Stereochemical Study on α-Alkylation of β-Branched α-Amino Acid Derivatives via Memory of Chirality

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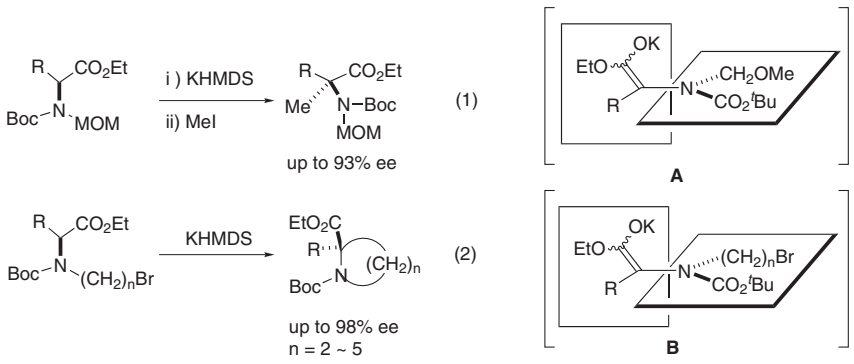
Received 21 March 2005

Abstract: α-Alkylation of *N*-Boc-*N*-MOM amino acid derivatives with an additional chiral center at the β-carbon proceeded with retention of configuration, irrespective of the chirality at the β-carbon. The C–N axial chirality of the enolate intermediates played a decisive role in the stereochemical course of the alkylation, while the central chirality of the β-carbon had little effect. Amino acid derivatives with contiguous quaternary and tertiary stereocenters are readily obtained in a stereochemically expectable manner.

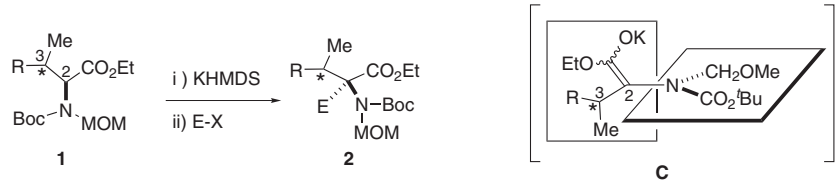
Key words: axial chirality, amino acid, memory of chirality, enolate, quaternary stereocenter

The stereoselective construction of chiral quaternary stereocenters is one of the most challenging tasks in current synthetic organic chemistry.[1] We have developed a direct method for the enantioselective construction of α,α-disubstituted α-amino acids from usual α-amino acids via memory of chirality.[2,3] Under these conditions, α-methylation of *N*-*tert*-butoxycarbonyl(Boc)-*N*-methoxymethyl(MOM)-α-amino acid derivatives takes place in up to 93% ee without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts [Scheme 1, (1)].[4] A chiral nonracemic enolate **A** with a chiral C–N axis has been proposed as the crucial intermediate for this novel asymmetric induction, whose racemization barrier is 16.0 kcal/mol (when R = CH_2Ph). The corresponding half-life of racemization is 22 hours at –78 °C.[4] We further developed a route for the straightforward synthesis of cyclic amino acids with a quaternary stereocenter from readily available α-amino acids via memory of chirality [Scheme 1, (2)].[5] An axially chiral enolate intermediate **B** was also proposed to be a crucial intermediate based on several experimental evidence.[5]

In the course of study of asymmetric synthesis based on memory of chirality, we became interested in the stereochemistry of α-alkylation of β-branched α-amino acid derivatives **1** that have chiral centers at C(2) and C(3) (Scheme 2). If the chiral information at C(2) is lost with formation of the enolate, the stereochemical course of α-alkylation of **1** should be totally controlled by the chirality at C(3). On the other hand, if the chirality of C(2) is preserved as C–N axial chirality as shown in **C**, the stereochemical course should be affected by chirality both at C(2) and C(3).



Scheme 1



Scheme 2

SYNTHESIS 2005, No. 8, pp 1368–1377
Advanced online publication: 25.04.2005
DOI: 10.1055/s-2005-865337; Art ID: E13305SS

Biographical Sketches

Takeo Kawabata was born in Osaka, Japan in 1955. He received his PhD in 1983 from Kyoto University under the guidance of Professor Eiichi Fujita. After working as a postdoctoral fellow (1983–1985) at Indiana University with Professor Paul A. Grieco, he joined Sagami Chemical Research Center as a researcher (1985–1989). He was appointed as Assistant Professor of the Institute for Chemical Research, Kyoto University, in 1989 and promoted to Associate Professor in 1998, and Professor in 2004. He received the Pharmaceutical Society of Japan Award for Young Scientists in 1995. His research interests include asymmetric synthesis, enolate chemistry, nucleophilic catalysis, and structural and functional investigation of heterochiral oligomers.

Jianyong Chen was born in 1966 in Suzhou, Jiangsu, China. He obtained his BSc (medicinal chemistry) in 1989 and MSc (medicinal chemistry) in 1992 from China Pharmaceutical University. From 1992 to 1996 he worked at the Department of Medicinal Chemistry of China Pharmaceutical University. He moved to Shanghai Institute of Materia Medica, Chinese Academy of Sciences in September 1996 and received his PhD (organic chemistry) in 1999. From August 1999 to October 2001, he worked as a postdoctoral fellow with Dr. Takeo Kawabata and Prof. Kaoru Fuji at the Institute of Chemical Research, Kyoto University, Japan. His research focused on asymmetric synthesis based on memory of chirality. Since 2001, he is working as a postdoctoral fellow at University of Michigan, USA.

Hideo Suzuki was born in Osaka, Japan in 1970. He received his PhD degree in 1998 from Kyoto University under the supervision of Professor Kaoru Fuji. He then joined Professor K. C. Nicolaou's group as a postdoctoral fellow at The Scripps Research Institute, USA, studying the total synthesis of Everninomicins. He moved to Array BioPharma, Colorado, in 2000. Since 2003, he is working for Takeda Pharmaceutical Company, Osaka, Japan. His research interests include asymmetric synthesis, natural product synthesis, process chemistry, and drug discovery.

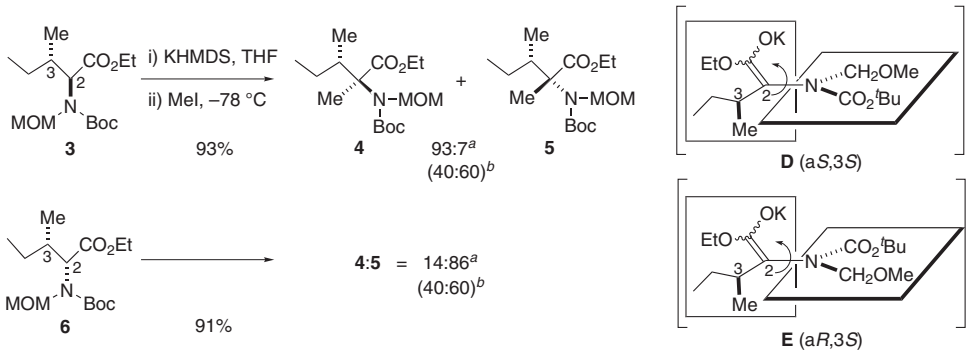
Kaoru Fuji was born in Osaka, Japan in 1938. He received both his BA and PhD degrees from Kyoto University. He was appointed Assistant Professor at the Institute for Chemical Research, Kyoto University, in 1967. After a postdoctoral stay with James P. Kutney at the University of British Columbia in Canada (1971–1973), he was promoted to Associate Professor in 1973, and Professor in 1983. During that time, he joined P. Gassman's group at the University of Minnesota as a research fellow (1981–1982). Dr. Fuji has been a recipient of the Pharmaceutical Society of Japan Award for Young Scientists (1980) and of the Pharmaceutical Society of Japan Award (1998), and held visiting positions at the Université Louis Pasteur de Strasbourg, France (1991 and 1994), at the Université Paris-Sud (1996) and at the Technical University of Vienna, Austria (2000). He joined Otsuka Pharmaceutical Company, Tokushima, as a counselor in 2002. In 2004, he moved to the Faculty of Pharmaceutical Sciences, Hiroshima International University, as a dean. His research interests include asymmetric synthesis, natural product synthesis, and design and synthesis of artificial receptors.

