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Asymmetric Desymmetrization of *Meso*-Pyrrolidine Derivatives by Enantiotopic Selective C-H Hydroxylation Using (Salen)manganese(III) Complexes

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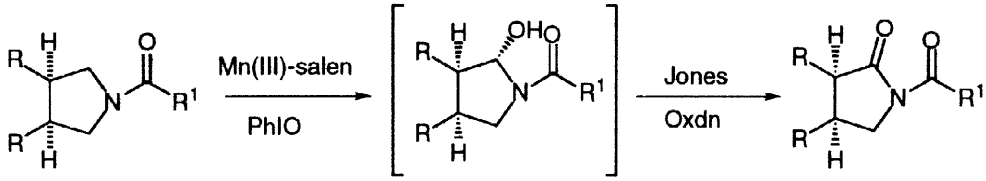
Abstract: Chiral (salen)manganese(III) complexes **1** catalyzed the asymmetric desymmetrization of *N*-protected *meso*-pyrrolidine derivatives **3**, **6-8**, **15** and **18** by enantiotopic selective C-H oxidation in the presence of terminal oxidant iodosylbenzene. The oxidation occurred chemoselectively at the carbon α to the nitrogen atom to afford optically active hydroxypyrrolidine derivatives **9**, **11**, **13**, **16**, **19** and **21** that were further oxidized to chiral lactams with Jones reagent. The *N*-protecting groups of the *meso*-pyrrolidine derivatives have notable effect on the enantioselectivity.

Introduction

Asymmetric catalytic C-H oxidation constitutes an appealing strategy in organic synthesis for introducing chirality in saturated hydrocarbons. Recently, much attention has been devoted to this topic and moderate to good enantioselectivities realized successfully in the catalytic oxidation of benzylic[1] and allylic[2] C-H bonds. We and others have reported that (salen)manganese(III) complexes (hereafter abbreviated as Mn-salen complex) are the excellent catalysts for enantioselective epoxidation of unfunctionalized alkenes[3] and C-H oxidation of prochiral benzylic substrates.[1b-c] Quite recently, we also disclosed that the well-designed Mn-salen complex **1a** efficiently catalyzed the asymmetric desymmetrization of *meso*-cyclic ethers by enantiotopic selective C-H oxidation.[4] The oxidative desymmerization of *meso*-cyclic ethers provides an effective approach for the synthesis of multi chiral centered optically active lactols that are versatile intermediates for the synthesis of naturally occurring compounds. This strategy should be applicable to other classes of *meso*-compounds and provide a useful tool for the synthesis of other chiral heterocyclic compounds. To explore this possibility, we examined the C-H oxidation of *meso*-pyrrolidine derivatives[5] and communicated the preliminary results that the oxidation of *meso*-*N*-acylpyrrolidines with Mn-salen complexes **1** and the subsequent Jones oxidation provided optically active lactams of 75-84% ee (Eq. 1).[6] The optically active lactams and intermediary hydroxypyrrolidine derivatives are useful chiral building blocks for the synthesis of nitrogen containing natural



(Eq. 1)

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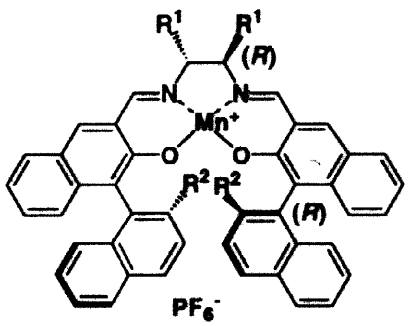
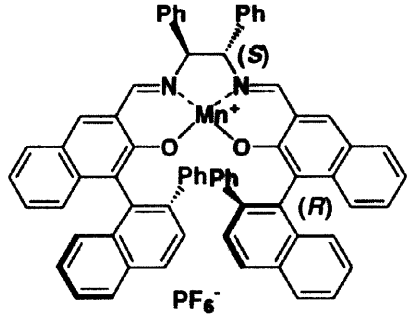
products.[7] Herein, we describe the detailed study on the oxidative desymmetrization of *N*-protected *meso*-pyrrolidine derivatives using **1** as the catalyst in the presence of terminal oxidant iodosylbenzene.

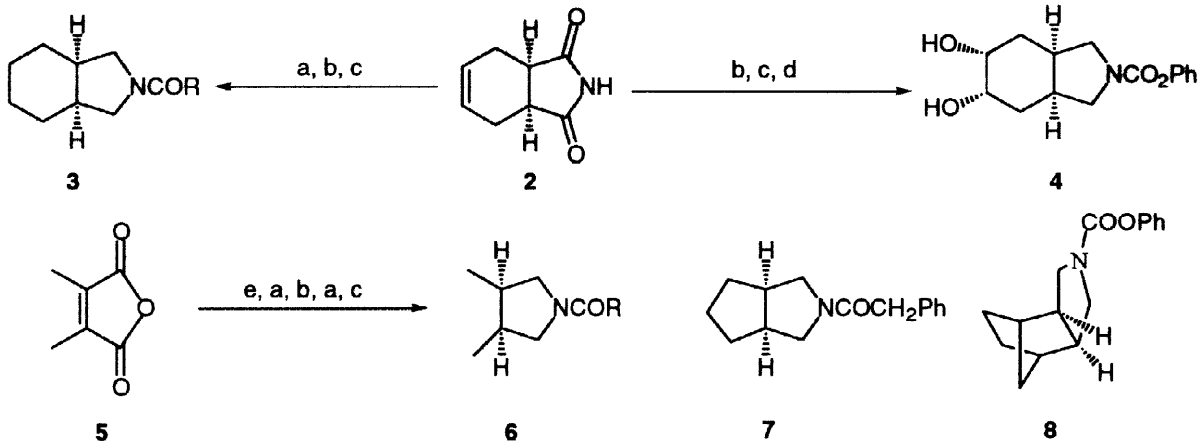


1



1e

a: R^1= -$(CH_2)_4$-, R^2= Ph
b: R^1= R^2=Ph
c: R^1= 3,5-$(Me)_2C_6H_3$-, R^2= Ph
d: R^1= Ph, R^2= 4-(TBDPS)C_6H_4-



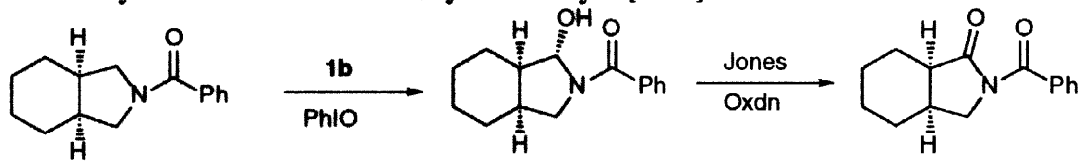
Scheme 1 (a) 10% Pd/C, MeOH, room temperature, 24 h; (b) $LiAlH_4$ (2.5 equiv.), THF, reflux, 30 h; (c) RCOCl, Et_3N, CH_2Cl_2, room temperature, 8h; (d) K_2OsO_4 $2H_2O$ (0.01 equiv.), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), DABCO (0.75 equiv.), *t*-BuOH-H_2O(1:1), room temperature, 24 h; (e) $BnNH_2$ (1 equiv.), THF, reflux, 10 h.

Results and Discussion

The *meso*-pyrrolidine derivatives **3**, **4**, **6**, **7** and **8** were prepared from the commercially available dicarboxylic acid derivatives (Scheme 1).[8,9] First, we examined the oxidation of *N*-benzoyl-8-azabicyclo[4.3.0]nonane **3a** as the standard substrate using Mn-salen complex **1** in various solvents in the presence of terminal oxidant, iodosylbenzene or pentafluoroiodosylbenzene.[6] The oxidation occurred preferentially at the carbon α to the nitrogen atom, affording optically active hydroxypyrrolidine derivative **9a** which behaved similarly to unreacted **3a** in SiO_2-chromatography. Thus the resulting mixture of compounds **9a** and **3a** was directly oxidized to chiral lactam **10a** by Jones reagent without purification. Enantiomeric excess of **10a** was determined by HPLC analysis (Table 1). Through these examinations, acetonitrile was found to be the

solvent of choice in both terms of enantioselectivity and chemical yield (Entry 7). The oxidation proceeded smoothly in chlorobenzene but enantioselectivity was suffered. The reaction with pentafluoroiodosylbenzene showed the same enantioselectivity as that with iodosylbenzene but the yield of **10a** was slightly better in the former reaction (Entry 7). We next examined the reaction using a series of Mn-salen complexes **1a-e** and found that complex **1b** was the most suitable catalyst for the oxidation of pyrrolidine derivative **3a**. Moderate enantioselectivity of 64% ee was obtained in the reaction at -25 °C (Entry 9). It is also noteworthy that, in accord with the desymmetrization of *meso*-furans, the (*R*,*R*)-complex **1b** was proven to be better catalyst for the present oxidation than the diastereomeric (*R*,*S*)-complex **1e** which was an excellent catalyst for benzylic hydroxylation[1b,c] and epoxidation (Entry 13).[3]

Table 1. Desymmetrization of *N*-Benzoyl-8-azabicyclo[4.3.0]nonane



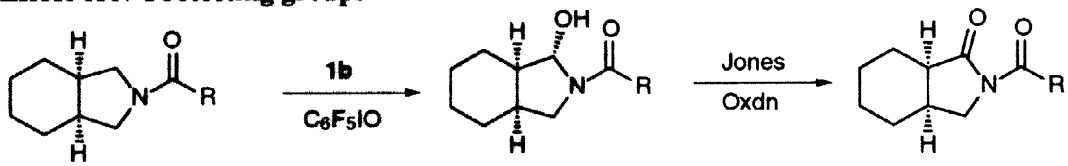
3a **9a** **10a**

Entry	Catalyst **1**	Solvent	Temp. (°C)	Time (h)	Yield(%)[a,b]	ee[d]
1	**a**	Chlorobenzene	rt	2	58	19
2	"	"	0	4	34	27
3	"	"	-20	12	41	33
4	"	Ethyl acetate	-20	12	27	4
5	"	Dichloromethane	-20	12	27	10
6	"	Acetone	-20	12	42[c]	42
7	"	Acetonitrile	-20	14	43, 47[c]	46
8	**b**	"	-20	12	43[c]	61
9	"	"	-25	14	55[c]	64
10	**c**	"	-25	14	56[c]	61
11	**d**	"	-25	14	41	29
12	**e**	"	0	4	37	5
13	"	"	-20	12	29	12

a) Carried out using 1 equivalent of iodosylbenzene as the terminal oxidant.
b) Isolated yield of **10a**.
c) Pentafluoroiodosylbenzene was used as the terminal oxidant.
d) Determined by HPLC analysis using DAICEL CHIRALCEL OD-H column (hexane/isopropanol 9:1).

