl bromide. The hydroxyl proton was abstracted by NaH and substituted by a benzyl group. As the reaction mixture was left overnight, in addition to mono-ether 1, di-ether 2 was also formed as a by-product but, 1 was the major product as we used equimolar amount of NaH. The desired product 1 was confirmed by the presence of a multiplet at δ 7.2–7.4 ppm having five protons integration in the 1H NMR spectrum. The strongly UV active and less-polar by-product 2 was discarded without taking spectroscopic data. The 3-benzyloxy propanol 3 was oxidized into the corresponding aldehyde 3 by Swern oxidation. It was confirmed by the disappearance of hydroxyl absorption and appearance of aldehydeic carbonyl absorption band at 1735 cm⁻¹ in the IR spectrum. The aldehyde 3 was treated with unstable fluorinated intermediate 5 which was formed by treating 2-bromo-3,3,3-trifluoro-propene 4 with LDA to form fluorinated substrate 6. The compound 6 was confirmed by reappearance of hydroxyl function in the IR spectrum at 3400 cm⁻¹. It was also confirmed by its fluorine NMR which exhibited singlet at δ 29.46 (characteristic for F₃C≡ moiety) in the 19F NMR spectrum. The preparation of substrate is illustrated in the Scheme 1.

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The prepared substrate 6 was treated with lipase PS (Pseudomonas cepacia, Amano Seiyaku Co. Ltd.), lipase MY (Candida rugosa, Meito Sangyo Co., Ltd.) and PL 266 (lipase QL, Alcaligenes sp., Meito Sangyo Co., Ltd.) in various solvents at 30° or 40 °C in the presence of vinyl acetate or chlorovinyl acetate as an acetylating agent for different time periods (Table I). It was observed that PL 266 in benzene at 40 °C in the presence of vinyl acetate is able to resolve the prepared racemic mixture 6. The conversion rate or the amount of ester accumulated 7a during the reaction was monitored by 19F NMR. After 24 hours the two components 6a and 7a were separated by column chromatography (Scheme 2). Their optical rotations were measured to be -29.37° at 14 °C for 6a and +46.21° at the same temperature for 7a.

**Determination of Optical Purity**

**Preparation of MTPA-ester**

At first, 6a was hydrogenated using palladium/charcoal which resulted three products 8, 9 and 10.

The compound 8 was confirmed by its 19F NMR which displayed doublet at δ 20.98 (double bond region, F3C–CH=). The desired compound 9 was also confirmed by its 19F NMR which exhibited

**Table I.**

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<th>Temp. (°C)</th>
<th>AcO-Agent</th>
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<td>40</td>
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a C.V.A.: chlorovinyl acetate, V.A.: vinyl acetate; b in percent.
signal at $\delta$ 11.68 as a triplet ($\text{F}_3\text{C}-\text{CH}_2-$). The compound 10 was identified by its fluorine and proton NMR which showed triplet at $\delta$ 11.59 in $^{19}$F NMR and the absence of aromatic protons in the $^1$H NMR spectra, respectively. The compound 9 was used for the preparation of MTPA-ester 11 by normal procedure (Scheme 3). Its purity was checked by gas chromatography and finally, by $^{19}$F NMR which showed 80% ee.

**Confirmation of optical purity**

The optical purity of ester 7a was also checked. In the first step, it was hydrogenated into 12 and then hydrolyzed by $\text{K}_2\text{CO}_3$ to afford alcohol 13 having opposite stereochemistry at C-3 with reference to 6a. Finally, compound 13 was also converted into the corresponding MTPA-ester which was also found to be 80% ee (Scheme 4).

**Improvement of optical purity**

After obtaining the alcohol 6a and acetate 7a in 80% ee, it was decided to improve the optical purity either by changing the time of reaction or the amount of enzyme used at 40 °C (Table II).

It was observed that when the reaction was left for longer period the conversion was very low. It was thought that may be this reaction is reversible after a long time or may be due to the atmospheric moisture. Due to these reason the substrate (racemic) 6 was acetylated chemically into 7 and treated with the same enzyme for three days. It was found that after longer period the some amount of alcohol was produced which was confirmed the reversibility of the reaction (Scheme 5).

**Preparation of E and Z alkenes**

The optically pure compound 6a was used for the preparation of E and Z alkenes (Scheme 6).

