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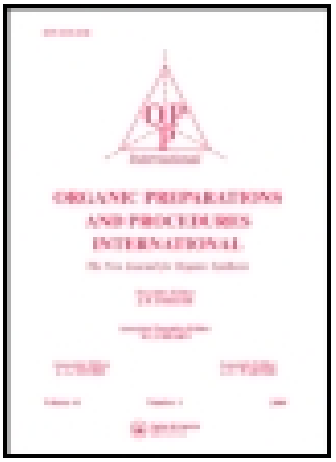

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IMPROVED SYNTHESIS OF (R)- AND (S)-β-METHYL-γBUTYROLACTONE

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IMPROVED SYNTHESIS OF (*R*)- AND (*S*)-β-METHYL-γ-BUTYROLACTONE

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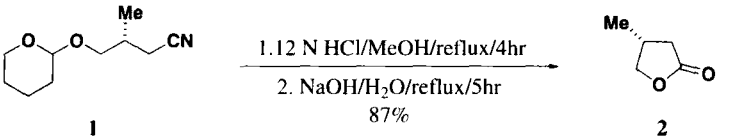
As part of a research program to design and synthesize optically active solvents based on the tetrahydrofuran scaffold for use in enantioselective organic and inorganic transformations, we required very large quantities of the title compounds. Mori has published[1] a five-step procedure for the preparation of (*S*)-(−)-β-methyl-γ-butyrolactone[2] from methyl (*R*)-(−)-3-hydroxy-2-methylpropionate (Roche ester).[3] The synthesis unfortunately suffers from an unacceptably low-yielding (23%) nitrile hydrolysis-lactonization reaction in the last step. The inefficiency of this process precluded the procurement of the large quantity of material needed for our work. We now report a substantially improved and simplified method for the conversion of nitrile **1** to the lactone **2** in 87% yield.



1 **2**

The intermediate **1** was synthesized in four steps according to the literature procedure in 85% overall yield.[4] We found that hydrolysis of the nitrile and concomitant unmasking of the alcohol with concentrated HCl in methanol gave the lactone directly; however, this approach suffered from variable yields, long reaction times and often resulted in a product contaminated with multiple side products which could only be removed by column chromatography. After considerable experimentation and optimization of reaction conditions, it was found that initial acidic hydrolysis of the nitrile to the amide, followed by further basic hydrolysis and reacidification afforded the pure lactone consistently in 85-90% yield on a multi-gram scale after simple distillation.

In summary, we have developed an efficient two-step procedure for the facile hydrolysis and lactonization of the nitrile **1** to give enantiomerically pure (*R*)-(+)-β-methyl-γ-butyrolactone in high yield. The present method is noteworthy in that it uses inexpensive reagents, features relatively short reaction times and requires no chromatographic separations. Moreover, since the title compounds are no longer readily available from commercial sources yet are also valuable building blocks for many polypropionate-derived natural products,[5] this new cost-effective procedure has the potential to meet the demand for these intermediates.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Varian Unity Plus 400-MHz spectrometer operating at 399.886 MHz in the indicated solvents. Optical rotations were performed on a Perkin-Elmer 241 polarimeter using a 1-cm^3 capacity quartz cell (1-dm path length) in the indicated solvent system at the recorded concentration. Thin layer chromatography (TLC) was performed using E. Merck silica gel (60 F 254) plates of 0.25 mm thickness. Visualization was accomplished with short wavelength ultraviolet light, and anisaldehyde dip reagent. All solvents and reagents were obtained from Fisher Scientific and used without further purification.

(*R*)-(+)-β-Methyl-γ-butyrolactone (2).[6]- To a stirred solution of the nitrile **1** (67.4 g, 0.368 mol) in MeOH (400 mL) was added 12N HCl (130 mL) at room temperature. The mixture was refluxed for 4 h. After cooling to room temperature, the solvent was removed under reduced pressure. Water (300 mL) and NaOH pellets (54.0 g, 1.35 mol) were added and the mixture again refluxed for 5 h. The cooled solution was extracted with dichloromethane (2 x 200 mL) and the organic fractions discarded. The aqueous fraction was carefully acidified with 12N HCl (60 mL), then extracted with chloroform (8 x 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was distilled through a short-path apparatus to afford pure **2** (32.0 g, 87%) as a colorless liquid, bp 92-94° (16 mmHg); $[\alpha]_D^{25}$ +25.4° (c = 5, MeOH), [*lit.*[7] $[\alpha]_D^{25}$ +24.7° (c = 4, MeOH)]; ^{1}H NMR ($CDCl_3$): δ 4.38 (1 H, dd, *J* = 7.0, 8.8 Hz), 3.84 (1 H, dd, *J* = 6.3, 8.8 Hz), 2.57-2.67 (2 H, m), 2.11 (1 H, dd, *J* = 10.5, 18.0 Hz), 1.13 (3 H, d, *J* = 6.5 Hz).

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REFERENCES

1. K. Mori, *Tetrahedron*, **39**, 3107 (1983).

2. (*S*)-(−)-β-Methyl-γ-butyrolactone was formerly available from the Aldrich Chemical Company, Inc. at a price of $19.00/100 mg.

3. Both enantiomers of this ester are available from Aldrich.

4. Prepared according to the procedure for the synthesis of the enantiomer of **1** in reference 1.

5. F. E. Ziegler and A. Kneisley, J. K. Thottathil and R. T. Wester, *J. Am. Chem. Soc.*, **110**, 5434 (1988); F. E. Ziegler, W. T. Cain, A. Kneisley, E. P. Stirchak and R. T. Wester, *ibid.*, **110**, 5442 (1988).

6. The antipode was prepared by the same procedure.

7. H. G. W. Leuenberger, W. Boguth, R. Barner, M. Schmidt and R. Zell, *Helv. Chim. Acta* **62**, 455 (1979).

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