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$TiCl_4$ promoted menthyl ester chiral auxiliary mediated synthesis of chiral *syn*-β-amino esters and applications of a representative *syn*-β-amino ester

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ABSTRACT

β-Amino esters were obtained in up to 78% yield with 72:28–96:4 diastereomeric ratios by the reaction of the chiral titanium enolate of menthyl esters, prepared using the $TiCl_4/Et_3N$ reagent system with prochiral imines. A representative *syn*-β-amino ester derivative has been used for the resolution of racemic mandelic acid to obtain a sample with >99% ee in a single step. A representative *syn*-β-amino ester was converted to the corresponding N-deprotected amino ester using the Pd–C/HCOOH reagent system, and then to the corresponding β-amino acid using the glacial CH_3COOH/HCl reagent system, and to the corresponding β-lactam derivative with partial epimerization by the reaction using C_2H_5MgBr.

1. Introduction

β-Amino acids and esters are useful building blocks for the synthesis of β-lactams, which are important structural elements in many therapeutic drug molecules.[1] β-Amino acid moieties are present in several natural products and bioactive molecules.[2] Amongst the several methods available for the synthesis of β-amino acid derivatives,[3] asymmetric Mannich-type reactions have attracted considerable interest.[4] The use of titanium enolates in Mannich-type reaction gave high levels of selectivity.[5] Herein, we report the diastereoselective synthesis of *syn*-β-amino esters by an asymmetric Mannich-type reaction using a $TiCl_4/Et_3N$ reagent system.

2. Results and discussion

The diastereoselective Mannich-type reaction of chiral imine **2** and ester **1** with $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino ester **3** in good yield with good diastereoselectivity (Scheme 1).[6]

However, it is difficult to remove and reuse the α-methylbenzylamine group present in the *syn*-β-amino ester product **3**. Accordingly, we have undertaken efforts to utilize chiral ester moieties, which can be easily removed and reused. The readily available, naturally occurring L-(−)-menthol **4** was chosen as a chiral auxiliary to prepare the chiral menthyl esters **5** and **6**. Menthol and its derivatives have proven applications as chiral handles in various asymmetric transformations.[7] The L-(−)-menthyl esters **5** and **6** were easily accessed by the reaction of L-(−)-menthol with the corresponding acid chloride and triethylamine in dichloromethane solvent under ambient conditions (Fig. 1).

Initially, the reaction between L-(−)-menthyl ester and *N*-benzylidenebenzylamine **7a** was screened with $TiCl_4$ in combination with different tertiary amines (Table 1, entries 1–4). The $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino esters in relatively good yield and with high selectivity (Scheme 2, Table 1, entries 4 and 7). The lowering of temperature below −45 °C did not increase the yield of selectivity of the amino ester product formed (Table 1, entry 6). The results are summarized in Table 1.

The major product **8a** was isolated from the diastereomeric mixture **8** by column chromatography. It readily forms a complex with (*R*)-(−)-mandelic acid **10a** in a CH_2Cl_2–acetone mixture at 25 °C (Scheme 3). Crystals suitable for X-ray single crystal structure analysis were obtained by crystallizing complex **11** from a toluene–isopropanol mixture.

The X-ray analysis of complex **11** revealed that the product has an (*R*,*R*) absolute configuration at the newly formed stereogenic centers. The crystal structure of the complex **11** is given in Figure 2.[8]

The reaction of L-(−)-menthyl butyrate **5** and imines **7b–g** with $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino esters **12–16** and **18** in moderate to good yield and with good selectivity (Scheme 4, Table 2, entries 1–5, 7). The *syn*-β-amino ester **17** was obtained by the reaction of D-(+)-menthyl butyrate and imine **7a** with the aforementioned reagent system (Table 2, entry 6). The diastereomeric ratios of the β-amino esters **12–18** were estimated from the ^1H NMR signals. The results are summarized in Table 2.

The imines derived from aliphatic amines gave better yield and selectivity compared to the aniline-derived imines (Table 2, entry 7). The stereochemistry of the major products **12–16** and **18** was assigned as *syn* by making a comparison of the ^1H NMR data of

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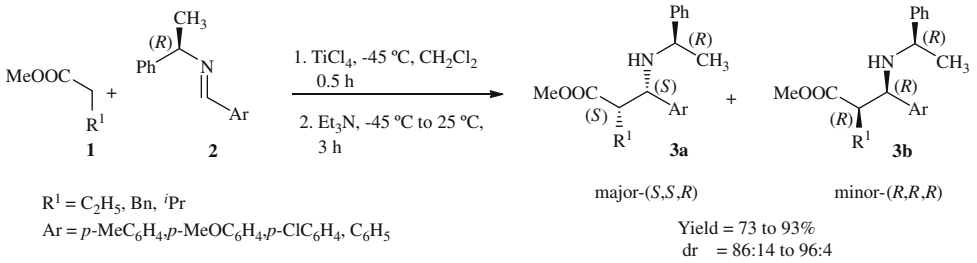


Scheme 1.

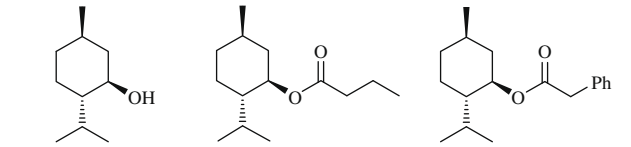


Figure 1.

Table 1
Reaction of menthyl ester and imine **7a** with $TiCl_4/R_3N$ reagent system[a]

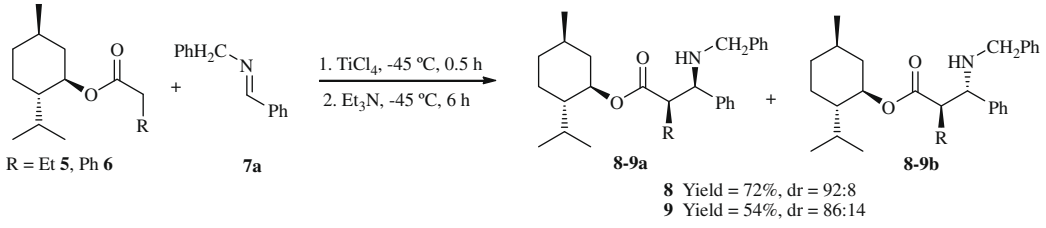
Entry	R_3N	$TiCl_4$ (equiv)	Temp (°C)	Yield[b] (%)
1	$^{i}Pr_2NEt$	2	−45	0
2	$^{i}Pr_2NCH_2Ph$	2	−45	<10
3	$^{n}Bu_3N$	2	−45	44
4[c]	Et_3N	2	−45	72
5	Et_3N	1	−45	36
6[d]	Et_3N	2	−65	70[e]
7[f]	Et_3N	2	−45	54

[a] Unless otherwise mentioned, all reactions were carried out using 2.2 mmol of menthyl ester **5** and 2 mmol of benzylidenebenzylamine **7a** in 20 mL of CH_2Cl_2. R_3N (2.1 mmol) was added after 0.5 h from the addition of $TiCl_4$ (4.5 mmol) at −45 °C and the reaction mixture was stirred for a further 6 h at −45 °C.
[b] Yields are for the isolated products.
[c] With $Ti(O^{i}Pr)_4$ and $TiCl_2(O^{i}Pr)_2$, the formation of product **8** was not observed.
[d] The reaction was carried out for 12 h.
[e] The diastereomeric ratios of entry 4 are similar to those of entry 6.
[f] The reaction was carried out with menthyl ester **6**.

