HETEROCYCLES, Vol. 52, No. 2, 2000, pp. 929 – 934, Received, 30th April, 1999

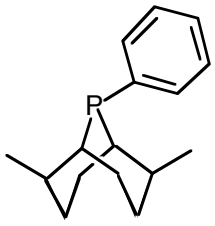
# SYNTHESIS OF NEW CHIRAL AMINES, 2,6-DIMETHYL-9-AZABICYCLO[3.3.1]NONANE AND ITS DERIVATIVES †

**Yasumasa Hamada*, Naoki Okamoto, and Osamu Hara**

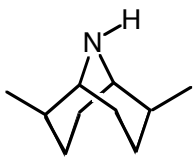
Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

**Abstract** - New chiral amines, 2,6-dimethyl-9-azabicyclo[3.3.1]nonane and its derivatives, were prepared starting from commercially available 1,5-dimethyl-1,5-cyclooctadiene followed by substitution reaction of the intermediate ditosylate with *p*-toluenesulfonamide under phase transfer conditions in 4 steps.

The design and development of the various chiral reagents used in asymmetric syntheses have received special attention in modern organic chemistry. Among them, nitrogen-containing chiral compounds constitute a major class of chiral reagents for asymmetric syntheses and have been widely used for obtaining a variety of optically active compounds.[1] We have recently been engaged in the development of the chiral auxiliaries[2] and reagents with the 9-heterobicyclo[3.3.1]nonane skeleton which contains part of structurally restricted adamantane and seems to serve for the efficient construction of an asymmetric environment. As part of these studies, we have succeeded in the synthesis of new monodentate chiral phosphines, (1*R*, 2*S*, 5*R*, 6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane (**1**) and its enantiomer ((*S*)-(+)- and (*R*)-(-)-9-PBNs), and demonstrated that these phosphines in combination with palladium are efficient catalysts for carbon-carbon bond forming reactions through asymmetric allylic alkylation.[3] For continuation of the studies on the chiral auxiliaries and reagents with the 9-heterobicyclo[3.3.1]nonane skeleton, we describe here the synthesis of 2,6-dimethyl-9-azabicyclo[3.3.1]nonane (**2**) and its relatives from commercially available 1,5-dimethyl-1,5-cyclooctadiene.[4] The achiral derivative, 9-azabicyclo[3.3.1]nonane, is known as norgranatanine and its lithio derivative has proved to be stable and strong base.[5]




(*R*)-9-PBN (**1**)

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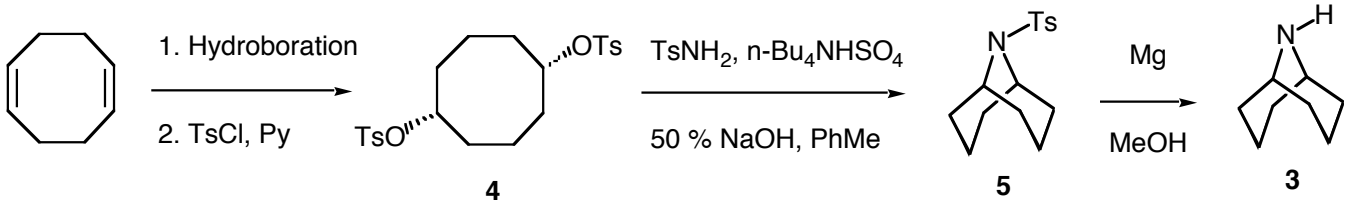
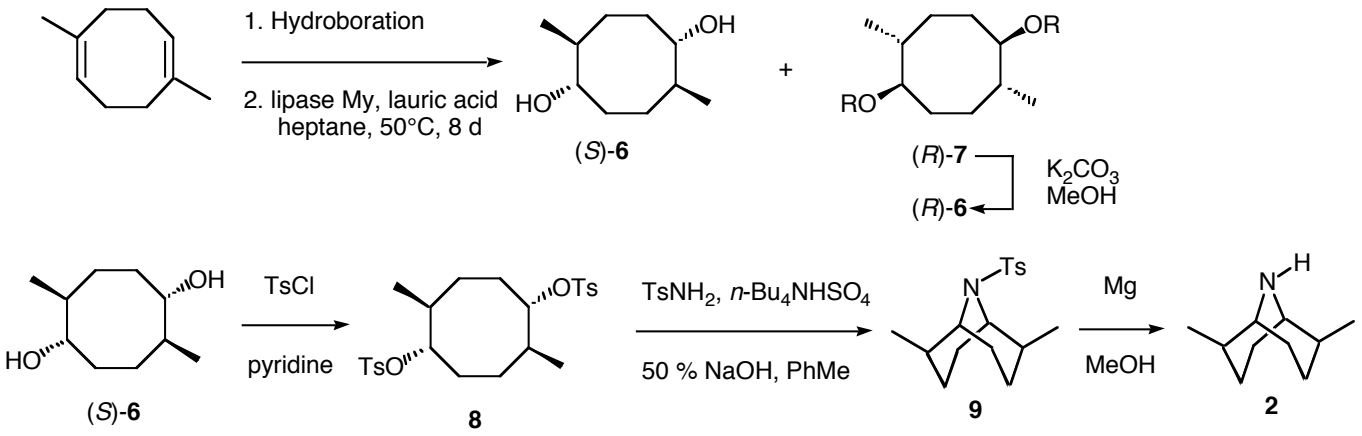
† Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

