

Asymmetric Synthesis of β -Amino- α -Hydroxy Acids through Lewis Acid-Mediated Addition of Ketene Acetal to Imines[#]

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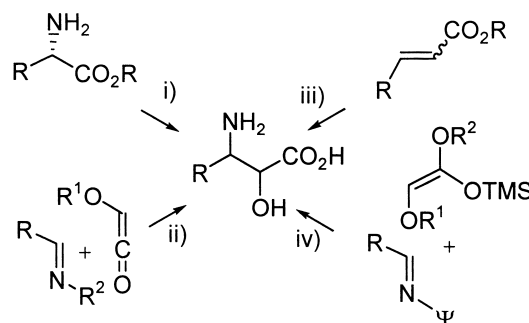
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Asymmetric synthesis of β -amino- α -hydroxy acids, key components of medicinally important molecules including Paclitaxel, KRI-1314, amastatin, and microginin, has been attained from the aldimine coupling of chiral imines *N*-alkylidene-(*S*)- or (*R*)- α -methylbenzylamine with (*Z*)- α -methoxyketene methyltrimethylsilyl acetal, followed by demethylation, hydrogenolysis, and hydrolysis.

During the last several years, enantioselective synthesis of β -amino- α -hydroxy acids has attracted much attention not only because of the synthetic interest to put the right functional moieties in the right positions in a stereospecific manner but also because of their presence in various medicinally important molecules.¹ Paclitaxel is a natural product isolated from the bark of *Taxus brevifolia* that is the most promising anticancer agent so far discovered.² This has (2*R*,3*S*)-3-(*N*-benzoylamino)-2-hydroxy-3-phenylpropionic acid as a side chain for the essential structural element for the activity. Another member of this class of compounds bearing 3-amino-2-hydroxy-5-methylhexanoate as a key component is amastatin isolated from *Streptomyces* sp., with immunoregulatory, antitumor, and antibacterial activity.³ β -Amino- α -hydroxy acid is also found in rennin inhibitor for antihypertensive agent, as the transition state mimic including KRI 1314.⁴ Microginin, a linear pentapeptide natural product isolated from blue-green alga *Microcystis aeruginosa*, possesses 3-amino-2-hydroxydecanoate as a *N*-terminal.⁵ This compound showed angiotension-converting enzyme inhibitory activity for the treatment of hypertense patients (Fig. 1).⁶

Ample examples were reported for the stereoselective synthesis⁷ based on several different approaches including i) homologation from chiral amino acids, ii) enantioselective introduction of amino and hydroxy groups to olefinic acids via either enantioselective dihydroxylation or epoxidation or aminohydroxylation, and iii) $[2\pi + 2\pi]$ cycloaddition between imines and ketenes to β -lactam and subsequent hydrolysis (Scheme 1). Another facile synthetic route can be designed with stereoselective aldimine-type coupling with ketene acetal, as shown in Scheme 1-iv.



Scheme 1.

Results and Discussion

A previous study of the condensation between chiral imine with α -silyloxyketene acetal led to a new synthetic route to the β -amino- α -hydroxy acids including paclitaxel side chain.⁸ With double stereodifferentiation by chiral imines, an equimolar amount of chiral boron catalysts yielded the desired stereochemical products of β -amino- α -hydroxy esters that were readily converted to the target molecules. However, some drawbacks were found in this process. The ketene acetal used for this reaction is (*Z*)-1-methoxy-1,2-bis(triethylsilyloxy)ethylene of which the synthesis required a low temperature like $-100\text{ }^{\circ}\text{C}$. The aldimine coupling reaction of this ketene acetal with chiral imine was carried out at $-78\text{ }^{\circ}\text{C}$ with consumption of equimolar amounts of expensive chiral catalyst.⁸ Therefore, a practical and inexpensive synthetic method from chiral imine with more readily available ketene acetal is required for the preparation of β -amino- α -hydroxy acids. Preliminary study in our laboratory for taxol side chain synthesis showed a possibility for this method to apply for various β -amino- α -hydroxy acids starting from stable chiral imines.⁹ Even an unstable imine generated in situ can also be reacted with ketene acetal to yield 3-amino-2-hydroxy-4-phenylbutyrate in a stereoselective man-

[#] This paper is part 14 in the series of "Lewis acid induced synthetic equivalents of imines and iminium ions". For part 13 see, H.-J. Ha, C.-J. Choi, Y.-G. Ahn, H. Yoon, Y. Dong and W. K. Lee, *J. Org. Chem.*, **65**, 8384 (2000).

ner.¹⁰ In this report is described the general aldimine route to enantioselective synthesis of β -amino- α -hydroxy acids involving aldimine coupling with readily available ketene acetal.

