Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 15, pp. 2579–2584, 1997

Printed in Great Britain
PII: S0957-4166(97)00312-1
0957-4166/97 $17.00 + 0.00

Novel synthetic approach to 1α,24(*R*)-dihydroxyvitamin D_3 using an asymmetric nitroaldol reaction

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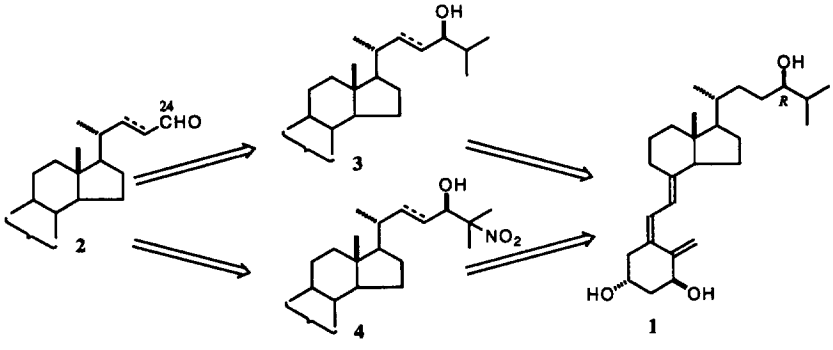
Abstract: Rare earth–K–(*S*)-BINOL complexes were used to catalyze the nitroaldol reaction of the CD-ring 24-aldehyde precursors with 2-nitropropane in a good stereoselective manner. The obtained nitroaldol compound was easily converted into a synthetic intermediate **12** of 1α,24(*R*)-dihydroxyvitamin D_3 **1** by a denitration reaction using 2,2′-azobisisobutyronitrile (AIBN) and Bu_3SnH. © 1997 Elsevier Science Ltd

Introduction

1α,24(*R*)-Dihydroxyvitamin D_3 **1**,[1] an active analogue of vitamin D_3, inhibits the growth of keratinocytes, induces keratinocyte differentiation[2] with less hypercalcemic activity, and is used as a therapeutic drug for psoriasis. Previously, we reported[3] the methodology for the diastereoselective total synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 **1**, which involved the diastereoselective isopropylation of 24-aldehyde precursors **2** with diisopropylzinc in the presence of chiral β-amino alcohols to give isopropylated adducts **3** as outlined in Scheme 1.



Scheme 1.

We report here another successful methodology, which includes the asymmetric nitroaldol reaction of the same 24-aldehyde precursors **2** with 2-nitropropane in the presence of rare earth metal–alkali metal–BINOL complexes. The nitroaldol reaction is one of the fundamental C–C bond-forming reactions to give nitro alcohols, which are useful intermediates for further transformations, for the synthesis of useful compounds.[4] In recent years, the catalytic asymmetric nitroaldol reaction using rare earth metal–alkali metal–BINOL complexes have been developed to expand the scope of the nitroaldol reaction[5] which prompted us to use the asymmetric addition reaction of the 24-aldehyde precursors **2** with 2-nitropropane to construct the side chain framework of 1α,24(*R*)-dihydroxyvitamin D_3 **1** via nitroaldol adducts **4**.

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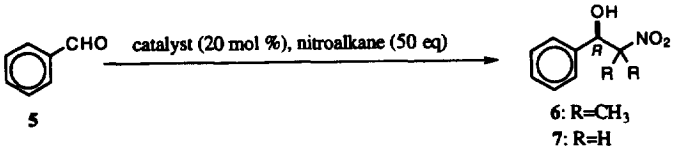
Results and discussion

