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Partial Asymmetric Synthesis of $\Delta^{1,9}$-2-Octalone with Chiral Enamine

Takeshi IGARASHI, Jun-ichi ODA and Yuzo INOUYE*

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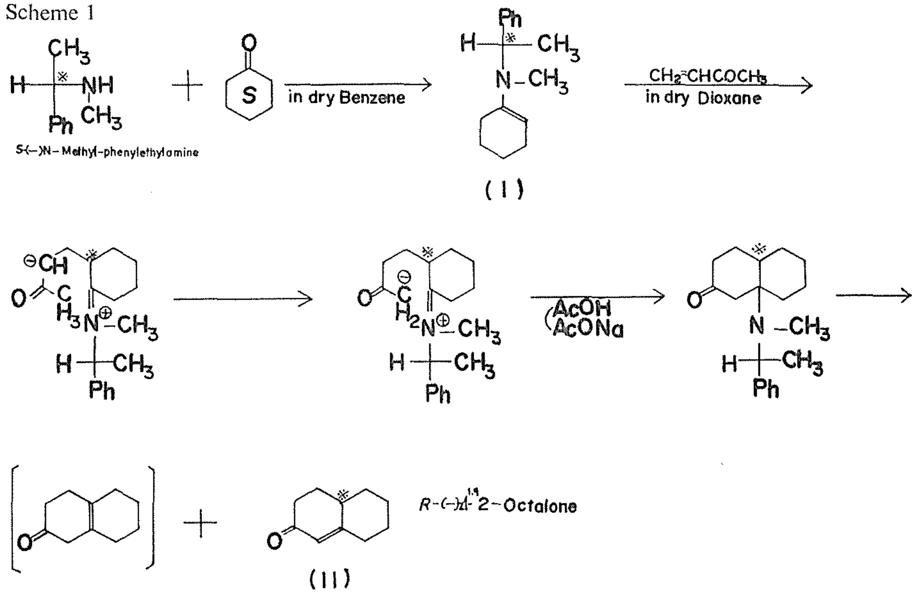
Sir:

In the previous communication,[1] the authors reported a partial asymmetric synthesis in the α-alkylation of enamine, and it has been proved that in the reaction, the nucleophilic attack of enamine to the double bond takes place according to the Prelog-Cram model of steric control of asymmetric induction.

At this time, we wish to report the addition reaction of a chiral enamine to an achiral C=C double bond. It was in expectation of a possible asymmetric induction, in which a higher optical yield could be expected, since the chiral center is closer to the reaction site. In this connection, we designed an asymmetric reaction of chiral N-methyl-α-phenylaminocyclohexene (I) with methylvinylketone, eventually giving rise to $\Delta^{1,9}$-2-octalone (II).

Enamine I, as the chiral reagent, was prepared by the N-alkylation of *S*-(−)-, and *R*-(+)-phenethylamine[2] ($[\alpha]_D^{20}$ −26.3° and +25.8° respectively) and followed by the reaction of cyclohexanone with use of p-toluenesulfonic acid as catalyst. Experimental condition was available with a slight modification in the literature.[3] (−)-

Scheme 1



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* 五十嵐 健, 小田 順一, 井上 雄三 : Laboratory of Plant Product Chemistry, Institute for Chemical Research, Kyoto University, Uji, Kyoto.

Enamine I was allowed to react with methylvinylketone in dry dioxane for 19 hrs at room temperature under stirring. After treatment of the resulting reaction mixture with acetic acid-sodium acetate buffer, (—)-$\Delta^{1,9}$-2-octalone (II) (yield 17%; $[\alpha]^{20}_{D}$ —20.24° (*c*, 21.5, EtOH) was obtained. On the other hand, the enantiomeric product (+)-II was isolated in the case of *R*-(+)-N-methylphenethylamine (Scheme 1).

The absolute configuration of the resulting chiral ketone II was established by the comparison of the ORD curve with that of the (—)-10α-methyl-$\Delta^{1,9}$-2-octalone (III) of the well-defined *R*-configuration.[4] The Cotton effect in 300–400 nm-region due to the optically active carbonyl chromophore was observed with both chiral ketones as

