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TETRAHEDRON: *ASYMMETRY*

# Stereoselective synthesis of (*R*)-(−)-denopamine, (*R*)-(−)-tembamide and (*R*)-(−)-aegeline via asymmetric reduction of azidoketones by *Daucus carota* in aqueous medium

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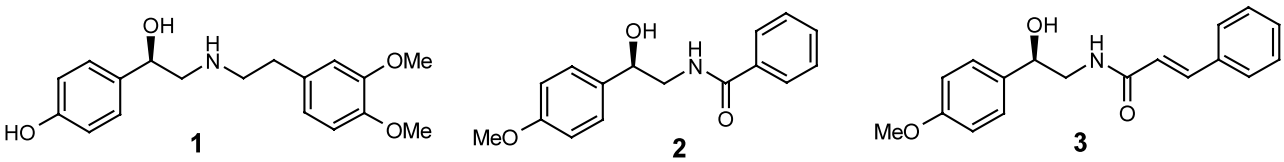
**Abstract**—A simple and efficient stereoselective synthesis of (*R*)-denopamine and other naturally occurring hydroxy amides from optically active (*R*)-2-azido-1-arylethanols, is described for the first time via reduction of the corresponding α-azidoarylketones with enzymes from *Daucus Carota* root, under mild and environmentally friendly conditions. The products are formed with high degrees of enantioselectivity. 

## 1. Introduction

Many chiral β-amino aryl ethanols are found to be potential synthetic precursors of pharmaceutically important molecules.[1] Recent studies have demonstrated that the two enantiomers of a chiral drug usually display different biological activities[2] and in most of the aryl ethanolamine drugs, the biological activity resides mainly in the (*R*)-enantiomer.[3] The increasing demand and interest in the stereoselective synthesis of these biologically useful molecules prompted us to take up their synthesis. The synthesis of (*R*)-denopamine **1**, a new selective β-antagonist for the treatment of congestive heart failure[4] and other naturally occurring biologically active molecules such as (*R*)-tembamide **2** and (*R*)-aegeline **3**, which are used in traditional Indian medicines and have been shown to have good hypoglycemic activity,[5] has now been achieved.

To date few methods have been reported for the synthesis of optically active (*R*)-denopamine **1**,[6] (*R*)-tembamide **2** and (*R*)-aegeline **3**,[7] these include either tedious chemical and biological methods[8] or require the use of expensive reagents with multi-step syntheses and low overall yields.[9] Recently, the asymmetric reduction of substituted α-amino ketones to β-amino alcohol derivatives[10] with high enantioselectivity using the Ru–BINAP complex has been reported.

Our continuous investigations on the development of new environmentally favorable bioreduction processes for the synthesis of chiral azido alcohols,[11] which are potential intermediates for aryl ethanolamine drugs[12] and our keen interest in the utility of such strategies for the total synthesis of enantiopure pharmaceutically important molecules led us to complete the study reported herein. Recently, plant cell cultures[13] and whole plant cells[14] have been considered as suitable biochemical systems for the stereoselective reduction of prochiral ketones. More recently, we have investigated the reduction of a variety of prochiral ketones with *Daucus carota* root in aqueous medium provided the corresponding alcohols[15] with good to excellent enantioselectivity and in high yield. Accordingly, we have focused our attention to extend this methodology to the preparation of key intermediates, i.e. (*R*)-chiral azido alcohols **5a** and **5b** from the corresponding α-azido aryl ketones **4a** and **4b**.

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## 2. Results and discussion

Initially, we investigated the reduction of α-azidoaryl ketones **4a** and **4b** with baker's yeast and *Daucus carota*, interestingly both of them gave the required azido alcohols **5a** and **5b** with high enantioselectivity and the results obtained with both biocatalysts are shown in Table 1. Based on the results shown in Table 1, we chose *Daucus carota* as the biocatalyst for the asymmetric reduction of azido ketones to optically active azido alcohols due to its operational simplicity, the easy isolation of the reaction products, the inexpensive and readily available biomaterial, the mild conditions and the high yield and enantioselectivity.