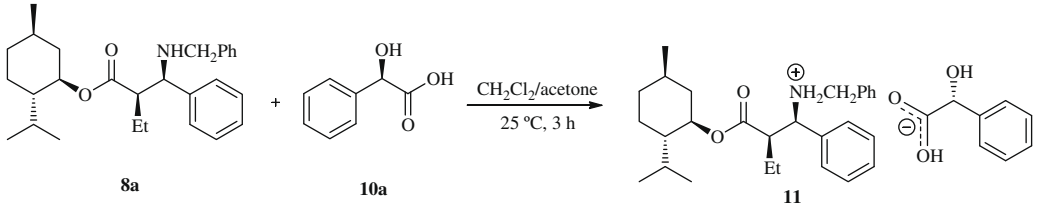
these products with the data for compound **8**. The ^1H NMR spectrum of the product mixture **15** is shown in Figure 3. The coupling constants of the –CH proton adjacent to the amine group of the minor *anti* product mixture is smaller (J = 2.8 and 2.4 Hz) compared to those of the major *syn*-product (J = 8.4 Hz) (Fig. 3).

Similar observations have been previously reported in some menthyl-derived *anti*- and *syn*-β-amino esters.[9a] From the diastereomeric mixture **15**, the major *syn*-β-amino ester product **15a** was isolated in pure form. The minor *anti* product mixture **15b** was also separated and the ^1H spectroscopic analysis revealed that it was a 1:1 mixture of *anti* diastereomers.

The origin of the asymmetric induction in the asymmetric Mannich-type reaction and the formation of the major product can be rationalized as outlined in Figure 4. It is reported in the literature that the presence of a chelating atom or a group in the substrate favors the preferential formation of the *Z*-titanium ester enolate over an *E*-enolate.[9b,c] In other cases, the equilibrium is favored to the *E*-enolate (alkyl group and O–Ti are *trans* to each other).[6,10] Based on the stereochemistry of the major product formed and the absence of chelating atom or group in the menthyl ester moiety, the preferred geometry of the titanium menthyl ester enolate participating in the reaction was assigned as *E*. The *Re* face attack of the *E*-titanium menthyl ester enolate onto the imine in **TS-1** is more favorable because the bulky isopropyl group is positioned far away from the C–C bond-forming side. Hence, the low-energy transition state **TS-1** would give the major product with an (*R*,*R*)-absolute configuration. The *Re* and *Si* face attack of the *Z*-titanium menthyl ester enolate onto the imine (**TS-II** and **TS-III**) is less favorable because of the enhancement in the steric interaction between ethyl and benzyl groups. Hence, these high-energy transi-



Scheme 2.



Scheme 3.

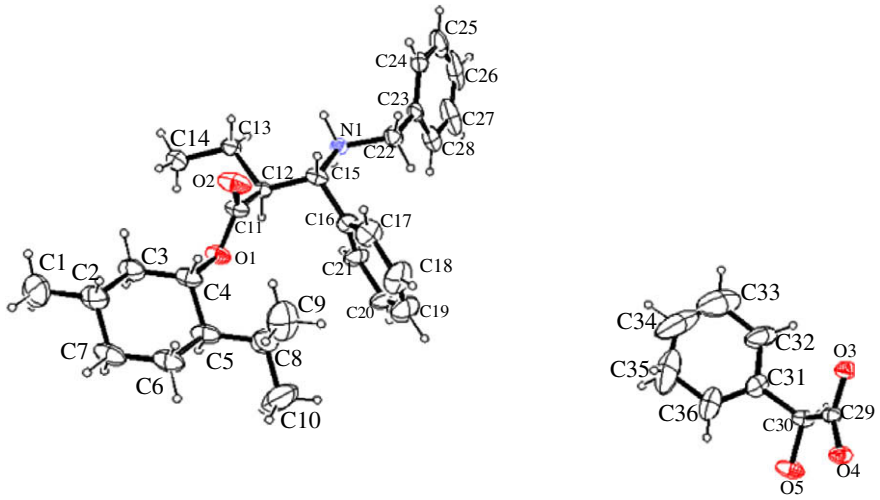
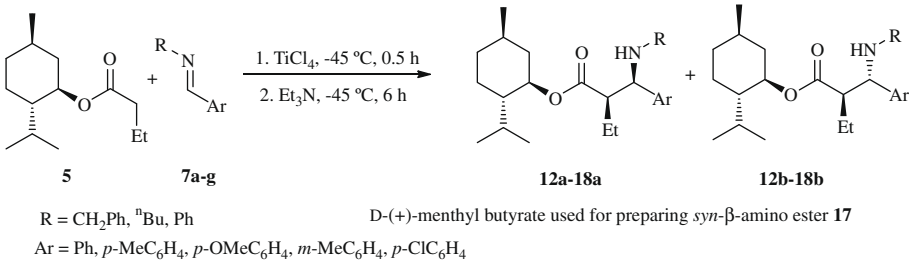


Figure 2. ORTEP representation of the crystal structure of complex **11** (thermal ellipsoids are drawn at 20% probability).



Scheme 4.

Table 2
Mannich-type reaction of menthyl ester **5** and imines with $TiCl_4/Et_3N$[a]

Entry	R (amine)	Ar (aldehyde)	Product	Yield[b] (%)	*syn*:*anti*[c]
1	$-CH_2Ph$ **7b**	*p*-MeC_6H_4	**12**	69	82:18
2	$-CH_2Ph$ **7c**	*p*-$OMeC_6H_4$	**13**	64	83:17
3	$-CH_2Ph$ **7d**	*m*-MeC_6H_4	**14**	71	96:4
4	$-^nBu$ **7e**	–Ph	**15**[d]	78	80:20
5	$-CH_2Ph$ **7f**	*p*-ClC_6H_4	**16**	54	79:21
6[e]	$-CH_2Ph$ **7a**	–Ph	**17**[f]	76	93:7
7[g]	–Ph **7g**	–Ph	**18**	45	72:28

[a] Unless otherwise mentioned, all reactions were carried out using 5.5 mmol of menthyl ester **5** and 5 mmol of imine in 40 mL of CH_2Cl_2. Et_3N (5 mmol) was added after 0.5 h via the addition of $TiCl_4$ (12 mmol) at −45 °C and the reaction mixture was stirred for 6 h at −45 °C.