To ascertain the effect of amino-protecting groups on the enantioselectivity, we examined the oxidation of series of *N*-acylated *meso*-8-azabicyclo[4.3.0]nonanes **3** with complex **1b** and pentafluoroiodosylbenzene in acetonitrile (Table 2). Both 4-nitro- and 4-methoxybenzoylated **3** showed the diminished selectivity suggesting that electronic effect did not exert a major role in enantioselection (Entries 2 and 4). Then, we studied the oxidation of **3** protected with propionyl, 4-methylbenzoyl, naphthoyl and phenylacetyl groups and found that good enantioselectivity of 76% ee was realized (at -27 °C) when *N*-phenylacetyl group was used as the protecting group (Entry 7). Consistently, the oxidation took place regio- and chemoselectively at the carbon α to the nitrogen atom in the pyrrolidine ring.

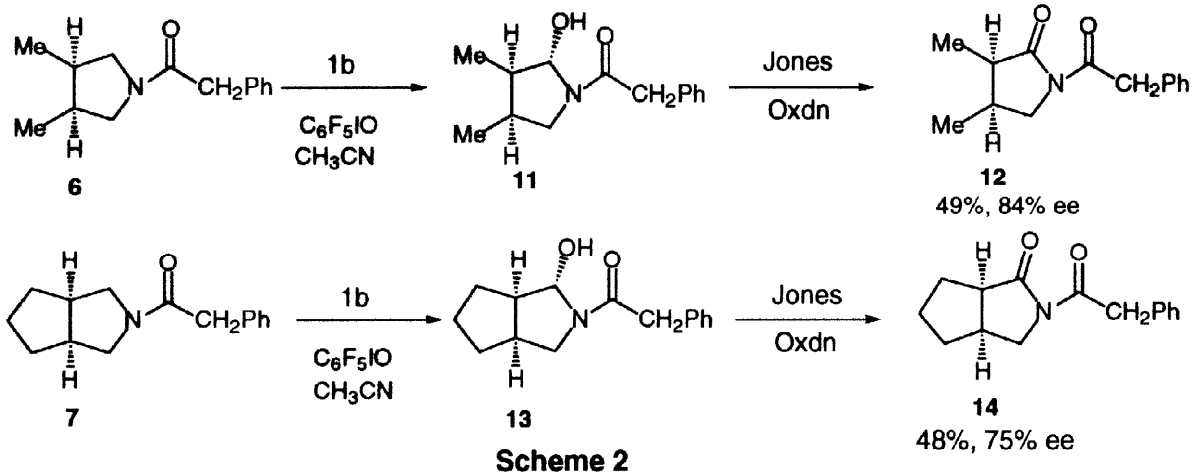
Table 2. Effect of *N*-Protecting groups



3 9 10

Entry	R	Temp.(°C)	Time (h)	Yield(%)[a,b]	ee[c]
1	Ethyl (**3b**)	-25	14	65	36[d]
2	4-Nitrophenyl (**3c**)	"	14	42	43[d]
3	4-Methylphenyl (**3d**)	"	12	41	39[d]
4	4-Methoxyphenyl (**3e**)	"	12	37	28[d]
5	Naphthyl (**3f**)	"	14	43	58[e]
6	Phenylmethyl (**3g**)	0	4	40	44[e,f]
7	"	-27	14	65	76[e,f]

a) Carried out in acetonitrile using 1 equivalent of pentafluoroiodosylbenzene as the terminal oxidant.
b) Isolated yield of **10**.
c) The % ee of **10**.
d) Determined by HPLC analysis using DAICEL CHIRALPAK AD column (hexane/isopropanol = 9:1).
e) Determined by HPLC analysis using DAICEL CHIRALCEL OD-H column (hexane/isopropanol = 9:1).
f) Accompanied with *ca.* 10 % of unidentified by-products

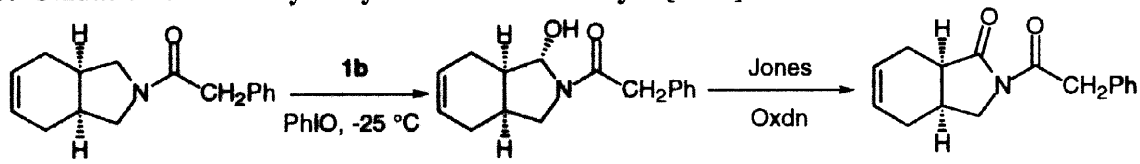


Scheme 2

Asymmetric desymmetrization of *meso*-pyrrolidines **6** and **7** also proceeded with good enantioselectivity under these optimized conditions (Scheme 2). We next examined the oxidation of *N*-phenylacetyl-*meso*-8-azabicyclo[4.3.0]non-3-ene **15** under the above reaction conditions. Interestingly, the oxidation took place chemoselectively at the carbon α to the nitrogen atom without affecting the double bond but enantioselectivity was unexpectedly low (Table 3, Entry 1). Thus, we re-examined the reaction conditions for this reaction, and found that chlorobenzene and toluene were more suitable solvents in this case and moderate enantioselectivity of 55% ee was observed in the reactions, though the chemical yield of **17** was insufficient (Table 3, Entries 5 and 6).

We further examined about the *N*-protecting group and found that carbamoyl group is a suitable one. For example, oxidation of *meso*-azabicyclo[4.3.0.]non-3-ene **18a** chemoselectively proceeded without affecting

Table 3. Oxidation of *N*-Phenylacetylated *Meso*-8-azabicyclo[4.3.0]non-3-ene



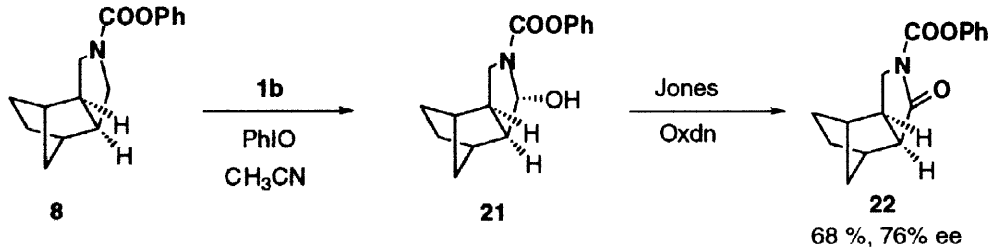
15 16 17

Entry	Solvent	Time (h)	Yield (%)[a,b]	ee (%)[c,d]
1	Acetonitrile	15	25	34
2	Acetone	17	19	51
3	2-Butanone	21	16	34
4	Fluorobenzene	21	23	46
5	Chlorobenzene	20	17	55
6	Toluene	21	19	55
7	Dichloromethane	23	13	19

a) Carried out using 1 equivalent of iodosylbenzene as the terminal oxidant.
b) Isolated yield of **17**.
c) The % ee of **17**.
d) Determined by HPLC analysis using DAICEL CHIRALCEL OD-H column (hexane/isopropanol = 9:1).

the double bond to give the desired α-hydroxy pyrrolidine **19a** with the improved enantioselectivity of 64% ee, though the chemical yield was still modest (Table 4, Entry 1). Unreacted **18a** was recovered intact (67%). Substrate **18b** protected by phenylcarbamoyl group also underwent C-H oxidation smoothly with high enantioselectivity to afford a mixture of the corresponding optically active hydroxypyrrolidine **19b** and lactam **20b** that were treated without separation by Jones reagent to give chiral lactam **20b** of 88% ee (Entry 2). Oxidation of substrate **18c** protected by benzylcarbamoyl group was also examined but enantioselectivity was diminished to some extent (Entry 4). Substrates **18e-g** bearing oxygen functionalties were also chemoselectively oxidized at the carbon α to the nitrogen atom with moderate to high enantioselectivities (Table 4, Entries 8-10). It is worth to mention that desymmetrization of **18f** and **18g** induces 4 asymmetric carbons at once. However, the best solvent varies with the substrate: acetonitrile was a better solvent for the reactions of these substrates **18b-d** than chlorobenzene (Entries 2,4 and 6), while chlorobenzene was a better solvent for the oxygenated substrates **18e-g** (Entries 8-10). Single recrystallization of **20e** from ethylacetate-hexane (1:1) provided optically pure **20e** with 11% yield (>99% ee).

