SUPPORTING INFORMATION

for

Highly Enantioselective Friedel-Crafts Alkylations of Pyrroles and Indoles with α' -Hydroxy Enones Under Cu(II)-Simple Bis(oxazoline) Catalysis.

Claudio Palomo,* Mikel Oiarbide, Bharat G. Kardak, Jesús M. García, Anthony Linden

E-mail: qoppanic@sc.ehu.es*Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, Apdo. 1072, 20080 San Sebastián, Spain.*e-mail: qoppanic@sc.ehu.es**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 . Ethanol, Isopropyl alcohol, and hexane 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[(4S)-4-*tert*-butyl-2-oxazoline and (S)-(-)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) were purchased from Aldrich Chemical, and used without further purification. Ligand 1,1'-bis[2-((4S)-(1,1-dimethylethyl)-1,3-oxazolinyl)]cyclopropane and the parent bisoxazolinyl cyclopropane derived from 2-amino indanol were 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

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

chloroform. Analytical high performance liquid 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, IA, OJ and Chiralcel OD columns.

Table S1. Reaction of α' -hydroxy enone **7a** [R: PhCH₂CH₂] with N-methyl pyrrole **8** promoted by bis(oxazoline)-metal complexes **A-D**.^a

cat.	R ¹	MX _n	time, h	Product 10a	
				yield, % ^a	ee, % ^b
A	<i>t</i> Bu	Mg(OTf) ₂	24	nr ^c	--
B	<i>t</i> Bu	Zn(OTf) ₂	22	99	17
C	Ph	Cu(OTf) ₂	2	78	7
D			2	76	62

^a Isolated yield after column chromatography. ^b Determined by HPLC. ^c Starting material recovered.

Table S2. Effect of the solvent in the reaction of α' -hydroxy enone **7a** [R: PhCH₂CH₂] with N-methyl pyrrole **8** catalyzed by complex **12**.^a

solvent	time, h	yield, % ^b	ee, % ^c
CH ₂ Cl ₂	3	86	92
THF	2	83	89
Et ₂ O	2	82	85
Toluene	20	80	88
CH ₃ CN	24	0	--

^a Reactions conducted at 0.5 mmole scale at r.t. Molar ratio of **7a**:**8**:**12** 1:2:0.1. ^b After column chromatography.

^c Determined by HPLC.

(3-Methyl-2-oxo-3-triethylsilyloxybutyl)-phosphonic acid dimethyl ester

(Procedure adapted from: a) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F., *J. Org. Chem.* **1986**, *51*, 2525-2529, and b) McCarthy, D. G.; Collins, C. C.; O'Driscoll, J. P.; Lawrence, S. E., *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667-3675.)

Methyl 2-hydroxyisobutyrate (6.9 mL, 60 mmol) was added under a nitrogen atmosphere to a solution of dimethyl amino pyridine (1.22 g, 10 mmol), triethylamine (10 mL, 50 mmol) and triethylchlorosilane (8.5 mL, 50 mmol) in 50 mL dichloromethane. The reaction mass was stirred at room temp for 24 hours. After filtering over celite to remove the salt, the filtrate was diluted with diethyl ether (150 mL) and the resulting solution was washed with brine (1 x 50 mL) and water (1 x 50 mL). The solvent was removed under reduced pressure to give the title compound. Yield: 12.6 g (92%). No further purification is needed.

Dimethyl methyl phosphonate (13.8 mL, 130 mmol, 2.5 eq) in dry THF (40 mL) was added drop-wise to a cold solution of n-BuLi (1.6 M in hexanes, 79 mL, 130 mmol) in

dry THF (80 mL) at -78°C under a nitrogen atmosphere. After stirring the resulting solution for 30 min, a solution of the crude triethylsilyl ether prepared above (12 g, 51 mmol) in dry THF (100 mL) was added drop-wise at -78°C . The mixture was stirred at the same temperature (-78°C) for 3h and then quenched at this temperature with saturated ammonium chloride solution (200 mL). After allowing reaction mass to come to room temperature, it was extracted with diethyl ether (3 x 250 mL), dried over MgSO_4 and the solvent was evaporated under reduced pressure to get the title compound. Yield: 17g (99 %). It was used for the next step without further purification.

Preparation of α' -hydroxy enones 7

α' -Hydroxy enones **7a-g** were prepared as previously described, starting from the corresponding aldehyde and either 3-hydroxy-3-methyl-2-butanone or (3-Hydroxy-3-methyl-2-oxo-butyl)-phosphonic acid dimethyl ester (Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188-9189).

2-Hydroxy-2-methyl-hex-4-en-3-one **7i**

Dried LiCl (1.17 g, 27 mmol) and Et_3N (3.8 mL, 27 mmol) were added successively to a solution of (3-methyl-2-oxo-3-(triethylsilyloxybutyl)-phosphonic acid dimethyl ester (9.0 g, 27 mmol) in dry MeCN (67 mL). The resulting milky suspension was stirred for 15 min at room temperature and acetaldehyde (1.5 mL, 27 mmol) was added dropwise. The mixture was stirred for 40 h, diluted with water and extracted with Et_2O . Evaporation of the solvent gives an oil which was dissolved in CH_3CN (50 mL) and HF (48% aqueous, 2 mL) was added dropwise. The mixture was stirred for 3 h, diluted with CH_2Cl_2 , washed with brine, dried and concentrated *in vacuo*. Flash chromatography (hexanes- EtOAc , 10:1) of the residue gave 2.5 g (72%) of the title compound. IR (CHCl_3 , cm^{-1}): 3421, 2968, 1646; ^1H NMR (300 MHz, CDCl_3) δ 7.15 (m, 1H), 6.46 (d, 1H, $J=15.3$ Hz), 3.98 (s, 1H), 1.96 (d, 3H, $J=6.6$ Hz), 1.39 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.1, 146.0, 123.9, 75.0, 26.2, 18.4.

General procedure for the catalytic Friedel-Crafts alkylation of either N-methyl pyrrole **8 or pyrrole **9** with enones **7****

2,2'-Isopropylidene bis[(4*S*)-4-tert-butyl-2-oxazoline] (tBu-BOX) (or the corresponding chiral ligand) (0.06 mmol) was weighted in a flame-dried flask and placed under N₂. Cu(OTf)₂ (18 mg, 0.05 mmol) was then added by rinsing with dry CH₂Cl₂ (1.0 mL) from a weighting boat directly into the reaction flask. After stirred at room temperature for 3 h, a solution of the corresponding α'-hydroxy enone **7** (0.5 mmol) in dry CH₂Cl₂ (0.5 mL) was cannulated into the solution followed by a 0.5 mL rinse, and the resulting mixture was stirred for a further 10 min at room temperature. Then N-methyl pyrrole **8** (89 μL, 1 mmol) was added dropwise by syringe directly into the reaction, and the mixture was stirred at room (or otherwise stated) temperature under N₂ for the stated time. The resulting reaction mixture was diluted with NH₄Cl (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 on SiO₂ eluting with 90% hexane and 10% EtOAc to yield pure compounds **10**.

For the reactions with pyrrole **9** to afford adducts **11**, the above procedure was employed using 67 μL (1 mmol) of pyrrole instead of N-methyl pyrrole.

General procedure for the preparation of racemic adducts.

The corresponding enone **7** (0.5 mmol) was weighted into an oven or flame-dried flask and placed under N₂. It was dissolved in 1.0 mL dry CH₂Cl₂. 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. Then either N-methyl pyrrole **8** or pyrrole **9** (1 mmol)

was added dropwise by syringe 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 NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10mL). The CH_2Cl_2 layers were combined, dried over anhydrous MgSO_4 and concentrated to give crude product. Subsequent purification by flash chromatography using gradient mixtures of ethyl acetate/n-hexane as eluent yields pure product.

