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Asymmetric synthesis of 3-amino-2-hydroxyalkanoates by Mannich reaction of menthyl acetate with imines and subsequent oxidation

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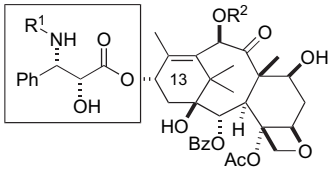
Abstract—Lithium amide-assisted Mannich-type reaction of menthyl acetate-derived lithium enolate with PMP-arylaldimines and subsequent in situ oxidation with oxaziridine gave *syn*-3-amino-3-aryl-2-hydroxypropanoates with high *syn*-selectivity and diastereoselectivity (with respect to menthyl moiety) in a one-pot procedure. Propargyl aldehyde-derived imines were also stereoselectively converted to the Mannich-oxidation products by a stepwise procedure.

1. Introduction

Asymmetric Mannich reaction of lithium enolates with imines is a fundamental asymmetric carbon–carbon bond forming reaction, giving 3-aminoalkanoates. We have been involved in this field and have developed highly efficient asymmetric Mannich reaction of lithium enolate of menthyl acetate with anisidine imines of arylaldehydes.[1] The key of this successful procedure is the concomitant use of lithium amide as an assisting agent for the Mannich reaction, giving lithiated 3-aminoenolate as a reactive product. The purpose of this article is to demonstrate the utility of this product enolate in a further transformation such as oxidation. Another purpose of this article is to report further application of lithium menthyl acetate enolate in the reaction with anisidine imines of propargyl aldehydes.

Anticancer taxoids, paclitaxel **1**, and docetaxel **2**,[2] have some barriers of which the major one is resource limitation. Semi-synthesis thereof from commercially available 10-deacetylbaccatin III and a C13 side chain has proven to be the solution (Fig. 1).[3] This situation has brought the necessity of the efficient synthesis of enantiopure side chain units, *syn*-3-amino-3-aryl-2-hydroxypropanoates. Over the last two decades, therefore, the asymmetric synthesis of the side chain units has attracted much attention from academic as well as industrial communities.[4] For examples, three types of direct synthesis have been reported for chiral *syn*-aminohydroxyphenylpropanoates. The Mannich-type addition of chiral *trans*-2-phenylcyclohexyl glycolate to an



1 Paclitaxel R^1 = Bz, R^2 = Ac
2 Docetaxel R^1 = Boc, R^2 = H

Figure 1. Taxane anticancer drugs.

imine has been one of the representatives for the highly efficient asymmetric synthesis, while the reaction of easily available menthyl ester has proven not to be selective.[4n] The one-pot reaction, asymmetric conjugate addition of a chiral lithium amide to cinnamate, and in situ oxidation of an enolate with an oxaziridine, provided a nice way, unfortunately, to an undesired *anti*-amino alcohol.[4u] The Mannich-type reaction of a lithium enolate of glycolate with a chiral sulfinylimine would have been a really efficient way if the chiral auxiliary was recyclable.[4a]

We have been involved in the asymmetric reaction of lithium ester enolates with aldimines, giving the corresponding β-lactams or 3-aminoalkanoates with high enantioselectivity.[1,5] The characteristic and appealing point of our reaction exists in the aiding use of lithium amide for the reactivity enhancement of lithium enolate **3**, in which dianion **5**, generated by further lithiation of an adduct ester with lithium amide, is the product (Scheme 1). Since the dianion **5** may be reactive enough to give an oxidation product at the α-position of an ester, we extended our study to the asymmetric

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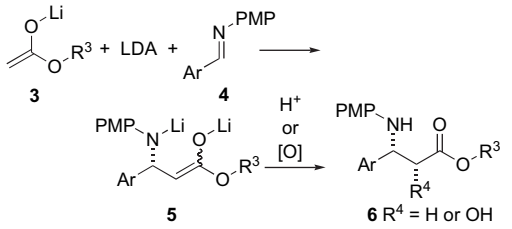
synthesis of the C13 side chain unit **6** (R^4=OH). We describe herein the diastereoselective (with respect to menthyl moiety) and *syn*-selective synthesis of *syn*-3-amino-3-aryl-2-hydroxypropanoates **6** by the one-pot, consecutive Mannich-oxidation reaction of lithium enolate of menthyl acetate with arylaldimines. Propargyl aldehyde-derived imines were also stereoselectively converted to the Mannich-oxidation products by a stepwise procedure.



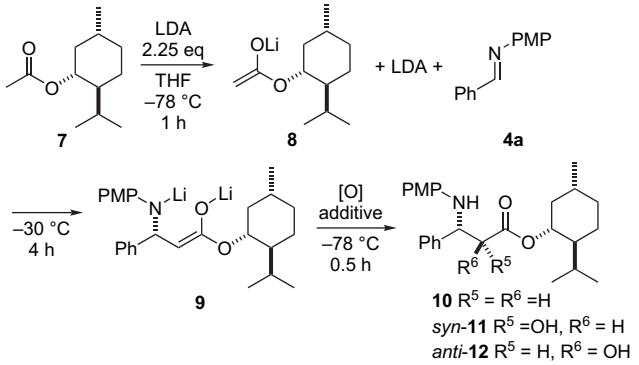
Scheme 1. Lithium amide-assisted Mannich-type reaction and subsequent oxidation.

