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for

The Catalytic, Enantioselective Conjugate Addition of Carbamates

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General

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 . Methanol, ethyl acetate, and benzene of chromatographic grade were used without distillation. Diisopropylamine was dried by refluxing over KOH and after distillation, stored with MS-4A. commercial $\text{Cu}(\text{OTf})_2$, $\text{Sc}(\text{OTf})_3$, $\text{Mg}(\text{OTf})_2$, and $\text{Zn}(\text{OTf})_2$ were used without purification. Chiral ligands 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline, (S)-(-)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) were purchased from Aldrich Chemical, and used without further purification. Ligand 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazoliny)]cyclopropane was synthesized according to Denmark.¹ Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0,25 mm silica gel 60-F plates. Visualization was accomplished with UV light and a solution obtained by admixing in 470 mL of water ammonium molybdate (21 g), cerium sulphate (1 g) and concentrated sulphuric acid (31 mL), followed by heating. Melting points were measured with a Mettler FP 80 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Varian Gemini-200, Bruker Avance-DPX-300, and Bruker Avance-500 spectrometers and are reported in ppm from internal tetramethylsilane (TMS) and chloroform. Analytical high performance liquid

¹ Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, 65, 5875-5878.

chromatography (HPLC) with chiral stationary phase was performed on Waters 600E and Hewlett Packard series 1050 chromatographs, equipped with a diode array UV detector, using Daicel Chiralpak AD, AS, and Chiralcel OD columns.

Preparation of α' hydroxy enones 1

General Procedure A: from commercial 3-hydroxy-3-methyl-2-butanone

To an oven or flame-dried 3-neck round bottom flask fitted with a low temperature thermometer and a dropping funnel loaded with $n-BuLi$ (2.5 M solution in hexanes, 80 mL, 200 mmol) under nitrogen was added dry THF (200 mL) and diisopropylamine (28 mL, 200 mmol). The solution was cooled to $-78^{\circ}C$ and $n-BuLi$ added dropwise such that the temperature remained below $-70^{\circ}C$. After the addition, the mixture was allowed to stir at $-78^{\circ}C$ for 1 h before adding 3-hydroxy-3-methyl-2-butanone (8.8 mL, 80 mmol) dropwise (again keeping the temperature below $-78^{\circ}C$). After complete addition, the mixture was allowed to stir at $-78^{\circ}C$ for a further 1 h before dropwise addition over a 45 min period of a solution of the corresponding aldehyde (240 mmol, 3 equiv.) in dry THF (30 mL). The mixture was stirred at $-78^{\circ}C$ and the reaction monitored by TLC (7:3 Hexane:EtOAc, product). After 2-3 h, the reaction was quenched with sat. NH_4Cl and then extracted with CH_2Cl_2 . The organic extracts were combined, dried over $MgSO_4$ and concentrated. The crude product was flash chromatographed (SiO_2) using a hexane: ethyl acetate gradient from 5:1 to 1:1. $CeCl_3 \cdot 7H_2O$ (1.5 mmol per 1 mmol substrate aldol) and NaI (1.5 mmol per 1 mmol substrate aldol) were successively added to a suspension of the aldol intermediate thus obtained in CH_3CN (10 mL/mmol) and the mixture was stirred at reflux for 3 h. After cooling at room temperature, the reaction was diluted with ether (200 mL) and washed with 0.5 M HCl (50 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the EtOAc extracts were combined, successively washed with 20 % $NaHSO_3$ (30 mL), $NaHCO_3$ (30 mL) and brine (30 mL), and dried over $MgSO_4$. Evaporation of solvent under reduced pressure gave a crude product which was flash chromatographed (SiO_2) using 9:1 hexane:ethyl acetate as eluent.

General Procedure B

Dried LiCl (1.05 g, 23.75 mmol) and Et₃N (3.3 mL, 22.85 mmol) were added successively to a solution of (3-Hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester² (7.0 g, 21.6 mmol) in dry MeCN (50 mL). The resulting milky suspension was stirred for 15 min at room temperature and the respective aldehyde (21.5 mmol) was added dropwise. The mixture was stirred for 48 h, diluted with water and extracted with Et₂O. Evaporation of the solvent gives an oil which was dissolved in CH₃CN (120 mL) and HF (48% aqueous, 1.2 mL) was added dropwise. The mixture was stirred for 3 h, diluted with CH₂Cl₂, washed with brine, dried and concentrated *in vacuo*. Flash chromatography (hexanes-EtOAc, 10:1) of the residue gave pure α -hydroxy enone.

2-Hydroxy-2-methyl-7-phenyl-hept-4-en-3-one 1a

The general procedure (Method A) was followed using hydrocinnamaldehyde (31.6 mL, 240 mmol). Yield 7.7g (42%). IR (CHCl₃, cm⁻¹): 3446, 2973, 1677, 1630; ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.21 (m, 6H), 6.41 (d, 1H, *J*=15.5Hz), 3.98 (s, 1H), 2.8 (t, 2H, *J*=8Hz), 2.59 (m, 2H), 1.34 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 202.3, 149.4, 140.6, 128.6, 128.5, 126.3, 123.1, 75.3, 34.5, 34.3, 26.3.

Using General Procedure B from hydrocinnamaldehyde (0.221g, 1.65 mmol), 0.270 g (74%) of the title compound was obtained.