2-Hydroxy-2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-7-phenyl-heptan-3-one

The title compound was prepared according to the general procedure starting from enone **7a** (109 mg, 0.5mmol). Yield 129 mg (86 %); Yellow thick oil; $[\alpha]_{\text{D}}^{25} = +10.80^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3475, 2959, 1710, 1480 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.28 (dd, 2H, $J=7.5\text{Hz}$), 7.19 (dd, 1H, $J=7.0\text{ Hz}$), 7.12 (d, 2H, $J=6.5\text{ Hz}$), 6.49 (d, 1H, $J=0\text{ Hz}$), 6.09 (dd, 1H $J=3.0\text{ Hz}$), 5.94 (d, 1H, $J=0$), 3.54 (s, 1H), 3.51 (s, 3H), 3.37 (m, 1H), 2.92 (dd, 1H, $J=7.5\text{ Hz}$), 2.77 (dd, 1H, $J=6.5\text{ Hz}$), 2.57 (m, 2H), 1.93 (m, 2H), 1.32 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) 213.3, 141.7, 135.4, 128.3, 128.3, 125.9, 121.0, 106.9, 104.2, 76.2, 42.8, 37.7, 33.6, 33.4, 31.1, 26.2, 26.0; MS (ESI): m/z : 299, 108; Elemental analysis calcd (%) for $\text{C}_{19}\text{H}_{25}\text{NO}_2$ (299.41): C 76.22, H 8.42, N 4.68; found: C 75.90, H 6.78, N 4.79; Chiral HPLC (Chiralcel OD column; hexane: iPrOH 95:5; 0.5 mL/min, 254nm, $R_{\text{t major}}$: 32.54 min, $R_{\text{t minor}}$: 23.42 min, 91.74 % e.e. By following the General Procedure using cat **13** the same compound was obtained in 80% yield (91% ee).

2-Hydroxy-2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-undecan-3-one

The title compound was prepared according to the general procedure starting from enone **7b** (85 mg, 0.5mmol). Yield 114 mg (82 %); yellow thick oil; $[\alpha]_D^{25} = +2.2^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3500, 2950, 1700, 1487. ^1H NMR (500 MHz, CDCl_3) δ 6.46 (d, 1H, $J = 0$ Hz), 6.04 (dd, 1H, $J = 3.5$ Hz), 5.85 (d, 1H, $J = 2.0$ Hz), 3.59 (s, 3H), 3.58 (s, 1H), 3.32 (m, 1H), 2.88 (dd, 1H, $J = 8.0$ Hz), 2.74 (dd, 1H, $J = 6.0$ Hz), 1.58 (q, 2H, $J = 7.5$ Hz), 1.34 (s, 3H), 1.23 (m, 8H), 1.22 (s, 3H), 0.86 (t, 3H, $J = 7$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 213.6, 136.3, 120.9, 106.7, 103.9, 76.3, 42.8, 36.5, 33.7, 31.7, 31.5, 29.3, 27.6, 26.3, 26.1, 22.6, 14.1; MS (ESI): m/z : 279, 94; Elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{29}\text{NO}_2$ (279.42): C 73.09, H 10.46, N 5.01; found: C 72.46, H 9.86, N 5.23 Chiral HPLC (Chiralcel OD column; hexane:iPrOH 95:5; 0.5 mL/min, 210nm, $R_{t\text{major}}$: 21.68 min, $R_{t\text{minor}}$: 14.26 min, 95.84 % e.e.

A 10 mg (4%) fraction of the dialkylated adduct (2-Hydroxy-5-{5-[1-(3-hydroxy-3-methyl-2-oxo-butyl)-heptyl]-1-methyl-1H-pyrrol-2-yl}-2-methyl-undecan-3-one, **S-1**) was also obtained from column.

Data of **S-1**: Yellow oil; $[\alpha]_D^{25} = -30.60^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3503, 2922, 1706, 1452; ^1H NMR (300 MHz, CDCl_3) δ 5.79 (s, 2H), 3.58 (s, 2H), 3.51 (s, 3H), 3.34 (m, 2H), 2.89 (dd, 2H, $J = 7.2$ Hz), 2.73 (dd, 2H, $J = 6$ Hz), 1.57 (m, 4H), 1.34 (s, 6H), 1.24 (m, 16H), 1.21 (s, 6H), 0.89 (t, 6H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 213.6, 135.2, 103.0, 76.2, 42.7, 36.3, 31.8, 31.7, 30.1, 29.2, 27.2, 26.1, 26.0, 22.5, 14.0; MS (ESI): m/z 476, 49.

2-Hydroxy-2,6-dimethyl-5-(1-methyl-1H-pyrrol-2-yl)-heptan-3-one

The title compound was prepared according to the general procedure starting from enone **7c** (78 mg, 0.5mmol). Yield 102 mg (86 %); yellow thick oil; $[\alpha]_D^{25} = +13.40^\circ$ ($c=1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3437, 2931, 1710, 1456; ^1H NMR (300 MHz, CDCl_3) δ 6.48 (d, 1H, $J=1.8$ Hz), 6.04 (dd, 1H, $J=2.7$ Hz), 5.82 (dd, 1H, $J=1.8$ Hz), 3.64 (s, 3H), 3.61 (s, 1H), 3.17 (m, 1H), 3.05 (dd, 1H, $J=10.5$ Hz), 2.76 (dd, 1H, $J=4.2$ Hz), 1.83 (m, 1H), 1.36 (s, 3H), 1.22 (s, 3H), 0.95 (d, 3H, $J=6.6$ Hz), 0.87 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 213.8, 135.2, 120.7, 106.4, 104.7, 76.3, 39.8, 37.7, 33.9, 33.5, 26.2, 20.3, 20.1; MS (ESI): m/z : 237, 108; Elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{23}\text{NO}_2$ (237.34): C 70.89, H 9.77, N 5.90; found: C 71.54, H 9.83, N 5.85; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 97:3; 0.5 mL/min, 254nm, $R_{t\text{major}}$: 15.40 min, $R_{t\text{minor}}$: 12.53 min, 94.72 % e.e.

1-Cyclohexyl-4-hydroxy-4-methyl-1-(1-methyl-1H-pyrrol-2-yl)-pentan-3-one

The title compound was prepared according to the general procedure starting from enone **7d** (98 mg, 0.5mmol). Yield 90 mg (65 %); yellow solid; m.p 146-149 $^\circ\text{C}$ (from hexane); $[\alpha]_D^{25} = -22.10^\circ$ ($c=1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3492, 2950, 1712, 1492; ^1H NMR (300 MHz, CDCl_3) δ 6.45 (d, 1H, $J=2.1$ Hz), 6.04 (dd, 1H, $J=3.3$ Hz), 5.80 (dd, 1H, $J=1.8$ Hz), 3.65 (s, 3H), 3.63 (s, 1H), 3.18 (m, 1H), 1.34 (s, 3H), 3.04 (dd, 1H, $J=9.9$ Hz), 2.79 (dd, 1H, $J=3.6$ Hz), 1.44-1.86 (m, 5H), 1.20 (s, 3H), 1.17 (m, 2H), 0.95 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.0, 135.4, 120.6, 106.4, 104.5, 76.3, 43.6, 39.7, 37.0, 33.9, 31.0, 30.6, 26.4, 26.4, 26.3, 26.2, 26.2. MS (ESI): m/z : 277, 108; Chiral HPLC (Chiralpak IA column; hexane:iPrOH 98:2; 0.5 mL/min, 210nm, $R_{t\text{major}}$: 17.75 min, $R_{t\text{minor}}$: 15.51 min, 92.86 % e.e.

A 34 mg (14%) fraction of dialkylated adduct **S-2** was also obtained from column.

