Acid-promoted hydroxylactonization of a $\delta, \varepsilon$-epoxy amide took place via both 6-exo-tet and 7-endo-tet processes, causing a considerable degree of racemization of the resulting $\delta$-hydroxyalkyl-$\delta$-lactone.

Key words: dihydroisocoumarin; epoxy amide; hydroxylactonization; racemization; Baldwin rule

Our recently completed total syntheses of bacillosarcins $A$ and $B$, herbicidal substances produced by Bacillus subtilis TF-B0611,2) as well as of two related natural products3) needed dihydroisocoumarin derivative 1 to be prepared as their common building block (Scheme 1). Although the preparation of 1 with a high enantiomeric excess (ee) of 96% was eventually accomplished by using an intermolecular epoxide ring-opening reaction as the key step, our initial approach to 1 via intramolecular epoxide ring opening of $\delta, \varepsilon$-epoxy amide 5 to hydroxy lactone 6a suffered from unexpected partial racemization, forcing us to abandon the original synthetic plan for 1. We disclose in this note our concise preparation of 5 and propose a plausible mechanism for the partial racemization.

The preparation of 5 began with the iodination of epoxy alcohol 2a that had been obtained in 88% ee by the Sharpless asymmetric epoxidation of (E)-5-methyl-2-hexen-1-ol according to a reported procedure.9) The ee of 2a was determined by comparing its specific rotation with the reported value and confirmed by a $^1$H-NMR analysis of corresponding ($R$)- and ($S$)-MTPA esters 2b. Resulting epoxy iodide 3 was converted into epoxy amide 5 in a 75% yield by treating 3 with the Lipshutz cuprate prepared from 4 by its successive treatment with -BuLi/TMEDA, CuCN, and LiCl.5–8) It is worth mentioning that 5 was obtained as a 1:1 mixture of diastereomers ascribable to atropisomerism due to restricted rotation about the Ar–CO single bond.9)

With 5 in hand, we set about the pivotal transformation, the hydroxylactonization of 5 into 6a. Although our literature search revealed that examples of this type of reaction, intramolecular epoxide ring opening of epoxy amides to produce hydroxy lactones,10,11) were scarcely preceded, in contrast to analogous transformations using epoxy carboxylic acids or epoxy esters as substrates, the conversion of 5 into 6a was successfully achieved by simply treating 5 with TFA in dichloromethane at room temperature, giving desired hydroxy lactone 6a in an acceptable yield of 54%. Lactone 6a was obtained as a single diastereomer, and its relative stereochemistry was confirmed by comparing its $^1$H- and $^{13}$C-NMR spectra with those of an authentic sample prepared by a different synthetic route.12) Surprisingly, however, a $^1$H-NMR analysis of ($R$)- and ($S$)-MTPA esters 6b prepared from 6a indicated the ee of 6a to be only 55%, down by 33% from the original ee value (88%) of starting material 2a. As shown in Scheme 2, we initially expected that the ring opening of protonated epoxide 7 would proceed via path a (6-exo-tet mode, the generally favored process from the Baldwin rule), giving desired lactone 6a as a single stereoisomer. The partial racemization that was observed during the acid-catalyzed hydroxylactonization process, however, suggests that ring opening also took place through path b (7-endo-tet mode), affording the enantiomer of 6a (ent-6a) via hydroxy iminium ion 8 and protonated amino acetal intermediate 9. We consider that this unexpected result could be based on the exceptional feature of three-membered rings (formally belonging to the tetrahedral system) that they can also behave like the trigonal system which generally favors both 7-endo and 6-exo ring-forming modes.13) Some related examples of such endo-type hydroxylactonization of $\gamma, \delta$-epoxy esters have in fact been reported in the literature.14)

In conclusion, we found that the hydroxy lactonization of $\delta, \varepsilon$-epoxy amide 5 to form lactone 6a can be effected by its treatment with TFA, but that the reaction was accompanied by a considerable degree of racemization ascribable to the concurrent 6-exo-tet and 7-endo-tet ring-forming processes.

Experimental
IR spectra were recorded by a Jasco FT/IR-4100 spectrometer, using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in CDCl$_3$ by a Varian Unity Plus-500 spectrometer (500 MHz for $^1$H and 125 MHz for $^{13}$C). Optical rotation values were measured with a Jasco DIP-371 polarimeter, and mass spectra were obtained with a JEOL JMS-700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for column chromatography. CH$_2$Cl$_2$ and THF employed for the reactions were respectively distilled from CaH$_2$ and Na$_2$benzenophenone.

