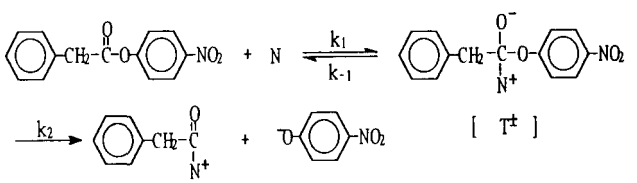
**Table 2.** $pK_a$ values of conjugate acid of the amines and second-order rate constants ($k_N$) for the aminolysis of *p*-nitrophenyl phenylacetate in water at 40 ℃

| amine | $pK_a$* | $k_N$ ($s^{-1}\cdot M^{-1}$) |
|---|---|---|
| piperidine | 11.2 | 0.186 |
| piperazine | 9.94 | 0.294 |
| morpholine | 8.78 | 0.0590 |
| 1-formyl piperidine | 7.98 | 0.0200 |

*values taken from reference 6.



**Scheme 1.**

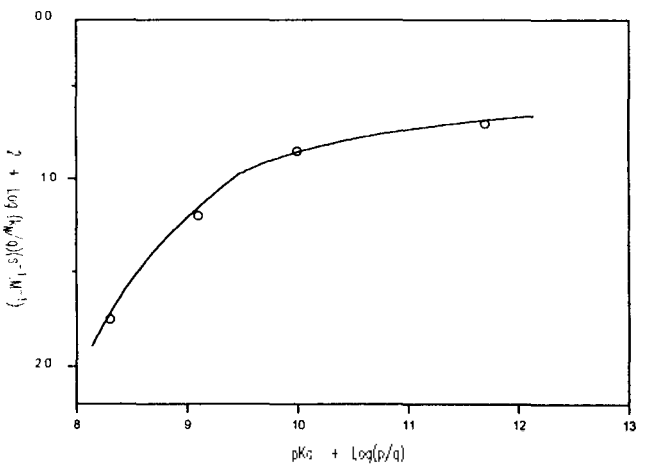



**Figure 2.** Brønsted plot for the nucleophilic reaction of *p*-nitrophenyl phenylacetate with secondary alicyclic amines against their basicity in water at 40 ℃, ionic strength 0.2 M. (the *q* and *p* values of amines were taken from reference 7.)

pKa of amine. The same results were found for the reactions of 2,4-dinitrophenyl acetate[10] and 2,4-dinitrophenylmethyl carbonate with secondary alicyclic amines.

The curved Brønsted plot obtained for the reaction of *N*-nitrophenyl phenylacetate with secondary alicyclic amine can be interpreted in terms of a tetrahedral intermediate ($T^{\pm}$ in Scheme 1, where *N* represents an amine) in the reaction path and a change in the rate determining step from $k_2$ to $k_1$ in Scheme 1 as the basicity of the amine increases..

Application of the steady state treatment to the tetrahedral intermediate leads to equation 2, where $k_N$ is the overall rate constant for the nucleophilic attack.

$$k_N = k_1k_2/(k_{-1}+k_2) \quad (2)$$

When the amine becomes more basic than the leaving group, $k_{-1} \ll k_2$, and according to equation 2 $k_N = k_1$, and the rate determining step should be formation of a tetrahedral intermediate. Where as, the nucleophilic amine is weakly basic, $k_{-1} \gg k_2$ and according to equation 2 $k_N = K_1k_2$, where $K_1$ is the equilibrium constant for the first step, and breakdown of a tetrahedral intermediate should be the rate determining step.

As we can see Figure 2, the slope in low $pK_a$ region ($\beta_2$) is 0.51 and in high $pK_a$ region ($\beta_1$) is 0.06 for breakdown and formation of a tetrahedral intermediate, respectively. These values are similar to the values found in the aminolysis of other reactive carbonyl compounds.[5-7]

**Acknowledgment.** This work was supported by the Basic Science Research Institute Program, Ministry of Education, 1994, Project No. BSRI-94-3402 and thanks for financial support of Dong-A University.

