Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 6, pp. 1295-1300, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00162-X

Highly Efficient Resolution of Benzopyrano[4,3-*c*]isoxazolidine Derivatives: Versatile Chiral Auxiliaries for Asymmetric Alkylation

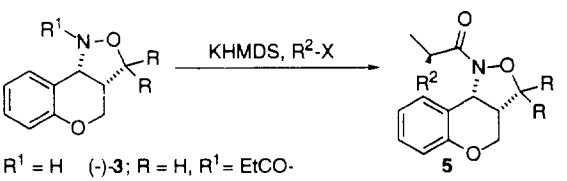
Atsushi Abiko*
Institute for Fundamental Research, Kao Corporation, Ichikai-machi, Haga-gun, Tochigi, 321-34 JAPAN.

William M. Davis and Satoru Masamune
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139 USA.

Abstract: Benzopyrano[4,3-c]isoxazolidine derivatives, newly developed chiral auxiliaries for asymmetric alkylation, were synthesized and resolved in a unique manner. Resolution could be executed so efficiently that both enantiomers were obtained with a single resolving reagent in excellent yields.

Recently we reported the synthesis and use of enantiomerically pure benzopyrano[4,3-c]isoxazolidine derivatives (**1** and **2**) as chiral auxiliaries for asymmetric alkylation (**Scheme 1**).[1] During the course of this investigation we found highly efficient methods for the resolution of compounds **1** and **2**. These methods were executed in a unique manner as detailed below.

Scheme 1: Asymmetric Alkylation of **3** and **4**

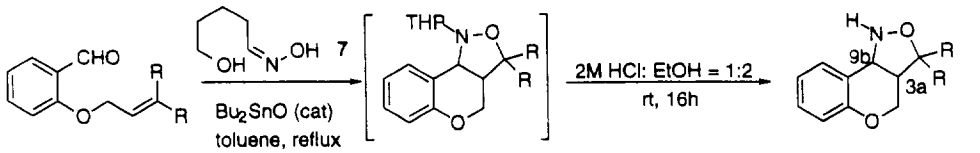


(+)-**1**; R = H, R^1 = H (-)-**3**; R = H, R^1 = EtCO-
(+)-**2**; R = Me, R^1 = H (-)-**4**; R = Me, R^1 = EtCO-

Results and discussion:

Syntheses of **1** and **2** are very simple and can be easily scaled up to more than 1 mole, and all of the starting materials for the preparation are inexpensive bulk chemicals. The isoxazolidine skeleton was constructed *via* an intramolecular [3+2] cycloaddition involving a nitrone.[2] Thus, an equimolar mixture of 2-allyloxybenzaldehyde **6** and 5-hydroxypentanal oxime **7** in toluene (1~2 M) was heated under reflux in the presence of as little as 1 mol% of Bu_2SnO for several hours with removal of the water generated. The tin catalyst was found to be essential for this transformation; prolonged heating without the catalyst or the use of more acidic catalyst such as PPTS caused total decomposition of the nitrone.[3] Simple acid hydrolysis followed by acid-base extraction afforded essentially pure **1** or **2**. (Upon basification most of **2** precipitated out.) Compound **1** was converted to its (+)-10-camphorsulfonic acid (CSA) salt for resolution. The total yield amounted to 70~90 % from the salicylaldehyde derivative, requiring no chromatographic purification. (**Scheme 2**)

Scheme 2: Synthesis of (±)-**1** and (±)-**2**



6a; R = H
6b; R = Me

8a; R = H
8b; R = Me

(±)-**1**; R = H (y. 75%)
(±)-**2**; R = Me (y. 90%)