1 $^{2}$R,IR)-2,3-Epoxy-5-methyl-1-hexanol (2a). To a stirred suspension of (−)-dipropyl tartrate (70 ml, 0.328 mmol), Ti(OiPr)$_4$ (65 ml, 0.219 mmol) and activated MS 3 A˚ (1.00 g) in CH$_2$Cl$_2$ (3.25 ml) was added TBHP (3.54 ml in toluene, 2.60 ml, 9.20 mmol) at −25°C. A solution of (E)-5-methyl-2-hexen-1-ol in CH$_2$Cl$_2$ (3.25 ml) was added after 45 min at −25°C, and the resulting mixture

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Abbreviations: TMEDA, $N,N',N'$-tetramethylethylenediamine; TFA, trifluoroacetic acid; MTPA, $\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenylacetyl
was stirred for 16h at the same temperature. The reaction was quenched by adding FeSO₄·7H₂O (2.6 g, 9.39 mmol) and 10% w/v aq. in-tartaric acid (13 ml) at -15 °C, and the mixture was filtered through a pad of Florisil. The filtrate was extracted with Et₂O, and the extract was successively washed with saturated aq. NaHCO₃ and brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed over SiO₂ (hexane/ethyl acetate = 5:1-2:1) to give 2a (435 mg, 76%) as a colorless oil. [α]D₃⁰ +36.7 (c 0.49, MeOH) (lit.⁶ [α]D₃⁰ -36.5 (c 0.053, MeOH) for ent-2 which was estimated to be 88% ee by an ee glc analysis); IR νmax: 3477 (s), 2955 (s), 1717 (s); 1H-NMR: δ 6.92 (1H, d, J = 3.3 Hz), 1.24–1.35 (2H, m), 1.72–1.84 (1H, m), 2.61 (1H, d, J = 6.5 Hz), 2.98 (1H, d, J = 6.3, 2.0 Hz), 3.64 (1H, ddd, J = 12.5, 5.4, 2.7 Hz), 3.92 (1H, ddd, J = 12.5, 5.4, 2.7 Hz); 13C-NMR: δ 34.19/34.20, 52.35, 100.68, 103.06, 121.21, 131.37/131.38; found: 131.1080, 131.1080 (M+H)⁺.

Determination of the ee of 2a. Compound 2a (2 mg) was treated with each of (R)- and (S)-MTPA chloride in pyridine to give the respective (S)- and (R)-MTPA esters (2b) which were then analyzed by 1H-NMR (500 MHz, CDCl₃) without chromatographic purification. The signals for the two protons on the MTPAO-bearing methylene carbon of the (R)-MTPA ester derived from 2a were observed at δ 4.24 (1H, dd, J = 12.1, 5.8 Hz) and δ 4.58 (1H, dd, J = 12.1, 3.3 Hz), while those of the MTPA ester formed from ent-2a contained in the sample of 2a as a small amount of contaminant appeared at δ 4.25 (1H, dd, J = 12.1, 6.2 Hz) and δ 4.54 (1H, dd, J = 12.1, 3.3 Hz). These chemical shifts were confirmed by the 1H-NMR spectrum of the (S)-MTPA esters obtained from 2a. A comparison of the two 1H-NMR spectra revealed the ee of 2a to be 88%.

(2S,3R)-2,3-Epoxy-1-iodo-5-methylhexane (3). To a stirred solution of 2a (847 mg, 6.51 mmol), Ph₃P (1.88 g, 7.16 mmol) and imidazole (797 mg, 11.7 mmol) in CH₂Cl₂ (50 ml) was added iodine (1.82 g, 7.16 mmol) at 0 °C under Ar, and the mixture was stirred at room temperature for 3 h. To this mixture were added saturated aq. NaHCO₃, and satd. aq. Na₂S₂O₅CO₂ at 0 °C, and the resulting mixture was extracted with Et₂O. The extract was successively washed with satd. aq. Na₂SO₄, satd. aq. NaHCO₃, and brine. Long (Na₂SO₄) and concentrated in vacuo. The residue was diluted with hexane/2-propanol (3:1) and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was chromatographed over SiO₂ (hexane/2-propanol = 4:1) to give 3 (1.284 g, 82%) as a colorless oil. [α]D₃⁰ +3.9 (c 0.3, CHCl₃); IR νmax: 2956 (s), 898 (m); 1H-NMR: δ 0.98 (6H, d, J = 6.5 Hz), 1.39 (1H, ddd, J = 13.5, 7.5, 5.5 Hz), 1.49 (1H, ddd, J = 13.5, 6.3, 6.0 Hz), 1.82 (1H, m, J = 5.5, 6.5 Hz), 2.83 (1H, ddd, J = 7.5, 6.3, 2.0 Hz), 2.98 (1H, ddd, J = 7.5, 6.3, 2.0 Hz), 3.05 (1H, dd, J = 10.3, 7.5 Hz), 3.26 ppm (1H, dd, J = 10.3, 6.3 Hz); 13C-NMR: δ 51.1, 25.2, 22.9, 26.3, 40.8, 85.4, 61.7; HRMS (EI) m/z: calcd. for C₇H₁₄O₂: 240.0011; found, 240.0014 (M⁺).
respective (S)- and (R)-MTPA esters (6b) which were then analyzed by 
$^1$H-NMR (500 MHz, CDCl$_3$) without chromatographic purification.
The signal for the methine proton on the lactone ring of the (R)-MTPA ester derived from 6a was observed at $\delta$ 4.53 (1H, dt, $J = 12.5$, 3.0 Hz), while that of the MTPA ester formed from ent-6a contained in the sample of 6a as a small amount of contaminant appeared at $\delta$ 4.39 (1H, ddd, $J = 12.4$, 4.4, 2.7 Hz). These chemical shifts were confirmed by the $^1$H NMR spectrum of the (S)-MTPA esters obtained from 6a.

A comparison of the two $^1$H-NMR spectra revealed the ee of 6a to be 55%.

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