Data of **S-2**: Yellow solid; $[\alpha]_{\text{D}}^{25} = +70.60^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3492, 2931, 1712, 1454; ^1H NMR (500 MHz, CDCl_3) δ 5.67 (s, 2H), 3.53 (s, 2H), 3.50 (s, 1H), 3.13 (m, 2H), 2.97 (dd, 2H, $J=10.5$ Hz, $J'=10$ Hz), 2.72 (dd, 2H, $J=4.0$ Hz), 1.75 (q, 1H, $J=12.5$ Hz), 1.63 (t, 1H, $J=12.0$ Hz), 1.38 (t, 2H, $J=10.0$ Hz), 1.13 (s, 6H), 1.13 (s, 6H), 1.13 (m, 4H), 0.86 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.1, 134.1, 103.6, 76.23, 43.7, 39.9, 37.6, 31.1, 30.6, 30.4, 26.4, 26.2, 26.1; Elemental analysis calcd (%) for $\text{C}_{29}\text{H}_{47}\text{NO}_4$ (473.69): C 73.53, H 10.00, N 2.96; found: C 73.75, H 10.25, N 3.00. (See the ORTEP diagram on the last page of SI).

By following the General Procedure, but using 6 mol equivalents of **8**, the title compound was obtained in 84% yield and 96.7% ee, without traces of dialkylated by-product **S-2**.

2-Hydroxy-2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-heptan-3-one

The title compound was prepared according to the general procedure starting from enone **7e** (71mg, 0.5mmol) and carrying out the reaction at -20°C . Yield 98 mg (88 %); yellow thick oil; $[\alpha]_{\text{D}}^{25} = -6.30^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3484, 2968, 1715, 1487; ^1H NMR (500 MHz, CDCl_3) δ 6.47 (d, 1H, $J=0.2$ Hz), 6.05 (dd, 1H, $J=3.5$ Hz), 5.84 (d, 1H, $J=2.0$ Hz), 3.61 (s, 1H), 3.60 (s, 3H), 3.27 (m, 1H), 2.90 (dd, 1H, $J=7.5$ Hz), 2.76 (dd, 1H, $J=6.5$ Hz), 1.61 (m, 2H), 1.34 (s, 3H), 1.23 (s, 3H), 0.85 (t, 3H, $J=7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 213.6, 136.0, 120.9, 106.7, 104.0, 76.3, 42.3, 33.7, 32.9, 29.2, 26.3, 26.1, 11.8; MS (ESI): m/z 223, 122; Chiral HPLC (Chiralcel OD

column, hexane:iPrOH 95:5; 0.5 mL/min, 210nm, $R_{t\text{major}}$: 16.86 min, $R_{t\text{minor}}$: 12.45 min., 93.73 % e.e.

2-Hydroxy-2,7-dimethyl-5-(1-methyl-1H-pyrrol-2-yl)-octan-3-one

The title compound was prepared according to the general procedure starting from enone **7f** (85 mg, 0.5mmol). Yield 85 mg (68 %); yellow thick oil; $[\alpha]_D^{25} = +11.50^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3475, 2959, 1710, 1470; ^1H NMR (500 MHz, CDCl_3) δ 6.45 (d, 1H, $J=2.5$ Hz), 6.04 (dd, 1H, $J=3.5$ Hz), 5.86 (d, 1H, $J=2.0$ Hz), 3.60 (s, 3H), 3.56 (s, 1H), 3.40 (m, 1H), 2.86 (dd, 1H, $J=7.5$ Hz), 2.68 (dd, 1H, $J=6.5$ Hz), 1.55 (m, 1H), 1.47 (m, 1H), 1.39 (m, 1H), 1.32 (s, 3H), 1.18 (s, 3H), 0.90 (d, 3H, $J=6.0$ Hz), 0.87 (d, 3H, $J=6.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 213.5, 136.3, 120.8, 106.8, 104.0, 76.3, 45.7, 43.3, 33.7, 29.5, 26.2, 25.9, 25.7, 23.1, 22.2; MS (ESI): m/z 251, 94; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 95:5; 0.5 mL/min, 210nm) $R_{t\text{major}}$: 21.44 min, $R_{t\text{minor}}$: 12.93 min., 88 % e.e.

A 18 mg (8%) fraction of the dialkylated adduct (2-Hydroxy-5-[5-(4-hydroxy-1-isobutyl-4-methyl-3-oxo-pentyl)-1-methyl-1H-pyrrol-2-yl]-2,7-dimethyl-octan-3-one, **S-3**) was also obtained from the column.

Data of **S-3**: Yellow waxy solid; $[\alpha]_D^{25} = -10.6^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3484, 1712, 1665; ^1H NMR (500 MHz, CDCl_3) δ 5.77 (s, 2H), 3.55 (s, 2H), 3.49 (s, 3H), 3.39 (m, 2H), 2.82 (dd, 2H, $J=7.5$ Hz), 2.64 (dd, 2H, $J=6.5$ Hz), 1.51 (m, 2H), 1.46-1.32 (m, 4H), 1.28 (s, 6H), 1.14 (s, 6H), 0.86 (d, 6H, $J=6.0$ Hz), 0.83 (d, 6H, $J=6.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 213.7, 135.1, 103.2, 76.2, 75.3, 69.0, 45.6, 43.4, 30.1, 29.9, 26.0, 25.9, 25.6, 24.4, 23.1, 22.2.

By following the General Procedure, but using 6 mol equivalents of **8** at -20°C, the title compound **10f** was obtained in 86% yield and 94% ee, without traces of dialkylation adduct **S-3**.

4-Hydroxy-4-methyl-1-(1-methyl-1H-pyrrol-2-yl)-1-phenyl-pentan-3-one

The title compound was prepared according to the general procedure starting from enone **7g** (95.12mg, 0.5mmol). Yield 128 mg (95 %); Yellow oil; $[\alpha]_D^{25} = -3.30$ ($c = 1$, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3456, 3071, 1707, 1489; ^1H NMR (500 MHz, CDCl_3) δ 7.20-7.28 (m, 5H), 6.56 (dd, 1H, $J=0$), 6.11(m, 2H), 4.68 (t, 1H, $J=7.0$ Hz, $J'=7.0$ Hz), 3.56 (s, 1H), 3.38 (s, 3H), 3.26 (dd, 1H, $J=7.5$ Hz, $J'=7.5$ Hz), 3.17 (dd, 1H, $J=8.5$ Hz, $J'=8.5$ Hz), 1.38 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 212.0, 142.6, 133.9, 128.6, 127.8, 126.7, 122.1, 106.4, 105.4, 76.3, 43.0, 38.1, 33.8, 26.2, 25.7; MS (ESI): m/z 271; Elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{21}\text{NO}_2$ (271.35): C 75.25, H 7.80, N 5.16; found: C 74.96, H 8.10, N 4.93; Chiral HPLC was performed on Waters 600 E (Chiralpak AD, Hexane:EtOH 94:06; 0.5 mL/min., 254nm) $R_{t\text{major}}$: 16.26 min, $R_{t\text{minor}}$: 20.13 min., 68 % e.e.

2-Hydroxy-2-methyl-7-phenyl-5-(1H-pyrrol-2-yl)-heptan-3-one

The title compound was prepared according to the general procedure starting from enone **7a** (109 mg, 0.5mmol) and pyrrole **9**. Yield 118 mg (83 %); Yellow red oil; $[\alpha]_D^{25} = +12.0^\circ$ ($c = 1$, CH_2Cl_2). IR (CH_2Cl_2 , cm^{-1}) 3384, 2974, 1709, 1455, 966, 701; ^1H NMR (300 MHz, CDCl_3) δ 8.38 (1H, bs), 7.16-7.34 (m, 5H), 6.68 (d, 1H, $J=1.8$ Hz), 6.17 (dd, 1H, $J=2.7$ Hz), 5.99 (d, 1H, $J=3.9$ Hz), 3.32 (m, 1H), 2.96 (dd, 1H, $J=7.5$ Hz), 2.80 (dd, 1H, $J=4.8$ Hz), 2.63 (m, 2H), 2.06 (m, 2H), 1.34 (s, 3H), 1.21 (s, 3H); ^{13}C

NMR (75 MHz, CDCl_3) δ 214.5, 141.8, 134.2, 128.4, 125.9, 116.3, 108.2, 104.0, 43.11, 36.42, 33.77, 33.51, 26.17, 25.95; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 95:5; 0.5 mL/min, 210nm, $R_{t\text{major}}$: 38.58 min, $R_{t\text{minor}}$: 47.62 min, 90.29 % e.e.

