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Regio- and stereoselective hydrogenolysis of optically active diols *via* transfer hydrogenation : Synthesis of α- arylpropionic acids

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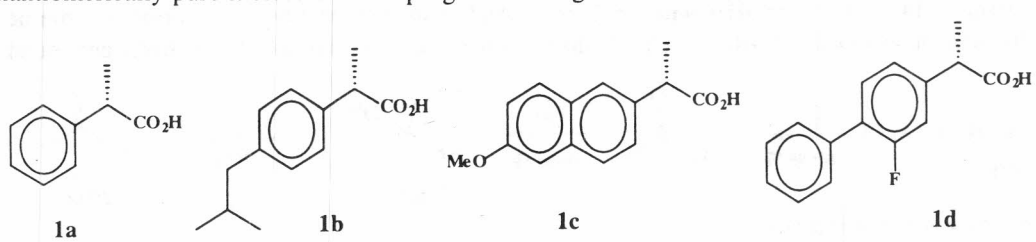
Asymmetric synthesis of α-arylpropionic acids, Ibuprofen **1b**, Naproxen **1c**, and Flurbiprofen **1d** have been achieved by employing Sharpless asymmetric dihydroxylation followed by the stereoselective hydrogenolysis of the chiral diols coupled with Jones' oxidation as the key steps. The regio- and stereoselective hydrogenolysis of the chiral diols at the benzylic position proceeds with retention of configuration for all the substrates studied.

α-Arylpropionic acids ("profens") such as Ibuprofen **1b**, Naproxen **1c**, Flurbiprofen **1d** etc. (**Figure 1**) have emerged as an important class of non-steroidal anti-inflammatory drugs (NSAID) having analgesic and antirheumatic properties.[1] Until now all profens except Naproxen are administered as racemic mixtures although the (*S*)-enantiomer displays the desired mode of function by inhibition of prostaglandin biosynthesis.[2] The use of racemate is justified to some extent since most (*R*)-antipodes have been found to undergo an enzymatically controlled *in vivo* racemization, the occurrence and mechanism of which are well documented.[2c] However, it is indispensible to realize the specificity of the required (*S*)-isomer and the toxicity and unnecessary load on the metabolite by the undesired (*R*)-isomer which is revealed by chemotherapeutic studies.[3] Thus optically active (*S*)-isomer is highly desirable. Moreover, presently much attention[4] is being paid to the problem of the manufacture of non-racemic chiral drugs.

Asymmetric synthesis of these molecules by chemical methods are still lacking efficient strategies and efforts to make enantiomerically pure molecule are in progress. Several methods[1] using classical resolution, enzymatic reaction and a few chemical syntheses are reported in the literature for the synthesis of these molecules. However, some of the methods are having drawbacks such as expensive reagents, low yield and optical purity, high pressure reactions etc.

Hence we sought to find synthetic methodology which would provide a general method to introduce the stereogenic center common to all of the NSAID's. We have developed a strategy whereby asymmetry is introduced into the molecule by means of Sharpless asymmetric dihydroxylation[5] (AD) and then the required stereogenic center is put in place by means of a highly regio- and stereospecific hydrogenolysis of the benzylic hydroxyl group with the retention of confi-guration followed by the Jones' oxidation (**Scheme I**).

We wanted to check the validity of our strategy first with an asymmetric synthesis of phenylpropionic acid **1a**. Then, having established the validity of the route, we turned our attention to the application of this strategy to the synthesis of representative members of this class of drugs.



1a **1b** **1c** **1d**

Figure 1

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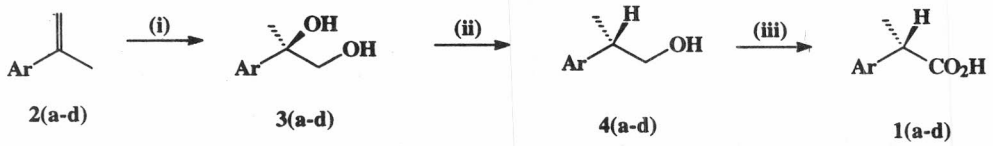


2(a-d) 3(a-d) 4(a-d) 1(a-d)

a : Ar = Phenyl
b : Ar = 4-Isobutylbenzene
c : Ar = 6-Methoxynaphthalene
d : Ar = 2-Fluorobiphenyl

Reagents: (i) AD mix-β, 28 hr; (ii) 10% Pd-C, $HCOONH_4$, ethanol, reflux, 6h; (iii) Jones' reagent, 8 hr

Scheme I

When this work was in progress Hamon and co-workers published[6] their work wherein the diol **3** was in turn converted to its epoxide and then the stereoselective hydrogenolysis of the benzylic epoxide bond produced the required stereogenic center.

