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Ireland–Claisen Rearrangement of 6-Methylene-1,4-oxazepan-2-ones

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The Ireland–Claisen rearrangement of 6-methylene-1,4-oxazepan-2-one-derived boron enolates leads to stereochemically defined, synthetically useful 4-(*E*)-ethylidene prolines. Detailed computational and experimental studies explain the stereochemical outcome of this transformation and suggest an unusual double-chelated transition state that involves two boron atoms. The scope of the method is also explored.

Introduction

A broad number of biologically active natural products, such as barmumycin (**1**),[1] limazepine E (**4**),[2] lucentamycin A (**5**),[3] eleganine A (**6**),[4] and many others (Figure 1), contain an (*E*)-4-ethylidene substituted proline fragment.

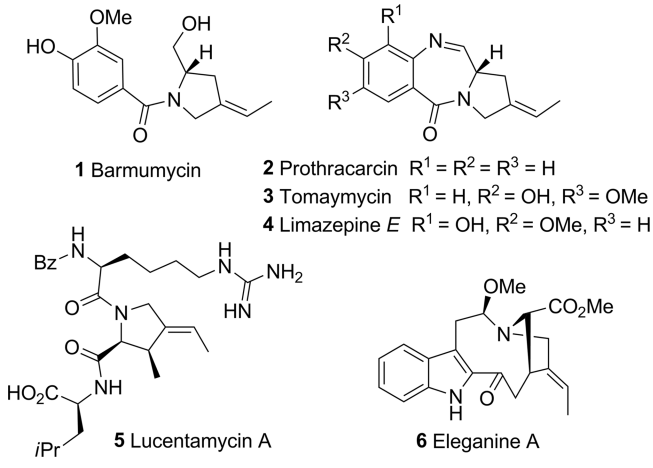

Figure 1. Examples of natural products that contain the 4-ethylidene proline fragment.

These types of natural products have interesting biological activities. For example, barmumycin (**1**) and lucentamycin A were found to be cytotoxic against various human tumor cell lines. Prothracarcin (**2**), tomaymycin (**3**), and limazepine E (**4**) belong to the pyrrolo[1,4]benzodiazepine (PBD) class[5] of natural products, the antitumor antibiotic properties of which are a result of their ability to covalently bind to the minor groove of DNA.[6] The crucial building block for the synthesis of all of these natural products is the proline fragment, which contains a C-4 ethylidene substituent in the (*E*) configuration relative to the nitrogen atom of the pyrrolidine ring. Although the total syntheses of several of these natural products have been reported, the stereoselective introduction of the double bond into these systems is still a considerable challenge. The classical Wittig olefination predominantly gives the undesired (*Z*) configuration of the double bond as shown in the total synthesis of prothracarcin (**2**) and tomaymycin (**3**),[7] and four extra steps were needed to invert its geometry. A Julia–Kocienski olefination reaction was employed in the total synthesis of barmumycin[1] (**1**), but the product was afforded in moderate yield with only slight selectivity (*E*/*Z*, 2:1) towards the desired (*E*) double bond isomer. Finally, the (*E*)-4-ethylidene proline fragment in lucentamycin A (**5**) was obtained by a long linear sequence, and the pyrrolidine ring was formed from an acyclic substrate that contained the ethylidene substituent.[8]

As a result of the preferred chair-like transition state, the Ireland–Claisen[9] rearrangement is known to be a reliable method for the stereoselective introduction of chiral centers and double bonds that have the desired configuration. The original method involved the enolization of an ester substrate by treatment with a strong base followed by trapping with a silyl chloride to give the intermediate silyl ketene acetal, which further underwent a [3,3] sigmatropic rearrangement.[10] Currently, soft enolization protocols are also known for the generation of ketene acetals by using a reactive Lewis acid in combination with a tertiary amine base.[11] Reports of this approach usually focus on Ireland–Claisen rearrangements of silyl ketene acetals, but phosphorus,[12] boron,[13] and several metal (Zn, Mg, and Al)[14] ketene acetals have also been successfully used in this transformation.

The high stereoselectivity and mild conditions of the Ireland–Claisen rearrangement prompted us to examine its

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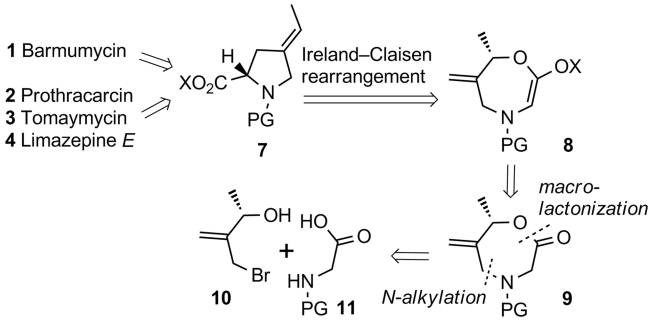
potential to solve the problems related to the introduction of an (*E*)-configured double bond in the synthesis of the 4-ethylidene proline derivatives. Recently, we developed a new approach to control the geometry of the exocyclic double bond by using a boron enolate in the Ireland–Claisen rearrangement, and this strategy was applied to the total syntheses of several natural products.[15] Herein, on the basis of our most recent experimental and computational studies, we report a revised stereochemical model for this transformation, which suggests the involvement of two boron atoms and an unusual double-chelated transition state.

Results and Discussion

The retrosynthetic analysis of some natural products that contain a 4-ethylidene proline fragment is outlined in Scheme 1.[15a] The common building block for the total syntheses of barmumycin (**1**) and PBDs **2**–**4** is 4-ethylidene proline **7**, which is accessible by employing an Ireland–Claisen rearrangement of ketene acetal **8**, which is derived from lactone **9**. The necessary lactone **9** is easily constructed from glycine derivative **11** and allylic bromide **10**.

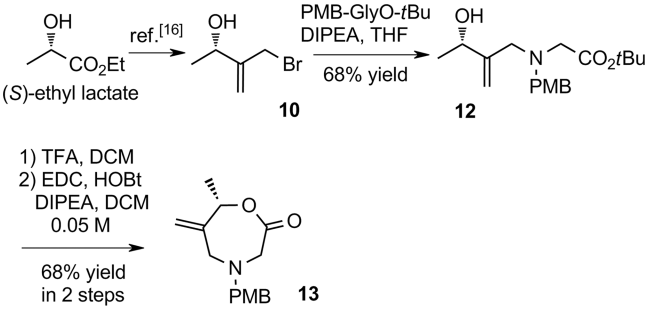


Scheme 1. Retrosynthetic analysis of some natural products (i.e., **1**–**4**) that contain a 4-ethylidene proline fragment (PG = protecting group).

Lactone **13** was prepared by starting from known allyl bromide **10**[16] and PMB-protected (PMB = *para*-methoxybenzyl) glycine *tert*-butyl ester[17] (Scheme 2).[15] The alkylation of this glycine derivative with bromide **10** gave tertiary amine **12**, which was further converted into lactone **13** through a deprotection–macrolactonization sequence.

