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Lipase-mediated asymmetric construction of 2-arylpropionic acids: enantiocontrolled syntheses of *S*-naproxen and *S*-ibuprofen

Toshikazu Bando, Yukiko Namba and Kozo Shishido *

Institute for Medicinal Resources, University of Tokushima, Sho-machi 1, Tokushima 770, Japan

Abstract: A general and enantiocontrolled synthetic route to 2-arylpropionic acids, represented by non-steroidal anti-inflammatory drugs *S*-naproxen **1a** and *S*-ibuprofen **1b**, has been developed by employing the lipase-mediated asymmetric acetylation of prochiral 2-aryl-1,3-propanediol **3**, which has been derived via a Heck reaction, as the key step.
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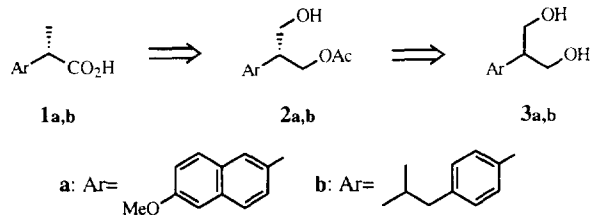
2-Arylpropionic acids **1**, bearing a single stereogenic tertiary center, are known well as an important class of non-steroidal anti-inflammatory agents which relieve inflammation by inhibiting cyclooxygenase and, thereby, regulating the arachidonic acid cascade.[1] Two representative members of this class are naproxen **1a** and ibuprofen **1b**. Since the pharmacological activity of the *S*-isomer of **1a,b** has been reported to be stronger than that of the *R*-isomer,[1a,2] development of an efficient and enantioselective synthetic route to *S*-2-arylpropionic acids **1** has received considerable attention.[3] As a part of our ongoing program to develop general and enantioselective routes to biologically important molecules using chemoenzymatic procedures,[4] we present here a concise construction of **1** by illustrating enantiocontrolled syntheses of *S*-naproxen **1a** and *S*-ibuprofen **1b**. This present synthesis is based on our previous construction of prochiral 2-aryl-1,3-propanediols **3** via a Heck reaction.[4] As shown in Scheme 1, our synthetic plan requires first the lipase-mediated asymmetric acetylation[5] of **3a,b** leading to the formation of monoacetates **2a,b**, which should involve an enantiomerically enriched tertiary stereogenic center at the benzylic position. Deoxygenation of the primary hydroxyl functionality in **2a,b** followed by oxidation should then deliver **1a,b**.

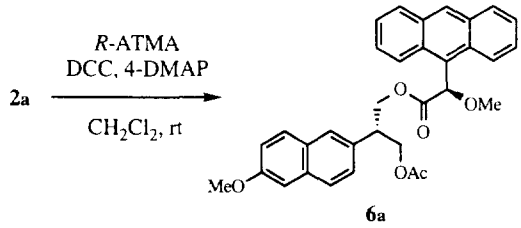


Scheme 1.

The prochiral diols **3a,b**, substrates for the key chemoenzymatic transformations, were prepared from commercially available 2-bromo-6-methoxynaphthalene and isobutylbenzene, respectively. On heating a solution of 2-bromo-methoxynaphthalene in HMPA with potassium iodide and copper(I) iodide at 150–160°C,[6] the iodide **4a** was obtained in 82% yield. The iodide **4b** was prepared quantitatively by treatment of isobutylbenzene with bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) in the presence of trifluoromethanesulfonic acid.[7] Heck reactions[8] between **4a,b** and 2-*tert*-butyl-4,7-dihydro-1,3-dioxepin[9] furnished **5a,b** in 75% and 84% yield, respectively. Oxidative cleavage of the double bond in **5a,b** using ozone, followed by reductive workup with $NaBH_4$, afforded cleanly the requisite prochiral diols **3a,b** in 52% and 64% yield, respectively. It should be mentioned that the present procedure for