Results and Discussion

For a model study, the synthesis of **1a** was carried out using α-methyl styrene **2a** (Aldrich, USA) as starting olefin. The optical purity of the final product 2-phenyl propanoic acid **1a** was found to be 60% ($[\alpha]_D$ = 48.4; *c* 1, EtOH). For the construction of a range of arylpropionic acids it was deemed desirable to develop the key intermediate olefins **2b-d**. The substituted aromatics **5b,c** were subjected to Friedel-Craft's acylation to get the corresponding acetophenones **6b,c** in good yield (80-95%). These compounds were converted to the corresponding tertiary alcohols **7b,c** by treating with methylmagnesium iodide. Here again the yields were good. Compounds **7b,c** had to be converted to the respective olefins. Among the various methods tried $POCl_3$/pyridine was found to be quite efficient (90% yield) for dehydration (**Scheme II**). Having completed the synthesis of key intermediates **2b,c**, we planned for the synthesis of various arylpropanoic acids.

(a) Asymmetric synthesis of Ibuprofen and Naproxen

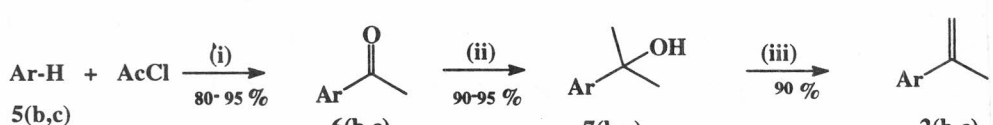
The olefins **2b** (m.p. 110 °C, yellow solid) and **5c** (m.p. 109-110 °C, yellow solid) were subjected to Sharpless asymmetric dihydroxylation using $(DHQD)_2$-PHAL as chiral auxiliary to furnish 85% of the diol **3b** [m.p. 67-70°C, $[\alpha]_D$ -7.01 (c 1.0, EtOH)] and **3c** [m.p. 119-122 °C, $[\alpha]_D$ -8.14 (c 1.15, EtOH)] with 75% ee. The *ee* of **3b** was determined by use of chiral shift reagent $Eu(hfc)_3$ on the derived acetate whereas that of **3c** was determined by comparing $[\alpha]_D$ value with the reported value.[7]

Hydrogenolysis of chiral benzylic alcohols with Raney Ni and Pd-C have been known to proceed with retention of configuration.[8] Thus, the diols **3b** and **3c** when subjected to hydrogenolysis over Pd-C in boiling absolute ethanol using $HCOONH_4$ as hydrogen source yielded **4b** and **4c** in 65% and 75% respectively with the retention of configuration (65% ee in each case). Here also the ee was calculated by complexing the derived acetate with the chiral shift reagent, $Eu(hfc)_3$. Mention must be made here that in Hamon's case[6] there was an inversion of configuration during the hydrogenolysis of the benzylic epoxide bond.

The alcohol **4b** [m.p. 101-103 °C, $[\alpha]_D$ +8.4 (*c* 1.15, EtOH)] and **4c** [m.p. 85-87 °C, $[\alpha]_D$ +2.2 (*c* 1.10, EtOH)] was subjected to Jones' oxidation using freshly prepared Jones' reagent[9] to get optically active α-arylpropionic acid **1b** [m.p. 54-56 ° C, $[\alpha]_D$ +38 (c 1.40, $CHCl_3$)] and **1c** [m.p. 154 °C, $[\alpha]_D$ +41.8 (c 1.0. $CHCl_3$)] in 40% and 35% yield respectively (65% *ee* in each case). The *ee* of the arylpropionic acid was low. The low optical purity of the final product could be because of partial racemisation during hydrogenolysis or during the strongly acidic Jones' oxidation.

b) Asymmetric synthesis of Flurbiprofen

(*S*)-Flurbiprofen **1d** has received a significant interest in recent years due to the profound and unexpected effects on the activities by the introduction of fluorine.[10] And also the ability of fluorine to mimic hydroxy functionalities and to act as hydrogen bond acceptor



5(b,c) 6(b,c) 7(b,c) 2(b,c)

b : Ar = 4-Isobutylbenzene
c : Ar = 6-Methoxynaphthalene

Reagents: (i) $AlCl_3$, CH_2Cl_2, (80-95%); (ii) MeMgI, ether, 0°C, (90-95 %); (iii) $POCl_3$, Pyridine (90%)

Scheme II

exert profound pharmacological effects in improving the activity and selectivity of bioactive compounds and drugs.[10] Here we also describe the synthesis of (S)-(+)-flurbiprofen **1d** *via* AD reaction and selective hydrogenolysis of the chiral diol under transfer hydrogenation conditions as key steps starting from racemic flurbiprofen **8** (**Scheme III**).