2. Results and discussion

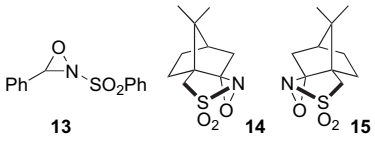
2.1. One-pot Mannich-oxidation tandem reaction

Successive treatment of L-menthyl acetate **7** with 2.25 equiv of LDA ($^iPr_2NLi$) in THF at −30 °C for 1 h to generate lithium enolate **8**, and benzaldehyde PMP (*p*-methoxyphenyl) imine **4a** at −30 °C for 4 h should produce dianion **9** that is protonated with water to give **10** (R^5=R^6=H) with 96:4 dr in 76% yield as has been previously reported.[1b] In the present study, dianion **9**, generated in situ, was treated with some oxidizing reagents. Treatment with MoOPD[6] (MoO_5/Py/DMPU (*N*,*N*′-dimethylpropyleneurea)) gave a complex mixture containing only trace amount of **11** and **12**. Promising result was obtained by oxidation with 2 equiv of racemic-oxaziridine **13**[7] at −78 °C for 0.5 h to give an *anti*-major 24:76 mixture of *syn*-**11** and *anti*-**12** in 58% yield (Table 1, entry 1). The *syn* structure of **11** was determined by

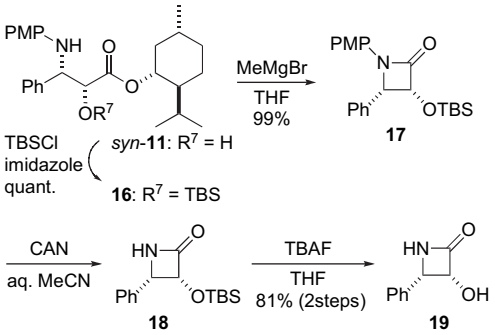
Table 1. One-pot Mannich-oxidation of L-menthyl acetate **7** with phenylimine **4a**



Entry	[O]	Additive	Yield/%	*syn*-**11**/*anti*-**12**
1	**13**	None	58	24:76
2	**14**	None	49	81:19
3	**15**	None	66	96:4
4	**15**	HMPA	63	92:8
5	**15**	DABCO	66	98.5:1.5



converting it to the established compound **19** as shown in Scheme 2. The ratio was determined by ^{1}H NMR, 0.40 ppm (*syn*) and 0.68 ppm (*anti*) for one methyl of the isopropyl group appeared as doublet. It is also interesting to describe that the diastereomer ascribable to L-menthyl group was not observed. Fortunately, recrystallization from a 1:1 mixture of methanol and hexane gave pure *anti*-**12** as colorless needles.[8] Treatment with (+)-camphorylsulfonyloxaziridine **14** at −78 °C for 0.5 h gave a *syn*-major 81:19 mixture of **11** and **12** (entry 2). Recrystallization from methanol gave *syn*-**11** as colorless needles. *syn*-Stereochemistry was determined by converting *syn*-**11** to the β-lactam **19** of the established stereochemistry (vide infra). Selectivity was more improved by the use of (−)-**15** at −78 °C for 0.5 h to give a 96:4 mixture of *syn*-**11** and *anti*-**12** (entry 3). Complexing ligand for lithium affected the level of diastereoselectivity. Although addition of HMPA ($PO(NMe_2)_3$)[9] gave a similar level of 92:8 *syn*/*anti*-selectivity and 4.5 equiv of DABCO (1,4-diazabicyclo[2.2.2]octane) exerted beneficial effect to give a 98.5:1.5 mixture of **11** and **12** in 66% yield (entries 4 and 5). Single recrystallization from methanol gave pure *syn*-**11** in 73% recovery.

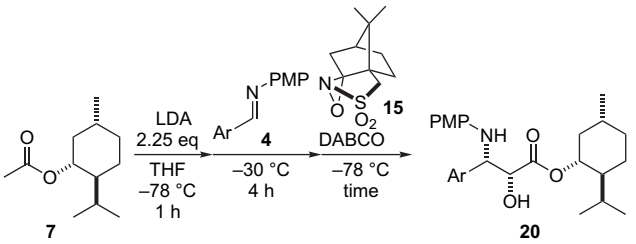


Scheme 2. Conversion of *syn*-**11** to *cis*-β-lactam **19**.

Conversion of *syn*-**11** into β-lactam **19**,[10] an established precursor for C13 side chain unit of taxol-derived anticancer drugs, was performed in four steps. The OH group of **11** was quantitatively converted to TBS ether **16** with TBSCl and imidazole in DMF at rt for 12 h. β-Lactamization with methylmagnesium bromide in THF at −10 °C for 1 h gave **17** in 99% yield. PMP group of **17** was removed by CAN oxidation in acetonitrile at 0 °C for 1 h and subsequent TBAF treatment of **18** in THF at 0 °C for 15 min gave β-lactam **19**[4b,11] in 81% yield over two steps, thus established the stereochemistry of **11**.

The one-pot Mannich-oxidation protocol was applied to imines **4b–e** as shown in Table 2. Arylimines **4** bearing electron donating 4-methoxyphenyl, electron withdrawing 4-chloro- and 4-trifluoromethyl-phenyl, and naphthyl groups were successfully converted to the corresponding

Table 2. One-pot Mannich-oxidation of L-menthyl acetate **7** with arylimines **4**



Entry	4	Ar	Temp/°C	Time/h	Yield%	*syn*/*anti*
1	**4b**	4-$MeOC_6H_4$	−30	4	65	96:4
2	**4c**	4-ClC_6H_4	−30	2	56	96:4
3	**4d**	4-$CF_3C_6H_4$	−40	3	43	90:10
4	**4e**	2-Naph	−40	3	50	98:2

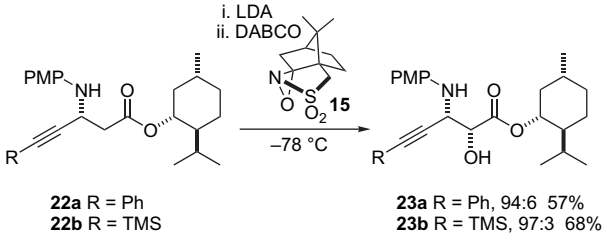
syn-3-amino-2-hydroxypropanoates **20** with 90:10 to 98:2 *syn*/*anti*-selectivity in 43–65% yield. Diastereomers ascribable to L-menthyl moiety were not observed.

