Enantioselective Reduction of *meso*-Cyclic-1,2-dicarboxylic Anhydrides and 1,2-Dicarboximides: Asymmetric Synthesis of Bicyclic Lactones and Hydroxylactams

Kenji MATSUKI,*[,a] Hirozumi INOUE,[a] Akihiko ISHIDA,[a] Mikio TAKEDA,[a] Masako NAKAGAWA,[b] and Tohru HINO[b]

Organic Chemistry Research Laboratory,[a] Tanabe Seiyaku Co., Ltd., 2–2–50, Kawagishi, Toda, Saitama 335, Japan and Faculty of Pharmaceutical Sciences, Chiba University,[b] 1–33 Yayoi-cho, Inage-ku, Chiba-shi 263, Japan.
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Chiral bicyclic lactones (3, 8, 9) and bicyclic hydroxylactams (10—13) were synthesized by highly enantioselective reduction of *meso*-cyclic-1,2-dicarboxylic anhydrides (1, 4) and *meso*-cyclic-1,2-dicarboximides (2) with lithium aluminum hydride ($LiAlH_4$)–alcohol(ROH)–(*R*)- or (*S*)-1,1′-bi-2-naphthol complex [(*R*)- or (*S*)-BINAL-H(ROH)]. Treatment of the hydroxylactams (10—13) with triethylsilane (Et_3SiH) and trifluoroacetic acid (CF_3CO_2H) gave chiral bicyclic lactams (14, 15) in quantitative yields. Removal of the *N*-4-methoxyphenyl group of the lactams (14, 15) with cerium(IV) ammonium nitrate (CAN) proceeded smoothly to give the corresponding *N*-unsubstituted lactams (16, 17) in high optical purity.

Keywords enantioselective reduction; chiral bicyclic lactone; chiral bicyclic hydroxylactam; chiral bicyclic lactam; *meso*-dicarboxylic anhydride; *meso*-dicarboximide

Enantioselective differentiation of prochiral functional groups in symmetrical bifunctional compounds such as *meso* compounds is an important strategy for creating new chiral centers. The synthesis of optically active compounds from *meso* dicarboxylic acids or their derivatives has been studied for some decades and in particular, enantioselective hydrolysis of *meso* or prochiral diesters by enzymatic methods has been extensively investigated.[1a] Although there have been several reports[1b] the asymmetric synthesis by chemical procedures, only a few methods have been reported for enantioselective reduction of symmetrical dicarboxylic acid derivatives.[2,3] In these cases the selectivities were not high. Therefore, a convenient and efficient method for the synthesis of optically active compounds from symmetrical dicarboxylic anhydrides or their derivatives is still desired.

We recently reported highly enantioselective reduction of *meso*-cyclic-1,2-dicarboxylic anhydrides (**1**) and 1,2-dicarboximides (**2**) with lithium aluminum hydride ($LiAlH_4$)–alcohol(ROH)–(*R*)- or (*S*)-1,1′-bi-2-naphthol complex [(*R*)- or (*S*)-BINAL-H(ROH)].[4] In this paper, we present full details of our work and additional new results.

Enantioselective Reduction of *meso*-Cyclic-1,2-dicarboxylic Anhydrides Enantioselective synthesis of bicyclic lactones (**3**, **8**, **9**), which are versatile intermediates for syntheses of natural products, can be achieved by enantioselective reduction of a carbonyl group in *meso*-1,2-dicarboxylic anhydrides (**1**) with two carbon centers of opposite chirality. Regarding asymmetric synthesis of bicyclic lactones, Osakada and his colleagues have reported the hydrogenation of *meso*-cyclic-1,2-dicarboxylic anhydrides using a Ru(II) complex with a chiral phosphine ligand as a catalyst, but the enantiomeric excess (ee) of products was unsatisfactory.[2]

(3a*S*,6a*R*)-1,3-Dibenzyldihydro-1*H*-furo[3,4-*d*]imidazole-2,4(3*H*,3a*H*)-dione (**3**), a key intermediate for (+)-biotin synthesis, has been prepared by chemoselective

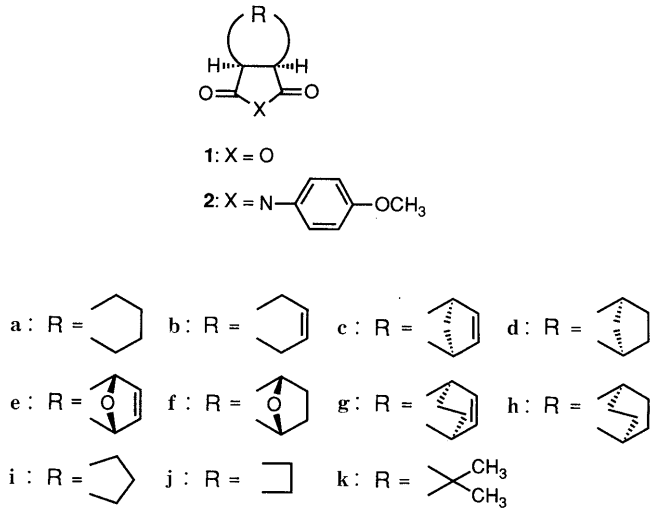


Chart 1

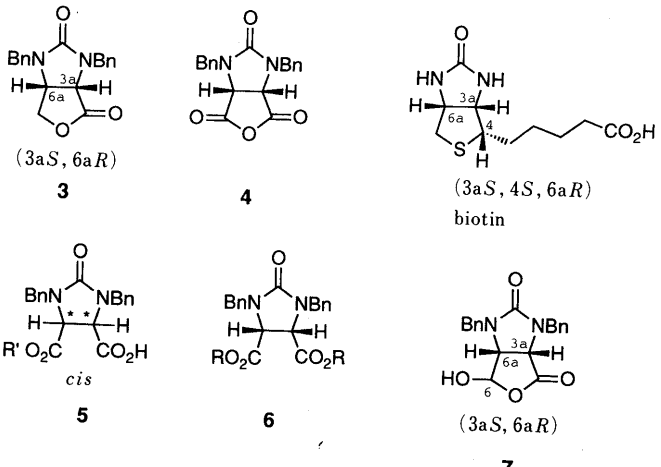


Chart 2

TABLE I. Enantioselective Reduction of the Anhydride **4** with Various Reducing Reagents

Entry	Reducing reagent[a]	Molar ratio [Reducing reagent/4]	Conditions[b]	Lactone **3**		
				Yield (%)	ee (%)[c]	$[\alpha]_D^{25}$ (°) ($c=1$, benzene)
1	I	2	A	—[d]	—	—
2	II	2	B	0	—	—
3	III	3	C	0	—	—
4	IV	2	B	0	—	—
5	V	2	B	23	3	+1.5
6	VI	2	A	74	0	—
7	VII	2.4	C	75	0	—
8	VIII	2.4	C	74	0	—
9	IX	2.4	C	71	0	—
10	X	3	C	69	7	+3.8
11	XI	3	C	75	3	+1.6
12	XII	2.5	C	28	0	—
13	XIII	3	C	44	6	+3.2
14	XIV	3	C	54	15	+8.9
15	XV	3	C	61	39	+22.8
16	XVI	1.5	D	Trace[e]	—	—
17	XVI	3	E	74	55	+31.8
18	XVI	3	F	76	90	+52.2
19	XVII	3	F	67	86	+49.8
20	XVIII	3	F	66	44	+25.6

a) Reducing reagent: I, BH_3–(*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (2 : 1)[9]; II, $NaBH_4$–(*S*)-proline (1 : 1)[10]; III, $NaBH_4$–(*R,R*)-tartaric acid (1 : 1.5)[11]; IV, BH_3–(*S*)-1,1′-bi-2-naphthol (1 : 1); V, $NaBH_4$–(*S*)-*N*-benzyloxycarbonylproline (1 : 3)[12]; VI, $NaBH_4$–$ZnCl_2$–1,2:5,6-diisopropylidene-D-glucofuranose (1 : 0.3 : 2)[13]; VII, $LiBH_4$–(*S*)-mandelic acid–*tert*-butanol (3 : 1 : 1.3); VIII, $LiBH_4$–(*S*)-*N*-benzoylserine–*tert*-butanol (3 : 1 : 1.3)[14]; IX, $LiBH_4$–(*S*)-*N*-toluenesulfonylserine–*tert*-butanol (3 : 1 : 1.3); X, $LiBH_4$–EtOH–(*S*)-1,1′-bi-2-naphthol (1 : 1 : 1); XI, $LiAlH_4$–(*S*)-menthol (1 : 3)[15]; XII, $LiAlH_4$–(2*S*,3*S*)-1,4-bis(pyrrolidinyl)butane-2,3-diol (1 : 1)[16]; XIII, $LiAlH_4$–(*S*)-2-(2,6-dimethylphenylamino)methylpyrrolidine (1 : 1.2) in ether[17]; XIV, $LiAlH_4$–EtOH–(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol (1 : 1 : 1); XV, $LiAlH_4$–(2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (1 : 2) in ether[18]; XVI, (*R*)-BINAL-H (EtOH); XVII, (*R*)-BINAL-H (MeOH); XVIII, (*R*)-BINAL-H (*tert*-BuOH). *b*) Reduction was carried out in THF except for entry 5 (CH_2Cl_2), 13 and 15 (ether–THF). Conditions: A, 0 °C; B, room temperature (r.t.); C, −78 °C-r.t.; D, −78 °C (5 h); E, −40 °C (5 h)-r.t.; F, −78 °C (5 h)-r.t. *c*) Based on $[\alpha]_D^{25}$ +58.2° ($c=1$, benzene).[5a] *d*) Complex mixture. *e*) The hydroxylactone **5**[5a] was obtained (41% yield).

reduction of the ester carbonyl of the chiral mono-ester (**5**), which was obtained by an optical resolution of racemic **5**, asymmetric enzymatic hydrolysis of the *meso*-diester **6**, or asymmetric alcoholysis of the *meso*-anhydride **4**.[5,6] Initially, the enantioselective reduction of the *meso*-1,2-dicarboxylic anhydride **4** to the chiral lactone **3** was taken as a model, and investigated by using chiral reducing reagents under various conditions. Table I summarizes the results. Among several reducing reagents screened, (*R*)-BINAL-H, prepared *in situ* according to Noyori's procedure,[7,8] is effective for this reduction, giving the desired (3a*S*,6a*R*)-lactone **3** in high optical purity. The use of the reducing reagents I and V—XV resulted in undesirable side reactions, a poor conversion into **3**, or a lowering of the optical purity of **3**. No reduction took place when the reducing reagents II, III and IV were used. The reduction of **4** with 1.5 molar amounts of (*R*)-BINAL-H(EtOH) gave the intermediary hydroxylactone (**7**),[5a] which was reduced to **3** in the presence of excess amounts of (*R*)-BINAL-H. The reduction of **4** using 3.0 molar amounts of (*R*)-BINAL-H in tetrahydrofuran (THF) at −78 °C, followed by gradual warming to room temperature and acid treatment, gave the (3a*S*,6a*R*)-lactone **3** (90% ee) in 76% yield. It was enriched to 95% ee by recrystallization from benzene–cyclohexane. This reduction would provide a convenient and practically useful route to (+)-biotin.

