ENANTIOSELECTIVE CREATION OF QUATERNARY CARBON CENTERS THROUGH ADDITION-ELIMINATION REACTION: ASYMMETRIC NITROOLEFINATION OF 3-SUBSTITUTED 2-OXINDOLES#

Kaoru Fuji,*[a] Takeo Kawabata,[a] Toshiumi Ohmori,[a] Muhong Shang,[a] and Manabu Node[b]

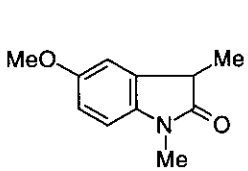
[a] Institute for Chemical Research, Kyoto University, Uji 611, Japan
[b] Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Abstract - Nitroolefination of 3-substituted 2-oxindoles with nitroenamine (**5**) afforded the corresponding products having quaternary carbon centers with high ee in good yield. Application of this method to concise syntheses of (-)-esermethole (**24**) and (-)-pseudophrynaminol (**28**) is described.

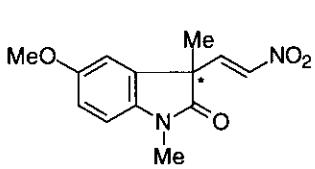
Asymmetric creation of quaternary carbon centers is a matter of infinite importance in organic synthesis.[1] Nearly ten years ago, we reported high asymmetric induction through addition-elimination process to construct a chiral carbon at the α-position of δ-lactones,[2] and the products were used as chiral building blocks for the total syntheses of optically active indole alkaloids[3,4] and diterpenoids.[5,6] Further studies on these lines led us to extend this method to 2-oxindoles. This paper focuses on the asymmetric nitroolefination of 3-substituted 2-oxindoles to form a quaternary center at C-3 with high enantiomeric excess (ee) and its application to concise syntheses of (-)-esermethole (**24**) and (-)-pseudophrynaminol (**28**).[7]

Nitroolefination of 3-Substituted 2-Oxindoles

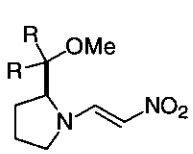
We began the study with a substrate (**1**) since it was expected to be the key intermediate for the synthesis of (-)-esermethole (**24**) (*vide infra*). Reactions of the lithium enolate generated from **1** and *n*-BuLi with (*S*)-nitroenamines (**3**~**5**) were carried out in various solvents. The results are summarized in Table 1. The nitroenamine (**3**) gave disappointing results in all solvent systems (9-23% ee, entries 1, 3, and 5).



1



2



3 : R = H
4 : R = Me
5 : R = Ph

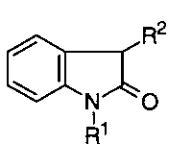
Replacing the counter cation of the enolate from lithium to zinc did not bring on the marked improvement of the ee (36-51% ee, entries 2 and 4), although we had previously observed a dramatic effect of zinc in the asymmetric nitroolefination of δ-lactones.[2] Nitroenamine (**4**), having dimethyl group on the side chain of the chiral auxiliary, brought some improvement on the enantioselectivity of the reaction up to 64% ee (entry 8). Furthermore, nitroenamine (**5**), having diphenyl group, dramatically increased the ee (94-95% ee, entries 9-11). The most satisfactory result was obtained when the reaction was carried out in toluene. The desired product (**2**) was obtained in 83% yield and 95% ee (entry 11). The absolute configuration of **2** was determined by the transformation into (-)-esermethole (**24**) (*vide infra*).

Table 1 Asymmetric Nitroolefination of **1** [a]

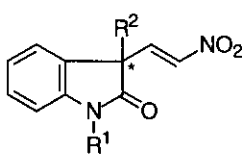
		reaction conditions			product (**2**)		
entry	nitroenamine	solvent	temp, °C	time, h	yield, %[b]	% ee	configuration
1	**3**	THF	-78 ~ -50	3	38	23	*R*
2[c]	**3**	THF	-78 ~ -30	4	77	36	*S*
3	**3**	DME	-78 ~ -70	2	25	10	*R*
4[c]	**3**	DME	-40 ~ 0	3	13	51	*R*
5	**3**	toluene	-78 ~ -40	3	32	9	*S*
6	**4**	THF	-78 ~ -40	5	42	~0	-
7	**4**	DME	-40 ~ -0	4	48	27	*S*
8	**4**	toluene	-78 ~ 0	5	52	64	*S*
9	**5**	THF	-50 ~ 0	3	54	95	*S*
10	**5**	DME	-50 ~ 0	2	57	94	*S*
11	**5**	toluene	-50 ~ 0	3	83	95	*S*

a) Three mol equivalents of lithium enolate, generated from **1** and *n*-BuLi, were used unless otherwise stated. b) Isolated yield. c) Zinc enolate wsa used.

Asymmetric nitroolefination of several 3-substituted 2-oxindoles using nitroenamine (**5**) was examined. Results are listed in Table 2. Presence of a substituent at the nitrogen is essential for the high asymmetric induction and chemical yield (entries 1 vs 2, 8 vs 10-12). Highly enantioselective nitroolefination of the lithium enolates of the oxindoles (**7**-**10**) and (**12**-**14**) proceeded in satisfactory chemical yields irrespective of the substituent R^2 (90-98% ee and 68-87% yield, entries 2-7 and 10-12). In the case of **11**, use of the zinc enolate gave much improved yield and ee (entry 8 vs 9).



