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Citation	Tetrahedron Asymmetry, 19(9), 1059-1067 https://doi.org/10.1016/j.tetasy.2008.04.013
Issue Date	2008-05-16
Doc URL	https://hdl.handle.net/2115/33049
Type	journal article
File Information	TETASY57110.pdf

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Stereoselective synthesis of a C1–C6 fragment of pinnatoxin A via a 1,4-addition/alkylation sequence

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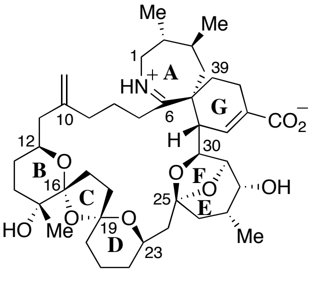
Abstract—A C1–C6 fragment of pinnatoxin A, (5*S*,6*R*)-5,6-dimethyl-3-methyleneoxepan-2-one, which features a γ,δ-*trans*-dimethyl-substituted α-methylene lactone, has been synthesized in an optically pure form from ethyl (*E*)-4-benzyloxy-2-butenoate through an auxiliary-based conjugate addition and alkylation reaction. The excellent diastereoselectivity (98:2) observed in the alkylation reaction would be a result of stereocontrol from both the adjacent stereocenter and the chiral oxazolidinone.

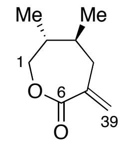
1. Introduction

Pinnatoxins[1] and pteriatoxins,[2] isolated and characterized by Uemura and co-workers in 1995 and 2001, respectively, are members of a class of marine toxins that are implicated in shellfish poisoning.[3] Structurally, these molecules feature a 27-membered carbocyclic ring that comprises a [6,5,6]-dispiroketal (BCD ring), a [5,6]-bicycloketal (EF ring), and a [6,7]-spiroimine (AG ring). Not surprisingly, the unprecedented molecular architecture and biological activity, in conjunction with the scarcity of the natural material, have provided an impetus to develop a route to this class of shellfish toxins.[4] The first total synthesis of (–)-pinnatoxin A was reported by Kishi and co-workers in 1998, leading to the absolute configurational assignment for the natural product.[5] They also established the complete stereochemistry of pinnatoxins B and C[6] and of pteriatoxins A–C[7] by total syntheses. A formal total synthesis of pinnatoxin A was documented by Hirama and co-workers,[8] and synthetic approaches have been pursued extensively in the laboratories of Ishihara and Murai,[9] Kitching[10] and Zakarian.[11]

As part of our own synthetic studies on these natural products, we have already reported a stereoselective construction of the [6,5,6]-dispiroketal ring system by exploiting a tandem hemiketal formation/hetero-Michael reaction sequence through the agency of LiOMe as a base.[12] To construct the G ring portion of these molecules, a biomimetic intramolecular Diels–Alder reaction appeared attractive due to the concurrent formation of the 27-membered carbocycle.



Pinnatoxin A (**1**)



C1–C6 Fragment (**2**)

Indeed, Kishi and co-workers accomplished total syntheses by an intramolecular cycloaddition-based approach.[5,7a] On the other hand, an intermolecular Diels–Alder approach has an advantage of allowing convenient access to simpler analogues for biological evaluation. The stereochemical arrangement of the G ring of pinnatoxins/pteriatoxins would require an exo-selective Diels–Alder reaction. In this regard, Roush and co-workers demonstrated the striking preference of conformationally *s-cis*-restricted enone and enoate dienophiles for exo cycloaddition.[13,14] Based on these precedents, we elected to take advantage of an intermolecular reaction using α-methylene lactone **2** as the dienophile for the synthesis of **1** and its congeners. Therefore, a practical route to optically pure lactone **2** needed to be developed. In this paper, we describe a stereoselective route to the lactone **2**, in which a chiral auxiliary, (*R*)-4-phenyl-2-oxazolidinone, plays a pivotal role as the source of asymmetry for the creation of both stereocenters at C2 and C3.

2. Results and discussion

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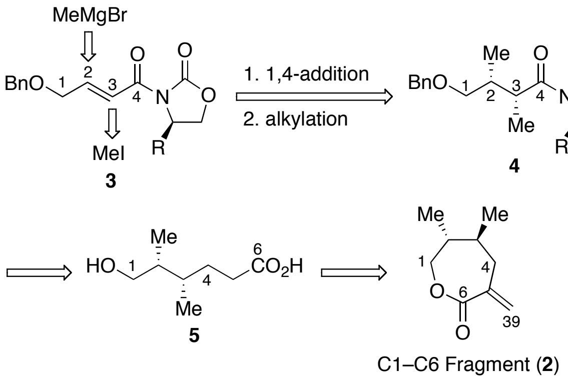
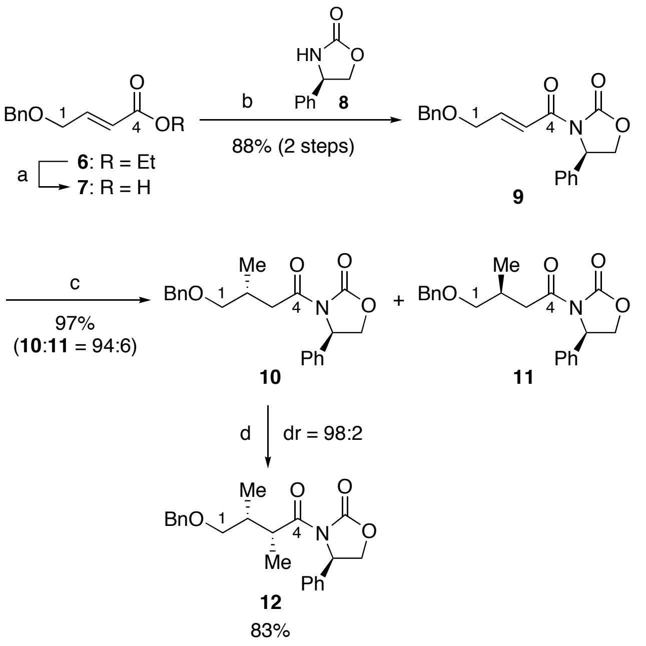
The C1–C6 fragment **2** features a 7-membered α-methylene lactone containing branched methyl groups with a 1,2-*trans* relationship. To construct the methyl-bearing stereocenters at C2 and C3, we planned to take advantage of asymmetric reactions using a common chiral oxazolidinone: 1,4-addition[15] of a methylmagnesium reagent to a chiral α,β-unsaturated 3-acyl-2-oxazolidinone **3** and subsequent alkylation with MeI (Scheme 1). However, to the best of our knowledge, the chiral oxazolidinone-based 1,4-addition/alkylation sequence has not been employed to install 1,2-dimethyl arrangements along acyclic backbones.[16] With regard to the oxazolidinone-based 1,4-addition reaction, Hruby and co-workers demonstrated that a phenyl-substituted auxiliary (R = Ph) is effective for asymmetric induction at the β-carbon. The major concern with this 1,4-addition/alkylation sequence was control of the configuration at the α-carbon (C3) by alkylation, since Evans and co-workers demonstrated that the phenyl group is a less effective substituent to shield the diastereoface of the lithium enolate in alkylations of *N*-butyryl-2-oxazolidinones with MeI at –30 °C than any other groups examined, providing a 4.24:1 mixture of alkylation products.[17]

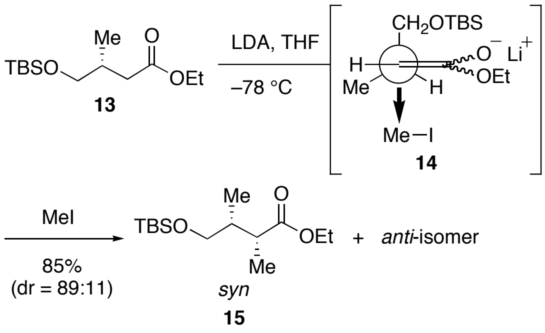


Scheme 1. Plan for the synthesis of C1–C6 fragment **2**.