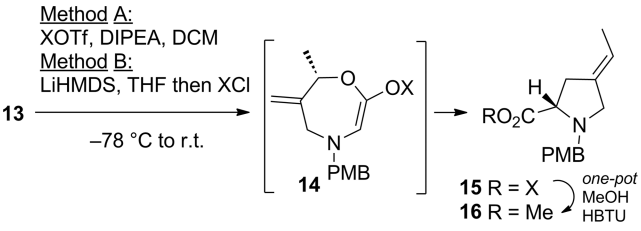
With lactone **13** in hand, we further investigated the Ireland–Claisen rearrangement, the results of which are shown in Table 1.

The use of silyl triflates resulted in either poor *E*/*Z* selectivity and low yields of the rearrangement products[18] or no reaction in the case of using TIPS triflate (Table 1, Entries 1–3). Employing the Kazmaier protocol[19] also failed (Table 1, Entry 5). On the other hand, the use of dibutylboron triflate [$(n\text{Bu})_2$BOTf] resulted in excellent selectivity and a high product yield (Table 1, Entry 4). Remarkably, additional experiments showed that the Ireland–Claisen rearrangement proceeded to full conversion at temperatures as low as 10 °C. To facilitate the product isolation, the resulting carboxylic acid boron or silicon esters were converted in situ into the corresponding methyl ester. Building



Scheme 2. Synthesis of lactone **13** (DIPEA = *N*,*N*-diisopropylethylamine, THF = tetrahydrofuran, TFA = trifluoroacetic acid, DCM = dichloromethane, EDC = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, HOBt = *N*-hydroxybenzotriazole).[15]

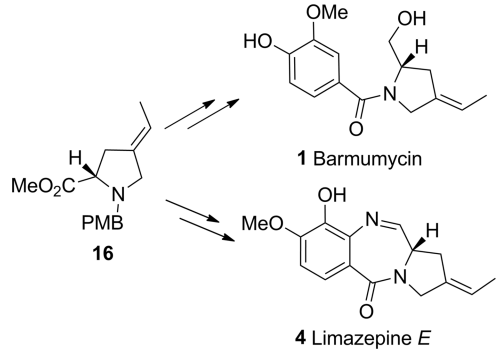
Table 1. Optimization of the Ireland–Claisen rearrangement of lactone **13** (LiHMDS = lithium hexamethyldisilazide).



Entry	X	Method	*E*/*Z*[a]	Isolated yield of **16**
1	TMS[b]	A	1:2	18
2	TBS[b]	A	1:1	15
3	TIPS[b]	A	–	–
4	$(n\text{Bu})_2$B	A	>95:5[c]	85
5	Zn	B	–	–

[a] The *E*/*Z* ratio was determined by using the integration of the signals in the ^{1}H NMR spectrum, and the geometry of the double bond of each isomer was assigned by NOE experiments. [b] TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl. [c] The minor isomer was not observed by NMR analysis.

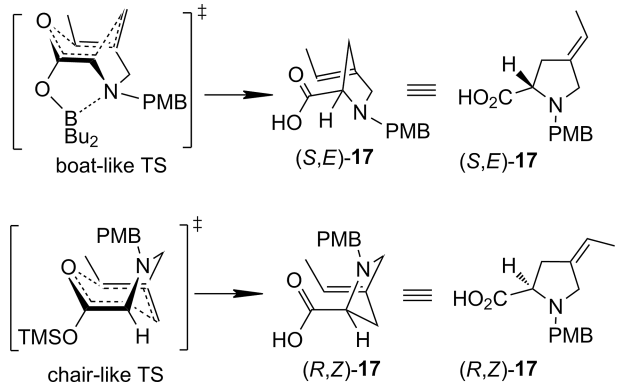
block **16** was then successfully converted into the two natural products – barmumycin (**1**) and limazepine E (**4**; Scheme 3).[15]



Scheme 3. The total synthesis of barmumycin (**1**) and limazepine E (**4**).[15]

We further proposed that the excellent *E*/*Z* stereoselectivity observed in the Ireland–Claisen rearrangement of boron enolates **14** (Table 1, Entry 4) could arise from the

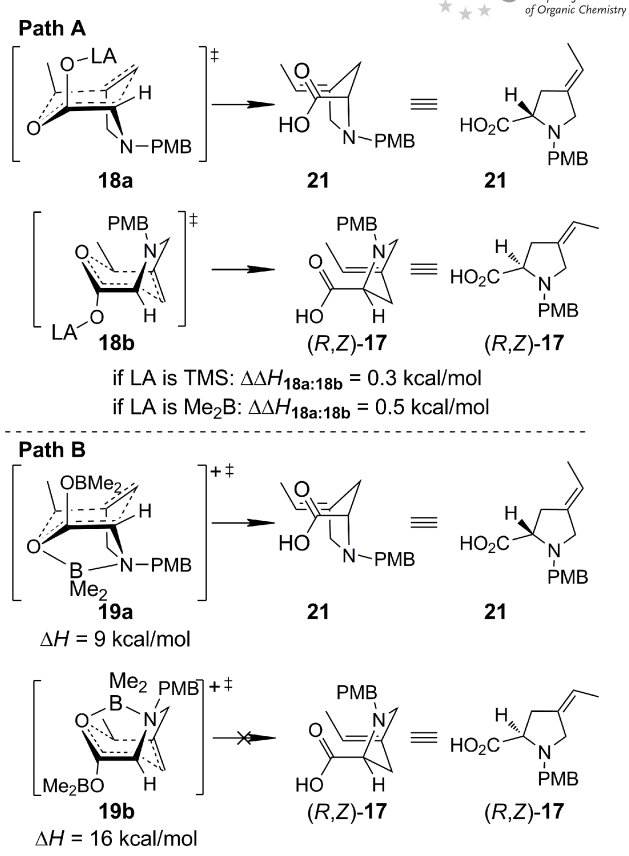
chelation of the boron atom with the nitrogen and oxygen atoms, which would stabilize the boat-like transition state (Scheme 4). This transition state would give the desired ethylidene proline **21**. In contrast, this stabilizing chelation is not possible with the silyl ketene acetals, and hence, (*R*,*Z*)-**17**, the undesired isomer, would be predominantly formed through the chair-like transition state (Scheme 4).



Scheme 4. Suggested stereochemical model.

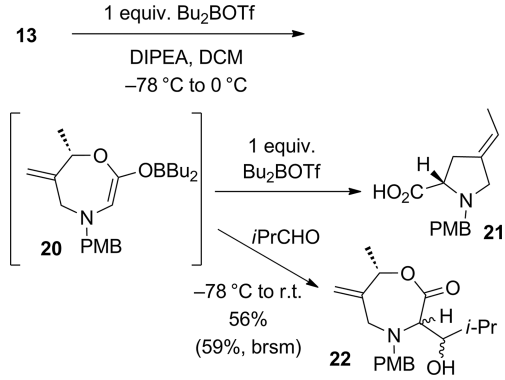
The relative energies of the two plausible transition states were determined by DFT calculations using the B3LYP/6-311++g(3dpf,2p)//B3LYP/6-31+g(d,p) method. The calculations confirmed the hypothesis that the nature of the Lewis acid used in the rearrangement has great impact on the transition-state geometry. Single coordinating Lewis acids (LA), such as those derived from TMS-OTf, bind to the exocyclic oxygen atom of the enolate (Scheme 5). This coordination has little influence on the stabilization of the transition state. Thus, both possible chair-like transition states **18a** and **18b** have similar energies and lead to a rearrangement with low selectivity. Similarly, DFT calculations predicted that the rearrangement of the corresponding dimethyl borane enolate, with the boron atom attached to the exocyclic oxygen atom, also occurred with low selectivity. In this case, the rearrangement led to two chair-like transition states **18a** and **18b** with a 0.5 kcal/mol relative enthalpy difference (Scheme 5, Path A).

