Tetrahedron: *Asymmetry* 19 (2008) 2789–2795

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Efficient asymmetric synthesis of the functionalized pyroglutamate core unit common to oxazolomycin and neooxazolomycin using Michael reaction of nucleophilic glycine Schiff base with α,β-disubstituted acrylate

Takeshi Yamada [a], Kazuhiko Sakaguchi [a], Tetsuro Shinada [a], Yasufumi Ohfune [a,*], Vadim A. Soloshonok [b,*]

[a] *Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan*
[b] *Department of Chemistry and Biochemistry, The University of Oklahoma, Norman, OK 73019, USA*

ARTICLE INFO

Article history:
Received 6 October 2008
Accepted 21 November 2008
Available online 20 January 2009

ABSTRACT

The functionalized pyroglutamate core unit, (2*R*,4*R*)-**3**, which could be converted into the β-lactone/pyrrolidine or γ-lactone/pyrrolidine ring system of oxazolomycin A **1** and neooxazolomycin **2**, and which possesses an exomethylene group at C3 as a scaffold for the construction of their C3 polyene segment, was synthesized by the Michael reaction of a glycine Schiff base **4** with the α,β-disubstituted acrylate **8** as the key step.

1. Introduction

Oxazolomycin A **1**, isolated in 1985 by Uemura et al.,[1] from the fermentation broth of *Streptomyces* sp., exhibits potent antibiotic properties against various gram positive bacteria and *Agrobacterium tumefaciens*,[2] strong anticancer activity,[1,3] and various antiviral activities.[4] In addition, oxazolomycin A inhibits crown gall formation in plants.[5] Due to its broad biological activity profile,[1,3] oxazolomycin A has received much attention as a candidate for antibiotic and anticancer drugs. Neooxazolomycin **2**, structurally related to **1**, has also been isolated from the same fermentation broth.[6] The structural features common to both **1** and **2** are characterized by the highly functionalized 2,3,3,4-tetrasubstituted pyroglutamate core unit and the conjugate diene and triene segment attached to C3. Their novel structures as well as their important biological activity profiles have attracted significant attention as important synthetic target molecules. Although a number of research groups have developed and studied the polyene segment[7] and the β-lactone/pyrrolidine or γ-lactone/pyrrolidine ring system[8] in **1** and **2**, an efficient construction of the functionalized pyroglutamate core unit remains a challenging target. Recently, Kende et al.[9] and Hatakeyama et al.[10] reported the total synthesis of neooxazolomycin **2**, although a total synthesis of oxazolomycin **1** has not yet been achieved. We considered that the pyroglutamate core unit, such as **3**, which possesses appropriate functional groups at C2 and C3, that is, the C2 hydroxymethyl substituent could readily cyclize to the β- or γ-lactone/pyrrolidine and the C3 exomethylene group would play a key role in assembling the polyene segment, can be viewed as a key synthetic intermediate of the total synthesis of these natural products. In this paper, we describe the synthesis of (2*R*,4*R*)-*tert*-butyl 2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate **3** (Fig. 1).

2. Results and discussion

Recently, we have developed an operationally convenient methodology for the generalized asymmetric synthesis of various types of β-substituted pyroglutamates **7a** (Scheme 1).[11,12] One of the methods involves the highly diastereoselective organic base-catalyzed Michael addition of the achiral glycine Schiff base derivative **4** with the chiral (*R*)- or (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidine-2-one **5a** to give the addition product **6a** as individual diastereoisomers in nearly quantitative yields in which the observed diastereoselectivity (>98% dr) was induced by the chiral oxazolidinone Michael

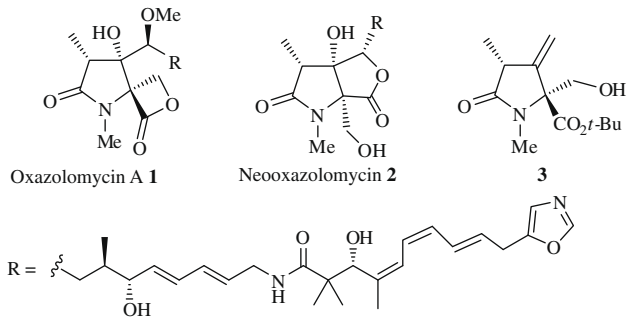

Figure 1.

* Corresponding authors. Tel.: +81 6 6605 2570; fax: +81 6 6605 3153 (Y.O.), tel.: +1 405 325 8279; fax: +1 405 325 6111 (V.A.S.).
E-mail addresses: ohfune@sci.osaka-cu.ac.jp (Y. Ohfune), vadim@ou.edu (V.A. Soloshonok).