[b] The structure of the products were confirmed by spectral data (IR, ^1H NMR, ^{13}C NMR, and mass spectrometry). Yields are for the isolated *syn:anti* mixture of products. The major products **12a**–**18a** are isolated in pure form from the mixture by crystallization from hexane. The yield, physical constant, and spectroscopic data for products **12a**–**18a** are given in Section 5.

[c] The diastereomeric ratios (*syn:anti*) were estimated from ^1H NMR (400 MHz) data.

[d] The *anti* product mixture was isolated from the *syn:anti* product mixture. The ^1H and ^{13}C NMR analyses revealed that the *anti* product is a 1:1 mixture of two *anti* diastereomers.

[e] The reaction was carried out with D-(+)-menthyl butyrate.

[f] The absolute configuration of the major isomer of the product **17** was assigned as (*S*,*S*) from the crystal structure of its complex with (*S*)-(+)-mandelic acid.

[g] After the addition of Et_3N, the reaction mixture was warmed to 0 °C for 2 h and then stirred at the same temperature for a further 12 h.

tion states **TS-II** and **TS-III** would give the minor *anti* products with (*S*,*R*)- and (*R*,*S*)-absolute configuration.

The *syn*-β-amino ester **17** obtained by the reaction of D-(+)-menthyl butyrate with benzylidenebenzylamine **7a** has a specific rotation equal in magnitude but opposite in direction to that of the compound **8**. We have observed that the major product **17a** does not form a precipitate with (*R*)-(−)-mandelic acid **10a** even after stirring for three days in CH_2Cl_2–acetone mixture at 25 °C. Under similar conditions, the major product **17a** readily forms a precipitate with (*S*)-(+)-mandelic acid **10b.** This difference in solubility of the diastereomeric complexes prompted us to examine the resolution of racemic mandelic acid **10** using the *syn*-β-amino ester **8a**. The *syn*-β-amino ester **8a** resolved the racemic mandelic acid **10** to >99% ee in a single step (Scheme 5**).** The complex **11** of the *syn*-β-amino ester **8a** and (*R*)-(−)-mandelic acid **10a** precipitated out leaving the (*S*)-(+)-mandelic acid in the filtrate fraction.

At room temperature, the *syn*-β-amino ester **8a** is partially soluble in acetone and completely soluble in CH_2Cl_2. Presumably, this may be the reason for the efficient resolution of racemic mandelic acid **10** by the *syn*-β-amino ester **8a** in the acetone–CH_2Cl_2 solvent system.

The *syn*-β-amino ester **8a** is easily recovered from the reaction mixture and can be reused without any loss in chirality. The crystalline nature and its high resistance to air and moisture would make the *syn*-β-amino ester **8a** an efficient reagent for the resolution of racemic carboxylic acids and hence it is a good addition to the pool of chiral resolving agents available for the resolution of racemic carboxylic acids.[11]

3. Synthesis of *N*-,*O*-deprotected derivatives and β-lactam product of *syn*-β-amino ester 8a

We have observed that N-debenzylation of the *syn*-β-amino ester **8a** can be readily carried out by reaction of the dispersion of Pd/C in formic acid and methanol (1:4 v/v) at 50 °C (Scheme 6). The

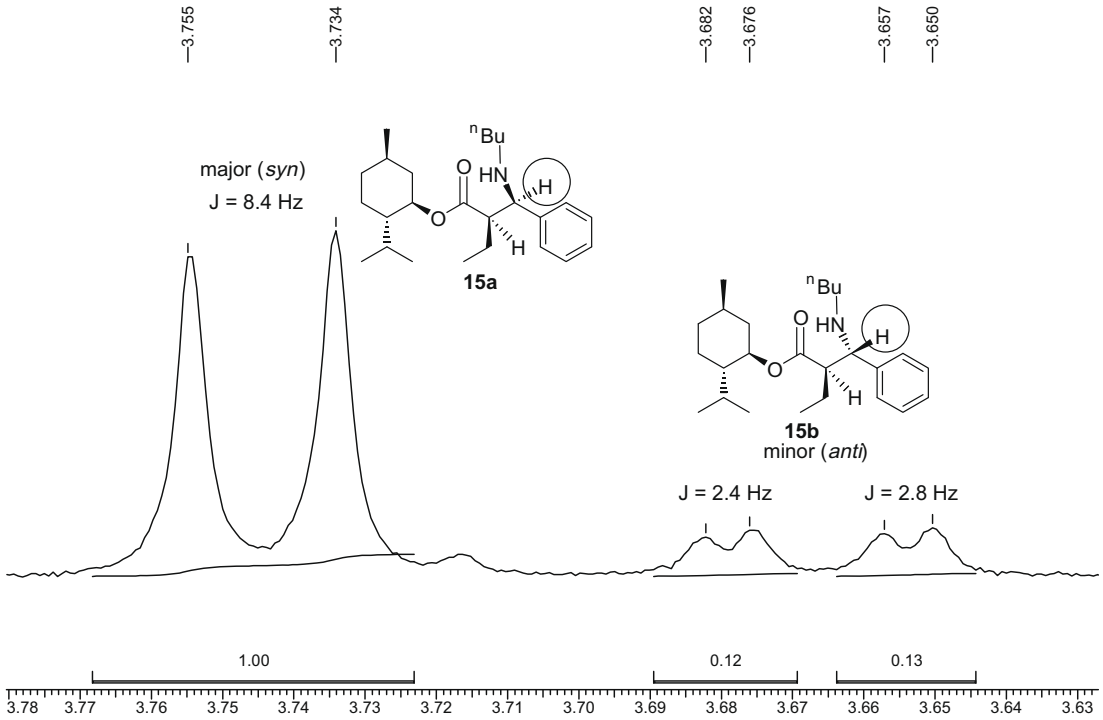


Figure 3. ^{1}H NMR spectrum of the product mixture **15**.