The first step of our present strategy involved the stereoselective reduction of 2-azido-1-aryl ketones **4a** and **4b** (Scheme 1) with *Daucus carota*, which provided the respective (*R*)-2-azido-1-aryl ethanols **5a** and **5b** with excellent enantiomeric excess (99–100%) and in high yield (85–92%). The enantiomeric excess of these azido alcohols was determined by chiral HPLC analysis and in this reduction; the observed stereochemistry could be explained on the basis of Prelog's rule[16] and the absolute configuration was confirmed by comparing their specific rotations with those of authentic samples.[11b,17]

Next, the azido alcohols **5a** and **5b** were reduced by hydrogenation over palladium on charcoal (5%) in methanol at room temperature for 2 h, which afforded the corresponding amino alcohols **6a** and **6b** in quantitative yields. We also investigated the reduction of **5a** with lithium aluminum hydride, which gave **6a** in good yield, whereas in the reduction of **5b** unwanted cleavage of the silyl protecting group was observed and 4-hydroxyphenylethanolamine was formed.

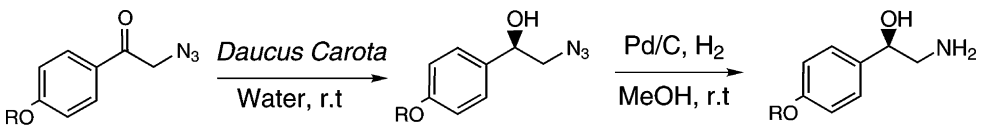
Acylation of **6a** with benzoyl chloride in the presence of 50% aqueous NaOH then gave **2** in 92% yield. Similarly amino alcohol **6a** was treated with cinnamoyl chloride to afford **3** in 90% yield. The specific rotation values of **2** and **3** were in good agreement with those reported in the literature (Scheme 2).[7]

In a similar manner, the reaction of **6b** and 3,4-dimethoxyphenylacetyl chloride under similar conditions provided the required hydroxyamide **7** in 88% yield. The amide group was then reduced to an amino group using borane in THF at 50°C, followed by deprotection of the silyl group with KF/MeOH, as described by Corey et al.,[7] to give (*R*)-(−)-denopamine **1** in good yield (75%) (Scheme 3).

**Table 1.** Reduction of azido ketones in aqueous media at room temperature

| Ketone | Product | Biocatalyst | Additive | Time (days) | Yield[c] | E.e. (%)[d] | Abs. conf.[e] |
|---|---|---|---|---|---|---|---|
| **4a** | **5a** | Baker's yeast[a] | Sucrose | 2 | 88 | 98 | *R* |
| **4a** | **5a** | *Daucus carota*[b] | | 2 | 92 | 99 | *R* |
| **4b** | **5b** | Baker's yeast | Sucrose | 3 | 78 | >99 | *R* |
| **4b** | **5b** | *Daucus carota* | | 3 | 85 | 100 | *R* |

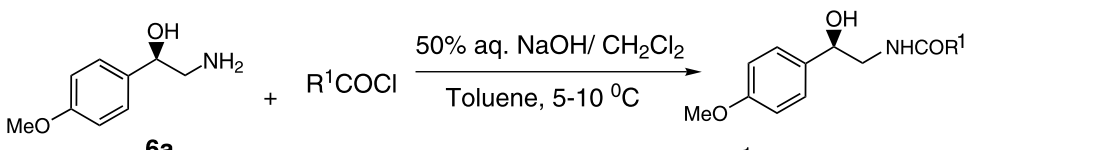
[a] Baker's yeast-mediated reactions were performed as reported in the literature.[11b]
[b] *Daucus carota*-mediated reactions were performed as reported in Section 4.
[c] Isolated yields after chromatographic purification.
[d] Determined by HPLC analysis using a Daicel chiral OD column: hexane/isopropanol = 8.5/1.5.
[e] The absolute configuration was assigned by analogy Ref. 11b.