2-Hydroxy-2-methyl-undec-4-en-3-one 1b

² Prepared in two steps (92% overall yield) from commercially available methyl 2-hydroxyisobutyrate, according to Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F., *J. Org. Chem.* **1986**, *51*, 2525-2529, and McCarthy, D. G.; Collins, C. C.; O'Driscoll, J. P.; Lawrence, S. E., *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667-3675.

The general procedure (Method A) was followed using n-heptanal (33.5 mL, 240 mmol). Yield 10.6g (64%). IR (CHCl₃, cm⁻¹): 3465, 2959, 1677, 1630, 1475; ¹H NMR (200 MHz, CDCl₃) δ 7.0 (m, 1H), 6.35 (d, 1H, *J* = 16.2 Hz), 4.04 (br s, 1H), 2.13 (q, 2H, *J* = 7.2 Hz), 1.36-1.32 (m, 2H), 1.25 (s, 6H), 1.17 (br s, 6H), 0.76 (t, 3H, *J* = 8.0 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 202.3, 150.8, 122.3, 75.2, 32.7, 31.5, 28.8, 27.9, 26.3, 22.5, 14.0.

2-Hydroxy-2-methyl-hept-4-en-3-one 1c

The general procedure (Method A) was followed using n-propanaldehyde (17.5 mL, 240 mmol). Yield 6.6g (56%). IR (CHCl₃, cm⁻¹): 3390, 2950, 1635, 1169, 974; ¹H NMR (500 MHz, CDCl₃) δ 7.15 (m, 1H), 6.38 (d, 1H, *J* = 15 Hz), 4.0 (s, 1H), 2.27 (m, 2H), 1.36 (s, 6H), 1.08 (t, 3H, *J* = 6.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 202.5, 152.3, 121.4, 75.2, 26.4, 25.9, 12.2.

2-Hydroxy-2, 7-dimethyl-oct-4-en-3-one 1d

The general procedure (Method A) was followed using isopentanaldehyde (25.7 mL, 240 mmol). Yield 7.78g (55%). IR (CHCl₃, cm⁻¹): 3465, 2940, 1696, 1621, 1456; ¹H NMR (200 MHz, CDCl₃) δ 6.93 (m, 1H), 6.32 (d, 1H, *J* = 15.2 Hz), 3.98 (br s, 1H), 1.98 (t, 2H, *J* = 8.5 Hz), 1.61 (m, 1H), 1.20 (s, 6H), 0.75 (d, 6H, *J* = 6.6 Hz); ¹³C NMR (50 MHz, CDCl₃) δ 202.2, 149.93, 123.5, 75.1, 41.9, 27.8, 26.2, 22.3.

2-Hydroxy-2,6-dimethyl-hept-4-en-3-one 1e

The general procedure (Method B) was followed using isobutyraldehyde (1.65 mL, 18.2 mmol). Yield 2.3 g (80 %); ¹H NMR (500 MHz, CDCl₃) δ 7.15 (dd, 1H, *J* = 15.3 Hz, *J'* = 8.5 Hz), 6.35 (d, 1H, *J* = 15.4 Hz), 4.0 (s, 1H), 2.5 (m, 1H), 1.4 (s, 6H), 1.1 (d, 6H, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 202.70, 157.07, 119.27, 75.18, 31.44, 26.36, 21.20.

1-Cyclohexyl-4-hydroxy-4-methyl-pent-1-en-3-one 1f

The general procedure (Method A) was followed using cyclohexylcarbaldehyde (29 mL, 240 mmol). Yield 7.0g (43%). IR (CHCl₃, cm⁻¹): 3456, 2940, 2846, 1696, 1621, 1475; ¹H NMR (200 MHz, CDCl₃) δ 6.86 (dd, 1H, *J*=15.4 Hz, *J'*= 6.8 Hz), 6.27 (d, 1H, *J*= 15.4 Hz), 4.04 (s, 1H), 2.0 (m, 1H), 1.60 (m, 4H), 1.17 (s, 6H), 1.1 (m, 6H); ¹³C NMR (50 MHz, CDCl₃) δ 202.6, 155.2, 119.9, 75.2, 40.8, 31.6, 26.2, 25.8, 25.6.

2-Hydroxy-2,6,6-trimethyl-hept-4-en-3-one 1g

(Procedure not optimized) 3-Hydroxy-3-methyl-2-butanone (5.0 g, 49 mmol) was dissolved in a mixture of MeOH (120 mL) and H₂O (40 mL). Freshly distilled *tert*-pentanal (7.5 g, 87.5 mmol) was then added followed by LiOH·H₂O (10.28 g, 245 mmol). The reaction was stirred at reflux for 3 h, and after removal of MeOH under reduced pressure, the aqueous residue was diluted with H₂O (40 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The CH₂Cl₂ extracts were combined, dried over MgSO₄ and concentrated. The crude product was flash chromatographed (SiO₂) using a 4:1 hexane:ethyl acetate mixture as eluent to get the title compound. Yield 2.3 g (18%). IR (CHCl₃, cm⁻¹) ν 3456, 2940, 1705, 1602, 1065; ¹H NMR (200 MHz, CDCl₃) δ 7.07 (d, 1H, *J*=15.6 Hz), 6.28 (d, 1H, *J*=15.8 Hz), 4.06 (br s, 1H), 1.3 (s, 6H), 1.0 (s, 9H); ¹³C NMR (50 MHz, CDCl₃) δ 203.0, 160.4, 117.2, 75.4, 34.1, 28.6, 26.4.

