Stereoselective Formal Synthesis of (+)-Allokainic Acid *via* Thiol-Mediated Acyl Radical Cyclization

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Stereoselective formal synthesis of (+)-allokainic acid was accomplished starting from L-glutamate by using a thiol-mediated acyl radical cyclization as a key step. The cyclization of a formylalkenoate proceeded in a highly diastereoselective manner to give *trans*-4,5-disubstituted pyrrolidin-3-one without the production of the *cis*-isomer. The pyrrolidinone was then converted into the established synthetic intermediate of (+)-allokainic acid *via* the iron-catalyzed coupling reaction with an isopropenyl Grignard reagent.

Key words (+)-allokainic acid; acyl radical cyclization; thiol; stereoselective synthesis

Construction of heterocyclic motifs is of great importance in synthetic organic chemistry because most of biologically significant molecules are heterocycles.[1)] Among those, pyrrolidine rings are abundantly found in bioactive alkaloids, such as nicotine, cocaine, and kainic acid. We have already reported the thiol-catalyzed acyl radical cyclization reaction of alkenals.[2)] In this reaction, acyl radicals are directly generated from aldehydes through hydrogen abstraction by an *in situ* generated thiyl radical, and undergo addition to an olefin moiety of the same molecule to give α-substituted cycloalkanones in high yield. The usefulness of this reaction was highlighted in the total synthesis of marine diterpenoid (−)-cyanthiwigin F.[3)] Herein, we report the acyl radical cyclization for the stereoselective pyrrolidine ring construction and its application to the synthesis of (+)-allokainic acid (**3**).[4—27)] We expected that the construction of N-containing heterocycles would be realized by utilizing this cyclization reaction (Chart 1).[28—36)] The acyl radical cyclization of N-containing cyclic formylalkenoate **1** would proceed *via* conformer **A** with the minimum 1,3-allylic strain to preferentially give *trans*-**2**, rather than *via* conformer **B** that gives *cis*-**2**.

Results and Discussion

First, the acyl radical cyclization of **6** was tested. Formylalkenoate **6** was prepared starting from known alcohol **4** (Chart 2).[37,38)] After *N*-alkylation with 1-bromo-2-(triethylsiloxy)ethane, an alkenoate moiety was installed by a Swern oxidation–Wittig olefination sequence. Removal of the triethylsilyl (TES) group and the oxidation of the resulting alcohol afforded **6**. The acyl radical cyclization of **6**, however, only gave a complex mixture, including no desired cyclized product, with a complete consumption of starting **6**. We speculated that the conformer **C** required for the cyclization would be unfavorable because of the steric repulsion between the *N*-benzyl and the siloxymethyl moiety (Chart 3). We, therefore, plan to fix the conformation by *N*,*O*-protection as cyclic carbamate **1**.

Cyclic formylalkenoate **1** was prepared from known ester **7** (Chart 4).[38,39)] *N*-Alkylation of **7** was successful when potassium *tert*-butoxide was used as a base with 18-crown-6 to give **8** in 87% yield.[38)] For the deprotonation of **7**, it was important to add a pre-mixed solution of the alkoxide and the crown ether to a solution of **7** cooled in an ice-water bath before the addition of the bromide. When the deprotonation was carried out at room temperature, not only **8** (67%) but also a significant amount of the *tert*-butyl ester analog of **8** was obtained (13%). When the alkoxide was added to a solu-

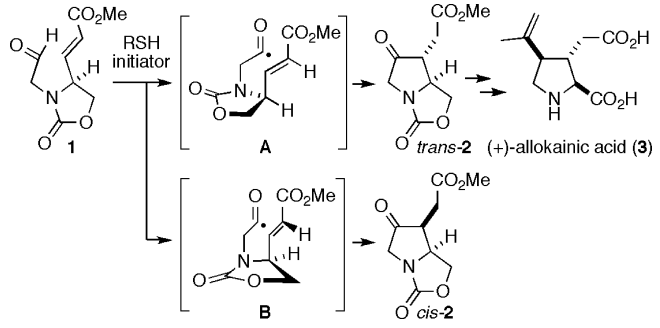

Chart 1. Acyl Radical Cyclization of **1** *via* Conformer **A** to Give *trans*-**2**, a Potential Intermediate for (+)-Allokainic Acid (**3**), and Conformer **B** to Give *cis*-**2**

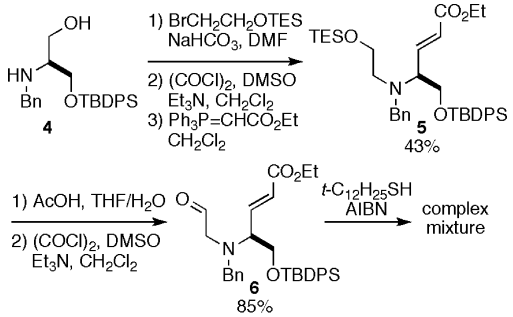

Chart 2. Preparation of **6** and Its Attempted Acyl Radical Cyclization

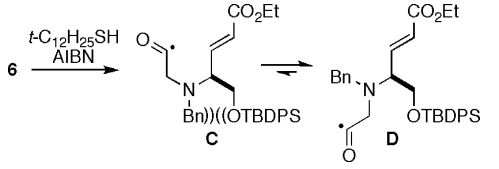

Chart 3. Conformers of Acyl Radical Generated from **6**: Conformer **C** Required for the Cyclization and Undesired Conformer **D**

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tion of the crown ether and **7**, the yield of **8** was dramatically decreased to 40%. The alkylation using sodium hydride or silver oxide was sluggish and not clean, resulting in low yield of **8** (14—25%) with partial recovery of **7** (0—53%).

Alkanoate **8** was dehydrogenated to alkenoate **9** by Ito–Saegusa oxidation in 69% yield. The same transformation was also achieved by selenylation–oxidative elimination sequence using lithium hexamethyldisilazide and phenylselenyl chloride, and then sodium periodate to give a desilylated analog of **9** in slightly lower yield (45%). Acidic removal of the TES group from **9** followed by Dess–Martin periodinane (DMP) oxidation afforded **1** in 62% yield.

First, the acyl radical cyclization of **1** was performed under our standard conditions: in refluxing benzene with 0.3 eq of *tert*-dodecanethiol and 2,2′-azobisisobutyronitrile (AIBN) (Table 1, entry 1).[2] Although the yield was quite low (3%), desired cyclized product *trans*-**2** was obtained as a sole diastereomer along with quantitative recovery of starting **1** (95%). The relative configuration of *trans*-**2** was confirmed by nuclear Overhauser effect spectroscopy (NOESY) cross peaks observed between the angular hydrogen and the α-proton of the ester moiety (see Experimental).

The yield of *trans*-**2** was increased when more than stoichiometric amounts of the thiol and the radical initiator were used; *trans*-**2** was obtained in 21% and 26% yield at 110 °C and 130 °C, respectively (entry 2, 3). The yield of deformylated **10** was, however, also increased to 9% at 110 °C (entry 2) and 15% at 130 °C (entry 3). The production of **10** could be explained by the decarbonylation of acyl radical **E** generated from **1** (Chart 5). Cyclization of **E** gives intermediate **F**, whose hydrogen abstraction from thiol affords *trans*-**2**. We hence expected that lower temperature should decelerate the entropy-increasing decarbonylation process. Thus, the reaction was performed at 70 °C using an excess amount of the initiator and the thiol (entry 4). Although a longer reaction time was required for the complete consumption of **1**, the yield of *trans*-**2** was increased to 38% while the production of **10** was decreased to 7%.