**4a, 4b** **5a, 5b** **6a, 6b**

4a R=Me
4b R=TBDMS

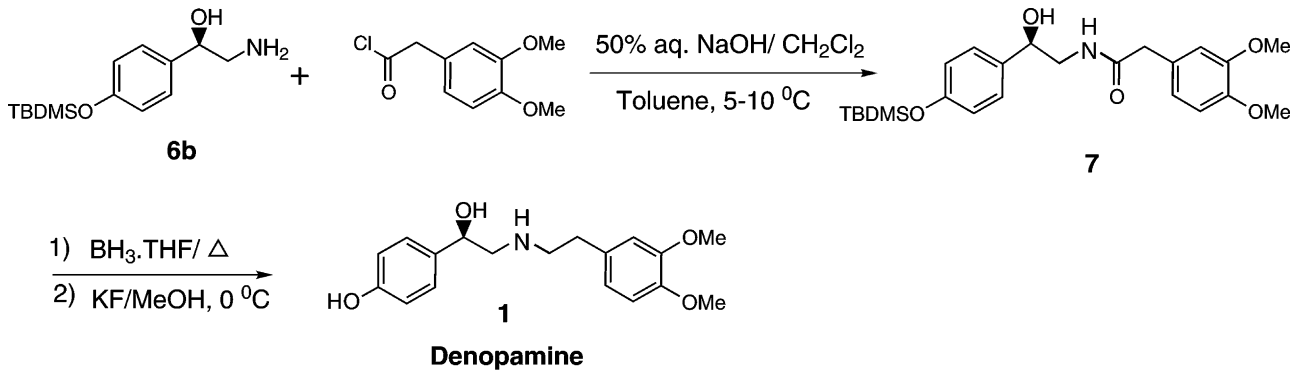
**Scheme 1.**




**6a**

**2** $R^1$= Ph, **Tembamide**
**3** $R^1$= trans- PhCH=CH-, **Aegeline**

**Scheme 2.**




**Scheme 3.**

## 3. Conclusion

In summary, we have established a convenient and simple procedure for the preparation of chiral azido alcohols from α-azido ketones with *Daucus carota* root reduction process, under milder conditions. We have also explained the importance of these optically active azido alcohols as precursors for the synthesis of a variety of pharmaceutically important molecules. Since this is a novel and alternative methodology to classical biochemical methods, it has wide scope and enables the synthesis of an analogous series of compounds. Further work is in progress and will appear in due course.

## 4. Experimental

### 4.1. General

Melting points were recorded on a Buchi R-535 apparatus. IR spectra were recorded on a Nicolet-740 FT-IR spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ solutions on Varian Gemini 200 and 50 MHz spectrometers and chemical shifts were reported in ppm. Mass spectra were recorded on VG micromass-7070H (70 eV). C,H,N analysis was performed on a Vario EL analyzer. Optical rotations were recorded on a Jasco Dip 360 digital polarimeter. HPLC analysis was performed on a Schimadzu liquid chromatography LC-6A, equipped with a SCE-6A, system controller, SPD-6A fixed wave length UV monitor detector and Chromatopac C-R4A data processor as integrator. The column was 4.6×250 mm chiralcel OD column (Daicel). The eluents were hexane–isopropanol (HPLC grade, 85:15) at a flow rate of 0.5 mL min$^{-1}$ and monitored at 254 nm wavelength. Baker's yeast type-1 was obtained from Sigma Chemicals Co. All starting materials were prepared according to the literature procedure. The fresh carrot roots were obtained from a local market.

