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Asymmetric Total Synthesis of Epolactaene. Part 1: Construction of Epoxy-γ-lactam Moiety and Deduction of Absolute Stereochemistry.†

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Abstract

Enantioselective construction of the epoxy-γ-lactam moiety of epolactaene (**1**) was completed in 11 steps from (*R*)-lactaldehyde derivatives. Key steps include: (i) the stereoselective aldol reaction between (*R*)-lactaldehyde and malonate ester; (ii) diastereospecific lactonization of malonate ester derivative **10**; (iii) cyclization of **16** to epoxy-γ-lactam derivative **2**. Both enantiomers, (*R*,*R*)-**2** and (*S*,*S*)-**2**, were synthesized, and their optical rotations were compared with that of (+)-epolactaene (**1**). The results suggest that the absolute configuration of **1** is (13*R*,14*R*).

Introduction

Neurotrophic factors (NTF) are known to be proteins essential for the growth and development or the survival and functional maintenance of neurons in the central and peripheral nervous systems.[1-6] Since a decreased availability of NTFs is thought to lead to various neural diseases involving senile dementia. For example, Alzheimer's disease, there is some speculation that NTF-like substances might be therapeutically

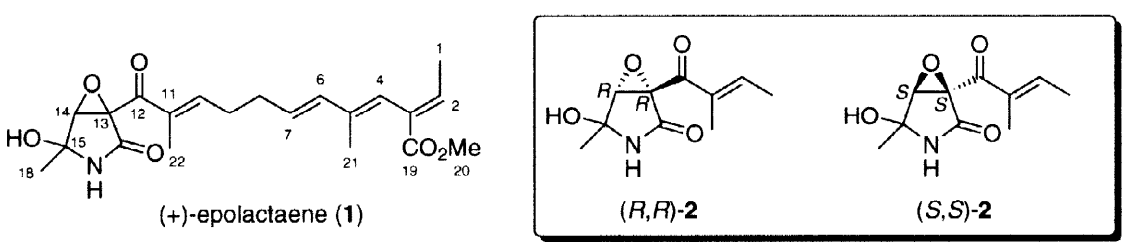

Figure 1

†With regard to this investigation, a patent application was filed before Japanese Patent Office on October 30, 1997 as a patent filing number of H09-297983.

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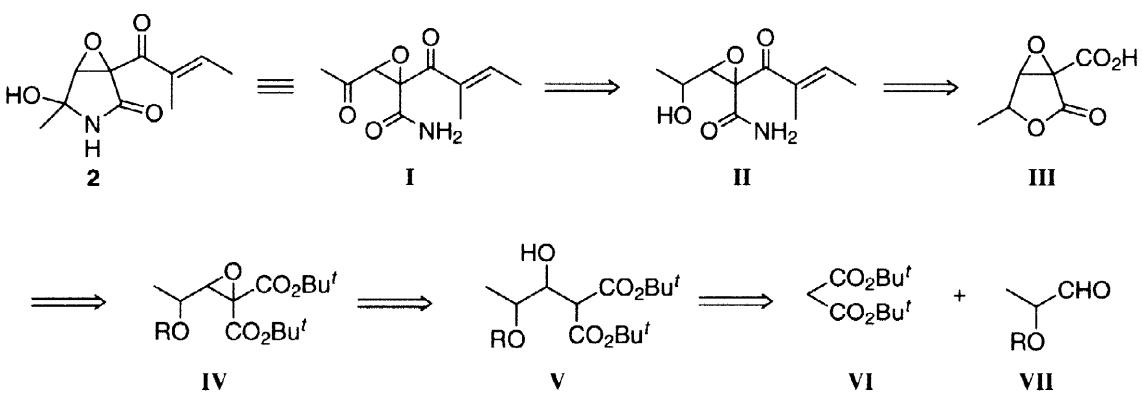
useful.[7,8] The neurotrophins trigger a variety of biological responses such as proliferation, differentiation, and survival of neuroblasts, as well as survival and adaptive responses of mature neurons.[9,10]

In 1995, Osada *et al.* isolated a novel compound, epolactaene (**1**) (Figure 1), from the culture broth of *Penicillium* sp. BM 1689-P,[11] which induces differentiation of the *human* neuroblastoma cell line, SH-SY5Y. Since epolactaene (**1**) is the first microbial metabolite effective for the neurite outgrowth activity[12,13] of the human neuroblastoma cell line, it has potential for development as a new drug for various neurodegenerative diseases such as dementia.[14] Furthermore, the initial structural assignment did not specify the absolute stereochemistry of the epoxy moiety, though it did establish the (*E,E,E*) geometry of the conjugated triene and the (*E*) configuration of the α,β-unsaturated ketone. In view of this remarkable biological activity and unique structure, this epolactaene (**1**) is a desirable target for synthesis. In addition, a total synthesis should enable to access to novel analogues for further development of the structure–activity relationships and for detailed studies of the mechanism of action. Recently, our group[15] and Hayashi *et al.*[16] achieved the total synthesis of **1** and determined its unknown absolute configuration to be (13*R*,14*R*). In this and the accompanying paper,[17] we give full details of the total synthesis of epolactaene (**1**). Here, we describe the synthesis of the optically active epoxy-γ-lactam derivatives, (*R,R*)-**2** and (*S,S*)-**2**, the model compounds of epolactaene, to deduce its absolute configuration.

Results and Discussion

Our synthetic strategy for the model compound **2** of epolactaene is summarized in Scheme 1. In brief, our assumptions were as follows. Since natural epolactaene is a diastereomeric mixture at the C15 position (approximately 5:1),[11] we can assume that epoxy-γ-lactam **2** is an equilibrium with the open form **I** which can be easily obtained by oxidation of **II**. Next, synthesis of **II** is achieved by transformation of the two carbonyl groups of **III**, respectively: carboxylic acid is converted to α,β-unsaturated ketone, and lactone is converted to primary amide. Diastereospecific lactonization of diester **IV** from alcohol **V** then produces epoxy-γ-lactone **III**, introducing a C13 quaternary stereogenic center. Finally, 1,2-diol **V** is furnished using our recent reported diastereoselective aldol reaction[18] between di-*tert*-butyl malonate **VI** and optically active *O*-protected lactaldehyde **VII**, converted from lactic acid derivative.



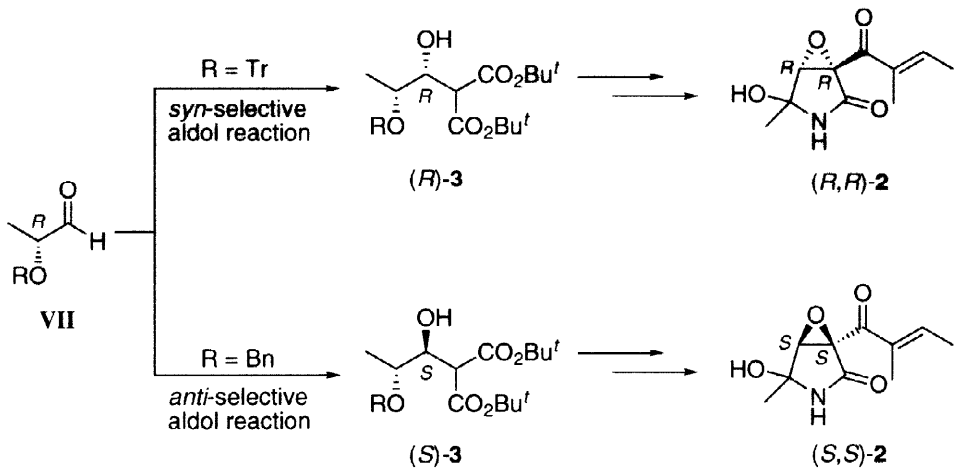
2 **I** **II** **III**

IV **V** **VI** **VII**

Scheme 1

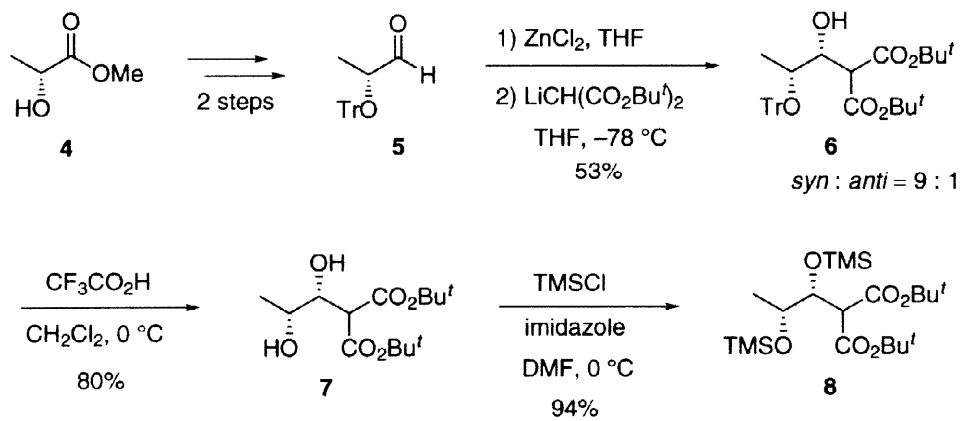
In this aldol reaction, we have reported that both *syn* and *anti* isomer are obtained stereoselectively by selection of *O*-protecting group in lactaldehyde **VII** (Scheme 2). (*R*)-2-Trityloxypropanal (R = Tr) provides *syn* isomer with a 14*R* stereocenter. On the other hand, (*R*)-2-benzyloxypropanal (R = Bn) affords *anti* isomer with a 14*S* stereocenter. According to our retro synthesis, (*R*)-**3** could be expected to transform to (*R,R*)-**2**,

and (*S*)-**3** to (*S*,*S*)-**2**. It is noteworthy that both enantiomers (*R*,*R*)-**2** and (*S*,*S*)-**2** are respectively synthesized from (*R*)-lactaldehyde **VII** by selecting an adequate protecting group, i.e., the trityl or benzyl group.