6 - 1 4



15 - 2 3

Table 2. Asymmetric Nitroolefination of 3-Substituted 2-Oxindoles with Nitroolefin (**5**)[a]

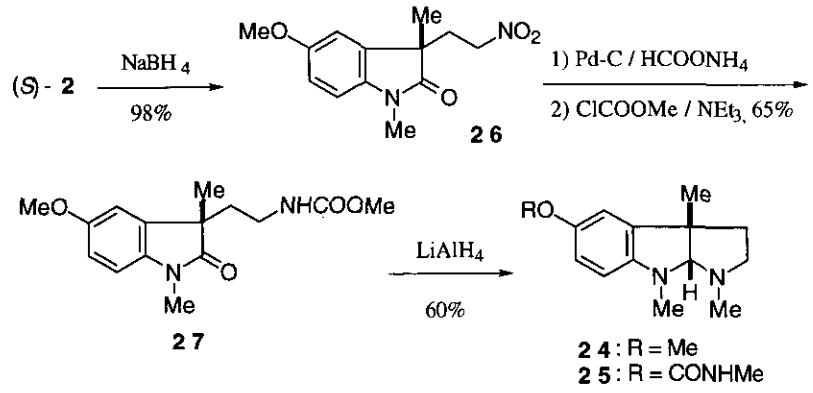
entry	substrate	R^1	R^2	solvent	temp, °C	time, h	product	yield, %[b]	% ee
1[c]	**6**	H	Me	THF	-78 ~ 0	5	**15**	70	61
2	**7**	Me	Me	THF	-78 ~ 0	5	**16**	68	98
3	**7**	Me	Me	toluene	-78 ~ 0	5	**16**	71	98
4	**8**	CH_2Ph	Et	THF	-78 ~ 0	3	**17**	28	94
5	**8**	CH_2Ph	Et	toluene	-30 ~ 0	2	**17**	82	92
6	**9**	CH_2Ph	CH_2Ph	toluene	-78 ~ 0	2	**18**	82	90
7	**10**	*p*-MeO-$C_6H_4CH_2$	$CH_2CH{=}CH_2$	toluene	-40 ~ 0	4	**19**	87	95
8	**11**	H	$CH_2CH{=}C(Me)_2$	THF			**20**	~0	-
9[c]	**11**	H	$CH_2CH{=}C(Me)_2$	THF	-78 ~ 0	5	**20**	88	78
10	**12**	Me	$CH_2CH{=}C(Me)_2$	toluene	-78 ~ 0	4	**21**	85	95
11	**13**	TBDMS	$CH_2CH{=}C(Me)_2$	THF	-30 ~ 0	4	**22**	86	97[d]
12	**14**	*p*-MeO-$C_6H_4CH_2$	$CH_2CH{=}C(Me)_2$	ether	-50 ~ 0	3	**23**	87	95

a) Three mol equivalents of lithium enolate, generated from substrate and *n*-BuLi were used unless otherwise stated. b) Isolated yield. c) Zinc enolate was used. d) Absolute configuration was determined to be*S* by the transformation to (-)-pseudophrynaminol (**28**) (see text).

Synthesis of (-)-Esermethole (24)

Since (-)-esermethole (**24**) was converted into a clinically important alkaloid, physostigmine (**25**)[8] to treat glaucoma and myasthenia gravis,[9] a number of syntheses of natural (-)-esermethole (**24**) have been reported.[10,11] The sequence of reactions starting from **2** is outlined in Scheme 1. Reduction of (*S*)-**2** (95% ee) with $NaBH_4$ afforded **26** in 92% yield. The nitro group of **26** was reduced to the corresponding amine which was converted into the carbamate (**27**) in 65% overall yield. Reductive cyclization[11g] of **27** with $LiAlH_4$ gave (-)-esermethole (**24**) in 60% yield.

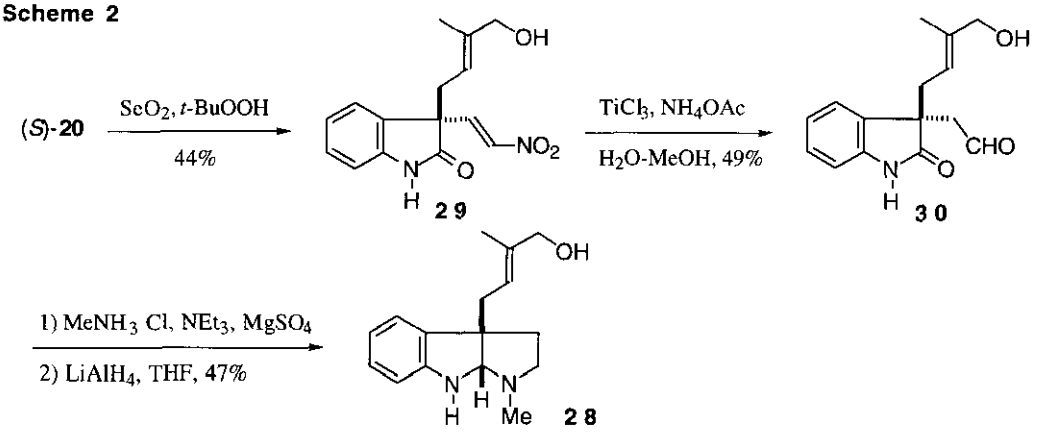
Scheme1



Synthesis of (-)-Pseudophrynaminol (28)

Pseudophrynaminol (**28**) was isolated from the skin of the Australian frog *Pseudophryne coriacea*.[12] This compound is expected to act as repugnant substances or neurotoxins to protect the animal from predation, since other indole alkaloids isolated from amphibian skin serve these roles.[13] A few syntheses of racemic **1** has been reported.[14] Recently, (-)-**28** was prepared through diastereoselective alkylation (up to 51% de) of an optically active 2-oxindole derivative.[15] Here, an enantioselective synthesis of (-)-**28** starting from **22** is described (Scheme 2). Removal of TBDMS group of (*S*)-**22** (97% ee) was readily accomplished by acid treatment to give **20** in 93% yield. Regioselective oxidation of **20** by means of selenium oxide oxidation[16] afforded **29** in 44% yield. Treatment of **29** with $TiCl_3$ in MeOH-NH_4OAc[17] furnished an aldehyde (**30**) in 49% yield. Imine-formation of **30** with methylamine followed by reductive cyclization[11g] with $LiAlH_4$ afforded (-)-**28** in 47% yield.