Our investigation commenced with the preliminary preparation of the known 9-azabicyclo[3.3.1]nonane (**3**) using a method developed by us. The hydroboration of 1,5-cyclooctadiene followed by tosylation of the resulting *cis*-1,5-cyclooctanediol provided the *cis*-ditosylate (**4**) in 68% yield. The double substitution reaction of **4** with *p*-toluenesulfonamide under phase transfer conditions at 70-80°C for 18 h afforded the desired *N*-toluenesulfonyl-9-azabicyclo[3.3.1]nonane (**5**) in 44% yield. Incidentally, the substitution reaction using benzamide and diphenylphosphinamide under the above conditions gave no desired product. Deprotection of the *N*-*p*-toluenesulfonyl group was achieved under the conditions using an excess of magnesium in methanol to yield the known 9-azabicyclo[3.3.1]nonane (**3**) in 36% yield.

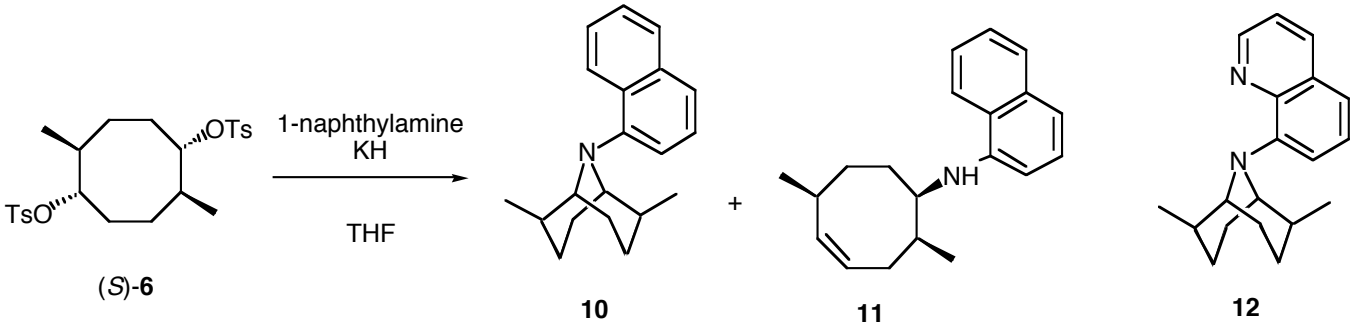



Similarly, the synthesis of 2,6-dimethyl-9-azabicyclo[3.3.1]nonane (**2**) was carried out from the commercially available 1,5-dimethyl-1,5-cyclooctadiene.[6] The diene was hydroborated using a combination of sodium borohydride and boron trifluoride etherate followed by treatment of alkaline hydrogen peroxide to afford the corresponding diol in 55% yield. The lipase-catalyzed esterification of the (*rac*)-diol (**6**) provided clean resolution to yield the (*S*)-diol (**6**) and the (*R*)-diester (**7**) with almost 100% ee.[7] After tosylation of (*S*)-**6**, the subsequent substitution reaction of **8** with *p*-toluenesulfonamide at 70-80°C for 21 h in toluene in the presence of *n*-$Bu_4NHSO_4$ and 50 % NaOH proceeded smoothly to furnish the *N*-*p*-toluenesulfonyl-2,6-dimethyl-9-azabicyclo[3.3.1]nonane (**9**) in 79% yield. An attempt to deprotect the *N*-*p*-toluenesulfonyl group of **9** under the typical conditions, sodium and liquid ammonia, failed to give the amine (**2**) due to its volatility. However, reductive cleavage of the *N*-*p*-toluenesulfonyl group using magnesium in methanol furnished the (1*R*,2 *S*,5 *R*,6 *S*)-2,6-dimethyl-9-azabicyclo[3.3.1]nonane (( *R*)-9-ABN, **2**) in 40% yield.




We next investigated the preparation of the *N*-substituted (*R*)-9-ABNs which will be of interest as chiral auxiliaries in asymmetric syntheses. We initially expected that mixing of (*S*)-**8** and 1-naphthylamine would

