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Control of the enantioselectivity of alkylation of phenylalanine derivatives by regulation of the aggregate structure of chiral enolate intermediates

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Abstract—Two strategies were introduced for the control of enantioselectivity of alkylation of phenylalanine derivatives by regulation of the aggregate structure of chiral enolate intermediates. Use of amino acid-dimers, **6** and **15**, was effective to minimize solvent- and electrophile-dependency of enantioselectivity of the alkylation. α-Allylation of **20** proceeded in improved selectivity of 82–88% ee under the control of aggregation of the intermediary enolate.

1. Introduction

Previous studies from our laboratory have demonstrated asymmetric induction based on the dynamic chirality of enolates.[1,2] Several *N*-*t*-butoxycarbonyl (Boc)-*N*-methoxymethyl (MOM)-amino acid derivatives undergo α-methylation upon treatment with potassium hexamethyldisilazide (KHMDS) followed by methyl iodide in 76–93% ee without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts (Scheme 1).[1,2b–d,3,4] Protective groups are readily removed by treatment with 6 M HCl to give optically active α-methyl amino acids. Chiral nonracemic enolate intermediate **A** with dynamic axial chirality along the C–N axis (R=CH_2Ph, $t_{1/2}$=22 h at −78°C) was proposed as a crucial intermediate for this asymmetric transformation.[1] Enantioselectivity of these reactions is, however, highly solvent- and electrophile-dependent, which could be ascribed to the complexity of the aggregate structure of enolate intermediates. In this paper, we described two approaches to regulation of the aggregate structure of enolates and their effects on the stereochemical course of the reactions.

2. Results and discussion

Results in Table 1 shows solvent- and electrophile-dependency of the enantioselectivity of alkylation of **1**. α-Methylation of **1** took place by treatment with KHMDS followed by methyl iodide to give **2** in 81% ee in a toluene–THF (4:1) solution, while the reaction in THF gave **2** in a lower selectivity of 35% ee (entries 1 and 2). Difference in the selectivity could be ascribed to the difference in the aggregate structure of intermediary enolates depending on the solvent. In a series of reactions in a toluene–THF solution, enantioselectivity of alkylation was affected by electrophiles. α-Allylation of **1** proceeded in lower enantioselectivity than α-methylation (entries 1 vs 3–5).

We often encounter comparable or even better stereoselectivity in the reactions of enolates with bulkier electrophiles rather than that with a small electrophile, methyl iodide.[5] The lower enantioselectivity observed in α-allylation of **1** implies that an intermediate of α-allylation may be different from that of α-methylation. We hypothesized that a few different aggregates exist in equilibrium in a toluene–THF solution and the higher-order aggregate (eg. enolate tetramer) reacts mainly with methyl iodide whereas the lower-order aggregate (eg. enolate dimer) reacts mainly with bulkier electrophiles.

If it is possible to control the aggregation of the enolate, both α-methylation and α-allylation would take place via a common aggregate intermediate, and this could lead to an improvement in the enantioselectivity of α-allylation.[6,7] Enolates generally form aggregates consisting of an oxygen–metal bond framework (Scheme 2, **B**).[8] They usually exist as a mixture of different aggregates in solution. The complexity of the aggregates is due, at least in part, to the *intermolecular* association of enolate subunits. We anticipated that the formation of stable *intramolecular* aggregate such as (**C**) or (**D**) would regulate the aggregate structure and affect the stereoselectivity of the reaction. Based on this hypothesis, we investigated two distinct

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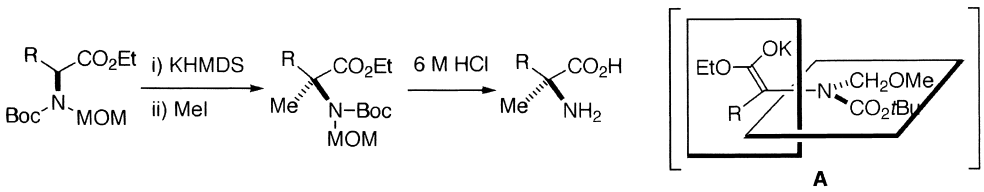
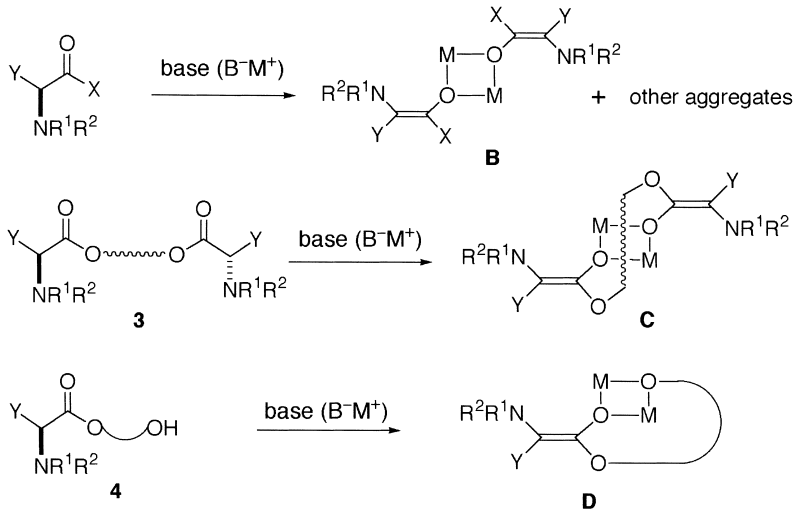


Scheme 1.

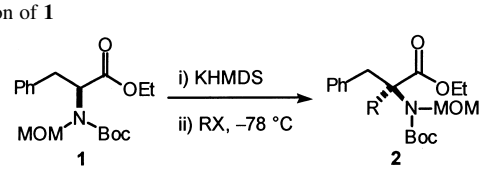


Scheme 2. Intermolecular aggregate **B** and intramolecular aggregates **C** and **D**.

strategies aimed at the controlled formation of intramolecular aggregates of enolates. The first one is an amino acid-dimer (**3**) that is expected to form, on treatment with a base, intramolecular aggregate (**C**) consisting of two enolate-subunits. The second one is an amino acid with hydroxyalkyl ester (**4**) that is expected to form intramolecular aggregate (**D**) enforced by the coordination of a metal alkoxide.[9]

As examples of general structure **3**, phenylalanine-dimers **5**–**8** were prepared. Condensation of two equivalents of *N*-Boc-phenylalanine and ethylene glycol in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) followed by introduction of MOM group on the nitrogen (KHMDS/MOMCl) gave **5** in 59% yield. Treatment of **5** with 2.2 mol equiv. of KHMDS in toluene–THF (4:1) at −78°C followed by addition of methyl iodide gave **9** as a 2.0:1 mixture of *dl*(chiral)-and *meso*-isomers (Table 2, entry 1). The enantiomeric purity of the *dl*(chiral)-isomer was 81% ee. Considering the amount of *meso*-isomer, total enantiomeric ratio (er) of **9** was 77:23. The corresponding reaction of **5** in THF gave **9** with total er of 72:28 (entry 2). α-Allylation of **5** gave **10** in 74:26 er in toluene–THF, which is comparable to the er (77:23) observed in α-methylation of **5** (entries 1 and 3). Thus, the effects of solvent and electrophile on the enantioselectivity of α-alkylation of **5** were less significant than that of **1**. The er (74:26) obtained in α-methylation of 1,3-propanediol-linked dimer **6** in toluene–THF was exactly same as that in THF (entries 5 and 6). These observations suggest that an enolate generated from **6** and KHMDS forms a single aggregate species (such as **C**) independently on solvents. The highest asymmetric induction of α-methylation and α-allylation was achieved with 1,4-butanediol-linked dimer **7** in toluene–THF, affording *dl*(chiral)-isomer **12** of 90% ee and *dl*(chiral)-isomer **13** of 81% ee, respectively (entries 7 and 9). Solvent-dependency on the enantioselectivity of α-methylation of **7** was slightly stronger than that of **6**, but was still much weaker than that of **1** (Table 1, entries 1, 2 vs Table 2, entries 7,8). Stereochemical results of α-methylation of **8** was similar to that of **7** (entries 7, 8 vs 11, 12).

