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Stereocontrolled synthesis of (1*S*)-1-(1*H*-imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methylpropan-1-ol as a potent $C_{17,20}$-lyase inhibitor

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Abstract—An efficient stereocontrolled synthesis of the potent $C_{17,20}$-lyase inhibitor, (1*S*)-1-(1*H*-imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methyl-1-propanol **1**, has been established. The stereogenic center of **1** was successfully constructed by a highly diastereoselective Grignard reaction of **2**, while a subsequent imidazole ring annulation afforded **1** in an enantiomerically pure form. The procedure enables a practical synthesis of **1** that can be conveniently carried out on a multigram scale.

1. Introduction

In our search for potential drugs for the treatment of androgen-dependent prostate cancer, we have identified (1*S*)-1-(1*H*-imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methyl-1-propanol **1** as a novel inhibitor of $C_{17,20}$-lyase,[1,2] a key enzyme involved in androgen biosynthesis. Compound **1** showed potent enzyme inhibitory activity for rat and human $C_{17,20}$-lyase with IC_{50} values of 21 and 28 nM, respectively, and markedly reduced the serum testosterone concentration in animal models and decreased the weights of androgen-dependent organs such as prostate and seminal vesicles in rats.[2] With the identification of **1** as a potent $C_{17,20}$-lyase inhibitor that may serve as a therapeutically useful agent for prostate cancer, an efficient stereocontrolled synthesis of **1** was initiated. Several methods for the preparation of chiral tertiary alcohols such as enantioselective Reformatsky reactions,[3] alkylzinc additions,[4] and diastereoselective Grignard reactions[5,6] have been reported. We envisioned that the stereogenic center of **1** bearing the two aromatic rings could be constructed by a diastereoselective Grignard alkylation of **2**, while a subsequent imidazole ring annulation would provide **1** in an enantiomerically pure form (Fig. 1).

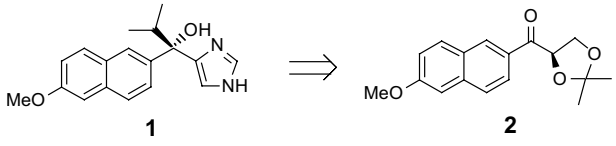

Figure 1.

2. Results and discussion

The synthetic approach that has been developed, summarized in Scheme 1, starts from the optically active ester **3**, which is commercially available or can be readily prepared from D-mannitol in large quantities according to the reported method.[7] Ester **3** was converted into the corresponding amide **4**, which was treated with Grignard reagent **5** prepared from 6-bromo-2-methoxynaphthalene, to give **2** without any loss of enantiomeric excess (99% ee confirmed by HPLC analysis using a Chiralcel® OD-R).[8] To set the benzylic stereocenter, a Grignard reaction was investigated. Initially this process was carried out using isopropylmagnesium bromide according to the literature.[5] Although treatment of **2** with isopropylmagnesium bromide gave the desired **7** (62%) as the major product, it also resulted in formation