afford the desired product. However, the result was disappointedly the complete recovery of the starting ditosylate. Finally, we found that the use of the potassium amide from 1-naphthylamine and potassium hydride in THF provided the (1*R*,2*S*,5*R*,6*S*)-*N*-(1-naphthyl)-2,6-dimethyl-9-azabicyclo[3.3.1]nonane (**10**) in 33% yield along with a considerable amount of the monosubstituted side product (**11**) (~68%), though the yield of **10** remained to be improved. By use of the proper conditions the *N*-(8-quinolinyl) derivative (**12**) was also obtained.




(*S*)-**6** **10** **11** **12**

In summary we have accomplished the syntheses of the known 9-azabicyclo[3.3.1]nonane (**3**) and new chiral amines, (1*R*,2*S*,5*R*,6*S*)-2,6-dimethyl-9-azabicyclo[3.3.1]nonane ((*R*)-9-ABN, **2**) along with its relatives (**10**) and (**12**), using a method developed by us. Applications of these chiral amines to asymmetric syntheses are now under investigation in this laboratory.

## EXPERIMENTAL

Melting points were measured with a Shibata melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-140 digital polarimeter with a sodium lamp. IR spectra were recorded on a JASCO FT/ IR-230 spectrophotometer. $^1$H NMR spectra were recorded on a JEOL JNM-GSX-500A (500 MHz), 400A(400 MHz), and α270 (270 MHz) spectrometers with tetramethylsilane as the internal standard unless otherwise indicated. Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel 60$F_{254}$/0.25 mm thick plates. Column chromatography was performed with silica gel (Fuji Davison Co.). THF was distilled from sodium/benzophenone ketyl. All other commercially available reagents were used as received.

### *cis*-1,5-Bis(*p*-toluenesulfonyloxy)cyclooctane (4)

To a stirred solution of the *cis*-1,5-cyclooctanediol (10.9 g, 75.6 mmol) in pyridine (100 mL) at 5°C was added in one portion *p*-toluenesulfonyl chloride (36 g, 189 mmol) and the reaction mixture was stirred at 5°C for 2 h and at rt for 16 h. After dilution of the mixture with ethyl acetate/*n*-hexane (9:1, 300 mL), the mixture was washed with 10% aqueous sulfuric acid (100 mL x 4) and saturated brine (100 mL x 1), dried over $MgSO_4$, and concentrated *in vacuo* to give the ditosylate (**4**) as colorless solids. Recrystallization from ethyl acetate/*n*-hexane gave the pure product (**4**) (23.3 g, 68%) as colorless crystals: mp 87-88°C; IR $\nu_{max}$(KBr): 2951, 1598, 1356, 1176, 1094, 898, 815, 665 cm$^{-1}$; $^1$H NMR ( 500 MHz, $CDCl_3$) δ 1.24-1.33 (m, 2 H), 1.64-1.78 (m, 10 H), 2.45 (s, 6 H), 4.52-4.54 (m, 2 H), 7.33 (d, *J* = 7.9 Hz, 4 H), 7.74-7.79 (m,

