Use of Bis-(Chiral α -Methylbenzyl)glycine Esters for Synthesis of Enantiopure **β -Hydroxyamino Esters**

Ayako Yamashita*, Emily B. Norton, R. Thomas Williamson, Douglas M. Ho[†], Sandra Sinishtaj^f and Tarek S. Mansour

Preparation of 4b

Using literature procedures, a mixture of dibenzylamine (26.5 ml, 0.138 mole) and tert-butyl bromoacetate (10 ml, 0.068 mole) in a mixture of ethanol and 1,4-dioxane (25 ml/25 ml) was heated at reflux for 4 h under nitrogen. After cooling, the mixture was concentrated *in vacuo*. The residue was treated with 1N KOH aqueous solution, and the aqueous layer was extracted with ether. The combined extracts were washed with saturated brine, dried over MgSO₄, and concentrated. The residue was chromatographed (silica gel, 10 % ether/hexanes), to give **4b** (20.7 g, 100 %) as a colorless solid. Mass (E/Z): 255.8 (M-tert-Bu +H). IRcm⁻¹: 1722. ¹H-NMR (δ , DMSO-d₆): 1.42 (9H, s), 3.04 (2H, s), 3.73 (4H, s), 7.07-8.60 (10H, m). Analysis for C₂₀H₂₅NO₂: Calcd: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.14; H, 8.09; N, 4.50.

Preparation of 4c

A mixture of (S)-(-)-N-benzyl- α -methylbenzylamine (3.6 g, 17 mmole), ethyl bromoacetate (2.5 ml, 17 mmole), and diisopropylethylamine (4.5 ml, 25.5 mmole) in a mixture of ethanol and 1,4-dioxane (20 ml/20 ml) was heated at reflux for 10 h under nitrogen. After cooling, the mixture was concentrated *in vacuo*, and the residue was suspended in EtOAc. The organic layer was washed with saturated brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed (silica gel, CH₂Cl₂), to give **4c** (5 g, 99 %) as a colorless oil. Mass (E/Z): 298.2 (M+H). IRcm⁻¹: 1733. ¹H-NMR (δ , DMSO-d₆): 1.16 (3H, t, J=5.7 Hz), 1.33 (3H, d, J=5.1 Hz), 3.07 (1H, d, J=12.9 Hz), 3.39 (1H, d, J=12.9 Hz), 3.63 (2H, s), 4.01 (1H, q, J=5.1 Hz), 4.05 (2H, q), 7.12-7.62 (10H, m). Analysis for C₁₉H₂₃NO₂: Calcd: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.76; H, 7.75; N, 4.50. $[\alpha]_D^{25} = -37 \pm 1$ (c=0.785; MeOH).

Preparation of 4d

A mixture of (R)-(+)-N-benzyl- α -methylbenzylamine (6.06 g, 28.7 mmole), ethyl bromoacetate (3.2 ml, 28.7 mmole), and diisopropylethylamine (9 ml, 51 mmole) in a mixture of ethanol and 1,4-dioxane (25 ml/25 ml) was heated at reflux for 10 h under nitrogen. After cooling, the mixture was concentrated *in vacuo*, and the residue was suspended in EtOAc. The organic layer was washed with saturated brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed (silica gel, CH₂Cl₂), to give **4d** (7 g, 82 %) as a white solid. Mass (E/Z): 298.2 (M+H). IRcm⁻¹: 1733. ¹H-NMR (δ , CDCl₃-d): 1.24 (3H, t, J=5.4 Hz), 1.40 (3H, d, J=5.1 Hz), 3.21 (1H, d, J=13.2 Hz), 3.42 (1H, d, J=13.2 Hz), 3.74 (2H, bs), 4.09-4.31 (3H, m), 6.99-7.54 (10H, m). Analysis for C₁₉H₂₃NO₂:

Calcd: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.51; H, 7.72; N, 4.21. $[\alpha]_D^{25} = +41 \pm 4$ (c=0.2345; MeOH).

