Supporting Information for:

Synthesis and SAR of *b*-Annulated 1,4-Dihydropyridines Define Cardiomyogenic Compounds as Inhibitors of TGFβ Signaling

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I) SYNTHETIC PROCEDURES AND ANALYTICAL DATA

Ethyl 4-(Biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by ethyl acetoacetate and using 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.06 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 2.12-2.33 (m, 4H), 2.35 (s, 3H), 4.08 (q, J = 7.2 Hz, 2H), 5.10 (s, 1H), 6.58 (br s, NH), 7.25-7.30 (m, 1H), 7.35-7.45 (m, 6H), 7.50-7.54 (m, 2H); LRMS calcd for $C_{27}H_{29}NO_3$ 415.21 $[M + H]^+$, found 438.20 $[M + Na]^+$. HPLC purity 96.5%, t_R = 7.63 min.

Methyl 4-(4-Fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7): The title compound was obtained according to the general procedure, using 4-fluorobenzaldehyde as the aldehyde. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.07 (s, 3H), 2.12-2.37 (m, 4H), 2.38 (s, 3H), 3.61 (s, 3H), 5.04 (s, 1H), 6.87 (t, J = 8.8 Hz, 2H), 7.22-7.27 (m, 2H); LRMS calcd for $C_{20}H_{22}FNO_3$ 343.16 $[M]^+$, found 344.42 $[M + H]^+$. HPLC purity 95.6%, t_R = 5.48 min.

Methyl 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8): The title compound was obtained according to the general procedure, using benzaldehyde as the aldehyde. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.07 (s, 3H), 2.13-2.37 (m, 4H), 2.39 (s, 3H), 3.61 (s, 3H), 5.07 (s, 1H), 5.76 (br s, 1H), 7.11 (td, J = 7.4 and 1.4 Hz, 1H), 7.20 (t, J = 7.1 Hz, 2H), 7.29 (d, J = 7.1 Hz, 2H); LRMS calcd for $C_{20}H_{23}NO_3$ 325.17 $[M]^+$, found 326.68 $[M + H]^+$. HPLC purity 97.7 %, t_R = 6.77 min.

Methyl 4-(4-*tert*-Butylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9): The title compound was obtained according to the general procedure, using 4-*tert*-butylbenzaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (s, 3H), 1.07 (s, 3H), 1.24 (s, 9H), 2.16-2.27 (m, 4H), 2.33 (s, 3H), 3.62 (s, 3H), 5.04 (s, 1H), 6.33 (s, 1H), 7.18 (s, 4H); LRMS calcd for $C_{24}H_{31}NO_3$ 381.50 $[M]^+$, found 382.35 $[M + H]^+$. HPLC purity 97.0%, t_R = 7.47 min.

Methyl 4-(Biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10): The title compound was obtained according to the general procedure, using 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.08 (s, 3H), 2.18 and 2.35 (AB system, J = 16.7 Hz, 2H), 2.22 and 2.26 (AB system, J = 8.9 Hz, 2H), 2.40 (s, 3H), 3.63 (s, 3H), 5.11 (s, 1H), 5.89 (br s, 1H), 7.29 (tt, J = 7.4 and 1.0 Hz, 1H), 7.34-7.45 (m, 6H), 7.53 (d, J = 7.9 Hz, 2H); LRMS calcd for $C_{26}H_{27}NO_3$ 401.21 $[M]^+$, found 402.15 $[M + H]^+$. HPLC purity 98.6 %, t_R = 7.34 min.

Methyl 4-(4-(1*H*-Pyrazol-1-yl)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11): The title compound was obtained according to the general procedure, using 4-(1*H*-pyrazol-1-yl)benzaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (s, 3H), 1.00 (s, 3H), 2.04-2.31 (m, 4H), 2.29 (s, 3H), 3.60 (s, 3H), 5.07 (s, 1H), 6.46 (t, J = 1.3 Hz, 1H), 7.42 (d, J = 5.3 Hz, 2H), 7.48 (br s, 1H), 7.50 (d, J = 4.1 Hz, 2H), 7.70 (d, J = 1.0 Hz, 1H), 7.87 (d, J = 1.4 Hz, 1H); LRMS calcd for $C_{23}H_{25}N_3O_3$ 390.19 $[M]^+$, found 391.87 $[M + H]^+$ and 414.0 $[M + Na]^+$. HPLC purity 98.6%, t_R = 5.58 min.

Ethyl 2-Ethyl-7,7-dimethyl-5-oxo-4-(4-(pyridin-2-yl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by ethyl acetoacetate and using 4-(2-pyridyl)benzaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (s, 3H), 1.01 (s, 3H), 1.16-1.22 (m, 6H), 2.09-2.34 (m, 4H), 2.65-2.78 (m, 2H), 4.05 (q, J = 6.9 Hz, 2H), 5.10 (s, 1H), 7.21-7.24 (m, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.70-7.77 (m, 2H), 7.82 (d, J = 8.4 Hz, 2H), 8.62 (d, J = 5.4 Hz, 1H); LRMS calcd for $C_{27}H_{30}N_2O_3$ 430.23 $[M]^+$, found 430.68 $[M + H]^+$. HPLC purity 100%, t_R = 9.79 min.

Methyl 4-(2-Fluorobiphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (13): The title compound was obtained according to the general procedure, using 4-(2-fluorophenyl)benzaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.09 (s, 3H),

2.18-2.38 (m, 4H), 2.40 (s, 3H), 3.65 (s, 3H), 5.11 (s, 1H), 6.07 (s, NH), 7.04 (dd, J = 7.2 and 0.9 Hz, 1H), 7.17 (dd, J = 4.7 and 0.9 Hz, 1H), 7.26 (t, J = 4.0 Hz, 1H), 7.31 (t, J = 4.4 Hz, 1H), 7.39 (t, J = 4.7 Hz, 2H), 7.49 (d, J = 4.2 Hz, 2H); LRMS calcd for $C_{26}H_{26}NO_3$ 419.19 $[M]^+$, found 420.07 $[M + H]^+$ and 442.0 $[M + Na]^+$. HPLC purity 98.4%, t_R = 7.32 min.

Methyl 4-(4'-(Methoxycarbonyl)biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (14): The title compound was obtained according to the general procedure, using methyl 4-(4-formylphenyl)benzoate as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.08 (s, 3H), 2.16-2.38 (m, 4H), 2.40 (s, 3H), 3.63 (s, 3H), 3.92 (s, 3H), 5.12 (s, 1H), 6.07 (s, NH), 7.38 (d, J = 5.0 Hz, 2H), 7.47 (d, J = 5.0 Hz, 2H), 7.59 (d, J = 4.0 Hz, 2H), 8.04 (d, J = 4.0 Hz, 2H); LRMS calcd for $C_{28}H_{29}NO_5$ 459.53 $[M]^+$, found 482.0 $[M + Na]^+$. HPLC purity 99.0%, t_R = 7.17 min.

2,2,2-Trifluoroethyl 4-(Biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by 2,2,2-trifluoroethyl 3-oxobutanoate and using 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.09 (s, 3H), 2.03-2.39 (m, 4H), 2.37 (s, 3H), 4.31-4.47 (m, 2H), 5.07 (s, 1H), 6.56 (br s, NH), 7.27 (d, J = 7.43 Hz, 1H), 7.36 (d, J = 7.43 Hz, 1H), 7.42 (t, J = 7.20 Hz, 2H), 7.52 (d, J = 9 Hz, 1H); LRMS calcd for $C_{27}H_{26}F_3NO_3$ 469.19 $[M]^+$, found 469.90 $[M + H]^+$. HPLC purity 96.7%, t_R = 7.69 min.

Isobutyl 4-(Biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by isobutyl 3-oxobutanoate and using 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.91 (s, 3H), 1.05 (s, 3H), 1.85-1.93 (m, 1H), 2.15 and 2.30 (AB system, J = 16.2 Hz), 2.20 and 2.23 (AB system, J = 10.3 Hz, 4H), 2.39 (s, 3H), 3.77-3.86 (m, 2H), 5.12 (s, 1H), 6.81 (br s, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.36-7.40 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 6.9 Hz, 2H); LRMS calcd for $C_{29}H_{33}NO_3$ 443.25 $[M]^+$, found 444.55 $[M + H]^+$. HPLC purity 95.5%, t_R = 9.04 min.

Isopentyl 4-(Biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by 3-methyl-1-butyl 3-oxobutanoate and 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.94 (s, 3H), 1.08 (s, 3H), 1.45 (q, J = 4.0 Hz, 2H), 1.52-1.59 (m, 1H), 2.15-2.35 (m, 4H), 2.41 (s, 3H), 4.0-4.08 (m, 2H), 5.08 (s, 1H), 5.83 (br s, NH), 7.28 (t, J = 7.4 Hz, 1H), 7.35-7.43 (m, 6H), 7.53 (d, J = 7.30 Hz, 2H); LRMS calcd for $C_{30}H_{35}NO_3$ 457.27 $[M]^+$, found 458.82 $[M + H]^+$. HPLC purity 96.6 %, t_R = 8.76 min.

4-Methoxybenzyl 4-(Biphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (18): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by 4-methoxybenzyl 3-oxobutanoate and using 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.07 (s, 3H), 2.14-2.34 (m, 4H), 2.39 (s, 3H), 3.74 (s, 3H), 4.94-5.11 (m, 3H), 5.84 (br s, NH), 6.78 (d, J = 8.82 Hz, 2H), 7.10 (d, J = 8.30 Hz, 2H), 7.30 (d, J = 8.30 Hz, 2H), 7.36-7.44 (m, 5H), 7.53 (d, J = 7.30 Hz, 2H); LRMS calcd for $C_{33}H_{33}NO_4$ 507.24 $[M]^+$, found 508.15 $[M + H]^+$ and 531.02 $[M + Na]^+$. HPLC purity 97.1 %, t_R = 7.25 min.