We next investigated the reduction of a variety of *meso*-cyclic-1,2-dicarboxylic anhydrides (**1a—k**) under similar conditions. Various anhydrides, upon treatment

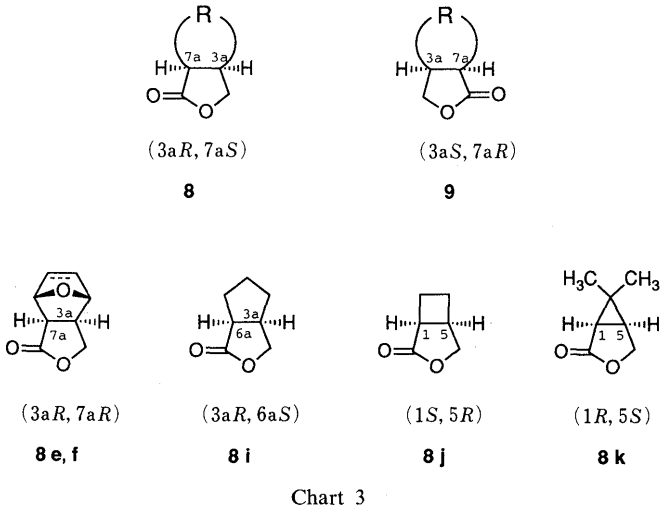


Chart 3

with 3.5—4.6 molar amounts of BINAL-H, gave the corresponding bicyclic lactones (**8**, **9**) in moderate chemical yields with high enantioselectivity (64—99% ee) (Table II). The ee of the lactones (**8**) was determined on the basis of their specific optical rotation in comparison with the known value or by chiral HPLC analysis.

The reduction of **1a—d**, **g—j** was enantiotopically selective for the carbonyl group attached to the chiral center with *R*-configuration. In the cases of **1e**, **f**, **k**, the reduction proceeded in the same manner as for other anhydrides to result in the (3a*R*,7a*R*)-enantiomers **8e**, **f** and (1*R*,5*S*)-enantiomer **8k**, respectively. Increase of

TABLE II. Reduction of the Anhydrides (**1**) with (*R*)-BINAL-H (EtOH)

Entry	Anhydride **1**	Lactone	Yield (%)	ee (%)[a]	$[\alpha]_D^{25}$ (°) (*c*, $CHCl_3$)	Reported $[\alpha]_D^{25}$ (°) (*c*, $CHCl_3$)	Reference
1	**1a**	**8a**	68	80	+38.9 (0.5)	+48.8 (0.5)	19)
2	**1b**	**8b**	52	78	−66.7 (1.0)[b]	−85.4 (2.63)[b]	20)
3	**1c**	**8c**	69	84 (85)[c]	+120.7 (0.5)	+143.2 (5.2)	21)
4	**1d**	**8d**	66	88	+134.5 (1.0)	+153.3 (1.01)	22)
5	**1e**	**8e**	63	99	+153.5 (0.5)	+155.0 (0.5)	23)
6	**1f**	**8f**	72	83	+95.1 (0.5)	+114.2 (16.7)	24)
7	**1g**	**8g**	68	99 (>95)[d]	+92.6 (0.5)	+92.0 (3.9)	21)
8	**1g**[e]	**9g**	72	>95[d]	−86.8 (0.5)		
9	**1h**	**8h**	65	95	+107.1 (0.5)	+113.0 (6.2)	21)
10	**1i**	**8i**	60	83	+80.0 (1.0)	+96.9 (1.0)	19)
11	**1j**	**8j**	61	64	+76.2 (1.0)	+118.7 (10)	19)
12	**1k**	**8k**	62	68	−61.0 (1.4)	−72.8 (1.4)[f]	25)

a) Determined on the basis of $[\alpha]_D$ value in comparison with the reported value. *b*) Measured in acetone at 20 °C. *c*) Determined by chiral HPLC analysis (Chiralcel OB-H). *d*) Determined by ^{1}H-NMR experiments.[21a,b] *e*) (*S*)-BINAL-H was used. *f*) The ee of this lactone was reported to be 81%.

steric bulkiness at the concave face improved the enantioselectivity (entries 3 and 4), while increase of steric bulkiness at the convex face lowered the selectivity (entries 5 and 6). When (*S*)-BINAL-H was used instead of (*R*)-BINAL-H, the (3a*S*,7a*R*)-lactone **9g** was obtained from **1g** in 72% yield.

After conversion[21a] of **9g** with excess methyl lithium (MeLi) into (2*R*,3*S*)-*cis-endo*-3-hydroxymethyl-2-(1-hydroxy-1-methylethyl)bicyclo[2.2.2]oct-5-ene (**23**), the ee of **9g** was determined to be >95% by ^{1}H-NMR experiments in the presence of tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)*d*-camphorato]europium [Eu(tfc)$_3$].[21a,b] The ^{1}H-NMR spectrum of the resulting (2*R*,3*S*)-diol (**23**) showed a singlet at δ 3.03 due to the geminal dimethyl protons, while the corresponding signal (δ 2.95) for the (2*S*,3*R*)-diol (**22**) derived from **8g** was not detectable.

Since the both enantiomers of 1,1′-bi-2-naphthol are commercially available, the bicyclic lactone with the desired configuration can be prepared by use of the appropriate enantiomer of binaphthol.

Enantioselective Reduction of *meso*-Cyclic-1,2-dicarboximides Concerning asymmetric reduction of *meso*-1,2-dicarboximides, Mukaiyama and his colleagues have described diastereoselective reduction of *meso*-imides derived from *R*-(−)-2-amino-2-phenylethanol and *meso*-1,2-dicarboxylic anhydrides.[25] Miller and Chamberlin also reported enantioselective reduction of *meso*-cyclohexylidene-*N*-benzyl tartarimide with chiral reducing reagents to afford up to 56% ee of the corresponding 5-hydroxy-2-pyrrolidinone, and the imide moiety remained intact during $LiAlH_4$–(*R*)-(+)-1,1′-bi-2-naphthol reduction.[3]

We examined the reduction of *meso*-cyclic-1,2-dicarboximides **2** having a 4-methoxyphenyl group as the *N*-substituent. The starting imides (**2a—d, i, k**) were readily prepared from **1** and 4-methoxyaniline according to the known method.[25] The reduction of *cis*-1,2-cyclohexane dicarboximide (**2a**) proceeded enantioselectively when it was carried out using 3.5 molar amounts of (*R*)-BINAL-H(MeOH). The isolated product was, however, a mixture of (3a*R*,7a*S*)-octahydro-3-hydroxy-1*H*-isoindol-1-one **10a** and **11a** (**10a**/**11a** ≒ 9 : 1), whose ratio depended on the conditions of work-up. The configurations of **10a** and **11a**

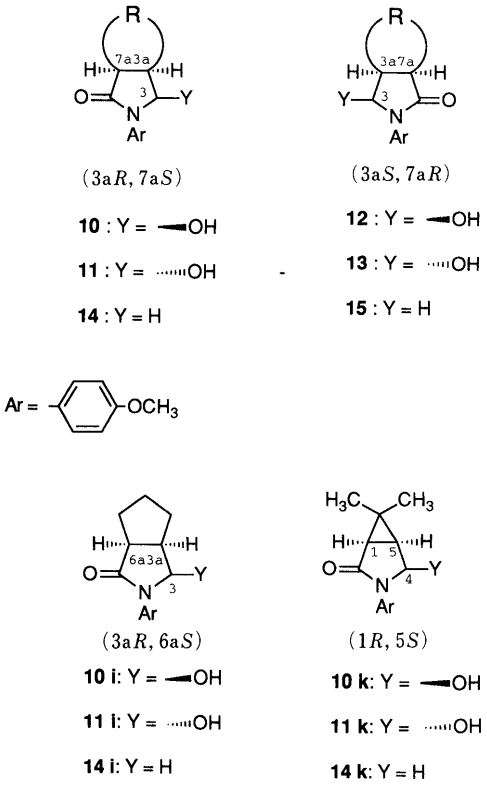


Chart 4

were deduced from the ^{1}H-NMR spectra to be $C_3\beta$-OH(3*R*) and $C_3\alpha$-OH(3*S*), respectively, by comparison with the literature values.[26] When the reduction was quenched with 10% HCl at −78 °C, the $C_3\beta$-hydroxy isomer (**10a**) was isolated as a sole product (85% yield). Acid treatment would lead to epimerization of the product to afford a mixture of **10a** and **11a**. The $C_3\alpha$-hydroxy isomer (**11a**) was obtained in 95% yield on treatment of **10a** with 10% HCl in THF at room temperature for 1 h. To confirm the enantioselectivity of the (*R*)-BINAL-H reduction, both compounds, **10a** and **11a**, were converted into (3a*R*,7a*S*)-octahydro-1*H*-isoindol-1-one (**14a**). Treatment of **10a** with Et_3SiH–CF_3CO_2H in dichloromethane (CH_2Cl_2) gave **14a** in a quantitative yield. The ee was