3-Pent-2-enoyl-oxazolidin-2-one 15

The title compound was prepared according to Hruby et al.³

2-(3-Methyl-butylidene)-malonic acid dimethyl ester 16

³ Chaozhong, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339-1350.

The title compound was prepared according to Cardillo et al.⁴

General procedure for the reaction of α' -hydroxy enones with carbamates catalysed by Sc(OTf)₃ (preparation of racemic adducts)

The corresponding enone **1** (0.5 mmol) was weighted into an oven or flame-dried flask and placed under N₂. The corresponding carbamate **2-5** (1 mmol) was then added by rinsing with dry CH₂Cl₂ (0.5 mL) from a weighting boat directly into the reaction flask. Sc(OTf)₃ (0.024 g, 0.05 mmol) was then added by rinsing with dry CH₂Cl₂ (1.0 mL) from a weighting boat directly into the reaction flask. The resulting solution was stirred at room temperature until disappearance of starting material as monitored by TLC. The mixture was then diluted with 0.1 M HCl (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The CH₂Cl₂ layers were combined, dried over anhydrous MgSO₄ and concentrated. The crude product was purified by column chromatography using gradient mixtures of ethyl acetate/dichloromethane as eluent.

General procedure for asymmetric 1,4-conjugate additions of carbamates **2-5**

2,2'-Isopropylidene bis[(4*S*)-4-tert-butyl-2-oxazoline] (tBu-BOX) (or the corresponding chiral ligand) (0.22 mmol) was weighted in a flame-dried flask and placed under N₂. Cu(OTf)₂ (72.3 mg, 0.2 mmol) was then added by rinsing with dry CH₂Cl₂ (3.0 mL) from a weighting boat directly into the reaction flask. After stirred at room

⁴ Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, 33, 1587-1594.

temperature for 3 h, a solution of the corresponding α' -hydroxy enone **1** (2 mmol) in dry CH_2Cl_2 (1.5 mL) was cannulated into the solution followed by a 1.5 mL rinse, and the resulting mixture was stirred for a further 30 min at room temperature. This solution was cannulated into a solution of benzyl carbamate **2** (0.605 g, 4 mmol) in dry CH_2Cl_2 (2.0 mL) followed by a 1.0 mL rinse, and the mixture was stirred at room temperature under N_2 for the stated time. The resulting reaction mixture was diluted with 0.1 M HCl (40 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The CH_2Cl_2 layers were combined, dried over anhydrous MgSO_4 and concentrated. The crude product was purified by column chromatography on SiO_2 eluting first with CH_2Cl_2 until total elution of the excess carbamate and then successively with 2%, 5% and 10% EtOAc in CH_2Cl_2 to yield pure compounds **11-14**.

N*-(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid *O*-benzyl ester **11a*

The title compound was prepared according to the general procedure starting from enone **1a** (0.436 g, 2 mmol). Yield 633 mg (86 %); white waxy solid which crystallizes to form clear rods from CH_2Cl_2 /hexane; m.p. 61-63°C; $[\alpha]_D = -15.0$ (c 0.5, CHCl_3); IR (CHCl_3 , cm^{-1}) 3408, 3325, 1701, 1536. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.31 (m, 4H), 7.29-7.26 (m, 2H), 7.19 (d, 1H, $J=7.5\text{Hz}$), 7.15 (d, 1H, $J=7\text{Hz}$), 5.23 (d, 1H, $J=7.5\text{Hz}$), 5.09 (d, 2H, $J=12.7\text{Hz}$), 4.07-4.01 (m, 1H), 3.58 (br.s, 1H), 2.89 (dd, 1H, $J=17.0\text{Hz}$, $J'=5.3\text{Hz}$), 2.80 (dd, 1H, $J=17.0\text{Hz}$, $J'=4.5\text{Hz}$), 2.75-2.69 (m, 1H), 2.65-2.59 (m, 1H), 1.99-1.93 (m, 1H), 1.85-1.78 (m, 1H), 1.32 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 213.4, 155.9, 141.1, 136.4, 128.5, 128.4, 128.3, 128.2, 128.1, 126.1, 76.5, 66.7, 48.0, 40.4, 35.9, 32.7, 26.3, 26.2; Elemental analysis calcd (%) for $\text{C}_{22}\text{H}_{27}\text{NO}_4$ (369.45): C 71.52, H 7.37, N 3.79; found: C 73.18, H 7.32, N 3.94. Chiral HPLC (Chiralpak AS column; iPrOH:hexane 5:95; 0.8 mL/min, 210 nm) $R_{t\text{major}} = 25.4$ min., $R_{t\text{minor}} = 34.2$ min., 96 % e.e.