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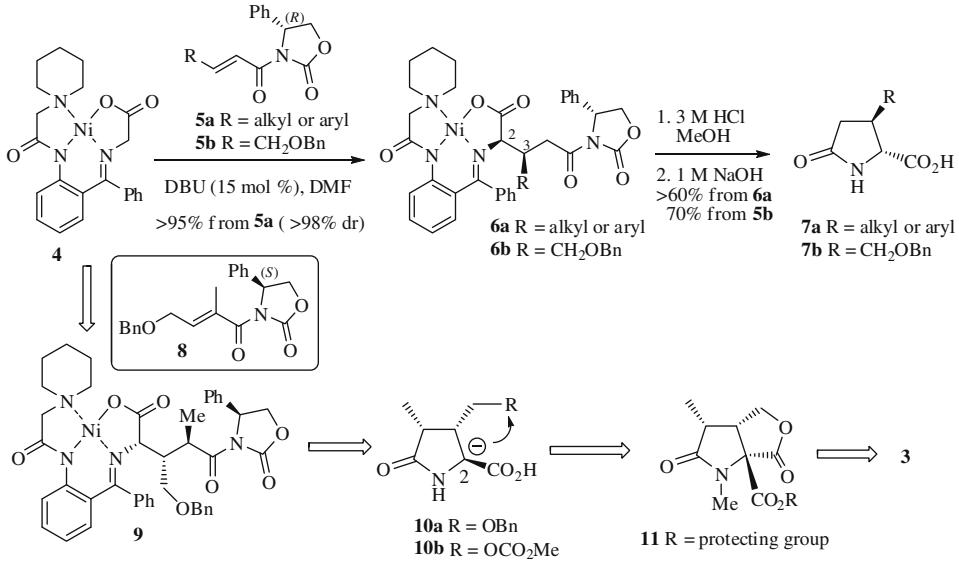
doi:10.1016/j.tetasy.2008.11.036



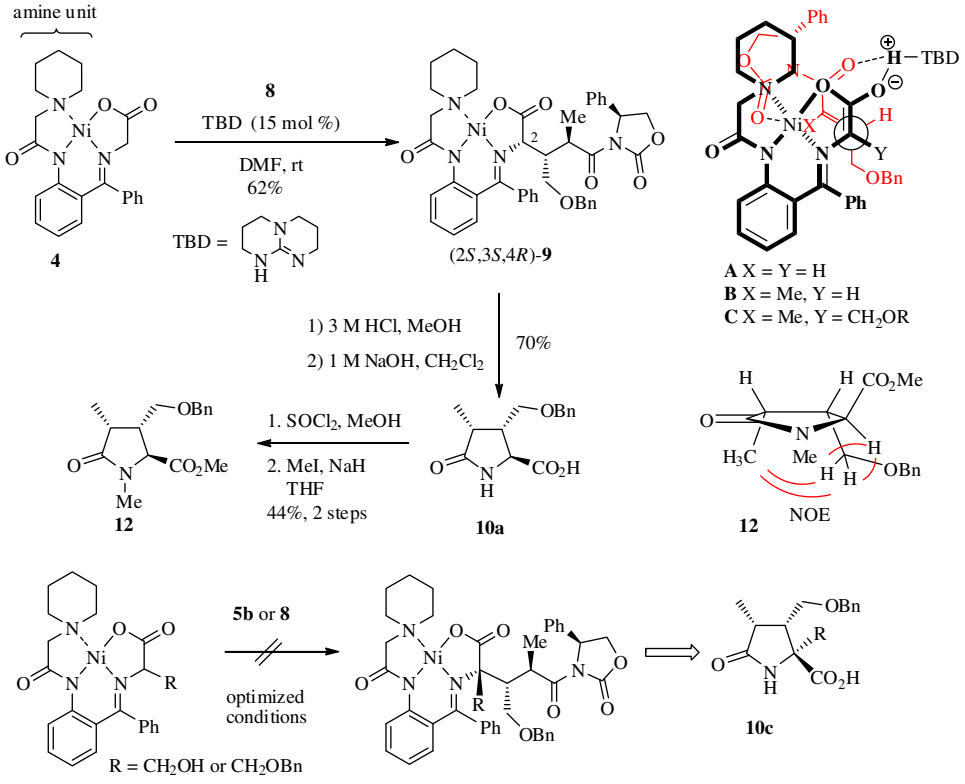
Scheme 1.

donor.[11b,12] The Michael adduct **6a** can be easily hydrolyzed under mild conditions and, upon workup, transformed into the optically active pyroglutamate **7a**. The corresponding Ni-ligand and the chiral auxiliary were recovered and recycled.[11b,12]

We envisioned that the 3,4-disubstituted pyroglutamic acid **10a** is an appropriate precursor for the preparation of the pyroglutamate core unit **3** via a γ-butyrolactone **11** from a carbonate **10b**. Considering the stereochemical requirements for **10a** as a starting compound for the synthesis of **3**, it was considered that the reaction of the glycine Schiff base **4** with the α,β-disubstituted acrylate possessing (*S*)-oxazolidinone **8** would undergo stereoselective Michael addition[11b,12] to give the Michael adduct, (2*S*,3*S*,4*R*)-**9**, which can be readily converted into the corresponding pyroglutamate, (2*S*,3*S*,4*R*)-**10a**, in a manner similar to the preparation of **7a** from **6a**. The use of **4** possessing the piperidine moiety as an amine unit was the choice for the glycine Schiff base in view of its high reactivity and the ease of its large-scale preparation compared to the dibutylamine- or pyridine-containing complexes.[11b] In addition, DBU as an organic catalyst was an extremely effective base for the Michael reaction of **4** with β-substituted acrylates **5a**.[11b] On the other hand, the Michael addition reactions of the α-methyl and/or β-alkoxymethyl substituted Michael acceptors such as **5b** and **8** are unprecedented regarding their reactivity and the product's diastereoselectivity (Scheme 1).