TABLE III. Reduction of the Dicarboximides **2** with (*R*)- or (*S*)-BINAL-H (MeOH)

Entry	Imide **2**	BINAL-H config.	Hydroxylactam Yield (%)		Lactam[a] ee[b] (%)		Lactone Yield (%)	Lactone $[\alpha]_D^{25}$ (°) (c=1, $CHCl_3$)	Lactone ee (%)
1	**2a**	*R*	**10a**, **11a**[c]	86	**14a**	88	**8a**	78	+45.8	94[d]
2		*S*	**12a**, **13a**[c]	91	**15a**	87	**9a**	82	−43.2	89[d]
3	**2b**	*R*	**10b**, **11b**[c]	79	**14b**	88	**8b**	84	−73.5[e]	86[f]
4		*S*	**12b**, **13b**[c]	77	**15b**	87	**9b**	81	+71.5[e]	84[g]
5	**2c**	*R*	**10c**[h]	86	**14c**	84				
6		*S*	**12c**[h]	91	**15c**	89				
7	**2d**	*R*	**10d**, **11d**[c]	55	**14d**	91				
8	**2i**	*R*	**10i**, **11i**[c]	78	**14i**	85	**8i**	80	+81.7	84[i]
9	**2k**	*R*	**10k**, **11k**[c]	94	**14k**	91	**8k**	86	−82.1	91[j]

a) Obtained in quantitative yields. *b*) Determined by HPLC analysis (Opti Pak XC). *c*) Obtained as a mixture of $C_3\alpha$- and $C_3\beta$-OH isomers. The reduction was quenched at 0 °C. *d*) Based on $[\alpha]_D^{25}$ +48.8° (c=0.5, $CHCl_3$).[19] *e*) Measured in acetone at 20 °C. *f*) Based on $[\alpha]_D^{20}$ −85.4° (c=2.63, acetone).[20] *g*) Based on $[\alpha]_D^{20}$ +85.2° (c=2.64, acetone).[20] *h*) The reduction was quenched at −30 °C. *i*) Based on $[\alpha]_D^{25}$ +96.9° (c=1, $CHCl_3$).[19] *j*) Based on $[\alpha]_D^{25}$ −72.8° (c=1.4, $CHCl_3$), 81% ee.[25]

determined to be 88% by chiral HPLC analysis. In a similar manner, the same isoindol-1-one **14a** was obtained (100%, 89% ee) from the $C_3\alpha$-hydroxy isomer **11a**. The absolute configuration was determined by converting **10a** into the known bicyclic lactone **8a** according to the literature.[25] $NaBH_4$ reduction of **10a** and subsequent acid hydrolysis gave **8a** (94% ee) in 78% yield. Under similar conditions to those used for **8a** and **14a**, the octahydro-3-hydroxy-1*H*-isoindol-1-one (**12a** and **13a**), prepared by reduction with (*S*)-BINAL-H, was converted into the lactone **9a** (89% ee) and the lactam **15a** (87% ee) in high yields, respectively. Similarly, reduction of the dicarboxamides (**2b—d**, **i**, **k**) with (*R*)- or (*S*)-BINAL-H afforded the hydroxylactams (**10—13b—d**, **i**, **k**) with high enantioselectivity (84—91% ee), and these were readily converted into the corresponding chiral lactams (**14b—d**, **i**, **k**, **15b**, **c**) and lactones (**8b**, **i**, **k**, **9b**) in high optical purity. The results are summarized in Table III. Conversion of **10c**, **d** into lactones (**8c**, **d**) was unsuccessful under the above conditions. As regards the absolute configuration of **10c**, **d** and **14c**, **d**, we postulate their configurations to be as shown in Chart 4 based upon the mode of reduction.

The 4-methoxyphenyl group of the chiral lactams (**14a—c**, **15a**, **c**) was easily removed by oxidation with cerium(IV) ammonium nitrate (CAN) (Chart 5).[27,28] Oxidation of **14a** (88% ee) with 3 molar amounts of CAN in aqueous acetonitrile (CH_3CN) gave **16a** (88% ee) in 80% yield. Similarly, removal of the 4-methoxyphenyl group of **14b** (88% ee), **14c** (89% ee), **15a** (87% ee), and **15c** (84% ee) readily proceeded at 10 °C to afford the corresponding *N*-unsubstituted lactams [**16b** (91% ee), **16c** (89% ee), **17a** (86% ee), and **17c** (88% ee)] in 79%, 85%, 88% and 81% yields, respectively without significant loss of optical purity.

The mechanism proposed by Noyori *et al.*,[7a] can be applied to the chiral recognition mechanism. The reduction would proceed through the preferential attack of (*R*)-BINAL-H on the carbonyl group attached to the *R*-center of the dicarboximide (**2**) from the convex face[26b] to afford the $C_3\beta$-hydroxy lactam (**10**). The transition state A would be more favorable owing to the n/π^* attractive

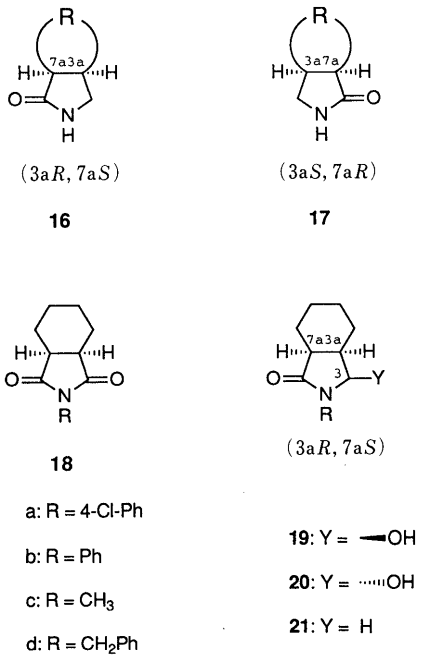


Chart 5

orbital interaction between the oxygene non-bonding orbital and the LUMO of the imide moiety, as compared with the transition state B (Fig. 1).

The results obtained by the (*R*)-BINAL-H reduction of dicarboximides (**18**) bearing various *N*-substituents are suggestive for this consideration. *N*-Aryl substitution of **18** was beneficial for the reduction, enhancing the formation of the (3a*R*,7a*S*)-enantiomer (**19**), while *N*-alkyl substitution decreased the enantioselectivity of the reduction products (**19**) (Table IV). The effectiveness of *N*-substituents for increasing the enantioselectivity of **19** was approximately in the order 4-chlorophenyl > phenyl > 4-methoxyphenyl > methyl > benzyl. Because of this observation, molecular orbital calculation by the Austin Model 1 (AM 1) method[29] of the stable conformation and the LUMO [or next lowest unoccupied orbital (NLUMO)[30]] of **2a** and **18** was carried out. The most stable conformation of **18** (R=H) was found to be the

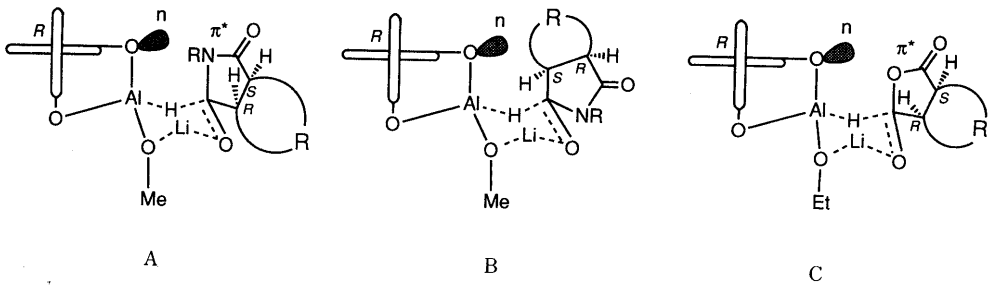


Fig. 1

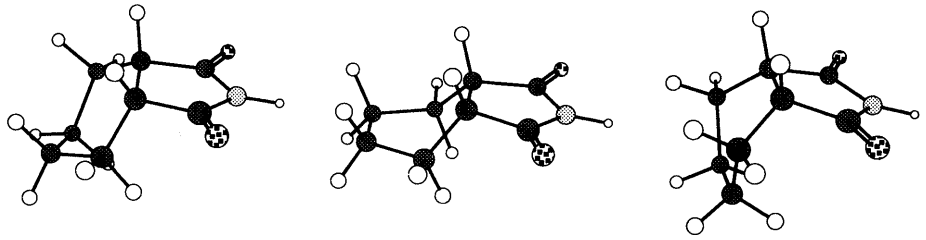


Fig. 2. The Stable Conformers of the Imide **18** (R = H)

TABLE IV. Reduction of *meso*-Imide (**18**) with (*R*)-BINAL-H (MeOH)

Entry	Imide	R	Hydroxylactam		Lactone (**8a**)			Lactam		
				Yield (%)	Yield (%)	ee (%)[a]	$[\alpha]_D^{25}$ (°)[b]		Yield (%)	ee (%)[c]
1	**18a**	4-Cl–Ph	**19a**	92	76	93	+45.2	**21a**	100	96
2	**18b**	Ph	**19b**	93	76	93	+45.3	**21b**	100	93
3	**2a**	4-MeO–Ph	**10a**	86	78	94	+45.8	**14a**	100	88
4	**18c**	CH_3	**19c**, **20c**[d]	89	76	77	+37.7		—	—
5	**18d**	CH_2Ph	**19d**, **20d**[d]	90	80	56	+27.5		—	—

a) Determined on the basis of $[\alpha]_D^{25}$ value in comparison with the reported value $[\alpha]_D^{25}$ +48.8° (c = 0.5, $CHCl_3$).[19] *b*) (c = 0.5, $CHCl_3$). *c*) Determined by chiral HPLC analysis (Opti Pak XC). *d*) Obtained as a mixture of $C_3\alpha$- and $C_3\beta$-OH isomers.

extended-boat form (Fig. 2) from the calculation of the heat of formation energy for its conformers. The results obtained by the AM 1 calculation of the stable conformation (extended-boat form) of **2a** and **18a—d** are shown in Table V. *N*-Aryl substituents would participate in the above-mentioned n/π* orbital interaction, lowering the NLUMO energy levels, compared with *N*-alkyl substituents. The substituent effect for lowering the LUMO (NLUMO) energy levels of imides was in the order 4-chlorophenyl > phenyl > 4-methoxyphenyl > methyl > benzyl. The order, thus obtained by calculation, is in accord with that of the enantioselectivity in the (*R*)-BINAL-H reduction of the dicarboximides (**2a**, **18a—d**).