Resolution of **1** was efficiently carried out. Thus, the (+)-CSA salt of (±)-**1** was crystallized from acetone (1 g of salt/10 ml of acetone) to afford the 1st crop (51 %; $[\alpha]_D^{25}$ +60.8, c 1.00, MeOH) which was found to be the pure (+)-isomer. Surprisingly, the 2nd crop obtained from the concentrated mother liquor (39 %; $[\alpha]_D^{25}$ -11.6, c 1.00, MeOH) was the pure (-)-isomer. Repetition of crystallization from acetone afforded the (+) and (-) salt *reciprocally* (alternately).[4] After six crystallizations total recovery of the enantiomerically pure salt amounted to 78 % for the (+) salt (>96 %ee) and 69 % for the (-) salt (>96 %ee). From these salts, (+)-**1**, $[\alpha]_D^{25}$ +62.4 (c 1.11, $CHCl_3$), mp 95-96 °C and (-)-**1**, $[\alpha]_D^{25}$ -62.4 (c 1.11, $CHCl_3$) were recovered quantitatively. The absolute configuration of (+)-**1** was determined to be [3a*S*, 9b*R*] by an X-ray analysis of the (+)-salt (**Figure 1**), and the enantiomeric purities of **1** and its propionyl derivative **3** were assessed by HPLC analysis on the Chiralcel OD column (Hexane : iPrOH = 9:1 as eluent). It should be emphasized that for this resolution one resolving reagent, (+)-CSA, afforded both enantiomers of **1** in optically pure form from the same resolving solution without seeding.

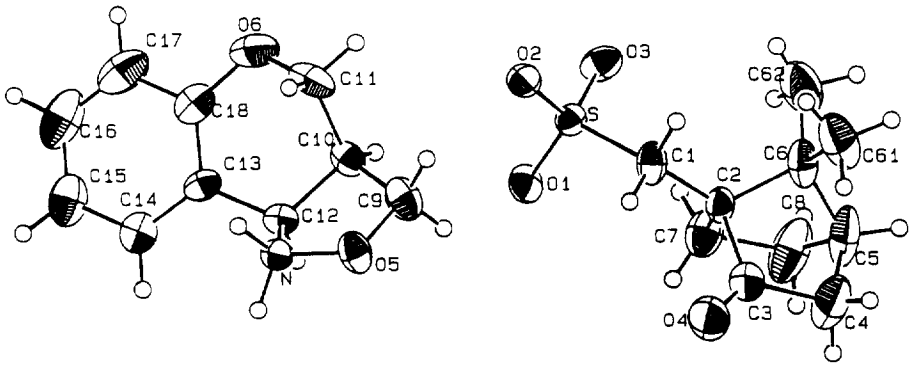
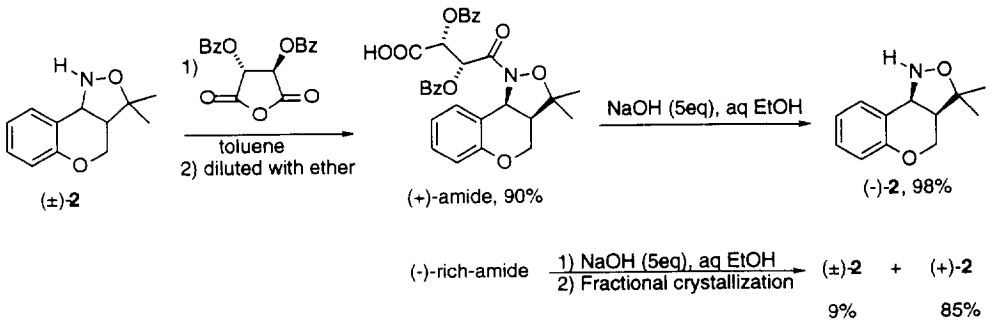


Figure 1. Crystal structure of the (+)-**1**-salt determined by X-ray crystallography

Both (+)- and (-)-**2** were obtained by resolution of (±)-**2** as its dibenzoyltartaramide derivative. Thus, treatment of (±)-**2** with L-dibenzoyltartaric anhydride afforded a mixture of isomeric monoamides, from which the (+)-isomer was crystallized in 91 % yield. The enantiomerically pure (-)-**2**, mp 85-86 °C; $[\alpha]_D^{25}$ -11.1 (c 1.14, $CHCl_3$) was liberated by alkaline hydrolysis quantitatively. The mother liquor of the crystalline amide was hydrolyzed and (+)-rich-**2** (84 %ee) was recovered, which first crystallized from ether to remove (±)-**2**, mp 120-121°C (9 %), and the enantiomerically pure (+)-**2**, mp 85-86 °C; $[\alpha]_D^{25}$ +11.1 (c 1.33, $CHCl_3$),

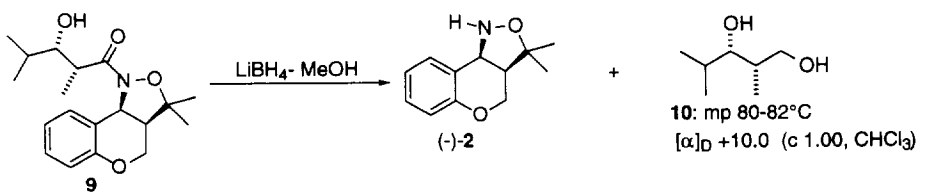
(85 %) was obtained by further crystallization from CH_2Cl_2 and hexane. Again this resolution was effected by the use of a single resolving agent to afford both enantiomers (**Scheme 3**).

