Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2021–2028

Synthetic studies on (1*S*)-1-(6,7-dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol as a selective $C_{17,20}$-lyase inhibitor

Nobuyuki Matsunaga,* Tomohiro Kaku, Akio Ojida† and Akihiro Tasaka

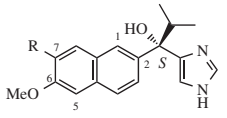
Medicinal Chemistry Research Laboratories II, Pharmaceutical Research Division: Takeda Chemical Industries, Ltd, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan

Received 27 April 2004; accepted 29 May 2004

Abstract—An asymmetric synthesis of the selective $C_{17,20}$-lyase inhibitor **2** has been established in eight steps from 2,3-dihydroxynaphthalene **9**. The key steps are the enantioselective oxidation of ketone **17** to the chiral α-hydroxy ketone **18** and the diastereoselective Grignard reaction of **18** to the (2*R*,3*S*)-diol **21**. In addition, a simple procedure for the preparation of imidazolyl 1,4-dimagnesium bromide has been established; the Grignard reaction of **11** using this reagent in the presence of cinchonine provided **2** with 44% ee.

1. Introduction

Prostate cancer is now the most prevalent cancer for males in the US and Europe. $C_{17,20}$-lyase, which is a key enzyme involved in androgen biosynthesis, is thought to be a promising target for the treatment of androgen-dependent prostate cancer. In previous papers,[1,2] we have described the synthesis and pharmacological profiles of $C_{17,20}$-lyase inhibitors. The active compound **1**, which had a potent $C_{17,20}$-lyase inhibition with IC_{50} values of 21 and 28 nM toward rat and human enzymes, respectively, showed significant in vivo effects in rat models.[2] The stereocontrolled synthesis of **1**, involving a diastereoselective Grignard reaction, was achieved,[3] with further studies revealing that **1** had a relatively potent inhibitory activity ($IC_{50} = 140$ nM) on rat steroid 11β-hydroxylase, which is responsible for the production of mineralocorticoids. During the search for selective inhibitors, (*S*)-1-(6,7-dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methyl-1-propanol **2** was identified as being a selective compound with IC_{50} values of 3.8 and >1000 nM for $C_{17,20}$-lyase and 11β-hydroxylase, respectively.[2] For extensive pharmacological studies, a practical stereocontrolled synthesis of **2** was initiated (Fig. 1).



1 (R=H)
2 (R=OMe)

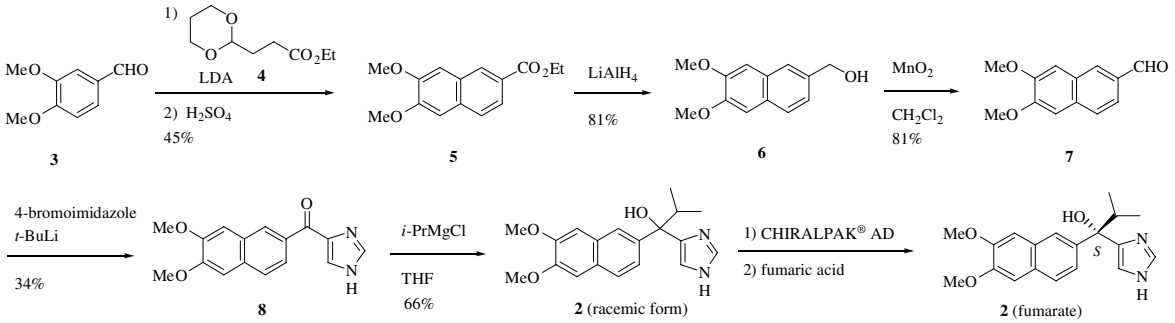
Figure 1.

2. Results and discussion

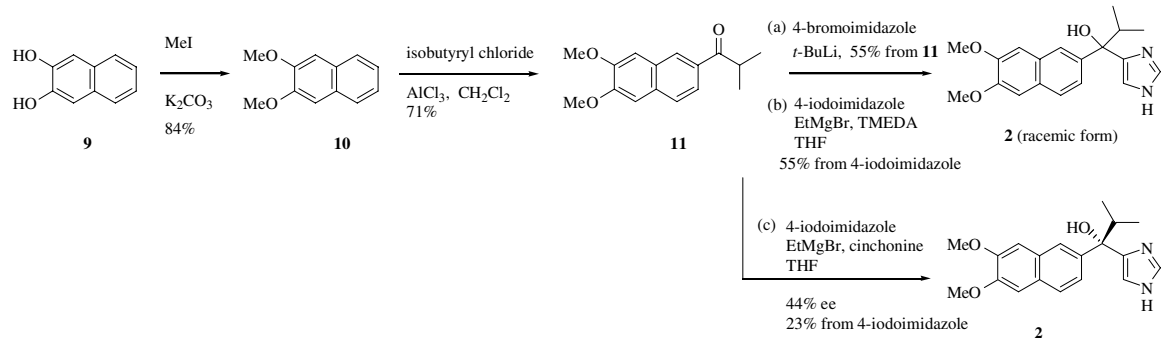
The initial synthetic route to **2** needed a five-step synthesis followed by a resolution using HPLC (Scheme 1).[2] For a convenient route to **2** in racemic form, we achieved a three-step synthesis from 2,3-dihydroxynaphthalene **9** as shown in Scheme 2. Methylation of **9** provided 2,3-dimethoxynaphthalene **10**, which was followed by a Friedel–Crafts acylation with isobutyryl chloride to provide ketone **11** in good yield. **11** was then applied to Katritzky's imidazole introduction[4] to afford **2**, in racemic form, in 55% yield. In these procedures, the imidazole introduction employing *t*-BuLi was not practical for a large scale synthesis. The facile generation

* Corresponding author. Fax: +81-6-6300-6206; e-mail: matsunaga_nobuyuki@takeda.co.jp
† Present address: Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Fukuoka 812-8581, Japan.