4-(Biphenyl-4-yl)-*N*-(4-methoxybenzyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (19): The title compound was obtained according to the general procedure but replacing methyl acetoacetate by *N*-(4-methoxybenzyl)-3-oxobutanamide and 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (s, 3H), 1.04 (s, 3H), 2.13 and 2.28 (AB system, J = 16.7 Hz, 2H), 2.19 and 2.21 (AB system, J = 3.9 Hz, 2H), 2.34 (s, 3H), 3.68 (s, 3H), 4.27 (ddd, J = 25.1, 14.8 and 5.4 Hz, 2H), 4.85 (s, 1H), 5.79 (t, J = 5.4 Hz, NH), 6.17 (s, 1H), 6.71 (d, J = 6.7 Hz, 2H), 6.90 (d, J = 6.7 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.36-7.45 (m, 6H), 7.53 (d, J = 7.4 Hz, 2H); LRMS calcd for $C_{33}H_{34}N_2O_3$ 505.26 $[M]^+$, found 506.48 $[M + H]^+$. HPLC purity 97.8%, t_R = 6.09 min.

Ethyl 4-(Biphenyl-4-yl)-7,7-dimethyl-5-oxo-2-(*n*-propyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (20): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by ethyl butyrylacetate and using 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.01 (t, J = 7.4 Hz, 3H), 1.08 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H), 1.63-1.72 (m, 2H), 2.15-2.36 (m, 4H), 2.67-2.72 (m, 1H), 2.78-2.84 (m, 1H), 4.07 (q, J = 7.4 Hz, 2H), 5.12 (s, 1H), 6.15 (br s, 1H), 7.28 (t, J = 8.4 Hz, 1H), 7.36-7.44 (m, 6H), 7.53 (br d, J = 7.9 Hz, 2H); LRMS calcd for $C_{29}H_{33}NO_3$ 443.25 $[M]^+$, found 444.55 $[M + H]^+$ and 467.08 $[M + Na]^+$. HPLC purity 96.4%, t_R= 8.19 min.

Methyl 4-(Biphenyl-4-yl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21): The title compound was obtained according to the general procedure, but replacing dimedone by 5-methylcyclohexane-1,3-dione and using 4-biphenylcarboxaldehyde as the aldehyde. Because of the presence of two centers of chirality (4- and 7-positions), a mixture of diastereomers was obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 + 1.05 (2 × d, J = 3.6 Hz, 3H), 2.01-2.47 (m, 5H), 2.40 (s, 3H), 3.63 (s, 3H), 5.11 + 5.15 (2 × s, 1H), 6.08 + 6.14 (2 × s, NH), 7.29 (t, J = 7.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H); LRMS calcd for $C_{25}H_{25}NO_3$ 387.18 $[M]^+$, found 388.05 $[M + H]^+$, 410 $[M + Na]^+$. HPLC purity 97.0%, t_R = 7.19 min.

Methyl 4-(Biphenyl-4-yl)-7-ethyl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (22): The title compound was obtained according to the general procedure, but replacing dimedone by 5-ethylcyclohexane-1,3-dione and using 4-biphenylcarboxaldehyde as the aldehyde. Because of the presence of two centers of chirality (4- and 7-positions), a mixture of diastereomers was obtained.^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, J = 7.4 Hz, 3H), 1.33-1.41 (m, 2H), 1.97-2.42 (m, 4H), 2.39 (s, 3H), 2.47 (d, J = 14.8 Hz, 1H), 3.63 (s, 3H), 5.11 + 5.16 (2 × s, 1H), 6.22 + 6.29 (2 × s, NH), 7.29 (t, J = 7.4 Hz, 1H), 7.33-7.44 (m, 6H), 7.52 (d, J = 7.9 Hz, 2H); LRMS calcd for $C_{26}H_{27}NO_3$ 401.20 $[M]^+$, found 401.67 $[M + H]^+$ and 424.07 $[M + Na]^+$. HPLC purity 98.6%, t_R = 6.50 min.

Methyl 4-(Biphenyl-4-yl)-7-isopropyl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (24): The title compound was obtained according to the general procedure, but replacing dimedone by 5-isopropylcyclohexane-1,3-dione and using 4-biphenylcarboxaldehyde as the aldehyde. Because of the presence of two centers of chirality (4- and 7-positions), a mixture of diastereomers was obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (dd, J = 5.4 and 6.7 Hz, 6H), 1.81-1.90 (m, 1H), 2.07 (dd, J = 13.3 Hz, 1H), 2.27-2.50 (m, 4H), 2.43 (s, 3H), 3.63 (s, 3H), 5.15 (s, 1H), 5.86 (s, NH), 7.29 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.9 Hz, 2H); LRMS calcd for $C_{27}H_{29}NO_3$ 415.21 $[M]^+$, found 416.07 $[M + H]^+$ and 438.2 $[M + Na]^+$. HPLC purity 95.8%, t_R = 7.03 min.

Methyl 4-(Biphenyl-4-yl)-7-isobutyl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (25): The title compound was obtained according to the general procedure, but replacing dimedone by 5-isobutyrylcyclohexane-1,3-dione and using 4-biphenylcarboxaldehyde as the aldehyde. Because of the presence of two centers of chirality (4- and 7-positions), a mixture of diastereomers was obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85-0.87 (m, 6H), 1.18-1.26 (m, 2H), 1.59-1.66 (m, 1H), 1.96-2.48 (m, 4H), 2.41 + 2.42 (2 × s, 3H), 3.63 (s, 3H), 5.11 + 5.15 (2 × s, 1H), 5.87 + 5.93 (2 × s, 1H), 7.29 (t, J = 6.9 Hz, 1H), 7.33-7.45 (m, 6H), 7.52-7.55 (m, 2H); LRMS calcd for $C_{28}H_{31}NO_3$ 429.23 $[M]^+$, found 430.35 $[M + H]^+$. HPLC purity 98.5%, t_R = 7.95 min.

Methyl 4-(Biphenyl-4-yl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (26): The title compound was obtained according to the general procedure, but replacing dimedone by 5-phenylcyclohexane-1,3-dione and using 4-biphenylcarboxaldehyde as the aldehyde. Because of the presence of two centers of chirality (4- and 7-positions), a mixture of diastereomers was obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41 + 2.43 (2 × s, 3H), 2.55-2.75 (m, 4H), 3.24-3.32 (m, 1H), 3.64 (s, 3H), 5.17 + 5.21 (2 × s, 1H), 6.08 + 6.18 (2 × s, NH), 7.19 (d, J = 6.9 Hz, 1H), 7.21-7.34 (m, 5H), 7.39-7.42 (m, 4H), 7.46 (d, J = 8.4 Hz, 2H), 7.53-7.55 (m, 2H); LRMS calcd for $C_{30}H_{27}NO_3$ 449.20 $[M]^+$, found 450.13 $[M + H]^+$ and 472.2 $[M + Na]^+$. HPLC purity 95.3%, t_R = 7.53 min.

Methyl 4-(Biphenyl-4-yl)-7-(4-(dimethylamino)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (27): The title compound was obtained according to the general procedure, but replacing dimedone by 5-(4-(dimethylamino)phenyl)cyclohexane-1,3-dione and using 4-biphenycarboxaldehyde as the aldehyde. Because of the presence of two centers of chirality (4- and 7-positions), a mixture of diastereomers was obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41 + 2.43 (2 × s, 3H), 2.49-2.74 (m, 5H), 2.87 (s, 3H), 2.93 (s, 3H), 3.64 (s, 3H), 5.17 + 5.20 (2 × s, 1H), 5.96 + 6.05 (2 × s, NH), 6.60 + 6.70 (2 × d, J = 8.4 Hz, 2H), 6.98 + 7.08 (2 × d, J = 8.9 Hz, 2H), 7.27-7.35 (m, 2H), 7.37-7.47 (m, 5H), 7.55 (d, J = 7.9 Hz, 2H); LRMS calcd for $C_{32}H_{32}N_2O_3$ 492.24 $[M]^+$, found 492.75 $[M + H]^+$. HPLC purity 96.4%, t_R = 5.73 min.

Methyl 4-(Biphenyl-4-yl)-2-ethyl-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (30): The title compound was obtained according to the general procedure, but replacing methyl acetoacetate by methyl 3-oxopentanoate and using 4-biphenylcarboxaldehyde as the aldehyde. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.08 (s, 3H), 1.25 (t, J = 9.0 Hz, 3H), 2.15-2.40 (m , 4H), 2.81 (dq, J = 3.0 and 9.0 Hz, 2H), 3.63 (s, 3H), 5.12 (s, 1H), 5.98 (s, NH), 7.34-7.44 (m, 7H), 7.55 (d, J = 9.0 Hz, 2H).

Methyl 4-(4-(1*H*-Indol-5-yl)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (33): The title compound was obtained according to the general procedure, using 1*H*-indol-5-ylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.07 (s, 3H), 2.16-2.52 (m, 4H), 2.40 (s, 3H), 3.64 (s, 3H), 5.12 (s, 1H), 5.91 (s, 1H), 6.57 (s, 1H), 7.18-7.22 (m, 2H), 7.28-7.49 (m, 4H), 7.76 + 7.79 (2 x s, 2H), 8.23 (br s, 1H); LRMS calcd for $C_{28}H_{28}N_2O_3$ 440.21 $[M]^+$, found 463.13 $[M + Na]^+$. HPLC purity 95.0%, t_R = 8.77 min.