Reaction of benzaldehyde with 2-nitropropane

Concerning the asymmetric nitroaldol reaction of aldehydes with 2-nitropropane, no example is known at this time.[5] We first started to examine the catalytic asymmetric nitroaldol reactions of benzaldehyde **5** with 2-nitropropane (Scheme 2). In the series of rare earth metal–alkali metal–BINOL complexes, lanthanum–lithium–BINOL (LLB) is reported to be the most efficient catalyst for the asymmetric nitroaldol reaction.[6] In the presence of LLB, prepared from $La(O^iPr)_3$, BuLi (3 eq) and (*S*)-BINOL (3 eq), [5 h] almost no addition reaction of 2-nitropropane to benzaldehyde occurred in THF at −30°C (Table 1, entry 1). When the reaction was carried out at 0°C or hexamethylphosphoramide (HMPA) was used as a co-solvent, nitroaldol reactions proceeded in 47% and 34% yield, respectively, without any stereoselectivity (Table 1, entries 2 and 3). These results indicated that LLB is not a suitable catalyst for the asymmetric nitroaldol reaction with 2-nitropropane. In the presence of lanthanum–potassium–BINOL[7] (LPB), which contains potassium instead of lithium for LLB and has not been reported as a catalyst for the asymmetric nitroaldol reaction, the nitroaldol reaction of benzaldehyde with 2-nitropropane was found to proceed with a moderate asymmetric induction (Table 1, entry 4). On the other hand, for the reaction with nitromethane, LPB was found to be less effective than LLB (Table 1, entries 5 and 6) showing specific effectiveness in the asymmetric reaction with 2-nitropropane.



5

6: R=CH_3
7: R=H

Scheme 2.

Reaction of 24-aldehyde precursors with 2-nitropropane

Instead of benzaldehyde, both a saturated 24-aldehyde precursor[3b] **8** and an α,β-unsaturated aldehyde[3b] **10** were subjected to the asymmetric nitroaldol reaction using LPB (Scheme 3). It was

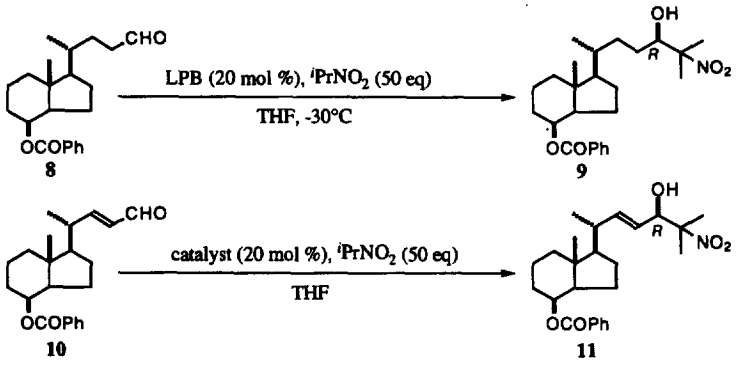
Table 1. Catalytic asymmetric nitroaldol reaction of benzaldehyde

entry	solvent	nitroalkane	catalyst*1	temperature	nitroaldol	yield*2	R : S*3
1	THF	$^iPrNO_2$	LLB	-30°C	**6**	almost no reaction	
2	THF	$^iPrNO_2$	LLB	0°C	**6**	47%	50 : 50
3	THF / HMPA (1 / 2)	$^iPrNO_2$	LLB	-30°C	**6**	34%	50 : 50
4	THF	$^iPrNO_2$	LPB	-30°C	**6**	61%	73 : 27
5	THF	$MeNO_2$	LPB	-50°C	**7**	71%	53 : 47
6	THF	$MeNO_2$	LLB	-50°C	**7**	91%	74 : 26

*1 LLB: lanthanum-lithium-(*S*)-BINOL, LPB: lanthanum-potassium-(*S*)-BINOL *2 Isolated yield

*3 Absolute configuration of **6** was estimated by reported results (ref. 5d) and that of **7** was estimated by comparison of elution order with commercially available (*R*)-(+)-2-methyl-1-phenyl-1-propanol using HPLC analysis (Chiralpak AD, hexane:EtOH=97.5:2.5) after denitration. R : S ratio was estimated by HPLC analysis using Chiralcel OD-H (hexane:^{i}PrOH=9:1).

found that the α,β-unsaturated aldehyde (71%, *R*:*S*=83:17) is a more preferable substrate than the saturated aldehyde (50%, *R*:*S*=50:50) with 2-nitropropane (Table 2, entries 1 and 2).



Scheme 3.

