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Stereoselective Reactions. XI.[1] Asymmetric Alkylation of Cyclohexanone *via* Chiral Chelated Lithioenamines Derived from D-Camphor Derivatives[2]

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Metalation and alkylation of the chiral imines prepared from cyclohexanone and methoxy amines (**2b**, **4c**, **6d**, and **7d**) derived from D-camphor derivatives provided, after hydrolysis, optically active 2-alkylcyclohexanones (**9**) in high enantiomeric purities of up to 99.5%.

Keywords——asymmetric synthesis; asymmetric alkylation; D-camphor; chiral methoxy amine; 2-alkylcyclohexanone; chelated lithioenamine

It has been shown that optically active *tert*-leucine *tert*-butyl ester is an excellent chiral reagent for asymmetric carbon–carbon bond-forming reactions such as hydrocyanation of chiral aldimines,[4] 1,4-addition of nucleophiles to chiral α,β-unsaturated aldimines,[5] and substitution at the α-position to the carbonyl group using chiral imines,[6] based on the principle of fixing the reactive conformation by an internal lignad. However, since it is somewhat tedious to resolve D,L-*tert*-leucine to obtain the optically active forms, we have been investigating various chiral bidental amines which could be prepared in a large quantity for use in such asymmetric reactions. As a part of our continuing studies on diastereoselective alkylation *via* lithioenamine, we describe here the synthesis of chiral methoxy amines (**2b**, **4c**, **6d**, and **7d**) derived from D-camphor derivatives, as well as the asymmetric alkylation of cyclohexanone using these reagents as chiral auxiliaries.

Results and Discussion

A. Synthesis of Chiral Methoxy Amines from D-Camphor Derivatives

The synthetic scheme for the preparation of chiral methoxy amines (**2b**, **4c**, **6d**, and **7d**)[7] from D-camphor derivatives is shown in Chart 1.

cis, *exo*-3-Amino-2-hydroxybornane (**2a**),[8,9] prepared from 3-hydroxyiminocamphor (**1**), was converted to the corresponding methoxy amine (**2b**) by treatment with potassium hydride and methyl iodide in tetrahydrofuran (THF)[10] in 49% yield from **1**.

Reduction of 3-*endo*-aminobornan-2-one (**3**) with lithium aluminum hydride[11] gave a mixture of *cis*, *endo*-3-amino-2-hydroxybornane (**4a**) and 3-*endo*-amino-2-*exo*-hydroxybornane (*endo,endo* : *endo,exo* = 72 : 28). Since it was difficult to isolate **4a** by recrystallization of the crude mixture or its hydrochloride, the crude reduction product was converted to the *N*-benzyloxycarbonyl (Z)-methoxyamine (**4b**) by treatment with KH and CH_3I in THF followed by reaction with ZCl and triethylamine (TEA) in methylene chloride. Then, pure **4b** was easily isolated by column chromatography on silica gel. Hydrogenolysis of **4b** with Pd–carbon catalyst to remove the Z group followed by vacuum distillation gave pure **4c** in 29% yield from **3**.