Initially, we examined reaction with the β-alkoxymethyl Michael acceptor **5b** without any α-substituent. The reaction under standard conditions was completed within 3 min to give the Michael adduct **6b** as the exclusive diastereomer (>98% dr).[13] Thus, it was found that the reaction tolerates the β-alkoxymethyl group. However, the α-methyl derivative **8**[14] did not react at all thus resulting in complete recovery of the starting material. After several unsuccessful trials, 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD),[12,15] slightly more basic than DBU, was found to catalyze the reaction to afford a mixture of the Michael adducts. A ^{1}H NMR analysis of the mixture indicated that it consists of 6 diastereomers (68:8:7:7:7:3). Fortunately, the major isomer was separated by silica gel column chromatography to give **9**, in 62% isolated yield.[16] The stereochemistry of **9**, with the desired (2*S*,3*S*,4*R*)-configuration[17], was ascertained by the NOE experiments of the N-methylated derivative **12**, prepared from **9** in 2 steps (Scheme 2). The stereochemical course of this transformation would be similar to the previously proposed mechanism by the authors[12] (Scheme 2), that is, the carbonyl group on the chiral oxazolidinone ring coordinates to Ni in which the phenyl group locates at the opposite face of the Ni-complex. The enolate oxygen and the amide carbonyl group are placed in close proximity to each other by TBD-H$^+$. The decreased diastereoselectivity in the 3,4-disubstituted adduct **9** (64% dr) in comparison to that of the 3-substituted adduct **6b** (>98% dr) may be due to steric repulsion between the α-methyl group of **8** and the central Ni atom of the glycine Schiff base **B** that destabilized the previously proposed rigid transition state **A**.[12] The use of the sterically more or less bulky amine unit (dibutylamine or pyrrolidine) instead of the piperidine unit of **4** did not affect the product's diastereoselectivity (dibutylamine as an amine unit, 0.5 equiv TBD, 24 h, 71% yield, dr = 71:12:9:4:2:2; pyrrolidine, 0.15 equiv TBD, 15 min, 66%, dr = 66:16 [a mixture of 3 diastereomers] 12:6.[16] An attempt was made to obtain the 2,3,4-trisubstituted pyroglutamic acid **10c**, which provides an extremely simple access to the synthesis of **3**. However, the reaction with the hydroxymethyl or benzyloxymethyl group-substituted glycine Shiff base was disappointing, and gave a complex mixture or the recovery of the starting material probably due to severe steric repulsion between the benzyloxymethyl group of the Michael acceptor **8** and the α-substituent of the Michael donor as depicted in **C** (Scheme 2).

The 3,4-disubstituted pyroglutamic acid **10a** with the requisite stereochemistry was prepared from **9** by an acidic workup followed by base treatment. Next, we turned our attention to the introduction of a carboxyl substituent at the C2 position. Our plan was an intramolecular trap of the carbonate from the ester enolate according to Danishefsky's protocol.[18] In order to differentiate the resulting ester groups at C2 for further transformation, the *tert*-butyl group was chosen for the carboxyl-protecting group of **10a**. Thus, the pyroglutamate **10a** was converted into the N-methylated *tert*-butyl ester **13** in two steps, which, upon the removal of the benzyl group and methyl carbonate formation of the resulting alcohol, gave the carbonate **14**. The treatment of **14** with NaHMDS gave a mixture of the desired γ-butyrolactone **15a** and its hydrolyzed product **15b**. Upon treatment of the mixture with diazomethane, only **15a** was isolated in 89% yield. To carry out the simultaneous nucleophilic opening of the lactone **15a** and incorporation of an appropriate leaving group at the resulting C3 hydroxymethyl group, the lactone **15a** was treated with the phenylselenide anion prepared from diphenyldiselenide.[19] The reaction proceeded

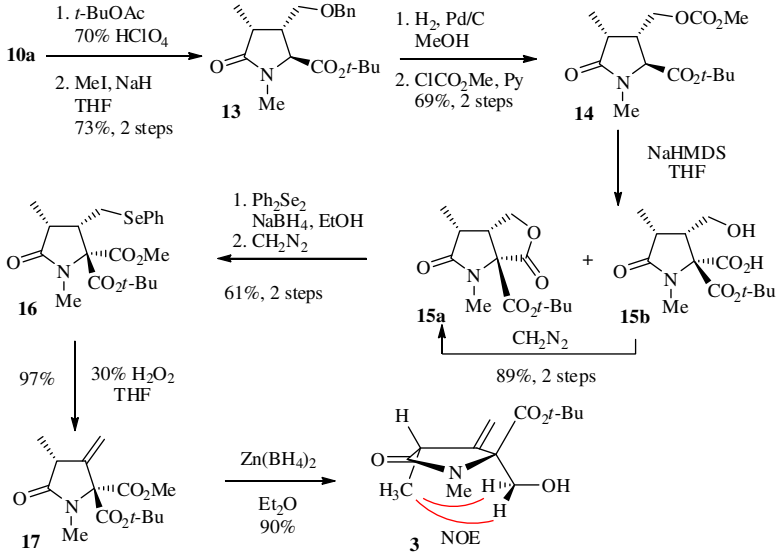


Scheme 2.

smoothly to give the ring-opened product, which, upon esterification with diazomethane, afforded the desired dicarboxyl group differentiated ester **16** in 61% yield (2 steps). Oxidative removal of the phenylselenyl group gave the exomethylene **17**. Chemoselective reduction of the methyl ester **17** with $Zn(BH_4)_2$ afforded **3**. No epimerization at C4 of the product **3** was ascertained by its NOE experiments as depicted in Scheme 3.

