Notes

Basic Hydrogen Peroxide Cleavage of a Bicyclic Ketone. A New Procedure for a Prostaglandin Intermediate

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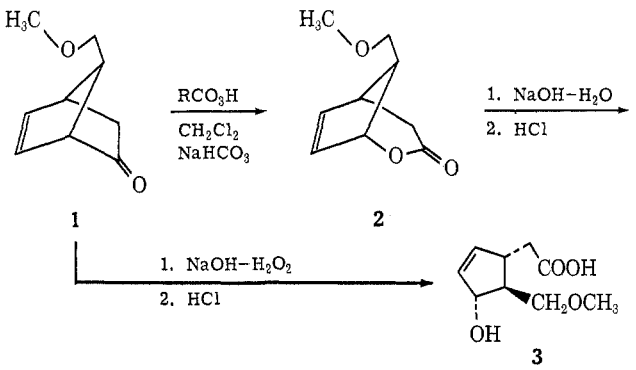
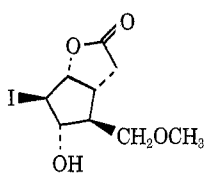
In work on improving the efficiency and simplicity of prostaglandin synthesis *via* the Corey method,[1] we questioned the need for isolating and then hydrolyzing the intermediate bicyclic lactone **2** in order to obtain hydroxy acid **3** for optical resolution.



Treatment of the ketone **1** (~85% pure) with 1.20 equiv of sodium hydroxide and 1.5 equiv of 30% hydrogen peroxide proceeded rapidly and exothermically to yield the desired product. This material could be isolated (quantitative) and resolved *via* *d*-ephedrine. Purification of this salt removed by-products formed from the oxidation of undesired isomers of the starting ketone. In addition, if *racemic* lactone **4** were desired,



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direct iodolactonization of the resulting basic solution should be feasible according to the existing procedure.[2] This procedure greatly reduces the time and cost of reagents involved and is readily adaptable to scaling up.[3] Although this reaction is reported[4] to give poor to fair yields with unstrained ketones, it should work reasonably well with other strained bicyclic ketones.

(1) E. J. Corey, T. K. Schaaf, W. Huber, V. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

(2) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(3) The sequence has been carried out without difficulty on a 500-g scale.

(4) Several examples of basic hydrogen peroxide cleavage of ketones are given in J. G. Wallace, "Hydrogen Peroxide in Organic Chemistry," E. I. du Pont de Nemours and Co., Wilmington, Del., pp 35–37.

Experimental Section

(±)-3α-Carboxymethyl-4β-methoxymethyl-5α-hydroxycyclopentene (3).—The ketone **1** (45.1 g, 0.29€ mol, 85% pure by vpc analysis) was dissolved in 125 ml of ether and mixed with a solution of 14.1 g (0.353 mol) of sodium hydroxide in 120 ml of water. The two-phase system was cooled (ice bath) and rapidly stirred while 53 ml of 30% hydrogen peroxide solution was added over a period of 40 min. The internal reaction temperature was maintained at 10–25°. After the addition, vpc analysis indicated that the ether phase was devoid of starting ketone. The aqueous phase was separated, washed with 100 ml of ether, and then neutralized (pH 6–7) with concentrated hydrochloric acid. Solid sodium sulfite was added cautiously to destroy excess hydrogen peroxide. The ethyl acetate (100 ml) was added, the mixture was cooled in ice–water, and concentrated hydrochloric acid was added to pH 3–4. The aqueous phase was separated and extracted with ethyl acetate (4 × 50 ml and 2 × 100 ml). The combined organic phases were combined, dried ($MgSO_4$), and concentrated to yield 42.0 g (78%) of the hydroxy acid as a colorless, viscous oil. Further acidification of the aqueous phase (with cooling) to pH 1.5–2 and extraction with ethyl acetate yielded an additional 13.0 g of **3**, total yield 55.0 g (99%); tlc analysis (silica gel; benzene:dioxane:HOAc, 20:20:1) indicated material indentical with hydroxy acid prepared by the published procedure.[1]

Resolution[5] of the Hydroxy Acid 3.—The hydroxy acid (55.0 g) was dissolved in 655 ml of ethyl acetate and thoroughly mixed with 49.8 g of *d*-(+)-ephedrine (Fluka) dissolved in 1455 ml of benzene. The first crop of crystals (~35 g) was redissolved in 1400 ml of 30% ethyl acetate–benzene and yielded 27.3 g of resolved salt, $[\alpha]^{25}D$ 37.5° (*c* 1.0780, MeOH) [lit.[1] $[\alpha]^{23}D$ 37.2° (*c* 1.0, MeOH)]. The overall yield (61.5%) takes into consideration the actual amount of desired ketone in the starting material.

Registry No.—**3**, 35672-36-7; hydrogen peroxide, 7722-84-1.

(5) The solvent system for resolution of the hydroxy acid has been modified from the original procedure[2] and allows for a severalfold decrease in the volume of solvent with no compromise in optical purity or number of crystallizations. The solvent system was developed by Dr. Niels Andersen.

Disaccharide Nucleosides of Benzimidazole

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This laboratory has been engaged in exploring methods of synthesis of disaccharide nucleosides, and reports concerning the synthesis of 9-β-melibiosyladenine[1] and 9-(2-deoxycellobiosyl)adenine[2] have appeared. The method of preparation of these compounds was based upon the coupling procedure devised by Davoll and Lowy,[3] in which a blocked glycosyl halide was condensed with the mercuric chloride salt of a purine base in a neutral solvent such as xylene or toluene. Similar techniques were used by Wol-

(1) L. M. Lerner, *J. Org. Chem.*, **32**, 3663 (1967).

(2) L. M. Lerner, *J. Med. Chem.*, **11**, 912 (1968).

(3) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **73**, 1650 (1951).