The key intermediate **12** was obtained from racemic flurbiprofen. The racemic flurbiprofen[11] was esterified with thionyl chloride and ethanol in quantitative yield to **9**. The ester was reduced by LAH to furnish the alcohol **10** (m.p. 56-58 °C, 78% yield). The alcohol **10** was tosylated to get **11** (m.p. 108-112 °C) by tosyl chloride in pyridine followed by LAH reduction to afford the isopropyl derivative **12** in 72% yield. The isopropyl derivative **12** was subjected to benzylic bromination to give the bromocompound **13** in 84% yield. It was dehydrobrominated using LiBr and Li_2CO_3 as base in DMF to obtain 2-(2-fluoro-4-biphenyl)prop-1-ene **14** (m.p. 60-64 °C) in 65% yield.

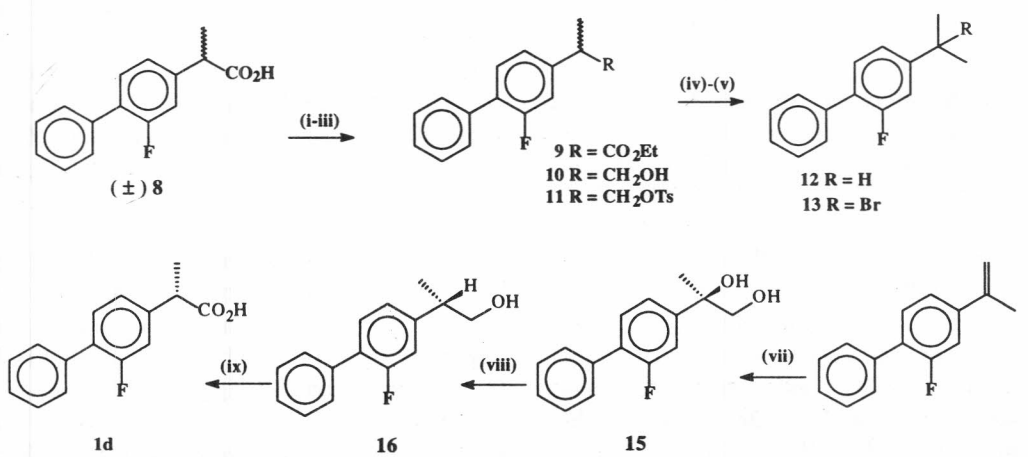
The olefin **14** was dihydroxylated using a AD mix-β to furnish the diol **15** [m.p. 96-99 °C, $[\alpha]_D$ -6.6 (*c* 1.5, EtOH)] with good enantiomeric excess (85% ee). The diol **15** was subjected to hydrogenolysis as in the case of **3b,c** to give the alcohol **16** [m.p. 55-58 °C, $[\alpha]_D$ +8.4 (*c* 1.1, EtOH), 74% yield] in 65% ee. The ee was determined by complexing the derived acetate with chiral shift reagent, $Eu(hfc)_3$. The alcohol **16** was oxidized to optically active α-arylpropionic acid **1d** by Jones' reagent in 72% yield and 57% ee.

In conclusion, the asymmetric synthesis of α-arylpropionic acids, Ibuprofen **1b**, Naproxen **1c**, Flurbiprofen **1d**, was achieved by employing Sharpless asymmetric dihydroxylation followed by stereoselective hydrogenolysis at the benzylic position as key steps. The chemical steps involved are efficient, easy to operate, economical and industrially useful.

Experimental Section

All melting points are uncorrected. IR spectra were recorded on Perkin-Elmer spectrophotometer model 683B or 1605 FT-IR, ^1H and ^{13}C NMR spectra in $CDCl_3$ with tetramethylsilane as internal standard on either FT-80A, Bruker WH-90 or Bruker AC-200 instruments and mass spectra recorded on Finnigan MAT-1020-B-70 eV mass spectrometer. All optical rotations were measured using Sodium D line on JASCO-181 digital polarimeter at room temperature. All solvents were distilled before use. Anhydrous Et_2O and THF were distilled from Na/benzophenone.