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.05.044



Scheme 1.

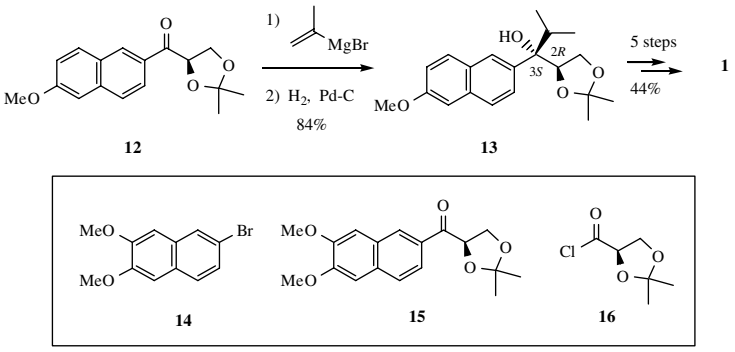


Scheme 2.

of imidazol-4-yl anions by addition of EtMgBr to *N*-protected 4-iodoimidazoles was reported by Turner and Lindell,[5] and we have explored a modified imidazole introduction using imidazolyl 1,4-dimagnesium bromide, which could generate 4-iodo-1*H*-imidazole and EtMgBr. During a survey of reaction conditions, optimal conditions for the preparation of imidazolyl 1,4-dimagnesium bromide that is applicable to a large scale synthesis, were established. The preparation was carried out as follows: 5 equiv of EtMgBr were added to a mixture of 4-iodoimidazole[6,7] (1 equiv) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 1.5 equiv) in THF, and the mixture heated at 60 °C for 1 h before being cooled to room temperature. Compound **11** (1.6 equiv) was added to the above mixture, and stirring continued at room temperature to give **2** (racemic form) in 55% yield. When TMEDA was not employed, it was found that the yield of racemic **2** decreased because the intermediate Grignard reagent separated out of the mixture in large quantities. Thus, we thought this procedure might provide an asymmetric reaction in the presence of a chiral ligand, whereas enantioselective alkylation of ketones has numerous difficulties. Several groups have already reported successful enantioselective alkylation,[8–13] but we tried the asymmetric imidazole introduction with a chiral ligand, instead of TMEDA, including diol derivatives such as di-*O*-lithio-(*S*)-2,2′-dihydroxy-1,1′-binaphthyl[8] and magnesium α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanolate,[9] and aminoalcohols and diamines such as cinchonine, quinidine, sparteine, and others. The best result was 44% ee with 23% isolated yield, which was when cinchonine was employed, although to the best of our knowledge, this is the first example of enantioselective introduction of a 4-imidazolyl group. These results led us to revise our approach.

Diastereoselective Grignard reactions are an effective method for providing chiral tertiary alcohols.[14–16] Our stereocontrolled synthesis of **1**[3] involved the diastereoselective Grignard reaction of chiral ketone **12** as the key step to establish the desired stereocenter (Scheme 3). To apply this chelation-controlled alkylation to the synthesis of **2**, the preparation of the bromonaphthalene **14** as a precursor of the chiral ketone **15** was investigated. However, our efforts revealed that the synthetic route employing **14** was impractical because the preparation of **14** itself required a multi-step synthesis. Also, an alternative approach to prepare **15** involving a Friedel–Crafts acylation of **10** with **16** under various conditions, resulted in quite poor yields. Consequently, another strategy was required; chiral α-hydroxy ketone **18** was employed for a novel stereocontrolled synthesis (Scheme 4). Friedel–Crafts acylations of **10** with D-lactic acid derivatives also gave poor yields, and the synthesis of the desired compound **18** being achieved by asymmetric oxidation of **17**. Ketone **17** was prepared by the Friedel–Crafts reaction of **10** with propionyl chloride using $AlCl_3$ in 77% yield.

The enantioselective α-hydroxylation of alkyl aryl ketones utilizing a chiral oxaziridine was reported by Davis and co-workers.[17,18] This procedure was applied to **17** (Table 1 in Scheme 4). The enolates of **17** were generated by the treatment of an appropriate base (1.2 equiv) in THF at −78 °C, with hydroxylation being



Scheme 3.