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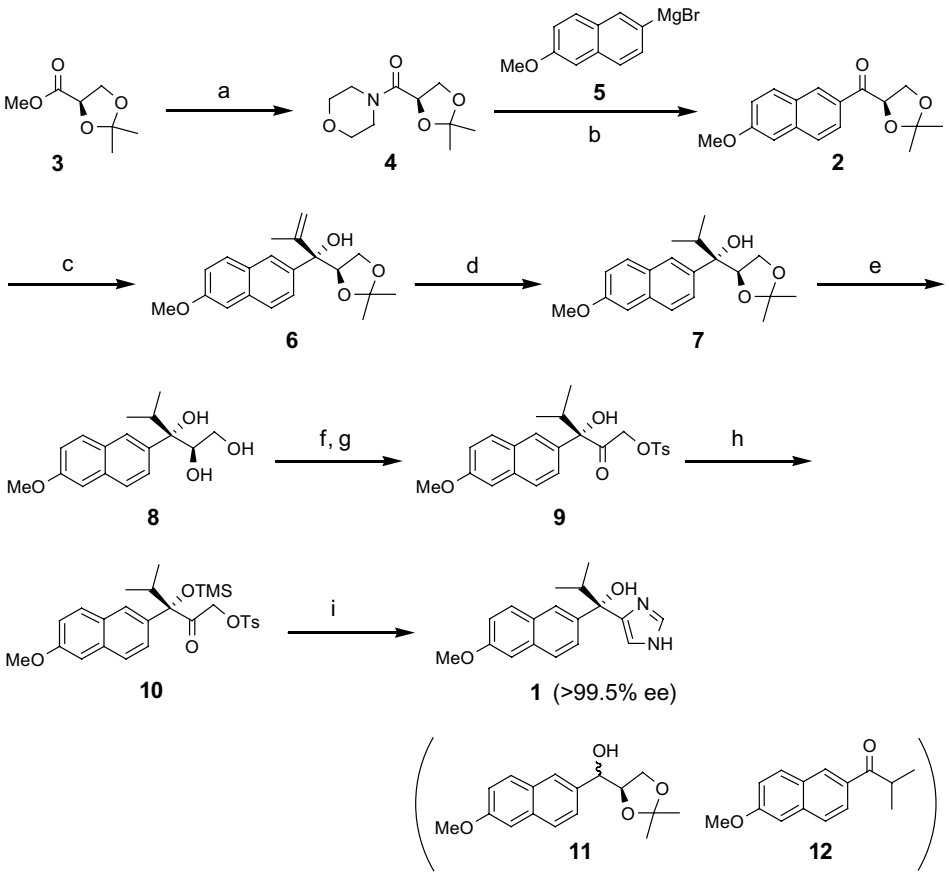

Scheme 1. Reagents and conditions: (a) morpholine, 90 °C, 71%; (b) **5**, THF, −20 to 0 °C, 81%; (c) isopropenylmagnesium bromide, −10 to 0 °C, THF; (d) H_2, Pd/C, AcOEt, rt, 84%, two steps; (e) 1 M HCl, THF–EtOH, 60 °C, 93%; (f) TsCl, pyridine, CH_2Cl_2, rt; (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −70 to −40 °C, 66%, two steps; (h) TMSCl, 2,6-lutidine, THF, rt; (i) formamidine acetate, saturated NH_3–MeOH, rt, 73%, two steps.

of the corresponding diastereomer (6%) and alcohol **11** (20%). The formation of **11** was due to hydride transfer from the Grignard reagent. During a survey of reaction conditions and reagents, the best results were obtained via a modified two-step procedure. Reaction of **2** with isopropenylmagnesium bromide exclusively gave **6** (>99% de) without formation of the undesired diastereomer and alcohol **11**. After hydrogenation of **6**, the desired **7** was obtained in good yield (84% in two steps). The absolute configuration of **7** was confirmed to be the (1*S*,2*R*)-form by X-ray crystallographic analysis (Fig. 2). The diastereoselectivity observed above is consistent with the prediction that the nucleophilic addition would occur specifically under chelation control as shown in Figure 3.

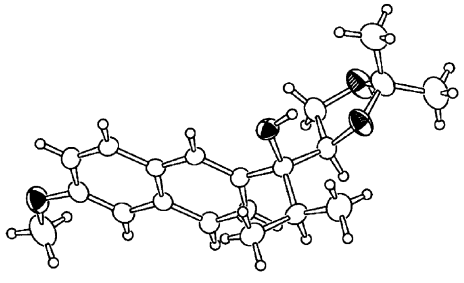

Figure 2. Crystal structure of **7**.

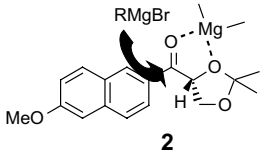

Figure 3.

The acid-catalyzed deprotection of **7** gave triol **8** in high yield, which was selectively tosylated at the primary hydroxyl group while subsequent Swern oxidation afforded **9**. Imidazole ring formation was carried out by using **9** and formamidine acetate under the conditions reported by Wong and Gluchowski[9] (i.e., 45 °C in liquid ammonia). However, this procedure gave only low yields (~30%) of **1**, with concomitant formation of ketone **12** as a major product, which was presumably formed via retro-benzoin condensation.[10] We found that the formation of **12** was effectively prevented by protection of the hydroxyl group of **9** with a trimethylsilyl (TMS) group, and that imidazole ring annulation occurred efficiently when saturated NH_3–MeOH was used as the solvent instead of liquid ammonia. Thus, treatment of **9** with TMSOTf gave **10** quantitatively, which without purification was reacted with formamidine in saturated NH_3–MeOH to afford **1** in good yield