In order to complete a formal synthesis of (+)-allokainic acid, introduction of an isopropenyl group was required. Initially, a nucleophilic substitution reaction under Anderson's condition was attempted.[40] The mixture of *trans*-**2** and **10** was treated with $LiAlH(O\textit{t}\text{-}Bu)_3$ to give *trans*-alcohol **11** in 33% yield along with lactone **12** (1%), which was probably produced by spontaneous cyclization of the *cis*-isomer of **11** (Chart 6). At the same time, deformylation product **10** was converted into the corresponding saturated ester and removed at this stage by silica gel column chromatography. Using $NaBH_4$ as a reducing agent in ethanol, the yield and the diastereoselectivity were less satisfactory to give **11** and **12** in

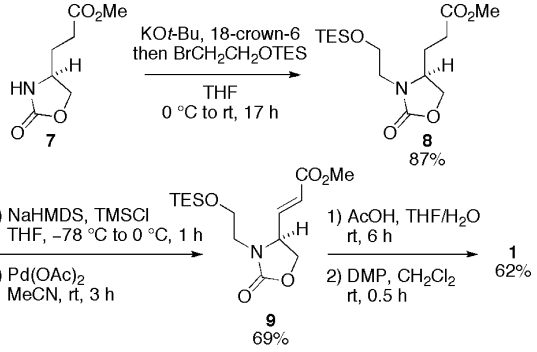


Chart 4. Preparation of **1** from Known Ester **7**

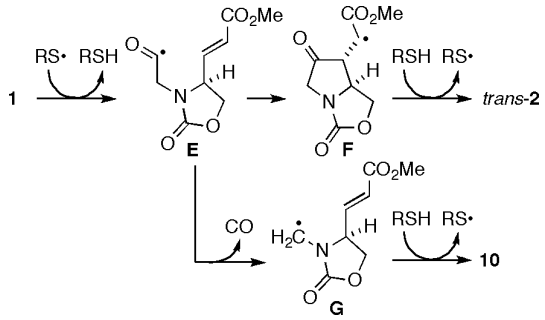


Chart 5. Formation of *trans*-**2** and **10** in Acyl Radical Cyclization of **1**

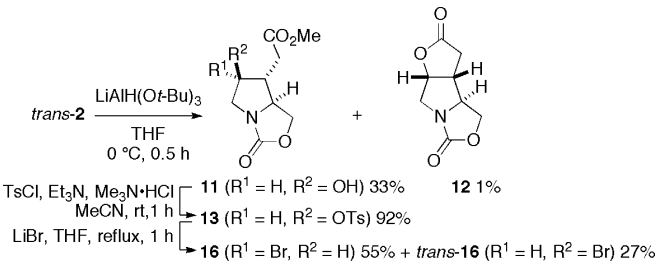
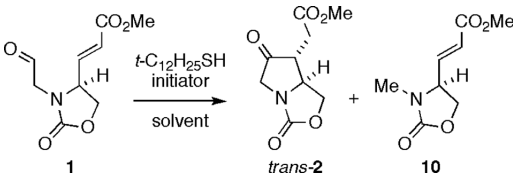


Chart 6. Conversion of *trans*-**2** to Tosylate **13** and Bromide **16**

Table 1. Acyl Radical Cyclization of Cyclic Formylalkenoate **1** to Give *trans*-**2** and **10**



Entry	Initiator (eq)	t-$C_{12}H_{25}SH$ (eq)	Solvent	Temp. (°C)	Time (h)	*trans*-**2** (%)	**10** (%)	**1** (%)
1	AIBN (0.3)	0.3	C_6H_6	80	19	3	2	95
2	V-40 (1.5)	3	PhMe	110	16	21	9	10
3[a]	V-40 (3)	4.5	PhCl	130	46	26	15	0
4[b]	AIBN (4)	10	PhMe	70	86	38	7	0

a) The reaction was started with V-40 (1.5 eq) and the thiol (3 eq), and 1.5 eq each of these were added to the reaction mixture after 34 h. *b*) The reaction was started with AIBN (1 eq) and the thiol (10 eq), and AIBN was portionwise (1 eq each) added to the reaction mixture after 12, 36, and 60 h.

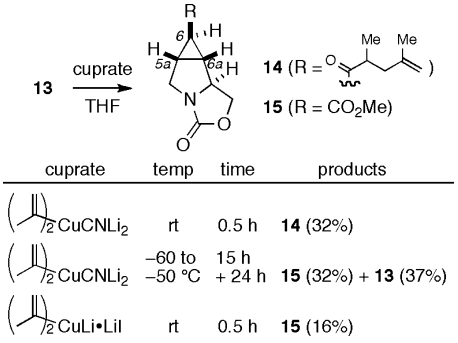


Chart 7. Unexpected Formation of Cyclopropanes **14** and **15** by the Reaction of Tosylate **13** with Cuprates

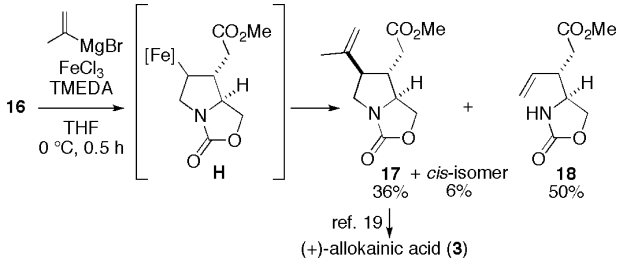


Chart 8. Formal Synthesis of (+)-Allokainic Acid (**3**)

12% and 5% yield, respectively. Tosylation of **11** under Tanabe's condition[41] proceeded smoothly to give **13**, which was separated from **12** at this stage.

Then, the isopropenylation with higher order cuprate was attempted using Anderson's condition (Chart 7). The expected substitution, however, failed to proceed, and unexpected cyclopropane **14** was obtained in 32% yield at room temperature. The reaction did not proceed at −60 °C, and at −50 °C, cyclopropanecarboxylate **15** was produced in 32% yield along with 37% recovery of tosylate **13**. These results show that the deprotonation at the α-position of the ester moiety is faster than the desired substitution and gives the enolate of **13**, which then undergoes 3-*exo*-*tet* cyclization to give **15**. At room temperature, ester **15** further reacts with two equiv of the cuprate to form **14** through 1,2-addition followed by 1,4-addition of the resulting intermediate α,β-unsaturated ketone. The use of the Gilman-type lithium iodide complex was unbeneficial and gave **15** in 16% yield. The stereochemistry of the ring fusion in **14** and **15** was assigned according to that of the parent molecule **13**, and the stereochemistry at the 6-positions was determined based on the small coupling constant (4.0 Hz) between the protons at the position and the adjacent protons. The relative configuration of the side chain in **14** was not determined, though only one of the diastereomers was obtained.