The stereoselectivity on the addition of ketene acetals to the corresponding imines toward β -amino- α -hydroxy acids depends on the stereochemistry of the imines and their transition states. All aldimines (**5**, **6**, **7**, and **8**) with *E* stereochemistry are stable enough to be prepared from aldehyde and benzylamine and can be isolated in quantitative yields.¹¹ *N*-Benzylidenbenzylamine (**5**) for the synthesis of 3-amino-2-hydroxy-3-phenylpropionic acid was the best candidate for the initial aldimine coupling reactions. This crucial coupling reaction of imine was carried out with readily available (*Z*)-1,2-dimethoxy-1-trimethylsilyloxyethylene (**13**),¹² in the presence of several different Lewis acids.¹³ All of the Lewis acids lead the reaction into the *syn* fashion in moderate yields. AlCl_3 , TMSCl and TMSTf showed the selectivity about 3:1 with the *syn* preference in good yield, while TiCl_4 , SnCl_4 and TiF_4 gave relatively poor stereoselectivity.⁹ The best reaction could be performed at room temp with 0.3 mol amount of MgBr_2 with

the desired stereochemistry by the *syn* (**14a**) to *anti* (**14b**) ratio of 84:16 at room temperature for 2 h. Other ketene acetals such as (*Z*)-1-*t*-butoxy-2-dimethoxy-1-trimethylsilyloxyethylene and (*Z*)-2-benzyloxy-1-methoxy-1-trimethylsilyloxyethylene were also tried with similar stereoselectivity in an early study.⁹

Once we have gotten the best reaction condition with a catalytic amount of MgBr_2 this was applied for other imines including *N*-(2-cyclohexylethylidene)benzylamine (**6**), *N*-(3-methylbutylidene)benzylamine (**7**), and *N*-octylidenbenzylamine (**8**). The stereochemical outcome from **6**, **7**, and **8** with (*Z*)-1,2-dimethoxy-1-trimethylsilyloxyethylene (**13**) yielded all *syn* products (**15a**, **16a**, and **17a**) with the ratios of 74:26, 72:28, and 76:24 in 78, 91, and 82% yields respectively (Scheme 2).

Once the reaction condition was established, we have studied extensively the diastereoselective synthesis of 3-amino-2-hydroxy-3-phenylpropionic acid with chiral imine of *N*-benzylidene-(*S*)- α -methylbenzylamine (**9**), while considering the additional factor of diastereofacial selectivity. The expected product of methyl (2*R*,3*S*)-2-methoxy-3-[(*S*)- α -methylbenzylamino]-3-phenylpropionate (**18**) could be obtained as a major

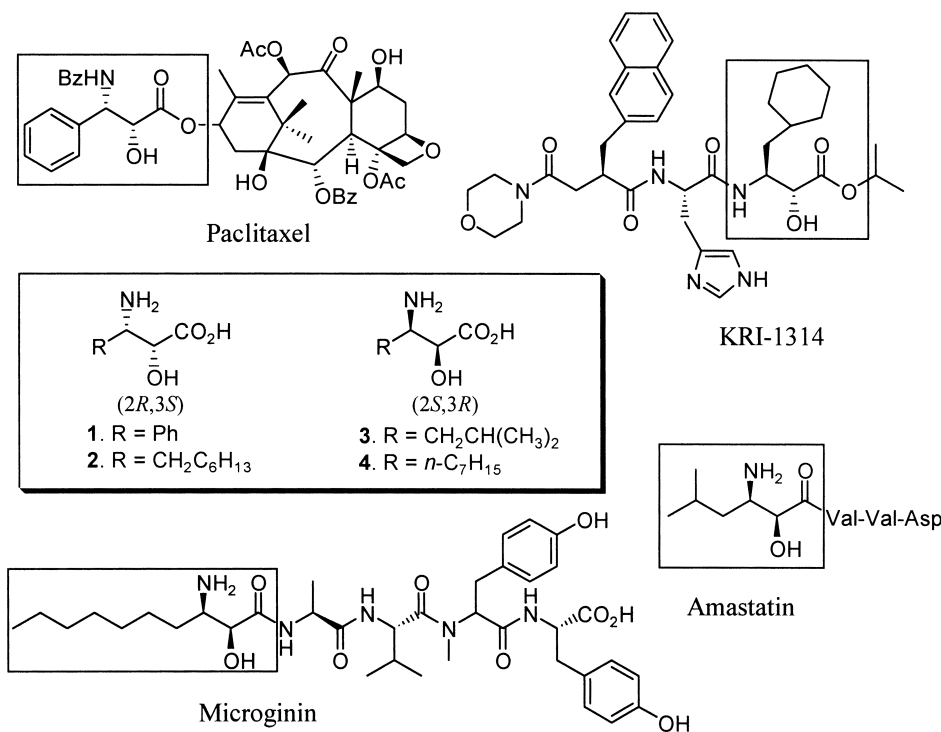
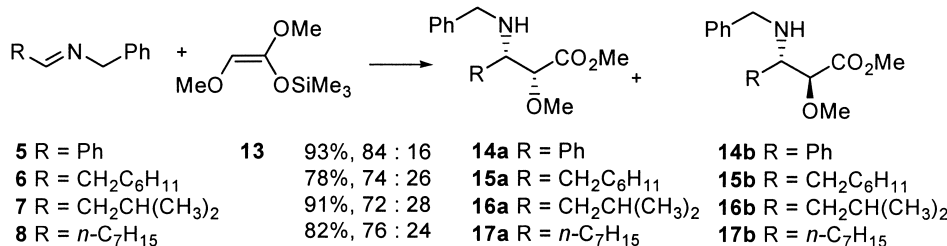
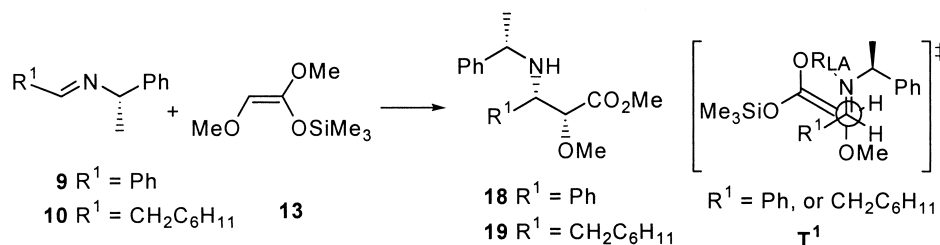