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## Radical Cyclization of β-Aminoacrylates: Expedient Synthesis of (+)-Monomorine 1 and (+)-Indolizidine 195B

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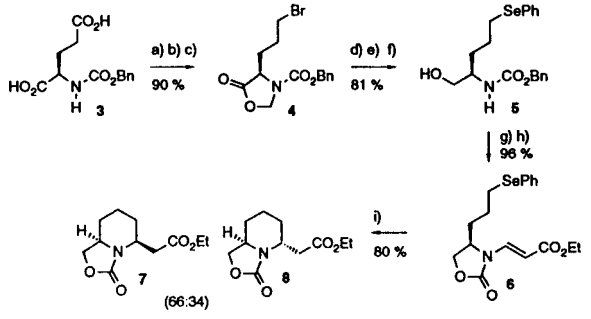
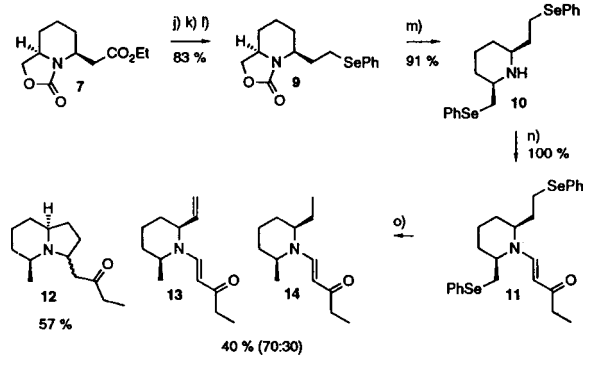
Indolizidine alkaloids offer attractive targets for synthesis because of their scarcity, exotic origin, and interesting biological activity. For example, (+)-monomorine 1(**1**)[1,2] is a trail pheromone of Pharaoh's ant (*Monomorium pharaonis* L.) and its epimer (+)-indolizidine 195B (**2**, bicyclic gephyrotoxin 195B)[3,4] was found in the skin extracts of neotropical poison dart frogs of the dendrobatid species.

Recently we reported that radical cyclization reactions of β-alkoxyacrylates[5] and β-aminoacrylates[6] might be used in the stereoselective synthesis of heterocyclic compounds. We now wish to report that **1** and **2** can be synthesized *via*



a) $(CH_2O)_n$, cat. p-TsOH, Toluene, Reflux; b) $BH_3$-THF, THF, 0 °C, 2 h; c) $CBr_4$, $PPh_3$, THF, 0 °C
d) $LiBH_4$, THF, -78 °C, 3 h; e) cat. KOMe, MeOH, r.t. 2 h; f) $(PhSe)_2$, $NaBH_4$, EtOH, 0 °C, 2 h
g) cat. KOMe, MeOH-THF, r.t. 12 h; h) $HCCCO_2Et$, NMM, DCM, r.t. 8 h
i) 1.3 eq. $Bu_3SnH$, 0.1 eq. AIBN, Benzene (0.025 M), Reflux, 6 h (Syringe Pump, 5 h)

**Scheme 1.**



j) LAH, THF, -40 °C, 1 h; k) $CBr_4$, $PPh_3$, DCM, r.t. 2 h; l) $(PhSe)_2$, $NaBH_4$, EtOH, 0 °C, 2 h
m) 2.0 eq. $PhSeSiMe_3$, 0.1 eq. $ZnI_2$, Toluene, Reflux, 4 h; n) HCCCOEt, DCM, Reflux, 3 days
o) 2.7 eq. $Bu_3SnH$, 0.1 eq. AIBN, Benzene (0.025 M), Reflux, 7 h (Syringe Pump, 6 h)