Preparation of 4e

A mixture of [S-(R*,R*)]-(-)-bis-(α -methylbenzyl)amine (5 g, 22.2 mmole), ethyl bromoacetate (2.5 ml, 22.2 mmole), and diisopropylethylamine (5.8 ml, 33.3 mmole) in 1,4-dioxane (25 ml) was heated at reflux for 20 h under nitrogen. After cooling, the mixture was concentrated *in vacuo*, and the residue was suspended in EtOAc. The organic layer was washed with saturated brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed (silica gel, CH₂Cl₂), to give **4e** (3.5 g, 25 %) as a pale yellow oil. Mass (E/Z): 312.2 (M+H). IRcm⁻¹: 1733. ¹H-NMR (δ , DMSO-d₆): 1.12 (3H, t, J=5.4 Hz), 1.28 (6H, d, J=5.1 Hz), 3.09 (1H, d, J=13.2 Hz), 3.49 (1H, d, J=13.2 Hz), 3.87-4.12 (4H, m), 7.20-7.39 (10H, m). Analysis for C₂₀H₂₅NO₂: Calcd: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.83; H, 7.99; N, 4.39. $[\alpha]_D^{25} = -9 \pm 2$ (c=0.748; MeOH).

Preparation of 4f

A mixture of [R-(R*,R*)]-(-)-bis-(α -methylbenzyl)amine (5 g, 22.2 mmole), ethyl bromoacetate (2.5 ml, 22.2 mmole), and diisopropylethylamine (5.8 ml, 33.3 mmole) in 1,4-dioxane (25 ml) was heated at reflux for 20 h under nitrogen. After cooling, the mixture was concentrated *in vacuo*, and the residue was suspended in EtOAc. The organic layer was washed with saturated brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed (silica gel, CH₂Cl₂), to give **4f** (1.2 g, 17 %) as a pale yellow oil. Mass (E/Z): 312.2 (M+H). IRcm⁻¹: 1749. ¹H-NMR (δ , CDCl₃-d): 1.18 (3H, t, J=5.4 Hz), 1.35 (6H, d, J=5.1 Hz), 3.18 (1H, d, J=13.2 Hz), 3.44 (1H, d, J=13.2 Hz), 3.92-4.00 (2H, m), 4.10 (2H, q), 7.20-7.39 (10H, m). Analysis for C₂₀H₂₅NO₂·0.2H₂O: Calcd: C, 76.25; H, 8.13; N, 4.45. Found: C, 76.44; H, 8.24; N, 4.43. $[\alpha]_D^{25} = +67 \pm 8$ (c=0.165; MeOH).

General Procedure for Aldol Reaction between 4 and 3:

Preparation of 5a and 6a:

To a solution of **4a** (7.3 g, 25.74 mmole) in anhydrous THF (130 ml), cooled at -78 °C under argon, was added a solution of LDA (13.0 ml, 25.74 mmole, 2.0 M solution in THF/heptane/ethylbenzene, purchased from Aldrich) over a period of 20 min via syringe. The resulting red solution was stirred under this condition for 1 hr, and to this mixture was added a solution of **3** (5.2 g, 25.74 mmole) in anhydrous THF (20 ml) via syringe over a period of 15 min. The resulting mixture was stirred at -78 °C for 4 hrs under argon, and diluted with ethyl acetate. The organic layer was separated, washed with saturated sodium bicarbonate aqueous solution and saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed (flash column, silica gel, CH₂Cl₂ : ether : MeOH = 95 : 4 : 1) to give a 4 : 1 mixture of **5a** and **6a** (11.5 g, 92 %) as a colorless oil. Mass (ES) m/z: 486.0 (M + H). The ratio of **5a** and **6a** was determined by H-NMR analysis.