2.2. Mannich reaction with propargyl aldehyde-derived imine and subsequent oxidation

The LDA or LICA (*c*Hex*i*PrNLi)-assisted Mannich reaction of lithium enolate of menthyl acetate **7** with a propargyl aldehyde-derived imine **21a** gave the corresponding Mannich product **22a** in high diastereoselectivity of 98:2 or 98.5:1.5, respectively (Table 3, entries 1 and 2). Unfortunately chemical yields were not satisfactory as low as 35% and 37%. More bulky lithium amides, TMSTrNLi and *t*-BuTrNLi, improved the chemical yield to 60% and 70%, while diastereoselectivity dropped to 81.5:18.5 and 91.5:8.5 (entries 3 and 4).

In the absence of any additive such as lithium amide, **22a** with 84.5:15.5 dr was obtained in 63% yield (entry 5). Dimethoxyethane (DME) as a solvent gave higher dr of 93:7 with 86% yield, while addition of DABCO was not beneficial (entries 6 and 7). In toluene, no diastereoselectivity was observed (entry 8). These solvent effects on dr and yield suggested the beneficial use of a coordinating ligand for lithium. Thus we turned our attention to ligand activation of lithium enolate **8**. We examined the reaction of **21a** with **8**, prepared from **7** and a slightly excess of LDA, in the presence of HMPA, DMPU, TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), and DABCO as a ligand for lithium. Although HMPA caused lower yield of 31% (entry 9), other activators worked well to give **22a** in 89–96% yield (entries 10–12). Especially, the reaction of **8** in the presence of DABCO in THF at −78 °C for 0.5 h gave **22a** in satisfactory 96% yield and 95.5:4.5 dr (entry 12). Under the same conditions, the reaction of **21b** (R^8=TMS) gave **22b** in 76% yield and 91.5:8.5 dr (entry 13). Recrystallization gave nearly diastereomerically pure **22a** and **22b**.

Mannich addition product **22a** was then converted to a dianion by treating with 3 equiv of LDA for 1 h, and then oxidized with **15** in the presence of 3 equiv of DABCO at −78 °C for 0.5 h to give **23a** with 94:6 *syn*/*anti* ratio in 57% yield. Recrystallization gave pure **23a**. Similarly **22b** was oxidized to **23b** with 97:3 *syn*/*anti* ratio in 68% yield. Recrystallization gave pure **23b** (Scheme 3).

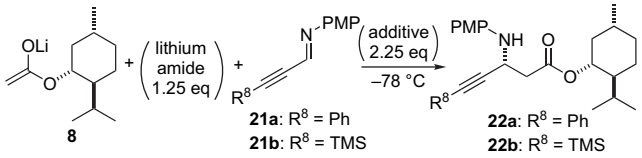


Scheme 3. *syn*-Selective oxidation of **22**.

3. Conclusion

A one-pot Mannich-oxidation sequential protocol for the asymmetric synthesis of C13 side chain unit for taxane

Table 3. Mannich-type reaction with propargyl aldehyde-derived imines **21**



Entry	Solvent	Lithiuim amide	Additive	Imine	Temp/°C	Time/h	Yield/%	dr
1	THF	LDA ($^iPr_2NLi$)	None	**21a**	−78	2	35	98:2
2	THF	LICA (*c*Hex*i*PrNLi)	None	**21a**	−78	2	37	98.5:1.5
3	THF	TMSTrNLi	None	**21a**	−78	2	60	81.5:18.5
4	THF	*t*-BuTrNLi	None	**21a**	−78	0.5	70	91.5:8.5
5	THF	None	None	**21a**	−78	2.5	63	84.5:15.5
6	DME	None	None	**21a**	−78	0.5	86	93:7
7	DME	None	DABCO	**21a**	−78	0.5	80	87.5:12.5
8	Toluene	None	None	**21a**	−20	4.5	56	0
9	THF	None	HMPA	**21a**	−78	0.5	31	Nd
10	THF	None	DMPU	**21a**	−78	1	95	83:17
11	THF	None	TMEDA	**21a**	−78	1	89	93.5:6.5
12	THF	None	DABCO	**21a**	−78	0.5	96	95.5:4.5
13	THF	None	DABCO	**21b**	−78	1	76	91.5:8.5

anticancer agents was developed. A two-step sequence was effective for propargyl aldehyde-derived imines to give *syn*-3-amino-2-hydroxyalkanoates with high *syn*/*anti*-selectivity. Since menthol belongs to a class of cost-effective chiral sources and is readily available, the use of menthyl acetate as a chiral acetate has a broad application. It is also remarkable to note that the lithium amide not only assists the activation of lithium ester enolates but also plays its original lithiation role of forming lithium enolate, which is a reactive nucleophile.

4. Experimental

4.1. General

Melting points are uncorrected. Reactions were carried out under Ar. Silica gel column chromatography was used for purification. IR spectra were expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shift values are expressed in parts per million relative to internal TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

