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An enantioselective formal synthesis of 4-demethoxydaunomycin using the catalytic asymmetric ring opening reaction of *meso*-epoxide with *p*-anisidine

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Abstract—A catalytic asymmetric formal synthesis of 4-demethoxydaunomycin (**3**) was achieved using a catalytic asymmetric ring opening reaction of *meso*-epoxide **9** as a key step. The epoxide opening reaction was promoted by 10 mol% of Pr-(*R*)-BINOL–Ph_3P=O complex to give the β-amino alcohol **11** in 80% yield with 65% enantiomeric excess (ee). Single recrystallization enhanced the enantiomeric purity of the β-amino alcohol **11** to 95% ee. The β-amino alcohol **11** was then converted to the known key intermediate **6** through several steps, including a methylation, Hofmann elimination, an oxymercuration, and addition of an ethynyl group in a highly diastereoselective manner.

1. Introduction

Daunomycin (**1**) and adriamycin (**2**) are prominent members of a class of clinically important anthracycline antibiotics[1] used most often in antitumor combination chemotherapy (Fig. 1). Their utility, however, is limited due to a number of side effects, the most serious being dose-dependent cardiotoxicity.[2] The 4-demethoxy analogs: 4-demethoxydaunomycin (idarubicin) (**3**) and 4-demethoxyadriamycin (**4**) were recently developed as artificial anthracyclines to improve the pharmacologic profile.[3] Because these non-natural analogs cannot be synthesized using the fermentation method, there have been a number of reports on the synthesis of **3** and **4**.[4] The antitumor activity of these compounds is strictly dependent on the chirality at C-9, and they are active only in their natural absolute configuration.[5] Therefore, much effort has been devoted to developing more efficient methods for the synthesis of enantiomerically pure aglycons.[6] Although catalytic asymmetric syntheses are effective methods in terms of 'atom-economy', there are only a few reports of catalytic asymmetric synthesis of **3**.[7] Thus, there is a high demand to develop a more efficient enantioselective method for synthesis. Herein, we report the short formal synthesis of (+)-4-demethoxydaunomycin (**3**) using the catalytic asymmetric ring opening reaction of *meso*-epoxide with *p*-anisidine as a key step.

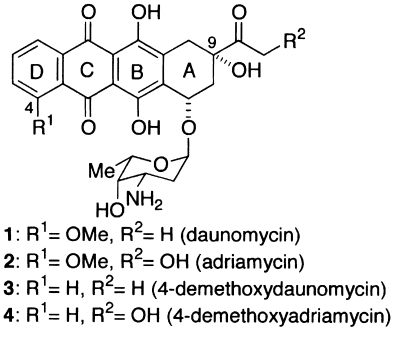
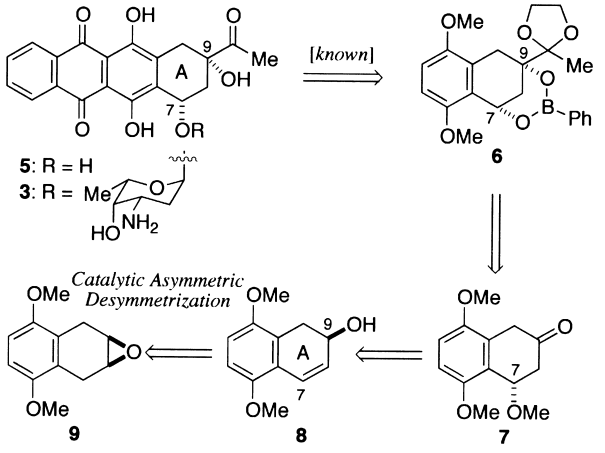


Figure 1. Structure of selected anthracycline antibiotics.

Our retrosynthetic analysis is outlined in Scheme 1. The synthetic target is benzeneboronate **6**,[8] which is known to



Scheme 1. Retrosynthetic analysis of 4-demethoxydaunomycine (**3**).

Keywords: 4-demethoxydaunomycin; catalytic asymmetric ring opening reaction; multifunctional catalyst.
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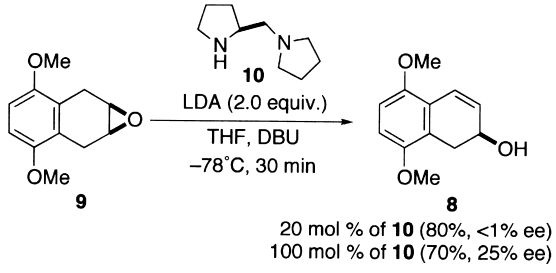
be coupled with bis(trimethylsiloxy)benzocyclobutane then efficiently converted to the aglycon: idarubicinone (**5**) in 65% yield (3 steps).[9] Our synthesis of the key intermediate **6** was designed by the use of a catalytic asymmetric desymmetrization of *meso*-epoxide **9** to introduce the chirality at C-9 with functionality at C-7 (**9→8**). In addition, our approach involves the transfer of stereochemical information around the cyclohexane ring (A-ring) by a series of 1,3-asymmetric induction events (**8→7** and **7→6**). Diastereoselective oxymercuration might transfer the chirality at C-9 in the allylic alcohol **8** to the chirality at C-7 in the β-methoxyalcohol **20** (Scheme 4), which would be oxidized to the β-methoxyketone **7**. Subsequent diastereoselective ethynylation followed by boronic ester formation would set all functionality in the A-ring and stereochemistry at C-7 and C-9, and thereby complete a formal total synthesis of 4-demethoxydaunomycin (**3**).