3. Conclusion

In conclusion, we have developed a simple and diastereoselective access to the 3,4-disubstituted pyroglutamic acid **10a** using the Michael addition of the achiral glycine Schiff base **4** with the chiral α,β-disubstituted acrylate derivative **8**. The quarternalization of C2 followed by introduction of the exomethylene group at C3 was carried out by the internal nucleophilic trap of the carbonate **14** and lactone opening with the phenylselenide anion. The total number of processes included was 12 steps, and the overall yield was 10%. The synthesized core unit **3** possesses the appropriate functional groups for the β-lactone or γ-lactone formation at C2, as well as an exomethylene group at C3 which could be a useful scaffold for stereoselective functionalization corresponding to the oxazolomycin's polyene segment. Further studies to assemble the exomethylene group directed toward the total synthesis of **1** and **2** are now in progress in our laboratories.



Scheme 3.

4. Experimental

4.1. General remarks

All reagents and solvents were purchased from either Aldrich Chemical Company, Inc., Merck & Co., Inc., Nacalai Tesque Co., Ltd, Tokyo Kasei Kogyo Co., Ltd, or Wako Pure Chemical Industries, Ltd., Kanto Chemical Co., Ltd, and used without further purification unless otherwise indicated. Tetrahydrofuran and ethyl alcohol (EtOH) of anhydrous grade were used. Optical rotations were taken on a JASCO P-1030 polarimeter with a sodium lamp (D line). FT-IR spectra were measured on a JASCO FT/IR-420 infrared spectrophotometer. ^{1}H NMR spectra were recorded on an either JEOL JNM-LA 300 (300 MHz), JEOL JNM-LA 400 (400 MHz), or Bruker AVANCE 600 (600 MHz) spectrometer. Chemical shifts of ^{1}H NMR were reported in parts per million (ppm, δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$, or CD_2HOD (δ = 3.30) in CD_3OD. ^{13}C NMR spectra were recorded on a JEOL JNM-LA 300 (75 MHz) or JEOL JNM-LA 400 (100 MHz) spectrometer. Chemical shifts of ^{13}C NMR were reported in ppm (δ) relative to $CHCl_3$ (δ = 77.0) in $CDCl_3$. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were obtained on a JEOL JMS-AX500 for fast atom bombardment ionization (FAB) or electron ionization (EI). All reactions were monitored by thin layer chromatography (TLC), which was performed with precoated plates (Silica Gel 60 F-254, 0.25 mm layer thickness, manufactured by Merck). TLC visualization was accomplished using UV lump (254 nm) or a charring solution (ethanoic molybdophosphoric acid and butanoic ninhydrin). Daisogel IR-60 1002W (40/63 mm) was used for flash column chromatography on silica gel.

4.2. (*R*)-3-((*E*)-4-(Benzyloxy)but-2-enoyl)-4-phenyloxazolidin-2-one 5b

A solution of phosphorane[14a,b] (14.6 g, 30.4 mmol) and 2-benzyloxymethyl acetoaldehyde[14c] (5.0 g, 30.5 mmol) in THF (150 mL) was stirred at room temperature for 2 days under an argon atmosphere. The reaction mixture was concentrated under reduced pressure to give a crude residue. The resulting residue was purified by column chromatography on silica gel (hexane/AcOEt = 5:1 to 2:1), and the resulting solid residue was recrystallized from AcOEt/hexane to give (*R*)-**5b** (4.11 g, 40%) as colorless needles. Mp 119 °C; $[\alpha]_D^{20.9} = -69.9$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 15.5, 1.7 Hz, 1H), 7.39–7.25 (m, 10H), 7.07 (dt, *J* = 15.5, 4.3 Hz, 1H), 5.48 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.69 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.55 (s, 2H), 4.27 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.19 (dd, *J* = 4.3, 1.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 153.5, 146.7, 138.9, 137.6, 129.1, 128.6, 128.4, 127.7, 127.7, 125.9, 120.2, 72.7, 69.9, 68.9, 57.7; IR (neat) 1778, 1689, 1643, 1332, 1200, 1105 cm^{-1}. HRMS(FAB) *m/z* (M+H)$^+$ calcd for $[C_{20}H_{20}NO_4]^+$ 338.1392, found 338.1373.

4.3. (2*R*,3*R*)-Methyl 3-((benzyloxy)methyl)-5-oxopyrrolidine-2-carboxylate, methyl ester of 7b