Methyl 2,7,7-Trimethyl-4-(4'-methylbiphenyl-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34): The title compound was obtained according to the general procedure, using 4-methylphenyl boronic acid as the boronic acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (s, 3H), 0.99 (s, 3H), 1.95-2.45 (m, 4H), 2.29 (s, 3H), 2.30 (s, 3H), 3.53 (s, 3H), 4.88 (s, 1H), 7.20 (t, J = 7.4 Hz, 4H), 7.46 (t, J = 8.2 Hz, 4H), 9.13 (br s, 1H); LRMS calcd for $C_{27}H_{29}NO_3$ 415.21 $[M]^+$, found 438.27 $[M + Na]^+$. HPLC purity: 97.1 %, t_R = 3.93 min.

Methyl 2,7,7-Trimethyl-5-oxo-4-(4'-(trifluoromethyl)biphenyl-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35): The title compound was obtained using 4-(trifluoromethyl)phenylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.09 (s, 3H), 2.17-2.37 (m, 4H), 2.41 (s, 3H), 3.64 (s, 3H), 5.12 (s, 1H), 5.84 (br s, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.63 (br s, 4H); LRMS calcd for $C_{27}H_{26}F_3NO_3$ 469.19 $[M]^+$, found 469.8 $[M + H]^+$. HPLC purity 98.6%, t_R = 6.82 min.

Methyl 4-(3'-Chlorobiphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36): The title compound was obtained according to the general procedure, using 3-chlorophenylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (s, 3H), 1.00 (s, 3H), 1.95-2.40 (m, 4H), 2.29 (s, 3H), 3.53 (s, 3H), 4.89 (s, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.34-7.60 (m, 4H), 7.63 (t, J = 1.9 Hz, 1H), 9.16 (br s, 1H); LRMS calcd for $C_{26}H_{26}ClNO_3$ 435.16 $[M]^+$, found 458.20 $[M + Na]^+$. HPLC purity 95.7 %, t_R = 7.88 min.

Methyl 2,7,7-Trimethyl-4-(2'-methylbiphenyl-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (37): The title compound was obtained according to the general procedure, using 2-methylphenylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (s, 3H), 1.00 (s, 3H), 1.97-2.47 (m, 4H), 2.17 (s, 3H), 2.30 (s, 3H), 3.55 (s, 3H), 4.92 (s, 1H), 7.10-7.25 (m, 8H), 9.14 (br s, 1H); LRMS calcd for $C_{27}H_{29}NO_3$ 415.21 $[M]^+$, found 438.27 $[M + Na]^+$. HPLC purity 96.9%, t_R = 7.65 min.

Methyl 4-(2'-Fluorobiphenyl-4-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (38): The title compound was obtained according to the general procedure, using 2-fluorophenylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (s, 3H), 1.00 (s,

3H), 1.97-2.45 (m, 4H), 2.29 (s, 3H), 3.54 (s, 3H), 4.90 (s, 1H), 7.21-7.29 (m, 5H), 7.36 (dd, J = 8.2 and 1.4 Hz, 2H), 7.46 (dt, J = 8.0 and 1.6 Hz, 1H), 9.16 (br s, 1H); LRMS calcd for $C_{26}H_{26}FNO_3$ 419.19 $[M]^+$, found 442.33 $[M + Na]^+$. HPLC purity 95.6%, t_R = 7.27 min.

Methyl 4-(Biphenyl-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (39): The title compound was obtained according to the general procedure, using phenylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 3H), 1.08 (s, 3H), 2.17-2.36 (m, 4H), 2.39 (s, 3H), 3.63 (s, 3H), 5.14 (s, 3H), 5.85 (s, 1H), 7.25-7.35 (m, 4H), 7.40 (t, J = 7.4 Hz, 2H), 7.51-7.54 (m, 3H); LRMS calcd for $C_{26}H_{27}NO_3$ 401.2 $[M]^+$, found 424.07 $[M + Na]^+$. HPLC purity 96.2 %, t_R = 7.37 min.

Methyl 4-(4'-Methoxybiphenyl-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (40): The title compound was obtained according to the general procedure, using 4-methoxyphenylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (s, 3H), 1.00 (s, 3H), 2.15-2.46 (m, 4H), 2.49 (s, 3H), 3.54 (s, 3H), 3.78 (s, 3H), 4.91 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.03-7.07 (m, 1H), 7.21-7.34 (m, 3H), 7.45 (d, J = 8.8 Hz, 2H), 9.10 (br s, NH); LRMS calcd for $C_{27}H_{29}NO_4$ 431.21 $[M]^+$, found 453.93 $[M + Na]^+$. HPLC purity 96.4%, t_R = 9.76 min.

Methyl 4-(3'-Chlorobiphenyl-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (41): The title compound was obtained according to the general procedure, using 3-chlorophenylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.09 (s, 3H), 2.16-2.38 (m, 4H), 2.39 (s, 3H), 3.63 (s, 3H), 5.13 (s, 1H), 5.86 (br s, 1H), 7.26-7.34 (m, 5H), 7.71 (td, J = 7.4 and 1.5 Hz, 1H), 7.49 (td, J = 9.8 and 1.9 Hz, 2H); LRMS calcd for $C_{26}H_{26}ClNO_3$ 435.16 $[M]^+$, found 458.07 $[M + Na]^+$. HPLC purity 95.1%, t_R = 8.22 min.

Methyl 2,7,7-Trimethyl-5-oxo-4-(3-(pyridin-3-yl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (42): The title compound was obtained according to the general procedure, using pyridine-3-ylboronic acid as the boronic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 3H), 1.07 (s, 3H), 2.15-2.34 (m, 4H), 2.38 (s, 3H), 3.62 (s, 3H), 5.14 (s, 1H), 6.45 (br s, NH), 7.31-7.37 (m, 4H), 7.52 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 8.54 (d, J = 3.9 Hz, 1H), 8.79 (br s, 1H); LRMS calcd for $C_{25}H_{26}N_2O_3$ 402.19 $[M]^+$, found 403.27 $[M + H]^+$. HPLC purity 98.7 %, t_R = 3.94 min.

A modification of the synthetic procedure of Shan et al. (2002) was used for the synthesis of 1,4-DHP enantiomers of **1**, **23** and **43**.[1]

(2*S*,3*R*)-Methyl 3-Hydroxy-2-(3-nitrobenzamido)butanoate (48): 7.5 g (0.063 mol) of L-threonine (**47**) was added in small aliquots to 22.5 g of thionyl chloride (0.189 mol) in 40 mL of MeOH that was chilled to 0°C prior to addition. The mixture was stirred at room temperature for 1.5 days and evaporated to dryness. Freshly prepared methyl (2*R*,3*S*)-2-amino-3-hydroxybutanoate hydrochloride was dissolved in 135 mL of EtOAc/water (2:1), cooled to 0°C, after which 12.9 g of K_2CO_3 (0.093 mol) was added. 11.69 g of 3-nitrobenzoyl chloride (0.063 mol) was added portion-wise while stirring. Stirring was continued at 0 °C for another 3 hours and then at room temperature overnight. The crude product obtained (16 g of a yellow oil, 90%) was >97% pure by TLC and was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): 1.30 (d, J = 6.4 Hz, 3H), 3.79 (s, 3H), 4.49 (qd, J = 6.4 and 2.9 Hz, 1H), 4.83 (dd, J = 8.4 and 2.5 Hz, 1H), 7.38 (d, J = 8.9 Hz, NH), 7.65 (t, J = 7.9 Hz, 1H), 8.00 (br s, OH), 8.24 (br d, J = 7.9 Hz, 1H), 8.37 (br d, J = 8.4 Hz, 1H), 8.72 (t, J = 2.0 Hz, 1H); LRMS calcd for $C_{12}H_{14}N_2O_6$ 282.09 $[M]^+$, found 265.95 $[M - OH]^+$. HPLC purity 98.0 %, t_R = 4.86 min.

(2*R*,3*S*)-4-Methoxy-3-(3-nitrobenzamido)-4-oxobutan-2-yl 4-(Biphenyl-4-yl)-2-methyl-5-oxo-7-(*n*-propyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (53): The title diastereomers were obtained according to the general procedure described in the manuscript, but using 5-(*n*-propyl)cyclohexane-1,3-dione instead of dimedone.

Diastereomer 53a: Yield: 326 mg (7%). %*de* = ≥99% (^{1}H NMR according to 4-CH, 2-CH_3 and $COOCH_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 0.83-0.87 (m, 3H), 1.12-1.14 (m, 2H), 1.24-1.31 (m, 5H), 1.96-2.47 (m, 5H), 2.44 (s, 3H), 3.79 (s, 3H), 4.91 (dd, *J* = 8.9 and 3.4 Hz, 1H), 5.00 + 5.04 (2 × s, 1H), 5.29 (s, NH), 5.38-5.43 (m, 1H), 6.32 + 6.39 (2 × s, NH), 7.05 (t, *J* = 8.9 Hz, 1H), 7.27-7.41 (m, 8H), 7.49 (q, *J* = 9.3 Hz, 1H), 8.05 (t, *J* = 8.9 Hz, 1H), 8.24 (t, *J* = 8.4Hz, 1H), 8.65 (br s, 1H); LRMS calcd for $C_{38}H_{39}N_3O_8$ 665.27 $[M]^+$, found 666.02 $[M + H]^+$ and 688.95 $[M + Na]^+$. HPLC purity 96.6%, t_R = 7.65 min.