4.1.1. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*S*)-2-hydroxy-3-(4-methoxyphenylamino)-3-phenylpropanoate *syn*-11 (Table 1, entry 5). A solution of L-menthyl acetate (396 mg, 2.0 mmol) in THF (3 mL) was added dropwise over 5 min at −78 °C to a solution of LDA (4.5 mmol) in THF (3 mL) and the resulting mixture was stirred at −78 °C for 0.5 h. A solution of imine **4a** (211 mg, 1.0 mmol) in THF (3 mL) was added dropwise over 10 min at −78 °C and the mixture was stirred at −30 °C for 2 h. A solution of DABCO (505 mg, 4.5 mmol) in THF (5 mL) was added at −78 °C to the mixture and the mixture was stirred for 0.5 h. Then, (−)-camphorylsulfonyloxaziridine **15** (688 mg, 3.0 mmol) in THF (3 mL) was added to the mixture. The mixture was stirred for 0.5 h at −78 °C and then quenched with satd ammonium chloride (20 mL) at −78 °C. The whole was extracted with ethyl acetate (30 mL×3). Combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. Concentration and column chromatography (hexane/Et_2O=4:1) gave a 98.5:1.5 mixture of **11** and **12** (280 mg, 66% yield) as colorless needles. Ratio was determined from the integration values of 0.40 ppm (*syn*) and 0.68 ppm (*anti*) by NMR. Recrystallization from methanol gave *syn*-**11** (205 mg) as colorless needles of mp 149.5–150 °C and $[\alpha]_D^{25}$ −38.4 (*c* 0.58, $CHCl_3$). ^1H NMR: 0.40 and 0.57 (each 3H, d, *J*=7.0 Hz), 0.86 (1H, m), 0.92 (3H, d, *J*=6.4 Hz), 0.97 (1H, m), 1.05 (1H, m), 1.39 (1H, m), 1.50 (1H, m), 1.63–1.70 (3H, m), 2.03 (1H, m), 3.16 (1H, br s), 3.67 (3H, s), 4.46 (1H, d, *J*=2.7 Hz), 4.81 (1H, ddd, *J*=4.3, 10.4, 10.4 Hz), 4.86 (1H, br s), 6.44 and 6.66 (each 2H, d, *J*=8.9 Hz), 7.24 (1H, m), 7.3 (2H, m), 7.38 (2H, d, *J*=7.7 Hz). ^{13}C NMR: 14.9 (CH_3), 20.5 (CH_3), 21.9 (CH_3), 22.6 (CH_2), 25.3 (CH_2), 31.3 (CH), 34.0 (CH), 40.7 (CH), 47.0 (CH_2), 55.6 (CH_3), 58.8 (CH), 74.9 (CH), 76.6 (CH), 114.5 (CH), 115.3 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 139.4 (CH), 140.2 (C), 152.0 (C), 172.7 (C). IR (KBr): 3395, 2951, 1720. EIMS *m*/*z*: 425 (M^+). Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29. Found: C, 73.28; H, 8.46; N, 3.22.

4.1.2. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*S*,3*S*)-2-hydroxy-3-(4-methoxyphenylamino)-3-phenylpropanoate *anti*-12 (Table 1, entry 1). Recrystallization of 24:76 *syn*/*anti* mixture (248 mg) from methanol/hexane (1:1 mL) gave pure *anti*-**12a** (65 mg) as colorless needles of mp 121–121.5 °C and $[\alpha]_D^{25}$ −18.5 (*c* 1.05, benzene). ^1H NMR: 0.68 and 0.84 (each 3H, d, *J*=7.0 Hz), 0.89 (1H, m), 0.91 (3H, d, *J*=6.4 Hz), 0.96–1.04 (2H, m), 1.36–1.45 (2H, m), 1.64–1.70 (3H, m), 1.83 (1H, m), 2.93 (1H, d, *J*=7.4 Hz), 3.69 (3H, s), 4.63 (2H, br s and dd are overlapped, *J*=3.4, 7.4 Hz), 4.70 (1H, ddd, *J*=4.3, 11.0, 11.0 Hz), 4.77 (1H, d, *J*=3.4 Hz), 6.58 (2H, d, *J*=9.2 Hz), 6.69 (2H, d, *J*=9.2 Hz), 7.24–7.29 (3H, m), 7.32 (2H, d, *J*=7.4 Hz). ^{13}C NMR: 15.8 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 23.0 (CH_2), 25.6 (CH_2), 31.3 (CH), 34.1 (CH), 40.8 (CH), 46.9 (CH_2), 55.7 (CH_3), 61.1 (CH), 75.1 (CH), 75.8 (CH), 114.8 (CH), 114.9 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 139.1 (C), 140.6 (C), 152.2 (C), 171.3 (C). IR (KBr): 3500, 1728. EIMS *m*/*z*: 425 (M^+). Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29. Found: C, 73.24; H, 8.17; N, 3.28.

4.1.3. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*S*)-2-*tert*-butyldimethylsiloxy-3-(4-methoxyphenylamino)-3-phenylpropanoate *syn*-16. A mixture of imidazole (37 mg, 0.54 mmol), TBDMSCl (40 mg, 0.27 mmol), and *syn*-**11** (23 mg) in 0.06 mL of DMF was stirred for 12 h at rt. Then ether (10 mL) and water (2 mL) were added. The organic layer was washed with water (2 mL×4) and dried over sodium sulfate and concentrated. Column chromatography (hexane/ether=9:1) gave *syn*-**16** (30 mg, quant) as a colorless gum of $[\alpha]_D^{25}$ −19.8 (*c* 1.18, $CHCl_3$). ^1H NMR: −0.40 (3H, s), −0.18 (3H, s), 0.39 and 0.59 (each 3H, d, *J*=7.0 Hz), 0.74 (9H, s), 0.84 (1H, m), 0.89 (3H, d, *J*=6.4 Hz), 0.94–1.02 (2H, m), 1.35 (1H, m), 1.46 (1H, m), 1.58–1.66 (3H, m), 1.92 (1H, m), 3.65 (3H, s), 4.39 (1H, d, *J*=2.5 Hz), 4.58 (1H, br s), 4.75 (1H, ddd, *J*=4.3, 11.0, 11.0 Hz), 4.81 (1H, br s), 6.39 (2H, d, *J*=8.9 Hz), 6.62 (2H, d, *J*=8.9 Hz), 7.19 (2H, t, *J*=7.2 Hz), 7.27 (2H, t, *J*=7.2 Hz), 7.32 (2H, d, *J*=7.2 Hz). ^{13}C NMR: −6.21 (CH_3), −5.67 (CH_3), 15.0 (CH_3), 18.2 (C), 20.7 (CH_3), 22.0 (CH_3), 22.7 (CH_2), 25.5 (CH_3), 25.5 (CH_2), 31.4 (CH), 34.2 (CH), 41.0 (CH), 47.1 (CH_2), 55.8 (CH_3), 60.4 (CH), 75.0 (CH), 77.1 (CH), 114.2 (CH), 114.7 (CH), 127.3 (CH), 127.4 (CH), 128.3 (CH), 140.0 (C), 140.7 (C), 151.7 (C), 171.2 (C). IR (KBr): 3422, 1747. EIMS *m*/*z*: 539 (M^+). HRMS *m*/*z*: calcd for $C_{32}H_{49}NO_4Si$: 539.3431. Found: 539.3426.