To a solution of Ni(II)-complex **4** (5.52 g, 11.5 mmol) in DMF (55 mL) was added the Michael acceptor (*R*)-**5b** (3.52 g, 10.4 mmol). After stirring the mixture for 10 min at room temperature, DBU (0.24 mL, 1.6 mmol) was added. The reaction was monitored by TLC (sample was quenched with brine, and the products were extracted with chloroform before being applied to the plate). After stirring at rt for 10 min, the reaction mixture was poured into water and stirred to initiate crystallization of the product. The crystalline product was filtered off, thoroughly washed with water, and dried in vacuo to afford addition products (2*R*,3*R*,4′*R*)-**6b**. A solution of **6b** in MeOH (400 mL) was slowly added with stirring to a mixture of 3 M HCl (40 mL) at 70 °C. Upon disappearance of the red color of the starting complex, the reaction mixture was evaporated in vacuo. 1 M NaOH and CH_2Cl_2 were added. After stirring at room temperature for 1 h, the mixture was filtrated and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and evaporated in vacuo, to afford a mixture of ligand and chiral auxiliary, which could be separated by recrystallization from AcOEt and hexane. The aqueous solution was acidified by 1 M HCl and extracted with AcOEt. The organic layers were dried over anhydrous $MgSO_4$, and evaporated in vacuo to afford **7b** (1.74 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (br s, 1H), 7.28–7.18 (m, 5H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 5.3 Hz, 1H), 3.55–3.44 (m, 2H), 2.75 (m, 1H), 2.48 (dd, *J* = 17.4, 9.3 Hz, 1H), 2.27 (dd, *J* = 17.4, 6.3 Hz, 1H). To a solution of **7b** (4.00 g, 16.0 mmol) in methanol (80 mL) was added thionyl chloride (2.4 mL, 32.0 mmol) dropwise at 0 °C under an argon atmosphere. The reaction mixture was warmed to room temperature and kept stirring for 3 h. Upon completion, the reaction mixture was evaporated, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash column chromatography on silica gel (AcOEt) to give the methyl ester of **7b** (4.26 g, 100%) as a colorless oil. $[\alpha]_D^{27.0} = -27.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.19 (m, 5H), 6.60 (br s, 1H), 4.50 (d, *J* = 12.2 Hz, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 4.09 (d, *J* = 4.6 Hz, 1H), 3.68 (s, 3H), 3.48 (d, *J* = 5.8 Hz, 2H), 2.79–2.69 (m, 1H), 2.44 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.19 (dd, *J* = 17.2, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 172.2, 137.7, 128.4, 127.8, 127.5, 73.1, 70.5, 57.4, 52.5, 38.5, 32.6; IR (neat) 3380, 2952, 2864, 1741, 1700, 1442, 1217, 1107, 744, 701 cm^{-1}; HRMS(FAB) *m/z* (M+H)$^+$ calcd for $[C_{14}H_{18}NO_4]^+$ 264.1236, found 264.1241.

4.4. (*S*)-3-((*E*)-4-(Benzyloxy)-2-methylbut-2-enoyl)-4-phenyloxazolidin-2-one 8

To a solution of (*S*)-4-phenyl oxazolidinone (16.3 g, 100 mmol) in THF (330 mL) was added *n*-BuLi (1.58 M in hexane, 63.3 mL, 100 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 10 min, then α-bromopropanoyl bromide (25 g, 117 mmol) was added. After stirring at −78 °C for 10 min, the mixture was warmed to room temperature and kept stirring for 20 min. The reaction mixture was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was dissolved in MeCN (120 mL), and triphenylphosphine (27 g, 103 mmol) was added under an argon atmosphere. After stirring at 50 °C for 24 h, 2 N NaOH (53 mL) was added at room temperature and stirred for 15 min. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The resulting phosphorane was dissolved in THF (500 mL), and 2-benzyloxymethyl acetoaldehyde[14c] (21.4 g, 150 mmol) was added. The reaction mixture was refluxed for 6 days under an argon atmosphere. The reaction mixture was concentrated under reduced pressure to give a crude residue. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 5:1 to 2:1), and the resulting solid residue was recrystallized from AcOEt/hexane to give (*S*)-**8** (21.4 g, 61%, *E*/*Z* = >30:1) as colorless needles. Mp 128 °C; $[\alpha]_D^{20.5} = +12.9$ (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.24 (m, 10H), 6.23 (ddd, *J* = 5.9, 5.9, 1.5 Hz, 1H), 5.45 (dd, *J* = 8.8, 7.1 Hz, 1H), 4.69 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.23 (dd, *J* = 8.8, 7.1 Hz, 1H), 4.22–4.17 (m, 2H), 1.84 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 153.3, 137.8, 137.7, 135.9, 132.5, 129.2, 128.9, 128.4, 127.9, 127.8, 126.3, 72.4, 69.9, 66.2, 58.3,

13.7; IR (neat) 1782, 1682, 1321, 1282, 1207, 1107, 1049, 764, 700 cm^{-1}; Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.8; H, 6.0; N, 4.0. Found: C, 70.9; H, 5.9; N, 4.0.

4.5. *N*-(2-Benzoyl-phenyl)-2-piperidyl-acetamide Ni(II) complex of (2*S*,3*S*,4*R*,4′*S*)- 3-benzyloxymethyl-4-methyl-5-[3′-(4′-phenyl-2′-oxazolidinonyl)] glutamic acid Schiff base 9

