^{13}C NMR (Me_2SO-d_6) 20.00, 32.08, 74.23, 112.31, 117.73, 120.44, 135.88, 143.08, 160.31, 165.24, 167.03 ppm.

Acknowledgment. I thank the National Institutes of Health (GM24474) for generous financial assistance.

Registry No. 1, 303-47-9; 3, 75716-69-7; 4, 75716-70-0; 5, 16281-39-3.

A 1,6-Eliminative Epoxide Cleavage in the Synthesis of an Ibuprofen Metabolite

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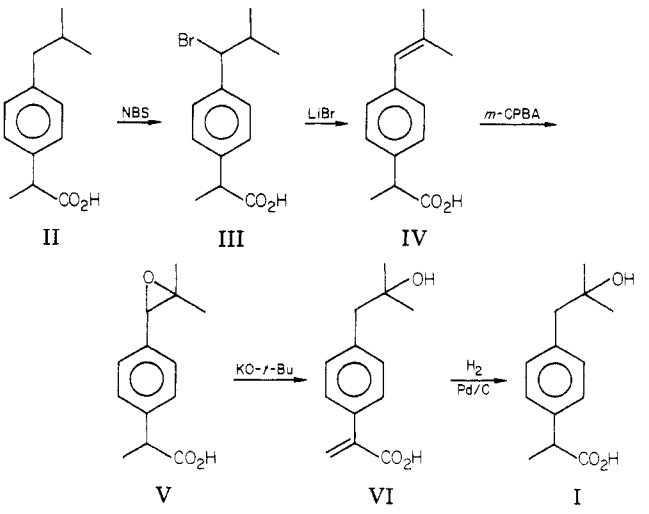
Received July 10, 1980

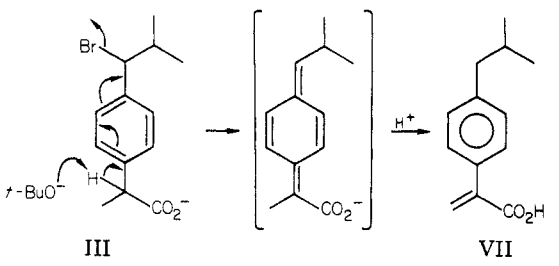
Previous syntheses of 2-[*p*-(2-methyl-2-hydroxypropyl)phenyl]propionic acid (I),[1,2] a major human metabolite of ibuprofen (II), were considered unsuitable for preparation of large quantities of pure I which were required for analytical studies. We report here a short, efficient synthesis of 2-[*p*-(2-methyl-2-hydroxypropyl)-phenyl]propionic acid, I, from ibuprofen, employing a novel 1,6-eliminative cleavage of an epoxide which may have general application for remote functionalization of appropriate aromatic side chains.

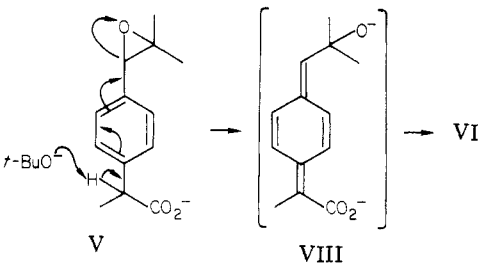
The key intermediate in this synthesis is the epoxide V which was obtained from II and subsequently converted to I by the method shown in Scheme I. Benzylic bromination of II with *N*-bromosuccinimide (NBS) provided a facile, selective entry into the isobutyl portion of the molecule. Although a benzylic proton was available in the propionic acid side chain, the α-COOH deactivated this position to attack.[3] Compound III was dehydrobrominated in DMF with LiBr to give the derivative IV in nearly quantitative yield. Initial attempts to effect this elimination with other bases such as Li_2CO_3, Et_2N-*i*-Pr, DBN, and DBU gave only 25–75% conversion to the olefin. Steric interactions of bromine and the *gem*-dimethyl group probably restrict formation of the trans configuration needed for the classic E2 elimination. The LiBr presumably coordinates with DMF to "lift" HBr from III in a cis fashion.[4] The olefin IV was treated with *m*-chloroperbenzoic acid (*m*-CPBA) to give the desired epoxide V. Attempts to hydrogenate V to give I directly using palladium or platinum catalysts in a variety of solvents were unsuccessful. During our investigation of methods to convert III to IV, we discovered an unusual reaction which became the key to the success of this synthesis. Treatment of III with potassium *tert*-butoxide in THF gave VII. The probable mechanism (Scheme II) involves a 1,6-elimination of HBr through the aromatic ring followed by rearomatization to the acrylic acid. Eliminations of the 1,6 variety involving a *p*-xylylene intermediate are proposed in one synthesis of [2.2]paracyclophanes.[5] In our synthesis of I we observed that treatment of V with potassium *tert*-butoxide gave VI, presumably through the intermediate VIII.