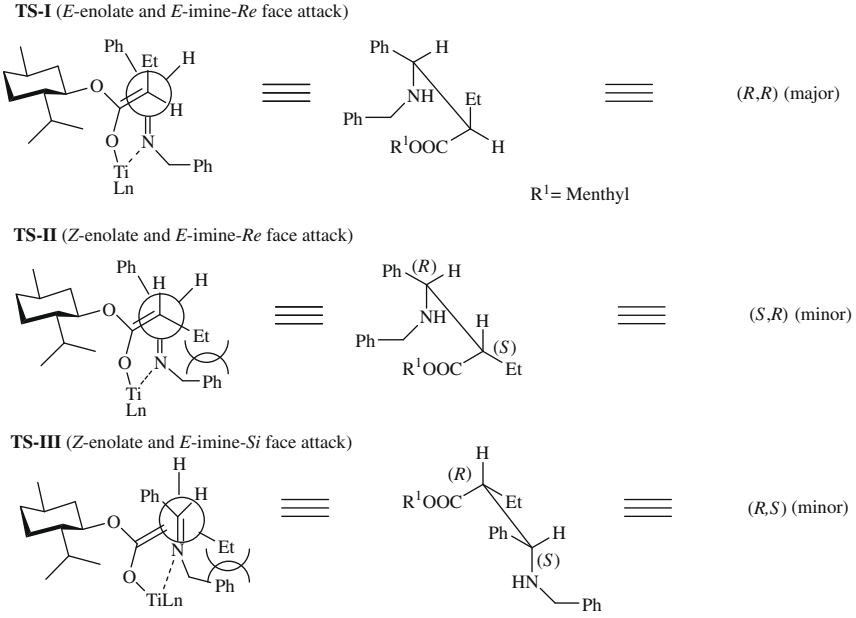
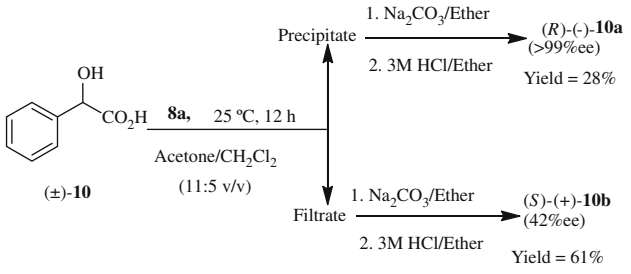


Figure 4. Stereochemical models.

debenzylated product **19** was obtained in 86% yield. We have found that the *syn*-β-amino acid **20** can be prepared by refluxing the *syn*-β-amino ester **8a** with a mixture of glacial acetic acid and conc. HCl albeit in a moderate 44% yield (Scheme 6). We have also examined the conversion of the representative *syn*-β-amino ester **8a** to the corresponding β-lactam using the C_2H_5MgBr reagent. In this reaction, the β-lactam product **21** was obtained in 56% yield with some partial epimerization even at 0 °C (Scheme 6) while the β-lactam was not formed in the reaction at −30 °C.

4. Conclusion

In conclusion, the chiral β-amino esters **8**, **9**, **12**–**18** were obtained in moderate to good yields with good selectivity by the asymmetric Mannich-type reaction of menthyl ester and imines using the $TiCl_4/Et_3N$ reagent system. The readily accessible *syn*-β-amino acid ester **8a** is useful for the resolution of racemic mandelic acid **10** in >99% ee in a single step and it is a promising resolving agent for the resolution of racemic carboxylic acids. The N-debenzylation of the *syn*-β-amino acid ester **8a** was carried out using a



Scheme 5.

Pd–C/HCOOH reagent system. The *syn*-β-amino acid **20** was synthesized by the hydrolysis of *syn*-β-amino ester **8a** with a glacial CH_3COOH/HCl reagent system. The β-lactam product **21** was obtained by the reaction of a C_2H_5MgBr reagent with *syn*-β-amino ester **8a**. Accordingly, the method described here for the synthesis and the application of the *syn*-β-amino esters has considerable potential for further exploitation.

5. Experimental section

5.1. Materials and methods

The melting points reported in this Letter are uncorrected and were determined using a Superfit capillary point apparatus. IR spectra were recorded on a JASCO FT-IR spectrophotometer Model 5300. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 Spectrometer with chloroform-*d* as a solvent and TMS as reference. Optical rotations were measured in an AUTOPOL-IV digital polarimeter (readability ±0.001°). Liquid chromatography (LC) and mass analysis (LC–MS) were performed on SHIMADZU-LCMS-2010A. Elemental analyses were carried out using a Perkin–Elmer elemental analyzer model-240C and a Thermo Finnigan analyzer series Flash EA 1112. HPLC analyses were performed on an SCL-10ATVP SHIMADZU instrument. The ee values were determined using CHIRALCEL OD-H column (4.6 × 250 mm) with eluents: hexane, 2-propanol, trifluoroacetic acid at a rate 0.5 mL/min, with the monitoring wave length 254 nm.

5.2. General procedure for the synthesis of L-(−)-menthyl ester 5 and 6

To a stirred solution of (L)-(−)-menthol (1.56 g, 10 mmol) in CH_2Cl_2 (30 mL), acid chloride was added (11 mmol) at 0 °C under N_2 atmosphere, followed by the slow addition of triethylamine (1.31 g, 1.81 mL, 13 mmol) in CH_2Cl_2 (10 mL) using a dropping funnel over a period of 10 min. The reaction mixture was slowly warmed to 25 °C and stirred at the same temperature for further 6 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed successively with 5% $NaHCO_3$ (20 mL), water (20 mL), and brine solution (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column (230–400 mesh) to isolate pure (L)-(−)-menthyl esters using hexane/EtOAc (99:1) as an eluent.

5.2.1. L-(−)-Menthyl butyrate 5

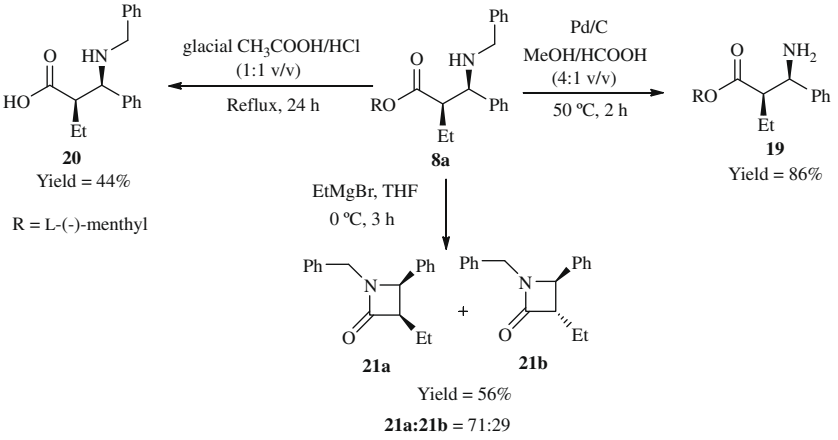
Yield: 2.01 g (89%); IR (neat): 2961, 2872, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.76 (d, J = 6.8 Hz, 3H), 0.88–1.08 (m, 12H), 1.34–1.50 (m, 2H), 1.62–1.68 (m, 4H), 1.85–2.10 (m, 2H), 2.26 (t, J = 7.3 Hz, 2H), 4.68 (dt, J = 10.8 Hz, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 13.7, 16.3, 18.7, 20.8, 22.1, 23.5, 26.3, 31.4, 34.4, 36.7, 41.0, 47.1, 73.9, 173.3; $[\alpha]_D^{25} = -74.7$ (*c* 1.1, C_2H_5OH). {Lit.[12] $[\alpha]_D^{25} = -75.8$ (*c* 1, C_2H_5OH)}.