The synthesis of lactone **2** was initiated by *N*-acylation of the D-phenylglycine-derived oxazolidinone **8**[15] with the known 4-benzyloxy-2-butenoic acid (**7**),[18] obtained by hydrolysis of ethyl ester **6**[19] with LiOH in aqueous THF, under Merck conditions [PivCl, Et_3N, LiCl, THF][20] to afford carboximide **9**, mp 115.5–116.5 °C, $[\alpha]_D^{26} = -67.3$ (*c* 2.07, $CHCl_3$), in 88% yield in two steps (Scheme 2). Conjugate addition of MeMgBr to the α,β-unsaturated imide **9** was carried out according to Hruby conditions[15] in the presence of $CuBr{\cdot}SMe_2$ in $THF/Me_2S/CH_2Cl_2$ (–78 → –30 °C) to produce a mixture of 1,4-adducts, **10** and its C2 epimer **11**, in 97% yield in a ratio of 94:6 as determined by 500 MHz ^1H NMR.[21] The minor diastereomer **11** could be removed by recrystallizations from 4:1 AcOEt/*n*-hexane, providing diastereomerically pure carboximide **10**, mp 68.5–69.0 °C, $[\alpha]_D^{22} = -52.8$ (*c* 2.08, $CHCl_3$), as colorless needles. Our effort was then directed toward the crucial methylation reaction. Gratifyingly, the reaction of the sodium enolate generated from **10** with MeI in THF at –78 °C exhibited excellent diastereoselectivity (98:2) for the desired alkylation product **12** with 1,2-*syn*-dimethyl stereocenters.[23] The excellent diastereoselection observed with **10** is attributed to the complementary influence on the facial bias imposed on the sodium enolate by the β-stereocenter as well as the chiral auxiliary.[24] In this context, McGarvey and Williams reported that a good level of 1,2-asymmetric induction from the β-substituent was observed in the methylation of ester enolates bearing oxygen substitution at a γ-position.[25] For example, treatment of the lithium enolate derived from ester **13** with MeI in THF at –78 °C afforded an 89:11 mixture of products favoring the *syn*-dimethyl-substituted ester **15** in 85% combined yield (Eq. 1). They reasoned that the homoallylic oxygen in the enolate would enhance the donor ability of the substituted carbon via lone pair participation, leading to the transition state **14**, wherein the electron-donating CH_2OTBS group is aligned anti to the forming bond and the sterically unencumbered hydrogen atom occupies the inside position. Based on the McGarvey precedent, the predominant



Scheme 2. *Reagents and conditions*: (a) LiOH, 5:1 THF/H_2O, 72 h; (b) PivCl, Et_3N, THF, –20 °C, 2 h, then oxazolidinone **8**, LiCl, rt, 3 h; (c) MeMgBr, $CuBr{\cdot}SMe_2$, 24:8:1 $THF/Me_2S/CH_2Cl_2$, –78 °C, 30 min, then –30 °C, 30 min; (d) NaHMDS, THF, –78 °C, 30 min, then MeI, 6 h.



(1)

formation of the 1,2-*syn* diastereomer **12** can be rationalized by the transition state **A**, wherein the benzyloxymethyl group at C2 and the phenyl group of the auxiliary act in concert to direct the alkylation from the *re*-face of the enolate (Figure 1).

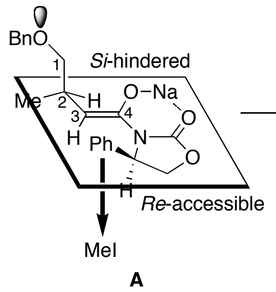
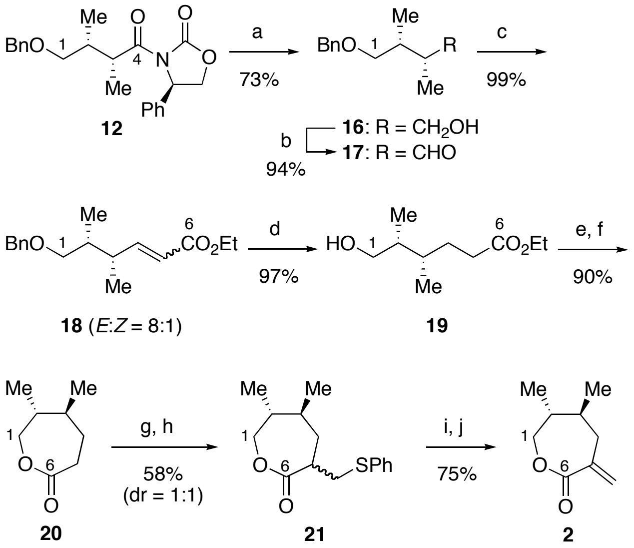


Figure 1. Stereochemical model for the predominant formation of *syn*-isomer **12**.

After chromatographic separation of the desired carboximide **12**, $[\alpha]_D^{20} = -82.0$ (*c* 2.01, $CHCl_3$), reductive removal of the chiral auxiliary with $LiBH_4$ in aqueous THF[26] afforded the primary alcohol **16**, $[\alpha]_D^{21} = +6.19$ (*c* 2.00, $CHCl_3$), in 73% yield along with 66% recovery of the auxiliary (Scheme 3). Oxidation of alcohol **16** with Dess–Martin periodinane[27] in CH_2Cl_2 was followed by Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate to give enoate **18** as an 8:1 *E*/*Z* mixture of olefin isomers in 93% yield in two steps. Hydrogenation of the C4–C5 olefin and hydrogenolytic cleavage of the C1 benzyl protecting group were effected in a single operation by treatment of **18** with $Pd(OH)_2/C$ in AcOEt under a hydrogen atmosphere to afford ε-hydroxyester **19**, $[\alpha]_D^{22} = -10.6$ (*c* 2.40, $CHCl_3$), in 97% yield. Saponification of **19** with KOH in MeOH and subsequent TsOH-catalyzed lactonization at high dilution (14 mM in benzene) provided 7-membered lactone **20**, $[\alpha]_D^{21} = -43.1$ (*c* 2.02, $CHCl_3$), in 90% yield in two steps.

With the 7-membered lactone **20** in hand, the remaining operation necessary for the synthesis of the C1–C6 fragment **2** was the α-methylidenation of lactone **20**. In this regard, Takeda and co-workers successfully utilized the Paterson procedure[28] for the conversion of ε-caprolactone to α-methylene-ε-caprolactone.[14b] Following this literature precedent, lactone **20** was uneventfully converted to the corresponding silyl ketene acetal, which, upon treatment with α-chlorothioanisole in the presence of a catalytic amount of $ZnBr_2$ in CH_2Cl_2, afforded α-(phenylthiomethyl)lactone **21** as a 1:1 mixture of diastereomers in 58% yield in two steps along with 13% recovery of the lactone **20**. Finally, oxidation of sulfide **21** with $NaIO_4$ in aqueous MeOH and subsequent elimination of the corresponding sulfoxide in refluxing toluene furnished the target α-methylene lactone **2**, $[\alpha]_D^{21} = -6.69$ (*c* 2.01, $CHCl_3$), in 75% yield in two steps.