(73% from **9**). The enantiomeric excess of **1** obtained by this procedure was confirmed to be >99.5% ee by HPLC analysis using a Chiralcel® OD-R. Physical data of the asymmetrically synthesized **1** {mp 178–180 °C, $[\alpha]_D^{23} = -49.6$ (*c* 0.5, MeOH)} were identical with those of the chromatographically separated **1** {mp 179–181 °C, $[\alpha]_D^{23} = -48.4$ (*c* 0.5, MeOH)}.[2]

3. Conclusion

The stereocontrolled synthesis described above allows the preparation of **1** in nine steps with 23% overall yield from the commercially available ester **3**, and is a practical and convenient procedure for the production of multigram quantities of **1**. Furthermore, the present synthetic approach is adaptable and should enable the preparation of a wide range of optically active analogues of **1** for biological evaluation.

4. Experimental

4.1. General methods

All commercially available substrates and reagents were used without purification. The melting points are uncorrected. The ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) with tetramethylsilane as an internal standard. Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} (E. Merck). Chromatographic separations were carried out on silica gel 60 (E. Merck, 70–230 mesh) and flash chromatography carried out on silica gel 60 (E. Merck, 230–400 mesh). HPLC analysis was performed using the following conditions: Chiralcel® OD-R (250 × 4.6 mm), mobile phase CH_3CN/pH 7.0 phosphate buffer (45:55), flow rate 0.5 mL/min, detection, UV (254 nm).

4.2. 4-{[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]carbonyl}-morpholine 4

A mixture of **3**[6] (64.5 g, 400 mmol) and morpholine (70 mL, 800 mmol) was heated at 90 °C for 16 h with stirring. After concentration in vacuo, the residue was purified by silica gel column chromatography (hexane–AcOEt = 4:1 to 1:1) to give **4** (60.8 g, 71%) as a pale yellow oil: $[\alpha]_D^{25} = -17.0$ (*c* 1.8, MeOH); ^{1}H NMR ($CDCl_3$) δ: 1.40 (6H, s), 3.47–3.86 (8H, m), 4.13 (1H, dd, $J = 6.8$, 8.4 Hz), 4.48 (1H, dd, $J = 6.0$, 8.6 Hz), 4.65 (1H, dd, $J = 6.0$, 6.8 Hz); IR (KBr): 2986, 2859, 1651, 1443, 1372, 1238, 1221, 1115, 1069, 847 cm^{-1}.

4.3. [(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](6-methoxy-2-naphthyl)methanone 2

To a cooled (−20 °C) solution of **4** (60.8 g, 282 mmol) in anhydrous THF (200 mL) was added dropwise a solution of **5** in THF (250 mL), which was prepared from 2-bromo-6-methoxynaphthalene (80.2 g, 338 mmol) and Mg (8.2 g, 338 mmol), while maintaining the temperature of the solution below −10 °C. After stirring for 20 min at −10 to 0 °C, the mixture was poured into 1 M HCl. The organic phase was separated and the aqueous phase extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in AcOEt, and the insoluble material filtered off. The filtrate was concentrated, and the residue recrystallized from diisopropyl ether to give **2** (65.3 g, 81%) as a colorless powder. The enantiomeric excess was determined to be 99% by HPLC analysis using a Chiralcel® OD-R: mp 116–117 °C; $[\alpha]_D^{25} = -14.9$ (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, s), 1.51 (3H, s), 3.95 (3H, s), 4.28–4.43 (2H, m), 5.40 (1H, dd, $J = 6.2$, 7.0 Hz), 7.14–7.26 (2H, m), 7.77 (1H, d, $J = 8.8$ Hz), 7.86 (1H, d, $J = 8.8$ Hz), 8. 02 (1H, dd, $J = 1.7$, 8.7 Hz), 8.48 (1H, s); IR (KBr): 1690, 1624, 1277, 1246, 1061, 1013, 897, 835, 822 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.38; H, 6.25.