The $E$ olefin 14 was prepared by treating compound 6a with Red-Al. It was confirmed by the presence of signal as ddq at $\delta$ 5.95 (1 H, $J = 2.01$, 15.62, 6.57 Hz, $\text{CF}_3\text{CH}$) and at $\delta$ 3.67 (1 H, ddq, $J = 4.01, 15.60, 2.01$ Hz, $\text{CF}_3\text{CH}=$$\text{CH}$) in the $^1$H NMR spectrum. The $Z$ olefin 15 was prepared by treating the same compound 6a with Lindlar cata-

<table>
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<th>No. solvent</th>
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</tr>
<tr>
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<td>27</td>
<td>equimolar</td>
</tr>
<tr>
<td>3 benzene</td>
<td>18000</td>
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</tr>
<tr>
<td>4 hexane</td>
<td>3000</td>
<td>12</td>
<td>two molar</td>
</tr>
</tbody>
</table>
lyst under hydrogen. It was also confirmed by its $^1$H NMR which displayed signals at $\delta$ 5.58 (1 H, ddq, $J = 1.23, 11.94, 8.76$ Hz, CF$_3$CH) and at $\delta$ 6.03 (1 H, dd, $J = 8.81, 11.94$ Hz, CF$_3$CH=CH) in the spectrum.

These $E$ and $Z$ optically pure olefins can be used as precursors for the syntheses of biologically active fluoro-hexoses having reverse stereochemistry at a chiral center. These sequences can also be applied for the syntheses of various natural products, especially in the area of carbohydrates containing fluorine atom/atoms.

**Experimental**

All commercially available reagents were used without further purification. All reactions involving air-sensitive materials were performed under nitrogen atmosphere. THF and CH$_2$Cl$_2$ were distilled from sodium/benzophenone and calcium hydride, respectively, under nitrogen immediately prior to use.

$^1$H and $^{13}$C NMR spectra were recorded on Varian Giemini-200 (200 MHz) or Varian VXR-500 (500 MHz) in CDCl$_3$. Chemical shifts were recorded in parts per million ($\delta$) downfield from internal tetramethylsilane (TMS). $^{19}$F NMR spectra were scanned by Hitachi R-1200F (56.451 MHz) in CDCl$_3$ and the chemical shifts were reported in ppm downfield from external trifluoro-acetic acid (TFA). Infrared (IR) spectra were obtained on JASCO A-102 or JASCO FT/IR-5000 spectrometers. Optical rotations were measured on JASCO DIP-140 digital polarimeter in chloroform. Silica gel column chromatography was performed (E. Merck, 70–230 mesh) by using mixtures of hexane:ethylacetate (v:v) as a mobile phase. Gas liquid chromatography (GLC) was conducted on Shimadzu GC-8A.

3-(Benzylxoy)-propanol (I)

To a stirring slurry of NaH (9.5 g) in DMF (160 ml), the propane diol (11.5 ml) was added dropwise at 0 °C under the nitrogen and the whole was stirred for 0.5 h. Then benzyllbormide (19 ml) was added gradually and the reaction mixture was left overnight. The reaction was quenched by NH$_4$Cl and the product was extracted with a mixture of hexane: diethyl ether (1:1). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude mass was purified by silica gel column chromatography using hexane:ethylacetate as a mobile phase. The first (less polar) product 2 eluted from column was discarded without taking spectroscopic data. The second product (polar) obtained from column was 1. The remaining DMF was removed by short path distillation. The whole reaction was repeated two times in order to obtain 1 in bulk.

**Yield:** 65%; **Mass** (FD): M$^+$ 166 m/z; **$^1$H NMR:** $\delta$ 1.95 (2 H, m, H-2), 3.63 (2 H, t, $J = 7.0$ Hz, H-3), 3.80 (2 H, dd, $J = 7.0, 5.1$ Hz, H-1), 4.45 (2 H, s, CH$_3$Ph), 7.2–7.4 (5 H, m, Ph).