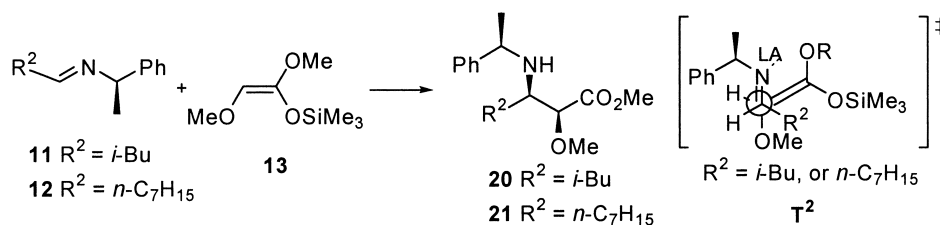
Fig. 1.



Scheme 2.



Scheme 3.



Scheme 4.

product among all four possible stereoisomers in 59% of isolated yield after flash column chromatography. (*syn:anti* = 84:16, diastereofacial ratio = 92:8).⁹ The diastereoselectivity was not much improved by changing methyl to *t*-butyl in the ketene acetal.⁹ The transition state of the reaction can be drawn as in the bracket of the Scheme 3 with *synclinal* orientation of imine activated by Lewis acid and with ketene acetal approaching to the less hindered face of the chiral imine (Scheme 3).¹⁴ The same results would be expected from the transition state with the *antiperiplanar* orientation.

This result showed the facile route for the enantioselective synthesis of several different β -amino- α -hydroxy acids with proper use of chiral α -methylbenzylamine auxiliaries. For the synthesis of compounds **2**, **3**, and **4** with common *syn* orientations of amine and hydroxy groups with the absolute configuration as (2*R*,3*S*) and as (2*S*,3*R*) could be achieved by utilizing (*S*)- α -methylbenzylamine and (*R*)- α -methylbenzylamine as chiral auxiliaries, respectively (Scheme 4).

Starting from chiral imine of *N*-benzylidene-(*S*)- α -methylbenzylamine (**9**) and *N*-(2-cyclohexylethylidene)-(*S*)- α -methylbenzylamine (**10**) with (*Z*)-1,2-dimethoxy-1-trimethylsilyloxyethylene (**13**) produced (2*R*,3*S*)- β -amino- α -methoxy esters (**18**, **19**) in 59 and 40% isolated yields from possible four diastereomers by flash column chromatography. Imines (**11** and **12**) bearing (*R*)- α -methylbenzylamine yielded (2*S*,3*R*)- β -amino- α -methoxy esters (**20**, **21**) in 44 and 39% isolated yields. Comparable diastereofacial selectivity as 84:16 was observed during the reaction of *N*-benzylidene-(*R*)- α -methylbenzylamine generated in situ with the same nucleophile.¹⁰ Unless we isolated and identified each of the possible four isomers with absolute stereochemistry, the exact value of facial selectivity would not be deduced.

The coupled product methyl (2*R*,3*S*)-2-methoxy-3-[(*S*)- α -methylbenzylamino]-3-phenylpropionate (**18**) for 3-amino-2-hydroxy-3-phenylpropionic acid was further treated for demethylation with 0.3 mol amount of BBr_3 at -78°C to give free hydroxy compound (**22**) with the minor product of β -lactam (3*R*,4*S*)-3-methoxy-1-[(*S*)- α -methylbenzyl]-4-phenylazetid-