Diastereomer 53b: Yield: 279 mg (6%). %*de* = ≥99% (^{1}H NMR); ^{1}H NMR (500 MHz, $CDCl_3$): 0.84-0.89 (m, 3H), 1.24-1.36 (m, 7H), 1.98-2.02 (m, 5H), 2.48 (s, 3H), 3.57 (s, 3H), 4.12 (q, *J* = 7.4 Hz, 1H), 4.74-4.76 (m, 1H), 5.09 + 5.14 (2 × s, 1H), 5.54-5.57 (m, 1H), 6.05 + 6.11 (2 × s, 1H), 6.51 (d, *J* = 8.9 Hz, 1H), 7.25-7.38 (m, 9H), 7.80 (d, *J* = 7.9 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.40 + 7.43 (2 × br s, 1H); LRMS calcd for $C_{38}H_{39}N_3O_8$ 665.27 $[M]^+$, found 666.02 $[M + H]^+$ and 688.95 $[M + Na]^+$. HPLC purity 98.1%, t_R = 7.92 min.

(2*R*,3*S*)-4-Methoxy-3-(3-nitrobenzamido)-4-oxobutan-2-yl 4-(3-Bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate Diastereomers (54): The title diastereomers were prepared according to the general protocol described in the manuscript, but using 3-bromobenzaldehyde as the aldehyde **5**.

Diastereomer 54a: Yield: 458 mg of a yellow solid (10%). TLC: R_f = 0.22 (tol/EtOAc, 1:1); %*de* = ≥98% (^{1}H NMR); ^{1}H NMR (500 MHz, $CDCl_3$): 0.89 (s, 3H), 1.07 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 3H), 2.19-2.36 (m, 4H), 2.48 (s, 3H), 3.63 (s, 3H), 4.73 (dd, *J* = 8.9 and 4.4 Hz, 1H), 5.03 (s, 1H), 5.49-5.54 (m, 1H), 5.92 (br s, NH), 6.54 (d, *J* = 8.4 Hz, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 7.24-7.27 (m, 1H), 7.31 (br s, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 8.00 (d, *J* = 7.4 Hz, 1H), 8.40 (br d, *J* = 7.4 Hz, 1H), 8.46 (br s, NH); LRMS calcd for $C_{31}H_{32}BrN_3O_8$ 655.14 $[M]^+$, found 655.95 $[M + H]^+$ and 678.75 $[M + Na]^+$. HPLC purity 89.1%, t_R = 6.56 min.

Diastereomer 54b: Yield: 550 mg of a yellow solid (12%). TLC: R_f = 0.20 (tol/EtOAc, 1:1); %*de* = ≥97% (^{1}H NMR); ^{1}H NMR (500 MHz, $CDCl_3$): 0.92 (s, 3H), 1.08 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 2.18-2.36 (m, 4H), 2.43 (s, 3H), 3.79 (s, 3H), 4.91 (dd, *J* = 8.9 and 3.4 Hz, 1H), 4.96 (s, 1H), 5.40-5.45 (m, 1H), 5.86 (br s, NH), 6.96 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 7.17 (br d, *J* = 9.3 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.37 (br s, 1H), 7.74 (t, *J* = 7.9 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 8.41 (br d, *J* = 8.4 Hz, 1H), 8.66 (br s, NH); LRMS calcd for $C_{31}H_{32}BrN_3O_8$ 655.14 $[M]^+$; found 655.95 $[M + H]^+$, 678.88 $[M + Na]^+$. HPLC purity 96.5%, t_R = 7.96 min.

4-(Biphenyl-4-yl)-2-methyl-5-oxo-7-(*n*-propyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid enantiomers (55a,b): The title enantiomers were obtained according to the general procedure, starting from 0.192 mmol affording **53** with 39% yield, 30 mg for **55a** (39%) and 30 mg for **55b** (39%) as off-white solids. Because of the presence of two centers of chirality (4- and 7-positions), a mixture of diastereomers was obtained. NMR analytical data was identical for both enantiomers:

Enantiomer 55a: ^{1}H NMR (300 MHz, CD_3OD): 0.88-0.93 (m, 3H), 1.31-1.38 (m, 4H), 2.06-2.61 (m, 5H), 2.36 + 2.37 (2 × s, 3H), 5.01 + 5.07 (2 × s, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.31-7.33 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.41-7.44 (m, 2H), 7.52-7.55 (m, 2H); LRMS calcd for $C_{26}H_{27}NO_3$ 401.20 $[M]^+$, found 402.15 $[M + H]^+$. HPLC purity 99.5%, t_R = 7.78 min.

Enantiomer 55b: ^{1}H NMR (300 MHz, CD_3OD): 0.87-0.94 (m, 3H), 1.29-1.39 (m, 4H), 2.03-2.61 (m, 5H), 2.36 + 2.37 (2 × s, 3H), 5.02 + 5.07 (2 × s, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.31 (dd, *J* = 8.4 and 2.9 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.42 (dd, *J* = 8.4 and 5.4 Hz, 2H), 7.52-7.55 (m, 2H); LRMS calcd for $C_{26}H_{27}NO_3$ 401.20 $[M]^+$, found 402.28 $[M + H]^+$. HPLC purity 96.6%, t_R = 6.84 min.

4-(3-Bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid Enantiomers (56a,b): The title enantiomers were prepared following the same protocol described above, but at a lower scale starting from 185 mg (0.28 mmol) of the respective diastereomer **54**. After the first chromatographic separation using CH_2Cl_2/MeOH (0-5%) as the eluent, a second purification

with hexanes/EtOAc (0-60%) was required to obtain >99% pure (HPLC) product with yields of 80 mg for **56a** (73%) and 77 mg for **56b** (70%) as off-white solids. Analytical data was identical for both enantiomers: TLC: R_f = 0.20 (CH_2Cl_2/MeOH, 95:5).

Enantiomer 56a: ^{1}H NMR (500 MHz, $CDCl_3$): 0.95 (s, 3H), 1.09 (s, 3H), 2.19-2.36 (m, 4H), 2.41 (s, 3H), 5.04 (s, 1H), 5.77 (br s, NH), 6.83-6.88 (m, 1H), 6.97-7.05 (m, 2H), 7.14-7.16 (m, 1H), 8.02 (br s, 1H); LRMS calcd for $C_{19}H_{20}BrNO_3$ 389.07 $[M]^+$, found 390.75 $[M + H]^+$. HPLC purity 98.9%, t_R = 6.48 min.

Enantiomer 56b: NMR data was identical to **56a**; LRMS calcd for $C_{19}H_{20}BrNO_3$ 389.07 $[M]^+$, found 389.75 $[M + H]^+$. HPLC purity 98.9%, t_R = 6.48 min.

Methyl 4-(Biphenyl-4-yl)-2-methyl-5-oxo-7-*n*-propyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate Enantiomers (23a,b): The title enantiomers were obtained according to the general procedure, but on a smaller scale starting with 0.07 mmol of **55** and replacing ethyl bromide with methyl iodide. The reaction was complete after 5 hours at room temperature.

Enantiomer 23a: Yield: 22 mg (76%) as a white solid. α_D^{29}= +82.31 (c = 0.4, $CHCl_3$); Because of the presence of two centers of chirality (4- and 7-position), a 1:1 mixture of diastereomers was obtained, resulting in two distinct resonances for certain signals both in ^{1}H and ^{13}C NMR spectra. ^{1}H NMR (500 MHz, $CDCl_3$): 0.85-0.89 (m, 3H), 1.29-1.33 (m, 4H), 2.01-2.08 (m, 2H), 2.17-2.31 (m, 2H), 2.37-2.49 (m, 1H), 2.39 + 2.40 (2 × s, 3H), 3.62 (s, 3H), 5.10 + 5.15 (2 × s, 1H), 6.27 + 6.34 (2 × s, NH), 7.28 (t, J = 8.4 Hz, 1H), 7.33-7.44 (m, 6H), 7.52 (br d, J = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.6 + 19.7, 19.8 + 20.0, 33.1 + 34.3, 33.9 + 34.1, 36.1, 37.7, 38.1, 43.7 + 43.9, 51.3, 105.6 + 105.8, 113.3, 127.0, 127.1, 127.2, 128.4 + 128.5, 128.8, 139.1, 141.5, 144.1 + 144.2, 146.2 + 146.3, 149.5 + 149.8, 168.1, 196.0 + 196.2; LRMS calcd for $C_{27}H_{29}NO_3$ 415.21 $[M]^+$, found 416.35 $[M + H]^+$. HPLC purity 100%, t_R = 7.70 min.

Enantiomer 23b: Yield: 24 mg (83%) as a white solid. α_D^{29}= −122.46 (c = 0.4, $CHCl_3$); As reported above for **23a**, diastereomers were observed in a 3:1 ratio for this 4-enantiomer. ^{1}H NMR (500 MHz, $CDCl_3$): 0.86-0.89 (m, 3H), 1.28-1.33 (m, 4H), 2.01-2.08 (m, 2H), 2.17-2.30 (m, 2H), 2.37-2.47 (m, 1H), 2.39 + 2.40 (2 × s, 3H), 3.63 (s, 3H), 5.10 + 5.15 (2 × s, 1H), 6.43 + 6.49 (2 × s, NH), 7.28 (t, J = 7.4 Hz, 1H), 7.33-7.44 (m, 6H), 7.51 (br d, J = 7.9 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): 19.6 + 19.7, 19.8 + 20.0, 33.1 + 34.2, 33.8 + 34.0, 36.1 + 36.4, 37.7 + 38.1, 43.7 + 43.9, 51.3, 105.6 + 105.8, 113.3, 127.0, 127.1, 127.2, 128.4 + 128.5, 128.83, 139.1, 141.4, 144.1 + 144.2, 146.2 + 146.3, 149.6 + 150.00, 168.1, 196.1 + 196.3; LRMS calcd for $C_{27}H_{29}NO_3$ 415.21 $[M]^+$, found 416.35 $[M + H]^+$. HPLC purity 99.7%, t_R = 7.67 min.