The stereochemical question was examined with a pair of diastereomers, L-isoleucine derivative **3** and D-*allo*-isoleucine derivative **6** (Scheme 3).[6] Treatment of **3** with 1.1 mole equivalent of potassium hexamethyl disilazide (KHMDS) in THF at –78 °C for 60 minutes followed by the addition of methyl iodide gave a mixture of diastereomers **4** and **5** in a 93:7 ratio and a combined yield of 93%. The same treatment of **6** gave a mixture of **4** and **5** in a 14:86 ratio and a combined yield of 91%. The stereochemistry of **5** was unambiguously determined to be (2*R*,3*S*) by an X-ray crystallographic analysis of the corresponding *p*-nitrobenzamide derivative.[6] α-Methylation of both **3** and **6** occurred with retention of configuration at C(2). α-Methylation of **3** gave **4** as a major diastereomer whereas **6** gave **5** as a major diastereomer, although both **3** and **6** have an (*S*)-chiral center at C(3). Thus, chirality at C(2) contributed decisively to the stereochemical course of the α-methylation of **3** and **6** even in the presence of the adjacent chiral center C(3). We assume **D** (a*S*,3*S*) and **E** (a*R*,3*S*) as the possible structures of chiral enolate intermediates generated from **3** and **6**, respectively, by analogy with our recent results.[2,3h,4,5] The C(2)–N axial chirality in **D** and **E** played a predominant role in the stereochemical course of α-methylation, while central chirality at C(3) had little effect.

When **3** was treated with KHMDS in THF at –78 °C for 60 minutes and then at 0 °C for 30 minutes, the subsequent addition of methyl iodide at –78 °C gave a mixture of **4** and **5** in a 40:60 ratio and a combined yield of 88%. The same treatment of **6** gave a mixture of **4** and **5** in exactly the same ratio and a combined yield of 90%. This indicates that warming to 0 °C caused epimerization of the chiral C–N axis, leading to complete thermodynamic equilibrium between **D** and **E** either from **3** or **6**.[7] The half-life of epimerization of the chiral C–N axis in **D** and **E** is estimated to be shorter than one second at 0 °C, on the assumption that the rotational barrier of the C–N axis in **D** and **E** is comparable to that of **A** (R = CH_2Ph, 16.0 kcal/mol at –78 °C) and $\Delta S^{\neq}$ of the restricted bond rotation is nearly zero.

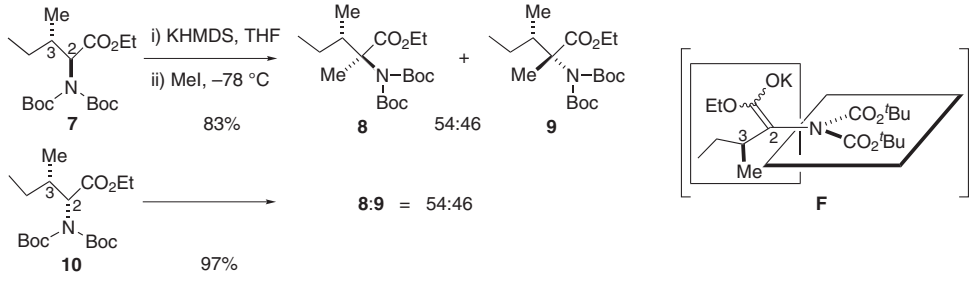
Since the Boc and MOM groups at the nitrogen seem to be essential for the generation of the C–N axial chirality, we next examined the reactions of the corresponding *N*,*N*-di-Boc derivatives **7** and **10** that do not generate axially chiral enolates (Scheme 4).[8] Upon α-methylation under the conditions identical to those for alkylation of **3** and **6**, **7** afforded a mixture of **8** and **9** in a 54:46 ratio and 83% yield.[9] The exactly same diastereomer ratio of **8** and **9** was obtained in the α-methylation of **10** (97% yield). The stereochemical course of the α-methylation of **7** and **10** was totally controlled by the chirality at C(3), irrespective of the chirality at C(2), which is in sharp contrast to the reactions of **3** and **6**. These results suggest that the reactions of both **7** and **10** share a common enolate intermediate **F**.[8]

From the studies with isoleucine derivatives **3** and **6**, it could be concluded that the stereochemical course of the α-methylation was controlled by the C–N axial chirality derived from central chirality at C(2), while central chirality at C(3) had little effect.[10] However, the effects of such



a) The enolate formation was performed at –78 °C for 1 h.
b) The enolate formation was performed at –78 °C for 1 h and then at 0 °C for 30 min.

