The Use of Magnesium Nitride for the Synthesis of Enantiomerically Pure 1,4-Dihydropyridines via the Hantzsch Reaction

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Abstract: Enantiomerically pure 1,4-dihydropyridines are prepared taking advantage of magnesium nitride as a useful and convenient source of 'solid ammonia'. The products possess various substituents at carbons 3, 4 and 5 of the dihydropyridine moiety.

Key words: 1,4-dihydropyridines, magnesium nitride, multicomponent reaction, Hantzsch esters, one-pot condensation

Significant attention has been devoted to 1,4-dihydropyridine derivatives due to their wide spectrum of biological activity. Compounds containing the 1,4-dihydropyridine moiety have been found to act as calcium modulators,[1] BACE-1 inhibitors,[2] drugs for the treatment of vasodilation,[3] a mineral corticoid receptor antagonist,[4] hepatoprotection, neuromodulatory, antiatherosclerosis, antidiabetes, antioxidant, antimutagenic and antitumor agents,[5] and also have an effect on the accumulation of tau.[6] 1,4-Dihydropyridines such as nifedipine, (Adalat®, Procardia®), amlodipine and nimodipine (Figure 1) are widely prescribed as antihypertensive drugs.[7] In addition, the dihydropyridine moiety has found application as an NADH analogue.[8] The classic method to prepare dihydropyridines was discovered by Hantzsch in 1882[9] and consists of a multicomponent reaction (MCR) between an aldehyde, a β-keto ester and a 30% aqueous ammonia solution as the nitrogen source.[4–7] Magnesium nitride (Mg_3N_2), a commercially available bench-stable solid, has been utilized by the Ley group, as an ammonia-releasing agent in the presence of proton sources.[10] In order to demonstrate the feasibility and utility of this reagent for the preparation of highly functionalized molecules, with special emphasis on those containing one or more stereocenters, we report herein our results on the synthesis of enantiomerically pure Hantzsch esters in good to satisfactory yields. In fact, the need for enantiomerically pure 1,4-dihydropyridines for biological testing[4,11] is well acknowledged, and hence research on their synthesis and bioactivity is highly warranted. Besides the preparation of enantiomerically pure compounds, it should be noted that, from a synthetic point of view, this work is based on the use of aprotic 1,4-dioxane as the solvent, instead of protic ethanol as reported by Ley.[10] In this way, slow decomposition of magnesium nitride, via the enolic form of the β-keto ester, takes place thereby allowing the use of stoichiometric amounts of magnesium nitride, the β-keto ester and the aldehyde.

A series of 1,4-dihydropyridines was synthesized via the one-pot condensation of an aldehyde, a β-keto ester and magnesium nitride in 1,4-dioxane (Scheme 1 and

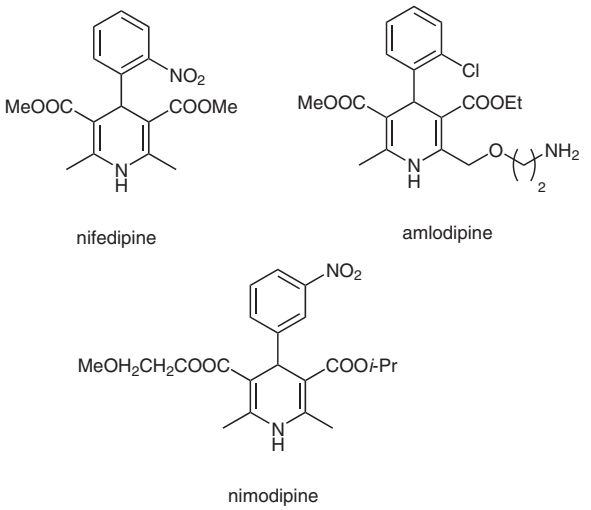
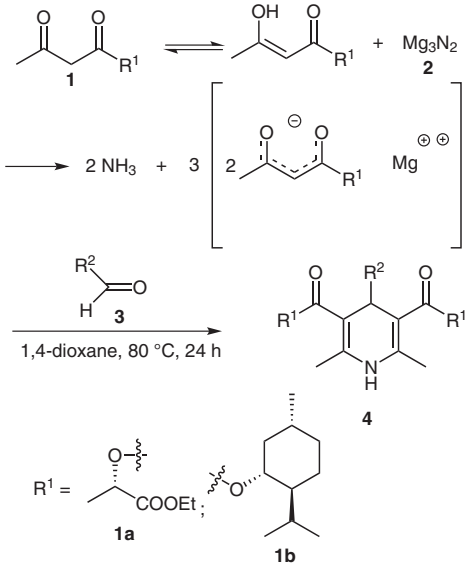


Figure 1 Some typical antihypertensive drugs based on the 1,4-dihydropyridine scaffold



Scheme 1 Preparation of 1,4-dihydropyridines **4a**–**p** in 1,4-dioxane

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Table 1). The starting optically active β-keto esters **1a** and **1b** were prepared in good yield by microwave-assisted transesterification in the absence of any catalyst.[12] Attempts to obtain the dihydropyridines **4a–p** under microwave-assisted organic synthesis (MAOS) conditions were not completely successful. In fact, even in the best cases, the yields were lower than those obtained by convective heating, whereas the time needed to complete the reaction was similar under both microwave and convective heating conditions. In summary, we have reported a simple protocol for the preparation of optically active 1,4-dihydropyridines in satisfactory yields.