General Procedure for Deprotection of Dibenzyl groupPreparation of 7a and 8a:

A 4 : 1 mixture of **5a** and **6a** (24 g, 49.43 mmole) was hydrogenated using 10 % Pd on carbon in absolute MeOH under atmospheric pressure at RT. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was chromatographed (silica gel, CH₂Cl₂/ether/MeOH = 95/4/1) to give **7a** (9.88 g, 65.5 %) as a colorless solid. Further elution gave 1.0 g (6.6 %) of a 1 : 1 mixture of **7a** and **8a**, and 3.5 g (23.2 %) of **8a** as a colorless oil. Recrystallization of **7a** from ethyl ether/n-hexane gave colorless prisms. The absolute stereochemistry of **7a** was determined by X-ray analysis. Mass (ES) *m/z*: 306.4 (M + H). IR *cm*⁻¹: 3452, 2877, 2922, 1720. ¹H-NMR (δ, DMSO-*d*₆): 1.18 (3H, t, *J*=7.2 Hz), 1.254 (3H, s), 1.38 (3H, s), 3.27 (3H, s), 3.33 (1H, s), 3.53 (1H, s), 3.79–3.67 (m, 2H), 4.12–4.01 (3H, m), 4.56 (1H, d, *J* = 6.0 Hz), 4.80 (1H, d, *J* = 6.0 Hz), 4.91 (1H, s), 5.13 (1H, d, *J* = 7.8 Hz). Analysis for C₁₃H₂₃NO₇: Calcd: C, 51.14; H, 7.59; N, 4.59. Found: C, 51.12; H, 7.63; N, 4.47. $[\alpha]_D^{25} = -71 \pm 2$ (CH₂Cl₂).

The spectra data for **8a**: Mass (ES) *m/z*: 306.4 (M + H). H-NMR (δ, DMSO-*d*₆): 1.19 (3H, t, *J* = 7.2 Hz), 1.25 (3H, s), 1.38 (3H, s), 1.83 (1H, bs), 3.24 (3H, s), 3.44–3.26 (1H, m), 3.48–3.26 (1H, m), 3.54–3.53 (1H, m), 4.14–4.04 (3H, m), 4.52 (1H, d, *J* = 6.0 Hz), 4.77 (1H, d, *J* = 6.0 Hz), 4.90 (1H, s), 5.36 (1H, d, *J* = 5.1 Hz). Compound **8a** was converted to the para-nitrophenyl urea as follows: A solution of **8a** (712 mg, 2.33 mmole) and para-nitrophenyl isocyanate (459 mg, 2.8 mmole) in anhydrous THF (5 ml) was stirred at RT under nitrogen for 24 hr. A mixture was concentrated *in vacuo*, and the residue was chromatographed (silica gel, CH₂Cl₂/ether/MeOH = 9/1/1), to give the urea **9a** (744.7 mg, 68.1 %) as a yellow solid. Mass (ES): 470 (M+H). IR *cm*⁻¹: 3374, 3320, 1702, 1684, 1612, 1599. ¹H-NMR (δ, DMSO-*d*₆): 1.20 (3H, t, *J* = 6.99 Hz), 1.26 (3H, s), 1.40 (3H, s), 3.27 (3H, s), 3.53–3.59 (m, 1H), 4.13–4.20 (3H, m), 4.56 (1H, d, *J*=5.94 Hz), 4.67 (1H, d, *J*=8.85 Hz), 4.82 (1H, d, *J*=5.94 Hz), 4.96 (1H, s), 5.85 (1H, d, *J*=6.24 Hz), 6.86 (1H, d, *J*=6.24 Hz), 7.61 (2H, d, *J*=9.03 Hz), 8.16 (2H, d, *J*=9.03 Hz), 9.64 (1H, s). Analysis for C₂₀H₂₇N₃O₁₀: Calcd: C, 51.17; H, 5.80; N, 8.95. Found: C, 50.97; H, 5.50; N, 8.97.

The absolute stereochemistry of **9a** was determined by X-ray analysis. Crystals suitable for X-ray analysis were obtained from MeOH/ CH₂Cl₂.

Aldol Reaction between 3 and 4b:

Aldol reaction was carried out as described above using **3** (404 mg, 2 mmole) and **4b** (567 mg, 2 mmole). A mixture of **5b** and **6b** (0.817 g, 80 %) was isolated by chromatography (silica gel column, CH₂Cl₂/ether/MeOH = 10/10/1). **5b** and **6b** were separated by further column chromatography.