### 4.2. General procedure for the reduction of 2-azido-1-aryl ketones 4a and 4b with *Daucus carota*

In a 1000 mL Erlenmeyer flask, freshly cut carrot root pieces (100 g, 1×1.5 cm) were suspended in water (400 mL) and an ethanolic solution of azido ketones **4a** and **4b** (1 g, 1.5 mL EtOH] was added to the suspension. The reaction mixture was then incubated in an orbital shaker (150 rpm) for 2 to 3 days at room temperature. The progress of the reaction was monitored by TLC and GC analysis. Finally, the suspensions were removed by filtration and washed with ether (2×20 mL). The combined filtrate was extracted with ether (2×30 mL), washed with brine and dried over $Na_2SO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh) using *n*-hexane:ethyl acetate (95:5) affording the pure azido alcohols **5a** and **5b** in good yield. The structure of these compounds was confirmed by spectral analysis and the enantiomeric excess was determined by the chiral HPLC.

**4.2.1. (*R*)-(−)-2-Azido-1-(4-methoxyphenyl)ethanol 5a**. Yield = 0.929 g (92%), colourless liquid; $[\alpha]_D^{25} = -40.1$ (*c* 1.02, $CHCl_3$); $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 2.10 (br s, 1H), 3.40 (m, 2H), 3.78 (s, 3H), 4.80 (dd, 1H, $J$ = 7.2, 4.0 Hz), 6.85 (d, 2H, $J$ = 7.8 Hz) 7.25 (d, 2H, $J$ = 7.8 Hz); $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 55.5, 58.2, 114.4, 127.5, 132.5, 159.8. MS (CI): $m/z$ 193 ($M^+$); IR ($CHCl_3$, cm$^{-1}$): 3426, 2100, 1024. Anal. calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.97; H, 5.68; N, 21.73%.

**4.2.2. (*R*)-(−)-2-Azido-1-(4-*tert*-butyldimethylsilyloxyphenyl)ethanol 5b**. Oil; yield = 0.879 g (85%); $[\alpha]_D^{25} = -59.5$ (*c* 1.00, $CHCl_3$); $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 0.20 (s, 6H), 1.00 (s, 9H), 2.35 (br s, 1H), 3.40 (m, 2H), 4.80 (m, 1H), 6.85 (d, 2H, $J$ = 7.4 Hz), 7.25 (d, 2H, $J$ = 7.4 Hz). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$: −4.46, 13.92, 25.62, 58.10, 73.09, 120.24, 127.00, 127.12, 133.14. MS (CI): $m/z$ 293 ($M^+$); IR ($CHCl_3$, cm$^{-1}$): 3422, 2086, 1026. Anal. calcd for $C_{14}H_{23}SiN_3O_2$: C, 57.30; H, 7.90; N, 14.32; Si, 9.57. Found: C, 57.38; H, 7.94; N, 14.38; Si, 9.63%.

**4.2.3. Synthesis of (*R*)-(−)-tembamide 2**. The azido alcohol **5a** (0.772 g, 4 mmol) was dissolved in MeOH (5 mL) and stirred under a hydrogen atmosphere (1 atm) in the presence of 5% Pd–C (20 mg) at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was concentrated to give amino alcohol **6a**. The residue was dissolved in DCM (5 mL), a solution