To improve the stereoselectivity of the nitroaldol reaction using the α,β-unsaturated aldehyde **10** with 2-nitropropane, other types of rare earth metal–alkali metal–BINOL complexes were examined. Complexes containing barium, magnesium, and sodium instead of lithium and potassium were found not to be effective catalysts for the nitroaldol reaction with 2-nitropropane (Table 2, entries 3–5). Both the yttrium and the samarium complexes showed catalytic activity (11% and 50% yield, respectively) but their stereoselectivities were not improved (*R*:*S*=43:57 and 83:17, respectively, Table 2, entries 6 and 7). Among the (*S*)-6,6′-bis((alkylsilyl)ethynyl)BINOLs, which were reported to be effective in the nitroaldol reaction,[5h] both La–Li–(*S*)-6,6′-bis((trimethylsilyl)ethynyl)BINOL and La–Li–(*S*)-6,6′-bis((triethylsilyl)ethynyl)BINOL gave the corresponding nitroaldol adduct with high stereoselectivities

Table 2. Catalytic asymmetric nitroaldol reaction of 24-aldehyde precursors with ^{i}PrNO$_2$

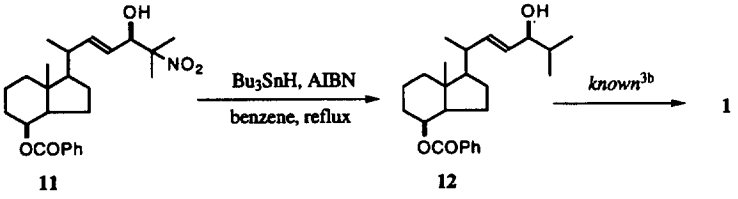
entry	aldehyde	catalyst*1	temperature	nitroaldol	yield*2	R : S*3
1	**8**	LPB	-30°C	**9**	50 %	50 : 50
2	**10**	LPB	-30°C	**11**	71 %	83 : 17
3	**10**	LSB	-30°C	**11**	almost no reaction	
4	**10**	LMB	-30°C	**11**	almost no reaction	
5	**10**	LBB	-30°C	**11**	almost no reaction	
6	**10**	YPB	-30°C	**11**	11 %	43 : 57
7	**10**	SPB	-30°C	**11**	51 %	83 : 17
8	**10**	LPB1	-30°C	**11**	60 %	92 : 8
9	**10**	LPB2	-30°C	**11**	70 %	93 : 7
10	**10**	LPB2	-50°C	**11**	65 %	94 : 6

*1 LPB: La-K-(*S*)-BINOL, LSB: La-Na-(*S*)-BINOL, LMB: La-Mg-(*S*)-BINOL, LBB: La-Ba-(*S*)-BINOL, SPB: samarium-K-(*S*)-BINOL, LPB1: La-K-(*S*)-6,6'-bis((trimethylsilyl)ethynyl)BINOL, YPB: yttrium-K-(*S*)-BINOL, LPB2: La-K-(*S*)-6,6'-bis((triethylsilyl)ethynyl)BINOL,

*2 Isolated yield *3 R : S ratio was estimated by HPLC analysis using Zorbax SIL (hexane:CH_2Cl_2:EtOH =90:10:0.4) for **9**, and Chiralcel OD-H (hexane:^{i}PrOH=9:1) for **10**.

(92:8 and 93:7, respectively, Table 2, entries 8 and 9). By lowering the reaction temperature to −50°C, the stereoselectivity was raised to 94:6 (Table 2, entry 10).

The denitration[8] of the obtained nitroaldol adduct **11** by Bu_3SnH in the presence of 2,2′-azobisisobutyronitrile (AIBN) gave the corresponding denitrated alcohol **12** in 70% yield, which is known as the key intermediate in the synthesis of 1α,24(*R*)-dihydroxyvitamin D_3[3b] **1** (Scheme 4). The present results demonstrate a novel asymmetric route to 1α,24(*R*)-dihydroxyvitamin D_3 **1**.



Scheme 4.

Conclusion

It was found that the asymmetric nitroaldol reactions of aldehydes with 2-nitropropane proceeded in the presence of rare earth metal–K–(*S*)-BINOL complexes, and that a conjugated double bond was needed for good asymmetric induction. The present methodologies were successfully applied to the reaction of the 24-aldehyde precursor of 1α,24(*R*)-dihydroxyvitamin D_3 **1** to give the nitroaldol adduct with high enantiomeric excesses. The obtained nitroaldol adduct was denitrated to the corresponding alcohol, which could be used as the key intermediate for the synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 **1** by the known procedure.[3b]

Experimental

IR spectra were recorded on a Shimadzu 8100M spectrometer. NMR spectra were obtained using a Varian Gemini 200 (200 MHz) spectrometer in $CDCl_3$. Chemical shifts and coupling constants (J) are given in ppm relative to internal tetramethylsilane and Hz, respectively. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and b (broad). Mass spectra (MS) were taken at 70 eV using a HP 5971 mass spectrometer. For high-performance liquid chromatography (HPLC) analysis, a Shimadzu Model LC-6A equipped with a Shimadzu SPD-6A UV detector (254 nm) and a Shimadzu C-R3A chromatopac was employed.