The optical purity of (+)-**23a** and (−)-**23b** were in both cases determined to be ≥96%*ee* by ^{1}H NMR spectroscopy. In this experiment 1.5 mg (+)Eu(hfc)$_3$ dissolved in 50 µL ($CDCl_3$) was added to 1.5 mg of the respective enantiomer in 550 µL ($CDCl_3$). NMR resonances of the OCH_3 (carboxylic ester) shifted differently upon addition of the chiral reagent for each enantiomer and was used to estimate %*ee*. Also, the OCH_3-singlet split up in two singlets due to the chiral 7-position revealing the existence of two diastereomers.

Methyl 4-(3-Bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate Enantiomers (57a,b): The title enantiomers **57** were prepared following the general protocol but starting from 70 mg (0.179 mmol) of the respective carboxylic acid enantiomer **56** and using 38 mg of methyl iodide (0.27 mmol, 1.5 eq) as the alkylating reagent. The reaction was complete after 5 hours at room temperature.

Enantiomer 57a: Yield: 58 mg (80%) as a light-yellow solid. TLC: R_f = 0.18 (hexanes/EtOAc, 6:4); α_D^{29}= −64.84 (c = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 0.95 (s, 3H), 1.08 (s, 3H), 2.16-2.36 (m, 4H), 2.39 (s, 3H), 3.61 (s, 3H), 5.04 (s, 1H), 5.88 (br s, 1H), 7.07 (t, J = 7.9 Hz, 1H), 7.22-7.17 (m, 2H),

7.37 (t, J = 1.5 Hz, 1H); LRMS calcd for $C_{20}H_{22}BrNO_3$ 404.30 $[M]^+$, found 405.5 $[M + H]^+$. HPLC purity 98.6%, t_R = 7.71 min.

Enantiomer 57b: Yield: 59 mg (81%) as a light-yellow solid. TLC: R_f = 0.18 (hexanes/EtOAc, 6:4); α_D^{29}= +73.96 (c = 0.4, $CHCl_3$); NMR data was identical to **56a**; LRMS calcd for $C_{20}H_{22}BrNO_3$ 404.3 [M], found 405.4 [M + H]. HPLC purity 100%, t_R = 7.83 min.

Methyl 4-(3-(1*H*-Indol-5-yl)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate enantiomers (43a,b): To a 5 mL microwave vial, 52 mg (0.129 mmol) of the respective bromo intermediate **57a,b**, 25 mg of 1*H*-indol-5-ylboronic acid (0.155 mmol), 16 mg of $Pd((Ph)_3)_4$ catalyst, and 0.15 mL of a 2M sodium carbonate in water dioxane/water (2/1.5 mL) was heated in a microwave for 15 minutes at 150 °C. Solvents were evaporated, the crude mixture dissolved in EtOAc, washed with water and dried over sodium sulfate and concentrated under reduced pressure. The crude products were purified by two flash chromatographies. For the first separation CH_2Cl_2/MeOH (0-5%) was used as the eluent and for the second chromatography hexane/EtOAc (0-60%) was used.

Enantiomer 43a: Yield: 30 mg (53%) as a light-yellow solid. TLC: R_f = 0.26 (hexane/EtOAc, 4:6); α_D^{29}= −49.35 (c = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 0.97, 1.08 (2 × s, 3H), 2.15-2.32 (m, 4H), 2.38 (s, 3H), 3.63 (s, 3H), 5.16 (s, 1H), 5.89 (br s, 1H), 6.58 (br t, 1H), 7.22 (m_c, 1H), 7.26 (m_c, 2H), 7.38 (m_c, 3H), 7.56 (m_c, 1H), 7.78 (m_c, 1H), 8.24 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 19.6 (2-CH_3), 27.3 (7-CH_3), 29.4 (7-CH_3), 32.9 (7-C), 36.7 (8-CH_2), 41.4 (4-CH), 51.07, 51.1 (OCH_3, 6-CH_2), 103.0 (3"-CH), 106.1 (3-C), 111.1 (7"-CH), 112.0 (5-C), 119.2, 122.1, 124.7, 125.4, 126.2, 127.0, 128.26, 128.31 (3"a-C), 134.0, 135.2, 142.2 (1'-C), 143.8 (5"-C), 147.2 (2-C), 148.0 (6-C), 168.0 (COO), 196.0 (CO); LRMS calcd for $C_{28}H_{28}N_2O_3$ 440.21 $[M]^+$, found 441.75 $[M + H]^+$. HPLC purity 99.1%, t_R = 7.55 min.

Enantiomer 43b: Yield: 28 mg (49%) as a light-yellow solid. TLC: R_f = 0.26 (hexane/EtOAc, 4:6); α_D^{29}= +48.5 (c = 0.4, $CHCl_3$); NMR data was identical to **43a**; LRMS calcd for $C_{28}H_{28}N_2O_3$ 440.21 $[M]^+$, found 441.68 $[M + H]^+$. HPLC purity 99.9%, t_R = 7.62 min.

The optical purity of (+)-**43a** and (−)-**43b** was in both cases determined to ≥96%*ee* by ^{1}H NMR spectroscopy. In this experiment 1.5 mg (+)Eu(hfc)$_3$ dissolved in 50 µL ($CDCl_3$) were added to 1.5 mg of the respective enantiomer in 550 µL ($CDCl_3$). NMR resonances of the 2-CH_3 and 7-CH_3 groups as well as for the OCH_3 (carboxylic ester) and 4-CH groups shifted differently upon addition of the chiral reagent for each enantiomer. Using the shifted resonances of the methyl ester OCH_3 group and 7-CH_3 groups, however, were suited best to estimate %*ee*.

I) REPRESENTATIVE NMR SPECTRA

1. ^{1}H, ^{13}C, ^{13}C DEPT, H-H-COSY, HSQC and HMBC spectra of 1:

^{1}H NMR (300 MHz, $CDCl_3$): 0.94 (s, 3H), 1.06 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 2.12-2.33 (m, 4H), 2.35 (s, 3H), 4.08 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 1H), 6.58 (br s, NH), 7.25-7.30 (m, 1H), 7.35-7.45 (m, 6H), 7.50-7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.4 ($OCH_2\underline{C}H_3$), 19.5 (2-CH_3), 27.3 (7-CH_3), 29.6 (7-CH_3), 32.8 (7-C), 36.5 (4-CH), 41.1 (8-CH_2), 50.9 (6-CH_2), 60.0 (OCH_2), 106.1 (3-C), 112.0 (4a-C), 126.8 (ArCH), 127.0 (ArCH), 128.5 (ArCH), 128.7 (ArCH), 138.9 (ArC), 141.3 (ArC), 143.8 (2-C), 146.4 (1'-C), 148.9 (8a-C), 167.6 (COOMe), 195.9 (CO).

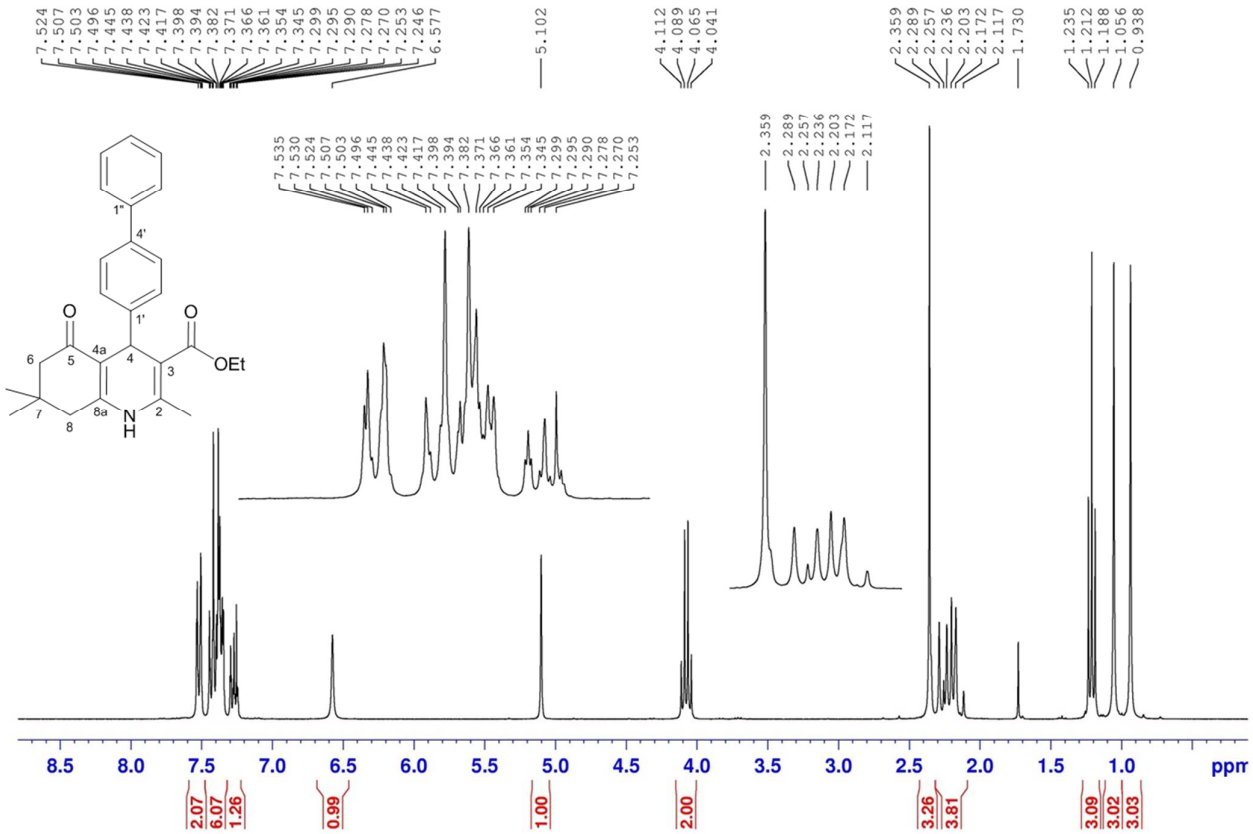


Figure S1: ^{1}H NMR spectrum of 1 (300 MHz).