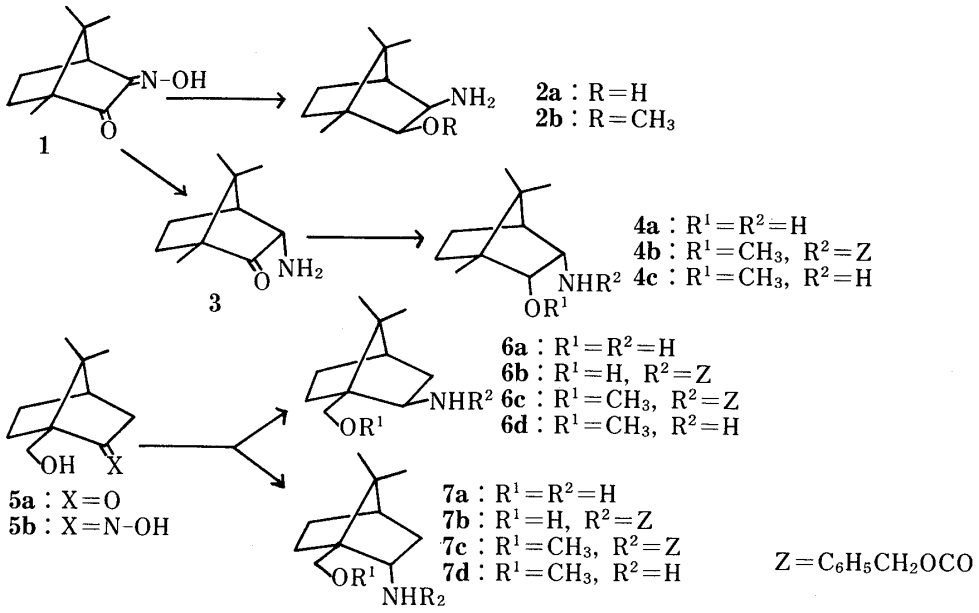


Chart 1

D-10-Hydroxycamphoroxime (**5b**), prepared from D-10-hydroxycamphor (**5a**)[12] was hydrogenated with Raney nickel at 50—70 °C for 2 h in methanol (initial pressure, 100 kg/cm^2) to give a mixture of 2-*exo*-amino derivative (**6a**) and 2-*endo*-amino derivative (**7a**) (**6a** : **7a** = 3 : 4), which without purification was converted to the *N*-Z derivatives. Chromatographic separation of the isomers afforded pure **6b** and **7b** in 26% and 34% yields, respectively, from **5b**. The stereochemistry of **6b** and **7b** at C_2 was determined by means of proton nuclear Overhauser effect (NOE) experiments. Upon irradiation of the C_8 methyl proton of **7b**, significant enhancement (about 15%) of the C_2 proton signal was observed, while no such enhancement was observed for **6b**. Removal of the Z group in **6b** and subsequent *O*-methylation provided the crude methoxy amine (**6d**). Since **6d** was not completely purified by distillation,[13] the crude mixture was converted to the *N*-Z derivative (**6c**), which was purified by column chromatography followed by deprotection of the Z group in **6c** and then vacuum distillation to afford pure **6d** in 42% yield from **6b**. Similarly, **7d** was prepared in 40% yield from **7b**.

B. Asymmetric Alkylation

The chiral imines (**8a—d**) were prepared by treating the methoxy amines (**2b**, **4c**, **6d**, and **7d**) with a slight excess of cyclohexanone in benzene under azeotropic conditions and purified by vacuum distillation in 80%—90% yield (Chart 2). Metalation of **8a—d** with lithium diisopropylamide (LDA) in THF at the temperature indicated in Table I, followed by alkylation with methyl iodide, propyl iodide, and allyl bromide, respectively, gave, after hydrolysis (10% aq. citric acid), (*R*)- or (*S*)-2-alkylcyclohexanones (**9a—c**), with recovery of

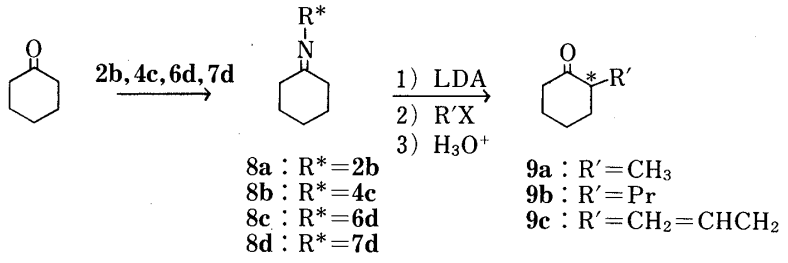
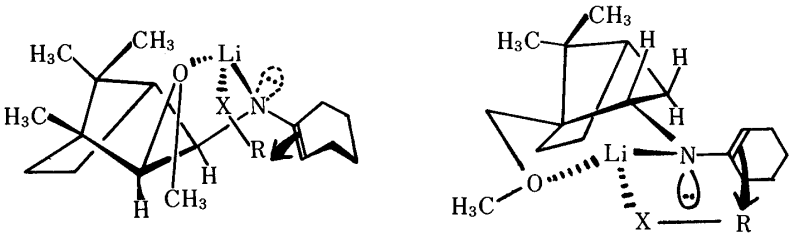