5.2.2. L-(−)-Menthylphenyl acetate 6

Yield: 2.25 g (82%); IR (neat): 3065, 3032, 2955, 1730, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.70 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 7.1 Hz, 3H), 0.90–0.93 (m, 4H), 0.96–1.10 (m, 2H), 1.33–1.50 (m, 2H), 1.64–1.79 (m, 3H), 1.98–2.0 (m, 1H), 3.61 (s, 2H), 4.69 (dt, J = 10.9 Hz, J = 4.4 Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 16.3, 20.7, 22.0, 23.5, 26.2, 31.4, 34.3, 40.8, 41.9, 47.1, 74.7, 126.9, 128.5, 129.2, 134.4, 171.2; $[\alpha]_D^{25} = -71.8$ (*c* 0.62, $CHCl_3$).

5.3. General procedure for the synthesis of chiral *syn*-β-amino esters derived from menthyl ester and imines

To a stirred solution of menthyl ester (5.5 mmol) and imine (5 mmol) in CH_2Cl_2 (40 mL) at −45 °C, a solution of $TiCl_4$ (12 mmol, 2.28 g, 1.3 mL) in 15 mL of CH_2Cl_2 was slowly added through an addition funnel over a period of 10 min under an N_2 atmosphere. After stirring for 0.5 h, triethylamine (0.70 mL, 5 mmol) was added and the reaction mixture was stirred at −45 °C for a further 6 h. The reaction was quenched with saturated aq K_2CO_3 (15 mL) solution, brought to room temperature, and filtered through a Buckner funnel. The organic layer was separated and the aqueous layer was counter extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The



Scheme 6.

residue was purified by flash column chromatography on silica gel (230–400 mesh) column using hexane/EtOAc (98:2) as an eluent.

5.3.1. Product mixture 8

Yield: 1.51 g (72%); dr = 92:8; The *syn*:*anti* diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of –CH proton adjacent to the menthyl oxygen moiety [For *syn* (δ 4.49 ppm, dt, J = 11 Hz, J = 4.4 Hz, 1H) and for *anti* products (δ 4.73–4.80 ppm, m, 0.09H)]. The *syn*:*anti* mixture was crystallized from hexane to obtain compound **8a** in pure form.

5.3.1.1. Compound 8a. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-(2*R*)-2-[(*R*)-1-benzylamino-1-phenylmethyl]butanoate: Yield 1.30 g (62%); mp 124–126 °C; IR (KBr): 3321, 3061, 2962, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.44 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H), 0.76–0.92 (m, 9H), 1.18–1.27 (m, 2H), 1.32–1.42 (m, 1H), 1.54–1.80 (m, 5H), 1.90–2.0 (m, 1H), 2.56–2.62 (m, 1H), 3.44 (d, J = 13.2 Hz, 1H), 3.59 (d, J = 13.2 Hz, 1H), 3.80 (d, J = 8.3 Hz, 1H), 4.49 (dt, J = 11.0 Hz, J = 4.4 Hz, 1H), 7.21–7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 15.9, 20.9, 22.1, 22.7, 23.0, 25.4, 31.4, 34.3, 41.0, 46.8, 51.5, 55.1, 63.7, 74.0, 126.9, 127.3, 128.0, 128.2, 128.4, 140.6, 141.9, 174.0; LC–MS: *m*/*z* 422 (M+1). Anal. Calcd: C, 79.76; H, 9.32; N, 3.32. Found: C, 79.45; H, 9.32; N, 3.49; $[\alpha]_D^{25} = -11.2$ (c 1, $CHCl_3$).

5.3.2. Product mixture 9

Yield: 1.26 g (54%); dr = 86:14; the diastereomeric ratio of the product mixture was calculated on the basis of the ^{1}H NMR analysis of the –CH proton adjacent to the –NH moiety [for minor product (δ 4.16 ppm, d, J = 10.8 Hz, 0.17H) and for major product (δ 4.23 ppm, d, J = 10.5 Hz, 1H)]. The diastereomeric mixture was crystallized from hexane to obtain compound **9a** in pure form.

5.3.2.1. Compound 9a. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-(2*R*,3*R*)-3-benzylamino-2,3-diphenyl propanoate: Yield: 1.0 g (43%); mp 136–138 °C; IR (KBr): 3323, 3061, 3028, 2953, 1711 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$, δ ppm): 0.29 (d, J = 6.8 Hz, 3H), 0.60 (d, J = 6.8 Hz, 3H), 0.74–0.77 (m, 4H), 0.83–0.90 (m, 3H), 1.06–1.13 (m, 1H), 1.23–1.27 (m, 1H), 1.47–1.56 (m, 3H), 1.81 (br s, 1H), 3.28 (d, J = 13.9 Hz, 1H), 3.52 (d, J = 13.7 Hz, 1H), 3.82 (d, J = 10.5 Hz, 1H), 4.23 (d, J = 10.5 Hz, 1H), 4.32–4.39 (m, 1H), 6.96 (d, J = 6.4 Hz, 2H), 7.19–7.22 (m, 3H), 7.26–7.35 (m, 6H), 7.45 (d, J = 6.8 Hz, 2H), 7.48 (d, J = 7.3 Hz, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$, δ ppm): 15.9, 20.8, 21.9, 23.0, 25.2, 31.3, 34.2, 40.3, 46.7, 50.8, 60.2, 63.6, 74.0, 126.8, 127.7, 127.9, 128.0, 128.2, 128.3, 128.6, 128.7, 128.8, 136.3, 140.1, 141.1, 171.3; LC–MS: *m*/*z* 470 (M+1); $[\alpha]_D^{25} = -12.8$ (c 0.25, $CHCl_3$).

5.3.3. Product mixture 12

Yield: 1.5 g (69%); dr = 82:18; The *syn:anti* diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of the –CH proton adjacent to the menthyl oxygen moiety [for *syn* (δ 4.48 ppm, dt, J = 11 Hz, J = 4.4 Hz, 1H) and for *anti* products (δ 4.68 ppm, dt, J = 11 Hz, J = 4.3 Hz, 0.22H)]. The *syn:anti* mixture was crystallized from hexane to obtain compound **12a** in pure form.