of 50% aqueous NaOH (1.10 g, 12 mmol) in water (6.5 mL) was added at 0–5°C and vigorously stirred for 10 min. To the resulting solution of **6a**, a solution of benzoyl chloride (5 mmol) in anhydrous toluene (3 mL) was added dropwise through a syringe over a period of 5 min. After the addition was complete, the reaction mixture was stirred for a further 20 min. The solvent was evaporated in vacuo and the residue was diluted with cold water. The precipitate was filtered and washed with water, dried in air and then recrystallized from ethanol:water (80:20) to afford pure (*R*)-(−)-tembamide **2**. Yield = 1.08 (92%), white crystalline solid; mp 154–155°C; $[\alpha]_D^{25} = -59.6$ (*c* 0.52, $CHCl_3$) [lit.[7] $[\alpha]_D^{24} = -59.8$ (*c* 0.4, $CHCl_3$)]; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$: 2.85 (br s, OH), 3.36–3.48 (m, 1H), 3.78 (s, 3H), 3.82–3.95 (m, 1H), 4.65 (dd, 1H, *J* = 7.6, 4.2 Hz), 6.52 (m, 1H), 6.85 (d, 2H, *J* = 8.2 Hz), 7.30 (d, 2H, *J* = 8.2 Hz), 7.38–7.45 (m, 3H), 7.75 (d, 2H, *J* = 8.2 Hz). $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$: 47.02, 54.44, 71.57, 112.87, 120.87, 126.87, 127.99, 128.63, 134.31, 139.17, 148.21, 165.83. MS: *m*/*z* 271 ($M^+$), IR (KBr, $cm^{-1}$): 3492, 3385, 1628, 1042. Anal. calcd for $C_{16}H_{17}NO_3$: C, 70.84; H, 6.26; N, 5.18. Found: C, 70.88; H, 6.28; N, 5.12%.

**4.2.4. Synthesis of (*R*)-(−)-aegeline 3**. The reduction of **5a** followed by treatment with cinnamoyl chloride under similar conditions gave (*R*)-(−)-aegeline **3**. Yield = 1.18 g (90%), white crystalline solid; mp 195–196°C (lit: 196–197). $[\alpha]_D^{25} = -36.1$ (*c* 0.45, $CHCl_3$) [lit.[7] $[\alpha]_D^{24} = -35.6$ (*c* 0.4, $CHCl_3$)]; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$: 3.18–3.35 (m, 1H), 3.57–3.70 (m, 1H), 3.80 (s, 3H), 4.72 (m, 1H), 5.12 (d, 1H, *J* = 3.3 Hz), 6.60 (d, 1H, *J* = 15.8 Hz), 6.85 (d, 2H, *J* = 8.4 Hz), 7.25–7.38 (m, 5H), 7.42–7.55 (m, 3H), 7.68 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$: 47.02, 54.44, 71.57, 112.87, 120.78, 126.39, 126.87, 127.99, 128.63, 134.31 and 139.17, 158.01, 165.83; MS(CI): *m*/*z* 297 ($M^+$). IR (KBr, $cm^{-1}$): 3458, 3328, 1632, 1039. Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.88; H, 6.38; N, 4.83%.

**4.2.5. Preparation of hydroxyamide 7**. To a stirred solution of amino alcohol **6b** (3 mmol) in DCM (5 mL) and 50% aq. NaOH (0.825 g, 9 mmol) in water (4.8 mL) was added a solution of 3,4-dimethoxyphenylacetyl chloride (4 mmol) in anhydrous toluene (3 mL) over a period of 5 min at 0–5°C and the reaction mixture was stirred for a further 20 min. The solvent was removed in vacuo and the residue was diluted with cold water and then extracted with ethyl acetate (2×20 mL) and dried over $Na_2SO_4$. The solvent was evaporated and the residue was chromatographed on silica gel (60–120 mesh) eluting with *n*-hexane:ethyl acetate (70:30) afforded the corresponding hydroxyamine **7** in pure form. Yield = 1.17 g, (88%); mp 37–38°C. $[\alpha]_D^{25} = -32.2$ (*c* 1.02, $CHCl_3$); $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 0.18 (s, 6H), 0.98 (s, 9H), 3.16–3.30 (m, 1H), 3.48 (s, 2H), 3.52–3.66 (m, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 4.69 (dd, 1H, *J* = 7.2, 4.0 Hz), 5.79 (t, 1H, *J* = 6.8 Hz), 6.75 (m, 5H), 7.10 (d, 2H, *J* = 8.6 Hz); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$: −4.82, 13.96, 42.60, 46.10, 55.30, 70.98, 111.10, 112.50, 117.88, 126.98, 128.12, 132.94, 147.75, 148.91, 157.08, 169.80; MS (CI): *m*/*z* 445 ($M^+$); IR (KBr, $cm^{-1}$): 3475, 3362, 1638, 1035. Anal. calcd for $C_{24}H_{35}SiNO_5$: C, 66.68; H, 7.94; N, 3.14; Si, 6.30. Found: C, 66.74; H, 7.98; N, 3.12; Si, 6.36%.