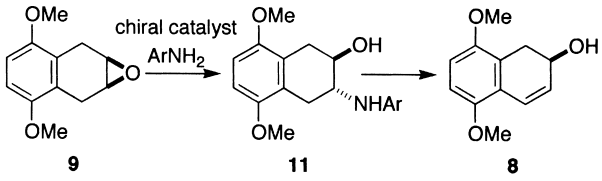
2. Results and discussion

The synthesis of the benzeneboronate **6** began with the readily available *meso*-epoxide **9**[10] subjected to a catalytic asymmetric desymmetrization. Desymmetrization of an achiral *meso* molecule to yield enantiomerically enriched products is proving to be a powerful synthetic tool.[11] The catalytic asymmetric epoxide rearrangement using a chiral lithium amide is one of the most widely used methods for preparing chiral allylic alcohols.[12] In our preliminary study of catalytic asymmetric epoxide rearrangements of *meso*-epoxide **9** using the chiral lithium amide, however, the epoxide rearrangement strategy for the synthesis of the allylic alcohol **8** produced unsatisfactory results (Scheme 2). Because of the high acidity of the benzylic proton of **9**, not only chiral lithium amide (20 mol%) but also non-chiral lithium amide (LDA, 200 mol%) reacted with the substrate to give the allylic alcohol **8** in low enantiomeric excess (<1% ee). Even using a stoichiometric amount of chiral lithium amide produced an unsatisfactory result (25% ee).

Thus, we chose a strategy based on the catalytic asymmetric ring opening reaction of *meso*-epoxide with amine (Scheme 3). The resulting chiral *trans*-β-amino alcohol **11** would be converted to the desired chiral allylic alcohol **8** by quaternary amine formation followed by Hofmann elimination. Recently, we and others achieved an efficient catalytic asymmetric ring opening reaction of *meso*-epoxide with various nucleophiles, such as trialkylsilyl azide,[13] trimethylsilyl cyanide,[14] thiol,[15] aryllithium,[16] halides,[17] and phenol.[18] In contrast to the great success of such nucleophiles, there are only a few reports employing an alkylamine[19] or an arylamine[20] as a nucleophile with low substrate generality, perhaps because of their high affinity to Lewis acids. Therefore, we planned to develop an efficient catalytic asymmetric ring opening reaction of *meso*-epoxide **9** with aniline derivatives, leading to the *trans*-β-amino alcohol **11**.



Scheme 2. Asymmetric epoxide rearrangement route.

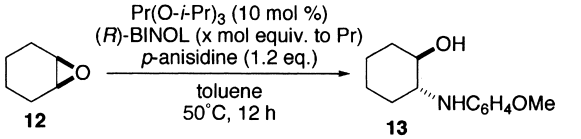


Scheme 3. Catalytic asymmetric ring opening reaction route.

On the basis of our previous results, we investigated the catalytic asymmetric ring opening reaction of cyclohexene oxide (**12**) as a model substrate using multifunctional asymmetric catalysts.[21] In screening of catalysts, including the Ga–Li–BINOL complex (GaLB), the alkali-metal free Ga–BINOL complex, and several alkali-metal free lanthanoid–BINOL complexes, the best result was obtained using the alkali-metal free Pr–BINOL complex as a catalyst and *p*-anisidine as a nucleophile, although the ee of **13** was still unsatisfactory. We also performed investigations on the ratio of $Pr(O\text{-}i\text{-}Pr)_3$ and BINOL (Table 1). In the absence of (*R*)-BINOL, the reaction did not proceed at all (entry 1), indicating ligand acceleration of the reaction.[22] Increasing the amount of (*R*)-BINOL relative to Pr increased both yields and ees (entries 2–7). The complex generated from $Pr(O\text{-}i\text{-}Pr)_3$ and (*R*)-BINOL in a ratio of 1:2 was the most effective asymmetric catalyst for the ring opening reaction of *meso*-epoxide **12**. The catalyst was easily prepared from $Pr(O\text{-}i\text{-}Pr)_3$ and (*R*)-BINOL, which were mixed in tetrahydrofuran followed by removal of tetrahydrofuran and resulting *i*-PrOH under reduced pressure. The residual pale green powder was used directly in the reaction. The absolute configuration of *trans*-β-amino alcohol **13** was determined to be (1*R*,2*R*) by comparing the measured optical rotations with the literature.[20b]

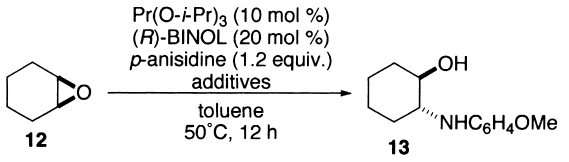
In the asymmetric epoxidation of enones promoted by alkali-metal free lanthanoid–BINOL complexes, addition of triphenylphosphine oxide ($Ph_3P{=}O$) and triphenylarsine

Table 1. Catalytic asymmetric ring opening reaction with *p*-anisidine. Effect of the ratio of (*R*)-BINOL to Pr



Entry	(*R*)-BINOL (xmol equiv. to Pr)	Yield (%)	ee (%)
1	–	No reaction	
2	0.33	30	9
3	0.5	53	13
4	1.0	68	22
5	1.5	72	28
6	2.0	73	30
7	3.0	70	23

Table 2. Catalytic asymmetric opening reaction with *p*-anisidine. Effect of additives



12 13

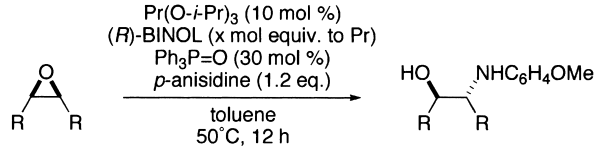
Entry	Additives (xmol%)	Yield (%)	ee (%)
1	–	73	30
2	Ph_3P═O (30)	87	35
3	Ph_3As═O (30)	40	34

oxide (Ph_3As═O) was effective for enhancing the reaction rate while maintaining high ee.[22] Thus, we next examined the influence of these additives (Table 2). The addition of Ph_3P═O induced higher solubility of the catalyst to the solvent to afford **13** with slightly higher ee (entry 2), whereas the addition of Ph_3As═O resulted in a decreased yield (entry 3).