N*-[1-(3-Hydroxy-3-methyl-2-oxo-butyl)-heptyl]-carbamic acid *O*-benzyl ester **11b*

The title compound was prepared according to the general procedure starting from enone **1b** (0.099 g, 0.5 mmol) and benzyl carbamate (0.151 g, 1.0 mmol). Yield 115mg (66%); white solid. M.p. 46-48°C (hexane:ethyl acetate); $[\alpha]_D = -18.6$ (c 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) 3477, 3334, 2910, 1718, 1571. ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.31 (m, 5H), 5.15 (d, 1H, $J = 2.9\text{Hz}$), 5.08 (s, 2H), 4.02-4.00 (m, 1H), 3.67 (br s, 1H), 2.8-2.79 (m, 2H), 1.53-1.52 (m, 2H), 1.34-1.33 (m, 8H), 1.29-1.26 (m, 6H), 0.89-0.86 (t, 3H, $J = 5.6\text{Hz}$); ^{13}C NMR (125 MHz, CDCl_3) δ 213.6, 156.0, 136.6, 128.6, 128.2, 128.1, 76.6, 66.7, 48.4, 40.5, 34.4, 31.7, 29.0, 26.4, 26.3, 22.6, 14.1; Elemental analysis calcd (%) for $\text{C}_{20}\text{H}_{31}\text{NO}_4$ (349.46): C 68.74, H 8.94, N 4.01; found: C 69.84, H 8.36, N 4.14; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.5 mL/min, 210 nm) $R_{t\text{major}} = 17.7$ min, $R_{t\text{minor}} = 27.9$ min, 92 % e.e.

N*-(1-Ethyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid *O*-benzyl ester **11c*

The title compound was prepared according to the general procedure starting from enone **1c** (0.284 g, 2 mmol). Yield 488 mg (83 %). Clear oil; $[\alpha]_D = -20.6$ (c 0.5, CHCl_3); IR (CHCl_3 , cm^{-1}) 3419, 3334, 1687, 1532; ^1H NMR (500 MHz, CDCl_3) δ 7.37-7.31 (m, 5H), 5.14 (d, 1H, $J = 6.5\text{Hz}$), 5.07 (q, 2H, $J = 13\text{Hz}$), 3.97-3.90 (m, 1H), 3.66 (br.s, 1H), 2.85 (dd, 1H, $J = 17.0\text{Hz}$, $J' = 5.3\text{Hz}$), 2.77 (dd, 1H, $J = 17.0\text{Hz}$, $J' = 4.3\text{Hz}$), 1.58 (dq, 2H, $J = 7.5\text{Hz}$, $J' = 6.5\text{Hz}$), 1.33 (s, 3H), 1.32 (s, 3H), 0.93 (t, 3H, $J = 7.5\text{Hz}$); ^{13}C NMR (125 MHz, CDCl_3) δ 213.5, 156.0, 136.4, 128.5, 128.1, 128.0, 76.5, 66.7, 49.8, 40.1, 27.3, 26.3, 26.2, 10.0; Elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{23}\text{NO}_4$ (293.36): C 65.51, H 7.90, N 4.77; found: C 65.35, H 8.19, N 4.70; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 5:95; 0.8 mL/min, 210 nm) $R_{t\text{major}} = 17.1$ min, $R_{t\text{minor}} = 24.6$ min, 96 % e.e.

N*-(4-Hydroxy-1-isobutyl-4-methyl-3-oxo-pentyl)-carbamic acid *O*-benzyl ester **11d*

The title compound was prepared according to the general procedure starting from enone **1d** (0.340 g, 2 mmol). Yield 456 mg (71 %). Clear oil; $[\alpha]_D = -27.4$ (c 0.5, CHCl_3); IR (CHCl_3 , cm^{-1}) 3409, 3344, 1696, 1536; ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.31 (m, 5H), 5.11 (d, 1H, $J=8.0\text{Hz}$), 5.07 (s, 2H), 4.13-4.06 (m, 1H), 3.66 (br s, 1H), 2.83 (dd, 1H, $J=17.3\text{ Hz}$, $J'=5.3\text{ Hz}$), 2.77 (dd, 1H, $J=17.3\text{ Hz}$, $J'=4.7\text{ Hz}$), 1.67-1.60 (m, 1H), 1.56-1.50 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.32-1.25 (m, 1H), 0.91 (t, 6H, $J=7.5\text{Hz}$); ^{13}C NMR (125 MHz, CDCl_3) δ 213.5, 155.9, 136.4, 128.5, 128.1, 128.0, 76.4, 66.7, 46.4, 43.4, 40.8, 26.3, 26.1, 25.0, 23.0, 21.9; Elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{27}\text{NO}_4$ (321.41): C 67.26, H 8.47, N 4.36; found: C 67.22, H 7.85, N 4.51; Chiral HPLC (Chiralpak AS column; $i\text{PrOH}$:hexane 4:96; 0.8 mL/min, 210 nm) $R_{t\text{major}} = 15.1\text{ min}$, $R_{t\text{minor}} = 22.4\text{ min}$, 96 % e.e.