1-Benzylxoy-6,6,6-trifluoro-4-hexyn-3-ol (6)

DMSO (20 ml) and dichloromethane (200 ml) were taken at −78 °C under nitrogen atmosphere and oxalyl-chloride (18.2 ml) was added. After 10 minutes stirring, the prepared benzyl-ether 1 (15.5 g) diluted with CH$_2$Cl$_2$ (150 ml) was added dropwise. After 0.5 h Et$_3$N (68.3 ml) was introduced into the reaction mixture and the reaction was left for further stirring about 0.5 h. Then the mixture was extracted with CH$_2$Cl$_2$. After drying over Na$_2$SO$_4$ it was purified by column chromatography using hexane:ethylacetate (4:1) which yielded 13.2 g of corresponding aldehyde 3.

The LDA was prepared by mixing treating diisopropyl amine (26 ml), THF (150 ml) and BuLi (68.6 ml) under nitrogen atmosphere at −78 °C. To this solution, a precooled solution of 2-bromo-3,3,3-trifluoropropene (8.32 ml) in THF (40 ml) was added dropwise. After 5 minutes, prepared aldehyde 3 (13 g) diluted with THF (78 ml) was introduced into the reaction mixture. The whole mixture was left for 0.5 h stirring and then quenched by NH$_4$Cl. The organic material was extracted with diethyl ether, dried over Na$_2$SO$_4$, and chromatographed on a silica gel column afforded compound 6.

**Elution:** Hexane:ethylacetate (4:1); **Yield:** 85%; **IR** (neat): ν 3400, 3100, 3075, 3025, 2950, 2925, 2275 cm$^{-1}$; **Mass** (FD): M$^+$ 258 m/z; **HRMS:** found 258.0852 m/z (Caled 258.0868 m/z for C$_{13}$H$_{13}$F$_3$O$_2$; $^1$H NMR: $\delta$ 1.98 (1 H, ddd, $J = 3.46, 5.57, 6.45$ Hz, H-2), 2.17 (1 H, dt, $J = 8.91, 14.77, 4.15$ Hz, H-2), 3.44 (1 H, d, $J = 6.84$ Hz, OH), 3.70 (1 H, ddd, $J = 4.15, 5.50, 9.64$ Hz, H-1), 3.86 (1 H, dt, $J = 3.54, 9.28$ Hz, H-1), 4.54 (2 H, s, CH$_3$Ph), 4.71 (1 H, dtq, $J = 3.81, 6.73, 2.97$ Hz, H-3), 7.2–7.4 (5 H, m, Ph); **$^{13}$C NMR:** $\delta$ 35.39, 60.91 (q, $J = 1.17$ Hz), 67.13, 72.03 (q, $J = 52.99$ Hz), 73.55, 87.50 (q, $J = 6.30$ Hz), 114.02 (q, $J = 257.46$ Hz), 127.73, 127.98, 128.53, 137.30; **$^{19}$F NMR:** $\delta$ 29.46 (d, $J = 2.77$ Hz).
**Enzymatic esterification**

The racemic alcohol 6 (11.0 g) was dissolved in hexane (85 ml). Then, vinyl acetate (7.27 ml) and PL 226 (Meito Sanyo Co., Ltd., 4.26 g) were added into it. The whole mixture was stirred at 40 °C for 12 hrs. After filtration and concentration, it was chromatographed on silica gel column using hexane:ethyl acetate which yielded optically active alcohol 6a and ester 7a. The physical properties of racemic alcohol 6 and optically active alcohol 6a were the same which were described previously, except the optical rotation.

**Yield:** 41%; \([\alpha\text{I}]^{23} +34°\ (c\ 1.26, CHCl_{3})\); optical purity: 96.3% ee

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**6-Benzoxy-1,1,1-trifluoro-4-acetoxy-2-hexyne (7a)**

**Elution:** Hexane:ethyl acetate (6:1); **Yield:** 59%; \([\alpha\text{I}]^{23} +40°\ (c\ 2.09, CHCl_{3})\); **Mass:** ([FD]; M\(^+\) 300 m/z (C\(_1\)H\(_{15}\)F\(_3\)O\(_3\)); **IR** (neat): n 3090, 3065, 3035, 2935, 2865, 2800, 1775 cm\(^{-1}\); **1H NMR:** \(\delta\ 2.06\ (3\ H, s, Ac), 2.0-2.3\ (2\ H, m, H-5), 3.53\ (1\ H, dt, J = 9.83, 5.70 Hz, H-6), 3.59\ (1\ H, dt, J = 9.86, 5.89 Hz, H-6), 4.46\ (1\ H, d, J = 11.94 Hz, CH\(_2\)Ph), 4.52\ (1\ H, d, J = 11.94 Hz, CH\(_2\)Ph), 5.63\ (1\ H, dq, J = 7.02, 2.88 Hz, H-4); **13C NMR:** \(\delta\ 20.63, 34.08, 60.04\ (q, J = 1.32 Hz), 64.85, 72.29\ (q, J = 52.87 Hz), 73.16, 84.40\ (q, J = 6.31 Hz), 113.81\ (q, J = 257.86 Hz), 127.75, 127.80, 128.46, 137.82, 169.39; **19F NMR:** \(\delta\ 28.38\ (d, J = 2.77 Hz).\)