Finally, the isopropenyl group was introduced by the iron-catalyzed coupling reaction under Cossy's condition.[42] Tosylate **13** was treated with lithium bromide to give **16** and the *trans*-isomer in 55% and 27% yield, respectively (Chart 6). The relative configuration of the products was determined by nOe experiments (see Experimental). The formation of the *trans*-isomer would be due to a re-substitution reaction of **16** with lithium bromide. The major isomer **16** was subjected to the iron-catalyzed reaction with isopropenylmagnesium bromide to give **17**, Hanessian's intermediate[19] of (+)-allokainic acid in 36% yield along with the *cis*-isomer in 6% yield (Chart 8). The production of byproduct **18** suggests that the moderate yield of the coupling reaction is probably due to β-elimination of alkyl–iron intermediate **H**. The coupling reaction with *trans*-**16** would also give **17** in similar efficiency because it was indicated that a radical process should be involved in the formation of an alkyl–iron intermediate from an alkyl bromide.[42]

Conclusion

We have tested the acyl radical cyclization of the N-containing formylalkenoates. Although the yield was not satisfactory, *trans*-4,5-disubstituted pyrrolidin-3-one was produced in a perfectly stereoselective manner. The product was converted into the known intermediate of (+)-allokainic acid (**3**) in 4 steps.

Experimental

General All melting points are uncorrected. IR spectra were expressed in cm^{-1}. ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts and coupling constants are presented in ppm δ and Hz respectively. ^{13}C peak multiplicity assignments were made based on distortionless enhancement by polarization transfer (DEPT) data. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The wavenumbers of maximum absorption peaks of IR spectroscopy were presented in cm^{-1}. All the reactions were conducted under argon atmosphere, except for reactions in aqueous media. Column chromatography was carried out with silica gel.

(2-Bromoethoxy)triethylsilane TESCl (128 g, 0.85 mol) was added dropwise over 10 min at 0 °C to a stirred solution of 2-bromoethanol (50 ml, 0.71 mol) and imidazole (121 g, 1.78 mol) in dry *N*,*N*-dimethylformamide (DMF) (710 ml). After the addition was completed, the mixture was stirred for 0.5 h at 0 °C. After addition of satd $NaHCO_3$ (400 ml), the mixture was extracted with AcOEt (300 ml×3). The combined organic layers were washed with water (300 ml×3) and brine (100 ml), and dried over Na_2SO_4. Concentration and column chromatography (hexane, then hexane/AcOEt=19/1) gave the titled compound (127 g, 75%) as colorless oil of bp 110 °C/22 mmHg: *Rf* 0.5 (hexane/AcOEt=19/1). ^{1}H-NMR: 0.63 (6H, q, *J*=8.0), 0.97 (9H, t, *J*=8.0), 3.40 (2H, t, *J*=6.7), 3.89 (2H, t, *J*=6.7). ^{13}C-NMR: 4.6 (CH_2), 6.8 (CH_3), 33.3 (CH_2), 63.5 (CH_2). IR (neat): 1095. Electron impact (EI)-MS *m*/*z*: 211 (M+2−Et), 209 (M^+−Et). *Anal.* Calcd for $C_8H_{19}BrOSi$: C, 40.17; H, 8.01. Found: C, 40.12; H, 8.18.

(*S*)-2-(Benzyl(2-(triethylsiloxy)ethyl)amino)-3-(*tert*-butyldiphenylsiloxy)propan-1-ol A mixture of alcohol **4**[37,38] (54 mg, 0.13 mmol), the above bromide (0.09 ml, 0.4 mmol), and $NaHCO_3$ (22 mg, 0.26 mmol) in DMF (0.4 ml) was stirred for 21 h at 100 °C. After addition of satd NH_4Cl (2 ml), the mixture was extracted with AcOEt (10 ml+5 ml×2). The combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=19/1) gave the titled compound (47 mg, 61%) as pale yellow oil: *Rf* 0.5 (hexane/AcOEt=19/1, developed three times). $[\alpha]_D^{25}$ −30.5 (*c*=1.33, $CHCl_3$). ^{1}H-NMR: 0.55 (6H, q, *J*=7.8), 0.92 (9H, t, *J*=7.8), 1.05 (9H, s), 2.65 (1H, dt, *J*=14.0, 4.3), 2.91 (1H, ddd, *J*=6.1, 8.0, 14.0), 3.08 (1H, m), 3.43—3.51 (3H, m), 3.57 (1H, dd, *J*=4.9, 11.0), 3.63 (1H, dd, *J*=6.1, 10.7), 3.75 (1H, d, *J*=14.0), 3.78 (1H, dd, *J*=5.8, 10.7), 3.88 (1H, d, *J*=14.0), 7.23 (1H, m), 7.28—7.29 (4H, m), 7.35—7.46 (6H, m) 7.65—7.66 (4H, m). ^{13}C-NMR: 4.2 (CH_2), 6.6 (CH_3), 19.0 (C), 26.8 (CH_3), 51.8 (CH_2), 56.0 (CH_2), 60.0 (CH_2), 61.41 (CH_2), 61.48 (CH_2), 62.6 (CH), 127.0 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 129.81 (CH), 129.84 (CH), 133.26 (C), 133.30 (C), 135.55 (CH), 135.59 (CH), 140.3 (C). IR (neat): 3448. FAB-MS *m*/*z*: 578 ($M+H^+$). High resolution (HR)-MS-FAB (*m*/*z*): $[M+H]^+$ Calcd for $C_{34}H_{52}NO_3Si_2$, 578.3486. Found: 578.3492.

Ethyl (*S*,*E*)-4-(Benzyl(2-(triethylsiloxy)ethyl)amino)-5-(*tert*-butyldiphenylsiloxy)pent-2-enoate (5) Oxalyl chloride (0.13 ml, 1.5 mmol) was added to a solution of dimethyl sulfoxide (DMSO) (0.18 ml, 2.6 mmol) in CH_2Cl_2 (7.0 ml) at −78 °C. After 5 min, a solution of the above alcohol (567 mg, 0.98 mmol) in CH_2Cl_2 (1.2 ml) was added over 5 min, and the mixture was stirred for another 20 min. Then, Et_3N (0.68 ml, 4.9 mmol) was added, and the mixture was warmed to −15 °C over 15 min. A solution of

$Ph_3P{=}CHCO_2Et$ (975 mg, 2.8 mmol) in CH_2Cl_2 (5.8 ml) was added to the mixture, which was then allowed to warm up to room temperature over 1 h. The mixture was poured into brine (10 ml). The two layers were separated and the aqueous layer was extracted with AcOEt (20 ml×3). The combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/Et_2O=19/1) gave alkenoate **5** (443 mg, 70%) as pale yellow oil: *Rf* 0.3 (hexane/Et_2O=19/1, developed three times). $[\alpha]_D^{25}$ +19.0 (c=1.00, $CHCl_3$). ^{1}H-NMR: 0.51 (6H, q, J=7.9), 0.89 (9H, t, J=7.9), 1.03 (9H, s), 1.30 (3H, t, J=7.4), 2.65—2.77 (2H, m), 3.47—3.55 (3H, m), 3.69 (1H, d, J=14.4), 3.75 (1H, dd, J=6.4, 10.2), 3.80 (1H, d, J=14.4), 3.86 (1H, dd, J=6.4, 10.2), 4.21 (2H, q, J=7.4), 6.02 (1H, dd, J=1.5, 15.9), 6.97 (1H, dd, J=6.7, 15.9), 7.20—7.44 (11H, m), 7.61—7.63 (4H, m). ^{13}C-NMR: 4.2 (CH_2), 6.6 (CH_3), 14.2 (CH_3), 19.1 (C), 26.7 (CH_3), 52.9 (CH_2), 56.5 (CH_2), 60.2 (CH_2), 62.3 (CH_2), 62.9 (CH), 64.0 (CH_2), 123.7 (CH), 126.9 (CH), 127.7 (CH), 128.2 (CH), 128.4 (CH), 129.7 (CH), 133.3 (C), 135.6 (CH), 140.2 (C), 146.2 (CH), 166.4 (C). IR (neat): 1720, 1651. FAB-MS *m/z*: 646 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{38}H_{56}NO_4Si_2$, 646.3748. Found: 646.3742.