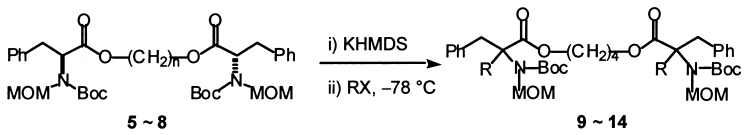
Table 1. Effects of solvent and electrophile on enantioselectivity of alkylation of **1**



Entry	RX	Solvent	Product	Yield (%)	ee (%)
1	MeI	toluene–THF=4:1	**2a**	96	81
2	MeI	THF	**2a**	93	35
3	CH_2=$CHCH_2I$	toluene–THF=4:1	**2b**	90	55
4	$(CH_3)_2C$=$CHCH_2Br$	toluene–THF=4:1	**2c**	87	69
5	*trans*-PhCH=$CHCH_2I$	toluene–THF=4:1	**2d**	88	48

We next examined reactions of phenylalanine-dimers **15** and **16** with a linker containing a heteroatom (Table 3). α-Methylation of diethylene glycol-linked dimer (**15**) in toluene–THF gave **17** in 73:27 er and that in THF gave **17** in 72:28 er (entries 1 and 2). Similarly, er of **18** obtained by α-allylation of **15** in toluene–THF was 74:26 and that in THF was 75:25 (entries 3 and 4). In these four distinct reactions, almost exactly same er's of products were obtained, indicating the intervention of a common intermediate for both α-methylation and α-allylation of **15** either

Table 2. Alkylation of amino acid-dimers **5**–**8**



Entry	Substrate	RX	Solvent	Product	Yield (%)	*dl*: *meso*	ee[a] (%)	Total er[b]
1	**5** (*n*=2)	MeI	Toluene–THF=4:1	**9**	65	2.0:1	81	77:23
2	**5** (*n*=2)	MeI	THF	**9**	70	2.3:1	63	72:28
3	**5** (*n*=2)	Allyl iodide	Toluene–THF=4:1	**10**	37	1.6:1	77	74:26
4	**5** (*n*=2)	Allyl iodide	THF	**10**	73	1.3:1	61	67:33
5	**6** (*n*=3)[c]	MeI	Toluene–THF=4:1	**11**	62	2.4:1	78	74:26
6	**6** (*n*=3)[c]	MeI	THF	**11**	88	2.0:1	71	74:26
7	**7** (*n*=4)	MeI	Toluene–THF=4:1	**12**	78	3.4:1	90	85:15
8	**7** (*n*=4)	MeI	THF	**12**	89	2.1:1	82	78:22
9	**7** (*n*=4)	Allyl iodide	Toluene–THF=4:1	**13**	78	1.9:1	81	76:24
10	**7** (*n*=4)	Allyl iodide	THF	**13**	91	1.3:1	52	65:35
11	**8** (*n*=5)	MeI	Toluene–THF=4:1	**14**	72	2.4:1	89	82:18
12	**8** (*n*=5)	MeI	THF	**14**	85	1.5:1	74	72:28

[a] Ee of the *dl*-isomer.
[b] Total enantiomeric ratio of combined *dl*- and *meso*-isomers.
[c] (*R*, *R*)-Isomer was used.

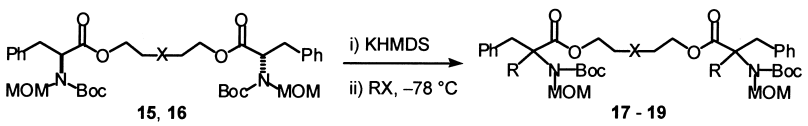
in toluene–THF or in THF. Stereochemical results similar to those of **15** were obtained in α-methylation of *N*-methyldiethanolamine-liked dimer (**16**) (entries 5 and 6).

We have shown that enantioselectivity of α-alkylation can be controlled by regulation of the aggregate structure of the enolate. Especially, enantioselectivity of the reactions of amino acid-dimer **15** was totally independent on solvent and electrophile. However, these reactions produce significant amounts of *meso*-isomers. In order to overcome this problem, we next examined reactions via assumed aggregate **D**. This approach is expected to improve the enantioselectivity of alkylation without formation of *meso*-isomers. As an example of general structure **4**, phenylalanine derivative **20** with a phenol group in its ester moiety was designed (Table 4). The phenoxide, formed by base-treatment of **20**, is expected to behave as a pseudo-enolate subunit to form intramolecular aggregate schematically shown in **D**.

Preparation of **20** was performed by condensation of *N*-Boc-*N*-MOM-phenylalanine and 2-(2-benzyloxyphenyl)ethanol in the presence of EDCI followed by hydrogenolysis in 80% yield. α-Alkylation of **20** was examined and the results are shown in Table 4. Treatment of **20** with 2.2 equiv. of KHMDS in toluene–THF (4:1) followed by methyl iodide at −78°C gave **21** in 88% ee (entry 1). The stereochemical course of the α-methylation was retention,[10] which parallels that of **1**.[1] α-Allylation of **20** proceeded with much improved selectivity of 82–87% ee (entries 3, 5, and 6). The degree of asymmetric induction in α-alkylation of **20** in a toluene–THF solution was comparable with several electrophiles (entries 1, 3, 5, and 6). The solvent effect of α-methylation of **20** was less significant than that of **1** (Table 4, entries 1, 2 vs Table 1, entries 1, 2). These results suggest that the reactive intermediate in these reactions would be a single aggregate species of a chiral nonracemic enolate, which may be shown as **E**.

To elucidate the effect of a phenolic OH groups of **20**, reactions of anisole derivative **25** were examined (Table 5). In both α-methylation and α-allylation, the enantioselectivity was comparable to that observed with **1** (Table 5, entries 1, 3 vs Table 1, entries 1, 3). Solvent-dependency on enantioselectivity of α-methylation of **25** was also comparable to that of **1** (Table 5, entries 1, 2 vs Table 1, entries 1, 2). The behavior of **25** in asymmetric α-alkylation is closer to that of ethyl ester **1** than that of phenol derivative **20**. The presence of the phenolic OH group in **20** is crucial for high asymmetric induction, which indicates that potassium

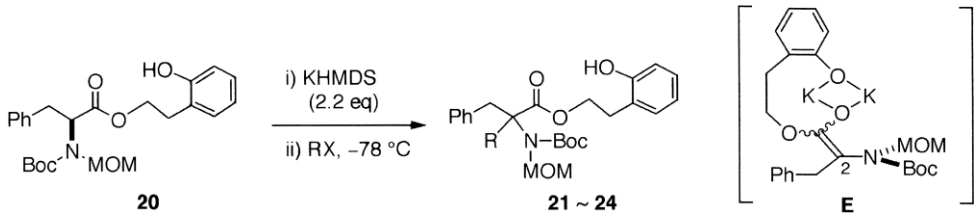
Table 3. Alkylation of amino acid-dimers **15** and **16**



Entry	Substrate	RX	Solvent	Product	Yield (%)	*dl*–*meso*	ee[a] (%)	Total er[b]
1	**15** (X=O)	MeI	Toluene–THF=4:1	**17**	51	2.2:1	68	73:27
2	**15** (X=O)	MeI	THF	**17**	68	1.6:1	75	72:28
3	**15** (X=O)	Allyl iodide	Toluene–THF=4:1	**18**	63	1.8:1	76	74:26
4	**15** (X=O)	Allyl iodide	THF	**18**	71	1.7:1	80	75:25
5	**16** (X=NMe)[c]	MeI	Toluene–THF=4:1	**19**	66	2.5:1	80	79:21
6	**16** (X=NMe)[c]	MeI	THF	**19**	73	1.5:1	76	73:27

[a] Ee of the *dl*-isomer.
[b] Total enantiometric ratio of combined *dl*- and *meso*-isomers.
[c] (*R*, *R*)-Isomer was used.

Table 4. Enantioselective alkylation of **20**



Entry	RX	Solvent	Product	Yield (%)	ee (%)
1	MeI	Toluene–THF=4:1	**21**	81	88[a]
2	MeI	THF	**21**	83	75[a]
3	CH_2=$CHCH_2I$	Toluene–THF=4:1	**22**	71	82
4	CH_2=$CHCH_2I$	THF	**22**	81	56
5	$(CH_3)_2C$=$CHCH_2Br$	Toluene–THF=4:1	**23**	47	87
6	*trans*-PhCH=$CHCH_2I$	Toluene–THF=4:1	**24**	89	83

[a] (*S*)-Isomer.