N*-(4-Hydroxy-1-isopropyl-4-methyl-3-oxo-pentyl)-carbamic acid *O*-benzyl ester **11e*

The title compound was prepared according to the general procedure starting from enone **1e** (0.312g, 2 mmol). Yield 323 mg (53 %). Pale yellow oil; $[\alpha]_D = -20.2$ (c 0.5, CHCl_3); IR (CHCl_3 , cm^{-1}) 3437, 3344, 1701, 1541; ^1H NMR (500 MHz, CDCl_3) δ 7.37-7.29 (m, 5H), 5.10 (d, 1H, $J=6.5\text{Hz}$), 5.07 (s, 2H), 3.88-3.82 (m, 1H), 3.66 (br s, 1H), 2.80 (d, 2H, $J=6\text{Hz}$), 1.95-1.86 (m, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 0.92 (t, 6H, $J=5.7\text{ Hz}$); ^{13}C NMR (125 MHz, CDCl_3) δ 213.4, 156.2, 136.4, 128.5, 128.1, 128.0, 76.6, 66.7, 53.7, 38.3, 31.3, 26.4, 26.3, 19.5, 18.5; Elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{25}\text{NO}_4$ (307.38): C 66.43, H 8.20, N 4.56; found: C 66.14, H 8.48, N 4.58; Chiral HPLC (Chiralpak AS column; $i\text{PrOH}$:hexane 4:96; 0.8 mL/min, 210 nm, $R_{t\text{major}} = 16.3\text{ min}$, $R_{t\text{minor}} = 20.7\text{ min}$, 98 % e.e.

(1-Cyclohexyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid benzyl ester **11f**

The title compound was prepared according to the general procedure starting from enone **1f** (0.98 g, 0.5 mmol) and benzyl carbamate (0.302 g, 2 mmol). Yield 100mg (57.6%). White solid; M.p. 88-89°C (ethyl acetate/hexane); $[\alpha]_D = -7.4$ (c 0.5, CH_2Cl_2); IR (KBr, cm^{-1}); 3370, 3328, 2935, 1710, 1560; ^1H NMR (200 MHz, CDCl_3) δ 7.36-7.33 (m, 5H), 5.15 (d, 1H, $J = 9.2$ Hz), 5.07 (s, 2H), 3.87 (m, 1H), 3.71 (br s, 1H), 2.83 (d, 2H, $J = 5.6$ Hz), 1.7 (m, 6H), 1.35-1.18 (br s, 6H), 1.18 (m, 3H), 1.0 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 213.7, 156.2, 136.6, 128.6, 128.2, 128.1, 76.7, 66.8, 53.0, 41.0, 38.0, 30.2, 29.2, 26.5, 26.4, 26.2, 26.1, 26.0; Elemental analysis calcd (%) for $\text{C}_{20}\text{H}_{29}\text{NO}_4$ (347.45): C 69.14, H 8.41, N 4.03; found: C 70.27, H 8.32, N 4.21; Chiral HPLC (Chiralcel OD column; iPrOH:hexane 10:90; 0.5 mL/min, 220 nm, $R_{t\text{major}} = 34.8$ min, $R_{t\text{minor}} = 42.4$ min, 94 % e.e.

(1-tert-Butyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid benzyl ester 11g

The title compound was prepared according to the general procedure starting from enone **1g** (0.075 g, 0.44mmol) and benzyl carbamate (0.133 g, 0.88 mmol). Yield 64mg (45%). White solid; M.p. 118-119°C ; $[\alpha]_D = -1.4$ (c 0.5, CH_2Cl_2); IR (KBr, cm^{-1}) ν 3267.5, 2967.5, 1726, 1677, 1541; ^1H NMR (200 MHz, CDCl_3) δ 7.42-7.35 (m, 5H), 5.1 (s, 2H), 4.85 (d, 1H, $J = 8.2$ Hz), 4.08 (br s, 1H), 3.7 (s, 1H), 2.89 (dd, 1H, $J = 3.6$ Hz, $J' = 14.8$ Hz), 2.5 (dd, 1H, $J = 10.6$ Hz, $J' = 15.6$ Hz), 1.34 (d, 6H, $J = 8.6$ Hz), 0.95 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 213.2, 156.4, 136.3, 128.4, 127.9, 77.4, 66.9, 56.3, 37.3, 34.7, 26.6; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.5 mL/min, 220 nm, $R_{t\text{major}} = 17.06$ min, $R_{t\text{minor}} = 21.06$ min, 94 % e.e.

(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid tert-butyl ester 12a

The title compound was prepared according to the general procedure starting from enone **1a** (0.109 g, 0.5 mmol) and tert-butyl carbamate (0.117 g, 1 mmol). Yield 154 mg (92%). White solid, M.p. 93-94°C (ethyl acetate/hexane); $[\alpha]_D = -18.4$ (*c* 0.5, CH₂Cl₂); IR (KBr, cm⁻¹) 3390, 3259, 1710, 1668. ¹H NMR (500 MHz, CDCl₃) δ 7.3-7.2 (m, 5H), 4.9 (s, 1H), 4.0 (br s, 1H), 3.7 (br s, 1H), 2.8 (br s, 2H), 2.7 (m, 1H), 2.6 (m, 1H), 1.9-1.8 (m, 2H), 1.45 (s, 9H), 1.34 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 213.6, 155.7, 141.2, 128.8, 126.1, 79.6, 47.9, 41.1, 36.4, 32.8, 28.6, 26.4; Elemental analysis calcd (%) for C₁₉H₂₉NO₄ (335.41): C 68.03, H 8.71, N 4.18; found: C 68.07, H 8.70, N 4.11; Chiral HPLC (Chiralcel OD column; iPrOH:hexane 10:90; 0.5 mL/min, 220 nm, *R*_t_{major} = 13.1 min, *R*_t_{minor} = 11.6 min, 90 % e.e.

