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ASYMMETRIC SYNTHESIS OF δ-OXOCARBOXYLIC ACIDS BY THE MICHAEL REACTION USING (2R,3S)-3,4-DIMETHYL-5,7-DIOXO-2-PHENYLPERHYDRO-1,4-OXAZEPINE

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(2R,3S)-3,4-Dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (I) was prepared from methyl hydrogen malonate and ℓ-ephedrine hydrochloride using 2-chloro-1-methylpyridinium tosylate as a coupling reagent. The Michael reaction of (I) to 2-cyclopenten-1-one catalyzed by 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), followed by hydrolysis and decarboxylation gave highly optically pure 3-cyclopentanoneacetic acid.

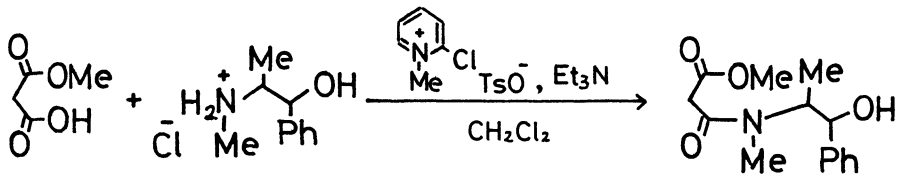
There have been reported many works on asymmetric synthesis in Michael-type reactions.[1] Most of these reactions have been demonstrated in the 1,4-addition of Grignard reagents to chiral α,β-unsaturated carbonyl compounds,[1d,e] but little study has been reported on asymmetric induction in Michael reaction of active methylene compounds possessing a chiral moiety.[2]

Recently we have shown that the 1,4-addition of Grignard reagents to (Z)-(2R,3S)-6-benzylidene-3,4-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine, followed by hydrolysis and decarboxylation gave highly optically pure 3-substituted 3-phenylpropionic acids in high yields.[3] This result suggested the synthetic utility of the chiral cyclic system ((2R,3S)-3,4-dimethyl-5,7-dioxo-2-phenyl-perhydro-1,4-oxazepine (I)).

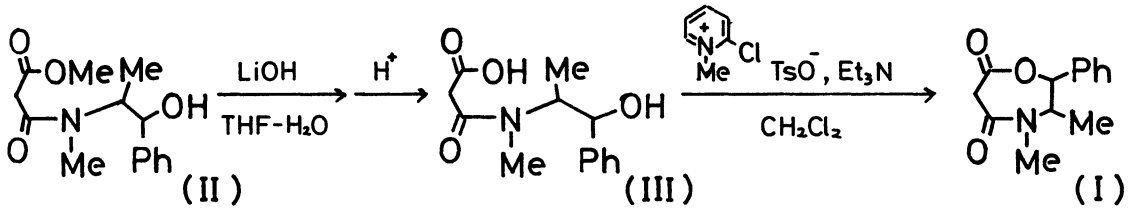
In the present communication, we wish to report the synthesis of (2R,3S)-3,4-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (I) and the result of the preliminary study on asymmetric induction in the Michael reaction of (I) to achiral α,β-unsaturated ketones.

The cyclic compound (I) was prepared from methyl hydrogen malonate and ℓ-ephedrine hydrochloride using 2-chloro-1-methylpyridinium tosylate, recently developed in our laboratory, as a coupling reagent.[4]

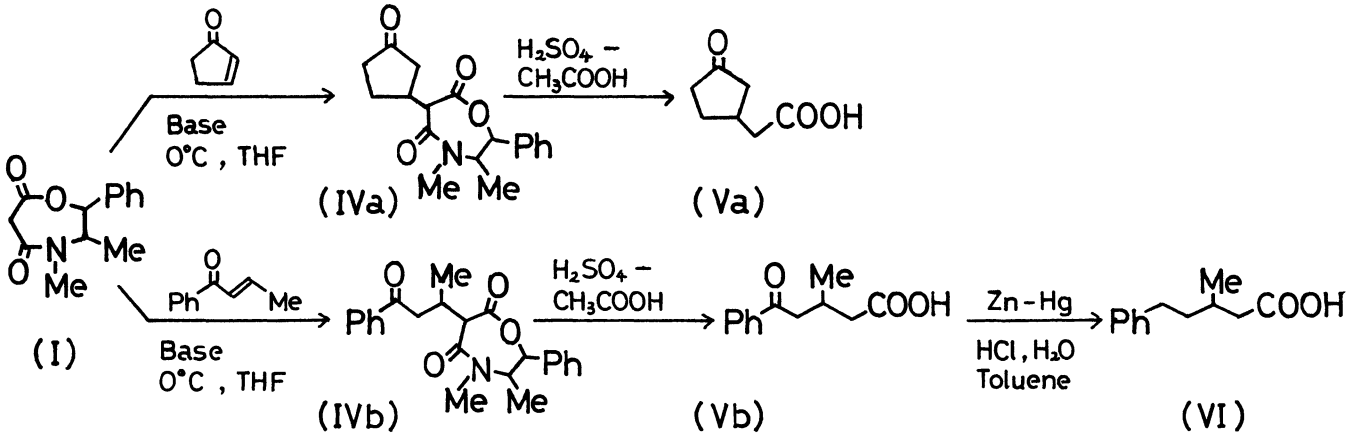
The experimental procedure for the synthesis of (I) is as follows: to a stirred dichloromethane (20 ml) solution of 2-chloro-1-methylpyridinium tosylate (18 mmol) and methyl hydrogen malonate (15 mmol), was added a dichloromethane (30 ml) suspension of ℓ-ephedrine hydrochloride (15 mmol), and triethylamine (54 mmol) at 0°C under an argon atmosphere within 10 minutes, and the reaction mixture was stirred overnight at room temperature. The dichloromethane solution was washed with water and the aqueous layer was extracted twice with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4 and condensed under reduced pressure. The residue was chromatographed on silica gel (eluted with dichloromethane-ether) and the hydroxyamide (II) was obtained in 64% yield. To the tetrahydrofuran (75 ml) solution of the hydroxyamide (II) (23 mmol) was added a solution of $LiOH \cdot H_2O$ (174 mmol) in water (75 ml), and the reaction mixture was stirred overnight at room temperature. After acidification (pH 2) with 6N hydrochloric acid, the reaction mixture was extracted with dichloromethane. The extract was dried over anhydrous Na_2SO_4, and the crude hydroxycarboxylic acid (III) was obtained by removing the solvent under reduced pressure. The dichloromethane (60 ml) solution of the crude hydroxycarboxylic acid (III) (21 mmol) was added dropwise to a stirred dichloromethane (70 ml) solution of 2-chloro-1-methylpyridinium tosylate (25 mmol) and triethylamine (50 mmol) at 0°C under an argon atmosphere, and the reaction mixture was stirred overnight at room temperature. After the reaction mixture was poured into a phosphate buffer solution (pH 7), the layers were separated and the aqueous 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 (eluted with dichloromethane-ether) and the cyclic compound (I) was obtained in 64% yield ($[\alpha]_D^{26}$ -92.1° (c 2, CH_2Cl_2), mp 124-126°C (benzene - hexane)) from the hydroxyamide (II). The structure of the cyclic compound (I) was supported by IR and NMR spectra and elemental analysis.



