Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12740–12746

Synthesis of the octahydroindole unit of aeruginosins via asymmetric hydrogenation of the Diels–Alder adducts of 2-amido-2,4-pentadienoate

Yoichiro Hoshina, Takayuki Doi and Takashi Takahashi*

Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro, Tokyo 152-8552, Japan

Received 31 August 2007; accepted 28 September 2007
Available online 2 October 2007

Abstract—An optically active octahydroindole, the core unit of aeruginosins (Choi) was synthesized. The Diels–Alder reaction of Danishefsky's diene with methyl (*Z*)-2-acetamido-2,4-pentadienoates provided the adducts regioselectively in good yield. The adducts were converted to the L-Choi precursor by asymmetric hydrogenation, followed by acid cyclization.

1. Introduction

Aeruginosin 298-A (**1a**), isolated from *Microcystis aeruginosa* (NIES-298), exhibited inhibitory activity toward serine proteases (Fig. 1).[1] Other aeruginosins[2] and related compounds, oscillarin (**1b**)[3] and aeruginosin EI461 (**1c**)[4,5] have also been studied for biological interests. Most of the aeruginosins have an unusual amino acid core structure 2-carboxy-6-hydroxyoctahydroindole (L-Choi), and aeruginosin EI461 (**1c**) has 3a,7a-di-*epi*-L-Choi.[5] From the interest of their binding mode to the target proteins[3,6] and chemical structures of L-Choi, the total synthesis of aeruginosins[3,5,7–9] and the synthesis of Choi[10,11] have been demonstrated by several groups. Recently, we have reported a combinatorial library synthesis of aeruginosin derivatives by peptide elongation at both C-terminus and N-terminus of a polymer-supported L-Choi, providing a 300 times more potent trypsin inhibitor.[12] Herein, we report an efficient synthesis of the Choi derivative via catalyst-controlled asymmetric hydrogenation as a key step.

Diels–Alder reaction is a powerful tool for the construction of a six-membered ring system. As for dienes, 1-methoxy-3-trimethylsiloxy-1,3-butadiene[13] (Danishefsky's diene) is widely used for the syntheses of 2-cyclohexenones due to its availability, high reactivity, and regioselectivity. It was reported that the protected L-Choi **2** utilized in the synthesis of aeruginosin 298-A was prepared from ketone (−)-*endo*-**3** by stereoselective reduction with LS-Selectride.[8b] Therefore, we planned the synthesis of (−)-*endo*-**3** as illustrated in Scheme 1, which includes Diels–Alder reaction of **6** and **7**, asymmetric hydrogenation of 2-amidoacrylate derivative **5**, and acid cyclization of **4**. To achieve the synthesis, we need to overcome the following two important points: (i) how the Diels–Alder reaction proceeds regioselectively at the γ,δ positions in **7** and (ii) which derivative related to **5** is suitable for catalyst-controlled asymmetric hydrogenation to induce stereochemistry at the 2-position independent of the cyclohexenyl group. The cyclization of **4**, after isomerization under thermodynamic conditions could provide **3**

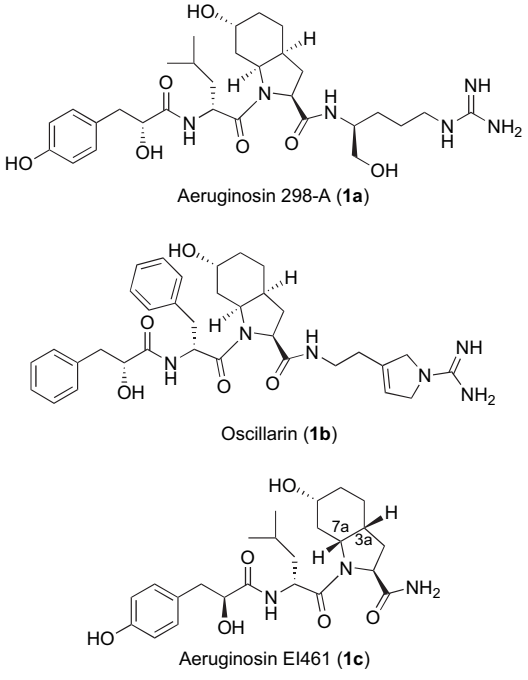
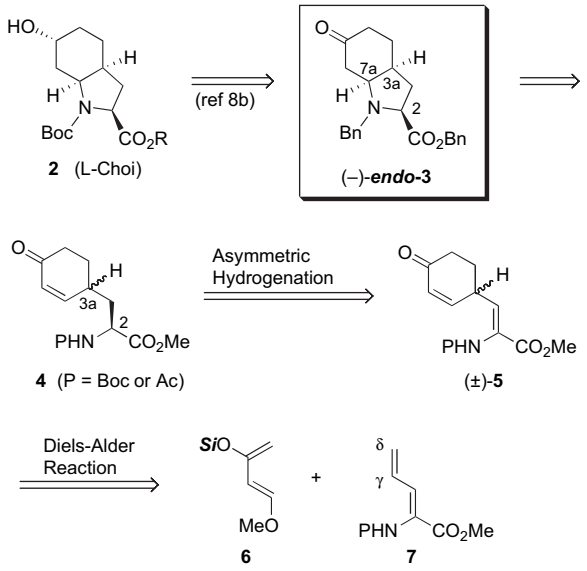


Figure 1. Structures of aeruginosin 298-A, oscillarin, and aeruginosin EI461.