A 20 mg (8%) fraction of the dialkylated adduct (2-Hydroxy-5-[5-(4-hydroxy-4-methyl-3-oxo-1-phenethyl-pentyl)-1H-pyrrol-2-yl]-2-methyl-7-phenyl-heptan-3-one, **S-4**) was also obtained from the column.

Data of **S-4**: Yellow red oil; $[\alpha]_{\text{D}}^{25} = -3.9^\circ$ ($c = 1$, CH_2Cl_2). ^1H NMR (500 MHz, CDCl_3) δ 8.18 (bs, 1H), 7.10-7.27 (m, 10H), 5.80 (d, 2H, $J = 2.5$ Hz), 3.19 (m, 2H), 2.86 (dd, 2H, $J = 9.0$ Hz), 2.71 (dd, 2H, $J = 5.0$ Hz), 2.55 (m, 4H), 1.94 (m, 4H), 1.29 (s, 6H), 1.16 (s, 6H).

2-Hydroxy-2-methyl-5-(1H-pyrrol-2-yl)-heptan-3-one

The title compound was prepared according to the general procedure starting from enone **7b** (99 mg, 0.5mmol) and pyrrole **9**. Yield 108 mg (82 %); Yellow red oil; $[\alpha]_{\text{D}}^{25} = +23.4^\circ$ ($c = 1$, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3411, 2940, 1707, 732 ^1H NMR (500 MHz, CDCl_3) δ 8.25 (bs, 1H), 6.62 (d, 1H, $J = 0$ Hz), 6.10 (dd, 1H, $J = 3.0$ Hz), 5.88 (d, 1H, $J = 0$ Hz), 3.57 (bs, 1H), 3.24 (m, 1H), 2.86 (dd, 1H, $J = 8.5$ Hz), 2.75 (dd, 1H, $J = 5.0$ Hz), 1.70 (m, 1H), 1.58 (m, 1H), 1.33 (s, 3H), 1.28 (m, 8H), 1.17 (s, 3H), 0.87 (t, 3H, $J = 7\text{Hz}$) ^{13}C NMR (125 MHz, CDCl_3) δ 214.9, 135.0, 116.1, 108.1, 103.8, 76.5, 43.0, 34.8, 33.9, 31.7, 29.3, 27.6, 26.2, 26.0, 22.6, 14.1; Chiral HPLC (Chiralpak IA column, Hexane: iPrOH 95:5; 0.5 mL/min., 254 nm) $R_{t\text{major}}$: 19.62 min; $R_{t\text{minor}}$: 23.12 min., 89 % e.e.

A 10 mg (4%) fraction of the dialkylated adduct (2-Hydroxy-5-{5-[1-(3-hydroxy-3-methyl-2-oxo-butyl)-heptyl]-1H-pyrrol-2-yl}-2-methyl-undecan-3-one, **S-5**) was also obtained from the column.

S-5

Data of **S-5**: Yellow red oil; ^1H NMR (500 MHz, CDCl_3) δ 8.11 (bs, 1H), 5.70 (d, 2H, $J=2.0$ Hz), 3.59 (s, 2H), 3.14 (m, 2H), 2.83 (dd, 2H, $J=9.0$ Hz), 2.68 (dd, 2H, $J=5.0$ Hz), 1.61 (m, 2H), 1.54 (m, 2H), 1.31 (s, 6H), 1.22 (m, 16H), 1.15 (s, 6H), 0.85 (t, 6H, $J=7.5$ Hz) ^{13}C NMR (125 MHz, CDCl_3) δ 214.6, 133.4, 103.6, 76.4, 42.9, 34.9, 33.9, 31.7, 29.2, 27.5, 26.2, 26.0, 22.6, 14.1.

By following the General Procedure, but using 6 mol equivalents of **9** and running the reaction at -20°C , the title compound was obtained in 87% yield and 91.46 % e.e., without traces of dialkylated by-product **S-5**.

General procedure for the catalytic Friedel-Crafts alkylation of indoles **14-17** with enones **7**

2,2'-Isopropylidene bis[(4*S*)-4-tert-butyl-2-oxazoline] (tBu-BOX) (or 1,1'-bis[2-((4*S*)-(1,1-dimethylethyl)-1,3-oxazolinyl)]cyclopropane) (0.05 mmol) was weighted in a flame-dried flask and placed under N_2 . $\text{Cu}(\text{OTf})_2$ (18 mg, 0.05 mmol) was then added by rinsing with dry CH_2Cl_2 (1.0 mL) from a weighting boat directly into the reaction flask. After stirred at room temperature for 3 h, a solution of the corresponding α' -hydroxy enone **7** (0.5 mmol) in dry CH_2Cl_2 (0.25 mL) was cannulated into the solution followed by a 0.25 mL rinse, and the resulting mixture was stirred for a further 10 min

at room temperature. Then corresponding indole **14-17** (1 mmol) was dissolved in 0.25 mL CH₂Cl₂ and added drop wise by syringe into the reaction flask followed by 0.25 mL rinse, and the mixture was stirred at room (or otherwise stated) temperature under N₂ until the disappearance of starting enone (TLC monitoring). The resulting reaction mixture was diluted with NH₄Cl (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 on SiO₂ eluting with 90% hexane and 10% EtOAc to yield pure compounds **18-21**.

2-Hydroxy-5-(1H-indol-3-yl)-2-methyl-7-phenyl-heptan-3-one

The title compound was prepared according to the general procedure (at reflux for 30 min) starting from enone **7a** (109 mg, 0.5 mmol). Yield 142 mg (85 %), brown thick oil; $[\alpha]_D = +27.2^\circ$ (*c* 1.0, CH₂Cl₂); IR (CH₂Cl₂, cm⁻¹) 3428, 1706, 1499, 1456, 742, 702; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (b, 1H), 7.69 (d, 1H, *J*=7.8 Hz), 7.41 (d, 1H, *J*=7.8 Hz), 7.14-7.29 (m, 7.0 Hz), 7.06 (d, 1H, *J*=2.1 Hz), 3.65 (m, 1H) 3.12 (dd, 1H, *J*=7.2 Hz), 2.92 (dd, 1H, *J*=8.1 Hz), 2.59 (m, 2H), 2.13 (m, 2H), 1.33 (s, 3H), 1.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 213.5, 142.2, 136.6, 128.3, 128.3, 126.3, 125.7, 122.0, 121.6, 119.4, 119.3, 118.2, 111.4, 76.3, 42.5, 36.9, 34.1, 32.5, 26.2, 25.8; Elemental analysis: Calcd for C₂₂H₂₅NO₂ (335.44): C 78.77, H 7.51, N 4.18; found: C 78.23, H 7.87, N 4.15; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 90:10; 0.5 mL/min, 254nm) *R*_t_{major}: 54.47 min, *R*_t_{minor}: 40.05 min, 98 % e.e.