Next, we examined the catalytic asymmetric ring opening reaction of several *meso*-epoxides using the asymmetric catalyst generated from Pr(O-*i*-Pr)$_3$, (*R*)-BINOL, and Ph_3P═O in ratios of 1:1.5:3 and 1:2:3 (Table 3). As shown, these asymmetric catalysts were also effective for cyclohexadiene mono oxide (**14**) and cyclopentene oxide (**16**) to afford desired *trans*-β-amino alcohols **15** and **17** with higher enantioselectivities (50–53% ee, entries 3–6). In the case of epoxide **18**, which is the 5,8-didemethoxy analog of epoxide **9**, *trans*-β-amino alcohols **19** was obtained with moderate enantioselectivities (36–38% ee, entries 7, 8). Not only electronic effect but also conformational effect might influence on enantiomeric selection. The absolute configuration of **15** was determined by transformation to **13** and that of **19** was determined on the basis of ^{1}H NMR analysis of the corresponding Mosher's ester.[23] The absolute configuration of **17** was tentatively determined on the basis of the result using aniline as a nucleophile.[20b]

We applied these catalyst systems for the catalytic asymmetric ring opening reaction of *meso*-epoxide **9** with *p*-anisidine (Table 4). The reaction proceeded using 10 mol% of the asymmetric catalyst generated from Pr(O-*i*-Pr)$_3$, (*R*)-BINOL, and Ph_3P═O in a ratio of 1:2:3

Table 3. Catalytic asymmetric ring opening reaction with *p*-anisidine. Applications to several *meso*-epoxides



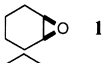
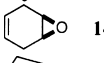
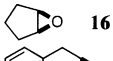
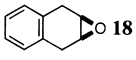
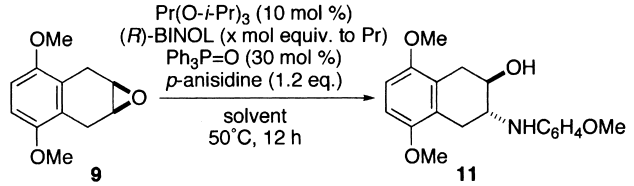
Entry	Epoxide	(*R*)-BINOL (x mol equiv. to Pr)	Product	Yield (%)	ee (%)	Configuration
1	 **12**	1.5	**13**	71	31	(1*R*,2*R*)
2		2.0		87	35	
3	 **14**	1.5	**15**	72	50	(1*R*,2*R*)
4		2.0		75	53	
5	 **16**	1.5	**17**	82	50	(1*R*,2*R*)
6		2.0		71	50	
7	 **18**	1.5	**19**	62	36	(1*R*,2*R*)
8		2.0		70	38	

Table 4. Catalytic asymmetric ring opening reaction with *p*-anisidine. Effects of the ratio of (*R*)-BINOL to Pr and solvent



9 11

Entry	(*R*)-BINOL (xmol equiv. to Pr)	Solvent	Yield (%)	ee (%)
1	1.0	Toluene	75	50
2	1.5	Toluene	73	59
3	2.0	Toluene	74	54
4[a]	1.5	Toluene	75	50
5[b]	1.5	Toluene	80	65
6	1.5	CH_2Cl_2	49	64
7	1.5	THF	10	20
8	1.5	DME	26	34

[a] Without Ph_3P═O.
[b] *p*-Anisidine was added slowly over 17 h.

to afford the desired *trans*-β-amino alcohol **11** in 74% yield with 54% ee (entry 3). We reinvestigated the ratio of BINOL to Pr(O-*i*-Pr)$_3$ and the solvent effects. In this case, the asymmetric catalyst generated from Pr(O-*i*-Pr)$_3$, (*R*)-BINOL, and Ph_3P═O in a ratio of 1:1.5:3 gave the best result (entry 2, 73% yield, 59% ee). The slow addition of *p*-anisidine had a slightly positive effect as well (entry 5, 80% yield, 65% ee). However, the use of solvent other than toluene gave less satisfactory result. The structure of the Pr–BINOL–Ph_3P═O complex is not yet clear. On the basis of the previous structural investigation on La–BINOL–Ph_3As═O,[22] we propose that the active catalyst is a 1:2:*x* complex of Pr–BINOL–Ph_3P═O. Laser desorption/ionization time-of-flight mass spectrometry (LDI TOF MS) of the complexes' solution supports our hypothesis. The peak observed in the negative mode (MW 709) corresponds to the molecular weight of the monomeric Pr(binaphthoxide)$_2$ complex. Although the affinity of Ph_3P═O to lanthanoid metals is lower than that of Ph_3As═O,[22] Ph_3P═O might coordinate with lanthanoid metals and contribute to the stability of the active