* Corresponding author. E-mail: ttak@apc.titech.ac.jp

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.078

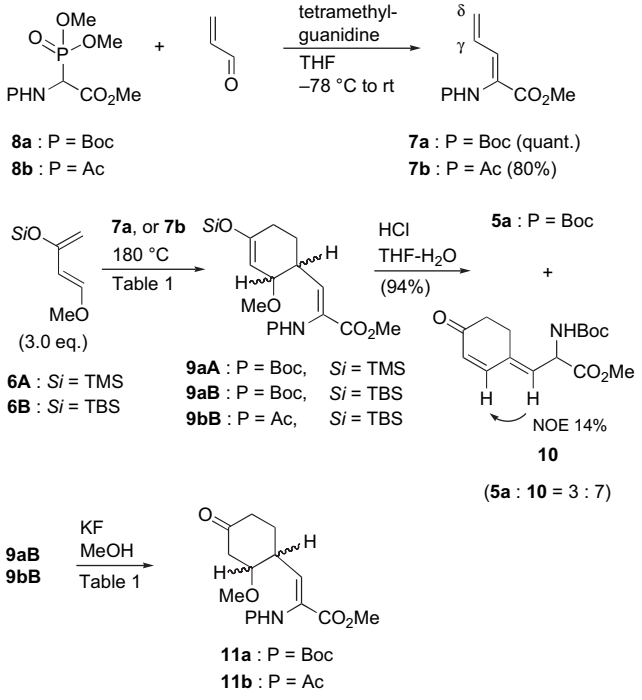
because it is easy to epimerize at the 3a position in **4** under strongly acidic conditions.



Scheme 1. Synthetic strategy of the key intermediate **3**.

2. Results and discussion

The Boc and acetyl protected dienamide esters **7a** and **7b** were prepared from the phosphonates **8a** and **8b** with acrolein by Burk method,[14] respectively (Scheme 2). The reaction of Danishefsky's diene **6A** with **7a** was carried out effectively at 180 °C in the absence of solvent for 30 min to provide **9aA** in 57% yield as an inseparable mixture of two diastereomers (Table 1, Entry 1). The reaction proceeded at the γ,δ positions in **7a** with complete regioselectivity. When the reaction was carried out at 180 °C in *p*-xylene, the yield decreased to 28% due to decomposition of **7a** (Entry 2). The reaction was complete in 10 min under microwave irradiation, whereas the yield was 42% in xylene and 39% in the absence of solvent (Entries 3 and 4). We next reacted diene **6B** with **7a**. The adduct **9aB** was provided in 62% yield (Entry 5). The reaction of **6B** with acetyl protected dienamide ester **7b** also afforded the corresponding adduct **9bB** in 69% (Entry 7). The *endo*/*exo* stereoselectivity, however, was not induced in all reactions.



Scheme 2. Preparation of Diels–Alder adducts **11**.

Table 1. Preparation of the precursor for asymmetric hydrogenation

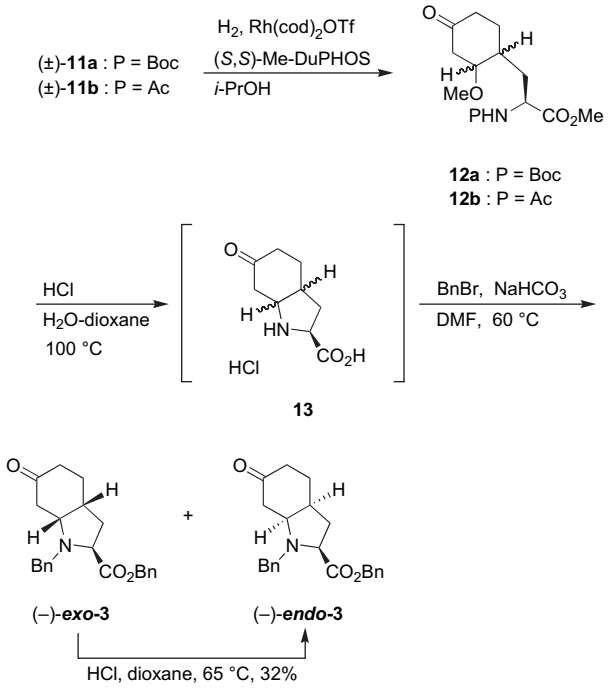
Entry	7	6	Conditions[a]	Yield of **9** (%)	Yield from **9** to **11** (%)	One-pot yield from **7** to **11** (%)
1	**7a**	**6A**	I	57 (59:41)[b]		
2	**7a**	**6A**	II	28 (57:43)[b]		
3	**7a**	**6A**	III	42 (54:46)[b]		
4	**7a**	**6A**	IV	39 (56:44)[b]		
5	**7a**	**6B**	I	62 (56:44)[b]	87 (57:43)	
6	**7a**	**6B**	I			59 (58:42)
7	**7b**	**6B**	I	69 (59:41)	91 (Cis)[c] 52 (Trans)[c]	
8	**7b**	**6B**	I			52 (90:10)

The numbers in parentheses refers to the ratio of cis:trans isomers (determined by ^{1}H NMR analysis).
[a] I: Neat, 180 °C, 30 min; II: xylene, 180 °C, 30 min; III: xylene, microwave, 180 °C, 10 min; IV: neat, microwave, 180 °C, 3 min.
[b] The cis and trans isomers were inseparable.
[c] The stereoisomers were partially separated before use.

Treatment of **9aA** with 5 mM aqueous HCl in THF[13] provided a 30:70 mixture of **5a** and **10** in which an alkenyl moiety isomerized to a conjugated ketone as thermodynamically stable form. Therefore, we needed not to form a conjugated ketone in a cyclohexane ring. We next converted **9aB** and **9bB** to **11a** and **11b** by treatment with KF in methanol, respectively (Entries 5 and 7). It is noted that removal of the TBS group in *cis*-**9bB** gave *cis*-**11b** in 91% yield, whereas the *trans*-**9bB** gave *trans*-**11b** in only 52% yield due to the fact that unknown polar products were formed (Entry 7). The cycloaddition and deprotection were sequentially performed in one pot. From **7a** and **6B**, **11a** was obtained in 59% overall yield as a 58:42 diastereomer mixture (Entry 6). From **7b** and **6B**, **11b** was obtained in 52% with a 90:10 ratio (Entry 8).