5.3.3.1. Compound 12a. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl(2*R*)-2-[(*R*)-1-benzylamino-1-(4-methyl phenyl)methyl]butanoate: Yield: 1.15 g (53%); mp 126–128 °C; IR(KBr): 3348, 2947, 2922, 2866, 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.43 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H), 0.75–0.91 (m, 9H), 1.17–1.19 (m, 2H), 1.33–1.38 (m, 1H), 1.54–1.78 (m, 5H), 1.93–2.0 (m, 1H), 2.33 (s, 3H), 2.54–2.59 (m, 1H), 3.43 (d, J = 13.1 Hz, 1H), 3.59 (d, J = 13.1 Hz, 1H,), 3.75 (d, J = 8.8 Hz, 1H), 4.48 (dt, J = 10.8, J = 4.4, 1H), 7.10–7.28 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 15.8, 20.9, 21.2, 22.0, 22.8, 23.0, 25.4, 31.3, 34.2, 41.0, 46.8, 51.4, 55.2, 63.4, 73.9, 126.8, 127.9, 128.2, 128.3, 129.0, 136.7, 138.9, 140.6, 174.0; LC–MS *m*/*z* 436 (M+1). Anal. Calcd: C, 79.95; H, 9.49; N, 3.22. Found: C 80.07; H, 9.47; N, 3.28; $[\alpha]_D^{25} = -8.0$ (c 1, $CHCl_3$).

5.3.4. Product mixture 13

Yield: 1.44 g (64 %); dr = 83:17; The *syn:anti* diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of –CH proton adjacent to menthyl oxygen moiety [For *syn* (δ 4.48 ppm, dt, J = 11 Hz, J = 4.4 Hz, 1H) and for *anti* products (δ 4.68 ppm, dt, J = 11 Hz, J = 4.3 Hz, 0.21 H)]. The *syn:anti* mixture was crystallized from hexane to obtain compound **13a** in pure form.

5.3.4.1. Compound 13a. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl(2*R*)-2-[(*R*)-1-benzylamino-1-(4-methoxyphenyl)methyl]butanoate: Yield: 1.15 g (51%); mp 150–152 °C; IR (KBr): 3346, 3026, 2951, 2860, 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.44 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H), 0.77–0.91 (m, 9H), 1.17–1.23 (m, 2H), 1.36–1.41 (m, 1H), 1.54–1.79 (m, 5H), 1.92–1.98 (m, 1H), 2.52–2.58 (m, 1H), 3.43 (d, J = 13.4 Hz, 1H), 3.59 (d, J = 13.9 Hz, 1H), 3.74 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 4.48 (dt, J = 11.0 Hz, J = 4.4 Hz, 1H), 6.84 (d, J = 8.3 Hz, 2H), 7.20–7.29 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 15.8, 20.8, 22.0, 22.9, 25.4, 31.3, 34.2, 41.0, 46.8, 51.3, 55.1, 55.3, 63.0, 73.9, 113.6, 126.8, 128.2, 128.3, 129.0, 133.9, 140.6, 158.8, 174.0; LC–MS: *m*/*z* 452 (M+1). Anal. Calcd: C, 77.12; H, 9.15; N, 3.10. Found: C, 77.16; H, 9.17; N, 3.29; $[\alpha]_D^{25} = -5.8$ (c 1, $CHCl_3$).

5.3.5. Product mixture 14

Yield: 1.55 g (71%); dr = 96:4; The *syn:anti* diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of a methyl proton [For *syn* (δ 0.72 ppm, d, J = 6.8 Hz, 3H) and for *anti* products (δ 0.65 ppm, d, J = 6.8 Hz, 0.13 H)]. The *syn:anti* mixture was crystallized from hexane to obtain compound **14a** in pure form.

5.3.5.1. Compound 14a. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl(2*R*)-2-[(*R*)-1-benzyl amino-1-(3-methylphenyl)methyl]butanoate: Yield: 1.45 g (67%); mp 112–114 °C; IR (KBr): 3319, 3024, 2957, 2868, 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.43 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H), 0.76–0.92 (m, 9H), 1.18–1.24 (m, 2H), 1.34–1.41 (m, 1H), 1.55–1.78 (m, 5H), 1.95–2.10 (m, 1H), 2.34 (s, 3H), 2.55–2.60 (m, 1H), 3.44 (d, J = 13.2 Hz, 1H), 3.59 (d, J = 13.2 Hz, 1H), 3.74(d, J = 8.6 Hz, 1H), 4.48 (dt, J = 10.3 Hz, J = 3.9 Hz, 1H), 7.04–7.10 (m, 3H), 7.17–7.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 15.8, 20.9, 21.5, 22.1, 22.8, 23.0, 25.4, 31.3, 34.2, 41.0, 46.8, 51.4, 55.1, 63.7, 73.9, 125.1, 126.9, 128.1, 128.2, 128.3, 128.6, 137.7, 140.5, 141.8, 173.9; LC–MS: *m*/*z* 436 (M+1). Anal. Calcd: C, 79.95; H, 9.49; N, 3.22. Found: C, 79.99; H, 9.46; N, 3.42; $[\alpha]_D^{25} = -7.4$ (c 1, $CHCl_3$).

5.3.6. Product mixture 15

Yield: 1.50 g (78%); dr = 80:20; The *syn:anti* diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of a –CH proton adjacent to the –NH moiety (cf. Fig. 3) [for *syn* (δ 3.74 ppm, d, J = 8.4 Hz, 1H) and for *anti* products (δ 3.65 ppm, d, J = 2.8 Hz, 0.13H and δ 3.68 ppm, d, J = 2.4 Hz, 0.12H)]. The *syn:anti* mixture was separated by flash column chromatography on silica gel (230–400 mesh) column using hexane/EtOAc (98:2) as an eluent.

5.3.6.1. Compound 15a. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*R*)-2-[(*R*)-1-butylamino-1-phenylmethyl]butanoate: Yield: 1.22 g (63%); mp 78–80 °C. IR (KBr): 3323, 2959, 2868, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.48 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H), 0.78–0.92 (m, 12H), 1.21–1.41 (m, 8H), 1.55–1.87 (m, 5H), 2.33–2.39 (m, 2H), 2.54 (br s, 1H), 3.74 (d, J = 8.4 Hz, 1H), 4.51 (dt, J = 11.0 Hz, J = 4.2 Hz, 1H), 7.20–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 14.0, 15.8, 20.4, 20.9, 22.0, 22.4, 23.0, 25.4, 31.3, 32.3, 34.2, 40.9, 46.8, 47.3, 55.0, 64.4, 73.9,

127.1, 127.8, 128.1, 142.3, 174.0; LC–MS: *m*/*z* 389 (M+1). Anal. Calcd: C, 77.47; H, 10.66; N, 3.61. Found: C, 77.47; H, 10.63; N, 3.52; $[\alpha]_D^{25} = -27.3$ (*c* 1, $CHCl_3$).

