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*Note*

# Partial Racemization Occurring in the Hydroxylactonization of a δ,ε-Epoxy Amide

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

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

Our recently completed total syntheses of bacilosarcins A and B,[1] herbicidal substances produced by *Bacillus subtilis* TP-B0611,[2] as well as of two related natural products[3] 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 δ,ε-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.[4] The ee of **2a** was determined by comparing its specific rotation with the reported value[4] 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 *s*-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 precedented, 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),[13] 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 γ,δ-epoxy esters have in fact been reported in the literature.[14]

In conclusion, we found that the hydroxylactonization of δ,ε-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. $CH_2Cl_2$ and THF employed for the reactions were respectively distilled from $CaH_2$ and Na/benzophenone.

*(2R,3R)-2,3-Epoxy-5-methyl-1-hexanol (**2a**).* To a stirred suspension of D-(−)-diisopropyl tartrate (70 ml, 0.328 mmol), Ti(O*i*Pr)$_4$ (65 ml, 0.219 mmol) and activated MS 3 Å (1.00 g) in $CH_2Cl_2$ (3.25 ml) was added TBHP (3.54 M in toluene, 2.60 ml, 9.20 mmol) at −25 °C. A solution of (*E*)-5-methyl-2-hexen-1-ol in $CH_2Cl_2$ (3.25 ml) was added after 45 min at −25 °C, and the resulting mixture

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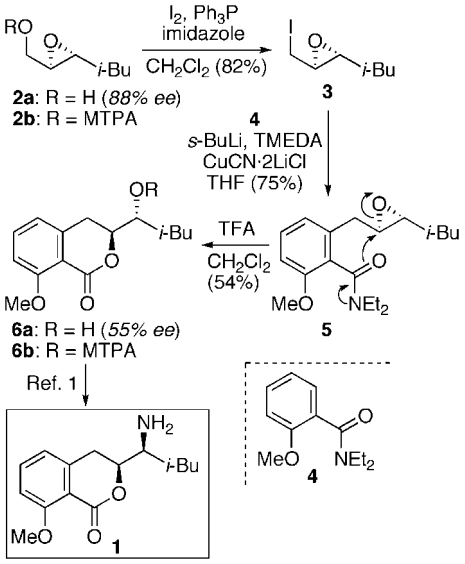
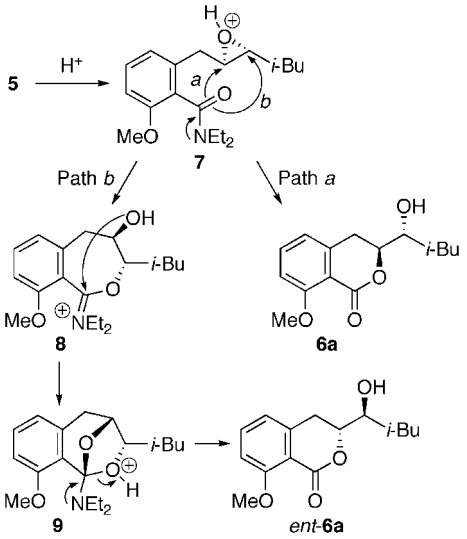
*Abbreviations*: TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TFA, trifluoroacetic acid; MTPA, α-methoxy-α-(trifluoromethyl)phenylacetyl