* Corresponding author. Email: shishido@ph.tokushima-u.ac.jp

the preparation of such diols is quite simple and efficient from the practical point of view and superior to the conventional method.[10] With the substrates for the key conversion in hand, we next turned to the search for optimum conditions for the lipase-mediated asymmetric acetylation of prochiral diols **3a,b** in organic solvents.[11] Of these, PPL-catalyzed conditions using vinyl acetate as an acyl donor in Et_2O proved to be the best choice. Thus, the enantiomerically enriched monoacetates **2a,b** were obtained in 80% and 76% yield, respectively. The enantiomeric excess of **2b** was >99% as determined by ^1H NMR analysis of its MTPA ester derivative.[12] However, for **2a** the MTPA method was found not to be applicable because of the ambiguous peak separation. The problem was nicely solved by employing the α-methoxy-α-(9-anthryl)acetic acid (ATMA) ester method developed by Kusumi.[13] Treatment of **2a** with *R*-ATMA in the presence of DCC and 4-DMAP provided the corresponding ester **6a**, whose ^1H NMR analysis indicated the enantiomeric excess is 89% (Scheme 2). The absolute configuration of the newly generated stereogenic center in **2b** was deduced to be *R* in terms of the empirical rule[14] based on the chemical shift of the corresponding MTPA ester. In the case of **2a**, however, the absolute configuration could not be determined at this stage: confirmation was made by the eventual conversion of **2a,b** into **1a,b**.



6a

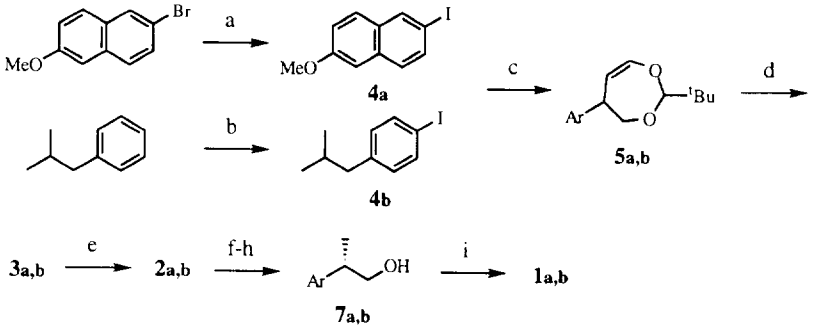
Scheme 2.

The monoacetates **2a,b** thus obtained were then submitted to the deoxygenation process of the primary hydroxyl functionality. Sequential tosylation and reductive removal of the resulting tosyloxy moiety with $NaBH_4$ in DMSO[11b] produced an easily separable mixture of *S*-2-arylpropanols **7a,b** and the corresponding acetates, which were converted into **7a,b** by treating with $LiAlH_4$ in THF at 0°C in 57% and 72% yield, respectively. Finally, oxidation of the primary hydroxyl group in **7a,b** under the conditions of Jones oxidation provided **1a,b** in 69% and 54% yield, respectively. The identities of our synthetic *S*-naproxen **1a** {mp 157–158°C (lit.[15] mp 157–158°C); $[\alpha]_D$ +60.0 (c=0.27, $CHCl_3$), (lit.[15] $[\alpha]_D$ +66.0 (c=1.00, $CHCl_3$))} and *S*-ibuprofen **1b** {mp 49°C (lit.[16] mp 51–53°C); $[\alpha]_D$ +53.2 (c=0.41, EtOH), (lit.[16] $[\alpha]_D$ +59.0 (c=2.00, EtOH))} were established by careful comparison of their IR, ^1H NMR, MS and TLC behavior with those of the authentic materials (Scheme 3).

In summary, new and concise syntheses of *S*-naproxen and *S*-ibuprofen, representatives of non-steroidal anti-inflammatory drugs, have been accomplished in enantiomerically pure forms based on the asymmetric acetylation of prochiral 2-aryl-1,3-propanediols. The strategy described herein should generally be applicable to the enantiocontrolled access to a wide variety of 2-arylpropionic acid derivatives.