Scheme 3: Resolution of (±)-**2**



The absolute stereochemistry of (-)-**2** was determined to be [3a*R*, 9b*S*] by an X-ray analysis of an aldol product **9**,[5] which was reduced by $LiBH_4$ and MeOH to the known (+)-diol **10** [6] with the recovery of (-)-**2** (**Scheme 4**). The enantiomeric purity of **2** and **4** was also determined by HPLC analysis.

Scheme 4:



It should be added that the resolutions as effective as described above are rarely found in the literature.[11]

Experimental:

2-Allyloxybenzaldehyde: ***6a*** [7]

A mixture of salicylaldehyde (106 ml, 1.0 mol), allyl bromide (90 ml, 1.05 mol) and K_2CO_3 (152 g, 1.1 mol) in acetone (1.5 L) was heated under reflux for 3 h. The cooled reaction mixture was filtered and the solid was washed with ether. Concentrated organic extracts were distilled under vaccum to give **6a** (153 g, 94%), bp 85-88 °C (0.25 mmHg).

2-(3-Methyl-2-butenyloxy)-benzaldehyde: ***6b*** [8]

A mixture of salicylaldehyde (90.6 ml, 0.85 mol), 1-chloro-3-methyl-2-butene (100 ml, 0.89 mol), NaI (15 g, 0.1 mol) and K_2CO_3 (138 g, 1.0 mol) in acetone (1.5 L) was heated under reflux for 3 h. The cooled reaction mixture was filtered and the solid was washed with ether. Concentrated organic extracts were distilled under vaccum to give **6b** (150 g, 93%), bp 115-117 °C (0.25 mmHg).

5-Hydroxypentanal oxime: **7** [9]

To a stirred solution of hydroxylamine hydrochloride (76.5 g, 1.1 mol) in H_2O (500 ml) was added dropwise 3,4-dihydro-2H-pyran (91.2 ml, 1.0 mol) at 0 °C during 1 h. Then the mixture was stirred at room temperature for 16 h, when the reaction became clear solution. The mixture was neutralized with 5 M NaOH, and extracted with ethyl acetate repeatedly. (After several extractions, the aqueous phase was concentrated and extraction was continued to ensure high recovery of the product.) Dried extracts were concentrated and the residue was recrystallized from $CHCl_3$ to give **7** (94 g, 80%).

1,3a,4,9b-Tetrahydro-cis-3H-[1]benzopyrano[4,3-c]isoxazole: (±)-**1**

A mixture of 2-allyloxybenzaldehyde **6a** (129 g, 0.8 mol), 5-hydroxypentanal oxime **7** (98 g, 0.84 mol) and Bu_2SnO (4g, 2 mol%) in toluene (800 ml) was heated under reflux with Dean-Stark apparatus for 4 h. Cooled reaction mixture was concentrated and the residue was dissloved in EtOH (1 L) and 2 M HCl (500 ml). After being stirred at room temperature for 16 h, the reaction was concentrated and the aqueous residue was extracted with ether (2 x 200 ml). The aqueous layer was basified with NH_4OH and extracted with CH_2Cl_2. Usual work-up gave crude (±)-**1**, 132 g, which was purified as (+)-CSA salt for resolution. Crude (±)-**1** was mixed with (+)-CSA (186 g) in warm acetone (1.3 L), and the solution was kept in a refrigerator overnight to give 250 g (total yield 75 % from **6a**) of crystalline salt.