Chart 2

TABLE I. Asymmetric Synthesis of 2-Alkylcyclohexanones (**9**)

Run	Chiral reagent	Metalation temp. (°C)	R′X	Yield[a] (%)	$[\alpha]_D^{25}$ (*c*, MeOH)	Optical purity[b] (Confign.)
1	**2b**	−78	CH_3I	54	−11.9° (2.56)	85 (*R*)[c]
2	**2b**		PrI	61	−25.7° (5.08)	91 (*R*)[d]
3	**2b**		$CH_2=CHCH_2Br$	68	−10.4° (3.01)	66 (*S*)[e]
4	**4c**	−78	CH_3I	42	+8.3° (4.53)	60 (*S*)[c]
5	**4c**		PrI	52	+23.8 (4.59)	84 (*S*)[d]
6	**4c**		$CH_2=CHCH_2Br$	43	+9.1° (3.85)	58 (*R*)[e]
7	**6d**	0	CH_3I	51	−11.1° (4.00)	79 (*R*)[c]
8	**6d**		PrI	21	−23.2° (4.01)	82 (*R*)[d]
9	**6d**		$CH_2=CHCH_2Br$	22	+8.9° (2.01)	56 (*S*)[e]
10	**7d**	−5—−10	CH_3I	46	+12.4° (5.02)	89 (*S*)[c]
11	**7d**		PrI	43	+28.1° (5.65)	>99.5 (*S*)[d]
12	**7d**		$CH_2=CHCH_2Br$	53	+12.8° (3.76)	81 (*R*)[e]

a) Isolation yield based on **8** after purification by column chromatography followed by vacuum distillation. *b*) Based on the highest rotation value in the literature. *c*) Based on $[\alpha]_D$ 14° (MeOH) reported in ref. 15. *d*) Based on $[\alpha]_D$ 28.2° (MeOH) reported in ref. 15. *e*) Based on $[\alpha]_D$ 15.8° (MeOH) reported in ref. 14.



10 **11**

Fig. 1

the optically pure methoxy amines for reuse. Although metalation of **8a** and **8b** with LDA was complete at −78 °C, much higher temperatures (−10—0 °C) were required to complete the metalation of **8c** and **8d**. The results are summarized in Table I. Enantiomeric excesses ranged from 56% to more than 99.5% with isolated yields from 21% to 68% based on the starting imines. An opposite sense of asymmetric induction was observed using chiral reagents **2b** *vs.* **4c** and **6d** *vs.* **7d**.

C. Stereochemical Mechanism

The experimental results can be explained in terms of the structures shown in Fig. 1 for **8a** and **8d**, which are similar to those reported by Meyers *et al.*[10,15] and us[6b] for this type of asymmetric alkylation.

When imines are metalated, the lithium ion becomes coordinated to the methoxyl ligand to form five-membered and six-membered complexes **10** and **11** from **8a** and **8d**, respectively. The cyclohexenyl ring on the nitrogen atom and the C_3-hydrogen are *cis* for steric reason in **10**, while the cyclohexenyl ring is equatorial in the stable chair conformation of **11**. In the alkylation step, the halogen of the alkyl halide is coordinated to the lithium cation. The halide is displaced in an S_N2 fashion by the π-orbital of the double bond in the conformation where the π-orbitals of the cyclohexene are parallel to the N–Li orbital and *trans* to the *N*-lone pair.[6]

Further studies aimed at utilizing this asymmetric alkylation to provide more complex and useful chiral ketones are in progress.