General procedure for the synthesis of La–K–(S)-BINOL complexes

To a solution of (*S*)-BINOL derivatives (2.0 mmol) in THF (4.5 mL) was added a solution of $La(O^iPr)_3$ (211 mg, 0.67 mmol; purchased from Soekawa Chemical Co., Ltd., Japan) in THF (6.9 mL) at 0°C. After being stirred for 1 h at room temperature, a 1.0 mol/L THF solution of KO^tBu (3.0 ml, 3.0 mmol) was added. The obtained solution was directly used as a catalyst (0.05 mol/L).

General procedure for the asymmetric nitroaldol reaction

To a solution of **an aldehyde** (0.15 mmol) and **a nitro compound** (7.5 mmol) in THF (2 mL) was added at −30°C a 0.05 mol/L THF solution of rare earth–alkali metal–(*S*)-BINOL complexes (0.6 mL, 0.03 mmol), and the resulting mixture was stirred for 96 h. After a 1 mol/L HCl solution was added, the mixture was extracted with EtOAc (25 mL). The separated extract was washed with brine (25 mL). Drying over $MgSO_4$ and filtration followed by evaporation of the solvent gave a crude product, which was passed through a silica gel pad (20 g) eluting with hexane and EtOAc (2:1). After evaporation of the solvent, the residue was subjected to preparative HPLC (silica gel, (hexane–EtOAc (10:1)) providing **the corresponding nitroaldol adduct**. The *R*/*S* ratio was estimated by HPLC analysis. The results are summarized in Tables 1 and 2.

2-Methyl-2-nitro-1-phenyl-1-propanol **6**[9]

9 was obtained from the reaction of benzaldehyde **5** with $^{i}PrNO_2$. The nitroaldol adduct **6** was subjected to HPLC analysis (Chiralcel OD-H 25 cm×4.6 mm I.D.) using hexane–^{i}Pr OH (90:10) as the mobile phase at 1.0 mL/min to estimate the ratio of **6*R*** and **6*S*** (**6*R***; 8.4 min, **6*S***; 11.7 min). An analytical sample was converted to 2-methyl-1-phenyl-1-propanol[10] by denitration[8] according to the procedure described below and then analyzed by HPLC (Chiralpak AD, hexane:EtOH=97.5:2.5, 1.0 mL/min, $t_R(R)$=8.1 min, $t_R(S)$=7.4 min) to determine an absolute configuration. IR (neat): 2997, 1534, 1468, 1401, 1373, 1350, 1293 cm^{-1}; ^{1}H NMR: δ 1.48 (s, 6H), 5.43 (b, 1H), 7.35–7.45 (m, 5H); MS (*m/z*):195 (M^+); High-resolution MS for $C_{10}H_{13}NO_3$ (M^+): Calcd. *m/z*: 195.0895; Found: 195.0963.

2-Nitro-1-phenyl-1-ethanol **7**[5d]

7 was obtained from the reaction of benzaldehyde **5** with $MeNO_2$. The nitroaldol adduct **7** was subjected to HPLC analysis (Chiralcel OD-H 25 cm×4.6 mm I.D.) using hexane–^{i}Pr OH (90:10) as the mobile phase at 1.0 mL/min to estimate the ratio of **7*R*** and **7*S*** (**7*R***; 12.1 min, 7*S*; 14.8 min). IR (neat): 3065, 1560, 1495, 1455, 1418, 1379, 1289 cm^{-1}; ^{1}H NMR: δ 2.80–2.90 (m, 1H), 4.45–4.70 (m, 2H), 5.40–5.55 (m, 1H), 7.30–7.45 (m, 5H); MS (*m/z*):167 (M^+); High-resolution MS for $C_8H_9O_3N$ (M^+): Calcd. *m/z*: 167.0583; Found: 167.0551.