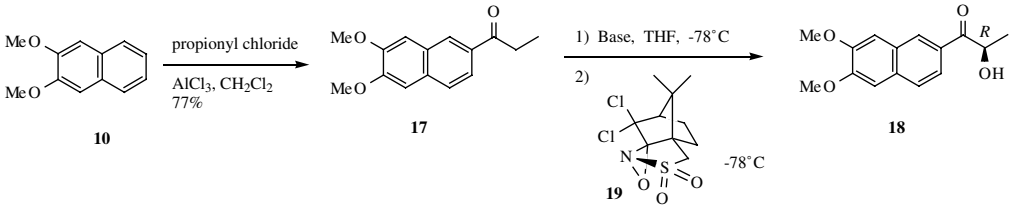
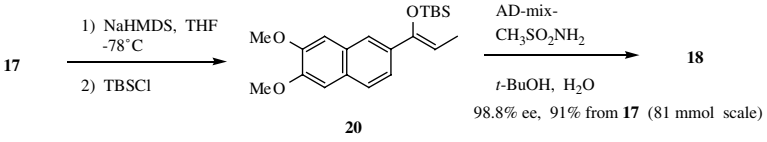


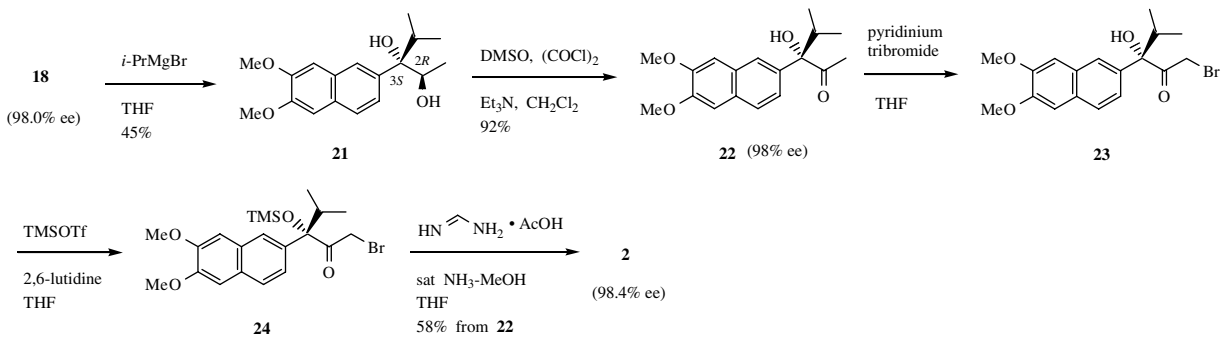
Table 1. Survey of Bases for Asymmetric a-Hydroxylation

Entry	Scale (mmol)	Base	**18** (%)	% ee
1	0.5	NaHMDS	86	95.4
2	0.5	LiHMDS	57	96.0
3	0.5	LDA	73	92.4
4	60	NaHMDS	90	95.0



Scheme 4.

accomplished by the addition of the (−)-(8,8-dichlorocamphorylsulfonyl)oxaziridine **19**[17] (1.2 equiv). A survey of bases revealed that sodium bis(trimethylsilyl)amide (NaHMDS) was the base of choice for this hydroxylation, affording (*R*)-hydroxyketone **18** in 95.4% ee and 86% yield (entry 1). Other bases such as lithium bis(trimethylsilyl)amide (LiHMDS) and lithium diisopropylamide (LDA) also exhibited high stereoselectivity with 96.0% ee and 92.4% ee, respectively; however moderate yields, 57% and 73%, respectively, were observed due to modest conversions (entries 2 and 3). Even in a larger scale reaction using NaHDMS 95% ee and 90% yield was obtained (entry 4). In addition, the enantiomeric excess of **18** shown in entry 4 was

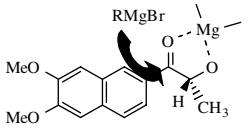


Scheme 5.

enhanced to 98.0% ee by washing the crystals with ether. The (*R*)-configuration of **18**, which is similar to Davis' results,[17] was determined by single-crystal X-ray analysis after conversion into **21**. The α-hydroxylation provided **18** with high enantioselectivity, but this reaction was not practical because the expensive chiral reagent **19** was stoichiometrically required. Therefore, a catalytic enantioselective reaction to obtain **18** was investigated.

Chiral α-hydroxy ketone synthesis via a catalytic asymmetric dihydroxylation of silyl enol ethers has previously been demonstrated by Sharpless and coworkers.[19] Applying this procedure, silyl enol ether **20** was prepared by generating the enolate of **17** in the presence of NaHMDS, followed by trapping with *tert*-butyldimethylsilyl chloride (TBSCl) (Scheme 4). The catalytic asymmetric dihydroxylation of **20** employing AD-mix-β (0.2 and 1 mol% with respect to $K_2OsO_2(OH)_4$ and $(DHQD)_2$–PHAL, respectively) in the presence of methanesulfonamide (1 equiv) at 0 °C successfully gave **18** in 98.8% ee and 91% yield, even in large scale reactions (81 mmol scale).

