

Alkoxycarbonylmethylation of (3*R*,10*bS*)-3-Phenyl-2,3,5,6-tetrahydro-10*bH*-oxazolo[2,3-*a*]isoquinoline

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As part of a series of studies on synthesis of chiral 1-alkyltetrahydroisoquinolines, asymmetric synthesis of 1-alkoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (IV) was investigated. Two synthetic approaches using intermolecular and intramolecular Reformatsky-type reactions from (3*R*,10*bS*)-3-phenyl-2,3,5,6-tetrahydro-10*bH*-oxazolo[2,3-*a*]isoquinoline (1) were attempted, but high stereoselectivity could not be obtained. For the purpose of determining the absolute structures of the compounds (2, 3) obtained by the Reformatsky-type reactions, transformation of 3a to a chiral 1,3,4,6,7,11*b*-hexahydro-2*H*-benzo[*a*]quinolizine (14) was investigated.

Keywords oxazolo[2,3-*a*]isoquinoline; diastereoselective alkylation; alkoxycarbonylmethylation; Reformatsky reaction; asymmetric synthesis; benzo[*a*]quinolizine

We previously succeeded in the synthesis of optically pure 1-alkyltetrahydroisoquinolines (I) from II via the diastereoselective alkylation of a chiral oxazolo[2,3-*a*]tetrahydroisoquinoline (III) with Grignard or alkyl-titanium reagents (Chart 1).^{1a-c} By using this method, we could achieve an asymmetric synthesis of I having a simple alkyl group, methyl, phenyl, benzyl, or phenethyl. This procedure of diastereoselective alkylation of III seemed to be applicable to the asymmetric synthesis of I having other substituents than an alkyl group on C₁. So, our attention was focused on chiral synthesis of 1-alkoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (IV), which would be a very useful chiron for asymmetric syntheses of naturally occurring isoquinoline alkaloids. In this paper, we describe the results of asymmetric synthesis

of IV by the Reformatsky-type reaction of chiral II and the determination of the absolute structure of IV.

The Reformatsky-type reaction of (3*R*,10*bS*)-3-phenyl-2,3,5,6-tetrahydro-10*bH*-oxazolo[2,3-*a*]isoquinoline (1)^{1b} with methyl bromoacetate using Zn–Ag–graphite²⁾ gave 2-(2-hydroxy-1-phenylethyl)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinolines (2a and 3a) in high yield, albeit without diastereoselectivity between (1*S*,1'*R*)-form (2a) and (1*R*,1'*R*)-form (3a) (Table I). On the other hand, reaction of 1 with methyl bromoacetate using Ti,³⁾ Ni,⁴⁾ Sn,⁵⁾ or Mg,⁶⁾ gave mainly 2a, b with a low diastereoselectivity, as indicated in Table I. Determination of the absolute structure of 2a, b is described later.

To achieve a high diastereoselectivity, we investigated the alkoxycarbonylmethylation of 1 with the reagent

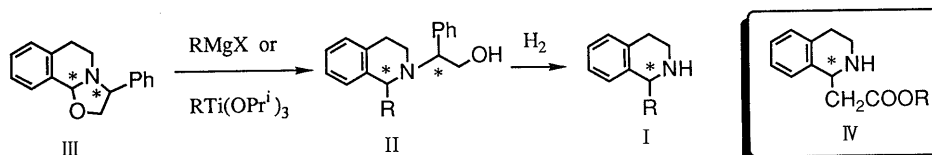
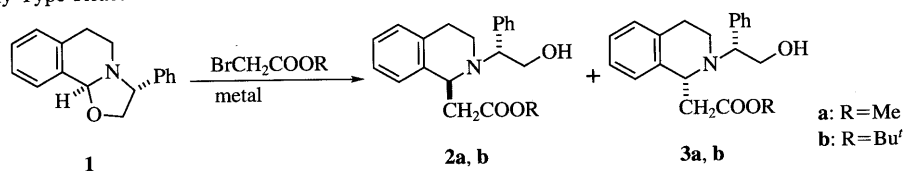


Chart 1

TABLE I. Reformatsky-Type Reaction of 1 with Bromoacetate and Metal



Reaction conditions					Product (2+3)	
Metal	R	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ratio (2:3)
Zn–Ag–graphite	Me	THF	–78	0.5	81	50:50
Zn–TiCl ₄	Me	THF	0	0.5	82	55:45
(Ph ₃ P) ₂ NiCl ₂ –Zn–Et ₄ Ni	Me	CH ₃ CN	r.t.	0.1	69	70:30
SnCl ₂ –LiAlH ₄	Me	THF	r.t.	12.0	79	60:40
Mg	Bu ^t	Et ₂ O	Reflux	0.5	77	54:46

r.t. = room temperature.

TABLE II. Reformatsky-Type Reaction of **1**

Reagent	Reaction conditions				Product (2+3)	
	R	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ratio (2:3)
$\text{Cl}_2\text{CeCH}_2\text{COOBu}^t$	Bu ^t	THF	-78	0.5	95	65:35
$\text{OTi}(\text{OPr}^i)_3$	Me	THF	-78	4.0	29	54:46
$\text{OTBDMS}^a)$	Me	CH_2Cl_2	-78	2.0	63	50:50

a) TMSOTf was used as a Lewis acid.