4.1.4. (3*R*,4*S*)-3-*tert*-Butyldimethylsiloxy-1-(4-methoxyphenyl)-4-phenylazetidin-2-one *cis*-17. To a solution of *syn*-**16** (74 mg, 0.137 mmol) in 5 mL of THF was added MeMgBr (0.5 M THF solution, 0.82 mL, 0.41 mmol) at −78 °C and the mixture was stirred for 1 h at −10 °C and quenched with satd ammonium chloride, and then extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with brine (20 mL) and dried over sodium sulfate, and then concentrated. Column chromatography (hexane/Et_2O=9:1) gave *cis*-**17** (54 mg, 99%) as colorless needles of mp 139–140 °C (hexane) and $[\alpha]_D^{25}$ −75.6 (*c* 0.75, $CHCl_3$). ^1H NMR: −0.15 (3H, s), 0.07 (3H, s), 0.64 (9H, s), 3.74 (3H, s), 5.11 (2H, m), 6.77–6.79 (2H, d, *J*=9.2 Hz), 7.28–7.33 (7H, m). ^{13}C NMR: −5.39 (CH_3), −4.87 (CH_3), 17.8 (C), 25.3 (CH_3), 55.4 (CH_3), 62.8 (CH),

77.6 (CH), 114.1 (CH), 118.9 (CH), 128.2 (CH), 128.2 (CH), 128.3 (CH), 131.0 (C), 134.1 (C), 156.2 (C), 165.5 (C). EIMS *m/z*: 383 (M^+). IR (KBr): 1720. Anal. Calcd for $C_{22}H_{29}NO_3Si$: C, 68.89; H, 7.62; N, 3.65. Found: C, 68.83; H, 7.60; N, 3.48.

4.1.5. (3*R*,4*S*)-3-*tert*-Butyldimethylsiloxy-1-(4-methoxyphenyl)-4-phenylazetidin-2-one *cis*-18. To a solution of *cis*-**17** (30 mg, 0.078 mmol) in 3 mL of acetonitrile was slowly added CAN (128 mg, 0.235 mmol) in water (10 mL) at 0 °C and the mixture was stirred for 1 h. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (15 mL×3). Combined organic layer was washed with brine (20 mL) and dried over sodium sulfate, and then concentrated to give a pale brown solid (27 mg). Column chromatography (benzene/ethyl acetate=30:1) gave *cis*-**18** (19.5 mg, 90%) as colorless fine needles of mp 108–110 °C and $[\alpha]_D^{25}$ +61.3 (*c* 0.62, $CHCl_3$). ^{1}H NMR: −0.17 (3H, s), 0.04 (3H, s), 0.64 (9H, s), 4.80 (1H, d, *J*=4.8 Hz), 5.06 (1H, dd, *J*=4.8, 2.3 Hz), 6.21 (1H, br s), 7.30–7.36 (5H, m). ^{13}C NMR: −5.50 (CH_3), −5.51 (CH_3), 17.7 (C), 25.2 (CH_3), 59.1 (CH), 79.6 (CH), 128.0 (CH), 128.0 (CH), 128.1 (CH), 136.3 (CH), 170.0 (C). EIMS *m/z*: 277 (M^+). IR (KBr): 3233, 1713. HRMS *m/z*: calcd for $C_{15}H_{23}NO_2Si$: 277.1498. Found: 277.1505.

4.1.6. (3*R*,4*S*)-3-Hydroxy-4-phenylazetidin-2-one 19. To *cis*-**18** (35 mg, 0.126 mmol) was added TBAF in THF (1.0 M, 0.38 mL) and the mixture was stirred for 15 min at 0 °C. Concentration and column chromatography (ethyl acetate/benzene=3:2) gave **19** (18.5 mg, 90%) as colorless fine needles of mp 182–183 °C (ethyl acetate) and $[\alpha]_D^{25}$ +178 (*c* 1.00, MeOH). ^{1}H NMR (DMSO-d_6): 4.69 (1H, d, *J*=4.6 Hz), 4.93 (1H, dd, *J*=4.6, 7.0 Hz), 5.83 (1H, d, *J*=7.0 Hz), 7.23–7.37 (5H, m), 8.47 (1H, br s). Spectroscopic data were identical with those reported for (3*R*,4*S*)-**19**.[12]