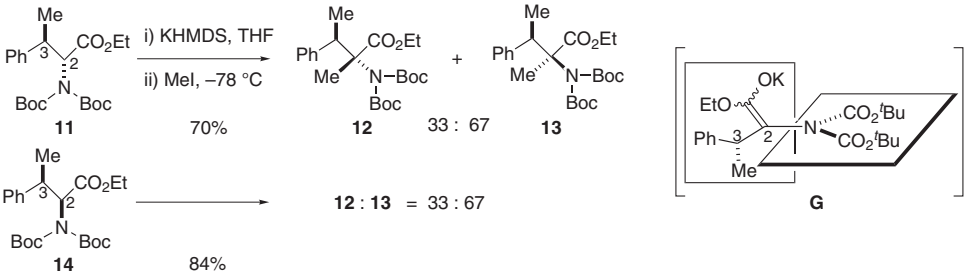
Scheme 3



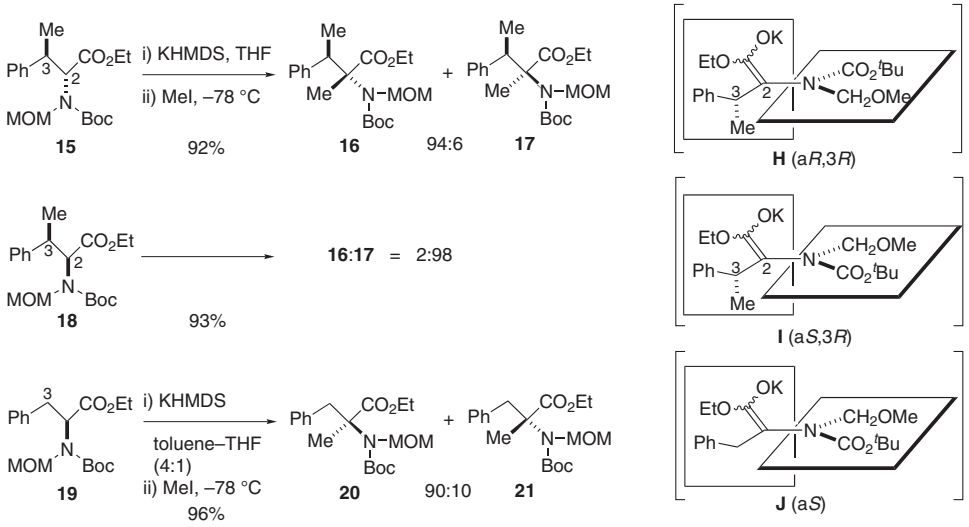
Scheme 4

a chiral center, that consists of ethyl, methyl, and hydrogen, on the stereochemical course of the α-alkylation must be intrinsically very small, and it is estimated to be $\Delta\Delta G^{\neq} = 0.06$ kcal/mol based on the reactions of **7** and **10** in Scheme 4. We then turned our attention to β-methylphenylalanine derivatives as substrates for further elucidation because a chiral center consisting of phenyl, methyl, and hydrogen is expected to show a more pronounced effect on the stereochemistry of α-alkylation (Scheme 5). At first, we examined reactions of *N*,*N*-di-Boc derivatives of β-methylphenylalanine, **11** and **14**. Since they do not generate axially chiral enolates,[11] the diastereomeric ratio observed in the α-methylation should be a measure of the effect of the C(3) chiral center. Upon α-methylation under conditions identical to those for **7** and **10**, **11** gave a mixture of **12** and **13** in a 33:67 ratio and in 84% yield. The exactly same diastereomer ratio of **12** and **13** was obtained from **14**, the C(2)-epimer of **11**. The stereochemical course was totally controlled by the chirality at C(3), independent of the chirality at C(2). These results again suggest that the reactions of both **11** and **14** share a common enolate intermediate **G**.[11] The effect of the C(3) chiral center in **11** and **14** was estimated to be $\Delta\Delta G^{\neq} = 0.27$ kcal/mol based on the ratio (33:67) and it is significantly larger than that of **7** and **10**. Then, α-methylation of *N*-Boc-*N*-MOM-β-methylphenylalanine derivative **15** was performed by treatment with KHMDS in THF at –78 °C for one hour followed by methyl iodide for 20 hours to give a mixture of **16** and **17** in a 94:6 ratio and a combined yield of 92% (Scheme 6). The same treatment of **18** gave a mixture of **16** and **17** in a 2:98 ratio and a combined yield of 93%. Thus, chirality at C(2) has a decisive effect on the stereochemical course of the α-methylation irrespective of the chirality of the adjacent C(3) chiral center. We assume **H** (a*R*,3*R*) and **I** (a*S*,3*R*) as the possible structures of chiral enolate intermediates generated from **15** and **18**, respectively. Comparing the stereoselectivity of α-methylation of **15** and **18** to that of **19**, which is lacking a chiral center at C(3), it might be expected that one of the diastereomers, **15** and **18**, would show higher stereoselectivity (*matched*) than **19**, the other would show lower stereoselectivity (*mismatched*) than **19**. Surprisingly, however, α-methylation of both **15** and **18** showed higher stereoselectivity in their α-methylation than that of **19**. This would be resulting from higher stereochemical purity of C–N axial chirality in **H** and **I** compared to **J** and/or the higher face selectivity in the reactions of **H** and **I** with methyl iodide compared to that of **J**.

The corresponding reactions using racemates of **15** and **18** were examined. α-Methylation of *rac*-**15** (*anti*) under the same conditions as applied for (2*R*,3*R*)-**15** gave racemic **16** and **17** in a 94:6 ratio and a combined yield of 93%. Similarly, α-methylation of *rac*-**18** (*syn*) gave racemic **16**



Scheme 5



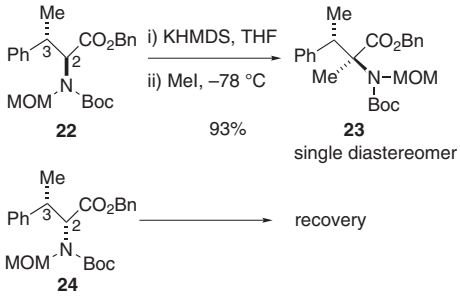
Scheme 6

and **17** in a 3:97 ratio and a combined yield of 91%. No significant difference in the stereochemistry of alkylation was observed between optically pure and racemic substrates. These results indicate that the aggregate structure of intermediary enolates does not significantly contribute to the stereochemical course of alkylation of **15** and **18**, which is in contrast to the case of **19**.[3h] In order to gain insight into the effect of the aggregate structure of enolate intermediates on stereoselectivity, solvent effects on the α-methylation of **3**, **6**, and **19** were examined. α-Methylation of **19** proceeded with the highest enantioselectivity in toluene–THF (4:1) to give **20** and **21** in a 90:10 ratio, while a 67:33 ratio was observed in THF.[3h] A much diminished solvent effect was observed in the α-methylation of **3** and **6**. α-Methylation of **3** and **6** in THF gave **4** and **5** in ratios of 93:7 and 14:86, respectively, as already described in Scheme 3, while in toluene–THF (4:1) **4** and **5** were obtained in ratios of 91:9 and 12:88 from **3** and **6**, respectively. These results led us to suggest that the aggregate structure of an enolate generated from **19** contributes significantly to the stereochemical course of α-alkylation, while a similar effect is not observed for the α-alkylation of **3** and **6**.

Complete control of the stereochemistry of α-methylation was achieved using the corresponding benzyl ester derivative **22**. α-Methylation of **22** under the standard conditions gave **23** as the only detectable product in 93% yield, while the reaction of **24** resulted in total recovery (Scheme 7).

Determination of the stereochemistry in **12**, **13**, **16**, and **17** was achieved by their transformation into either **25** or **26**.[12] Treatment of a 94:6 mixture of **16** and **17** obtained from the reaction of **15** with 6 M HCl at 100 °C followed by purification with ion exchange resin gave a 94:6 mixture of **25** and **26**. The stereochemistry of **25** and **26** thus obtained was determined by comparison of the ^{1}H NMR spectral data with those reported in the literature.[12] Similarly, the stereochemistry in **12** and **13** was determined by the transformation into **25** and **26**, respectively (Figure 1).

Although the stereochemistry in **12**, **13**, **16**, and **17** could be assigned based on the transformation into the known amino acids, **25** and **26**, some ambiguity remained because of no obvious difference between the ^{1}H NMR spectra of **25** and **26**.[12] Thus, the stereochemistry in **16** and **17**



Scheme 7

was further confirmed by NOE measurements carried out with the corresponding tetrahydroisoquinoline derivatives **27** and **28**, respectively (Figure 2). Removal of the nitrogen substituents of a 94:6 mixture of **16** and **17** by treatment with 4 M HCl in ethyl acetate followed by Pictet–Spengler reaction gave, after purification by column chromatography, diastereomerically pure **27**. Similarly, a 2:98 mixture of **16** and **17** was transformed into diastereomerically pure **28**.[13] NOE's between C(3)-Me/C(4)-H and C(3)-Me/C(4)-Me were observed in **27**, which is consistent with the most stable conformation **K** generated by molecular modeling of **27** with MM3* force field.[14] *syn*-Orientation between C(3)-Me and C(4)-H in **28** was indicated by the observation of the strong NOE in between, which is consistent with the most stable conformation **L** with the 3,4-dimethyl groups in diaxial conformation.[14]