The reduction of *meso*-1,2-dicarboxylic anhydride (**1**) with (*R*)-BINAL-H would proceed through the transition state C (Fig. 1) to give the chiral γ-hydroxylactone intermediate in the first stage and then lead to the hydroxycarboxylate or lactone (**8**) by further reduction with excess of the reducing reagent at the second stage.

The hydroxylactams (**10—13**) provided by enantioselective reduction of **2** are useful precursors for the preparation of nitrogen-containing compounds based on the *N*-acyliminocyclization strategy.[31] The chiral lactones (**8**, **9**)

TABLE V. The LUMO (NLUMO) Energy Level of the Imides (**2a**, **18**)

R	Imide	Energy (eV)	
		LUMO	NLUMO
4-Cl–Ph	**18a**		0.23143
Ph	**18b**		0.35422
4-MeO–Ph	**2a**		0.36939
Me	**18c**	0.44425	
$PhCH_2$	**18d**		0.47084

are also important as versatile intermediates for synthesis of biologically active compounds or natural products. In practice, (3a*R*,7a*S*)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (**8c**) can be utilized as a building block for syntheses of prostanoids, prostaglandin, boschnialactone, and a potent thromboxane A_2/prostaglandin H_2 receptor antagonist.[21a,32] The chiral lactones (**8b**, **k**, **9a**) are also important precursors for syntheses of brefeldin A, carbaprostacyclin, chrysanthemic acid, and trandolapril.[25,33]

Thus, the asymmetric syntheses of bicyclic lactones (**8**, **9**) and bicyclic hydroxylactams (**10—13**) were ac-

complished by the reduction of prochiral *meso*-cyclic-1,2-dicarboxylic anhydrides (**1**) and 1,2-dicarboximides (**2**) with (*R*)- or (*S*)-BINAL-H. The reduction appears to provide a practical method for the preparation of optically active lactones and hydroxylactams which can serve as versatile building blocks for synthesis of natural products or their mimics.

Experimental

All melting points were taken in open capillary tubes on a melting point apparatus (Büchi 535) without correction. Infrared (IR) spectra were taken with an Analect RFX-65 spectrometer. ^{1}H-NMR spectra were measured with a Gemini 300 (Varian, 300 MHz), a JNM FX-200 (JEOL, 200 MHz) or a JNM GSX-400 (JEOL, 400 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. The mass spectra (MS), chemical ionization mass spectra (CI-MS), and FAB-MS were obtained with an INCOS 50 (Finnigan MAT Inc.) or a JMS HX-100 (JEOL) spectrometer. Optical rotations were measured on a Horiba SEPA-200 digital polarimeter. Chiral high-performance liquid chromatographic (HPLC) analysis was done with a Hitachi 638-30 (ultraviolet detection). Elemental analyses were obtained by using a Perkin-Elmer 2400, a Yanagimoto MT-3 or a YEW ion-chromato IC-7000. The (*R*)-(+)- and (*S*)-(−)-1,1′-bi-2-naphthols [>99% ee (HPLC)] were purchased from Environmental Research Center Co., Ltd. (*R*)- and (*S*)-BINAL-H(ROH) were prepared from $LiAlH_4$, EtOH or MeOH, and (*R*)- or (*S*)-1,1′-bi-2-naphthol (1 : 1 : 1 mol ratio) in THF according to Noyori's method.[7] The anhydrides **1a**—**c**, **e** and **1g** were commercial products, and **1d**, **f**, **h**—**k** and **4**[6,34-39] were prepared according to the literature. The imides **2b**—**d**, **18a**—**c** and **d**[26,40-44] were also prepared according to the literature. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

Reduction of *cis*-1,3-Dibenzyl-1*H*-furo[3,4-*d*]imidazole-2,4,6(3*H*,3a*H*,6a*H*)-trione (4) Reduction with (*R*)-BINAL-H (EtOH): A solution of **4** (390 mg, 1.1 mmol) in THF (40 ml) was added dropwise to a suspension of (*R*)-BINAL-H (EtOH) (3.5 mmol) in THF (25 ml) at −78 °C. The mixture was stirred for 5 h at −78 °C, then gradually warmed to room temperature. A 10% HCl solution was added under ice-cooling, and the whole was concentrated *in vacuo*. The residue was taken up into ethyl acetate (AcOEt), washed with brine, and the solution was dried and concentrated to give a mixture of (*R*)-binaphthol and lactone, which was separated by column chromatography on silica gel (×30). Elution with hexane–AcOEt (4 : 1) gave 950 mg (95% recovery) of (*R*)-binaphthol. Further elution with hexane–AcOEt (7 : 3) gave 284 mg (76%) of (3a*S*,6a*R*)-1,3-dibenzyldihydro-1*H*-furo[3,4-*d*]imidazole-2,4(3*H*,3a*H*)-dione (**3**) as colorless crystals, mp 116—118 °C (lit.[5a] mp 120—121 °C), $[\alpha]_D^{25}$ +52.2° (*c*=1.0, benzene). Recrystallization from benzene–cyclohexane afforded 223 mg (60%, 95% ee) of **3**, mp 118—119 °C, $[\alpha]_D^{25}$ +55.0 °C (*c*=1.0, benzene).

Reduction with the Reducing Reagent XV: A solution of 1.20 g (5.5 mmol) of (2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol in ether (20 ml) was added dropwise to a solution of 1 M $LiAlH_4$–ether solution (5.5 ml) in ether (30 ml) at 0 °C.[18] To this mixture, a solution of **4** (300 mg, 0.89 mmol) in THF (30 ml) was added at −78 °C. The reaction mixture was stirred for 5 h at −78 °C and gradually warmed to room temperature. A 10% HCl solution was added under ice-cooling, and the whole was extracted with AcOEt (300 ml). The extract was washed with brine, dried and concentrated. The residue was purified by short-column chromatography on silica gel (×10). Elution with $CHCl_3$ gave 176 mg (61%, 39% ee) of **3**, mp 105—107 °C, $[\alpha]_D^{25}$ +22.8° (*c*=1.0, benzene).

Reduction of 1 with (*R*)-(+)- or (*S*)-(−)-BINAL-H (EtOH) The general procedure is exemplified by reduction of **1c** with (*R*)-BINAL-H (EtOH). Reductions of **1a**, **b**, **i**—**k** were carried out at −78 °C for 18 h followed by gradual warming to 0 °C. The lactones **8a**, **b**, **i**—**k** were isolated by Kugelrohr distillation, after removal of binaphthol by recrystallization. The ee of **8** and **9** was determined on the basis of the $[\alpha]_D$ value in comparison with the reported value. Yields and optical purities of **8** and **9** are given in Table II. Melting points or boiling points, and spectral data for **8a**—**b**, **d**—**k** were consistent with those of authentic samples.[19-21a,24]

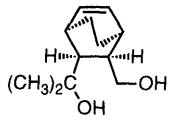
(3a*R*,4*S*,7*R*,7a*S*)-3a,4,7,7a-Tetrahydro-4,7-methanoisobenzofuran-1(3*H*)-one (**8c**): A solution of 250 mg (1.5 mmol) of *cis-endo*-3,6-methano-4-cyclohexene-1,2-dicarboxylic anhydride (**1c**) in THF (20 ml) was added dropwise to a suspension of (*R*)-BINAL-H (EtOH) (7.0 mmol) in THF (35 ml) at −78 °C. The mixture was stirred for 5 h at −78 °C and gradually warmed to room temperature, then a 10% HCl solution was added under ice-cooling. The whole was extracted with AcOEt (450 ml). The organic layer was washed with brine, dried and concentrated to give a mixture of (*R*)-binaphthol and lactone which was separated by column chromatography on aluminium oxide (×30). Elution with $CHCl_3$–hexane (2 : 3) gave 157 mg (69%) of **8c** as colorless crystals, mp 119—121 °C (lit.[21a] 120—122 °C). Further elution with $CHCl_3$ gave 1.96 g (98% recovery) of (*R*)-binaphthol. Chiral HPLC analysis was carried out under the following conditions: column, Chiralcel OB-H; eluent, hexane–EtOH (250 : 1) at 1.0 ml/min; t_R, **8c** (37.6 min), **9c** (45.3 min).

(3a*S*,4*R*,7*S*,7a*R*)-3a,4,7,7a-Tetrahydro-4,7-ethanoisobenzofuran-1(3*H*)-one (**9g**): Reduction of **1g** (270 mg, 1.5 mmol) with (*S*)-BINAL-H (EtOH) (7.0 mmol) gave 180 mg of **9g** as colorless crystals, mp 90—91 °C. Spectral data of **9g** were consistent with those of **8g**. *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.85; H, 7.33.