4.1.7. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*S*)-2-hydroxy-3-(4-methoxyphenylamino)-3-(4-methoxyphenyl)propanoate *syn*-20b (Table 2, entry 1). The 96:4 *syn*/*anti* ratio was determined from the integration values of 4.41 ppm (*syn*) and 4.45 ppm (*anti*). Recrystallization (204 mg) from ethanol gave *syn*-**20b** (120 mg) as colorless needles of mp 124–124.5 °C and $[\alpha]_D^{25}$ −27.8 (*c* 1.00, benzene). ^{1}H NMR: 0.40 and 0.58 (each 3H, d, *J*=7.0 Hz), 0.82–1.09 (6H, m), 1.41 (1H, m), 1.50 (1H, m), 1.60–1.70 (3H, m), 2.01 (1H, m), 3.68 (3H, s), 3.77 (3H, s), 4.41 (1H, d, *J*=2.8 Hz), 4.77–4.83 (2H, m), 6.43 (2H, d, *J*=8.9 Hz), 6.65 (2H, d, *J*=8.9 Hz), 6.85 (2H, d, *J*=8.6 Hz), 7.29 (2H, d, *J*=8.6 Hz). ^{13}C NMR: 15.0 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 31.4 (CH), 34.1 (CH), 40.7 (CH), 47.1 (CH_2), 55.2 (CH_3), 55.7 (CH_3), 58.3 (CH), 75.0 (CH), 77.1 (CH), 114.1 (CH), 114.7 (CH), 114.7 (CH), 128.1 (CH), 131.3 (C), 140.3 (C), 152.1 (C), 159.0 (C), 172.3 (C). IR (KBr): 3398, 1720. EIMS *m/z*: 455 (M^+). Anal. Calcd for $C_{27}H_{37}NO_5$: C, 71.18; H, 8.19; N, 3.07. Found: C, 71.15; H, 8.27; N, 3.04.

4.1.8. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*S*)-2-hydroxy-3-(4-methoxyphenylamino)-3-(4-chlorophenyl)propanoate *syn*-20c (Table 2, entry 2). Column chromatography (Hex/Et_2O=4:1) gave a 96:4 *syn*/*anti* mixture as a pale brown gum of $[\alpha]_D^{25}$ −37.1 (*c* 1.26, benzene). The ratio was determined from the integration values of 6.67 ppm (*syn*) and 6.48 ppm (*anti*). The spectral data of major isomer: ^{1}H NMR: 0.39 and 0.56 (each 3H, d, *J*=7.0 Hz), 0.83–1.08 (6H, m), 1.39 (1H, m), 1.49 (1H, m), 1.62–1.68 (3H, m), 2.02 (1H, m), 3.22 (1H, dd, *J*=1.2 Hz, 2.8 Hz), 3.68 (3H, s), 4.41 (1H, m), 4.50 (1H, br s), 4.78–4.82 (2H, m), 6.41 and 6.67 (each 2H, d, *J*=8.9 Hz), 7.30 and 7.33 (each 2H, d, *J*=8.9 Hz). ^{13}C NMR: 14.9 (CH_3), 20.5 (CH_3), 21.9 (CH_3), 22.6 (CH_2), 25.4 (CH_2), 31.4 (CH), 34.0 (CH), 40.7 (CH), 47.0 (CH_2), 55.7 (CH_3), 58.3 (CH), 74.7 (CH), 76.9 (CH), 114.5 (CH), 114.7 (CH), 128.5 (CH), 128.8 (CH), 133.2 (C), 138.1 (C), 139.8 (C), 152.2 (C), 172.6 (C). IR (KBr): 3395, 1728. EIMS *m/z*: 460 (M^+). HRMS *m/z*: calcd for $C_{26}H_{34}ClNO_4$: 459.2176. Found: 459.2171.

4.1.9. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*S*)-2-hydroxy-3-(4-methoxyphenylamino)-3-[4-(trifluoromethyl)phenyl]propanoate *syn*-20d (Table 2, entry 3). The 90:10 *syn*/*anti* ratio was determined from the integration values of 0.40 ppm (*syn*) and 0.49 ppm (*anti*). Recrystallization (100 mg) from 1 mL of ethanol gave *syn*-**20d** (75 mg) as colorless needles of mp 133.0–133.5 °C and $[\alpha]_D^{25}$ −36.1 (*c* 1.07, benzene). ^{1}H NMR: 0.40 and 0.57 (each 3H, d, *J*=7.0 Hz), 0.92 (3H, d, *J*=6.4 Hz), 0.95–1.10 (3H, m), 1.39 (1H, m), 1.50 (1H, m), 1.62–1.69 (3H, m), 2.03 (1H, m), 3.33 (1H, br s), 3.68 (3H, s), 4.45 (1H, d, *J*=2.2 Hz), 4.54 (1H, br s), 4.82 (1H, ddd, *J*=10.7, 10.7, 4.3 Hz), 4.91 (1H, br s), 6.42 and 6.67 (each 2H, d, *J*=8.9 Hz), 7.51 and 7.58 (each 2H, d, *J*=7.9 Hz). ^{13}C NMR: 14.9 (CH_3), 20.5 (CH_3), 21.9 (CH_3), 22.7 (CH_2), 25.5 (CH_2), 31.4 (CH), 34.0 (CH), 40.7 (CH), 47.1 (CH_2), 55.7 (CH_3), 58.5 (CH), 74.6 (CH), 77.2 (CH), 114.5 (CH), 114.8 (CH), 124.2 (q, $^1J_{C-F}$=270.7 Hz, C), 125.6 (q, $^3J_{C-F}$=4.1 Hz, CH), 127.5 (CH), 129.8 (q, $^2J_{C-F}$=31.9 Hz, C), 139.6 (C), 143.9 (C), 152.4 (C), 172.5 (C). IR (KBr): 3394, 1720. EIMS *m/z*: 493 (M^+). Anal. Calcd for $C_{27}H_{34}F_3NO_3$: C, 65.70; H, 6.94; N, 2.84. Found: C, 65.45; H, 7.04; N, 2.75.