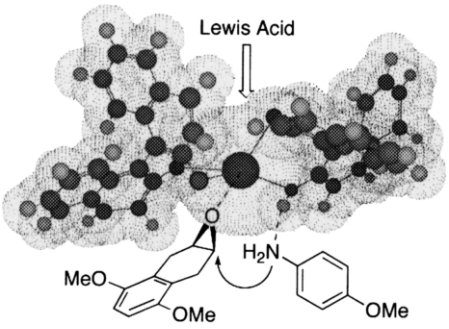
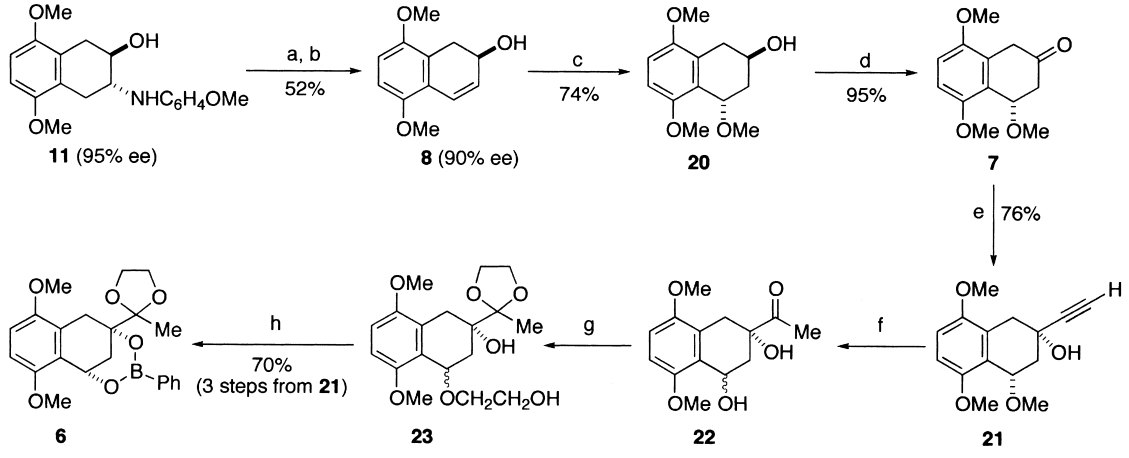


Figure 2. Possible transition state of ring opening reaction of epoxide **9** with *p*-anisidine.

monomeric species. The possible transition states leading to **11** are shown in Fig. 2. The Pr–BINOL–Ph_3P═O complex would promote the ring opening reaction of *meso*-epoxides with *p*-anisidine through activation of epoxide. The enantiomeric induction in the present system can be understood by fixation of the position of the epoxide coordinating to the Lewis acidic center metal and the orientation of *p*-anisidine through a hydrogen bond between the nitrogen and phenolic protons.[18] The absolute configuration of **11** was determined by transformation to **20** (vide infra).

Large quantities of the enantiomerically enriched *trans*-β-amino alcohol **11** (65% ee) allowed for the completion of the key intermediate **6** (Scheme 4). A single recrystallization of **11** (65% ee) from CH_2Cl_2–heptane enhanced its enantiomeric purity to 95% ee in 40% recrystallization yield. Methylation of the *trans*-β-amino alcohol **11** gave a quaternary ammonium salt, which was directly treated with an excess amount of BuLi to afford the allylic alcohol **8** in 52% yield (2 steps) with slight decrease of ee (90% ee). Other bases such as KHMDS or KO-*t*-Bu dehydrated the resulting allylic alcohol **8** to afford 1,4-dimethoxynaphtharene. To synthesize the β-methoxyalcohol **20**, oxymercuration of the allylic alcohol **8** with $Hg(OAc)_2$ in methanol followed by reduction with $NaBH_4$ was examined. In the second reaction, the addition order of the reagents is crucial. The addition of $NaBH_4$ to the reaction mixture gave no desired β-methoxyalcohol **20** with recovery of the starting material **8** in ca. 70% yield. In these reaction conditions, the elimination reaction of the radical intermediate might proceed to give **8** in preference to reduction due to the easy formation of elimination product **8**. This led us to investigate the reverse addition method. When the reaction mixture of oxymercuration was added slowly to a 5% aqueous NaOH solution of $NaBH_4$,[24] the radical intermediate was reduced immediately with an excess amount of $NaBH_4$ to afford the β-methoxyalcohol **20** in 74% yield (2 steps). Moreover, oxymercuration proceeded in a completely diastereo- and regiocontrolled manner. Mercury(II) acetate reacts with olefins from the same side with a hydroxyl group.[25] The relative configuration of **20** was determined by NOE experiments and coupling constant analysis of **20** and 9-*epi*-**20**, which was prepared by reduction of ketone **7** (Fig. 3). The absolute configuration of **20** was unequivocally determined by converting to its Mosher's ester.[23] The hydroxyl group of **20** was oxidized to a ketone using Dess–Martin periodinane to afford **7** in 95% yield. The addition of an ethynyl group to the ketone **7** with a cerium reagent prepared from ethynylmagnesium bromide and cerium(III) chloride gave the propargyl alcohol **21** (76%) in a highly diastereoselective manner (>10:1).[26] The relative configuration of **21** was determined by considering relative and absolute configurations of **20** and **6**. The ethynyl group of **21** was hydrated to give the ketone **22** using mercury(II) sulfate as a catalyst. Under these conditions, the methoxy group was substituted by water at the same time. ^1H NMR revealed that the diastereomeric ratio of the hydroxyl group was ca. 1:1. The carbonyl group of **22** was protected as cyclic ethyleneketal with excess ethylene glycol, $MgSO_4$, and 10 mol% of *p*-toluenesulfonic acid to afford **23** in which the hydroxyl group was substituted by ethylene glycol. Decreasing the amount of ethylene glycol, for example 3 equiv. of ethylene glycol in benzene, resulted in a decreased yield due to aromatization. Subsequent treatment of the crude diol **23** with phenylboronic acid gave the known key intermediate **6** in 70% overall yield from **21** (3 steps). The spectral data were identical to those previously



Scheme 4. Synthesis of the key intermediate **6**: *Reagents and conditions*: (a) CH_3I (10 equiv.), K_2CO_3 (2.0 equiv.), methanol, reflux, 24 h; (b) BuLi (3.0 equiv.), THF, −78°C, 1 h; (c) (i) $Hg(OAc)_2$ (1.1 equiv.), methanol, rt, (ii) $NaBH_4$ (3.0 equiv.), 5% NaOH aq, 50°C; (d) Dess–Martin periodinane (1.5 equiv.), CH_2Cl_2 0°C, 2 h; (e) ethynylmagnesium bromide (2.0 equiv.), $CeCl_3$ (2.0 equiv.), THF −78 to −30°C, 2 h; (f) $HgSO_4$ (20 mol%), 2% H_2SO_4 aq, acetone, rt, 40 h; (g) TsOH·H_2O (10 mol%), $MgSO_4$ (3.0 equiv.), ethylene glycol, 60°C, 24 h; (h) $PhB(OH)_2$ (3.0 equiv.), TsOH·H_2O (10 mol%), toluene, rt, 12 h.