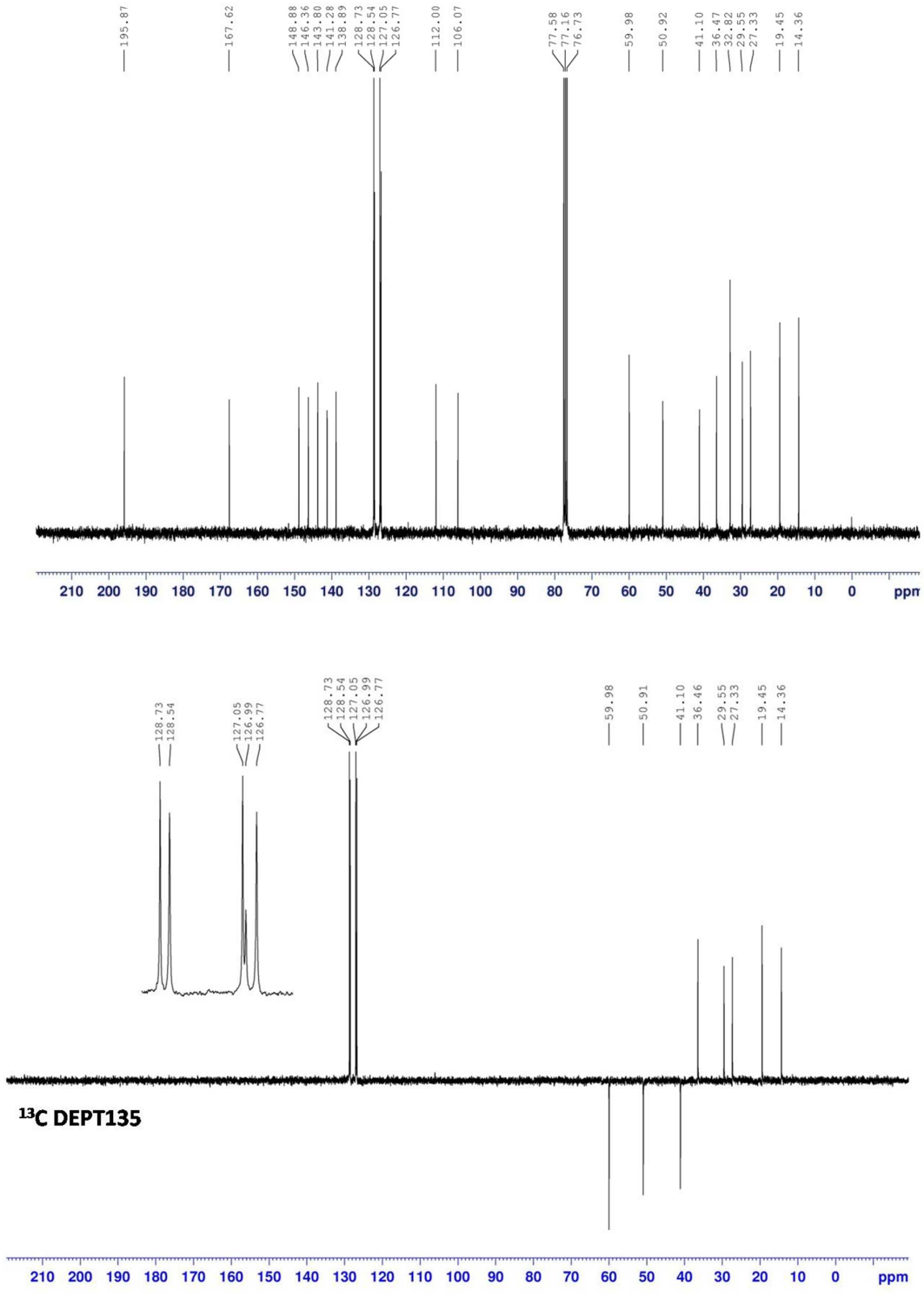
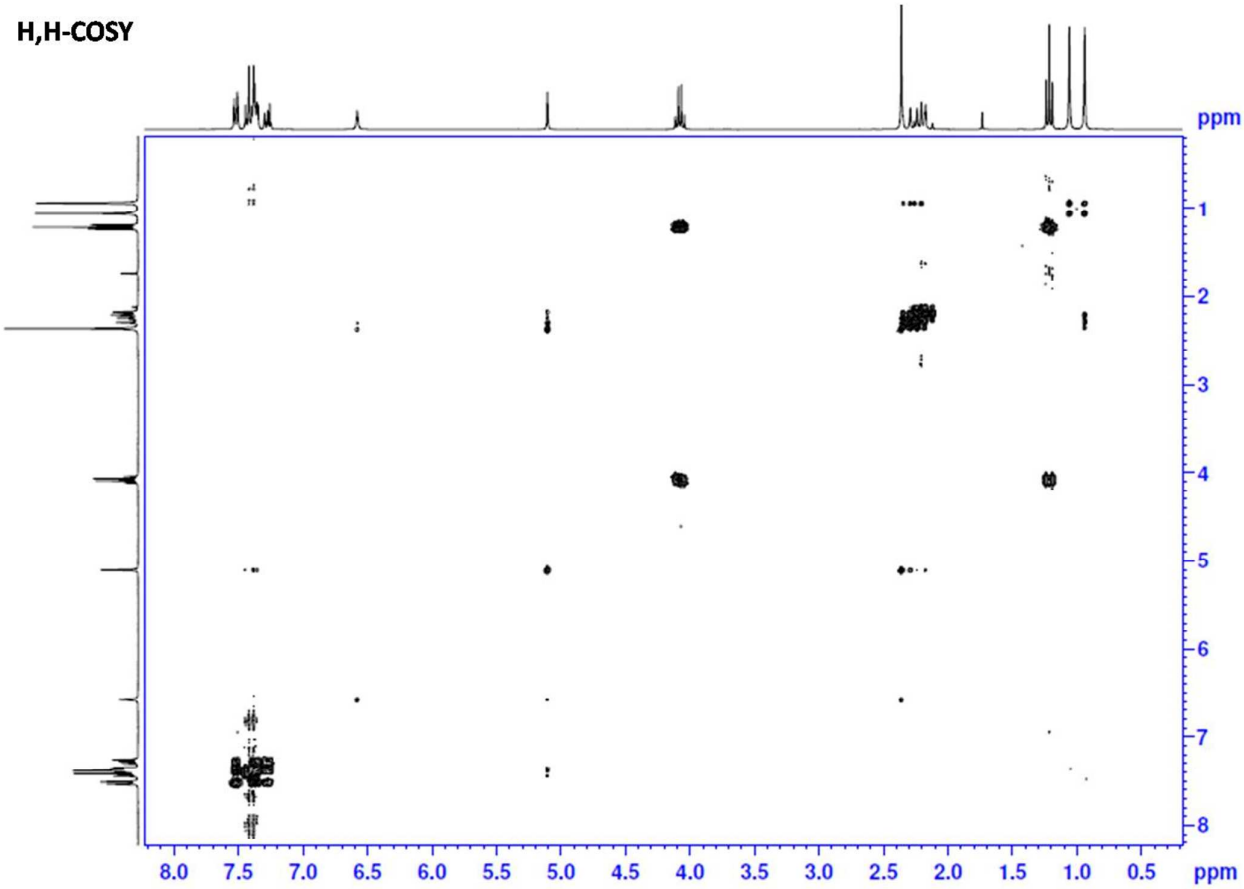
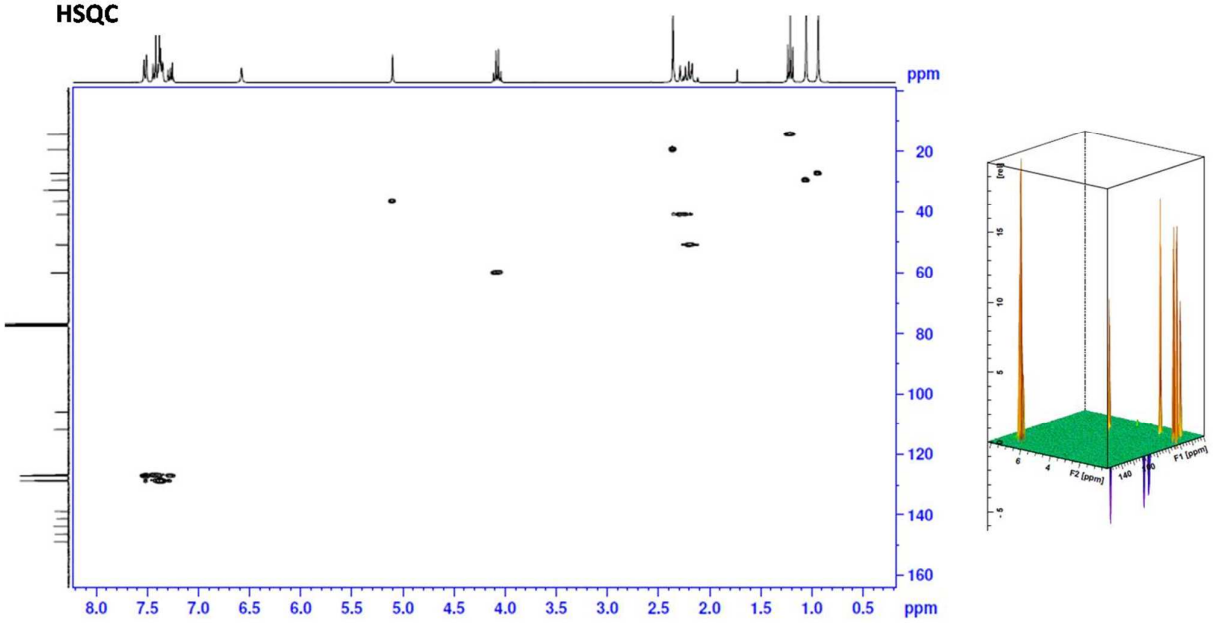


Figure S2: ^{13}C and ^{13}C-DEPT NMR spectra of 1 (75 MHz).