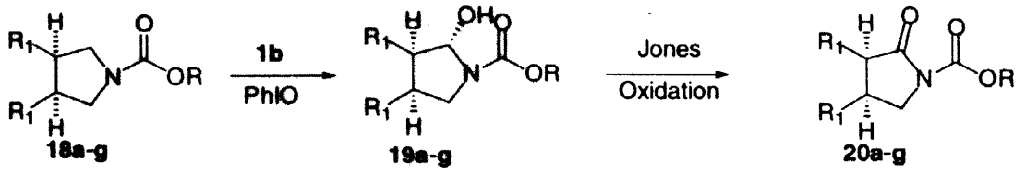
The oxidation of *N*-protected *meso*-norbornane derivative **8** using complex **1b** also provided the optically active hydroxypyrrolidine derivative **21** that was further oxidized to chiral lactam **22** with good enantioselectivity (Scheme 3).

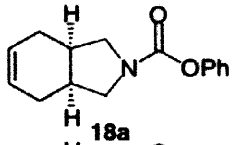
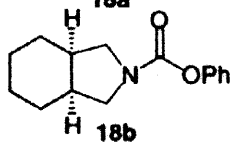
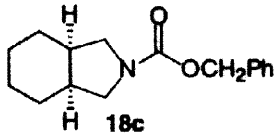
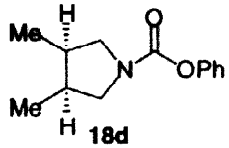
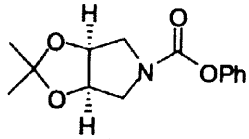
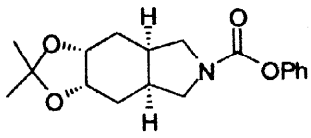
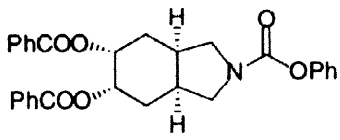


8 21 22
68 %, 76% ee

Scheme 3

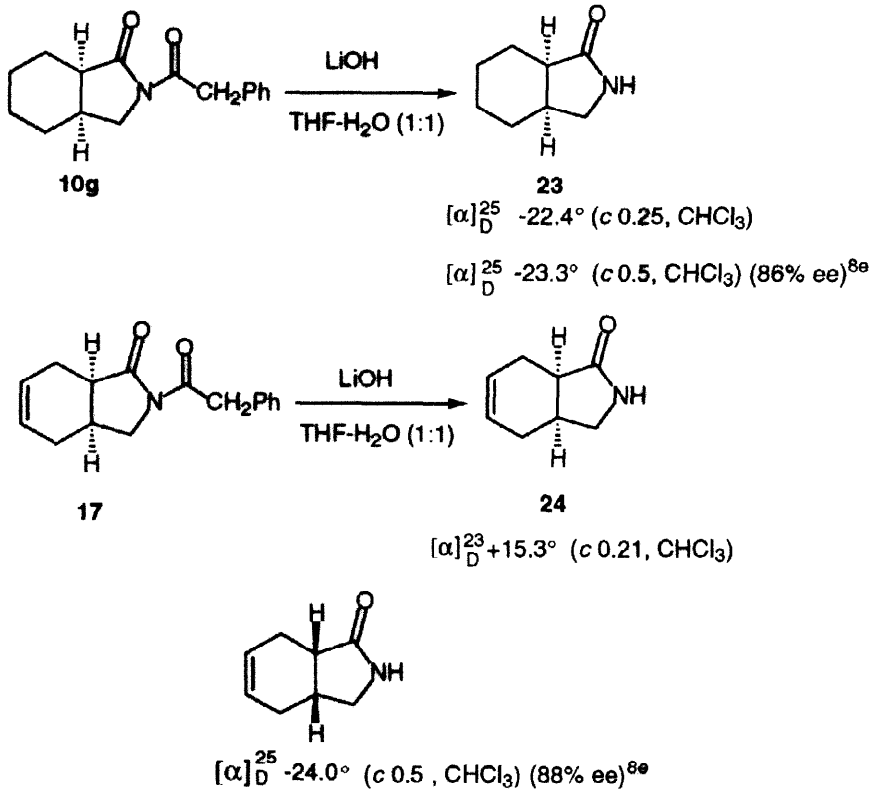
Table 4. Oxidation of *N*-Carbamoylated *Meso*-Pyrrolidine Derivatives.



Entry	Susbrate	Solvent	Time (h)	Yield (%)[a,b]	ee (%)[c]
1	 18a	C_6H_5Cl	32	29	64[d]
2	 18b	CH_3CN	32	70	88[e]
3	18b	C_6H_5Cl	32	65	80
4	 18c	CH_3CN	32	56	77[e]
5	18c	C_6H_5Cl	34	39	63[e]
6	 18d	CH_3CN	32	57	82[e]
7	18d	C_6H_5Cl	34	52	76[e]
8	 18e	C_6H_5Cl	46	35(11)[f]	79(>99)[g]
9	 18f	C_6H_5Cl	28	51	63[g]
10	 18g	C_6H_5Cl	32	55	68[g]

a) Carried out using 1 equivalent of iodosylbenzene as the terminal oxidant.
b) Isolated yield of **20**.
c) The % ee of **20**.
d) Determined by HPLC analysis using DAICEL CHIRALCEL OD-H column (hexane/isopropanol = 9:1).
e) Determined by HPLC analysis using DAICEL CHIRALCEL OJ column (hexane/isopropanol = 4:1).
f) Accompanied with unidentified byproduct (7%).
g) Determined by HPLC analysis using DAICEL CHIRALPAK AD column (hexane/isopropanol = 2:1).

The absolute configuration of the lactams **10g** and **17** was determined to be 1*S*,6*R* after their conversion to the corresponding known lactams (Scheme 4).



Scheme 4

The stereochemistry of the hydroxy groups in the intermediary hydroxy pyrrolidines is considered to be *exo* for the steric reason. Actually, the X-ray analysis of **19b** supported this consideration (see, Experimental Section).

In conclusion, we have developed an efficient and useful synthetic method for the synthesis of optically active hydroxypyrrolidines and lactams from *meso*-pyrrolidine derivatives by enantioselective C-H oxidation. These two chiral compounds, hydroxypyrrolidines and lactams, are versatile synthetic intermediates for the synthesis of nitrogen-containing natural products[7] and the new method described here provides a useful tool for the synthesis of this class of compounds.

Experimental Section

Materials and Methods. Iodosylbenzene was purchased from Tokyo chemical Industry Co., Ltd. Manganese(II) acetate tetrahydrate was purchased from Nacalai Tesque Inc. Sodium hexafluorophosphate was purchased from Aldrich Chemical Co., Inc. ^{1}H NMR spectra were recorded at 270 MHz on a JEOL EX-270 spectrometer. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in $CDCl_3$). NOE experiment was performed with Varian Unity-Inova 600 600MHz. IR spectra were obtained with a Shimadzu FTIR-8600 spectrophotometer. Mass spectra were recorded on a Shimadzu QP-5000 mass spectrometer. High resolution FAB mass spectra were obtained from JEOL JMX-SX/SX 102A spectrometer using *m*-nitrobenzyl alcohol matrix. Optical rotation was measured with a JASCO DIP-360 automatic digital polarimeter. Column chromatography was conducted on silica gel BW-820MH, 70-200 mesh

ASTM, high performance liquid chromatography on Hitachi L-4000 equipped with an appropriate optically active column, as described in the footnotes of Tables. The reaction temperature was controlled with EYELA COOL ECS 50. Solvents were dried and distilled shortly prior to use. Reactions were carried out under nitrogen atmosphere.

Preparation of Chiral Mn-salen (1b).

$Mn(OAc)_2$ $4H_2O$ (24.5 mg, 0.1 mmol) was added to a solution of (*R, R*)-(+)-1,2-diphenylethylenediamine (21.2 mg, 0.1 mmol) in absolute EtOH (7 ml) and the reaction mixture was stirred at room temperature for 1 h. To this solution was added (*aR*)-3-formyl-2-hydroxy-2'-phenyl-1,1'-binaphthyl (74.8 mg, 0.2 mmol) and the whole mixture was stirred at 60 °C for 6 h in air. Cooled to room temperature, $NaPF_6$ (84 mg, 0.5 mmol) was added and the reaction mixture further stirred for 20 h. Concentrated in vacuo, and the residue was chromatographed on silica gel (dichloromethane/methanol = 1/0 to 19/1) to afford **1b** (96%) as dark brown crystals. IR(KBr): 3528, 1607, 1584, 1560, 856, 751 cm^{-1}. HRMS (*m/z*). Calcd for $C_{68}H_{46}O_2N_2Mn$(-PF6) (M^+): 977.2942. Found: 977.2940. Anal. Calcd for $C_{68}H_{46}O_2N_2MnPF_6$ $2H_2O$: C, 70.45; H, 4.35; N, 2.42. Found: C, 70.21; H, 14.41; N, 2.38.

General Procedure for the Synthesis of *meso*-8-Azabicyclo[4.3.0]nonanes (3).

***cis*-Cyclohexane-1,2-dicarboximide.** 10% Pd/C (0.3 g) was added to a solution of *cis*-1,2,3,6-tetrahydrophthalimide (3.0 g, 19.9 mmol) in methanol (100 ml), and the reaction mixture was stirred under hydrogen at room temperature for 28 h. Filtration and evaporation of the solvent afforded *cis*-cyclohexane-1,2-dicarboximide as colorless crystals (3.0 g, 98%). M.p. 122-123 °C. ^1H NMR ($CDCl_3$): δ 7.80(s, 1H), 2.87-2.96(m, 2H), 1.76-1.83(m, 4H), 1.45-1.51(m, 4H). IR(KBr): 3128, 2956, 2945, 2925, 2883, 1759, 1710, 1461, 1365, 1338, 1195, 1174, 1136, 1072, 1047, 937, 842, 742 cm^{-1}. MS(*m/z*): 153(M^+), 138, 125, 111, 99, 82, 67(100), 54.