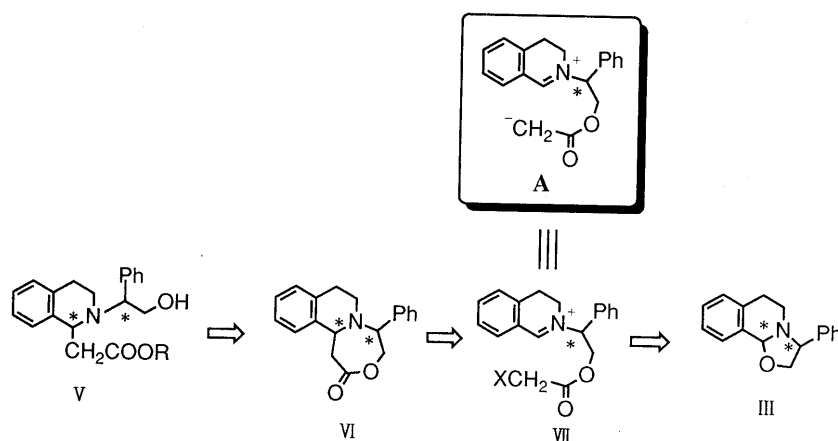


Chart 2

containing Ce, Ti, or Si (Table II). Reaction of **1** with organocerium reagent,⁷⁾ which was prepared by treatment of lithium *tert*-butyl acetate with cerium chloride, gave mainly **2a** with low diastereoselectivity and in high yield. Reaction of **1** with organotitanium reagent,⁸⁾ which was prepared by treatment of the lithium enolate of methyl acetate with chlorotitanium triisopropoxide, gave mainly **2a** with low diastereoselectivity and in low yield. Reaction of **1** with organosilicon reagent, 1-*tert*-butyldimethylsiloxy-1-methoxyethane,⁹⁾ in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave **2b** and **3b** in a moderate yield without diastereoselectivity.

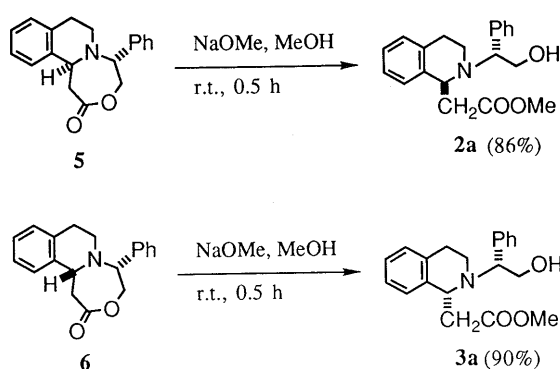
Attempts to develop a highly diastereoselective Reformatsky-type reaction of **1** with organometal reagents were unsuccessful. Then, we thought that an intramolecular Reformatsky-type reaction instead of the intermolecular one might give **2** or **3** with a high diastereoselectivity (Chart 2). A chiron such as **A** might give a chiral 5-phenyl-1,2,4,5,7,8-hexahydro-12bH-[1,4]oxazepino[4,5-*a*]isoquinolin-2-one (**VI**), which would give a chiral **V** upon methanolysis. We therefore investigated the intramolecular Reformatsky-type reaction (Table III). Heating of **1** with bromoacetyl bromide gave 2-(2-bromoacetoxy-1-phenylethyl)-3,4-dihydroisoquinolinium bromide (**4**). Treatment of the crude **4** with

bis(triphenylphosphino)nickel chloride and zinc in the presence of tetraethylammonium iodide gave a diastereomeric mixture of **5** and **6** (Table III). Determination of the absolute structures of **5** and **6** was performed by methanolysis of each compound to **2a** and **3a**, respectively (Chart 3). Consequently, it was proved that the intramolecular Reformatsky-type reaction did not proceed in a high yield and gave only a modest diastereoselectivity. However, it is of interest that this reaction mainly gave **6**, which corresponded to the minor product (**3a**) in the intermolecular Reformatsky-type reaction of **1** with methyl bromoacetate.

Next, in order to elucidate the absolute structure of **3a**, we planned to correlate **3a** with a known product, 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (**14**),¹⁰⁾ the absolute structure of which has already been established (Chart 4). Thus, hydrogenolysis⁹⁾ of optically pure **3a** using palladium hydroxide-carbon as a catalyst gave (*R*)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-**7**]. However, as can be seen from Table IV, it became apparent that increasing the amount of the catalyst and prolonging the reaction time caused a decrease in the enantiomeric purity of (*R*)-**7**. Determination of the enantiomeric excess of (*R*)-**7** was performed on the basis of the result of chiral HPLC of 2-(2-methoxycarbonyl-

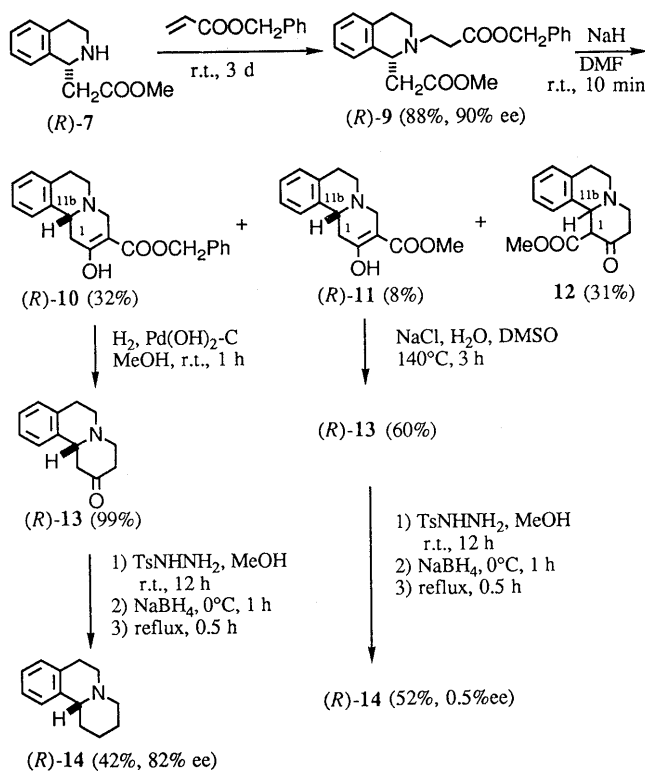
TABLE III. Intermolecular Cyclization of Chiral Isoquinolinium Salt (4)