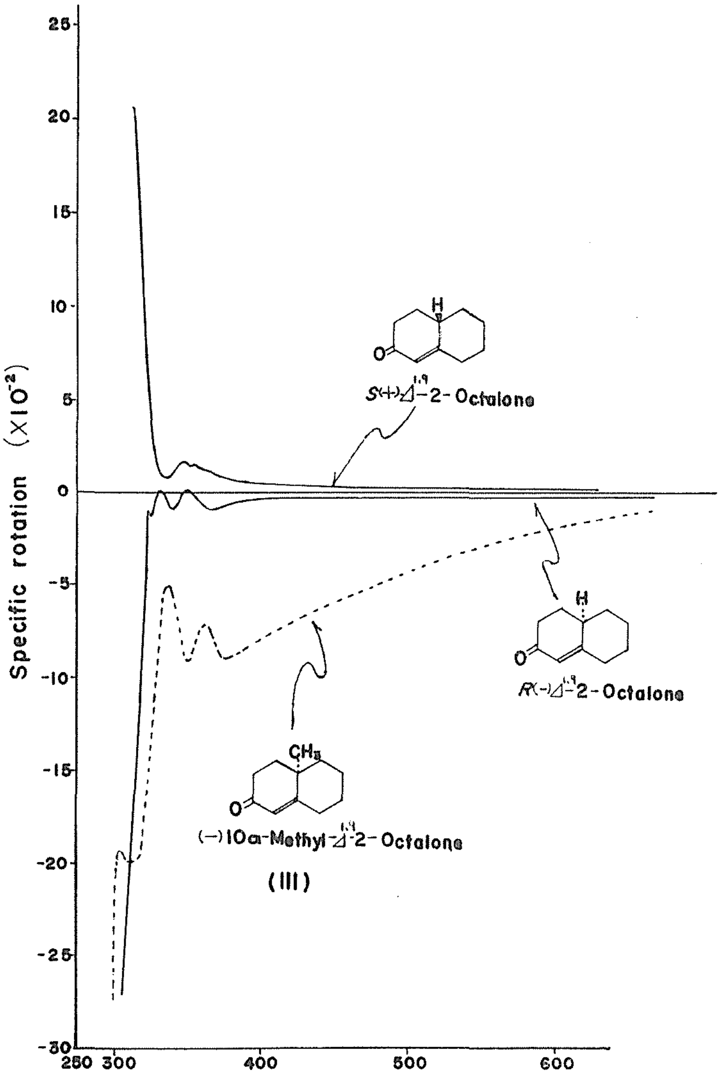

Fig. 1. The Cotton curves of *S*(+)-$\Delta^{1,9}$-2-octalone(II),R(—)-$\Delta^{1,9}$-2-octalone (II) and (—)10-Methyl-$\Delta^{1,9}$-2-octalone(III).

shown in Fig. 1. It was found that (*R*)-(−)-III and (−)-II exhibited similar negative Cotton effect in this region, so that the *R*-configuration was tentatively assigned to (−)-octalone II, while (+)-octalone, showing a positive Cotton effect, was assigned the *S*-configuration.

In view of the information on the absolute configuration of asymmetric center and reaction mechanism, it seems likely that the stereochemical-determining step in the present system is the electrophilic addition of $\alpha\beta$-unsaturated ketone to a β-position of enamine. As visualized in the Fig. 2, one might consider that three conformations are possible at this stage, among which the conformation IV seems to be most sterically preferred to V and VI, since the tricovalent nitrogen atom causes the methyl group on C_1 to interfere with a hydrogen atom attached to the double bond. Actually, inspection of the scale models indicates that the conformation IV is sterically more favored than the other. It may therefore be safely predicted that the addition to the enamine should take place preferentially from the least-hindered side (*re-si* face) of the conformation IV to give the final product II in preponderance.

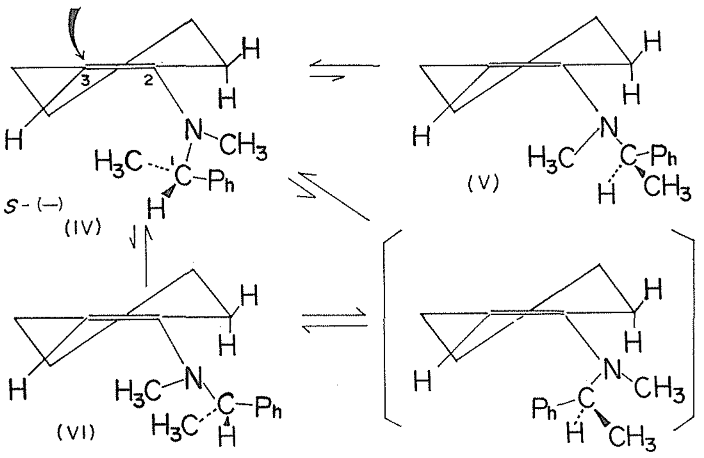

Fig. 2. Three Conformations (IV,V,VI) of Steric Course.

The above mentioned argument on the steric course coupled with its reaction mechanism of the present asymmetric system is in good agreement with the experimental finding.

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