However, dimethyl borane can also bind to two Lewis basic atoms and form a bridge between the endocyclic oxygen and nitrogen atoms. A second equivalent of dimethylborane would coordinate in this fashion to result in significant steric hindrance between the bridging dimethyl borane and the exocyclic methyl group in chair-like transition state **19b** as opposed to that found in boat-like transition state **19a**. As a result of the large energy difference between transition states **19a** and **19b** ($\Delta\Delta H$ = 7 kcal/mol), the Ireland–Claisen rearrangement must proceed with high selectivity and yield only **21**(Scheme 5, Path B) These computational results are in line with the experimental data reported in Table 1. The presence of two borane species in the transition state was confirmed experimentally. Hence, the addition of 1 equiv. of dibutylboron triflate to lactone **13** led to formation of boron enolate **20**, which did not undergo the rearrangement to give proline derivative **21** (Scheme 6). The rearrangement took place only after the addition of the



Scheme 5. DFT analysis of transition states.

second equivalent of dibutylboron triflate, which resulted in the formation of the desired (*E*)-ethylidene proline **21**. Ketene acetal **20** was further treated with isobutyraldehyde to give aldol product **22**.



Scheme 6. Studies of ketene acetal **20** formation (brsm = based on recovered starting material).

The formation of ketene acetal **20** was also observed in the ^{1}H NMR spectrum of the crude reaction mixture (Figure 2).[20] Here, we observed an upfield shift of the signals that correspond to protons H_a, H_b, and H_e after treating lactone **13** with 1 equiv. of dibutylboron triflate. A new signal H_g also appeared, which corresponds to the newly formed double bond in ketene acetal **20**. After treatment of intermediate **20** with another equivalent of dibutylboron triflate, the characteristic proton signals H_a, H_b, H_e, and H_g

disappeared, and a multiplet for proton H_k in the double bond of ethylidene proline **21** appeared. These experimental results are in good agreement with those proposed as a result of the in silico calculations.

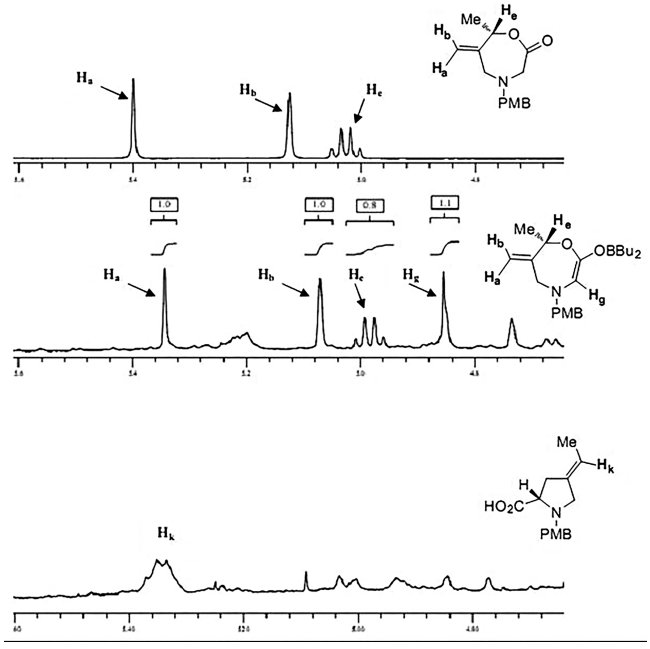
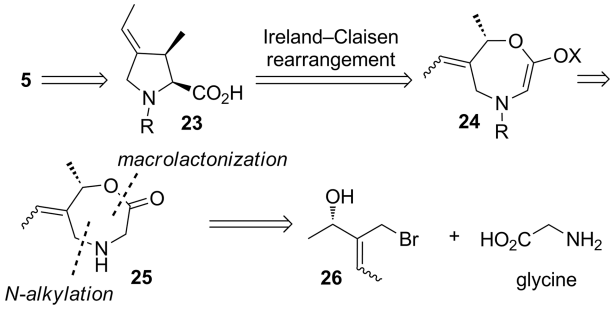


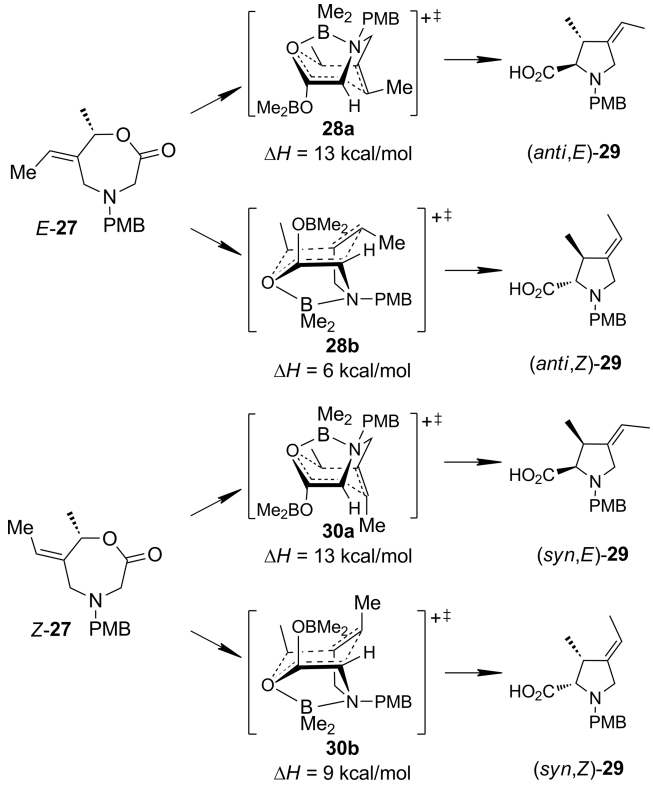
Figure 2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of crude reaction mixture.

Next we turned our attention to the total synthesis of lucentamycin A (**5**). Our retrosynthetic analysis is outlined in Scheme 7. The crucial building block of this strategy is ethylidene proline **23**, which may be accessible by employing an Ireland–Claisen rearrangement of ketene acetal **24**, which is derived from lactone **25**. The necessary lactone **25** could be synthesized form two simple building blocks – glycine and allyl bromide **26**.



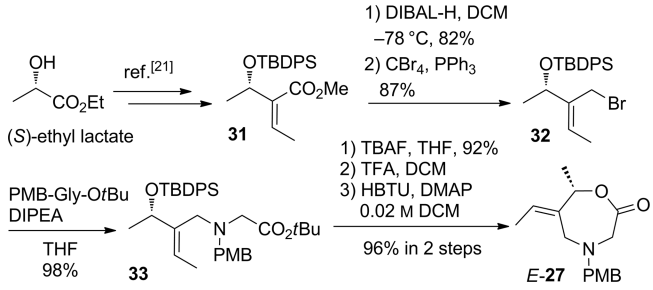
Scheme 7. Retrosynthetic analysis of lucentamycin A (**5**).

