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ASYMMETRIC SYNTHESIS OF β-SUBSTITUTED γ-BUTYROLACTONES

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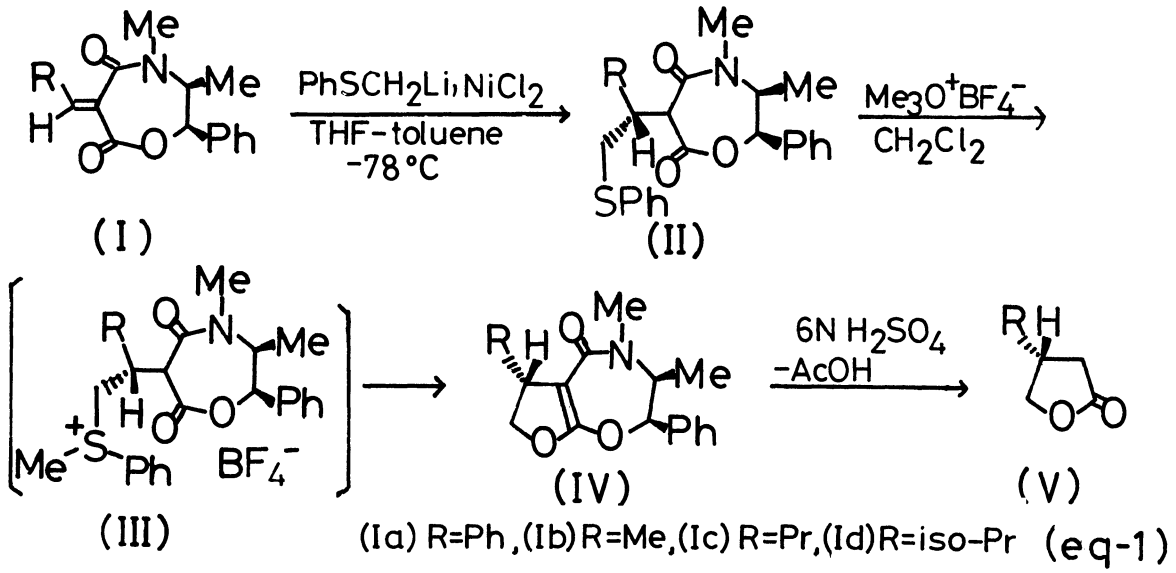
Highly optically pure β-substituted γ-butyrolactones (V) were obtained in good yields by the reaction of (E)-(2R,3S)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (I) with phenylthiomethyllithium, followed by i) treatment with trimethyloxonium tetrafluoroborate and ii) acid hydrolysis.

Optically active β-substituted γ-butyrolactone is known to be a useful chiral synthon in organic synthesis.[1] Concerning the preparation of this type of optically active lactones, no effective preparative method by a resolution of racemic lactones or an asymmetric reaction has been reported.[2]

In the previous paper, we showed that optically active β-substituted γ-butyrolactones (V) were produced in high asymmetric yields by the reaction of (E)-(2R,3S)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (I) with dimethylsulfoxonium methylide, but the chemical yields of the lactones (V) were low in general.[3]

Now we wish to report an efficient method for the asymmetric synthesis of β-substituted γ-butyrolactones (V). When (E)-(2R,3S)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (I) was allowed to react with phenylthiomethyllithium in the presence of a catalytic amount of nickel(II) chloride, the adduct (II) was obtained in a high yield. The methylation of this adduct (II) with trimethyloxonium tetrafluoroborate gave the sulfonium salt (III), which in turn was cyclized to form a dihydrofuran derivative by the preferential attack of carbonyl oxygen of the ester to α-carbon of the sulfonio group. Acid hydrolysis of the dihydrofuran (IV) afforded the highly optically pure β-substituted γ-butyrolactone (V) in a good yield (eq-1).



(Ia) R=Ph, (Ib) R=Me, (Ic) R=Pr, (Id) R=iso-Pr (eq-1)