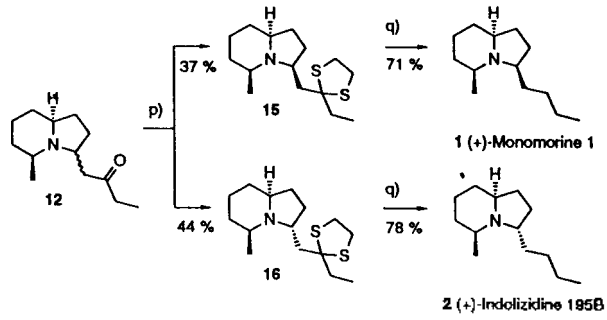
**Scheme 2.**

sequential radical cyclizations of intermediates derived from D-glutamic acid.

The Cbz-protected D-glutamic acid **3** was converted into the corresponding oxazolidinone,[7] which was then reduced with borane-THF, and the product alcohol was transformed into the bromide **4**. Lithium borohydride reduction, removal of the N-hydroxymethyl group under basic conditions, and phenyl selenide substitution gave the selenide **5** in good yield. Prolonged basic treatment converted **5** into the cyclic carbamate derivative, which reacted with ethyl propiolate in the presence of N-methylmorpholine to give the β-amino-acrylate **6** in excellent yield (Scheme 1). Radical cyclization of **6** was carried out under standard high dilution conditions to yield a 2 : 1 mixture of the piperidine-2-acetate derivatives **7** and **8** in 80% yield.[8]

The major, *cis* isomer **7** was then converted into the selenide **9** *via* the corresponding alcohol and bromide. The cleavage of the cyclic carbamate was accomplished when **9** reacted with phenylselenotrimethylsilane in the presence of zinc iodide to yield the bis(phenylseleno) piperidine derivative **10**. The β-amino vinyl ketone **11** was obtained in excellent yield from **10** and 1-pentyn-3-one (Scheme 2). The second radical cyclization under high dilution conditions gave an inseparable mixture of indolizidine derivatives **12** in 57% yield. A mixture of two piperidinyl by-products **13** and **14** was also obtained.[9]

The dithioketal derivatives **15** and **16** were obtained in



p) $HSCH_2CH_2SH$, $BF_3$-$OEt_2$, DCM, $N_2$, r.t.; q) Ra-Ni, abs. EtOH, r.t. 3 h

**Scheme 3.**

37 and 44% yield from the mixture of the ketones **12**. The dithioketal **15** reacted with Raney Ni to yield (+)-monomorine 1(**1**) in useful yield (Scheme 3). (+)-Indolizidine 195B (**2**) was likewise obtained from **16** in good yield.[10]

The most salient feature of the present synthesis is that both six- and five-membered rings in the indolizidine system were formed by stepwise radical cyclizations, of a β-amino-acrylate and a β-amino vinyl ketone, respectively. It is apparent that the radical cyclization of these stabilized enamine derivatives will provide novel and practical routes to more complex azacyclic systems, and future progress will be reported in due course.

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8. The *cis* isomer **7** was assigned as the major product following the results of the closely related studies reported in the reference 6. The assignment was confirmed by the synthesis of the final products **1** and **2**.
9. Formation of **13** probably involves intramolecular hydrogen abstraction of the intermediate primary radical.
10. They were identified by comparing with the known physical and spectroscopic data from the literature.

## Selective Conversion of 4,5-Epoxypentanoic Acids Esters to the Corresponding γ-Ketoesters Using Tetrabutylammonium Dihydrogentrifluoride

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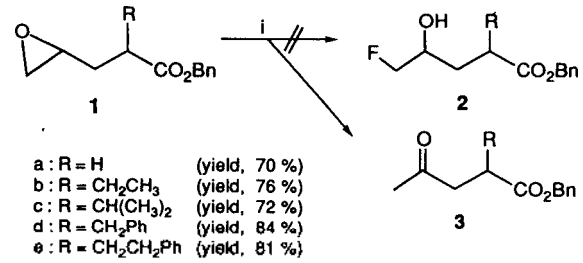
Oxiranes constitute an important class of compounds to synthetic chemistry:[1] They are easily prepared and very reactive. Furthermore, they bear very versatile chemical reactivity. Thus, a large variety of carbon[1c,d] as well as oxygen,[1a] sulfur,[1a] nitrogen[1c] and halogen[1f] nucleophiles can cleave oxirane rings, generating a diverse nature of functionalities. This unusual chemical property of epoxides has made oxiranes as one of the most frequently used intermediates for organic synthesis.

