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A Modification of the Asymmetric Dihydroxylation Approach to the Synthesis of (*S*)-2-Arylpropanoic Acids

Hiroyuki Ishibashi,* Momoe Maeki, Junko Yagi, Masashi Ohba, and Tae Kanai

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan

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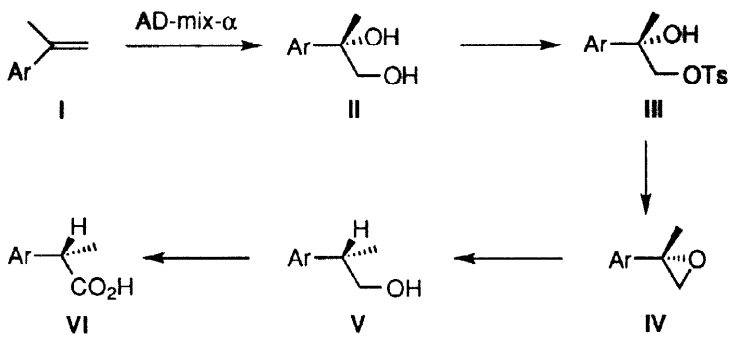
Abstract: Catalytic hydrogenolysis of (*S*)-2-phenyl-1,2-propanediol (**2**), prepared by an asymmetric dihydroxylation of α-methylstyrene (**1**) with AD-mix-α, over Pearlman's catalyst gave (*S*)-2-phenyl-1-propanol (**3**). This method was applied to the synthesis of optically active 2-arylpropanoic acid anti-inflammatory agents, (*S*)-ibuprofen (**8**) and (*S*)-naproxen (**13**). © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

2-Arylpropanoic acids are an important class of non-steroidal anti-inflammatory agents.[1] It has been shown that a higher level of activity is associated with the (*S*)-configuration at the chiral center of, for example, naproxen [2-(6-methoxy-2-naphthyl)propanoic acid].[2] For this reason, many investigations have been carried out with the objective of preparing 2-arylpropanoic acids in the enantiomerically pure (*S*)-configuration.[3]

Quite recently, Hamon and his coworkers[4] reported a new synthesis of optically active (*S*)-naproxen and (*S*)-flurbiprofen using a Sharpless asymmetric dihydroxylation of alkenes with AD-mix-α[5] as a key step. The sequence of the reactions involved the conversion of the optically active (*S*)-diols **II**, prepared from **I**, into the epoxides **IV** *via* the tosylates **III**. The required stereogenic center of the (*S*)-2-arylpropanoic acids **VI** was assembled by catalytic hydrogenolysis of the epoxides **IV** followed by oxidation of the resulting primary alcohols **V** (Scheme 1). The authors reported that "*direct hydrogenolysis of the benzylic tertiary hydroxy group in the intermediates II leading to V was not very satisfactory.*" We found, however, that the conversion of **II** to **V** can be effected by catalytic hydrogenolysis over Pearlman's catalyst [palladium hydroxide on carbon, moist] to give **V** in good yields. In this paper, we report an application of this method to the synthesis of optically active (*S*)-ibuprofen and (*S*)-naproxen.

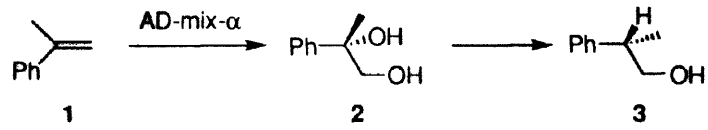


Scheme 1.