Scheme 2

Initially, we attempted the synthesis of (*R*,*R*)-**2** using *syn*-selective aldol reaction. *Syn*-selective aldol reaction between (*R*)-2-trityloxypropanal (**5**), derived from commercially available methyl (*R*)-lactate (**4**) in 2 steps,[19] and lithium enolate, derived from di-*tert*-butyl malonate, in THF at –78 °C in the presence of zinc chloride, was achieved in the same manner as the racemic compound[18] to give *syn* aldol adduct **6** in 53% yield (85% yield based on 62% conversion of the aldehyde **5** by ^{1}H NMR analysis) with 9:1 selectivity (Scheme 3). Removal of the trityl protecting group from **6** was performed by exposure to trifluoroacetic acid in dichloromethane (CH_2Cl_2) at 0 °C to afford alcohol **7** in 80% yield. The resulting diol **7** was silylated with chlorotrimethylsilane (TMSCl) and imidazole in *N*,*N*-dimethylformamide (DMF) to obtain bissilylether **8** (94%). This **8** could be purified by silica gel flash column chromatography to give pure *syn* isomer.

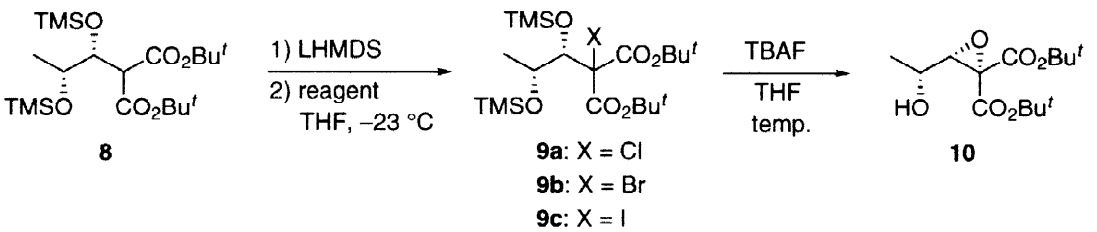


Scheme 3

The next task was to construct epoxide (results summarized in Table 1). By deprotonating of the active proton of **8** with lithium hexamethyldisilazide (LHMDS) in THF at –23 °C and exposing it to *N*-chlorosuccinimide (NCS), α-chloromalonate ester **9a** was produced, then it was used in the next step without purification. Unfortunately, when **9a** was treated with tetrabutylammonium fluoride (TBAF) in THF at 0 °C, an undesired retro aldol reaction occurred and no epoxide **10** was produced (entry 1). Using *N*-bromosuccinimide (NBS) or iodine instead of NCS provided α-bromomalonate ester **9b** or α-iodomalonate ester **9c**, respec-

tively. Treatment of **9b** with TBAF in THF at 0 °C gave the desired epoxide **10** in 47% yield in 2 steps (entry 2). Finally, treatment of **9c** with TBAF at a lower temperature (−46 to −15 °C) afforded **10** in 53% yield from **8** (entry 3) without retro aldol product. The epoxyalcohol **10** was converted to (*S*)- and (*R*)-MTPA esters respectively. ^{1}H NMR analysis of both MTPA esters shows that no racemization was occurred during above the aldol reaction.

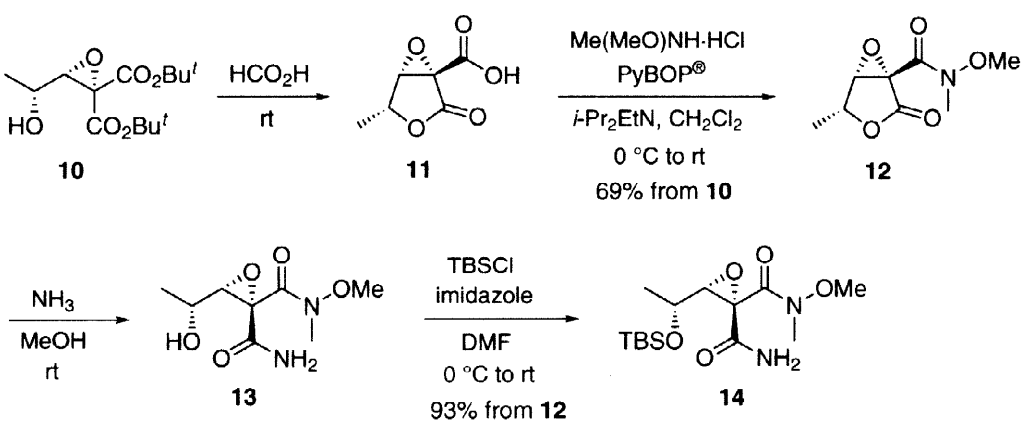
Table 1



entry	reagent	X	temp.	yield (%)[a]
1	NCS	Cl	0 °C	0
2	NBS	Br	0 °C	47
3	I_2	I	−46 to −15 °C	53

[a] Yield for 2 steps.

Hydrolysis of the two *tert*-butyl ester of **10** with formic acid at room temperature provided dicarboxylic acid, and this product then facilitated concomitant diastereospecific cyclization to produce epoxy-γ-lactone **11** (Scheme 4). Unfortunately, the next step, conversion of the carboxylic acid to Weinreb amide,[20] was quite difficult. Use of standard methods (chloroformate ester or the Yamaguchi procedure) resulted in no product formation. Treatment of dicyclohexylcarbodiimide (DCC) gave the desired Weinreb amide **12** in 53% yield (for 2 steps). Finally, dehydroxylation was achieved using 1*H*-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate[21] (PyBOP®), *N*,*O*-dimethylhydroxylamine hydrochloride, and *N*,*N*-diisopropylethylamine in CH_2Cl_2 at 0 °C to furnish Weinreb amide **12** in 69% overall yield from **10**. The *cis* arrangement of **12** between C14 and C15 was firmly established by an X-Ray crystallographic analysis[15] (see ORTEP drawing, Figure 2). Next, after ammonolysis of **12** to open the lactone ring, the resulting alcohol was protected by the *tert*-butyldimethylsilyl (TBS) group to provide **14** in 93% yield from **12**.



Scheme 4

For the synthesis of (*R*,*R*)-**2**, all that remained to be done was to introduce the side chain and construct the γ-lactam ring, and these steps were achieved as shown in Scheme 5. Excess of commercially available (*E*)-2-bromobut-2-ene was converted to its lithio derivative by halogen–metal exchange with *tert*-butyllithium in THF at –78 ℃, and the resulting vinyllithium coupled with Weinreb amide **14** to afford (*E*)-α,β-unsaturated ketone **15** in 82% yield.