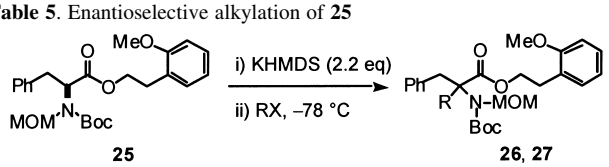
phenoxide contributes to the intramolecular aggregation of the enolate intermediate probably as a pseudo-enolate subunit as shown in **E**.

Asymmetric α-alkylation of **20** is assumed to proceed via a chiral nonracemic enolate intermediate **E** with dynamic axial chirality along the C(2)–N axis, by analogy to our previous study with **1**.[1] We then investigated the behavior of the enolate intermediate generated from **20** toward racemization. When **20** was treated with KHMDS in toluene–THF (4:1) at −78°C for 30 min and then at −40°C for 30 min, the reaction of the resulting enolate with methyl iodide at −78°C gave **21** in 68% ee (*cf*. 88% ee after 30 min of base treatment at −78°C, Table 4, entry 1). The half-life of racemization of the chiral enolate is roughly estimated to be ~80 min at −40°C, assuming first-order kinetics for racemization.[1] On the other hand, the same treatment of **1** gave **2** in 5% ee (*cf*. 81% ee after 30 min of base treatment at −78°C, Table 1, entry 1), which corresponds to a half-life of racemization of ~7 min at −40°C. Thus, the formation of an intramolecular aggregate enhances the stability of the chiral enolate against racemization (ie., enhancement of the memory effect of chirality).[11]

3. Conclusions

We have shown two strategies for the control of enantioselectivity of alkylation of phenylalanine derivatives by regulation of the aggregate structure of chiral enolate intermediates. Use of amino acid-dimers, especially **6** and **15**, was effective to minimize solvent- and electrophile-dependency of enantioselectivity of their alkylation. Use of **20** with a phenol group in its ester moiety was successful in improving the enantioselectivity of α-allylation. We expect that these protocols may have potentially general applicability to the control of reactivity and selectivity of the reactions via enolate intermediates.

Table 5. Enantioselective alkylation of **25**



Entry	RX	Solvent	Product	Yield (%)	ee (%)
1	MeI	Toluene–THF=4:1	**26**	95	77
2	MeI	THF	**26**	88	51
3	Allyl iodide	Toluene–THF=4:1	**27**	90	58

4. Experimental

4.1. General

Melting points were measured using a Yanagimoto micro point apparatus and uncorrected. NMR spectra were obtained with a Varian Gemini 200 (200 MHz) spectrometer or a JEOL JMN-GX 400 spectrometer, chemical shifts being given in ppm units (tetramethylsilane or chloroform as internal standards, indicating 0 or 7.24, respectively). IR spectra were recorded with a JACSO FT/IR-300 spectrometer. Specific rotations were measured with a Horiba SEPA-200 automatic digital polarimeter. MS spectra were recorded with a JEOL JMS-DX300 mass spectrometer. TLC analyses and preparative TLC were performed on commercial glass plates bearing a 0.25 mm layer and a 0.5 mm layer of Merck Kiesel-gel 60 F_{254}, respectively. Silica gel column chromatography was carried out with Wakogel C-200, Fuji Silysia BW-1277H, or Nacalai Tesque Silica gel 60 (150–325 mesh). Dry solvents (THF, ether, hexane, dichloromethane, and toluene; <50 ppm water contents) were purchased from Kanto Chemical Co., Inc. and used without further treatment.

4.2. General procedure for alkylation of 1

Each substrate was dried azeotropically with toluene prior to use. A KHMDS solution in THF[†] (0.50 M, 1.1 mL, 0.55 mmol) was diluted with 3 mL of toluene. A solution of substrate (0.5 mmol) in toluene (1.5 mL) was added to the KHMDS solution at −78°C. After stirring for 30 min, electrophile (1.5–5.0 mmol) was added. Stirring was continued for 16–17 h at −78°C. The mixture was poured into saturated aq. NH_4Cl and extracted with ethyl acetate. The organic phase

[†] Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

was washed with saturated aq. $NaHCO_3$ and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by preparative TLC.

4.2.1. *N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α-(2-propenyl)-phenylalanine ethyl ester (2b). Colorless oil. HPLC conditions: Daicel Chiralpak AD, 2-PrOH–hexane=1:99, 1.0 mL/min, t_R=10, 12 min. $[\alpha]_D^{16}$ (55% ee)=−38 (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.21 (m, 3H), 7.09–7.03 (m, 2H), 5.92–5.70 (m, 1H), 5.28–5.21 (m, 1H), 5.20–5.14 (m, 1H), 4.86–4.46 (br, 1H), 4.30–4.05 (br m, 2H), 3.68 (br d, *J*=12.0 Hz, 1H), 3.46 (br d, *J*=13.6 Hz, 1H), 3.30 (s, 3H), 3.15 (d, *J*=13.6 Hz, 1H), 2.90–2.65 (br m, 1H), 2.54 (br dd, *J*=13.6, 7.4 Hz, 1H), 1.52 (s, 9H), 1.27 (br t, *J*=7.1 Hz, 3H). IR (neat) 2978, 1742, 1701, 1375, 1294 cm^{-1}. MS *m/z* 377 (M^+, 0.3), 336 (3), 286 (30), 236 (25), 186 (100). Anal. calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.39. Found: C, 66.59; H, 8.32; N, 3.64.

4.2.2. *N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α-(3,3-dimethyl-2-propenyl)-phenylalanine ethyl ester (2c). Colorless oil. HPLC conditions: Daicel Chiralpak AD, 2-PrOH–hexane=1:99, 1.0 mL/min, t_R=10, 12 min. $[\alpha]_D^{16}$ (69% ee)=−22 (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.21 (m, 3H), 7.06–7.01 (m, 2H), 5.23 (br t, *J*=6.0 Hz, 1H), 4.90–4.52 (br, 1H), 4.17–4.07 (br q, *J*=7.1 Hz, 2H), 3.73 (d, *J*=11.3 Hz, 1H), 3.43 (br, 1H), 3.30 (s, 3H), 3.14 (d, *J*=13.7 Hz, 1H), 2.95–2.60 (br, 1H), 2.50–2.25 (br, 1H), 1.77 (s, 3H), 1.61 (s, 3H), 1.51 (s, 9H), 1.25 (br t, *J*=7.1 Hz, 3H). IR (neat) 1978, 1743, 1698, 1454, 1367, 1293 cm^{-1}. MS *m/z* 405 (M^+, 0.5), 373 (5), 336 (5), 314 (10), 274 (10), 258 (15), 214 (100), 182 (40). Anal. calcd for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45. Found: C, 67.93; H, 8.81; N, 3.40.

4.2.3. *N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α-(3-phenyl-2-propenyl)-phenylalanine ethyl ester (2d). Colorless oil. HPLC conditions: Daicel Chiralpak AD, 2-PrOH–hexane=1:99, 1.0 mL/min, t_R=16, 21 min. $[\alpha]_D^{16}$ (48% ee)=−22 (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.62–7.18 (m, 8H), 7.17–7.04 (m, 2H), 6.52 (d, *J*=15.7 Hz, 1H), 6.18 (td, *J*=15.7, 7.7 Hz, 1H), 4.71–4.60 (br, 1H), 4.28–4.08 (br m, 2H), 3.78 (d, *J*=12.2 Hz, 1H), 3.58–3.38 (br, 1H), 3.32 (s, 3H), 3.22 (d, *J*=13.6 Hz, 1H), 2.94 (dd, *J*=12.9, 7.7 Hz, 1H), 2.71 (br dd, *J*=12.9, 7.7 Hz, 1H), 1.52 (s, 9H), 1.25 (t, *J*=7.1 Hz, 3H). IR (neat) 2979, 1739, 1698, 1374, 1294, 1080 cm^{-1}. MS *m/z* 421 (M^+, 2), 362 (3), 348 (5), 322 (10), 292 (100). Anal. calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.73; N, 3.09. Found: C, 71.18; H, 7.80; N, 2.97.