Table 1 Synthesis of Optically Active 1,4-Dihydropyridines **4a–p**

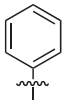
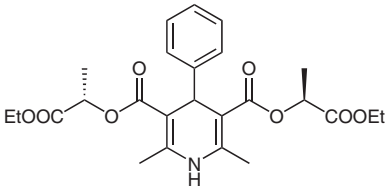
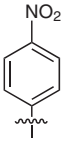
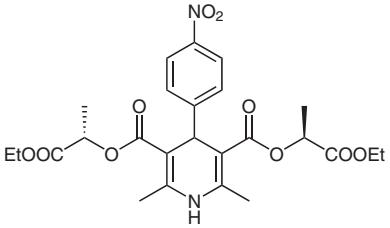
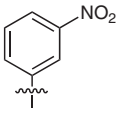
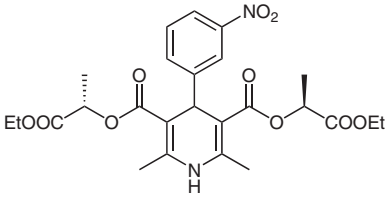
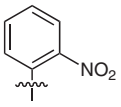
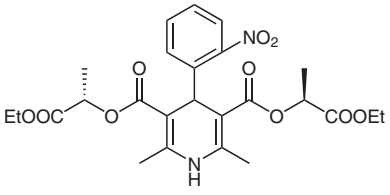
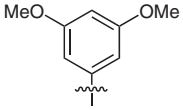
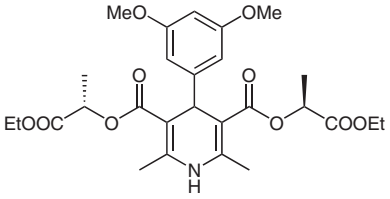
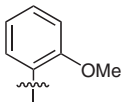
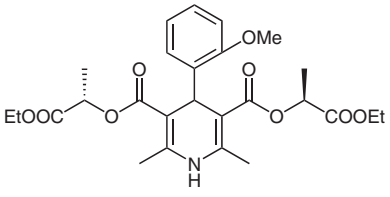
Entry	R^1	Product	Yield (%)
1		 **4a**	95
2		 **4b**	66
3		 **4c**	66
4		 **4d**	46
5		 **4e**	41
6		 **4f**	43

Table 1 Synthesis of Optically Active 1,4-Dihydropyridines **4a–p** (continued)

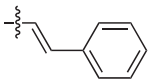
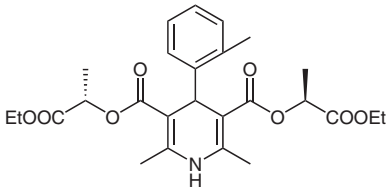
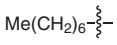
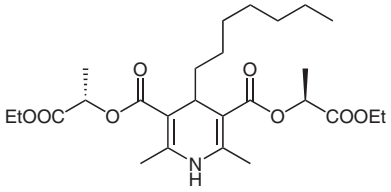
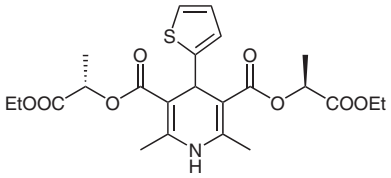
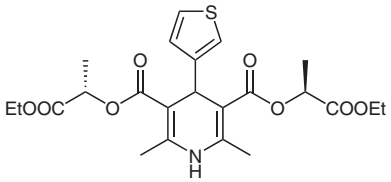
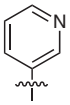
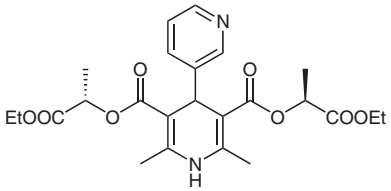
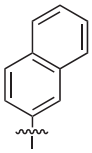
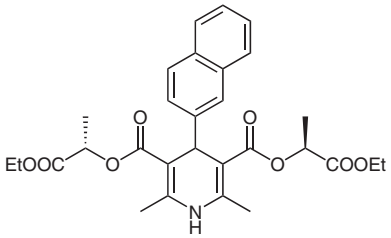
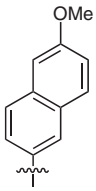
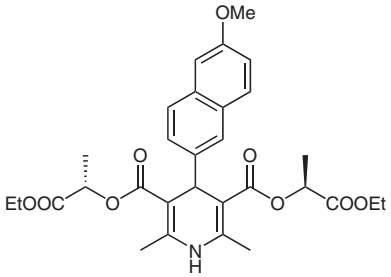
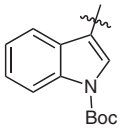
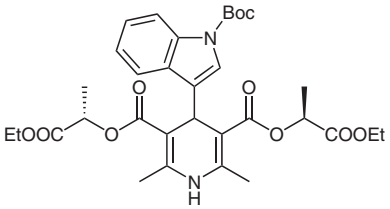
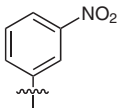
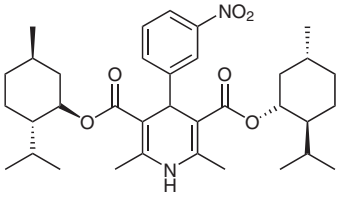
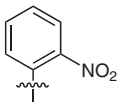
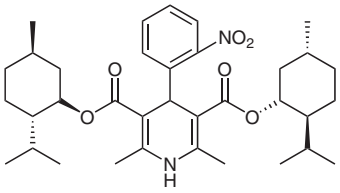
Entry	R^1	Product	Yield (%)
7		 **4g**	65
8		 **4h**	58
9		 **4i**	28
10		 **4j**	73
11		 **4k**	58
12		 **4l**	52
13		 **4m**	26

