Supporting Information for the Paper

A Combinatorial Scaffold Approach Based Upon a Multicomponent Reaction

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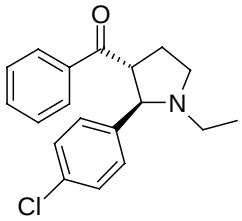
General

All the commercial available compounds were used without further purification. Magnesium iodide (MgI_2 >99%) (Riedel-de Haën) and potassium *tert*-butoxide (KO^tBu >95%) (Aldrich) were stored over an argon atmosphere and quickly weighted before use. Et_2Al-I (25 wt% solution in toluene) was purchased from Acros. Tetrahydrofuran (THF, bottle with crown-cap), Dimethylsulfoxide (DMSO, bottle with crown-cap) and Acetonitrile (CH_3CN, stored over 4Å MS) (Fluka) were used without further purification. All reactions were carried out in vials purchased from Supelco.

Purification of compounds was achieved by flash chromatography using CH_2Cl_2/MeOH as the eluting mixture. All ^1H and ^{13}C-NMR spectra were recorded using a Varian XL 400MHz. NMR spectra were recorded in $CDCl_3$ solutions; chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.2±0.06 ppm). Diastereoisomeric ratios were determined by ^1H-NMR analysis. UV-purity was determined using a Waters HPLC-system (600E pump, 2700 autosampler, 996 PDA-detector, UV scan: 190-450 nm).

General Procedure for the MgI_2-Promoted One-Pot Three-Component Synthesis of Pyrrolidines

***anti*-3-Benzoyl-2-(4-chloro-phenyl)-1-ethyl-pyrrolidine (1)**



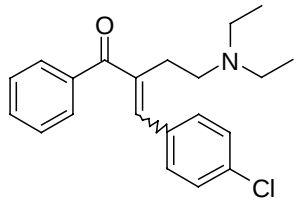
In a 7 mL vial, at room temperature, 4-chlorobenzaldehyde (140 mg; 1.0 mmoL; 1.0 eq.), MgI_2 (278 mg; 1.0 mmol; 1.0 eq) and cyclopropyl-phenyl-ketone (146 mg; 138 μL; 1.0 mmol; 1.0 eq.) were added sequentially to a solution of ethylamine (0.5 mL; 1.0 mmol; 1.0 eq.; 2.0M in THF) in THF (4.0 mL) and the resulting mixture was shaken at 80 °C. After 6h, the reaction was cooled to ambient temperature and then quenched with saturated aqueous $Na_2S_2O_3$ solution (2 mL). The mixture was extracted with EtOAc (5 mL) and the organic phase washed with a saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL), dried over Na_2SO_4, filtered and concentrated. The corresponding crude reaction mixture, consisting of a >99:1 mixture of diastereoisomers, was purified by flash chromatography on silica gel (CH_2Cl_2+MeOH 4%) to afford the major diastereoisomer **1** (218 mg; 69% yield) as an oil.

Data for *anti* diastereoisomer **1**: R_f : 0.6 (silica gel, CH_2Cl_2+MeOH 5%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.76-7.73 (m, 2H); 7.51-7.46 (m, 1H); 7.38-7.32 (m, 4H); 7.25-7.21 (m, 2H); 3.84-3.74 (m, 2H); 3.42-3.34 (m, 1H); 2.61 (dq, 1H, *J*=7.2 Hz and 4.6 Hz); 2.45-2.34 (m, 2H); 2.14 (dq, 1H, *J*=7.1 Hz and 4.9 Hz); 2.03-1.96 (m, 1H); 0.87 (t, 3H, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 200.7; 141.3; 136.7; 133.3; 133.1; 129.3 (2C); 128.8 (2C); 128.7 (3C); 128.7; 71.0; 55.2; 52.5; 47.9; 28.8; 13.8. HRMS (Ion Mode: FAB$^+$) calcd for $C_{19}H_{20}ClNO$ (M^++1): 314.1311, found: 314.1300.