4.1.10. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*S*)-2-hydroxy-3-(4-methoxyphenylamino)-3-(naphthalen-2-yl)propanoate *syn*-20e (Table 2, entry 4). A 98:2 *syn*/*anti* ratio was determined from the integration values of 6.48 ppm (*syn*) and 6.56 ppm (*anti*). Recrystallization (237 mg) from 10 mL of ethanol gave *syn*-**20e** (197 mg) as colorless needles of mp 146–147 °C and $[\alpha]_D^{25}$ −28.8 (*c* 1.00, benzene). ^{1}H NMR: 0.40 and 0.57 (each 3H, d, *J*=7.0 Hz), 0.86 (1H, m), 0.92 (3H, d, *J*=6.7 Hz), 0.95–1.10 (2H, m), 1.40 (1H, m), 1.50 (1H, m), 1.61–1.70 (3H, m), 2.02 (1H, m), 3.21 (1H, d, *J*=3.1 Hz), 3.65 (3H, s), 4.55 (1H, dd, *J*=3.1, 2.7 Hz), 4.83 (1H, ddd, *J*=4.3, 10.8, 10.8 Hz), 5.01 (1H, br s), 6.48 and 6.63 (2H, d, *J*=8.9 Hz), 7.41–7.45 (2H, m), 7.52 (1H, dd, *J*=8.6, 1.6 Hz), 7.78–7.83 (4H, m). ^{13}C NMR: 14.9 (CH_3), 20.5 (CH_3), 21.9 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 31.4 (CH), 34.0 (CH), 40.7 (CH), 47.1 (CH_2), 55.7 (CH_3), 59.2 (CH), 75.0 (CH), 76.8 (CH), 114.7 (CH), 114.8 (CH), 125.0 (CH), 125.8 (CH), 126.1 (CH), 126.2 (CH), 127.7 (CH), 128.0 (CH), 128.5 (CH), 133.0 (C), 133.4 (C), 137.1 (C), 140.2 (C), 152.2 (C), 172.7 (C). IR (KBr): 3395, 1720. EIMS *m/z*: 475 (M^+). Anal. Calcd for $C_{30}H_{37}NO_4$: C, 75.76; H, 7.84; N, 2.94. Found: C, 75.59; H, 7.79; N, 2.99.

4.1.11. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (3*R*)-3-(4-methoxyphenylamino)-5-phenylpent-4-ynoate 22a (Table 3, entry 12). A solution of L-menthyl acetate (396 mg, 2.0 mmol) in THF (3 mL) was added dropwise over 5 min at −78 °C to a preformed solution of LDA (2.25 mmol) in THF (3 mL). The mixture was stirred at −78 °C for 0.5 h. Then DABCO (505 mg, 4.5 mmol) in THF (5 mL) was added at −78 °C to the mixture. A solution of imine **21a** (235 mg, 1.0 mmol) in THF (3 mL) was added dropwise over 10 min at −78 °C to the mixture and the mixture was stirred at −78 °C for 0.5 h. The reaction was quenched with satd ammonium chloride (20 mL) at −78 °C and extracted with AcOEt (30 mL×3). Combined organic layers were washed with brine (20 mL) and dried over sodium sulfate, and then concentrated to give a pale yellow solid (655 mg). Column chromatography (hexane/AcOEt=15:1) gave **22a** (420 mg, 96% yield) as pale yellow solid. The ratio of two diastereomers was determined to be 95.5:4.5 from the integration values of 0.67 ppm (3*R*) and 0.71 ppm (3*S*). Recrystallization (330 mg) from 2 mL of 2-propanol gave (3*R*)-**22a** as colorless needles of mp 106–107.0 °C and $[\alpha]_D^{25}$ +96.4 (*c* 1.00, $CHCl_3$). ^{1}H NMR: 0.67 and 0.79 (each 3H, d, *J*=7.2 Hz), 0.84 (1H, m), 0.87 (3H, d, *J*=6.4 Hz), 0.96–1.08 (2H, m), 1.37 (1H, m), 1.47 (1H, m), 1.64–1.69 (2H, m), 1.86 (1H, m), 2.03 (1H, m), 2.85 (1H, m), 3.03 (1H, m), 3.76 (3H, s), 4.00 (1H, br s), 4.66 (1H, m), 4.76 (1H, m), 6.77 and 6.81 (each 2H, d, *J*=7.9 Hz), 7.23–7.27 (3H, m), 7.33 (2H, d, *J*=7.9 Hz). ^{13}C NMR: 16.0 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 23.2 (CH_2), 26.0 (CH_2), 31.3 (CH), 34.1 (CH), 41.0 (CH), 41.1 (CH), 44.7 (CH_2), 47.0 (CH_2), 55.7 (CH_3), 74.8 (CH), 83.4 (C), 88.6 (C), 114.7 (CH), 116.7 (CH), 122.7 (CH), 128.2 (CH), 128.2 (CH), 131.8 (C), 140.2 (C), 153.4 (C), 170.2 (C). IR (KBr): 3364, 1724. EIMS *m*/*z*: 433 (M^+). HRMS *m*/*z*: calcd for $C_{28}H_{35}NO_3$: 433.2617. Found: 433.2621.

4.1.12. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (3*R*)-3-(4-methoxyphenylamino)-5-(trimethylsilyl)-pent-4-ynoate 22b (Table 3, entry 13). Column chromatography (hexane/Et_2O=9:1) gave **22b** (76%) as pale yellow solid. The diastereomer ratio was determined to be 91.5:8.5 from the integration values of 0.70 ppm (3*R*) and 0.74 ppm (3*S*). Recrystallization (300 mg) from 0.5 mL of hexane/2-propanol (1:1) gave 97:3 mixture (175 mg) as pale brown fine needles of mp 71.0–72.0 °C and $[\alpha]_D^{25}$ +62.4 (*c* 0.99, benzene). ^{1}H NMR: 0.10 (9H, s), 0.71 and 0.83 (each 3H, d, *J*=7.0 Hz), 0.88–0.91 (4H, m), 0.98–1.06 (2H, m), 1.36 (1H, m), 1.48 (1H, m), 1.64–1.69 (2H, m), 1.84 (1H, m), 2.00 (1H, m), 2.74 (2H, d, *J*=6.4 Hz), 3.76 (3H, s), 3.86 (1H, br s), 4.44 (1H, dd, *J*=6.4, 6.4 Hz), 4.73 (1H, ddd, *J*=4.6, 11.0, 11.0 Hz), 6.71 and 6.80 (each 2H, d, *J*=8.8 Hz). ^{13}C NMR: −0.26 (CH_3), 16.0 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 23.2 (CH_2), 26.0 (CH_2), 31.3 (CH), 34.1 (CH), 40.6 (CH), 40.8 (CH), 44.7 (CH_2), 46.8 (CH_2), 55.5 (CH_3), 74.6 (CH), 87.8 (C), 105.1 (C), 114.5 (CH), 116.6 (CH), 140.1 (C), 153.2 (C), 170.0 (C). IR (KBr): 3368, 1732. EIMS *m*/*z*: 429 (M^+). Anal. Calcd for $C_{25}H_{39}NO_3Si$: C, 69.88; H, 9.15; N, 3.26. Found: C, 69.86; H, 9.00; N, 3.29.