Preparation of 4-isobutylacetophenone 6b and 2-Acetyl-6-methoxynaphthalene 6c. To a stirred solution of either isobutylbenzene **5b** or 6-methoxy-naphthalene **5c** (0.01 mole) and anhyd. $AlCl_3$ (2 g, 0.015 mole) in dry CH_2Cl_2 (100 mL), acetyl chloride (1.1 mL, 0.01 mole)was added dropwise. The reaction mixture was stirred for 12 hr at 25 °C and decomposed with ice-cold water and dil. HCl. It was then extracted with CH_2Cl_2, washed with brine and dried over anhyd. Na_2SO_4. Removal of solvent under reduced pressure gave the corresponding ketone **6b** and **6c** which was further purified by column chromatography (2% ethyl acetate in pet. ether). **6b**: light yellow solid; m.p. 99-100 °C, yield 95%; IR (Nujol): 1750, 1690, 1460, 1330, 1180, 1020 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (d, *J*=7Hz, 6H), 1.75 (m, 1H), 2.55 (d, *J*= 4Hz, 1H), 2.60 (s, 1H), 7.2 (d, *J*= 7Hz, 2H), 7.95 (d, *J*=6.2Hz, 2H); **6c:** b.p. 230-235 °C, yield: 88%; IR (Neat). 1760, 1685, 1610, 1460, 1320, 1020 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ



Reagents: (i) $SOCl_2$, EtOH; (ii) LAH, THF; (iii) TsCl, Et_3N; (iv) LAH, THF; (v) NBS, CCl_4; (vi) LiBr, Li_2CO_3, DMF; (vii) AD mix-β; (viii) Pd-C, $HCOONH_4$, ethanol; (ix) Jones' oxidation

Scheme III

2.7 (s, 3H), 3.95 (s, 3H), 7.2 (m, 2H), 7.8 (m, 2H), 8.1 (d, *J*= 7Hz, 1H), 8.45 (s, 1H).

Peparation of alcohols 7b and 7c. To a solution of freshly prepared MeMgI [prepared from Mg (0.24 g , 0.01 mole) and CH_3I (1.4 g, 0.01 mole) in dry ether (20 mL) was added a solution of the ketone (**6b** or **6c**, 0.01 mole) in dry ether (40 mL) at 20 °C for 10 hr and gently refluxed for 30 min. It was then cooled to 0 °C and quenched with saturated solution of NH_4Cl followed by extraction with ether provided the alcohol **7b** and **7c** in 90% yield. **7b**: light yellow solid; m.p. 120-121 °C; yield: 95%; IR (Nujol): 3400, 1470, 1370, 780, 610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (d, *J*=7Hz, 6H), 1.6 (s, 6H), 1.95 (m, 1H), 2.2 (s, 1H, -OH), 2.51 (d, *J*= 7.14 Hz, 2H), 7.1 (d, *J*= 7.0 Hz, 2H), 7.45 (d, *J*= 7.15 Hz, 2H); **7c**: Yellow solid, m.p. 91-96 °C; yield: 90%; IR (Nujol: 3400, 1600, 1420, 1380, 1210 cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$): δ 1.52 (s, 6H), 1.95 (brs, 1H), 3.95 (s, 3H), 7.2 (m, 2H), 7.85 (m, 2H), 7.95 (m, 2H).

Preparaion of olefins 2b and 2c. To an ice cooled solution of the alcohol **7b** or **7c** (0.01 mole) in dichloromethane (40 mL) was added pyridine (1.31 mL, 0.015 mole). To the above solution was added freshly distilled $POCl_3$ (1.0 mL, 0.01 mole) dropwise under vigorous stirring. The reaction mixture was allowed to stir at 25 °C overnight. Usual work-up gave the olefin **2b** and **2c** in good yield. **2b**: yellow solid; m.p. 110 °C; yield: 90%; IR (Nujol): 1500, 1460, 1380, 1200, 810 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 0.9 (d, *J*= 8 Hz, 6H), 1.95 (m, 1H), 2.1 (s, 3H), 2.5 (d, *J*= 8.1 Hz, 2H), 5.1 (d, *J*=8.0 Hz, 1H), 5.4 (d, *J*= 7.99 Hz, 1H), 7.1 (d, *J*= 9.6 Hz, 2H), 7.45 (d, *J*= 9.6 Hz, 2H); **2c**: yellow solid; m.p. 109-110 °C; yield: 90%; IR (Nujol): 1610, 1500, 1450, 1390,1000, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H), 3.95 (s, 3H), 5.2 (d, *J*= 8.0 Hz, 1H), 5.45 (d, *J*= 7.9 Hz, 1H), 7.1 (m, 2H), 7.6-7.9 (m, 4H).