Experimental[16]

***cis*, *exo*-3-Amino-2-methoxybornane (2b)**——The hydrochloride of *cis*, *exo*-3-amino-2-hydroxybornane (**2a**)[11] was prepared from 3-hydroxyiminocamphor (**1**) and purified by repeated recrystallization from 2-propanol–ether. Pure **2a** was obtained after neutralization of the hydrochloride with 10% aq. NaOH in 60% yield from **1**, mp 215—217.5 °C (pentane), $[\alpha]_D^{20}$ −7.23° (*c*=2.05, EtOH) (lit.[11] mp 213—214 °C). A solution of **2a** (3.2 g, 19 mmol) in 25 ml of anhydrous THF was added dropwise to a stirred suspension of potassium hydride (3.57 g, about 23% oil suspension, 20.5 mmol, hexane washed) in 50 ml of THF at room temperature under nitrogen. The resulting pale yellow gelatinous mixture was stirred at room temperature for 30 min, then a solution of methyl iodide (1.14 ml, 18.4 mmol) in THF (30 ml) was added over a period of 2 h. After stirring at room temperature for 1 h, the insoluble materials were filtered off and the filtrate was concentrated *in vacuo* to give a residual oil, which was dissolved in ether. The ethereal layer was washed with satd. aq. NaCl and dried over K_2CO_3. Filtration and evaporation *in vacuo* gave an oily residue, which was purified by bulb-to-bulb distillation to afford pure **2b** (2.84 g, yield 82%) as a colorless oil of bp 120—125 °C (3 mmHg). $[\alpha]_D^{20}$ −76.9° (*c*=3.2, benzene). NMR ($CDCl_3$): 0.76, 0.90, 1.16 (3×3H, three s, 3×CH_3), 0.7—1.8 (m, 5H, 2×CH_2, C_4-H), 3.02 (2H, s, C_2- and C_3-H), 3.38 (3H, s, OCH_3). MS *m/e*: 184 [$(M+1)^+$], 183 (M^+).

***cis*, *endo*-3-Amino-2-methoxybornane (4c)**——3-*endo*-Aminobornan-2-one (**3**)[11a] (7.91 g, 47.3 mmol) was reduced with $LiAlH_4$ (1.83 g, 48.2 mmol) at −20——18 °C according to the reported procedure[11b] to give a mixture of **4a** and 3-*endo*-amino-2-*exo*-hydroxybornane (*endo,endo* : *endo,exo* = 72 : 28), which was methylated as described for the preparation of **2b**, followed by reaction with ZCl (5.64 ml, 40 mmol) and TEA (6.6 ml, 47.4 mmol) in CH_2Cl_2 at room temperature for 1.5 h to afford a crude **4b** after usual work-up. *cis*, *endo*-3-*N*-Benzyloxycarbonylamino-2-methoxybornane (**4b**) was isolated by column chromatography (silica gel, hexane : AcOEt = 40 : 1) in 46% yield from **3**, $[\alpha]_D^{24}$ +47.7° (*c*=2.14, benzene). IR ν_{max}^{film} cm^{-1}: 3430, 1720. NMR ($CDCl_3$): 0.83 (6H, s, C_9- and C_{10}-CH_3), 0.90 (3H, s, C_8-CH_3), 1.05—2.05 (4H, 2×CH_2), 1.92 (1H, m, C_4-H), 3.31 (3H, s, OCH_3), 3.38 (1H, d, *J*=10 Hz, C_2-H), 4.12 (1H, m, C_3-H), 5.05 (2H, s, CH_2Ph), 5.31 (1H, d, *J*=6 Hz, NH), 7.30 (5H, aromatic protons). MS *m/e*: 317 (M^+). Hydrogenolysis of **4b** (5.35 g, 16.9 mmol) followed by bulb-to-bulb distillation gave pure **4c** (1.92 g, yield 62.2%) as a colorless oil of bp 78—82 °C (8 mmHg), $[\alpha]_D^{22}$ +62.9° (*c*=2.6, benzene). IR ν_{max}^{film} cm^{-1}: 3400, 1590. NMR ($CDCl_3$): 0.87 (9H, s, C_8-, C_9- and C_{10}-CH_3), 1.05—1.95 (5H, m, C_4-H, 2×CH_2), 1.53 (2H, s, NH_2), 3.10—3.65 (2H, m, C_2- and C_3-H), 3.41 (3H, s, OCH_3). High-resolution MS *m/e* (M^+): Calcd for $C_{11}H_{21}N_1O_1$: 183.1623. Found: 183.1651.