4.1.13. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*,3*S*)-3-(4-methoxyphenylamino)-2-hydroxy-5-phenylpent-4-ynoate 23a. To a THF solution of 0.3 M LDA (1.5 mL, 0.45 mmol) was added THF solution of pure **22a** (65 mg, 0.15 mmol, 1.5 mL) at −78 °C and the mixture was stirred for 1 h at −30 °C. A solution of DABCO (50 mg, 0.45 mmol) in THF (1.5 mL) was added and the mixture was stirred for 0.5 h at −78 °C. Then, (−)-**15** (52 mg, 0.23 mmol) in THF (1.5 mL) was added at −78 °C and the mixture was stirred for 0.5 h. The reaction was quenched with satd ammonium chloride (5 mL) and extracted with ethyl acetate (10 mL×3). Combined organic layers were washed with brine (20 mL) and dried over sodium sulfate, and then concentrated to give a yellow solid (101 mg). Column chromatography (hexane/AcOEt=7:1) gave **23a** (38 mg, 57%) as a pale yellow solid. The 94:6 ratio was determined from the integration values of 6.70 ppm (*syn*) and 6.74 ppm (*anti*). Recrystallization (20 mg) from 1.5 mL of methanol gave pure **23a** (15 mg) as colorless fine needles of mp 164.0–165.0 °C and $[\alpha]_D^{25}$ +65.4 (*c* 1.00, benzene). ^{1}H NMR: 0.44 and 0.64 (each 3H, d, *J*=7.0 Hz), 0.84–0.91 (4H, m), 0.95–1.08 (2H, m), 1.38 (1H, m), 1.49 (1H, m), 1.62–1.69 (2H, m), 1.75 (1H, m), 2.04 (1H, m), 3.43 (1H, br s), 3.75 (3H, s), 4.07 (1H, br s), 4.55 (1H, d, *J*=2.5 Hz), 4.71 (1H, br s), 4.81 (1H, ddd, *J*=11.0, 11.0, 4.3 Hz), 6.70 and 6.80 (each 2H, d, *J*=9.2 Hz), 7.22–7.26 (3H, m), 7.34–7.36 (2H, m). ^{13}C NMR: 15.1 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 22.7 (CH_2), 25.5 (CH_2), 31.4 (CH), 34.0 (CH), 40.7 (CH), 47.0 (CH_2), 49.5 (CH), 55.7 (CH_3), 73.1 (CH), 77.1 (CH), 84.0 (C), 86.6 (C), 114.6 (CH), 116.3 (CH), 122.6 (CH), 128.1 (CH), 128.2 (CH), 131.9 (C), 139.7 (C), 153.3 (C), 171.8 (C). IR (KBr): 3425, 1728. EIMS *m*/*z*: 449 (M^+). HRMS *m*/*z*: calcd for $C_{28}H_{35}NO_4$: 449.2566. Found: 449.2574.

4.1.14. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (3*R*)-2-hydroxy-3-(4-methoxyphenylamino)-5-(trimethylsilyl)pent-4-ynoate 23b. Column chromatography (hexane/Et_2O=6:1) gave **23b** (68%) as a pale yellow solid. A 97:3 *syn*/*anti* ratio was determined from the integration values of 0.64 ppm (*syn*) and 0.74 ppm (*anti*). Recrystallization (90 mg) from a 1:1 mixture of 2-propanol and hexane (0.5 mL) gave pure **23b** (71 mg) as colorless fine needles of mp 124.5–125.0 °C and $[\alpha]_D^{25}$ +50.1 (*c* 0.69, benzene). ^{1}H NMR: 0.10 (9H, s), 0.45 and 0.64 (each 3H, d, *J*=7.0 Hz), 0.84–0.91 (4H, m), 0.97–1.04 (2H, m), 1.34 (1H, m), 1.48 (1H, m), 1.61–1.70 (3H, m), 2.02 (1H, m), 3.36 (1H, br s), 3.75 (3H, s), 3.95 (1H, br s), 4.45 and 4.50 (each 1H, d, *J*=2.4 Hz), 4.76 (1H, ddd, *J*=11.0, 11.0, 4.3 Hz), 6.64 and 6.78 (each 2H, d, *J*=8.9 Hz). ^{13}C NMR: −0.18 (CH_3), 15.0 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 22.6 (CH_2), 25.4 (CH_2), 31.3 (CH), 34.0 (CH), 40.6 (CH), 47.0 (CH_2), 49.4 (CH), 55.6 (CH_3), 72.8 (CH), 76.9 (CH), 88.8 (C), 103.0 (C), 114.5 (CH), 116.3 (CH), 139.6 (C), 153.2 (C), 171.6 (C). IR (KBr): 3433, 1728. EIMS *m*/*z*: 445 (M^+). Anal. Calcd for $C_{25}H_{39}NO_4Si$: C, 67.37; H, 8.82; N, 3.14. Found: C, 67.31; H, 8.66; N, 3.09.

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