Scheme 2



In conclusion, we have developed highly enantioselective nitroolefination of 3-substituted 2-oxindoles. Steric bulk of the side chain of the chiral nitroenamines has been shown to have critical importance on the high ee of the nitroolefination. This method provides a straightforward entry to the synthesis of optically active indole alkaloids such as physostigmine and pseudophrynaminol.

ACKNOWLEDGMENT

This work was supported by the JSPS Fellowship for Japanese Junior Scientists (T. O.).

EXPERIMENTAL SECTION

General. Melting points were measured using a Yanagimoto Micro Melting Point Apparatus and were uncorrected. NMR spectra were obtained with a Varian Gemini 200 (200 MHz) spectrometer, chemical shifts being given in ppm units (tetramethylsilane or chloroform as internal standards, indicating 0 or 7.24

ppm, respectively). IR spectra were recorded with a JACSO A-202 or a PERKIN ELMER 1720-X diffracting grating infrared spectrophotometer. Specific rotation was measured with a Horiba SEPA-200 automatic digital polarimeter. MS spectra were recorded with a JEOL JMS-DX300 mass spectrometer. TLC analyses and preparative TLC were performed on commercial glass plates bearing 0.25-mm layer and 0.5-mm layer of Merck Kiesel-gel 60 F_{254}, respectively. Silica gel column chromatography was carried out with Wakogel C-200 or Nacalai tesque silica gel 60 (150-325 mesh). Tetrahydrofuran (THF), ether, and toluene were distilled over benzophenone ketyl before each use. Dichloromethane was distilled from calcium hydride.

(*S*)-2-(1-Methoxy-1-methylethyl)-1-(2-nitrovinyl)pyrrolidine (4) : A Mixture of (*S*)-2-(1-methoxy-1-methylethyl)pyrrolidine[18] (5.44 g, 38 mmol) and 1-morpholino-2-nitroethene[19] (6.01 g, 38 mmol) in methanol (100 mL) was heated under reflux for 3 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography (dichloromethane : acetone = 100 : 1) to afford **4** (5.47 g, 67 % yield) as pale yellow needles: mp 80-82 °C (ethanol): $[\alpha]_D^{22}$ -9.1° (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.07 (s, 3H), 1.17 (s, 3H), 1.7~2.2 (m, 4H), 3.2~3.3 (m, 2H), 3.25 (s, 3H), 3.72 (t, *J* = 7.2 Hz, 1H), 6.62, 8.60 (ABq, *J* = 10.9 Hz, 2H); IR (KBr) ν 3000, 1610, 1470, 1300, 1230 cm^{-1}; MS *m/z* 214 (M^+). Anal. Calcd for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.10; H, 8.75; N, 13.00.

Optical purity of (*S*)-**4** was determined to be >99% ee by HPLC analysis (Daicel Chiralpak AD, 2-propanol:hexane=40:60).

(*S*)-2-Methoxydiphenylmethyl-1-(2-nitrovinyl)pyrrolidine (5) : A Mixture of (*S*)-diphenyl(pyrrolidine-2-yl)methanol[18] (5.08 g, 19 mmol) and 1-morpholino-2-nitroethene (3.60 g, 23 mmol) in methanol (70 mL) was heated at 70 °C overnight. After evaporation of the solvent, the residue was purified by silica gel column chromatography (dichloromethane) followed by recrystallization from ethanol to afford **5** (4.52 g, 70% yield) as pale yellow prisms: mp 185-187 °C (ethanol); $[\alpha]_D^{20}$ - 485° (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.5~2.9 (m, 4H), 2.8~3.0 (m, 2H), 2.97 (s, 3H), 4.84 (dd, 1H, *J* = 2.4, 9.3 Hz, 1H), 6.52, 8.60 (ABq, *J* = 10.9 Hz, 2H), 7.5~7.6 (m, 10H); IR (KBr) ν 3130, 3050, 2950, 1610, 1470, 1310, 1250 cm^{-1}; MS *m/z* 338 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.18; H, 6.74; N, 8.03.

Optical purity of (*S*)-**5** was determined to be >99% ee by HPLC analysis (Daicel Chiralpak AD, 2-propanol:hexane=20:80, flow (1 mL/min), t_R= 74 min (*S*) and 88 min (*R*).

General Procedure for Nitroolefination in Table 1. Synthesis of 1,3-Dimethyl-5-methoxy-3-(2-nitrovinyl)-2-oxindole (2) (entry 11): *n*-BuLi (1.50 M in hexane, 1.0 mL, 1.5 mmol) was added to a solution of **1**[11c] (286 mg, 1.5 mmol) in toluene (2.5 mL) at 0 °C. After being stirred at 0 °C for 20 min, the solution was transferred *via* cannula to a solution of **5** (169 mg, 0.5 mmol) in toluene (2 mL) precooled at -78 °C. The mixture was immediately warmed to -50 °C and then gradually warmed to 0 °C during a period of 3 h. The reaction mixture was poured into 2.5 M aq HCl and extracted with ether. The organic phase was successively washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (dichloromethane) to afford **2** (109 mg, 83% yield). The optical purity of **2** was determined to be 95% ee by ^{1}H-NMR analysis with $Eu(hfc)_3$:: pale yellow oil: $[\alpha]_D^{22}$ -89° (*c* 0.4, $CHCl_3$) (95% ee);^{1}H-NMR ($CDCl_3$) δ 7.05, 7.32 (ABq, *J* = 13.6 Hz, 2H), 6.8-6.95 (m, 3H), 3.86 (s, 3H) 3.25 (s, 3H), 1.62 (s, 3H) ; IR (neat) ν 2940, 1710, 1600, 1530, 1340 cm^{-1}; MS *m/z* 338 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98 ; H, 6.55 ; N, 8.28. Found : C, 71.18 ; H, 6.74; N, 8.03.