***cis*-8-Azabicyclononane.** To a stirred slurry of $LiAlH_4$ (1.86 g, 49 mmol) in 15 ml of dry THF, a solution of *cis*-cyclohexane-1,2-dicarboximide (3.0 g, 19.6 mmol) in THF (50 ml) was added dropwise at such a rate that the solvent in the flask refluxed gently.[8a] After the addition of the imide was complete, the solution was refluxed for 30 h. The mixture was cooled and the excess of $LiAlH_4$ decomposed by the addition of H_2O. The precipitate that formed was filtered off and THF evaporated. The residue was extracted with ether and dried over Na_2SO_4. Evaporation of the solvent provided *cis*-8-azabicyclononane which was distilled under reduced pressure (1.96 g, 80% yield). ^1H NMR ($CDCl_3$): δ 2.92(dd, *J*=6.9 and 10.6 Hz, 2H), 2.74(dd, *J*=5.6 and 10.6 Hz, 2H), 2.02-2.12(m, 3H), 1.32-1.75(m, 8H). MS(*m/z*): 125(M^+), 124, 95, 81, 67, 55.

Acylation. Acid chloride (2 mmol) was added to a stirred solution of *cis*-8-azabicyclo[4.3.0]nonane (0.25 g, 2 mmol) and triethylamine(0.3 ml, 2.2 mmol) in dichloromethane(5 ml) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for additional 8 h. Dichloromethane was removed in vacuo, and the residue was dissolved in ethylacetate (25 ml). The organic layer was successively washed with saturated $NaHCO_3$ (3 x 10 ml) solution and brine (3 x 10 ml). Drying (Na_2SO_4) and evaporation of the solvent provided residue which was distilled or purified on column chromatography (hexane/ethyl acetate, 7:3) to afford **3** with 90-95 % yields.

***N*-Benzoyl-*meso*-8-azabicyclo[4.3.0]nonane (3a).** Colorless liquid. ^1H NMR($CDCl_3$): δ 7.28-7.53 (m, 5H), 3.52-3.62(m, 2H), 3.41-3.47(m, 1H), 3.14-3.30(m, 1H), 2.10-2.36(m, 2H), 1.34-1.67(m, 8H). IR(neat): 3050,

2925, 2854, 1620, 1575, 1479, 1446, 1336, 1176, 1070, 790 cm^{-1}. MS(*m/z*): 229(M^+), 186, 172, 146, 124, 105, 77, 51. Anal. Calcd for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.34; H, 8.44; N, 6.05.

***N*-Propionyl-*meso*-8-azabicyclo[4.3.0]nonane (3b).** Colorless liquid. ^1H NMR ($CDCl_3$): δ 3.33-3.46(m, 3H), 3.25(dd, *J*=5.6 and 9.9 Hz, 1H), 2.17-2.31 (m, 4H), 1.35-1.85 (m, 8H), 1.21 (t, *J*=7.60 Hz, 3H). IR(neat): 2927, 2854, 1643, 1463, 1434, 1375, 813 cm^{-1}. HRMS(*m/z*). Calcd for $C_{11}H_{19}ON$ (M^++1): 182.1545. Found: 182.1545.

***N*-4-Nitrobenzoyl-*meso*-8-azabicyclo[4.3.0]nonane (3c).** Colorless powder. M.p. 96-97 °C. ^1H NMR ($CDCl_3$): δ 8.25-8.29 (m, 2H), 7.66-7.69(m, 2H), 3.54-3.68(m, 2H), 3.41(dd, *J*=6.6 and 10.2 Hz, 1H), 3.21(dd, *J*=5.0 and 10.6 Hz, 1H), 2.21-2.41(m, 2H), 1.26-1.71(m, 8H). IR(KBr): 2930, 2860, 1625, 1593, 1517, 1436, 1338, 1317, 867, 721 cm^{-1}. MS (*m/z*): 275(M^++1), 274, 257, 231, 217, 191, 175, 150(100), 134, 120, 108, 104, 76, 50. Anal. Calcd for $C_{15}H_{18}O_3N_2$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.40; H, 6.56; N, 10.11.

***N*-4-Methylbenzoyl-*meso*-8-azabicyclo[4.3.0]nonane (3d).** Colorless liquid. ^1H NMR ($CDCl_3$): δ 7.41-7.65(m, 2H), 7.18-7.26(m, 2H), 3.56-3.62(m, 2H), 3.46(dd, *J*=6.6 and 10.6 Hz, 1H), 3.30(dd, *J*=6.3 and 10.3 Hz, 1H), 2.3(s, 3H), 2.14-2.42(m, 2H), 1.33-1.65(m, 8H). IR(neat): 2925, 2854, 1624, 1569, 1421, 1180, 831, 752 cm^{-1}. HRMS(*m/z*). Calcd for $C_{16}H_{21}ON$ (M^++1): 244.1702. Found: 244.1701.

***N*-4-Methoxybenzoyl-*meso*-8-azabicyclo[4.3.0]nonane (3e).** Colorless liquid. ^1H NMR ($CDCl_3$): δ 7.50-7.55 (m, 2H), 6.88-6.93 (m, 2H), 3.8 (s, 3H), 3.47-3.60(m, 3H), 3.31-3.37(m, 1H), 2.18-2.35(m, 2H), 1.34-1.82(m, 8H). IR(neat): 2927, 2854, 1608, 1620, 1514, 1423, 1404, 1253, 1174, 1114, 1029, 842, 763 cm^{-1}. HRMS(*m/z*). Calcd for $C_{16}H_{21}O_2N$ (M^+): 260.1650. Found: 260.1651.

***N*-Naphthoyl-*meso*-8-azabicyclo[4.3.0]nonane (3f).** Colorless liquid. ^1H NMR ($CDCl_3$): δ 7.86-7.90(m, 2H), 7.31-7.54(m, 5H), 3.74(dd, *J*=2.6 and 7.3 Hz, 2H), 3.16(dd, *J*=6.9 and 10.6 Hz, 1H), 2.96(dd, *J*=5.6 and 10.6 Hz, 1H), 2.30-2.39(m, 1H), 2.14-2.18(m, 1H), 1.26-1.62(m, 8H). IR(neat): 3053, 2925, 2852, 1633, 1508, 1463, 1384, 802, 731, 781 cm^{-1}. HRMS(*m/z*). Calcd for $C_{19}H_{21}ON$ (M^++1): 280.1701. Found: 280.1707.

***N*-Phenylacetyl-*meso*-8-azabicyclo[4.3.0]nonane (3g).** Colorless crystals. M.p. 53-54 °C. ^1H NMR($CDCl_3$): δ 7.23-7.34(m, 5H), 3.65(s, 2H), 3.39-3.41(m, 3H), 3.25-3.31(dd, *J*=5.6 and 9.9 Hz, 1H), 2.14-2.23(m, 2H), 1.35-1.54(m, 8H). IR(KBr): 2925, 2860, 2841, 1632, 1448, 1481, 1182, 725 cm^{-1}. MS(*m/z*): 243(M^+), 200, 168, 152(100), 124, 109, 95, 91, 67, 55. Anal. Calcd for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.78; H, 8.79; N, 5.55.

Synthesis of *N*-Phenylacetyl-*meso*-3,4-dimethylpyrrolidine (6).

***N*-Benzyl-3,4-dimethylmaleimide.** To a stirred solution of 3,4-dimethylmaleic anhydride (1.26g, 10 mmol) in THF (5 ml), was added benzylamine (1.1 ml, 10 mmol) dropwise at 0 °C.[8a] The reaction mixture was refluxed for 10 h and cooled to room temperature. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate (50 ml). The organic layer was washed with brine solution and dried over Na_2SO_4. Evaporation of the solvent in vacuo provided *N*-benzyl-3,4-dimethylmaleimide (96%). ^1H NMR ($CDCl_3$): δ 7.2-7.35(m, 5H), 4.62(d, *J*=2.3 Hz, 2H), 1.94(s, 3H), 1.93(s, 3H). IR(KBr): 1701, 1434, 1406, 732 cm^{-1}. MS(*m/z*): 215(M^+), 197, 186, 172, 132, 110, 104, 91, 65, 55.

***N*-Benzyl-3,4-dimethylsuccinimide.** Hydrogenation of *N*-benzyl-3,4-dimethylmaleimide in the presence of 10% Pd/C in methanol according to the procedure for the synthesis of **3**, afforded *N*-benzyl-3,4-dimethylsuccinimide as a mixture of *cis* and *trans* (13:1) isomers (98%). M.p. 50-51 °C. MS(*m/z*): 218(M^+), 217, 189, 174, 160, 134, 132, 106, 104, 91, 65, 56(100). ^1H NMR ($CDCl_3$) for *cis* compound: δ 7.24-7.37(m,

5H), 4.63(s, 2H), 2.87-2.93(m, 2H), 1.20(d, *J*=6.9 Hz, 6H). IR(KBr): 2979, 1697, 1400, 1342, 752 cm^{-1}.

***N*-Benzyl-3,4-dimethylpyrrolidine**. The *N*-benzyl-3,4-dimethylsuccinimide mixture (*cis* and *trans*) was reacted with $LiAlH_4$ in THF according to the procedure for the synthesis of **3** to afford a mixture of *cis* and *trans* *N*-benzyl-3,4-dimethylpyrrolidines in 70% yield as colorless liquid.[8a] ^1H NMR ($CDCl_3$) for *cis* -isomer: δ 7.20-7.31(m, 5H), 3.57(s, 2H), 2.99(dd, *J*=7.3 and 8.6 Hz, 2H), 2.2-2.31((m, 2H), 1.94(m, 2H), 0.88(d, *J*=5.9 Hz, 6H).