4.4. (1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(6-methoxy-2-naphthyl)-2-methyl-2-propen-1-ol 6

To a cooled (−20 °C) solution of **2** (75.0 g, 262 mmol) in anhydrous THF (400 mL) was added dropwise a solution of isopropenylmagnesium bromide, which was prepared from 2-bromopropene (41.9 g, 472 mmol) and Mg (11.5 g, 472 mmol), while maintaining the temperature of the reaction mixture below −10 °C. The mixture was stirred for a further 20 min at −10 to 0 °C and then diluted with saturated NH_4Cl, after which the organic phase was separated, and the aqueous phase extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give **6** as a pale yellow solid, which was used in the next reaction without further purification. An analytical sample was obtained by recrystallization from AcOEt–hexane (colorless prisms): mp 133–134 °C; $[\alpha]_D^{23} = +107.5$ (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, s), 1.50 (3H, s), 1,62 (3H, s), 2.80 (1H, br s), 3.46 (1H, dd, $J = 6.6$, 8.2 Hz), 3.73 (1H, dd, $J = 8.3$, 8.2 Hz), 3.91 (3H, s), 4.89 (1H, dd, $J = 6.6$, 8.2 Hz), 5.12 (1H, s), 5.40 (1H, s), 7.13–7.18 (2H, s), 7.43 (1H, dd, $J = 1.8$, 8.6 Hz), 7.67–7.76 (2H, m), 7.87 (1H, s); IR (KBr): 3557, 2994, 2948, 1267, 1209, 1161, 1032, 897, 855, 812 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.30; H, 7.21.

4.5. (1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(6-methoxy-2-naphthyl)-2-methylpropan-1-ol 7

A solution of **6** and 10% Pd–C (10 g) in AcOEt (400 mL) was vigorously stirred for 24 h at room temperature under an H_2 atmosphere (1 atm). The resulting mixture was filtered and concentrated in vacuo, the residue passed through a silica gel plug (elution with hexane–AcOEt = 3:1), and the eluate concentrated to give a pale yellow solid. The solid was recrystallized from hexane to

afford **7** (64.8 g, 75%) as colorless needles. The mother liquor was concentrated and the residue recrystallized from hexane to give an additional quantity of **7** (7.67 g, 9%) as colorless needles: mp 105–106 °C; $[\alpha]_D^{25} = +46.3$ (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ: 0.84 (3H, d, $J = 6.8$ Hz), 0.95 (3H, d, $J = 6.8$ Hz), 1.44 (3H, s), 1.46 (3H, s), 2.11–2.28 (1H, m), 2.43 (1H, br s), 3.44–3.59 (2H, m), 3.91 (3H, s), 4.78 (1H, dd, $J = 6.5$, 8.1 Hz), 7.13–7.18 (2H, m), 7.43 (1H, dd, $J = 1.8$, 8.6 Hz), 7.67–7.80 (3H, m); IR (KBr): 3548, 2984, 1607, 1466, 1381, 1368, 1265, 1221, 1177, 1067, 1038, 849 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.69; H, 7.83.

4.6. Single-crystal X-ray analysis of 7

An analytical sample of **7** for X-ray analysis was obtained by recrystallization from diisopropyl ether. X-ray measurement was preformed on a Rigaku AFC5R diffractometer with Cu-Kα radiation. Crystal data for **7**: $C_{20}H_{26}O_4$, $M = 330.42$, monoclinic, space group $C2$ (#5), $a = 20.478(4)$ Å, $b = 5.878(4)$ Å, $c = 15.359(3)$ Å, $\beta = 92.76(2)°$, $V = 1846(1)$ Å^3, $D_{calcd} = 1.188$ g cm^{-3}, $Z = 4$; final *R*-values were $R1 = 0.040$ for 2337 reflections with Fo $> 4\sigma$ (Fo), $wR2 = 0.113$ for all the 2759 reflections. The absolute configuration was supported by the Flack parameter[11] of $-0.03(29)$. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 231491).