The zinc enolate was prepared by the treatment of the corresponding lithium enolate solution prepared as above with 0.72- 0.78 M zinc chloride solution in ether[20] at -40 °C, then at -20 °C for 30 min. The zinc enolate solution was treated with **3** according to the procedure described above at the temperature indicated in the Table 1, entries 2 and 4.

1-Benzyl-3-ethyl-2-oxindole (8): *n*-BuLi (1.58 M in hexane, 6.33 mL, 10 mmol) was added to a solution of 1-benzyl-2-oxindole[21] (2.23 g, 10 mmol) in THF (20 mL) at -78 °C and the mixture was stirred at 0 °C for 20 min. After being cooled at -78 °C, the mixture was treated with ethyl iodide (3.90 mL, 50 mmol) and the resulting solution was gradually warmed to rt. The reaction mixture was quenched with saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was successively washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 5) to afford **8** (0.97 g, 38% yield): colorless crystals: mp 77-79 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 6.9-7.4 (m, 8H), 6.72 (d, *J* = 7.7 Hz, 1H), 4.99,4.87 (ABq, *J* = 15.6 Hz, 2H), 3.54 (t, *J* = 5.6 Hz, 1H) 2.10 (dq, *J* = 7.4, 5.7 Hz), 0.93 (t, *J* = 7.4 Hz, 3H) ; IR(KBr) ν 2960, 2925, 2870, 1715, 1610 cm^{-1}; MS *m/z* 251 (M^+). Anal. Calcd for $C_{17}H_{16}NO$: C, 81.24 ; H, 6.82 ; N, 5.57. Found : C, 81.32 ; H, 6.84 ; N, 5.48.

1,3-Dibenzyl-2-oxindole (9): pale yellow needles (ethyl acetate-hexane): mp 120-122 °C; ^{1}H-NMR ($CDCl_3$) δ 6.9-7.3 (m, 13H), 6.59 (d, *J* = 7.7 Hz, 1H), 4.67, 5.08 (ABq, *J* = 16 Hz, 2H), 3.89 (q, *J* = 3.9 Hz, 1H), 3.55 (dd, *J* = 3.8, 13.6 Hz, 1H), 3.17 (dd, *J* = 8.1, 13.6 Hz, 1H) ; IR (KBr) ν 3025, 1715, 1610, 1485, 1465, 1360 cm^{-1}; HRMS calcd for $C_{22}H_{19}NO$ (M^+) 313.1465. Found 313.1450.

3-Allyl-1-(4-methoxybenzyl)-2-oxindole (10): pale yellow prisms (ethyl acetate-hexane): mp 56-58 °C;^{1}H-NMR ($CDCl_3$) δ 6.7-7.3 (m, 8H), 5.65-5.9 (m, 1H), 5.12 (d, *J* = 18.6 Hz, 1H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.94, 4.82 (ABq, *J* = 15.4 Hz, 2H), 3.81 (s, 3H), 3.58 (t, *J* = 6.1 Hz, 1H), 2.5-3.0 (m, 2H) ; IR (KBr) ν 2830, 2350, 1715, 1705, 1610, 990 cm^{-1}; MS *m/z* 293 (M^+). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79 ; H, 6.53 ; N, 4.77. Found : C, 77.64 ; H, 6.52 ; N, 4.84.

3-(3-Methylbut-2-enyl)-2-oxindole (11): *n*-BuLi (1.63 M in hexane, 123 mL, 200 mmol) was added to a solution of 2-oxindole (13.7 g, 100 mmol) in THF (350 mL) at -78 °C. After being stirred for 1 h, the mixture was treated with 1-bromo-3-methyl-2-butene (15.0 mL, 150 mmol) and stirred at -78 °C for additional 1h. The reaction mixture was warmed to -50 °C and stirred for 3 h, then quenched with saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was successively washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 5) to afford **11** (16.6 g, 83% yield): pale yellow needles: mp 100-102 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 8.6-9.1 (br, 1H), 6.8-7.3 (m, 4H), 5.16 (t, *J* = 6.7 Hz, 1H), 3.49 (dd, *J* = 5.0, 7.7 Hz), 2.5-2.8 (m, 2H), 1.71 (s, 3H), 1.62 (s, 3H); IR (KBr) ν 3170, 1715, 1670, 1620, 1240, 830 cm^{-1}; MS *m/z* 201 (M^+). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58 ; H, 7.51 ; N, 6.96. Found : C, 77.28 ; H, 7.59 ; N, 6.83.

1-Methyl-3-(3-methylbut-2-enyl)-2-oxindole (12): pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 7.2-7.35 (m, 2H), 6.95-7.1 (m, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 5.05-5.2 (m, 2H), 3.43 (dd, *J* = 3.4, 4.9 Hz, 1H), 3.21 (s, 3H), 2.4-2.85 (m, 2H), 1.69 (s, 3H), 1.58 (s, 3H); IR (neat) ν 3050, 2970, 2910, 1720, 1610, 1490, 1250, 1120 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10 ; H, 7.96 ; N, 6.51. Found : C, 77.75 ; H, 8.06 ; N, 6.44: HRMS calcd for $C_{14}H_{17}NO$ (M^+) 215.1309. Found : 215.1295.

1-*tert*-Butyldimethylsilyl-3-(3-methylbut-2-enyl)-2-oxindole (13): To a solution of **11** (101 mg, 0.5 mmol) in dichloromethane (1 mL) was added *tert*-butyldimethylsilyl triflate (0.69 mL, 3.0 mmol) and 2,6-lutidine (0.52 mL, 4.5 mmol). After being stirred for 2 h, the reaction mixture was poured into saturated aq $NaHCO_3$ and extracted with ether. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone :

hexane = 1 : 5) to afford **13** (144 mg, 92% yield) as pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.9-7.3 (m, 4H), 4.95-5.1 (m, 1H), 3.47 (t, *J* = 5.7 Hz, 1H), 2.67 (t, *J* = 6.8 Hz, 2H), 1.65 (s, 3H), 1.61 (s, 3H), 1.02 (s, 9H), 0.55 (d, *J* = 5.9 Hz, 6H); IR ($CHCl_3$) ν 2955, 2930, 1705, 1610, 1480, 1460, 1270, 1255, 1215, 1170 cm^{-1}; HRMS calcd for $C_{19}H_{29}NOSi$ (M^+) 315.2017. Found 315.2107.