Experimental

Melting points were determined by a Yanagimoto MP-S2 apparatus and are uncorrected. Ir spectra were recorded on Perkin Elmer 1720FT-IR and Hitachi 215 spectrophotometers. ^1H and ^{13}C NMR spectra were recorded at 200 MHz on a JEOL JMS FX-200 spectrometer and at 400 MHz (100 MHz for ^{13}C) on GSX-400 spectrometer in deuteriochloroform solutions with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Ordinary mass spectra and high resolution mass spectra were measured with a JEOL JMS-D300 mass spectrometer. Optical rotations were determined on a Union Giken PM-201 polarimeter. Tlc was



Scheme 3. *Reagents and conditions*: a, KI, CuI, HMPA, 150–160°C, 82%; b, IPy_2BF_4, CF_3SO_3H, CH_2Cl_2, rt, 100%; c, 2-*tert*-butyl-4,7-dihydro-1,3-dioxepin, $Pd(OAc)_2$, Ph_3P, $^iPr_2NEt$, DMF, 80°C, 75% for **5a**, 84% for **5b**; d, O_3, CH_2Cl_2 then $NaBH_4$, MeOH, −78°C→0°C→rt, 52% for **3a**, 64% for **3b**; e, PPL, vinyl acetate, Et_2O, rt, 80% for **2a**, 76% for **2b**; f, TsCl, Et_3N, 4-DMAP, CH_2Cl_2, 0°C; g, $NaBH_4$, DMSO, 60°C; h, $LiAlH_4$, THF, 0°C, 57% for **7a**, 72% for **7b**; i, Jones ox., 0°C, 69% for **1a**, 54% for **1b**.

carried out with E. Merck Silica gel GOF-254 (0. 25 mm thickness) precoated tlc plates. Column chromatography was carried out with silica gel (Kieselgel 60, 70–230 mesh, E. Merck). All reactions were run under an atmosphere of argon. Solvents were freshly distilled prior to use: tetrahydrofuran (THF), toluene and diethyl ether (Et_2O) were distilled from sodium: dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) were distilled from phosphorus pentoxide and kept over 4A molecular sieves. Unless otherwise noted, all reaction mixtures were dried, after workup, over anhydrous magnesium sulfate.

2-Iodo-6-methoxynaphthalene ***4a***

A solution of 2-bromo-6-methoxynaphthalene (5.0 g, 21.1 mmol), KI (52.5 g, 316 mmol) and CuI (20.0 g, 105 mmol) in HMPA (60 ml) was heated at 160°C for 12 h. After cooling to 0°C, the mixture was treated with 5% HCl, extracted with Et_2O and filtered. The filtrate was washed with sat. $Na_2S_2O_3$ and brine, and dried. Evaporation of the solvent followed by chromatography on silica gel (hexane–ethyl acetate, 95:5, v/v) gave the iodide **4a** (4.94 g, 82%) as a colorless solid: mp 146–147°C; ^1H NMR ($CDCl_3$) δ 3.91 (3H, s), 7.11–7.69 (5H, m), 8.14 (1H, s); MS (EI) m/z 284; HRMS Calcd for $C_{11}H_9OI$: 283.9698. Found: 283.9683.

4-Isobutyliodobenzene ***4b***[17]

A solution of trifluoromethanesulfonic acid (1.80 g, 12 mmol) in CH_2Cl_2 (9 ml) was added dropwise to a stirred solution of IPy_2BF_4 (2.5 g, 6.6 mmol) and isobutylbenzene (0.80 g, 6 mmol) in CH_2Cl_2 (19 ml) at room temperature and the resulting mixture was stirred for 0.5 h. The mixture was treated with sat. $Na_2S_2O_3$ and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel (hexane) to give the iodide **4b** (1.70 g, 100%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.88 (6H, d, J=6.6 Hz), 1.84 (1H, m), 2.41 (2H, d, J=7.3 Hz), 6.89 (2H, d, J=8.1 Hz), 7.58 (2H, d, J=8.1 Hz); MS (EI) m/z 260 (M^+); HRMS Calcd for $C_{10}H_{13}I$: 260.0062. Found: 260.0066.

