of **2a**, **14**, and **13**, in a ratio of 35:60:5 as determined by NMR. Attempts to convert more of mesylate **2a** into product by use of additional dimethylcuprate under similar conditions afforded less **14** and more of the dimethyl ketone **13**.

Acknowledgment. This research was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, by Biomedical Sciences Support Grant No. RR 07033-14 of The National Institutes of Health, and by the Science and Education Administration of the U.S. Department of Agriculture under Grant No. 7800894.

Registry No. **1a**, 504-02-9; **1b**, 126-81-8; **2a**, 75700-18-4; **2b**, 18922-00-4; **7a**, 5682-75-7; **7b**, 17530-69-7; **8a**, 56671-81-9; **8b**, 13271-49-3; **9a**, 56671-82-0; **9b**, 56671-85-3; **10**, 5323-87-5; **11a**, 6135-22-4; **11b**, 31039-88-0; **12**, 75700-19-5; **13**, 2979-19-3; **14**, 1193-18-6; dimethylamine, 124-40-3; benzyl mercaptan, 100-53-8.

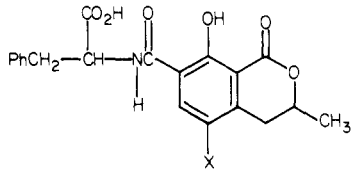
A Facile Synthesis of Ochratoxin A

George A. Kraus

Department of Chemistry, Iowa State University, Ames, Iowa 50011

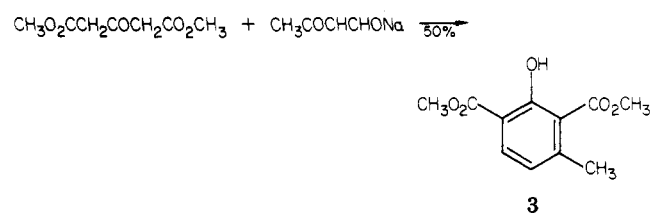
Received July 21, 1980

Ochratoxin A (1) was isolated by Steyn and co-workers[1] from some strains of *Aspergillus ochraceus*. Interest in this toxic metabolite and related compounds such as ochratoxin B (2) is prompted by the health hazard they pose because of their occurrence in agricultural products.



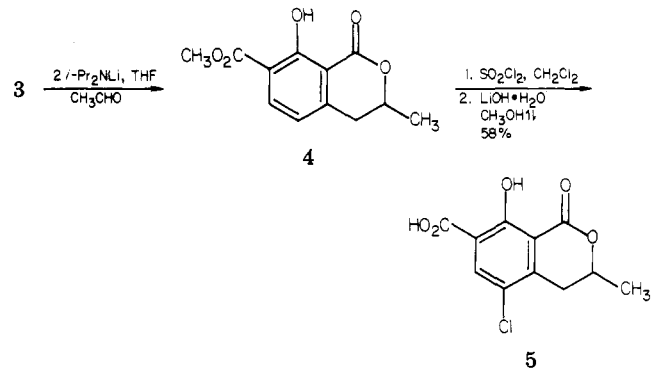
1, X = Cl
2, X = H

In addition, the availability of more highly oxygenated analogues for structure–activity studies is currently limited. Although two syntheses of 1 have been previously reported,[2] both are lengthy routes which proceed in low overall yield. In conjunction with another project, diester **3** was prepared in one step from dimethyl 3-oxopentanedicarboxylate and the sodium salt of (hydroxymethylene)acetone.[3] The transformation of **3** into the known acid **5** which has been converted into ochratoxin A in one step is the subject of this note. The reaction sequence is shown in Scheme I.



3

Scheme I



Diester **3** was deprotonated with 2 equiv of lithium diisopropylamide in tetrahydrofuran (THF)–hexamethylphosphorictriamide at −78 °C. After the addition of freshly distilled acetaldehyde and aqueous acid workup, lactone **4** could be isolated in 69% yield. Chlorination of **4** with sulfuryl chloride in methylene chloride[4] afforded a chloro lactone which was immediately suspended in methanol and saponified with lithium hydroxide. The melting point of the resulting acid **5** was in close agreement with the literature[2] melting point. Since the overall yield from commercially available starting material is 20%, this route is by far the most efficient preparation of ochratoxin intermediates and should be amenable to considerable variation.

Experimental Section

General. THF was distilled from lithium aluminum hydride. Melting points were determined on a Fisher-Johns melting-point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on Hitachi Perkin-Elmer R20 B. The ^{13}C NMR spectrum was determined on a JEOLCO FX-90Q.

Methyl 3,4-Dihydro-8-hydroxy-3-methyl-1*H*-2-benzopyran-1-one-7-carboxylate (4). To a solution of 14.9 mmol of lithium diisopropylamide prepared from 2.4 M *n*-butyllithium (6.2 mL, 14.9 mmol) and diisopropylamine (2.24 mL, 16 mmol) in 10 mL of THF at −78 °C was added diester **3** (1.54 g, 6.9 mmol) in 3 mL of THF over 3 min. After the deep red solution was stirred for 10 min, neat acetaldehyde (1.2 mL, 21.5 mmol) was added and the solution was stirred for 5 min at −78 °C and 15 min at 0 °C. The reaction was quenched at 0 °C with acetic acid (1.99 g) and diluted with ether and water. The aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel to afford 1.13 g of yellow solid. The solid had a melting point of 108–110 °C; NMR ($CDCl_3$) δ 1.53 (d, 3 H, J = 6 Hz), 2.6–3.2 (m, 2 H), 3.93 (s, 3 H), 4.4–4.8 (m, 1 H), 6.72 (d, 1 H, J = 9 Hz), 8.03 (d, 1 H, J = 9 Hz).