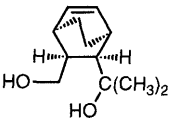
(2*S*,3*R*)-*cis-endo*-3-Hydroxymethyl-2-(1-hydroxy-1-methylethyl)-bicyclo[2.2.2]oct-5-ene (22) For ^{1}H-NMR experiments using Eu(tfc)$_3$ (0.4 eq), the (2*S*,3*R*)-diol (**22**) was prepared from **8g** according to the literature.[21a,b] ^{1}H-NMR ($CDCl_3$–Eu(tfc)$_3$) δ: 1.6—1.9 (2H, m), 2.1—2.35 (2H, m), 2.43 (3H, s, *gem* CH_3), 2.95 (3H, s, *gem* CH_3), 3.43 (1H, s), 3.69 (1H, s), 3.97 (1H, br s), 5.83 (1H, br s), 6.90—7.15 (2H, m), 7.20—7.75 (1H, m), 8.4 (1H, br s).

(2*R*,3*S*)-*cis-endo*-3-Hydroxymethyl-2-(1-hydroxy-1-methylethyl)-bicyclo[2.2.2]oct-5-ene (23) A 1.0 M MeLi solution in ether (1.3 ml) was added to a solution of **9g** (72 mg, 0.44 mmol) in THF (2 ml) at −78 °C. The mixture was stirred for 30 min at −78 °C and gradually warmed to room temperature, then a solution of acetic acid (75 mg, 1.3 mmol) in water (10 ml) was added under ice-cooling. The whole was extracted with ether (30 ml). The extract was washed with brine and dried. Removal of the solvent gave 85 mg (99%) of the (2*R*,3*S*)-diol (**23**) as colorless crystals, mp 95—96 °C, $[\alpha]_D^{25}$ +34.4° (*c*=0.5, $CHCl_3$). IR (Nujol): 3200 cm^{-1}. CI-MS *m/z*: 197 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.33 (3H, s), 1.1—1.4 (2H, m), 1.5—1.6 (2H, m), 2.07 (1H, d, *J*=9 Hz), 2.3—2.6 (3H, m), 3.56 (1H, dd, *J*=3.5, 11.5 Hz), 3.80 (1H, dd, *J*=10, 11.5 Hz), 4.40 (2H, br s), 6.14 (1H, t, *J*=7 Hz), 6.25 (1H, t, *J*=7 Hz). *Anal.* Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.37; H, 10.39.

No geminal methyl proton signal of **22** was detectable in ^{1}H-NMR-Eu(tfc)$_3$ experiments on **23**. ^{1}H-NMR [$CDCl_3$-Eu(tfc)$_3$] δ: 1.6—1.9 (2H, m), 2.1—2.35 (2H, m), 2.43 (3H, s, *gem* CH_3), 3.03 (3H, s, *gem* CH_3), 3.48 (1H, s), 3.76 (1H, s), 4.07 (1H, br s), 6.20 (1H, br s), 6.90—7.15 (2H, m), 7.20—7.75 (1H, m), 8.8 (1H, br s).



22



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***N*-(4-Methoxyphenyl)-*cis*-cyclohexane-1,2-dicarboximide (2a)** A solution of the imide **2b** (5.00 g, 19 mmol) in AcOEt (50 ml) and THF (50 ml) was hydrogenated over 10% Pd–C (0.10 g) at room temperature for 1 h under atmospheric pressure of hydrogen. Removal of the catalyst and evaporation of the solvent, followed by recrystallization from AcOEt, gave 4.83 g (96%) of **2a** as colorless needles, mp 161.5—162.5 °C. IR (Nujol): 1710 cm^{-1}. MS *m/z*: 259 (M^+, 100), 149. ^{1}H-NMR (DMSO-d_6) δ: 1.3—1.5 (4H, m), 1.6—1.9 (4H, m), 3.08 (2H, m), 3.79 (3H, s), 6.95—7.05 (2H, m), 7.10—7.20 (2H, m). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.43; H, 6.54; N, 5.36.

***N*-(4-Methoxyphenyl)-*cis*-cyclopentane-1,2-dicarboximide (2i)** A solution of **1i** (1.50 g, 11 mmol) in THF (10 ml) was added to a solution of 4-methoxyaniline (1.32 g, 11 mmol) in THF (10 ml) at 10 °C. The mixture was stirred for 3 h at room temperature, and then concentrated. Acetic anhydride (Ac_2O) (10 ml) and sodium acetate (NaOAc) (85 mg) were added to the residue, and the mixture was stirred for 3 h at 100 °C. After removal of Ac_2O *in vacuo*, water was added to the residue. The whole was extracted with AcOEt. The organic layer was washed with 10% HCl and saturated $NaHCO_3$ solution, and dried. Removal of the solvent followed by recrystallization from AcOEt–hexane gave 1.78 g (68%) of **2i** as colorless needles, mp 129—130 °C. IR (Nujol): 1710 cm^{-1}. MS *m/z*: 245 (M^+, 100), 149. ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.4 (6H, m),

3.2—3.4 (2H, m), 3.82 (3H, s), 6.9—7.3 (4H, m). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.53; H, 6.14; N, 5.68.

***N*-(4-Methoxyphenyl)-*cis*-2,2-dimethylcyclopropane-1,3-dicarboximide (2k)** A mixture of **1k** (1.00 g, 7.2 mmol) and 4-methoxyaniline (0.90 g, 7.2 mmol) in THF (15 ml) was stirred for 3 h at room temperature, and then concentrated. Ac_2O (7 ml) and NaOAc (60 mg) were added to the residue, and the mixture was stirred for 3 h at 100 °C. After removal of Ac_2O *in vacuo*, water was added to the residue and the mixture was worked up in the usual way. Recrystallization from AcOEt–hexane gave 1.35 g (77%) of **2k** as colorless prisms, mp 147.0—148.5 °C. IR (Nujol): 1720, 1710 cm^{-1}. MS *m/z*: 245 (M^+, 100), 149. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, s), 1.41 (3H, s), 2.47 (2H, s), 3.81 (3H, s), 6.9—7.2 (4H, m). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.61; H, 6.16; N, 5.66.

Reduction of 2 with (*R*)- or (*S*)-BINAL-H(MeOH) The general procedure is examplified by reduction of **2a** with (*R*)-BINAL-H. Reductions of **2c—k** were carried out at −78 °C for 20 h followed by gradual warming to −30 °C. Reduction of **2c** was halted by adding 10% HCl solution at −30 °C. (*R*)-BINAL-H reduction gave a mixture of **10** and **11**, which was easily epimerized to **11** on treatment with 10% HCl solution in THF. (*S*)-BINAL-H reduction afforded a mixture of **12** and **13**, epimerizing to **13** under similar conditions. Yields are given in Table III.

(3*R*,3a*R*,7a*S*)-Octahydro-3-hydroxy-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**10a**): A solution of **2a** (520 mg, 2.0 mmol) in THF (50 ml) was added dropwise to a suspension of (*R*)-BINAL-H(MeOH) (7.0 mmol) in THF (35 ml) at −78 °C. The mixture was stirred for 20 h at −78 °C, then the reaction was quenched by the addition of 10% HCl solution at 0 °C, and the whole was extracted with AcOEt (200 ml × 3). The extract was washed with saturated $NaHCO_3$ solution and brine, dried and concentrated to give a mixture of **10a**, **11a**, and (*R*)-binaphthol, which was separated by column chromatography on silica gel (× 30). Elution with $CHCl_3$ gave 1.92 g (96% recovery) of (*R*)-binaphthol. Further elution with $CHCl_3$–MeOH (49 : 1) gave 449 mg (86%) of a mixture of **10a** and **11a** (≒9 : 1) as a colorless solid.

When the reduction was quenched by adding 10% HCl solution at −78 °C and the mixture was carefully worked up, **10a** was isolated as a sole product. **10a**: yield 85%, colorless crystals, mp 139—140 °C, $[\alpha]_D^{25}$ −15.6° (*c* = 0.5, $CHCl_3$). IR (Nujol): 3260, 1660 cm^{-1}. MS *m/z*: 261 (M^+), 149, 123 (100). ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.1 (8H, m), 2.4—2.7 (2H, m), 2.63 (1H, d, *J* = 7.0 Hz, C_3-OH), 3.80 (3H, s), 5.50 (1H, dd, *J* = 5.5, 7.0 Hz, C_3-H), 6.8—7.0 (2H, m), 7.2—7.4 (2H, m). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.07; H, 7.19; N, 5.27.

(3*S*,3a*R*,7a*S*)-Octahydro-3-hydroxy-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**11a**): A 10% HCl solution (1 ml) was added to a solution of **10a** (60 mg, 0.23 mmol) in THF (10 ml) at room temperature. The mixture was stirred for 1 h at room temperature, then diluted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution and brine, then dried and concentrated *in vacuo* to afford 59 mg (98%) of **11a** as colorless crystals, mp 124—126 °C, $[\alpha]_D^{25}$ +27.7° (*c* = 0.5, $CHCl_3$). IR (Nujol): 3320, 1670 cm^{-1}. MS *m/z*: 261 (M^+), 149, 123 (100). ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.4 (8H, m), 2.1—3.1 (2H, m), 3.15 (1H, d, *J* = 6.3 Hz, C_3-OH), 3.80 (3H, s), 5.02 (1H, dd, *J* = < 1, 6.3 Hz, C_3-H), 6.8—7.0 (2H, m), 7.2—7.4 (2H, m). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.09; H, 7.29; N, 5.27.