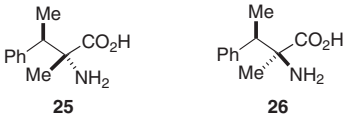


Figure 1

In conclusion, α-alkylation of β-branched *N*-Boc-*N*-MOM-α-amino acid derivatives proceeded in retention of the configuration, irrespective of the chirality at the β-carbon. The stereochemical course of the alkylation was controlled by the C–N axial chirality derived from central chirality at the α-carbon, while central chirality at the β-carbon had little effect. This provides a straightforward method for the preparation of amino acid derivatives with

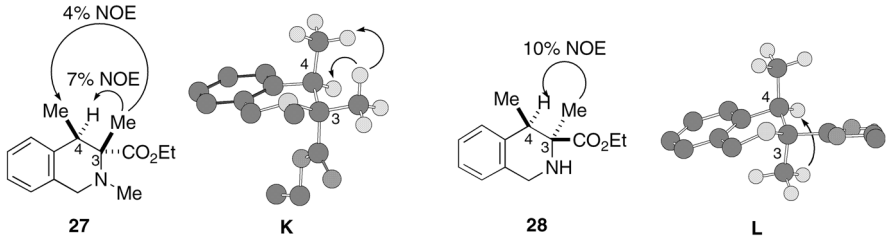


Figure 2 NOE's observed in **27** and **28** and their most stable conformations **K** and **L**. Hydrogen atoms, except C(3)-Me, C(4)-Me, and C(4)-H, in **K** and **L** are omitted for clarity.

contiguous quaternary and tertiary stereocenters in a stereochemically expectable manner.[15,16]

Melting points were measured using a Yanagimoto micro point apparatus and are uncorrected. NMR spectra were obtained with a Varian Gemini 200 (200 MHz) spectrometer or a JEOL JMN-GX 400 spectrometer, with chemical shifts given in ppm (internal standards: TMS or $CHCl_3$, indicating 0 or 7.24, respectively). IR spectra were recorded on a JASCO FT/IR-300 spectrometer. Specific rotations were measured with a Horiba SEPA-200 automatic digital polarimeter. Mass spectra were recorded on a JEOL JMS-DX300 mass spectrometer. TLC analyses and preparative TLC were performed on commercial glass plates bearing a 0.25 mm layer or 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, Et_2O, hexane, CH_2Cl_2, and toluene; <50 ppm water contents) were purchased from Kanto Chemical Co., Inc. and used without further treatment.

(2*S*,3*S*)-*N*-*tert*-Butoxycarbonyl-*N*-(methoxymethyl)isoleucine Ethyl Ester (3)

N,*N*-Diisopropylethylamine (6.97 mL, 40mmol) and di-*tert*-butyl dicarbonate (4.80 g, 22 mmol) were added to a solution of (2*S*,3*S*)-isoleucine ethyl ester hydrochloride (3.91 g, 20 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The mixture was warmed to r.t. and stirred for 20 h, then poured into sat. aq NH_4Cl (50 mL) and extracted with EtOAc (300 mL). The organic layer was washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, EtOAc–hexane, 1:9) to give (2*S*,3*S*)-*N*-(*tert*-butoxycarbonyl)isoleucine ethyl ester as a colorless oil (5.13 g, 99% yield).

$[\alpha]_D^{19}$ +16 (*c* 1.0, $CHCl_3$).

IR (neat): 3371, 2971, 2935, 1715, 1505, 1456, 1367 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.04 (d, *J* = 7.8 Hz, 1 H), 4.26–4.13 (m, 3 H), 1.89–1.80 (m, 1 H), 1.48–1.39 (m, 1 H), 1.45 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.23–1.12 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

MS (EI): *m*/*z* (%) = 259 (M^+), 244, 214, 203, 186, 158, 147, 130.

Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 59.94; H, 9.80; N, 5.34.

Potassium hexamethyldisilazide (KHMDS)[17] (0.46 M in THF, 12.3 mL, 5.7 mmol) was added to a solution of (2*S*,3*S*)-*N*-(*tert*-butoxycarbonyl)isoleucine ethyl ester (1.55 g, 6.0 mmol) in THF (5 mL) at –78 °C. After 30 min, chloromethyl methyl ether (1.37 mL, 18 mmol) was added and the mixture was gradually warmed to r.t. during a period of 20 h. The mixture was poured into sat. aq NH_4Cl (50 mL) and extracted with EtOAc (300 mL). The organic layer was washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:9) to give **3** as a colorless oil (1.68 g, 93% yield).

$[\alpha]_D^{19}$ –44 (*c* 1.0, $CHCl_3$).

IR (neat): 2978, 1742, 1707, 1367, 1300, 1255, 1143, 1083 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.86–4.67 (m, 2 H), 4.33 (br m, 0.5 H), 4.21–4.10 (m, 2 H), 3.92 (br d, *J* = 8.1 Hz, 0.5 H), 3.34 (br s, 3 H), 2.14–1.98 (m, 1 H), 1.56–1.39 (m, 1 H), 1.47 (s, 9 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 1.15–1.01 (m, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H).

MS (EI): *m*/*z* (%) = 303 (M^+), 272, 247, 230, 202, 172, 146, 130.

Anal. Calcd for $C_{15}H_{29}NO_5$: C, 59.38; H, 9.63; N, 4.62. Found: C, 59.18; H, 9.82; N, 4.61.

(2*R*,3*S*)-*N*-*tert*-Butoxycarbonyl-*allo*-isoleucine Ethyl Ester

Prepared from (2*R*,3*S*)-*allo*-isoleucine ethyl ester hydrochloride according to the procedure for (2*S*,3*S*)-*N*-(*tert*-butoxycarbonyl)isoleucine ethyl ester in 96% yield.

$[\alpha]_D^{19}$ –17 (*c* 1.2, $CHCl_3$).

IR (neat): 3373, 2971, 2935, 1716, 1505, 1458, 1367 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.98 (d, *J* = 9.2 Hz, 1 H), 4.34 (dd, *J* = 3.6, 9.2 Hz, 1 H), 4.25–4.14 (m, 2 H), 1.96–1.85 (m, 1 H), 1.50–1.40 (m, 1 H), 1.45 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.23–1.15 (m, 1 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H).

MS (EI): *m*/*z* (%) = 259 (M^+), 244, 214, 203, 186, 158, 147, 130.

Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.04; H, 9.88; N, 5.39.

(2*R*,3*S*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-*allo*-isoleucine Ethyl Ester (6)

Prepared from (2*R*,3*S*)-*N*-*ter*t-butoxycarbonyl-*allo*-isoleucine ethyl ester according to the procedure for **3** in 78% yield.

$[\alpha]_D^{19}$ +48 (*c* 1.2, $CHCl_3$).

IR (neat): 2974, 1745, 1705, 1367, 1295, 1176, 1086 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.84–4.67 (m, 2 H), 4.26 (br d, *J* = 8.7 Hz, 0.5 H), 4.20–4.10 (m, 2 H), 3.86 (br d, *J* = 9.0 Hz, 0.5 H), 3.35, 3.32 (2 br s, 3 H), 2.23–2.09 (m, 1 H), 1.62–1.51 (m, 1 H), 1.46 (s, 9 H), 1.27 (br t, *J* = 6.3 Hz, 3 H), 1.20–1.07 (m, 1 H), 0.93 (t, *J* = 7.3 Hz, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H).

MS (EI): *m*/*z* (%) = 303 (M^+), 272, 247, 230, 202, 172, 146, 130.

Anal. Calcd for $C_{15}H_{29}NO_5$: C, 59.38; H, 9.63; N, 4.62. Found: C, 59.33; H, 9.76; N, 4.57.