Asymmetric hydrogenation of enamides (±)-**11a** (cis:trans=58:42) and (±)-**11b** (cis:trans=90:10) was performed utilizing an Rh–(*S*,*S*)-Me-DuPHOS system (Scheme 3).[15,16] Both of the enamides underwent asymmetric hydrogenation in the presence of 5 mol % of [(COD)Rh–(*S*,*S*)-Me-DuPHOS]OTf in 2-propanol[17] under H_2 (0.1 MPa) leading to the corresponding amino acid derivatives **12a** and **12b** in quantitative yields, respectively, as a mixture of diastereomers (Table 2). Therefore, the enantiomeric excesses of the products were analyzed after conversion to cis-fused (−)-*exo*-**3** and (−)-*endo*-**3**, reported previously.[8b] As shown in Scheme 3, treatment of **12** with 6 M aqueous HCl/dioxane at 100 °C induced elimination of methanol, removal of the protecting groups, and sequential cyclization to form the bicyclic amino acid **13**. Dibenzylation of **13** in situ afforded (−)-*exo*-**3** and (−)-*endo*-**3**, which were isolated by silica gel column

chromatography. The yields and enantiomeric excesses (ee's) determined by chiral HPLC analysis are summarized in Table 2. From the Boc protected derivative **12a**, **3** was obtained with low ee's (up to 41% ee) (Entry 1). On the other hand, from the acetyl protected derivative **12b**, highly enantiorich compounds were obtained, (−)-*exo*-**3** in 32% (95% ee) and (−)-*endo*-**3** in 21% (95% ee) (Entry 2). Both (±)-*cis*-**11b** and (±)-*trans*-**11b** were independently converted to **3** in the same yields and ee's (Entries 3 and 4). *Thus, this asymmetric hydrogenation proceeded efficiently by the catalyst-control without influence of the stereochemistry on the cyclohexyl group.*[16] The higher H_2 pressure gave lower ee's (Entry 5). The difference in the ee values derived from the protecting groups would be caused by the enantioselectivity of the asymmetric hydrogenation step. The bidentate chelation of a substrate–Rh–(*S*,*S*)-Me-DuPHOS complex would be weaker in the *N*-Boc derivative than in the *N*-acetyl derivative due to the steric effect and/or less electron donation of the O-*t*-Bu group.[16,18] The optical purity of (−)-*endo*-**3** was further enriched (>99% ee) by recrystallization from ethanol/hexane. The absolute stereochemistry was determined by the optical rotation of *exo*-**3** and *endo*-**3**.[8b,10] Acid-mediated isomerization of (−)-*exo*-**3** to (−)-*endo*-**3** was performed in 32% yield with recovery of (−)-*exo*-**3** (43%) as we reported previously.[12a,19] Chiral HPLC analysis proved that this isomerization proceeded without loss of optical purity. It has been reported that (−)-*endo*-**3** and (−)-*exo*-**3** are easily converted to the protected L-Choi (**2**) and 3a,7a-di-*epi*-L-Choi, respectively.[5,8b]



Scheme 3. The synthesis of (−)-*exo*-**3** and (−)-*endo*-**3**.

In summary, we have demonstrated the synthesis of the optically pure octahydroindole that is a core unit of aeruginosins (L-Choi). The Diels–Alder reaction of Danishefsky-type diene **6** with the dienamides **7** in the absence of solvent provided the adducts as a mixture of stereoisomers with complete regioselectivity. The adduct **11b** underwent asymmetric hydrogenation catalyzed by an Rh–DuPHOS system inducing high enantiomeric excess at the 2-position in **12b**. Finally, acid cyclization provided the cis-fused (−)-*endo*-**3** with 95% ee and (−)-*exo*-**3** with 95% ee. This synthetic methodology will be useful for the synthesis of Choi derivatives by utilization of other substituted Danishefsky's dienes and/or substituted 2-(acetoamido)pentadienoates.

Table 2. Yields of **12** and **3**, and enantiomeric excesses of **3**

Entry	**11**	Yields and ee's[a] (%)		
		12	(−)-*exo*-**3**	(−)-*endo*-**3**
1[b]	(±)-**11a** (58:42)	>99	35 (37)	23 (41)
2[b]	(±)-**11b** (90:10)	>99	32 (95)	21 (95)
3[b]	(±)-*cis*-**11b**	96	32 (93)	25 (94)
4[b]	(±)-*trans*-**11b**	95	35 (95)	27 (94)
5[c]	(±)-*cis*-**11b**	94	37 (85)	29 (82)

[a] The numbers in parentheses refer to the enantiomeric excesses determined by chiral HPLC analysis.
[b] Rh catalyst (5 mol %), 0.1 MPa, 3 h.
[c] Rh catalyst (5 mol %), 0.4 MPa, 14 h.

3. Experimental

3.1. General information

^{1}H spectra were recorded on JEOL Model ECP-400 (400 MHz) or ECA-400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform-*d*: δ 7.26, dimethylsulfoxide-d_6: δ 2.50). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, and m=multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on JEOL Model ECP-400 (100 MHz) or ECA-400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform-*d*: δ 77.0, dimethylsulfoxide-d_6: δ 39.6). Infrared spectra were recorded on Perkin-Elmer Spectrum One or Shimadzu IRPrestige-21 FT-IR spectrometer. Mass spectra were obtained on JMN1100 (FAB) or (ESI-TOF) mass spectrometers. Analytical thin-layer chromatography was performed on silica gel TLC plates. Visualization was accomplished with UV light and ethanol solution of phosphomolybdic acid or ninhydrin/H_2O/1-butanol solution followed by heating. Column chromatography was performed on Merck silica gel 60 (0.063–0.200 mm) or Nacalai silica gel 60 (spherical, neutrality). Optical rotations were measured with JASCO P-1020 or Horiba SEPA-300 polarimeter. Chiral HPLC was performed on Shimadzu LC-10 series system. The column was Daicel Chiralcel OJ or OD-H 4.6×250 mm. Peak areas were integrated with 214 nm.

3.1.1. Methyl 2-*tert*-butoxycarbonylamino-2-(dimethoxyphosphinyl)acetate (8a). A solution of methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate (2.3 g, 7.0 mmol) and $(Boc)_2O$ (1.8 mL, 7.7 mmol) in MeOH (25 mL) was treated with 5% palladium–carbon (0.23 g) under a hydrogen atmosphere (0.1 MPa) for 24 h. The reaction

mixture was filtered through Celite®, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=1/2–EtOAc) to afford **8a** (2.1 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (9H, s), 3.78–3.89 (9H, m), 4.88 (1H, dd, J=9.2, 22.7 Hz), 5.35 (1H, br d, J=8.2 Hz).