[1R-[1α(3R,6R*),3aβ,4α,7aα]]-6-[4-(Benzoyloxy)octahydro-7a-methyl-1H-inden-1-yl]-2-methyl-2-nitro-heptan-3-ol* **9**

9 was obtained from the reaction of [1*R*-[1α(4*R**),3aβ,4α,7aα]]-4-[4-(benzoyloxy)octahydro-7a-methyl-1*H*-inden-1-yl]pentan-1-al **8** with $^{i}PrNO_2$. A nitroaldol adduct **9** was subjected to HPLC analysis (Zorbax SIL 25 cm×4.6 mm I.D.) using hexane–CH_2Cl_2–EtOH (90:10:0.4) as the mobile phase at 2.0 mL/min to estimate the ratio of **9*R*** and **9*S*** (**9*R***; 17.8 min, **9*S***; 20.7 min). The absolute configuration at C-3 was estimated by comparison of an elution order with the authentic sample, which was obtained by hydrogenation of nitroaldol **11** (**11*R***:**11*S***=83:17) over Pd/C, using HPLC analysis. IR (neat): 2949, 1716, 1541, 1271 cm^{-1}; ^{1}H NMR: δ 0.94 (d, 3H, *J*=6 Hz), 1.05 (s, 3H), 1.05–2.35 (m, 17H), 1.56 (s, 3H), 3.85–4.00 (m, 1H), 5.35–5.45 (m, 1H), 7.40–7.60 (m, 3H), 8.00–8.10 (m, 1H); MS (*m/z*): 431 (M^+); High-resolution MS for $C_{25}H_{37}O_3$ $(M-46)^+$: Calcd. *m/z*: 385.2743; Found: 385.2689.

[1R-[1α(3R,4E,6R*),3aβ,4α,7aα]]-6-[4-(Benzoyloxy)octahydro-7a-methyl-1H-inden-1-yl]-2-methyl-2-nitro-4-hepten-3-ol* **11**

11 was obtained from the reaction of [1*R*-[1α(2*E*,4*R**),3aβ,4α,7aα]]-4-[4-(benzoyloxy)-octahydro-7a-methyl-1*H*-inden-1-yl]-2-penten-1-al **10** with $^{i}PrNO_2$. The nitroaldol adduct **11** was subjected to HPLC analysis (Chiralcel OD-H 25 cm×4.6 mm I.D.) using hexane–^{i}Pr OH (90:10) as the mobile phase at 1.0 mL/min to estimate the ratio of **11*R*** and **11*S*** (**11*R***; 7.4 min, **11*S***; 8.6 min). IR (neat): 2948, 1717, 1541, 1271 cm^{-1}; ^{1}H NMR: δ 1.04 (d, 3H, *J*=6 Hz), 1.05 (s, 3H), 1.05–2.25 (m, 15H), 1.52 (s, 6H), 4.45–4.55 (m, 1H), 5.25–5.45 (m, 2H), 5.60–5.80 (m, 1H), 7.40–7.60 (m, 3H), 8.00–8.10 (m, 1H); MS (*m/z*): 429 (M^+); High-resolution MS for $C_{25}H_{35}NO_5$ (M^+): Calcd. *m/z*: 429.2515; Found: 429.2505.

Conversion of nitroaldol adduct to a synthetic intermediate **12** *of 1α,24(*R*)-dihydroxyvitamin D_3* **1**

To a solution of [1*R*-[1α(3*R**,4*E*,6*R**),3aβ,4α,7aα]]-6-[4-(benzoyloxy)octahydro-7a-methyl-1*H*-inden-1-yl]-2-methyl-2-nitro-4-hepten-3-ol **11** (11 mg, 0.026 mmol) in benzene (2 mL) was added AIBN (16 mg, 0.098 mmol) and Bu_3SnH (0.06 mL, 0.223 mmol). The resulting mixture was refluxed for 2 h. Removal of the solvent gave a crude product, which was subjected to column chromatography on silica gel (20 g) using hexane and EtOAc (20:1) as the eluent to obtain [1*R*-[1α(3*R**,4*E*,6*R**),3aβ,4α,7aα]]-6-[4-(benzoyloxy)-octahydro-7a-methyl-1*H*-inden-1-yl]-2-methyl-4-hepten-3-ol **12** (7 mg, 0.018 mmol, 70%).[3b] The absolute configuration at C-3 was confirmed by HPLC analysis after hydrogenation.[3d] IR (neat): 3500, 2953, 2870, 1717, 1410, 1314,

1113 cm^{-1}; ^1H NMR: δ 0.85–1.00 (m, 9H), 1.1–2.40 (m, 18H), 3.80 (t, 1H, *J*=6 Hz), 5.43 (b, 1H), 5.40–5.65 (m, 2H), 7.40–7.60 (m, 3H), 8.00–8.10 (m, 1H); MS (*m/z*): 384 (M^+).