*2-*tert*-Butyl-4,5-dihydro-5-(6-methoxynaphth-2-yl)-1,3-dioxepin* ***5a***

A mixture of **4a** (2.32 g, 8.17 mmol), 2-*tert*-butyl-4,7-dihydro-1,3-dioxepin (1.53 g, 9.79 mmol), $^iPr_2NEt$ (3.17 g, 24.5 mmol), $Pd(OAc)_2$ (0.055 g, 0.25 mmol) and Ph_3P (0.128 g, 0.49 mmol) in DMF (2.5 ml) was stirred at 80°C for 14 h. After removal of the solvent, the residue was extracted with CH_2Cl_2 and the extracts were washed with sat. $Na_2S_2O_3$ and brine, and dried. Evaporation of the solvent followed by chromatography on silica gel (hexane–ethyl acetate, 98:2, v/v) gave **5a** (1.9 g, 75%) as a colorless solid: mp 133–134°C; ^1H NMR ($CDCl_3$) δ 1.05 (9H, s), 3.30 (1H, dd, J=11.0 and 11.2 Hz), 3.97 (3H, s), 4.05 (1H, m), 4.19 (1H, m), 4.31 (1H, s), 4.94 (1H, d, J=7.6 Hz), 6.51 (1H, dd,

J=2.9 and 7.7 Hz), 7.18 (2H, m), 7.32 (1H, m), 7.73 (3H, m); MS (EI) m/z 312 (M^+); HRMS Calcd for $C_{20}H_{24}O_3$: 312.1725. Found: 312.1725. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.91; H, 7.94.

*2-*tert*-Butyl-4,5-dihydro-5-(4-isobutylphenyl)-1,3-dioxepin* ***5b***

According to the procedure described for **5a**, the product **5b** (1.07 g, 84%) was obtained from the iodide **4b** (1.45 g, 5.6 mmol) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, d, J=6.6 Hz), 0.98 (9H, s), 1.84 (1H, m), 2.45 (2H, d, J=7.1 Hz), 3.14 (1H, t, J=11.3 Hz), 3.84 (1H, m), 4.09 (1H, ddd, J=1.4, 5.6 and 11.5 Hz), 4.20 (1H, br d, J=7.6 Hz), 6.40 (1H, dd, J=2.9 and 7.6 Hz), 7.08 (2H, d, J=8.4 Hz), 7.14 (2H, d, J=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.9, 30.2, 35.8, 45.0, 47.9, 111.4, 113.5, 127.6, 129.3, 138.0, 140.3, 145.1; MS (EI) m/z 288 (M^+); HRMS Calcd for $C_{19}H_{28}O_2$: 288.2089. Found: 288.2078.

2-(6-Methoxynaphth-2-yl)-1,3-propanediol ***3a***

O_3 was bubbled through a stirred solution of **5a** (4.2 g, 13.5 mmol) in CH_2Cl_2 at −78°C. After releasing excess O_3, the solvent was removed and the residue was taken up into MeOH (100 ml). To a stirred solution was added $NaBH_4$ (776 mg, 20.25 mmol) at 0°C and the mixture was further stirred at room temperature for 12 h. Evaporation of the solvent left a residue which was extracted with AcOEt, the extract was washed with brine, dried and evaporated. The residue was chromatographed on silica gel (ethyl acetate) to give the diol **3a** (1.63 g, 52%) as a colorless solid: mp 143–145°C; IR (KBr) cm^{-1} 3250; ^{1}H NMR ($CDCl_3$) δ 2.20 (2H, br s, D_2O exchangeable), 3.48 (1H, m), 3.92 (3H, s), 4.04 (4H, m), 7.14 (2H, m), 7.33 (1H, d, J=8.5 Hz), 7.68 (3H, m); MS (EI) m/z 232 (M^+); HRMS Calcd for $C_{14}H_{16}O_3$: 232.1099. Found: 232.1106. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 71.99; H, 6.99.