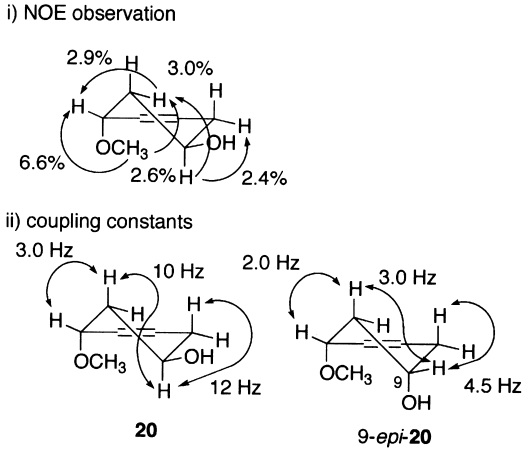


Figure 3. NOE observation and coupling constants of **20**. The aromatic part of **20** is simplified for clarity.

reported. The optical rotation of the synthetic product ($[\alpha]_D^{25}$=+28, *c* 0.5, $CHCl_3$, 90% ee) was well within the limits of polarimetric error for the reported value ($[\alpha]_D^{20}$=+35, *c* 0.5, $CHCl_3$, >99% ee).[27]

3. Conclusions

In summary, we succeeded in a catalytic asymmetric formal synthesis of 4-demethoxydaunomycin (**3**) using the catalytic asymmetric ring opening reaction of *meso*-epoxide **9** with *p*-anisidene as a key step. The catalytic asymmetric ring opening reaction of **9** was promoted by a new multifunctional asymmetric catalyst system: Pr(O-*i*-Pr)$_3$-(*R*)-BINOL–Ph_3P=O complex to afford the desired β-amino alcohol **11** (80% yield, 65% ee), which was successfully converted to the known key intermediate **6**. Further optimization of the reaction, determination of the structure of the catalyst, and application for other *meso*-epoxides are currently in progress.

4. Experimental

4.1. General method and material

Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier transform infrared spectrometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ are reported on the δ scale relative to $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR) as an internal reference. The following abbreviations are used to multiplicities: 's' (singlet), 'd' (doublet), 't' (triplet), 'm' (multiplet), 'br' (broad). Optical rotations are measured on a JASCO P-1010 polarimeter. EIMS were measured on a JEOL JMS-BU20 GCmate. Column chromatography was carried out with silica gel Merck 60 (230–400 mesh ASTM). The enatiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UVIDEC-100-IV, measured at 250 nm; column, DAICEL CHIRALPAK OD or OD-H; mobile phase, hexane-2-propanol; flow rate 1.0 mL min^{-1}. Reactions were carried out in dry solvents under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Toluene was distilled from sodium. Praseodymium triisopropoxide (Pr(*O*-*i*-Pr)$_3$) was purchased from Kojundo Chemical Laboratory, 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax: +81-492-84-1351). Other reagents were purified by usual methods.

4.2. General procedure for the catalytic asymetric ring opening reaction of *meso*-epoxide with *p*-anisidine

(*R*)-1,1′-Binaphthol ((*R*)-BINOL) (428 mg, 1.5 mmol), which was dried under reduced pressure overnight, was dissolved in THF (20 mL). To this solution was added a solution of praseodymium triisopropoxide (Pr(O-*i*-Pr)$_3$) (1.0 mmol, 0.2 M in THF) at room temperature and the resulting mixture was stirred for 30 min. Addition of Ph_3P=O (858 mg, 3.0 mmol) to this solution was followed by stirring for 1 h at room temparature, then the mixture was concentrated at the same temperature under reduced pressure for 6 h to give Pr-(*R*)-BINOL–Ph_3P=O complex as a pale green powder. To a solution of the complex in toluene (40 mL) was added epoxide **9** (2.06 g, 10 mmol) followed by slow addition of a solution of *p*-anisidine (1.44 g, 12 mmol) in toluene (5.0 mL) using a syringe pump technique for 17 h at 50°C. The reaction was quenched by addition of saturated aqueous citric acid (100 mL) and diethyl ether (100 mL). The aqueous layer was separated and neutralized by 2N aq. NaOH and the resulting suspension was extracted with diethyl ether (200 mL). The organic layer was washed with sat. NH_4Cl (100 mL) and brine (100 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 10/1) to afford β-amino alcohol **11** (3.11 g, 80%, 65% ee) (Table 4, entry 5) as a white powder. Enrichment of enantiomeric excess was achieved by recrystllization. White powder of **11** (3.11 g) was dissolved in CH_2Cl_2 (20 mL) and heptane (200 mL) at 50°C. The resulting mixture was allowed to stand for two days to afford nearly enantiomerically pure **11** (1.20 g, 40%, 95% ee).