Recently, Landini and his associates reported that tetrabutylammonium dihydrogentrifluoride is a readily available, convenient, and highly efficient catalyst for the regioselective hydrofluorination of many epoxides to afford fluorohydrins when used in conjunction with a molar excess of potassium hydrogen difluoride under solid-liquid phase transfer conditions.[2] The fluorohydrins thus obtained are thought to be of considerable importance as versatile intermediates for the preparation of diverse fluorine-containing compounds of medicinal interest. In connection with other project, we were interested in obtaining fluoromethyl ketones and we thought that these compounds may be prepared by simple oxidation of fluorohydrins which are obtainable from appropriate epoxides using the reagent of Landini.[2] However, when we carried out the reaction with benzyl ester of 2-benzyl-4,5-epoxypentanoic acid under the conditions of Landini, hoping to obtain the ester of 2-benzyl-5-fluoro-4-hydroxypentanoic acid, there was obtained an unexpected product of a methyl ketone instead. We wish to report preliminary results of this regioselective isomerization reaction of epoxyesters to the corresponding methyl ketoesters under unusual conditions.




**Scheme 1.**

The 4,5-epoxyesters were readily prepared by epoxidating the corresponding olefines with *m*-chloroperbenzoic acid. The epoxides thus obtained were treated with the hydrofluorinating agent[3] as described by Landini *et al.*[2] Thus, a heterogeneous mixture of epoxide **1**, catalytic amount of tetrabutylammonium dihydrogentrifluoride and an excess of potassium hydrogen difluoride was heated at 120 ℃ until the epoxide is no longer detectable by TLC. It took about 5 h. The reaction mixture was then dissolved in methylene chloride and the solution was filtered on celite. The crude product obtained by concentration of the filtrate was purified by column chromatography, giving the corresponding γ-ketoester[4] in satisfactory yield (Scheme 1).[5] Structural assignments for the products was supported by the spectral data: two carbonyl absorption bands (e.g., 1717 and 1731 $cm^{-1}$ for **3d**) in their IR spectra and a characteristic singlet magnetic resonance signal for methyl protons in the region of δ 2.0-2.1 ppm in the NMR spectra. The mass spectral data and results of microelemental analyses were in agreement with the structures.

It is worthy noting that the present regioselective isomerization of the 4,5-epoxyesters to γ-ketoesters is contrary to the result of Landini *et al.* In fact, when we first observed the formation of the ketoester **3d** from the reaction of **1d**, dismayed by the unexpected result we repeated the experiments of Landini *et al.*[2] Their results were reproduced. These are first examples which demonstrate that the reagent of Landini does not necessarily transform oxiranes to the corresponding fluorohydrins, but to cause isomerization of the oxiranes to the ketoesters in cases of 4,5-epoxyesters. Although the reason for the alternate reaction path in case of epoxyesters is not apparent presently to us and remains to be clarified, the present observation is important in view of the fact that the method of Landini has been known as an unique route to fluorohydrins which are valuable intermediates for the preparation of compounds having pharmacological interests. An additional work to this end and for finding the limitation of the regioselective isomerization is in progress.

Most of ring opening as well as isomerization reactions of monosubstituted epoxides are known to suffer from a lack of regioselectivity.[6] In this regard, the present protocol for the conversion of the epoxide in the epoxyesters to the corresponding methyl ketones may itself have a synthetic value