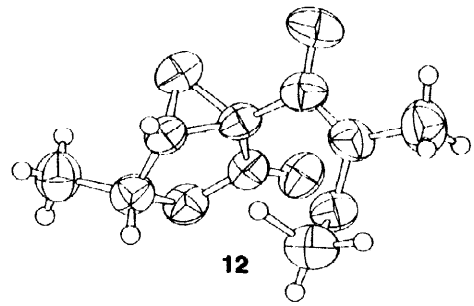


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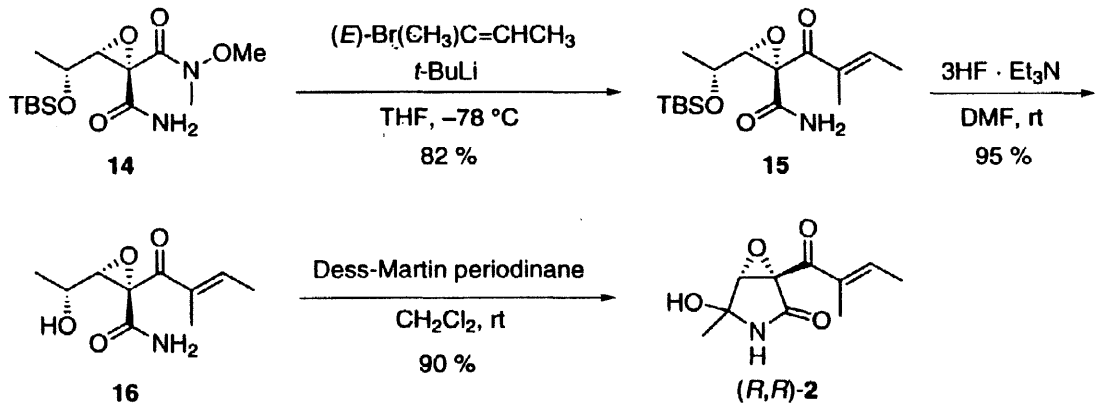
Figure 2

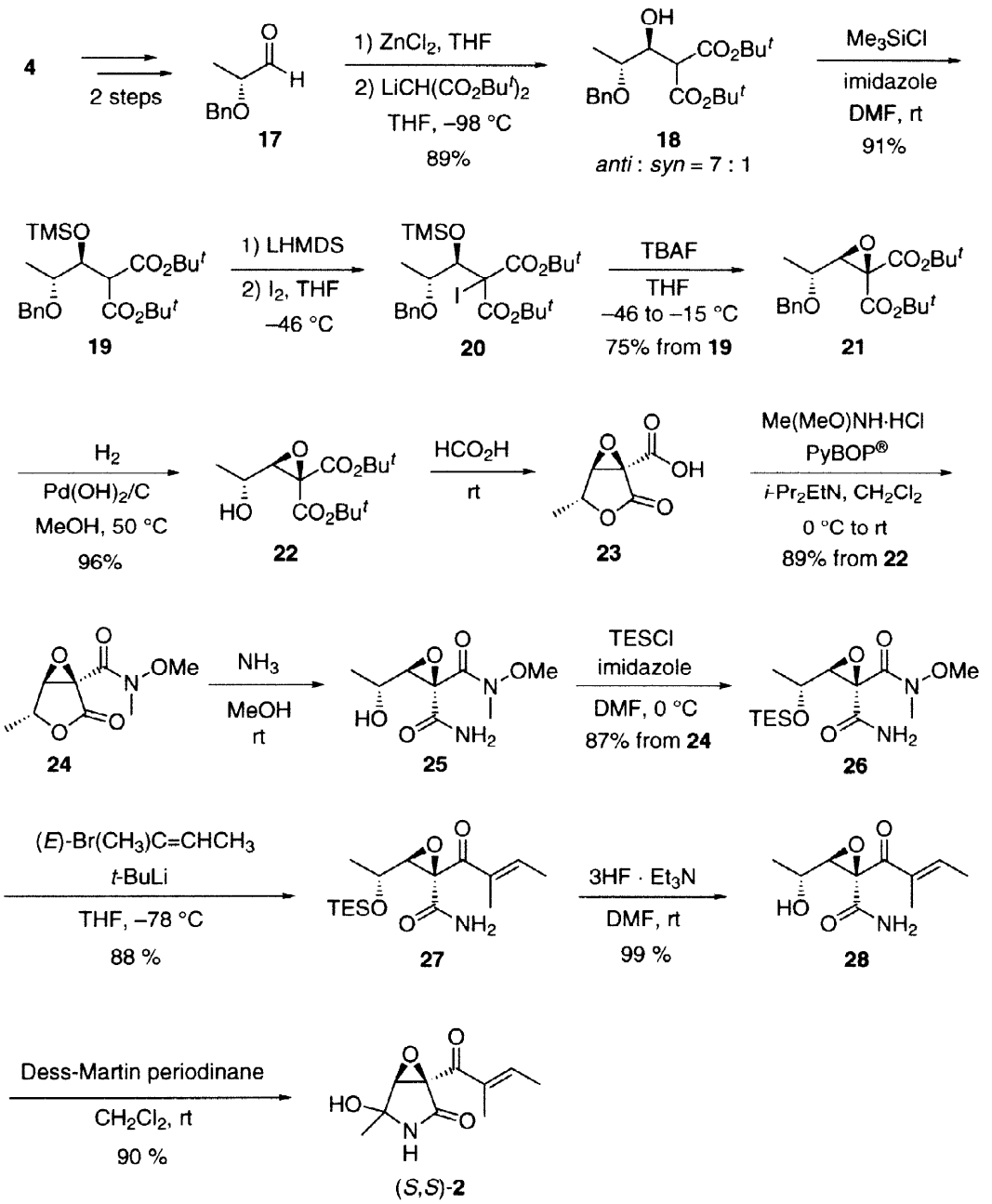


Scheme 5

Finally, triethylamine trihydrofluoride in DMF removed the silicon group from **15** (95%), Dess–Martin oxidation[22] of the resulting alcohol provided corresponding ketone, and this ketone cyclized spontaneously as we expected to produce the desired compound (*R*,*R*)-**2** in 90% yield. The (*R*,*R*)-**2** was obtained ca. 4:1 diastereomeric mixture at C15 as with epolactaene (**1**) (ca. 5:1).

As discussed in the retro synthesis, (*S*,*S*)-**2** could also be synthesized from the same starting material, methyl (*R*)-lactate (**4**). Our attempt of the synthesis is described in Scheme 6. (*R*)-2-Benzyloxypropanal (**17**),[23] derived through two-step conversion from methyl (*R*)-lactate (**4**), was subjected to the aldol reaction with lithium enolate of di-*tert*-butyl malonate in THF in the presence of zinc chloride at –98 ℃ to afford aldol product **18** (*anti*:*syn* = 7:1) in 89% yield. Silylation of the alcohol with trimethylsilyl group gave **19** in 91% yield. Then, conversion of **19** to iodide **20** by LHMDS and iodine followed by treatment with TBAF at –15 ℃ provided epoxide **21** in good yield (75% from **19**). Removal of the benzyl protection from **21** byhydrogenation with palladium hydroxide on carbon (Pearlman's catalyst) at 50 ℃ provided epoxyalcohol **22** in 96% yield. The epoxyalcohol **22** was converted to (*S*)- and (*R*)-MTPA esters respectively. ^{1}H NMR analysis of both MTPA esters shows that no racemization was occurred during the *anti* selective aldol reaction. Transformation of **22** to the target compound (*S*,*S*)-**2** was accomplished through the same method as the synthesis of (*R*,*R*)-**2**, by the following sequence: (a) hydrolysis of the two ester groups with formic acid and diastereospecific lactonization; (b) conversion of the carboxylic acid to Weinreb amide **24** with *N*,*O*-

dimethylhydroxylamine hydrochloride and PyBOP® (89% from **22**); (c) ammonolysis to furnish ammonium amide **25**; (d) silylation of the alcohol with chlorotriethylsilane (TESCl) to obtain silylether **26** in 87% overall yield from **24**; (e) coupling with the vinyllithium generated from (*E*)-2-bromobut-2-ene and *tert*-butyllithium to provide (*E*)-α,β-unsaturated ketone **27** in 88% yield; (f) desilylation of **27** using triethylamine trihydrofluoride to give **28** (99%); (g) Dess–Martin oxidation and spontaneous lactamization to afford the desired (*S*,*S*)-**2** in 90% yield. During the synthesis, the structure of Weinreb amide **24** was confirmed by X-Ray crystallographic analysis[24] (see ORTEP drawing in Figure 3).



Scheme 6

Physical and spectroscopic data on the resulting (*S*,*S*)-**2** are of course, identical with those on (*R*,*R*)-**2**, except the sign of the optical rotation ((*R*,*R*)-**2**: $[\alpha]^{22}_{D}$ +10.0 (*c* 0.10 MeOH); (*S*,*S*)-**2**: $[\alpha]^{22}_{D}$ −10.6 (*c* 0.10 MeOH). In addition, ^{1}H and ^{13}C NMR spectra of **2** are in good agreement with those of epolactaene (**1**) (Table 1), a finding which supports the use of **2** as an appropriate model compound of the natural product.

When the sign of the optical rotation of epolactaene (**1**) (lit.[11] $[\alpha]^{22}_{D}$ +32 (*c* 0.1, MeOH)) was compared with those of (*R*,*R*)-**2** and (*S*,*S*)-**2**, (*R*,*R*)-**2** coincided with **1**. This result suggests that the absolute configuration of (+)-epolactaene is (13*R*,14*R*).