Scheme 3. *Reagents and conditions*: (a) $LiBH_4$, H_2O, THF, 0 °C, 3 h, then rt, 1.5 h; (b) Dess–Martin periodinane, CH_2Cl_2, 10 min; (c) $(EtO)_2P(O)CH_2CO_2Et$, ^{t}BuOK, THF, −78 °C, 30 min, then 0 °C, 30 min; (d) H_2, 20% $Pd(OH)_2/C$, AcOEt, 5 h; (e) KOH, MeOH, 4 h; (f) TsOH, benzene (14 mM), reflux, 1 h; (g) LDA, THF, −78 °C, 1 h, then TMSCl, −78 °C, 30 min and rt, 1 h; (h) $PhSCH_2Cl$, $ZnBr_2$, CH_2Cl_2, 12 h; (i) $NaIO_4$, 9:1 $MeOH/H_2O$, 24 h; (j) toluene, reflux, 3 h.

3. Conclusion

We have achieved the stereoselective synthesis of a C1–C6 fragment of pinnatoxin A in 14 steps with an overall yield of 13.7%. The foregoing synthetic sequence demonstrated the utility of phenyl-substituted oxazolidinone as a common chiral auxiliary to set the contiguous methyl-bearing stereocenters in a *syn* stereochemical relationship through a 1,4-addition of MeMgBr and subsequent alkylation with MeI wherein the facial bias conferred on the enolate was reinforced by the adjacent stereocenter created by the 1,4-addition. This is the first example of a stereoselective construction of a 1,2-*syn*-dimethyl array via the chiral oxazolidinone-based 1,4-addition/alkylation sequence. Efforts to complete the total synthesis of pinnatoxin A (**1**) using an intermolecular Diels–Alder strategy are in progress in our laboratory and will be reported in due course.[29]

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO P-1030 digital polarimeter with a sodium lamp. Infrared (IR) spectra were recorded on JASCO FT/IR-5300 or FT/IR-4100 spectrometers and absorbance bands are reported in wavenumbers (cm^{-1}). ^{1}H NMR spectra were recorded on JEOL JNM-ECA500 (500 MHz) or Bruker ARX500 (500 MHz) spectrometers with tetramethylsilane (δ 0.00) or C_6H_6 (δ

7.20) as an internal standard. Coupling constants (*J*) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration and assignment. Pinnatoxin numbering is used for proton assignments of all compounds. ^{13}C NMR spectra were recorded on JEOL JNM-EX270 (67.8 MHz), JNM-AL400 (100.6 MHz) or JNM-ECX400P (99.6 MHz) spectrometers with $CDCl_3$ (δ 77.0) as an internal standard. Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded on JEOL JMS-FABmate and JMS-HX110 spectrometers, respectively, by the Center for Instrumental Analysis, Hokkaido University.

Column chromatography was carried out on Kanto silica gel 60 N (63–210 μm). Analytical TLC was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and anisaldehyde or phosphomolybdic acid stain, followed by heating.

Reagents and solvents were purified by standard means or used as received unless otherwise noted. Dehydrated stabilizer free THF was purchased from Kanto Chemical Co., Inc. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5 and redistilled from calcium hydride prior to use. Diisopropylamine ($^iPr_2NH$) and TMSCl were distilled from calcium hydride prior to use.

$CuBr{\cdot}SMe_2$[30] and Dess–Martin periodinane[31] were prepared according to literature procedures.

4.2. [4*R*,3(2*E*)]-3-(4-Benzyloxy-2-butenoyl)-4-phenyl-2-oxazolidinone (9). Lithium hydroxide monohydrate (4.67 g, 111 mmol) was added to a solution of ethyl 4-benzyloxy-2-butenoate[19] (**6**, 12.3 g, 55.6 mmol) in 5:1 THF/H_2O (240 mL). After stirring for 72 h, THF was removed in vacuo, and the residue was partitioned between Et_2O (100 mL) and 2 M aqueous $NaHSO_4$ (150 mL). The aqueous layer was extracted with AcOEt (300 mL). The combined organic extracts were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (11.0 g, slightly yellow solid), which was used without further purification.

Trimethylacetyl chloride (9.3 mL, 61.2 mmol) was added to a solution of the crude carboxylic acid **7** (11.0 g) and Et_3N (24 mL, 167 mmol) in THF (200 mL) at –25 °C under an argon atmosphere. After stirring at –20 °C for 2 h, LiCl (3.5 g, 83.5 mmol) and 2-oxazolidinone **8**[15] (10.0 g, 61.2 mmol) were added, and the mixture was allowed to warm to room temperature. After stirring for 3 h, the reaction mixture was poured into an ice-cooled, two-layer mixture of Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (150 mL), and the whole mixture was extracted with AcOEt (300 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (2×100 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (21.7 g, brown solid), which was recrystallized from 1:1 *n*-hexane/AcOEt to give carboximide **9** (13.9 g, 74%) as colorless plates. Concentration of the mother liquor followed by purified by column chromatography (silica gel 110 g, 3:1 *n*-hexane/AcOEt) gave **9** (2.56 g, 14%) as a white solid: TLC R_f = 0.24 (3:1 *n*-hexane/AcOEt); mp 115.5–116.5 °C; $[\alpha]_D^{26}$ = –67.3 (*c* 2.07, $CHCl_3$); IR (nujol) 2924, 2855, 1796, 1767, 1682, 1644, 1462, 1379, 1366, 1333, 1209, 1138, 972, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.21 (dd, *J* = 2.0, 4.5 Hz, 2H, C1-H_2), 4.29 (dd, *J* = 3.9, 8.8 Hz, 1H, one of CH_2O), 4.57 (s, 2H, PhCH_2O), 4.71 (t, *J* = 8.8 Hz, 1H, one of CH_2O), 5.49 (dd, *J* = 3.9, 8.8 Hz, 1H, PhC*H*N), 7.08 (dt, *J* = 15.4, 4.5 Hz, 1H, C2-*H*), 7.27–7.40 (m, 10H, Ar*H*), 7.54 (dt, *J* = 15.4, 2.0 Hz, 1H, C3-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 56.7 (CH), 68.8 (CH_2), 69.8 (CH_2), 72.6 (CH_2), 120.2 (CH), 125.8 (CH), 127.58 (CH), 127.63 (CH), 128.3 (CH), 128.5 (CH), 129.0 (CH), 137.6 (C), 138.8 (C), 146.4 (CH), 153.4 (C), 164.0 (C); FAB-HRMS *m*/*z* calcd for $C_{20}H_{20}NO_4$ $(M+H)^+$ 338.1392, found 338.1400; Anal. calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15, found: C, 71.27; H, 5.61; N, 4.26.