5b: Mass (E/Z):514 (M+H). IR *cm*⁻¹: 3428, 2974, 2936, 1726. ¹H-NMR (δ, DMSO-*d*₆): 1.23 (3H, s), 1.33 (3H, s), 1.45 (9H, s), 3.01 (1H, bs), 3.33 (3H, s), 3.47 (1H, d, *J*=2.7 Hz), 3.89 (2H, d, *J*=5.4 Hz), 3.94 (1H, bs), 4.18 (1H, bs), 4.20 (2H, d, *J*=5.4 Hz), 4.75 (1H, s), 4.81 (1H, d, *J*=4.2 Hz), 5.56 (1H, d, *J*=6.0 Hz), 7.12–7.90 (10H, m). Analysis for C₂₉H₃₉NO₇: Calcd: C, 67.82; H, 7.65; N, 2.73. Found: C, 67.92; H, 7.63; N, 2.43. $[\alpha]_D^{25} = +2 \pm 2$ (MeOH). **6b**: Mass (E/Z): 514.2 (M+H). IR *cm*⁻¹: 3436, 2978, 2938, 1727. ¹H-NMR (δ, DMSO-*d*₆): 1.19 (3H, s), 1.33 (3H, s), 1.49 (9H, s), 3.32 (3H, s), 3.38 (1H,

d, $J=3.0$ Hz), 3.68 (2H, d, $J=10.8$ Hz), 3.76-3.79 (1H, m), 3.99 (2H, d, $J=10.8$ Hz), 4.28 (1H, d, $J=3.0$ Hz), 4.44 (1H, d, $J=4.5$ Hz), 4.62 (1H, d, $J=4.5$ Hz), 4.81 (1H, s), 5.31 (1H, d, $J=4.5$ Hz), 7.12-7.50 (10H, m). Analysis for $C_{29}H_{39}NO_7$: Calcd: C, 67.82; H, 7.65; N, 2.73. Found: C, 68.15; H, 7.61; N, 2.43.

Aldol Reaction between 3 and 4c:

Aldol reaction was carried out as described above using **3** (404 mg, 2.0 mmole) and **4c** (654.3 mg, 2.2 mmole). A mixture of **5c** and **6c** (755.8 mg, 76 %) was isolated by chromatography (silica gel column, 15 % ether in hexanes). The ratio of **5c** and **6c** was determined by 1H -NMR analysis to be 2 : 1. A mixture of **5c** and **6c** was hydrogenated using 10 % Pd on carbon in abs MeOH at RT. The resulting unprotected amines **7c** and **8c** were separated, and their structures were determined by comparison of their 1H -NMR and TLC analyses with those of two authentic samples **7a** and **8a**, to confirm **7c** = **7a** and **8c** = **8a**.

Aldol Reaction between 3 and 4d:

Aldol reaction was carried out as described above using **3** (404 mg, 2.0 mmole) and **4d** (654.3 mg, 2.2 mmole). A mixture of **5d** and **6d** (772.8 mg, 77 %) was isolated by chromatography (silica gel column, 15 % ether in hexanes). The ratio of **5d** and **6d** was determined by H-NMR analysis to be 2.6 : 1. A mixture of **5d** and **6d** (430 mg, 0.86 mmole) was hydrogenated using 10 % Pd on carbon (60 mg) in abs MeOH at RT. The resulting amino-alcohols **7d** and **8d** were separated, and were characterized by comparison of their 1H -NMR and TLC analyses with those of two authentic samples **7a** and **8a**, to confirm **7d** = **7a** and **8d** = **8a**.