PII: S0040-4020(99)00279-3

RESULTS AND DISCUSSION

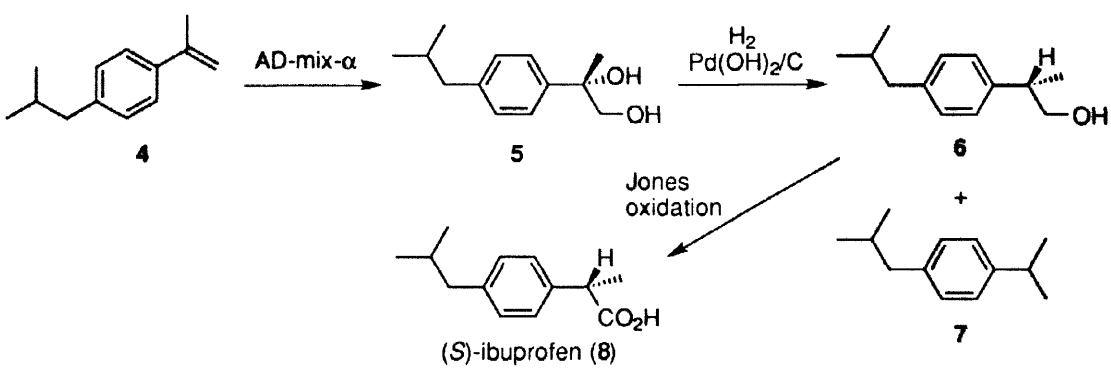
First, we examined the reduction of the diol **2** (92% ee), prepared from α-methylstyrene (**1**), with Et_3SiH in CF_3CO_2H at 50 °C. These conditions gave the expected (*S*)-primary alcohol **3** in 52% yield. However, HPLC analysis showed the ee of **3** to be only 12%. This result clearly indicates that the reduction of **2** with Et_3SiH occurred predominantly in an S_N1 manner. A similar result was obtained with Et_3SiH in the presence of BF_3-Et_2O at room temperature, which gave (*S*)-**3** in 58% yield with 12% ee.



Scheme 2.

We then reinvestigated the catalytic hydrogenolysis of **2** leading to **3**. In fact, the compound **2** was rather resistant to hydrogenolysis over 10% Pd-C at atmospheric pressure. A yield of only 24% of the desired compound **3** was obtained after stirring the mixture for 7 h at room temperature and then for 7 h at 40 °C in the presence of an equal amount of Pd-C in EtOH; a substantial amount of the starting material **2** was recovered unchanged (73%). We soon found, however, that the catalytic hydrogenolysis of **2** proceeded smoothly over an equal amount of Pearlman's catalyst at room temperature in EtOH to give **3** in 55% yield at the complete expense of the starting material **2**. HPLC analysis showed the ee of (*S*)-**3** obtained from (*S*)-**2** (92% ee) to be 89%, which strongly suggested that the hydrogenolysis of **2** essentially proceeded with an inversion. When a catalytic amount of Pearlman's catalyst was used, the hydrogenolysis of **2** became much more sluggish.

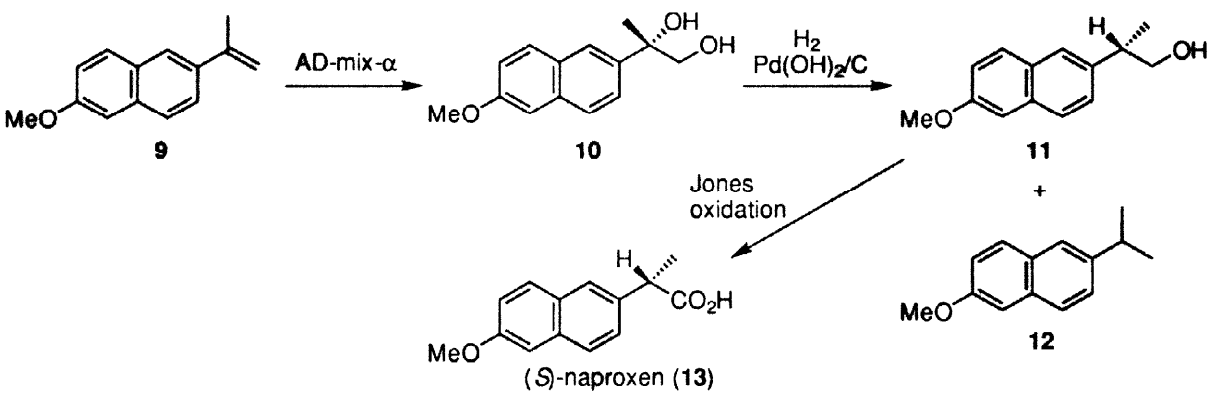
Encouraged by the success of the direct conversion of **II** to **V** in Scheme 1, we next examined a synthesis of (*S*)-ibuprofen (**8**) and (*S*)-naproxen (**13**). The requisite (*S*)-diol **5** (94% ee) for the synthesis of **8** was obtained by dihydroxylation of **4** with AD-mix-α in quantitative yield. Hydrogenolysis of **5** over Pearlman's catalyst gave the expected (*S*)-alcohol **6** in 57% yield. In this case, somewhat surprisingly, the compound **7**, in which both hydroxy groups of **5** were hydrogenated, was also obtained in 19% yield. Although the exact mechanism for the formation of **7** from **5** is not yet clear, it is assumed that the compound **5** is converted into the alkene **4** under the reaction conditions employed, and then the compound **4** is hydrogenated to give **7**. This