2-Hydroxy-5-(1H-indol-3-yl)-2-methyl-undecan-3-one

The title compound was prepared according to the general procedure starting from enone **7b** (99 mg, 0.5 mmol) and carrying out the reaction at 0°C for 12 h. Yield 132 mg (85 %); Off white solid; m.p.74-75 °C (from hexane); $[\alpha]_D^{25} = +19.4^\circ$ (*c* 1.0, CH₂Cl₂). IR (CH₂Cl₂, cm⁻¹) 3418, 2922, 1708, 732. ¹H NMR (500 MHz, CDCl₃) δ 8.13 (b, 1H), 7.67 (d, 1H, *J*=8.0 Hz), 7.34 (d, 1H, *J*=8.0 Hz), 7.20 (t, 1H, *J*=7.0 Hz), 7.13 (t, 1H, *J*=7.5 Hz), 6.96 (d, 1H, *J*=3.0 Hz), 3.83 (s, 1H), 3.60 (m, 1H), 3.06 (dd, 1H, *J*=7.0 Hz), 2.89 (dd, 1H, *J*=7.0 Hz), 1.84 (m, 1H), 1.74 (m, 1H), 1.35 (s, 3H), 1.25 (m, 8H), 1.08 (s, 3H), 0.86 (t, 3H, *J*=6.5 Hz); ¹³C NMR (125 MHz, CDCl₃) 214.0, 136.6, 126.5, 122.0, 121.9, 121.5, 121.4, 119.4, 119.3, 119.2, 118.8, 111.6, 76.4, 42.7, 35.4, 32.7, 31.8, 29.3, 27.8, 26.3, 25.9, 25.8, 22.7; Chiral HPLC (Chiralcel OD column, hexane:iPrOH 90:10; 0.5 mL/min, 254nm) *R*_t_{major}: 33.26 min, *R*_t_{minor}: 24.75 min, 95.51 % e.e.

2-Hydroxy-5-(1H-indol-3-yl)-2,6-dimethyl-heptan-3-one

The title compound was prepared according to the general procedure (at reflux for 4 h) starting from enone **7c** (78 mg, 0.5 mmol). Yield 110 mg (81 %); Off white waxy solid; $[\alpha]_D = +45.6$ (*c* 1.0, CH₂Cl₂); IR (CH₂Cl₂, cm⁻¹) 3415, 2962, 1709, 750. ¹H NMR (500 MHz, CDCl₃) δ 8.16 (b, 1H), 7.71 (d, 1H, *J*=7.5 Hz), 7.35 (d, 1H, *J*=7.8 Hz), 7.11- 7.23 (m, 2H), 6.94 (d, 1H, *J*=2.1 Hz), 3.78 (b, 1H), 3.45 (m, 1H), 3.17 (dd, 1H, *J*=9.0 Hz), 2.95 (dd, 1H, *J*=4.5 Hz), 2.16 (m, 1H), 1.33 (s, 3H), 1.04 (s, 3H), 1.03 (d, 3H, *J*=6.6 Hz), 0.89 (d, 3H, *J*=6.9 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 213.9, 136.3, 126.9, 121.89, 121.83, 119.5, 119.2, 117.7, 111.2, 76.4, 39.5, 39.1, 32.1, 26.2, 25.9, 21.1, 20.6. Chiral HPLC (Chiralcel OD column; hexane:iPrOH 90:10; 0.5 mL/min, 210nm) *R*_t_{major}: 34.07 min, *R*_t_{minor}: 21.51 min, 95 % e.e.

1-Cyclohexyl-4-hydroxy-1-(1H-indol-3-yl)-4-methyl-pentan-3-one

The title compound was prepared according to the general procedure (25°C for 24h) starting from enone **7d** (98 mg, 0.5 mmol). Yield 125 mg (80 %); Off white solid; m.p. 114-115 °C(from hexane); $[\alpha]_D^{25} = +51.4^\circ$ (*c* 1.0, CH₂Cl₂); IR (CH₂Cl₂, cm⁻¹) 3420, 2850, 1705, 738. ¹H NMR (500 MHz, CDCl₃) δ 7.94 (b, 1H), 7.33 (d, 1H, *J*=8.5 Hz), 7.17 (dd, 1H, *J*=8.0 Hz), 7.11 (dd, 1H, *J*=7.0 Hz), 6.92 (s, 1H), 3.66 (b, 1H), 3.42 (m, 1H), 3.11 (dd, 1H, *J*=9.5 Hz), 2.94 (dd, 1H, *J*=5.0 Hz), 0.88-1.89 (m, 11H), 1.31 (s, 3H), 0.98 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 214.1, 136.4, 127.0, 122.0, 121.8, 119.6, 119.3, 117.8, 111.3, 76.4, 41.9, 39.3, 38.4, 31.7, 31.0, 26.59, 26.51, 26.4, 26.3, 25.9; Elemental analysis: Calcd for C₂₀H₂₇NO₂ (313.43) : C 76.64, H 8.68, N 4.47; found: C 76.87, H 7.84, N 4.54; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 90:10; 0.5 mL/min, 254nm) R_tmajor: 36.80 min, R_tminor: 21.22 min, 95.65 % e.e.

1-(4-Chloro-phenyl)-4-hydroxy-1-(1H-indol-3-yl)-4-methyl-pentan-3-one

The title compound was prepared according to the general procedure starting from enone **7h** (112.5 mg, 0.5 mmol). Yield 162 mg (95 %); White solid; m.p. 58-59 °C (Hexane); $[\alpha]_D = -12.3^\circ$ (*c* 1.0, CH₂Cl₂); IR (CH₂Cl₂, cm⁻¹) 3428, 1711, 1494, 1461; ¹H NMR (500 MHz, CDCl₃) δ 8.01 (b, 1H), 7.39 (d, 1H, *J*=8 Hz), 7.35 (d, 1H, *J*=7.5 Hz), 7.22-7.26 (m, 4H), 7.18 (dd, 1H, *J*=7.5 Hz, *J'*=7.5 Hz), 7.05 (dd, 1H, *J*=7 Hz, *J'*=7 Hz), 6.99 (s, 1H), 4.93 (t, 1H, *J*=7.5 Hz, *J'*=7.5 Hz), 3.52 (s, 1H), 3.34 (dd, 2H, *J*=3.5 Hz, *J'*=3.5 Hz), 1.27 (s, 3H), 1.17 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 212.3, 142.3, 136.7, 132.3, 129.3, 128.6, 126.3, 122.5, 121.2, 119.8, 119.4, 118.6, 111.3, 76.4, 42.3, 37.3, 26.2, 26.1; Elemental analysis: Calcd for C₂₀H₂₀ClNO₂ (341.83): C 70.27, H 5.90, N 4.10; found C 69.70, H 5.83, N 3.92. Chiral HPLC was performed on HP series 1050

(Chiralpak AD column. Hexane:2-PrOH 90:10; 0.5 mL/min., 210nm) $R_{t\text{major}}$: 53.80 min, $R_{t\text{minor}}$: 74.0 min., 82.85 % e.e.

2-Hydroxy-5-(1H-indol-3-yl)-2-methyl-hexan-3-one

The title compound was prepared according to the general procedure (0°C for 3 h) starting from enone **7i** (69 mg, 0.5 mmol). Yield 80 mg (65 %); Reddish white solid; m.p 89-92°C (from hexane); $[\alpha]_D = -8.6^\circ$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3420, 2969, 1714, 732. ^1H NMR (500 MHz, CDCl_3): δ 7.99 (bs, 1H), 7.65 (d, 1H, $J=7.0$ Hz), 7.37 (d, 1H, $J=8.0$ Hz), 7.21 (dd, 1H, $J=7.5$ Hz), 7.13 (dd, 1H, $J'=7.5$ Hz), 7.00 (s, 1H), 3.82 (s, 1H), 3.76 (m, 1H), 3.06 (dd, 1H, $J'=3.5$ Hz), 2.83 (dd, 1H, $J=9$ Hz), 1.41 (d, 3H, $J=5.5$ Hz), 1.33 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 213.9, 136.6, 126.2, 122.1, 120.8, 120.4, 119.4, 119.2, 111.5, 76.5, 43.9, 26.8, 26.4, 26.1, 20.9; Elemental analysis: Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ (245.14): C 73.44, H 7.81, N 5.71; found: C 73.23, H 7.46, N 5.65; Chiral HPLC (Chiralpak OJ column; hexane:iPrOH 80:20; 0.5 mL/min, 254nm) $R_{t\text{major}}$: 52.03 min, $R_{t\text{minor}}$: 46.70 min, 97.61 % e.e.