4 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 18.58, 21.58, 32.46, 82.47, 127.51, 129.77, 134.26, 144.57. Anal. Calcd for $C_{22}H_{28}O_6S_2$: C, 58.39; H, 6.24. Found: C, 58.37; H,6.29.

***N*-*p*-Toluenesulfonyl-9-azabicyclo[3.3.1]nonane (5)**

A mixture of the ditosylate (**4**) (45.3 g, 100 mmol), *p*-toluenesulfonamide (17.1 g, 100 mmol), and *n*-$Bu_4NHSO_4$ (6.8 g, 20 mmol) in 50 % aqueous sodium hydroxide (40 mL) and toluene (300 mL) was heated to 70-80°C for 18 h. The mixture was cooled to rt, diluted with ethyl acetate/*n*-hexane (1:1, 200 mL), and washed with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*. The residue was chromatographed on silica gel (BW-200, 100 g, *n*-hexane-ethyl acetate (8:1)) to give the sulfonamide (**5**) (12.4 g, 44%) as colorless crystals: mp 143-145°C (*n*-hexane); IR $\nu_{max}$(KBr): 2912, 2848, 1335, 1159, 672 cm$^{-1}$; $^1$H NMR ( 500 MHz, $CDCl_3$) δ 1.43-1.75 (m, 7 H), 1.80-1.88 (m, 3 H), 1.92-2.07 (m, 2 H), 2.41 (s, 3 H), 4.06-4.08 (m, 1H), 4.28-4.29 (m, 1H), 7.26-7.27 (m, 2 H), 7.71-7.75 (m, 2 H). Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.51; H, 7.64; N, 5.02.

**9-Azabicyclo[3.3.1]nonane (3)**

To a stirred solution of the sulfonamide (**5**) (1 g, 3.58 mmol) in methanol (23 mL) at rt was added in one portion magnesium turnings (429 mg, 7.9 mg atom) and the reaction mixture was stirred at rt overnight. The mixture was acidified with concentrated hydrochloric acid (3.6 mL) and condensed *in vacuo*. The residue was diluted with water and washed with $CH_2Cl_2$. The aqueous layer was adjusted to pH 12 with 1N NaOH and extracted with $CH_2Cl_2$. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to leave the amine (**3**) (160 mg, 36%) as a pale yellow oil. The analytical sample was obtained as the picrate: mp 225-227°C (lit.,[5a] 225°C); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.70-2.40 (m, 14 H), 3.76 (m, 1 H), 4.28 (m, 1 H), 8.93 (s, 2 H).