4.3. General procedure for preparation of phenylalanine-dimers 5, 6, 15, and 16

A solution of (*S*)-*N*-*t*-butoxycarbonylphenylalanine (400 mg, 1.5 mmol), ethyleneglycol (50 mg, 0.8 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (318 mg, 1.65 mmol) and 4-dimethylpyridine (18 mg, 0.15 mmol) in dichloromethane (5 mL) was stirred at 0°C to rt overnight. The mixture was diluted with ethyl acetate and washed successively with water, saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 4:1, hexane–AcOEt) to give (2*S*)-2-*t*-butoxycarbonylamino-3-phenylpropionic acid 2-[(2*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-propionyloxy]ethyl ester (320 mg, 77% yield). To a solution of this material (320 mg, 0.58 mmol) in THF (2 mL), a KHMDS solution (0.47 M in THF, 2.34 mL, 1.1 mmol) was added to at −78°C. After stirring for 10 min, chloromethyl methyl ester (0.44 mL, 5.8 mmol) was added and stirring was continued for additional 20 h at −78°C. The mixture was poured into saturated aq. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, dioxane–hexane=1:10) to give **5** (290 mg, 77% yield) as colorless oil.

4.3.1. (2*S*)-2-(*tert*-Butoxycarbonyl-methoxymethyl-amino)-3-phenylpropionic acid 2-[(2*S*)-2-(*tert*-butoxycarbonyl-methoxymethylamino)-3-phenylpropionyloxy]-ethyl ester (5). Colorless oil. $[\alpha]_D^{20}$=−102 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.10 (m, 10H), 4.69 (d, *J*=10.4 Hz, 1H), 4.57 (d, *J*=11.1 Hz, 1H), 4.45–4.15 (m, 6H), 4.03 (d, *J*=11.1 Hz, 1H), 3.93 (m, 1H), 3.40–3.25 (m, 4H), 3.17, 3.10 (two s, 6H), 1.46 (s, 18H). IR (neat) 2975, 1746, 1707 cm^{-1}. MS *m/z* (rel intensity) 644 (M^+, 0.4), 612 (50), 512 (30), 423 (50), 352 (40), 321 (100), 289 (50), 204 (50), 132 (90). Anal. calcd for $C_{34}H_{48}N_2O_{10}$: C, 63.34; H, 7.50; N, 4.34%. Found: C, 63.07; H, 7.68; N, 4.27%.

4.3.2. (2*R*)-2-(*tert*-Butoxycarbonyl-methoxymethyl-amino)-3-phenylpropionic acid 3-[(2*R*)-2-(*tert*-butoxycarbonyl-methoxymethylamino)-3-phenyl-propionyloxy]-propyl ester (6). Colorless oil. $[\alpha]_D^{20}$=104 (*c* 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.14 (m, 10H), 4.70 (d, *J*=10.9, 39–3.25 (Hz, 1H), 4.58 (d, *J*=11.1 Hz, 1H), 4.32–4.07 (m, 6H), 4.03 (d, *J*=11.1 Hz, 1H), 3.91 (d, *J*=10.9 Hz, 1H), 3.39–3.25 (m, 4H), 3.19, 3.12 (two s, 6H), 1.99 (m, 2H), 1.47 (s, 18H). IR (neat) 2976, 1743, 1706 cm^{-1}. MS *m/z* (rel intensity) 658 (M^+, 0.4), 626 (30), 526 (20), 435 (30), 379 (40), 335 (40), 303 (90), 218 (50), 132 (100). Anal. calcd for $C_{35}H_{50}N_2O_{10}$: C, 63.81; H, 7.65; N, 4.25%. Found: C, 63.55; H, 7.65; N, 4.24%.

4.3.3. (2*S*)-2-(*tert*-Butoxycarbonyl-methoxymethyl-amino)-3-phenylpropionic acid 2-{(2*S*)-2-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-3-phenyl-propionyloxy]-ethoxy}-ethyl ester (15). Colorless oil. $[\alpha]_D^{20}$=−102 (*c* 0.86, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.15 (m, 10H), 4.73–4.69 (m, 1H), 4.60–4.55 (m, 1H), 4.40–4.15 (m, 6H), 4.05–3.98 (m, 1H), 3.87 (d, *J*=10.9 Hz, 1H), 3.74–3.60 (m, 4H), 3.40–3.25 (m, 4H), 3.32–3.12 (m, 6H), 1.47 (s, 18H). ^1H NMR (400 MHz, *d*-toluene, 100°C) δ 7.07 (m, 10H), 4.70 (br d, *J*=11.1 Hz, 2H), 4.45–4.35 (m, 2H), 4.27 (d, *J*=11.1 Hz, 2H), 4.17–4.00 (m, 4H), 3.46–3.22 (m, 8H), 3.14 (s, 6H), 1.39 (s, 18H). IR (neat) 2976, 1743, 1707 cm^{-1}. MS *m/z* (rel intensity) 688 (M^+, 0.2), 656 (15), 525 (10), 465 (20), 365 (20), 333 (30), 164 (40), 132 (90), 57 (100). HRMS, *m/z* calcd for $C_{36}H_{52}N_2O_{11}$: 688.3571, found: 688.3531.

4.3.4. (2*R*)-2-(*tert*-Butoxycarbonyl-methoxymethyl-amino)-3-phenylpropionic acid 2-({(2*R*)-2-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-3-phenyl-propionyloxy]-ethyl}-methylamino)-ethyl ester (16). Colorless oil. $[\alpha]_D^{20}$=87 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz,

$CDCl_3$) δ 7.30–7.14 (m, 10H), 4.69, 4.58 (two d, J=11.0, 11.4 Hz, ratio=3:2, 2H), 4.34–4.10 (m, 6H), 4.06, 3.91 (two d, J=11.4, 11.0 Hz, ratio=2:3, 2H), 3.40–3.15 (m, 4H), 3.18, 3.11 (two s, ratio=3:2, 6H), 2.69 (m, 4H), 2.31 (s, 3H), 1.47 (s, 18H). IR (neat) 2975, 1742, 1706 cm^{-1}. MS *m/z* (rel intensity) 701 (M^+, 2), 670 (5), 438 (4), 379 (100), 247 (60). Anal. calcd for $C_{37}H_{55}N_3O_{10}$: C, 63.32; H, 7.90; N, 5.99%. Found: C, 63.07; H, 8.01; N, 5.96%.

4.4. General procedure for preparation of phenylalanine-dimers 7 and 8

A solution of (*S*)-*N*-*tert*-butoxycarbonyl-*N*-(methoxymethyl)phenylalanine (see the procedure for 20) (1.4 g, 4.3 mmol), 1,5-pentanediol (224 mg, 2.15 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (990 mg, 5.16 mmol) and 4-dimethylpyridine (52 mg, 0.43 mmol) in dichloromethane (15 mL) was stirred at 0°C to rt for 15 h. The mixture was diluted with ethyl acetate and washed successively with water, saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 5:1, hexane–AcOEt) to give **8** (950 mg, 64% yield) as colorless oil.

4.4.1. (2*S*)-2-(*tert*-Butoxycarbonyl-methoxymethylamino)-3-phenylpropionic acid 4-[(2*S*)-2-(*tert*-butoxycarbonyl-methoxymethylamino)-3-phenyl-propionyloxy]-butyl ester (7). Colorless oil. $[\alpha]_D^{20}=-100$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.13 (m, 10H), 4.70, 4.58 (d, J=10.9, 11.4 Hz, 2H), 4.30–4.05 (m, 6H), 1.75–1.63 (br s, 4H), 1.47 (s, 18H) ^1H NMR (400 MHz, *d*-toluene, 100°C) δ 7.17–7.03 (m, 10H), 4.69 (d, J=10.5 Hz, 2H), 4.44–4.35 (m, 2H), 4.30 (d, J=10.5 Hz, 2H), 4.03–3.90 (m, 4H), 3.40, 3.37 (dd, J=5.6, 5.8 Hz, 2H), 3.32–3.22 (m, 2H), 3.13 (s, 6H), 1.48 (s, 4H), 1.39 (s, 18H). IR (neat) 2972, 1742, 1704, 1427, 1367, 1298, 1169, 1140, 1092, 701 cm^{-1}. MS *m/z* (rel intensity) 672 (M^+, 0.2), 640 (20), 449 (30), 409 (30), 393 (20), 317 (100), 132 (90). Anal. calcd for $C_{36}H_{52}N_2O_{10}$: C, 64.27; H, 7.79; N, 4.16. Found: C, 64.14; H, 7.89; N, 4.12.