### 4.3. Synthesis of (*R*)-(−)-denopamine 1

To a solution of hydroxy amide **7** (0.890 g, 2 mmol) in dry THF (5 mL), a solution of $BH_3$·THF (1 M, 3 mL, 3 mmol) was added. The resulting mixture was stirred at 50°C for 2 h under an $N_2$ atmosphere and then cooled to room temperature and cautiously quenched with methanol (0.3 mL). The solvent was evaporated and the residue was dissolved in dry methanol (4 mL), cooled to 0°C and KF (2 mmol) in methanol (1 mL) was added. Anhydrous methanolic HCl (1 M, 2.5 mL, 2.5 mmol) was added and the mixture was stirred for 4 h at room temperature. The solvent was removed and the residue was diluted with ethyl acetate (20 mL), washed with 10% aqueous NaCl (3 mL), and dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the solid obtained was recrystallized from *n*-hexane:ethyl acetate (70:30) to afford pure (*R*)-denopamine **1**. Yield = 0.477 g (75%), mp 164–165°C. $[\alpha]_D^{25} = -27.8$ (*c* 1.02, MeOH) [lit.[6a] $[\alpha]_D^{24} = -27.5$ (*c* 0.95, MeOH)]; $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 3.02–3.38 (m, 6H), 3.79 (s, 3H), 3.81 (s, 3H), 5.18 (dd, 1H, *J* = 3.6, 1.8 Hz), 6.68–6.88 (m, 5H), 7.21 (d, 2H, *J* = 8.2 Hz); $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 34.88, 50.95, 52.76, 56.10, 72.52, 111.32, 114.46, 119.85, 126.98, 132.10, 134.30, 147.88, 149.20, 158.42, 159.33; MS (CI): *m*/*z* 318 ($M^+$); IR (KBr, $cm^{-1}$): 2938, 1622, 1585. HRMS calcd for $C_{18}H_{23}NO_4$: 318.1704; Found: 318.1658.

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## References

1. (a) Roth, H. J.; Kleeman, A. *Pharmaceutical Chemistry, Drug Synthesis*; Ellis Harwood: UK, 1988; Vol. 1, p. 144; (b) Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett*. **1994**, *31*, 5551; (c) Hieble, J. P.; Bondinell, W.; Ruffolo, R. R., Jr. *J. Med. Chem*. **1995**, *38*, 3415; (d) Hieble, J. P.; Bondinell, W.; Ruffolo, R. R., Jr. *J. Med. Chem*. **1995**, *38*, 3681; (e) Ramachandran, P. V.; Gong, B.; Brown, H. C. *Chirality* **1995**, *7*, 103.
2. (a) Millership, J. S.; Fitzpatrick, A. *Chirality* **1993**, *5*, 573 and references cited therein; (b) Brittain, R. T.; Farmer, J. B.; Marshall, R. J. *Br. J. Pharmacol*. **1973**, *48*, 144; (c) Chapman, I. D.; Buchheit, K. H.; Manley, P.; Morley, J. *Trends J. Pharmacol. Sci*. **1992**, *13*, 231; (d) Stinson, S. C. *Chem. Eng. News* **2000**, *78*, 59.
3. (a) Ruffolo, R. R., Jr. *Tetrahedron* **1991**, *47*, 9953; (b) Lunts, L. H. C.; Main, B. G.; Tucker, H. In *Medicinal Chemistry*, *The Role of Organic Chemistry in Drug Research*; Roberts, S. M.; Price, B. J., Ed.; Academic Press: New York, 1985; pp. 49–92.