α-Methylation of 3: (2*S*,3*S*)- and (2*R*,3*S*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α-methylisoleucine Ethyl Esters (4 and 5), and (2*S*,3*S*)-*N*-*p*-Nitrobenzoyl-α-methylisoleucine Ethyl Ester

A solution of **3** (dried azeotropically with toluene prior to use, 152 mg, 0.5 mmol) in THF (4.5 mL) was added to a solution of KHMDS[17] (0.50 M in THF, 1.1 mL, 0.55 mmol) at –78 °C. After 60 min, MeI (0.31 mL, 5.0 mmol) was added and the mixture was stirred at –78 °C for 20 h, then poured into sat. aq NH_4Cl (20 mL) and extracted with EtOAc (150 mL). The organic layer was washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, EtOAc–hexane, 1:12) to give an inseparable mixture (154 mg) of **4** and **5**, and a trace amount (≤4%) of **3**. The combined yield of **4** and **5** and the diastereomeric ratio were determined by 400 MHz ^1H NMR spectroscopy to be 93% and 93:7, respectively.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.12, 5.08 (2 d, *J* = 11.8, 11.7 Hz, ratio = 1:<10, 1 H), 4.58, 4.53 (2 d, *J* = 11.7, 11.8 Hz, ratio = 93:7, 1 H), 4.20–4.06 (m, 2 H), 3.36, 3.35 (2 s, ratio = 93:7, 3 H), 2.37–2.17 (m, 1 H), 1.92–1.80, 1.55–1.42 (2 m, ratio = 1:>10, 1 H), 1.49 (s, 3 H), 1.45 (s, 9 H), 1.26, 1.25 (2 t, *J* = 7.3, 7.3 Hz, ratio = >10:1, 3 H), 1.02, 0.84 (2 d, *J* = 6.6, 6.8 Hz, ratio = 93:7, 3 H), 1.00–0.85 (m, 1 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

MS (EI): *m*/*z* (%) = 317 (M^+), 286, 260, 244, 216, 186, 160, 140, 112.

Exact mass calcd for $C_{16}H_{31}NO_5$: 317.2202; found: *m*/*z* 317.2217.

An analytically pure sample of the mixture of **4** and **5** was obtained by removing the trace amount of **3** through selective ester hydrolysis (10% KOH/dioxane = 4:1, Bu_4NI, 50 °C). The diastereomeric ratio of **4** to **5** did not alter before and after hydrolysis.

IR (neat): 2976, 1740, 1702, 1409, 1367, 1299, 1252, 1173, 1104, 1084 cm^{-1}.

Anal. Calcd for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41. Found: C, 60.58; H, 9.99; N, 4.40.

The mixture (120 mg) was dissolved in 4 M HCl in EtOAc (3 mL) and the solution was stirred at r.t. for 1 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2 (2 mL) and treated with *N,N*-diisopropylethylamine (0.20 mL, 1.1 mmol) and *p*-nitrobenzoyl chloride (140 mg, 0.76 mmol) at r.t. for 4 h. Work-up followed by purification by flash column chromatography ($CHCl_3$–acetone, 60:1) gave a mixture of (2*S*,3*S*)- and (2*R*,3*S*)-*N*-*p*-nitrobenzoyl-α-methylisoleucine ethyl ester (110 mg, 94% yield). Recrystallization from Et_2O–hexane (2:1) gave diastereomerically and analytically pure (2*S*,3*S*)-*N*-*p*-nitrobenzoyl-α-methylisoleucine ethyl ester.

Colorless needles (ether–hexane), mp 135–136 °C.

$[\alpha]_D^{18}$ +14 (*c* 1.1, $CHCl_3$).

IR (KBr): 3439, 2971, 1728, 1663, 1603, 1525, 1510, 1482 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 8.30 (d, *J* = 8.7 Hz, 2 H), 8.05 (d, *J* = 8.7 Hz, 2 H), 7.96 (br s, 1 H), 4.15 (q of ABq, J_{AB} = 10.7 Hz, J_{AX} = 7.0 Hz, $\Delta\nu_{AB}$ = 15.9 Hz, 2 H), 1.98–1.83 (m, 2 H), 1.56 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.18–1.10 (m, 1 H), 0.96 (t, *J* = 7.2 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H).

MS (EI): *m*/*z* (%) = 322 (M^+), 293, 277, 265, 249, 219, 167, 150, 134, 104, 92, 76.

Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.60; H, 6.99; N, 8.66.

α-Methylation of 6: (2*R*,3*S*)-*N*-*p*-Nitrobenzoyl-α-methyl-*allo*-isoleucine Ethyl Ester

α-Methylation of **6** was performed according to the procedure for the methylation of **3**. The reaction residue was purified by flash column chromatography (SiO_2, EtOAc–hexane, 1:12) to give an inseparable mixture (154 mg) of **4** and **5**, and a trace amount (≤6%) of **6**. The combined yield of **4** and **5** and the diastereomeric ratio were determined by 400 MHz ^1H NMR spectroscopy to be 91% and 14:86, respectively. The mixture (129 mg) was treated with 4 M HCl in EtOAc followed by *p*-nitrobenzoyl chloride to give a mixture of (2*S*,3*S*)- and (2*R*,3*S*)-*N*-*p*-nitrobenzoyl-α-methylisoleucine ethyl ester (118 mg, 90% yield). Recrystallization from Et_2O–hexane (2:1) gave diastereomerically and analytically pure (2*R*,3*S*)-*N*-*p*-nitrobenzoyl-α-methylisoleucine ethyl ester.

Colorless prisms (ether–hexane), mp 129–130 °C.

$[\alpha]_D^{18}$ –17 (*c* 1.0, $CHCl_3$).

IR (KBr): 3437, 2973, 1727, 1663, 1523, 1482 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 8.30 (d, *J* = 8.7 Hz, 2 H), 8.06 (d, *J* = 8.7 Hz, 2 H), 7.88 (s, 1 H), 4.15 (q of ABq, J_{AB} = 10.7 Hz, J_{AX} = 7.0 Hz, $\Delta\nu_{AB}$ = 7.6 Hz, 2 H), 2.04–1.97 (m, 1 H), 1.68–1.61 (m, 1 H), 1.58 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.13–1.09 (m, 1 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

MS (EI): *m*/*z* (%) = 322 (M^+), 293, 277, 265, 249, 219, 167, 150, 134, 104, 92, 76.

Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.50; H, 6.96; N, 8.44.

(2*S*,3*S*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)isoleucine Ethyl Ester (7)

Potassium hexamethyldisilazide (KHMDS)[17] (0.51 M in THF, 5.56 mL, 2.8 mmol) was added to a solution of (2*S*,3*S*)-*N*-(*tert*-butoxycarbonyl)isoleucine ethyl ester (777 mg, 3.0 mmol) in THF (20 mL) at –78 °C. After 30 min, di-*tert*-butyl dicarbonate (1.31 g, 6.0 mmol) was added and the mixture was gradually warmed to r.t. during a period of 20 h. The reaction mixture was poured into sat. aq NH_4Cl (30 mL) and extracted with EtOAc (150 mL). The organic layer was washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:15) to give **7** as a colorless oil (710 mg, 66% yield).

$[\alpha]_D^{19}$ –43 (*c* 1.0, $CHCl_3$).