**Scheme 1.** Preparation of δ,ε-Epoxy Amide **5** and Its Hydroxylactonization to **6a**.




**Scheme 2.** Plausible Mechanism for the Partial Racemization of **6a**.

was stirred for 16 h at the same temperature. The reaction was quenched by adding $FeSO_4 \cdot 7H_2O$ (2.6 g, 9.39 mmol) and 10% w/v aq. DL-tartaric acid (13 ml) at −15 °C, and the mixture was filtered through a pad of Florisil. The resulting filtrate was extracted with $Et_2O$, and the extract was successively washed with saturated aq. $NaHCO_3$ and brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (hexane/ethyl acetate = 5:1–2:1) to give **2a** (435 mg, 76%) as a colorless oil. $[\alpha]^{22}_D$ +36.7 (*c* 0.49, MeOH) (lit.[4]) $[\alpha]^{20}_D$ −36.5 (*c* 0.053, MeOH) for *ent*-**2** which was estimated to be 88% ee by a chiral GLC analysis); IR $\nu_{max}$: 3449 (s), 2957 (s); $^1$H-NMR δ: 0.96 (3H, d, *J* = 3.5 Hz), 0.99 (3H, d, *J* = 3.5 Hz), 1.29–1.56 (2H, m), 1.74–1.90 (2H, m), 2.90 (1H, ddd, *J* = 4.5, 2.7, 2.7 Hz), 2.98 (1H, ddd, *J* = 6.3, 5.4, 2.7 Hz), 3.64 (1H, ddd, *J* = 12.5, 6.6, 3.9 Hz), 3.92 (1H, ddd, *J* = 12.5, 5.4, 2.7 Hz); $^{13}$C-NMR δ: 23.0, 23.5, 26.9, 41.3, 55.5, 59.2, 62.3; HRMS (FAB) *m/z*: calcd. for $C_7H_{15}O_2$, 131.1072; found, 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 $^1$H-NMR (500 MHz, $CDCl_3$) 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 $^1$H-NMR spectrum of the (*S*)-MTPA esters obtained from **2a**. A comparison of the two $^1$H-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), $Ph_3P$ (1.88 g, 7.16 mmol) and imidazole (797 mg, 11.7 mmol) in $CH_2Cl_2$ (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. $NaHCO_3$ and satd. aq. $Na_2S_2CO_3$ at 0 °C, and the resulting mixture was extracted with $Et_2O$. The extract was successively washed with satd. aq. $Na_2SO_3$, satd. aq. $NaHCO_3$ and brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was diluted with hexane/$Et_2O$ (3:1) and filtered though a pad of Celite. The filtrate was concentrated *in vacuo*, and the residue was chromatographed over $SiO_2$ (hexane/EtOAc = 4:1) to give **3** (1.284 g, 82%) as a colorless oil. $[\alpha]^{22}_D$ −2.0 (*c* 0.3, $CHCl_3$); IR $\nu_{max}$: 2956 (s), 898 (m); $^1$H-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, 6.0, 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); $^{13}$C-NMR δ: 5.1, 22.5, 22.9, 26.3, 40.8, 58.4, 61.7; HRMS (EI) *m/z*: calcd. for $C_7H_{13}OI$, 240.0011; found, 240.0014 ($M^+$).