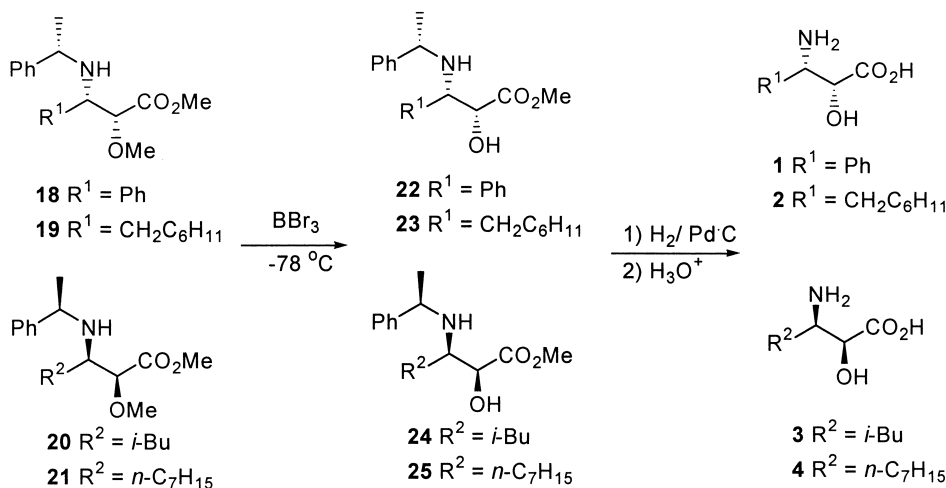
2-one in 75% and 15% isolated yields, respectively.⁹ This indicates that demethylation competes with lactamization. A greater amount of lactamized product was obtained by elevation of the reaction temperature to 0°C . In the same manner, treatment of methyl (2*R*,3*S*)-4-cyclohexyl-2-methoxy-3-[(*S*)- α -methylbenzylamino]butyrate (**19**), methyl (2*S*,3*R*)-2-methoxy-5-methyl-3-[(*R*)- α -methylbenzylamino]hexanoate (**20**), and methyl (2*S*,3*R*)-2-methoxy-3-[(*R*)- α -methylbenzylamino]decanoate (**21**) with BBr_3 yielded demethylated products (**23**, **24**, **25**) in 62, 72, and 67% yields, respectively (Scheme 5) with 10–15% of lactamized products.

Each of β -amino- α -hydroxy esters (**22**, **23**, **24**, and **25**) was further transformed by sequential reactions of hydrogenolysis and hydrolysis to afford the target β -amino- α -hydroxy acids (**1**, **2**, **3**, and **4**) in more than 75% yields by the known methods.¹⁰

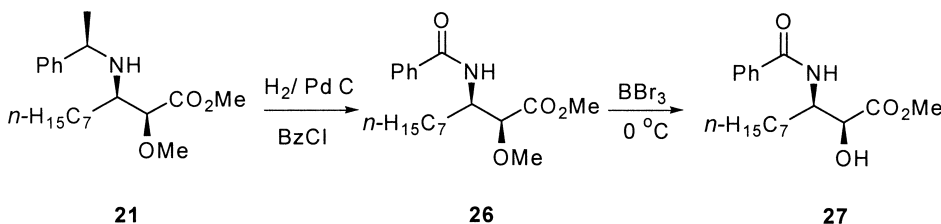
In case of 3-amino-2-hydroxydecanoate, α -methylbenzyl group at the nitrogen of the initial adduct methyl (2*S*,3*R*)-2-methoxy-3-[(*R*)- α -methylbenzylamino]decanoate (**21**) was replaced with benzoyl by hydrogenation in the presence of equimolar amount of benzoyl chloride in 82% yield. Demethylation of the methoxy to free hydroxy group at this stage (**26**) with benzoyl at the amine succeeded with BBr_3 in much better yield than the same reaction with the compound **21** bearing the α -methylbenzyl group (Scheme 6).

Removal of methyl from methoxy of **26** by BBr_3 proceeded in 89% yield with complete suppression of lactamization. Such better yield of demethylation from **26** compared with **21** can be explained by Lewis acidic character of boron that would be an essential element to remove methyl from methoxy group. With the substrate **21**, BBr_3 was deactivated to a great extent by the strong base of α -methylbenzylamine. However this would be suppressed in **26** which has a benzamide of which the nitrogen is not quite basic.

In conclusion we have showed the aldimine coupling of chiral imines *N*-alkylidene-(*S*)- or (*R*)- α -methylbenzylamine with (*Z*)- α -methoxyketene methyltrimethylsilyl acetal would be the general route for asymmetric synthesis of β -amino- α -



Scheme 5.



Scheme 6.

hydroxy acids, key components of medicinally important molecules.

Experimental

General. ¹H NMR and ¹³C NMR spectra were recorded on a Varian 200 or 400 (200 and 400 MHz for ¹H and 50.3 and 100.6 MHz for ¹³C). Chemical shifts were given in ppm using TMS as internal standard. Mass spectra were obtained using a Hewlett Packard Model 5985B spectrometer or a Kratos Concept 1-S double focusing mass spectrometer. Elemental analysis was performed on a Pekin-Elmer 240 DS elemental analyzer. Melting point was measured by Mel-II capillary melting point apparatus. Optical rotation was measured with Rudolph Research Autopole 3 polarimeter. The silica gel used for column chromatography was Merck 200–230 mesh. Thin-layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness.