By using our theoretical model, we hypothesized that the stereochemistry at the β-carbon of proline derivative **29** would be determined by the double-bond geometry of lactone **27** (Scheme 8). Thus, treatment of (*E*)-**27** with dimethylboron triflate leads to (*anti*,*Z*)-**29**. This reaction should proceed with high selectivity, as there is an energy difference of 7 kcal mol^{-1} between the favored transition state **28b** and unfavorable **28a**. On the other hand, the treatment of (*Z*)-**27** with dimethylboron triflate leads to (*syn*,*Z*)-**29**. In this case, the selectivity may be lower, as the energy difference between transition states **30a** and **30b** is 4 kcal mol^{-1}. The higher energy of transition state **30b** over **28b** can be attributed to the presence of three axial substituents in the former compared to two axial substituents in the latter.



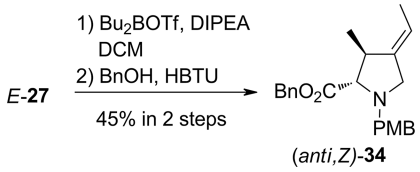
Scheme 8. Theoretical model for stereochemical control in the formation of proline **29**.

To support the theoretical model, both double-bond isomers of lactone **27** were synthesized. First, lactone (*E*)-**27** was prepared by starting from known acrylate **31**[21] (Scheme 9). Ester **31** was converted into the desired allyl bromide by using a DIBAL-H reduction/Appel reaction sequence. The resulting bromide **32** was further used in the alkylation of PMB-protected glycine *tert*-butyl ester.[22] Alcohol and carboxylic acid protecting groups were subsequently cleaved, and the intermediate hydroxy acid under-



Scheme 9. Synthesis of lactone (*E*)-**27** [TBDPS = *tert*-butyldiphenylsilyl, DIBAL-H = diisobutylaluminum hydride, TBAF = tetra-*n*-butylammonium fluoride, HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DMAP = 4-(dimethylamino)pyridine].

went a macrolactonization under high dilution to give the desired product (*E*)-**27**. With lactone (*E*)-**27** in hand, we then examined the Ireland–Claisen rearrangement (Scheme 10).



Scheme 10. Ireland–Claisen rearrangement of lactone (*E*)-**27**.

By using our previously determined conditions,[11] we were able to isolate the Ireland–Claisen rearrangement product (*anti*,*Z*)-**34** in moderate yield as a single diastereomer. The relative *anti* stereochemistry of the obtained 4-ethylidene proline derivative was unambiguously determined by a NOESY experiment (Figure 3), and this was in full agreement with our theoretical model (Scheme 8). Although the obtained proline (*anti*,*Z*)-**34** could not be used in the total synthesis of lucentamycin A (**5**), it could successfully be used in the synthesis of the C-3 and C-4 *anti*-ethylidene proline fragments found, for example, in eleganine A (**6**, Figure 1). The Ireland–Claisen rearrangement allows the generation of three out of the four stereochemical elements in a single step.

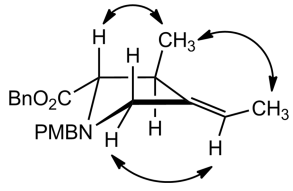
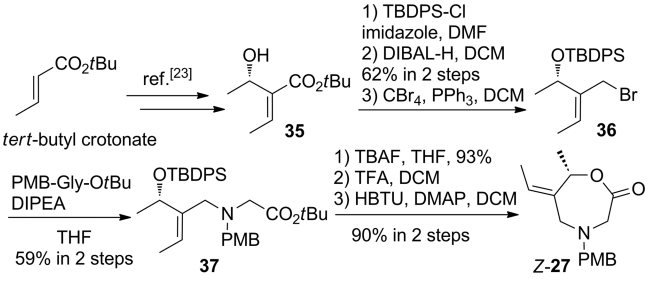


Figure 3. Overhauser effects of proline (*anti*,*Z*)-**34** 2D NOESY spectrum.

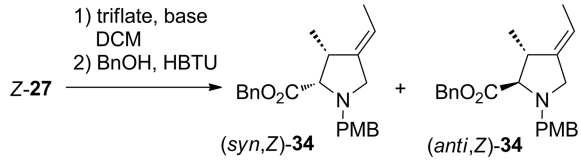
Next, lactone (*Z*)-**27** was prepared in a similar manner as (*E*)-**27** (Scheme 11). The known acrylate **35**[23] was first protected and then converted into the corresponding allyl bromide **36**, which was needed for the alkylation of the PMB-protected glycine *tert*-butyl ester. Finally, the protecting group cleavage–macrolactonization sequence gave the desired lactone (*Z*)-**27** in high yield.



Scheme 11. Synthesis of lactone (*Z*)-**27** (DMF = *N*,*N*-dimethylformamide).

With lactone (*Z*)-**27** in hand, we turned our attention toward the Ireland–Claisen rearrangement. A series of reagents were first screened to optimize this reaction (Table 2). Interestingly, the rearrangement was sensitive to the base that was used, and only Et_3N in combination with sterically small boron triflates (Table 2, Entries 2 and 5) could be used to isolate significant amounts of the desired ethylidene proline **34**. Again in this case, the product that resulted from the less favorable transition state **30a** [corresponding to (*syn*,*E*)-**29**; Scheme 8] was not formed. Instead, a mixture of isomers (*syn*,*Z*)-**34** and (*anti,Z*)-**34** was formed. The isomers could be separated by using semipreparative chiral HPLC. The relative stereochemistry of (*syn*,*Z*)-**34** was determined by a 2D NOESY experiment (Figure 4), whereas the spectrum of (*anti*,*Z*)-**34** was identical to that of **34** (Scheme 10).

Table 2. Optimization of the Ireland–Claisen rearrangement of lactone (*Z*)-**27**.



Entry	Triflate	Base	(*anti*,*Z*)-**34**/(*syn*,*Z*)-**34**[a]	% Yield
1	Et_2BOTf	Me_2NEt	–	trace
2	Et_2BOTf	Et_3N	3:2	23
3	Et_2BOTf	DIPEA	–	trace
4	Bu_2BOTf	Me_2NEt	–	trace
5	Bu_2BOTf	Et_3N	1:2	40
6	Bu_2BOTf	NMM[b]	–	trace
7	Bu_2BOTf	2,6-lut[b]	–	trace
8	Bu_2BOTf	DIPEA	–	trace
9	Cy_2BOTf[b]	Et_3N	–	trace

[a] The *syn*/*anti* ratio was determined by the integration of the signals in the ^1H NMR spectrum. [b] NMM = *N*-methylmorpholine, 2,6-lut = 2,6-lutidine, Cy = cyclohexyl.

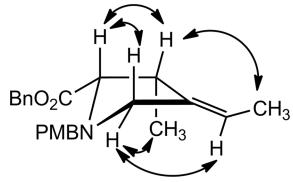
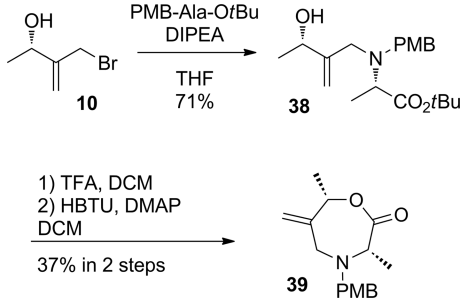


Figure 4. Overhauser effects of proline (*syn,Z*)-**34** 2D NOESY spectrum.