3.1.2. Methyl 2-acetylamino-2-(dimethoxyphosphinyl)-acetate (8b). A solution of methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate (5.7 g, 17 mmol) and acetic anhydride (4.4 mL, 47 mmol) in MeOH (48 mL) was treated with 10% palladium–carbon (0.59 g) under a hydrogen atmosphere (0.3 MPa) for 24 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated under vacuum. The residue was crystallized from EtOAc and hexane to afford **8b** (3.7 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s), 3.80–3.86 (9H, m), 5.24 (1H, dd, J=8.9, 22.2 Hz), 6.40 (1H, br d, J=7.8 Hz).

3.1.3. Methyl (*Z*)-2-*tert*-butoxycarbonylamido-2,4-pentadienoate (7a). To a solution of the phosphate **8a** (1.3 g, 4.4 mmol) in THF (14 mL) was added 1,1,3,3-tetramethylguanidine (0.55 mL, 4.4 mmol) and acrolein (0.33 mL, 4.4 mmol) in THF (5 mL) at −78 °C. After stirring for 15 min at the same temperature, the resulting solution was warmed to room temperature for 1 h. The reaction mixture was quenched with 1 mol/L HCl and extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=4/1) to afford **7a** (1.0 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (9H, s), 3.81 (3H, s), 5.47 (1H, d, J=10.6 Hz), 5.58 (1H, d, J=16.9 Hz), 6.19 (1H, br s), 6.58 (1H, ddd, J=10.6, 10.6, 16.9 Hz), 6.93 (1H, d, J=11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 52.3, 80.7, 124.0, 124.4, 130.7, 131.6, 153.2, 165.5; IR (neat) 3333, 2980, 1707, 1492, 1367, 1261, 1164, 1049, 997, 776 cm^{-1}.

3.1.4. Methyl (*Z*)-2-acetamidopenta-2,4-dienoate (7b). To a solution of the phosphate **8b** (960 mg, 4.0 mmol) in THF (16 mL) was added 1,1,3,3-tetramethylguanidine (0.67 mL, 5.3 mmol) and acrolein (0.36 mL, 4.8 mmol) in THF (8 mL) at −78 °C. After stirring for 30 min at the same temperature, the resulting solution was warmed to room temperature for 2 h. The reaction mixture was quenched with 1 mol/L HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=1/1–EtOAc) to afford **7b** (540 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H, s), 3.81 (3H, s), 5.49 (1H, d, J=9.6 Hz), 5.60 (1H, d, J=16.5 Hz), 6.41–6.54 (1H, m), 7.05 (1H, d, J=11.0 Hz), 7.09 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 52.4, 123.8, 124.9, 131.7, 132.8, 165.3, 169.0; IR (KBr) 2953, 1728, 1674, 1552, 1437, 1261, 1009, 770 cm^{-1}.

3.1.5. Methyl (*Z*)-2-*tert*-butoxycarbonylamino-3-[4-(trimethylsilyloxy)-2-methoxycyclohex-3-enyl]-acrylate (9aA, mixture of diastereomers). The mixture of the dienamide **7a** (150 mg, 0.66 mmol) and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**6A**, 0.39 mL, 2.0 mmol) was heated at 180 °C for 30 min. The reaction mixture was purified by silica gel column chromatography (spherical, neutrality, hexane/EtOAc=2/1–EtOAc only) to afford **9aA** (150 mg, 57%, cis:trans=59:41 (determined by ^{1}H NMR)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 and 0.33 (9H, s), 1.46 and 1.47 (9H, s), 1.56–1.70 (1H, m), 1.85–2.25 (3H, m), 2.57–2.69 and 2.73–2.84 (1H, m), 3.31 and 3.32 (3H, s), 3.66–3.73 and 3.82–3.90 (1H, m), 3.77 and 3.78 (3H, s), 5.00 and 5.09 (1H, br s and d, J=4.3 Hz), 6.06 and 6.12 (1H, br s), 6.72 and 6.79 (1H, d and s, J=9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2 and 0.3, 22.9, 28.1, 28.7 and 29.0, 37.5 and 37.9, 52.2, 55.9 and 56.1, 75.9, 80.4, 102.8, 103.5, 137.2, 153.5 and 153.7, 154.4, 165.5; IR (neat) 3335, 2955, 1728, 1660, 1489, 1368, 1253, 1167, 1084, 884, 846, 759 cm^{-1}.

3.1.6. Mixture of methyl 2-*tert*-butoxycarbonylamino-3-(4-oxocyclohex-2-enyl)acrylate (5a) and methyl (3*E*)-2-*tert*-butoxycarbonylamino-3-(4-oxocyclohex-2-enylidene)propionate (10). To a solution of the trimethylsilyl ether **9aA** (140 mg, 0.35 mmol) in THF (1 mL) was added 0.005 mol/L HCl (1 mL) at room temperature. After stirring for 2 h at this temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the aqueous solution was extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. The solution was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=3/1–3/2) to afford mixture of **5a** and **10** (99 mg, total yield 94%, **5a**:**10**=3:7 (determined by ^{1}H NMR)). Compound **5a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (9H, s), 1.86–1.98 (1H, m), 2.19–2.28 (1H, m), 2.43 (1H, ddd, J=4.9, 11.6, 16.7 Hz), 2.68–2.80 (1H, m), 3.50–3.60 (1H, m), 3.81 (3H, s), 6.07 (1H, dd, J=2.4, 10.1 Hz), 6.19 (1H, br s), 6.42 (1H, d, J=10.2 Hz), 6.90 (1H, dd, J=2.7, 10.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 28.1, 30.7, 37.1, 52.5, 80.9, 126.6, 129.3, 129.7, 133.8, 150.9, 164.9, 198.7. Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 2.49–2.64 (2H, m), 2.85–3.09 (2H, m), 3.77 (3H, s), 5.14 (1H, br t, J=8.0 Hz), 5.25–5.39 (1H, m), 5.59 (1H, d, J=9.3 Hz), 5.99 (1H, d, J=10.0 Hz), 6.97 (1H, d, J=10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 28.1, 36.1, 51.9, 52.8, 80.2, 128.1, 129.6, 137.9, 147.6, 154.7, 170.7, 198.9; IR (KBr) 3343, 2978, 1694, 1487, 1250, 1161, 1049, 864, 756 cm^{-1}; MS (FAB) *m*/*z*: 296 $[M+H]^+$.