4.3. [4*R*,3(3*R*)]-3-(4-Benzyloxy-3-methylbutanoyl)-4-phenyl-2-oxazolidinone (10). MeMgBr in THF (0.93 M, 127 mL, 119 mmol) was added to a suspension of $CuBr{\cdot}SMe_2$ (32.5 g, 158 mmol) in 3:2 THF/Me_2S (400 mL) at –78 °C under an argon atmosphere. After stirring at –78 °C for 20 min and at 0 °C for 20 min, the yellow suspension was cooled to –78 °C, and a solution of carboximide **9** (13.3 g, 39.4 mmol) in 6:1 THF/CH_2Cl_2 (140 mL) was added. After stirring at –78 °C for 30 min, the mixture was warmed to –30 °C over 30 min and stirred at this temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (150 mL), and the mixture was extracted with AcOEt (300 mL). The organic extract was successively washed with saturated aqueous NH_4Cl (2×150 mL), H_2O (80 mL) and brine (2×80 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the slightly yellow solid (14.4 g), whose ^1H NMR [integration of C3-H, desired isomer **10** (2.68 ppm), undesired isomer **11** (2.86 ppm)] revealed a **10**/**11** ratio of 94:6. Purification of the crude product by column chromatography (silica gel 300 g, 100:1 CH_2Cl_2/AcOEt) afforded a mixture of 1,4-adducts (13.6 g, 97%) as a white solid, which was recrystallized twice from 4:1 AcOEt/*n*-hexane to afford desired isomer **10** (7.06 g, 51%) as colorless needles. Concentration of the mother liquor followed by two recrystallizations from 4:1 AcOEt/*n*-hexane gave **10** (2.03 g, 15%) as colorless needles. This sequence was repeated again to provide another crop of carboximide **10** (877 mg, 6%), resulting in combined yield of 72%: TLC R_f = 0.23 (4:1 *n*-hexane/AcOEt); mp 68.5–69.0 °C; $[\alpha]_D^{22}$ = –52.8 (*c* 2.08, $CHCl_3$); IR (nujol) 2922, 2855, 1782, 1699, 1462, 1381, 1300, 1200, 1121, 1036, 762, 729, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.8 Hz, 3H, C2-CH_3), 2.42 (m, 1H, C2-*H*), 2.68 (dd, *J* = 6.2, 16.1 Hz, 1H, one of C3-H_2), 3.25 (dd, *J* = 7.3, 16.1 Hz, 1H, one of C3-H_2), 3.31 (dd, *J* = 7.6, 9.2 Hz, 1H, one of C1-H_2), 3.39 (dd, *J* = 5.6, 9.2 Hz, 1H, one of C1-H_2), 4.14 (dd, *J* = 3.8, 8.8 Hz, 1H, one of CH_2O), 4.36 (t, *J* = 8.8 Hz, 1H, one of CH_2O), 4.42 (d, *J* = 11.8 Hz, 1H, one of PhCH_2O), 4.44 (d, *J* = 11.8 Hz, 1H, one of PhCH_2O), 5.23 (dd, *J* = 3.8, 8.8 Hz, 1H, PhC*H*N), 7.23–7.37 (m, 10H, Ar*H*); ^{13}C NMR

(67.8 MHz, $CDCl_3$) δ 17.1 (CH_3), 30.6 (CH), 39.2 (CH_2), 57.4 (CH), 69.5 (CH_2), 72.7 (CH_2), 75.0 (CH_2), 125.8 (CH), 127.36 (CH), 127.43 (CH), 128.2 (CH), 128.4 (CH), 129.0 (CH), 138.6 (C), 139.2 (C), 153.7 (C), 172.0 (C); FAB-HRMS *m*/*z* calcd for $C_{21}H_{24}NO_4$ $(M+H)^+$ 354.1705, found 354.1718; Anal. calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96, found: C, 71.30; H, 6.62; N, 3.84.

4.4. [4*S*,3(3*R*)]-3-(4-Benzyloxy-3-methylbutanoyl)-4-phenyl-2-oxazolidinone (*ent*-11). Trimethylacetyl chloride (0.01 mL, 76.1 μmol) was added to a solution of (*R*)-4-benzyloxy-3-methylbutanoic acid[22] (12.0 mg, 57.6 μmol) and Et_3N (0.03 mL, 0.215 mmol) in THF (1 mL) at –25 °C under an argon atmosphere. After stirring at –20 °C for 2 h, LiCl (3.7 mg, 87.3 μmol) and oxazolidinone *ent*-**8** (9.5 mg, 58.2 μmol) were added, and the mixture was allowed to warm to room temperature. After stirring for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the mixture was extracted with AcOEt (15 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (2×5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (21.7 mg, yellow oil), which was purified by column chromatography (silica gel 4 g, 4:1 *n*-hexane/AcOEt) to give *ent*-**11** (19.1 mg, 94%) as a colorless oil: TLC $R_f = 0.23$ (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{18} = +43.5$ (*c* 1.08, $CHCl_3$); IR (film) 3032, 2961, 2927, 2857, 1781, 1706, 1455, 1385, 1325, 1200, 1121, 1096, 758, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, $J = 6.9$ Hz, 3H, C2-CH_3), 2.37 (m, 1H, C2-*H*), 2.86 (dd, $J = 8.0$, 16.6 Hz, 1H, one of C3-H_2), 3.04 (dd, $J = 5.7$, 16.6 Hz, 1H, one of C3-H_2), 3.30 (dd, $J = 6.9$, 9.2 Hz, 1H, one of C1-H_2), 3.35 (dd, $J = 5.7$, 9.2 Hz, 1H, one of C1-H_2), 4.21 (dd, $J = 3.4$, 8.6 Hz, 1H, one of CH_2O), 4.42 (s, 2H, PhCH_2O), 4.56 (t, $J = 8.6$ Hz, 1H, one of CH_2O), 5.31 (dd, $J = 3.4$, 8.6 Hz, 1H, PhC*H*N), 7.20–7.40 (m, 10H, Ar*H*); ^{13}C NMR (99.6 MHz, $CDCl_3$) δ 17.0 (CH_3), 30.2 (CH), 39.8 (CH_2), 57.6 (CH), 69.9 (CH_2), 72.9 (CH_2), 74.8 (CH_2), 125.9 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH), 128.6 (CH), 129.1 (CH), 138.5 (C), 139.2 (C), 153.7 (C), 171.9 (C); FAB-HRMS *m*/*z* calcd for $C_{21}H_{24}NO_4$ $(M+H)^+$ 354.1705, found 354.1715.