(II)



The Michael reaction of (I) to α,β-unsaturated ketones was carried out under several conditions (See Table).



The typical reaction procedure is described for entry 5 using 2-cyclopenten-1-one as a Michael acceptor: to the stirred tetrahydrofuran (2.5 ml) solution of the cyclic compound (I) (0.86 mmol) was added a tetrahydrofuran (2.5 ml) solution of DBU (0.26 mmol) and then added a tetrahydrofuran (2.5 ml) solution of 2-cyclopenten-1-one (1.29 mmol) at 0°C under an argon atmosphere. After stirring for 3 days, the reaction mixture was poured into a phosphate buffer solution (pH 7). The layers were separated and the aqueous 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 (eluted with dichloromethane-ether) and the Michael adduct (IVa) was isolated as a mixture of diastereomers. To the acetic acid (5 ml) solution of the Michael adduct (IVa) was added 6N sulfuric acid (10 ml). After refluxing for 6 hr, the reaction mixture was extracted with dichloromethane and the extract was condensed under reduced pressure. The residue was chromatographed on silica gel (eluted with dichloromethane-methanol) and 3-cyclopentanoneacetic acid (Va) was isolated in 43% yield. Further it was purified for the measurement of specific rotation by bulb-to-bulb distillation (160-180°C (bath temperature)/ 1 mmHg).

Table Asymmetric synthesis of δ-oxocarboxylic acids

	Michael acceptor	Base	Additive	Overall yield of (V) (%)	$[\alpha]_D$ (°)	C ($CHCl_3$)	Optical purity (%)
1	2-cyclopenten-1-one	t-BuOK	-	43	$[\alpha]_D^{29}$+8.58	2.04	16[b]
2		Ph_3CLi	-	32	$[\alpha]_D^{27}$-4.67	2.57	9[b]
3		t-BuOK	$NiCl_2$[a]	31	$[\alpha]_D^{26}$-3.95	2.53	7[b]
4			dicyclohexyl-18-crown-6[a]	53	$[\alpha]_D^{24}$+40.59	2.02	76[b]
5		DBU	-	43	$[\alpha]_D^{28}$+50.71	2.53	96[b]
6	1-phenyl-2-buten-1-one	t-BuOK	-	42	$[\alpha]_D^{23}$+0.97[c]	2.07	-
7		DBU	-	64	$[\alpha]_D^{24}$-17.70[c]	2.66	-
					$[\alpha]_D^{23}$-15.15[c]	neat	55[d]

a) This additive was used (0.3 molar equiv. based on I). b) Based on the reported rotation of 3-cyclopentanoneacetic acid (Va) $[\alpha]_D^{21}$-53.1°.[5] c) $[\alpha]_D$ was measured for 3-methyl-5-phenylpentanoic acid (VI) obtained from δ-oxocarboxylic acid (Vb) by Clemmensen reduction in a usual manner.[6] d) The reported maximum rotation of 3-methyl-5-phenylpentanoic acid (VI) $[\alpha]_D^{25}$ (neat) is -27.5°.[7]

The result shows that the Michael reaction of the cyclic compound (I) catalyzed by DBU or t-BuOK in the presence of dicyclohexyl-18-crown-6, followed by hydrolysis and decarboxylation gave the highly optically pure δ-oxocarboxylic acids and this preliminary work showed the utility of the cyclic compound (I) on asymmetric induction in Michael reaction and related reactions. Further investigations on the reaction mechanism involving the specific effect of the catalysts and the scope of the present reaction are now in progress.

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