4.4.2. (2*S*)-2-(*tert*-Butoxycarbonyl-methoxymethylamino)-3-phenyl-propionic acid 5-[(2*S*)-2-(*tert*-butoxycarbonyl-methoxymethylamino)-3-phenyl-propionyloxy]-pentyl ester (8). (>99% ee) Colorless oil. HPLC conditions: Daicel Chiralcel AD, hexane–2-propanol=97:3, 1.0 mL/min, t_R=36 (*S*, *S*), 45 (*meso*), 49 (*R*, *R*) min. $[\alpha]_D^{20}=-108$ (*c* 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.14 (m, 10H), 4.70 (d, J=10.8 Hz, 1H), 4.58 (d, J=11.4 Hz, 1H), 4.30–4.00 (m, 6H), 3.89 (d, J=10.8 Hz, 1H), 3.40–3.15 (m, 4H), 3.19, 3.12 (two s, 6H), 1.70–1.60 (m, 6H), 1.50–1.35 (m, 2H), 1.47 (s, 18H). IR (neat) 2975, 1741, 1706 cm^{-1}. MS *m/z* (rel intensity) 686 (M^+, 10), 654 (20), 554 (20), 463 (40), 423 (30), 363 (40), 331 (90), 164 (50), 132 (100). Anal. calcd for $C_{37}H_{54}N_2O_{10}$: C, 64.70; H, 7.92; N, 4.08%. Found: C, 64.53; H, 8.09; N, 4.00%.

4.5. General procedure for asymmetric alkylation

A KHMDS solution in THF (0.44 M in THF, 0.55 mmol) was diluted with 3 mL of toluene. A solution of **5** in toluene (2 mL) was added to the KHMDS solution at −78°C. After stirring for 30 min, methyl iodide (0.31 mL, 5 mmol) was added and stirring was continued for 18 h at −78°C. The mixture was poured into saturated aq. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, ethyl acetate–hexane=1:3) to give **9** (110 mg, 65%, *dl* (81% ee): *meso*=2:1). The ratio of *dl*- to *meso*-isomer and the ee of *dl*-isomer were determined by HPLC analysis.

4.5.1. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenyl-propionicacid 2-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionyloxy]-ethyl ester (9). *dl* (63% ee): *meso*=2.3:1. Colorless solids. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=98:2, 0.7 mL/min, t_R=34, 39, 42 (*meso*) min. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 6H), 7.06–7.04 (m, 4H), 4.85–4.55 (m, 2H), 4.50–4.20 (m, 4H), 3.75–3.50 (m, 4H), 3.23 (s, 6H), 3.00 (d, J=13.4 Hz, 2H), 1.51 (s, 18H), 1.49 (s, 6H). IR (neat) 2977, 1743, 1703 cm^{-1}. MS *m/z* (rel intensity) 672 (M^+, 0.1) 640 (1.5), 581 (4), 549 (7), 509 (5), 449 (50), 317 (100), 218 (50), 146 (60). HRMS, *m/z* calcd for $C_{36}H_{52}N_2O_{10}$: 672.3622, found: 672.3639.

4.5.2. 2-Benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-pent-4-enoic acid 2-[2-benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-pent-4-enoyloxy]-ethyl ester (10). *dl* (77% ee): *meso*=1.6:1. Colorless oil. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=98:2, 0.7 mL/min, t_R=35, 37 (*meso*), 44 min. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 6H), 7.08–7.04 (m, 4H), 5.86–5.75 (m, 2H), 5.24–5.19 (m, 4H), 4.80–4.50 (m, 2H), 4.31 (br s, 4H), 3.75–3.65 (m, 2H), 3.50–3.40 (m, 2H), 3.26 (s, 6H), 3.15 (d, J=13.8 Hz, 2H), 2.85–2.73 (m, 2H), 2.60–2.53 (m, 2H), 1.51 (s, 18H). IR (neat) 2978, 1745, 1696 cm^{-1}. MS *m/z* (rel intensity) 724 (M^+, 0.2), 693 (1.2), 601 (20), 501 (50), 419 (70), 331 (100), 244 (90). HRMS, *m/z* calcd for $C_{40}H_{56}N_2O_{10}$: 724.3935, found: 724.3962.

4.5.3. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionic acid 3-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenyl-propionyloxy]-propyl ester (11). *dl* (71% ee): *meso*=2.0:1. Colorless oil. HPLC conditions: Daicel Chiralcel OD, hexane–2-propanol=98:2, 0.5 mL/min, t_R=20, 23 (*meso*), 27 min. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 6H), 7.10–7.04 (m, 4H), 5.10–4.55 (m, 2H), 4.30–4.10 (m, 4H), 3.75–3.50 (m, 4H), 3.24 (s, 6H), 3.00 (d, J=14.6 Hz, 2H), 2.01 (t, J=6.3 Hz, 2H), 1.51–1.46 (m, 24H). IR (neat) 2977, 1740, 1698 cm^{-1}. MS *m/z* (rel intensity) 686 (M^+, 0.05) 654 (1), 595 (2), 463 (90), 419 (90), 332 (100), 319 (90), 232 (90), 146 (80). HRMS, *m/z* calcd for $C_{37}H_{54}N_2O_{10}$: 686.3779, found: 686.3754.

4.5.4. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionic acid 4-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenyl-propionyloxy]-butyl ester (12). *dl* (82% ee): *meso*=2.1:1.

Colorless oil: HPLC conditions: Daicel Chiralcpak AD, hexane–2-propanol=97:3, 0.6 mL/min, t_R=36, 49 (*meso*), 54 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 10H), 7.10–7.02 (m, 4H), 4.87–4.55 (br m, 2H), 4.25–3.45 (br m, 8H), 3.24 (s, 6H), 3.00 (d, J=13.6 Hz, 2H), 1.78–1.66 (m, 4H), 1.51, 1.48, 1.46 (three s, 24H). ^{1}H NMR (400 MHz, *d*-toluene, 100°C) δ 7.06 (s, 10H), 5.04, 4.75 (br s and d, J=11.9 Hz, ratio=1:3, 2H), 4.15–3.90 (m, 4H), 3.96 (d, J=11.9 Hz, 2H), 3.71, 3.37 (two d, J=13.6, 13.6 Hz, 2H), 3.22 (s, 6H), 3.19, 3.12 (two d, J=13.6, 13.6 Hz, 2H), 1.61, 1.51, 1.49 (three s, 10H), 1.42 (s, 18H). IR (neat) 2977, 1740, 1699, 1455, 1374, 1297, 1258, 1165, 1140, 1091, 757 cm^{-1}. MS *m/z* (rel intensity) 700 (M^+, 0.1), 668 (1), 521 (2), 433 (20), 391 (20), 345 (100), 146 (60), 57 (60). HRMS calcd for $C_{38}H_{56}N_2O_{10}$, M^+ 700.3935, found *m/z* 700.3923.

4.5.5. 2-Benzyl-2-(*tert*-butoxycarbonyl-methoxymethyl-amino)-pent-4-enoic acid 4-[2-benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-pent-4-enoyloxy]-butyl ester (13). *dl* (52% ee): *meso*=1.3:1. Colorless oil: HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=97:3, 1.0 mL/min, t_R=19, 27 (*meso*), 37 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 6H), 7.10–7.00 (m, 4H), 5.86–5.71 (m, 2H), 5.19, 5.18 (two d, J=10.7, 17.2 Hz, 4H), 4.82–4.48 (br m, 2H), 4.20–3.95 (br m, 4H), 3.85–3.32 (br m, 4H), 3.27 (s, 6H), 3.14 (d, J=13.6 Hz, 2H), 2.85–2.70 (br m, 2H), 2.61–2.50 (m, 2H), 1.71 (br s, 4H), 1.50 (s, 18H). ^{1}H NMR (400 MHz, *d*-toluene, 100°C) δ 7.06 (s, 10H), 5.92–5.80 (m, 2H), 5.09, 5.08 (two d, J=19.6, 9.0 Hz, 4H), 4.70 (d, J=12.1 Hz, 2H), 4.10–4.00 (m, 6H), 3.58 (d, J=13.6 Hz, 2H), 3.28 (d, J=13.6 Hz, 2H), 3.27 (s, 6H), 2.92 (dd, J=7.0, 7.0 Hz, 2H), 2.70 (dd, J=7.0, 7.0 Hz, 2H), 1.60 (s, 4H), 1.41 (s, 18H). IR (neat) 2978, 1741, 1698, 1454, 1405, 1373, 1295, 1218, 1175, 1136, 1082, 755, 705 cm^{-1}. MS *m/z* (rel intensity) 752 (M^+, 0.1), 721 (0.5), 661 (1), 529 (10), 447 (10), 397 (30), 172 (30), 91 (30), 57 (100). HRMS calcd for $C_{42}H_{60}N_2O_{10}$, M^+ 752.4248, found *m/z* 752.4263.