1-(4-Methoxybenzyl)-3-(3-methylbut-2-enyl)-2-oxindole (14): *n*-BuLi (1.54 M in hexane, 13.0 mL, 20 mmol) was added to a solution of 1-(4-methoxybenzyl)-2-oxindole (5.06 g, 20 mmol) in THF (60 mL) at -78 °C. The mixture was warmed to 0 °C and stirred for 1 h, then cooled at -78 °C and treated with 1-bromo-3-methyl-2-butene (2.60 mL, 30 mmol). After being stirred at -50 °C for 3 h, the reaction mixture was warmed at -30 °C and stirred for 2 h, then quenched with saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was successively washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 7) to afford **14** (3.25 g, 51% yield): pale yellow prisms: mp 64-66 °C (hexane); ^{1}H-NMR ($CDCl_3$) δ 6.7-7.3 (m, 8H), 5.0-5.2 (m, 1H), 4.70, 5.03 (ABq, *J* = 15.5 Hz, 2H), 3.79 (s, 3H), 3.56 (t, *J* = 6.2 Hz, 1H), 2.6-2.85 (m, 2H), 1.66 (s, 3H), 1.60 (s, 3H) ; IR (KBr) ν 2950, 2900, 1700, 1610, 1510, 1240 cm^{-1}; MS *m/z* 321 (M^+). Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47 ; H, 7.21 ; N, 4.36. Found : C, 78.47 ; H, 7.26 ; N, 4.27.

3-Methyl-3-(2-nitrovinyl)-2-oxindole (15): yellow oil: $[\alpha]_D^{20}$ -23° (*c* 0.4, $CHCl_3$) (61% ee); ^{1}H-NMR ($CDCl_3$) δ 8.94 (br s, 1H), 7.05, 7.36 (ABq, *J* = 13.5 Hz, 2H), 7.01-7.38 (m, 4H), 1.67 (s, 3H) ; IR (neat) ν 3250, 2930, 1715, 1620, 1525, 1470, 1350, 1195, 960 cm^{-1}; HRMS calcd for $C_{11}H_{10}N_2O_3$ 218.0667 (M^+), Found 218.0698.

HPLC conditions: Daicel Chiralpak AD, 2-propanol:hexane=2:98, flow (1 mL/min), t_R=50 min (minor) and 55 min (major).

1,3-Dimethyl-3-(2-nitrovinyl)-2-oxindole (16): pale yellow oil: $[\alpha]_D^{22}$ -37° (*c* 0.9, $CHCl_3$) (98% ee); ^{1}H-NMR ($CDCl_3$) δ 6.9-7.5 (m, 4H), 7.05, 7.36 (ABq, *J* = 13.6 Hz, 2H), 3.28 (s,3H), 1.65 (s, 3H) ; IR (neat) ν 3100, 2980, 1710, 1610, 1520, 1340, 1250 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.09 ; H, 5.21 ; N, 12.06. Found : C, 61.70 ; H, 5.18 ; N, 11.89 ; HRMS calcd for $C_{12}H_{12}N_2O_3$ 232.0848 (M^+), Found 232.0857.

HPLC conditions: Daicel Chiralpak AD, 2-propanol:hexane=2:98, flow (1 mL/min), t_R=29 min (minor) and 40 min (major).

1-Benzyl-3-ethyl-3-(2-nitrovinyl)-2-oxindole (17): yellow oil: $[\alpha]_D^{22}$ -46° (*c* 0.8, $CHCl_3$) (92% ee); ^{1}H-NMR ($CDCl_3$) δ 6.8-7.5 (m, 9H), 7.08, 7.45 (ABq, *J* = 13.5 Hz, 2H), 5.05, 4.88 (ABq, *J* = 15.6 Hz, 2H), 2.0-2.3 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H) ; IR (neat) ν 2960, 2930, 1700, 1610, 1520, 1345 cm^{-1}; MS *m/z* 322 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79 ; H, 5.63 ; N, 8.65. Found : C, 70.70 ; H, 5.63 ; N, 8.69.

HPLC conditions: Daicel Chiralpak AD, 2-propanol:hexane=5:95, flow (1 mL/min), t_R=13 min (minor) and 16 min (major).

1,3-Dibenzyl-3-(2-nitrovinyl)-2-oxindole (18): yellow powder: $[\alpha]_D^{22}$ +39° (*c* 0.6, $CHCl_3$) (90% ee); ^{1}H-NMR ($CDCl_3$) δ 7.12, 7.58 (ABq, *J* = 13.5 Hz, 2H), 7.05-7.35 (m, 9H), 6.9-7.0 (m, 2H), 6.65-6.75 (m, 2H), 6.5-6.6 (m, 1H), 4.54, 5.0 (ABq, *J* = 16.1 Hz, 2H), 3.40 (ABq, *J* = 5.1, 12.9 Hz, 2H) ; IR (KBr) ν 3040, 1720, 1650, 1610, 1520, 1350 cm^{-1}; MS *m/z* 384 (M^+). Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98 ; H, 5.24 ; N, 7.29. Found : C, 74.74 ; H, 5.22 ; N, 7.18.

HPLC conditions: Daicel Chiralpak AD, 2-propanol:hexane=15:85, flow (1 mL/min), t_R=13 min (minor) and 18 min (major).