Acknowledgements

The authors gratefully acknowledge S. Sugihara for his technical assistance.

References

1. Morisaki, M.; Koizumi, N.; Ikekawa, N., *J. Chem. Soc. Perkin Trans. I* **1975**, 1421.
2. (a) Tanaka, H.; Abe, E.; Miyaura, C.; Kurihashi, T.; Konno, K.; Nishii, Y.; Suda, T., *Biochem. J.* **1982**, *204*, 713; (b) Matsumoto, K.; Hashimoto, K.; Kiyoshi, M.; Yamamoto, M.; Yoshikawa, K., *J. Dermatol.* **1990**, *17*, 97; (c) Matsunaga, T.; Yamamoto, M.; Mimura, H.; Ohta, T.; Kiyoshi, M.; Ohba, T.; Naruchi, T.; Hosoi, J.; Kuroki, T., *J. Dermatol.* **1990**, *17*, 135; (d) Kobayashi, T.; Okumura, H.; Azuma, Y.; Kiyoki, M.; Matsumoto, K.; Hashimoto, K.; Yoshikawa, K., *J. Dermatol.* **1990**, *17*, 707.
3. (a) Okamoto, M.; Tabe, M.; Fujii, T.; Tanaka, T., *Tetrahedron: Asymmetry* **1995**, *6*, 767; (b) Okamoto, M.; Fujii, T.; Tanaka, T., *Tetrahedron* **1995**, *51*, 5543.
4. (a) Martin, O. R.; Lai, W., *J. Org. Chem.* **1993**, *58*, 176; (b) Kolter, T.; Echten-Decket, G. V.; Sandhoff, K., *Tetrahedron* **1994**, *50*, 13425; (c) Barlaam, B.; Boivin, J.; Elkaim, L.; Elton-Farr, S.; Zard, S. Z., *Tetrahedron* **1995**, *51*, 1684; (d) Chandler, M.; Conroy, R.; Cooper, A. W. J.; Lamount, R. B.; Scicinski, J. J.; Smart, J. E.; Storer, R.; Weir, N. G.; Wilson, R. D.; Wyatt, P. G., *J. Chem. Soc. Perkin Trans. I* **1995**, 1189.
5. (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M., *J. Am. Chem. Soc.* **1992**, *114*, 4418; (b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M., *Tetrahedron Lett.* **1993**, *34*, 851; (c) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M., *Tetrahedron Lett.* **1993**, *34*, 855; (d) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M., *Tetrahedron Lett.* **1993**, *34*, 2657; (e) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.;Okamura, K.; Shibasaki, M., *J. Am. Chem. Soc.* **1993**, *115*, 10372; (f) Sasai, H.; Kim, W.S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T., *Tetrahedron Lett.* **1994**, *35*, 6123; (g) Sasai, H.; Yamada, Y. M. A.; Shibasaki, M., *Tetrahedron* **1994**, *50*, 12313; (h) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M., *J. Org. Chem.* **1995**, *60*, 7388.
6. Steinhagen, H.; Helmchen, G., *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2339.
7. Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M., *J. Org. Chem.* **1995**, *60*, 6656.
8. (a) Tanner, D. D.; Blackburn, E. V.; Diaz, G. E., *J. Am. Chem. Soc.* **1981**, *103*, 1557; (b) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A., *Tetrahedron Lett.* **1981**, *22*, 1705; (c) Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Kaji, A., *Tetrahedron* **1985**, *41*, 4013.
9. Fernandez, R.; Gasch, C.; Gomez-Sanchez, A.; Vilchez, J. E., *Tetrahedron Lett.* **1991**, *32*, 3225.
10. MacLeod, R.; Welch, F. J.; Mosher, H. S., *J. Am. Chem. Soc.* **1960**, *82*, 876.

(Received in Japan 6 June 1997; accepted 11 July 1997)