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ASYMMETRIC SYNTHESIS OF CYCLOPROPANES AND γ-BUTYROLACTONES BY THE REACTION OF DIMETHYLSULFOXONIUM METHYLIDE WITH (E)-(2R,3S)-6-ALKYLIDENE-3,4-DIMETHYL-2-PHENYLPERHYDRO-1,4-OXAZEPINE-5,7-DIONE

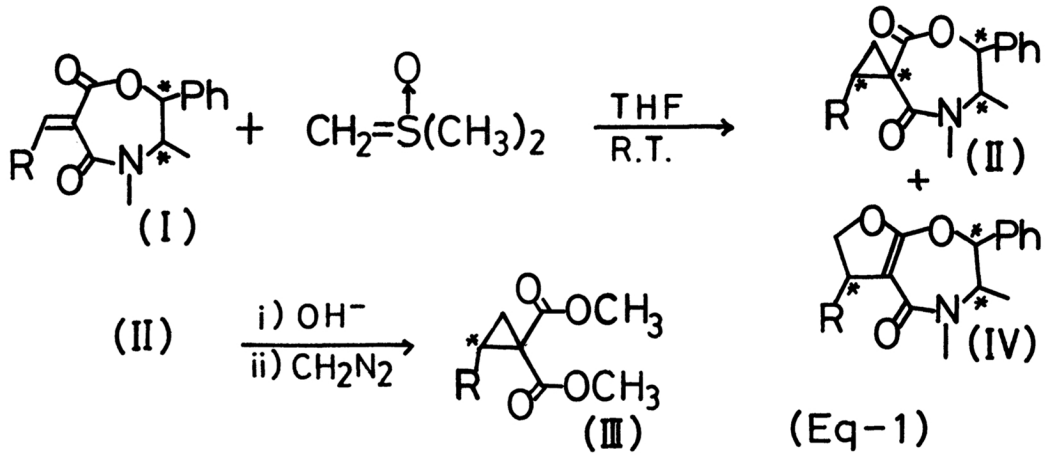
Teruaki MUKAIYAMA, Katsumi FUJIMOTO, and Takeshi TAKEDA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Dihydrofuran and cyclopropane derivatives are produced by the reaction of (E)-(2R,3S)-6-alkylidene-3,4-dimethyl-2-phenyl-perhydro-1,4-oxazepine-5,7-diones with dimethylsulfoxonium methylide. The cyclopropane derivatives are hydrolyzed and esterified to give highly optically pure (>90%e.e.) dimethyl 2-alkylcyclopropane-1,1-dicarboxylates. Highly optically pure (>90%e.e.) 3-substituted γ-butyrolactones are obtained by the hydrolysis of the dihydrofuran derivatives.

Many works[1),2)] have been reported on the asymmetric synthesis of cyclopropane derivatives, for example, the reactions of α,β-unsaturated esters of optically active alcohols with sulfoxonium ylid or diazo compounds, the reaction of optically active ylid with α,β-unsaturated carbonyl compounds, and chiral metal complex catalyzed carbenoid reactions. But no highly optically active cyclopropane was obtained by these methods. Recently, the syntheses of highly optically active phenyl and 1-alkenylcyclopropane derivatives were reported by employing chiral coper(I)[3)] and cobalt(II) complexes.[4)]

In the previous papers, we reported the asymmetric synthesis of 3-substituted alkanoic acids by the reaction of organometallic compounds, such as Grignard reagents and lithium dialkylcuprates, with (E)-(2R,3S)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (I).[5)] High asymmetric induction achieved in the reaction prompted us to investigate further asymmetric reactions utilizing the optically active oxazepines.

In this communication, we wish to report the asymmetric synthesis of highly optically pure 2-substituted cyclopropane-1,1-dicarboxylic esters and 3-substituted γ-butyrolactones. The treatment of (E)-(2R,3S)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-diones (I) with dimethylsulfoxonium methylide in tetrahydrofuran (THF) at room temperature, followed by hydrolysis with potassium hydroxide and esterification with diazomethane gives cyclopropane dicarboxylic esters with high enantiomeric excess (Eq-1). It was observed that less than 10% of the dihydrofuran derivatives are always produced as shown in the equation.



A typical procedure for the preparation of the optically active cyclopropanes is as follows; a THF solution of dimethylsulfoxonium methylide was prepared by the method reported by Corey and Chaykovsky.[6] To the THF solution (2ml) of (E)-(2R,3S)-6-ethylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (Ib) (1 mmol), a THF solution (1.3 ml) of dimethylsulfoxonium methylide (1 mmol) was added in one portion under an argon atmosphere at room temperature. After stirring for 2h, the reaction mixture was poured into a phosphate buffer solution (pH 7). The organic layer was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4 and condensed under reduced pressure to give the crude adduct (IIb). The crude adduct was dissolved in an ethanol (10 ml) solution of potassium hydroxide (1.5g). After refluxing for 3h, the reaction mixture was acidified with 3N hydrochloric acid at 0°C, and extracted with dichloromethane. The extracts were combined, dried over anhydrous Na_2SO_4, and condensed under reduced pressure. The residue was dissolved in methanol (10 ml) and treated with diazomethane. Excess diazomethane was decomposed by the addition of acetic acid. The mixture was poured into 5% $NaHCO_3$, and the organic layer was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2-Et_2O) and dimethyl 2-methylcyclopropane-1,1-dicarboxylate was obtained in 54% yield. The enantiomeric ratios of the esters were determined by quantitative NMR analysis using optically active shift reagent (tris-[3-(trifluoromethylhydroxymethylene)-d-camphorato] europium(III), in CCl_4.