Reaction conditions			Product (5+6)	
(Ph ₃ P) ₂ NiCl ₂ : Zn : Et ₄ NI (eq)	Temp.	Time (h)	Yield (%)	Ratio (5 : 6)
0 : 5.0 : 0	Reflux	3	40	31 : 69
0 : 5.0 : 0	r.t.	24	19	31 : 69
0.05 : 1.5 : 1.0	r.t.	3	47	40 : 60
0.50 : 1.5 : 1.0	r.t.	3	40	30 : 70



ethyl)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-8] which was obtained by Michael reaction of (*R*)-7 with methyl acrylate as mentioned below.

The Michael reaction of (*R*)-7 with excess benzyl acrylate¹¹ gave 2-(2-benzyloxycarbonylethyl)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-9] in 88% yield. On the basis of the chiral HPLC analysis, the enantiomeric purity of (*R*)-9 was 90% ee. The Dieckmann condensation of (*R*)-9 (90% ee) gave three products, 3-benzyloxycarbonyl-2-hydroxy-1,6,7,11b-tetrahydro-4*H*-benzo[*a*]quinolizine [(*R*)-10], 2-hydroxy-3-methoxycarbonyl-1,6,7,11b-tetrahydro-4*H*-benzo[*a*]quinolizine [(*R*)-11], and 1-methoxycarbonyl-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (**12**) in 32%, 8%, and 31% yields, respectively. Compound **12** showed no optical rotation. The structures of these products (**10**–**12**) were determined from the ¹H-NMR spectral data. The ¹H-NMR spectrum of **12** showed two doublet peaks (*J* = 10 Hz) at δ 4.66 and 3.95 ppm assigned to the 1 and 11b protons in **12**, respectively. The ¹H-NMR spectrum of **11** showed a singlet peak at δ 11.90 ppm assigned to the enol proton and multiplet peaks at δ 3.58–3.65 ppm assigned to the 11b proton in **11**. The structure of **10** was supported by the similarity of the ¹H-NMR signals of **10** to those of **11**. Demethoxycarbonylation of the compound [(*R*)-11], which is a candidate intermediate for synthesis of the final product [(*R*)-14], by Krapcho's method¹² did not proceed with retention of configuration. Namely, reaction of (*R*)-11 with sodium chloride in aqueous dimethylsulfoxide (DMSO)¹²



at 140 °C for 3 h gave 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one [(*R*)-13], which showed a very small [α]_D value. Moreover, the value of enantiomeric excess of (*R*)-14 derived from (*R*)-13 in our hand was only 0.5% based on a comparison with literature data¹⁰ (see Experimental), indicating that racemization had occurred during the demethoxycarbonylation of (*R*)-11. On the other hand, a careful debenzoylation of (*R*)-10 followed by spontaneous decarboxylation afforded (*R*)-13 [$[\alpha]_D = +108^\circ$]. Finally, (*R*)-13 was converted to (*R*)-14 by successive treatments with tosylhydrazine and sodium borohydride.¹³ Compound (*R*)-14 in our hands showed a positive optical rotational value ($[\alpha]_D = +181^\circ$) and its enantiomeric excess was calculated as 82%. Therefore, the absolute structures of **2a** and **3a** can be depicted as shown.

Consequently, we could not find an effective method

TABLE IV. Hydrogenation of **3a**

Reaction conditions		Yield of (R)-7 (%)	Optical purity of (R)-8 (% ee)
20% Pd(OH) ₂ -C/ 3a (mg/mmol)	Time (h)		
50	24	Quant.	23
30	24	Quant.	65
30	2	73	95
5	72	87	77

for the intermolecular or the intramolecular Reformatsky-type reaction of **1** with a high diastereoselectivity, despite the findings in the Grignard reaction of **1**.^{1a)} The Grignard reaction and the Reformatsky-type reaction of **1** are considered to proceed *via* immonium intermediates as in the reaction¹⁴⁾ of 1,3-oxazolidine with the Grignard reagents. The difference of diastereoselectivity among the Grignard reaction, the intermolecular Reformatsky-type reaction, and the intramolecular Reformatsky-type reaction might be related to the reactivity of the immonium intermediates and/or the existence of *sp*² carbon next to the reaction site of organometallic reagents.

To elucidate the reaction mechanisms in detail, we needed diastereomerically pure **1** and its diastereomer, which were, however, obtained as an inseparable, unstable oily mixture.^{1c)} Further work is in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. Mass spectra (MS) were recorded on a VG-70SE spectrometer. ¹H-NMR spectra were run on a Hitachi R-1500 (60 MHz) spectrometer. Optical rotations were measured on a JASCO DIP-4 spectrometer. Analytical HPLC was performed with a Shimadzu SPD-6A instrument on a chiral phase column, Chiralcel OD (Daicel) or a silica gel column, Chemcosorb 5Si-U (Chemco). Merck Silica gel 60 (230–400 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography. Extracts were dried over anhydrous MgSO₄.