Conversion of **18** (98.0% ee) into **2** was achieved as shown in Scheme 5. Treatment of **18** with isopropylmagnesium bromide predictably provided the (2*R*,3*S*)-diol **21** in a diastereoselective manner in 45% yield. As no diastereoisomer was observed in this case, the two-step procedure described in our previous paper[3] (reaction using isopropenyl magnesium bromide followed by catalytic hydrogenation) was not adopted. A high degree of diastereoselectivity could be explained by the relatively rigid chelate transition state and the carbanion attack on the chelate from the less hindered side (Fig. 2). The absolute configuration of **21** was determined by a single-crystal X-ray analysis (Fig. 3). Oxidation of **21** under Swern conditions afforded hydroxyketone **22** in 92% yield with 98% ee. The α-bromination of **22** was carried out using pyridinium tribromide to give bromoketone **23**. The imidazole ring construction was accomplished in a two-step procedure as described previously.[3] The tertiary hydroxyl group of **23** was silylated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of 2,6-lutidine to give the protected intermediate **24**. Treatment of the intermediate with formamidine acetate in saturated NH_3–MeOH furnished **2** with 98.4% ee in 58% yield over the final three steps. The asymmetric synthesis of **2** was then completed in just eight steps from the commercially available 2,3-dihydroxynaphthalene. The enantiomeric excess was enhanced to >99.9% when **2** was obtained as the fumarate salt. Physical data of the asymmetrically synthesized **2** (fumarate), {mp 117–120 °C, $[\alpha]_D^{20} = -34.4$ (*c* 1.00, MeOH)}, were identical with those of the chromatographically separated **2** (fumarate), {mp 116–120 °C, $[\alpha]_D^{20} = -35.3$ (*c* 1.01, MeOH)}.[2]



18

Figure 2.

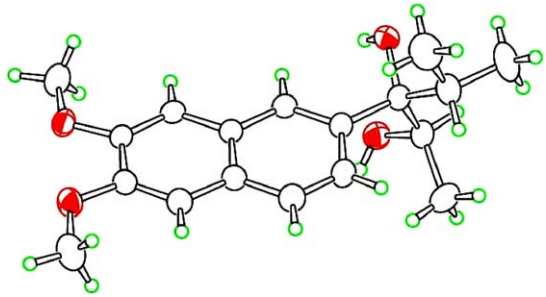


Figure 3. Crystal structure of **21**.

3. Conclusions

An asymmetric synthesis of the selective $C_{17,20}$-lyase inhibitor **2** has been established in eight steps from 2,3-dihydroxynaphthalene **9**. The key steps involved are the enantioselective oxidation of ketone **17** to the chiral α-hydroxy ketone **18** and the diastereoselective Grignard reaction of **18** to the (2*R*,3*S*)-diol **21**. In addition, α-haloketones such as **24** could be good intermediates for azole derivatives, with their asymmetric synthesis offering efficient procedures for the synthesis of chiral tertiary alcohols carrying azole moieties. Furthermore, a facile procedure for the preparation of imidazolyl 1,4-dimagnesium bromide has been established; the stereocontrolled imidazole ring introduction with this reagent and cinchonine provided **2** in moderate enantiomeric excess.

4. Experimental

4.1. Chemistry

Melting points were determined on a Yanaco MP-500V micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Shimadzu FTIR-8200PC spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in ppm with tetramethylsilane as the internal standard, coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, br s = broad singlet. Column chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck).

4.2. 2,3-Dimethoxynaphthalene 10

To a mixture of 2,3-dihydroxynaphthalene **9** (204.80 g, 1.28 mol) and potassium carbonate (883.9 g, 6.40 mol) in DMF (800 mL) was added methyl iodide (544.9 g,

3.84 mol) over 30 min with ice-cooling. The cooling bath was removed and an exothermic reaction proceeded. After the exothermic reaction was completed, the mixture was stirred at room temperature for 18 h and poured into water. The crystals that separated out of the solution were collected, washed with water, and dried. Recrystallization from AcOEt–hexane gave **10** as colorless needles (201.85 g, 84%). Mp 119–120 °C. IR ν_{max}^{KBr} cm^{-1}: 1508, 1489, 1254, 1163, 1117, 1003, 853, 754. ^1H NMR ($CDCl_3$) δ: 4.00 (6H, s), 7.12 (2H, s), 7.29–7.38 (2H, m), 7.64–7.74 (2H, m). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.53; H, 6.35.

4.3. 1-(6,7-Dimethoxy-2-naphthyl)-2-methylpropan-1-one 11

To a mixture of **10** (149.7 g, 795.3 mmol) and isobutyryl chloride (120.0 mL, 1.15 mol) in dichloromethane (800 mL) was added $AlCl_3$ (180.0 g, 1.35 mol) portionwise at 0–15 °C. The mixture was stirred at room temperature for 3 h, poured onto crushed ice, and diluted with 1 M HCl. After separation of the layers, the aqueous phase was extracted further with dichloromethane. The combined organic layers were washed with 1 M NaOH and brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from AcOEt–hexane to give **11** as colorless crystals (146.0 g, 71%). Mp 107 °C (AcOEt–hexane). IR (KBr): 2971, 1674, 1487, 1262, 1217 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.27 (6H, d, $J = 6.6$ Hz), 3.60–3.80 (1H, m), 4.03 (6H, s), 7.15 (1H, s), 7.23 (1H, s), 7.73 (1H, d, $J = 8.4$ Hz), 7.91 (1H, dd, $J = 1.6$, 8.4 Hz), 8.34 (1H, d, $J = 1.6$ Hz). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.28; H, 7.01.