2-*exo*-Amino-10-methoxybornane (6d) and 2-*endo*-Amino-10-methoxybornane (7d)——The oxime (**5b**) was prepared from D-10-hydroxycamphor (**5a**)[12] by the usual procedure in 65% yield, mp 170—173 °C (pet. ether). A mixture of **5b** (3.88 g, 21.2 mmol) and W-4 Raney nickel (38.8 ml, methanol suspension) was hydrogenated under 100 kg/cm² pressure of hydrogen at 50—70 °C for 2 h. Raney nickel was removed by filtration, and the methanol was removed *in vacuo* to give an oil, which was treated with ZCl (3.2 ml, 22.4 mmol) and TEA (3.4 ml, 24.4 mmol) in CH_2Cl_2 (93 ml) at room temperature for 1.5 h. After usual work-up, the crude product was subjected to column chromatography (silica gel, hexane : AcOEt = 3 : 1) to give **6b** (less polar compound, 1.58 g, yield 26%) and **7b** (polar compound, 2.1 g, yield 34%) as crystals. Analytical samples of **6b** and **7b** were obtained by recrystallization from AcOEt–hexane. **6b**: mp 136—137.5 °C. $[\alpha]_D^{24}$ −26.9° (*c*=2.50, MeOH). IR ν_{max}^{film} cm^{-1}: 3360, 3290, 1680, 1540. NMR ($CDCl_3$): 0.85 (6H, s, C_8- and C_9-CH_3), 1.0—2.0 (7H, m, 3×CH_2, C_4-H), 3.15—3.90 (2H, m, C_2-H, OH), 3.15—3.90 (2H, m, CH_2OH), 4.89 (1H, d, *J*=6 Hz, NH), 5.10 (2H, s, CH_2Ph), 7.32 (5H, s, aromatic protons). *Anal.* Calcd for $C_{19}H_{21}N_1O_3$: C, 71.29; H, 8.25; N, 4.62. Found: C, 71.26; H, 8.44; N, 4.60. **7b**: mp 119.5—121 °C. IR ν_{max}^{KBr} cm^{-1}: 3400, 3290, 1680, 1540. NMR ($CDCl_3$): 0.82 (1H, dd, *J*=13, 5.5 Hz, C_3-H_a), 0.93 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.15—2.05 (5H, m, 2×CH_2, C_4-H), 2.38 (1H, m, C_3-H_b), 3.51 (1H, br s, OH), 3.32 (1H, d, *J*=13 Hz, one of CH_2OH), 3.60 (1H, d, *J*=13 Hz, one of CH_2OH), 4.35 (1H, m, C_2-H), 5.10 (2H, s, CH_2Ph), 7.33 (5H, s, aromatic protons). *Anal.* Calcd for $C_{19}H_{28}N_1O_3$: C, 71.29; H, 8.25; N, 4.62. Found: C, 71.36; H, 8.53; N, 4.50. A mixture of **6b** (3.45 g, 11.3 mmol) and 5% Pd–C (1.35 g) in methanol (64 ml) was hydrogenated at room temperature for 1.5 h. After removal of the catalyst by filtration, the methanol was evaporated off *in vacuo* to afford **6a** (2.0 g, yield quant., mp 238—242 °C, $[\alpha]_D^{20}$ −48.1° (*c*=2.6, MeOH)), which was used without further purification. Methylation (KH, THF, 45—50 °C, 1 h; CH_3I, r.t., 0.5 h) of **6a** (1.94 g, 10.6 mmol) and subsequent benzyloxycarbonylation afforded **6c** (1.95 g, oil, yield 58%) after column chromatography, $[\alpha]_D^{20}$ −48.6° (*c*=2.8, benzene). **6d** (828 mg) was obtained as an oil of bp 105—115 °C (2 mmHg) in 73% yield after catalytic hydrogenation of the Z group, $[\alpha]_D^{20}$ −56.2° (*c*=3.3, MeOH). IR ν_{max}^{film} cm^{-1}: 3400, 1580, 1450. NMR ($CDCl_3$): 0.80, 1.03 (2×3H, two s, C_8- and C_9-CH_3), 1.1—2.20 (7H, m, 3×CH_2, C_4-H), 1.42 (2H, s, NH_2), 2.80—3.75 (3H, m, CH_2OH, C_2-H), 3.30 (3H, s, OCH_3). High-resolution MS *m/e* (M^+): Calcd for $C_{11}H_{21}N_1O_1$: 183.1624. Found: 183.1665. **7d** was obtained in 40% yield from **7b** as described for the preparation of **6d**. **7a**: mp 206—212 °C. $[\alpha]_D^{20}$ +14.8° (*c*=2.47, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3440, 3320, 1620, 1562. NMR ($CDCl_3$): 0.89 (6H, s, C_8- and C_9-CH_3), 0.4—2.10 (7H, m, 3×CH_2, C_4-H), 3.12 (3H, br s, NH_2, OH), 3.41 (1H, m, C_2-H), 3.56, 3.85 (2×1H, two d, *J*=10 Hz, CH_2OH). **7c**: Oil, $[\alpha]_D^{20}$ −4.3° (*c*=3.46, benzene). IR ν_{max}^{film} cm^{-1}: 3350, 1700. NMR ($CDCl_3$): 0.90, 0.95 (2×3H, two s, C_8- and C_9-CH_3), 0.80—2.00 (6H, m, C_3-H_a, C_4-H, 2×CH_2), 2.38 (1H, m, C_3-H_b), 3.20 (3H, s, OCH_3), 3.30 (2H, s, CH_2OH), 4.02 (1H, m, C_2-H), 5.06 (2H, s, CH_2Ph), 5.20 (1H, br d, *J*=7 Hz, NH), 7.26 (5H, s, aromatic protons). **7d**: Oil, $[\alpha]_D^{20}$ +30.8° (*c*=3.25, MeOH). IR ν_{max}^{film} cm^{-1}: 3400, 1600, 1455. NMR ($CDCl_3$): 0.69 (1H, dd, *J*=13, 5 Hz, C_3-*endo*-H), 0.91 (6H, s, C_8- and C_9-CH_3), 1.00—2.60 (6H, m, C_3-*exo*-H, C_4-H,