The *anti* stereochemistry was determined by *NOESY* experiments on a pure stereoisomer **1**. **No** *NOESY* correlations were observed between $\mathbf{H_2 \rightarrow H_3}$.

General Procedure for the Et_2AlI-Promoted One-Pot Three-Component Synthesis of -(Aminoethyl)- , -Enones

(*E/Z*)-2-(4-Chloro-benzylidene)-4-(2-diethylamino-ethyl)-1-phenyl-butan-1-one (2a and 2b)

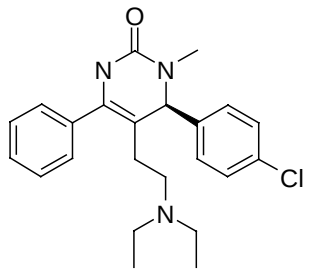


In a 7 mL vial, at room temperature, 4-chloro-benzaldehyde (140 mg; 1.0 mmol; 1.0 eq.), Et_2Al-I (1.17 mL; 1.2 mmol; 1.2 eq.) and cyclopropyl-phenyl-ketone (146 mg; 138 μL; 1.0 mmol; 1.0 eq.) were added sequentially to a solution of diethylamine (73 mg; 104 μL; 1.0 mmol; 1.0 eq.) in CH_3CN (4.0 mL). The resulting mixture was vigorously shaken at room temperature for 15 h and then KO^{t}Bu (168 mg, 1.5 mmol, 1.5 eq.) was added. After 2h the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (2 mL) and the mixture was extracted with EtOAc (5 mL). The organic phase was washed with a saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL), dried over Na_2SO_4, filtered and concentrated. The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2+MeOH 4%) to afford an 85:15 mixture of *E/Z* stereoisomers **2a**/**2b** (204 mg; 60% yield) as an oil.

Data for the *E/Z* stereoisomeric mixture **2a**/**2b**: R_f : 0.38 (silica gel, CH_2Cl_2+MeOH 5%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.86-7.83 (m, 2H, *Z*); 7.81-7.77 (m, 2H, *E*); 7.58-7.53 (m, 1H, *E*); 7.49-7.43 (m, 3H); 7.40-7.34 (m, 4H, *E*); 7.31-7.29 (m, 2H, *Z*); 7.27-7.25 (m, 2H, *Z*); 7.06 (s, 1H, *E*); 7.05-7.02 (m, 2H, *Z*); 6.76 (s, 1H, *Z*); 2.96-2.89 (m, 2H); 2.74-2.68 (m, 6H); 2.63-2.50 (m, 8H); 1.01 (t, 6H, *J*=7.1 Hz, *E*); 0.97 (t, 6H, *J*=7.2 Hz, *Z*). ^{13}C NMR (100 MHz, $CDCl_3$) 200.0 (*Z*); 198.8 (*E*); 141.3; 141.1; 139.9; 138.5; 136.1; 134.6; 134.5; 134.2; 133.4; 132.2; 130.6; 130.0; 129.9; 129.6; 129.0; 128.6; 128.5; 128.4; 51.9 (*Z*); 51.2 (*E*); 46.8 (*E*); 46.5 (*Z*); 34.7 (2C, *Z*); 25.7 (2C, *E*); 11.7 (2C, *E*); 11.5 (2C, *Z*). HRMS (Ion Mode: FAB$^+$) calcd. for $C_{21}H_{24}ClNO$ (M^++1): 342.1624, found: 342.1629.

The diastereoselectivity was determined by integration of the peaks at 7.06 (**2a**) and 6.76 (**2b**).