H,H-COSY


ppm
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

HSQC


ppm
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40
60
80
100
120
140
160
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
F2 [ppm]
F1 [ppm]

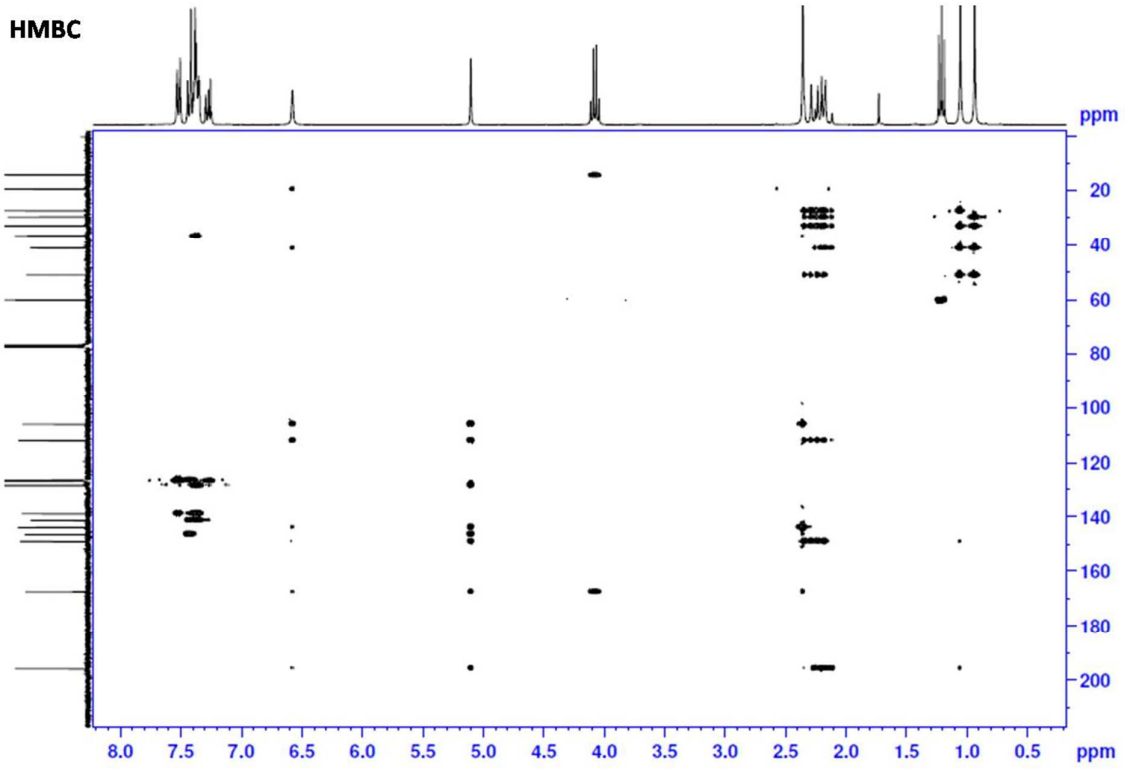

Figure S3: 2D-NMR spectra of 1.

2. ^{1}H spectra of 52a/b diastereomers

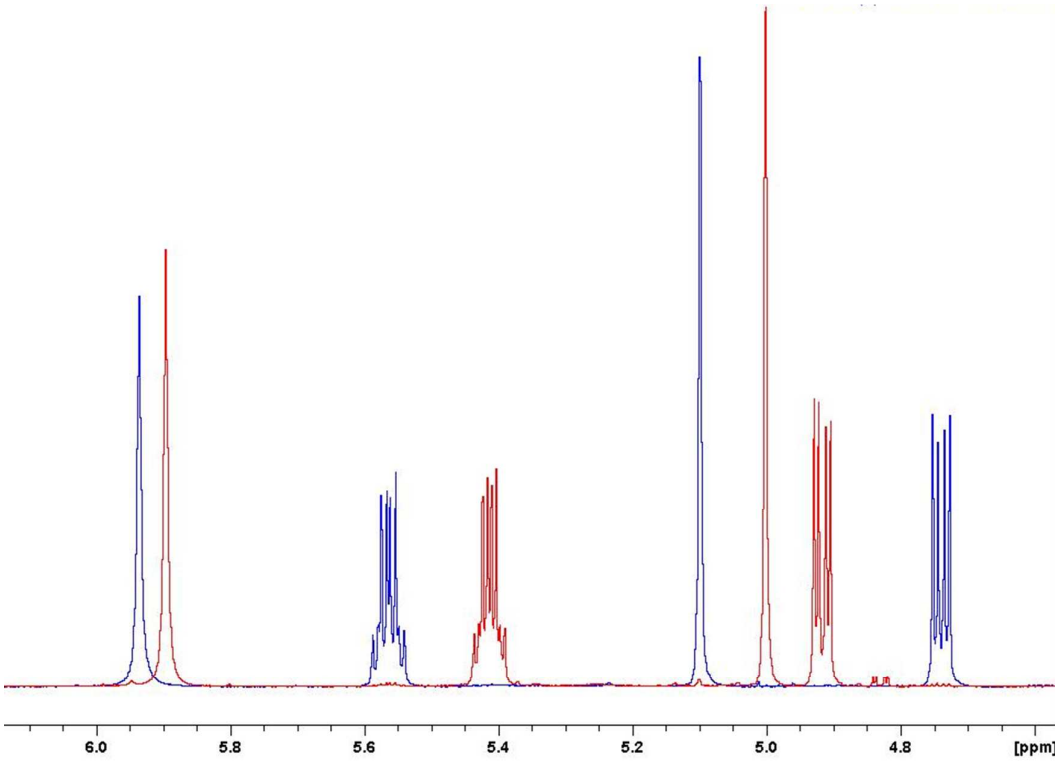

Figure S4: Overlay of ^{1}H NMR spectra of 52a/52b diastereomers. Blue = 52a, Red = 52b (≥ 99%*de*)

3. (+)Eu(hfc)$_3$ ^{1}H NMR shift reagent experiments

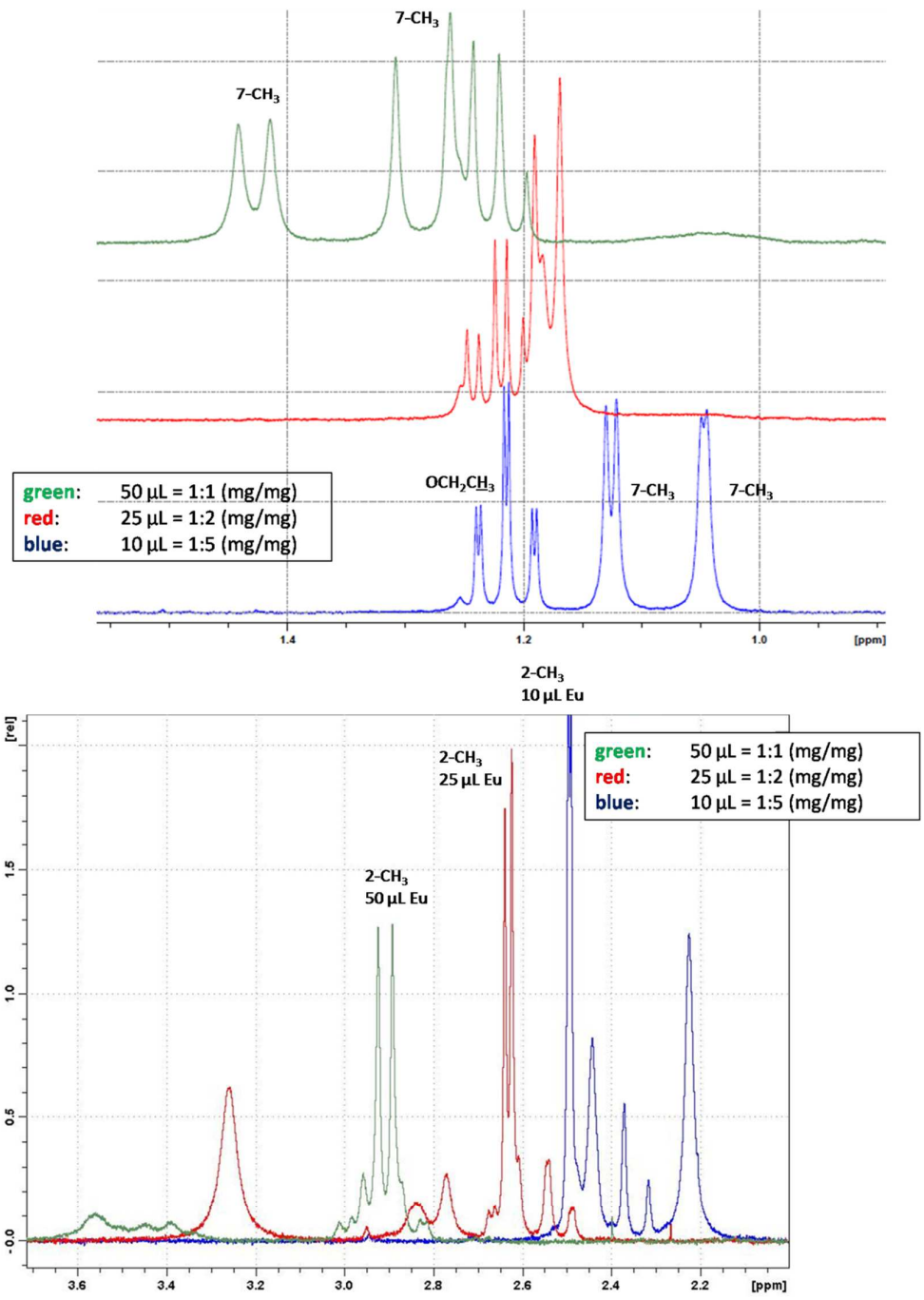

Figure S5: (+)Eu(hfc)$_3$ ^{1}H NMR shift reagent experiments for racemic 1. 2 mg (+)Eu(hfc)$_3$/50 µL ($CDCl_3$) were added sequentially to 2 mg of **1** in 550 µL ($CDCl_3$).