$2\times CH_2$), 1.36 (2H, s, NH_2), 3.26 (3H, s, OCH_3), 3.32 (2H, s, CH_2OH), 3.25—3.60 (1H, m, C_2-H). High-resolution MS *m/e* (M^+): Calcd for $C_{11}H_{21}N_1O_1$: 183.1621. Found: 183.1611.

Preparation of the Imines (8a—d)——The procedure for the preparation of *cis,exo*-3-cyclohexylideneamino-2-methoxybornane is described as an example. A solution of cyclohexanone (0.69 ml, 6.65 mmol) and **2b** (1.15 g, 6.27 mmol) in benzene (25 ml) was heated under reflux using a Dean-Stark apparatus for 8 h. The solvent was removed *in vacuo*, and the residue was distilled to give **8a** (1.47 g, yield 89%) as a pale yellow oil of bp 160—170 °C (2 mmHg), $[\alpha]_D^{20}$ −23.2° (*c*=5.23, benzene). IR ν_{max}^{film} cm^{-1}: 1655. NMR ($CDCl_3$): 0.84, 0.94, 1.12 ($3\times 3H$, three s, $3\times CH_3$), 0.7—2.6 (15H, m, $7\times CH_2$, C_4-H), 2.9—3.7 (2H, m, C_2- and C_3-H), 3.28 (3H, s, OCH_3).