3.1.7. Methyl (*Z*)-2-*tert*-butoxycarbonylamino-3-[4-(*tert*-butyldimethylsilyloxy)-2-methoxycyclohex-3-enyl]acrylate (9aB, mixture of diastereomers). The mixture of the dienamide **7a** (110 mg, 0.5 mmol) and *trans*-3-(*tert*-butyldimethylsilyloxy)-1-methoxy-1,3-butadiene (**6B**, 0.36 mL, 1.5 mmol) was heated at 180 °C for 30 min. The reaction mixture was purified by silica gel column chromatography (spherical, neutrality, hexane/EtOAc=8/1–4/1) to afford **9aB** (138 mg, 62%, cis:trans=56:44 (determined by ^{1}H NMR)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 and 0.17 (6H, s), 0.92 (9H, s), 1.46 (9H, s), 1.56–1.68 (1H, m), 1.87–2.22 (3H, m), 2.56–2.67 and 2.73–2.82 (1H, m), 3.31 and 3.32 (3H, s), 3.66–3.72 and 3.83–3.88 (1H, m), 3.77 and 3.78 (3H, s), 5.00 and 5.09 (1H, br s and d, J=4.3 Hz),

6.06 and 6.16 (1H, br s), 6.72 and 6.80 (1H, d and s, J=9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6 and −4.5, 17.9, 22.9, 25.5, 28.0, 28.6 and 29.0, 37.4 and 37.8, 52.0 and 52.1, 55.8 and 56.0, 75.8, 80.2 and 80.5, 102.8, 103.5, 137.1, 153.4 and 153.6, 154.1 and 154.5, 165.3 and 165.4; IR (neat) 3337, 2932, 1727, 1661, 1473, 1368, 1251, 1168, 1084, 878, 839, 780 cm^{-1}.

3.1.8. Methyl (*Z*)-2-acetylamino-3-[4-(*tert*-butyldimethylsilanoxy)-2-methoxycyclohex-3-enyl]acrylate (9bB, mixture of diastereomers). The mixture of the dienamide **7b** (170 mg, 1.0 mmol) and *trans*-3-(*tert*-butyldimethylsilyloxy)-1-methoxy-1,3-butadiene (**6B**, 0.72 mL, 3.0 mmol) was heated at 180 °C for 30 min. The reaction mixture was purified by silica gel column chromatography (spherical, neutrality, hexane/EtOAc=2/1–EtOAc only) to afford **9bB** (270 mg, 69%, cis:trans=59:41 (determined by ^{1}H NMR)). The two isomers were partially separated by silica gel column chromatography (spherical, neutrality, hexane/EtOAc=2/1–EtOAc only) into *cis*-**9bB** and *trans*-**9bB**. *cis*-**9bB**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.15 (3H, s), 0.16 (3H, s), 0.90 (9H, s), 1.45–1.54 (1H, m), 1.71–1.83 (1H, m), 1.90–2.07 (2H, m), 1.93 (3H, s), 2.63–2.70 (1H, m), 3.18 (3H, s), 3.63 (3H, s), 3.78 (1H, br t, J=3.9 Hz), 5.05 (1H, d, J=4.1 Hz), 6.43 (1H, d, J=9.6 Hz), 9.25 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ −4.5, 17.7, 22.3, 23.0, 25.5, 28.4, 35.9, 51.8, 55.2, 74.7, 103.6, 127.4, 136.4, 153.9, 164.8, 168.9; IR (neat) 3271, 2930, 2859, 1732, 1634, 1371, 1200, 1082, 839, 779 cm^{-1}. *trans*-**9bB**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.15 (6H, s), 0.90 (9H, s), 1.44–1.55 (1H, m), 1.71–1.80 (1H, m), 1.90–2.05 (2H, m), 1.94 (3H, s), 2.60–2.71 (1H, m), 3.17 (3H, s), 3.63 (3H, s), 3.65–3.70 (1H, m), 4.94 (1H, d, J=3.7 Hz), 6.24 (1H, d, J=9.6 Hz), 9.28 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ −4.5, 17.8, 22.3, 23.2, 25.5, 27.5, 35.7, 51.9, 54.7, 77.5, 103.5, 128.4, 136.0, 153.6, 164.8, 168.9; IR (neat) 3269, 2930, 2859, 1732, 1645, 1514, 1435, 1371, 1240, 1084, 874, 779 cm^{-1}.

3.1.9. Methyl (*Z*)-2-*tert*-butoxycarbonylamino-3-(2-methoxy-4-oxocyclohexyl)acrylate (11a, mixture of diastereomers). To a solution of the adduct **9aB** (140 mg, 0.30 mmol) in MeOH (1.5 mL) was added KF (19 mg, 0.33 mmol) at room temperature. After stirring for 1.5 h at this temperature, the resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=2/1–1/1) to afford **11a** (87 mg, 87%, cis:trans=57:43 (determined by ^{1}H NMR)). The two isomers were partially separated by silica gel column chromatography (hexane/EtOAc=3/1–1/1). *cis*-**11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, s), 1.80–1.93 (1H, m), 2.21 (1H, m), 2.30–2.54 (3H, m), 2.74 (1H, dd, J=4.8, 14.7 Hz), 3.04 (1H, m), 3.34 (3H, s), 3.80 (3H, s), 3.85 (1H, br s), 6.34 (1H, br s), 6.64 (1H, d, J=9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 28.1, 39.7, 39.8, 44.1, 52.4, 56.8, 80.0, 80.7, 126.3, 134.6, 153.5, 165.3, 208.9; IR (KBr) 3227, 2934, 1707, 1651, 1541, 1362, 1258, 1165 cm^{-1}; MS (FAB) *m*/*z*: 328 [M+H]$^+$. *trans*-**11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41–1.62 (1H, m), 1.48 (9H, s), 2.12–2.25 (1H, m), 2.30–2.49 (3H, m), 2.82–2.98 (2H, m), 3.25–3.41 (1H, m), 3.31 (3H, s), 3.80 (3H, s), 6.17 (1H, br s), 6.68 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 28.1, 39.5, 40.6, 46.2, 52.3, 56.8, 80.7, 82.2, 129.7, 132.2, 153.4, 165.1, 207.7; IR (KBr) 1732, 1695, 1655, 1634, 1541, 1364, 1304, 1263, 1202, 1157 cm^{-1}; MS (FAB) *m*/*z*: 328 [M+H]$^+$.