**(1*S*,2*S*,5*S*,6*S*)-1,5-Bis(*p*-toluenesulfonyloxy)-2,6-dimethylcyclooctane (8)**

To a stirred solution of the (*S*)-diol (**6**) (3.46 g, 20 mmol) in pyridine (20 mL) at 0°C was added *p*-toluenesulfonyl chloride (15.3 g, 80 mmol) and the reaction mixture was stirred at 0°C for 21 h. After treatment with water (10 mL) at 5°C for 1 h, the mixture was diluted with ethyl acetate/*n*-hexane (9:1, 300 mL), washed with 1 M $KHSO_4$ (100 mL x 5), water (50 mL x 1), saturated aqueous $NaHCO_3$ (100 mL x 1), water (50 mL x 1), and saturated brine (100 mL x 1), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was triturated with *n*-hexane-ether and the resulting white solids were filtered, washed with *n*-hexane, and dried *in vacuo* to give the ditosylate (**8**) (9.11 g, 95%) as unstable colorless solids. The analytical sample was obtained by recrystallization with $CH_2Cl_2$-ether-*n*-hexane to give the pure (*S*)-**8** as colorless crystals: mp 92-94°C (decomp); $[\alpha]_D^{20}$ +40.02° (c 1.84, $CHCl_3$); IR $\nu_{max}$(KBr): 1362, 1171, 897, 668, 552 cm$^{-1}$; $^1$H NMR ( 270 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.9 Hz, 6 H), 1.21-1.29 (m, 2 H), 1.67-1.91 (m, 8 H), 2.43 (s, 6 H), 4.26-4.33 (m, 2 H), 7.33 (d, *J* = 8.6 Hz, 4 H), 7.77 (d, *J* = 8.3 Hz, 4 H). Anal. Calcd for $C_{24}H_{32}O_6S_2$: C, 59.97; H, 6.71. Found: C, 59.81; H, 6.91.

**(1*R*,2*S*,5*R*,6*S*)-*N*-*p*-Toluenesulfonyl-2,6-dimethyl-9-azabicyclo[3.3.1]nonane (9)**

A mixture of the (*S*)-ditosylate (**8**) (4.33 g, 9 mmol), *p*-toluenesulfonamide (1.54 g, 9 mmol), and *n*-$Bu_4NHSO_4$ (1.02 g, 3 mmol) in 50 % aqueous sodium hydroxide (2 mL) and toluene (50 mL) was heated to 70-80°C for 21 h with stirring. The mixture was cooled to rt, diluted with benzene (200 mL), and washed with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (BW820MH, 50 g, *n*-hexane-ethyl acetate (10:1)) to give the product (**9**) (2.19 g, 79%) as colorless solids: mp 105-107°C (*n*-hexane); $[\alpha]_D^{19}$ -30.4° (c 1.09, $CHCl_3$); IR $\nu_{max}$(KBr): 2959, 2921, 1318, 1157, 1112, 679 $cm^{-1}$; $^1H$ NMR ( 500 MHz, $CDCl_3$) δ 0.86 (d, *J* = 7 Hz, 6 H), 1.01-1.07 (m, 2 H), 1.30-1.35 (m, 2H), 1.57-1.63 (m, 2 H), 1.83-1.98 (m, 4 H), 2.40 (s, 3 H), 3.76 (m, 2 H), 7.25 (d, *J* = 7.9 Hz, 2 H), 7.70 (d, *J* = 8.2 Hz, 2 H). Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.14; H, 8.19; N, 4.43.

**(1*R*,2*S*,5*R*,6*S*)-2,6-Dimethyl-9-azabicyclo[3.3.1]nonane (2) ((*R*)-9-ABN)**

To a stirred solution of the sulfonamide (**9**) (600 mg, 1.95 mmol) in methanol (12.5 mL) was added in one portion magnesium turnings (474 mg, 19.52 mg atom) and the mixture was stirred at rt overnight. The reaction mixture was then sonicated at 0°C for 3.5 h. The mixture was acidified with concentrated hydrochloric acid (3.5 mL) and condensed *in vacuo*. The residue was diluted with water and washed with $CH_2Cl_2$. The aqueous layer was adjusted to pH 12 with 1N NaOH and extracted with $CH_2Cl_2$. The organic layer was washed with saturated brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to leave the amine (**2**) (120 mg, 40%) as a pale yellow oil. The analytical sample was obtained as the picrate (257 mg, 34 %): mp 257-258°C (decomp); $[\alpha]_D^{25}$ +74.1° (c 0.345, $CHCl_3$); IR $\nu_{max}$(KBr): 2967, 1640, 1608, 1560, 1368, 1318, 1278 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J* = 7.3 Hz, 6 H), 1.49-1.54 (m, 2 H), 1.71-1.75 (m, 2 H), 2.04-2.06 (m, 2 H), 2.16-2.24 (m, 2 H), 2.34-2.42 (m, 2 H), 3.47-3.51 (m, 2 H), 8.95 (s, 2 H). Anal. Calcd for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 49.92; H,5.71; N, 14.52.

