Intramolecular Nucleophilic Epoxidation of γ-Amino-α,β-Unsaturated Esters with an *N*-Hydroperoxymethyl Group

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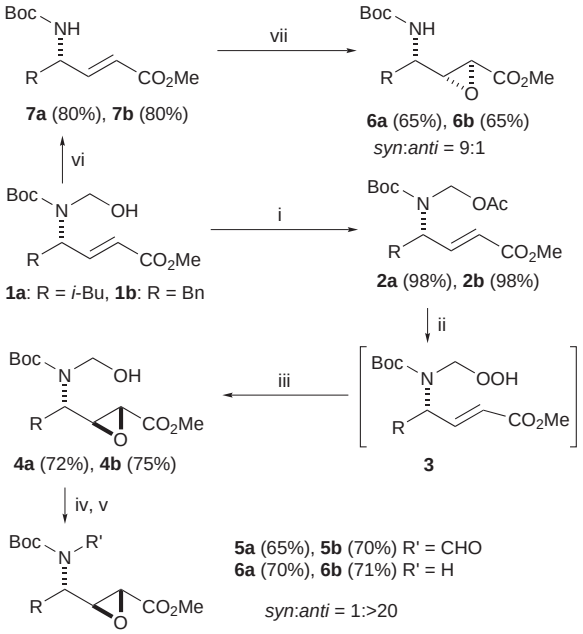
Abstract: Intramolecular nucleophilic epoxidation reactions of γ-amino-α,β-unsaturated esters have been studied for the first time with a hydroperoxymethyl group attached to the nitrogen atom. The epoxidation was fast under mild basic conditions and highly *anti* selective (>20:1) when the alkyl group is small.

Key words: asymmetric synthesis, ring-opening, peroxides, nucleophile, intramolecular epoxidation, amino epoxide

Stereoselective epoxidation of olefins is one of the important subjects in organic synthesis because epoxides can undergo regio- and stereoselective attack by various nucleophiles.[1] Substrate-directed control of stereoselectivity has been well utilized for this purpose without using chiral catalysts or ligands.[2] We have been interested in stereoselective synthesis of γ-amino-α,β-epoxy esters because they can serve as useful chiral building blocks for bioactive products with an amino alcohol moiety.[3] In principle, they can be efficiently prepared from an amino group-directed epoxidation of γ-amino-α,β-unsaturated esters that are derived from a Wittig olefination of readily available α-amino aldehydes.

However, intermolecular epoxidation reactions of α,β-unsaturated esters with peroxyacids such as MCPBA are generally slow and base is often necessary to effect the reactions.[4] Sometimes stronger base is used to achieve a successful epoxidation.[5] The stereoselectivities in all of these epoxidation reactions are *syn* to the allylic amino group.[5a,6] We have found out that a facile and stereoselective epoxidation reaction of γ-amino-α,β-unsaturated esters is possible with intramolecular addition of an *N*-hydroperoxymethyl group under mild basic conditions.[7] High *anti* selectivity obtained in the present study is complementary to the usual *syn* selectivity of the intermolecular epoxidation reactions. We believe it is the first report of the stereoselective intramolecular epoxidation reaction of electron-poor alkenes, whereas there have been several scattered reports on the intramolecular regio- or stereoselective epoxidation reactions of electron-rich alkenes.[8]

We planned to introduce the *N*-hydroperoxymethyl group by reacting the *N*-hydroxymethyl group of γ-amino-α,β-unsaturated esters **1** with H_2O_2 (Scheme 1). Compounds **1** were prepared as reported.[9,10] Introduction of the *N*-hydroperoxymethyl group was facilitated after acetylation of the *N*-hydroxymethyl group of **1**, and **2** were treated with aqueous H_2O_2 under acidic conditions for four hours in the presence of $MgSO_4$.[11] After filtration of $MgSO_4$ from the resulting mixture, the epoxidation reaction was completed within 30 minutes at room temperature by sequential addition of MeOH and K_2CO_3 to the filtrate. It should be noted that the epoxidation was very fast even under mild basic conditions probably because of the intramolecular nature of the reaction.



Scheme 1 *Reagents and conditions*: (i) Ac_2O, DMAP, TEA, CH_2Cl_2; (ii) 30% aq H_2O_2, *p*-TsOH, $MgSO_4$, DME; (iii) K_2CO_3, MeOH; (iv) PDC, CH_2Cl_2; (v) Cs_2CO_3, MeOH; (vi) *p*-TsOH, CH_2Cl_2, reflux; (vii) MCPBA, CH_2Cl_2.