Table 1 Synthesis of Optically Active 1,4-Dihydropyridines **4a–p** (continued)

Entry	R^1	Product	Yield (%)
14		 **4n**	22
15		 **4o**	50
16		 **4p**	25

All starting materials, unless otherwise stated, were purchased and used without any further purification. Solvents were distilled and dried according to standard procedures. All the reactions were run in a sealed tube under a nitrogen atmosphere. Column chromatography was performed using Merck KGaA Silicagel 60 (230-400 Mesh-ASTM). Melting points were obtained using a Stuart Scientific SMP3 Melting Point apparatus and are not corrected. Optical rotations were obtained using a Perkin Elmer 343 polarimeter. IR spectra were recorded on a Nicolet 380 FT-IR infrared spectrometer. NMR spectroscopy was performed on a Varian-Mercury 400 spectrometer using the residual signal of the solvent as the internal standard. The chemical shifts are reported in ppm and coupling constants (*J*) are reported in Hz. GC–MS spectra were recorded using Agilent Technologies 6850 and 5975 GC-Mass instrumentation. LC–MS spectra were obtained using an Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Elemental analysis were performed at CNR-ISMAR, Bologna, Italy.

(2*S*)-1-Ethoxy-1-oxopropan-2-yl 3-Oxobutanoate (1a)

(*S*)-(–)-Ethyl lactate (0.3 mol, 35 mL) and ethyl acetoacetate (0.15 mol, 19.5 mL), in a 50 mL flask, were heated at reflux temperature in a microwave oven (Milestone/MicroSynth) at 500 W for 3 h. During this time the EtOH produced during the transesterification was removed by side-arm distillation. The excess (*S*)-(–)-ethyl lactate was removed by rotary evaporation. The residue was found to consist of 24.2 g (80% conversion) of the target compound. The analytical data (including the optical rotation) was analogous with the literature.[12]

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 3-Oxobutanoate (1b)

The title product was prepared using the previously reported microwave-assisted organic synthesis technique.[12]

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a); Typical Procedure

A mixture of benzaldehyde (**3a**) (0.203 mL, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol) in anhyd 1,4-dioxane (3 mL) in a 5 mL sealed tube was stirred for 24 h at 80 °C. The mixture was cooled, dissolved in ice-cold H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over $MgSO_4$, the solvent removed in vacuo and the product purified by flash chromatography on silica gel (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.896 g (95%); $[\alpha]_D^{20}$ +133.43 (*c* 0.7, $CHCl_3$).

IR (film): 1740, 1695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.42 (d, *J* = 6.9 Hz, 3 H), 1.46 (d, *J* = 6.9 Hz, 3 H), 2.34 (s, 3 H), 2.35 (s, 3 H), 4.07 (m, 2 H), 4.18 (m, 2 H), 4.96 (q, *J* = 7.1 Hz, 1 H), 5.03 (q, *J* = 6.9 Hz, 1 H), 5.07 (s, 1 H), 5.97 (s, 1 H, NH), 7.13–7.31 (m, 5 H, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.96, 14.06, 16.87, 17.04, 19.51, 19.85, 39.45, 60.94, 61.13, 68.24, 68.44, 103.15, 103.88, 126.11, 127.73, 128.14, 145.27, 147.45, 166.65, 166.70, 171.20, 171.47.

MS (ESI): *m*/*z* = 474 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{31}NO_8$: C, 63.41; H, 6.60; N, 2.96. Found: C, 63.60; H, 6.62.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4b)

The product was prepared according to the typical procedure from 4-nitrobenzaldehyde (**3b**) (0.302 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow solid; yield: 0.681 g (66%); mp 55 °C; $[\alpha]_D^{20}$ +63.64 (*c* 1.1, $CHCl_3$).

IR (film): 1735, 1701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.42 (d, *J* = 6.8 Hz, 3 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 2.26 (s, 3 H), 2.38 (s, 3 H), 4.05 (m, 2 H), 4.20 (m, 2 H), 4.96 (q, *J* = 6.8 Hz, 1 H), 5.00 (q, *J* = 6.8 Hz, 1 H), 5.15 (s, 1 H), 6.43 (s, 1 H), 7.47 (d, *J* = 9.6 Hz, 2 H), 8.07 (d, *J* = 9.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.94, 14.03, 16.90, 17.01, 19.34, 19.56, 39.83, 61.02, 61.37, 68.33, 68.55, 101.83, 102.61, 123.17, 129.08, 145.64, 146.55, 154.79, 166.10, 166.15, 170.95, 171.46.