2-(4-Isobutylphenyl)-1,3-propanediol ***3b***

According to the procedure for **3a**, **5b** (1.07 g, 3.7 mmol) was converted into the diol **3b** (0.50 g, 64%) as colorless prisms: mp 81–83°C (hexane–ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, d, J=6.6 Hz), 1.85 (1H, m), 2.11 (2H, br s, D_2O exchangeable), 2.45 (2H, d, J=7.3 Hz), 3.10 (1H, m), 4.00 (4H, m), 7.12 (4H, s); ^{13}C NMR ($CDCl_3$) δ 22.4, 30.2, 45.0, 49.3, 66.1, 127.7, 129.5, 136.4, 140.6; MS (EI) m/z 208 (M^+); HRMS Calcd for $C_{13}H_{20}O_2$: 208.1464. Found: 208.1473.

(2R)-(+)-3-Acetoxy-2-(6-methoxynaphth-2-yl)-1-propanol ***2a***

PPL (0.22 g) was added to a solution of **3a** (0.13 g, 0.576 mmol) and vinyl acetate (0.12 g, 1.44 mmol) in Et_2O (13 ml) and the mixture was stirred at room temperature for 6 h. After filtration, the filtrate was evaporated to give a residue which was chromatographed on silica gel (hexane–ethyl acetate, 8:2, v/v) to afford **2a** (0.13 g, 80%) as a colorless solid: $[\alpha]_D$ +17.6 (c=0.54, $CHCl_3$); mp 101–103°C; IR ($CHCl_3$) cm^{-1} 3600, 1730; ^{1}H NMR ($CDCl_3$) δ 2.04 (3H, s), 3.28 (1H, m), 3.90 (2H, d, J=6.1 Hz), 3.91 (3H, s), 4.45 (2H, d, J=6.8 Hz), 7.14 (2H, m), 7.33 (1H, dd, J=1.7 and 8.3 Hz), 7.67 (3H, m). MS (EI) m/z 274 (M^+); HRMS Calcd for $C_{16}H_{18}O_4$: 274.1205. Found: 274.1210. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.66; H, 6.71.

(2R)-(+)-3-Acetoxy-2-(4-isobutylphenyl)-1-propanol ***2b***

According to the procedure for **2a**, monoacetate **2b** (0.40 g, 76%), as a pale yellow oil, was obtained from PPL (0.22 g) and **3b** (0.44 g, 2.1 mmol): $[\alpha]_D$ +15.6 (c=0.56, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3350, 1740; ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, d, J=6.6 Hz), 1.85 (1H, m), 2.05 (3H, s), 2.45 (2H, d, J=7.1 Hz), 3.13 (1H, m), 3.85 (2H, d, J=6.4 Hz), 4.37 (2H, d, J=6.4 Hz), 7.11 (2H, d, J=8.8 Hz), 7.16 (2H, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 22.2, 22.4, 30.2, 45.0, 46.8, 63.9, 65.2, 127.8, 129.5, 136.1, 140.7, 171.4; MS (EI) m/z 250 (M^+); HRMS Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1587.