Ethyl (*S*,*E*)-4-(Benzyl(2-hydroxyethyl)amino)-5-(*tert*-butyldiphenylsiloxy)pent-2-enoate A solution of **5** (50 mg, 0.080 mmol) in AcOH/tetrahydrofuran (THF)/H_2O (1/1/3, 0.4 ml) was stirred for 16 h at room temperature. After satd $NaHCO_3$ (5 ml) was added, the mixture was extracted with $CHCl_3$ (5 ml×3). The combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=5/1) gave the titled alcohol (42 mg, 99%) as colorless oil: *Rf* 0.6 (hexane/AcOEt=5/1, developed three times). $[\alpha]_D^{25}$ +61.3 (c=1.64, $CHCl_3$). ^{1}H-NMR: 1.04 (9H, s), 1.29 (3H, t, J=7.2), 2.65 (1H, dt, J=13.5, 3.4), 2.94 (1H, ddd, J=4.3, 9.2, 13.5), 3.42 (1H, m), 3.51 (1H, m), 3.55—3.62 (3H, m), 3.81—3.85 (2H, m), 4.19 (2H, q, J=7.2), 5.77 (1H, d, J=15.9), 6.80 (1H, dd, J=7.9, 15.9), 7.27—7.43 (11H, m), 7.52—7.53 (2H, m), 7.59—7.61 (2H, m). ^{13}C-NMR: 14.1 (CH_3), 19.0 (C), 26.7 (CH_3), 51.2 (CH_2), 55.7 (CH_2), 59.2 (CH_2), 60.5 (CH_2), 61.6 (CH), 63.5 (CH_2), 124.8 (CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 128.6 (CH), 128.9 (CH), 129.8 (CH), 129.9 (CH), 132.9 (C), 133.0 (C), 135.59 (CH), 135.65 (CH), 139.1 (C), 143.5 (CH), 165.9 (C). IR (neat): 3456, 1720, 1651. FAB-MS *m/z*: 532 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{32}H_{42}NO_4Si$, 532.2883. Found: 532.2879.

Ethyl (*S*,*E*)-4-(Benzyl(2-oxoethyl)amino)-5-(*tert*-butyldiphenylsiloxy)-pent-2-enoate (6) Oxalyl chloride (0.03 ml, 0.3 mmol) was added to a solution of DMSO (0.04 ml, 0.6 mmol) in CH_2Cl_2 (1.1 ml) at −78 °C. After 5 min, a solution of the above alcohol (110 mg, 0.21 mmol) in CH_2Cl_2 (1.2 ml) was added over 2 min, and the mixture was stirring for another 20 min at −78 °C. Then, Et_3N (0.15 ml, 1.1 mmol) was added, and the mixture was warmed to room temperature over 20 min. The reaction was quenched by addition of water (5 ml) and the solution was extracted with $CHCl_3$ (10 ml×3). The combined organic layers were washed with brine (5 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=19/1) gave aldehyde **6** (91 mg, 86%) as pale yellow oil: *Rf* 0.2 (hexane/AcOEt=19/1, developed three times). $[\alpha]_D^{25}$ +10.7 (c=1.43, $CHCl_3$). ^{1}H-NMR: 1.05 (9H, s), 1.30 (3H, t, J=7.0), 3.29 (1H, dd, J=1.9, 17.7), 3.45 (1H, dd, J=1.9, 17.7), 3.51 (1H, m), 3.73 (1H, d, J=13.6), 3.79—3.87 (3H, m), 4.21 (2H, q, J=7.0), 6.00 (1H, dd, J=1.2, 15.9), 6.92 (1H, dd, J=6.7, 15.9), 7.28—7.47 (11H, m), 7.62—7.65 (4H, m), 9.50 (1H, dd, J=1.9, 1.9). ^{13}C-NMR: 14.1 (CH_3), 19.1 (C), 26.8 (CH_3), 57.0 (CH_2), 60.5 (CH_2), 60.9 (CH_2), 63.2 (CH), 64.2 (CH_2), 124.3 (CH), 127.7 (CH), 127.9 (CH), 128.6 (CH), 128.9 (CH), 129.9 (CH), 132.9 (C), 133.0 (C), 135.6 (CH), 135.7 (CH), 138.4 (C), 144.8 (CH), 166.1 (C), 202.6 (CH). IR (neat): 1720, 1651. FAB-MS *m/z*: 530 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{32}H_{40}NO_4Si$, 530.2727. Found: 530.2721.

Methyl (*S*)-2-Oxo-3-(2-(triethylsiloxy)ethyl)oxazolidine-4-acrylate (8) To a solution of **7**[38,39] (9.8 g, 57 mmol) in THF (110 ml) was added a mixture of 18-crown-6 (1.5 g, 5.7 mmol) and a 1.0 M solution of *t*-BuOK in THF (68 ml, 68 mmol) at 0 °C. After 30 min, (2-bromoethoxy)triethylsilane (16 ml, 69 mmol) was added to the mixture, which was then warmed up to room temperature. After 17 h, the reaction was quenched by addition of satd. NH_4Cl (200 ml). The mixture was extracted with AcOEt (100 ml×5). The combined organic layers were washed with brine (50 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=2/1) gave **8** (16.6 g, 87%) as pale brown oil: *Rf* 0.2 (hexane/AcOEt=1/1). $[\alpha]_D^{25}$ −3.7 (c=1.08, $CHCl_3$). ^{1}H-NMR: 0.60 (6H, q, J=8.0), 0.95 (9H, t, J=8.0), 1.92 (1H, m), 2.11 (1H, m), 2.31, (2H, m), 3.17 (1H, m), 3.55 (1H, m), 3.70 (3H, s), 3.78 (2H, m), 3.96 (1H, dd, J=6.2, 8.5), 4.06 (1H, m), 4.36 (1H, dd, J=8.5, 8.5). ^{13}C-NMR: 3.8 (CH_2), 6.3 (CH_3), 26.4 (CH_2), 28.2 (CH_2), 44.0 (CH_2), 51.5 (CH_3), 55.1 (CH), 60.9 (CH_2), 66.5 (CH_2), 157.8 (C), 172.5 (C). IR (neat): 1747. FAB-MS *m/z*: 332 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{30}NO_5Si$, 332.1893. Found: 332.1878.