MS (ESI): *m*/*z* = 519 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.83; N, 5.40. Found: C, 58.03; H, 5.84.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c)

The product was prepared according to the typical procedure from 3-nitrobenzaldehyde (**3c**) (0.302 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.684 g (66%); $[\alpha]_D^{20}$ +60.9 (*c* 1.1, $CHCl_3$).

IR (film): 1738, 1701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 6.8 Hz, 3 H), 1.24 (t, *J* = 6.8 Hz, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.49 (d, *J* = 6.8 Hz, 3 H), 2.37 (s, 3 H), 2.41 (s, 3 H), 4.04 (m, 2 H), 4.20 (m, 2 H), 4.97 (q, *J* = 6.8 Hz, 1 H), 5.00 (q, *J* = 7.2 Hz, 1 H), 5.16 (s, 1 H), 6.17 (s, 1 H, NH), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.68 (dt, *J* = 1.4 Hz, *J* = 7.7 Hz, 1 H), 8.01 (ddd, *J* = 1.0 Hz, *J* = 1.4 Hz, *J* = 8.2 Hz, 1 H), 8.14 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.88, 14.02, 16.82, 16.95, 19.13, 19.37, 39.85, 60.90, 61.45, 68.23, 68.53, 101.83, 102.73, 121.25, 123.44, 128.58, 134.80, 145.71, 146.78, 147.83, 149.81, 166.09, 166.22, 170.91, 171.74.

MS (ESI): *m*/*z* = 541 $[M + 23]^+$.

Anal. Calcd for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.83; N, 5.40. Found: C, 59.59; H, 5.99.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d)

The product was prepared according to the typical procedure from 2-nitrobenzaldehyde (**3d**) (0.151 g, 1 mmol), β-keto ester **1a** (0.404 g, 2 mmol) and Mg_3N_2 (**2**) (0.50 g, 0.5 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.236 g (46%); $[\alpha]_D^{20}$ +55.0 (*c* 1.0, $CHCl_3$).

IR (film): 1735, 1701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 6.8 Hz, 3 H), 1.26 (t, *J* = 6.8 Hz, 3 H), 1.41 (d, *J* = 7.2 Hz, 3 H), 1.45 (d, *J* = 7.6 Hz, 3 H), 2.26 (s, 3 H), 2.41 (s, 3 H), 3.96 (m, 2 H), 4.19 (m, 2 H), 4.92 (q, *J* = 6.8 Hz, 1 H), 5.01 (q, *J* = 7.2 Hz, 1 H), 6.09 (s, 1 H), 6.77 (br s, 1 H, NH), 7.25 (t, *J* = 8.4 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.00, 13.05, 14.96, 15.26, 15.46, 33.34, 59.73, 60.37, 67.47, 67.55, 101.48, 102.00, 123.19, 125.98, 131.05, 132.02, 142.16, 145.20, 145.63, 146.10, 165.37, 165.89, 170.09, 171.16.

MS (ESI): *m*/*z* = 519 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.83; N, 5.40. Found: C, 59.71; H, 6.01.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 4-(3,5-Dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e)

The product was prepared according to the typical procedure from 3,5-dimethoxybenzaldehyde (**3e**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.441 g (41%); $[\alpha]_D^{20}$ +40.0 (*c* 1.1, $CHCl_3$).

IR (film): 1740, 1698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.0 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.49 (d, *J* = 7.6 Hz, 3 H), 2.34 (s, 3 H), 2.35 (s, 3 H), 3.75 (s, 6 H), 4.14 (m, 4 H), 5.00 (q, *J* = 7.2 Hz, 1 H), 5.06 (q, *J* = 7.2 Hz, 1 H), 5.07 (s, 1 H), 5.84 (s, 1 H, NH), 6.27 (s, 1 H), 6.50 (s, 1 H), 6.51 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.74, 13.89, 16.82, 16.93, 18.88, 19.20, 39.31, 54.94, 60.82, 61.08, 68.02, 68.29, 97.51, 102.13, 102.98, 106.47, 145.04, 146.08, 149.92, 160.05, 166.66, 170.01, 171.59.

MS (ESI): *m*/*z* = 534 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{35}NO_{10}$: C, 60.78; H, 6.61; N, 2.63. Found: C, 60.96; H, 6.63.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 4-(2-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f)

The product was prepared according to the typical procedure from 2-methoxybenzaldehyde (**3f**) (0.272 g, 2 mmol), β-keto ester **1a** (0.808 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over $MgSO_4$ and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.431 g (43%); $[\alpha]_D^{20}$ +55.56 (*c* 0.9, $CHCl_3$).