Aldol Reaction between 3 and 4e:

Aldol reaction was carried out as described above using **3** (384 mg, 1.9 mmole) and **4e** (623 mg, 2.0 mmole). A mixture of **5e** and **6e** (738.9 mg, 76 %) was isolated by chromatography (silica gel column, 2 % MeOH in CH_2Cl_2). The ratio of **5e** and **6e** was determined by H-NMR analysis to be 1 : 199. Further column chromatography isolated compounds **5d** and **6d**. **5e**: Mass (E/Z): 514 (M+H). **6e**: Mass (E/Z): 514 (M+H). IR cm^{-1} : 3411, 2972, 2937, 1725. 1H -NMR (δ , DMSO- d_6): 0.97 (3H, t, $J=5.4$ Hz), 1.28 (3H, s), 1.40 (3H, s), 1.47 (6H, d, $J=5.1$ Hz), 3.33 (3H, s), 3.65 (1H, d, $J=2.7$ Hz), 3.80 (2H, q), 3.86-3.88 (1H, m), 4.21 (2H, d, $J=6.3$ Hz), 4.54-4.57 (2H, m), 4.88 (1H, dd, $J=0.6, 4.5$ Hz), 4.92 (1H, s), 5.21 (1H, d, $J=4.8$ Hz), 7.00-7.40 (10H, m). Analysis for $C_{29}H_{39}NO_7$: Calcd: C, 67.82; H, 7.65; N, 2.73. Found: C, 67.55; H, 7.43; N, 2.73. $[\alpha]_D^{25} = -64 \pm 1$ (MeOH). The absolute stereochemistry of **6e** was determined by X-ray analysis. Crystals of **6e** suitable for X-ray were obtained as colorless needles from ether/hexanes.

Aldol Reaction between 3 and 4f:

Aldol reaction was carried out as described above using **3** (384 mg, 1.9 mmole) and **4f** (624 mg, 2.0 mmole). A mixture of **5f** and **6f** (697 mg, 71 %) was isolated by chromatography (silica gel column, 15 % ether in hexanes). The ratio of **5f** and **6f** was determined by 1H -NMR analysis to be 2.5 : 1. A

mixture of **5f** and **6f** was hydrogenated using 10 % Pd on carbon in abs MeOH at RT. The resulting amino-alcohols **7f** and **8f** were separated, and were characterized by comparison of their $^1\text{H-NMR}$ and TLC analyses with those of two authentic samples **7a** and **8a**, to confirm **7f** = **7a** and **8f** = **8a**.

Aldol Reaction between **4e** and trimethylacetaldehyde:

Aldol reaction was carried out as described above using **4e** (624 mg, 2.0 mmole) and trimethylacetaldehyde (0.217 ml, 2.0 mmole). Column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{hexanes}$ = 1/1) isolated **10a** (563 mg, 71 %) as a colorless oil. Mass (E/Z): 398.2 (M+H). $^1\text{H-NMR}$ (δ , $\text{CDCl}_3\text{-d}$): 0.93 (9H, s), 0.95 (3H, t, $J=7.14$ Hz), 1.60 (3H, d, $J=7.32$ Hz), 1.62 (3H, d, $J=7.32$ Hz), 3.58 (1H, s), 3.73 (1H, d, $J=10.2$ Hz), 3.77-3.94 (2H, m), 4.54 (1H, d, $J=10.3$ Hz), 4.65 (2H, q), 6.99-7.42 (10 H, m). Analysis for $\text{C}_{25}\text{H}_{35}\text{NO}_3$: Calcd: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.70; H, 8.90; N, 3.53. $[\alpha]_{\text{D}}^{25} = -54 \pm 1$ ($c=1.006$; MeOH). Hydrogenation of **10a** (340 mg, 0.855 mmole) using 10 % Pd/C in abs MeOH gave the corresponding amino ester **12a**, recrystallized from hexanes. Mass (E/Z): 190.1 (M+H). $^1\text{H-NMR}$ (δ , DMSO-d_6): 0.89 (9H, s), 1.20 (3H, t, $J=5.4$ Hz), 2.41 (2H, bs), 3.17 (1H, t, $J=4.5$ Hz), 3.36 (1H, d, $J=4.5$ Hz), 3.98-4.20 (2H, m), 4.78 (1H, d, $J=6.0$ Hz). Analysis for $\text{C}_9\text{H}_{19}\text{NO}_3 \cdot 0.3\text{H}_2\text{O}$: Calcd: C, 55.53; H, 10.15; N, 7.202. Found: C, 55.58; H, 10.20; N, 7.13. $[\alpha]_{\text{D}}^{25} = +8 \pm 1$ ($c=1.042$, MeOH).