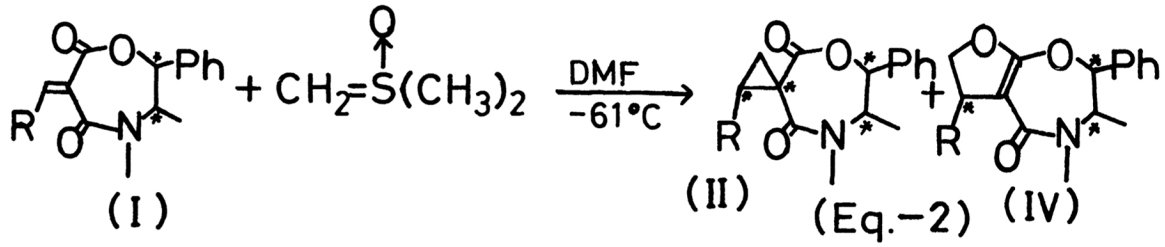
Table I Synthesis of optically active cyclopropanedicarboxylic esters

R	Synthetic yield(%)	e.e.(%)	$[\alpha]_D$(t°C, c)[a]
(IIIa) Ph-	63	>90[b]	+106 (30, 4.86)
(IIIb) CH_3-	54	>90	+47 (30, 0.72)
(IIIc) $(CH_3)_2CH$-	64	>90	+19 (30, 0.95)
(IIId) CH_3-$(CH_2)_2$-	62	>90	+36 (30, 1.35)

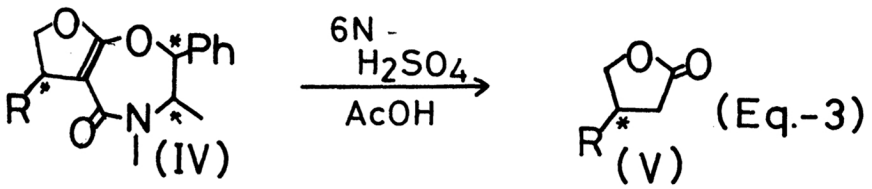
a) Ethanol used as a solvent. b) Tris-[3-(trifluoromethylhydroxymethylene)-d-camphorato] praseodymium(III) was used as optically active shift reagent.

As listed in Table I, the present reaction provides a useful method for asymmetric synthesis of cyclopropane derivatives, including aliphatic and aromatic ones, in high optical yields.

As mentioned before, it was found that a small amount of dihydrofuran derivatives were always produced along with the cyclopropane derivatives. The ratio of the two compounds depends on the reaction conditions. When (Ia-d) were allowed to react with dimethylsulfoxonium methylide in dimethylformamide (DMF) at -61°C, the dihydrofuran derivatives (IV) were produced in 8-57% yields along with the cyclopropane derivatives (II) in 69-29% yields, which were the normal products of the reactions of sulfoxonium ylid with α,β-unsaturated carbonyl compounds[7] (Eq-2).



The dihydrofuran derivatives (IV) are hydrolyzed to give highly optically pure 3-substituted γ-butyrolactones (V) in good yields (Eq-3).



A typical procedure for this reaction is as follows; to a suspension of sodium hydride (1 mmol) in DMF (2 ml) was added 1.0 mmol of trimethylsulfoxonium iodide at room temperature. After stirring for 20 min, the reaction mixture was cooled to -61°C. One mmol of 6-benzylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione in DMF (1 ml) cooled to -61°C was poured into the DMF solution of the ylid in one portion. Stirring was continued for 6h at -61°C. The reaction mixture was poured into a phosphate buffer solution (pH 7) and the organic layer was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel ($CHCl_3$), and the dihydrofuran derivative (IVa) (57%) and the cyclopropane derivative (IIa) (29%) were obtained. The dihydrofuran derivative (IVa) was dissolved in acetic acid (10 ml) and 6N sulfuric acid (20 ml). And the solution was refluxed for 6h. The organic layer was extracted with dichloromethane, the extracts were combined, dried over anhydrous Na_2SO_4, and condensed under reduced pressure. The residue which was the almost pure lactone was distilled according to the Kugel-Rohr method. In a similar manner, several optically active 3-substituted γ-butyrolactones were obtained.

Table II Synthesis of optically active γ-butyrolactones

R	Yield(%) (II)	Yield(%) (IV)	Overall Yield(%)	$[\alpha]_D$(t°C, c, solvent)	e.e.(%)	R,S
(Va) Ph-	29	57	43	+51(28,8.62,EtOH)	>90[a]	–
(Vb) CH_3-	37	54	20	+22(28,2.01,MeOH)	>90[b]	R[8]
(Vc) $(CH_3)_2CH$-	68	19	12	-12(23,neat)	>99[c]	S[9]
(Vd) $CH_3(CH_2)_2$-	69	8	–	–	–	–

a) Determined by Jones' method[10] using optically active shift reagent (tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)) in $CDCl_3$.

b) 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-methylbutane, obtained by reduction of (Vb) with lithium aluminium hydride, followed by treatment with acetyl chloride.

c) Determined by its specific rotation based on $[\alpha]_D^{20}$+12° for optically pure lactone.[9]

There have been reported several method for the preparation of 3-substituted γ-butyrolactones[11], however, the artificial asymmetric synthesis of 3-substituted γ-butyrolactone has not yet been known.[8] Though the yields of the lactones are not yet sufficient except for the case of 3-phenyl γ-butyrolactone, it is noted that this reaction provides a simple synthetic tool for the preparation of highly optically active 3-substituted γ-butyrolactones.

Further study on the asymmetric synthesis using the optically active (E)-(2R, 3S)-6-alkylidene-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione is now in progress.

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