3-Allyl-1-(4-methoxybenzyl)-3-(2-nitrovinyl)-2-oxindole (19): yellow oil: $[\alpha]_D^{22}$ -18° (*c* 0.7, $CHCl_3$) (95% ee); ^{1}H-NMR ($CDCl_3$) δ 7.06, 7.45 (ABq, *J* = 13.6 Hz, 2H), 5.35-5.60 (m, 1H), 5.05-5.2 (m, 2H), 4.77, 4.98 (ABq, *J* = 15.4 Hz, 2H), 3.80 (s, 3H), 2.83 (d, *J* = 7.2 Hz, 2H) ; IR (KBr) ν 2830 , 2350, 1710, 1610, 1520, 1340 cm^{-1}; MS *m/z* 364 (M^+). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.21 ; H, 5.53 ; N, 7.69. Found : C, 69.51 ; H, 5.49 ; N, 7.52.

HPLC conditions: Daicel Chiralpak AS, 2-propanol:hexane=7:93, flow (1 mL/min), t_R=21 min (major) and 24 min (minor).

3-(3-Methylbut-2-enyl)-3-(2-nitrovinyl)-2-oxindole (20): yellow oil: $[\alpha]_D^{22}$ -21° (*c* 1.0, $CHCl_3$) (97% ee); ^{1}H-NMR ($CDCl_3$) δ 9.4-9.6 (br, 1H), 7.0-7.4 (m, 4H), 7.05, 7.45 (ABq, *J* = 13.7 Hz, 2H), 4.96 (t, *J* = 7.3 Hz, 1H), 2.75 (d, *J* = 7.3 Hz, 2H), 1.64 (s, 3H), 1.54 (s, 3H); IR (neat) ν 3200, 1700, 1620, 1520, 1470, 1350 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16 ; H, 5.92 ; N, 10.29. Found : C, 66.51 ; H, 6.06 ; N, 9.93; HRMS calcd for $C_{15}H_{16}N_2O_3$ (M^+) 272.1161. Found 272.1163.

HPLC conditions: Daicel Chiralpak AD, 2-propanol:hexane=5:95, flow (1 mL/min), t_R=13 min (*R*) and 16 min (*S*).

1-Methyl-3-(3-methylbut-2-enyl)-3-(2-nitrovinyl)-2-oxindole (21): pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 6.9-7.5 (m, 4H), 6.89, 7.57 (ABq, J = 13.6 Hz, 2H), 4.8-5.0 (m, 1H), 3.26 (s, 3H), 2.72 (d, J = 8.8 Hz, 2H), 1.65 (s, 3H), 1.53 (s, 3H); IR (neat) ν 2850, 1710, 1650, 1610, 1520, 1345, 1250 cm^{-1}; MS *m/z* 286 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11 ; H, 6.34 ; N, 9.78. Found : C, 66.86 ; H, 6.40 ; N, 9.75.

HPLC conditions: Daicel Chiralpak AD, 2-propanol:hexane=2:98, flow (1 mL/min), t_R=12 min (minor) and 17 min (major).

General Procedure for Nitroolefination in Table 2. Synthesis of (*S*)-1-*tert*-Butyldimethylsilyl-3-(3-methylbut-2-enyl)-3-(2-nitrovinyl)-2-oxindole (22) (entry 11): *n*-BuLi (1.67 M in hexane, 4.79 mL, 8.0 mmol) was added to a solution of **13** (2.52 g, 8.0 mmol) in THF (24 mL) at -78 °C. After being stirred for 30 min, the enolate solution was transferred *via* cannula to a solution of **5** (0.68 g, 2.0 mmol) in THF (6 mL) precooled at -78 °C. The mixture was immediately warmed to -30 °C then gradually warmed to 0 °C during a period of 4 h. The reaction mixture was poured into 2.5 M aq HCl and extracted with ether. The organic phase was successively washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (acetone : hexane = 1 : 20) to afford **22** (0.66 g, 86% yield). The optical purity of **22** was determined to be 97% ee by HPLC analysis after its conversion to **20**: (**22**) pale yellow oil: $[\alpha]_D^{22}$ -16° (*c* 1.3, $CHCl_3$) (97% ee); ^{1}H-NMR ($CDCl_3$) δ 7.05-7.35 (m, 4H), 7.07, 7.41 (ABq, J = 13.5 Hz, 2H), 4.73 (br t, J = 8.0 Hz,1H), 2.78 (dd, J = 13.5, 8.6 Hz, 1H), 2.59 (dd, J = 13.5, 7.0 Hz, 1H), 1.58 (s, 3H), 1.54 (s, 3H); 1.00 (s, 9H), 0.54 (s, 6H); IR ($CHCl_3$) ν 2960, 2930, 2860, 1710, 1610, 1530, 1465, 1355, 1255, 1165 cm^{-1}; MS *m/z* 386 (M^+). Anal. Calcd for $C_{21}H_{30}N_2O_3Si$: C, 65.25 ; H, 7.82 ; N, 7.25. Found : C, 65.49 ; H, 7.94 ; N, 7.34.

The zinc enolate was prepared by the treatment of the corresponding lithium enolate solution prepared as above with 0.72- 0.78 M zinc chloride solution in ether[20] at -40 °C, then at -20 °C for 30 min. The zinc enolate solution was treated with **5** according to the procedure described above at the temperature indicated in the Table 2, entries 1 and 9.

1-(4-Methoxybenzyl)-3-(3-methylbut-2-enyl)-3-(2-nitrovinyl)-2-oxindole (23): yellow oil: $[\alpha]_D^{22}$ +13° (c 1.3, $CHCl_3$) (95% ee); ^{1}H-NMR ($CDCl_3$) δ 6.7-7.3 (m, 8H), 7.08, 7.48 (ABq, J = 13.5 Hz, 2H), 4.75-4.9 (m, 1H), 4.68, 5.10 (ABq, J = 15.7 Hz, 2H), 3.81 (s, 3H), 2.81 (dq, J = 13.9, 8.4 Hz, 2H), 1.62 (s, 3H), 1.58 (s, 3H); IR (neat) ν 2900, 1710, 1610, 1520, 1340, 1245 cm^{-1};

MS *m/z* 392 (M^+). Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39 ; H, 6.16 ; N, 7.14. Found : C, 70.43 ; H, 6.18 ; N, 7.17.