**(1*R*,2*S*,5*R*,6*S*)-*N*-(1-Naphthyl)-2,6-dimethyl-9-azabicyclo[3.3.1]nonane (10)**

To a stirred mixture of 1-naphthylamine (53 mg, 0.37 mmol) and 35 % KH (89 mg, 0.77 mmol) in THF (2 mL) at 5 °C was added a solution of the (*S*)-ditosylate (**8**) (178 mg, 0.37 mmol) in THF (3 mL) and the reaction mixture was kept at the same temperature with stirring for 4.5 h. The reaction mixture was then allowed to warm to rt and stirred for 2 h. After dilution with water, the reaction mixture was extracted three times with ethyl acetate, washed with water and saturated brine, and dried over sodium sulfate. Concentration of the organic layer and chromatography of the residue using an eluant (ethyl acetate/*n*-hexane = 1:49) gave the amine (**10**) (34 mg, 33%) as colorless crystals: mp 128-129°C (*n*-pentane); $[\alpha]_D^{22}$ –375° (c 1, $CHCl_3$); IR $\nu_{max}$(KBr):2927, 1570, 1406, 768 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.9 (br s, 6 H), 1.45 (m, 2 H), 1.53 (m, 2 H), 1.76 (m, 2 H), 2.08 (br s, 2 H), 2.49 (m, 2 H), 3.60 (d, 2 H, *J* = 6.4 Hz), 7.01 (m, 1 H), 7.26-7.30 (m, 2 H), 7.36-7.41 (m, 2 H), 7.77 (dd, 1 H, *J* = 7.7, 1.6 Hz), 7.99 (dd, 1 H, *J* = 7.6, 1.5 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 21.2, 24.5, 26.2, 35.0, 58.8, 113.1, 119.5, 123.9, 124.3, 125.2, 125.9, 127.6, 128.5, 135.3, 151.8. Anal. Calcd for $C_{20}H_{25}N$: C, 85.96; H, 9.01; N, 5.01. Found: C, 85.78; H, 9.11; N, 4.86.

**(1*R*,2*S*,5*R*,6*S*)-*N*-(8-Quinolinyl)-2,6-dimethyl-9-azabicyclo[3.3.1]nonane (12)**

To a stirred mixture of 8-aminoquinoline (173 mg, 1.2 mmol) and 35 % KH (275 mg, 2.4 mmol) in THF (5 mL) at 5 ℃ was added a solution of the (S)-ditosylate (**8**) (480 mg, 1 mmol) in THF (5 mL) and the reaction mixture was kept at the same temperature for 30 min with stirring. The reaction mixture was then allowed to warm to rt and stirred overnight. After dilution with water, the reaction mixture was extracted three times with ethyl acetate, and the combined extracts were washed with water and saturated brine, and dried over sodium sulfate. Concentration of the organic layer and chromatography of the residue using an eluant (ethyl acetate/*n*-hexane = 1:49) gave the product (**12**) (27 mg, 10%) which solidified as colorless crystals: mp 65-67℃; $[\alpha]_D^{22}$ –514° (c 0.33, $CHCl_3$); IR $\nu_{max}$(KBr):2918, 1562, 1496, 1470 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7 Hz, 6 H), 1.35-1.55 (m, 4 H), 1.76-1.81 (m, 2 H), 2.12-2.21 (m, 2 H), 2.52-2.60 (m, 2 H), 4.18 (br s, 2 H), 7.02-7.10 (m, 2 H), 7.25-7.33 (m, 2 H), 8.00 (dd, *J* = 8.3, 2.0 Hz, 1H), 8.73 (dd, *J* = 4, 1.8 Hz, 1 H). HRMS (FAB) Calcd for $C_{19}H_{24}N_2$: 280.1939. Found: 280.1938. Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 80.98; H, 8.89; N, 9.46.

**ACKNOWLEDGEMENT**

We thank Mr. H. Uchida of Meito Sangyo Co. for the generous gift of lipase My.

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