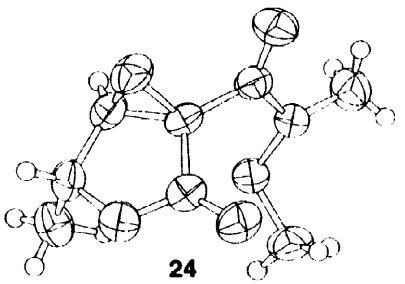


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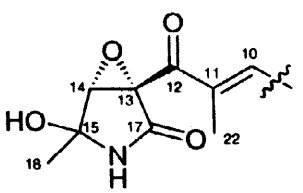
Figure 3

Table 2



	^{13}C NMR		^{1}H NMR	
Position	Model	Natural[a]	Model	Natural[a]
10	145.8	150.1	7.02 qd (7.2, 1.3) 1H	7.01 td (7.3, 1.0) 1H
11	138.1	137.2		
12	191.9	192.1		
13	63.9	63.9		
14	66.0	66.1	4.00 s 1H	3.98 s 1H
15	84.7	84.8		
17	172.3	172.2		
18	22.2	22.2	1.51 s 3H	1.51 s 3H
22	10.8	11.1	1.83 s 3H	1.82 s 3H

[a] ref. 11

Conclusion

In this paper, we delineate the construction of the optically active epoxy-γ-lactam moiety and synthesis of the model compounds of epolactaene the absolute configuration of which was deduced as (13*R*,14*R*). The key steps involved were (i) stereoselective aldol reaction, (ii) construction of epoxide, and (iii) stereospecific lactonization. We concluded that this transformation can be used as a general procedure for the synthesis of the

derivatives of epolactaene or other naturally occurring epoxy-γ-lactam compounds.[25] In the following paper, we describe details of our total synthesis of epolactaene.

Experimental Section

General

Unless otherwise noted, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All other dry solvents were purchased from Aldrich in SureSeal™ containers. All other commercially obtained reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-EX-270 spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. In NMR spectral lists, chemical shifts which are assigned to minor isomer, are marked with an asterisk. Infrared spectra were recorded on a JASCO FT-IR-8900 spectrometer. Optical rotations were measured on a JASCO P-1030 or DIP-370 polarimeter. Mass spectra were obtained on a JEOL HX-100, an SX-102A or a JMS-AX-505H mass spectrometer. Analytical TLC was performed on 0.25 mm pre-coated Merck silica gel 60 F_{254} plates. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh).

Di-*tert*-butyl 2-[(1*R*, 2*R*)-1-hydroxy-2-(trityloxy)propyl]malonate (6):

Zinc chloride (0.5 M in THF, 0.25 mL, 0.12 mmol) was added to a solution of aldehyde **5** (35.3 mg, 0.11 mmol) in THF (1 mL) at room temperature. The reaction mixture was stirred for 1.5 hours and then cooled to –78 °C. A solution of di-*tert*-butyl malonate (45 μL, 0.22 mmol) in THF (1 mL), pretreated with LHMDS (1.0 M in THF, 0.20 mL, 0.20 mmol) at –78 °C for 20 min, was added to the reaction mixture through a cannula. After stirring another 20 min at this temperature, a saturated aqueous NH_4Cl solution was added to this mixture and the organic material was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 5–10% ethyl acetate in hexane) provided 31.6 mg (53%) of aldol adduct **6** as a colorless oil: IR (film) υ_{max} 3558, 2979, 2934, 1728, 1491, 1450, 1252, 1139, 1067, 849, 760, 707 cm^{-1}; $[\alpha]^{22}_D$ +11.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 and 0.85* (each d, *J* = 6.2 Hz, *J** = 6.1 Hz, 3 H), 1.38 and 1.34* (each s, 9 H), 1.48 and 1.40* (each s, 9 H), 3.37 (d, *J* = 8.8 Hz, 1 H), 3.52-3.58 (m, 1 H), 3.54 (d, *J* = 6.6 Hz, 1 H), 3.93-3.99 (m, 1 H), 7.19-7.33 (m, 9 H), 7.44-7.51 (m, 6 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.5, 27.9 (x 6), 55.2, 71.2, 73.2, 81.8, 82.0, 86.8, 127.1 (x 3), 127.7 (x 6), 128.9 (x 6), 144.7 (x 3), 167.1, 168.5; HRMS, calcd for $C_{33}H_{40}O_6Na$ $(M + Na)^+$ 555.2723, found 555.2719.

Di-*tert*-butyl 2-[(1*R*, 2*R*)-1,2-dihydroxypropyl]malonate (7):

Trifluoroacetic acid (15 μL, 0.19 mmol) was added to a solution of **6** (50.7 mg, 0.095 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After stirring for 20 min, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, the organic material was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 15–40% ethyl acetate in hexane) afforded 22.2 mg (80%) of diol **7** as a colorless oil: IR (film) υ_{max} 3468, 2979, 2935, 1729, 1370, 1299, 1256, 1144, 1060, 983, 848 cm^{-1}; $[\alpha]^{22}_D$ +7.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 and 1.27* (each d, *J* = 6.5 Hz, *J** = 6.3 Hz, 3 H), 1.48 (s, 9 H), 1.49 (s, 9 H), 2.45 (br s, 1 H), 3.45 and 3.50* (each d, *J* = 5.9 Hz, *J** = 5.3 Hz, 1 H), 3.66 (br s, 1 H), 3.73-3.83 (m, 1 H), 3.92 (br t, *J* = 4.7 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.4, 27.9 (x 6), 55.9, 68.3, 74.2, 82.5, 82.8, 167.4, 168.5; HRMS, calcd for $C_{14}H_{27}O_6$ $(M + H)^+$ 291.1808, found 291.1767.

Di-*tert*-butyl 2-[(1*R*, 2*R*)-1,2-[bis(trimethylsilyl)oxy]propyl]malonate (8):

TMSCl (23 μL, 0.18 mmol) was added to a solution of **7** (20.3 mg, 0.073 mmol) and imidazole (30.0 mg, 0.44 mmol) in DMF (1.0 mL) at 0 ℃. After stirring for 1 hour, a saturated aqueous $NaHCO_3$ solution was added, the organic material was extracted with hexane, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 3% ethyl acetate in hexane) gave 30.2 mg (94%) of bissilyl ether as a 9:1 diastereomeric mixture. This mixture was separated by flash chromatography (SiO_2, 0–2% ethyl acetate in hexane) to obtain 25.4 mg of *syn* product **8**: IR (film) υ_{max} 2979, 2960, 1748, 1732, 1479, 1457, 1369, 1297, 1252, 1140, 1102, 843, 749 cm^{-1}; $[\alpha]^{22}_D$ +28.6 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.10 (s, 9 H), 0.14 (s, 9 H), 1.16 (d, *J* = 6.3 Hz, 3 H), 1.45 (s, 9 H), 1.46 (s, 9 H), 3.52 (d, *J* = 7.9 Hz, 1 H), 3.89 (qd, *J* = 6.3 Hz, 3.9 Hz, 1 H), 4.22 (dd, *J* = 7.9 Hz, 3.9 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 0.3 (x 3), 0.7 (x 3), 18.7, 28.0 (x 6), 56.6, 69.7, 74.3, 81.1 (x 2), 167.0, 167.2; HRMS, calcd for $C_{20}H_{42}O_6Si_2Na$ $(M + Na)^+$ 457.2418, found 457.2396. For the *anti* isomer: IR (film) υ_{max} 2979, 2961, 1748, 1732, 1456, 1370, 1289, 1251, 1144, 1038, 1010, 897, 843, 750 cm^{-1}; $[\alpha]^{22}_D$ –7.7 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (s, 18 H), 1.09 (d, *J* = 6.2 Hz, 3 H), 1.45 (s, 9 H), 1.46 (s, 9 H), 3.27 (d, *J* = 8.4 Hz, 1 H), 3.79 (qd, *J* = 6.2 Hz, 3.3 Hz, 1 H), 4.20 (dd, *J* = 8.4 Hz, 3.3 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 0.1 (x 3), 0.5 (x 3), 17.2, 27.9 (x 6), 58.2, 69.0, 75.5, 81.1, 81.5, 166.6, 166.9; HRMS, calcd for $C_{20}H_{42}O_6Si_2Na$ $(M + Na)^+$ 457.2418, found 457.2399. Anal. Calcd for $C_{20}H_{42}O_6Si_2$: C, 55.26; H, 9.74. Found: C, 54.92; H, 9.51.

Di-*tert*-butyl 2-[(1*S*, 2*R*)-1,2-[bis(trimethylsilyl)oxy]propyl]-2-iodomalonate (9c):

LHMDS (1.0 M in THF, 38 mL, 38 mmol) was added to a solution of **8** (10.9 g, 25 mmol) in THF (150 mL) at –23 ℃. After mixing for 1 hour, and then cooling to –46 ℃, iodine (9.64 g, 38 mmol) in THF (50 mL) was mixed in and the stirring was continued for another 1 hour at –23 ℃. Next, a saturated aqueous NH_4Cl solution was mixed in, the organic material was extracted with hexane, and the combined organic extracts were washed with a 1 M solution of $Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting crude iodide **9c** was used in the next step without purification: ^1H NMR (270 MHz, $CDCl_3$) δ 0.14 (s, 9H), 0.18 (s, 9H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.46 (s, 9H), 1.47 (s, 9 H), 3.86 (d, *J* = 3.0 Hz, 1 H), 4.28 (qd, *J* = 6.3 Hz, 3.0 Hz, 1 H).