4.5.6. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionic acid 5-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenyl-propionyloxy]-pentyl ester (14). *dl* (74% ee): *meso*=1.5:1. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 6H), 7.08–7.04 (m, 4H), 4.85–4.55 (m, 2H), 4.20–4.00 (m, 4H), 3.75–3.50 (m, 4H), 3.25 (s, 6H), 3.00 (d, J=13.6 Hz, 2H), 1.70–1.60 (m, 2H), 1.55–1.40 (m, 4H), 1.51 (s, 18H), 1.48 (s, 6H). IR (neat) 2977, 1739, 1699 cm^{-1}. MS *m/z* (rel intensity) 714 (M^+, 0.1) 682 (0.5), 591 (2.3), 503 (2.7), 359 (100), 267 (10), 178 (10), 146 (30). HRMS, *m/z* calcd for $C_{39}H_{58}N_2O_{10}$: 714.4092, found: 714.4092. Determination of the ratio of *dl*- to *meso*-isomers and ee of the *dl*-isomer was performed with the corresponding benzoly derivative.

4.5.7. 2-Benzoylamino-2-methyl-3-phenylpropionic acid 5-(2-benzoylamino-2-methyl-3-phenyl-propionyloxy)-pentyl ester. Colorless oil. HPLC conditions: Daicel Chiralcel OD, hexane–2-propanol=85:15, 0.9 mL/min, t_R=24, 28 (*meso*), 37 min. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J=7.0 Hz, 4H), 7.52–7.47 (m, 2H), 7.40 (t, J=7.8 Hz, 4H), 7.30–7.20 (m, 4H), 7.10–7.04 (m, 4H), 6.75 (s, 2H), 4.19 (ABX, J_{AB}=10.9 Hz, $\Delta\nu_{AB}$=13.9 Hz, J_{AB}=6.8 Hz, 4H), 3.65 (d, J=13.4 Hz, 2H), 3.31 (d, J=13.4 Hz, 2H), 1.80–1.70 (m, 8H), 1.60–1.40 (m, 4H). IR (neat) 2921, 2860, 1732, 1650, 1538, 1455 cm^{-1}. MS *m/z* (rel intensity) 634 (M^+, 1), 543 (30), 513 (10), 422 (10), 266 (20), 238 (30), 105 (100). HRMS calcd for $C_{39}H_{42}N_2O_6$, M^+ 634.3043, found *m/z* 634.3036.

4.5.8. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionic acid 2-{2-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenyl-propionyloxy]-ethoxy}-ethyl ester (17). *dl* (68% ee): *meso*=2.2:1. Colorless oil. HPLC conditions: Daicel Chiralpak AD, hexane–ethanol=98:2, 0.8 mL/min, t_R=20, 26 (*meso*), 32 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 6H), 7.11–7.04 (m, 4H), 5.15–4.20 (m, 4H), 4.27 (br t, J=4.7 Hz, 4H), 3.75–3.50 (m, 6H), 3.25 (s, 6H), 3.01 (d, J=13.3 Hz, 2H), 1.51, 1.49 (two s, 18H), 1.46 (s, 6H). ^{1}H NMR (400 MHz, *d*-toluene, 100°C) δ 7.06 (s, 10H), 4.76 (d, J=11.9 Hz, 2H), 4.25–4.10 (m, 4H), 3.96 (d, J=11.9 Hz, 2H), 3.70 (d, J=13.4 Hz, 4H), 3.50 (br t, J=5.1 Hz, 8H), 3.23 (s, 6H), 3.12 (d, J=13.4 Hz, 2H), 1.50 (s, 6H), 1.42 (s, 18H). IR (neat) 2978, 1740, 1698 cm^{-1}. MS *m/z* (rel intensity) 716 (M^+, 0.005), 656 (1.5), 593 (1.7), 537 (2.3), 361 (100), 349 (30), 146 (50). HRMS, *m/z* calcd for $C_{38}H_{56}N_2O_{11}$: 716.3884, found: 716.3857.

4.5.9. 2-Benzyl-2-(*tert*-butoxycarbonyl-methoxymethyl-amino)-pent-4-enoic acid 2-{2-[2-benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-pent-4-enoyloxy]-ethoxy}-ethyl ester (18). *dl* (76% ee): *meso*=1.8:1. Colorless oil. HPLC conditions: Daicel Chiralpak AD, hexane–ethanol=97:3, 0.8 mL/min, t_R=17, 20 (*meso*), 24 min. ^{1}H NMR (400 MHz, $CDCl_3$, 20°C) δ 7.30–7.20 (m, 6H), 7.07–7.05 (m, 4H), 5.85–5.75 (m, 2H), 5.20 (dd, J=13.8, 2.0 Hz, 4H), 4.80–4.50 (m, 2H), 4.30–4.10 (m, 4H), 3.75–3.63 (m, 6H), 3.50–3.35 (m, 2H), 3.28 (s, 6H), 3.15 (d, J=13.6 Hz, 2H), 2.85–2.74 (m, 2H), 2.57–2.52 (m, 2H), 1.51 (s, 18H). ^{1}H NMR (400 MHz, *d*-toluene, 100°C) δ 7.13–7.00 (m, 10H), 5.94–5.80 (m, 2H), 5.15–5.05 (m, 4H), 4.71 (d, J=11.8 Hz, 2H), 4.20–4.10 (m, 4H), 4.02 (d, J=11.8 Hz, 2H), 3.58 (d, J=13.8 Hz, 2H), 3.55–3.45 (m, 4H), 3.33–3.24 (m, 8H), 2.94 (dd, J=6.5, 6.5 Hz, 2H), 2.70 (dd, J=6.5, 6.5 Hz, 2H), 1.41 (s, 18H). IR (neat) 2978, 1743, 1698 cm^{-1}. MS *m/z* (rel intensity) 768 (M^+, 0.2) 737 (0.4), 645 (6), 557 (6), 463 (20), 413 (80), 172 (50), 57 (100). HRMS, *m/z* calcd for $C_{42}H_{60}N_2O_{11}$: 768.4197, found: 768.4175.

4.5.10. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionic acid 2-({2-[2-(*tert*-butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenyl-propionyloxy]-ethyl}-methylamino)-ethyl ester (19). *dl* (76% ee): *meso*=1.5:1. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 20°C) δ 7.30–7.20 (m, 6H), 7.07–7.04 (m, 4H), 4.85–4.55 (m, 2H), 4.34–4.05 (m, 4H), 3.75–3.50 (m, 4H), 3.24 (s, 6H), 3.00 (d, J=13.3 Hz, 2H), 2.71 (br t, J=5.8 Hz, 4H), 2.34 (s, 3H), 1.51 (s, 18H), 1.48 (s, 6H). IR (neat) 2976, 1740, 1698 cm^{-1}. MS *m/z* (rel intensity) 729 (M^+, 1) 698 (1), 638 (8), 393 (70), 247 (100), 215 (40), 146 (40). HRMS, *m/z* calcd for $C_{39}H_{59}N_3O_{10}$: 729.4200, found: 729.4183. Determination of the ratio of *dl*- to *meso*-isomers and ee of the *dl*-isomer was performed with the corresponding benzoly derivative.