[1-(3-Hydroxy-3-methyl-2-oxo-butyl)-heptyl]-carbamic acid tert-butyl ester 12b

The title compound was prepared according to the general procedure starting from enone **1b** (0.099 g, 0.5 mmol) and tert-butyl carbamate (0.117 g, 1 mmol). Yield 120 mg (76%). White waxy solid; M.p. 49-50°C (ethyl acetate/hexane); $[\alpha]_D = -21.6$ (*c* 0.5, CH₂Cl₂). IR (KBr, cm⁻¹) 3477, 3334, 2910, 1718, 1571; ¹H NMR (300 MHz, CDCl₃) δ 4.87 (br s, 1H), 3.87 (m, 2H), 2.78 (br s, 2H), 1.54 (br s, 2H), 1.42 (s, 9H), 1.34 (br s, 8H), 1.27 (br s, 6H), 0.88 (t, 3H, *J*=6.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 213.6, 155.6, 79.4, 48.0, 41.0, 34.7, 31.7, 28.9, 28.3, 26.2, 22.5, 14.0; Elemental analysis calcd (%) for C₁₇H₃₃NO₄ (315.45): C 64.73, H 10.54, N 4.44; found: C 65.60, H 9.77, N 4.50; Chiral HPLC (Chiralpak AD column; iPrOH:hexane 3:97; 0.5 mL/min, 220 nm, *R*_t_{major} = 30.0 min, *R*_t_{minor} = 75 min, 96.5 % e.e.

(4-Hydroxy-1-isobutyl-4-methyl-3-oxo-pentyl)-carbamic acid tert-butyl ester 12d

The title compound was prepared according to the general procedure starting from enone **1d** (0.510 g, 3 mmol) and tert-butyl carbamate (0.702 g, 6 mmol). Yield 746mg (86.6%). White solid; M. p. 63-64°C (ethyl acetate/hexane); $[\alpha]_D = -29.0$ (*c* 0.5, CH₂Cl₂); IR (KBr, cm⁻¹) 3287.5, 2987.5, 1696, 1677, 1541; ¹H NMR (200 MHz, CDCl₃) δ 4.83 (d, 1H, *J*= 8.8 Hz), 4.06 (m, 1H), 3.9 (s, 1H), 2.8 (m, 2H), 1.6 (m, 1H), 1.43 (s, 9H), 1.36 (s, 6H), 0.92 (d, 6H, *J*= 5.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 213.6, 155.6, 79.4, 46.2, 43.7, 41.5, 28.4, 26.2, 25.0, 22.95, 22.94; Elemental analysis calcd (%) for C₁₅H₂₉NO₄ (287.40): C 62.69, H 10.17, N 4.87; found: C 62.66, H 9.39, N 4.80; Chiral HPLC (Chiralpak AD column; iPrOH:hexane 4:96; 0.5 mL/min, 210 nm, *R*_t_{major} = 22.22 min, *R*_t_{minor} = 19.08 min, 96 % e.e.

(1-Cyclohexyl-4-hydroxy-4-methyl-3-oxo-pentyl)-carbamic acid tert-butyl ester 12f

The title compound was prepared according to the general procedure starting from enone **1f** (0.180 g, 0.51 mmol) and tert-butyl carbamate (0.120 g, 1.02 mmol). Yield 135 mg (85%); White solid; M. p. 96-97°C (ethyl acetate/hexane); $[\alpha]_D = -16.8$ (*c* 0.5, CH₂Cl₂); IR (KBr, cm⁻¹) 3387, 3365, 2912, 1725, 1660; ¹H NMR (200 MHz, CDCl₃) δ 4.9-4.8 (d, 1H, *J*=7.6 Hz), 3.9 (br s, 1H), 3.8 (br s, 1H), 2.7 (m, 2H), 1.7 (m, 6H), 1.42 (s, 9H), 1.4 (s, 6H), 1.2 (s, 3H), 0.96 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 213.8, 155.8, 79.4, 52.6, 41.2, 38.6, 30.0, 29.6, 29.126.3, 26.0; Elemental analysis calcd (%) for C₁₇H₃₁NO₄ (313.43): C 65.14, H 9.97, N 4.47; found: C 66.17, H 9.84, N 4.61; Chiral HPLC (Chiralpak AD column; iPrOH:hexane 5:95; 0.5 mL/min, 210 nm, *R*_t_{major} = 17.2 min, *R*_t_{minor} = 22.3 min, 91 % e.e.

(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid methyl ester 13a

The title compound was prepared according to the general procedure starting from enone **1a** (0.150 g, 0.688 mmol) and methyl carbamate (0.103 g, 1.38 mmol). Yield 103 mg (51%); White waxy solid; M. p. 45-46°C (ethyl acetate/hexane); $[\alpha]_D = -9.8$ (c 0.5, CH₂Cl₂); IR (KBr, cm⁻¹) 3475, 3362, 2950, 1710, 1527; ¹H NMR (200 MHz, CDCl₃) δ 7.3-7.17 (m, 5H), 5.20 (d, 1H, J = 7.4Hz), 4.05 (br s, 1H), 3.67 (s, 3H), 2.9-2.7 (m, 4H), 1.86 (m, 2H), 1.36 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 213.6, 156.7, 141.3, 128.6, 126.2, 76.5, 52.2, 48.1, 40.5, 36.1, 32.8, 26.3; Elemental analysis calcd (%) for C₁₆H₂₃NO₄ (293.16): C 65.51, H 7.90, N 4.77; found: C 66.43, H 8.04, N 4.88; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.8 mL/min, 220 nm, $R_{t\text{major}}$ = 30.7 min, $R_{t\text{minor}}$ = 41.2 min, >99 % e.e.