Di-*tert*-butyl 2-[(1*S*, 2*R*)-1,2-[bis(trimethylsilyl)oxy]propyl]-2-chloromalonate (9a):

^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (s, 9H), 0.16 (s, 9H), 1.18 (d, *J* = 6.3 Hz, 3 H), 1.47 (s, 9H), 1.48 (s, 9 H), 4.14 (qd, *J* = 6.3 Hz, 3.3 Hz, 1 H), 4.26 (d, *J* = 3.3 Hz, 1 H).

Di-*tert*-butyl 2-[(1*S*, 2*R*)-1,2-[bis(trimethylsilyl)oxy]propyl]-2-bromomalonate (9b):

^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (s, 9H), 0.16 (s, 9H), 1.18 (d, *J* = 6.3 Hz, 3 H), 1.47 (s, 9H), 1.48 (s, 9 H), 4.17 (d, *J* = 3.3 Hz, 1 H), 4.28 (qd, *J* = 6.1 Hz, 3.3 Hz, 1 H).

Di-*tert*-butyl (*S*)-3-[(*R*)-1-hydroxyethyl]oxirane-2,2-dicarboxylate (10):

TBAF (1.0 M in THF, 63 mL, 63 mmol) was added to a solution of the resulting crude iodide **9c** in THF (200 mL) at –46 ℃. The reaction mixture was allowed to warm slowly to –15 ℃ and stirred for another 1 hour. Water was added, the organic material was extracted with ether, and the combined organic extracts were washed with a 1 M solution of $Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Purification by flash chromatography (SiO_2, 15–35% ethyl acetate in hexane) furnished 3.80 g (53% from **7**) of epoxide **10** as a colorless oil: IR (film) υ_{max} 3469, 2981, 2937, 1743, 1459, 1396, 1372, 1343, 1250, 1160, 1124, 1022, 846 cm^{-1}; $[\alpha]^{22}_D$ –40.0 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.6 Hz, 3 H), 1.50 (s, 9 H), 1.51 (s, 9 H), 2.00 (br d, *J* = 4.9 Hz, 1 H), 3.42 (d, *J* = 6.4 Hz, 1 H), 3.65-3.73 (m, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.4, 27.8 (x 6), 61.0, 65.1, 65.9, 83.4, 84.0, 163.7, 164.6; HRMS, calcd for $C_{14}H_{24}O_6Na$ $(M + Na)^+$ 311.1471, found 311.1472.

(*S*)-MTPA ester of **10**: IR (film) υ_{max} 2983, 2941, 1748, 1455, 1396, 1372, 1336, 1248, 1169, 1124, 1070, 1022, 848, 811, 765, 719 cm^{-1}; $[\alpha]^{22}_{D}$ −71.3 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.6 Hz, 3 H), 1.49 (s, 9 H), 1.55 (s, 9 H), 3.53 (d, *J* = 8.7 Hz, 1 H), 3.56 (d, *J* = 1.3 Hz, 3 H), 4.93 (dq, *J* = 8.7 Hz, 6.6 Hz, 1 H), 7.38-7.43 (m, 3 H), 7.53-7.57 (m, 2 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 16.5, 27.8 (x 3), 27.9 (x 3), 55.5, 60.6, 61.5, 72.1, 84.2, 84.3, 84.8 (q, *J* = 27.9 Hz), 123.2 (d, *J* = 288.3 Hz), 127.5, 128.4 (x 2), 129.7 (x 2), 131.9, 163.1, 164.1, 165.5; HRMS, calcd for $C_{24}H_{31}F_3O_8Na$ $(M + Na)^+$ 527.1869, found 527.1864.

(*R*)-MTPA ester of **10**: IR (film) υ_{max} 2983, 2941, 1749, 1455, 1396, 1372, 1337, 1248, 1169, 1125, 1070, 1023, 848, 811, 765, 719 cm^{-1}; $[\alpha]^{22}_{D}$ +2.5 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.39 (d, *J* = 6.5 Hz, 3 H), 1.50 (s, 9 H), 1.55 (s, 9 H), 3.56 (d, *J* = 8.8 Hz, 1 H), 3.61 (d, *J* = 1.3 Hz, 3 H), 4.89 (dq, *J* = 8.8 Hz, 6.5 Hz, 1 H), 7.40-7.44 (m, 3 H), 7.51-7.56 (m, 2 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 16.1, 27.8 (x 3), 27.9 (x 3), 55.7, 60.9, 61.5, 72.1, 84.2, 84.3, 84.3 (q, *J* = 27.5 Hz), 123.2 (d, *J* = 288.4 Hz), 127.2, 128.5 (x 2), 129.6 (x 2), 132.2, 163.1, 164.0, 165.5; HRMS, calcd for $C_{24}H_{31}F_3O_8Na$ $(M + Na)^+$ 527.1869, found 527.1863.

(1*R*, 4*R*, 5*S*)-4-Methyl-2-oxo-3,6-dioxabicyclo[3.1.0]hexane-1-carboxylic acid (11):

Formic acid (1.0 mL) was added to the epoxide **10** (14.0 mg, 0.049 mmol) and the mixture was stirred for 10 hours at room temperature. The formic acid was removed *in vacuo*. The resulting epoxylactone **11** was used in the next step without purification: ^1H NMR (270 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.5 Hz, 3 H), 4.45 (d, *J* = 1.2 Hz, 1 H), 4.76 (qd, *J* = 6.5 Hz, 1.2 Hz, 1 H).

***N*-Methoxy-*N*-methyl (1*R*, 4*R*, 5*S*)-4-methyl-2-oxo-3,6-dioxabicyclo[3.1.0]hex-ane-1-carboxamide (12)**:

Diisopropylethylamine (34 μL, 0.19 mmol), *N,O*-dimethylhydroxylamine hydrochloride (9.6 mg, 0.098 mmol), and PyBOP® (38.5 mg, 0.074 mmol) were added successively to a solution of the resulted epoxylactone **11** in CH_2Cl_2 (1 mL) at 0 ℃. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Water was added to the mixture, the organic material was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 40–60% ethyl acetate in hexane) provided 6.7 mg (69% from **10**) of Weinreb amide **12** as colorless prisms: mp 101-102 °C; IR (KBr) υ_{max} 2987, 2951, 2929, 1779, 1677, 1489, 1380, 1338, 1074, 999, 935, 778, 639, 542 cm^{-1}; $[\alpha]^{22}_{D}$ −20.5 (*c* 0.20, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.4 Hz, 3 H), 3.28 (s, 3 H), 3.74 (s, 3 H), 4.20 (s, 1 H), 4.71 (d, *J* = 6.4 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.9, 32.2, 59.3, 61.3, 62.3, 74.9, 161.4, 167.2; HRMS, calcd for $C_8H_{12}NO_5$ $(M + H)^+$ 202.0715, found 202.0702. Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.82; H, 5.54; N, 6.87.

***N*-Methoxy-*N*-methyl (2*S*, 3*S*)-2-carbamoyl-3-[(*R*)-1-hydroxyethyl]oxirane-2-carboxamide (13)**:

A saturated ammonia solution in methanol (4 mL) was added to a solution of the Weinreb amide **12** (100 mg, 0.50 mmol) in methanol (1 mL) at room temperature. After stirring for 30 min, ammonia and methanol were removed *in vacuo* to yield amide **13**, which was used in the next step without any purification: ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.5 Hz, 3 H), 3.25 (br s, 3H), 3.56 (br. d, *J* = 8.4 Hz , 1 H), 3.79 (s, 3H), 3.75-3.85 (m, 1H), 5.76 (br s, 1H), 6.43 (br s, 1H).