2-Hydroxy-2-methyl-5-(2-methyl-1H-indol-3-yl)-7-phenyl-heptan-3-one

The title compound was prepared according to general procedure starting from enone **7a** (109 mg, 0.5 mmol) and substituted indole **15** (131 mg). Yield 155mg (89 %); Yellow waxy solid; $[\alpha]_D = +52.2^\circ$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3411, 2973, 1709, 1458, 700; ^1H NMR (300 MHz, CDCl_3) δ 7.89 (s, 1H), 7.66 (d, 1H, $J=7.2$ Hz), 7.09-7.31 (m, 8H), 3.58 (m, 1H), 3.31 (dd, 1H, $J=8.7$ Hz), 2.90 (dd, 1H, $J=5.4$ Hz), 2.54 (m, 2H), 2.35 (s, 3H), 2.14 (m, 2H), 1.33 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 213.8, 142.2, 135.7, 132.0, 128.4, 128.2, 126.9, 125.7, 120.8, 119.1, 118.7, 112.3, 110.6, 76.4, 41.6, 36.3, 34.2, 32.4, 26.1, 25.5, 11.9; Elemental analysis: Calcd for

$C_{23}H_{27}NO_2$ (349.47): C 79.05, H 7.79, N 4.01; found: C 79.42, H 6.79, N 4.02; Chiral HPLC (Chiralpak AD column; hexane:iPrOH 90:10; 0.5 mL/min, 254nm) $R_{t\text{major}}$: 41.35 min, $R_{t\text{minor}}$: 30.06 min, 93 % e.e.

2-Hydroxy-5-(5-methoxy-1H-indol-3-yl)-2-methyl-7-phenyl-heptan-3-one

The title compound was prepared according to the general procedure starting from enone **7a** (109 mg, 0.5 mmol) and 5-methoxy indole **16** (147 mg). Yield 175mg (96 %); Yellow waxy solid; $[\alpha]_D = +43.2^\circ$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3415, 2933, 1709, 1483, 700; 1H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.90- 7.32 (m, 9H), 3.91 (s, 3H), 3.74 (sb, 1H), 3.65 (m, 1H), 3.10 (dd, 1H, $J=6.6$ Hz), 2.91 (dd, 1H, $J=7.2$ Hz), 2.62 (m, 2H), 2.14 (m, 2H), 1.35 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 153.9, 142.2, 131.8, 128.4, 128.3, 126.9, 125.7, 122.3, 118.1, 112.0, 101.5, 76.3, 56.0, 42.6, 37.0, 34.0, 32.2, 26.2, 25.9; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 90:10; 0.5 mL/min, 210nm, $R_{t\text{major}}$: 78.85 min, $R_{t\text{minor}}$: 61.85 min, 97.1 % e.e.

2-Hydroxy-2-methyl-5-(1-methyl-1H-indol-3-yl)-7-phenyl-heptan-3-one

The title compound was prepared according to the general procedure starting from enone **7a** (109 mg, 0.5 mmol) and N-methyl indole **17** (131 mg). Yield 150 mg (86 %); Yellow waxy solid; $[\alpha]_D = +28.4^\circ$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3457, 2931, 1709, 1468, 966, 740; 1H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, 1H, $J=6.9$ Hz), 7.12-7.36 (m,

8H), 6.91 (s, 1H), 3.79 (s, 3H), 3.65 (m, 1H), 3.10 (dd, 1H, $J=6.3$ Hz), 2.93 (dd, 1H, $J=6.9$ Hz), 2.62 (m, 2H), 2.18 (m, 2H), 1.34 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 213.5, 142.3, 137.3, 128.4, 128.2, 126.8, 126.4, 125.7, 121.6, 119.4, 118.8, 116.7, 109.4, 76.2, 42.8, 37.1, 34.1, 32.6, 32.4, 26.3, 25.9; Elemental analysis: Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_2$ (349.47): C 79.05, H 7.79, N 4.01; found: C 79.10, H 6.63, N 4.05; Chiral HPLC (Chiralpak AD column; hexane:iPrOH 90:10; 0.5 mL/min, 254nm) $R_{t\text{major}}$: 18.61 min, $R_{t\text{minor}}$: 22.67 min, 98.10 % e.e.

Assignment of the configuration for the adducts

The absolute configuration (*R*) of adduct **10c** was determined by transforming it into aldehyde **23** and comparison of the optical rotation of its alcohol derivative with published values (see below). The same configuration (*R*) for adducts **10d,g** and the opposite (*S*) for the rest of adducts **10** and **11** was assumed based on a uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

The absolute configuration (*S*) of adduct **18i** was determined by transforming it into methyl ester **26** and comparison of its optical rotation with published values (see below). The same configuration (*S*) for adducts **18a,b**, **19-21** and the opposite (*R*) for adducts **18c,d,h** was assumed based on a uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

The assignment of the relative configuration for the dialkylated adduct from enone **7d** was determined by X-ray diffraction analysis (see below). The configuration of the rest of dialkylated adducts was assigned by analogy.

Elaboration of adducts into aldehydes. General Procedure

In a round bottom flask, under nitrogen atmosphere, to a solution of the Friedel-Crafts adduct (1 mmol) in THF (3 ml), cooled to 0°C (ice bath), was added drop wise a solution of Borane in THF (1M soln, 2.24 ml, 2 mmol) keeping temperature at 0°C. The reaction was stirred at the same temperature until TLC analysis indicates completion of the reaction (around 3 hours). While keeping cool (0 °C), methanol (3ml) was added and then the mixture was allowed to come to room temperature and stirred for an additional 30 minutes. Evaporation of solvent afforded the crude diol compound used as is for the next step. In a round bottom flask, under nitrogen atmosphere at 0 °C, the diol crude was dissolved in dry dichloromethane (25 mL) and a previously prepared mixture

of $\text{NaIO}_4\text{-SiO}_2^2$ (2 gm, 2 mmol of oxidant) was added in portions over a period of 5-10 min. The reaction mass was allowed to come to room temperature and stirred until TLC analysis indicated reaction completion (around 3 hours). If necessary for completion, additional excess of pre-adsorbed NaIO_4 on Silica might be added. The mixture was filtered and the silica washed with dichloromethane (20 ml). The combined layers were evaporated under reduced pressure to give the crude aldehyde compound, which was characterized as the corresponding alcohol after reduction with NaBH_4 , as follows:

In a round bottom flask, under nitrogen atmosphere, the crude aldehyde was dissolved in dry ethanol (3 ml) and, after cooling to 0°C , NaBH_4 (38 mg, 1 mmol) was added in portions over a period of about 5 minutes. The reaction was stirred at the same temperature until TLC analysis indicated completion of the reaction (around 20 minutes). Then, the reaction was quenched with NaHCO_3 , extracted with dichloromethane (10 ml) and the extracts washed with water. Drying of the organic layer over anhydrous MgSO_4 and concentration afforded the crude alcohol product, which was purified by column chromatography (Silica gel, 10:90 EtOAc: Hexane)

3-(1-Methyl-1H-pyrrol-2-yl)-5-phenyl-pentanal

The title compound was prepared according to the general procedure starting from **10a** (237 mg, 1.0 mmol). Yield and data of the alcohol (over the three steps): 120 mg (72 %); Red thick oil ; $[\alpha]_D^{25} = +31.10^\circ$ ($c = 1$, MeOH) ^1H NMR (300 MHz, CDCl_3) δ 6.50 (m, 5H), 6.08 (dd, 1H), 5.86 (m, 2H), 3.55 (s, 1H), 3.46 (m, 1H), 2.65 (m, 2H), 1.98 (m, 2H), 1.78 (m, 1H), 0.89 (q, 6H, $J = 7.2\text{ Hz}$). ^{13}C NMR (75 MHz, CDCl_3) δ 135.43, 120.87, 106.49, 105.21, 61.70, 39.60, 35.06, 33.49, 20.40, 19.94. Chiral HPLC (Chiralpak OD column; hexane:iPrOH 90:10; 0.5 mL/min, 220nm) $R_{t\text{major}}$: 27.42 min, $R_{t\text{minor}}$: 17.14 min, 90.13 % e.e.