(4-Hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-carbamic acid ethyl ester 14a

The title compound was prepared according to the general procedure starting from enone **1a** (0.050g, 0.229 mmol) and urethane (0.41 g, 0.46 mmol). Yield 52mg (74%). Colorless oil; $[\alpha]_D = -12.2$ (c 0.5, CH₂Cl₂); IR (KBr, cm⁻¹) 3409, 2987, 1705, 1545; ¹H NMR (200 MHz, CDCl₃) δ 7.36 -7.19 (m, 5H), 5.23 (d, 1H, J = 3.4 Hz), 4.1 (m, 3H), 2.87 (t, 2H, J = 7.3 Hz), 2.7-2.59 (m, 2H), 2.2-1.8 (m, 2H), 1.35 (s, 6H), 1.3-1.2 (m, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 213.7, 155.5, 141.3, 128.5, 126.0, 61.0, 48.0, 40.7, 36.2, 32.8, 26.4, 14.7; Elemental analysis calcd (%) for C₁₇H₂₅NO₄ (307.18): C 66.43, H 8.20, N 4.56; found: C 64.66, H 8.11, N 4.11; Chiral HPLC (Chiralpak AS column; iPrOH:hexane 4:96; 0.8 mL/min, 220 nm, $R_{t\text{major}}$ = 21.9 min, $R_{t\text{minor}}$ = 30.6 min, 96 % e.e.

2-(1-Benzyloxycarbonylamino-3-methyl-butyl)-malonic acid dimethyl ester

The title compound was prepared following the general procedure applied to α -hydroxy enones starting from alkylidene **16** (0.050 g, 0.25mmol) and benzyl carbamate (0.076 g, 0.5 mmol). Yield 70mg (80%); Colorless liquid; IR (CHCl_3 , cm^{-1}) 3448, 2968, 1738.8, 1513; ^1H NMR (200 MHz, CDCl_3) δ : 7.35 (s, 5H), 5.6 (d, 1H, $J=10\text{Hz}$), 5.08 (d, 2H, $J=1.2\text{ Hz}$), 4.4 (m, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 3.65 (d, 1H, $J=6.3\text{ Hz}$), 1.64 (m, 1H), 1.30 (m, 2H), 0.94 (t, 6H, $J=4.8\text{ Hz}$); ^{13}C NMR (75 MHz, CDCl_3) δ 168.7, 168.2, 155.9, 136.7, 128.5, 66.7, 55.2, 52.7, 49.1, 42.6, 25.0, 23.1, 21.9; Chiral HPLC (Chiralpak OD column; iPrOH:hexane 3:97; 0.5 mL/min, 220 nm, $R_{t\text{major}} = 28.1\text{ min}$, $R_{t\text{minor}} = 30.7\text{ min}$, ~00 % e.e.

Chemical correlation of Cbz adduct **11e** and Boc adduct **12e**

To a solution of **11e** (0.030 g, 0.093 mmol) and $(\text{Boc})_2\text{O}$ (0.041 g, 0.186 mmol) in ethyl acetate (3mL) was added activated Pd on charcoal (10%, 3 mg) and the mixture was kept under hydrogen atmosphere at room temperature for several hours till the starting material disappeared. Then the suspension was filtered through a pad of celite and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (eluent, ethyl acetate/hexane) to get the title compound which showed identical physical and spectroscopic data than authentic **12e**. Yield 0.024 g (90%).

Procedure for cleavage of α' -hydroxy ketones **11-12** with sodium periodate

A solution of sodium periodate (1.50 g, 7 mmol) in H_2O (10 mL) was added to a solution of the corresponding α -hydroxy ketone **11/12** (0.7 mmol) in methanol (1 mL) and after complete addition the reaction was stirred at room temperature until starting material disappeared as monitored by TLC (several hours). Methanol was then removed under reduced pressure and the reaction mixture extracted several times with CH_2Cl_2 . The organic layers were combined, washed with saturated sodium bicarbonate solution and then dried over anhydrous MgSO_4 and concentrated.

Data for acid 17a: **17a**

The above procedure was used starting from **11a** (0.235 g, 0.7 mmol). Yield 0.197 g (96%).

Data for acid 17d: **17d**

The above procedure was used starting from **11d** (0.225 g, 0.7 mmol). Yield 0.177g (91%). The obtained compound showed identical physical and spectroscopic data to those reported.⁵ $[\alpha]_D^{25} = -28.7$ ($c=2.9$, CHCl_3) [Lit.⁵ data for *R* isomer: $[\alpha]_D^{25} = +29.5$ ($c=2.5$, CHCl_3)].

Data for acid 18a **18a**

Yield 0.087 g (99%). The compound thus obtained showed identical physical and spectroscopic data than that published.⁶

Data for acid 18d **18d**

⁵ El Marini, A.; Roumestant; Viallefont, P.; Razafindramboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, 1104-1108.

⁶ Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, 81, 2141-2156.