Alkoxycarbonylmethylation of (3R,10bS)-3-Phenyl-2,3,5,6-tetrahydro-10bH-oxazolo[2,3-a]isoquinoline (1**) (Tables I and II). (A) With Methyl Bromoacetate and Zinc-Silver-Graphite Under an Ar atmosphere, a small piece of potassium (0.64 g, 16.4 mmol) was added to graphite powder at 170 °C with vigorous stirring to give a bronze K-graphite (C₈K),²⁾ which was allowed to cool. A mixture of ZnCl₂ (2.17 g, 15.9 mmol) and AgOAc (0.27 g, 16.1 mmol) was added to a suspension of the K-graphite in dry tetrahydrofuran (THF, 20 ml). The reaction started spontaneously and vigorously. After reflux ceased, the reaction mixture was heated at reflux for a further 30 min. This suspension of Zn-Ag-graphite in THF was used in the next reaction. A mixture of **1** (81% de, 1.00 g, 3.98 mmol) and methyl bromoacetate (1.14 ml, 12.0 mmol) in dry THF (10 ml) was added to the suspension obtained above at –78 °C and the mixture was stirred at the same temperature for 0.5 h. The reaction mixture was poured into saturated NH₄Cl solution and the whole was filtered. The filtrate was extracted with Et₂O. The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The diastereomeric ratio (50:50) of (1S,1'R)-2-(2-hydroxy-1-phenylethyl)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (**2a**) and (1R,1'R)-2-(2-hydroxy-1-phenylethyl)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (**3a**) was determined by HPLC analysis of the residue (column, Chemcosorb 5Si-U; column temperature, room temperature; eluent, AcOEt:hexane = 1:2; flow rate, 1.0 ml/min; wave-**

length, 254 nm; retention times, 7.0 min (**3a**) and 16.5 min (**2a**). The residue was dissolved in AcOEt and purified by column chromatography (SiO₂, AcOEt:hexane = 1:3) to give 1.06 g (81%) of a mixture of **2a** and **3a**. This mixture in AcOEt was subjected to column chromatography (SiO₂).

Elution with AcOEt and hexane (1:6) gave 0.49 g (36%) of **3a** as colorless needles, mp 113–114 °C (Et₂O and hexane). [α]_D²⁵ –33.9° (*c* = 1.02, CHCl₃). IR (Nujol) ν : 3500, 1715 cm^{–1}. ¹H-NMR (60 MHz, CDCl₃) δ : 2.15–3.28 (7H, m), 3.67 (3H, s), 3.40–4.17 (3H, m), 4.49–4.82 (1H, m), 6.86–7.44 (9H, m). FAB-MS (positive ion mode) *m/z*: 326 [(M+1)⁺]. Anal. Calcd for C₂₀H₂₃NO₃: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.53; H, 7.28; N, 4.33.

Elution with AcOEt and hexane (1:3) gave 0.51 g (38%) of **2a** as colorless plates, mp 79 °C (cyclohexane). [α]_D²⁵ –6.8° (*c* = 0.80, CHCl₃). IR (Nujol) ν : 3510, 1700 cm^{–1}. ¹H-NMR (60 MHz, CDCl₃) δ : 2.15 (1H, br), 2.25–3.54 (6H, m), 3.67 (3H, s), 3.76–3.97 (3H, m), 4.17–4.30 (1H, m), 6.58–7.15 (4H, m), 7.23 (5H, s). FAB-MS (positive ion mode) *m/z*: 326 [(M+1)⁺]. Anal. Calcd for C₂₀H₂₃NO₃: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.64; H, 7.28; N, 4.05.

(B) With Methyl Bromoacetate and Zn-TiCl₄ Under an Ar atmosphere, TiCl₄ (1 M hexane solution, 1.0 ml, 1.0 mmol) was added to the suspension of Zn powder (525 mg, 8.00 mmol) in dry THF (10 ml).³⁾ The mixture was stirred at room temperature for 15 min, then cooled to 0 °C. A mixture of **1** (81% de, 500 mg, 1.99 mmol) and methyl bromoacetate (0.76 ml, 8.00 mmol) in dry THF (5 ml) was added over 10 min and stirring was continued at the same temperature for a further 0.5 h. The reaction mixture was poured into saturated NH₄Cl solution. After filtration of the mixture, the filtrate was extracted with Et₂O. The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The diastereomeric ratio (55:45) of **2a** and **3a** was determined by HPLC analysis of the residue. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂, AcOEt:hexane = 1:3) to give 532 mg (82%) of a mixture of **2a** and **3a**.

(C) With Methyl Bromoacetate and Zn-(Ph₃P)₂NiCl₂-Et₄NI Under an argon atmosphere, dry CH₃CN (6 ml) was added to a mixture of Zn powder (525 mg, 8.00 mmol), (Ph₃P)₂NiCl₂ (260 mg, 0.40 mmol), and Et₄NI (2.05 g, 8.00 mmol), and the mixture was stirred at room temperature for 10 min.⁴⁾ A mixture of **1** (81% de, 500 mg, 1.99 mmol) and methyl bromoacetate (0.76 ml, 8.00 mmol) in dry CH₃CN (5 ml) was added, and the whole was stirred at the same temperature for 10 min. The reaction mixture was poured into saturated NH₄Cl solution. After filtration, the filtrate was extracted with Et₂O. The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The diastereomeric ratio (70:30) of **2a** and **3a** was determined by HPLC analysis of the residue. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂, AcOEt:hexane = 1:3) to give 460 mg (69%) of a mixture of **2a** and **3a**.