4.2.1. (2*R*,3*R*)-5,8-Dimethoxy-3-(4-methoxyphenylamino)-1,2,3,4-tetrahydronaphthalene-2-ol (11). ^{1}H NMR ($CDCl_3$) δ 6.77 (d, *J*=9.0 Hz, 2H), 6.73 (d, *J*=9.0 Hz, 2H), 6.64 (d, *J*=8.5 Hz, 1H), 6.61 (d, *J*=8.5 Hz), 3.82 (ddd, *J*=5.5, 6.0, 6.0 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.47 (ddd, *J*=5.5, 9.5, 9.5 Hz, 1H), 3.36 (dd, *J*=6.0, 6.0 Hz, 1H), 2.61 (dd, *J*=9.5, 17.0 Hz, 1H), 2.30 (dd, *J*=9.5, 17.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 152.98, 151.26, 141.57, 124.44, 116.24, 114.90, 107.59, 107.28, 70.24, 57.13, 55.52, 31.30, 29.89; FTIR (KBr) ν 3541, 3310, 2956, 2833 cm^{-1}; MS (*m*/*z*) 121 (base peak), 143, 173, 292, 329 (M^+); $[\alpha]_D^{24}$=−95 (*c* 1.1, $CHCl_3$, 95% ee); HRMS calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1614; HPLC: CHIRALCEL OD-H, 2-propanol/hexane 1/9, flow 0.7 mL min^{-1}, t_R 44.2 min (*S*) and 48.7 min (*R*); mp 153–156°C.

4.2.2. (1*R*,2*R*)-2-(4-Methoxyphenylamino)cyclohexane-1-ol (13).[20b] $[\alpha]_D^{26}$=−23 (*c* 1.1, CH_2Cl_2, 31% ee) (Table 3, entry 1); HPLC: CHIRALCEL OD, 2-propanol/

hexane 1/9, flow 1.0 mL min^{-1}, t_R 12.8 min (*S*) and 18.8 min (*R*).

4.2.3. (1*R*,2*R*)-2-(4-Methoxyphenylamino)-4-cyclohexene-1-ol (15). ^1H NMR ($CDCl_3$) δ 6.77 (d, *J*=8.5 Hz, 2H), 6.71 (d, *J*=8.5 Hz, 2H), 5.56–5.63 (m, 2H), 3.75 (s, 3H), 3.70–3.75 (m, 1H), 3.37 (ddd, *J*=5.5, 9.0, 9.0 Hz, 1H), 2.55–2.61 (m, 2H), 2.15–2.21 (m, 1H), 1.84–1.90 (m, 1H), ^{13}C NMR ($CDCl_3$) δ 152.96, 141.48, 124.76, 116.40, 116.22, 114.87, 70.38, 57.36, 55.73, 33.13, 31.95; FTIR (KBr) ν 3372, 3027, 2910, 2832, 1511 cm^{-1}; MS (*m/z*) 165, 188, 201, 219 (M^+); $[\alpha]_D^{24}=-48$ (*c* 0.9, $CHCl_3$, 53% ee) (Table 3, entry 4); HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1256; HPLC: CHIRALCEL OD, 2-propanol/hexane 1/9, flow 1.0 mL min^{-1}, t_R 11.5 min (*S*) and 15.5 min (*R*).

4.2.4. (1*R*,2*R*)-2-(4-Methoxyphenylamino)cyclopentane-1-ol (17). ^1H NMR ($CDCl_3$) δ 6.76 (d, *J*=8.8 Hz, 2H), 6.63 (d, *J*=8.8 Hz, 2H), 4.01–4.04 (m, 1H), 3.72 (s, 3H), 3.51–3.54 (m, 1H), 2.20–2.28 (m, 1H), 1.96–2.01 (m, 1H), 1.58–1.83 (m, 3H), 1.33–1.41 (m, 1H); ^{13}C NMR δ 144.31, 134.23, 114.95, 114.82, 78.32, 63.09, 55.81, 32.90, 31.21, 20.97; MS (*m/z*) 162, 174, 189, 207 (M^+); HRMS calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1259; $[\alpha]_D^{28}=-17$ (*c* 1.1, $CHCl_3$, 50% ee) (Table 3, entry 5); HPLC: CHIRALCEL OD, 2-propanol/hexane 1/9, flow 0.5 mL min^{-1}, t_R 41.8 min (*S*) and 60.3 min (*R*).

4.2.5. (2*R*,3*R*)-3-(4-Methoxyphenylamino)-1,2,3,4-tetrahydronaphthalene-1-ol (19). ^1H NMR ($CDCl_3$) δ 7.01–7.14 (m, 4H), 6.79 (d, *J*=8.5 Hz, 1H), 6.75 (d, *J*=8.5 Hz, 1H), 3.87–3.93 (m, 1H), 3.52–3.58 (m, 1H), 3.26–3.31 (m, 2H), 2.93 (dd, *J*=8.5, 14.5 Hz, 1H), 2.62 (dd, *J*=9.0, 14.5 Hz, 1H); FTIR (neat) ν 3372, 3027, 2910, 2832, 1511 cm^{-1}; MS (*m/z*) 117, 136, 269 (M^+); $[\alpha]_D^{28}=-66$ (*c* 0.3, $CHCl_3$, 36% ee) (Table 3, entry 7); HRMS calcd for $C_{13}H_{17}NO_2$ 269.1416, found 269.1423; HPLC: CHIRALCEL OD, 2-propanol/hexane 1/9, flow 1.0 mL min^{-1}, t_R 18.4 min (*S*) and 25.5 min (*R*).