3,4-dimethylpyrrolidine. A mixture of *cis* and *trans* *N*-benzyl-3,4-dimethylpyrrolidines was debenzylated using 10% Pd/C in methanol under hydrogen to afford a mixture of *cis* and *trans* 3,4-dimethylpyrrolidnes as described for synthesis of **3** (hydrogenation).[8c] ^1H NMR($CDCl_3$) for *cis*-isomer(liquid): δ 3.11(dd, *J*=6.9 and 10.9 Hz, 2H), 2.8(s, 1H), 2.52(dd, *J*=6.3 and 10.6 Hz, 2H), 2.0-2.20(m, 2H), 0.89(d, *J*=6.6 Hz, 6H).

***N*-Phenylacetyl-*meso*-3,4-dimethylpyrrolidine**. A mixture of *cis* and *trans* 3,4-dimethylpyrrolidines was treated with phenylacetyl chloride as described for the synthesis of **3** to provide **6** of a mixture of *cis* and *trans* isomers. Two isomers were separated on silica gel column chromatography using solvents hexane and ethyl acetate (8:2). Data for the *meso*-isomer **6**: ^1H NMR ($CDCl_3$): δ 7.23-7.34 (m, 5H), 3.63(s, 2H,), 3.48-3.59(m, 2H), 3.23(dd, *J*= 5.6 and 11.8 Hz, 1H), 3.11(dd, *J*=5.9 and 10.0 Hz, 1H), 2.13-2.32(m, 2H), 0.92(d, *J*=1.7 Hz, 3H), 0.89(d, *J*=1.6 Hz, 3H). IR(neat): 2960, 2873, 1624, 1496, 1456, 1191, 1147, 1076, 723 cm^{-1}. HRMS(*m/z*) Calcd for $C_{14}H_{19}ON$ (M^++1): 218.1542. Found: 218.1545.

***N*-Phenylacetyl-*meso*-7-azabicyclo[3.3.0]octane (7)**. Obtained as a colorless liquid from *cis*-cyclopentane-1,2-dicarboxylic anhydride according to the above described procedure for the synthesis of **6** in over all 30% yield. ^1H NMR($CDCl_3$): δ 7.23-7.34(m, 5H), 3.68(s, 2H), 3.57-3.71(m, 2H), 3.32(dd, *J*=4.3 and 12.5 Hz, 1H), 3.2(dd, *J*=3.6 and 10.6 Hz, 1H), 2.57-2.64(m, 2H), 1.57-1.84(m, 6H). IR(neat): 2950, 2868, 1638, 1456, 696 cm^{-1}. MS(*m/z*): 229(M^+), 215, 200, 152, 138(100), 110, 95, 91, 67, 55.

***N*-Phenylacetyl-*meso*-8-azabicyclo[4.3.0]non-3-ene (15)**. Prepared by the reduction of *cis*-1,2,3,6-tetrahydrophthalimide and subsequent acylation as described for the synthesis of **3** in over all 70% yield. ^1H NMR($CDCl_3$): δ 7.23-7.31(m, 5H), 5.59-5.67(m, 2H), 3.64(s, 2H), 3.47-3.57(m, 2H), 3.34(dd, *J*=5.3 and 11.9 Hz, 1H), 3.21(dd, *J*=6.3 and 9.6 Hz, 1H), 2.28-2.38(m, 4H), 1.81-1.88(m, 2H). IR(neat): 3026, 2935, 2881, 2839, 1639, 1496, 1456, 1425, 1159, 1029, 723, 669 cm^{-1}. MS(*m/z*): 241(M^+), 150, 122, 107, 91(100), 93, 80, 65, 53. Anal. Calcd for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.8 Found: C, 79.37; H, 7.99; N, 5.74.

General Procedure for the Synthesis of *N*-Phenylcarbamoylated-*meso*-Pyrrolidine Derivatives (8 and 18). Phenyl chloroformate (0.25 ml, 2 mmol) was added to a stirred solution of *meso*-pyrrolidine derivative (2 mmol) and triethylamine (0.28 ml, 2 mmol) in dry THF (5 ml) at 0 °C. The reaction mixture was stirred for additional 5 h at room temperature and concentrated in vacuo. The residue was dissolved in ethyl acetate and successively washed with saturated $NaHCO_3$ solution (3 x 15 ml) and brine (3 x 10 ml). Drying(Na_2SO_4) and evaporation of the solvent gave residue which was purified on silica gel column chromatography using hexane and ethyl acetate as eluent.

***N*-Phenyloxycarbonyl-*meso*-8-azatricyclo[4.3.0.$1^{2,5}$]decane (8)**. *meso*-8-Azatricyclo[4.3.0.$1^{2,5}$]decane was synthesized from *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride in overall 60% yield as colorless crystals according to the procedure described for the synthesis of **6**. M.p. 56-57 °C. ^1H NMR($CDCl_3$): δ 7.10-7.35(m, 5H), 3.16-3.32(m, 2H), 3.7-3.84(m, 2H), 2.62-2.68(m, 2H), 2.57-2.59(m, 2H), 1.36-1.52(m, 6H). IR(KBr):2876, 1717, 1406, 1178, 750 cm^{-1}. MS(*m/z*): 257(M^+), 164(100), 136, 121, 93, 79, 67, 56. Anal.

Calcd for $C_{16}H_{19}O_2N$: C, 74.66; H, 7.44; N, 5.44. Found: C, 74.15; H, 7.37; N, 5.35.

***N*-Phenyloxycarbonyl-*meso*-8-azabicyclo[4.3.0]non-3-ene (18a)**. Synthesized as colorless crystals from *cis*-1,2,3,6-tetrahydrophthalimide in 72% yield according to the procedure described for **15**. M.p. 44-45 °C. ^{1}H NMR($CDCl_3$): δ 7.07-7.41(m, 5H), 5.62-5.70(m, 2H), 3.66(dd, *J*=6.7 and 10.3 Hz, 1H), 3.56(dd, *J*=5.9 and 10.6 Hz, 1H), 3.27-3.39(m, 2H), 2.25-2.46(m, 4H), 1.94-2.01(m, 2H). IR(neat): 3026, 2941, 2883, 2839, 1780, 1724, 1593, 1494, 1398, 1209, 1053, 688, 754 cm^{-1}. MS(*m/z*): 243(M^+), 214, 188, 150, 122, 107, 93, 79, 77, 51. Anal. Calcd for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.84; H, 7.02; N, 5.65.

***N*-Phenyloxycarbonyl-*meso*-8-azabicyclo[4.3.0]nonane (18b)**. Synthesized as colorless crystals according to the procedure described above. M.p. 34-35 °C. ^{1}H NMR($CDCl_3$): δ 7.35-7.42 (m, 2H), 7.12-7.25(m, 3H), 3.33-3.60(m, 4H), 2.21-2.30(m, 2H), 1.37-1.75(m, 8H). IR(neat): 2928, 2860, 1780, 1720, 1595, 1492, 1394, 1211, 1182, 1078, 752, 686 cm^{-1}. MS(*m/z*): 245(M^+), 214, 164, 152(100), 135, 124, 109, 94, 81, 67, 55. Anal. Calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.8; N, 5.71. Found: C, 73.37; H, 7.81; N, 5.63.

***N*-Benzyloxycarbonyl-*meso*-8-azabicyclo[4.3.0]nonane (18c)**. Obtained as colorless liquid according to the procedure described above. ^{1}H NMR($CDCl_3$): δ 7.26-7.42(m, 5H), 5.13(d, *J*=3.4 Hz, 2H), 3.23-3.45(m, 4H), 2.14-2.24(m, 2H), 1.33-1.69(m, 8H). IR(neat): 2927, 2856, 1706, 1417, 1448, 1359, 1172, 1124, 1107, 1091, 875, 767, 698 cm^{-1}. MS(*m/z*): 259(M^+), 214, 168, 152, 124, 92, 91(100), 84, 65, 55. Anal. Calcd for $C_{16}H_{21}O_2N$: C, 74.09; H, 8.17; N, 5.40. Found: C, 73.90; H, 8.90; N, 5.55.

***N*-Phenyloxycarbonyl-*meso*-3,4-dimethylpyrrolidine (18d)**. Obtained as colorless crystals according to the procedure described above. M.p. 43-44 °C. ^{1}H NMR ($CDCl_3$): δ 7.12-7.38(m, 5H), 3.67(dd, *J*=6.6 and 10.6 Hz, 1H), 3.58(dd, *J*=6.6 and 10.9 Hz, 1H), 3.17-3.30(m, 2H), 2.25-2.39(m, 2H), 1.0(d, *J*=2.3 Hz, 3H), 0.98(d, *J*=2.3 Hz, 3H). IR(neat): 2964, 2877, 1766, 1728, 1606, 1593, 1398, 1211, 1163, 1055, 754, 68 cm^{-1}. MS(*m/z*): 219(M^+), 219, 126, 94, 83, 69, 55(100). Anal. Calcd for $C_{13}H_{17}O_2N$: C, 71.19; H, 7.82; N, 6.39. Found: C, 71.16; H, 7.79; N, 6.33.

Synthesis of*N*-Phenyloxycarbonyl-*meso*-3,4-isopyropylenedioxy-pyrrolidine (18e).

***N*-Phenyloxycarbonyl-3-pyrroline**: To a stirred solution of 3-pyrroline (0.77 ml, 10 mmol), triethylamine (1.4 ml, 10 mmol) in THF (10 ml) was added phenyl chloroformate (1.25 ml, 10 mmol) dropwise at 0 °C. The reaction mixture was warmed up to room temperature, stirred for 5 h, and concentrated in vacuo. The residue was dissolved in ethyl acetate (30 ml) and successively washed with saturated $NaHCO_3$ solution and brine. Drying (Na_2SO_4) and evaporation of the solvent afforded *N*-phenyloxycarbonyl-3-pyrroline (1.72 g, 91%) as colorless crystals. M.P. 90 °C.