The diastereoselectivity of the intramolecular epoxidation was determined at the stage of **6** because the diastereomeric mixtures of **4** and **5** were not separated on the ^1H NMR spectra. The ratio of **6-*anti*** to **6-*syn*** epoxides was more than 20:1 by ^1H NMR, indicating that the in situ intramolecular epoxidation reaction gave the *anti*-epoxides with high selectivity. The minor epoxides **6-*syn*** were obtained separately from **7** as major products by the intermolecular epoxidations with MCPBA as reported.[3a] The minor products from the MCPBA epoxidation of **7** were

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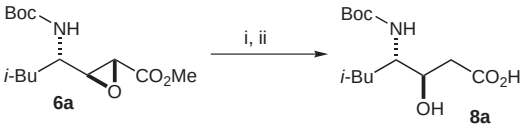
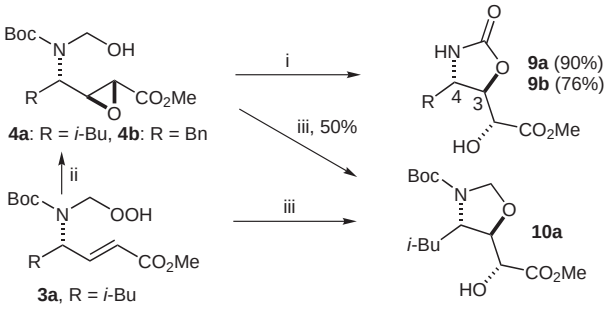
the same as the major products **6-*anti*** derived from the intramolecular epoxidation. The assignment of the relative configuration was confirmed by transformation of **6a** into **8a**, a diastereomeric derivative of statine, with regioselective reduction (Scheme 2).[12a] The ^{1}H NMR and ^{13}C NMR spectra of the major product matched those in the literature.[12b]



Scheme 2 *Reagents and conditions*: (i) SmI_2, DMAE, HMPA, THF, 60%; (ii) NaOH, MeOH–H_2O, 70%.

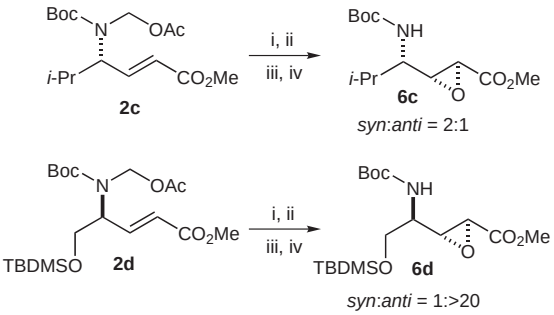
Further evidence for the *anti* configuration was obtained from measurement of the vicinal coupling constant between the protons at C-3 and C-4 of oxazolidinones **9** (Scheme 3). When treated with silica gel, **4** underwent a completely regio- and stereoselective ring closure to give **9**.[13] A ^{1}H NMR analysis of **9a** and **9b** showed $J_{3,4}$ of 4.6 Hz and 4.2 Hz, respectively, which are typical values for the *trans* oxazolidinones of comparable structure.[13,14b] The similar *cis* oxazolidinones were reported to have a larger coupling constant of 7–10 Hz.[14] The peroxide intermediate **3a** that was isolated by flash column chromatography in 70% yield reacted as expected to give epoxide **4a** in 80% yield under similar conditions (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) SiO_2, MeOH; (ii) K_2CO_3, MeOH at 0.08 M, 80%; (iii) K_2CO_3, MeOH at 1.0 M, 65%.

Interestingly, **3a** reacted at higher concentration to give directly oxazolidine **10a** that was produced presumably by an in situ attack of the *N*-hydroxymethyl group of **4a** on the epoxide ring. The formation of **10a** from **3a** via **4a** was confirmed by an independent synthesis of **10a** by treating **4a** in MeOH with K_2CO_3 although the yield was lower (50%).

The intramolecular epoxidation protocol was extended to a couple of other γ-amino-α,β-unsaturated esters, **2c** and **2d**, that were obtained from L-valine and D-serine, respectively (Scheme 4). The high selectivity for the *anti* epoxide **6d** was observed with **2d**, whereas the opposite *syn* selectivity was shown with **2c**. Their relative stereochemistry was determined similarly as described above.



Scheme 4 *Reagents and conditions*: (i) 30% aq H_2O_2, *p*-TsOH, $MgSO_4$, DME; (ii) K_2CO_3, MeOH; (iii) PDC, CH_2Cl_2; (iv) Cs_2CO_3, MeOH.