4.5.11. 2-Benzoylamino-2-methyl-3-phenylpropionic acid 2-{[2-(2-benzoylamino-2-methyl-3-phenylpropionyloxy)-ethyl]-methylamino}-ethyl ester. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=85:15, 1.0 mL/min, t_R=62, 74 (*meso*), 93 min. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (m, 4H), 7.48 (tt, J=6.3, 2.5 Hz, 2H), 7.39 (t, J=6.3 Hz, 4H), 7.23–7.18 (m, 4H), 7.12–7.08 (m, 4H), 6.76 (s, 2H), 4.27 (ABX, J_{AB}=11.4 Hz, $\Delta\nu_{AB}$=12.9 Hz, J_{AX}=6.0 Hz, 4H), 3.61, 3.60 (two d, J=13.5 Hz, 2H), 3.33 (d, J=13.5 Hz, 2H), 2.78 (t, J=6.0 Hz, 4H), 2.37 (s, 3H), 2.00–1.90 (m, 2H), 1.73 (s, 6H). IR (neat) 3305, 2939, 1734, 1645, 1578, 1531 cm^{-1}. MS *m/z* (rel intensity) 649 (M^+, 10), 558 (50), 366 (100), 275 (25), 238 (15). HRMS calcd for $C_{39}H_{43}N_3O_6$, M^+ 649.3151, found *m/z* 649.3149.

4.5.12. Preparation of (*S*)-*N*-*tert*-butoxycarbonyl-*N*-(methoxymethyl)phenylalanine 2-(2-hydroxyphenyl) ethyl ester (20). A KHMDS solution (0.45 M in THF, 33.3 mL, 15.0 mmol) was added to a solution of (*S*)-*N*-*tert*-butoxycarbonylphenylalanine benzyl ester[‡] (5.60 g, 15.8 mmol) in THF (20 mL) at −78°C. After stirring for 10 min, chloromethyl methyl ether (2.43 mL, 32.0 mmol) was added and stirring was continued for additional 21 h at −78°C. The mixture was poured into saturated aq. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, dioxane–hexane=1:10) to give (*S*)-*N*-*tert*-butoxycarbonyl-*N*-(methoxymethyl)phenylalanine benzyl ester (5.00 g, 79% yield) as a colorless oil. $[\alpha]_D^{20}$=−79 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.10 (m, 10H), 5.18 (ABq, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=20.3 Hz, 2H), 4.70, 4.56 (two d, J=10.8, 11.3 Hz, ratio=2:1, 1H), 4.34–4.14 (m, 1H), 3.98, 3.85 (two d, J=11.3, 10.8 Hz, ratio=1:2, 1H), 3.49–3.16 (m, 2H), 3.11, 3.00 (two s, ratio=2:1, 3H), 1.43 (s, 9H). IR (neat) 2976, 1742, 1707, 1455, 1428, 1367, 1299, 1170, 1092 cm^{-1}. MS *m/z* (rel intensity) 399 (M^+, 12), 367 (30), 311 (50), 298 (30), 267 (30), 208 (45), 132 (45), 91 (100). Anal. calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51%. Found: C, 68.91; H, 7.33; N, 3.49%.

A mixture of (*S*)-*N*-*tert*-butoxycarbonyl-*N*-methoxymethylphenylalanine benzyl ester (3.60 g, 11.7 mmol) and 10% Pd–C (0.36 g) in ethyl acetate (10 mL) was vigorously stirred under hydrogen atmosphere for 15 h. The mixture was filtered and the filtrate was evaporated in vacuo to give pure (*S*)-*N*-*tert*-butoxycarbonyl-*N*-(methoxymethyl)phenylalanine as a colorless oil (2.70 g, 92% yield). $[\alpha]_D^{20}$=−122 (*c* 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 7.32–7.16 (m, 5H), 4.76, 4.60 (two d, J=10.5, 11.1 Hz, ratio=3:2, 1H), 4.28 (t, J=8.5 Hz, 2/5H), 4.21 (dd, J=10.4, 4.6 Hz, 3/5H), 4.01, 3.83 (two d, J=11.1, 10.5 Hz, ratio=2:3, 1H), 3.40–3.15 (m, 2H), 3.23, 3.11 (two s, ratio=3:2, 3H), 1.50, 1.48 (two s, ratio=3:2, 9H). IR (neat) 3480, 2977, 1710, 1428, 1299, 1168 cm^{-1}. MS *m/z* (rel intensity) 309 (M^+, 10), 293 (20), 277 (15), 221 (40), 204 (20), 177 (25), 148 (40), 91 (65), 57 (100). HRMS calcd for $C_{16}H_{23}NO_5$; 309.1576, found 309.1563.

[‡] Dhaon, M. K., Olsen, R. K., Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

A solution of (*S*)-*N*-*tert*-butoxycarbonyl-*N*-(methoxymethyl)phenylalanine (100 mg, 0.32 mmol), 2-(2-benzyloxyphenyl)ethanol (88 mg, 0.38 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (92 mg, 0.48 mmol) and 4-dimethylaiminopyridine (4 mg, 0.03 mmol) in dichloromethane (3 mL) was stirred at 0°C for 1 h. The mixture was diluted with ethyl acetate and washed successively with water, saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, ethyl acetate–hexane=1:4) to give (*S*)-*N*-*tert*-butoxycarbonyl-*N*-(methoxymethyl)-phenylalanine 2-(2-benzyloxyphenyl)ethyl ester (140 mg, 84% yield). A mixture of this compound (56 mg, 0.11 mmol) and 10% Pd–C (6 mg) in ethyl acetate (2 mL) was vigorously stirred under hydrogen atmosphere for 20 h. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by preparative TLC (SiO_2, ethyl acetate–hexane=1:2) to give **20** (44 mg, 95% yield). Colorless oil. HPLC conditions: Daicel Chiralpak AD, 2-PrOH–hexane=5:95, 0.8 mL/min, t_R=21 (*S*), 29 (*R*) min. $[\alpha]_D^{20}$ (98% ee)=−84 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.06 (m, 7H), 6.87–6.76 (m, 2H), 6.13, 5.96 (two br s, ratio=1:2, 1H), 4.67, 4.57 (two d, J=11.0, 11.5 Hz, ratio=2:1, 1H), 4.44–4.17 (m, 3H), 4.07, 3.93 (two d, J=11.5, 11.0 Hz, ratio=1:2, 1H), 3.38–2.91 (m, 4H), 3.15, 3.10 (two s, ratio=2:1, 3H), 1.47, 1.45 (two s, ratio=1:2, 9H). IR (neat) 3381, 2976, 1741, 1708 cm^{-1}. MS *m/z* 429 (rel intensity) (M^+, 15), 397 (20), 297 (40), 120 (100), 91 (20). Anal. calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26%. Found: C, 66.79; H, 7.37; N, 3.18%.

4.5.13. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionic acid 2-(2-methoxyphenyl)-ethyl ester (25). Colorless oil. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=99:1, 1.0 mL/min, t_R=20 (S), 30 (*R*) min. $[\alpha]_D^{20}$ (97% ee)=−83 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.10 (m, 7H), 6.90–6.80 (m, 2H), 4.66, 4.55 (two d, J=10.9, 11.3 Hz, ratio=5:2, 1H), 4.42–4.10 (m, 3H), 4.07, 3.88 (two d, J=11.3, 10.9 Hz, ratio=2:5, 1H), 3.80 (s, 3H), 3.38–2.90 (m, 4H), 3.13, 3.05 (two s, ratio=5:2, 3H), 1.47 (s, 9H). IR (neat) 2973, 1741, 1707, 1495, 1428, 1367, 1245, 1172 cm^{-1}. MS *m/z* (rel intensity) 443 (M^+, 10), 342 (5), 312 (10), 252 (20), 220 (15), 164 (20), 135 (100). Anal. calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16%. Found: C, 67.58; H, 7.51; N, 3.09%.

4.6. General procedure for asymmetric alkylation of 20 and 25

A KHMDS solution in THF (0.45 M, 2.40 mL, 1.08 mmol) was diluted with 6 mL of toluene. A solution of **20** (dried azeotropically with toluene prior to use, 215 mg, 0.50 mmol) in toluene (4.0 mL) was added to the KHMDS solution at −78°C. After stirring for 30 min, methyl iodide (0.16 mL, 2.6 mmol) was added and stirring was continued for 15 h at −78°C. The mixture was poured into saturated aq. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2,

ethyl acetate–hexane=1:3) to give **21** (180 mg, 81% yield, 88% ee).