***N*-Phenyloxycarbonyl-*meso*-3,4-isopyropylenedioxypyrrolidine**: A solution of *N*-phenyloxycarbonyl-3-pyrroline (0.567 g, 3 mmol) and K_2OsO_4 $2H_2O$(10 mg, 0.03 mmol) in *t*-BuOH (20 ml) and H_2O (20 ml) was added to a mixture of DABCO (84 mg, 0.75 mmol), $K_3Fe(CN)_6$ (3.05 g, 9 mmol), and K_2CO_3 (1.25 g, 9 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, Na_2SO_3 (15.55 g, 123.4 mmol) was added, and further stirred for another 0.5 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 15 ml). The combined organic layers were concentrated in vacuo to give the residue which was diluted with ethyl acetate (50 ml), washed successively with 1M sulfuric acid, aqueous $NaHCO_3$ (3 x 15 ml) and brine (3 x 15 ml). Drying (Na_2SO_4) and evaporation of the solvent gave *N*-phenyloxycarbonyl-*meso*-3,4-dihydroxypyrrolidine as a thick liquid (435 mg, 65%): ^{1}H NMR ($CDCl_3$): δ 7.09-7.39(m, 5H), 4.20-4.21(m, 2H), 3.42-3.78(m, 4H). IR(neat): 3400, 2949, 1705, 1595, 1418, 1209 cm^{-1}. The diol was stirred with 2,2-dimethoxypropane (1.2 ml) and catalytic amount of *p*-toluenesulfonic acid in DMF (5

ml) for 24 h at 50 °C. The mixture was cooled to room temperature, diluted with ethyl acetate (50 ml), and washed successively with aqueous $NaHCO_3$ (3 x 15 ml) and brine (3 x 15 ml). Drying (Na_2SO_4) and evaporation of the solvent gave residue which was purified on column chromatography (hexane/ethyl acetate, 6:4) to give **18e** (446 mg, 87%) as colorless crystals. M.P. 80 °C. ^1H NMR ($CDCl_3$): δ 7.11-7.38(m, 5H), 4.79(d, *J*=2.9 Hz, 2H), 3.93(dd, *J*=12.5, 19.8 Hz, 2H), 3.45-3.57(m, 2H), 1.53(s, 3H), 1.36(s, 3H). IR(KBr): 2872, 1780, 1398, 1198, 1053 cm^{-1}. HRMS(*m/z*): Calcd for $C_{14}H_{17}O_4N$ (M^++1): 264.1236. Found: 264.1236.

***N*-Phenyloxycarbonyl-*meso*-3,4-isopyropylenedioxy-8-azabicyclo[4.3.0]nonane (18f).** Synthesized from **4** according to the procedure described for **18e**. M.p. 72-73 °C. ^1H NMR ($CDCl_3$): δ 7.11-7.38(m, 5H), 4.0-4.31(m, 2H), 3.78-3.93(m, 2H), 3.17-3.27(m, 2H), 2.60-2.64(m, 2H), 2.00-2.06(m, 2H), 1.35-1.53(m, 2H), 1.51(s, 3H), 1.36(s, 3H). IR(KBr): 3060, 2985, 2960, 2930, 2869, 1728, 1589, 1433, 1377, 1365, 1218, 1191, 1170, 1043, 1060, 752 cm^{-1}. MS(*m/z*): 317(M^+), 302, 224(100), 166, 123, 95, 79, 77, 59. Anal. Calcd for $C_{18}H_{23}O_4N$: C, 68.12, H, 7.3; N, 4.41. Found: C, 67.92; H, 7.30; N, 4.35.

***N*-Phenyloxycarbonyl-3,4-dibenzoyloxy-*meso*-8-azabicyclo[4.3.0]nonane (18g).** Usual *N*-benzoylation of **4** with benzoyl chloride afforded **18g** as colorless crystals in 95% yield. M.p. 144-145 °C. ^1H NMR($CDCl_3$): δ 7.14-8.04(m, 15H), 5.40-5.53(m, 2H), 3.75(dd, *J*=7.3 and 10.9 Hz, 1H), 3.56-3.70(m, 2H), 3.49(dd, *J*=5.0, and 10.9 Hz, 1H), 2.29-2.40(m, 2H), 2.66-2.79(m, 2H), 1.91-2.07(m, 2H). IR(KBr): 2950, 2879, 1118, 1720, 1705, 1600, 1390, 1284, 1215, 1118, 713 cm^{-1}. Anal. Calcd for $C_{29}H_{27}O_6N$: C, 71.74; H, 5.61; N, 2.88. Found: C, 70.57; H, 5.64; N, 2.89.

General Procedure for the Oxidative Desymmerization of *meso*-Pyrrolidine Derivatives Using Mn-Salen Complexes 1 as the Catalysts.

Iodosylbenzene (22 mg, 0.1 mmol) was added at once to a precooled solution of *N*-protected *meso*-pyrrolidine derivative **18** (0.1 mmol) and **1b** (2.2 mg, 2 μmol) in acetonitrile (1 ml) under nitrogen at -25 °C. After stirring 32-46 h, the reaction mixture was quenched by adding dimethyl sulfide and concentrated *in vacuo*. The residue was passed through a short column of silica gel (ethyl acetate/hexane) to afford hydroxy pyrrolidine derivative **19** . Crude **19** was dissolved in acetone (5 ml) and cooled to 10 °C under nitrogen. To this solution was added aqueous CrO_3 reagent (25 μl, 1.7M)[10] rapidly with stirring. After 20 min, few drops of isopropanol was added, and the solution was concentrated *in vacuo* . The residue was dissolved in ethyl acetate (15 ml), and washed with saturated $NaHCO_3$ solution. Drying (Na_2SO_4), and evaporation of the solvent gave a residue which was purified by silica gel column chromatography using ethyl acetate/hexane. Enantiomeric excess of lactam **20** was determined by HPLC analysis using optically active column.

***N*-Benzoyl-8-azabicyclo[4.3.0]non-7-one (10a).** Colorless liquid. Yield 55% (64% ee). $[\alpha]_D^{23}$ + 24.75° (*c* 0.65, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.38-7.60(m, 5H), 3.8(dd, *J*=5.9 and 11.6 Hz, 1H), 3.68(dd, *J*=2.0 and 11.2 Hz, 1H), 2.68-2.72(m, 1H), 2.40-2.46(m, 1H), 2.04-2.09(m, 1H), 1.89-1.91(m, 1H), 1.13-1.86(m, 6H). IR(neat): 2933, 2854, 1747, 1670, 1448, 1321, 1292, 689 cm^{-1}. MS (*m/z*): 243(M^+), 138, 105, 77, 51. Anal. Calcd for $C_{15}H_{17}O_2N$: C, 74.04; H, 7.05; N, 5.76. Found: C, 74.05; H, 7.06; N, 5.66.

***N*-Propionyl-8-azabicyclo[4.3.0]non-7-one (10b).** Colorless crystals. M.p. 34-36 °C. Yield 65% (36% ee). $[\alpha]_D^{22}$ +11.89° (*c* 0.41, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.58 (d, *J*=4.0 Hz, 2H), 2.89-3.02 (m, 2H), 2.65-2.82 (m, 1H), 2.30-2.38(m, 1H), 2.07-2.27(m, 1H), 1.05-1.78(m, 10H). IR(KBr): 2978, 2936, 2856, 1736, 1697, 1371, 1244 cm^{-1}. MS(*m/z*): 195(M^+), 167, 152, 140, 124, 112, 95, 81, 67, 57. Anal. Calcd for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.52; H, 8.78; N, 7.17.

***N*-4-Nitrobenzoyl-8-azabicyclo[4.3.0]non-7-one (10c)**. Colorless crystals. M.p. 91-92 °C. Yield 42% (43% ee). $[\alpha]_D^{24}$ + 7.7° (*c* 0.12, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.25-2.29(m, 2H), 7.67-7.70 (m, 2H), 3.75-3.83(m, 2H), 2.72-2.75(m, 1H), 2.45-2.48(m, 1H), 1.92-2.07(m, 1H), 1.86-1.92(m, 1H), 1.20-1.69(m, 6H). IR(KBr): 2932, 2853, 1749, 1663, 1605, 1524, 1350, 1226, 1168, 1116, 866, 712 cm^{-1}. MS(*m/z*): 288(M^+), 233, 150(100), 138, 120, 104, 81, 76, 50. Anal. Calcd for $C_{15}H_{16}O_4N_2$: C, 62.48; H, 5.60; N, 9.72. Found: C, 62.35; H, 5.61; N, 9.65.

***N*-4-Methylbenzoyl-8-azabicyclo[4.3.0]non-7-one (10d)**. Colorless powder. M.p. 61-62 °C. Yield 41% (39% ee). $[\alpha]_D^{24}$ + 14.7° (*c* 0.21, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.50(d, *J*=8.3 Hz, 2H), 7.21 (d, *J*=8.6 Hz, 2H), 3.82(dd, *J*=5.9 and 11.2 Hz, 1H), 3.65(dd, *J*=1.9 and 11.2 Hz, 1H), 2.67-2.71 (m, 1H), 2.33-2.45(m, 1H), 2.4(s, 3H), 2.04-2.16(m, 1H), 1.24-1.69(m, 7H). IR(KBr): 2926, 2858, 2889, 1736, 1670, 1610, 1319, 1292, 756 cm^{-1}. MS(*m/z*): 257(M^+), 242, 229, 238, 120, 119(100), 91, 65, 53. Anal. Calcd for $C_{16}H_{19}O_2N$: C, 74.67; H, 7.45; N, 5.45. Found: C, 74.55; H, 7.36; N, 5.38.