IR (neat): 2979, 1748, 1705, 1456, 1368, 1311, 1237, 1130 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.53 (d, *J* = 9.5 Hz, 1 H), 4.15 (q of ABq, J_{AB} = 10.7 Hz, J_{AX} = 7.0 Hz, $\Delta\nu_{AB}$ = 14.4 Hz, 2 H), 2.29–2.22 (m, 1 H), 1.49 (s, 18 H), 1.48–1.38 (m, 1 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.10 (d, *J* = 6.5 Hz, 3 H), 1.07–0.99 (m, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^1H NMR (400 MHz, C_6D_6): δ = 4.87 (d, *J* = 9.4 Hz, 1 H), 3.96 (q of ABq, J_{AB} = 10.9 Hz, J_{AX} = 7.0 Hz, J_{AB} = 23.8 Hz, 2 H), 2.58–2.51 (m, 1 H), 1.67–1.59 (m, 1 H), 1.40 (s, 18 H), 1.27–1.22 (m, 1 H), 1.20 (d, *J* = 6.5 Hz, 3 H), 0.96 (t, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

MS (EI): *m*/*z* (%) = 359 (M^+), 303, 286, 258, 247, 202, 186, 147, 130.

Anal. Calcd for $C_{18}H_{33}NO_6$: C, 60.14; H, 9.25; N, 3.90. Found: C, 59.94; H, 9.37; N, 3.90.

(2*R*,3*S*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)-*allo*-isoleucine Ethyl Ester (10)

Prepared from (2*R*,3*S*)-*N*-(*tert*-butoxycarbonyl)-*allo*-isoleucine ethyl ester according to the procedure for **7** in 85% yield.

$[\alpha]_D^{19}$ +41 (*c* 1.0, $CHCl_3$).

IR (neat): 2979, 1747, 1456, 1368, 1314, 1235, 1132 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.56 (d, *J* = 9.2 Hz, 1 H), 4.15 (q of ABq, J_{AB} = 10.9 Hz, J_{AX} = 7.1 Hz, $\Delta\nu_{AB}$ = 14.2 Hz, 2 H), 2.33–2.26 (m, 1 H), 1.82–1.72 (m, 1 H), 1.49 (s, 18 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.21–1.16 (m, 1 H), 0.95 (t, *J* = 7.5 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H).

^1H NMR (400 MHz, C_6D_6): δ = 4.88 (d, *J* = 9.0 Hz, 1 H), 3.97 (q of ABq, J_{AB} = 10.9 Hz, J_{AX} = 7.2 Hz, $\Delta\nu_{AB}$ = 26.2 Hz, 2 H), 2.61–2.54 (m, 1 H), 1.96–1.87 (m, 1 H), 1.39 (s, 18 H), 1.36–1.23 (m, 1 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.97 (t, *J* = 7.2 Hz, 3 H), 0.96 (t, *J* = 7.5 Hz, 3 H).

MS (EI): *m*/*z* (%) = 359 (M^+), 303, 286, 258, 247, 202, 186, 147, 130.

Anal. Calcd for $C_{18}H_{33}NO_6$: C, 60.14; H, 9.25; N, 3.90. Found: C, 59.98; H, 9.38; N, 4.01.

(2*R*,3*R*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)-β-methylphenylalanine Ethyl Ester (11)

Potassium hexamethyldisilazide (KHMDS)[17] (0.53 M in THF, 1.81 mL, 0.95 mmol) was added to a solution of (2*R*,3*R*)-*N*-*tert*-butoxycarbonyl-β-methylphenylalanine ethyl ester (307mg, 1.0 mmol)[18] in THF (5 mL) at –78 °C. After 30 min, di-*tert*-butyl dicarbonate (436 mg, 2.0 mmol) was added and the mixture was gradually warmed to r.t. during a period of 20 h. The mixture was poured into aq NH_4Cl (20 mL) and extracted with EtOAc (150 mL). The organic layer was washed with brine (20 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:15) to give **11** (273 mg, 67% yield) as a colorless oil.

$[\alpha]_D^{20}$ +67 (*c* 1.1, $CHCl_3$).

IR (neat): 2980, 2934, 1748, 1455, 1367, 1260, 1130, 1029 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.11 (m, 5 H), 4.97 (d, *J* = 10.0 Hz, 1 H), 4.29–4.12 (m, 2 H), 3.63–3.52 (m, 1 H), 1.50 (d, *J* = 6.8 Hz, 3 H), 1.37 (s, 18 H), 1.26 (t, *J* = 7.0 Hz, 3 H).

^1H NMR (400 MHz, C_6D_6): δ = 7.30–7.01 (m, 5 H), 5.32 (d, *J* = 10.0 Hz, 1 H), 4.08–3.90 (m, 3 H), 1.59 (d, *J* = 6.8 Hz, 3 H), 1.29 (s, 18 H), 0.96 (t, *J* = 7.0 Hz, 3 H).

MS (EI): *m*/*z* (%) = 407 (M^+), 351, 306, 295, 250, 234, 202, 190, 146, 141.

Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.97; H, 8.13; N, 3.35.

(2*S*,3*R*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)-β-methylphenylalanine Ethyl Ester (14)

Prepared from (2*S*,3*R*)-*N*-*tert*-butoxycarbonyl-β-methylphenylalanine ethyl ester[18] according to the procedure for (2*R*,3*R*)-*N*,*N*-bis(*tert*-butoxycarbonyl)-β-methylphenylalanine ethyl ester in 77% yield.

$[\alpha]_D^{20}$ –75 (*c* 1.2, $CHCl_3$).

IR (neat): 2979, 1795, 1749, 1455, 1368, 1234, 1148, 1038 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.13 (m, 5 H), 5.17 (d, *J* = 9.9 Hz, 1 H), 4.09–3.94 (m, 2 H), 3.70–3.58 (m, 1 H), 1.55 (s, 18 H), 1.17 (d, *J* = 7.3 Hz, 3 H), 1.12 (t, *J* = 7.0 Hz, 3 H).

^1H NMR (400 MHz, C_6D_6): δ = 7.54–7.02 (m, 5 H), 5.59 (d, *J* = 9.9 Hz, 1 H), 4.03–3.93 (m, 1 H), 3.86–3.67 (m, 2 H), 1.42 (s, 18 H), 1.35 (d, *J* = 7.3 Hz, 3 H), 0.76 (t, *J* = 7.0 Hz, 3 H).

MS (EI): *m*/*z* (%) = 407 (M^+), 351, 306, 295, 250, 234, 202, 190, 146, 141.

Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.64; H, 8.18; N, 3.41.

α-Methylation of 11: A 33:67 Mixture of (2*R*,3*R*)- and (2*S*,3*R*)-*N*,*N*-Bis(*tert*-butoxycarbonyl)-α,β-dimethylphenylalanine Ethyl Esters (12 and 13)

α-Methylation of **11** was performed according to the procedure for α-methylation of **3**. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:10) to yield an inseparable mixture (196 mg) of **12** and **13**, and a trace amount of **11**. The combined yield of **12** and **13** and the diastereomeric ratio were determined by 400 MHz ^1H NMR spectroscopy to be 84% and 33:67, respectively.

IR (neat): 2978, 1745, 1715, 1455, 1339, 1127 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 7.60–7.02 (m, 5 H), 4.30–3.88 (m, 3 H), 1.80, 1.60 (2 s, ratio = 33:67, 3 H), 1.72, 1.58 (2 d, *J* = 7.5, 7.7 Hz, ratio = 33:67, 3 H), 1.54, 1.45 (2 s, ratio = 33:67, 18 H), 0.96, 0.93 (2 d, *J* = 7.7, 7.2 Hz, ratio = 67:33, 3 H).