The stereoselectivity observed in the present study could be rationalized based on the more favorable N-eclipsed allylic conformation (Figure 1). In contrast to the *N*-hydroxymethyl group used for (–)-statine,[9] an H-eclipsed allylic conformation would be disfavored because of the dipole-dipole repulsion between the peroxy group and the double bond. The selectivity shown here is opposite to that of the conjugate addition of the *N*-hydroxymethyl group described in the synthesis of (–)-statine. When the alkyl group R is bulky, however, the N-eclipsed conformation should be disfavored due to the $A^{1,3}$-strain. Therefore, the valine derivative **2c** having an isopropyl side chain produced the *syn* epoxide as a major product with low selectivity.

In summary, we have demonstrated an efficient and highly stereoselective synthesis of *anti*-γ-amino-α,β-epoxy esters via the first examples of an intramolecular nucleophilic epoxidation of readily available γ-amino-α,β-unsaturated esters. The *anti* selectivity in the present study is complementary to the usual *syn* selectivity of the intermolecular epoxidation reactions with MCPBA. The present results can be applied directly to prepare an amino diol moiety that is present in biologically active compounds. For example, (2*S*,3*S*,4*S*)-3,4-dihydroxy-L-glutamic acid, a selective agonist of mGluR1,[15] can be prepared from **4d** by a neighboring group-assisted regio- and stereoselective epoxide opening as shown in Scheme 3. Application of this strategy to the synthesis of dihydroxyglutamic acid is currently underway in our laboratory.

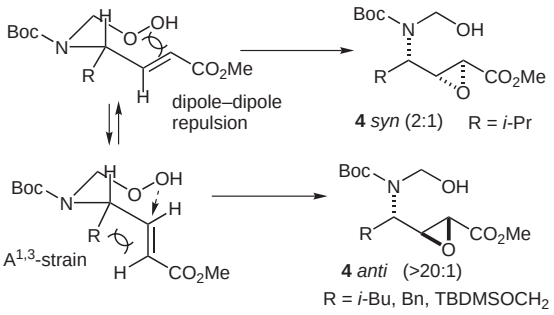


Figure 1 Favored conformations of the intramolecular epoxidation.

Preparation of Compound 2a

To a solution of **1a**[9] (106 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (72 mg, 0.70 mmol), TEA (71 mg, 0.70 mmol) and DMAP (4 mg, 0.04 mmol). The mixture was stirred for 1 h at r.t. The resulting mixture was partitioned between H_2O (2 × 20 mL) and Et_2O (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane–EtOAc) to give **2a** (118 mg, 98%) as colorless oil. R_f = 0.50 (2:1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, 3 H, *J* = 6.2 Hz), 0.95 (d, 3 H, *J* = 6.2 Hz), 1.35–1.55 (m, 2 H), 1.48 (s, 9 H), 1.55–1.70 (m, 1 H), 2.04 (s, 3 H), 3.74 (s, 3 H), 4.50–4.95 (m, 1 H), 5.20 (br s, 1 H), 5.40 (d, 1 H, *J* = 10.8 Hz), 5.86 (dd, 1 H, *J* = 15.8, 1.5 Hz), 6.88 (dd, 1 H, *J* = 15.8, 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 22.0, 22.9, 24.5, 28.2, 40.9, 51.7, 54.3, 69.9, 81.4, 121.3, 147.6, 155.5, 166.6, 171.8. Anal. Calcd for $C_{17}H_{29}NO_6$: C, 59.46; H, 8.51; N, 4.08. Found: C, 59.41; H, 8.69; N, 3.95.

Preparation of Compound 3a

To a solution of **2a** (110 mg, 0.32 mmol) in DME (5 mL) was added 30% aq H_2O_2 (300 mg, 2.65 mmol), *p*-TsOH (6 mg, 0.03 mmol) and $MgSO_4$ (300 mg). The mixture was stirred for 7 h at r.t. The resulting mixture was concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane–EtOAc) to give **3a** (71 mg, 70%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 60 °C): δ = 0.926 (d, 3 H, *J* = 6.3 Hz), 0.933 (d, 3 H, *J* = 6.3 Hz), 1.40–1.65 (m, 2 H), 1.47 (s, 9 H), 1.65–1.80 (m, 1 H), 3.72 (s, 3 H), 4.45–4.65 (m, 1 H), 4.99 (d, 1 H, *J* = 11.9 Hz), 5.09 (d, 1 H, *J* = 11.9 Hz), 5.87 (dd, 1 H, *J* = 15.8, 1.5 Hz), 7.00 (dd, 1 H, *J* = 15.8, 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 22.6, 24.5, 28.3, 41.1, 51.5, 55.5, 81.0, 81.6, 121.3, 148.0, 155.9, 166.9. IR (KBr): 3364, 1705, 1684, 1157 cm^{-1}.