4-Methyl-3-(1-methyl-1H-pyrrol-2-yl)-pentanal

² Adsorbed sodium meta periodate on silica was prepared according to Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, 62, 2622, as follows: NaIO_4 (25 gm) and water (50 ml) are mixed with stirring at 70°C , and then silica gel (60 mesh, 100 gm) is added and the mixture vigorously stirred for 1 hour. The resulting powder can be stored for weeks and used as it is.

The title compound was prepared according to the general procedure starting from **10c** (237 mg, 1.0 mmol). Yield and data of the alcohol (over the three steps): 141 g (78%): $[\alpha]_D = +31.1$ (c 1.0, CH₃OH); Literature data³ for (S)-enantiomer $[\alpha]_D = -20^\circ$ (c 1.0, CH₃OH). All other spectroscopic and physical data were identical to those previously reported.⁴ Chiral HPLC (Chiralpak OD column; hexane : iPrOH 90:10; 0.5 mL/min, 254 nm) $R_{t\text{major}}$: 15.67 min, $R_{t\text{minor}}$: 11.97 min, 95.04 % e.e.

3-(1H-Indol-3-yl)-5-phenyl-pentanal

The title compound was prepared according to the general procedure starting from **18a** (335 mg, 1.0 mmol). Yield and data of the alcohol (over the three steps): 225 mg (80 %); Yellow waxy solids, $[\alpha]_D = +7.8^\circ$ (c 1.0, CH₂Cl₂); IR (CH₂Cl₂) 3417, 3314, 2928, 2857, 700. ¹H NMR (300 MHz, CDCl₃) δ 8.05 (b, 1H), 7.69 (d, 1H, $J=7.8$ Hz), 7.41(d,1H, $J=8.1$ Hz), 7.12- 7.31 (m,7H), 7.05 (d,1H, $J=2.1$ Hz), 3.63 (m, 2H), 3.13 (m, 1H), 2.60 (m, 2H), 2.12 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) 142.6, 136.7, 128.4, 128.2, 126.8, 125.6, 122.0, 121.2, 119.5, 119.2, 119.0, 111.2, 61.5, 38.9, 38.0, 33.9, 33.4; Elemental analysis : Calcd for C₁₉H₂₁NO (279.38): C 81.68, H 7.58, N 5.01; found : C 81.79, H 8.10, N 4.81; Chiral HPLC (Chiralcel OD column. Hexane : iPrOH 80:20; 0.5 mL/min., 210 nm) $R_{t\text{major}}$: 22.06 min, $R_{t\text{minor}}$: 16.92 min., 95.75 % ee.

Elaboration of adducts into carboxylic acid esters. General Procedure.

In an oven-dried flask, the corresponding adduct **18** (1mmol) was dissolved in 4 mL of dry diethyl ether. The solution was cooled to 0°C using ice bath and periodic acid

³ Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371.

(274 mg, 1.2 mmol) was added slowly in portions over a period of 5-10 minutes. During the course of the reaction, black coloured solids are generated which stick to the walls of reaction flask. The reaction was stirred at 0°C until completion (TLC analysis, around 9-10 hours). After completion, reaction was quenched with 10% aqueous sodium sulfite (5 mL) and the mixture was extracted with diethyl ether (3 x 20 mL). Organic layers were combined and washed with water (2 x 10 mL). The organic layer was dried over MgSO₄ and the solvent evaporated under reduced pressure to give the crude carboxylic acid which was directly submitted to methylation. Trimethylsilyl diazomethane (2M solution in hexanes, 0.548 mL, 1.1 mmol) (**caution: diazo derivatives are explosive under certain conditions and should be handled with care**) was added dropwise to a solution of crude carboxylic acid (1 mmol) in benzene (20 mL) and methanol (2 mL) at room temperature. After 20 min of stirring, solvents were removed under reduced pressure to afford the corresponding crude ester which was purified by flash column chromatography (gradient eluent: ethyl acetate/hexane).

3-(1H-Indol-3-yl)-5-phenyl-pentanoic acid methyl ester

The title compound was prepared according to the general procedure starting from **18a** (335 mg, 1.0 mmol). Yield 185 mg (60 %); brown thick oil, $[\alpha]_D = + 7.0^\circ$ (*c* 1.0, CH₂Cl₂); IR (CH₂Cl₂) ¹H NMR (300 MHz, CDCl₃) δ 8.09 (b, 1H), 7.69 (d, 1H, *J*=7.5 Hz), 7.41 (d, 1H, *J*=7.5 Hz), 7.29 (t, 1H, *J*=8.0 Hz), 7.16 (t, 1H, *J*=6.5 Hz), 7.07 (s, 1H), 3.62 (s, 3H), 3.56 (m, 1H), 2.81 (d, 1H, *J*=7.2 Hz), 2.61 (m, 2H), 2.16 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 173.2, 142.2, 128.4, 128.2, 125.7, 121.9, 121.3, 119.3, 119.2, 111.2, 51.5, 41.1, 37.1, 33.8, 33.3. Elemental analysis: Calcd for C₂₀H₂₁NO₂ (307.16): C 78.15, H 6.89, N 4.45; found: C 77.75, H 6.94, N 4.68; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 90:10; 0.5 mL/min, 254nm) *R*_t_{major}: 42.91 min, *R*_t_{minor}: 31.45 min, 98.50 % e.e.

3-(1H-Indol-3-yl)-butyric acid methyl ester

The title compound was prepared according to the general procedure starting from **18i** (245 mg, 1.0 mmol). Yield 145 mg (67 %); brown thick oil, $[\alpha]_D = + 4.0$ (c 1.10, CH_2Cl_2); Lit⁴ $[\alpha]_D = + 2.7$ (c 1.10, CH_2Cl_2); All other spectroscopic and physical data were identical to those previously reported.⁵

Elemental analysis: Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2$ (217.11): C 71.87, H 6.96, N 6.45; found: C 71.36, H 6.87, N 6.41; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 90:10; 0.5 mL/min, 254nm) $R_{t\text{major}}$: 36.05min, $R_{t\text{minor}}$: 25.33 min, 93.64 % e.e.

Elaboration of adducts into ketones. General Procedure

nBuLi (2.5 M in hexanes, 1.2 mL, 3 mmol) or MeLi (1.4 M in Et_2O , 2.14 mL, 3 mmol) was added to a solution of adduct **18a** (1 mmol) in THF (3 mL) at -78°C and the solution was stirred at 0°C for 1.5 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (5 mL) and the resulting mixture was allowed to warm to room temperature, after which the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (15 mL). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. The residue thus obtained was subjected to oxidative scission by treatment with NaIO_4 , under the following conditions. The crude residue from the previous reaction was dissolved in a mixture of methanol (6 mL) and water (3 mL). To this solution, NaIO_4 (1.25 g, 6 mmol) was added at room temperature in 2 portions with 3 hours of interval between each. During stirring of the mixture at room temperature, brown colored precipitates are developed. After completion of the reaction as monitored by TLC analysis (around 6 h), the reaction mass was diluted with dichloromethane (30 mL), washed with water (10 mL) and 5% aq. sodium sulfite solution (10 mL). The combined organic layer was dried over MgSO_4 and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (Silica gel, EtOAc/Hexane).

⁴ Evans, D. A.; Scheidt, K. A.; Frandrick, K. R.; Lam, H. W.; Wu, J., *J. Am. Chem. Soc.* **2003**, 125, 10780-10781.