Methyl (*S*,*E*)-2-Oxo-3-(2-(triethylsiloxy)ethyl)oxazolidine-4-acrylate (9) To a solution of **8** (13.6 g, 41 mmol) in THF (260 ml) was added freshly distilled TMSCl (10 ml, 82 mmol) and a 1.0 M solution of NaHMDS in THF (82 ml, 82 mmol) at −78 °C. The mixture was stirred for 1 h at 0 °C and transferred *via* cannula into a suspension of $Pd(OAc)_2$ (11 g, 49 mmol) in CH_3CN (180 ml) at room temperature. After 3 h, the reaction was quenched by addition of satd. NH_4Cl (100 ml). The resulting salts were removed by filtration through a celite pad. The filtrate was extracted with AcOEt (200 ml×3). The combined organic layers were washed with brine (100 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=3/1) gave **9** (9.3 g, 69%) as pale yellow oil: *Rf* 0.5 (hexane/AcOEt=3/1). $[\alpha]_D^{25}$ +5.1 (c=1.88, $CHCl_3$). ^{1}H-NMR: 0.60 (6H, q, J=8.1), 0.95 (9H, t, J=8.1), 3.09 (1H, ddd, J=4.0, 8.5, 14.5), 3.52 (1H, ddd, J=3.5, 4.5, 14.5), 3.72 (1H, ddd, J=4.0, 4.5, 10.5), 3.78 (3H, s), 3.81 (1H, ddd, J=3.5, 8.5, 10.5), 4.01 (1H, dd, J=6.5, 8.5), 4.45 (1H, t, J=8.5), 4.65 (1H, dt, J=6.5, 8.5), 6.04 (1H, d, J=15.5), 6.76 (1H, dd, J=8.5, 15.5). ^{13}C-NMR: 4.2 (CH_2), 6.7 (CH_3), 44.5 (CH_2), 51.9 (CH_3), 58.1 (CH), 61.2 (CH_2), 66.4 (CH_2), 125.7 (CH), 143.1 (CH), 157.6 (C), 165.5 (C). IR (neat): 1759, 1658. FAB-MS *m/z*: 330 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{15}H_{28}NO_5Si$, 330.1737. Found: 330.1754.

Methyl (*S*,*E*)-3-(2-Hydroxyethyl)-2-oxooxazolidine-4-acrylate A solution of **9** (23.9 g, 71 mmol) in AcOH/THF/H_2O (2/5/15, 390 ml) was stirred for 6 h at room temperature. After addition of satd $NaHCO_3$ (250 ml), the mixture was saturated with NaCl and extracted with $CHCl_3$ (200 ml×18). The combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=3/1, then AcOEt) gave the titled alcohol (14.1 g, 92%) as colorless solids of mp 70—72 °C: *Rf* 0.5 (AcOEt). $[\alpha]_D^{25}$ +6.1 (c=1.0, $CHCl_3$). ^{1}H-NMR: 3.19 (1H, ddd, J=4.0, 7.1, 15.0), 3.53 (1H, ddd, J=3.7, 5.8, 15.0), 3.76—3.85 (2H, m), 3.78 (3H, s), 4.06 (1H, dd, J=6.6, 8.7), 4.51 (1H, dd, J=8.5, 8.7), 4.58 (1H, dt, J=6.6, 8.5), 6.09 (1H, d, J=15.8), 6.78 (1H, dd, J=8.5, 15.8). ^{13}C-NMR: 45.1 (CH_2), 52.1 (CH_3), 58.1 (CH), 61.0 (CH_2), 66.7 (CH_2), 126.3 (CH), 142.9 (CH), 158.7 (C), 165.6 (C). IR (KBr): 3417, 1728, 1659. FAB-MS *m/z*: 216 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_9H_{14}NO_5$, 216.0872. Found: 216.0858.

Methyl (*S*,*E*)-2-Oxo-3-(2-oxoethyl)oxazolidine-4-acrylate (1) To a solution of the above alcohol (5.4 g, 25 mmol) in CH_2Cl_2 (180 ml) was added Dess–Martin periodinane (12.7 g, 30 mmol). After 1 h, *i*-PrOH (11 ml) was added, and the resulting suspension was stirred for 1 h at room temperature. The solid material was filtered off through a celite pad. Concentration of the filtrate and column chromatography (hexane/AcOEt=1/2) twice gave aldehyde **1** (4.4 g, 75%) as colorless oil: *Rf* 0.35 (hexane/AcOEt=1/4, developed three times). $[\alpha]_D^{25}$ +38.9 (c=2.05, $CHCl_3$). ^{1}H-NMR: 3.78 (3H, s), 3.85 (1H, d, J=19.3), 4.11 (1H, m), 4.35 (1H, d, J=19.3), 4.56—4.62 (2H, m), 6.04 (1H, d, J=15.6), 6.73 (1H, m), 9.59 (1H, s). ^{13}C-NMR: 51.8 (CH_3), 52.0 (CH_2), 57.3 (CH), 66.8 (CH_2), 126.6 (CH), 141.7 (CH), 157.9 (C), 165.2 (C), 195.5 (CH). IR (neat): 1728, 1658. FAB-MS *m/z*: 214 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_9H_{12}NO_5$, 214.0715. Found: 214.0714.

Methyl (7*R*,7a*S*)-3,6-Dioxohexahydropyrrolo[1,2-*c*]oxazole-7-acetate (*trans*-2) and Methyl (*S*,*E*)-3-Methyl-2-oxooxazolidine-4-acrylate (10) (Table 1, Entry 4) A solution of aldehyde **1** (3.5 g, 17 mmol), AIBN (2.7 g, 17 mmol), and *tert*-dodecanethiol (38 ml, 170 mmol) in toluene (1.1 l) was heated at 70 °C for 86 h. During that period, additional portions of AIBN (2.7 g, 17 mmol each) were added after 12, 36, and 60 h. Concentration of the reaction mixture and column chromatography (hexane/AcOEt=1/1) of the resulting crude material gave a 10 : 1 mixture of *trans*-**2** and **10** (1.56 g, 38% and 4%, respectively) as yellow oil and **10** (84 mg, 3%) as yellow oil. The ratio of *trans*-**2** and **10** was determined based on the integration area of ^{1}H-NMR signals at 3.58 (the α-CH_2 of the ketone moiety of *trans*-**2** in $CDCl_3$) and 2.87 ppm (NCH_3 of **10**). The mixture of *trans*-**2** and **10** was further purified by another column chromatography (hexane/AcOEt=1/1) to give *trans*-**2**, which was characterized as below.

trans-**2**: *Rf* 0.37 (hexane/AcOEt=1/1, developed three times). $[\alpha]_D^{25}$ −106.3 (c=2.1, $CHCl_3$). ^{1}H-NMR (CD_2Cl_2): 2.57 (1H, dd, J=8.0, 17.0), 2.64 (1H, ddd, J=3.0, 8.0, 9.0), 2.87 (1H, dd, J=3.0, 17.0), 3.56 (1H, d, J=18.5), 3.68 (3H, s), 4.11 (1H, d, J=18.5), 4.16 (1H, ddd, J=3.5, 7.5, 9.0), 4.52 (1H, dd, J=3.5, 9.5), 4.71 (1H, dd, J=7.5, 9.5). ^{13}C-NMR: 31.2 (CH_2), 48.9 (CH), 52.2 (CH_3), 52.4 (CH_2), 61.0 (CH), 68.1 (CH_2), 160.2 (C), 171.5 (C), 210.5 (C). IR (neat): 1761, 1734. FAB-MS *m/z*: 214 ($M+H^+$). HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_9H_{12}NO_5$, 214.0715. Found: 214.0710. The relative configuration was determined to be as drown by NOESY cross peaks observed between the angular NCH (4.16 ppm) and one of the α-CH_2

of the ester moiety (2.57 ppm).