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**6-Benzoxy-1,1,1-trifluoro-4-acetoxyhexane (12)**

To a suspension of 10% Pd–C (0.03 g) in anhydrous ethanol (15 ml) under hydrogen, was added compound 7a (387 mg), and the whole mixture was stirred overnight. After removal of the catalyst (Pd–C) by filtration, the solution was concentrated. The crude product so obtained, was purified by silica gel column chromatography.

**Elution:** Hexane:ethanol acetate (9:1); **Yield:** 98.2%; \([\alpha\text{I}]^{23} +8.69°\ (c\ 1.105, CHCl_{3})\); **IR** (neat): n 3020, 1735, 1216 cm\(^{-1}\); **MS** (FD); M\(^+\) 304 m/z (C\(_1\)H\(_{19}\)F\(_3\)O\(_3\)); **1H NMR:** \(\delta\ 1.90\ (2\ H, q, J = 6.27 Hz, H-5), 2.00\ (3\ H, s, Ac), 2.11–2.22\ (4\ H, m, H-3 and H-2), 3.49\ (1\ H, dt, J = 9.52, 6.47 Hz, H-6), 3.51\ (1\ H, dt, J = 9.52, 5.86 Hz, H-6), 4.47\ (2\ H, s, CH\(_2\)Ph), 5.09\ (1\ H, dq, J = 3.42, 6.43 Hz, H-4), 7.12\ (5\ H, m, Ph).

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**1-Benzoxy-6,6,6-trifluorohexen-3-ol (13)**

Compound 12 (387 mg) was dissolved in methanol (15 ml) and K\(_2\)CO\(_3\) (288 mg) was added into it at room temperature. After 2 hrs. of stirring, the methanol was removed by vacuum and water was added. The product was extracted with ethylacetate and purified by silica gel column chromatography.

**Elution:** Hexane:ethylacetate (8:1); **Yield:** 86%; \([\alpha\text{I}]^{23} +17.98°\ (c\ 1.19, CHCl_{3})\); **Mass** (FD); M\(^+\) 262 m/z (C\(_3\)H\(_{17}\)F\(_2\)O\(_2\)); **1H NMR:** \(\delta\ 1.88\ (4\ H, m, H-2 and H-4), 2.25\ (2\ H, m, H-5), 3.68\ (1\ H, ddd, J = 4.15, 5.50, 9.64 Hz, H-1), 3.78\ (1\ H, dt, J = 3.54, 9.28 Hz, H-1), 3.89\ (1\ H, dtq, J = 3.81, 6.73, 2.97 Hz, H-3), 4.52\ (2\ H, s, CH\(_2\)Ph), 7.33\ (5\ H, m, Ph).

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**Catalytic hydrogenation of 1-Benzoxy-6,6,6-trifluoro-4-hexen-3-ol (6a)**

The optically pure alcohol 6a (515 mg), was dissolved in ethanol (30 ml) and treated with 10% Pd–C (0.04 g under hydrogen. The reaction was left overnight. After filtration, the crude material was chromatographed on silica gel column. After purification two products could be identified. The spectroscopic data of compound 8 having double bond is identified as Z olefin 15. The data of desired saturated compound 9 is identical to compound 13; \([\alpha\text{I}]^{23} +12.80°\ (c\ 1.27, CHCl_{3}).\)

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**Preparation and purification of MTPA-ester**

The optically pure saturated alcohols 9 and 13 having opposite stereochemistry at C-3, were converted into their corresponding MTPA-esters separately. In each case, 0.5 m.mol alcohol was dissolved in anhydrous CH\(_2\)Cl\(_2\) and MTPA-Cl (0.13 ml), 4-dimethylaminopyridine (catalytic amount) and triethyl amine (0.08 ml) were added into it at room temperature under nitrogen overnight. Then, the mixture was quenched with 1 N HCl and extracted with CH\(_2\)Cl\(_2\). The crude materials were passed through silica gel column and the optical purity was checked by GLC and fluoride NMR.