Aldol Reaction between **4f** and trimethylacetaldehyde:

Aldol reaction was carried out as described above using **4f** (645 mg, 2.07 mmole) and trimethylacetaldehyde (0.217 ml, 2.0 mmole). Column chromatography (silica gel, CH_2Cl_2) isolated **11b** (563 mg, 88 %) as a colorless oil. Mass (E/Z): 398.2 (M+H). $^1\text{H-NMR}$ (δ , $\text{CDCl}_3\text{-d}$): 0.93 (9H, s), 0.95 (3H, t, $J=5.79$ Hz), 1.62 (6H, d, $J=6.84$ Hz), 3.58 (1H, s), 3.73 (1H, d, $J=9.33$ Hz), 3.79-3.94 (2H, m), 4.58 (1H, d, $J=10.3$ Hz), 4.65 (2H, q), 6.995-7.229 (10 H, m). Analysis for $\text{C}_{25}\text{H}_{35}\text{NO}_3$: Calcd: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.13; H, 8.97; N, 3.55. $[\alpha]_{\text{D}}^{25} = +69 \pm 1$ ($c=1.018$; MeOH). Hydrogenation of **11b** (450 mg, 1.13 mmole) using 10 % Pd/C in abs MeOH gave the corresponding amino ester **12b**, recrystallized from hexanes. Mass (E/Z): 190.1 (M+H). $^1\text{H-NMR}$ (δ , DMSO-d_6): 0.91 (9H, s), 1.20 (3H, t, $J=5.4$ Hz), 3.32 (2H, bs), 3.32-3.37 (1H, bs), 3.757 (1H, d, $J=2.7$ Hz), 4.081 (2H, q), 5.255 (1H, d, $J=3.9$ Hz). $[\alpha]_{\text{D}}^{25} = -5 \pm 1$ ($c=0.02$, MeOH).

Aldol Reaction between **4e** and iso-butyraldehyde:

Aldol reaction was carried out as described above using **4e** (624 mg, 2.0 mmole) and iso-butyraldehyde (0.2 ml, 2.2 mmole). Column chromatography (silica gel, 1 % MeOH in CH_2Cl_2) isolated **10c** (500 mg, 65 %) as a colorless oil and **11c** (91 mg, 12 %) as a colorless solid.

10c : Mass (E/Z): 384.2 (M+H). IR cm^{-1} : 3514, 2966, 1703. $^1\text{H-NMR}$ (δ , DMSO-d_6): 0.92-1.070 (9H, overlapping d, d, t), 1.53 (6H, d, $J=6.93$ Hz), 1.83-1.90 (1H, m), 3.28 (1H, d, $J=8.73$ Hz), 3.56 (1H, d, $J=4.44$ Hz), 3.69-3.74 (1H, m), 3.78-3.88 (2H, m), 4.55 (2H, q, $J=6.87$ Hz), 6.90-7.48 (10 H, m). Analysis for $\text{C}_{24}\text{H}_{33}\text{NO}_3$: Calcd: C, 75.16; H, 8.67; N, 3.65. Found: C, 74.89; H, 8.85; N, 3.60. $[\alpha]_{\text{D}}^{25} = -53 \pm 1$ ($c=1.043$; MeOH).

11c: Mass (E/Z): 384.2 (M+H). ¹H-NMR (δ, DMSO-d₆): -0.35 (3H, d, J=6.96 Hz), 0.68 (3H, d, J=6.96 Hz), 1.27 (3H, t, J=7.05 Hz), 1.27-1.35 (1H, m), 1.48 (6H, d, J=6.81 Hz), 3.03 (1H, d, J=9.84 Hz), 3.66-3.71 (1H, m), 4.03-4.11 (1H, m), 4.12-4.22 (1H, m), 4.51-4.56 (3H, m), 6.95-7.26 (10 H, m). Analysis for C₂₄H₃₃NO₃: Calcd: C, 75.16; H, 8.67; N, 3.65. Found: C, 75.09; H, 8.92; N, 3.71. [α]_D²⁵ = +12 ± 1 (c=1.051; MeOH). The absolute stereochemistry of **11c** was determined by X-ray analysis. Crystals of **11c** suitable for X-ray analysis were obtained as colorless prisms from ether/hexanes.