HPLC conditions: Daicel Chiralpak AS, 2-propanol:hexane=8:92, flow (1 mL/min), t_R=22 min (minor) and 27 min (major).

(*S*)-1,3-Dimethyl-5-methoxy-3-(2-nitroethyl)-2-oxindole (26) : A mixture of (*S*)-**2** (95% ee) (205 mg, 0.78 mmol) and sodium borohydride (44 mg, 1.2 mmol) in dioxane-methanol (3:1, 4 mL) was stirred at rt for 3 h. The mixture was poured into saturated aq NH_4Cl and extracted with ether. The organic phase was washed with saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (dichloromethane) to afford (*S*)-**26** (202 mg, 98% yield): colorless needles: mp 96-97 °C (benzene-heptane): $[\alpha]_D^{22}$ -3.3° (*c* 0.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 6.75-6.95 (m, 3H), 4.0-4.4 (m, 2H), 3.84 (s, 3H), 3.23 (s, 3H), 2.4-2.8 (m, 2H), 1.45 (s, 3H); IR (KBr) ν 2965, 1710, 1600, 1550, 1500, 1360, 1290, 1205, 1125, 1030 cm^{-1}; MS *m/z* 264 (M^+). Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08 ; H, 6.10 ; N, 10.60. Found : C, 58.95 ; H, 6.23 ; N, 10.47.

(*S*)-1,3-Dimethyl-5-methoxy-3-{2-(methoxycarbonylamino)ethyl}-2-oxindole (27) and (-)-esermethole (24): A mixture of (*S*)-**26** (82 mg, 0.31 mmol), 10% Pd-C (8.2 mg), and ammonium formate (0.38 g, 6.2 mmol) in ethanol (5 mL) was heated under reflux for 30 min. The mixture was filtered and washed with ethanol. The filtrate was concentrated *in vacuo* and the residue was treated with saturated aq $NaHCO_3$ and extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give the corresponding amine (64 mg) which was used in following reaction without purification. To the solution of the amine (60 mg) in dichloromethane (8 mL) was added triethylamine (72 μL, 0.51 mmol) and methyl chloroformate (31 μL, 0.38 mmol). After being stirred for 2 h at rt, the reaction mixture was poured into saturated aq NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate : hexane = 3 : 1) to afford (*S*)-**27** [11c,h] (48mg, 65% overall yield){$[\alpha]_D^{22}$ -23° (*c* 1.2, $CHCl_3$)}, which was treated with lithium aluminum hydride according to the literature[11g] gave **24** in 60% yield, $[\alpha]_D^{22}$ -126° (*c* 0.4, benzene); lit.,[11a] $[\alpha]_D^{34}$ -134° (*c* 0.35, benzene). Spectral data were identical with those from the authentic sample (S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Chem. Pharm. Bull.*, 1982, **30**, 2641).

(*S*)-3-(*E*-4-Hydroxy-3-methylbut-2-enyl)-3-(2-nitrovinyl)-2-oxindol (29): A solution of (*S*)-**20** (438 mg, 1.6 mmol) in dichloromethane (2 mL) obtained from (*S*)-**22** (97% ee) was added to a solution of selenium dioxide (92 mg, 0.80 mmol), *tert*-butyl hydroperoxide (0.65 g, 5.8 mmol), and salicylic acid (0.22 g, 1.6 mmol) in dichloromethane (5 mL). After being stirred at rt for 48 h, the mixture was diluted with dichloromethane and washed successively with 10% aq KOH (three times), saturated aq NaCl, and water. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 2 : 1) to afford (*S*)-**29** (202 mg, 44% yield) as yellow amorphous: $[\alpha]_D^{22}$ -14° (*c* 1.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.3-9.32 (br, 1H), 6.95-7.35 (m, 4H), 7.05, 7.43 (ABq, *J* = 13.6 Hz, 2H), 5.19 (t, *J* = 6.4 Hz, 1H), 3.88 (s, 2H), 2.7-2.8 (m, 2H), 2.4-2.6 (br, 1H), 1.59 (s, 3H); HRMS calcd for $C_{15}H_{16}N_2O_4$ (M^+) 288.1110. Found 288.1122.

(*S*)-[3-(*E*-4-Hydroxy-3-methylbut-2-enyl)-2-oxindol-3-yl]acetaldehyde (30): To a solution of ammonium acetate (1.98 g, 26 mmol) in methanol-water (4:3, 16 mL) was added 20% aq titanium(III) chloride (2.1 mL, 2.6 mmol) followed by a solution of (*S*)-**29** (200 mg, 0.52 mmol) in methanol (3 mL). After being stirred at rt for 3 h, the mixture was extracted with ether. The organic layer was successively washed with saturated aq $NaHCO_3$ and saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate : hexane = 5 : 1) to afford (*S*)-**30** (86 mg, 49% yield) as pale yellow oil: $[\alpha]_D^{22}$ -31° (*c* 1.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.55 (s, 1H), 8.1-8.2 (br, 1H), 6.9-7.3 (m, 4H), 5.20 (br t, *J* = 7.7 Hz, 1H), 3.90 (s, 2H), 3.10 (s, 2H), 2.59 (d, *J* = 7.7 Hz, 2H), 1.58 (s, 3H); HRMS calcd for $C_{15}H_{17}NO_3$ (M^+) 259.1207. Found 259.1199.