Preparation of the diols 3a, 3b and 3c. To a well stirred mixture of $K_3Fe(CN)_6$ (6.6 g, 20 mmole), K_2CO_3 (2.7 g, 20 mmole), H_2O (20 mL), *t*-BuOH (20 mL), OsO_4 (0.1 mL, 0.4 *M* in toluene) and $(DHQD)_2$-PHAL (25 mg, 0.1 mmole) at 0 °C was added $MeSO_2NH_2$ (475 mg, 5 mmole) followed by **2a** or **2b** or **2c** (5 mmole). After 28 hr solid $NaHSO_3$ (5g) was added, the mixture was stirred for 1 hr, extracted with EtOAc (3 × 25 mL) and the organic layer was washed with dil. HCl (2*M*), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give **3a, 3b** or **3c**. Compound **3a** : colourless liquid yield : 82% IR ($CHCl_3$): 3500-3350, 1440, 1360, 1210, 1025, 860 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.85 (br s, 1H), 3.25 (s, 1H), 3.45 (m, 1H), 3.53 (m, 1H), 7.2-7.45 (m 5H); MS: m/z (% rel. intensity) : 152 (M^+, 90), 101 (40), 78 (80); $[\alpha]_D$: –7.56 (*c* 2, EtOH); **3b**: light yellow solid; m.p. 67-70 °C; yield: 85%; IR (Nujol): 3500-3450, 1520, 1470, 1370, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (d, *J*= 7.1 Hz, 6H), 1.5 (s, 3H), 1.8 (m, 1H), 2.4 (brs, 1H), 2.51 (d, *J*= 7.0 Hz, 2H), 3.51 (d, *J*= 14 Hz, 1H), 3.8 (d, *J*= 14 Hz, 1H), 7.1 (d, *J*= 9 Hz, 2H), 7.45 (d, *J*= 9.0 Hz, 2H); $[\alpha]_D$: –7.01 (*c* 1.00. EtOH); **3c**: yellow solid; m.p. 119-122 °C; yield: 85%; IR (Nujol): 3500-3450, 1520, 1470, 1370, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.6 (s, 3H), 2.2 (brs, 1H), 3.7 (d, *J*= 7.6 Hz, 1H), 3.8 (d, *J*= 7.6 Hz, 1H), 3.95 (s, 3H), 7.1 (d, *J*= 7.5 Hz, 2H), 7.5 (d, *J*= 7.6 Hz, 1H), 7.7 (d, *J*= 7.6 Hz, 2H), 7.9 (d, *J*= 7.65 Hz, 1H); MS: m/z (% rel. intensity): 232 (M^+, 30), 201 (100), 185 (80), 171 (10), 157 (40); $[\alpha]_D$: –8.14 (*c* 1.15, EtOH).

Preparation of alcohols 4a, 4b and 4c. In a two-necked 100 mL round bottom flask equipped with a magnetic stirrer and reflux condenser, **3a** or **3b** or **3c** (0.01 mole) was dissolved in EtOH (25 mL), 10% Pd-C (Aldrich, 50 mg), $HCOONH_4$ (325 mg, 5 mmole) was added to this solution and heated to reflux. After 6 hr, the suspension was allowed to cool and then filtered through a pad of Celite. The ethanolic solution was concentrated under reduced pressure to get the crude product with no traces of starting material. Compound **4a:** colourless liquid yield: 65%; IR ($CHCl_3$) 3400-3350, 1465, 1040, 1010, 780, 700 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) : δ 1.24 (d, 3H, *J*=7.2Hz), 1.66 (br s, 1H), 2.5-3.25 (m, 1H), 3.58 (d, 2H, *J*=6.2Hz), 7.16 (m, 5H), $[\alpha]_D$: +3.54 (*c* 2 EtOH); **4b**: white solid; m.p. 101-103 °C; yield: 65%; IR (Nujol): 3400, 1610, 1580, 1410, 920, 810 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (d, *J*= 7.1 Hz, 6H), 1.2 (d, *J*= 7.0 Hz, 3H), 1.51 (brs, 1H), 1.9 (m, 1H), 2.45 (d, *J*=6.9 Hz, 2H), 2.95 (m, 1H), 3.7 (d, *J*= 6.9 Hz, 2H), 7.1 (m, 4H); MS: m/z (% rel. intensity): 192 (M^+, 50), 136 (80), 78 (90); $[\alpha]_D$: +8.4 (*c* 1.15, EtOH); **4c**: white solid; m.p. 85-87 °C; yield : 75%; IR (Nujol): 3400, 1620, 1590, 1420, 980, 810 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9-1.0 (d, *J*= 3.5 Hz, 3H), 1.2 (brs, 1H), 2.85 (m, 1H), 3.4 (d, *J*= 3.4 Hz, 2H), 3.7 (s, 3H), 6.9-7.5 (m, 6H); MS: m/z (% rel. intensity): 216 (M^+, 50), 185 (100), 170 (30), 153 (20), 141 (20), 11 (15); $[\alpha]_D$: +2.52 (*c* 1.10, EtOH).