Scheme 3.

was presumably the case for the reduction of **2**, but that the corresponding product (isopropylbenzene) was not isolated was probably due to its volatility. Finally, Jones oxidation of the alcohol **6** gave (*S*)-ibuprofen (**8**) in 83% yield. HPLC analysis of **8** showed its ee to be 90%.

The (*S*)-diol **10** for the synthesis of (*S*)-naproxen (**13**) was prepared from **9** with 98% ee. Hydrogenolysis of **10** over Pearlman's catalyst gave the desired (*S*)-alcohol **11** in good yield. In this instance, however, small amounts of unidentified products were also formed. One of them seemed to be the isopropyl derivative **12** and the others were probably compounds in which the aromatic double bonds of **11** and/or **12** were partially hydrogenated. In an attempt to diminish the formation of these undesired products, the effect of temperature (at 0 °C), of solvent (THF, THF-H_2O, AcOH), and of additive (aq HaOH, aq $HClO_4$) on the hydrogenolysis of **10** were examined, but no satisfactory result was obtained. Therefore, the above mixture, without further purification, was then subjected to the Jones oxidation to give (*S*)-naproxen (**13**) in 37% yield (based on **10**), whose recrystallization from hexane/acetone gave the enantiomerically pure **13**, mp 152-154 °C (lit.[6] mp 152-154 °C).



Scheme 4.

Thus, the method described above provides an alternative simple route to the synthesis of optically active (*S*)-2-arylpropanoic acids using an asymmetric dihydroxylation of alkenes, though the catalytic hydrogenolysis of diols often gave undesired by-products.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8100 spectrophotometer. ^1H NMR spectra were measured on a JEOL JNM-EX-270 spectrometer for solutions in $CDCl_3$. δ Values quoted are relative to tetramethylsilane. Optical rotations were measured with a Horiba SEPA-300 polarimeter. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX 102A. HPLC was performed on a Daicel Chiralcel OJ-R column attached to a Tosoh CCPD-8020 system, and peaks were located by using a UV absorbance detector operated at 254 nm. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure. Pearlman's catalyst [palladium hydroxide, 20 wt. % Pd (dry basis) on carbon, moist] was purchased from Aldrich Chem. Co.

(*S*)-2-Phenyl-1,2-propanediol (2). 2-Phenylpropene (**1**) (236 mg, 2 mmol) was added to an ice-cooled solution of AD-mix-α (2.8 g) in *tert*-BuOH (10 mL) and water (10 mL), and the mixture was stirred at 0 °C for 6 h. Sodium sulfite (3.0 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 h, and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 2:1) to give **2**[5] (317 mg, 100%) as an oil [92% ee by HPLC (H_2O/CH_3CN, 9:1; 0.5 mL/min; retention time: (*S*)-**2**, 16.0 min; (*R*)-**2**, 20.2 min)]: IR (neat) ν 3400 cm^{-1}; ^1H NMR (270 MHz) δ 1.54 (s, 3 H, Me), 1.82 (br s, 1 H, OH), 2.58 (s, 1 H, OH), 3.64 (dd, J = 11.2, 5.6 Hz, 1 H, one of CH_2), 3.80 (d, J = 11.2 Hz, 1 H, one of CH_2), 7.22-7.50 (m, 5 H, ArH).