Physical Data of 8b—d——**8b**: Oil, bp 140—160 °C (2 mmHg). $[\alpha]_D^{25}$ +87.0° (*c*=2.51, benzene). IR ν_{max}^{film} cm^{-1}: 1660. NMR ($CDCl_3$): 0.90 (9H, s, $3\times CH_3$), 1.10—2.60 (15H, m, C_4-H, $7\times CH_2$), 3.10—3.65 (2H, m, C_2- and C_3-H), 3.42 (3H, s, OCH_3). **8c**: Oil, bp 170—180 °C (2 mmHg). $[\alpha]_D^{20}$ −66.0° (*c*=3.18, benzene). IR ν_{max}^{film} cm^{-1}: 1655. NMR ($CDCl_3$): 0.88, 1.15 ($2\times 3H$, two s, $2\times CH_3$), 1.00—2.80 (17H, m, $8\times CH_2$, C_4-H), 3.19 (3H, s, OCH_3), 3.12—3.75 (3H, m, CH_2OH, C_2-H). **8d**: Oil, bp 140—150 °C (2 mmHg). $[\alpha]_D^{20}$ +61.0° (*c*=3.77, benzene). IR ν_{max}^{film} cm^{-1}: 1660. NMR ($CDCl_3$): 0.92, 1.02 ($2\times 3H$, two s, $2\times CH_3$), 0.7—2.50 (17H, m, $8\times CH_2$, C_4-H), 3.19 (3H, s, OCH_3), 3.10—3.40 (2H, m, CH_2OH), 4.00 (1H, dd, *J*=12, 3 Hz, C_2-H).

Alkylations of Imines with Alkyl Halides——The procedure for the alkylation of **8a** with propyl iodide (Table I, run 2) is described as an example. Other alkylations were conducted under the same conditions as described here except for the metalation temperature. Butyl lithium (1.98 ml of a 1.52 M solution in hexane) was added to a solution of diisopropylamine (0.42 ml, 3.0 mmol) in anhydrous THF (5.5 ml) at −78 °C. The mixture was stirred at −78 °C for 30 min, then a solution of **8a** (660 mg, 2.5 mmol) in THF (5.5 ml) was added at −78 °C over a period of 5 min, and the whole was stirred at −78 °C for 50 min. A solution of propyl iodide (0.27 ml, 2.75 mmol) in THF (2 ml) was added over a period of 10 min, and stirring was continued at −78 °C for 2 h, then 2 ml of cold 10% aq. citric acid was added. The mixture was poured into 9 ml of cold 10% aq. citric acid and stirred for 20 min, then extracted with ether ($\times 2$). The combined ether extracts were washed with 0.5% aq. $NaHCO_3$, water, and satd. aq. NaCl, and dried over $MgSO_4$. The ether was removed *in vacuo* to give a residual oil, which was subjected to column chromatography (silica gel, pentane : ether = 8 : 1) to afford **9a** (261 mg, yield 74%) as an oil. Pure **9a** (134 mg, yield 61%) was obtained by bulb-to-bulb distillation, bp 140—150 °C (40 mmHg), $[\alpha]_D^{18}$ −25.7° (*c*=5.1, MeOH).

References and Notes

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7) 2-*exo*-Amino-3-*endo*-(*tert*-butoxycarbonyl)bornane (bp 125—127 °C (2 mmHg), $[\alpha]_D^{22}$ −12.4° (*c*=2.34, benzene)) was also synthesized from D-camphor by the following procedure: a) dimethylcarbonate, NaH, THF, reflux, b) $NH_2OH\cdot HCl$, CH_3COONa, MeOH, reflux, c) Raney Ni, MeOH, d) ZCl, TEA, CH_2Cl_2, e) aq. NaOH, f) isobutylene, conc. H_2SO_4, CH_2Cl_2, g) 5% Pd–C. However, alkylation of the imine prepared from cyclohexanone did not proceed under the conditions described in section B.
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9) The reduction of **1** with lithium alminium hydride in ether gave a mixture of **2a** and its *cis, endo* derivative (ratio about 9 : 1), and **2a** was not completely purified by recrystallization at this stage. Pure **2a** was obtained by repeated recrystallization of the hydrochloride salt of the crude reduction mixture from 2-propanol–ether, followed by neutralization.
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13) In the small-scale experiments, pure **6d** and **7d** were obtained from **6a** and **7a**, respectively, by vacuum distillation of the crude reaction mixture.
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grating infrared spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a JNM-PS 100 (100 MHz) and JNM-FX 100 (100 MHz) or a Hitachi R-24 (60 MHz) spectrometer. Data are recorded in parts per million (ppm) downfield from internal tetramethylsilane. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a JASCO DIP-181. Mass spectra (MS) were recorded with a JEOL JMS-01 5G-Z mass spectrometer.