Synthesis of Methyl 3-benzylamino-2-methoxy-3-phenylpropionate (14): Anhydrous MgBr₂ (206 mg, 1.12 mmol) was added into the solution of the imines (**5**) (728 mg, 3.73 mmol) in CH₂Cl₂ at room temperature. The resultant solution was stirred for 15 min before adding (Z)-1,2-dimethoxy-1-trimethylsilyloxyethene (723 mg, 410 mmol) in drops. After 1 h for completion, the reaction mixture was dumped into the H₂O. The reaction product was extracted with EtOAc (50 mL × 3). The organic layer was washed by 100 mL each of water and brine, dried by anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 1.34 g of **14a** and **14b** in 93% yield. In the same manner **15**, **16**, and **17** were obtained. For **14a**, ¹H NMR δ 2.37 (s, 1H), 3.27 (s, 3H), 3.30 (d, 1H, *J* = 12.2 Hz), 3.45 (s, 3H), 3.59 (d, 1H, *J* = 12.2 Hz), 3.76 (d, 1H, *J* = 6.5 Hz), 3.95 (d, 1H, *J* = 6.5 Hz),

7.13–7.31 (m, 10H); ¹³C NMR δ 50.7, 51.6, 58.6, 63.7, 85.6, 126.9, 127.9, 128.1, 128.2, 128.3, 128.4, 138.8, 140.2, 171.4. For **14b**, ¹H NMR δ 2.10 (s, 1H), 3.28 (s, 3H), 3.45 (d, 1H, *J* = 13.4 Hz), 3.55 (s, 3H), 3.63 (d, 1H, *J* = 13.4 Hz), 3.94 (d, 1H, *J* = 5.4 Hz), 4.01 (d, 1H, *J* = 5.4 Hz), 7.16–7.30 (m, 10H); ¹³C NMR δ 50.8, 51.6, 58.9, 63.1, 84.4, 127.0, 127.7, 128.0, 128.1, 128.37, 128.4, 139.0, 140.0, 171.4. For **15a**, ¹H NMR, δ 0.68–0.91 (m, 2H), 1.07–1.34 (m, 6H), 1.47–1.62 (m, 6H), 2.91 (dt, 1H, *J* = 6.6, 3.2 Hz), 3.35 (s, 3H), 3.63 (s, 3H), 3.65–3.70 (m, 2H), 7.13–7.23 (m, 5H); ¹³C NMR δ 26.2, 26.3, 33.4, 34.5, 38.5, 50.8, 51.6, 55.8, 58.9, 82.1, 126.7, 128.1, 128.2, 140.7, 172.5. For **15b**, ¹H NMR δ 0.58–0.95 (m, 2H), 1.05–1.39 (m, 6H), 1.40–1.59 (m, 6H), 2.19 (dt, 1H, *J* = 6.4, 3.2 Hz), 3.36 (d, 3H, *J* = 12.4 Hz), 3.68 (s, 3H), 3.65–3.89 (m, 2H), 7.08–7.29 (m, 5H); ¹³C NMR δ 26.4, 26.5, 28.8, 32.3, 34.0, 34.2, 38.4, 51.7, 56.3, 59.0, 69.8, 81.5, 126.9, 128.1, 128.3, 140.5, 176.7. For **16a**, ¹H NMR δ 0.72 (d, 3H, *J* = 2.2 Hz), 0.75 (d, 3H, *J* = 2.0 Hz), 1.24 (t, 2H, *J* = 7.1 Hz), 1.45 (bs, 1H), 1.51 (oct, 1H, *J* = 6.8 Hz), 2.82 (dt, 1H, *J* = 4.8, 3.8 Hz), 3.27 (s, 3H), 3.55 (s, 3H), 3.59–3.64 (m, 3H), 7.05–7.15 (m, 5H); ¹³C NMR δ 22.5, 22.6, 24.8, 39.8, 50.7, 51.4, 56.5, 58.7, 81.8, 126.6, 127.8, 128.0, 140.5, 172.3. For **16b**, ¹H NMR δ 0.68 (d, 3H, *J* = 6.2 Hz), 0.81 (d, 3H, *J* = 6.6 Hz), 0.91–1.05 (m, 1H), 1.27–1.41 (m, 1H), 1.53 (bs, 1H), 1.52–1.79 (m, 1H), 2.89 (dt, 1H, *J* = 9.8, 3.6 Hz), 3.35 (s, 3H), 3.68 (s, 3H), 3.70–3.78 (m, 2H), 3.93 (d, 1H, *J* = 3.8 Hz), 7.13–7.30 (m, 5H); ¹³C NMR δ 21.5, 23.6, 24.5, 39.9, 51.3, 51.7, 57.2, 59.0, 81.4, 126.9, 128.1, 128.2, 140.5, 172.4. For **17a**, ¹H NMR δ 0.74 (t, 3H, *J* = 6.8 Hz), 1.13 (bs, 1H), 1.31–1.42 (m, 2H), 1.47 (bs, 1H), 2.74 (dt, 1H, *J* = 6.6, 3.2 Hz), 3.28 (s, 3H), 3.57 (s, 3H), 3.54–3.71 (m, 3H), 7.04–7.16 (m, 5H); ¹³C NMR δ 14.1, 22.6, 26.2, 29.2, 29.6, 30.6, 31.7, 50.9, 51.7, 58.7, 58.9, 82.1, 126.8, 128.2, 128.3, 140.7, 172.5. For **17b**, ¹H NMR δ 0.81 (t, 3H, *J* = 6.2 Hz), 1.03–1.53 (m, 14H), 2.81 (dt,

1H, $J = 5.8, 4.1$ Hz), 3.34 (s, 3H), 3.63 (s, 3H), 3.66–3.78 (m, 3H), 7.12–7.26 (m, 5H); ^{13}C NMR δ 14.0, 22.5, 26.1, 29.1, 29.5, 30.5, 31.7, 50.8, 51.5, 58.6, 58.8, 82.0, 126.7, 128.0, 128.1, 140.6, 172.4.