Resolution of (±)-1:

(±)-**1**:(+)-CSA salt (68 g) was dissolved in 680 ml of boiling acetone. After being cooled to room temperature, the 1st crop of the crystalline was collected, 17.5 g $[\alpha]_D^{25}$ +60.8 (c 1.00, MeOH) (51 %). The mother liquor and washings were concentrated to *ca.* 400 ml and were let to stand overnight at room temperature to afford the 2nd crop, 13.3 g $[\alpha]_D^{25}$ -11.6 (c 1.00, MeOH) (39 %). Crystallization was repeated as above afforded the following crops: 3rd 5.4 g $[\alpha]_D^{25}$ +59.8 (c 1.00, MeOH) (16 %), 4th 6.0 g $[\alpha]_D^{25}$ -11.4 (c 1.00, MeOH) (18 %), 5th 3.6 g $[\alpha]_D^{25}$ +60.3 (c 1.00, MeOH) (11 %), 6th 3.7 g $[\alpha]_D^{25}$ -11.6 (c 1.00, MeOH) (12 %). Total yield of the (+)-salt was 78 % and the (-)-salt yielded 69 % after 6 crystallizations. Recrytallization of each from acetone afforded the diastereomerically pure salt with over 95 % recovery.

The (+)-salt: $[\alpha]_D^{25}$ +61.5 (c 1.10, MeOH); mp 185-187 °C (dec); IR (Nujol) ν 1740 cm^{-1}; ^1H NMR (CD_3OD) δ 7.20-7.40 (2H, m), 6.80-7.00 (2H, m), 5.12 (1H, m), 4.78 (2H, s), 4.50 (1H, m), 4.25 (2H, m), 3.82 (1H, m), 3.15 (1H, m), 2.63 (1H, m), 2.45 (1H, m), 2.20 (1H, m), 1.90 (2H, m), 1.75 (1H, m), 1.50 (1H, m), 1.28 (1H, m), 0.98 (3H, s), 0.71 (3H, s); ^{13}C NMR (CD_3OD) δ 183.8, 157.1, 144.1, 132.7, 132.3, 123.3, 119.1, 114.7, 88.8, 74.9, 64.9, 59.6, 58.4, 44.1, 43.6, 40.1, 27.8, 25.8, 20.4, 20.1; MS m/z 232(2), 177(69), 151(66), 145(70), 131(50), 123(48), 109(100), 81(78), 67(41); HRMS calcd for $C_{20}H_{28}NO_6S$ (MH^+): 410.1637, found 410.1640. Anal. Calcd for $C_{20}H_{27}NO_6S$: C, 58.66; H, 6.65; N, 3.42. Found: C, 58.53; H, 6.43; N, 3.49.

The (-)-salt: $[\alpha]_D^{25}$ -12.0 (c 1.15, MeOH); mp 186-188 °C (dec); HRMS calcd for $C_{20}H_{28}NO_6S$ (MH^+): 410.1637, found 410.1648. Anal. Calcd for $C_{20}H_{27}NO_6S$: C, 58.66; H, 6.65; N, 3.42. Found: C, 58.83; H, 6.49; N, 3.45.

(+)- and (-)-**1** were obtained quantitatively by treatment of the (+)- and (-)- salts, respectively, with 1M NaOH and extraction with CH_2Cl_2.

[3a*S*, 9b*R*]-(+)-**1**: $[\alpha]_D^{25}$ +62.4 (c 1.11, $CHCl_3$); mp 95-96 °C; IR (Nujol) ν 3180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (1H, d, J = 6.5Hz), 7.20 (1H, m), 7.00 (2H, m), 5.00 (1H, br), 4.20-4.50 (3H, m) 3.75 (2H, m),

3.10 (1H, m); ^{13}C NMR ($CDCl_3$) δ 155.5, 131.3, 129.4, 121.6, 118.5, 117.3, 72.8, 65.2, 57.3, 40.7; MS m/z 177 (M^+, 27), 145 (100), 131 (38), 115 (17), 91 (16), 77 (14), 65 (13), 51 (13), 39 (21); HRMS calcd for $C_{10}H_{11}NO_2$: 177.0790, found 177.0787. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.26; N, 7.87.

[3a*R*, 9b*S*]-(-)-**1**: $[\alpha]_D^{25}$ -62.4 (c 1.11, $CHCl_3$); mp 95-96 °C; HRMS calcd for $C_{10}H_{11}NO_2$: 177.0790, found 177.0791. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.27; N, 7.88.