(2S)-(−)-2-(6-Methoxynaphth-2-yl)-1-propanol ***7a***

p-Toluenesulfonyl chloride (89 mg, 0.47 mmol), Et_3N (58 mg, 0.58 mmol) and 4-DMAP (2 mg, 0.016 mmol) were added successively to a stirred solution of **2a** (107 mg, 0.39 mmol) in CH_2Cl_2 (2 ml) at 0°C. After being stirred at room temperature for 3 h, water was added and the mixture was extracted with CH_2Cl_2. The extracts were washed with brine, dried and evaporated to give the tosylate (121 mg, 73%) as colorless solid, $[\alpha]_D$ −1.4 (c=1.07, $CHCl_3$); mp 94–96°C; IR ($CHCl_3$) cm^{-1} 1740; ^1H NMR ($CDCl_3$) δ 1.98 (3H, s), 2.37 (3H, s), 3.44 (1H, m), 3.92 (3H, s), 4.33 (4H, m), 7.17 (3H, m), 7.63 (3H, m); MS (EI) m/z 428 (M^+); HRMS Calcd for $C_{23}H_{24}O_6S$: 428.1293. Found: 428.1297. Anal. Calcd for $C_{23}H_{24}O_6S$: C, 64.47; H, 5.65. Found: C, 64.10; H, 5.69, which was used for the next reaction without further purification. $NaBH_4$ (40 mg, 1.06 mmol) was added to a solution of the tosylate (91 mg, 0.212 mmol) in DMSO (1.8 ml) at 0°C. After being stirred at 60°C for 26 h, the mixture was extracted with benzene, and the extracts were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel (hexane–ethyl acetate, 95:5, v/v) to give the 2-(6-methoxynaphth-2-yl)-1-acetoxypropane (5.7 mg, 11%) as a colorless solid, $[\alpha]_D$ −7.1 (c=0.14, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1730; ^1H NMR ($CDCl_3$) δ 1.37 (3H, d, J=7.1 Hz), 2.01 (3H, s), 3.23 (1H, m), 3.92 (3H, s), 4.24 (2H, m), 7.13 (2H, m), 7.34 (1H, d, J=8.5 Hz), 7.58 (1H, s), 7.70 (2H, d, J=8.5 Hz). From the later fractions (hexane–ethyl acetate, 8:2, v/v), **7a** (36 mg, 78%) was obtained as a colorless solid, $[\alpha]_D$ −12.7 (c=0.50, $CHCl_3$); mp 89–91°C; IR ($CHCl_3$) cm^{-1} 3600; ^1H NMR ($CDCl_3$) δ 1.35 (3H, d, J=7.0 Hz), 3.11 (1H, m), 3.78 (2H, d, J=7.0 Hz), 3.92 (3H, s), 7.15 (2H, m), 7.35 (1H, dd, J=2.0 and 8.5 Hz), 7.61 (1H, s), 7.71 (2H, m); MS (EI) m/z 216 (M^+); HRMS Calcd for $C_{14}H_{16}O_2$: 216.1151. Found: 216.1147.

The acetate obtained above (11 mg, 0.043 mmol) was reduced with $LiAlH_4$ (2 mg, 0.043 mmol) at room temperature in THF (5 ml) to give **7a** (10 mg, 100%).

(2S)-(−)-2-(4-Isobutylphenyl)-1-propanol ***7b***

According to the procedure for **7a**, the tosylate (440 mg, 74%), $[\alpha]_D$ −2.4 (c=0.66, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1710; ^1H NMR ($CDCl_3$) δ 0.89 (6H, d, J=6.6 Hz), 1.85 (1H, m), 1.96 (3H, s), 2.43 (2H, d, J=7.1 Hz), 2.44 (3H, s), 3.26 (1H, m), 4.25 (2H, m), 7.02 (4H, s), 7.29 (2H, d, J=8.5 Hz), 7.69 (2H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.6, 22.3, 30.1, 43.5, 45.0, 64.1, 70.3, 127.6, 127.9, 129.4, 129.8, 132.6, 134.2, 141.1, 144.8, 170.4; MS (EI) m/z 404 (M^+); HRMS Calcd for $C_{22}H_{28}O_5S$: 404.1658. Found: 404.1662, was obtained from **2b** (370 mg, 1.40 mmol) as a colorless oil. $NaBH_4$ (190 mg, 4.95 mmol) was added to a solution of the tosylate (420 mg, 0.99 mmol) in DMSO (8 ml) at 0°C. After being stirred at 60°C for 12 h, the mixture was extracted with benzene, and the extracts were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give the 2-(4-isobutylphenyl)-1-acetoxypropane (150 mg, 64%) as a colorless solid: $[\alpha]_D$ −3.8 (c=0.92, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1720; ^1H NMR ($CDCl_3$) δ 0.89 (6H, d, J=6.8 Hz), 1.29 (3H, d, J=6.8 Hz), 1.85 (1H, m), 2.02 (3H, s), 2.44 (2H, d, J=7.1 Hz), 3.06 (1H, m), 4.09 (1H, dd, J=6.8 and 10.8 Hz), 4.19 (1H, dd, J=7.4 and 10.8 Hz), 7.08 (2H, d, J=8.3 Hz), 7.13 (2H, d, J=8.3 Hz); MS (EI) m/z 234 (M^+); HRMS Calcd for $C_{15}H_{22}O_2$: 234.1619. Found: 234.1623. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.44; H, 9.65. From the later fractions, **7b** (67 mg, 35%) was obtained as a colorless oil: $[\alpha]_D$ −16.4 (c=1.04, $CHCl_3$) {for the *R*-isomer; $[\alpha]_D$ +11.6 (c=0.97, $CHCl_3$)}; IR ($CHCl_3$) cm^{-1} 3600; ^1H NMR ($CDCl_3$) δ 0.90 (6H, d, J=6.6 Hz), 1.26 (3H, d, J=7.1 Hz), 1.85 (1H, m), 2.45 (2H, d, J=7.3 Hz), 2.92 (1H, m), 3.69 (2H, d, J=6.8 Hz), 7.10 (2H, d, J=8.3 Hz), 7.15 (2H, d, J=8.3 Hz); MS (EI) m/z 192 (M^+); HRMS Calcd for $C_{13}H_{20}O$: 192.1515. Found: 192.1500.