Synthesis of Methyl α -Methoxy- β -(α -methylbenzyl)amino Carboxylate. The reactions were carried out in the same way as for the compounds **14** with the imines (**9–12**) derived from (*R*)- or (*S*)- α -methylbenzylamine instead of benzylamines.

Methyl (2*R*,3*S*)-2-methoxy-3-[(*S*)- α -methylbenzylamino]-3-phenylpropionate (18**):** ^1H NMR δ 1.17 (d, 3H), 2.20 (brs, 1H), 3.22 (s, 3H), 3.51 (q, 1H), 3.54 (s, 3H), 3.78 (d, 1H), 4.11 (d, 1H), 7.09–7.24 (m, 10H); ^{13}C NMR δ 21.7, 51.6, 54.1, 58.8, 61.9, 85.3, 126.6, 126.7, 127.5, 127.9, 128.2, 139.4, 145.9, 171.6. $[\alpha]_D^{22} + 0.91^\circ$ (c 0.93, CH_2Cl_2). Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_3$: C, 72.8; H, 7.40; N, 4.47%. Found: C, 72.6; H, 7.69; N, 4.34%.

Methyl (2*R*,3*S*)-4-Cyclohexyl-2-methoxy-3-[(*S*)- α -methylbenzylamino]butyrate (19**):** ^1H NMR δ 0.61–1.58 (m, 13H), 1.24 (d, 3H, $J = 6.4$ Hz), 3.35 (s, 3H), 3.38–3.81 (m, 3H), 3.74 (s, 3H), 7.11–7.45 (m, 5H); ^{13}C NMR δ 24.5, 26.0, 26.2, 26.4, 32.7, 33.6, 33.7, 39.9, 51.4, 53.8, 55.3, 58.6, 81.4, 126.7, 128.0, 128.3, 145.8, 172.5. $[\alpha]_D^{22} - 36.7^\circ$ (c 1.2, CH_2Cl_2). Anal. Calcd for $\text{C}_{20}\text{H}_{31}\text{NO}_3$: C, 72.0; H, 9.37; N, 4.20%. Found: C, 72.1; H, 9.51; N, 4.42%.

Methyl (2*S*,3*R*)-2-Methoxy-5-methyl-3-[(*R*)- α -methylbenzylamino]hexanoate (20**):** ^1H NMR δ 0.56 (d, 3H, $J = 6.6$ Hz), 0.74 (d, 3H, $J = 6.6$ Hz), 1.12–1.19 (m, 5H), 1.31–1.65 (m, 2H), 2.63 (dt, 1H, $J = 6.4, 1.8$ Hz), 3.15 (s, 3H), 3.34 (s, 3H), 3.41–3.62 (m, 2H), 6.97–7.07 (m, 5H); ^{13}C NMR δ 21.7, 22.5, 24.1, 24.2, 41.2, 50.7, 54.3, 54.8, 58.2, 80.9, 126.5, 127.8, 145.6, 172.2. $[\alpha]_D^{22} + 40.3^\circ$ (c 1.6, CH_2Cl_2). Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_3$: C, 69.5; H, 9.28; N, 4.77%. Found: C, 69.4; H, 9.11; N, 4.49%.

Methyl (2*S*,3*R*)-2-Methoxy-3-[(*R*)- α -methylbenzylamino]decanoate (21**):** ^1H NMR δ 0.80 (t, 3H, $J = 6.8$ Hz), 0.94–1.52 (m, 12H), 1.18 (d, 3H, $J = 6.6$ Hz), 1.53 (s, 1H), 2.74 (dt, 1H, $J = 6.2, 3.0$ Hz), 3.32 (s, 3H), 3.71 (s, 3H), 3.59–3.76 (m, 2H), 7.08–7.23 (m, 5H); ^{13}C NMR δ 14.1, 22.6, 24.6, 26.2, 29.2, 29.4, 31.8, 32.1, 51.6, 55.5, 56.9, 58.9, 81.5, 126.8, 128.2, 146.0, 172.7. $[\alpha]_D^{22} + 14.3^\circ$ (c 0.74, CH_2Cl_2). Anal. Calcd for $\text{C}_{20}\text{H}_{33}\text{NO}_3$: C, 71.6; H, 9.91; N, 4.18%. Found: C, 71.6; H, 9.77; N, 4.09%.