We speculate that the rearrangement of lactone (*Z*)-**27** still proceeds through the favored boron-chelated transition state **30b** (Scheme 8). However, under the reaction conditions, the chiral center at the C-2 position of ethylidene proline (*syn*,*Z*)-**34** partially epimerizes to form the more stable isomer (*anti*,*Z*)-**34**.

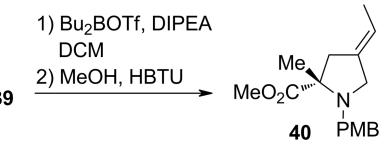
To expand the scope of this transformation, we also synthesized lactone **39**, which has an additional methyl group at its C-3 position (Scheme 12). The Ireland–Claisen rearrangement of this substrate would provide a proline derivative that has a chiral quaternary carbon.



Scheme 12. Synthesis of lactone **39**.

We began the synthesis with the alkylation of commercially available PMB-protected alanine *tert*-butyl ester with known allyl bromide **10**.[16] The obtained intermediate **38** was further converted into the desired lactone **39** in a similar manner as described for **13** (Scheme 2). With lactone **39** in hand, we investigated the Ireland–Claisen rearrangement as summarized in Table 3.

Table 3. Optimization of the Ireland–Claisen rearrangement of lactone **39**.



Entry	Triflate	Base	*E*/*Z*[a]	% Yield
1	Bu_2BOTf	Et_3N	1:2	43
2	Bu_2BOTf	DIPEA	–	trace
3	Cy_2BOTf	Et_3N	1:2	47
4	Cy_2BOTf	DIPEA	–	trace

[a] The *E*/*Z* ratio was determined by the integration of the signals in the ^{1}H NMR spectrum.

Et_3N was determined to be the preferred base (Table 3, Entries 1 and 4), However, all attempts of the rearrangement led to the formation of an inseparable mixture of (*E*) and (*Z*) isomers in moderate yields. Understanding the reasons for the poor stereocontrol in the Ireland–Claisen rearrangement of lactone **39** is a topic of ongoing investigation, and the results of these studies will be reported in due course.

Conclusions

We have developed an efficient method for the fully stereoselective and high yielding synthesis of (*E*)-4-ethylidene proline by using an Ireland–Claisen rearrangement. The computational and experimental studies suggest an unusual mechanistic pathway, in which two molecules of boron triflate are involved in the preferred transition state. The obtained (*E*)-4-ethylidene proline was used in the total syntheses of barmumycin (**1**) and limazepine E (**4**). Although the method has some limitations when applied to the synthesis of more complex (*E*)-4-ethylidene proline derivatives, it has a good potential for the synthesis of the C-3 and C-4 *anti*- ethylidene proline fragments that are found, for example, in eleganine A (**6**).

Experimental Section

General Methods: Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. Petroleum ether with a boiling range 60–80 °C was used. Flash chromatography was carried out by using Merck Kieselgel (230–400 mesh). Thin layer chromatography was performed on Merck Kieselgel 60F254. The NMR spectroscopic data were recorded with Bruker Fourier (300 MHz), Varian Mercury (400 MHz), and Varian Unity Inova (600 MHz) spectrometers. Chemical shift values are referenced against the residual proton in the deuterated solvents for ^{1}H NMR and the deuterated solvent for ^{13}C NMR. The multiplicities of the signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). Infrared spectra were recorded as films in the range 4000–600 cm^{-1}. HRMS was performed on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer. Optical rotations were measured by using a Rudolph Research Analytical Autopol VI polarimeter. LC–MS analyses were performed on a Shimadzu Prominence chromatograph connected to an Applied Biosystems API 2000 mass spectrometer [column: Phenomenex Gemini 5 μm C_{18}, 50 × 2 mm; eluent: MeCN (+ 0.1% HCOOH)/H_2O (+ 0.1% HCOOH)]. Preparative LC–MS purification was performed by using a Waters 600 chromatograph connected to a Waters 3100 mass spectrometer [column: Xterra 10 μm C_{18}, 10 × 150 mm; eluent: MeOH (+ 0.1% HCOOH)/H_2O (+ 0.1% HCOOH)].

NMR Experiment: Lactone **13** (100 mg, 0.383 mmol) was placed in a microwave tube and dried overnight over P_2O_5 in a vacuum drying chamber. The tube was tightly sealed and purged with argon (3×). Dry $CDCl_3$ (2 mL) and DIPEA (445 mg, 3.444 mmol), which was freshly distilled from sodium, were added, and the resulting mixture was then cooled to –78 °C, treated with dibutylboron triflate (104 mg, 0.383 mmol), and then warmed to room temp. A few drops of the reaction mixture were removed with a dry syringe, placed in an NMR tube (sealed with a rubber septum and purged with Ar), and diluted with dry $CDCl_3$. The spectra, which were recorded after 15 min and 3 h, looked very similar. The reaction mixture was again cooled to –78 °C and treated with dibutylboron triflate (104 mg, 0.383 mmol). The resulting mixture was warmed to room temp., and an NMR sample was then prepared as described above.

(7*S*)-3-(1-Hydroxy-2-methylpropyl)-4-(4-methoxybenzyl)-7-methyl-6-methylene-1,4-oxazepan-2-one (22): Lactone **13** (100 mg, 0.383 mmol) was placed in a microwave tube and dried overnight over P_2O_5 in a vacuum drying chamber. The tube was tightly sealed and purged with argon (3×). Dry DCM (2 mL) and DIPEA (445 mg, 3.444 mmol), which was freshly distilled from sodium, were added, and the mixture was cooled to –78 °C and treated with dibutylboron triflate (104 mg, 0.383 mmol). The mixture was placed in an ice bath, stirred for 10 min, and then recooled to –78 °C. Then, freshly distilled isobutyraldehyde (82 mg, 1.148 mmol) was added, and the mixture was warmed to ambient temperature, stirred overnight, and then diluted with brine. The resulting solution was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography [petroleum ether (Pet)/EtOAc, 9:1 to 1:1) to give **22** (72 mg, 56%, 63% brsm) as a pale yellow oil. ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 7.11 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 5.42 (s, 1 H), 5.04 (q, J = 6.4 Hz, 1 H), 4.95 (s, 1 H), 4.05–4.00 (m, 1 H), 3.86 (d, J = 8.8 Hz, 1 H), 3.78 (s, 3 H), 3.55 (d, J = 13.3 Hz, 1 H), 3.36 (2 H, AB m), 3.20 (d, J = 13.5 Hz, 1 H), 2.63 (d, J = 3.5 Hz, 1 H), 2.35, (septet, J = 6.6 Hz), 1.54 (d, J = 6.54 Hz, 3 H), 1.07 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.01, 158.80, 138.58, 129.72, 129.65, 117.79, 113.82, 75.04, 72.53, 65.89, 59.65, 55.19, 50.33, 28.21, 20.25, 17.83, 14.57 ppm. HRMS (ESI): calcd. for $C_{19}H_{28}NO_4$ $[M + H]^+$ 334.2016; found 334.2018. IR (film): $\tilde{\nu}$ = 3503, 2958, 1717, 1612, 1512, 1245 cm^{-1}.