10: *Rf* 0.33 (hexane/AcOEt=1/1, developed three times). $[\alpha]_D^{25}$ −8.3 (c=0.4, $CHCl_3$). ^{1}H-NMR: 2.82 (3H, s), 3.79 (3H, s), 4.01 (1H, dd, J=6.7, 8.9), 4.25—4.30 (1H, m), 4.48 (1H, dd, J=8.9, 8.9), 6.09 (1H, d, J=15.6), 6.77 (1H, dd, J=8.6, 15.6). ^{13}C-NMR: 29.6 (CH_3), 52.1 (CH_3), 58.9 (CH), 66.2 (CH_2), 126.0 (CH), 142.4 (CH), 158.2 (C), 165.5 (C). IR (neat): 1759, 1720, 1666. FAB-MS m/z: 186 ($M+H^+$). HR-MS-FAB (m/z): $[M+H]^+$ Calcd for $C_8H_{12}NO_4$, 186.0766. Found: 186.0764.

Methyl (6*S*,7*R*,7a*S*)-6-Hydroxy-3-oxohexahydropyrrolo[1,2-*c*]oxazole-7-acetate (11), (3a*R*,3b*S*,8a*R*)-Hexahydro-2*H*-furo[3′,2′:3,4]pyrrolo[1,2-*c*][1,3]oxazole-2,6-dione (12), and Methyl (*S*)-3-Methyl-2-oxooxazolidine-4-propionate To an ice-cooled and stirred suspension of $LiAlH(Ot\text{-}Bu)_3$ (890 mg, 3.5 mmol) in THF (8 ml), a solution of the 10 : 1 mixture of *trans*-**2** and **10** (543 mg, 2.35 and 0.23 mmol, respectively) in THF (2 ml) was added. After 30 min, the reaction mixture was poured into water (20 ml). After addition of 10% HCl (10 ml), the aqueous layer was saturated with NaCl, and the mixture was extracted with $CHCl_3$ (30 ml×26). The combined organic layers were dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=1/3) gave a 33 : 1 mixture of **11** and **12** (168 mg, 33% and 1%, respectively) as yellow oil with $[\alpha]_D^{25}$ −5.02 (c=1.00, $CHCl_3$) and the titled propionate (19 mg, 43%) as yellow oil. The ratio of **11** and **12** was determined based on the integration area of ^{1}H-NMR signals at 3.40—3.46 ppm (the overlapping α-CH_2 of the ester moieties of **11** and **12**) and 5.11 ppm (the OCH of **12**).

11: *Rf* 0.3 (hexane/AcOEt=1/3, developed three times). ^{1}H-NMR: 2.25 (1H, m), 2.43 (1H, dd, J=8.3, 16.8), 2.63 (1H, dd, J=6.8, 16.8), 2.76 (1H, br s), δ: 3.42 (1H, dd, J=6.1, 12.3), 3.65 (1H, dd, J=3.9, 12.3), 3.68—3.75 (4H, m), 4.24 (1H, m), 4.34 (1H, dd, J=4.2, 8.9), 4.56 (1H, dd=8.9, 8.9). ^{13}C-NMR: 34.9 (CH_2), 49.0 (CH), 52.1 (CH_3), 53.4 (CH_2), 63.1 (CH), 68.5 (CH_2), 77.9 (CH), 161.8 (C), 172.6 (C). IR (neat): 3425, 1736. FAB-MS m/z: 216 ($M+H^+$). HR-MS-FAB (m/z): $[M+H]^+$ Calcd for $C_9H_{14}NO_5$, 216.0872. Found: 216.0894.

12: ^{1}H-NMR: 2.50 (1H, dd, J=17.8), 2.71 (1H, m), 2.84 (1H, dd, J=8.3, 17.8), 3.45 (1H, dd, J=2.2, 13.9), 3.75 (1H, m), 4.26—4.31 (2H, m), 4.61 (1H, dd, J=7.6, 9.3), 5.11 (1H, ddd, J=2.4, 6.8, 6.8). ^{13}C-NMR: 31.6 (CH_2), 44.4 (CH), 52.5 (CH_2), 63.5 (CH), 66.3 (CH_2), 83.8 (CH), 160.3 (C), 174.1 (C). IR (KBr): 1743. FAB-MS m/z: 184 ($M+H^+$). HR-MS-FAB (m/z): $[M+H]^+$ Calcd for $C_8H_{10}NO_4$, 184.0610. Found: 184.0619.

The propionate: *Rf* 0.5 (hexane/AcOEt=1/3, developed three times). $[\alpha]_D^{25}$ +23.7 (c=0.36, $CHCl_3$). ^{1}H-NMR: 1.88 (1H, m), 2.10 (1H, dddd, J=3.4, 7.0, 8.8, 12.5), 2.32—2.36 (2H, m), 2.86 (3H, s), 3.78—3.69 (4H, m), 3.94 (1H, dd, J=6.7, 8.9), 4.38 (1H, J=8.9, 8.9). ^{13}C-NMR: 26.7 (CH_2), 28.3 (CH_2), 29.1 (CH_3), 52.0 (CH_3), 56.3 (CH), 66.5 (CH_2), 166.9 (C), 172.8 (C). IR (neat): 1744. FAB-MS m/z: 200 ($M+H^+$). HR-MS-FAB (m/z): $[M+H]^+$ Calcd for $C_8H_{14}O_4N$, 188.0923. Found: 188.0928.

Methyl (6*S*,7*R*,7a*S*)-3-Oxo-6-(tosyloxy)hexahydropyrrolo[1,2-*c*]oxazole-7-acetate (13) To a solution of a 13 : 1 mixture of **11** and **12** (135 mg, 0.59 and 0.047 mmol, respectively) in CH_3CN (1.3 ml), was added $Me_3N\cdot$HCl (60 mg, 0.63 mmol), Et_3N (0.22 ml, 1.6 mmol), and TsCl (181 mg, 0.95 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. After addition of water (5 ml), the mixture was extracted with $CHCl_3$ (10 ml×3), and the combined organic layers were dried over Na_2SO_4. Concentration and column chromatography ($CHCl_3$/AcOEt=9/1) gave tosylate **13** (201 mg, 92%) as colorless columns of mp 143—144 °C and recovered **12** (5 mg, 58% recovery) as white solids.