3.1.10. One-pot reaction from 7a to 11a. The mixture of the diene **7a** (100 mg, 0.45 mmol) and *trans*-3-(*tert*-butyldimethylsilyloxy)-1-methoxy-1,3-butadiene (**6B**, 0.32 mL, 1.4 mmol) was heated at 180 °C for 30 min. After cooling to room temperature, MeOH (3 mL) and KF (81 mg, 1.4 mmol) were added to the reaction mixture. After stirring for 40 min at this temperature, the reaction mixture was quenched with aqueous water, and extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=3/1–3/2) to afford **11a** (87 mg, 59%, cis:trans=58:42 (determined by ^{1}H NMR)).

3.1.11. Methyl (*Z*)-2-acetylamino-3-(*cis*-2-methoxy-4-oxocyclohexyl)acrylate (*cis*-11b). To a solution of the silyl ether *cis*-**9bB** (400 mg, 1.0 mmol) in MeOH (5 mL) was added KF (99 mg, 1.7 mmol) at room temperature. After stirring for 1 h at this temperature, the resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10/1) to afford *cis*-**11b** (250 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79–1.90 (1H, m), 2.04–2.21 (1H, m), 2.17 (3H, s), 2.30–2.50 (3H, m), 2.70–2.79 (1H, m), 2.93 (1H, br t, J=10.1 Hz), 3.34 (3H, s), 3.81 (3H, s), 3.88 (1H, br s), 6.77 (1H, d, J=10.1 Hz), 7.11 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 25.4, 39.8, 40.1, 44.0, 52.5, 56.7, 79.9, 125.1, 136.5, 165.1, 168.9, 209.1; IR (neat) 3281, 2953, 1732, 1715, 1694, 1487, 1371, 1244, 1092, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{13}H_{19}NO_5+H]^+$ 270.1341, found 270.1343.

3.1.12. Methyl (*Z*)-2-acetylamino-3-(*trans*-2-methoxy-4-oxocyclohexyl)acrylate (*trans*-11b). To a solution of the silyl ether *trans*-**9bB** (210 mg, 0.56 mmol) in MeOH (3 mL) was added KF (51 mg, 0.87 mmol) at room temperature. After stirring for 1 h at this temperature, the resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10/1) to afford *trans*-**11b** (78 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47–1.61 (1H, m), 2.08–2.26 (1H, m), 2.14 (3H, s), 2.30–2.49 (3H, m), 2.70–2.86 (1H, m), 2.92 (1H, dd, J=3.7, 13.7 Hz), 3.28–3.39 (1H, m), 3.33 (3H, s), 3.80 (3H, s), 6.32 (1H, d, J=9.6 Hz), 7.56 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 26.2, 39.6, 41.3, 46.1, 52.6, 56.9, 82.3, 129.1, 134.4, 164.7, 169.2, 207.7; IR (neat) 3304, 2953, 1715, 1645, 1520, 1435, 1373, 1211, 1088 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{13}H_{19}NO_5+H]^+$ 270.1341, found 270.1347.

3.1.13. One-pot reaction from 7b to 11b. The mixture of the diene **7b** (150 mg, 0.91 mmol) and *trans*-3-(*tert*-butyldimethylsilyloxy)-1-methoxy-1,3-butadiene (**6B**, 0.65 mL, 2.7 mmol) was heated at 180 °C for 30 min. After cooling to room temperature, MeOH (3 mL) and KF (160 mg, 2.7 mmol) were added to the reaction mixture. After stirring for 1 h at this temperature, the resulting solution was concentrated under vacuum. The residue was purified by silica

gel column chromatography ($CHCl_3$/MeOH=10/1) to afford **11b** (130 mg, 52%, cis:trans=90:10 (determined by ^1H NMR)).

3.1.14. Conversion of 11a to 3. A solution of $Rh(COD)_2OTf$ (2.3 mg, 0.0050 mmol) and (*S*,*S*)-Me-DuPHOS (1.5 mg, 0.0050 mmol) in 2-propanol (0.5 mL) was stirred for 1 h to prepare [(COD)Rh–(*S*,*S*)-Me-DuPHOS]OTf. To a solution of (±)-**11a** (33 mg, 0.10 mmol, cis:trans=58:42) in 2-propanol (0.5 mL) was added [(COD)Rh–(*S*,*S*)-Me-DuPHOS]OTf (5 mol %) in 2-propanol (0.5 mL), and the reaction mixture was stirred under a hydrogen atmosphere (0.1 MPa) for 3 h. The resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=3/2–1/1) to afford **12a** (34 mg, quant.).

To a solution of **12a** (34 mg, 0.10 mmol) in dioxane (1 mL) was added 6 mol/L HCl (1 mL), and the reaction mixture was stirred for 7 h at 100 °C. After removing the solvent under vacuum, the residue was dissolved in DMF (1 mL). $NaHCO_3$ (50 mg, 0.60 mmol) and benzyl bromide (0.048 mL, 0.40 mmol) were added to the solution, and the resulting solution was stirred at 60 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under vacuum. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/EtOAc=2/1) to afford (−)-*exo*-**3** (13 mg, 35%, 37% ee) and (−)-*endo*-**3** (8.6 mg, 23%, 41% ee). The spectral data of **3** are shown in Section 3.1.18.