4.6.1. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenylpropionic acid 2-(2-hydroxyphenyl)-ethyl ester (21). Colorless oil. Enantiomeric excess of **4** was determined by HPLC analysis with Daicel Chiralpak AD, hexane–2-propanol=97:3, flow 1.0 mL/min, t_R=40 (*S*), 44 (*R*) min. $[\alpha]_D^{20}$ (88% ee)=−68 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.20 (m, 3H), 7.13–7.08 (m, 2H), 7.05–7.01 (m, 2H), 6.86–6.80 (m, 2H), 6.50, 6.26 (two br s, 1H), 4.85–4.55 (br m, 1H), 4.45–4.20 (br m, 2H), 3.80–3.50 (br m, 2H), 3.25 (s, 3H), 3.02–2.95 (m, 3H), 1.49 (s, 9H), 1.45 (s, 3H). IR (neat) 3408, 2978, 1740, 1702 cm^{-1}. MS *m/z* (rel intensity) 443 (M^+, 20), 352 (95), 252 (40), 146 (25), 120 (100), 91 (25). Anal. calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16%. Found: C, 67.68; H, 7.67; N, 3.21%.

4.6.2. 2-Benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-pent-4-enoic acid 2-(2-hydroxyphenyl)-ethyl ester (22). Colorless needles (toluene-hexane), mp 121.5–123°C. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=97:3, flow 1.0 mL/min, t_R=39, 45 min. $[\alpha]_D^{20}$ (82% ee, before recrystallization)=−40 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.20 (m, 3H), 7.15–7.08 (m, 2H), 7.05–6.96 (m, 2H), 6.88–6.78 (m, 2H), 6.39, 6.12 (two br s, ratio=2:1, 1H), 5.80–5.65 (br m, 1H), 5.14–4.98 (m, 2H), 4.75–4.45 (br, 1H), 4.34–4.15 (m, 2H), 3.73–3.30 (br, 2H), 3.29 (s, 3H), 3.15–3.06 (m, 1H), 2.97 (br t, *J*=6.8 Hz, 2H), 2.70–2.48 (m, 2H), 1.50, 1.47 (two s, ratio=2:1, 9H). IR (neat) 3411, 2977, 1740, 1703 cm^{-1}. MS *m/z* (rel intensity) 469 (M^+, 10), 437 (15), 278 (30), 218 (50), 172 (20), 120 (100). Anal. calcd for $C_{27}H_{35}NO_6$: C, 69.06; H, 7.50; N, 2.98%. Found: C, 68.97; H, 7.71; N, 2.91%.

4.6.3. 2-Benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-5-methyl-hex-4-enoic acid 2-(2-hydroxyphenyl)-ethyl ester (23). Colorless oil. Daicel Chiralpak AD, hexane–2-propanol=96:4, flow 0.6 mL/min, t_R=33, 37 min. $[\alpha]_D^{20}$ (87% ee)=−25 (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.19 (m, 3H), 7.13–7.07 (m, 2H), 7.01–6.96 (m, 2H), 6.86–6.80 (m, 2H), 6.54, 6.29 (two br s, ratio=2:1, 1H), 5.18 (br s, 1H), 4.75–4.47 (br m, 1H), 4.23 (br t, *J*=6.8 Hz, 2H), 3.77–3.33 (br m, 2H), 3.30 (s, 3H), 3.15 (d, *J*=13.6 Hz, 1H), 2.95 (t, *J*=7.0 Hz, 2H), 2.75–2.63 (br m, 1H), 2.46–2.35 (br m, 1H), 1.71 (s, 3H), 1.53 (s, 3H), 1.49 (br s, 9H). IR (neat) 3400, 2977, 2920, 1703, 1455, 1370, 1295 cm^{-1}. MS *m/z* (rel intensity) 497 (M^+, 5), 465 (40), 409 (50), 374 (50), 306 (20), 274 (20), 246 (15), 199 (30), 121 (100), 91 (70). HRMS calcd for $C_{29}H_{39}NO_6$, 497.2777; found 497.2790.

4.6.4. 2-Benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-5-phenyl-pent-4-enoic acid 2-(2-hydroxyphenyl)-ethyl ester (24). Colorless crystals (ether), mp 51–53°C. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=97:3, flow 0.8 mL/min, t_R=82, 89 min. $[\alpha]_D^{20}$ (87% ee, before recrystallization)=−11 (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.20 (m, 8H), 7.13–7.01 (m, 4H), 6.88–6.79 (m, 2H), 6.35–5.85 (br, 3H), 4.75–4.51 (br, 1H), 4.31–4.16 (m, 2H), 3.83–3.35 (br m, 2H), 3.32 (s, 3H), 3.18 (d, *J*=13.5 Hz, 1H), 2.96 (t of ABq, J_{AX}=7.3 Hz, J_{AB}=14.5 Hz, $\Delta\nu_{AB}$=15.6 Hz, 2H), 2.83–2.65 (m, 2H), 1.50 (br s, 9H). IR (neat) 3357, 2931, 1698, 1455, 1370, 1294 cm^{-1}. MS *m/z* (rel intensity) 545 (M^+, 15), 513 (10), 384 (40), 247 (50), 121 (100), 120 (80), 91 (70). HRMS calcd for $C_{33}H_{39}NO_6$; 545.2777, found 545.2764.

4.6.5. 2-(*tert*-Butoxycarbonyl-methoxymethylamino)-2-methyl-3-phenyl-propionic acid 2-(2-methoxyphenyl)-ethyl ester (26). Colorless oil. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=99:1, 1.0 mL/min, t_R=17, 24 min. $[\alpha]_D^{20}$ (77% ee)=−68 (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.15 (m, 5H), 7.04 (d, *J*=7.8 Hz, 1H), 7.03 (d, *J*=7.5 Hz, 1H), 6.87 (td, *J*=7.5, 0.9 Hz, 1H), 6.84 (d, *J*=8.2 Hz, 1H), 4.83–4.55 (br, 1H), 4.41–4.20 (br m, 2H), 3.82 (s, 3H), 3.71 (br d, *J*=12.1 Hz, 1H), 3.65–3.45 (br, 1H), 3.23 (s, 3H), 3.03–2.91 (m, 3H), 1.51 (s, 9H), 1.44 (s, 3H). IR (neat) 2978, 1739, 1799, 1496, 1373, 1297 cm^{-1}. MS *m/z* (rel intensity) 457 (M^+, 20), 411 (10), 366 (40), 266 (100), 178 (20), 135 (100), 91 (30). Anal. calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06%. Found: C, 68.20; H, 7.88; N, 3.01%.

4.6.6. 2-Benzyl-2-(*tert*-butoxycarbonyl-methoxymethylamino)-pent-4-enoic acid 2-(2-methoxyphenyl)-ethyl ester (27). Colorless oil. HPLC conditions: Daicel Chiralpak AD, hexane–2-propanol=99:1, 1.0 mL/min, t_R=18, 22 min. $[\alpha]_D^{20}$ (58% ee)=−35 (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.15 (m, 5H), 7.06–6.99 (m, 2H), 6.87 (t, *J*=7.5 Hz, 1H), 6.84 (d, *J*=8.4 Hz, 1H), 5.77–5.64 (m, 1H), 5.12 (d, *J*=9.1 Hz, 1H), 5.09 (d, *J*=15.9 Hz, 1H), 4.80–4.50 (br, 1H), 4.35–4.17 (br m, 2H), 3.81 (s, 3H), 3.75–3.65 (br, 1H), 3.50–3.25 (br, 1H), 3.27 (s, 3H), 3.13 (d, *J*=13.6 Hz, 1H), 2.96 (t of ABq, J_{AX}=7.0 Hz, J_{AB}=13.6 Hz, $\Delta\nu_{AB}$=9.8 Hz, 2H), 2.80–2.69 (br m, 1H), 2.65–2.57 (m, 1H), 1.50 (s, 9H). IR (neat) 2977, 1741, 1701, 1496, 1370, 1293, 1245 cm^{-1}. MS *m/z* (rel intensity) 483 (M^+, 5), 392 (40), 342 (25), 292 (100), 204 (25), 172 (45), 135 (100), 134 (70), 91 (50). Anal. calcd for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90%. Found: C, 69.37; H, 7.70; N, 2.95%.

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