13: *Rf* 0.3 ($CHCl_3$/AcOEt=9/1). $[\alpha]_D^{25}$ −39.0 (c=1.00, $CHCl_3$). ^{1}H-NMR: 2.40—2.55 (5H, m), 2.46 (1H, dd, J=8.6, 16.6), 3.30 (1H, dd, J=6.1, 13.2), 3.64—3.78 (5H, m), 4.36 (1H, dd, J=4.2, 9.5), 4.54 (1H, dd, J=8.3, 9.5), 4.91 (1H, m), 7.37 (2H, d, J=8.3), 7.78 (2H, d, J=8.3). ^{13}C-NMR: 21.7 (CH_3), 33.8 (CH_2), 47.5 (CH), 50.7 (CH_2), 52.1 (CH_3), 62.3 (CH), 68.2 (CH_2), 84.4 (CH), 127.8 (CH), 130.1 (CH), 132.9 (C), 145.6 (C), 160.4 (C), 171.4 (C). IR (KBr): 1751, 1728, 1365, 1173. EI-MS m/z: 369 (M^+). *Anal.* Calcd for $C_{16}H_{19}NO_7S$: C, 52.02; H, 5.18; N, 3.79. Found: C, 51.74; H, 5.12; N, 3.78.

(5a*S*,6*R*,6a*R*,6b*S*)-6-(2,4-Dimethylpent-4-enoyl)hexahydrocyclopropa[*c*]pyrrolo[1,2-*c*]oxazol-3-one (14) To a solution of 2-bromopropene (0.18 ml, 2.0 mmol) in THF (10 ml) at −78 °C, was added 1.76 M *t*-BuLi in pentane (2.3 ml, 4.0 mmol) dropwise. After 1 h, the mixture was transferred rapidly by cannula (1.0 ml THF wash) into a stirred suspension of CuCN (89 mg, 1.0 mmol, dried by a heat-gun *in vacuo*) in THF (1.0 ml) at −78 °C. After 5 min, the cooling bath was removed. After complete dissolution of the CuCN was observed, the reaction mixture was re-cooled to −78 °C, and a solution of tosylate **13** (74 mg, 1.0 mmol) in THF (2.0 ml) cooled to −78 °C was rapidly added by cannula (0.5 ml THF wash). After 5 min, the cooling bath was removed. After 0.5 h, the reaction was quenched by the addition of 1 N HCl (10 ml), and the mixture was diluted with water (20 ml) and extracted with AcOEt (30 ml×3). The combined organic layers were washed with brine (15 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=2/1) gave **14** (16 mg, 32%, a single diastereomer) as colorless oil: *Rf* 0.6 (hexane/AcOEt=1/1, developed three times). $[\alpha]_D^{25}$ +28.3 (c=0.55, $CHCl_3$). ^{1}H-NMR: 1.12 (3H, dd, J=2.5, 8.5), 1.73 (3H, s), 1.99 (1H, dd, J=4.0, 4.0), 2.04 (1H, dd, J=10.0, 18.0), 2.21 (1H, m), 2.38—2.45 (2H, m), 2.89 (1H, ddq, J=9.0, 10.0, 8.5), 3.11 (1H, dd, J=2.5, 15.5), 4.02 (1H, m), 4.09 (1H, dd, J=7.5, 15.5), 4.24 (1H, dd, J=8.0, 11.5), 4.56 (1H, dd, J=11.0, 11.5), 4.69 (1H, d, J=1.5), 4.80 (1H, d, J=1.5). ^{13}C-NMR: 15.8 (CH_3), 22.3 (CH_3), 33.7 (CH), 35.9 (CH), 38.6 (CH), 40.8 (CH_2), 45.2 (CH), 51.5 (CH_2), 62.6 (CH), 68.0 (CH_2), 112.5 (CH_2), 142.6 (C), 161.7 (C), 209.6 (C). IR (neat): 1743, 1690, 1643. FAB-MS m/z: 250 ($M+H^+$). HR-MS-FAB (m/z): $[M+H]^+$ Calcd for $C_{14}H_{20}NO_3$, 250.1443. Found: 250.1445. The relative configuration of the tricyclic core was determined based on coupling constants of ^{1}H-NMR (see the text). The stereochemistry of the side chain was not determined.

Methyl (5a*S*,6*R*,6a*R*,6b*S*)-3-Oxohexahydrocyclopropa[*c*]pyrrolo[1,2-*c*]oxazole-6-carboxylate (15). Method A To a solution of 2-bromopropene (0.14 ml, 1.6 mmol) in THF (8 ml) at −78 °C, was added 1.76 M *t*-BuLi in pentane (1.8 ml, 3.2 mmol) dropwise. After 1 h, the mixture was transferred rapidly by cannula (1.0 ml THF wash) into a stirred suspension of CuCN (88 mg, 0.96 mmol, dried by a heat-gun *in vacuo*) in THF (1.0 ml) at −78 °C. After 5 min, the cooling bath was removed. After complete dissolution of the CuCN was observed, the reaction mixture was re-cooled to −78 °C and rapidly added by cannula to a solution of tosylate **13** (74 mg, 0.2 mmol) in THF (3.0 ml) cooled at −78 °C. After 5 min, the reaction was stirred for 15 h at −60 °C and then for further 24 h at −50 °C. The reaction was quenched by the addition of 1 N HCl (10 ml). The reaction mixture was diluted with water (20 ml) and extracted with AcOEt (20 ml×3). The combined organic layers were washed with brine (10 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=2/1) gave cyclopropanecarboxylate **15** (16 mg, 32%) as white solids of mp 131—133 °C and recovered tosylate **13** (22 mg, 37%). The relative configuration was determined based on coupling constants of ^{1}H-NMR (see the text).

15: *Rf* 0.4 (hexane/AcOEt=1/1, developed three times). $[\alpha]_D^{25}$ +5.6 (c=0.016, $CHCl_3$). ^{1}H-NMR: 1.69 (1H, dd, J=4.0, 4.0), 2.25 (1H, ddd, J=1.5, 4.0, 11.5), 2.49 (1H, m), 3.09 (1H, dd, J=2.5, 15.5), 3.69 (3H, s), 3.99 (1H, m), 4.10 (1H, dd, J=8.0, 15.5), 4.26 (1H, dd, J=7.5, 11.5), 4.56 (1H, dd, J=10.5, 11.5). ^{13}C-NMR: 31.4 (CH), 32.3 (CH), 34.1 (CH), 51.3 (CH_2), 52.1 (CH_3), 62.4 (CH_2), 67.8 (CH), 161.7 (C), 171.1 (C). IR (KBr): 1751, 1728. FAB-MS m/z: 198 ($M+H^+$). HR-MS-FAB (m/z): $[M+H]^+$ Calcd for $C_9H_{12}NO_4$, 198.0766. Found: 198.0767.

Method B To a solution of 2-bromopropene (0.17 ml, 1.9 mmol) in THF (9 ml) at 0 °C, was added 1.76 M *t*-BuLi in pentane (2.2 ml, 3.9 mmol) dropwise. After 1 h, the mixture was transferred rapidly by cannula into a stirred suspension of CuI (217 mg, 1.14 mmol, dried by a heat-gun *in vacuo*) in THF (1.0 ml) at 0 °C. After 30 min, the mixture was cooled to −78 °C and then rapidly added by cannula to a solution of tosylate **13** (71 mg, 0.19 mmol) in THF (4.0 ml) cooled at −78 °C. After 30 min, the cooling bath was removed, and the mixture was stirred for further 30 min. The reaction was quenched by the addition of 1 N HCl. The aqueous layer was extracted with AcOEt (30 ml×3). The combined organic layers were washed with brine (20 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=1/1) gave **15** (6 mg, 16%) as white solids.