***N*-Methoxy-*N*-methyl (2*S*, 3*S*)-3-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-carbamoyl-oxirane-2-carboxamide (14)**:

TBSCl (151 mg, 1.0 mmol) was added to a solution of the crude amide **13** and imidazole (136 mg, 2.0 mmol) in DMF (3 mL) at 0 ℃. After the reaction mixture was allowed to warm to room temperature, the

mixture was stirred for 1 hour, a saturated aqueous $NaHCO_3$ solution was added, and the organic material was extracted with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Purification by flash chromatography (SiO_2, 30–60% ethyl acetate in hexane) afforded 155 mg (93% from **12**) of TBS ether **14** as a colorless foam: IR (KBr) υ_{max} 3397, 3298, 3244, 2955, 2931, 2859, 1690, 1668, 1591, 1374, 1259, 1110, 1034, 942, 924, 841, 779 cm^{-1}; $[\alpha]^{22}_D$ –49.3 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 1.25 (d, *J* = 6.3 Hz, 3 H), 3.23 (br s, 3 H), 3.55 (br d, *J* = 8.0 Hz, 1 H), 3.70-3.78 (m, 1 H), 3.79 (s, 3 H), 6.05 (br s, 1 H), 6.24 (br s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ –4.7, –4.5, 18.1, 20.3, 25.7 (x3), 32.4, 61.5, 62.1, 66.7, 67.2, 165.2, 167.7; HRMS, calcd for $C_{14}H_{29}N_2O_5Si$ $(M + H)^+$ 333.1846, found 333.1848. Anal. Calcd for $C_{14}H_{28}N_2O_5Si$: C, 50.58; H, 8.49; N, 8.43. Found: C, 50.27; H, 8.29; N, 8.30.

(2*R*, 3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-(2-methylbut-2-enoyl)-oxirane-2-carboxamide (15):

tert-Butyllithium (1.64 M in THF, 1.0 mL, 1.7 mmol) was added dropwise to a solution of (*E*)-2-bromobut-2-ene (122 mg, 0.90 mmol) in THF (2 mL) at –78 °C. The reaction mixture was stirred for 20 min at this temperature, a solution of TBS ether **14** (50.0 mg, 0.15 mmol) in THF (1 mL) was added dropwise at –78 °C, and the stirring was continued for another 20 min at the same temperature. A saturated aqueous NH_4Cl solution was added, the organic material was extracted with ether, and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 20–30% ethyl acetate in hexane) provided 40.5 mg (82%) of enone **15** as a colorless foam: IR (KBr) υ_{max} 3435, 3316, 2956, 2931, 2859, 1696, 1671, 1646, 1600, 1472, 1399, 1373, 1313, 1260, 1169, 1002, 924, 835, 782, 607 cm^{-1}; $[\alpha]^{22}_D$ –80.3 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 1.28 (d, *J* = 6.5 Hz, 3 H), 1.80 (s, 3 H), 1.94 (d, *J* = 7.1 Hz, 3 H), 3.26 (d, *J* = 8.0 Hz, 1 H), 3.64-3.75 (m, 1 H), 6.02 (br s, 1 H) , 6.46 (br s, 1 H), 7.07 (q, *J* = 7.1 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ –4.7, –4.5, 10.9, 15.2, 18.0, 20.3, 25.7 (x3), 65.1, 66.8, 67.5, 136.0, 144.8, 167.1, 192.7; HRMS, calcd for $C_{16}H_{30}NO_4Si$ $(M + H)^+$ 328.1944, found 328.1923.

(2*R*, 3*S*)-3-[(*R*)-1-Hydroxyethyl]-2-(2-methylbut-2-enoyl)oxirane-2-carboxamide (16):

Triethylamine trihydrofluoride (20 μL) was added to a solution of enone **15** (37.2 mg, 0.11 mmol) in DMF (1 mL) at room temperature, and the reaction mixture was stirred for 3 days. After the solvent was concentrated, the resulting residue was purified by flash chromatography (SiO_2, 40–70% ethyl acetate in hexane) to give 23.0 mg (95%) of alcohol **16** as a colorless foam: IR (KBr) υ_{max} 3459, 3430, 3294, 3171, 1679, 1641, 1602, 1438, 1377, 1325, 1298, 1258, 1167, 1108, 1071, 984, 895, 836, 747, 682, 629, 575 cm^{-1}; $[\alpha]^{22}_D$ –119.9 (*c* 0.50, MeOH); ^1H NMR (270 MHz, CD_3OD) δ 1.24 (d, *J* = 6.5 Hz, 3 H), 1.78 (s, 3 H), 1.92 (d, *J* = 6.9 Hz, 3 H), 3.23 (d, *J* = 8.1 Hz, 1 H), 3.63 (dq, *J* = 8.1 Hz, 6.5 Hz, 1 H), 7.08 (q, *J* = 6.9 Hz, 1 H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 11.0, 15.0, 19.5, 66.1, 66.8, 67.1, 137.1, 144.8, 170.3, 194.1; HRMS, calcd for $C_{10}H_{15}NO_4$ M^+ 213.1001, found 213.1008.

(1*R*, 5*R*)-4-Hydroxy-4-methyl-1-(2-methylbut-2-enoyl)-6-oxa-3-azabicyclo-[3.1.0]hexan-2-one ((*R*,*R*)-2):

Dess–Martin periodinane (119 mg, 0.28 mmol) was added to a solution of alcohol **16** (12.0 mg, 0.056 mmol) in CH_2Cl_2 (1 mL) at room temperature, and the reaction mixture was stirred for 15 min at this temperature. A 1 M solution of $Na_2S_2O_3$ and a saturated aqueous $NaHCO_3$ solution were added, the organic material was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 30–50% ethyl acetate in hexane) furnished 10.7 mg (90%) of (*R*,*R*)-**2** as a colorless foam: IR (KBr) υ_{max} 3273, 2927, 1698, 1674, 1660, 1636, 1423,

1383, 1272, 1230, 1170, 1115, 1076, 948, 853, 767, 651 cm^{-1}; $[\alpha]^{22}_D$ +10.0 (*c* 0.10, MeOH); ^1H NMR (270 MHz, CD_3OD) δ 1.51 and 1.59* (each s, 3 H), 1.83 (d, *J* = 1.3 Hz, 3 H), 1.93 (d, *J* = 7.2 Hz, 3 H), 4.00 and 4.06* (each s, 1 H), 7.08 and 6.92* (each qq, *J* = 7.2 Hz, 1.3 Hz, *J** = 6.6 Hz, 1.3 Hz, 1 H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 10.8, 15.1, 22.2, 63.9, 66.0, 84.7, 138.1, 145.8, 172.3, 191.9; HRMS, calcd for $C_{10}H_{13}NO_4$ M^+ 211.0845, found 211.0841.

Di-*tert*-Butyl 2-[(1*S*, 2*R*)-2-benzyloxy-1-hydroxypropyl]malonate (18):

Zinc chloride (0.5 M in THF, 0.24 mL, 0.12 mmol) was added to a solution of aldehyde **17** (15.9 mg, 0.10 mmol) in THF (1 mL) at room temperature. The reaction mixture was stirred for 1.5 hours and then cooled to –98 °C. A solution of di-*tert*-butyl malonate (33.4 μL, 0.15 mmol) in THF (1 mL), pretreated with LHMDS (1.0 M in THF, 0.14 mL, 0.14 mmol) at –98 °C for 20 min, was added to the reaction mixture through a cannula, and the stirring was continued for another 20 min at this temperature. A saturated aqueous NH_4Cl solution was added, the organic material was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 5–10% ethyl acetate in hexane) provided 32.8 mg (89%) of aldol adduct as a 7:1 diastereomeric mixture. This mixture was separated by flash chromatography (SiO_2, 5–8% ethyl acetate in hexane) to obtain 26.2 mg of *anti* product **18** as a colorless oil: IR (film) υ_{max} 3503, 2979, 2934, 1735, 1716, 1455, 1394, 1369, 1290, 1255, 1142, 1093, 846, 741, 698 cm^{-1}; $[\alpha]^{22}_D$ –22.2 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.3 Hz, 3 H), 1.45 (s, 9 H), 1.47 (s, 9 H), 3.53-3.59 (m, 1 H), 3.57 (d, *J* = 7.5 Hz, 1 H), 3.67 (d, *J* = 4.3 Hz, 1 H), 4.04 (td, *J* = 7.5 Hz, 4.3 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 4.62 (d, *J* = 11.5 Hz, 1 H), 7.27-7.36 (m, 5 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.9, 27.9 (x 3), 28.0 (x 3), 54.8, 71.0, 74.2, 76.3, 82.2, 82.3, 127.6, 127.7 (x 2), 128.4 (x 2), 138.3, 167.8, 168.8; HRMS, calcd for $C_{21}H_{32}O_6Na$ $(M + Na)^+$ 403.2097, found 403.2115. For the *syn* isomer: IR (film) υ_{max} 3535, 2979, 2934, 1729, 1455, 1394, 1370, 1293, 1254, 1142, 1091, 1073, 849, 745, 699 cm^{-1}; $[\alpha]^{22}_D$ –1.8 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.3 Hz, 3 H), 1.44 (s, 9 H), 1.47 (s, 9 H), 3.17 (d, *J* = 7.9 Hz, 1 H), 3.51 (d, *J* = 7.9 Hz, 1 H), 3.64 (qd, *J* = 6.3 Hz, 2.6 Hz, 1 H), 4.08 (td, *J* = 7.9 Hz, 2.6 Hz, 1 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 7.27-7.36 (m, 5 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.6, 27.9 (x6), 54.6, 71.0, 73.4, 74.7, 81.9, 82.1, 127.6, 127.9 (x 2), 128.3 (x 2), 138.2, 167.0, 168.3; HRMS, calcd for $C_{21}H_{32}O_6Na$ $(M + Na)^+$ 403.2097, found 403.2093.