(*S*)-(-)-Pseudophrynaminol (28) : A mixtur of (*S*)-**30** (85 mg, 0.33 mmol), methylamine hydrochloride (22 mg, 0.33 mmol), anhydrous magnesium sulfate (234 mg, 1.9 mmol), and triethylamine (46 μL, 0.33 mmol) in THF (8 mL) was stirred at rt for 25 h. Lithium aluminum hydride (124 mg, 3.3 mmol) was added and the resulting mixture was heated under reflux of THF for 2 h. After being cooled at rt, the mixture was quenched with ethyl acetate (2 mL) followed by saturated aq $NaHCO_3$ (2 mL). The mixture was extracted with ethyl acetate and the organic layer was washed with saturated aq NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (methanol : chloroform = 1 : 4) to afford (*S*)-(-)-pseusophrynaminol (40 mg, 47% yield). {$[\alpha]_D^{20}$ -80°

(c 1.0, $CHCl_3$)}; lit.,[15] $[\alpha]_D^{29}$ -82.8° (c 0.98, $CHCl_3$), Spectral data of **28** were identical with those reported.[12]

REFERENCES

Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

1. K. Fuji, *Chem. Rev.*, 1993, **93**, 2037.
2. (a) K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, and S. Terada *J. Am. Chem. Soc.*, 1986, **108**, 3855. (b) K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, T. Taga, K. Machida, and G. Snatzke, *J. Am. Chem. Soc.*, 1989, **111**, 7921.
3. (a) M. Node, H. Nagasawa, and K. Fuji, *J. Am. Chem. Soc.*, 1987, **109**, 7901. (b) M. Node, H. Nagasawa, and K. Fuji, *J. Org. Chem.*, 1990, **55**, 517.
4. M. Node, X.-J. Hao, and K. Fuji, *Chem. Lett.*, 1991, 57.
5. (a) M. Node, X.-J. Hao, H. Nagasawa, and K. Fuji, *Tetrahedron Lett.*, 1989, **30**, 4141. (b) X.-J. Hao, M. Node, and K. Fuji, *J. Chem. Soc., Perkin Trans. I*, 1992, 1505.
6. K. Fuji, S.-Z. Zheng, M. Node, and X.-J. Hao, *Chem. Pharm. Bull.*, 1991, **39**, 202.
7. Parts of this work have been published in a preliminary form: K. Fuji, T. Kawabata, T. Ohmori, and M. Node, *Synlett*, **1995**, 367.
8. M. Polonovski and C. Nitzberg, *Bull. Soc. Chim. Fr. Sér. 4*, 1916, **19**, 33.
9. (a) A. Brossi, *J. Med. Chem.*, 1990, **33**, 2311. (b) M. Sano, K. Bell, K. Marder, and L. Stricks, *Clinical Pharm.*, 1993, **16**, 61.
10. For a review, see: S. Takano and K. Ogasawara, *The Alkaloids*; ed. by A. Brossi,: Academic Press: New York, 1989; Vol. 36, p. 25.
11. For asymmetric synthesis reported since ref. 10, see: (a) S. Takano, M. Moriya, Y. Iwabuchi, and K. Ogasawara, *Chem. Lett.*, 1990, 109. (b) M. Node, A. Itoh, Y. Masaki, and K. Fuji, *Heterocycles*, 1991, **32**, 1705. (c) T. B. K. Lee and G. S. K. Wong, *J. Org. Chem.*, 1991, **56**, 872. (d) S. Takano, M. Moriya, and K. Ogasawara, *J. Org. Chem.*, 1991, **56**, 5982. (e) J. P. Marino, S. Bogdan, and K. Kimura, *J. Am. Chem. Soc.*, 1992, **114**, 5566. (f) Q. Yu, W. Luo, Y. Li, and A. Brossi, *Heterocycles*, 1993, **36**, 1279. (g) A. Ashimori, T. Matsuura, L. E.Overmann, and D. J. Poon, *J. Org. Chem.*, 1993, **58**, 6949. (h) M. Pallavicini, E. Valoti, L. Villa, and F. Lianza, *Tetrahedron: Asymmetry*, 1994, **5**, 111. (i) M. Pallavicini, E. Valoti, L. Villa, and I. Resta, *Tetrahedron: Asymmetry*, 1994, **5**, 363.
12. T. F. Spande, M. W. Edwards, L. K. Pannell, J. W. Daly, V. Erspamer, and P. Melchiorri, *J. Org. Chem.*, 1988, **53**, 1222.
13. (a) C. W. Myers and J. W. Daly, *Sci., Am.*, 1983, **248**(2), 97. J. W. Daly, R. J. Highet, and C. W. Myers, *Toxicon*, 1984, **22**, 905. (b) V. Erspamer, G. Falconieri-Erspamer, P. Melchiorri, and G. Mazzani, *Neuropharmacology*, 1985, **24**, 783. (c) G. Falconieri-Erspamer, V. Erspamer, and P. Melchiorri, *Neuropharmacology*, 1986, **25**, 807.
14. (a) M. O. Mitchell and P. W. Le Quesne, *Tetrahedron Lett.*, 1990, **31**, 2681. (b) P. G. Cozzi, C.

Palazzi, D. Potenza, C. Scolastico, and W. Y. Sun, *Tetrahedron Lett.*, 1990, **31**, 5661.

15. W. Y. Sun, Y. Sun, Y. C. Tang, and J. Q. Hu, *Synlett*, 1993, 337.
16. M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 5526.
17. J. E. McMurry and J. Melton, *J. Org. Chem.*, 1973, **38**, 4367.
18. D. Enders, H. Kipphardt, P. Gerdes, L. J. Breñ-valle, and V. Bhushan, *Bull. Soc. Chim. Belg.*, 1988, **97**, 692.
19. M. Fanlgues, L. Rene, and R. Royer, *Synthesis*, 1982, 260.
20. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. A.m. Chem. Soc.*, 1973, **95**, 3310.
21. N. Hirose, S. Souda, and S. Toyoshiama, *Yakugakuzasshi*, 1971, **91**, 1323.

Received, 22nd July, 1997