Scheme I



Scheme II





The acrylic acid derivative VI was purified by recrystallization and then reduced quantitatively by catalytic hydrogenation with Pd/C to racemic I. The overall yield of I, from ibuprofen, by this method was 45% (70% from III). Since the hydrogenation of VI with an asymmetric rhodium catalyst has been reported to give predominately the *R* (or *S*) enantiomer of I,[6] a stereoselective dimension of the synthetic pathway is available.

Experimental Section

Solvents were of reagent grade and were used without further purification. Reaction products were purified further when necessary by recrystallization.

Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets and visualized under UV light. A Varian EM 390 spectrometer was used for the NMR spectra (Me_4Si as the internal reference). Mass spectra, melting points, and microanalyses were performed by the Physical and Analytical Chemistry Department at The Upjohn Company.

2-[*p*-(1-Bromo-2-methylpropyl)phenyl]propionic Acid, III. A solution of 240 g (1.16 mol) of ibuprofen (The Upjohn Company), and 2.5 L of CCl_4 was refluxed for 10 min under N_2, cooled to room temperature, and then treated with 190 g (1.06 mol) of

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(4) R. P. Holysz, *J. Am. Chem. Soc.*, 75, 4432 (1953).
(5) (a) D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 4, 204 (1971); (b) H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.*, 82, 1428 (1960).
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0022-3263/81/1946-0202$01.00/0

N-bromosuccinimide and 300 mg of benzoyl peroxide. The mixture was refluxed for 6 h, stirred overnight at room temperature, and filtered. The filtrate was concentrated to a reddish-brown oil which was diluted with 1.5 L of hexane to give crystals. The product was collected on a filter and washed four times with 200-mL portions of hexane and then dried to constant weight to afford 185 g of III, mp 112.5–117.1 °C. A second crop of 27 g of slightly less pure compound resulted in a total yield of 55%. Yields varied from 55–73% in this reaction. Identification was confirmed by NMR and mass spectral data: NMR ($CDCl_3$, Me_4Si) δ 0.9 (d, 3 H), 1.2 (d, 3 H), 1.5 (d, 3 H), 2.1–2.5 (m, 1 H), 3.7 (q, 1 H), 4.7 (d, 2 H), 7.2 (s, 4 H); mass spectrum (70 eV), *m/e* (relative intensity) 286 (M^+, 0.6), 284 (M^+, 0.6), 205 (M^+–Br, 100). Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.74; H, 5.96. Found: C, 54.53; H, 5.91).

2-[*p*-(2-Methylprop-1-ene)phenyl]propionic Acid, IV. A solution of 100 g (0.35 mol) of III, 72 g (0.83 mol) of lithium bromide, and 1.5 L of DMF was heated under nitrogen between 80–100 °C for 5 h. The reaction was judged complete (by NMR of an aliquot) at this time. The solution was cooled to room temperature, diluted with 5 L of H_2O and extracted with three 1-L portions of ether. The ether extracts were combined and washed with two 1-L portions of water and 500 mL of brine. After the solution was dried over $MgSO_4$, the ether was removed in vacuo to give 73 g (100%) of a yellow oil. The quality (estimated at 95% by NMR analysis) was suitable for the next step without further purification; NMR ($CDCl_3$, Me_4Si) δ 1.5 (d, 3 H), 1.82 (s, 3 H), 1.90 (s, 3 H), 3.7 (q, 1 H), 6.2 (s, 1 H), 7.2 (d, 4 H).

2-[*p*-(2-Methyl-1,2-epoxypropyl)phenyl]propionic Acid, V. To a well-stirred solution of 73 g (0.35 mol) of IV in 750 mL of CH_2Cl_2 at room temperature under N_2 was added a slurry of 72 g (0.37 mol, 85% quality) of *m*-chloroperbenzoic acid in 700 mL of CH_2Cl_2. The reaction was slightly exothermic and was maintained below 35 °C with a water bath. After 2 h the reaction was judged complete by TLC, and the volume was reduced to 500 mL in vacuo. Upon dilution with an equal volume of hexane, *m*-chlorobenzoic acid (*m*-CBA) precipitated. The solids were filtered and washed with hexane to dissolve any V. The filtrate was concentrated to an oil and again diluted with 500 mL of hexane. More *m*-chlorobenzoic acid was removed by filtration (total of 46 g). The filtrate was concentrated to an oil which was used in the next step without further purification. An NMR of the product showed only epoxide and *m*-CBA present: NMR ($CDCl_3$, Me_4Si) δ 1.0 (s, 3 H), 1.4 (s, 3 H), 1.5 (d, 3 H), 3.7 (q, 1 H), 3.8 (s, 1 H), 7.3 (s, 4 H).