MS (EI): *m*/*z* (%) = 421 (M^+, 1), 348 (5), 316 (50), 264 (50), 216 (60), 192 (60), 160 (100).

Exact mass calcd for $C_{23}H_{35}NO_6$: 421.2465; found: *m*/*z* 421.2469.

(2*R*,3*R*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-β-methylphenylalanine Ethyl Ester (15)

Potassium hexamethyldisilazide (KHMDS)[17] (0.53 M in THF, 3.01mL, 1.59 mmol) was added to a solution of (2*R*,3*R*)-*N*-*tert*-butoxycarbonyl-β-methylphenylalanine ethyl ester (512 mg, 1.67 mmol)[18] in THF (6 mL) at –78 °C. After 30 min, chloromethyl methyl ether (0.38 mL, 5.00 mmol) was added and the mixture was gradually warmed to r.t. during a period of 20 h. The mixture was poured into aq NH_4Cl (20 mL) and extracted with EtOAc (150 mL). The organic layer was washed with brine (20 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:12) to give **15** (472mg, 81% yield) as a colorless oil.

$[\alpha]_D^{20}$ +97 (*c* 1.1, $CHCl_3$).

IR (neat): 2977, 1743, 1704, 1455, 1367, 1297, 1175, 1084, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.09 (m, 5 H), 4.53, 4.42 (2 d, *J* = 10.6, 11.2 Hz, ratio = 1:2, 2 H), 4.30–4.11 (m, 3 H), 3.67–3.47 (m, 1 H), 3.12, 3.06 (2 s, ratio = 1:2, 3 H), 1.44, 1.34 (2 s, ratio = 1:2, 9 H), 1.40 (t, *J* = 4.6 Hz, 3 H), 1.30 (d, *J* = 6.3 Hz, 3 H).

MS (EI): *m*/*z* (%) = 351 (M^+), 320, 278, 246, 220, 190, 178, 146, 105.

Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.32; N, 3.99. Found: C, 64.74; H, 8.44; N, 4.03.

(2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-β-methylphenylalanine Ethyl Ester (18)

Prepared from (2*S*,3*R*)-*N*-*tert*-butoxycarbonyl-β-methylphenylalanine ethyl ester[18] according to the procedure for **15** in 72% yield.

$[\alpha]_D^{20}$ –72.3 (*c* 1.2, $CHCl_3$).

IR (neat): 2977, 1714, 1455, 1368, 1144, 1084 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.10 (m, 5 H), 4.86, 4.79 (2 br s, ratio = 1:1, 2 H), 4.70, 4.39 (2 br s, ratio = 1:1, 1 H), 3.94 (br s, 2 H), 3.49 (br s, 1 H), 3.38 (br s, 3 H), 1.52 (s, 9 H), 1.25 (d, *J* = 7.0 Hz, 3 H), 1.07, 0.98 (2 br s, ratio = 1:1, 3 H).

MS (EI): *m*/*z* (%) = 351 (M^+), 320, 278, 246, 220, 190, 178, 146, 105.

Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.32; N, 3.99. Found: C, 64.93; H, 8.48; N, 3.93.

α-Methylation of 15: A 94:6 Mixture of (2*R*,3*R*)- and (2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α,β-dimethylphenylalanine Ethyl Esters (16 and 17)

A solution of **15** (dried azeotropically with toluene prior to use, 176 mg, 0.50 mmol) in THF (4.5 mL) was added to a solution of KHMDS (0.50 M in THF, 1.1 mL, 0.55 mmol) at –78 °C. After 60 min, MeI (0.31 mL, 5.0 mmol) was added and the mixture was stirred at –78 °C for 20 h, then poured into aq NH_4Cl (20 mL) and extracted with EtOAc (150 mL). The organic layer was washed with brine (30 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:10) to give an inseparable mixture (168 mg) of **16** and **17**, and a trace amount of **15**. The combined yield of **16** and **17** and the diastereomeric ratio were determined by 400 MHz ^1H NMR spectroscopy to be 92% and 94:6, respectively.

$[\alpha]_D^{20}$ +128 (*c* 1.0, $CHCl_3$).

IR (neat): 2978, 1742, 1698, 1455, 1376, 1297 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.10 (m, 5 H), 4.41–3.83 (m, 4 H), 3.41–3.28 (m, 1 H), 3.34, 3.18 (2 s, ratio = 6:94, 3 H), 1.57 (s, 3 H), 1.54 (d, *J* = 7.0 Hz, 3 H), 1.49 (s, 9 H), 1.27 (t, *J* = 6.8 Hz, 3 H).

MS (EI): *m*/*z* (%) = 365 (M^+), 351, 334, 292, 277, 260, 234, 204, 192, 160, 128.

Exact mass calcd for $C_{20}H_{31}NO_5$: 365.2202; found: *m*/*z* 365.2178.

α-Methylation of 18: A 2:98 Mixture of (2*R*,3*R*)- and (2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α,β-dimethylphenylalanine Ethyl Esters (16 and 17)

α-Methylation of **18** was performed according to the procedure for α-methylation of **15**. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:10) to give an inseparable mixture (170 mg) of **16** and **17**, and a trace amount of **18**. The combined yield of **16** and **17** and the diastereomeric ratio were determined by 400 MHz ^1H NMR spectroscopy to be 93% and 2:98, respectively.

$[\alpha]_D^{20}$ –46.9 (*c* 0.66, $CHCl_3$).

IR (neat): 2978, 1698, 1455, 1369, 1088 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.11 (m, 5 H), 4.99 (d, *J* = 11.9 Hz, 1 H), 4.22 (d, *J* = 11.9 Hz, 1 H), 4.17–4.03 (m, 2 H), 3.69 (q, *J* = 7.3 Hz, 1 H), 3.34, 3.18 (2 s, ratio = 98:2, 3 H), 1.49 (s, 9 H), 1.43 (s, 3 H), 1.33 (d, *J* = 7.3 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

MS (EI): *m*/*z* (%) = 365 (M^+), 351, 334, 292, 277, 260, 234, 204, 192, 160, 128.

Exact mass calcd for $C_{20}H_{31}NO_5$: 365.2202; found: *m*/*z* 365.2198.

(2*S*,3*S*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-β-methylphenylalanine Benzyl Ester (22)

Prepared from (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-β-methylphenylalanine benzyl ester[18] according to the procedure for **15** in 78% yield.

$[\alpha]_D^{20}$ –61 (*c* 1.0, $CHCl_3$).

IR (neat): 2973, 1704, 1455, 1367, 1173, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.11 (m, 10 H), 5.29–5.08 (m, 2 H), 4.56–4.11 (m, 3 H), 3.71–3.48 (m, 1 H), 3.00, 2.89 (2 s, ratio = 1:1, 3 H), 1.39, 1.26 (2 s, ratio = 1:1, 9 H), 1.35 (d, *J* = 6.4 Hz, 3 H).

MS (EI): *m*/*z* (%) = 413 (M^+), 381, 325, 308, 282, 252, 208, 182, 146, 121.

Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.44; H, 7.59; N, 3.33.

(2*R*,3*S*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-β-methylphenylalanine Benzyl Ester (24)

Prepared from (2*R*,3*S*)-*N*-*tert*-butoxycarbonyl-β-methylphenylalanine benzyl ester[18] according to the procedure for **15** in 80% yield.