Reduction of 2 with Triethylsilane. BF_3-Et_2O (0.06 mL, 0.5 mmol) was added slowly to a stirred ice-colled mixture of **2** (152 mg, 1 mmol) and Et_3SiH (0.32 mL, 2 mmol) during 15 min, and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into 3 N NaOH and the whole was extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give (*S*)-2-phenyl-1-propanol (**3**)[7] (78 mg, 58%) as an oil [12% ee by HPLC (H_2O/CH_3CN, 3:1; 0.6 mL/min; retention time: (*S*)-**3**, 17.3 min; (*R*)-**3**, 20.1 min)]: IR (neat) ν 3360 cm^{-1}; ^1H NMR (270 MHz) δ 1.28 (d, J = 6.9 Hz, 3 H, Me), 1.60 (br s, 1 H, OH), 2.95 (sextet, J = 6.9 Hz, 1 H, CH), 3.69 (d, J = 6.9 Hz, 2 H, CH_2), 7.22-7.43 (m, 5 H, ArH).

Hydrogenolyis of 2 over Pearlman's Catalyst. A solution of **2** (120 mg, 0.79 mmol) in EtOH (5 mL) containing Pearlman's catalyst (120 mg) was stirred at room temperature under hydrogen gas for 2 h. The catalyst was filtered off and washed with hot EtOH (5 mL). The combined organic layers were concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **3** (59 mg, 55%) as an oil: $[\alpha]_D^{22}$ -15.0 (*c* 0.64, benzene) for 89% ee [by HPLC (H_2O/CH_3CN, 3:1; 0.4 mL/min; retention time: (*S*)-**3**, 26.7 min; (*R*)-**3**, 32.0 min)] [lit.[7] $[\alpha]_D^{19}$ -19.0 (*c* 0.83, benzene) for >95% ee].

4-Isobutylisopropenylbenzene (4). To a solution of butyllithium (6.5 mL as a 1.6 mol/L hexane solution, 10 mmol) in dry diethyl ether (25 mL) was added slowly methyltriphenylphosphonium bromide (3.57 g, 10 mmol) at room temperature, and the mixture was stirred at the same temperature for 4 h. 4-Isobutylacetophenone (1.8 mL, 10 mmol) was added to the mixture, and the mixtrure was stirred at room temperature overnight. The precipitated salts were removed by filtration and the filtrate was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane) to give **4** (722 mg, 41%) as an oil: ^1H NMR (270 MHz) δ 0.91 (d, J = 6.6 Hz, 6 H, CH*Me*$_2$), 1.86 (nonet, J = 6.9 Hz, 1 H, CH), 2.14 (s, 3 H, C=CMe), 2.47 (d, J = 7.3 Hz, 2 H, C*H*$_2$CHMe$_2$), 5.03 (s, 1 H, one of C=CH_2), 5.35 (s, 1 H, one of C=CH_2), 7.10 (d, J = 7.9 Hz, 2 H, ArH), 7.39 (d, J = 8.2 Hz, 2 H, ArH); HRMS calcd for $C_{13}H_{18}$ 174.1408, found 174.1407.

(*S*)-2-(4-Isobutylphenyl)-1,2-propanediol (5). According to a procedure similar to that described above for the preparation of **2**, compound **4** (504 mg, 2.9 mmol) was treated with AD-mix-α (4.2 g). After work-up, the crude material was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **5** (598 mg, 99%), mp 57.5-58 °C (from hexane): $[\alpha]_D^{27}$ +16 (*c* 0.19, $CHCl_3$) for 94% ee [by HPLC (H_2O/CH_3CN, 65:35; 1.0 mL/min; retention time: (*S*)-**5**, 5.2 min; (*R*)-**5**, 5.9 min)]; ^1H NMR (270 MHz) δ 0.90 (d, J = 6.6 Hz, 6 H, CH*Me*$_2$), 1.53 (s, 3 H, ArCH*Me*), 1.75-1.93 (m, 1 H, C*H*Me$_2$), 1.81 (br s, 1 H, OH), 2.46 (d, J = 7.3 Hz, 2

H, ArCH_2), 2.51 (br s, 1 H, OH), 3.62 (dd, J = 10.5, 7.1 Hz, 1 H, one of CH_2OH), 3.79 (d, J = 10.5 Hz, 1 H, one of CH_2OH), 7.14 (d, J = 7.9 Hz, 2 H, ArH), 7.35 (d, J = 7.9 Hz, 2 H, ArH). *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.78; H, 9.78.