IR (film): 1740, 1691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.40 (d, *J* = 6.9 Hz, 3 H), 1.45 (d, *J* = 6.9 Hz, 3 H), 2.21 (s, 3 H), 2.32 (s, 3 H), 3.72 (s, 3 H), 3.95 (m, 2 H), 4.19 (m, 2 H), 4.87 (q, *J* = 7.1 Hz, 1 H), 4.98 (q, *J* = 7.1 Hz, 1 H), 5.28 (s, 1 H), 6.65 (br s, 1 H, NH), 6.78 (m, 2 H), 7.08 (dt, *J* = 1.8 Hz, *J* = 7.4 Hz, 1 H), 7.21 (dd, *J* = 1.8 Hz , *J* = 7.5 Hz , 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.79, 13.99, 16.76, 16.80, 18.86, 19.23, 35.36, 55.08, 60.64, 61.10, 67.80, 67.99, 101.31, 102.13, 110.51, 119.67, 127.16, 131.26, 135.37, 145.04, 146.08, 157.24, 167.05, 167.27, 171.36, 172.11.

MS (ESI): *m*/*z* = 504 $[M + H]^+$.

Anal. Calcd for $C_{26}H_{33}NO_9$: C, 62.02; H, 6.61; N, 2.78. Found: C, 62.20; H, 6.63.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (4g)

The product was prepared according to the typical procedure from *trans*-cinnamaldehyde (**3g**) (0.264 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.645 g (65%); $[\alpha]_D^{20}$ +44.55 (*c* 0.9, $CHCl_3$).

IR (film): 1741, 1698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 6.8 Hz, 3 H), 1.26 (t, *J* = 6.8 Hz, 3 H), 1.51 (d, *J* = 6.4 Hz, 3 H), 1.53 (d, *J* = 6.4 Hz, 3 H), 2.32 (s, 3 H), 2.33 (s, 3 H), 4.16 (m, 4 H), 4.69 (d, *J* = 6.0 Hz, 1 H), 5.08 (q, *J* = 6.8 Hz, 1 H), 5.12 (q, *J* = 7.2 Hz, 1 H), 5.99 (s, 1 H, NH), 6.36 (m, 2 H), 7.14–7.31 (m, 5 H, Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.02, 14.08, 17.05, 17.11, 19.46, 19.60, 36.33, 61.05, 61.15, 68.25, 68.36, 100.54, 101.23, 126.25,

126.78, 128.28, 128.37, 128.73, 131.76, 137.83, 145.49, 146.18, 166.63, 166.74, 171.33, 171.49.

MS (ESI): m/z = 500 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{33}NO_8$: C, 64.92; H, 6.66; N, 2.80. Found: C, 65.18; H, 6.69.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 4-Heptyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h)

The product was prepared according to the typical procedure from octanal (**3h**) (0.256 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.572 g (58%); $[\alpha]_D^{20}$ +52.00 (*c* 0.9, $CHCl_3$).

IR (film): 1741, 1696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.0 Hz, 3 H), 1.19–1.41 (complex pattern, 18 H), 1.48 (d, *J* = 7.2 Hz, 3 H), 1.49 (d, *J* = 6.8 Hz, 3 H), 2.23 (s, 3 H), 2.26 (s, 3 H), 3.95 (t, *J* = 5.6 Hz, 1 H), 4.18 (m, 4 H), 5.05 (q, *J* = 7.2 Hz, 1 H), 5.06 (q, *J* = 6.8 Hz, 1 H), 6.32 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.03, 14.06, 16.95, 16.98, 19.12, 19.16, 22.62, 24.70, 29.39, 29.92, 31.92, 32.70, 36.95, 60.94, 61.12, 68.05, 68.09, 101.93, 102.47, 146.00, 146.39, 167.11, 167.41, 171.58, 171.71.

MS (ESI): m/z = 496 $[M + H]^+$.

Anal. Calcd for $C_{26}H_{41}NO_8$: C, 63.01; H, 8.34; N, 2.83. Found: C, 63.17; H, 8.36.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(thien-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4i)

The product was prepared according to the typical procedure from thiophene-2-carbaldehyde (**3i**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.268 g (28%); $[\alpha]_D^{20}$ +33.08 (*c* 1.3, $CHCl_3$).

IR (Nujol): 1737, 1697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.6 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.48 (d, *J* = 7.1 Hz, 3 H), 1.50 (d, *J* = 7.1 Hz, 3 H), 2.36 (s, 3 H), 4.19 (m, 4 H), 5.06 (q, *J* = 7.1 Hz, 1 H), 5.10 (q, *J* = 7.1 Hz, 1 H), 5.42 (s, 1 H), 6.01 (s, 1 H, NH), 6.86 (m, 2 H), 7.05 (dd, *J* = 1.4 Hz, *J* = 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.04, 14.08, 16.96, 17.07, 19.52, 19.79, 34.25, 61.06, 61.17, 68.45, 68.59, 102.89, 103.31, 123.13, 123.46, 126.41, 144.96, 145.64, 151.34, 166.38, 166.44, 171.23, 171.37.

MS (ESI): m/z = 480 $[M + H]^+$.

Anal. Calcd for $C_{23}H_{29}NO_8S$: C, 57.61; H, 6.10; N, 2.92. Found: C, 57.80; H, 6.30.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(thien-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4j)

The product was prepared according to the typical procedure from thiophen-3-carbaldehyde (**3j**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.704 g (73%); $[\alpha]_D^{20}$ +52.35 (*c* 1.7, $CHCl_3$).