The acetate obtained above (170 mg, 0.73 mmol) was converted into **7b** (140 mg, 97%) by reduction with $LiAlH_4$ (28 mg, 0.73 mmol) at 0°C in THF (3.5 ml).

(S)-(+)-Naproxen ***1a***

Three drops of Jones reagent {prepared as 10 ml aqueous solution containing CrO_3 (2.67 g, 26.7 mmol) and conc. H_2SO_4 (4.2 g, 42 mmol)} was added to a stirred solution of **7a** (15 mg, 0.069 mmol) in acetone (5 ml) at 0°C and the resulting mixture was stirred for 0.5 h at the same temperature. To the mixture, 1 M solution of KH_2PO_4 and 10% aq. $Na_2S_2O_5$ were added and the resulting mixture was diluted with Et_2O. After filtration using Celite, the filtrate was adjusted to pH 2 by the addition of 10% HCl and extracted with Et_2O. The extracts were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel (ethyl acetate) to give **1a** (11 mg, 69%) as a colorless solid: $[\alpha]_D$ +60 (c=0.27, $CHCl_3$) {lit.[15] $[\alpha]_D$ +66 (c=1.00, $CHCl_3$)}; mp 157–158°C (lit.[15] mp 152–154°C); IR ($CHCl_3$) cm^{-1} 3500, 1710; ^1H NMR ($CDCl_3$) δ 1.59 (3H, d, J=7.3 Hz), 3.85 (1H, m), 3.91 (3H, s), 7.13 (2H, d, J=8.4 Hz), 7.41 (1H, d, J=10.0 Hz), 7.70 (3H, d, J=8.4 Hz); MS (EI) m/z 230 (M^+); HRMS Calcd for $C_{14}H_{14}O_3$: 230.0943. Found: 230.0940.

(S)-(+)-Ibuprofen ***1b***

According to the procedure for **1a**, **7b** (46 mg, 0.26 mmol) was oxidized with Jones reagent (0.1 ml) at 0°C to afford **1b** (29 mg, 54%) as a colorless solid after silica gel chromatography (etyl acetate): $[\alpha]_D$ +53.2 (c=0.41, EtOH) {lit.[16] $[\alpha]_D$ +60.0 (c=2.00, EtOH)}; mp 49°C (lit.[16] mp 50–52°C); IR ($CHCl_3$) cm^{-1} 3500, 1710; ^1H NMR ($CDCl_3$) δ 0.82 (6H, d, J=6.6 Hz), 1.43 (3H, d, J=7.1 Hz), 1.75 (1H, m), 2.37 (2H, d, J=7.2 Hz), 3.64 (1H, q, J=7.2 Hz), 7.02 (2H, d, J=8.1 Hz), 7.15 (2H, d, J=8.1 Hz); MS (EI) m/z 206 (M^+); HRMS Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1303.

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