4.5. [4*R*,3(2*R*,3*R*)]-3-(4-Benzyloxy-2,3-dimethylbutanoyl)-4-phenyl-2-oxazolidinone (12). A solution of carboximide **10** (14.1 g, 40.0 mmol) in THF (50 mL plus 2×4 mL rinse) was added to a 0.5 M solution of NaHMDS in THF (104 mL, 52.0 mmol) at –78 °C under an argon atmosphere. After stirring for 30 min, MeI (12.5 mL, 199 mmol) was added, and the mixture was stirred for 6 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the mixture was extracted with AcOEt (300 mL). The organic extract was successively washed with saturated aqueous NH_4Cl (2×80 mL) and brine (100 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (15.0 g, yellow oil), whose diastereomeric ratio was determined to be 98:2 by ^1H-NMR [integration of the benzylic proton at C4 of the oxazolidinone, desired *syn*-isomer **12** (4.91 ppm), undesired *anti*-isomer (5.45 ppm)]. Purification of the crude product by column chromatography (silica gel 300 g, 6:1 → 4:1 → 2:1 *n*-hexane/AcOEt) afforded *syn*-isomer **12** (12.2 g, 83%) as a colorless oil, along with a 6.3:1 mixture of **10** and *anti*-isomer (2.22 g) as a white solid: TLC $R_f = 0.36$ (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{20} = -82.0$ (*c* 2.01, $CHCl_3$); IR (film) 3032, 2969, 2932, 2878, 1779, 1705, 1454, 1383, 1319, 1204, 1098, 982, 741, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, $J = 7.0$ Hz, 3H, C2-CH_3), 1.03 (d, $J = 6.9$ Hz, 3H, C3-CH_3), 2.31 (m, 1H, C2-*H*), 3.39 (t, $J = 9.3$ Hz, 1H, one of C1-H_2), 3.47 (dd, $J = 5.2$, 9.3 Hz, 1H, one of C1-H_2), 3.83 (dq, $J = 8.9$, 6.9 Hz, 1H, C3-*H*), 3.92–3.99 (m, 2H, CH_2O), 4.39 (d, $J = 11.4$ Hz, 1H, one of PhCH_2O), 4.46 (d, $J = 11.4$ Hz, 1H, one of PhCH_2O), 4.91 (dd, $J = 4.7$, 8.4 Hz, 1H, PhC*H*N), 7.15–7.18 (m, 2H, Ar*H*), 7.25–7.39 (m, 8H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.7 (CH_3), 14.9 (CH_3), 35.6 (CH), 40.0 (CH), 57.4 (CH), 69.1 (CH_2), 72.7 (CH_2), 75.4 (CH_2), 125.4 (CH), 127.4 (CH), 127.5 (CH), 128.1 (CH), 128.2 (CH), 128.9 (CH), 138.6 (C), 139.5 (C), 153.6 (C), 176.5 (C); FAB-HRMS *m*/*z* calcd for $C_{22}H_{26}NO_4$ $(M+H)^+$ 368.1862, found 368.1871; Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81, found: C, 71.99; H, 6.94; N, 3.78. Data for [4*R*,3(2*S*,3*R*)]-isomer: TLC $R_f = 0.23$ (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{23} = -16.6$ (*c* 1.28, $CHCl_3$); IR (nujol) 2924, 2854, 1786, 1701, 1457, 1377, 1319, 1211, 1083, 749, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, $J = 6.9$ Hz, 3H, C2-CH_3), 1.08 (d, $J = 6.9$ Hz, 3H, C3-CH_3), 2.16 (m, 1H, C2-*H*), 3.14–3.24 (m, 2H, C1-H_2), 3.83 (quintet, $J = 6.9$ Hz, 1H, C3-*H*), 4.22–4.33 (m, 3H, one of CH_2O, PhCH_2O), 4.68 (t, $J = 9.2$ Hz, 1H, one of CH_2O), 5.45 (dd, $J = 4.6$, 9.2 Hz, 1H, PhC*H*N), 7.22–7.38 (m, 10H, Ar*H*); ^{13}C NMR (99.6 MHz, $CDCl_3$) δ 13.0 (CH_3), 15.9 (CH_3), 36.4 (CH), 40.5 (CH), 57.8 (CH), 69.5 (CH_2), 72.0 (CH_2), 72.8 (CH_2), 126.2 (CH), 127.36 (CH), 127.39 (CH), 128.3 (CH), 128.6 (CH), 129.0 (CH), 138.5 (C), 139.0 (C), 153.4 (C), 176.1 (C); FAB-HRMS *m*/*z* calcd for $C_{22}H_{26}NO_4$ $(M+H)^+$ 368.1862, found 368.1848.

4.6. (2*R*,3*R*)-4-Benzyloxy-2,3-dimethyl-1-butanol (16). A 2.0 M solution of $LiBH_4$ in THF (21.5 mL, 43.0 mmol) was added to a solution of carboximide **12** (12.7 g, 34.6 mmol) in THF (120 mL) and H_2O (0.78 mL, 43.2 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was poured into an ice-cooled, two-layer mixture of Et_2O (10 mL) and saturated aqueous NH_4Cl (60 mL), and the whole mixture was extracted with AcOEt (150 mL). The organic extract was successively washed with saturated aqueous NH_4Cl (80 mL) and brine (2×80 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (13.5 g, white solid), which was purified by column chromatography (silica gel 250 g, 8:1 *n*-hexane/AcOEt → 4:1 CH_2Cl_2/AcOEt) to give alcohol **16** (5.22 g, 73%) as a colorless oil, along with recovered oxazolidinone **8** (3.7 g) as a white solid: TLC $R_f = 0.31$ (3:1 *n*-hexane/AcOEt); $[\alpha]_D^{21} = +6.19$ (*c* 2.00, $CHCl_3$); IR (film) 3387 (br), 3030, 2876, 1454, 1364, 1094, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, $J = 7.0$ Hz, 6H, C2-CH_3, C3-CH_3), 1.70 (m, 1H, C3-*H*), 1.87 (m, 1H, C2-*H*), 2.20 (br s, 1H, O*H*), 3.38 (dd, $J = 7.2$, 9.3 Hz, 1H, one of C1-H_2), 3.42 (dd, $J = 4.8$, 9.3 Hz, 1H, one of C1-H_2), 3.48 (dd, $J = 5.8$, 11.1 Hz, 1H, one of C4-H_2), 3.60 (dd, $J = 5.0$, 11.1 Hz, 1H, one of C4-H_2), 4.51 (d, J = 11.9 Hz, 1H, one of PhCH_2O), 4.53 (d, J = 11.9 Hz, 1H, one of PhCH_2O), 7.25–7.38 (m, 5H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.8 (CH_3), 13.1 (CH_3), 34.4 (CH), 37.4 (CH), 65.7 (CH_2), 72.9 (CH_2), 73.9 (CH_2), 127.36 (CH), 127.42 (CH), 128.1 (CH), 138.0 (C); EI-HRMS *m*/*z* calcd for $C_{13}H_{20}O_2$ $(M)^+$ 208.1463, found 208.1465; Anal. calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68, found: C, 74.84; H, 9.71.

4.7. (2*R*,3*R*)-4-Benzyloxy-2,3-dimethylbutanal (17). A solution of alcohol **16** (2.77 g, 13.3 mmol) in CH_2Cl_2 (9 mL) was added to a solution of Dess–Martin periodinane (6.80 g, 16.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C under an argon atmosphere. After stirring at room temperature for 10 min, the reaction was quenched with a mixture of 1 M aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL), and the whole mixture was extracted with AcOEt (600 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (4×100 mL) and brine (100 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (2.90 g, colorless oil), which was purified by column chromatography (silica gel 40 g, 10:1 *n*-hexane/AcOEt) to give aldehyde **17** (2.57 g, 94%) as a colorless oil: TLC R_f = 0.32 (10:1 *n*-hexane/AcOEt); $[\alpha]_D^{21}$ = –39.8 (*c* 2.16, $CHCl_3$); IR (film) 2967, 2876, 1723, 1454, 1364, 1100, 737, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J = 6.9 Hz, 3H, C2-CH_3), 1.00 (d, J = 7.0 Hz, 3H, C3-CH_3), 2.34 (m, 1H, C2-*H*), 2.53 (m, 1H, C3-*H*), 3.31 (dd, J = 8.2, 9.3 Hz, 1H, one of C1-H_2), 3.43 (dd, J = 5.2, 9.3 Hz, 1H, one of C1-H_2), 4.48 (d, J = 12.1 Hz, 1H, one of PhCH_2O), 4.49 (d, J = 12.1 Hz, 1H, one of PhCH_2O), 7.25–7.38 (m, 5H, Ar*H*), 9.65 (d, J = 1.7 Hz, 1H, C4-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 8.6 (CH_3), 12.8 (CH_3), 33.5 (CH), 48.1 (CH), 72.8 (CH_2), 127.3 (CH), 128.1 (CH), 138.0 (C), 204.5 (CH); EI-HRMS *m*/*z* calcd for $C_{13}H_{18}O_2$ $(M)^+$ 206.1307, found 206.1315; Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80, found: C, 75.49; H, 8.79.