Preparation of α-arylpropionic acids 1a, 1b and 1c. To a solution of the alcohol (**4a** or **4b** or **4c**, 1 mmole) in acetone (4 mL) was treated dropwise with Jones' reagent (3 mL) [prepared from 26 g of Cr(VI) oxide, 23 mL of concentrated H_2SO_4 and 77 mL of water] at 0 °C and stirred for 8 hr. Then the mixture was diluted with water and extracted with chloroform (3 × 50 mL). The organic phase was treated with saturated $NaHCO_3$ solution (2 × 50 mL). The combined aqueous extracts were acidified to *p*H 1-2 with dil. H_2SO_4 and extracted with chloroform (5 × 50 mL). After drying over anhyd.

Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (pet. ether: EtOAc; 8 : 2). Compound **1a:** low melting solid, yield 42%, IR (Nujol) 3400-2800, 1710, 1605, 1510, 1455, 1075, 950, 865, 710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.52 (d, 3H, *J*=7.2 Hz), 3.62 (q, 1H, *J*=7.2 Hz), 7.2 (m,5H), 8.3 (br s, 1H); MS (m/z) (rel. intensity): 150 (M^+, 3), 105 (100), 91 (29), 77 (72), 63 (8); $[\alpha]_D$: + 48.4 (*c* 1, EtOH), lit.[12] $[\alpha]_D$: +81.1 (*c* 1.0, EtOH); **1b**: colourless solid; m.p. 54-56 °C; yield: 40%; IR ($CHCl_3$): 2710, 1700, 1600, 1280, 1000 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (d, 6H), 1.51 (d, 3H), 1.84 (m, 1H), 2.4 (brd, 2H), 3.5 (q, 1H), 6.9-7.4 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 181.2, 140.7, 136.5, 129.3, 127.2, 45.01, 45.00, 22.38, 18.06; MS (m/z) (rel. intensity): 206 (M^+, 45), 167 (100), 119 (55), 107 (52), 77 (12), 57 (10); $[\alpha]_D$: +38.0 (*c* 1.40, $CHCl_3$), lit.[13] $[\alpha]_D$: +60 (*c* 1.0, EtOH); **1c**: colourless solid; m.p. 154 °C; yield: 35%; IR ($CHCl_3$): 2700, 1701, 1640, 1320, 1100 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$): δ 1.70 (d, 3H), 3.76 (q, 1H), 3.87 (s, 3H), 7.1-7.85 (m, 6H); MS (m/z) (rel. intensity): 230 (M^+, 40), 185 (100), 170 (35), 153 (10), 141 (20), 115 (15); $[\alpha]_D$: +41.8 (*c* 1.55, $CHCl_3$), lit.[14] $[\alpha]_D$: +65.5 (*c* 1.0, $CHCl_3$).

Preparation of 2-(2-fluoro-4-biphenyl)ethylpropionate 9. A flame dried 100 mL RB flask fitted with a reflux condenser and $CaCl_2$ guard tube was charged with racemic flurbiprofen (976 mg, 4 mmole) and dry ethanol (20 mL) and cooled to 0 °C in an ice bath. Freshly distilled thionyl chloride (590 mg, 349 µL, 5 mmole) was added dropwise and the mixture was refluxed for 6 hr. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using EtOAc : pet.ether (9 : 1) to yield a colourless thick liquid (1g). yield 94 %; (Thick liquid); IR (Neat):2980, 1735, 1620, 1580, 1420, 1235, 1180 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6-7.1 (m, 8H), 4.16 (q, *J* = 6.5 Hz, 2H), 3.75 (q, *J* = 8 Hz, 1H), 1.55 (d, *J*=9.6 Hz, 3H), 1.76 (t, *J* = 8 Hz, 3H).