(3*R* and 3*S*,3a*S*,7a*R*)-Octahydro-3-hydroxy-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**12a** and **13a**): Reduction of **2a** (500 mg, 1.9 mmol) with (*S*)-BINAL-H(MeOH) (7.0 mmol) gave 456 mg (91%) of a mixture of **12a** and **13a** (≒10 : 1) as a colorless solid. The ratio of isomers was determined from ^{1}H-NMR spectrum. IR (Nujol): 3300, 1670, 1660 cm^{-1}. MS *m/z*: 261 (M^+), 149, 123 (100). ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.4 (8H, m), 2.1—3.1 (2H, m), 2.63 (0.9H, d, *J* = 7.0 Hz, C_3-OH), 3.15 (0.1H, d, *J* = 6.3 Hz, C_3-OH), 3.80 (3H, s), 5.02 (0.1H, dd, *J* = < 1, 6.3 Hz, C_3-H), 5.50 (0.9H, dd, *J* = 5.5, 7.0 Hz, C_3-H), 6.8—7.0 (2H, m), 7.2—7.4 (2H, m).

(3*S*,3a*R*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-3-hydroxy-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**11b**): Reduction of **2b** (450 mg, 1.7 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave 357 mg (79%) of a mixture of **10b** and **11b** (≒10 : 1) as a colorless solid. Treatment of the mixture (100 mg, 0.39 mmol) with 10% HCl solution (1 ml) in THF (10 ml) gave 97 mg (97%) of **11b** as colorless crystals, mp 140—142 °C, $[\alpha]_D^{25}$ −20.0° (*c* = 0.5, $CHCl_3$). IR (Nujol): 3300, 1670 cm^{-1}. MS *m/z*: 259 (M^+, 100). ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.0 (1H, m), 2.2—2.9 (4H, m), 3.0—3.2 (1H, m), 3.05 (1H, d, *J* = 5.8 Hz, C_3-OH), 3.80 (3H, s), 5.09 (1H, dd, *J* = 1.2, 5.8 Hz, C_3-H), 5.6—6.0 (2H, m), 6.8—7.0 (2H, m), 7.3—7.5 (2H, m). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.61; H, 6.53; N, 5.32.

(3*R* and 3*S*,3a*S*,7a*R*)-2,3,3a,4,7,7a-Hexahydro-3-hydroxy-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**12b** and **13b**): Reduction of **2b** (450 mg, 1.7 mmol) with (*S*)-BINAL-H(MeOH) (7.0 mmol) gave 349 mg (77%) of a mixture of **12b** and **13b** (≒10 : 1) as a colorless solid. IR (Nujol): 3400, 1670, 1660 cm^{-1}. MS *m/z*: 259 (M^+, 100). ^{1}H-NMR ($CDCl_3$) δ: 1.8—3.20 (6H, m), 2.78 (0.9H, d, *J* = 8.4 Hz, C_3-OH), 3.07 (0.1H, d, *J* = 5.9 Hz, C_3-OH), 3.80 (3H, s), 5.09 (0.1H, dd, *J* = 1.2, 5.9 Hz, C_3-H), 5.43 (0.9H, dd, *J* = 5.7, 8.4 Hz, C_3-H), 5.6—6.0 (2H, m), 6.8—7.0 (2H, m), 7.3—7.5 (2H, m).

(3*R*,3a*R*,4*R*,7*S*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-3-hydroxy-4,7-methano-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**10c**): Reduction of **2c** (500 mg, 1.9 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave 435 mg (86%) of **10c** as colorless crystals, mp 139—140 °C, $[\alpha]_D^{25}$ +118.3° (*c* = 0.5, MeOH). IR (Nujol): 3260, 1640 cm^{-1}. CI-MS *m/z*: 272 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.7 (2H, m), 2.39 (1H, d, *J* = 7.6 Hz, C_3-OH), 3.1—3.5 (4H, m), 3.79 (3H, s), 5.56 (1H, dd, *J* = 7.4, 7.6 Hz, C_3-H), 6.2—6.35 (2H, m), 6.8—7.0 (2H, m), 7.3—7.5 (2H, m). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.43; H, 6.31; N, 4.98.

(3*S*,3a*S*,4*S*,7*R*,7a*R*)-2,3,3a,4,7,7a-Hexahydro-3-hydroxy-4,7-methano-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**12c**): Reduction of **2c** (500 mg, 1.9 mmol) with (*S*)-BINAL-H(MeOH) (7.0 mmol) gave 458 mg (91%) of **12c** as colorless crystals, mp 138.5—140 °C, $[\alpha]_D^{25}$ −118.8° (*c* = 0.5, MeOH). Spectral data of **12c** were consistent with those of **10c**. *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.57; H, 6.30; N, 5.01.

(3*S*,3a*R*,4*S*,7*R*,7a*S*)-Octahydro-3-hydroxy-4,7-methano-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**11d**): Reduction of **2d** (500 mg, 1.8 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave 277 mg (55%) of a mixture of **10d** and **11d** (≒10 : 1) as a colorless solid. Treatment of the mixture (100 mg, 0.37 mmol) with 10% HCl solution (1 ml) in THF (10 ml) gave 95 mg (95%) of **11d** as colorless crystals, mp 246—247 °C, $[\alpha]_D^{25}$ +116.8° (*c* = 0.25, MeOH). IR (Nujol): 3260, 1640 cm^{-1}. MS *m/z*: 273 (M^+, 100). ^{1}H-NMR ($CDCl_3$) δ: 1.2—1.7 (6H, m), 2.4—2.75 (3H, m), 3.00 (1H, dd, *J* = 5.5, 10.3 Hz), 3.32 (1H, d, *J* = 7.3 Hz, C_3-OH), 3.80 (3H, s), 5.23 (1H, dd, *J* = < 1, 7.3 Hz, C_3-H), 6.8—7.0 (2H, m), 7.3—7.5 (2H, m). *Anal.* Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.01; H, 7.00; N, 4.91.

(3*S*,3a*R*,6a*S*)-Hexahydro-3-hydroxycyclopenta[*c*]pyrrol-1(2*H*)-one (**11i**): Reduction of **2i** (450 mg, 1.8 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave 354 mg (78%) of a mixture of **10i** and **11i** (≒10 : 1) as a colorless solid. Treatment of the mixture (100 mg, 0.40 mmol) with 10% HCl solution (1 ml) in THF (10 ml) gave 96 mg (96%) of **11i** as colorless crystals, mp 128—130 °C, $[\alpha]_D^{25}$ +49.6° (*c* = 0.25, $CHCl_3$). IR (Nujol): 3200, 1650 cm^{-1}. MS *m/z*: 247 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.3 (6H, m), 2.5—3.3 (2H, m), 3.14 (1H, d, *J* = 6.3 Hz, C_3-OH), 3.80 (3H, s), 5.14 (1H, dd, *J* = < 1, 6.3 Hz, C_3-H), 6.8—7.0 (2H, m), 7.3—7.5 (2H, m). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.28; H, 6.74; N, 5.51.

(1*R*,4*S*,5*S*)-6,6-Dimethyl-4-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[3.1.0]hexan-2-one (**11k**): Reduction of **2k** (470 mg, 1.9 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave 445 mg (94%) of a mixture of **10k** and **11k** (≒4 : 1) as a colorless solid. Treatment of the mixture (100 mg, 0.39 mmol) with 10% HCl solution (1 ml) in THF (10 ml) gave 98 mg (98%) of **12k** as colorless crystals, mp 97—98 °C, $[\alpha]_D^{25}$ +59.3° (*c* = 0.3, $CHCl_3$). IR (Nujol): 3200, 1650 cm^{-1}. MS *m/z*: 247 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, s), 1.16 (3H, s), 1.78 (1H, d, *J* = 6 Hz), 1.99 (1H, dd, *J* = 1.7, 6.0 Hz), 3.66 (1H, d, *J* = 10 Hz, C_4-OH), 3.78 (3H, s), 5.07 (1H, dd, *J* = 1.7, 10 Hz, C_4-H), 6.7—6.8 (2H, m), 7.3—7.5 (2H, m). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.25; H, 6.97; N, 5.44.

Conversion of Hydroxylactam (10—13) into Lactam (14, 15) The general procedure is exemplified by conversion of **10a** into **14a**. Yields and optical purities of **14** and **15** are given in Table III. Chiral HPLC analysis was carried out under the following conditions: column, Opti Pak XC; eluent, hexane–2-propanol (80 : 20), 1.0 ml/min.

(3a*R*,7a*S*)-Octahydro-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**14a**): A solution of Et_3SiH (0.25 ml) and CF_3CO_2H (0.25 ml) in CH_2Cl_2 (0.5 ml) was added to a solution of **10a** (150 mg, 0.54 mmol) in CH_2Cl_2 (5 ml) at room temperature. The mixture was stirred for 1 h at room

temperature, then poured into ice-water, and the organic layer was washed with saturated $NaHCO_3$ solution and brine, dried and concentrated to give 146 mg (100%) of **14a** as colorless crystals, mp 77—78 °C, $[\alpha]_D^{25}$ −3.2° (c=0.5, $CHCl_3$). IR (Nujol): 1690 cm^{-1}. MS m/z: 245 (M^+, 100). ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.2 (8H, m), 2.36—2.50 (1H, m), 2.62—2.70 (1H, m), 3.33 (1H, dd, J=2.3, 9.5 Hz), 3.80 (3H, s), 3.81 (1H, dd, J=5.8, 9.5 Hz), 6.8—7.0 (2H, m), 7.4—7.6 (2H, m). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.68; H, 7.79; N, 5.69. Chiral HPLC: t_R, **14a** (7.2 min), **15a** (10.8 min).

(3a*S*,7a*R*)-Octahydro-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**15a**): Treatment of the mixture (110 mg, 0.42 mmol) of **12a** and **13a** with Et_3SiH–CF_3CO_2H gave 103 mg of **15a** as colorless crystals, mp 77—78 °C, $[\alpha]_D^{25}$ +4.4° (c=0.5, $CHCl_3$). Spectral data of **15a** were consistent with those of **14a**. *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.59; H, 7.76; N, 5.51.