Yield 0.157 g (92%). The compound thus obtained showed identical physical and spectroscopic data than that published.⁵

Preparation of ester using Trimethyl silyl diazomethane:

Trimethylsilyl diazomethane (2M solution in hexanes, 0.165 mL, 0.33 mmol) (**explosive**) was added dropwise to a solution of acid **17/18** (0.3 mmol) in benzene (5 mL) and methanol (0.5 mL) at room temperature. After 20 min of stirring, solvents were removed under reduced pressure to get the corresponding crude ester which was purified by flash column chromatography (gradient eluent: ethyl acetate/hexane).

Data for ester 19d

Yield 0.270 g (74%). Chemical correlation of this compound and Boc-derivative **20d** confirmed identity and configuration (see below).

Data for ester 20a

Yield 0.088 g (98%). The compound thus obtained showed identical physical and spectroscopic data than that published.⁷ $[\alpha]_{\text{D}}^{25} = -8.7$ ($c=1.8$, CHCl_3) [Lit. data for *R* isomer: $[\alpha]_{\text{D}}^{25} = +7.2$ ($c=1.8$, CHCl_3)].

Data for ester 20d

⁷ El Marini, A.; Roumestant; Viallefont, P.; Razafindramboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, 1104-1108.

Yield 0.150 g (95%). The compound thus obtained showed identical physical and spectroscopic data than that published.⁷ $[\alpha]_{\text{D}}^{25} = -21.9$ ($c=1.47$, CH_3OH) [Lit.⁷ $[\alpha]_{\text{D}}^{25} = -22.8$ ($c=1.47$, CH_3OH)].

FGI: Cbz to Boc group

To a solution of adduct **19d** (174 mg, 0.59 mmol) and $(\text{Boc})_2\text{O}$ (259 mg, 1.18 mmol) in ethyl acetate (5.0 mL) was added 10% activated Pd on charcoal and the mixture was kept under hydrogen atmosphere at room temperature for several hours till the starting material was disappeared. Then the suspension was filtered through a pad of celite and evaporated under reduced pressure. The residue was purified by column chromatography (gradient eluent of Hexane: ethyl acetate) to get the title ester compound. Yield 0.130 g (85%). The compound thus obtained showed identical physical and spectroscopic data than that published.⁶ $[\alpha]_{\text{D}}^{25} = -21.9$ ($c=1.47$, Methanol) [Lit. $[\alpha]_{\text{D}}^{25} = -22.8$ ($c=1.48$, Methanol)].

1a¹H NMR ¹³C NMR

^1H NMR

^{13}C NMR

1c¹H NMR ¹³C NMR

1d¹H NMR ¹³C NMR

^1H NMR

^{13}C NMR

^1H NMR

^{13}C NMR

1g¹H NMR ¹³C NMR

11a¹H NMR ¹³C NMR

11b¹H NMR ¹³C NMR

11c¹H NMR ¹³C NMR

^1H NMR

^{13}C NMR

11e¹H NMR ¹³C NMR

^1H NMR

^{13}C NMR

11g¹H NMR ¹³C NMR

12a¹H NMR ¹³C NMR

12b¹H NMR ¹³C NMR

^1H NMR

^{13}C NMR

^1H NMR

^{13}C NMR

13a¹H NMR ¹³C NMR

¹H NMR

¹³C NMR

¹H NMR ¹³C NMR

¹H NMR

¹³C NMR

^1H NMR

^{13}C NMR

^1H NMR

^1H NMR

rac-11a **11a**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.436	MM	2.9519	1.66433e4	93.96838	98.1968
2	34.205	MM	2.3225	305.61594	2.19311	1.8032

rac-11b **11b**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.694	MM	2.6588	7477.41455	46.87159	95.8491
2	27.873	MM	2.8419	323.82446	1.89910	4.1509

rac-11c **11c**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.146	MM	1.9395	1.47286e4	126.56786	97.6234
2	24.624	MM	1.7084	358.55582	3.49790	2.3766

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.125	MM	2.0383	1.15045e4	94.06971	97.5042
2	22.408	MM	2.2875	294.47495	2.14552	2.4958

rac-11e **11e**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.336	MM	1.8388	9658.24414	87.54135	98.9665
2	20.693	MM	1.2916	100.85738	1.30144	1.0335

Retention Time (min)	Area	% Area	Height
34,809	12977659	97,00	127364
42,425	400944	3,00	4460

Retention Time (min)	Area	% Area	Height
17,076	24005579	96,92	235024
21,067	763498	3,08	7900

rac-12a

12a

Retention Time (min)	Area	% Area	Height
11,615	631146	4,90	24219
13,110	12250728	95,10	400790

rac-12b **12b**

Retention Time (min)	Area	% Area	Height
26,750	104631	1,78	1436
30,046	5785131	98,22	45163

rac-12d **12d**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.089	MM	1.5875	242.23987	2.54318	1.9252
2	22.223	MM	2.5295	1.23404e4	81.30984	98.0748

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.245	MM	1.7430	668.27991	6.39004	4.4651
2	22.334	VV	1.6275	1.42985e4	104.03514	95.5349

rac-14a **14a**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.923	MM	2.6171	2.50359e4	159.43698	98.0971
2	30.610	MM	2.1385	485.65616	3.78506	1.9029

rac-19d **19d**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.437	MM	0.5841	1704.13281	48.62803	2.2017
2	17.562	MM	0.9636	7.56983e4	1309.35278	97.7983

rac-20d **20d**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.927	MM	1.8223	528.91943	4.83756	3.2768
2	22.097	MM	2.7113	1.56125e4	95.97194	96.7232