Synthesis of Methyl α -Hydroxy- β -(α -methylbenzyl)amino Carboxylate. BBr_3 (10 mg, 0.40 mmol) was added into the solution of methyl (2*R*,3*S*)-2-methoxy-3-[(*S*)- α -methylbenzylamino]-3-phenylpropionate (**18**) (376 mg, 1.20 mmol) in CH_2Cl_2 (30 mL) at -78°C . The resultant reaction mixture was stirred for 2 h at -78°C before adding H_2O (30 mL). The solution was neutralized with 2M NaOH solution. The reaction product was extracted with EtOAc (50 mL) three times. The extracts were washed by 100 mL each of water and brine, dried by anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 269 mg of methyl (2*R*,3*S*)-2-hydroxy-3-[(*S*)- α -methylbenzylamino]-3-phenylpropionate (**22**) as the major product with 51 mg of lactamized product (3*R*,4*S*)-3-hydroxy-1-[(*S*)- α -methylbenzyl]-4-phenylazetidin-2-one as the minor one.

Methyl (2*R*,3*S*)-2-Hydroxy-3-[(*S*)- α -methylbenzylamino]-3-phenylpropionate (22**):** ^1H NMR δ 1.18 (d, 3H, $J = 6.4$ Hz), 3.54 (q, 1H, $J = 6.4$ Hz), 3.71 (s, 3H), 4.06 (d, 1H, $J = 3.4$ Hz), 4.19 (d, 1H, $J = 3.4$ Hz), 7.10–7.30 (m, 10H); ^{13}C NMR δ 22.5, 52.4, 54.5, 61.4, 74.4, 126.5, 127.3, 127.4, 127.7, 128.5, 128.6, 140.2, 145.7. Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3$: C, 72.2; H, 7.07; N, 4.68%. Found: C, 72.4; H, 6.98; N, 4.74%.

(3*R*,4*S*)-3-methoxy-1-[(*S*)- α -methylbenzyl]-4-phenylazetidin-2-one ^1H NMR δ 1.24 (d, 3H), 2.90 (s, 3H), 4.37 (d, 1H), 4.45 (d, 1H), 5.01 (q, 1H), 7.18–7.39 (m, 10H); ^{13}C NMR δ 19.0, 51.7, 58.0, 60.9, 84.8, 127.4, 127.9, 128.1, 128.5, 128.7, 128.8, 135.2, 139.5, 166.8. $[\alpha]_D^{22} + 68.9^\circ$ (c 0.48, CH_2Cl_2). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$: C, 76.8; H, 6.81; N, 4.98%. Found: C, 76.6; H, 6.73; N, 4.74%.

Methyl (2*R*,3*S*)-4-Cyclohexyl-2-hydroxy-3-[(*S*)- α -methylbenzylamino]butyrate (23**):** ^1H NMR δ 0.61–1.58 (m, 13H), 1.29 (3H, $J = 6.4$ Hz), 2.01 (brs, 2H), 2.98 (t, 1H, $J = 6.8$ Hz), 3.59 (q, 1H, $J = 6.6$ Hz), 3.82 (s, 3H), 4.00 (s, 1H), 7.17–7.43 (m, 5H); ^{13}C NMR δ 24.1, 26.1, 26.3, 26.4, 33.0, 33.4, 34.0, 41.2, 52.2, 54.0, 55.9, 71.4, 126.4, 127.2, 128.4, 145.3, 175.4. $[\alpha]_D^{22} - 56.6^\circ$ (c 0.41, CH_2Cl_2). Anal. Calcd for $\text{C}_{19}\text{H}_{29}\text{NO}_3$: C, 71.4; H, 9.15; N, 4.38%. Found: C, 71.7; H, 9.29; N, 4.18%.

(3*R*,4*S*)-4-Cyclohexylmethyl-3-methoxy-1-[(*S*)- α -methylbenzyl]azetidin-2-one: ^1H NMR δ 0.64–1.58 (m, 13H), 1.57 (d, 3H, $J = 7.4$ Hz), 3.47 (s, 3H), 3.49–3.54 (m, 1H), 4.28 (d, 1H, $J = 4.4$ Hz), 4.76 (q, 1H, $J = 7.0$ Hz), 7.12–7.33 (m, 5H); ^{13}C NMR δ 19.9, 26.1, 26.2, 26.3, 33.1, 33.4, 34.4, 34.8, 36.3, 52.0, 56.4, 59.1, 83.3, 126.9, 127.6, 128.6, 140.2, 167.5. $[\alpha]_D^{22} + 32.7^\circ$ (c 1.2, CH_2Cl_2).

Methyl (2*S*,3*R*)-2-Hydroxy-5-methyl-3-[(*R*)- α -methylbenzylamino]hexanoate (24**):** ^1H NMR δ 0.64 (d, 3H, $J = 6.8$ Hz), 0.78 (d, 6H, $J = 6.8$ Hz), 1.25 (d, 3H, $J = 6.8$ Hz), 1.06–1.72 (m, 3H), 2.90 (dt, 1H, $J = 7.2, 2.0$ Hz), 3.63 (q, 1H, $J = 6.8$ Hz), 3.79 (s, 3H), 3.98 (d, 1H, $J = 1.8$ Hz), 7.12–7.60 (m, 5H). Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_3$: C, 68.7; H, 9.02; N, 5.01%. Found: C, 68.9; H, 9.25; N, 5.24%.