To a solution of Ni-complex **4** (847 mg, 1.94 mmol) in DMF (9 mL) was added (*S*)-**8** (620 mg, 1.77 mmol). After stirring the mixture for 10 min at room temperature, TBD (37 mg, 0.27 mmol) was added. The reaction was monitored by TLC (sample was quenched with brine, and the products were extracted with chloroform before being applied to the plate). After stirring at room temperature for 15 min, the reaction mixture was poured into water and stirred to initiate crystallization of the product. The crystalline product was filtered off, thoroughly washed with water, and dried in an oven. The crude mixture was purified by flash column chromatography on silica gel (CH_2Cl_2/acetone = 10:1 to 5:1) to give (2*S*,3*S*,4*R*,4′*S*)-**9** (858 mg, 62%) as a reddish solid. Mp 144–145 °C; $[\alpha]_D^{21.2} = +2376.3$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 8.6 Hz, 1H), 7.45 (m, 1H), 7.35–7.05 (14H), 6.81 (br d, *J* = 7.6 Hz, 1H), 6.68–6.66 (2H), 5.13 (dd, *J* = 7.9, 2.0 Hz, 1H), 4.19 (d, *J* = 12.0 Hz, 1H), 4.09–4.01 (3H), 3.91 (br d, *J* = 16.2 Hz, 1H), 3.83 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.61 (d, *J* = 16.2 Hz, 1H), 3.56 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.45–3.38 (m, 3H), 3.28–3.17 (m, 2H), 2.86 (m, 1H), 2.54 (m, 1H), 1.76–1.22 (m, 6H), 1.39 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 177.1, 176.5, 172.5, 153.2, 142.9, 139.5, 138.4, 134.0, 133.4, 133.0, 129.8, 129.2, 129.2, 129.1, 128.6, 128.1, 127.9, 127.8, 127.3, 127.0, 126.1, 125.4, 123.7, 121.1, 72.5, 70.1, 69.3, 68.4, 60.0, 58.1, 55.7, 54.3, 43.6, 38.4, 22.9, 19.8, 19.2, 10.8; IR (neat) 2361, 1778, 1637, 751 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{43}H_{45}N_4O_7Ni]^+$ 787.2642, found 787.2657.

4.6. (2*S*,3*S*,4*R*)-3-((Benzyloxy)methyl)-4-methyl-5-oxopyrrolidine-2-carboxylic acid 10a

To a solution of the Ni-complex (2*S*,3*S*,4*R*,4′*S*)-**9** (3.90 g, 4.95 mmol) in MeOH (200 mL) was slowly added aqueous 3 N HCl (20 mL) with stirring at 70 °C. Upon disappearance of the red color of the starting complex, the reaction mixture was evaporated in vacuo. 1 M NaOH and CH_2Cl_2 were added. After stirring at room temperature for 1 h, the mixture was filtrated and extracted with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$ and evaporated in vacuo to afford a mixture of ligand and (*S*)-chiral auxiliary, which could be separated by recrystallization from AcOEt and hexane. The aqueous solution was acidified by 1 M HCl and extracted with AcOEt. The organic layers were dried over $MgSO_4$, and evaporated in vacuo to afford (2*S*,3*S*,4*R*)-**10a** (958 mg, 70%) as a colorless oil. $[\alpha]_D^{25.7} = +24.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (br s, 1H), 7.57 (s, 1H), 7.32–7.18 (m, 5H), 4.38 (s, 2H), 4.29 (d, *J* = 7.8 Hz, 1H), 3.60–3.50 (m, 2H), 2.98 (m, 1H), 2.67 (m, 1H), 1.13 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 174.8, 137.6, 130.0, 128.3, 127.6, 73.2, 66.3, 57.1, 41.0, 38.7, 10.5; IR (neat) 3295, 2879, 1712, 1662, 1454, 1369, 1232, 1099 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{14}H_{18}NO_4]^+$ 264.1236, found 264.1239.

4.7. (2*S*,3*S*,4*R*)-Methyl 3-((benzyloxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate 12

To a stirred solution of (2*S*,3*S*,4*R*)-**10a** (78 mg, 0.30 mmol) in MeOH (1.5 mL) was added thionyl chloride (44 mL, 0.6 mmol) dropwise at 0 °C under an argon atmosphere. The mixture was warmed to room temperature and kept stirring for 2 h. Upon completion, the reaction mixture was evaporated, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash column chromatography on silica gel (AcOEt) to give the (2*S*,3*S*,4*R*)-methyl pyroglutamate (78 mg, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 6.50 (br s, 1H), 4.39 (d, *J* = 2.0 Hz, 2H), 4.29 (d, *J* = 7.1 Hz, 1H), 3.56 (s, 3H), 3.53–3.47 (2H), 3.01 (m, 1H), 2.65 (dq, *J* = 7.4, 7.4 Hz, 1H), 1.14 (d, *J* = 7.4 Hz, 3H). To a solution of (2*S*,3*S*,4*R*)-methyl pyroglutamate (38.6 mg, 0.14 mmol) in THF (1.5 mL) was added sodium hydride (8 mg, 0.34 mmol) at 0 °C under an argon atmosphere. After stirring for 5 min, methyl iodide (20 mL, 0.32 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, then quenched with saturated NH_4Cl and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1:1) to give (2*S*,3*S*,4*R*)-**12** (19.1 mg, 47%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.27 (5H), 4.44 (s, 2H), 4.17 (d, *J* = 8.4 Hz, 1H), 3.65 (s, 3H), 3.53–3.47 (m, 2H), 3.00 (m, 1H), 2.63 (dq, *J* = 7.8, 7.8 Hz, 1H), 1.17 (d, *J* = 7.8 Hz, 3H).