Hydrogenolysis of 5. According to a procedure similar to that described above for the preparation of **3**, compound **5** (392 mg, 1.88 mmol) was subjected to the hydrogenolysis in the presence of Pearlman's catalyst (392 mg) in EtOH (10 mL) for 6 h. After work-up, the crude material was chromatographed on silica gel (hexane/AcOEt, 2:1). The first eluent gave 4-isobutylisopropylbenzene (**7**)[8] (64 mg, 19%) as an oil: ^{1}H NMR (270 MHz) δ 0.90 (d, J = 6.6 Hz, 6 H, CH_2CHMe_2), 1.24 (d, J = 6.9 Hz, 6 H, $ArCHMe_2$), 1.75-1.93 (m, 1 H, CH_2CHMe_2), 2.43 (d, J = 7.3 Hz, 2 H, ArCH_2), 2.80-2.96 (m, 1 H, ArCH), 7.02-7.18 (m, 4 H, ArH). The second eluent gave (*S*)-2-(4-isobutylphenyl)-1-propanol (**6**) (204 mg, 57%) as an oil: $[\alpha]_D^{27}$ -16.9 (*c* 1.21, $CHCl_3$) [lit.[9] $[\alpha]_D$ -16.4 (*c* 1.04, $CHCl_3$)]; ^{1}H NMR (270 MHz) δ 0.90 (d, J = 6.6 Hz, 6 H, $CHMe_2$), 1.27 (d, J = 7.3 Hz, 3 H, ArCHMe), 1.57 (br s, 1 H, OH), 1.75-1.96 (m, 1 H, CHMe$_2$), 2.44 (d, J = 7.3 Hz, 2 H, ArCH_2), 2.85-3.0 (m, 1 H, ArCH), 3.69 (d, J = 6.6 Hz, 2 H, CH_2OH), 7.10, 7.15 (ABq, J = 8.3 Hz, 2 H each, ArH); HRMS calcd for $C_{13}H_{20}O$ 192.1514, found 192.1517.

(*S*)-Ibuprofen (8). To a solution of CrO_3 (1.34 g, 13.4 mmol) in water (2 mL) was added conc. H_2SO_4 (1.15 mL) at 0 °C, and the mixture was diluted with water until the total volume of this solution was 5 mL. A 1 mL of this solution (Jones' reagent) was added to an ice-cooled solution of **6** (93 mg, 0.48 mmol) in acetone (10 mL), and the mixture was stirred at room temperature for 2 h. 2-Propanol (0.2 mL) was added to the mixture and the whole was stirred at room temperature for 30 min. Water (20 mL) and diethyl ether (20 mL) were added to the reaction mixture and the organic layer was separated. The aqueous layer was further extracted with diethyl ether, and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 2:1) to give **8** (82 mg, 83%): $[\alpha]_D^{27}$ +48.4 (*c* 0.28, EtOH) for 90% ee [by HPLC (0.2 M H_3PO_4-KH_2PO_4/CH_3CN, 65:35; 1.0 mL/min; retention time: (*S*)-**8**, 20.7 min; (*R*)-**8**, 22.1 min)] [lit.[9] $[\alpha]_D$ +53.2 (*c* 0.41, EtOH), lit.[10] $[\alpha]_D$ +57 (EtOH) for 90% ee]; ^{1}H NMR (270 MHz) δ 0.89 (d, J = 6.6 Hz, 6 H, $CHMe_2$), 1.50 (d, J = 6.9 Hz, 3 H, ArCHMe), 1.75-1.95 (m, 1 H, CHMe$_2$), 2.44 (d, J = 7.3 Hz, 2 H, ArCH_2), 3.71 (q, J = 6.9 Hz, 1 H, ArCH), 7.10, 7.22 (ABq, J = 7.9 Hz, 2 H each, ArH).