5-Chloro-3,4-dihydro-8-hydroxy-3-methyl-1*H*-2-benzopyran-1-one-7-carboxylic Acid (5). To a solution of 4 (0.361 g, 1.53 mmol) in 3 mL of methylene chloride at ambient temperature was added sulfuryl chloride (0.50 mL, 5.18 mmol). The solution was stirred under a nitrogen atmosphere for 20 h, concentrated in vacuo, and suspended in 5 mL of methanol. Lithium hydroxide monohydrate (0.700 g, 16.6 mmol) was added to the suspension and the suspension was heated to reflux under a nitrogen atmosphere for 20 h. After the solution had cooled, most of the methanol was removed in vacuo. The semisolid was dissolved in water and extracted once with ether and the aqueous layer was then acidified to pH 2 with 3 N HCl. The solution was extracted twice over sodium sulfate, concentrated in vacuo, and recrystallized from acetone–methanol to afford 0.189 g of a white solid with a melting point of 246 °C: NMR (Me_2SO-d_6) δ 1.5 (d, 3 H, J = 6 Hz), 2.6–3.2 (m, 2 H), 4.3–4.8 (m, 1 H), 8.0 (s, 1 H);

(1) Van der Merwe, K. J.; Steyn, P. S.; Fourie, L. *J. Chem. Soc. C.* **1965**, 7083.
(2) Steyn, P. S.; Holzapfel, C. W. *Tetrahedron* **1967**, *23*, 4449. Roberts, J. C.; Woollven, P. *J. Chem. Soc. C.* **1970**, 278.
(3) Prelog, V.; Metzler, O.; Jesen, O. *Helv. Chim. Acta* **1947**, *30*, 675.
(4) Efforts to selectively chlorinate 1,4-dihydro-8-hydroxy-3-methyl-1*H*-2-benzopyran-1-one were initiated in an earlier approach to 1 by John Pezzanite.

0022-3263/81/1946-0201$01.00/0

^{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

Richard R. Kurtz* and David J. Houser

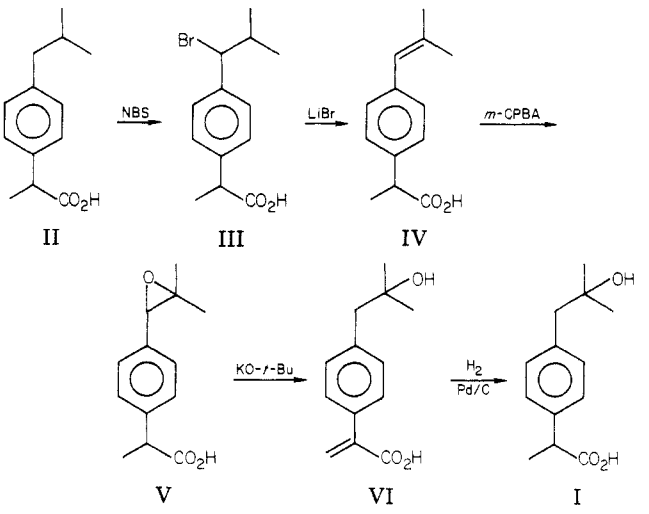
The Upjohn Company, Research Laboratories, Kalamazoo, Michigan, 49001

Received July 10, 1980

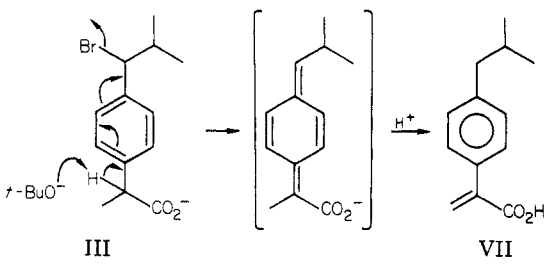
Previous syntheses of 2-[*p*-(2-methyl-2-hydroxypropyl)phenyl]propionic acid (I),[1,2] a major human metabolite of ibuprofen (II), were considered unsuitable for preparation of large quantities of pure I which were required for analytical studies. We report here a short, efficient synthesis of 2-[*p*-(2-methyl-2-hydroxypropyl)-phenyl]propionic 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.

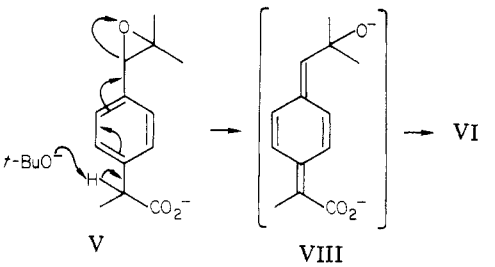
The key intermediate in this synthesis is the epoxide V which was obtained from II and subsequently converted to I by the method shown in Scheme I. Benzylic bromination of II with *N*-bromosuccinimide (NBS) provided a facile, selective entry into the isobutyl portion of the molecule. Although a benzylic 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

(1) R. A. Johnson, C. M. Hall, W. C. Krueger, and H. C. Murray, *Biorg. Chem.*, 2, 99 (1973).
(2) R. J. Reischer and W. J. Wechter, private communication.
(3) Bromination α to a carboxylate with *N*-bromosuccinimide has been reported, but much more vigorous conditions are required which involve in situ formation of an acyl halide. J. G. Gleason and D. N. Harpp, *Tetrahedron Lett.*, 3431 (1970).
(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).
(6) Belgian Patent 840,354, Oct 4, 1976, to The Boots Company, Ltd.

0022-3263/81/1946-0202$01.00/0