4.8. (2*S*,3*S*,4*R*)-*tert*-Butyl-3-((benzyloxy)methyl)-1,4-dimethyl-5-oxopyrrolidine-2-carboxylate 13

To a solution of (2*S*,3*S*,4*R*)-**10a** (493 mg, 1.78 mmol) in *t*-BuOAc (2.5 mL) was added 70% $HClO_4$ aq (3 drops) at room temperature. The reaction mixture was stirred at room temperature for 40 h, then quenched with saturated $NaHCO_3$ solution, and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1:4) to give the *t*-butyl ester (451 mg, 80%) as a colorless oil. $[\alpha]_D^{25.4} = +14.9$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 5.93 (br s, 1H), 4.43 (s, 2H), 4.18 (d, *J* = 7.6 Hz, 1H), 3.54 (d, *J* = 5.4 Hz, 2H), 2.93 (m, 1H), 2.61 (dq, *J* = 7.6, 7.6 Hz, 1H), 1.39 (s, 9H), 1.15 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 169.6, 137.6, 128.1, 127.4, 127.4, 82.1, 73.0, 66.3, 57.0, 41.0, 38.3, 27.7, 10.7; IR (neat) 3246, 1707, 1454, 1369, 1228, 1157, 1097, 752 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{18}H_{26}NO_4]^+$ 320.1862, found 320.1866. To a solution of the resulting *t*-butyl ester (28.4 mg, 0.09 mmol) in THF (1.0 mL) was added sodium hydride (2.6 mg, 0.11 mmol) at 0 °C under an argon atmosphere. After stirring for 5 min, methyl iodide (7 mL, 0.11 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, then quenched with saturated NH_4Cl, and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1:1) to give (2*S*,3*S*,4*R*)-**13** (23.7 mg, 80%) as a colorless oil. $[\alpha]_D^{26.1} = +25.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.17 (m, 5H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 3.94 (d, *J* = 9.0 Hz, 1H), 3.50 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.37 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.86 (dtd, *J* = 8.9, 8.9, 6.7 Hz, 1H), 2.72 (s, 3H), 2.53 (m, 1H), 1.35 (s, 9H), 1.09 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 169.5, 128.3, 127.7, 127.7, 82.5, 73.4, 66.7, 64.2, 37.9, 37.8, 28.7, 27.9, 11.9; IR (neat) 2360, 1732, 1697, 1457, 1369, 1226, 1156, 1100 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{19}H_{28}NO_4]^+$ 334.2018, found 334.2010.

4.9. ((2*S*,3*S*,4*R*)-2-(*tert*-Butoxycarbonyl)-1,4-dimethyl-5-oxopyrrolidin-3-yl)methyl methyl carbonate 14

To a solution of (2*S*,3*S*,4*R*)-**13** (851 mg, 2.55 mmol) in MeOH (30 mL) was added Pd/C (85 mg, 10 wt %). The reaction mixture

was stirred at room temperature for 12 h under H_2. The reaction mixture was filtered and concentrated under reduced pressure. To a stirred solution of crude alcohol in pyridine (25 mL) was added methyl chlorocarbonate (1.0 mL, 16.8 mmol) dropwise at 0 °C under an argon atmosphere. After stirring for 5 h at 0 °C, the mixture was warmed to room temperature and kept stirring for 5 h. The reaction mixture was quenched with 1 M HCl and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1:2) to give (2*S*,3*S*,4*R*)-**15** (538 mg, 70%) as a colorless oil. $[\alpha]_D^{27.0} = +27.5$ (*c* 3.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 11.0, 7.4 Hz, 1H), 4.10 (dd, *J* = 11.0, 8.3 Hz, 1H), 4.01 (d, *J* = 8.8 Hz, 1H), 3.73 (s, 3H), 3.00–2.91 (1H), 2.76 (s, 3H), 2.61–2.53 (dq, *J* = 7.6, 7.6 Hz, 1H), 1.43 (s, 9H), 1.13 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 169.2, 155.3, 83.1, 64.6, 63.7, 54.9, 37.7, 36.8, 28.8, 27.8, 11.9; IR (neat) 3476, 2978, 1741, 1695, 1447, 1275, 1157, 963, 793 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{14}H_{24}NO_6]^+$ 302.1604, found 302.1613.

4.10. (3*R*,3a*S*,6a*R*)-*tert*-Butyl-hexahydro-1,3-dimethyl-2,6-dioxo-1*H*-furo[3,4-*b*]pyrrole- 6a-carboxylate 15a

A solution of (2*S*,3*S*,4*R*)-**14** (538 mg, 1.8 mmol) in THF (18.5 mL) was treated with NaHMDS (1.9 M in THF, 2.0 mL, 3.8 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 15 min, then quenched with saturated NH_4Cl, and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 2:1 to 1:1) to give the γ-butyrolactone **15a** (185 mg, 39%). The aqueous solution was acidified by 1 N HCl and extracted with AcOEt. The organic layers were dried over $MgSO_4$, and evaporated in vacuo to afford hydrolysis product **15b** (281 mg). To a solution of diazomethane in ether was added a solution of **15b** in ether at 0 °C, stirred for 30 min, and concentrated in boiled water bath. The residue was purified by flash column chromatography (hexane/AcOEt = 1:1) to give **15a** (240 mg, 50%) as a colorless oil. $[\alpha]_D^{25.1} = +88.7$ (*c* 1.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 9.5, 8.6 Hz, 1H), 4.09 (dd, *J* = 9.5, 7.3 Hz, 1H), 3.37–3.31 (m, 1H), 2.93 (s, 3H), 2.73–2.65 (1H), 1.45 (s, 9H), 1.14 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 169.8, 166.1, 84.9, 70.2, 67.2, 43.4, 37.1, 27.9, 27.4, 10.6; IR (neat) 2980, 1783, 1743, 1711, 1371, 1259, 1151, 1037, 836 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{13}H_{20}NO_5]^+$ 270.1341, found 270.1340.