5.3.6.2. Compound 15b. (1*R*,2*S*,5R)-2-Isopropyl-5-methylcyclohexyl (2*R*)-2-[(*S*)-1-butylamino-1-phenylmethyl]butanoate (1:1 mixture of anti diastereomers): Yield: 0.28 g (14%), Gummy liquid. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.76–0.83 (m, 18H), 0.90–0.93 (m, 14H), 1.03–1.53 (m, 22H), 1.68–1.71 (m, 4H), 1.96–2.11 (m, 4H), 2.26–2.31 (m, 4H), 2.43–2.49 (m, 2H), 3.65 (d, *J* = 2.8 Hz, 1H), 3.68 (d, *J* = 2.4 Hz, 1H), 4.74–4.83 (m, 2H), 7.23–7.26 (m, 6H), 7.31–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.7, 13.9, 15.9, 16.0, 20.3, 20.4, 20.8, 20.9, 22.0, 22.1, 23.0, 23.1, 23.5, 25.7, 25.8, 31.3, 31.4, 32.2, 32.3, 34.3, 40.9, 41.0, 46.8, 46.9, 47.0, 55.4, 55.5, 65.2, 65.6, 74.0, 74.1, 127.1, 127.2, 127.5, 127.6, 128.4, 142.2, 174.7, 174.9.

5.3.7. Product mixture 16

Yield: 1.23 g (54%); dr = 79:21; The *syn:anti* diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of a –CH proton adjacent to the menthyl oxygen moiety [For *syn* (δ 4.48, dt, *J* = 11 Hz, *J* = 4.4 Hz, 1H) and for *anti* products (δ 4.75–4.84 ppm, m, 0.27 H)]. The *syn:anti* mixture was crystallized from hexane to obtain compound **16a** in pure form.

5.3.7.1. Compound 16a. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl(2*R*)-2-[(*R*)-1-benzylamino-1-(4-chlorophenyl)methyl]butanoate: Yield: 0.8 g (35%); mp 128–130 °C; IR (KBr): 3321, 3061, 2962, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.45 (d, *J* = 6.8 Hz, 3H), 0.70–0.92 (m, 12H), 1.10–1.23 (m, 2H), 1.34–1.42 (m, 1H), 1.55–1.80 (m, 5H), 1.89–1.97 (m, 1H), 2.56–2.59 (m, 1H), 3.36–3.46 (m, 1H), 3.52–3.61 (m, 1H), 3.72–3.81 (m, 1H), 4.48 (dt, *J*= 11 Hz, *J* = 4.4 Hz, 1H), 7.22–7.31 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 15.9, 20.9, 22.1, 22.7, 23.0, 25.4, 31.4, 34.2, 40.9, 46.7, 51.4, 55.0, 63.6, 73.9, 126.9, 127.3, 128.0, 128.2, 128.3, 140.5, 141.9, 173.9; LC–MS *m*/*z* 456 (M^+). Anal. Calcd: C, 73.74; H, 8.40; N, 3.07; Cl, 7.77. Found: C 73.70; H, 8.47; N, 3.19; $[\alpha]_D^{25} = -3.2$ (*c* 1, $CHCl_3$).

5.3.8. Compound 17a

(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl (2*S*)-2-[(*S*)-1-benzylamino-1-phenylmethyl]butanoate: The crystallization of **17** was carried out in a similar manner to **8**. Yield: 1.40 g (66%); mp 124–126 °C; $[\alpha]_D^{25} = +11.4$ (*c* 1, $CHCl_3$).

5.3.9. Product mixture 18

Yield: 0.91 g (45%); dr = 72:28; The *syn:anti* diastereomeric ratio was calculated on the basis of ^{1}H NMR analysis of a methyl proton [For *syn* (δ 0.42 ppm, d, *J* = 6.8 Hz, 3H) and for *anti* products (δ 0.49 ppm, d, *J* = 6.8 Hz, 1.2 H)]. The *syn:anti* mixture was crystallized from hexane to obtain compound **18a** in pure form.

5.3.9.1. Compound 18. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl(2*R*)-2-[(*R*)-1-anilino-1-phenylmethyl]butanoate: Yield: 0.50 g (25%); mp 174–176 °C; IR (KBr): 3389, 3051, 2953, 1703 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$, δ ppm): 0.42 (d, *J* = 6.8 Hz, 3H), 0.66 (d, *J* = 6.8 Hz, 3H), 0.83–0.92 (m, 9H), 1.25–1.42 (m, 3H), 1.56–1.65 (m, 3H), 1.75–1.89 (m, 2H), 2.69–2.75 (m, 1H), 4.31 (br s, 1H), 4.60–4.66 (m, 2H), 6.48 (d, *J* = 8 Hz, 2H), 6.62 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 2H), 7.18–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 12.4, 15.6, 20.8, 20.9, 22.1, 23.0, 25.7, 31.5, 34.3, 41.1, 47.0, 54.8, 59.5, 74.6, 113.5, 117.6, 127.2, 127.3, 128.5, 129.1, 141.2, 147.2, 173.3; LC–MS: *m*/*z* 408 (M+1). Anal. Calcd: C, 79.56; H, 9.15; N, 3.44. Found: C 79.58; H, 9.17; N, 3.48; $[\alpha]_D^{25} = -21.4$ (*c* 0.5, $CHCl_3$).

5.4. Procedure for the preparation of mandelic acid complexes 11 of *syn*-β-amino esters 8a

The *syn*-β-amino ester **8a** (0.42 g, 1 mmol) was taken in CH_2Cl_2/acetone mixture (3 mL, 1:1 v/v ratio) and stirred for 10 min till complete dissolution occurs. To that mixture, (*R*)-(−)-mandelic acid **10a** (0.152 g, 1 mmol) was added and the contents were stirred at 25 °C for 3 h. The precipitate formed was filtered off and crystallized from toluene–isopropanol mixture to obtain the crystals of complex **11** suitable for X-ray structure analysis.

5.5. Procedure for the resolution of racemic mandelic acid 10 using *syn*-β-amino esters 8a

The *syn*-β-amino ester **8a** (2.1 g, 5 mmol) was taken in acetone–CH_2Cl_2 mixture (16 mL, 11:5 v/v ratio) and stirred for 10 min until complete dissolution occurs. Racemic mandelic acid **10** (0.765 g, 5 mmol) was added and the contents were stirred at 25 °C for 12 h and the precipitate was filtered. The precipitate was suspended in a mixture of ether and 2 M Na_2CO_3 and stirred until dissolution occurred. The aqueous layer was treated with dilute HCl (3 M)/ether and the mandelic acid was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to obtain the (*R*)-(−)-**10a** mandelic acid enantiomer (>99% ee, 28% yield). The filtrate part was concentrated and the residue was treated as outlined above to obtain the (*S*)-(+)-**10b** enantiomer (42% ee, 61% yield). After decomposition: Precipitate: Yield 0.215 g (28%); $[\alpha]_D^{25} = -147.0$ (*c* 0.5, ethanol) [Lit[13] $[\alpha]_D^{25} = -145.6$ (*c* 0.43, ethanol, For >99% ee (*R*)-(−)-mandelic acid); enantiomeric purity >99% ee (Determined by HPLC using chiral column, chiralcel OD-H[14] solvent system, hexane/2-propanol/trifluoroacetic acid = 900:100:2.5, v/v flow rate 0.5 mL/min, 254 nm, Retention times: 16.2 min for minor (*S*) and 19.8 min for major (*R*) isomer). From filtrate: Yield 0.470 g (61%); $[\alpha]_D^{25} = +60.4$ (*c* 1, ethanol); enantiomeric purity 42% ee, retention times: 15.7 min for major (*S*) isomer and 20.1 min for minor (*R*) isomer.