Hydrogenation of **10c** (400 mg, 1.043 mmole) using 10 % Pd/C in abs MeOH gave the corresponding amino ester **12c** as a colorless oil. Mass (E/Z): 176.1 (M+H). ¹H-NMR (δ, CDCl₃-d): 0.963 (3H, d, J=6.42 Hz), 0.99 (3H, d, J=6.45 Hz), 1.30 (3H, t, J=7.11 Hz), 1.89-1.92 (1H, m), 2.42-2.45 (3H, bs), 3.45 (1H, d, J=5.28 Hz), 3.61 (1H, d, J=3.75 Hz), 4.22 (2H, q, J=7.10 Hz). [α]_D²⁵ = +9 ± 1 (c=1.022, MeOH).

A mixture of **12c** (2.0 g, 5.219 mmole) with N-(benzyloxycarbonyloxy)succinimide (3.13 g, 12.56 mmole), diisopropylethylamine (2.2 ml, 12.63 mmole) and DMAP (200 mg, 1.64 mmole) in anhydrous CH₂Cl₂ was stirred at RT under nitrogen for 24 h. After a usual work-up procedure, the residue was chromatographed (silica gel, 5 % MeOH in CH₂Cl₂), to give the Bis-CBZ derivative **13c** (2.034g, 81 %). Mass (E/Z): 444.0 (M+H), 887.4 (2M+H). IRcm⁻¹: 1787, 1738, 1531. ¹H-NMR (δ, CDCl₃-d): 0.96 (3H, d, J=6.59 Hz), 1.05 (3H, d, J=6.59 Hz), 1.24 (3H, t, J=7.08 Hz), 2.06-2.13 (1H, m), 4.15-4.19 (2H, m), 4.71-4.74 (2H, m), 5.11 (2H, s), 5.16 (2H, s), 5.640 (1H, d, J=7.92 Hz), 7.26-7.60 (10H, m). Analysis for C₂₄H₂₉NO₇: Calcd: C, 65.00; H, 6.59; N, 3.16. Found: C, 65.21; H, 6.74; N, 3.09. [α]_D²⁵ = -15 ± 2 (c=0.4455; MeOH). The relative stereochemistry of **13c** was determined by X-ray analysis. Crystals of **13c** suitable for X-ray were obtained as colorless needles from ether/hexanes. The supplementary publication number for the X-ray for **13c** is CCDC 214753.

Aldol Reaction between **4f** and iso-butyaldehyde:

Aldol reaction was carried out as described above using **4f** (625 mg, 2.07 mmole) and iso-butyaldehyde (0.2 ml, 2.2 mmole). Column chromatography (silica gel, 1 % MeOH in CH₂Cl₂) isolated **10d** (182 mg, 24 %) as a solid, and **11d** (542 mg, 71 %) as a colorless oil.

10d: Mass (E/Z): 384.2 (M+H). ¹H-NMR (δ, DMSO-d₆): -0.35 (3H, d, J=5.1 Hz), 0.68 (3H, d, J=5.1 Hz), 1.28 (3H, t, J=5.4 Hz), 1.32-1.36 (1H, m), 1.48 (6H, d, J=5.1 Hz), 3.04 (1H, d, J=7.2 Hz), 3.71-3.66 (1H, m), 4.07-4.10 (1H, m), 4.13-4.22 (1H, m), 4.52-4.67 (3H, m), 7.04-7.25 (10 H, m). Analysis for C₂₄H₃₃NO₃: Calcd: C, 75.16; H, 8.67; N, 3.65. Found: C, 74.86; H, 8.75; N, 3.64. [α]_D²⁵ = -13 ± 1 (c=1.034; MeOH). The absolute stereochemistry of **10d** was determined by X-ray analysis. Crystals of **10d** suitable for X-ray analysis were obtained as colorless prisms from ether/hexanes.