(3a*R*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**14b**): Treatment of the mixture (110 mg, 0.42 mmol) of **10b** and **11b** with Et_3SiH–CF_3CO_2H gave 103 mg of **14b** as colorless crystals, mp 98—100 °C, $[\alpha]_D^{25}$ −38.9° (c=0.5, $CHCl_3$). IR (Nujol): 1685 cm^{-1}. MS m/z: 243 (M^+, 100). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.65 (5H, m), 2.83 (1H, ddd, J=3.0, 8.0, 8.0 Hz), 3.39 (1H, dd, J=3.0, 9.4 Hz), 3.80 (3H, s), 3.92 (1H, dd, J=5.9, 9.4 Hz), 5.65—5.85 (2H, m), 6.8—7.0 (2H, m), 7.8—8.0 (2H, m). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.90; H, 7.02; N, 5.70. Chiral HPLC: t_R, **14b** (8.4 min), **15b** (14.1 min).

(3a*S*,7a*R*)-2,3,3a,4,7,7a-Hexahydro-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**15b**): Treatment of the mixture (100 mg, 0.39 mmol) of **12b** and **13b** with Et_3SiH–CF_3CO_2H gave 97 mg of **15b** as colorless crystals, mp 98—100 °C, $[\alpha]_D^{25}$ +40.4° (c=0.5, $CHCl_3$). Spectral data of **15b** were consistent with those of **14b**. *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.12; H, 7.00; N, 5.58.

(3a*R*,4*R*,7*S*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-4,7-methano-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**14c**): Treatment of 100 mg (0.37 mmol) of **10c** with Et_3SiH–CF_3CO_2H gave 94 mg of **14c** as colorless crystals, mp 90—92 °C, $[\alpha]_D^{25}$ +140.6° (c=0.5, $CHCl_3$). IR (Nujol): 1680 cm^{-1}. CI-MS m/z: 256 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.44 (1H, br d, J=8.4 Hz), 1.62 (1H, dd, J=1.4, 8.4 Hz), 2.8—3.0 (1H, m), 3.05—3.15 (1H, m), 3.19 (1H, dd, J=3, 10 Hz), 3.27 (1H, dd, J=4.5, 9.5 Hz), 3.35—3.45 (1H, m), 3.78 (3H, s), 3.83 (1H, dd, J=9.5, 10 Hz), 6.19 (1H, dd, J=3, 5.8 Hz), 6.31 (1H, dd, J=3, 5.8 Hz), 6.8—7.5 (4H, m). *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.27; H, 6.71; N, 5.40. Chiral HPLC: t_R, **14c** (8.7 min), **15c** (12.1 min).

(3a*S*,4*S*,7*R*,7a*R*)-2,3,3a,4,7,7a-Hexahydro-4,7-methano-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**15c**): Treatment of 100 mg (0.37 mmol) of **12c** with Et_3SiH–CF_3CO_2H gave 95 mg of **15c** as colorless crystals, mp 88—90 °C, $[\alpha]_D^{25}$ −131.2° (c=0.5, $CHCl_3$). Spectral data of **15c** were consistent with those of **14c**. *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.25; H, 6.69; N, 5.42.

(3a*R*,4*S*,7*R*,7a*S*)-Octahydro-4,7-methano-2-(4-methoxyphenyl)-1*H*-isoindol-1-one (**14d**): Treatment of the mixture (100 mg, 0.37 mmol) of **10d** and **11d** with Et_3SiH–CF_3CO_2H gave 95 mg of **14d** as colorless crystals, mp 129—131 °C, $[\alpha]_D^{25}$ +111.6° (c=0.5, $CHCl_3$). IR (Nujol): 1680 cm^{-1}. CI-MS m/z: 258 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.65 (6H, m), 2.3—2.8 (3H, m), 2.99 (1H, dd, J=5.6, 10.3 Hz), 3.57 (1H, dd, J=2.2, 10.3 Hz), 3.80 (3H, s), 3.87 (1H, dd, J=9.2, 10.3 Hz), 6.8—7.6 (4H, m). *Anal.* Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.47; H, 7.36; N, 5.26. Chiral HPLC: t_R, **14d** (8.3 min), **15d** (12.8 min).

(3a*R*,6a*S*)-Hexahydrocyclopenta[*c*]pyrrol-1(2*H*)-one (**14i**): Treatment of the mixture (100 mg, 0.40 mmol) of **10i** and **11i** with Et_3SiH–CF_3CO_2H gave 93 mg of **14i** as colorless crystals, mp 79—81 °C, $[\alpha]_D^{25}$ +42.0° (c=0.5, $CHCl_3$). IR (Nujol): 1670 cm^{-1}. MS m/z: 231 (M^+, 100). ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.20 (6H, m), 2.80 (1H, m), 3.08 (1H, ddd, J=2.8, 9.2, 9.2 Hz), 3.43 (1H, dd, J=3.0, 9.9 Hz), 3.80 (3H, s), 4.04 (1H, dd, J=8.5, 9.9 Hz), 6.8—7.5 (4H, m). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.71; H, 7.41; N, 5.94. Chiral HPLC: t_R, **14i** (7.8 min), **15i** (10.2 min).

(1*R*,5*S*)-6,6-Dimethyl-3-(4-methoxyphenyl)-3-azabicyclo[3.1.0]-hexan-2-one (**14k**): Treatment of the mixture (100 mg, 0.40 mmol) of **10k** and **11k** with Et_3SiH–CF_3CO_2H gave 95 mg of **14k** as colorless crystals, mp 65—67 °C, $[\alpha]_D^{25}$ −26.8° (c=0.5, $CHCl_3$). IR (Nujol): 1675 cm^{-1}. MS m/z: 231 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, s), 1.16 (3H, s), 1.96 (1H, dd, J=1.9, 6.6 Hz), 1.72 (1H, dd, J=6.6, 6.6 Hz), 3.57 (1H, br d, J=10.7 Hz), 3.78 (3H, s), 3.98 (1H, dd, J=6.6, 10.7 Hz), 6.7—7.5 (4H, m). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.71; H, 7.41; N, 5.94. Chiral HPLC: t_R, **14k** (8.1 min), **15k** (9.4 min).

Conversion of Hydroxylactam (10—13) into Lactone (8—9) The general procedure is exemplified by conversion of **10a** into **8a**. The ee of **8** and **9** was determined by comparing the $[\alpha]_D$ value with the reported value. Yields and optical purities of **8** and **9** are given in Table III. Boiling points and spectral data of **9a**, **b**, **8b**, **i**—**k** were consistent with those of authentic samples.[19,20,25]

The (3a*R*,7a*S*)-Lactone (**8a**): $NaBH_4$ (75 mg, 2.0 mmol) was added to a solution of **10a** (200 mg, 0.77 mmol) in 60% ethanol (15 ml). The mixture was stirred for 5 h at 50 °C. A 10% HCl solution was added to the mixture under ice-cooling, the whole was extracted with AcOEt. The organic layer was washed with brine, dried and concentrated. After the addition of 2 N H_2SO_4 (15 ml) to the residue, the mixture was stirred at 80 °C for 2 h and extracted with ether. The organic layer was washed with brine, dried and concentrated. Kugelrohr distillation of the residue gave 84 mg of **8a** as a colorless oil, bp 160 °C (10 mmHg), (lit.[19] 86 °C (2 mmHg)).

Removal of the 4-Methoxyphenyl Group of the Lactam (14, 15) The general procedure is exemplified by removal of the 4-methoxyphenyl group of **14a** by oxidation with CAN. Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OB-H; eluent, hexane–2-propanol (50 : 1), 1.0 ml/min.

(3a*R*,7a*S*)-Octahydro-1*H*-isoindol-1-one (**16a**): A solution of CAN (1.27 g, 2.3 mmol) in H_2O (20 ml) was added to a solution of 180 mg (0.73 mmol, 88% ee) of **14a** in CH_3CN (20 ml) at 5 °C. The mixture was stirred for 1 h at 5 °C and extracted with AcOEt. The organic layer was washed with water, saturated $NaHCO_3$ solution, sodium sulfite solution and brine, then dried and concentrated. The residue was purified by column chromatography on silica gel (× 20). Elution with $CHCl_3$–MeOH (19 : 1) gave 81 mg (80%) of **16a** as colorless crystals, mp 94—95 °C, $[\alpha]_D^{25}$ +24.0° (c=0.5, $CHCl_3$). IR (Nujol): 3200 (NH), 1680 cm^{-1}. MS m/z: 139 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.1—2.1 (8H, m), 2.3—2.50 (2H, m), 2.94 (1H, ddd, J=2, 2, 9.3 Hz), 3.37 (1H, dd, J=6.0, 9.3 Hz), 6.2 (1H, br s). *Anal.* Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.05; H, 9.43; N, 9.78. Chiral HPLC: t_R, **16a** (11.1 min), **17a** (13.8 min); 88% ee.

(3a*S*,7a*R*)-Octahydro-1*H*-isoindol-1-one (**17a**): Treatment of 90 mg (0.37 mmol, 87% ee) of **15a** with CAN (650 mg, 1.2 mmol) gave 45 mg (88%) of **17a** as colorless crystals, mp 93—95 °C, $[\alpha]_D^{25}$ −23.3° (c=0.5, $CHCl_3$), 86% ee. Spectral data of **17a** were consistent with those of **16a**. *Anal.* Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.00; H, 9.42; N, 9.86.