(*S*,*E*)-2-{1-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}but-2-en-1-ol (SI-1): To a stirred solution of ester **31** (2.860 g, 7.476 mmol) in dry DCM (25 mL) was slowly added DIBAL-H (1.2 M in toluene, 3.23 g, 22.427 mmol) at –78 °C. After 4 h, the mixture was quenched by adding MeOH, and the resulting mixture was warmed to room temp. and diluted with a saturated Rochelle salt solution. The mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (Pet/EtOAc, 10:1) to give alcohol SI-**1** (2.170 g, 82%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4 H), 7.46–7.34 (m, 6 H), 5.31 (q, J = 7.0 Hz, 1 H), 4.35 (q, J = 6.3 Hz, 1 H), 4.29 (d, J = 5.5 Hz, 2 H), 2.44 (t, J = 5.5 Hz, 1 H), 1.61 (d, J = 7.0 Hz, 3 H), 1.20 (d, J = 6.3 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.57, 135.94, 135.89, 133.78, 133.39, 129.74, 129.69, 127.55, 127.47, 124.01, 75.61, 57.83, 26.97, 23.27, 19.10, 12.88 ppm. $[\alpha]_D$ = –26.50 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{22}H_{31}SiO_2$ $[M + H]^+$ 355.2106; found 355.2089. IR (film): $\tilde{\nu}$ = 3418, 3071, 1669 cm^{-1}.

(*S*,*Z*)-{[3-(Bromomethyl)pent-3-en-2-yl]oxy}(*tert*-butyl)diphenylsilane (32): To a stirred solution of alcohol **SI**-1 (2.17 g, 6.120 mmol) and PPh_3 (1.76 g, 6.732 mmol) in dry DCM under argon was added CBr_4 (2.23 g, 6.732 mmol) at 0 °C, and the resulting mixture was warmed to ambient temperature. The reaction mixture was stirred for 2 h and then concentrated in vacuo. The residue was purified by flash column chromatography (Pet/EtOAc, 10:1) to give **32** (2.550 g, 87%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.61 (m, 4 H), 7.45–7.33 (m, 6 H), 5.57 (q, J = 7.0 Hz, 1 H), 4.36 (q, J = 6.4 Hz, 1 H), 4.02 (2 H, AB m), 1.63 (d, J = 7.0 Hz, 3 H), 1.28 (d, J = 6.4 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.52, 135.87, 135.82, 134.24, 133.79, 129.57, 129.55, 127.47, 127.41, 127.12, 72.80, 26.98, 26.10, 23.68, 19.25, 13.20 ppm. $[\alpha]_D$ = 65.84 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{22}H_{30}SiO^{79}Br$ $[M + H]^+$ 417.1244; found 417.1243; calcd. for $C_{22}H_{30}SiO^{81}Br$ $[M + H]^+$ 419.1223; found 419.1224. IR (film): $\tilde{\nu}$ = 2961, 1662 cm^{-1}.

***tert*-Butyl (*S*,*E*)-2-[(2-{1-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}but-2-en-1-yl)(4-methoxybenzyl)amino]acetate (33):** A mixture containing 2-[(4-methoxybenzyl)amino]acetate (361 mg, 1.437 mmol), bromide **32** (400 mg, 0.958 mmol), and DIPEA (247 mg, 1.916 mmol) in dry THF (3 mL) was stirred in a sealed tube for 7 d under argon. The reaction mixture was concentrated in vacuo, and the residue was diluted with a saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (Pet/EtOAc, 20:1) to give **33** (3.240 g, 98%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.59 (m, 4 H), 7.41–7.28 (m, 6 H), 7.06 (d, J = 8.6 Hz, 2 H), 6.73 (d, J = 8.6 Hz, 2 H), 5.85 (q, J = 7.0 Hz, 1 H), 4.35 (q, J = 6.6 Hz, 1 H), 3.77 (s, 3 H), 3.58 (2 H, AB m), 3.26 (d, J = 13.3 Hz, 1 H), 3.03 (d, J = 11.7 Hz, 1 H), 2.95 (2 H, AB m), 1.64 (d, J = 7.0 Hz, 3 H), 1.43 (s, 9 H), 1.06 (d, J = 6.3 Hz, 3 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.14, 158.48, 140.28, 135.87, 134.85, 134.69, 134.31, 131.51, 130.01, 129.38, 127.36, 127.31, 122.42, 113.41, 80.40, 71.36, 57.12, 55.19, 53.53, 49.34, 28.18, 27.06, 23.90, 19.30, 13.05 ppm. $[\alpha]_D$ = –19.16 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{36}H_{50}SiNO_4$ $[M + H]^+$ 588.3519; found 588.3495. IR (film): $\tilde{\nu}$ = 2962, 1734, 1661, 1512, 1247, 1144 cm^{-1}.

***tert*-Butyl (*S*,*E*)-2-{[2-(1-Hydroxyethyl)but-2-en-1-yl](4-methoxybenzyl)amino}acetate (SI-2):** A mixture containing ester **33** (100 mg, 0.170 mmol) and TBAF·3H_2O (80 mg, 0.255 mmol) in dry THF (1 mL) was stirred in a sealed tube for 5 d under argon. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (Pet/EtOAc, 20:1) to give SI-**2** (55 mg, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, J = 9.0 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 5.70 (q, J = 6.6 Hz, 1 H), 5.41 (br. s, 1 H), 4.26 (q, J = 7.04 Hz, 1 H), 3.80 (s, 3 H), 3.76 (d, J = 12.9 Hz, 1 H), 3.55 (d, J = 12.5 Hz, 1 H), 3.36 (2 H, AB m), 3.15 (2 H, AB m), 1.66 (d, J = 7.0 Hz, 3 H), 1.46 (s, 9 H), 1.17 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.34, 158.98, 137.88, 130.55, 129.77, 124.51, 113.79, 81.31, 73.25, 57.67, 55.21, 54.06, 50.12, 28.10, 22.00, 12.93 ppm. HRMS (ESI): calcd. for $C_{20}H_{31}NO_4$ [M + H] 350.2337; found 250.2320. $[\alpha]_D$ = 9.60 (c = 1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3070, 2962, 1734, 1247 cm^{-1}.