2-[*p*-(2-Methyl-2-hydroxypropyl)phenyl]propenoic Acid, VI. To a solution of V, obtained in the previous step (~80 g, 0.3 mol) in 1 L of THF at 15 °C under N_2 was added dropwise over 2 h 550 mL of 20% potassium *tert*-butoxide in THF. As the pH became neutral, a milky slurry resulted, and as the pH became basic an orange mixture was observed. The reaction was followed by TLC. After disappearance of starting material the reaction was quenched by the dropwise addition of 1 N HCl over a 20-min period at 15 °C. The two-phase, acidic system was diluted with 700 mL of ether, and the aqueous phase was removed. The organic phase was washed twice with 1 L of H_2O and once with 500 mL of saturated sodium chloride and dried over $MgSO_4$. The mixture was filtered, and the filtrate concentrated to a yellow oil. The oil was azeotroped with 500 mL of cyclohexane and then slurried with another 500 mL of cyclohexane until crystallization occurred. The solids were filtered, washed twice with fresh cyclohexane, and dried to constant weight to give 52.4 g as a first crop and 7.3 g as a second crop. The yield from IV to VI was 78%. Recrystallization of 50 g of VI from acetone/cyclohexane afforded 30.9 g of material, mp 110–114 °C (single zone by TLC), and 13.4 g of a less pure second crop; NMR ($CDCl_3$, Me_4Si) δ 1.3 (s, 6 H), 2.8 (s, 2 H), 6.0 (s, 1 H), 6.3 (s, 1 H), 6.5 (s, 1 H), 7.1–7.5 (m, 4 H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.90; H, 7.27. Found C, 70.72; H, 7.44.

2-[*p*-(2-Methyl-2-hydroxypropyl)phenyl]propionic Acid, I. A mixture of 27 g (0.12 mol) of VI, 250 mL of THF, and 1 g of 10% Pd/C was placed in a Parr hydrogenation apparatus and reduced under 50 psi of H_2 at room temperature for 1.5 h. The resulting mixture was filtered through a Celite pad, and the filtrate concentrated to a yellow oil. The oil was slurried in 400 mL of cyclohexane for a few minutes and crystallization of a white solid was observed. The solids were filtered, washed with fresh cyclohexane, and dried to constant weight at 50 °C in vacuo to give 27.2 g (quantitative yield) of I, mp 120–122 °C. TLC and NMR data were identical with those of authentic material;[7] NMR ($CDCl_3$, Me_4Si) δ 1.2 (s, 6 H), 1.5 (d, 3 H), 2.7 (s, 2 H), 3.7 (q, 1 H), 5.9 (s, 2 H), 7.1–7.3 (m, 4 H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.20; H, 8.46.

2-[*p*-(2-Methylpropyl)phenyl]propenoic Acid, VII. To a solution of 5 g (0.018 mol) of III in 100 mL of tetrahydrofuran (THF) was added 25 mL of 20% potassium *tert*-butoxide in THF. The mixture became cloudy and after 15 min was poured onto 100 mL of ice-cold 5% HCl and extracted with 100 mL of ether. The ether solution was washed twice with 50 mL of water and once with 25 mL of saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to an oil. The oil was dissolved in 25 mL of hexane and stored overnight in a freezer. The solids were collected on a filter, washed with cold hexane, and dried to give 1.96 g of VII (55%, additional material can be obtained in a second crop): mp 88.5–92.8 °C; NMR ($CDCl_3$, Me_4Si) δ 0.91 (d, 6 H), 1.5–2.2 (m, 1 H), 2.3 (d, 2 H), 6.0 (s, 1H), 6.5 (s, 1 H), 7.1–7.45 (m, 4 H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 76.47; H, 7.84. Found: C, 75.87; H, 7.97.

Registry No. I, 51146-55-5; II, 15687-27-1; III, 75625-98-8; IV, 75625-99-9; V, 75626-00-5; VI, 75626-01-6; VII, 6448-14-2.

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Improved Synthesis of Fluoroveratroles and Fluorophenethylamines via Organolithium Reagents[1]

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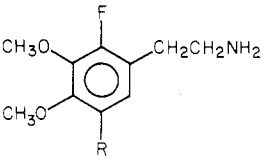
Received January 25, 1980

The introduction of fluorine into biologically active molecules often induces interesting new pharmacological properties.[2] The reported[3] synthesis of [2-(2-fluoro-3,4-dimethoxyphenyl)ethyl]amine, 1, is lengthy and requires



1, R = H
2, R = F

a low-yield photochemical Schiemann reaction for the introduction of fluorine. Therefore, we wished to find an improved synthesis which would afford 1 as well as the difluoro analogue 2.

It is known[4,5] that 3-fluoroveratrole can be converted to 2-fluoro-3,4-dimethoxyphenylacetonitrile via the benzyl

(1) Presented in part at the 13th Middle Atlantic Regional Meeting of the American Chemical Society, West Long Branch, NJ, March 21, 1979, Paper OR-17.

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