4.3. Procedure for the synthesis of the key intermediate 6 from β-amino alcohol 11

4.3.1. (*R*)-5,8-Dimethoxy-1,2-dihydronaphthalene-2-ol (8). To a solution of β-amino alcohol **11** (300 mg, 0.911 mmol, 95% ee) in methanol (5.0 mL) was added MeI (1.30 g) and K_2CO_3 (251 mg) at room temperature. The resulting mixture was refluxed for 24 h. The reaction was concentrated under reduced pressure to give crude quaternary ammonium salt as a white solid, which was directly used to the next step. The crude solid was suspended in THF (5.0 mL) and a solution of BuLi (3.0 mmol, 1.48 M in hexane) was added to the mixture at −78°C. The resulting mixture was stirred for 1 h at the same temperature. The reaction was quenched by addition of saturated NH_4Cl (50 mL) and diethyl ether (50 mL). The organic layer was separated, washed with brine (50 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 4/1) to afford allylic alcohol **8** (97 mg, 2 steps 52, 90% ee) as a white solid; ^1H NMR ($CDCl_3$) δ 6.93 (d, *J*=9.5 Hz, 1H), 6.72 (d, *J*=9.0 Hz, 1H), 6.67 (d, *J*=9.0 Hz, 1H), 6.11 (dd, *J*=4.0, 9.5 Hz, 1H), 3.79 (s, 6H), 4.41–4.45 (m, 1H), 3.12 (dd, *J*=6.0, 17.0 Hz, 1H), 2.86 (dd, *J*=9.5, 17.0 Hz, 1H); ^{13}C NMR δ 151.21, 149.72, 128.59, 122.35, 122.26, 110.50, 108.94, 63.75, 56.03, 55.94, 29.83; FTIR (KBr) ν 3314, 2958, 2823, 1485 cm^{-1}; MS (*m/z*) 145, 173, 188, 206 (M^+); $[\alpha]_D^{25}=+161$ (*c* 1.5, CH_2Cl_2, 90% ee); HPLC: CHIRALCEL OD, 2-propanol/hexane 2/98, flow 1.0 mL min^{-1}, t_R 34.8 min (*S*) and 37.8 min (*R*).

4.3.2. (2*R*,4*S*)-4,5,8-Trimethoxy-1,2,3,4-tetrahydronaphthalene-2-ol (20). To a solution of allylic alcohol **8** (402 mg, 1.95 mmol) in 40 mL of methanol was added mercury(II) acetate (750 mg 2.34 mmol) at room temperature, and the resulting mixture was stirred for 2 h. After the disappearance of starting allylic alcohol was established by TLC, the reaction mixture was added dropwise to a mixture of $NaBH_4$ (72 mg, 6.0 mmol) and 10% aqueous NaOH solution (40 mL) at 50°C. After completion of addition, methanol was removed under reduced pressure, and then diethyl ether (200 mL) was added to the mixture. The aqueous layer was separated and extracted with diethyl ether (100 mL). The combined organic layers were washed with saturated NH_4Cl (200 mL) and brine (200 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 1/1) to afford β-methoxyalcohol **20** (343 mg, 74%) as a colorless oil. The absolute configuration was determined by converting to its MTPA ester; ^1H NMR ($CDCl_3$) δ 6.72 (d, *J*=8.0 Hz, 1H), 6.68 (d, *J*=8.0 Hz, 1H), 4.67 (t, *J*=3.0 Hz, 1H), 4.25–4.32 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.45 (s, 3H), 3.27 (ddd, *J*=1.0, 5.0, 16.0 Hz, 1H), 2.40–2.45 (m, 1H), 2.28 (dd, *J*=10.0, 16.0 Hz, 1H), 1.60 (br, 1H), 1.52 (ddd, *J*=3.0 12.0, 12.0 Hz, 1H); ^{13}C NMR δ 152.0, 151.2, 125.9, 125.9, 109.9, 108.3, 72.6, 63.9, 57.2, 56.0, 55.8, 33.1, 25.7; FTIR (neat) ν 3396, 2937, 2832, 1482 cm^{-1}; MS (*m/z*) 189, 207, 238 (M^+); $[\alpha]_D^{26}=-45$ (*c* 1.1, $CHCl_3$, 90% ee); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1206.

4.3.3. (*S*)-4,5,8-Trimethoxy-3,4-dihydro-1*H*-naphthalene-2-one (7). To a solution of β-methoxyalcohol **20** (780 mg, 3.3 mmol) in CH_2Cl_2 (50 mL) was added Dess–Martin periodinane (2.10 g, 4.95 mmol) at 0°C. The resulting mixture was stirred at room temperature for 1.5 h. The mixture was diluted with CH_2Cl_2 (50 mL) and quenched by addition of saturated aq. $NaHCO_3$ (200 mL). The mixture was stirred for 20 min and filtered through a pad of Celite. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 4/1) to afford ketone **7** (735 mg, 95%) as a yellow oil; ^1H NMR ($CDCl_3$) δ 6.79 (d, *J*=9.0 Hz, 1H), 6.75 (d, *J*=9.0 Hz, 1H), 5.13 (dd, *J*=3.0, 3.0 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.66 (d, *J*=21.5 Hz, 1H), 3.39 (d, *J*=21.5 Hz, 1H), 3.23 (s, 3H), 2.91 (dd, *J*=3.0, 16.0 Hz, 1H), 2.49 (dd, *J*=3.0, 16.0 Hz, 1H); ^{13}C NMR δ 208.1, 151.2, 150.8, 124.9, 124.5, 110.7, 108.9, 70.6, 56.1, 56.0,55.8, 44.2, 37.3; FTIR (neat) ν 2937, 1720, 1487, 1261, 1082 cm^{-1}; MS (*m/z*) 176, 204, 236 (M^+); $[\alpha]_D^{26}=-133$ (*c* 0.8, CH_2Cl_2, 90% ee); HRMS calcd for $C_{13}H_{16}O_4$ 236.1048, found 236.1046.