(*S*,*E*)-6-Ethylidene-4-(4-methoxybenzyl)-7-methyl-1,4-oxazepan-2-one [(*E*)-27]: To a stirred solution of ester SI-**2** (1.330 g, 3.344 mmol) in DCM (20 mL) was added TFA (20 mL), and the dark reaction mixture was stirred for 4 h and then concentrated in vacuo. The residue was dissolved in dry DCM (10 mL), and over a period of approximately 1 h, the solution was added to a vigorously stirred slurry that contained *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU, 3.804 g, 10.033 mmol) and DMAP (2.451 g, 20.065 mmol) in dry DCM (150 mL). The resulting mixture was stirred overnight and then diluted with brine. The mixture was extracted with DCM (2×) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (Pet/EtOAc 4:1 to 1:1) to give (*E*)-**27** (880 mg, 96% in two steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 5.93 (q, J = 6.8 Hz, 1 H), 5.18 (q, J = 6.6 Hz, 1 H), 3.80 (s, 3 H), 3.73 (d, J = 16.6 Hz, 1 H), 3.57 (2 H, AB m), 3.51 (d, J = 15.1 Hz, 1 H), 3.44 (d, J = 16.6 Hz, 1 H), 3.28 (d, J = 14.3 Hz, 1 H), 1.61 (d, J = 6.8 Hz, 3 H), 1.51 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.34, 158.94, 133.66, 129.89, 129.68, 126.68, 113.79, 77.18, 58.32, 58.14, 55.22, 54.37, 18.64, 13.31 ppm. $[\alpha]_D$ = 58.4 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1594; found 276.1607. IR (film): $\tilde{\nu}$ = 2934, 1717, 1513, 1247 cm^{-1}.

Benzyl (2*S*,3*S*,*E*)-4-Ethylidene-1-(4-methoxybenzyl)-3-methylpyrrolidine-2-carboxylate [(*anti*,*Z*)-34]: Lactone (*E*)-**27** (50 mg, 0.182 mmol) was placed in a MW tube and dried overnight over P_2O_5 in a vacuum drying chamber. The tube was tightly sealed and purged with argon (3×). Dry DCM (0.5 mL) and DIPEA (140 mg, 1.090 mmol), which was freshly distilled from sodium, were added, and the mixture was cooled in an ice bath and then treated with dibutylboron triflate (149 mg, 0.545 mmol). The mixture was warmed to ambient temperature over 3 h, and then benzyl alcohol (196 mg, 1.816 mmol) was added followed by HBTU (206 mg, 0.545 mmol). The obtained mixture was stirred for 16 h and then diluted with a saturated aqueous sodium hydrogen carbonate solu-

tion. The mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC–MS to give (*anti*,*Z*)-**34** (30 mg, 45%) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 5 H), 7.21 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 5.31 (q, J = 7.4 Hz, 1 H), 3.85 (d, J = 12.4 Hz, 1 H), 3.79 (s, 3 H), 3.46 (2 H, AB m), 3.14 (d, J = 12.0 Hz, 1 H), 3.11 (d, J = 5.7 Hz, 1 H), 2.96–2.93 (m, 1 H), 1.56 (d, J = 6.7 Hz, 3 H), 1.23 (d, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.66, 158.88, 140.70, 135.80, 130.35, 128.53, 128.26, 116.53, 113.62, 73.43, 66.45, 57.68, 57.61, 55.23, 39.89, 19.13, 13.84 ppm. HRMS (ESI): calcd. for $C_{23}H_{28}NO_3$ $[M + H]^+$ 376.2031; found 376.2096. $[\alpha]_D$ = –13.5 (c = 1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2927, 1730, 1248 cm^{-1}.

***tert*-Butyl (*S*,*E*)-2-{1-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}but-2-enoate (SI-3):** A mixture of alcohol **35** (4.016 g, 21.567 mmol), TBDPS-Cl (8.892 g, 32.351 mmol), and imidazole (4.404 g, 64.702 mmol) in dry DMF (20 mL) in a sealed tube was stirred for 4 d under argon. The reaction mixture was concentrated in vacuo, and the residue was diluted with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (Pet/EtOAc, 10:1 to 5:1). The fractions that contained the desired product were concentrated in vacuo and used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 2 H), 7.63–7.60 (m, 2 H), 7.44–7.30 (m, 6 H), 6.63 (q, J = 7.4 Hz, 1 H), 4.85 (q, J = 6.6 Hz, 1 H), 1.80 (d, J = 7.4 Hz, 3 H), 1.42 (s, 9 H), 1.30 (d, J = 6.6 Hz, 3 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.41, 137.88, 137.19, 135.82, 134.34, 133.83, 129.49, 129.45, 127.46, 127.40, 79.96, 66.46, 28.12, 26.92, 23.23, 19.21, 14.30 ppm. $[\alpha]_D$ = –8.64 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{26}H_{36}SiNaO_3$ $[M + Na]^+$ 447.2326; found 447.2317. IR (film): $\tilde{\nu}$ = 2973, 1703, 1648, 1274, 1092 cm^{-1}.

(*S*,*Z*)-2-{1-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}but-2-en-1-ol (SI-4): Compound SI-**4** was obtained in a similar manner as that described for the preparation of SI-**1**. Pale yellow oil (4.740 g, 62% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 2 H), 7.67–7.64 (m, 2 H), 7.47–7.35 (m, 6 H), 5.43 (q, J = 6.65 Hz, 1 H), 4.86 (q, J = 7.0 Hz, 1 H), 4.40 (d, J = 12.5 Hz, 1 H), 4.13 (d, J = 12.5 Hz, 1 H), 2.64 (br. s, 1 H), 1.35 (d, J = 7.0 Hz, 3 H), 1.16 (d, J = 6.5 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.83, 135.82, 135.72, 134.14, 133.71, 129.63, 127.53, 127.40, 67.33, 33.58, 26.96, 23.47, 19.23, 13.24 ppm. $[\alpha]_D$ = –10.82 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{22}H_{29}SiNaO_2$ $[M + Na]^+$ 377.1907; found 377.1930. IR (film): $\tilde{\nu}$ = 3411, 2930, 1589, 1111, 1073 cm^{-1}.

(*S*,*E*)-{[3-(Bromomethyl)pent-3-en-2-yl]oxy}(*tert*-butyl)diphenylsilane (36): Compound **36** was obtained in a similar manner as that described for the preparation of **32** and used in the next step without full purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 2 H), 7.63–7.60 (m, 2 H), 7.45–7.32 (m, 6 H), 5.65 (q, J = 7.0 Hz, 1 H), 4.74 (q, J = 6.6 Hz, 1 H), 4.35 (d, J = 9.8 Hz, 1 H), 3.90 (d, J = 9.8 Hz, 1 H), 1.41 (d, J = 7.0 Hz, 3 H), 1.31 (d, J = 6.6 Hz, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.98, 135.97, 135.87, 134.30, 133.87, 129.78, 127.67, 127.55, 67.49, 67.42, 27.10, 23.61, 19.39, 13.42 ppm. $[\alpha]_D$ = –34.28 (c = 1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2961, 1652, 1111 cm^{-1}.

***tert*-Butyl (*S*,*Z*)-2-[(2-{1-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}but-2-en-1-yl)(4-methoxybenzyl)amino]acetate (37):** Compound **37** was obtained in a similar manner as that described for the preparation of **33**. Pale yellow oil (1.070 g, 59% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 2 H), 7.58–7.56 (m, 2 H), 7.43–7.28 (m, 6 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 8.6 Hz, 2 H), 5.47 (q, J = 7.4 Hz, 1 H), 4.64 (q, J = 6.3 Hz, 1 H), 3.78 (s, 3 H), 3.67 (2 H, AB m), 3.36 (d, J = 14.0 Hz, 1 H), 3.12–3.09 (m, 3 H), 1.45 (s, 9 H), 1.43 (d, J = 7.4 Hz, 3 H), 1.18 (d, J = 6.3 Hz, 3 H), 1.00 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.19, 158.50, 139.53, 135.83, 135.77, 134.59, 134.03, 131.28, 130.01, 129.41, 129.36, 127.40, 127.34, 121.59, 113.49, 80.39, 67.72, 57.38, 55.48, 55.19, 54.02, 28.23, 26.94, 22.75, 19.21, 12.97 ppm. $[\alpha]_D$ = 1.64 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{36}H_{50}SiNO_4$ $[M + H]^+$ 588.3504; found 588.3506. IR (film): $\tilde{\nu}$ = 2930, 1733, 1612, 1145, 1111 cm^{-1}.