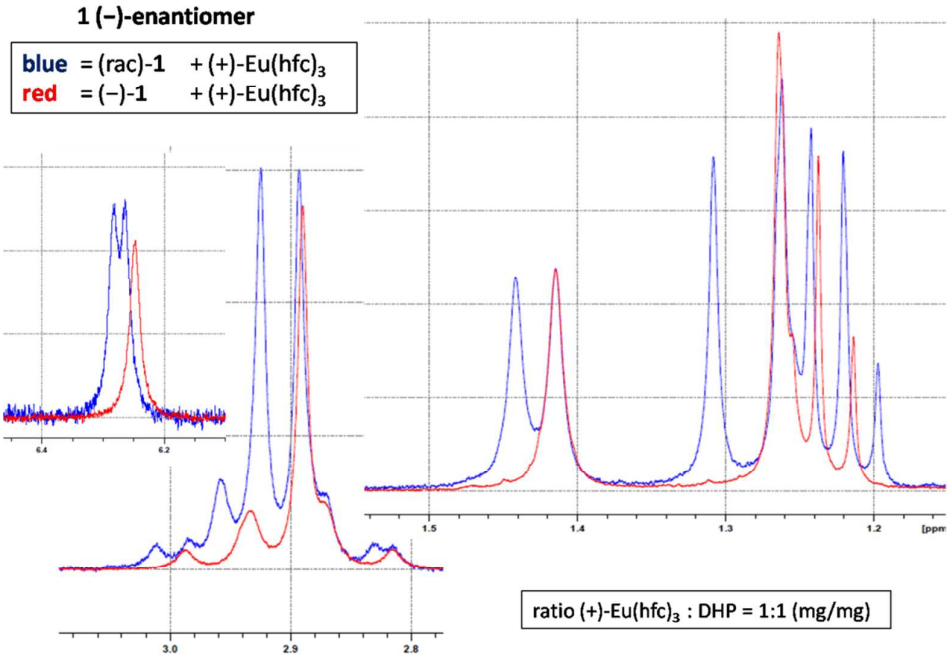

Figure S6: (+)Eu(hfc)$_3$ ^{1}H NMR shift reagent experiments for single enantiomers of (–)-1. 1.5 mg (+)Eu(hfc)$_3$/50 µL ($CDCl_3$) was added to 1.5 mg of (−)-**1** in 550 µL ($CDCl_3$). Overlay of ^{1}H spectra of racemic and enantiopure material from separate NMR experiments. Resonances for the 7-methyl groups were used to estimate %*ee* which was ≥96%.

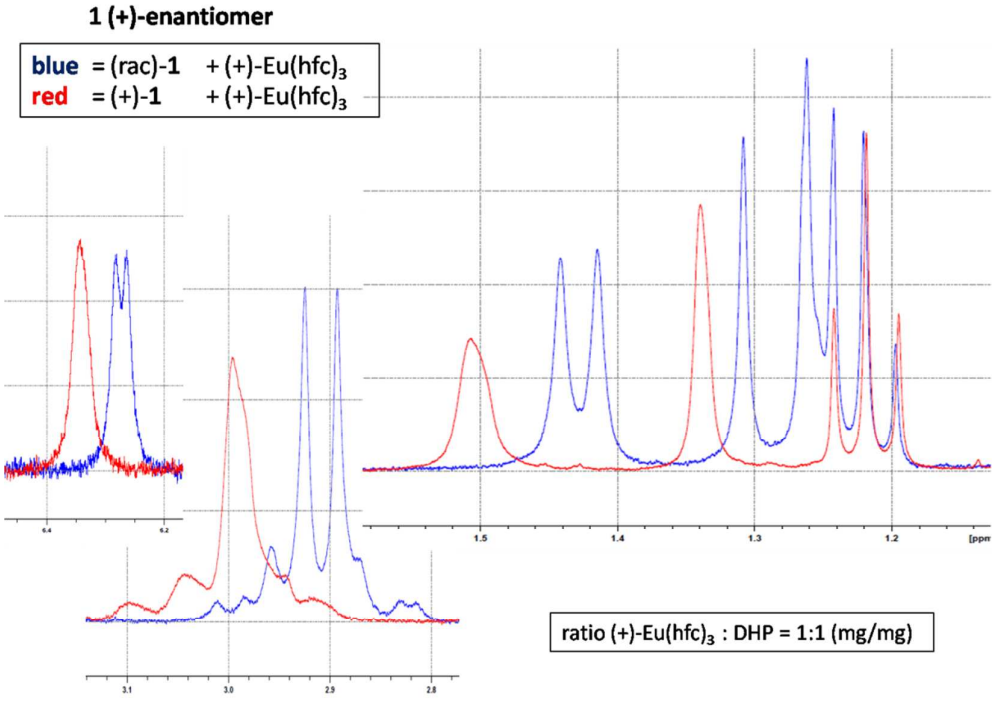

Figure S7: (+)Eu(hfc)$_3$ ^{1}H NMR shift reagent experiments for single enantiomers of (+)-1. 1.5 mg (+)Eu(hfc)$_3$/50 µL ($CDCl_3$) was added to 1.5 mg of (+)-**1** in 550 µL ($CDCl_3$). Overlay of ^{1}H spectra of racemic and enantiopure material from separate NMR experiments. Resonances for the 7-methyl groups were used to estimate %*ee* which was ≥96%.

II) CALCIUM TRANSIENTS IN HL-1 CELLS

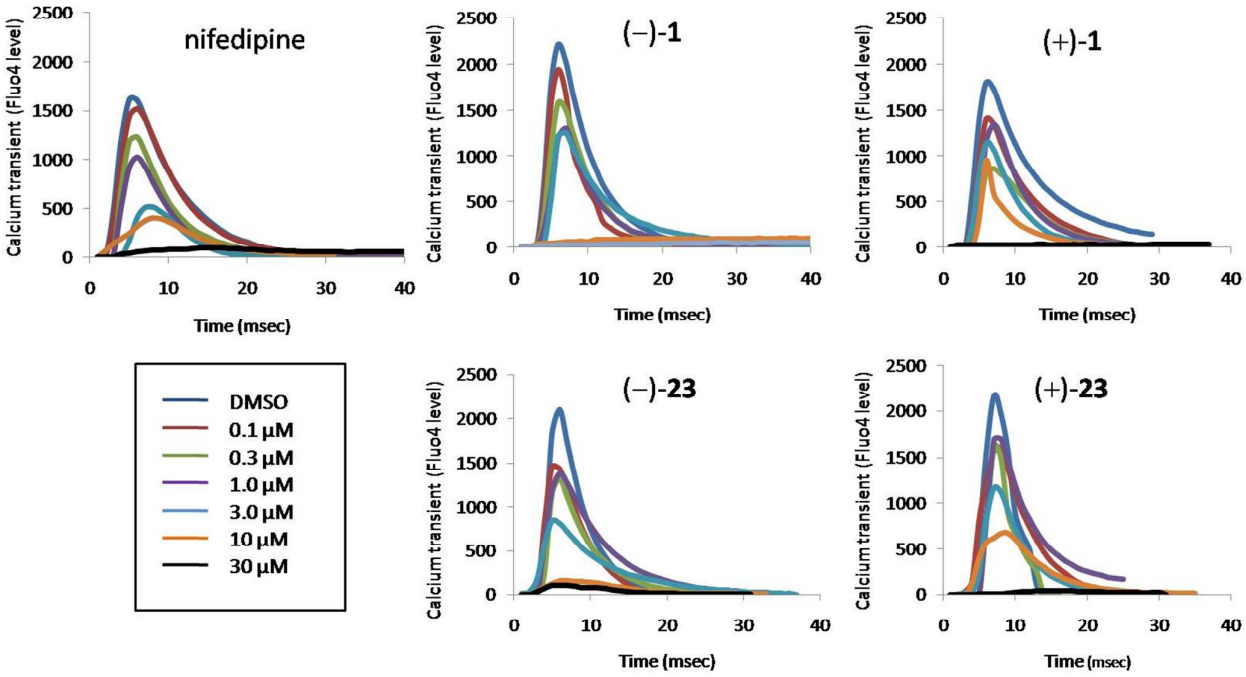

Figure S8: Representative Calcium transients in HL-1 cells.

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2. Claycomb, W. C.; Lanson, N. A., Jr.; Stallworth, B. S.; Egeland, D. B.; Delcarpio, J. B.; Bahinski, A.; Izzo, N. J., Jr. HL-1 cells: a cardiac muscle cell line that contracts and retains phenotypic characteristics of the adult cardiomyocyte. *Proc. Natl. Acad. Sci. U.S.A.* **1998,** 95 (6), 2979-2984.