Preparation of 2-(2-fluoro-4-biphenyl)propanol 10. A flame dried 100 mL RB flask fitted with a reflux condenser was charged with LAH (75 mg, 2 mmole) and dry ether (10 mL) and cooled in an ice bath under argon atmosphere. The ester **9** (544 mg, 2 mmole) in dry ether (2 mL) was added dropwise and the reaction mixture was refluxed for 8 hr (monitored by TLC), cooled to rt and was quenched with ethyl acetate. Extracted with ether (3 × 15 mL) dried over anhyd. sodium sulfate and evaporated to dryness. The crude product was purified by flash column chromatography to afford the alcohol as a white low melting solid (358 mg), yield 78 %; mp 56-58 °C; IR (Nujol): 3315, 2980, 1620, 1580, 1485, 1420, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.65-7.25 (m, 6H), 7.15-7.0 (m, 2H), 3.75 (d, J = 8.5 Hz, 2H), 3.02 (m, 1H), 1.7 (bs, OH), 1.35 (d, J = 10Hz, 3H).

Preparation of 2-(2-fluoro-4-biphenyl) *p*-toluenesulfonylpropionate 11. To a solution of the alcohol **10** (460 mg, 2 mmole) and Et_3N (506 mg, 697 µL, 5 mmole) in dry CH_2Cl_2 (2 mL) was added tosyl chloride (401 mg, 2.1 mmole) in CH_2Cl_2 (2 mL) dropwise at 0 °C under argon atmosphere. The reaction mixture was stirred overnight at rt (monitored by TLC). The solvent was evaporated to dryness and the crude solid was purified by flash column chromatography to afford the tosylate as a white solid (706 mg),yield 92 %; m.p. 108-112 °C; IR (Nujol): 2910, 1600, 1455, 1370, 1880, 970 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.7 -7.25 (m, 10H), 7.05-6.85 (m, 2H), 4.1 (d, *J* = 8 Hz, 2H), 3.15 (m, 1H), 2.40 (s, 3H), 1.32 (d, *J* = 10Hz, 3H); MS (m/z, rel. intensity, %) 384 (M^+, 3), 272 (9), 230 (7), 212, (100), 199 (45), 178 (32), 155 (20), 104 (38), 91 (35).

Preparation of 2-(2-fluoro-4-biphenyl)propane 12. A flame dried 100 mL RB flask fitted with a reflux condenser was charged with LAH (76 mg, 2 mmole) and dry ether (8 mL) and cooled in an ice bath under argon atmosphere. The tosylate **11** (768 mg, 2 mmole) in dry ether (2 mL) was added dropwise and the reaction mixture was refluxed for 8 hr (monitored by TLC), cooled to rt , quenched with ethyl acetate, extracted with ether (3 × 15 mL), dried over anhyd. sodium sulfate and evaporated to dryness. The crude product was purified by flash column chromatography to afford the isopropyl derivative as a colourless liquid (316 mg), yield 74 %; oily liquid; IR (Neat): 3000, 2950, 1520, 1435, 1380, 1360, 1050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6-7.05 (m, 8H), 2.95 (m, 1H), 0.98 (d, *J* = 7.5 Hz, 3H), 0.9 (d, *J* = 7 Hz, 3H); MS (m/z, rel. intensity, %) 214 (M^+, 50), 199 (90), 181 (100), 170 (10), 165 (26), 152 (18).

Preparation of 2-bromo-2-(2-fluoro-4-biphenyl)-propane 13. A flame dried 50 mL RB flask fitted with a reflux condenser was charged with the isopropyl derivative **12** (428 mg, 2 mmole) and benzoyl peroxide (10 mg) in dry CCl_4 (10mL) and was treated in portions with NBS (445 mg, 2.5 mmole) at 0 °C. The reaction mixture was stirred for 1 hr at rt and then refluxed for 2 hr. The reaction mixture was cooled and poured into ice water, neutralized with aq. ammonia and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with dil. HCl and dried over anhyd. sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography using EtOAc : pet.ether (1 : 9) as eluent to afford a light yellow solid (400 mg, 68%). The product was directly used for dehydrobromination.

Preparation of 2-(2-fluoro-4-biphenyl)prop-1-ene 14. A flame dried 50 mL 2-necked RB flask fitted with a reflux condenser was charged with the bromocompound

(588 mg, 2 mmole), LiBr (260 mg, 3 mmole), and Li_2CO_3 (222 mg, 3 mmole) under argon atmosphere. The reaction mixture was refluxed for 5 hr (monitored by TLC), cooled to rt and poured into water, washed with brine and extracted with ether (3 × 15 mL). The organic layer was dried over anhyd.sodium sulfate, filtered and evaporated to an yellow oil which was purified by flash column chromatography (EtOAc : pet.ether, 0.5 : 9.5) to furnish a colourless solid (322 mg, 76%), m.p. : 60-64 °C; IR (Nujol): 2990, 1610, 1500, 1450, 1395, 1050, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.55-7.05 (m, 8H), 5.45 (d, J = 7.9 Hz, 1H), 5.2 (d, J = 8 Hz, 1H), 2.15 (s, 3H); MS (m/z, rel. intensity, %) : 212 (M^+, 32), 201 (85), 181 (100), 170 (14), 167 (12), 150 (15).