IR (film): 1740, 1698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 3 H), 1.26 (t, *J* = 6.6 Hz, 3 H), 1.45 (d, *J* = 7.2 Hz, 3 H), 1.50 (d, *J* = 7.2 Hz, 3 H), 2.32 (s, 3 H), 2.33 (s, 3 H), 4.17 (m, 4 H), 5.03 (q, *J* = 6.8 Hz, 1 H), 5.06 (q, *J* = 7.2 Hz, 1 H), 5.20 (s, 1 H), 6.15 (br s, 1 H, NH), 6.98 (m, 1 H), 7.06 (dd, *J* = 1.2 Hz, *J* = 5.0 Hz,1 H), 7.12 (dd, *J* = 3.0 Hz, *J* = 4.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.05, 14.07, 16.96, 17.08, 19.43, 19.63, 34.33, 61.07, 61.20, 68.30, 68.46, 102.43, 103.00, 120.55, 124.49, 127.69, 145.22, 145.81, 147.50, 166.66, 166.72, 171.35, 171.49.

MS (ESI): m/z = 480 $[M + H]^+$.

Anal. Calcd for $C_{23}H_{29}NO_8S$: C, 57.61; H, 6.10; N, 2.92. Found: C, 57.80; H, 6.30.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(pyridin-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4k)

The product was prepared according to the typical procedure from pyridine-3-carbaldehyde (**3k**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 9:1).

White solid; yield: 0.549 g (58%); mp 127 °C; $[\alpha]_D^{20}$ +74.00 (*c* 1.0, $CHCl_3$).

IR (film): 1741, 1699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 6.8 Hz, 3 H), 1.43 (d, *J* = 7.1 Hz, 3 H), 1.48 (d, *J* = 7.1 Hz, 3 H), 2.33 (s, 3 H), 2.36 (s, 3 H), 4.04 (m, 2 H), 4.18 (m, 2 H), 4.95 (q, *J* = 7.1 Hz, 1 H), 5.00 (q, *J* = 7.1 Hz, 1 H), 5.04 (s, 1 H), 6.90 (s, 1 H, NH), 7.16 (dd, *J* = 4.7 Hz, *J* = 7.7 Hz, 1 H), 7.64 (m, 1 H), 8.36 (m, 1 H), 8.52 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.95, 14.05, 16.89, 17.02, 19.19, 19.41, 37.55, 60.97, 61.29, 68.26, 68.48, 101.99, 102.74, 123.04, 135.92, 143.19, 145.69, 146.59, 147.14, 149.65, 166.28, 166.29, 171.02, 171.51.

MS (ESI): m/z = 475 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{30}N_2O_8$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.91; H, 6.39.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(naphthalen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4l)

The product was prepared according to the typical procedure from naphthalene-2-carbaldehyde (**3l**) (0.312 g, 2 mmol), β-keto ester **1a** (0.808 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over $MgSO_4$ and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.543 g (52%); $[\alpha]_D^{20}$ +49.60 (*c* 1.0, $CHCl_3$).

IR (film): 1744, 1699 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.1 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.39 (d, *J* = 7.1 Hz, 3 H), 1.44 (d, *J* = 7.1 Hz, 3 H), 2.36 (s, 6 H), 3.95 (m, 2 H), 4.16 (m, 2 H), 4.90 (q, *J* = 7.1 Hz, 1 H), 5.02 (q, *J* = 7.1 Hz, 1 H), 5.23 (s, 1 H), 5.87 (s, 1 H, NH), 7.36 (m, 2 H), 7.49 (dd, *J* = 1.8 Hz, *J* = 8.7 Hz, 1 H), 7.68–7.77 (complex pattern, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.53, 13.93, 16.82, 16.93, 18.98, 19.30, 39.70, 60.72, 61.18, 68.01, 68.35, 102.34, 103.26, 124.94, 125.37, 126.52, 127.12, 127.21, 127.28, 127.67, 132.19, 133.16, 144.98, 145.09, 146.07, 166.71, 171.19, 171.79.

MS (ESI): m/z = 524 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{33}NO_8$: C, 66.53; H, 6.35; N, 2.68. Found: C, 66.71; H, 6.37.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 2,6-Dimethyl-4-(6-methoxynaphthalen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4m)

The product was prepared according to the typical procedure from 6-methoxynaphthalene-2-carbaldehyde (**3m**) (0.300 g, 1.6 mmol), β-keto ester **1a** (0.649 g, 3.2 mmol) and Mg_3N_2 (**2**) (0.083 g, 0.8 mmol). The reaction mixture was stirred for 29 h at 90–100 °C, and then at r.t. for an additional 48 h. The crude mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried over $MgSO_4$ and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.224 g (26%); $[\alpha]_D^{20}$ +54.27 (*c* 1.0, $CHCl_3$).

IR (film): 1740, 1691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.42 (d, *J* = 7.1 Hz, 3 H), 1.47 (d, *J* = 7.1 Hz, 3 H), 2.35 (s, 3 H), 2.38 (s, 3 H), 3.89 (s, 3 H), 3.94 (m, 2 H), 4.18 (m, 2H), 4.91 (q, *J* = 7.1 Hz, 1 H), 5.01 (q, *J* = 7.1 Hz, 1 H), 5.19 (s, 1 H), 6.16 (s, 1 H, NH), 7.01–7.13 (m, 2 H), 7.46 (dd, *J* = 1.8 Hz, *J* = 8.5 Hz, 1 H), 7.61 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.72, 14.03, 16.90, 17.03, 18.40, 19.74, 39.52, 55.23, 60.85, 61.16, 68.15, 68.42, 102.96, 103.81, 105.51, 118.17, 126.12, 126.41, 127.73, 128.74, 129.27, 133.18, 142.91, 144.38, 145.44, 157.11, 166.72, 166.78, 171.20, 171.61.