Preparation of Compound 4a

To a solution of **3a** (52 mg, 0.16 mmol) in MeOH (2 mL) was added K_2CO_3 (34 mg, 0.25 mmol). The reaction was complete within 30 min. The resulting mixture was partitioned between H_2O (2 × 20 mL) and Et_2O (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane–EtOAc) to give **4a** (42 mg, 80%) as colorless oil. R_f = 0.28 (2:1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$, 60 °C): δ = 0.91 (d, 3 H, *J* = 6.7 Hz), 0.93 (d, 3 H, *J* = 6.7 Hz), 1.35–1.55 (m, 2 H), 1.49 (s, 9 H), 1.55–1.75 (m, 1 H), 3.30 (dd, 1 H, *J* = 5.9, 1.8 Hz), 3.41 (d, 1 H, *J* = 1.8 Hz), 3.70–3.90 (m, 1 H), 3.76 (s, 3 H), 4.62–4.74 (m, 1 H), 4.74–4.84 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 23.2, 24.3, 28.3, 38.3, 51.9, 52.5, 55.0, 59.9, 69.2, 81.5, 155.6, 169.1. IR (KBr): 3420, 1720, 1680 cm^{-1}. This compound **4a** was so reactive that it began to cyclize to **9a** during storage at r.t. Conformational isomerism of **4a** made some of the NMR peaks blurred.

Conversion of 2a to 4a without Isolation of 3a

To a solution of **2a** (110 mg, 0.32 mmol) in DME (5 mL) was added 30% aq H_2O_2 (300 mg, 2.65 mmol), *p*-TsOH (6 mg, 0.03 mmol) and $MgSO_4$ (300 mg). The reaction mixture was stirred for 7 h at r.t. After filtration of $MgSO_4$ from the resulting mixture, MeOH (2.5 mL) and K_2CO_3 (133 mg, 0.96 mmol) was added in sequence. The reaction was complete within 30 min. The resulting mixture was partitioned between H_2O (2 × 20 mL) and Et_2O (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane–EtOAc) to give **4a** (73 mg, 72%) as colorless oil.

Preparation of Compound 6a

To a solution of **5a** (47 mg, 0.15 mmol) in MeOH (5 mL) was added Cs_2CO_3 (49 mg, 0.15 mmol). The mixture was stirred for 0.5 h at r.t. The resulting mixture was partitioned between H_2O (2 × 20 mL) and Et_2O (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane–EtOAc) to give **6a** (30 mg, 70%) as white solid. R_f = 0.34 (2:1 hexane–EtOAc). ^{1}H NMR (300 MHz, DMSO, 70 °C): δ = 0.82 (d, 3 H, *J* = 6.6 Hz), 0.86 (d, 3 H, *J* = 6.6 Hz), 1.20–1.50 (m, 2 H), 1.36 (s, 9 H), 1.50–1.75 (m, 1 H), 3.01 (dd, 1 H, *J* = 5.7, 1.8 Hz), 3.40–3.55 (m, 1 H), 3.47 (d, 1 H, *J* = 1.8 Hz), 3.66 (s, 3 H), 6.82 (br d, 1 H, *J* = 9.3 Hz). ^{13}C NMR (75 MHz, DMSO): δ = 21.5, 23.0, 24.0, 28.0, 48.4, 50.0, 51.1, 52.2, 59.4, 77.9, 155.6, 169.1. Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.49; H, 8.93; N, 4.74.

Preparation of Compound 9a

To a solution of **4a** (40 mg, 0.13 mmol) in MeOH (5 mL) was added SiO_2 (145 mg). The mixture was stirred for 2.5 d at r.t. The resulting mixture was filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (1:1 hexane–EtOAc) to give **9a** (36 mg, 90%) as colorless oil. R_f = 0.07 (2:1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.918 (d, 3 H, *J* = 6.4 Hz), 0.922 (d, 3 H, *J* = 6.4 Hz), 1.20–1.40 (m, 1 H), 1.45–1.70 (m, 2 H), 3.83 (s, 3 H), 3.82–3.93 (m, 1 H), 4.43 (dd, 1 H, *J* = 4.6, 3.6 Hz), 4.50 (d, 1 H, *J* = 3.6 Hz), 6.28 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 22.9, 24.6, 45.3, 51.1, 52.9, 71.1, 82.3, 159.0, 171.2. MS (CI): *m/z* (%) = 232 (100) $[M + 1]^+$, 142 (17), 90 (20). HRMS (CI): *m/z* calcd for $C_{10}H_{18}NO_5$: 232.1185; found: 232.1184.

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