4. (a) Yokoyama, H.; Yanagisawa, T.; Taira, N. *J. Cardiovasc. Pharmacol.* **1988**, *12*, 323; (b) Bristow, M. R.; Hershberger, R. E.; Port, J. D.; Minobe, W.; Rasmussen, R. *Mol. Pharmacol.* **1989**, *35*, 295.
5. Shoeb, A.; Kapil, R. S.; Popli, S. P. *Phytochemistry* **1973**, *12*, 2071.
6. (a) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442; (b) Kawagucki, T.; Saito, K.; Matsuki, K.; Iwakuma, T.; Takeda, M. *Chem. Pharm. Bull.* **1993**, *4*, 639.
7. Brown, R. F. C.; Jackson, W. R.; Mc Carthy, T. D. *Tetrahedron: Asymmetry* **1993**, *4*, 205.
8. (a) Ikezaki, M.; Umino, N.; Gaino, M.; Aoe, K.; Iwakuma, T.; Ohishi, T. *Yakugaku. Zasshi* **1986**, *106*, 80; (b) Noguchi, K.; Irie, K, Japan Patent 79 70, 233, 1979, *Chem. Abstr.* **1979**, *91* 630; (c) Kuck, A. M.; Albonico, S. M.; Deulofeu, V. *J. Chem. Soc., Section C* **1967**, 1327; (d) Gu, J.-X.; Zu-Yi, L.; Guo-Qiang, L. *Tetrahedron* **1993**, *49*, 5803.
9. Senuma, M.; Yamato, E.; Koumato, T.; Gaino, M.; Kawaguchi, T.; Iwakuma, T. *Chem. Expt.* **1989**, *4*, 245.
10. (a) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510; (b) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703; (c) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529.
11. (a) Yadav, J. S.; Reddy, P. T.; Hashim, S. R. *Synlett* **2000**, 1469; (b) Yadav, J. S.; Reddy, P. T.; Nanda, S.; Rao, A. B. *Tetrahedron: Asymmetry* **2001**, *12*, 63 and references cited therein.
12. (a) Lu, S. F.; Herbet, B.; Haufe, G.; Laue, K. W.; Padgett, W. L.; Oshunleti, O.; Daly, J. W.; Kirk, K. L. *J. Med. Chem.* **2000**, *43*, 1611; (b) Procopiou, P. A.; Merton, G. E.; Todd, M.; Webb, G. *Tetrahedron: Asymmetry* **2001**, *12*, 2005.
13. (a) Naoshima, Y.; Akakabe, Y. *J. Org. Chem.* **1989**, *54*, 4237; (b) Naoshima, Y.; Akakabe, Y. *Phytochemistry* **1991**, *30*, 3595; (c) Akakabe, Y.; Takahashi, M.; Kamazawa, M.; Kikuchi, K.; Tachibana, H.; Obtani, H.; Noashima, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1295.
14. (a) Chadha, A.; Manohar, M.; Soundrarajan, T.; Lokeswari, T. S. *Tetrahedron: Asymmetry* **1996**, *7*, 1571; (b) Baldassarre, F.; Bertoni, G.; Chiappe, C.; Marioni, F. *J. Mol. Catal.-B Enzym.* **2000**, *11*, 55.
15. Yadav, J. S.; Nanda, S.; Reddy, P. T.; Rao, A. B. *J. Org. Chem.* **2001**, in press.
16. (a) Prelog, V. *Helv. Pure Appl. Chem.* **1964**, *9*, 119; (b) Sih, C.-J.; Chen, C.-S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570.
17. Guy, A.; Dubffet, T.; Doussot, J.; Falguieres, A. G. *Synlett* **1991**, 403.