***N*-4-Methoxybenzoyl-8-azabicyclo[4.3.0]non-7-one (10e)**. Colorless powder. M.p. 63-64 °C. Yield 37% (28% ee). $[\alpha]_D^{23}$ + 20.18° (*c* 0.17, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.63(d, *J*=8.6 Hz, 2H), 6.90(d, *J*=8.9 Hz, 2H), 3.85(s, 3H), 3.82(dd, *J*=5.6 and 11.2 Hz, 1H), 3.65(dd, *J*=1.7 and 10.9 Hz, 1H), 2.67-2.71(m, 1H), 2.41-2.45(m, 1H), 2.06-2.11(m, 1H), 1.82-1.90(m, 1H), 1.34-1.69(m, 6H). IR(KBr): 2936, 2853, 1726, 1670, 1602, 1510, 1319, 1254, 845, 767, 609 cm^{-1}. MS(*m/z*): 274(M^++1), 273, 245, 135(100), 107, 92, 77, 63. Anal. Calcd for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.28; H, 6.95; N, 4.88.

***N*-Naphthoyl-8-azabicyclo[4.3.0]non-7-one (10f)**. Colorless liquid. Yield 43 % (58% ee). $[\alpha]_D^{23}$ + 17.03° (c 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.79-8.70(m, 3H), 7.44-7.59(m, 4H), 3.85-3.90(m, 2H), 2.67-2.47(m, 1H), 1.91-1.99(m, 1H), 2.46-2.47((m, 1H), 1.67-1.70(m, 1H), 1.08-1.55(m, 6H). IR(neat): 3057, 2932, 2855, 1749, 1668, 1508, 1317, 783, 631 cm^{-1}. MS(*m/z*): 293(M^+), 265, 171, 155(100), 138, 127, 115, 101, 83, 67, 55. Anal. Calcd for $C_{19}H_{19}O_2N$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.69; H, 6.49; N, 4.65.

(1*S*,6*R*)-*N*-Phenylacetyl-8-azabicyclo[4.3.0]non-7-one (10g). Colorless liquid. Yield 65% (76% ee). $[\alpha]_D^{25}$ + 11.3° (*c* 0.23, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.21-7.35 (m, 5H), 4.30(s, 2H), 3.59(d, *J*=3.7 Hz, 2H), 2.66-2.72 (m, 1H), 2.26-2.38 (m, 1H), 2.06-2.17(m, 1H), 1.13-1.79(m, 7H). IR(neat): 2938, 2855, 1786, 1751, 1717, 1309, 1290, 1170, 877, 696 cm^{-1}. MS(*m/z*): 257(M^+), 140, 118, 95, 91, 67, 55. Anal. Calcd for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44, N, 5.44. Found: C, 74.57, H, 7.56, N, 5.32.

***N*-Phenylacetyl-3,4-dimethylpyrrolidin-4-one (12)**. Colorless liquid. Yield 49% (84% ee). The enantiomeric excess of **12** was determined by CHIRALPAK AD column (100:1, hexane/isopropanol). $[\alpha]_D^{25}$ +8.4° (*c* 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.15-7.28(m, 5H), 4.2(d, *J*=2.3 Hz, 2H), 3.68(dd, *J*=6.3 and 11.6 Hz, 1H), 3.43-3.48(dd, *J*=3.6 and 11.6 Hz, 1H), 2.62-2.72(m, 1H), 2.3-2.45(m, 1H), 1.10(d, *J*=7.3 Hz, 3H), 0.90(d, *J*=7.3 Hz, 3H). IR(neat): 2933, 2854, 1786, 1751, 1716, 1309, 1290, 1267, 1170, 696 cm^{-1}. HRMS(*m/z*). Calcd for $C_{14}H_{17}O_2N$ (M^++1): 232.1337. Found: 232.1338.

***N*-Phenylacetyl-7-azabicyclo[3.3.0]octan-6-one (14)**. Colorless liquid. Yield 48% (75% ee). Enantiomeric excess of **14** was determined by CHIRALCEL OD-H column (9:1, hexane/isopropanol). $[\alpha]_D^{25}$ + 9.8° (*c* 0.1 $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.21-7.31(m, 5H), 4.26(d, *J*=5.3 Hz, 2H), 3.91(dd, *J*=3.6 and 12.2 Hz, 1H), 3.54(dd, *J*=2.5 and 12.2 Hz, , 1H), 3.04-3.12(m, 1H), 2.67-2.72(m, 1H), 1.46-2.03(m, 6H). IR(neat): 2933, 2855, 1741, 1671, 1363, 1251 cm^{-1}. MS(*m/z*): 243(M^+), 126, 118(100), 91, 65, 56. Anal. Calcd for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.88; H, 7.15; N, 5.72.

(1*S*,6*R*)-*N*-Phenylacetyl-8-azabicyclo[4.3.0]non-3-en-7-one (17). Colorless powder. Yield 17% (55% ee).

M.p. 45-46 °C. $[\alpha]_D^{22}$+39.2° (*c* 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.20-7.34 (m, 5H), 5.70-5.74(m, 2H), 4.28(d, *J*=3.0 Hz, 2H), 3.62-3.74(m, 2H), 2.81-2.88(m, 1H), 2.18-2.58(m, 5H). IR(neat): 2844, 1740, 1700, 1697, 1364, 1252 cm^{-1}. HRMS(*m/z*). Calcd for $C_{16}H_{17}O_2N$ (M^++1): 256.1338. Found: 256.1338.

***N*-Phenyloxycarbonyl-8-azabicyclo[4.3.0]non-3-en-7-one (20a)**. Colorless powder. Yield 29% (64% ee). M.p. 88-89 °C. $[\alpha]_D^{23}$+ 19.17° (*c* 0.41, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.36-7.42(m, 2H), 7.13-7.27(m, 3H), 5.70-5.77(m, 2H), 3.90(dd, *J*=5.6 and 10.9 Hz, 1H), 3.69(dd, *J*=2.3 and 10.6 Hz, 1H), 2.82-2.88(m, 1H), 2.51-2.63(m, 2H), 2.25-2.40(m, 2H), 1.88-1.98(m, 1H). IR(KBr): 3032, 2843, 1759, 1728, 1364, 1319, 1310, 1201, 1182, 750, 666 cm^{-1}. HRMS(*m/z*). Calcd for $C_{15}H_{15}O_3N$ (M^++1): 258.1128. Found: 258.1130.

***N*-Phenyloxycarbonyl-8-azabicyclo[4.3.0]non-7-one (20b)**. Colorless crystals. M.p. 65-66 °C. Yield 70% (88% ee). $[\alpha]_D^{24}$ – 12.1° (*c* 0.17, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.29-7.46(m, 5H), 3.48(dd, *J*=1.9 and 10.6 Hz, 1H), 2.59-2.65(m, 1H), 2.09-2.31(m, 2H), 1.18-1.84(m, 8H). IR(KBr): 3070, 2920, 2856, 1794, 1710, 1375, 1286, 1170, 960, 763, 692 cm^{-1}. MS(*m/z*): 259(M^+), 215, 166, 138, 109, 95(100), 81, 67, 55. Anal. Calcd for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.33, H, 6.74; N, 5.13.

***N*-Benzyloxycarbonyl-8-azabicyclo[4.3.0]non-7-one (20c)**. Colorless liquid. Yield 56% (77% ee). $[\alpha]_D^{23}$ – 8.90° (*c* 0.47, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.29-7.46(m, 5H), 5.28(d, *J*=3.3 Hz, 2H), 3.68(dd, *J*=5.9 and 10.9 Hz, 1H), 3.49(dd, *J*=2.0 and 10.6 Hz, 1H), 2.59-2.65(m, 1H), 2.31(m, 1H), 2.09-2.13(m, 1H), 1.18-1.84(m, 7H). IR(neat): 2933, 2854, 1786, 1716, 1309, 1290, 1170, 977, 696 cm^{-1}. HRMS(*m/z*). Calcd for $C_{16}H_{19}O_3N$: (M^++1): 274.1443. Found: 274.1443.

***N*-Phenyloxycarbonyl-3,4-dimethylpyrrolidin-4-one (20d)**. Colorless crystals. M.p. 49-50 °C. Yield 60% (82% ee). $[\alpha]_D^{23}$ –4.3° (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.17-7.42(m, 5H), 3.94(dd, *J*=6.6, and 10.9 Hz, 1H), 3.58(dd, *J*=5.0 and 10.9 Hz, 1H), 2.61-2.80(m, 1H), 2.46-2.58(m, 1H), 1.19(d, *J*=7.26 Hz, 3H), 1.06(d, *J*=6.93, 3H). IR(KBr): 2972, 2939, 2877, 1798, 1759, 1730, 1494, 1315, 1164, 947, 689 cm^{-1}. HRMS(*m/z*). Calcd for $C_{13}H_{15}O_3N$ (M^++1): 234.1127. Found: 234.1130.

***N*-Phenyloxycarbonyl-3,4-isopropylenedioxy-pyrrolidin-2-one (20e)**. Colorless crystals. M.p. 220 °C. Yield 35% (79% ee), [11% yield, >99% ee after single crystallization from ethylacetate/hexane(1:1), $[\alpha]_D^{23}$ –36° (*c* 0.18, $CHCl_3$)]. ^1H NMR ($CDCl_3$): δ 7.18-7.43(m, 5H), 4.74-4.81(m, 2H), 4.2(d, *J*=12.5 Hz, 1H), 3.98(dd, *J*=3.9 and 12.5 Hz, 1H), 1.53(s, 3H), 1.43(s, 3H). IR(KBr): 1753, 1734, 1309, 1196, 1215, 1101 cm^{-1}. HRMS(*m/z*). Calcd for $C_{14}H_{15}O_5N$ (M^++1): 278.1028. Found: 278.1028.