(D) With Methyl Bromoacetate and SnCl₂-LiAlH₄ Under an Ar atmosphere, LiAlH₄ (152 mg, 4.00 mmol) was added portionwise to a suspension of SnCl₂ (1.14 g, 8.00 mmol) in dry THF (10 ml).⁵⁾ The mixture was stirred for 15 min, then cooled to 0 °C. A mixture of **1** (81% de, 500 mg, 1.99 mmol) and methyl bromoacetate (0.76 ml, 8.00 mmol) in dry THF (5 ml) was added and the whole was stirred at room temperature for 12 h. The reaction mixture was poured into saturated KHCO₃ solution, and extracted with Et₂O. The Et₂O layer was washed with

water, dried, and evaporated *in vacuo*. The diastereomeric ratio (60:40) of **2a** and **3a** was determined by the HPLC analysis of the residue. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂, AcOEt:hexane=1:3) to give 508 mg (79%) of a mixture of **2a** and **3a**.

(E) With *tert*-Butyl Bromoacetate and Mg A suspension of Mg (0.19 g, 7.96 mmol, activated by iodine) in dry Et₂O (10 ml) was gently refluxed with stirring under an Ar atmosphere.⁶⁾ A mixture of **1** (81% de, 500 mg, 1.99 mmol) and *tert*-butyl bromoacetate (1.87 ml, 8.00 mmol) in dry Et₂O (15 ml) was added dropwise to the refluxing solution over 5 min and the whole was refluxed for a further 0.5 h. The mixture was poured into saturated NH₄Cl solution and extracted with Et₂O. The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The diastereomeric ratio (54:46) of reaction products, (1*S*,1'*R*)-1-*tert*-butoxycarbonylmethyl-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (**2b**) and (1*R*,1'*R*)-1-*tert*-butoxycarbonylmethyl-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (**3b**), was determined by HPLC analysis of the residue (column, Chemcosorb 5Si-U; column temperature, room temperature; eluent, AcOEt:hexane=1:3; flow rate, 1.0 ml/min; wavelength, 254 nm; retention times, 5.0 min (**3b**) and 14.2 min (**2b**)). The residue was dissolved in AcOEt and purified by column chromatography (hexane) to give 600 mg (77%) of a mixture of **2b** and **3b**. This mixture in AcOEt was subjected to a column chromatography (SiO₂).

Elution with AcOEt and hexane (1:6) gave 0.27 g (37%) of **3b** as colorless needles, mp 109–110 °C (Et₂O and hexane). [α]_D²⁶ –10.3° (*c*=0.60, EtOH). IR (Nujol) ν : 3490, 1702 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 1.46 (9H, s), 2.30–3.28 (7H, m), 3.40–4.08 (3H, m), 4.46–4.79 (1H, m), 6.86–7.13 (4H, m), 7.30 (5H, s). FAB-MS (positive ion mode) *m/z*: 368 [(M+)⁺]. Anal. Calcd for C₂₃H₂₉NO₃: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.02; H, 7.99; N, 3.56.

Elution with AcOEt and hexane (1:3) gave 0.28 g (38%) of **2b** as a colorless syrup. [α]_D²⁶ +6.7° (*c*=0.60, EtOH). IR (neat) ν : 3460, 1725 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 1.47 (9H, s), 2.52 (1H, br), 2.22–3.31 (6H, m), 3.77–3.98 (3H, m), 4.22–4.55 (1H, m), 6.78–7.16 (4H, m), 7.24 (5H, s). FAB-MS (positive ion mode) *m/z*: 368 [(M+)⁺].

(F) With Cerium Reagent A solution of lithio *tert*-butylacetate (2.90 g, 24.1 mmol) in dry THF (10 ml) was added at –78 °C to a suspension of dry CeCl₃ prepared from CeCl₃·7H₂O (9.00 g, 24.2 mmol) in dry THF (40 ml) under an Ar atmosphere and the mixture was stirred at the same temperature for 1.5 h.⁷⁾ A solution of **1** (81% de, 2.00 g, 7.97 mmol) in dry THF (10 ml) was added to the above-mentioned mixture and the whole was stirred at the same temperature for 0.5 h. The mixture was poured into saturated NH₄Cl solution. After filtration, the filtrate was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with water, dried, and evaporated *in vacuo*. The diastereomeric ratio (65:35) of reaction products, **2a** and **3a**, was determined by the HPLC analysis of the residue. The residue was dissolved in AcOEt and purified by column chromatography (hexane) to give 2.77 g (95%) of a mixture of **2a** and **3a**.

(G) With Titanium Reagent Under an Ar atmosphere, methyl acetate (1.27 ml, 16.0 mmol) was added dropwise at –78 °C to a THF (40 ml) solution of lithium diisopropylamide (LDA) which was prepared from diisopropylamine (2.45 ml, 16.0 mmol) and *n*-BuLi (1.48 M in hexane; 10.76 ml, 15.9 mmol).^{8a,b)} Stirring was continued at the same temperature for 0.5 h, then chlorotitanium triisopropoxide (3.80 ml, 15.9 mmol) was added and the mixture was stirred at –78 °C. A solution of **1** (81% de, 1.00 g, 3.98 mmol) in dry THF (10 ml) was added and the whole was stirred at the same temperature for 4 h, then poured into saturated NH₄Cl solution. After filtration, the filtrate was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with water, dried, and evaporated *in vacuo*. The diastereomeric ratio (54:46) of the reaction products, **2a** and **3a**, was determined by HPLC analysis of the residue. The residue was dissolved in AcOEt and purified by column chromatography (hexane) to give 0.36 g (29%) of a mixture of **2a** and **3a**.