5.6. Procedure for the N-debenzylation of *syn*-β-amino ester 8a

To a stirred solution of *syn*-β-amino ester **8a** (0.42 g, 1 mmol) in a mixture of methanol and formic acid (100%) (20 mL, 4:1 v/v), Pd/C (50 mg, 5% by weight) was added under a nitrogen atmosphere. The reaction mixture was heated to 50 °C for 2 h. The reaction mixture was brought to room temperature, filtered, and neutralized slowly by adding 3 M NaOH solution until the solution became slightly basic. The reaction mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with water (20 mL), brine (15 mL), dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (230–400 mesh) column using hexane/EtOAc (95:5) as an eluent.

5.6.1. Compound 19 (1*R*,2*S*,5*R*)-2-isoproyl-5-methylcyclohexyl-(2*R*)-2-[(*R*)-1-amino-1-phenyl methyl]butanoate

Yield: 0.28 g (86%); mp 96–98 °C; IR (KBr): 3371, 3308, 3061, 2955, 1714 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$, δ ppm): 0.43 (d, *J* = 6.8 Hz, 3H), 0.69–0.96 (m, 12H), 1.16–1.37 (m, 3H), 1.57–1.85 (m, 7H), 2.54–2.60 (m, 1H), 4.07 (d, *J* = 8.6 Hz, 1H), 4.50 (dt, *J* = 10.8 Hz, *J* = 4.2 Hz, 1H), 7.21–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 15.8, 20.8, 22.0, 22.6, 23.0, 25.3, 31.3, 34.2, 40.9, 46.7, 55.9, 57.6, 73.9, 127.0, 127.3, 128.4, 144.1, 173.9; LC–MS: *m*/*z* 332 (M+1). Anal. Calcd: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.20; H, 10.02; N, 4.29. $[\alpha]_D^{25} = -61.7$ (*c* 0.5, $CHCl_3$).

5.7. Procedure for the hydrolysis of *syn*-β-amino ester 8a

The *syn*-β-amino ester **8a** (0.42 g, 1 mmol) was taken in a mixture of glacial acetic acid and hydrochloric acid (10 mL, 1:1 v/v) and refluxed for 24 h. The solvents were distilled off and the residue was taken in 5 mL of distilled water. A saturated sodium bicarbonate solution was added dropwise to the mixture until it became slightly basic. The aqueous solution was extracted with ether (3×15 mL) and the combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (230–400 mesh) column using hexane/EtOAc (90:10) as an eluent. Yield: 0.12 g (44%); mp 80–82 °C; IR (KBr): 3400, 3034, 2964, 1684, 1624, 1583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 0.74 (t, J = 7.2 Hz, 3H), 1.26–1.31 (m, 1H), 1.65–1.72 (m, 1H), 2.77 (br s, 1H), 3.80 (d, J = 13.2 Hz, 1H), 4.11–4.21 (m, 2H), 7.26–7.40 (m, 10H), 8.75 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 12.3, 20.7, 49.0, 50.0, 61.5, 128.6, 128.9, 129.1, 129.3, 129.5, 129.8, 132.0, 133.4, 177.3; LC–MS m/z 284 (M+1). Anal. Calcd. C, 76.29; H, 7.47; N, 4.94. Found: C, 76.35; H, 7.48; N, 5.0; $[\alpha]_D^{25} = +43.4$ (c 0.15, $CHCl_3$).

5.8. Procedure for the synthesis of β-lactam 21

To a stirred solution of *syn*-β-amino ester **8a** (0.42 g, 1 mmol) in dry THF (10 mL), a solution of ethylmagnesium bromide (0.13 g, 1 mmol) in 5 mL of dry THF was added slowly at 0 °C under an N_2 atmosphere over a period of 10 min. The reaction mixture was stirred at 0 °C for 3 h and then quenched with saturated NH_4Cl solution. The reaction mixture was diluted with ether (20 mL) and the organic layer was separated. The aqueous layer was extracted with ether (2×15 mL) and the combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (230–400 mesh) using hexane/EtOAc (95:5) as an eluent. Yield 0.23 g (56%); dr 71:29; IR (neat): 3030, 2926, 1738 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$, δ ppm): (for the diastereomeric mixture) 0.69 (t, J = 7.3 Hz, 3H), 0.99–1.10 (m, 1H), 1.37–1.48 (m, 1H), 3.19–3.24 (m, 1H), 3.78 (d, 1H, J = 14.9 Hz), 4.51 (d, J = 5.4 Hz, 1H), 4.80 (d, J = 14.6 Hz, 1H), 7.06–7.30 (m, 12H). Additional signals for the minor isomer: 0.90 (t, J = 7.3 Hz, 3H), 1.60–1.67 (m, 1H), 1.71–1.80 (m, 1H), 2.89–2.92 (m, 1), 3.64 (d, J = 14.9 Hz, 1H), 3.97 (s, 1H), 4.79–4.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): (for the diastereomeric mixture) 11.4, 11.7, 18.7, 21.7, 44.1, 44.2, 57.1, 57.7, 59.9, 62.0, 126.4, 127.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.4, 135.7, 170.2, 170.7; mass m/z 266 (M+1).

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8. *Crystal data*: For complex **11**: Molecular formula: $C_{36}H_{47}NO_5$ [$C_{28}H_{40}NO_2$, $C_8H_7O_3$], MW = 573.75, orthorhombic, space group: $P2(1)$ 2(1) 2(1), a = 9.694(3) Å, b = 16.116(6) Å, c = 21.580(12) Å, α = 90°, β = 90°, γ = 90°, V = 3371(3) $Å^3$, Z = 4, ρ_c = 1.130 Mg M^{-3}, μ = 0.074 mm^{-1}, T = 298(2) K. Of the 9909 reflections collected, 5934 were unique (R_{int} = 0.0520). Refinement on all data converged at R_1 = 0.0552, wR_2 = 0.0990. (CCDC deposition number: 677361).
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