Di-*tert*-Butyl 2-[(1*S*, 2*R*)-2-benzyloxy-1-[(trimethylsilyl)oxy]propyl]malonate (19):

TMSCl (31 μL, 0.24 mmol) was added to a solution of **18** (77.6 mg, 0.20 mmol) and imidazole (40.8 mg, 0.60 mmol) in DMF (1 mL) at 0 °C. After the reaction mixture was allowed to warm to room temperature and stirred for 30 min, a saturated aqueous $NaHCO_3$ solution was added, the organic material was extracted with hexane, and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 25% ethyl acetate in hexane) gave 84.0 mg (91%) of TMS ether **19** as a colorless oil: IR (film) υ_{max} 2979, 2935, 1746, 1731, 1455, 1393, 1369, 1290, 1249, 1143, 1035, 879, 845, 749, 698 cm^{-1}; $[\alpha]^{22}_D$ –7.0 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (s, 9 H), 1.16 (d, *J* = 6.3 Hz, 3 H), 1.40 (s, 9 H), 1.47 (s, 9 H), 3.39 (d, *J* = 7.8 Hz, 1 H), 3.52 (qd, *J* = 6.3 Hz, 3.9 Hz, 1 H), 4.40 (dd, *J* = 7.8 Hz, 3.9 Hz, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.60 (d, *J* = 12.0 Hz, 1 H), 7.25-7.38 (m, 5 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 0.5 (x 3), 14.4, 27.9 (x 3), 28.0 (x 3), 57.8, 70.7, 73.0, 75.8, 81.3, 81.5, 127.4, 127.7 (x 2), 128.2 (x 2), 138.7, 166.7, 167.0; HRMS, calcd for $C_{24}H_{40}O_6SiNa$ $(M + Na)^+$ 475.2492, found 475.2509. Anal. Calcd for $C_{24}H_{40}O_6Si$: C, 63.68; H, 8.91. Found: C, 63.88; H, 8.92.

Di-*tert*-Butyl 2-[(1*S*, 2*R*)-2-benzyloxy-1-[(trimethylsilyl)oxy]propyl]-2-iodo-malonate (20):

LHMDS (1.0 M in THF, 0.10 mL, 0.10 mmol) was added to a solution of **19** (35.8 mg, 0.079 mmol) in THF (1 mL) at –46 °C. The reaction mixture was stirred for 1 hour, iodine (27.9 mg, 0.11 mmol) in THF (1

mL) was added, and the stirring was continued for another 30 min. A saturated aqueous NH_4Cl solution was added, the organic material was extracted with hexane, and the combined organic extracts were washed with a 1 M solution of $Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. The resulting crude iodide **20** was used in the next step without purification: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.18 (s, 9 H), 1.17 (d, *J* = 6.2 Hz, 3 H), 1.38 (s, 9 H), 1.46 (s, 9 H), 3.83 (qd, *J* = 6.2 Hz, 3.9 Hz, 1 H), 4.02 (d, *J* = 3.9 Hz, 1 H), 4.49 (d, *J* = 12.2 Hz, 1 H), 4.59 (d, *J* = 12.2 Hz, 1 H), 7.24-7.38 (m, 5 H).

Di-*tert*-Butyl (*R*)-3-[(*R*)-1-(benzyloxy)ethyl]oxirane-2,2-dicarboxylate (21):

TBAF (1.0 M in THF, 0.16 mL, 0.16 mmol) was added to a solution of the resulting crude iodide **20** in THF (2 mL) at –46 °C. The reaction mixture was allowed to warm slowly to –15 °C and stirred for 1 hour. Water was added, the organic material was extracted with hexane, and the combined organic extracts were washed with a 1 M solution of $Na_2S_2O_3$ and water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Purification by flash chromatography (SiO_2, 5–8% ethyl acetate in hexane) furnished 22.3 mg (75% from **19**) of epoxide **21** as a colorless oil: IR (film) υ_{max} 2980, 2936, 1742, 1456, 1395, 1371, 1340, 1280, 1247, 1164, 1121, 965, 838, 811, 737, 698 cm^{-1}; $[\alpha]^{22}_D$ +42.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.3 Hz, 3 H), 1.49 (s, 9 H), 1.51 (s, 9 H), 3.44 (d, *J* = 6.3 Hz, 1 H), 3.60 (quin, *J* = 6.3 Hz, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 7.25-7.38 (m, 5 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.1, 27.9 (x 6), 61.3, 64.2, 71.4, 71.8, 83.2, 83.6, 127.6 (x 3), 128.3 (x 2), 138.2, 163.8, 164.9; HRMS, calcd for $C_{21}H_{31}O_6$ $(M + H)^+$ 379.2121, found 379.2099.

Di-*tert*-Butyl (*R*)-3-[(*R*)-1-hydroxyethyl]oxirane-2,2-dicarboxylate (22):

A suspension of **21** (37.7 mg, 0.10 mmol) and palladium hydroxide on charcoal (10 mg) in methanol (1 mL) was stirred under H_2 atmosphere at 50 °C for 4 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2, 10–20% ethyl acetate in hexane) provided 27.5 mg (96%) of alcohol **21** as colorless prisms: mp 44-46 °C; IR (KBr) υ_{max} 3481, 2982, 2938, 1746, 1736, 1478, 1461, 1395, 1373, 1338, 1281, 1246, 1160, 1129, 973, 852, 836, 812 cm^{-1}; $[\alpha]^{22}_D$ +22.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (d, *J* = 6.4 Hz, 3 H), 1.51 (s, 9 H), 1.54 (s, 9 H), 2.55 (br d, *J* = 4.9 Hz, 1 H), 3.30 (d, *J* = 6.6 Hz, 1 H), 3.64 (d quin, *J* = 6.4 Hz, 1.4 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.2, 27.9 (x 6), 60.8, 64.6, 66.5, 83.9, 84.1, 164.5, 164.8; HRMS, calcd for $C_{14}H_{24}O_6Na$ $(M + Na)^+$ 311.1471, found 311.1479. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.20; H, 8.36.

(*S*)-MTPA ester of **22**: IR (film) υ_{max} 2983, 2940, 1752, 1455, 1396, 1372, 1344, 1255, 1171, 1120, 1061, 1024, 964, 837, 810, 765, 720 cm^{-1}; $[\alpha]^{22}_D$ –13.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 1.50 (d, *J* = 7.2 Hz, 3 H), 1.54 (s, 9 H), 3.40 (d, *J* = 7.9 Hz, 1 H), 3.55 (d, *J* = 1.2 Hz, 3 H), 5.00 (dq, *J* = 7.9 Hz, 7.2 Hz, 1 H), 7.37-7.44 (m, 3 H), 7.52-7.57 (m, 2 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.5, 27.8 (x 6), 55.4, 61.6, 61.7, 68.9, 83.8, 84.4, 84.7 (q, *J* = 28.1 Hz), 123.2 (d, *J* = 288.7 Hz), 127.5, 128.4 (x 2), 129.7 (x 2), 132.0, 163.1, 163.9, 165.1; HRMS, calcd for $C_{24}H_{31}F_3O_8Na$ $(M + Na)^+$ 527.1869, found 527.1872.

(*R*)-MTPA ester of **22**: IR (film) υ_{max} 2983, 2940, 1750, 1455, 1396, 1372, 1344, 1254, 1169, 1119, 1061, 1024, 966, 836, 809, 766, 720 cm^{-1}; $[\alpha]^{22}_D$ +48.2 (*c* 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.5 Hz, 3 H), 1.49 (s, 9 H), 1.50 (s, 9 H), 3.52 (d, *J* = 8.5 Hz, 1 H), 3.60 (d, *J* = 1.0 Hz, 3 H), 4.98 (dq, *J* = 8.5 Hz, 6.5 Hz, 1 H), 7.37-7.45 (m, 3 H), 7.51-7.54 (m, 2 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.3, 27.8 (x 6), 55.6, 61.6, 61.7, 68.9, 84.0, 84.4, 84.6 (q, *J* = 27.3 Hz), 123.1 (d, *J* = 288.4 Hz), 127.2, 128.4 (x 2), 129.7 (x 2), 132.0, 163.0, 163.9, 165.0; HRMS, calcd for $C_{24}H_{31}F_3O_8Na$ $(M + Na)^+$ 527.1869, found 527.1856.