4.8. Ethyl (4*S*,5*R*)-6-benzyloxy-4,5-dimethyl-2-hexenoate (18). Triethyl phosphonoacetate (3.8 mL, 18.6 mmol) was added to a suspension of ^{t}BuOK (2.08 g, 18.5 mmol) in THF (50 mL) at 0 °C under an argon atmosphere. After stirring at room temperature for 30 min, the solution was cooled to –78 °C, and a solution of aldehyde **17** (2.54 g, 12.3 mmol) in THF (8 mL plus 2×1 mL rinse) was added. After 30 min, the reaction mixture was allowed to warm to 0 °C and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (30 mL), and the whole mixture was extracted with AcOEt (150 mL). The organic extract was successively washed with saturated aqueous NH_4Cl (40 mL) and brine (40 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (5.30 g, slightly yellow oil), which was purified by column chromatography (silica gel 150 g, 20:1 *n*-hexane/AcOEt) to give α,β-unsaturated esters (*E*)-**18** (3.02 g, 89%) and (*Z*)-**18** (368 mg, 11%) as colorless oils. Data for (2*E*,4*S*,5*R*)-isomer (*E*)-**18**: TLC R_f = 0.29 (10:1 *n*-hexane/AcOEt); $[\alpha]_D^{22}$ = –46.2 (*c* 2.09, $CHCl_3$); IR (film) 2969, 2876, 1719, 1651, 1454, 1368, 1265, 1184, 737, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J = 6.9 Hz, 3H, C2-CH_3), 1.00 (d, J = 6.8 Hz, 3H, C3-CH_3), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.89 (m, 1H, C2-*H*), 2.49 (m, 1H, C3-*H*), 3.29 (dd, J = 6.3, 9.3 Hz, 1H, one of C1-H_2), 3.37 (dd, J = 6.4, 9.3 Hz, 1H, one of C1-H_2), 4.19 (q, J = 7.1 Hz, 2H, OC$H_2$$CH_3$), 4.48 (s, 2H, PhC$H_2$O), 5.78 (dd, J = 0.9, 15.7 Hz, 1H, C5-*H*), 6.93 (dd, J = 7.6, 15.7 Hz, 1H, C4-*H*), 7.25–7.36 (m, 5H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.5 (CH_3), 14.2 (CH_3), 14.6 (CH_3), 37.6 (CH), 37.9 (CH), 60.0 (CH_2), 72.9 (CH_2), 73.3 (CH_2), 120.1 (CH), 127.31 (CH), 127.34 (CH), 128.1 (CH), 138.3 (C), 153.3 (CH), 166.6 (C); EI-HRMS *m*/*z* calcd for $C_{17}H_{24}O_3$ $(M)^+$ 276.1725, found 276.1741; Anal. calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75, found: C, 73.78; H, 8.68. Data for (2*Z*,4*S*,5*R*)-isomer (*Z*)-**18**: TLC R_f = 0.35 (10:1 *n*-hexane/AcOEt); $[\alpha]_D^{24}$ = +22.6 (*c* 1.99, $CHCl_3$); IR (film) 2976, 2874, 1721, 1644, 1454, 1416, 1182, 1098, 1032, 737, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.3 Hz, 3H, C2-CH_3), 1.00 (d, J = 6.3 Hz, 3H, C3-CH_3), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.74 (m, 1H, C2-*H*), 3.24 (dd, J = 7.7, 9.2 Hz, 1H, one of C1-H_2), 3.43 (dd, J = 5.0, 9.2 Hz, 1H, one of C1-H_2), 3.46 (m, 1H, C3-*H*), 4.15 (q, J = 7.1 Hz, 2H, OC$H_2$$CH_3$), 4.46 (d, J = 12.0 Hz, 1H, one of PhCH_2O), 4.47 (d, J = 12.0 Hz, 1H, one of PhCH_2O), 5.71 (d, J = 11.5 Hz, 1H, C5-*H*), 6.09 (t, J = 11.5 Hz, 1H, C4-*H*), 7.24–7.35 (m, 5H, Ar*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 14.5 (CH_3), 17.1 (CH_3), 35.1 (CH), 38.6 (CH), 59.7 (CH_2), 72.8 (CH_2), 74.1 (CH_2), 118.3 (CH), 127.2 (CH), 127.3 (CH), 128.1 (CH), 138.5 (C), 154.4 (CH), 166.1 (C); EI-HRMS *m*/*z* calcd for $C_{17}H_{24}O_3$ $(M)^+$ 276.1725, found 276.1713.

4.9. Ethyl (4*S*,5*R*)-6-hydroxy-4,5-dimethylhexanoate (19). $Pd(OH)_2$ on carbon (20%, 123 mg) was added to a solution of enoate **18** (3.29 g, 11.9 mmol) in AcOEt (30 mL) under an argon atmosphere, and the mixture was vigorously stirred for 5 h under 1 atm of hydrogen. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. Purification of the crude product (2.29 g, slightly yellow oil) by column chromatography (silica gel 65 g, 4:1 *n*-hexane/AcOEt) afforded hydroxyester **19** (2.19 g, 97%) as a colorless oil: TLC R_f = 0.13 (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{22}$ = –10.6 (*c* 2.40, $CHCl_3$); IR (film) 3428 (br), 2961, 2928, 1736, 1181, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, J = 6.7 Hz, 3H, C3-CH_3), 0.84 (d, J = 6.8 Hz, 3H, C2-CH_3), 1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.50 (m, 1H, one of C4-H_2), 1.55–1.75 (m, 3H, C2-*H*, C3-*H*, one of C4-H_2), 2.24–2.40 (m, 2H, C5-H_2), 3.48–3.57 (m, 2H, C1-H_2), 4.13 (q, J = 7.2 Hz, 2H, OC$H_2$$CH_3$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.3 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 29.7 (CH_2), 32.3 (CH_2), 32.7 (CH), 39.2 (CH), 60.1 (CH_2), 66.0 (CH_2), 174.0 (C); FAB-HRMS *m*/*z* calcd for $C_{10}H_{21}O_3$ $(M+H)^+$ 189.1491, found 189.1504; Anal. calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71, found: C, 63.71; H, 10.71.

4.10. (5*S*,6*R*)-5,6-Dimethyloxepan-2-one (20). KOH (85%, 2.18 g, 33.0 mmol) was added to a solution of hydroxyester **19** (2.07 g, 11.0 mmol) in MeOH (20 mL) at 0 °C. After stirring at room temperature for 4 h, the solvent was removed in vacuo, and the residue was partitioned between AcOEt (150 mL) and 2 M aqueous $NaHSO_4$ (35 mL). The organic extract was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.96 g), which was used without further purification.