***tert*-Butyl (*S*,*Z*)-2-{[2-(1-Hydroxyethyl)but-2-en-1-yl](4-methoxybenzyl)amino}acetate (SI-5):** Compound SI-**5** was obtained in a similar manner as that described for the preparation of SI-**2**. Pale yellow oil (1.180 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.73 (br. s, 1 H), 5.35 (q, J = 7.0 Hz, 1 H), 4.77 (q, J = 6.3 Hz, 1 H), 3.85 (d, J = 12.9 Hz, 1 H), 3.80 (s, 3 H), 3.50 (2 H, AB m), 3.25 (d, J = 16.4 Hz, 1 H), 3.03–2.97 (m, 2 H), 1.64 (d, J = 7.0 Hz, 3 H), 1.46 (s, 9 H), 1.16 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.17, 158.94, 137.97, 130.57, 129.48, 124.98, 113.75, 81.22, 66.38, 58.42, 57.42, 55.22, 53.93, 28.09, 22.67, 13.05 ppm. $[\alpha]_D$ = –23.56 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{20}H_{32}NO_4$ $[M + H]^+$ 350.2326; found 350.2359. IR (film): $\tilde{\nu}$ = 3446, 2974, 1734, 1612, 1157 cm^{-1}.

(*S*,*Z*)-6-Ethylidene-4-(4-methoxybenzyl)-7-methyl-1,4-oxazepan-2-one [(*Z*)-27]: Compound (*Z*)-**27** was obtained in a similar manner as that described for the preparation of (*E*)-**27**. Pale yellow oil (730 mg, 90% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.64 (q, J = 7.0 Hz, 1 H), 5.29 (q, J = 6.6 Hz, 1 H), 3.80 (s, 3 H), 3.57 (s, 2 H), 3.47–3.40 (m, 3 H), 3.12 (d, J = 12.5 Hz, 1 H), 1.72 (d, J = 7.0 Hz, 3 H), 1.58 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.31, 158.92, 134.45, 130.20, 129.87, 129.51, 127.87, 113.77, 74.23, 58.54, 57.76, 55.26, 55.19, 19.88, 13.17 ppm. $[\alpha]_D$ = 9.20 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{16}H_{22}NO_3$ $[M + Na]^+$ 276.1594; found 276.1599. IR (film): $\tilde{\nu}$ = 2934, 1718, 1611, 1247, 1078 cm^{-1}.

Benzyl (2*S*,3*R*,*E*)-4-Ethylidene-1-(4-methoxybenzyl)-3-methylpyrrolidine-2-carboxylate [(*syn*,*Z*)-34]: Compound (*syn*,*Z*)-**34** was obtained in a similar manner as that described for the preparation of (*anti*,*Z*)-**34** by starting from (*Z*)-**27**. Et_3N was used instead of DIPEA. After purification of the isomeric mixture by preparative HPLC–MS, the *syn* and *anti* isomers were successfully separated by using semipreparative chiral HPLC. The product was obtained as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 5 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 5.24–5.16 (m, 3 H), 3.99 (d, J = 12.5 Hz, 1 H), 3.79 (s, 3 H), 3.56 (d, J = 13.7 Hz, 1 H), 3.42 (J = 6.6 Hz, 1 H), 3.25 (d, J = 12.5 Hz, 1 H), 3.12–3.06 (m, 1 H), 2.88 (d, 1 H), 1.58 (d, J = 7.4 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H) ppm.

***tert*-Butyl (*S*)-2-{[(*S*)-3-Hydroxy-2-methylenebutyl](4-methoxybenzyl)amino}propanoate (38):** Compound **38** was obtained in a similar manner as that described for the preparation of **33**. Pale yellow oil (710 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.10 (s, 2 H), 4.98 (s, 1 H), 4.30 (q, J = 6.3 Hz, 1 H), 3.80 (s, 3 H), 3.64–3.52 (m, 3 H), 3.30 (2 H, AB m), 1.50 (s, 9 H), 1.24 (d, J = 7.1 Hz, 3 H), 1.19 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.51, 158.85, 147.81, 130.33, 130.28, 114.17, 113.78, 81.23, 70.23, 56.22, 55.17, 54.55, 53.68, 28.17, 21.20, 12.16 ppm. $[\alpha]_D$ = –65.80

(c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{20}H_{32}NO_4$ $[M + H]^+$ 350.2331; found 350.2336. IR (film): $\tilde{\nu}$ = 3440, 2977, 1724, 1612, 1513, 1252 cm^{-1}.

(3*S*,7*S*)-4-(4-Methoxybenzyl)-3,7-dimethyl-6-methylene-1,4-oxazepan-2-one (39): Compound **39** was obtained in a similar manner as that described for the preparation of (*E*)-**27**. Pale yellow oil (140 mg, 37% over two steps). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.42 (s, 1 H), 5.02–4.96 (m, 2 H), 4.08 (q, J = 6.7 Hz, 1 H), 3.80 (s, 3 H), 3.65 (d, J = 13.5 Hz, 1 H), 3.37 (2 H, AB m), 3.17 (d, J = 13.4 Hz, 1 H), 1.54 (d, J = 6.5 Hz, 3 H), 1.44 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.54, 158.74, 139.73, 130.44, 129.83, 116.83, 113.73, 74.49, 58.81, 58.77, 55.23, 49.27, 18.06, 16.39 ppm. $[a]_D$ = –146.70 (c = 1, $CHCl_3$). HRMS (ESI): calcd. for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1600; found 176.1597.

Methyl (*S*,*E*)-4-Ethylidene-1-(4-methoxybenzyl)-2-methylpyrrolidine-2-carboxylate and Methyl (*S*,*Z*)-4-Ethylidene-1-(4-methoxybenzyl)-2-methylpyrrolidine-2-carboxylate (40): Compounds **40** were obtained in a similar manner as that described for the preparation of (***anti***,*Z*)-**34** by starting from **39**. The separation of isomers was not successful. The product was obtained as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$, mixture of isomers): δ = 7.28–7.24 (m, 2 H), 6.87–6.83 (m, 2 H), 5.23 (br. s), 3.81–3.71 (m, 7 H), 3.54–3.31 (m, 3 H), 2.87–2.80 (m, 1 H), 2.49–2.40 (m, 1 H), 1.54 (d, 2 H, J = 7.0 Hz), 1.48–1.43 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers): δ = 175.21, 158.58, 135.96, 131.64, 129.54, 129.45, 114.84, 113.61, 67.65, 56.34, 55.24, 53.88, 53.14, 53.02, 51.44, 44.84, 41.29, 20.89, 20.55, 14.50, 14.39 ppm.

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