Preparation of 2-(2-fluoro-4-biphenyl)-1, 2-dihydroxypropane 15. A double jacketed 100 mL flask was charged with $K_3Fe(CN)_6$ (987 mg, 3 mmole), K_2CO_3 (414 mg, 3 mmole), $(DHQD)_2$-PHAL (20 mg, 0.025 mmole) in t-BuOH : H_2O (1 : 1, 10 mL) at 0 °C. A solution of OsO_4 (20 μL, 2.54 mg, 0.01 mmole; 0.5 *M* in toluene) was added and stirred for 10 min. The olefin **14** (212 mg, 1 mmole) was added and the reaction mixture was stirred for 30 hr quenched with sodium meta bisulfite (1.04 mg, 6 mmole) and extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), dried over anhyd. sodium sulfate, filtered and evaporated to get a light yellow solid which was further purified by flash column chromatography (EtOAc : pet.ether, 1 : 1) to furnish a colourless solid (216 mg), yield 88 %; m.p. 96-99 °C; IR (Nujol):3350, 2975, 1585, 1435, 1220, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.6-7.15 (m, 8H), 3.76 (d, J = 11.5 Hz, 1H), 3.62 (d, J = 11.5 Hz, 1H), 2.85 (bs, 2OH), 1.5 (s, 3H); MS (m/z, rel. intensity, %) 246 (M^+, 1), 231 (3), 214 (20), 199 (57), 181 (54), 170 (37), 152 (50), 129 (49), 115 (20), 105 (100), 91 (90), 77 (96); $[\alpha]_D^{25}$ – 6.6 (*c*, 1.5 , EtOH).

Preparation of 2-(*S*)-2-(2-fluoro-4-biphenyl)propanol 16. A flame dried 100 mL RB flask fitted with a reflux condenser was charged with the diol **15** (492 mg, 2 mmole), ammonium formate (378 mg, 6 mmole) and 10% Pd-C (25 mg) in dry ethanol (10 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 16 hr (monitored by TLC). The solvent was evaporated to dryness and the crude solid was washed with water and extracted with ether (3 × 15 mL). After removal of the ether under reduced pressure, the crude product was purified by flash column chromatography [EtOAc : pet.ether, (2 : 8)] to yield a low melting solid (294 mg), yield 64 %; mp 55-58 °C; IR (Nujol): 3310, 2930, 1620, 1580, 1480, 1415, 1250, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.65-7.25 (m, 6H), 7.15-7.0 (m, 2H), 3.75 (d, J = 8.5 Hz, 2H), 3.02 (m, 1H), 1.7 (bs, OH), 1.35 (d, J = 10Hz, 3H); MS (m/z, rel. intensity, %): 230 (M^+, 35), 212 (18), 199 (100), 178 (38), 170 (15), 165 (18), 152 (16), 133 (6), 115 (5), 91 (10), 77 (8); $[\alpha]_D^{25}$ + 8.4 (*c*, 1.1, EtOH).

Preparation of 2-(*S*)-2-(2-fluoro-4-biphenyl)propionic acid 1d. A solution of the alcohol **16** (460 mg, 2 mmole) in acetone (10 mL) was treated dropwise with Jones' reagent (6 mL) [prepared from Cr(VI)oxide (26g), con. H_2SO_4 (23 mL) and water (77 mL)] at 0 °C and stirred for 8h. The reaction mixture was diluted with water (10 mL) and extracted with chloroform (3 × 15 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2 × 10 mL). The combined aqueous extracts were acidified with dil. H_2SO_4 and extracted with chloroform (4 × 20 mL).The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using EtOAc : pet.ether (2 : 8) to furnish a colourless solid (352 mg), yield 72%; mp 118 - 121 °C; IR (Nujol) :3210, 1720, 1410, 1315 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.2 (b, 1H), 7.5-7.15 (m, 8H), 3.8 (q, J = 8 Hz, 1H), 1.6 (d, J = 9.2 Hz, 3H); MS (m/z, rel. intensity, %): 244 (M^+, 45), 199 (100), 183 (30), 178 (35), 170 (18), 159 (7), 152 (15), 133 (12), 99 (15), 85 (12), 77 (18); $[\alpha]_D^{25}$ + 25.4 (*c*, 1.8, EtOH); Lit[15] : + 44.7 (*c* 1, EtOH).

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