MS (ESI): *m*/*z* = 554 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{35}NO_9$: C, 65.09; H, 6.37; N, 2.53. Found: C, 65.30; H, 6.39.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl] 4-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4n)

The product was prepared according to the typical procedure from *tert*-butyl-3-formyl-1*H*-indole-1-carboxylate (**3n**) (0.492, 2.0 mmol), β-keto ester **1a** (0.808 g, 2.0 mmol) and Mg_3N_2 (**2**) (0.100 g, 1.0 mmol). The reaction mixture was stirred for 29 h at 90–100 °C, and then at r.t. for an additional 48 h. The crude mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried over $MgSO_4$ and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.272 g (22%); $[\alpha]_D^{20}$ +38.34 (*c* 0.8, $CHCl_3$).

IR (CH_2Cl_2): 1732, 1699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.1 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 1.43 (d, *J* = 7.1 Hz, 3 H), 1.64 (s, 9 H), 2.28 (s, 3 H), 2.35 (s, 3 H), 3.80–3.99 (complex pattern, 2 H), 4.19 (m, 2 H), 4.91 (q, *J* = 7.1 Hz, 1 H), 5.00 (q, *J* = 7.1 Hz, 1 H), 5.34 (s, 1 H), 6.59 (br s, 1 H, NH), 7.02 (d, *J* = 2.4 Hz, 1 H), 7.15–7.24 (complex pattern, 2 H), 7.38 (s, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.60, 13.98, 16.82, 16.89, 19.07, 19.47, 28.13, 30.70, 60.76, 61.20, 68.11, 68.38, 83.24, 102.72, 110.87, 114.80, 120.44, 121.98, 123.55, 124.40, 129.66, 144.48, 145.69, 166.78, 171.14, 171.80.

MS (ESI): *m*/*z* = 613 $[M + H]^+$.

Anal. Calcd for $C_{32}H_{40}N_2O_{10}$: C, 62.73; H, 6.58; N, 4.57. Found: C, 62.91; H, 6.60.

Bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4o)

The product was prepared according to the typical procedure from 3-nitrobenzaldehyde (**3c**) (0.302 g, 2 mmol), β-keto ester **1b** (0.960 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The mixture was stirred for 28 h at 90–100 °C. The crude mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$ and purified by flash chromatography (Et_2O–cyclohexane, 30:70).

Yellow solid; yield: 0.589 g (50%); mp 151 °C; $[\alpha]_D^{20}$ –26.25 (*c* 0.8, $CHCl_3$).

IR (Nujol): 1700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.49 (d, *J* = 7.1 Hz, 3 H), 0.58 (d, *J* = 7.1 Hz, 3 H), 0.76 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.72–2.08 (complex pattern, 18 H), 2.33 (s, 3 H), 2.43 (s, 3 H), 4.67 (dt, *J* = 4.3 Hz, *J* = 11.2 Hz, 2 H), 5.10 (s, 1 H), 5.64 (br s, 1 H, NH), 7.38 (t, *J* = 8.1 Hz, 1 H), 7.62 (dt, *J* = 1.4 Hz, *J* = 8.1 Hz, 1 H), 8.01 (ddd, *J* = 1.0 Hz, *J* = 2.4 Hz, *J* = 5.9 Hz, 1 H), 8.14 (t, *J* = 2.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.64, 16.87, 19.61, 20.91, 22.06, 22.85, 23.91, 25.52, 31.46, 34.35, 39.96, 41.05, 41.58, 47.27, 47.54, 73.33, 74.10, 103.19, 104.10, 121.23, 123.39, 128.68, 134.60, 144.25, 145.37, 148.05, 150.13, 166.69.

MS (ESI): *m*/*z* = 595 $[M + H]^+$.

Anal. Calcd for $C_{35}H_{50}N_2O_6$: C, 70.68; H, 8.47; N, 4.71. Found: C, 70.93; H, 8.50.

Bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4p)

The product was prepared according to the typical procedure from 2-nitrobenzaldehyde (**3d**) (0.302 g, 2 mmol), β-keto ester **1b** (0.960 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The mixture was stirred for 24 h at 90–100 °C, then at 120 °C for 8 h, and then at r.t. for an additional 48 h. The crude mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$ and purified by flash chromatography (Et_2O–cyclohexane, 30:70).