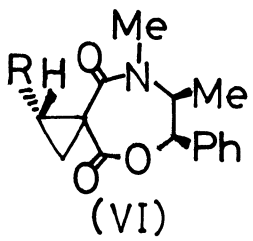
A typical experimental procedure is as follows; to a suspension of nickel(II) chloride (0.069 g, 0.53 mmol) and (E)-(2R,3S)-6-isobutylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (Id) (0.754 g, 2.62 mmol) in toluene (10 ml) was added a THF (10 ml) solution of phenylthiomethyllithium (5.24 mmol)[4] at -78°C over 15 min. The reaction mixture was stirred for 2 h at -78°C, the mixture was quenched with a phosphate buffer solution (pH 7). The organic layer was extracted with dichloromethane, and the extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel ($CHCl_3$) in order to remove the excess thioanisole. A dichloromethane solution (4 ml) of the diastereomeric mixture of the adducts (II) thus obtained was added to a suspension of trimethyloxonium tetrafluoroborate (0.809 g, 5.47 mmol) in dichloromethane (4 ml) at 0°C, and the mixture was allowed to warm up to room temperature. After stirring overnight, the solvent was removed under reduced pressure. The residue was dissolved in a mixture of acetic acid (2.6 ml) and 6N sulfuric acid (5.2 ml), and the mixture was heated to reflux for 6 h, cooled and extracted with dichloromethane. The combined extract was washed with saturated aq sodium hydrogencarbonate, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residual oil was separated by silica gel thin-layer chromatography (CH_2Cl_2) to give β-isopropyl-γ-butyrolactone (V d). The isolated product was further purified by short path vacuum distillation (0.257 g, 76%, >90%e.e.). In a similar manner several optically active lactones (V) were synthesized, and the results are summarized in the Table.

Table. Synthesis of optically active β-substituted γ-butyrolactones (V)

R	Overall Yield(%)	$[\alpha]_D^\circ$(t°C, c, solvent)	e.e.(%)	Config.
Ph[a)]	83	+47(27, 8.2, EtOH)	>90[b)]	
Me	61	+23(25, 4.2, MeOH)	>90[c)]	R[1a)]
Pr	63	+6.7(26, 3.9, EtOH)	>90[c)]	R[5)]
iso-Pr	76	-13(24, neat)	>90[c)]	S[2)]

a) The addition was carried out in THF at -100°C.
b) Determined by Jones' method[6)] using optically active shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium(III), in $CDCl_3$.
c) Determined by quantitative NMR analysis using optically active shift reagent, tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium(III), in CCl_4 for 1,4-diacetoxy-2-alkylbutane, obtained by reduction of Vb-Vd with lithium aluminium hydride, followed by treatment with acetic anhydride and pyridine.

In the present synthesis, no cyclopropane derivative (VI) was obtained in contrast to the result that VI was the major product when the oxazepine (I) was treated with dimethylsulfoxonium methylide.[3)] The selective formation of the dihydrofuran (IV) or the cyclopropane (VI) by the respective two reactions may be explained as follows: In the case of the reaction of I with the sulfoxonium ylide, the cyclization proceeds under basic condition via the enolate anion intermediate. Consequently, more nucleophilic carbanion preferentially attacks the α-carbon of sulfoxonio group to give the cyclopropane (VI). On the other hand, only the attack of electronegative carbonyl oxygen of the ester occurs under neutral or acidic condition. Therefore the dihydrofuran (IV) is selectively produced via the sulfonium salt (III) formed by the alkylation of the adduct (II).



(VI)

It should be noted that the present reaction provides a simple synthetic tool for the synthesis of the highly optically pure β-substituted γ-butyrolactones (V). Further study on the asymmetric reaction utilizing (2R,3S)-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione is now in progress.

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References and Notes

1) a) H. G. W. Leuenberger, W. Boguth, R. Barner, M. Schmid, and R. Zell, Helv. Chim. Acta, 62, 455 (1979).
b) M. Schmid and R. Barner, Helv. Chim. Acta, 62, 464 (1979).

2) The following two methods for the preparation of optically active β-substituted γ-butyrolactone are reported; i)microbiological synthesis of β-methyl-γ-butyrolactone[1a] and ii)preparation of β-isopropyl-γ-butyrolactone by the chemical degradation of the naturally occurring compound (R. D. Allan, R. W. Dunlop, M. J. Kendall, R. J. Wells, and J. K. MacLeod, Tetrahedron Lett., 1973, 3.).

3) T. Mukaiyama, K. Fujimoto, and T. Takeda, Chem. Lett., 1979, 1207.

4) E. J. Corey and D. Seebach, J. Org. Chem., 31, 4097 (1966).

5) The configuration of the lactone was determined by measurement of specific rotation of the corresponding diol: K. Freudenberg, W. Lwowski, and W. Hohmann, Justus Liebigs Ann. Chem., 594, 76 (1955).

6) a) I. J. Jacovac and J. B. Jones, J. Chem. Soc., Chem. Commun., 1978, 722.
b) I. J. Jacovac and J. B. Jones, J. Org. Chem., 44, 2165 (1979).

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