N,N-*Diethyl-2-[(2R,3R)-2,3-epoxy-5-methylhexyl]-6-methoxybenzamide (****5****).* To a stirred solution of TMEDA (773 ml, 5.12 mmol) in THF (20 ml) was added *s*-BuLi (1.0 M in hexane, 5.12 ml, 5.12 mmol) at −78 °C under Ar. After 10 min, a solution of **4** (1.04 g, 5.00 mmol) in THF (6.0 ml) was added over 15 min, and the resulting mixture was stirred for 30 min. To the mixture was added a solution of CuCN (224 mg, 2.50 mmol) and LiCl (212 mg, 5.00 mmol) in THF (8.25 ml) over 10 min. The mixture was gradually warmed to −15 °C over 50 min and stirred at −15 °C for an additional 10 min. A solution of **3** (300 mg, 1.25 mmol) in THF (3.0 ml) was then added to the resulting yellow suspension at −78 °C, and the mixture was gradually warmed to room temperature and stirred overnight. The reaction was quenched with satd. aq. $NH_4Cl$, and the mixture was extracted with $Et_2O$. The extract was successively washed with water and brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (hexane/ethyl acetate = 5:1–4:1) to give **5** (300 mg, 75%) as a colorless oil. $[\alpha]^{22}_D$ +13.8 (*c* 0.94, $CHCl_3$); IR $\nu_{max}$: 2961 (s), 1631 (s); $^1$H-NMR δ: 0.89 (0.5 × 3H, d, *J* = 6.3 Hz), 0.92 (0.5 × 3H, d, *J* = 6.3 Hz), 0.93 (0.5 × 3H, d, *J* = 6.5 Hz), 0.94 (0.5 × 3H, d, *J* = 6.5 Hz), 1.02 (0.5 × 3H, t, *J* = 7.3 Hz), 1.03 (0.5 × 3H, t, *J* = 7.3 Hz), 1.24 (0.5 × 3H, t, *J* = 7.3 Hz), 1.26 (0.5 × 3H, t, *J* = 7.3 Hz) 1.34–1.45 (2H, m), 1.72–1.84 (1H, m), 2.61 (0.5 × 1H, dd, *J* = 14.5, 7.5 Hz), 2.65 (0.5 × 1H, dd, *J* = 14.5, 6.0 Hz), 2.74–2.96 (3H, m), 3.07–3.19 (2H, m), 3.43 (1H, dq, *J* = 20.0, 7.3 Hz), 3.75 (1H, dq, *J* = 20.0, 7.3 Hz), 3.78 (3H, s), 6.79 (1H, d, *J* = 7.8 Hz), 6.91 (0.5 × 1H, d, *J* = 7.8 Hz), 6.99 (0.5 × 1H, d, *J* = 7.8 Hz), 7.25 (0.5 × 1H, t, *J* = 7.8 Hz), 7.29 (0.5 × 1H, t, *J* = 7.8 Hz); $^{13}$C-NMR δ: 12.8, 13.71/13.73, 22.40/22.43, 22.95/22.97, 26.3/26.4, 35.6, 38.5, 41.0, 42.6/42.7, 55.5, 57.8/58.0, 58.2/58.4, 108.8/108.9, 121.7/122.3, 126.5, 129.3/129.4, 135.3/135.8, 155.3, 167.8/167.9; HRMS (FAB) *m/z*: calcd. for $C_{19}H_{30}O_3N$, 320.2226; found, 320.2234 ($[M+H]^+$).

*(S)-3-[(R)-1-Hydroxy-3-methylbutyl]-8-methoxyisochroman-1-one (****6a****).* To a stirred solution of **5** (30 mg, 0.0939 mmol) in $CH_2Cl_2$ (2.0 ml) was added TFA (7.0 ml, 0.0939 mmol) at room temperature. After 13.5 h, the reaction was quenched with satd. aq. $NaHCO_3$, and the mixture was extracted with $CH_2Cl_2$. The extract was washed with brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (hexane/ethyl acetate = 4:1) to give **6a** (13.4 mg, 54%) as a colorless oil. $[\alpha]^{22}_D$ −64 (*c* 0.62, $CHCl_3$); IR $\nu_{max}$: 3477 (s), 2955 (s), 1717 (s); $^1$H-NMR δ: 0.95 (3H, d, *J* = 6.6 Hz), 0.98 (3H, d, *J* = 6.6 Hz), 1.21–1.34 (1H, m), 1.52 (1H, ddd, *J* = 14.4, 10.2, 6.0 Hz), 1.79–1.93 (1H, m), 2.18 (1H, d, *J* = 3.9 Hz), 2.78 (1H, dd, *J* = 16.2, 2.7 Hz), 3.20 (1H, dd, *J* = 16.2, 12.6 Hz), 3.96 (3H, s), 4.20–4.12 (1H, m), 4.31 (1H, ddd, *J* = 12.6, 3.2, 2.7 Hz), 6.85 (1H, d, *J* = 7.2 Hz), 6.92 (1H, d, *J* = 8.7 Hz), 7.47 (1H, d, *J* = 8.4 Hz); $^{13}$C-NMR δ: 21.8, 23.5, 24.6, 28.0, 40.6, 56.2, 69.8, 81.0, 110.8, 113.5, 119.7, 134.7, 142.1, 161.2, 162.4; HRMS (FAB) *m/z*: calcd. for $C_{15}H_{21}O_4$, 265.1440; found, 265.1435 ($[M+H]^+$).

*Determination of the ee of* ***6a****.* Compound **6a** (2 mg) was treated with each of (*R*)- and (*S*)-MTPA chloride in pyridine to give the

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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