4.7. (2*R*,3*S*)-3-(6-Methoxy-2-naphthyl)-4-methylpentane-1,2,3-triol 8

A solution of **7** (72.0 g, 218 mmol) in 1 M HCl–THF–EtOH (1:1:2, 480 mL) was heated at 60 °C for 2 h. After removal of the solvent, the residue was diluted with water, and the mixture extracted with AcOEt (×2). The combined organic layers were washed with saturated $NaHCO_3$ and brine, followed by drying over $MgSO_4$. After removal of the solvent, the residue was recrystallized from hexane–AcOEt (4:1) to give **8** (54.8 g, 87%) as a colorless powder. The mother liquor was concentrated and the residue recrystallized from diisopropyl ether to give an additional quantity of **8** (3.98 g, 6%) as a colorless powder: mp 131–132 °C; $[\alpha]_D^{23} = +15.6$ (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ: 0.78 (3H, d, $J = 6.8$ Hz), 0.93 (3H, d, $J = 6.8$ Hz), 2.33–2.47 (1H, m), 3.09 (3H, br s), 3.53 (2H, d, $J = 4.2$ Hz), 3.92 (3H, s), 4.32 (1H, dd, $J = 4.2$, 4.2 Hz), 7.12–7.18 (2H, m), 7.36 (1H, dd, $J = 8.7$, 1.7 Hz), 7.66–7.79 (3H, m); IR (KBr): 3537, 3428, 2973, 2959, 1605, 1391, 1265, 1223, 1165, 1030, 883, 855 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.43; H, 7.51.

4.8. (3*S*)-3-Hydroxy-3-(6-methoxy-2-naphthyl)-4-methyl-2-oxopentyl *p*-toluenesulfonate 9

To a cooled (0 °C) solution of **8** (57.0 g, 196 mmol) in anhydrous CH_2Cl_2 (350 mL) were added pyridine (47.6 mL, 588 mmol) and *p*-toluenesulfonyl chloride (41.2 g, 216 mmol). After stirring for 12 h at room temperature, the reaction mixture was successively washed with 1 M HCl (×2), and saturated $NaHCO_3$ followed by drying over $MgSO_4$. The solution was concentrated in vacuo to give the tosylate as a pale yellow viscous oil, which was used for the next reaction without further purification.

To a cooled (−70 °C) solution of oxalyl chloride (34.2 mL, 392 mmol) in anhydrous CH_2Cl_2 (250 mL) was added dropwise a solution of DMSO (55.6 mL, 784 mmol) in anhydrous CH_2Cl_2 (50 mL). After stirring for 5 min, a solution of the tosylate in anhydrous CH_2Cl_2 (200 mL) was added dropwise over 1 h, and the reaction mixture stirred for 30 min at −50 to −40 °C. After cooling to −70 °C, triethylamine (200 mL) was added dropwise over 30 min, and the mixture then allowed to warm to room temperature. The resulting mixture was diluted with water and extracted with CH_2Cl_2 (×2). The combined organic layers were washed with water and dried over $MgSO_4$. After removal of the solvent, the obtained solid was filtered and washed with AcOEt. The filtrate was concentrated and the residue passed through a silica gel plug (eluting with CH_2Cl_2) after which the eluant was concentrated to give a brown solid. The solids were combined and recrystallized from AcOEt to give **9** (47.4 g, 55%) as a colorless powder. The mother liquor was concentrated and the residue purified by column chromatography on silica gel (hexane–AcOEt = 4:1) followed by recrystallization from AcOEt to give an additional amount of **9** (9.43 g, 11%) as a colorless powder: mp 155–156 °C; $[\alpha]_D^{23} = -125.3$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ: 0.72 (3H, d, $J = 6.8$ Hz), 0.94 (3H, d, $J = 6.8$ Hz), 2.34 (3H, s), 2.78–2.92 (1H, m), 3.05 (1H, s), 3.93 (3H, s), 5.00 (2H, s), 7.10–7.21 (4H, m), 7.39 (1H, dd, $J = 1.9$, 8.7 Hz), 7.62 (2H, d, $J = 8.2$ Hz), 7.71 (2H, d, $J = 8.6$ Hz), 7.83 (1H, s); IR (KBr): 3555, 1736, 1406, 1362, 1260, 1190, 1175, 1034, 1017, 845, 814 cm^{-1}. Anal. Calcd for $C_{24}H_{26}O_6S$: C, 65.14; H, 5.92. Found: C, 65.02; H, 5.83.