TsOH (41.9 mg, 0.22 mmol) was added to a solution of the crude hydroxycarboxylic acid **5** (1.96 g) in benzene (800 mL), and the mixture was refluxed for 1 h. After the solvent was removed by distillation at atmospheric pressure, the residue was partitioned between AcOEt (300 mL) and saturated aqueous $NaHCO_3$ (60 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (80 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration by atmospheric fractional distillation furnished the crude product (1.89 g), which was purified by column chromatography (silica gel 40 g, 5:2 *n*-hexane/Et_2O) to give lactone **20** (1.41 g, 90%) as a white solid: TLC R_f = 0.28 (3:1 *n*-hexane/AcOEt); mp 41.0–42.0 °C; $[\alpha]_D^{21}$ = –43.1 (*c* 2.02, $CHCl_3$); IR (nujol) 2922, 1750, 1458, 1377, 1277, 1074, 903 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.9 Hz, 3H, C2-C*H*$_3$), 1.04 (d, *J* = 6.2 Hz, 3H, C3-C*H*$_3$), 1.38–1.51 (m, 2H, C3-*H*, one of C4-*H*$_2$), 1.57 (m, 1H, C2-*H*), 1.89 (m, 1H, one of C4-*H*$_2$), 2.60–2.69 (m, 2H, C5-*H*$_2$), 4.03 (dd, *J* = 8.4, 12.9 Hz, 1H, one of C1-*H*$_2$), 4.07 (dd, *J* = 2.1, 12.9 Hz, 1H, one of C1-*H*$_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.5 (CH_3), 20.4 (CH_3), 30.2 (CH_2), 32.4 (CH_2), 39.8 (CH), 40.0 (CH), 72.9 (CH_2), 175.8 (C); EI-HRMS *m*/*z* calcd for $C_8H_{14}O_2$ $(M)^+$ 142.0994, found 142.0997; Anal. calcd for $C_8H_{14}O_2$: C, 67.58; H, 9.92, found: C, 67.68; H, 9.73.

4.11. (5*S*,6*R*)-5,6-Dimethyl-3-(phenylthiomethyl)oxepan-2-one (21). BuLi in *n*-hexane (1.56 M, 11.6 mL, 18.1 mmol) was added to a solution of ^{i}Pr$_2$NH (2.6 mL, 18.6 mmol) in THF (20 mL) at –30 °C under an argon atmosphere. After stirring for 30 min, the solution was cooled to –78 °C, and a solution of lactone **20** (12.8 g, 9.00 mmol) in THF (10 mL) was added. After 1 h, TMSCl (2.3 mL, 18.1 mmol) was added, and the resulting mixture was stirred for 30 min. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 1 h. After the volatile elements were removed in vacuo, the residue was suspended in pentane (60 mL) and filtered through a plug of Celite. Evaporation of the filtrate in vacuo furnished the crude product (2.91 g), which was used without further purification.

$ZnBr_2$ (20.3 mg, 90.1 μmol) was added to a solution of the crude silyl ketene acetal and α-chlorothioanisole (1.8 mL, 13.4 mmol) in CH_2Cl_2 (30 mL) under an argon atmosphere. After stirring for 12 h, the volatile elements were removed in vacuo, and the residue (5.21 g, orange oil) was purified by column chromatography (silica gel 90 g, 8:1 *n*-hexane/AcOEt) to give sulfide **21** (1.37 g, 58%) as a colorless oil, along with recovered lactone **20** (168 mg, 13%) as a white solid: TLC R_f = 0.39 (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{23}$ = –1.20 (*c* 2.01, $CHCl_3$); IR (film) 2963, 2930, 1732, 1584, 1480, 1381, 1262, 1179, 1154, 1094, 741, 693 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.34 (d, *J* = 6.9 Hz, 1.5H, C2-C*H*$_3$), 0.55–0.65 (m, 3H, C3-C*H*$_3$), 0.73 (m, 0.5H, C3-*H*), 0.77 (d, *J* = 6.9 Hz, 1.5H, C2-C*H*$_3$), 0.84 (m, 0.5H, C2-*H*), 0.93–1.09 (m, 1H, C2-*H*, one of C4-*H*$_2$), 1.27 (m, 0.5H, C3-*H*), 1.41–1.53 (m, 1H, C4-*H*$_2$), 1.79 (dd, *J* = 3.4, 14.3 Hz, 0.5H, one of C4-*H*$_2$), 2.50–2.60 (m, 1H, C5-*H*), 2.76–2.87 (m, 1H, one of C*H*$_2$SPh), 3.23 (dd, *J* = 9.7, 13.2 Hz, 0.5H, one of C1-*H*$_2$), 3.28 (dd, *J* = 3.4, 13.2 Hz, 0.5H, one of C1-*H*$_2$), 3.41 (dd, *J* = 1.7, 13.2 Hz, 0.5H, one of C1-*H*$_2$), 3.605 (d, *J* = 13.2 Hz, 0.5H, one of C1-*H*$_2$), 3.609 (dd, *J* = 4.6, 13.7 Hz, 0.5H, one of C*H*$_2$SPh), 3.65 (dd, *J* = 4.6, 13.7 Hz, 0.5H, one of C*H*$_2$SPh), 6.95 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.03 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.04 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.28 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.31 (d, *J* = 7.4 Hz, 1H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.3 (CH_3), 16.4 (CH_3), 19.0 (CH_3), 20.6 (CH_3), 30.8 (CH_2), 34.0 (CH), 36.0 (2×CH_2), 36.9 (CH), 37.3 (CH), 37.4 (CH_2), 39.7 (CH), 40.8 (CH), 41.2 (CH), 67.8 (CH_2), 73.3 (CH_2), 126.27 (CH), 126.32 (CH), 128.9 (CH), 129.5 (CH), 129.6 (CH), 135.5 (C), 135.6 (C), 175.90 (C), 175.93 (C); EI-HRMS *m*/*z* calcd for $C_{15}H_{20}O_2S$ $(M)^+$ 264.1184, found 264.1177; Anal. calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.63; S, 12.13, found: C, 68.02; H, 7.55; S, 12.15.

4.12. (5*S*,6*R*)-5,6-Dimethyl-3-methyleneoxepan-2-one (2). A solution of sodium periodate (1.17 g, 5.47 mmol) in H_2O (4 mL) was added to a solution of sulfide **21** (1.31 g, 4.96 mmol) in MeOH (36 mL). After stirring for 24 h, the mixture was filtrated through a Celite pad, and the filtrate was evaporated in vacuo. The residue was partitioned between AcOEt (50 mL) and H_2O (20 mL), and the aqueous layer was extracted with AcOEt (50 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.50 g), which was purified by column chromatography (silica gel 45 g, 1:2 *n*-hexane/AcOEt) to give sulfoxide (1.23 g, 89%) as a white wax.