4.4. 1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol 2 (as the racemic form)

4.4.1. Imidazole introduction into 11 using 4-bromoimidazole and *t*-BuLi. To a solution of 4-bromoimidazole (6.02 g, 41.0 mmol) in THF (75 mL) was added *t*-BuLi (1.54 M in pentane, 60.0 mL, 92.4 mmol) at −78 °C. The mixture was allowed to warm to 0 °C and stirred for 1 h. The mixture was then cooled to −78 °C and a solution of **11** (8.00 g, 31.0 mmol) in THF (30 mL) added dropwise. The mixture was warmed to room temperature and stirred for an additional 72 h. The reaction was quenched with aqueous NH_4Cl and the mixture extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated, and the residue chromatographed on silica gel using CH_2Cl_2–MeOH (30:1) as an eluent followed by recrystallization from AcOEt–hexane to give **2** (racemic form, 5.50 g, 55%). Mp 162–163 °C. IR (KBr): 3322, 2965, 1510, 1254, 1163, 731 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.81 (3H, d, $J = 6.6$ Hz), 1.00 (3H, d, $J = 6.6$ Hz), 2.60–2.78 (1H, m), 3.96 (3H, s), 3.97 (3H, s), 6.98 (1H, d, $J = 1.0$ Hz), 7.07 (1H, s), 7.11 (1H, s), 7.41–7.49 (2H, m), 7.61 (1H, d, $J = 8.4$ Hz), 7.89 (1H, d, $J = 1.4$ Hz). Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.83; H, 6.76; N, 8.42.

4.4.2. Improved imidazole introduction using 4-iodoimidazole and EtMgBr. 4-Iodo-1*H*-imidazole. To a solution of imidazole (136.78 g, 2.01 mol) in 2.3 M NaOH (6 L) was added a mixture of KI (1120 g, 6.76 mol) and iodine (1022 g, 6.76 mol) in water (3 L). The mixture was stirred at room temperature for 3 h and then neutralized by the addition of 6 M HCl and crushed ice. The precipitate was collected by filtration, washed with water and cold EtOH, and dried to give 4,5-diiodo-1*H*-imidazole (554.0 g, 87%). ^1H NMR ($CDCl_3$+DMSO-d_6) δ: 7.64 (1H, s), 7.71 (1H, s). A solution of potassium sulfite (4324 g, 27.32 mol) in water (8.0 L) was added portionwise to a heated (70 °C) solution of 4,5-diiodo-1*H*-imidazole (1082 g, 3.29 mol) in DMF (8.0 L). The mixture was heated at 95–100 °C for 6 h, cooled to room temperature, and filtered. The filtrate was diluted with brine (16 L) and extracted with AcOEt–THF (1:1) three times. The organic layers were combined and concentrated to dryness. The residue was dissolved in hot AcOEt and the insoluble inorganic salt filtered off. The crystals separated out of the AcOEt solution were collected and dried to give 4-iodo-1*H*-imidazole (194.0 g). The filtrate was washed with water and brine, dried over $MgSO_4$, and concentrated. The residual crystals were collected and washed with diisopropylether to give 4-iodo-1*H*-imidazole (268.9 g). Yield 71%. Mp 140 °C (H_2O). (lit.[6] 137–138 °C). ^1H NMR ($CDCl_3$+CD_3OD) δ: 7.12 (1H, d, $J = 1.4$ Hz), 7.55 (1H, d, $J = 1.4$ Hz). Anal. Calcd for $C_3H_3IN_2$: C,18.58; H, 1.56; N, 14.44. Found: C, 18.52; H, 1.54; N, 14.47.

Imidazole introduction into **11** *with imidazolyl-1,4-dimagnesium bromide*. To a mixture of 4-iodo-1*H*-imidazole (1.50 g, 7.7 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (1.74 mL, 11.5 mmol) in THF (10 mL) was added dropwise EtMgBr in THF (1.0 M; 39 mL, 39.0 mmol) with ice-cooling. The mixture was stirred at 60 °C for 1 h and then cooled to room temperature. **11** (3.30 g, 12.8 mmol) was then added portionwise and the mixture stirred at room temperature for 3.5 h. The reaction was quenched with aqueous NH_4Cl and the mixture extracted with several portion of AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using AcOEt–MeOH = 50:1 as an eluent to give **2** (racemic form, 1.40 g, 55%).

4.4.3. Enantioselective imidazole introduction using cinchonine. To a mixture of 4-iodo-1*H*-imidazole (1.50 g, 7.7 mmol) and cinchonine (3.44 g, 11.5 mmol) in THF (20 mL) was added dropwise EtMgBr in THF (1.0 M; 47 mL, 47 mmol) with ice-cooling. The mixture was stirred at 60 °C for 1 h and then cooled with an ice-bath. **11** (3.30 g, 12.8 mmol) in THF (15 mL) was then added dropwise and the mixture stirred at 5 °C for 8 h. The reaction was quenched with aqueous NH_4Cl and the mixture was extracted with several portion of AcOEt. The organic layers were combined, dried over $MgSO_4$ and concentrated, with the residue chromatographed on silica gel using AcOEt–MeOH = 50:1 as an eluent to give **2** (0.58 g, 23%, 43% ee).