4-(1H-Indol-3-yl)-6-phenyl-hexan-2-one

The title compound was prepared according to the general procedure starting from **18a** (335 mg, 1.0 mmol) and methyllithium. Yield 247 mg (85 %); Yellow waxy solids, $[\alpha]_D = +12.6^\circ$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3416, 2923, 1706, 1455, 742, 701; ^1H NMR (300 MHz, CDCl_3) δ 8.19 (sb, 1H), 7.72 (d, 1H, $J=7.8$ Hz), 7.42 (d, 1H, $J=7.8$ Hz), 7.16-7.34 (m, 7H), 7.03 (d, 1H, $J=2.1$ Hz), 3.60 (m, 1H), 3.00 (dd, 1H, $J=6.9$ Hz), 2.89 (dd, 1H, $J=6.6$ Hz), 2.62 (t, 2H, $J=7.5$ Hz), 2.17 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 208.9, 142.3, 136.6, 128.5, 128.3, 126.5, 125.8, 122.0, 121.6, 119.3, 118.2, 111.5, 50.2, 37.5, 33.9, 32.7, 30.5; Elemental analysis: Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}$ (291.39): C 82.44, H 7.26, N 4.81; found: C 80.22, H 6.90, N 4.50; Chiral HPLC (Chiralcel OD column; hexane:iPrOH 90:10; 0.5 mL/min, 210nm) $R_{t,\text{major}}$: 34.48 min, $R_{t,\text{minor}}$: 31.38 min, 94.58 % e.e.

3-(1H-Indol-3-yl)-1-phenyl-nonan-5-one

The title compound was prepared according to the general procedure starting from **18a** (335 mg, 1.0 mmol) and butyllithium. Yield 273 mg (82 %); Yellow waxy solid; $[\alpha]_D = +20.0^\circ$ (c 1.0, CH_2Cl_2); IR (CH_2Cl_2 , cm^{-1}) 3414, 2934, 1708, 739. ^1H NMR (300 MHz, CDCl_3) δ 8.21 (sb, 1H), 7.72 (d, 1H, $J=7.8$ Hz), 7.41 (d, 1H, $J=8.1$ Hz), 7.15-7.33 (m, 7H), 7.03 (d, 1H, $J=2.1$ Hz), 3.61 (m, 1H), 2.99 (dd, 1H, $J=6.9$ Hz), 2.86 (dd, 1H, $J=6.6$ Hz), 2.61 (t, 2H, $J=6.9$ Hz), 2.32 (m, 2H), 2.15 (m, 2H), 1.49 (m, 2H), 1.24 (m, 2H), 0.86 (t, 3H, $J=6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 211.1, 142.4, 136.7, 128.4, 128.3, 126.5, 125.7, 121.9, 121.6, 119.4, 119.2, 118.4, 111.4, 149.4, 43.1, 37.4, 34.0, 32.7, 25.7, 22.2, 13.8; Elemental analysis: Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}$ (333.21): C 82.84, H 8.16, N 4.20; found: C 82.24, H 9.48, N 3.95; Chiral HPLC (Chiralcel OD column,

hexane:iPrOH 95:05; 0.5 mL/min, 254nm) $R_{t_{\text{major}}}$:22.11 min, $R_{t_{\text{minor}}}$: 20.49 min, 97 %
e.e.

7i
(^1H NMR)

7i
(^{13}C NMR)

10a
(¹H NMR)

10a
(¹³C NMR)

10c
(^1H NMR)

10c
(^{13}C NMR)

10d
(^1H NMR)

10d
(^{13}C NMR)

10e
(¹H NMR)

10e
(¹³C NMR)

10f
(^1H NMR)

10f
(^{13}C NMR)

10g
(¹H NMR)

10g
(¹³C NMR)

11a
(¹H NMR)

11a
(¹³C NMR)

11b
(^1H NMR)

11b
(^{13}C NMR)

S-3 (^1H NMR) **S-3** (^{13}C NMR)

S-5 (¹H NMR) **S-5** (¹³C NMR)

18a
(^1H NMR)

18a
(^{13}C NMR)

18b
(^1H NMR)

18b
(^{13}C NMR)

18c
(^1H NMR)

18c
(^{13}C NMR)

18d
(^1H NMR)

18d
(^{13}C NMR)

18h
(^1H NMR)

18h
(^{13}C NMR)

18i
(¹H NMR)

18i
(¹³C NMR)

19a
(^1H NMR)

19a
(^{13}C NMR)

20a
(^1H NMR)

20a
(^{13}C NMR)

21a
(^1H NMR)

21a
(^{13}C NMR)

from **22**
(^1H NMR)

from **22**
(^{13}C NMR)

from **23**
(^1H NMR)

from **23**
(^{13}C NMR)

25
(^1H NMR)

25
(^{13}C NMR)

26
(¹H NMR)

26
(¹³C NMR)

27
(¹H NMR)

27
(¹³C NMR)

Retention Time (min)	Area	% Area	Height
23,425	677701	4,13	15100
32,540	15720492	95,87	222085

Retention Time (min)	Area	% Area
14,264	7949	2,08
21,683	373367	97,92

Retention Time (min)	Area	% Area	Height
12,538	630355	2,64	22768
15,409	23204920	97,36	698598

Retention Time (min)	Area	% Area
15,515	21269	1,64
17,750	1276155	98,36

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
12.455	MM	0.5002	319.58551	10.64757	3.1652
16.865	MM	0.5907	9777.20215	275.86365	96.8348

Retention Time (min)	Area	% Area
12,930	143622	3,09
21,440	4500758	96,91

Retention Time (min)	Area	% Area
16,264	1112660	84,23
20,138	208337	15,77

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
38.589	MM	2.2455	1.21590e5	902.49377	95.2475
47.620	MM	2.7191	6066.97607	37.18782	4.7525

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
17.149	MM	0.9905	1888.89844	31.78224	5.7470
27.427	MM	1.1280	3.09788e4	457.70676	94.2530

Retention Time (min)	Area	% Area
11,972	517352	2,48
15,672	20360172	97,52

Retention Time (min)	Area	% Area
40,050	2492334	1,21
54,476	202894248	98,79

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
24.703	MM	1.5823	1130.21045	11.90457	1.8684
33.266	MM	1.7848	5.93598e4	554.30847	98.1316

Retention Time (min)	Area	% Area
23,480	3112839	2,47
36,263	122884604	97,53

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
21.227	MM	1.0373	2920.99927	33.54160	2.1796
36.830	MM	2.0417	1.31092e5	1070.13342	97.8204

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
53.802	MM	3.4520	1.44395e5	697.15009	91.4274
74.006	MM	3.4512	1.35391e4	65.38279	8.5726

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
47.174	MM	2.4482	797.05127	5.42600	1.3565
52.064	MM	4.8097	5.79593e4	200.84288	98.6435

Retention Time (min)	Area	% Area
30,062	3100764	3,42
41,353	87523558	96,58

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
61.856	MM	3.8355	1000.21326	4.34627	1.4332
78.856	MM	3.9796	6.87902e4	288.09320	98.5668

Retention Time (min)	Area	% Area
18,618	95499357	99,05
22,670	918619	0,95

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
16.928	MM	0.8599	543.19012	10.52861	2.1249
22.063	MM	1.2171	2.50195e4	342.62158	97.8751

Retention Time (min)	Area	% Area
31,452	1021043	0,75
42,916	135317513	99,25

Retention Time (min)	Area	% Area
25,333	5780738	3,18
36,050	176050587	96,82

Retention Time (min)	Area	% Area
31,383	1119397	2,76
34,735	39504355	97,24

RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
20.409	MM	0.6174	249.96851	4.89606	1.4211
22.118	MM	1.1920	1.73393e4	242.43062	98.5789

ORTEP diagram of **S-2**

CPBK106 (L0429)

S-2