X-ray Crystal Structure Analysis of the (+)-1-salt:

Crystal Data: $C_{20}H_{27}NO_6S$, FW = 409.50, crystal size 0.430 x 0.280 x 0.320 mm, orthorhombic, space group $P2_12_12_1$ (#19), a = 7.225(1) Å, b = 9.635(1) Å, c = 29.888(3) Å, V = 2080.6(7) Å^3, Z = 4, D_c = 1.307 g cm^{-3}, μ (Mo Kα) = 1.81 cm^{-1}. Intensity data were measured at 23°C on a Enraf-Nonius CAD-4 diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71069 Å) using the ω-2θ scan technique to $2\theta_{max}$ = 54.9°, and 4059 unique reflections were collected. The structure was solved by the direct method and refined anisotropically by the full-matrix least-squares to R = 0.055, R_w = 0.044 and S = 1.38.[10] Hydrogen atoms were included but not refined.

1,3a,4,9b-Tetrahydro-3,3-dimethyl-cis-3H-[1]benzopyrano [4,3-c]isoxazole: (±)-**2.**

A mixture of 2-(3-methyl-2-butenyloxy)-benzaldehyde **6b** (190 g, 1 mol), **7** (120 g,1.03 mol) and Bu_2SnO (5 g, 2 mol%) in toluene (1 L) was heated under reflux for 5 h with a Dien-Stark apparatus. When the reaction was cooled to room temperature, crystalline adduct (160 g, 55 %) was deposited and isolated by filtration. The mother liquor was concentrated to afford 150 g of residue, which was combined with the crystalline adduct and hydrolyzed in 2 M HCl (600 ml) and EtOH (1.2 L) at room temperature overnight. After being concentrated and extracted with ether, the aqueous solution was basified with NH_4OH at 0 °C to give a precipitate. Total yield of crystalline (±)-**2** amounted to 170 g (75 %) including the 2nd crop. Extraction of the aqueous mother liquor with CH_2Cl_2 afforded an additional 34 g (15 %) of (±)-**2**.

Adduct (**8b**): mp 205-206 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H), 6.90 (m, 2H), 4.57 (1H, d, J = 6.0 Hz), 4.20 (4H, m), 3.60 (1H, m), 2.40 (1H, dt, J = 6.0, 6.0 and 6.8 Hz), 1.40 and 1.30 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 155.3, 131.1, 129.1, 122.6, 120.7, 119.6, 87.1 79.0, 68.0, 64.3, 54.5, 46.9, 29.5, 29.3, 25.6, 23.8, 22.7; MS m/z 289(18), 231(20), 205(98), 173(100), 137(96), 131(94), 85(96), 67(39), 57(36); HRMS calcd for $C_{17}H_{23}NO_3$: 289.1678 found 289.1677; Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.56; H, 8.09; N, 4.66.

(±)-**2**: mp 120-121 °C; IR (Nujol) ν 3170, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (1H, m), 7.22 (1H, m), 6.95 (2H, m), 4.50 (1H, d, J = 6.6 Hz), 4.20 (1H, dd, J = 4.8 and 5.1 Hz), 3.82 (1H, dd, J = 10.8 and 13.2 Hz), 2.55 (1H, m), 1.44 (3H, s), 1.30 (3H, s); ^{13}C NMR ($CDCl_3$) δ 155.1, 131.0, 129.2, 121.4, 119.2, 117.1, 84.8, 63.5, 57.7, 48.1, 28.6, 21.3; MS m/z 205 (M^+, 63), 173 (31), 137 (100), 120 (56), 91 (49); Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.09; H, 7.33; N, 6.79.

Resolution of (±)-2:

A mixture of (±)-**2** (66 g, 0.32 mol) and L-dibenzoyltartaric anhydride (110 g, 0.32 mol) in toluene (300 ml) was stirred at room temperature for 1 h, and then diluted with ether (500 ml) at 0 °C with stirring. After 1 h at 0 °C, the crystalline amide was collected by filtration and washed with ether to afford (+)-amide. 80 g (91 %): $[\alpha]_D^{25}$ +125.1 (c 2.45, $CHCl_3$); mp 150-152 °C; IR (Nujol) ν 3490, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0-8.1 (4H, m), 7.35-7.62 (7H, m), 7.02 (1H, br), 6.94 (1H, t , J = 7 Hz), 6.74 (1H, d, J = 7 Hz), 6.30 (1H, t, J = 7