$[\alpha]_D^{20}$ +53 (*c* 0.5, $CHCl_3$).

IR (KBr): 2979, 1737, 1695, 1421, 1366, 1303, 1166, 1085, 1018 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.03 (m, 10 H), 4.98–4.41 (m, 5 H), 3.59–3.45 (m, 1 H), 3.31, 3.26 (2 s, ratio = 1:1, 3 H), 1.48 (s, 9 H), 1.25 (d, *J* = 7.0 Hz, 3 H).

MS (EI): *m*/*z* (%) = 413 (M^+), 381, 325, 308, 282, 252, 208, 182, 146, 121.

Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.49; H, 7.58; N, 3.30.

α-Methylation of 22: (2S,3*S*)-*N*-*tert*-Butoxycarbonyl-*N*-methoxymethyl-α,β-dimethylphenylalanine Benzyl Ester (23)

α-Methylation of **22** (207 mg, 0.50 mmol) was performed according to the procedure for α-methylation of **15**. The residue was purified by flash column chromatography (SiO_2, Et_2O–hexane, 1:10) to give diastereomerically pure **23** (199 mg, 93% yield) as a colorless oil.

$[\alpha]_D^{20}$ +57 (*c* 1.1, $CHCl_3$).

IR (neat): 2976, 1703, 1455, 1367, 1088 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.15 (m, 10 H), 5.08 (ABq, J_{AB} = 12.4 Hz, $\Delta\nu_{AB}$ = 42.3 Hz, 2 H), 4.95 (d, *J* = 12.8 Hz, 1 H), 4.22 (d, *J* = 12.8 Hz, 1 H), 3.70 (q, *J* = 7.3 Hz, 1 H), 3.21 (s, 3 H), 1.46 (s, 3 H), 1.45 (s, 9 H), 1.35 (d, *J* = 7.3 Hz, 3 H).

MS (EI): *m*/*z* (%) = 427 (M^+), 396, 382, 352, 340, 322, 308, 296, 282, 266, 222, 208, 190, 176, 160, 146.

Exact mass calcd for $C_{25}H_{33}NO_5$: 427.2359 (M^+); found: *m*/*z* 427.2356.

***N*-Methyl-(3*R*,4*R*)-3,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Ethyl Ester (27)**

A 94:6 mixture of **16** and **17** (176 mg) was dissolved in 4 M HCl in EtOAc (3 mL) and the solution was stirred at r.t. for 1 h. The mixture was poured into sat. aq Na_2CO_3 (20 mL) and extracted with EtOAc (150 mL). The organic layer was washed with brine (30 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, $CHCl_3$–MeOH, 20:1) to give a 94:6 mixture of (2*R*,3*R*)- and (2*S*,3*R*)-α,β-dimethylphenylalanine ethyl ester as a colorless oil.

$[\alpha]_D^{20}$ +25 (*c* 1.0, $CHCl_3$).

IR (neat): 2976, 1728, 1453, 1118 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 5 H), 4.23–4.15, 4.10–4.01 (2 m, ratio = 6:94, 2 H), 3.19 (q, *J* = 7.3 Hz, 1 H), 1.45 (br s, 2 H), 1.35 (d, *J* = 7.3 Hz, 3 H), 1.34 (s, 3 H), 1.19 (t, *J* = 7.3 Hz, 3 H).

MS (EI): *m*/*z* (%) = 222 (MH^+), 206, 186, 174, 160, 148, 133, 116, 105.

Exact mass calcd for $C_{13}H_{20}NO_2$ (MH^+): 222.1494; found: *m*/*z* 222.1500.

A solution of this mixture (75 mg) in 37% aq HCl and 37% aq HCHO (1:1, 6 mL) was heated under reflux for 3 h. The mixture was basified with sat. aq Na_2CO_3 (20 mL) and extracted with EtOAc (120 mL). The organic layer was washed with brine (20 mL), dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, $CHCl_3$–MeOH, 15:1) to give diastereomerically and analytically pure **27** (29 mg, 35% yield) as a colorless oil.

$[\alpha]_D^{20}$ +4.7 (*c* 0.7, $CHCl_3$).

IR (neat): 2978, 1726, 1445, 1372, 1200, 1104, 1020 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 7.13–6.96 (m, 4 H), 3.99 (q, *J* = 7.0 Hz, 2 H), 3.90 (ABq, J_{AB} = 16.0 Hz, $\Delta\nu_{AB}$ = 39.9 Hz, 2 H), 3.25 (q, *J* = 7.0 Hz, 1 H), 2.56 (s, 3 H), 1.32 (s, 3 H), 1.18 (d, *J* = 7.0 Hz, 3 H), 1.06 (t, *J* = 7.0 Hz, 3 H).

MS (EI): *m*/*z* (%) = 246 ($M - H^+$), 230, 218, 188, 173, 158, 144.

Exact mass calcd for $C_{15}H_{20}NO_2$ ($M - H^+$): 246.1494; found: *m*/*z* 246.1488.

(3*S*,4*R*)-3,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Ethyl Ester (28)

Treatment of a 2:98 mixture of **16** and **17** (140 mg) according to the procedure for **27** gave diastereomerically pure **28** in 71% yield.

$[\alpha]_D^{20}$ –44 (*c* 0.5, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.00 (m, 4 H), 4.26 (q of ABX, J_{AB} = 13.1 Hz, J_{AX} = 7.3 Hz, $\Delta\nu_{AB}$ = 5.7 Hz, 2 H), 4.12 (s, 2 H), 2.95 (q, *J* = 7.0 Hz, 1 H), 2.18 (br s, 1 H), 1.38 (s, 3 H), 1.33 (t, *J* = 7.0 Hz, 3 H), 1.15 (d, *J* = 7.0 Hz, 3 H).

IR (neat): 2976, 1732, 1455, 1373, 1214, 1136 cm^{-1}.

MS (EI): *m*/*z* (%) = 233 (M^+), 218, 204, 160, 144, 115.

Exact mass calcd for $C_{14}H_{19}NO_2$: 233.1416; found: *m*/*z* 233.1407.

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(7) A similar temperature-dependent decrease in ee was also observed in the α-methylation of **19**: When enolate formation was performed at –78 °C for 30 min, the subsequent methylation at –78 °C gave a product of 81% ee. When enolate formation was performed at –78 °C for 30 min and then at –40 °C for 30 min, the subsequent methylation at –78 °C gave a product of 5% ee. Enolate formation at –78 °C for 30 min and then at 0 °C for 30 min gave a product of 0% ee. This can be rationalized by temperature-dependent epimerization of the chiral enolate intermediate **J** via bond rotation of the C(2)–N axis. Details are discussed in reference 2.

(8) Enolate **F** generated from **7** or **10** is not axially chiral along the C(2)–N axis because of the same two substituents on the nitrogen atom, even if the bond rotation is restricted at –78 °C.

(9) The stereochemistry of **8** and **9** was determined after their conversion into the corresponding *p*-nitrobenzamide derivatives, see ref. 6.

(10) Similar stereochemical results were observed in the α-allylation of **3** and **6**, see reference 6.

(11) Enolate **G** generated from **11** or **14** is not axially chiral along the C(2)–N axis because of the same two substituents on the nitrogen atom, even if the bond rotation is restricted at –78 °C.

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(13) While *N*-methylation took place during the transformation from **16** into **27**, it did not during that from **17** into **28**, probably due to the steric hindrance caused by diaxial 3,4-dimethyl groups in **28**.

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