4.5. 1-(6,7-Dimethoxy-2-naphthyl)propan-1-one 17

To a mixture of **10** (122.35 g, 650.0 mmol) and propionyl chloride (97.90 g, 1.06 mol) in dichloromethane (700 mL) was added $AlCl_3$ (162.9 g, 1.22 mol) with ice-cooling. The mixture was stirred at 0 °C for 2 h, poured onto crushed ice and diluted with 1 M HCl. After the separation of the layers, the aqueous phase was further extracted with dichloromethane. The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was collected and washed with diisopropylether to give **17** as colorless crystals. Recrystallization from AcOEt–hexane gave colorless plates (122.85 g, 77%). Mp 101–103 °C. IR ν_{max}^{KBr} cm^{-1}: 1680, 1493, 1264, 1217, 1173, 1140, 920, 856. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, t, $J = 7.2$ Hz), 3.11 (2H, q, $J = 7.2$ Hz), 4.03 (6H, s), 7.15 (1H, s), 7.23 (1H, s), 7.72 (1H, d, $J = 8.4$ Hz), 7.91 (1H, dd, $J = 8.4$, 1.6 Hz), 8.34 (1H, d, $J = 1.6$ Hz). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.66; H, 6.48.

4.6. (2*R*)-1-(6,7-Dimethoxy-2-naphthyl)-2-hydroxypropan-1-one 18

4.6.1. Asymmetric oxidation using Davis reagent. To a solution of **17** (14.65 g, 60.0 mmol) in THF (240 mL) was added 1 M sodium bis(trimethylsilyl)amide solution in THF (72.0 mL, 72.0 mmol) at −70 °C over 30 min and the mixture stirred for 1 h. A solution of (−)-(8,8-dichlorocamphorylsulfonyl)oxazirizine **19** (21.47 g, 72.0 mmol) in THF (60 mL) was added over 1 h and the mixture then stirred at −70 °C for an additional 0.5 h. The reaction was quenched by the addition of aqueous NH_4Cl, and the mixture allowed to warm to room temperature. After separation of the layers, the aqueous phase was further extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using hexane–AcOEt (3:1 to 2:1) as an eluent to give **18** as colorless crystals (14.04 g, 90% yield, 95.0% ee). The crystals were suspended in ether and collected by filtration to give 98.0% ee of **18** (12.90 g, 83% yield). The % ees were determined by HPLC [Chiralpak® AD 0.46×25 cm column; *n*-hexane–EtOH (85:15) as an eluent; flow rate 0.8 mL/min]. Mp 138–139 °C (ether). $[\alpha]_D^{20} = +55.0$ (*c* 1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1674, 1487, 1262. ^1H NMR ($CDCl_3$) δ: 1.52 (3H, d, $J = 6.8$ Hz), 3.90 (1H, d, $J = 6.8$ Hz), 4.03 (3H, s), 4.04 (3H, s), 5.28 (1H, quintet, $J = 6.8$ Hz), 7.16 (1H, s), 7.24 (1H, s), 7.76 (1H, d, $J = 8.8$ Hz), 7.86 (1H, dd, $J = 8.8$, 1.8 Hz), 8.30 (1H, d, $J = 1.8$ Hz). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.08; H, 5.98.

4.6.2. Asymmetric oxidation using AD-mix-β. To a solution of **17** (19.85 g, 81.3 mmol) in THF (350 mL) was added 40% sodium bis(trimethylsilyl)amide solution in THF (46.0 g, 100.3 mmol) at −70 °C over 40 min, after which the mixture was stirred for 1 h. A solution of TBSCl (14.77 g, 98.0 mmol) in hexane (30 mL) was added over 30 min, and stirring continued at −70 °C for 10 min. The mixture was allowed to warm to room temperature, stirred for an additional 0.5 h, and diluted with water. After separation of the layers, the aqueous phase was extracted further with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the silyl enol ether **20** as an oil. Compound **20** was dissolved in *t*-BuOH (500 mL) and water (400 mL) and the mixture was cooled to 5 °C. Methanesulfonamide (8.09 g, 82.0 mmol) and AD-mix-β (114.8 g) were added and the mixture stirred at 5 °C for 43 h and at room temperature for 90 h. Solid sodium sulfite (81.3 g) was added and the mixture stirred for an additional 1 h. Water and AcOEt were added and the layers separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using hexane–AcOEt (4:1 to 3:2) as an eluent to give 98.8% ee of **18** as colorless crystals (19.29 g, 91% yield,). The crystals were suspended in ether and collected by filtration to give 99.7% ee of **18** (16.64 g, 79% yield).

4.7. (2*R*,3*S*)-3-(6,7-Dimethoxy-2-naphthyl)-4-methylpentane-2,3-diol 21

To a solution of **18** (30.00 g, 115.3 mmol, 98.0% ee) in THF (300 mL) was added isopropylmagnesium bromide (470 mmol) in THF at −10 °C over 45 min. The mixture was stirred at 0–4 °C for 14 h and quenched with aqueous NH_4Cl. After separation of the layers, the aqueous phase was extracted further with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2–MeOH (300:1 to 100:1) as an eluent. The product was crystallized from ether-diisopropylether to give **21** (15.90 g, 45%). Recrystallization from diisopropylether gave colorless prisms. Mp 99.5–100.5 °C. $[\alpha]_D^{20} = +13.9$ (*c* 1.01, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3480, 2971, 1512, 1493, 1250, 1165, 1132, 1007, 860, 754. ^1H NMR ($CDCl_3$) δ: 0.86 (3H, d, $J = 6.6$ Hz), 0.93 (3H, d, $J = 6.6$ Hz), 1.05 (3H, d, $J = 6.4$ Hz), 2.41 (1H, septet, $J = 6.6$ Hz), 2.65 (1H, s), 3.99 (6H, s), 4.32 (1H, quint, $J = 6.4$ Hz), 7.11 (1H, s), 7.15 (1H, s), 7.28 (1H, dd, $J = 8.4$, 1.8 Hz), 7.65 (1H, d, $J = 8.4$ Hz), 7.74 (1H, d, $J = 1.8$ Hz). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.11; H, 8.11.