A solution of the sulfoxide (1.23 g, 4.39 mmol) in toluene (10 mL) was refluxed for 3 h. The solvent was evaporated in vacuo, and the residue (1.22 g) was purified by column chromatography (silica gel 35 g, 6:1 *n*-hexane/Et_2O) to give α-methylene lactone **2** (572 mg, 84%) as a white solid: TLC R_f = 0.34 (4:1 *n*-hexane/AcOEt); mp 30.0–31.0 °C; $[\alpha]_D^{21}$ = –6.69 (*c* 2.01, $CHCl_3$); IR (nujol) 2963, 2930, 1732, 1462, 1308, 1181, 1140, 1032, 934, 802 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.9 Hz, 3H, C2-C*H*$_3$), 1.04 (d, *J* = 6.4 Hz, 3H, C3-C*H*$_3$), 1.46–1.62 (m, 2H, C2-*H*, C3-*H*), 2.17 (dd, *J* = 10.7, 14.6 Hz, 1H, one of C4-*H*$_2$), 2.50 (dd, *J* = 3.2, 14.6 Hz, 1H, one of C4-*H*$_2$), 3.94 (dd, *J* = 6.7, 12.6 Hz, 1H, one of C1-*H*$_2$), 4.15 (dd, *J* = 2.1, 12.6 Hz, 1H, one of C1-*H*$_2$), 5.43 (s, 1H, one of C5=C*H*$_2$), 5.75 (s, 1H, one of C5=C*H*$_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.2 (CH_3), 19.9 (CH_3), 38.2 (CH_2), 38.2 (CH), 39.3 (CH), 72.4 (CH_2), 123.5 (CH_2), 141.0 (C), 172.4 (C); EI-HRMS *m*/*z* calcd for $C_9H_{14}O_2$ $(M)^+$ 154.0994, found 154.0999; Anal. calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15, found: C, 69.92; H, 9.19.

Acknowledgments

This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" and Priority Areas 18032002 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and by the Akiyama Foundation. We thank Ms. H. Matsumoto, A. Maeda, S. Oka, M. Kiuchi, and Mr. T. Hirose of the Center for Instrumental Analysis, Hokkaido University for technical assistance in mass and elemental analyses.

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Stereoselective synthesis of a C1–C6 fragment of pinnatoxin A via a 1,4-addition/alkylation sequence

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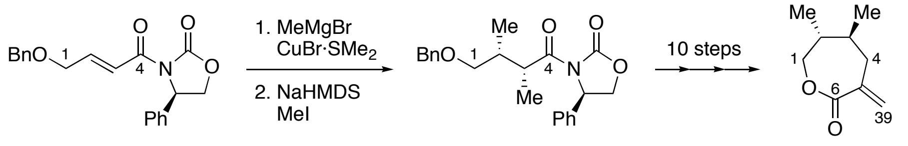
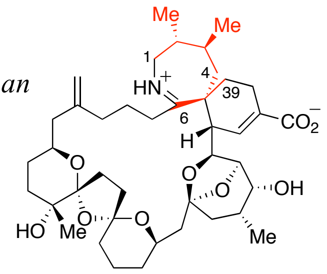


C1–C6 Fragment



Pinnatoxin A

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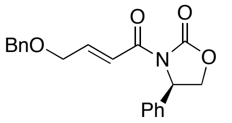

$[\alpha]_D^{26} = -67.3$ (*c* 2.07, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (*R*)

$C_{20}H_{19}NO_4$

[4*R*,3(2*E*)]-3-(4-Benzyloxy-2-butenoyl)-4-phenyl-2-oxazolidinone

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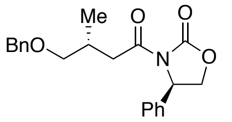
Seiichi Nakamura, Fumiaki Kikuchi and Shunichi Hashimoto*



$[\alpha]_D^{22} = -52.8$ (*c* 2.08, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: [4*R*,3(3*R*)]

$C_{21}H_{23}NO_4$

[4*R*,3(3*R*)]-3-(4-Benzyloxy-3-methylbutanoyl)-4-phenyl-2-oxazolidinone

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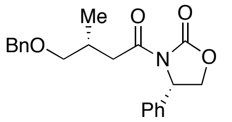
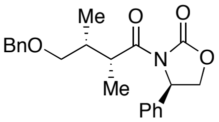


$[\alpha]_D^{18} = +43.5$ (*c* 1.08, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: [4*S*,3(3*R*)]

$C_{21}H_{23}NO_4$

[4*S*,3(3*R*)]-3-(4-Benzyloxy-3-methylbutanoyl)-4-phenyl-2-oxazolidinone

Seiichi Nakamura, Fumiaki Kikuchi and Shunichi Hashimoto*



$[\alpha]_D^{20} = -82.0$ (*c* 2.01, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: [4*R*,3(2*R*,3*R*)]

$C_{22}H_{25}NO_4$

[4*R*,3(2*R*,3*R*)]-3-(4-Benzyloxy-2,3-dimethylbutanoyl)-4-phenyl-2-oxazolidinone

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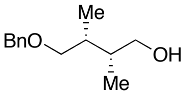
Seiichi Nakamura, Fumiaki Kikuchi and Shunichi Hashimoto*

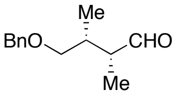


$[\alpha]_D^{21} = +6.19$ (*c* 2.00, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (2*R*,3*R*)

$C_{13}H_{20}O_2$

(2*R*,3*R*)-4-Benzyloxy-2,3-dimethyl-1-butanol

Seiichi Nakamura, Fumiaki Kikuchi and Shunichi Hashimoto*

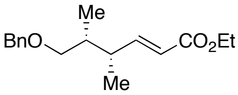


$[\alpha]_D^{21} = -39.8$ (*c* 2.16, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (2*R*,3*R*)

$C_{13}H_{18}O_2$

(2*R*,3*R*)-4-Benzyloxy-2,3-dimethylbutanal

Seiichi Nakamura, Fumiaki Kikuchi and Shunichi Hashimoto*



$[\alpha]_D^{22} = -46.2$ (*c* 2.09, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (4*S*,5*R*)

$C_{17}H_{24}O_3$

Ethyl (2*E*,4*S*,5*R*)-6-benzyloxy-4,5-dimethyl-2-hexenoate

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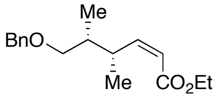

$C_{17}H_{24}O_3$

Ethyl (2*Z*,4*S*,5*R*)-6-benzyloxy-4,5-dimethyl-2-hexenoate

$[\alpha]_D^{24} = +22.6$ (*c* 1.99, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (4*S*,5*R*)

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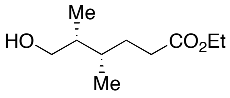

$C_{10}H_{20}O_3$

Ethyl (4*S*,5*R*)-6-hydroxy-4,5-dimethylhexanoate

$[\alpha]_D^{22} = -10.6$ (*c* 2.40, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (4*S*,5*R*)

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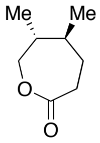

$C_8H_{14}O_2$

(5*S*,6*R*)-5,6-Dimethyloxepan-2-one

$[\alpha]_D^{21} = -43.1$ (*c* 2.02, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (5*S*,6*R*)

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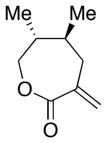

$C_9H_{14}O_2$

(5*S*,6*R*)-5,6-Dimethyl-3-methyleneoxepan-2-one

$[\alpha]_D^{21} = -6.69$ (*c* 2.01, $CHCl_3$)
Source of chirality: D-phenylglycine
Absolute configuration: (5*S*,6*R*)