4.11. (2*R*,3*S*,4*R*)-2-*tert*-Butyl 2-methyl 1,4-dimethyl-5-oxo-3-((phenylselanyl)methyl) pyrrolidine-2,2-dicarboxylate 16

To a mixture of **15a** (235 mg, 0.87 mmol) and Ph_2Se_2 (569 mg, 1.87 mmol) in EtOH (9.2 mL) was added $NaBH_4$ (129 mg, 3.42 mmol) at 0 °C. After stirring at room temperature for 30 min, the mixture was heated to 60 °C and kept stirring for 1 h. The reaction mixture was quenched with 1 M KOH and extracted with Et_2O. The aqueous layer was acidified with 1 M citric acid and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To a solution of diazomethane in ether was added a solution of the crude mixture in ether at 0 °C. The mixture was stirred for 30 min and concentrated in boiled water bath. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 3:1) to give (2*R*,3*S*,4*R*)-**16** (235 mg, 61%) as a yellow oil. $[\alpha]_D^{26.7} = -52.8$ (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.48 (m, 2H), 7.26–7.21 (m, 3H), 3.76 (s, 3H), 3.17 (dd, *J* = 12.3, 4.5 Hz, 1H), 3.11–3.03 (m, 1H), 2.87 (s, 3H), 2.82–2.69 (m, 2H), 1.36 (s, 9H), 1.11 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 168.5, 166.1, 133.8, 129.2, 129.0, 127.7, 84.1, 75.6, 52.7, 43.4, 38.3, 28.8, 27.7, 24.3, 11.5; IR (neat) 1736, 1706, 1251, 1155 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{20}H_{28}NO_5Se]^+$ 442.1133, found 442.1128.

4.12. (2*R*,4*R*)-2-*tert*-Butyl 2-methyl 1,4-dimethyl-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate 17

A solution of (2*R*,3*S*,4*R*)-**16** (49.0 mg, 0.11 mmol) in THF (2.0 mL) was treated with 30% aqueous H_2O_2 (0.2 mL) at room temperature. After the reaction mixture was stirred at room temperature for 3 h, quenched with saturated Na_2SO_3 solution at 0 °C, and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 3:1) to give (2*R*,4*R*)-**17** (30.7 mg, 97%) as a pale yellow oil. $[\alpha]_D^{25} = -84.0$ (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (m, 1H), 5.32 (dd, *J* = 2.4, 0.7 Hz, 1H), 3.81 (s, 3H), 3.09 (m, 1H), 2.97 (s, 3H), 1.47 (s, 9H), 1.31 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 167.5, 165.4, 142.7, 112.9, 83.9, 76.2, 53.1, 39.8, 28.3, 27.7, 16.2; IR (neat) 2979, 1739, 1714, 1664, 1455, 1430, 1375, 1255, 1157, 1074, 1049 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{14}H_{22}NO_5]^+$ 284.1498, found 284.1497.

4.13. (2*R*,4*R*)-*tert*-Butyl 2-(hydroxymethyl)-1,4-dimethyl-3-methylene-5-oxopyrrolidine-2-carboxylate 3

To a solution of (2*R*,4*R*)-**17** (4.8 mg, 0.017 mmol) in ether (120 μL) was added $Zn(BH_4)_2$ (0.14 M in ether, 120 μL, 0.017 mmol) at room temperature under an argon atmosphere. After the reaction mixture was stirred at room temperature for 24 h, quenched with water, and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1:2) to give (2*R*,4*R*)-**3** (3.9 mg, 90%) as a colorless powder. $[\alpha]_D^{25.0} = -85.7$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (d, *J* = 2.8 Hz, 1H), 5.23 (dd, *J* = 2.8, 0.6 Hz, 1H), 4.05 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.90 (dd, *J* = 12.2, 6.3 Hz, 1H), 3.08 (m, 1H), 2.89 (s, 3H), 2.13 (br s, 1H), 1.43 (s, 9H), 1.29 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 169.0, 145.7, 109.8, 83.0, 73.9, 64.4, 39.9, 27.8, 26.9, 15.9; IR (neat) 3309, 2981, 1725, 1681, 1656, 1459, 1436, 1398, 1369, 1257, 1164, 1139, 1076, 1014 cm^{-1}; HRMS(FAB) *m/z* $(M+H)^+$ calcd for $[C_{13}H_{22}NO_4]^+$ 256.1549, found 256.1551.

Acknowledgments

This study was supported by Grants-in-Aid (16201045 and 19201045) for Scientific Research from the Japan Society for the Promotion of Science (JSPS).

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16. The ratio was determined from the ^{1}H NMR (600 MHz) spectra of the crude product. The relative structure of the other diastereomers except for the major isomer **9** could not be determined because of the difficulty of isolating of each diastereomer from the mixture.
17. The absolute structure was assigned to (2*S*,3*S*,4*R*)-**9**, by analogy with the related transformation from **4** to the Michael adduct (2*R*,3*R*)-**6a** using the (*R*)-oxazolidinone Michael acceptor.[11b,12]
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