(H) With Silyl Reagent Under an argon atmosphere, TMSOTf (1.00 M in CH₂Cl₂; 0.5 ml, 0.5 mmol) was added at –78 °C to a solution of **1** (81% de, 0.50 g, 1.99 mmol) in CH₂Cl₂ (5 ml).⁹⁾ The mixture was stirred at –78 °C for 10 min, then a solution of 1-*tert*-butyldimethylsiloxy-1-methoxyethane (1.13 g, 6.00 mmol) in dry CH₂Cl₂ (5 ml) was added. The reaction mixture was stirred at the same temperature for 2 h, then poured into saturated KHCO₃ solution. After filtration, the filtrate was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with water, dried, and evaporated *in vacuo*. The residue was dissolved in a mixed solution of CH₃CN (95 ml) and 40% HF solution in water and the whole was stirred

at room temperature overnight, then neutralized with saturated KHCO₃ solution and extracted with Et₂O. The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The diastereomeric ratio (50:50) of reaction products, **2b** and **3b**, was determined by HPLC analysis of the residue. The residue was dissolved in AcOEt and purified by column chromatography (hexane) to give 407 mg (63%) of a mixture of **2b** and **3b**.

(R)-2-(2-Bromoacetoxy-1-phenyl)ethyl-3,4-dihydroisoquinolinium Bromide (4) Bromoacetyl bromide (0.77 ml, 8.83 mmol) was added to a solution of **1** (81% de, 1.10 g, 4.38 mmol) in dry CH₂Cl₂ (10 ml) and the mixture was refluxed for 2 h, then cooled. Dry Et₂O (50 ml) was added to the mixture to produce a gummy precipitate. After decantation of the Et₂O layer, the residue was dissolved in dry CH₂Cl₂ (5 ml). Under vigorous stirring, dry Et₂O (50 ml) was added to the CH₂Cl₂ solution to produce crystalline precipitates. The supernatant was removed by decantation and dry Et₂O was added to the residue with stirring. After repeating this procedure, crude **4** was obtained and used for the next reaction.

Methoxycarbonylmethylation of 4 (Table III). (A) With Zn at Reflux A dry CH₃CN solution (40 ml) of **4** was added to a mixture of Zn powder (1.43 g, 22.0 mmol) in dry CH₃CN (40 ml) and the mixture was refluxed for 3 h, then poured into saturated NH₄Cl solution. After filtration of the mixture, CH₃CN in the filtrate was evaporated *in vacuo* and the residue was extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with water and dried. The solvent was removed *in vacuo*. The diastereomeric ratio (31:69) of reaction products, (5*R*,12*bS*)-5-phenyl-1,2,4,5,7,8-hexahydro-12*bH*-[1,4]oxazepino[4,5-*a*]isoquinolin-2-one (**5**) and (5*R*,12*bR*)-5-phenyl-1,2,4,5,7,8-hexahydro-12*bH*-[1,4]oxazepino[4,5-*a*]isoquinolin-2-one (**6**), was determined by HPLC analysis of the residue (column, Chemcosorb 5Si-U; column temperature, room temperature; eluent, AcOEt:hexane=1:1; flow rate, 1.0 ml/min; wavelength, 254 nm; retention times, 6.1 min (**6**) and 18.1 min (**5**)). The residue was dissolved in AcOEt and purified by column chromatography.

Elution with AcOEt and hexane (1:7) gave 0.35 g (27%) of **6** as a colorless syrup. [α]_D²⁶ +45.5° (*c*=0.18, CHCl₃). IR (neat) ν : 1750 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.13–3.49 (6H, m), 3.66–3.92 (1H, m), 4.02–4.52 (3H, m), 6.90–7.81 (9H, m). FAB-MS (positive ion mode) *m/z*: 294 [(M+)⁺].

Elution with AcOEt and hexane (1:2) gave 0.17 g (13%) of **5** as a colorless needles, mp 149–150 °C (CHCl₃ and hexane). [α]_D²⁶ –51.0° (*c*=0.11, CHCl₃). IR (Nujol) ν : 1735 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.51–3.77 (6H, m), 3.96–4.27 (1H, m), 4.34–4.97 (3H, m), 6.94–7.82 (9H, m). FAB-MS (positive ion mode) *m/z*: 294 [(M+)⁺]. Anal. Calcd for C₁₉H₁₉NO₂: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.35; H, 6.47; N, 4.64.

(B) With Zn at Room Temperature A dry CH₃CN solution (40 ml) of **4** was added to a suspension of Zn powder (1.43 g, 22.0 mmol) in dry CH₃CN (5 ml) and the mixture was stirred at room temperature for 24 h, then worked-up by the same procedure as mentioned above. The diastereomeric ratio (31:69) of reaction products, **5** and **6**, was determined by HPLC analysis of the residue. Separation of the mixture by column chromatography gave 0.08 g (6%) of **5** and 0.17 g (13%) of **6**, respectively.

(C) With (Ph₃P)₂NiCl₂ (5% mol), Zn, and Et₄NI A dry CH₃CN solution (40 ml) of **4** was added to a mixture of Zn powder (0.43 g, 6.61 mmol), (Ph₃P)₂NiCl₂ (143 mg, 0.22 mmol), and Et₄NI (1.13 g, 4.39 mmol) in dry CH₃CN (5 ml). The reaction mixture was stirred at room temperature for 3 h,⁶⁾ then worked-up by the same procedure as mentioned above. The diastereomeric ratio (40:60) of reaction products, **5** and **6**, was determined by HPLC analysis of the residue. Separation of the mixture by column chromatography gave 0.24 g (18%) of **5** and 0.37 g (29%) of **6**, respectively.