4.8. X-ray structure of 21

An analytical sample of **21** for X-ray analysis was obtained by recrystallization from AcOEt–hexane. The X-ray measurement was preformed on a Rigaku AFC5R diffractometer with Cu-Kα radiation. Crystal data for **21**: $C_{18}H_{24}O_4 \cdot 1/4H_2O$, $M_r = 308.9$, triclinic, space group $P\bar{1}$ (#1), $a = 12.456(1)$ Å, $b = 16.140(3)$ Å, $c = 9.656(1)$ Å, $\alpha = 101.70(1)°$, $\beta = 109.83(1)°$, $\gamma = 93.83(1)°$, $V = 1768.7(5)$ Å^3, $D_{calc} = 1.160$ g cm^{-3}, $Z = 4$; Final *R*-values were $R1 = 0.035$ for 10,404 reflections with $F_o > 4\sigma(F_o)$, $wR2 = 0.104$ for all the 11,938 reflections. The absolute configuration was determined by the

Flack parameter[20] of −0.05(11). Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 235615).

4.9. (3*S*)-3-(6,7-Dimethoxy-2-naphthyl)-3-hydroxy-4-methylpentan-2-one 22

To a solution of oxalyl chloride (8.7 mL, 100 mmol) in CH_2Cl_2 (150 mL) was added DMSO (15.5 mL, 200 mmol) below −50 °C and the mixture stirred at −70 °C for 0.5 h. A solution of **21** (15.00 g, 49.3 mmol) in CH_2Cl_2 (100 mL) was added, the mixture stirred at −40 °C for 0.5 h and then cooled to −60 °C. Triethylamine (45.0 mL, 323 mmol) was added, and the mixture allowed to warm to 10 °C, stirred for an additional 0.5 h, and diluted with aqueous NH_4Cl. After separation of the layers, the aqueous phase was further extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The residue was crystallized from 2-propanol to give **22** as colorless prisms (13.64 g, 92%). The % ee was determined to be 98% ee by HPLC [Chiralpak® AD 0.46×25 cm column; *n*-hexane–EtOH (85:15) as an eluent; flow rate 0.8 mL/min]. Mp 132.5–134.5 °C. $[\alpha]_D^{20} = +10.7$ (*c* 0.99, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3461, 2976, 1692, 1510, 1493, 1260, 1219, 1167, 1140, 1005, 856. ^{1}H NMR ($CDCl_3$) δ: 0.94 (3H, d, $J = 6.6$ Hz), 0.95 (3H, d, $J = 6.6$ Hz), 2.17 (3H, s), 2.92 (1H, septet, $J = 6.6$ Hz), 4.00 (6H, s), 4.57 (1H, s), 7.11 (1H, s), 7.14 (1H, s), 7.48 (1H, dd, $J = 8.4$, 1.8 Hz), 7.70 (1H, d, $J = 8.4$ Hz), 7.89 (1H, d, $J = 1.8$ Hz). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.41; H, 7.39.

4.10. (3*S*)-1-Bromo-3-(6,7-dimethoxy-2-naphthyl)-3-hydroxy-4-methylpentan-2-one (23)

To a solution of **22** (13.00 g, 43.0 mmol) in THF (280 mL) was added pyridinium tribromide (15.13 g, 47.3 mmol) with ice-cooling. The mixture was stirred at room temperature for 42 h, diluted with aqueous $Na_2S_2O_3$, and extracted with AcOEt. The extract was washed with aqueous citric acid and aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using hexane–acetone (15:1 to 4:1) as an eluent to give **23** as crystals (containing a small amount of **22**, 13.16 g, 71% yield). IR ν_{max}^{KBr} cm^{-1}: 2969, 1721, 1508, 1489, 1256, 1167, 1009, 855. ^{1}H NMR ($CDCl_3$) δ: 0.84 (3H, d, $J = 7.2$ Hz), 1.04 (3H, d, $J = 7.2$ Hz), 2.95 (1H, septet, $J = 7.2$ Hz), 4.00 (6H, s), 4.20 (2H, s), 7.11 (1H, s), 7.14 (1H, s), 7.43 (1H, dd, $J = 8.4$, 1.8 Hz), 7.70 (1H, d, $J = 8.4$ Hz), 7.87 (1H, d, $J = 1.8$ Hz).