***N*-Phenyloxycarbonyl-3,4-isopropylenedioxy-8-azabicyclo[4.3.0]non-7-one (20f)**. Colorless crystals. M.p. 125-126 °C. Yield 51% (63% ee). $[\alpha]_D^{23}$ +11.8° (*c* 0.38, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.17-7.42(m, 5H), 4.40-4.49(m, 1H), 4.39-4.42(m, 1H), 4.11(dd, *J*=8.6 and 11.2 Hz, 1H), 3.58(dd, *J*=3.6 and 11.2 Hz, 1H), 2.97-3.07(m, 1H), 2.69-2.81(m, 1H), 2.35-2.40(m, 1H), 1.90-1.99(m, 1H), 1.49(s, 3H), 1.36(s, 3H), 1.25-1.68(m, 2H). IR(KBr): 2920, 1784, 1701, 1387, 1306, 1190, 1037, 764, 687 cm^{-1}. HRMS(*m/z*). Calcd for $C_{18}H_{21}O_5N$(M^++1): 332.1497. Found: 332.1498.

***N*-Phenyloxycarbonyl-3,4-dibenzoyloxy-8-azabicyclo[4.3.0]non-7-one (20g)**. Colorless powder. Yield 55% (68% ee). M.p. 144-145 °C. $[\alpha]_D^{23}$ + 59° (*C* 0.15, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.21-8.07(m, 15H), 5.35(t, *J*=2.3 *Hz*, 1H) 5.18-5.24(m, 1H), 3.95(dd, *J*=5.6 and 11.2 Hz, 1H), 3.73(d, *J*=11.2 Hz, 1H), 2.99-3.10(m, 1H), 2.79-2.85(m, 1H), 2.56-2.63(m, 1H), 2.35-2.46(m, 2H), 1.79-2.18(m, 1H). IR(KBr): 2957, 1794, 1742, 1724, 1308, 1209, 754, 690 cm^{-1}. HRMS(*m/z*). Calcd for $C_{29}H_{25}O_7N$ (M^+): 500.1707. Found: 500.1709.

***N*-Phenyloxycarbonyl-8-azatricyclo[4.3.0.1^{2,5}]decan-7-one (22)**. Colorless crystals. M.p. 110-111 °C. Yield 68% (76% ee). The enantiomeric excess of **22** was determined by CHIRALCEL OJ column (4:1, hexane and

isopropanol). $[\alpha]_D^{23}$ –59.4° (*c* 0.36, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.18-7.39(m, 5H), 3.81-3.88(m, 2H), 3.06(dd, *J*=5.6 and 10.7 Hz, 1H), 2.61-2.75(m, 2H), 2.42(s, 1H), 1.54-1.57(m, 6H). IR(KBr): 2973, 2939, 1894, 1729, 1303, 1271, 1209, 712 cm^{-1}. MS(*m/z*): 271(M^+), 227, 192, 178, 150, 122, 107, 94, 79(100), 77, 56. Anal. Calcd for $C_{16}H_{17}O_3N$: C, 70.82; H, 6.32; N, 5.16. Found: 70.81; H, 6.31; N, 5.17.

8-Azabicyclo[4.3.0]non-7-one (23). To a stirred solution of **10g** (0.8 mmol, 20 mg) in THF and water (1 ml, 1:1) was added LiOH H_2O (17 mg). The reaction mixture was stirred at room temperature for 1h and concentrated in vacuo. The aqueous layer was extracted with ethyl acetate (10 ml) and the combined organic layers were washed with brine. Drying (Na_2SO_4) and evaporation of the solvent provided **23** as colorless crystals (10.8 mg, 100%, 76% ee). Enantiomeric excess of **23** was determined by CHIRALCEL OB-H column (20:1, hexane/isopropanol). $[\alpha]_D^{25}$ -22.4° (*c* 0.25, $CHCl_3$) [Lit.[8e] (86% ee) $[\alpha]_D^{25}$ -23.3° (*c* 0.5, $CHCl_3$)]. M.p. 94-95 °C. ^1H NMR ($CDCl_3$): δ 5.77(s, 1H), 3.37(dd, *J*=5.9 and 9.6 Hz, 1H), 2.94(d, *J*=9.2 Hz, 1H), 2.40-2.44(m, 2H), 2.0-2.03(m, 1H), 1.20-1.74(m, 7H). IR(KBr): 3240, 2932, 2855, 1701, 1655, 1445, 1259, 1061, 759 cm^{-1}. MS(*m/z*): 139(M^+), 110, 96, 84, 67, 54.

8-Azabicyclo[4.3.0]non-3-en-7-one (24). According to the procedure described for **23**, the phenylacetyl group of **17** was removed to afford **24** as the colorless crystals with 100% yield (54% ee). The enantiomeric excess of **24** was determined by CHIRALCEL OB-H column (20:1, hexane/isopropanol). $[\alpha]_D^{23}$ +15.3° (*c* 0.21, $CHCl_3$) [Lit.[8e] (88% ee) $[\alpha]_D^{23}$ -24.0° (*c* 0.5, $CHCl_3$)]. M.p. 74-75 °C. ^1H NMR ($CDCl_3$): δ 5.71-5.81(m, 2H), 5.50(s, 1H), 3.49(dd, *J*=4.3 and 8.9 Hz, 1H), 3.0(d, *J*=9.9 Hz, 1H), 1.88-2.60(m, 6H). IR(KBr): 3231, 3022, 1701, 1678, 1263, 1191 cm^{-1}. MS(*m/z*): 137(M^+), 122, 108, 96, 79, 77, 51.

***N*-Phenyloxycarbonyl-7-hydroxy-8-azabicyclo[4.3.0]nonane (19b).** Iodosylbenzene (22 mg, 0.1 mmol) was added to the precooled stirred solution of *N*-phenyloxycarbonyl-8-azabicyclo[4.3.0]nonane **18b** (24.5 mg, 0.1 mmol) and **1b** (2.2 mg, 2 μmol) in acetonitrile (1 ml) under nitrogen at -25 °C. After 32 h, the reaction mixture was quenched by adding dimethyl sulfide, and concentrated *in vacuo*. The residue was purified on silica gel column chromatography (ethyl acetate/hexane, 1:1) to afford **19b** which was contaminated with a trace amount of the diastereomeric isomer at C7. 73% yield (88% ee). Enantiomeric excess of **19b** was determined by HPLC analysis using CHIRALCEL OB-H column (hexane/isopropanol, 20:1). M.p. 98-99 °C. $[\alpha]_D^{24}$ +46.7° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.13-7.40(m, 5H), 5.28-5.33(m, 1H), 3.72(dd, *J*=7.2 and 10.5 Hz, 1H), 3.39-3.57(m, 1H), 2.52-2.60(m, 1H), 2.11-2.17(m, 1H), 1.31-1.72(m, 8H). IR(KBr): 3456, 2916, 1717, 1382, 1195, 746 cm^{-1}. MS(*m/z*): 261(M^+), 168, 150, 124, 94(100), 79, 65, 55. Recrystallization of **19b** from ethylacetate/hexane (2:8) provided a single crystal whose structure was determined by X-ray analysis (Fig. 1). Crystallographic data: $C_{15}H_{19}NO_3$, M = 261.32, orthorhombic, space group $P2_12_12_1$, a = 10.5443(4) Å, b = 24.1956(8) Å, c = 5.2838(1) Å, V = 1348.03(8) $Å^3$; Z = 4; D_C = 1.288 g cm^{-3}, μ(Cu-Kα) = 7.27 cm^{-1}, R_1 = 0.030, Rw= 0.035 for 1156 reflections and 174 variables, *GOF* = 1.54. Data were collected on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu-Kα at 25 °C. Structural analysis was performed using the teXsan crystallographic software package. The structure was solved by the direct methods (SIR92) and expanded using Fourier techniques. All non-hydrogen atoms were refined anisotropically and the hydrogen atoms were included but not refined.

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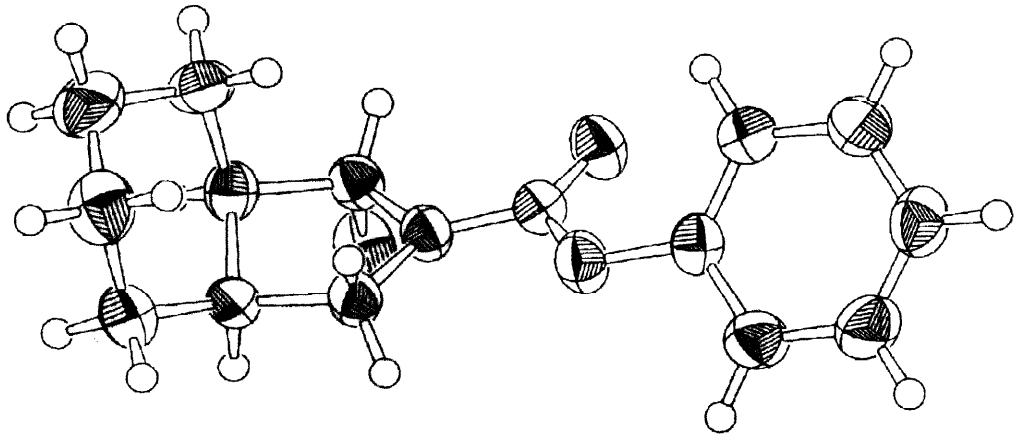

Figure 1. ORTEP drawing of **19b** with thermal ellipsoids at 50% probability level.

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