4.9. (3*S*)-3-(6-Methoxy-2-naphthyl)-4-methyl-2-oxo-3-[(trimethylsilyl)oxy]pentyl *p*-toluenesulfonate 10

To a cooled (0 °C) solution of **9** (40.0 g, 90.4 mmol) and 2,6-lutidine (21.1 mL, 118 mmol) in anhydrous THF (400 mL) was added dropwise trimethylsilyl trifluoromethanesulfonate (21.4 mL, 118 mmol) and the mixture stirred for 30 min at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched with water and the resulting mixture diluted with 1 M HCl, and extracted with AcOEt (×2). The combined organic layers were successively washed with water, saturated $NaHCO_3$, and brine, followed by drying over $MgSO_4$. The solvent was removed in vacuo to give **10** as a pale yellow solid, and this material was used for the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ: 0.14 (9H, s), 0.89 (3H, d, $J = 6.8$ Hz), 0.93 (3H, d, $J = 6.8$ Hz), 2.36 (3H, s), 2.76–2.89 (1H, m), 3.93 (3H,

s), 5.07 (2H, s), 7.11–7.20 (4H, m), 7.31 (1H, dd, $J = 1.9$, 8.1 Hz), 7.64–7.71 (5H, m); IR (KBr): 1736, 1375, 1366, 1208, 1182, 1011, 851 cm^{-1}.

4.10. (1*S*)-1-(1*H*-Imidazol-4-yl)-1-(6-methoxy-2-naphthyl)-2-methylpropan-1-ol 1

In a round bottomed flask, **10** and formamidine acetate (14.2 g, 136 mmol) was dissolved in anhydrous THF (40 mL), after which freshly prepared saturated NH_3–MeOH solution (200 mL) was added, and the reaction mixture stirred for 60 h at room temperature. After removal of the solvent, the residue was diluted with water and extracted with AcOEt (×2) and the combined organic layers washed with brine, dried over $MgSO_4$ then concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH = 20:1 to 10:1) to give a brown viscous oil which was crystallized from AcOEt to give **1** (17.2 g, 64%) as a pale yellow powder. The mother liquor was concentrated and the residue was purified by column silica gel chromatography followed by recrystallization from AcOEt to give an additional amount of **1** (2.52 g, 9%) as a pale yellow powder. The enantiomeric excess of **1** was >99.5% as determined by HPLC using a Chiralcel® OD-R: mp 178–180 °C; $[\alpha]_D^{23} = -49.6$ (*c* 0.5, MeOH); ^1H NMR ($CDCl_3 + CD_3OD$) δ: 0.81 (3H, d, $J = 6.8$ Hz) 1.00 (3H, d, $J = 6.8$ Hz), 2.78–2.64 (1H, m), 3.91 (3H, s), 7.00 (1H, d, $J = 1.0$ Hz), 7.15–7.09 (2H, m), 7.56–7.51 (2H, m), 7.75–7.65 (2H, m), 7.91 (1H, d, $J = 1.4$ Hz); IR (KBr): 3140, 2984, 2957, 1464, 1222, 1028, 856, 806, 652 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.77; H, 6.79; N, 9.31.

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References and notes

1. Matsunaga, N.; Kaku, T; Itoh, F.; Tanaka, T.; Hara, T.; Miki, H.; Iwasaki, M.; Aono, T.; Yamaoka, M.; Kusaka, M.; Tasaka, A. *Bioorg. Med. Chem.* **2004**, *12*, 2251.
2. Matsunaga, N.; Kaku, T; Ojida, A; Tanaka, T.; Hara, T.; Yamaoka, M.; Kusaka, M.; Tasaka, A. *Bioorg. Med. Chem.* (in press).
3. (a) Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051; (b) Soai, K.; Oshio, A.; Saito, T. *J. Chem. Soc., Chem. Commun.* **1993**, 811.
4. (a) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970; (b) Yus, M.; Ramón, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 2291; (c) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445.
5. Méric, R.; Vigneron, J.-P. *Bull. Soc. Chim. Fr.* **1973**, 327.
6. Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031.
7. (a) Chittenden, G. J. *Carbohydr. Res.* **1980**, *84*, 350; (b) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6; (c) Lichtenthaler, F. W.; Jarglis, P.; Lorenz, K. *Synthesis* **1988**, 790.
8. Tasaka, A.; Tamura, N.; Matsushita, Y.; Teranishi, K.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **1993**, *41*, 1035.
9. (a) Wong, W. C.; Gluchowski, C. *Synthesis* **1995**, 139; (b) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic, 1997.
10. Miyashita, A.; Suzuki, Y.; Okumura, Y.; Iwamoto, K.; Higashino, T. *Chem. Pharm. Bull.* **1998**, *46*, 6.
11. Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.