(1*S*,4*R*,5*R*)-4-Methyl-2-oxo-3,6-dioxabicyclo[3.1.0]hexane-1-carboxylic acid (23):

Formic acid (1.0 mL) was added to the epoxide **22** (87.7 mg, 0.30 mmol) and stirred for 12 hours at room temperature. Formic acid was removed *in vacuo* to yield epoxylactone **23**, which was used in the next step without purification: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.50 (d, J = 6.8 Hz, 3 H), 4.35 (s, 1 H), 4.74 (q, J = 6.8 Hz, 1 H).

_N_-Methoxy-_N_-methyl (1_S_, 4_R_, 5_R_)-4-methyl-2-oxo-3,6-dioxabicyclo[3.1.0]hex-ane-1-carboxamide (24):

Diisopropylethylamine (0.21 mL, 1.22 mmol), _N,O_-dimethylhydroxylamine (59.5 mg, 0.61 mmol), and PyBOP® (23.9 mg, 0.46 mmol) were added successively to a solution of the resulting epoxylactone **23** in CH_2Cl_2 (2 mL) at 0 ℃. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Water was added, the organic material was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 40–60% ethyl acetate in hexane) provided 54.7 mg (89% from **22**) of Weinreb amide **24** as colorless prisms: mp 114-115 °C; IR (KBr) υ_{max} 3066, 2996, 2949, 1773, 1697, 1475, 1378, 1330, 1238, 1176, 1073, 1002, 983, 932, 864, 782, 639, 546 cm^{-1}; $[\alpha]^{22}_D$ +1.8 (_c_ 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.47 (d, J = 6.8 Hz, 3 H), 3.29 (s, 3 H), 3.75 (s, 3 H), 4.11 (s, 1 H), 4.73 (q, J = 6.8 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.4, 32.2, 58.1, 61.1, 63.7, 75.5, 161.5, 167.1; HRMS, calcd for $C_8H_{12}NO_5$ (M + H)$^+$ 202.0715, found 202.0705. Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.55; H, 5.52; N, 6.82.

_N_-Methoxy-_N_-methyl (2_R_, 3_R_)-2-carbamoyl-3-[(_R_)-1-hydroxyethyl]oxirane-2-carboxamide (25):

A saturated ammonia solution in methanol (5 mL) was added to a solution of the Weinreb amide **24** (200 mg, 0.99 mmol) in methanol (3 mL) at room temperature. After stirring for 30 min, ammonia and methanol were removed *in vacuo*. The resulting amide **25** was used in the next step without any purification: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (d, J = 6.4 Hz, 3 H), 3.23 (br s, 3 H), 3.42 (d, J = 8.2 Hz, 1 H), 3.69-3.84 (m, 1 H), 3.77 (s, 3 H), 4.04 (br s, 1 H), 6.56 (br s, 1 H), 6.73 (br s, 1 H).

_N_-Methoxy-_N_-methyl (2_R_, 3_R_)-2-carbamoyl-3-[(_R_)-1-[(triethylsilyl)oxy]ethyl]-oxirane-2-carboxamide (26):

TESCl (0.33 mL, 2.0 mmol) was added to a solution of the resulted crude amide **25** and imidazole (204 mg, 3.0 mmol) in DMF (10 mL) at 0 ℃. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. A saturated aqueous $NaHCO_3$ solution was added, the organic material was extracted with ethyl acetate, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* after filtration. Purification by flash chromatography (SiO_2, 40–70% ethyl acetate in hexane) afforded 288 mg (87% from **24**) of TES ether **26** as a colorless foam: IR (KBr) υ_{max} 3434, 3251, 2959, 2877, 1709, 1666, 1598, 1459, 1414, 1393, 1107, 1031, 846, 780, 749, 732, 612 cm^{-1}; $[\alpha]^{22}_D$ +55.9 (_c_ 0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.59 (q, J = 7.9 Hz, 6 H), 0.95 (t, J = 7.9 Hz, 9 H), 1.34 (d, J = 6.1 Hz, 3 H), 3.23 (br s, 3 H), 3.50 (br d, J = 3.5 Hz, 1 H), 3.77 (s, 3 H), 3.80-3.86 (m, 1 H), 5.91 (br s, 1 H), 6.19 (br s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 4.7 (x 3), 6.7 (x 3), 21.7, 32.4, 61.5, 63.2, 64.4, 65.7, 165.5, 167.3; HRMS, calcd for $C_{14}H_{29}N_2O_5Si$ (M + H)$^+$ 333.1846, found 333.1831. Anal. Calcd for $C_{14}H_{29}N_2O_5Si$: C, 50.58; H, 8.49; N, 8.43. Found: C, 50.49; H, 8.46; N, 8.39.

(2_S_, 3_R_)-2-(2-Methylbut-2-enoyl)-3-[(_R_)-1-[(triethylsilyl)oxy]ethyl]oxirane-2-carboxamide (27):

tert-Butyllithium (1.64 M in THF, 1.0 mL, 1.7 mmol) was added dropwise to a solution of (_E_)-2-bromobut-2-ene (122 mg, 0.90 mmol) in THF (2 mL) at −78 ℃. The reaction mixture was stirred for 15 min at this temperature. A solution of TES ether **26** (50.0 mg, 0.15 mmol) in THF (1 mL) was added dropwise at −78 ℃

and the stirring was continued for another 30 min. A saturated aqueous NH_4Cl solution was added, and the organic material was extracted with ether, and the combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 20–30% ethyl acetate in hexane) provided 43.2 mg (88%) of enone **27** as a colorless foam: IR (KBr) υ_{max} 3420, 3248, 2957, 2877, 1705, 1676, 1642, 1607, 1410, 1105, 1080, 998, 920, 841, 779, 749, 726 cm^{-1}; $[\alpha]^{22}_D$ +57.3 (*c* 0.50, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.61 (q, *J* = 7.9 Hz, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.34 (d, *J* = 6.1 Hz, 3 H), 1.81 (s, 3 H), 1.94 (d, *J* = 7.0 Hz, 3 H), 3.17 (d, *J* = 7.5 Hz, 1 H), 3.74-3.85 (m, 1 H), 6.15 (br s, 1 H), 6.49 (br s, 1 H), 7.21 (qd, *J* = 7.0 Hz, 1.2 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 4.9 (x 3), 6.7 (x 3), 10.8, 15.3, 21.7, 65.3, 65.9, 66.2, 135.9, 146.0, 166.8, 193.2; HRMS, calcd for $C_{16}H_{30}NO_4Si$ $(M + H)^+$ 328.1944, found 328.1935.

(2*S*, 3*R*)-3-[(*R*)-1-Hydroxyethyl]-2-(2-methylbut-2-enoyl)oxirane-2-carboxamide (28):

Triethylamine trihydrofluoride (20 μL) was added to a solution of enone **27** (26.4 mg, 0.081 mmol) in DMF (1 mL) at room temperature and the reaction mixture was stirred for 1 hour. The solvent was concentrated, and the resulting residue was purified by flash chromatography (SiO_2, 50–80% ethyl acetate in hexane) to give 17.0 mg (99%) of alcohol **28** as a colorless foam: IR (KBr) υ_{max} 3375, 3313, 2976, 2925, 1695, 1660, 1635, 1611, 1401, 1380, 1268, 1118, 1086, 971, 906, 849, 685, 625 cm^{-1}; $[\alpha]^{22}_D$ +55.4 (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.4 Hz, 3 H), 1.80 (s, 3 H), 1.94 (d, *J* = 6.4 Hz, 3 H), 3.18 (d, *J* = 7.9 Hz, 1 H), 3.67-3.78 (m, 2 H), 6.53 (br s, 1 H), 6.75 (br s, 1 H) , 7.21 (q, *J* = 6.4 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 10.8, 15.3, 20.3, 65.2, 65.4, 66.1, 135.8, 146.1, 167.8, 192.9; HRMS, calcd for $C_{10}H_{16}NO_4$ $(M + H)^+$ 214.1079, found 214.1069.

(1*S*, 5*S*)-4-Hydroxy-4-methyl-1-(2-methylbut-2-enoyl)-6-oxa-3-azabicyclo-[3.1.0]hexan-2-one ((*S*,*S*)-2):

Dess–Martin periodinane (80.6 mg, 0.19 mmol) was added to a solution of alcohol **28** (7.9 mg, 0.037 mmol) in CH_2Cl_2 (0.5 mL) at room temperature and the reaction mixture was stirred for 15 min at this temperature. A 1 M solution of $Na_2S_2O_3$ and a saturated aqueous $NaHCO_3$ solution were added, the organic material was extracted with ethyl acetate, and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* after filtration. Flash chromatography (SiO_2, 30–50% ethyl acetate in hexane) furnished 7.0 mg (90%) of (*S*,*S*)-**2** as a colorless foam: $[\alpha]^{22}_D$ –10.6 (*c* 0.10, MeOH); HRMS, calcd for $C_{10}H_{14}NO_4$ M^+ 212.0923, found 212.0916.

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