3.1.15. Methyl 2-acetylamino-3-(*cis*-2-methoxy-4-oxocyclohexyl)propionate (*cis*-12b, mixture of diastereomers). A solution of $Rh(COD)_2OTf$ (2.3 mg, 0.0050 mmol) and (*S*,*S*)-Me-DuPHOS (1.5 mg, 0.0050 mmol) in 2-propanol (0.5 mL) was stirred for 1 h to prepare [(CODRh–(*S*,*S*)-Me-DuPHOS)]OTf. To a solution of *cis*-**11b** (27 mg, 1.0 mmol) in 2-propanol (0.5 mL) was added [(COD)Rh–(*S*,*S*)-Me-DuPHOS]OTf (5 mol %) in 2-propanol (0.5 mL), and the reaction mixture was stirred under a hydrogen atmosphere (0.1 MPa) for 3 h. The resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10/1) to afford *cis*-**12b** (26 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 1.52–1.61 (1H, m), 1.69–1.82 (1H, m), 1.85–2.03 and 2.08–2.17 (3H, m), 2.06 (3H, s), 2.27–2.43 (3H, m), 2.70–2.80 (1H, m), 3.31 and 3.36 (3H, s), 3.66 and 3.87 (1H, br s), 3.77 (3H, s), 4.62–4.72 (1H, m), 6.01 and 6.07 (1H, br d, J=8.2, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 25.9 and 27.0, 34.4 and 34.6, 36.7 and 36.8, 39.8 and 40.2, 43.8, 50.2 and 50.4, 52.5, 56.4 and 56.6, 78.6 and 80.3, 170.1, 173.2, 209.7 and 209.8; IR (neat) 3306, 2953, 1748, 1715, 1435, 1373, 1207, 1089 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{13}H_{21}NO_5+H]^+$ 272.1498, found 272.1495.

3.1.16. Methyl 2-acetylamino-3-(*trans*-2-methoxy-4-oxocyclohexyl)propionate (*trans*-12b, mixture of diastereomers). A solution of $Rh(cod)_2OTf$ (2.3 mg, 0.0050 mmol) and (*S*,*S*)-Me-DuPHOS (1.5 mg, 0.0050 mmol) in 2-propanol (0.5 mL) was stirred for 1 h to prepare [(*S*,*S*)-Me-DuPHOS-Rh(cod)]OTf. To a solution of *trans*-**11b** (27 mg, 1.0 mmol) in 2-propanol (0.5 mL) was added [(*S*,*S*)-Me-DuPHOS-Rh(cod)]OTf (5 mol %) in 2-propanol (0.5 mL), and the reaction mixture was stirred under a hydrogen atmosphere (0.1 MPa) for 3 h. The resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10/1) to afford *trans*-**12b** (26 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 1.28–1.48 (1H, m), 1.65–1.93 (2H, m), 2.02–2.39 (5H, m), 2.04 and 2.06 (3H, s), 2.76–2.90 (1H, m), 3.09–3.17 and 3.18–3.28 (1H, m), 3.32 and 3.34 (3H, s), 3.75 and 3.77 (3H, s), 4.61–4.74 (1H, m), 6.32 and 6.58 (1H, d, J=7.8 and 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 26.6 and 27.2, 34.5, 37.3 and 38.1, 39.6 and 39.9, 45.0 and 45.6, 50.1 and 50.7, 52.4 and 52.5, 56.3 and 56.4, 81.9, 169.8 and 170.3, 172.7 and 173.0, 208.4 and 208.5; IR (neat) 3304, 2953, 1715, 1645, 1520, 1435, 1373, 1211, 1088 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{13}H_{21}NO_5+H]^+$ 272.1498, found 272.1494.

3.1.17. Methyl 2-acetylamino-3-(2-methoxy-4-oxocyclohexyl)propionate (12b, mixture of diastereomers). A solution of $Rh(cod)_2OTf$ (23 mg, 0.050 mmol) and (*S*,*S*)-Me-DuPHOS (15 mg, 0.050 mmol) in 2-propanol (5 mL) was stirred for 1 h to prepare [(*S*,*S*)-Me-DuPHOS-Rh(cod)]OTf. To a solution of (±)-**11b** (270 mg, 1.0 mmol, cis:trans=90:10) in 2-propanol (5 mL) was added [(*S*,*S*)-Me-DuPHOS-Rh(cod)]OTf (5 mol %) in 2-propanol (5 mL), and the reaction mixture was stirred under a hydrogen atmosphere (0.1 MPa) for 3 h. The resulting solution was concentrated under vacuum. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=10/1) to afford **12b** (270 mg, cis:trans=91:9 (determined by ^1H NMR), quant.).

3.1.18. Conversion of 12b to 3. Benzyl (2*S*,3a*R*,7a*R*)- and (2*S*,3a*S*,7a*S*)-1-benzyl-6-oxooctahydroindole-2-carboxylate ((−)-*exo*-3 and (−)-*endo*-3). To a solution of **12b** (270 mg, 1.0 mmol, cis:trans=91:9) in dioxane (10 mL) was added 6 mol/L HCl (10 mL), and the reaction mixture was stirred for 7 h at 100 °C. After removing the solvent under vacuum, the residue was dissolved in DMF (10 mL). $NaHCO_3$ (420 mg, 5.0 mmol) and benzyl bromide (0.36 mL, 3.0 mmol) were added to the solution, and the resulting solution was stirred at 60 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc=6/1–2/1) to afford (−)-*exo*-**3** (120 mg, 32%, 95% ee) and (−)-*endo*-**3** (76 mg, 21%, 95% ee). (−)-*exo*-**3**: $[\alpha]_D^{27}$ −51.1 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (1H, dq, J=5.2, 14.2 Hz), 1.85 (1H, dt, J=8.2, 13.3 Hz), 1.98–2.10 (2H, m), 2.22 (1H, ddd, J=4.8, 6.0, 19.7 Hz), 2.41 (1H, ddd, J=4.6, 10.5, 18.8 Hz), 2.55 (2H, d, J=5.0 Hz), 2.80 (1H, m), 3.51 (1H, d, J=13.3 Hz), 3.57 (1H, d, J=8.2 Hz), 3.74 (1H, dt, J=4.6, 9.6 Hz), 3.87 (1H, d, J=13.3 Hz), 5.06 (1H, d, J=11.9 Hz), 5.17 (1H, d, J=12.4 Hz), 7.07–7.42 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 33.1, 34.1, 35.2, 42.0, 52.0, 59.1, 61.7, 65.7, 126.9, 128.1, 128.2, 128.4, 128.6, 135.6, 138.4, 173.5, 212.2; IR (neat) 3030,

2941, 1728, 1495, 1454, 1148 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{23}H_{25}NO_3+H]^+$ 364.1913, found 364.1916.