(D) With (Ph₃P)₂NiCl₂ (50% mol), Zn, and Et₄NI A dry CH₃CN solution (40 ml) of **4** was added to a mixture of Zn powder (0.43 g, 6.61 mmol), (Ph₃P)₂NiCl₂ (1.43 g, 0.22 mmol), and Et₄NI (1.13 g, 4.39 mmol) in dry CH₃CN (5 ml). The reaction mixture was stirred at room temperature for 3 h,⁴⁾ then worked-up by the same procedure as mentioned above. The diastereomeric ratio (30:70) of reaction products, **5** and **6**, was determined by HPLC analysis of the residue. Separation of the mixture by column chromatography gave 0.24 g (13%) of **5** and 0.37 g (27%) of **6**, respectively.

Methanolysis of 5 and 6 Under an Ar atmosphere, NaOMe (0.5 M in MeOH; 1.70 ml, 0.85 mmol) was added to a solution of **5** (50 mg, 0.17 mmol) in absolute MeOH (3 ml). The mixture was stirred at room temperature for 0.5 h, poured into ice water and extracted with Et₂O.

The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography. Elution with AcOEt and hexane (1:3) gave 48 mg (86%) of **2a**. The same reaction of **6** (50 mg, 0.17 mmol) gave 50 mg (90%) of **3a**.

(R)-1-Methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline [(R)-7] A mixture of 20% Pd(OH)₂-C (in the amount shown in Table IV; Aldrich Co. Ltd.; moist) and **2a** in MeOH was stirred at room temperature under a hydrogen atmosphere. The catalyst was filtered off on a Celite bed, and the filtrate was evaporated *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂). Elution with AcOEt and hexane (1:9) gave (R)-**7** as a yellow oil. Yields are shown in Table IV. Instrumental data for (R)-**7**, which gave (R)-**8** having 95% ee in the next reaction, were as follows: $[\alpha]_D^{26} + 95.2^\circ$ ($c=1.00$, CHCl₃, 95% ee). IR (neat) ν : 3340, 1725 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.28 (1H, br), 2.62–3.41 (6H, m), 3.71 (3H, s), 4.30–4.64 (1H, m), 7.01–7.36 (4H, m). FAB-MS (positive ion mode) m/z : 206 [(M+1)⁺].

(R)-2-(2-Methoxycarbonylethyl)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline [(R)-8] A mixture of (R)-**7** and methyl acrylate [10-fold excess based on (R)-**7**] was stirred at reflux for 6 h. Excess methyl acrylate was removed *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂). Elution with AcOEt and hexane (1:4) gave (R)-**8** as a colorless oil. The enantiomeric ratio of reaction products, (R)-**8** and (S)-**8**, was determined by HPLC analysis (column, Chiralcel OD; column temperature, room temperature; eluent, 2-propanol:hexane=1:9; flow rate, 1.0 ml/min; wavelength, 254 nm; retention times, 6.2 min [(R)-**8**] and 8.5 min [(S)-**8**]). The chemical and optical yields are listed in Table IV. Instrumental data for (R)-**8** having 95% ee were as follows: $[\alpha]_D^{26} - 17.2^\circ$ ($c=2.02$, MeOH, 95% ee). IR (neat) ν : 1740 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.28–3.40 (10H, m), 3.65, 3.69 (each 3H, each s), 4.02–4.38 (1H, m), 7.09 (4H, s). FAB-MS (positive ion mode) m/z : 292 [(M+1)⁺].

(R)-2-(2-Benzoyloxycarbonylethyl)-1-methoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline [(R)-9] A mixture of (R)-**7** (1.60 g, 7.80 mmol) and benzyl acrylate (5.43 g, 31.2 mmol)¹¹ in dry CH₃CN (20 ml) was stirred at room temperature for 3 d. Excess CH₃CN was removed *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂). Elution with AcOEt and hexane (1:7) gave 2.53 g (88%) of (R)-**9** as colorless prisms, mp 37 °C (ether and hexane). The enantiomeric ratio (90% ee) of the reaction products, (R)-**9** and (S)-**9**, was determined by HPLC analysis (column, Chiralcel OD; column temperature, room temperature; eluent, 2-propanol:hexane=1:9; flow rate, 1.0 ml/min; wavelength, 254 nm; retention times, 7.6 min [(R)-**9**] and 11.7 min [(S)-**9**]). $[\alpha]_D^{18} - 14.7^\circ$ ($c=1.10$, MeOH). IR (Nujol) ν : 1740, 1720 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.26–3.18 (8H, m), 3.67 (3H, s), 4.02–4.39 (1H, m), 5.11 (2H, s), 7.10 (4H, s), 7.33 (4H, s). FAB-MS (positive ion mode) m/z : 368 [(M+1)⁺]. Anal. Calcd for C₂₂H₂₅NO₄: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.71; H, 6.79; N, 3.73.

The Dieckmann Condensation of [(R)-9] Under an Ar atmosphere, NaH (62.7% in material oil; 610 mg, 15.9 mmol) was added portionwise at room temperature to a solution of (R)-**9** (90% ee, 4.86 g, 13.2 mmol) in dry *N,N*-dimethylformamide (DMF, 50 ml). The reaction mixture was stirred at the same temperature for 10 min, then poured into saturated NH₄Cl solution and extracted with Et₂O. The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂).