(3a*R*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-1*H*-isoindol-1-one (**16b**): Treatment of 90 mg (0.37 mmol, 88% ee) of **14b** with CAN (650 mg, 1.2 mmol) gave 40 mg (79%) of **16b** as colorless crystals, mp 73—75 °C, $[\alpha]_D^{25}$ −24.0° (c=0.5, $CHCl_3$). IR (Nujol): 3200 (NH), 1700, 1680 cm^{-1}. MS m/z: 137 (M^+, 100). ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.7 (6H, m), 2.99 (1H, dd, J=2.5, 9.4 Hz), 3.49 (1H, dd, J=6.2, 9.4 Hz), 5.76 (2H, m), 6.3 (1H, br s). *Anal.* Calcd for $C_8H_{11}NO$: C, 70.03; H, 8.09; N, 10.21. Found: C, 70.16; H, 7.97; N, 9.87. Chiral HPLC: t_R, **16b** (17.5 min), **17b** (26.5 min); 91% ee.

(3a*R*,4*R*,7*S*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-4,7-methano-1*H*-isoindol-1-one (**16c**): Treatment of 70 mg (0.30 mmol, 89% ee) of **14c** with CAN (490 mg, 0.90 mmol) gave 36 mg (85%) of **16c** as colorless crystals, mp 133—135 °C, $[\alpha]_D^{25}$ +128.0° (c=0.2, $CHCl_3$). IR (Nujol): 3240 (NH), 1680, 1650 cm^{-1}. CI-MS m/z: 150 (MH^+), 84 (100). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (1H, ddd, J=1.5, 1.5, 8.4 Hz), 1.59 (1H, ddd, J=1.5, 1.7, 8.4 Hz), 2.78 (1H, ddd, J=1, 3.2, 10.1 Hz), 2.85—3.1 (3H, m), 3.2—3.3 (1H, m), 3.34 (1H, dd, J=9, 10.1 Hz), 6.0 (1H, br s), 6.17 (1H, dd, J=2.9, 5.5 Hz), 6.27 (1H, dd, J=2.9, 5.5 Hz). *Anal.* Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.34; H, 7.33; N, 9.10. Chiral HPLC: t_R, **16c** (15.3 min), **17c** (18.5 min); 89% ee.

(3a*S*,4*S*,7*R*,7a*R*)-2,3,3a,4,7,7a-Hexahydro-4,7-methano-1*H*-isoindol-1-one (**17c**): Treatment of 95 mg (0.35 mmol, 84% ee) of **15c** with CAN (580 mg, 1.1 mmol) gave 47 mg (81%) of **17c** as colorless crystals, mp 133—135 °C, $[\alpha]_D^{25}$ −128.8° (c=0.2, $CHCl_3$), 88% ee. Spectral data of **17c** were consistent with those of **16c**. *Anal.* Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.33; H, 7.24; N, 9.09.

Reduction of 18 with (*R*)-BINAL-H(MeOH) Reduction of **18** was carried out under the condition used for reduction of **2**. Yields of **19** and **20** are given in Table IV.

(3*R*,3a*R*,7a*S*)-Octahydro-3-hydroxy-2-(4-chlorophenyl)-1*H*-isoindol-1-one (**19a**): Reduction of **18a** (450 mg, 1.7 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave 417 mg of **19a** as colorless crystals, mp

135—137 °C, $[\alpha]_D^{25}$ −26.4° (c=0.25, $CHCl_3$). IR (Nujol): 3480, 3260, 1680, 1660 cm^{-1}. MS m/z: 267 (M^++2), 265 (M^+), 155, 153, 129, 127 (100), 67. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.1 (8H, m), 2.45—2.65 (2H, m), 2.65 (1H, d, J=8.1 Hz, C_3-OH), 5.59 (1H, dd, J=5.5, 8.1 Hz, C_3-H), 7.3—7.5 (4H, m). *Anal.* Calcd for $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; Cl, 13.34; N, 5.27. Found: C, 63.16; H, 6.05; Cl, 13.23; N, 5.17.

(3*R*,3a*R*,7a*S*)-Octahydro-3-hydroxy-2-phenyl-1*H*-isoindol-1-one (**19b**): Reduction of **18b** (450 mg, 2.0 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave 423 mg of **19b** as colorless crystals, mp 136—138 °C, $[\alpha]_D^{25}$ −33.6° (c=0.25, $CHCl_3$). IR (Nujol): 3460, 3260, 1670, 1650 cm^{-1}. MS m/z: 231 (M^+), 119, 93 (100), 77. ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.1 (8H, m), 2.5—2.6 (2H, m), 2.63 (1H, d, J=7.6 Hz, C_3-OH), 5.62 (1H, dd, J=5.4, 7.6 Hz, C_3-H), 7.1—7.5 (5H, m). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.66; H, 7.41; N, 6.03.

(3*R* and 3*S*,3a*R*,7a*S*)-Octahydro-3-hydroxy-2-methyl-1*H*-isoindol-1-one (**19c** and **20c**): Reduction of **18c** (500 mg, 3.0 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave a mixture (478 mg) of **19c** and **20c** (≒7:3) as a colorless solid. IR (Nujol): 3240, 1660 cm^{-1}. MS m/z: 169 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.1 (8H, m), 2.1—2.8 (1H, m), 2.84 (0.7H, s), 2.89 (0.3H, s), 3.12 (0.7H, d, J=8.3 Hz), 3.52 (0.3H, d, J=7.0 Hz), 4.65 (0.3H, dd, J=<1, 7.0 Hz, C_3-H), 5.05 (0.7H, dd, J=5.2, 8.3 Hz, C_3-H).[26]

(3*S*,3a*R*,7a*S*)-Octahydro-3-hydroxy-2-benzyl-1*H*-isoindol-1-one (**20d**): Reduction of **18d** (600 mg, 2.5 mmol) with (*R*)-BINAL-H(MeOH) (7.0 mmol) gave a mixture (545 mg) of **19d** and **20d** (≒3:2) as a colorless solid. Treatment of the mixture (100 mg, 0.41 mmol) with 10% HCl solution (1 ml) in THF (10 ml) gave 92 mg (92%) of **20d** as colorless crystals, mp 106.5—108.5 °C, $[\alpha]_D^{25}$ −40.4° (c=0.5, $CHCl_3$). IR (Nujol): 3280, 1650 cm^{-1}. MS m/z: 245 (M^+), 227, 91 (100). ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.3 (9H, m), 2.7—2.9 (1H, m), 2.69 (1H, d, J=6.6 Hz), 4.21 (1H, d, J=14.7 Hz), 4.55 (1H, dd, J=1.3, 6.4 Hz, C_3-H), 4.83 (1H, d, J=14.7 Hz), 7.2—7.4 (5H, m). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.70; H, 7.77; N, 5.71.

Conversion of the Hydroxylactams (19 and 20) into the Lactone (8a) Conversion of **19** and **20** into **8a** was carried out under the same conditions used for conversion of **10a** into **8a**. Yields and optically purities of **8a** are given in Table IV. The ee of **8a** was determined on the basis of the $[\alpha]_D$ value in comparison with the reported value.

Conversion of the Hydroxylactams (19) into the Lactam (21) Conversion of **19** into **21** was carried out under the conditions used for conversion of **10a** into **14a**. Yields and optically purities of **21** are given in Table IV. Chiral HPLC analysis was carried out under the following conditions: column, Opti Pak XC; eluent, hexane–2-propanol (85:15) 1.0 ml/min.

(3a*R*,7a*S*)-Octahydro-2-(4-chlorophenyl)-1*H*-isoindol-1-one (**21a**): Treatment of **19a** (100 mg, 0.38 mmol) with Et_3SiH–CF_3CO_2H gave 94 mg of **21a** as colorless crystals, mp 105—107 °C, $[\alpha]_D^{25}$ −2.0° (c=0.5, $CHCl_3$). IR (Nujol): 1680 cm^{-1}. MS m/z: 251 (M^++2), 249 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.3 (8H, m), 2.40—2.52 (1H, m), 2.64—2.73 (1H, m), 3.34 (1H, dd, J=2.2, 9.3 Hz), 3.80 (1H, dd, J=5.8, 9.3 Hz), 7.2—7.7 (4H, m). *Anal.* Calcd for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; Cl, 14.20; N, 5.61. Found: C, 67.59; H, 6.48; Cl, 13.97; N, 5.37. Chiral HPLC: t_R, **21a** (4.8 min), enantiomer of **21a** (6.3 min).

(3a*R*,7a*S*)-Octahydro-2-phenyl-1*H*-isoindol-1-one (**21b**): Treatment of **19b** (100 mg, 0.43 mmol) with Et_3SiH–CF_3CO_2H gave 93 mg of **21b** as colorless crystals, mp 87.5—89 °C, $[\alpha]_D^{25}$ −4.8° (c=0.5, $CHCl_3$). IR (Nujol): 1690 cm^{-1}. MS m/z: 215 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.2 (8H, m), 2.40—2.52 (1H, m), 2.64—2.73 (1H, m), 3.39 (1H, dd, J=2.2, 9.4 Hz), 3.83 (1H, dd, J=5.8, 9.4 Hz), 7.0—7.7 (5H, m). *Anal.* Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.23; H, 7.86; N, 6.29. Chiral HPLC: t_R, **21b** (6.4 min), enantiomer of **21b** (7.1 min).

Molecular Orbital Calculations The structural modeling and all calculations were performed on an IRIS 4D/80GT 3D-graphics workstation (Silicon Graphics Inc.) using the molecular modeling program SYBYL (Tripos Associates Inc.). Models of **18** were built with R=H, and minimized with MAXIMIN 2 (with Tripos force field) in SYBYL. Possible conformations were searched by using the RANDOM SEARCH command of SYBYL, then each conformer was minimized using the semiempirical molecular orbital method AM 1 as implemented in the MOPAC program.[45] The lowest energy conformation (extended-boat form) was chosen, then all compounds were constructed by adding *N*-substituent groups (R=Me, $PhCH_2$, Ph, 4-Cl-Ph, 4-MeO-Ph) followed by geometry optimization with AM 1.

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