4.3.4. (2*S*,4*S*)-2-Ethynyl-4,5,8-trimethoxy-1,2,3,4-tetrahydronaphthalene-2-ol (21). 0.5 M THF solution of ethynylmagnesium bromide was freshly prepared from 1.0 M THF solution of ethylmagnesium bromide and acetylene. Cerium(III) chloride (anhydrous, 600 mg 2.5 mmol) was dried under reduced pressure for 1 h at 100°C and then for 5 h at 140°C. After suspending cerium chloride in THF (3.0 mL), it was sonicated for 2 h. The resulting slurry was vigorously stirred for 12 h. The solution of ethynylmagnesium bromide (5.0 mL, 2.5 mmol 0.5 M in THF) was added at −78°C and the resulting mixture was stirred at −30°C for 1 h. A solution of ketone **7** (295 mg 1.25 mmol) in THF (3.0 mL) was added to the mixture at the same temperature and stirred for 2 h. The reaction was quenched by addition of saturated NH_4Cl aq. (50 mL), extracted with diethyl ether (50 mL), washed with 1N HCl (50 mL), saturated $NaHCO_3$ aq. (50 mL) and brine (50 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 4/1) to afford propargyl alcohol **21** (248 mg, 76%) as a white powder; ^{1}H NMR ($CDCl_3$) δ 6.76 (d, J=8.5 Hz, 1H), 6.72 (d, J=8.5 Hz, 1H), 5.15 (s, 1H), 4.73 (dd, J=1.0, 3.5 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.50 (s, 3H), 3.47 (dd, J=1.0, 17.0 Hz, 1H), 2.81 (d, J=17.0 Hz, 1H), 2.74 (ddd, J=1.0, 1.0, 13.5 Hz, 1H), 2.49 (s, 1H), 1.94 (dd, J=3.5, 13.5 Hz, 1H); ^{13}C NMR δ 151.8, 151.4. 123.7, 123.5, 110.3, 108.3, 71.8, 70.4, 67.9, 65.4, 56.0, 55.8, 38.3, 36.1, 17.4; FTIR (neat) ν 3425, 3268, 2926, 1482 cm^{-1}; MS (*m*/*z*) 179, 199, 230, 262(M^+); $[\alpha]_D^{25}$=−9.1 (*c* 0.4, CH_2Cl_2, 90% ee); HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1205.

4.3.5. (3*S*)-*cis*-[1-(1,1-Ethylenedioxy)ethyl]-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene-1,3-diyl benzeneboronate (6). To a solution of propargyl alcohol **21** (150 mg, 0.573 mmol) in acetone (1.5 mL) and 2% aqueous H_2SO_4 (0.15 mL) was added mercury(II) sulfate (34 mg, 0.107 mmol) at room temperature. The resulting mixture was stirred for 40 h at the same temperature. The reaction was quenched by addition of saturated $NaHCO_3$ aq. (2 mL). Acetone was evaporated under reduced pressure, and then ethyl acetate (10 mL) and water (10 mL) were added to the residue. The organic layer was separated, washed with brine, and dried over Na_2SO_4. The organic solvent was evaporated under reduced pressure to afford crude **22** (148 mg). The crude **22** was dissolved in ethylene glycol (3 mL), and then *p*-toluenesulfonic acid monohydrate (10 mg, 0.057 mmol) and $MgSO_4$ (192 mg, 1.6 mmol) was added at room temperature. The resulting mixture was stirred for 24 h at 60°C. The reaction was quenched by addition of saturated $NaHCO_3$ aq. (2 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted with ethyl acetate (2×5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was pumped up for 3 h at 50°C to afford crude **23** (ca. 150 mg) as a mixture with small amount of ethylene glycol. This crude mixture was used for the next step without further purification; ^{1}H NMR ($CDCl_3$) δ 6.71 (d, J=8.0 Hz, 1H), 6.67 (d, J=8.0 Hz, 1H), 4.91 (dd, J=2.0, 3.0 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.6–4.2 (m, 8H), 3.04 (dd, J=2.0, 16.5 Hz, 1H), 2.67 (d, J=16.5 Hz, 1H), 2.42 (ddd, J=2.0, 2.0, 13.5 Hz), 1.67 (dd, J=3.0, 13.5 Hz, 1H); MS (*m*/*z*) 259, 274, 310, 350; HRMS calcd for $C_{18}H_{26}O_7$ 254.1679, found 254.1684. To a solution of the crude **23** in toluene (2.0 mL) was added phenylboronic acid (208 mg, 1.71 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.057 mmol) at room temperature. The resulting mixture was stirred for 12 h at the same temperature. After completion of the reaction, saturated $NaHCO_3$ (2 mL) and ethyl acetate (10 mL) were added. The organic layer was separated, washed with brine (10 mL), and dried over $NaSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 8/1) to afford benzeneboronate **6** (158 mg, 3 steps 70%) as an oily solid; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J=6.7 Hz, 2H), 7.18–7.27 (m, 2H), 6.65 (s, 2H), 5.58 (dd, J=1.5, 1.5 Hz, 1H), 3.99–4.10 (m, 4H), 3.81 (s, 3H), 3.69 (s, 3H), 3.11 (d, J=18.3 Hz, 1H), 2.86 (d, J=18.3 Hz, 1H), 2.31 (dd, J=1.5, 13.5 Hz, 1H), 1.91 (dd, J=1.5, 13.5 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR δ 152.25, 151.53, 134.17, 130.65, 130.64, 127.59, 127.46, 123.98, 127.59, 127.46, 123.98, 111.79, 109.97, 109.42, 76.05, 66.19, 66.06, 61.99, 57.00, 55.80, 33.08, 31.31, 22.71, 19.87; FTIR (neat) ν 2958, 1601, 1484, 1321 cm^{-1}; MS (*m*/*z*) 177, 259, 310, 396 (M^+); $[\alpha]_D^{25}$=+28.5 (*c* 0.5, $CHCl_3$, 90% ee) (lit.[27] $[\alpha]_D^{20}$=+35.8 (*c* 0.5, $CHCl_3$)); HRMS calcd for $C_{22}H_{25}BO_6$ 396.1744, found 396.1737.

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