(*S*)-2-(6-Methoxy-2-naphthyl)-1,2-propanediol (10). According to a procedure similar to that described above for the prepation of **2**, compound **9**[11] (1.98 g, 10 mmol) was treated with AD-mix-α (12 g). After work-up, the crude material was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **10**[4,12] (1.88 g, 81%) [98% ee by HPLC (H_2O/CH_3CN, 2:1; 0.5 mL/min; retention time: (*S*)-**10**, 10.5 min; (*R*)-**10**, 11.7 min)]: ^{1}H NMR (270 MHz) δ 1.61 (s, 3 H, CMe), 1.84 (br s, 1 H, OH), 2.70 (br s, 1 H, OH), 3.70 (d, J = 11.2 Hz, 1 H, one of CH_2OH), 3.80 (d, J = 11.2 Hz, 1 H, one of CH_2OH), 3.92 (s, 3 H, OMe), 7.10-7.19 (m, 2 H, ArH), 7.49 (dd, J = 8.6, 1.7 Hz, 1 H, ArH), 7.74 (d, J = 8.6 Hz, 2 H, ArH), 7.87 (d, J = 1.3 Hz, 1 H, ArH).

(*S*)-Naproxen (13). According to a procedure similar to that described above for the preparation of **3**, compound **10** (464 mg, 2 mmol) was subjected to the hydrogenolysis in the presence of Pearlman's catalyst (464 mg) in EtOH (20 mL) for 2 h. After filtration of the catalyst, the solvent was evaporated off to give **11**[4]

(417 mg) containing a small quantity of by-products. This mixture was then subjected to the Jones oxidation according to a procedure similar to that described for the preparation of **8**. After work-up, the the crude material was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **13** (167 mg, 37% based on **10**), whose recrystallization from hexane/acetone gave the enantiomerically pure **13**, mp 152-154 °C (lit.[6] mp 152-154 °C): $[\alpha]_D^{28}$ +64.2 (*c* 1.00, $CHCl_3$) [lit.[6] $[\alpha]_D$ +66 ($CHCl_3$)]; ^1H NMR (270 MHz) δ 1.59 (d, *J* = 6.9 Hz, 3 H, CMe), 3.88 (q, *J* = 7.3 Hz, 1 H, CH), 3.91 (s, 3 H, OMe), 7.0-7.17 (m, 2 H, ArH), 7.41 (dd, *J* = 8,6, 2.0 Hz, 1 H, ArH), 7.66-7.73 (m, 3 H, ArH).

REFERENCES

1. Rieu, J.-P.; Boucherie, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.
2. Shen, T. Y. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 460; Gu, Q.-M.; Chen, C.-S.; Sih, C. J. *Tetrahedron Lett.* **1986**, *27*, 1763.
3. For an excellent review on the synthesis of optically active 2-arylpropanoic acids, see: Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, pp. 163-192.
4. Griesbach, R. C.; Hamon, D. P. G.; Kennedy, R. J. *Tetrahedron: Asymmetry* **1997**, *8*, 507.
5. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
6. Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203.
7. Eliel, E. L.; Freeman, J. P. *J. Am. Chem. Soc.* **1952**, *74*, 923.
8. Marshall, W.S. *Ger. Offen.* **1971**, 2,064,825 (*Chem. Abstr.* **1971**, *75*, 101301c).
9. Bando, T.; Namba, Y.; Shishido, K. *Tetrahedron: Asymmetry* **1997**, *8*, 2159.
10. Kaiser, D. G.; Vangiessen, G. J.; Reischer, R. J.; Wechter, W. J. *J. Pharm. Sci.* **1976**, *65*, 269.
11. Yadav, V. S.; Mysorekar, S. M. *Syn. Commun.* **1989**, *19*, 1057.
12. Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.