4.11. (1*S*)-1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol 2

To a mixture of **23** (4.19 g, 11.0 mmol) and 2,6-lutidine (2.6 mL, 22.0 mmol) in THF (40 mL) was added trimethylsilyl trifluoromethanesulfonate (2.6 mL, 14.3 mmol) with ice-cooling and stirring continued for 1 h. 2,6-Lutidine (1.3 mL, 11.0 mmol) and trimethylsilyl trifluoromethanesulfonate (1.3 mL, 7.0 mmol) were then additionally added, and the reaction mixture stirred for a further 0.5 h. The mixture was diluted with 1 M HCl and extracted with AcOEt. The extract was washed with water and aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give **24**; IR ν_{max}^{KBr} cm^{-1}: 2959, 1734, 1510, 1489, 1256, 843. ^{1}H NMR ($CDCl_3$) δ: 0.23 (9H, s), 0.93 (3H, d, $J = 6.8$ Hz), 0.97 (3H, d, $J = 6.8$ Hz), 2.86 (1H, septet, $J = 6.8$ Hz), 4.00 (3H, s), 4.02 (3H, s), 4.28 (2H, s), 7.10 (2H, s), 7.30 (1H, dd, $J = 8.8$, 2.2 Hz), 7.64–7.70 (2H, m). Compound **24** was dissolved in THF (4 mL) and cooled to −15 °C. Saturated NH_3 solution in methanol (23 mL) and formamidine acetate (1.83 g, 17.6 mmol) were added, and the mixture was stirred at −15 °C for 15 min and at room temperature for 39 h. After removal of the solvent, the residue was partitioned between AcOEt and brine. After separation of the layers, the organic phase was extracted with 1 M HCl (2×100 mL). The combined aqueous HCl layers were made alkaline by the addition of 2 M NaOH (150 mL) and then extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2–MeOH (50:1 to 20:1) as an eluent to give **2** as an amorphous solid (2.90 g, 58% from **22**). The enantiomeric excess was determined to be 98.4% by HPLC [Chiralcel® OJ-R 0.46×15 cm column; CH_3CN-10 mM (pH 7) phosphate buffer (30:70) as an eluent; flow rate 0.5 mL/min]. $[\alpha]_D^{20} = -45.3$ (*c* 1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 2971, 1510, 1489, 1254, 1163, 1005, 855, 731. ^{1}H NMR ($CDCl_3$) δ: 0.81 (3H, d, $J = 6.8$ Hz), 1.01 (3H, d, $J = 6.8$ Hz), 2.70 (1H, septet, $J = 6.8$ Hz), 3.98 (6H, s), 7.00 (1H, s), 7.08 (1H, s), 7.12 (1H, s), 7.47 (1H, dd, $J = 8.4$, 1.8 Hz), 7.51 (1H, s), 7.62 (1H, d, $J = 8.4$ Hz), 7.90 (1H, d, $J = 1.8$ Hz).

4.12. (1*S*)-1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol fumarate [fumarate of 2]

To a solution of **2** (2.78 g, 8.5 mmol) in methanol (10 mL) was added fumaric acid (1.00 g, 8.6 mmol). The solvent was removed to about a half volume and the residual mixture then diluted with AcOEt (10 mL). After 5 days, the crystals that had separated out of the solution were collected by filtration, washed with AcOEt, and dried to give the fumarate of **2** (2.61 g). The enantiomeric excess was determined to be >99.9% by HPLC [Chiralcel® OJ-R 0.46×15 cm column; CH_3CN-10 mM (pH 7) phosphate buffer (30:70) as an eluent; flow rate 0.5 mL/min]. Mp 117–120 °C [lit.[2] mp 116–120 °C]. $[\alpha]_D^{20} = -34.4$ (*c* 1.00, MeOH) {lit.[2] $[\alpha]_D^{20} = -35.3$ (*c* 1.01, MeOH)}. IR ν_{max}^{KBr} cm^{-1}: 3669, 3279, 3125, 2965, 1698, 1512, 1262, 1208, 1165, 849, 646. ^{1}H NMR (DMSO-d_6) δ: 0.66 (3H, d, $J = 5.4$ Hz), 0.84 (3H, d, $J = 5.4$ Hz), 2.60–2.80 (1H, m), 3.86 (6H, s), 5.10–5.30 (1H, br), 6.61 (2H, s), 7.00 (1H, s), 7.20–7.22 (2H, m), 7.54 (1H, d, $J = 8.8$ Hz), 7.61 (1H, d, $J = 8.8$ Hz), 7.67 (1H, s), 7.90 (1H, s). Anal. Calcd for $C_{19}H_{22}N_2O_3 \cdot C_4H_4O_4 \cdot 0.5H_2O$: C, 61.19; H, 6.03; N, 6.20. Found: C, 61.05; H, 6.00; N, 6.37.

Acknowledgements

We thank Drs. A. Miyake and T. Naka for helpful discussions throughout this work and Mr. A. Fujishima and Ms. K. Higashikawa for single-crystal X-ray analysis.

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. Ojida, A; Matsunaga, N.; Kaku, T; Tasaka, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1555.
4. Katritzky, A. R.; Slawinski, J. J.; Brunner, F.; Gorun, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1139.
5. Turner, R. M.; Lindell, S. D. *J. Org. Chem.* **1991**, *56*, 5739.
6. Dickens, J. P.; Dyer, R. L.; Hamill, B. J.; Harrow, T. A.; Bible, R. H., Jr.; Finnegan, P. M.; Henrick, K.; Owston, P. G. *J. Org. Chem.* **1981**, *46*, 1781.
7. Pauly, H.; Arauner, E. *J. Prakt. Chem.* **1928**, *118*, 33.
8. Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597.
9. Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117.
10. Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905.
11. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
12. Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 1291.
13. Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051.
14. Méric, R.; Vigneron, J.-P. *Bull. Soc. Chim. France* **1973**, 327.
15. Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031.
16. Brown, J. D. *Tetrahedron: Asymmetry* **1992**, *3*, 1551.
17. Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274.
18. Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679–6690.
19. Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067.
20. Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.