Methyl (6*R*,7*R*,7a*S*)-6-Bromo-3-oxohexahydropyrrolo[1,2-*c*]oxazole-7-acetate (16) and Methyl (6*S*,7*R*,7a*S*)-6-Bromo-3-oxohexahydropyrrolo-[1,2-*c*]oxazole-7-acetate (*trans*-16) Tosylate **13** (128 mg, 0.35 mmol) was dissolved in dry THF (3.5 ml), and LiBr (304 mg, 3.5 mmol) was added to the solution. The mixture was heated under reflux for 2.5 h. After addition of water (5 ml), the mixture was extracted with AcOEt (10×3 ml). The combined organic layers were washed with brine (5 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=2/1) gave bromide **16** (54 mg, 55%) as colorless solids of mp 77—78 °C and *trans*-**16** (26 mg, 27%) as yellow solids of mp 65—67 °C.

16: *Rf* 0.50 (hexane/AcOEt=1/1, developed three times). $[\alpha]_D^{25}$ +48.5 (c=1.00, $CHCl_3$). ^{1}H-NMR: 2.19 (1H, m), 2.56 (1H, dd, J=6.3, 16.9), 2.74 (1H, dd, J=7.8, 16.9), 3.72 (3H, s), 3.81 (1H, dd, J=1.5, 13.5), 3.98 (1H, ddd, J=3.5, 8.0, 10.0), 4.32 (1H, dd, J=3.5, 9.5), 4.36 (1H, dd, J=6.1, 13.5), 4.56 (1H, dd, J=8.0, 9.5), 4.86 (1H, m). ^{13}C-NMR: 33.6 (CH_2), 44.8 (CH), 52.1 (CH_3), 54.9 (CH), 57.0 (CH_2), 61.5 (CH), 66.1 (CH_2), 161.8 (C), 171.4 (C). IR (KBr): 1744. FAB-MS m/z: 280 ($M+2+H^+$), 278 ($M+H^+$). HR-MS-FAB (m/z): $[M+H]^+$ Calcd for $C_9H_{13}BrNO_4$, 278.0028. Found:

278.0031. The relative configuration was determined by stronger nOe (3%, see below) observed between the BrCH and β-CH of the bromine atom at 4.86 and 2.19 ppm, respectively, and the absence of that between the BrCH and the α-CH_2 of the ester moiety.

trans-**16**: *Rf* 0.46 (hexane/AcOEt=1/1, developed three times). $[\alpha]_D^{25}$ −28.8 (c=1.00, $CHCl_3$). ^{1}H-NMR: 2.37 (1H, dd, J=9.9, 16.6), 2.53 (1H, dddd, J=4.0, 8.3, 8.3, 9.9), 2.85 (1H, dd, J=4.0, 16.6), 3.72 (3H, s), 3.78 (1H, dd, J=7.8, 12.6), 3.81 (1H, ddd, J=4.9, 8.3, 8.3), 3.90 (1H, dd, J=6.3, 12.6), 4.07 (1H, m), 4.46 (1H, dd, J=4.9, 9.5), 4.58 (1H, dd, J=8.3, 9.5). ^{13}C-NMR: 34.3 (CH_2), 48.5 (CH), 50.4 (CH), 52.1 (CH_3), 54.0 (CH_2), 62.9 (CH), 68.1 (CH_2), 160.5 (C), 171.3 (C). IR (KBr): 1736. FAB-MS *m/z*: 280 (M+2+H$^+$), 278 (M+H$^+$). HR-MS-FAB (*m/z*): [M+H]$^+$ Calcd for $C_9H_{13}BrNO_4$, 278.0028. Found: 278.0031. The relative configuration was determined by weaker nOe (1%, see above) observed between the BrCH and β-CH of the bromine atom at 4.07 and 2.53 ppm, respectively, and that observed between the BrCH and the α-CH_2 of the ester moiety at 2.37 ppm (3%).

Methyl (6*R*,7*S*,7a*S*)-3-Oxo-6-(prop-1-en-2-yl)hexahydropyrrolo[1,2-*c*]-oxazole-7-acetate (17), Methyl (6*S*,7*S*,7a*S*)-3-Oxo-6-(prop-1-en-2-yl)-hexahydropyrrolo[1,2-*c*]oxazole-7-acetate, and Methyl (*S*)-3-((*S*)-2-Oxo-oxazolidin-4-yl)pent-4-enoate (18) A mixture of a 0.5 M solution of isopropenylmagnesium bromide in THF (52 ml, 0.52 mmol) and TMEDA (0.04 ml, 0.2 mmol) was added dropwise over 7 min to a solution of bromide **16** (46 mg, 0.17 mmol) and $FeCl_3$ (3 mg, 0.02 mmol) in THF (0.2 ml) at 0 °C. After 30 min, the reaction was quenched by addition of satd NH_4Cl (2 ml). The mixture was extracted with AcOEt (10 ml×3). The combined organic layers were washed with brine (5 ml) and dried over Na_2SO_4. Concentration and column chromatography (hexane/AcOEt=1/1) gave a 71 : 11 : 18 mixture of **17**, *cis*-isomer, and **16** (21 mg, 36%, 6%, and 8%, respectively) as white solids of mp 77—78 °C with $[\alpha]_D^{25}$ +10.1 (c=0.525, $CHCl_3$), and **18** (17 mg, 50%) as colorless oil. ^{1}H- and ^{13}C-NMR, and IR were in good agreement with those reported for **17** and the *cis*-isomer.[19] The ratio of **17**, *cis*-isomer, and **16** was determined based on the integration area of ^{1}H-NMR signals at 4.45—4.58 (the overlapping OCH_2 of the three compounds), 4.24 (the other OCH_2 of the *cis*-isomer), and 3.98 ppm (the NCH of **16**).

17: *Rf* 0.6 (hexane/AcOEt=1/1, developed three times). lit.[19] $[\alpha]_D$ +4.0 (c=1.0, $CHCl_3$). FAB-MS *m/z*: 240 (M+H$^+$). HR-MS-FAB (*m/z*): [M+H]$^+$ Calcd for $C_{12}H_{18}NO_4$, 240.1236. Found: 240.1241.

18: *Rf* 0.1 (hexane/AcOEt=1/1, developed three times). $[\alpha]_D^{25}$ −8.6 (c=0.40, $CHCl_3$). ^{1}H-NMR: 2.39 (1H, dd, J=7.8, 15.5), 2.44 (1H, dd, J=6.3, 15.5), 2.69 (1H, m), 3.69 (3H, s), 3.93 (1H, m), 4.16 (1H, dd, J=6.0, 8.9), 4.47 (1H, dd, J=8.9, 8.9), 5.13 (1H, br s), 5.25 (1H, d, J=17.2), 5.28 (1H, d, J=10.2), 5.67 (1H, ddd, J=8.6, 10.2, 17.2). ^{13}C-NMR: 35.3 (CH_2), 44.3 (CH), 51.9 (CH_3), 54.5 (CH), 67.8 (CH_2), 119.9 (CH_2), 134.4 (CH), 159.4 (C), 171.8 (C). IR (KBr): 1766, 1728, 1643. FAB-MS *m/z*: 200 (M+H$^+$). HR-MS-FAB (*m/z*): [M+H]$^+$ Calcd for $C_9H_{14}NO_4$, 200.0923. Found: 200.0927.

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