Hz), 6.22 (1H, d, J = 2.9 Hz), 5.99 (1H, d, J = 2.9 Hz), 5.44 (1H, d, J = 7.8 Hz), 4.25 (1H, dd, J = 5.0 and 11.0 Hz), 3.74 (1H, t, J = 11.0 Hz), 2.72 (1H, ddd, J = 5.1, 7.8 and 10.9 Hz), 1.54 (3H, s), 1.45 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.0, 165.2, 164.8, 153.9, 133.1, 130.7, 129.7, 129.6, 128.0, 127.9, 121.2, 120.4, 116.0, 98.2, 86.0, 71.3, 70.1, 63.8, 53.6, 45.9, 25.3, 19.2; MS m/z 528 (M-H_2O), 396, 274, 205, 173, 137, 131, 105; HRMS calcd for $C_{30}H_{28}NO_9$ (MH^+): 546.1764, found 546.1771; Anal. Calcd for $C_{30}H_{27}NO_9$ C, 66.05; H, 4.99; N, 2.57. Found: C, 66.10; H, 4.79; N, 2.57.

Enantiomerically pure (-)-**2** was obained from diastereomerically pure (+)-amide: Thus, (+)-amide (80 g, 0.15 mol) was treated with NaOH (30 g, 0.75 mol) in H_2O (500 ml) and EtOH (300 ml) at room temperature for 3 h. Concentration of the reaction mixture afforded a crystalline solid, which was collected by filtration to give (-)-**2**, 27 g (90 %). Extraction of the mother liquor with CH_2Cl_2 afforded further 2.5 g of (-)-**2**. The total yield was 98 % after recrystallization from CH_2Cl_2 and hexane.

[3a*R* 9b*S*]-(-)-**2**: mp 85-86 °C; $[\alpha]_D^{25}$ -11.1 (c 1.14, $CHCl_3$); HRMS calcd for $C_{12}H_{15}NO_2$: 205.1103 found 205.1099; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.92; H, 7.31; N, 6.80.

Enantiomerically pure (+)-**2** was obtained from the (-)-amide-rich filtrate of the crystallization of (+)-amide: Thus, the filtrate of the (+)-amide described above was hydrolyzed with NaOH (40 g, 1 mol) in H_2O (500 ml) and EtOH (300 ml) at room temperature for 3 h to afford 36 g of (+)-**2** (84 %ee), which was crystallized from ether (250 ml) to give 6 g (9 %) of (±)-**2** and further crystallization from CH_2Cl_2 and hexane afforded 28 g (85 %) of (+)-**2**.

[3a*S*, 9b*R*]-(+)-**2**: mp 85-86 °C, $[\alpha]_D^{25}$ +11.1 (c 1.33, $CHCl_3$); HRMS calcd for $C_{12}H_{15}NO_2$: 205.1103 found 205.1099; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.47; H, 7.22; N, 6.87.

Reduction of **9**

To a stirred solution of **9** (743 mg, 2.23 mmol) and MeOH (231 μl, 5.73 mmol) in THF (5 ml) was added a 2 M solution of $LiBH_4$ (2.85 ml, 5.73 mmol) in THF at 0 °C. The resulting solution was stirred at room temperature for 16 h and quenched by dropwise addition of 2 M HCl. After being stirred for 2 h at room temperature, the reaction was worked up as usual. Silica gel chromatography afforded (-)-**2** (317 mg, 81 %) and **10** (139 mg, 88 %), mp 80-82 °C, $[\alpha]_D^{25}$ +10.0 (c 1.00, $CHCl_3$) {lit.[6] $[\alpha]_D$ +11.3 (c = 0.6, $CHCl_3$) }.

References and Notes:

1. Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 793.
2. Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1977**, 1117. see also Orlek, B. S.; Sammes, P. G.; Walker, D. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1412.
3. Abiko, A. *Chemistry Letters* in press.
4. Saigo, K.; Sugiura, I.; Shida, I.;Tachibana, K.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2915.
5. Unfortunately, the *R* value of the final refinement (0.083) was not adequate to draw the accurate structure of **9**, however, the stereochemistry of the molecule was established as shown.
6. Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874.
7. McKervey, M. A.; Ye, T. *J. Chem. Soc., Chem. Commun.* **1992**, 823.
8. Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1993**, *58*, 2068.
9. Mzengeza, S.; Whitney, R. A. *J. Chem. Soc., Chem. Commun.* **1984**, 606.
10. All calculations were done using the TAXSAN crystallographic software package of Molecular Structure Corporation (1985).
11. S. M. gratefully acknowledges the National Institutes of Health, USA (CA48175) for financial support.

(*Received in Japan* 3 *April* 1995)