**((E)-1-Benzoxy-6,6,6-trifluoro-4-hexen-3-ol (14)**

To a stirring solution of Red-Al (0.53 ml) in toluene (5 ml) at _-78 °C was added optically pure alcohol 6a (0.387 g). After stirring for 3 hrs., the mixture was quenched with 1 N HCl and the product was extracted with ethylacetate. The crude olefin was purified by silica gel column chromatography.

**Elution:** Hexane:ethyl acetate (4:1); **Yield:** 90.4%; \([\alpha\text{I}]^{23} +5.06°\ (c\ 1.304, CHCl_{3})\); **Mass** (HRMS): Found M\(^+\) 260.2561 m/z (Calcd for C\(_3\)H\(_{17}\)F\(_2\)O\(_2\) m/z 260.1024); **IR** (neat): n 3450, 3075, 3050, 2950, 2875, 1650 cm\(^{-1}\); **1H NMR:** \(\delta\ 1.7–2.1\ (2\ H, m, H-2), 3.41\ (1\ H, d, J = 3.81 Hz, CH\(_2\)Ph).\)
OH), 3.65 (1 H, dt, J = 9.34, 4.27 Hz, H-1), 3.73 (1 H, dt, J = 9.38, 4.04 Hz, H-1), 4.4–4.6 (1 H, m, H-3), 4.52 (2 H, s, CH₂Ph), 5.95 (1 H, ddq, J = 2.01, 15.62, 6.57 Hz, H-5), 6.37 (1 H, ddq, J = 4.01, 15.60, 2.01 Hz, H-4), 7.2–7.4 (5 H, m, Ph); ¹³C NMR: δ 35.38 (q, J = 1.32 Hz), 68.33, 69.78, 75.53, 117.90 (q, J = 33.65 Hz), 123.37 (q, J = 268.84 Hz), 127.77, 128.01, 128.58, 137.44, 141.78 (q, J = 6.30 Hz); ¹⁹F NMR: δ 15.01 (d, J = 5.53 Hz).

(Z)-1-Benzoxo-6,6,6-trifluoro-4-hexen-3-ol (15)

A solution of optically active alcohol 6a (2 g) in hexane (40 ml) and Lindlar catalyst (0.31 g) was added into it under hydrogen. After 2 hrs., catalyst was removed by filtration and the solution was concentrated under reduced pressure, which was then purified by column chromatography to afford olefin 15.

Elution: Hexane:ethyl acetate (9:1); Yield: 63%; [α]D +5.89° (c 1.083, CHCl₃); Mass (HRMS): Found M⁺ 260.2561 m/z (Calcd 260.1024 for C₁₃H₁₅F₃O₂ m/z); IR (neat): v 3425, 3075, 3050, 2950, 2875, 1650, 675 cm⁻¹; ¹H NMR: δ 1.6–2.1 (2 H, m, H-2), 3.31 (1 H, d, J = 3.25 Hz, OH), 3.66 (1 H, ddd, J = 4.06, 4.90, 8.91 Hz, H-1), 3.73 (1 H, ddd, J = 2.56, 4.88, 9.38 Hz, H-1), 4.48 (1 H, d, J = 11.9 Hz, CH₂Ph), 4.55 (1 H, d, J = 11.72 Hz, CH₂Ph), 4.7–5.0 (1 H, m, H-3), 5.58 (1 H, ddq, J = 1.23, 11.94, 8.76 Hz, H-5), 6.03 (1 H, dd, J = 8.81, 11.94 Hz, H-4), 7.2–7.5 (5 H, m, Ph); ¹³C NMR: δ 36.18, 67.53 (q, J = 1.42 Hz), 68.29, 73.41, 117.72 (q, J = 34.47 Hz), 122.87 (q, J = 272.00 Hz), 127.75, 127.90, 128.53, 137.62, 144.48 (q, J = 5.19 Hz); ¹⁹F NMR: δ 20.92 (d, J = 8.24 Hz).

Acknowledgements

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