(3*S*,4*R*)-4-Isobutyl-3-methoxy-1-[(*R*)- α -methylbenzyl]azetidin-2-one: ^1H NMR δ 0.72 (d, 6H, $J = 6.4$ Hz), 0.78 (d, 3H, $J = 6.4$ Hz), 1.19–1.62 (m, 7H), 3.52 (s, 3H), 4.31 (dt, 1H, $J = 8.2, 2.1$ Hz), 4.81 (q, 1H, $J = 8.0$ Hz), 7.25–7.33 (m, 5H); ^{13}C NMR δ 19.7, 22.2, 22.9, 25.3, 37.6, 52.0, 56.8, 59.0, 83.3, 127.1, 127.7, 128.7, 140.1, 167.7. $[\alpha]_D^{22} - 24.4^\circ$ (c 0.56, CH_2Cl_2).

Methyl (2*S*,3*R*)-2-Hydroxy-3-[(*R*)- α -methylbenzylamino]decanoate (25**):** ^1H NMR δ 0.82 (t, 3H, $J = 7.4$ Hz), 1.18–1.69 (m, 12H), 3.48 (q, 1H, $J = 6.0$ Hz), 3.71 (s, 3H), 3.94 (d, 1H, $J = 1.9$ Hz), 7.06–7.28 (m, 5H); ^{13}C NMR δ 14.2, 22.6, 26.1, 29.1, 29.3, 31.7, 33.2, 52.1, 55.8, 56.8, 71.1, 126.4, 127.1, 128.4, 145.3, 173.5. $[\alpha]_D^{22} + 24.9^\circ$ (c 1.28, CH_2Cl_2). Anal. Calcd for $\text{C}_{19}\text{H}_{31}\text{NO}_3$: C, 70.9; H, 9.72; N, 4.36%. Found: C, 71.2; H, 9.88; N, 4.52%.

Methyl (2*S*,3*R*)-3-Benzoylamino-2-methoxydecanoate (26**):** In CH_3OH (15 mL) were dissolved Pd–C (60 mg) and compound **21** (291 mg, 0.87 mmol). Into this solution was introduced H_2 gas with a balloon; the mixture was stirred at rt until all starting material was consumed on TLC for 15 h. The mixture was filtered and concentrated under reduced pressure. This crude reaction product was dissolved in a mixture of THF (5 mL) and water (5 mL). Benzoyl chloride (122 mg, 0.87 mmol) was added dropwise to this solution at 0°C maintaining pH 9–10 with NaOH solution. After addition was completed the resultant reaction mixture was stirred vigorously for 30 min. The reaction product was extracted with EtOAc (50 mL) three times. The extracts were washed by 100 mL each of water and brine, dried by anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 238 mg of the titled compound in 82% yield. ^1H NMR δ 0.81 (t, 3H, $J = 7.0$ Hz), 1.18–1.69 (m, 12H), 3.41 (s, 3H), 3.67 (s, 3H), 3.85 (s, 1H), 4.48 (q, 1H, $J = 7.4$ Hz), 6.31 (d, 1H, $J = 8.8$ Hz), 7.21–7.71 (m, 5H); ^{13}C NMR δ 14.1, 22.6, 26.1, 29.1, 29.3, 31.7, 32.1, 51.8, 53.0,

71.8, 126.9, 128.5, 131.5, 134.4, 167.2, 174.2. $[\alpha]_D^{22} + 1.86^\circ$ (c 1.28, CH_2Cl_2). Anal. Calcd for $\text{C}_{19}\text{H}_{29}\text{NO}_4$: C, 68.0; H, 8.71; N, 4.18%. Found: C, 68.0; H, 8.72; N, 4.02%.

Methyl (2S,3R)-3-Benzoylamino-2-hydroxydecanoate (27): BBr_3 (32.5 mg, 0.13 mmol) was added into the solution of methyl (2S,3R)-3-benzoylamino-2-methoxydecanoate (**26**) (134 mg, 0.40 mmol) in CH_2Cl_2 (30 mL) at -78°C . After 10 min the cooling bath was removed and the resultant reaction mixture was stirred for 2 h before adding H_2O (30 mL). The solution was neutralized with Na_2CO_3 solution. The reaction product was extracted with CH_2Cl_2 (30 mL) three times. The extracts were washed by 50 mL each of water and brine, dried by anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 114 mg of the titled compound as a white solid in 89% yield. Mp $64\text{--}65^\circ\text{C}$; ^1H NMR δ 0.80 (t, 3H, $J = 7.0$ Hz), 1.19–1.68 (m, 12H), 3.71 (s, 3H), 4.23 (s, 1H), 4.51 (q, 1H, $J = 7.6$ Hz), 6.28 (d, 1H, $J = 9.2$ Hz), 7.29–7.66 (m, 5H); ^{13}C NMR δ 14.1, 22.6, 26.1, 29.1, 29.3, 31.7, 32.1, 51.8, 53.0, 71.8, 126.9, 128.5, 131.5, 134.4, 167.2, 174.2. $[\alpha]_D^{22} + 23.8^\circ$ (c 2.2, CH_2Cl_2). Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_4$: C, 67.3; H, 8.47; N, 4.36%. Found: C, 67.1; H, 8.68; N, 4.43%.

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