Yellow solid; yield: 287 mg (25%); mp 93 °C; $[\alpha]_D^{20}$ +20.87 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 1687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.46 (d, *J* = 7.1 Hz, 3 H), 0.51 (d, *J* = 7.1 Hz, 3 H), 0.65 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 6 H), 0.88 (d, *J* = 7.1 Hz, 9 H), 0.90–1.94 (complex pattern, 12 H), 2.27 (s, 3 H), 2.34 (s, 3 H), 4.64 (dq, *J* = 4.3 Hz, *J* = 9.8 Hz, 2 H), 5.78 (br s, 1 H, NH), 5.96 (s, 1 H), 7.23 (m, 1 H), 7.46 (dt, *J* = 1.2 Hz, *J* = 7.1 Hz, 1 H), 7.56 (dd, *J* = 1.2 Hz, *J* = 7.9 Hz, 1 H), 7.81 (dd, *J* = 1.2 Hz, *J* = 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.58, 16.34, 19.71, 19.99, 20.62, 20.99, 20.98, 22.84, 23.54, 25.24, 26.33, 31.42, 31.50, 34.08, 34.18, 39.68, 40.22, 40.72, 46.14, 46.40, 73.37–73.42, 74.16–74.21, 103.92, 104.45, 124.21, 126.61, 131.60, 132.76, 143.45, 143.76, 145.00, 147.42, 166.80, 166.97.

MS (ESI): *m*/*z* = 595 $[M + H]^+$.

Anal. Calcd for $C_{35}H_{50}N_2O_6$: C, 70.68; H, 8.47; N, 4.71. Found: C, 70.96; H, 8.80.

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References

(1) (a) Yamamoto, T.; Niwa, S.; Ohno, S.; Onishi, T.; Matsueda, H.; Koganei, H.; Uneyama, H.; Fujita, S.; Takeda, T.; Kito,

M.; Ono, Y.; Saitou, Y.; Takahara, A.; Iwata, S.; Shoji, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 798. (b) Dagnino, L.; Li-Kwong-Ken, M. C.; Wolowyk, M. W.; Wynn, H.; Triggle, C. R.; Knaus, E. E. *J. Med. Chem.* **1986**, *29*, 2524. (c) Dagnino, L.; Li-Kwong-Ken, M. C.; Wynn, H.; Wolowyk, M. W.; Triggle, C. R.; Knaus, E. E. *J. Med. Chem.* **1987**, *30*, 640.

(2) Choi, S.-J.; Cho, J.-H.; Im, I.; Lee, S.-D.; Jang, J.-Y.; Oh, Y.-M.; Jung, Y.-K.; Jeon, E.-S.; Kim, Y.-C. *Eur. J. Med. Chem.* **2010**, *45*, 2578.

(3) Iwanami, M.; Shibanuma, T.; Fujimoto, M.; Kaway, R.; Tamazawa, K.; Takenaka, T.; Takahashi, K.; Murakami, M. *Chem. Pharm. Bull.* **1979**, *27*, 1426.

(4) Arhancet, G. B.; Woodard, S. S.; Dietz, J. D.; Garland, D. J.; Wagner, G. M.; Iyanar, K.; Collins, J. T.; Blinn, J. R.; Numann, R. E.; Hu, X.; Huang, H.-C. *J. Med. Chem.* **2010**, *53*, 4300.

(5) (a) Zhang, B.-l.; He, W.; Shi, X.; Huan, M.-l.; Huang, Q.-j.; Zhou, S.-y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 805. (b) Briede, J.; Daija, D.; Stivrina, M.; Duburs, G. *Cell. Biochem. Funct.* **1999**, *17*, 89. (c) Klusa, V. *Drugs Future* **1995**, *20*, 135.

(6) Evans, C. G.; Jinwal, U. K.; Makley, L. N.; Dickey, C. A.; Gestwicki, J. E. *Chem. Commun.* **2011**, *47*, 529.

(7) Chang, C.-C.; Cao, S.; Kang, S.; Kai, L.; Tian, X.; Pandey, P.; Dunne, S. F.; Luan, C.-H.; Surmeier, D. J.; Silverman, R. B. *Bioorg. Med. Chem.* **2010**, *18*, 3147.

(8) (a) Che, J.; Lam, Y. *Synlett* **2010**, 2415. (b) Hoffman, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. (c) Rueping, M.; Suiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (d) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

(9) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.

(10) (a) Bridgwood, K. L.; Veitch, G. E.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3627. (b) Veitch, G. E.; Bridgwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623. (c) Veitch, G. E.; Bridgwood, K. L.; Rands-Trevor, K.; Ley, S. V. *Synlett* **2008**, 2597.

(11) (a) Sobolev, A.; Franssen, M. C. R.; Vigante, B.; Cekavicus, B.; Makarova, N.; Duburs, G.; de Groot, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3251. (b) Sobolev, A.; Franssen, M. C. R.; Vigante, B.; Cekavicus, B.; Zhalubovskis, R.; Kooijman, H.; Spek, A. L.; Duburs, G.; de Groot, A. *J. Org. Chem.* **2002**, *67*, 401. (c) Sobolev, A.; Franssen, M. C. R.; Makarova, N.; Duburs, G.; de Groot, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4559. (d) Boatto, G.; Nieddu, M.; Faedda, M. V.; De Caprariis, P. *Chirality* **2003**, *15*, 494. (e) de Castro, M.; Salazar, L.; Sinisterra, J. *Tetrahedron: Asymmetry* **1997**, *8*, 857.

(12) Gianotti, M.; Martelli, G.; Spunta, G.; Campana, E.; Panunzio, M.; Mendozza, M. *Synth. Commun.* **2000**, *30*, 1725.