Elution with AcOEt and hexane (1:10) gave 1.41 g (32%) of (R)-3-benzoyloxycarbonyl-2-hydroxy-1,6,7,11b-tetrahydro-4H-benzo[*a*]quinolizine [(R)-**10**] as light yellow needles (ether and hexane), mp 70–71 °C. $[\alpha]_D^{16} + 257^\circ$ ($c=0.43$, MeOH). IR (Nujol) ν : 1661, 1617 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.25–3.85 (9H, m), 5.24 (2H, s), 7.15 (4H, s), 7.37 (5H, m), 11.91 (1H, s, OH). EI-MS m/z : 335 (M⁺). Anal. Calcd for C₂₁H₂₁NO₃: C, 75.20; H, 6.31; N, 4.18. Found: C, 74.72; H, 6.34; N, 3.97.

Elution with AcOEt and hexane (1:7) gave 0.27 g (8%) of (R)-2-hydroxy-3-methoxycarbonyl-1,6,7,11b-tetrahydro-4H-benzo[*a*]quinolizine [(R)-**11**] as colorless needles, mp 118–119 °C (ether and hexane). $[\alpha]_D^{16} + 338^\circ$ ($c=0.81$, MeOH). IR (Nujol) ν : 1665, 1625 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.23–3.76 (9H, m), 3.78 (3H, s), 7.15 (4H, s), 11.90 (1H, s). Anal. Calcd for C₁₅H₁₇NO₃: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.68; H, 6.55; N, 5.14.

Elution with AcOEt and hexane (1:1) gave 1.02 g (31%) of 1-methoxycarbonyl-1,3,4,6,7,11b-hexahydro-2H-benzo[*a*]quinolizine-

2-one (**12**) as colorless prisms, mp 98 °C (ether and hexane). IR (Nujol) ν : 1775, 1730 cm⁻¹. ¹H-NMR (60 MHz, pyridine-*d*₅) δ : 2.13–3.56 (8H, m), 3.74 (3H, s), 3.95, 4.66 (each 1H, each d, $J=10$ Hz), 7.02–7.46 (4H, m). FAB-MS (positive ion mode) m/z : 260 [(M+1)⁺]. Anal. Calcd for C₁₅H₁₇NO₃: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.47; H, 6.44; N, 5.15.

Synthesis of (R)-1,3,4,6,7,11b-Hexahydro-2H-benzo[*a*]quinolizine [(R)-14] from (R)-10 A mixture of 20% Pd(OH)₂-C (150 mg; Aldrich Co. Ltd.; moist) and (R)-**10** (1.41 g, 3.84 mmol) in MeOH (30 ml) was stirred at room temperature for 1 h under a hydrogen atmosphere. The catalyst was filtered off on a Celite bed and the filtrate was evaporated *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂). Elution with AcOEt and hexane (1:3) gave 0.83 g (99%) of (R)-1,3,4,6,7,11b-hexahydro-2H-benzo[*a*]quinolizine-2-one [(R)-**13**] as colorless needles, mp 76 °C (cyclohexane). $[\alpha]_D^{16} + 108^\circ$ ($c=1.00$, MeOH). IR (Nujol) ν : 1710 cm⁻¹. ¹H-NMR (60 MHz, CDCl₃) δ : 2.20–3.40 (10H, m), 3.42–3.80 (1H, m), 7.15 (4H, s). FAB-MS (positive ion mode) m/z : 202 [(M+1)⁺]. Anal. Calcd for C₁₃H₁₅NO: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.66; H, 7.53; N, 7.01.

A mixture of (R)-**13** (400 mg, 1.99 mmol) and *p*-toluenesulfonylhydrazide (740 mg, 3.98 mmol) in MeOH (25 ml) was stirred at room temperature for 12 h. NaBH₄ (750 mg, 19.8 mmol) was added portionwise at 0 °C for 1 h, then the mixture was refluxed for 30 min and allowed to cool.¹³ The MeOH was removed *in vacuo* to reduce the volume to half the initial volume. Saturated KHCO₃ (70 ml) was added to the mixture and the whole was extracted with Et₂O. The Et₂O layer was washed with water and dried. The solvent was removed *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography (Al₂O₃). Elution with AcOEt and hexane (1:15) gave 155 mg (42%) of (R)-**14** as a colorless oil. $[\alpha]_D^{16} + 181^\circ$ ($c=0.754$, pyridine) {lit.¹⁰ $[\alpha]_D^{16} + 222^\circ$ ($c=0.022$, pyridine)}. ¹H-NMR (60 MHz, CDCl₃) δ : 1.27–2.14 (6H, m), 2.17–3.46 (7H, m), 6.98–7.28 (4H, m). FAB-MS (positive ion mode) m/z : 188 [(M+1)⁺].

Synthesis of (R)-1,3,4,6,7,11b-Hexahydro-2H-benzo[*a*]quinolizine [(R)-14] from (R)-11 A mixture of (R)-**11** (2.60 g, 10.0 mmol), NaCl (1.17 g, 20.0 mmol), and DMSO (10 ml) in the presence of two drops of water was heated at 140 °C for 3 h with stirring.¹² The mixture was poured into ice water and extracted with Et₂O. The Et₂O layer was washed with water, dried, and evaporated *in vacuo*. The residue was dissolved in AcOEt and purified by column chromatography (SiO₂). Elution with AcOEt and hexane (1:1) gave 1.21 g (60%) of (R)-**13** as colorless plates, mp 77 °C (cyclohexane).

Reduction¹³ of this (R)-**13** to (R)-**14** was performed by the procedure described above. (R)-**14**; yield (52%), $[\alpha]_D^{24} + 1.1^\circ$ ($c=0.81$, pyridine) {lit.¹⁰ $[\alpha]_D^{16} + 222^\circ$ ($c=0.022$, pyridine)}.

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