The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [Daicel Chiralpak OJ, 10% *i*-PrOH in hexane, flow rate 1.0 mL/min, t_R 17.3 min (2*S*,3a*R*,7a*R*)-isomer and 22.8 min (2*R*,3a*S*,7a*S*)-isomer, detected at 214 nm]. (−)-*endo*-**3**: $[\alpha]_D^{27}$ −47.5 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (1H, ddd, *J*=6.0, 8.7, 12.8 Hz), 1.82–1.98 (2H, m), 2.18 (1H, ddd, *J*=4.8, 8.2, 17.6 Hz), 2.34 (1H, ddd, *J*=8.4, 8.4, 12.7 Hz), 2.39–2.49 (2H, m, H-3a), 2.49–2.55 (1H, m), 2.59 (1H, dd, *J*=5.3, 15.8 Hz), 3.09 (1H, dt, *J*=4.9, 8.4 Hz), 3.33 (1H, t, *J*=8.2 Hz), 3.63 (1H, d, *J*=13.7 Hz), 3.85 (1H, d, *J*=13.7 Hz), 4.86 (2H, s), 7.17–7.39 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 34.6, 34.7, 36.6, 42.1, 56.1, 61.6, 65.5, 66.2, 127.2, 128.0, 128.1, 128.4, 129.5, 135.6, 136.6, 173.2, 211.6; IR (KBr) 3030, 2941, 1717, 1454, 1184, 752, 700 cm^{-1}; HRMS (ESI-TOF) calcd for $[C_{23}H_{25}NO_3+H]^+$ 364.1913, found 364.1912. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [Daicel Chiralpak OD-H, 1% *i*-PrOH in hexane, flow rate 1.0 mL/min, t_R 37.2 min (2*S*,3a*S*,7a*S*)-isomer and 30.1 min (2*R*,3a*R*,7a*R*)-isomer, detected at 214 nm]. (−)-*endo*-**3** (64 mg, 95% ee) was recrystallized from EtOH/hexane to give optically pure (−)-*endo*-**3** (40 mg, 63%, >99% ee). $[\alpha]_D^{28}$ −48.6 (*c* 1.00, $CHCl_3$); lit. $[\alpha]_D^{20}$ −58.1 (*c* 1.00, $CHCl_3$).[8b,10]

Acknowledgements

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 14103013).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.078.

References and notes

1. Murakami, M.; Okita, Y.; Matsuda, H.; Okino, T.; Yamaguchi, K. *Tetrahedron Lett.* **1994**, *35*, 3129–3132.
2. (a) Aeruginosin 98-A,B: Murakami, M.; Ishida, K.; Okino, T.; Okita, Y.; Matsuda, H.; Yamaguchi, K. *Tetrahedron Lett.* **1995**, *36*, 2785–2788; (b) aeruginosin 102: Matsuda, H.; Okino, T.; Murakami, M.; Yamaguchi, K. *Tetrahedron* **1996**, *52*, 14501–14506; (c) aeruginosin 205: Shin, H.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *J. Org. Chem.* **1997**, *62*, 1810–1813; (d) aeruginosin 103: Kodani, S.; Ishida, K.; Murakami, M. *J. Nat. Prod.* **1998**, *61*, 1046–1048; (e) aeruginosin 89: Ishida, K.; Matsuda, H.; Okino, T.; Murakami, M. *Tetrahedron* **1999**, *55*, 10971–10988.
3. Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064–6071.
4. Ploutno, A.; Shoshan, M.; Carmeli, S. *J. Nat. Prod.* **2002**, *65*, 973–978.
5. Valls, N.; Vallribera, M.; Carmeli, S.; Bonjoch, J. *Org. Lett.* **2003**, *5*, 447–450.
6. (a) Sandler, B.; Murakami, M.; Clardy, J. *J. Am. Chem. Soc.* **1998**, *120*, 595–596; (b) Steiner, J. L. R.; Murakami, M.; Tulinsky, A. *J. Am. Chem. Soc.* **1998**, *120*, 597–598.
7. Wipf, P.; Methot, J.-L. *Org. Lett.* **2000**, *2*, 4213–4216.
8. (a) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2000**, *122*, 11248–11249; (b) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem.—Eur. J.* **2001**, *7*, 3446–3460; (c) Valls, N.; Vallribera, M.; López-Canet, M.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 4945–4950.
9. (a) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206–11207; (b) Fukuta, Y.; Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Nemoto, T.; Kisugi, T.; Okino, T.; Shibasaki, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5433–5438.
10. Bonjoch, J.; Cantena, J.; Isábal, E.; López-Canet, M.; Valls, N. *Tetrahedron: Asymmetry* **1996**, *7*, 1899–1902.
11. Toyooka, N.; Okumura, M.; Himiyama, T.; Nakazawa, A.; Nemoto, H. *Synlett* **2003**, 55–58.
12. (a) Doi, T.; Hoshina, Y.; Mogi, H.; Yamada, Y.; Takahashi, T. *J. Comb. Chem.* **2006**, *8*, 571–582; (b) Hoshina, Y.; Yamada, Y.; Tanaka, H.; Doi, T.; Takahashi, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2904–2907.
13. (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808; (b) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406; (c) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996–7000.
14. (a) Burk, M. J.; Allen, J. G.; Kiesman, W. F. *J. Am. Chem. Soc.* **1998**, *120*, 657–663; (b) Teoh, E.; Campi, E. M.; Jackson, W. R.; Robinson, A. J. *New J. Chem.* **2003**, *27*, 387–394.
15. The asymmetric hydrogenation of **9aA** utilizing a rhodium catalyst [Rh–DuPHOS] resulted in a complex mixture.
16. (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519; (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125–10138.
17. The reaction in methanol resulted in the formation of dimethyl acetal of **12**.
18. Glaser, R.; Geresh, S. *Tetrahedron* **1979**, *35*, 2381–2387.
19. Acid isomerization of its methyl ester was demonstrated by Bonjoch et al. (see Ref 8b). It was explained that the equilibrium is due to acid-mediated β-elimination of the β-amino ketone, vinylogous enolization, and intramolecular Michael readdition.