11d: Mass (E/Z): 384.2 (M+H). ¹H-NMR (δ, DMSO-d₆): 0.86 (3H, d, J=5.1 Hz), 0.89-1.03 (6H, overlapping d, t), 1.43 (6H, d, J=5.1 Hz), 2.09-2.09 (1H, m), 3.36 (1H, d, J=5.7 Hz), 3.63-3.79 (3H, m), 4.53 (2H, q, J=5.1 Hz), 4.67 (1H, d, J=4.8 Hz), 7.13-7.35 (10 H, m). Analysis for C₂₄H₃₃NO₃:

Calcd: C, 75.16; H, 8.67; N, 3.65. Found: C, 75.24; H, 9.02; N, 3.64. $[\alpha]_D^{25} = +57 \pm 1$ (c=1.022; MeOH).

Hydrogenation of **11d** using 10 % Pd/C in abs MeOH gave the unprotected amino ester **12d** as a colorless oil. Mass (E/Z): 176.1 (M+H). $^1\text{H-NMR}$ (δ , DMSO- d_6): 0.83 (3H, d, J=5.1 Hz), 0.88 (3H, d, J=5.1 Hz), 1.20 (3H, t, J=5.1 Hz), 1.84-1.90 (1H, m), 3.261-3.32 (3H, m), 3.40 (1H, d, J=4.5 Hz), 4.08 (2H, q, J=5.1 Hz), 4.835 (1H, bs). $[\alpha]_D^{25} = -4 \pm 1$ (c=1.052, MeOH).

A mixture of **12d** (1.38 g, 7.69 mmole) with N-(benzyloxycarbonyloxy)succinimide (4.22 g, 16.92 mmole), diisopropylethylamine (2.95 ml, 16.92 mmole) and DMAP (100 mg, 0.82 mmole) in anhydrous CH_2Cl_2 (80 ml) was stirred at RT under nitrogen for 24 h. After a usual work-up procedure, the residue was chromatographed (silica gel, 5 % MeOH in CH_2Cl_2), to give the Bis-CBZ derivative **13d** (755 mg, 22 %) as a colorless solid, and the mono-N-CBZ derivative **14d** (1.51 g, 63 %) as a colorless oil. **13d**: Mass (E/Z): 444.3 (M+H), 887.5 (2M+H). IR cm^{-1} : 1747, 1717. $^1\text{H-NMR}$ (δ , CDCl_3 - δ): 0.96 (3H, d, J=6.66 Hz), 1.04 (3H, d, J=6.66 Hz), 1.24 (3H, t, J=7.08 Hz), 2.00-2.13 (1H, m), 4.14-4.21 (2H, m), 4.71-4.74 (2H, m), 5.110 (2H, bs), 5.166 (2H, bs), 5.305 (1H, d, J=7.38 Hz), 7.258-7.604 (10H, m). Analysis for $\text{C}_{24}\text{H}_{29}\text{NO}_7$: Calcd: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.60; H, 6.72; N, 3.23. $[\alpha]_D^{25} = -40 \pm 4$ (c=0.343; MeOH). **14d**: Mass (E/Z): 310.2 (M+H), 619.3 (2M+H). IR cm^{-1} : 3437, 2964, 1723. $^1\text{H-NMR}$ (δ , CDCl_3 - δ): 0.99 (3H, d, J=7.59 Hz), 1.01 (3H, d, J=7.59 Hz), 1.30 (3H, t, J=7.08 Hz), 1.65-1.80 (1H, m), 2.50 (1H, d, J=7.7 Hz), 3.48-3.49 (1H, m), 4.22-4.24 (2H, m), 4.49-4.52 (1H, m), 5.12 (2H, bs), 5.76 (1H, d, J=7.35 Hz), 7.26-7.63 (5H, m). Analysis for $\text{C}_{16}\text{H}_{23}\text{NO}_5 \cdot 0.1\text{H}_2\text{O}$: Calcd: C, 61.76; H, 7.51; N, 4.50. Found: C, 61.54; H, 7.41; N, 4.95. $[\alpha]_D^{25} = +12 \pm 4$ (c=0.32; MeOH).