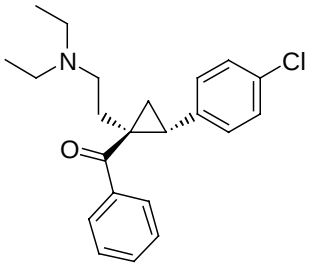
6-(4-Chloro-phenyl)-5-(2-diethylamino-ethyl)-1-methyl-4-phenyl-5,6-dihydro-3*H*-pyrimidin-2-one (3)



In a 20 mL vial, at room temperature, NaOEt (408 mg; 6.0 mmol; 6.0 eq) and N-methylurea (444 mg; 6.0 mmol; 6.0 eq.) were added sequentially to a solution of **2** (341 mg; 1.0 mmol; 1.0 eq.) in DMF (10.0 mL) and the resulting mixture was vigorously shaken for 12h at room temperature. The reaction was then quenched with few drops of water and the mixture was washed with a saturated aqueous $NaHCO_3$ solution (3 mL), brine (3 mL) and extracted with EtOAc (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2+MeOH 4%→6%) to afford the substituted pyrimidin-2-one **3** (193 mg; 48% yield) as an oil.

Data for **3**: R_f : 0.41 (silica gel, CH_2Cl_2+MeOH 5%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.41-7.24 (m, 9H); 6.60 (s, 1H, *NH*); 4.78 (s, 1H); 2.74 (s, 3H); 2.36 (ddd, 1H, *J*=15.8 Hz and 10.5 Hz and 5.2 Hz); 2.26 (q, 4H, *J*=7.2 Hz); 2.18 (ddd, 1H, *J*=15.5 Hz and 10.2 Hz and 5.5 Hz); 2.04 (ddd, 1H, *J*=15.9 Hz and 10.5 Hz and 5.3 Hz); 1.75 (ddd, 1H, *J*=15.4 Hz and 10.3 Hz and 5.2 Hz); 0.80 (t, 6H, *J*=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 153.2; 140.1; 134.8; 134.3; 132.5; 129.3; 129.1; 129.0; 128.9; 128.7; 107.8; 66.3; 51.3; 46.8; 32.8; 25.9; 11.7. HRMS (Ion Mode: FAB^+) calcd for $C_{23}H_{28}ClN_3O$ (M^++1): 398.2000, found: 398.2004.

***anti*-1-Benzoyl-2-(4-chlorophenyl)-1-(2-diethylamino-ethyl)-cyclopropane (4)**



In a 20 mL dry vial, at room temperature, trimethylsulfoxonium iodide (616 mg, 2.8 mmol, 2.8 eq.) was added to a solution of NaH (110 mg, 2.4 mmol, 2.4 eq.; 55-60% in mineral oil, pre-washed with heptane) in dry DMSO (5.0 mL). The reaction mixture

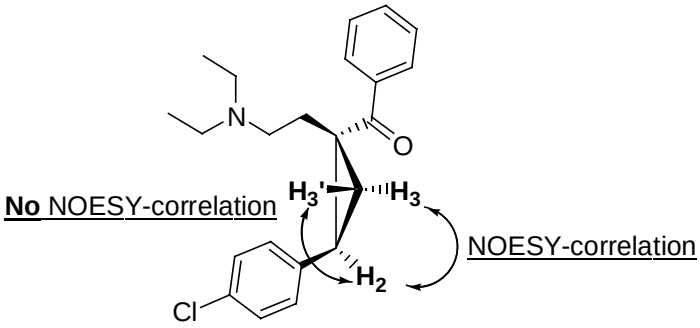
was flushed under a stream of argon and the vial was quickly capped. After 1 h shaking, the temperature was raised up to 60 C and the vial was shaken for another hour. A solution of **2** (341 mg; 1.0 mmol; 1.0 eq.) in dry DMSO (2.0 mL) was then added drop wise to the suspension, and the mixture was kept at 60 C. After 1.5 hours the mixture was cooled to room temperature, quenched with water (20 mL) and extracted with EtOAc (3 25 mL). The collected organic phases were dried over Na_2SO_4, filtered and concentrated. The corresponding crude product was purified by column chromathography (CH_2Cl_2+MeOH 6%) to afford **4** (270 mg, 76%) as an oil.
Data for **4**: R_f: 0.46 (silica gel, CH_2Cl_2+MeOH 10%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.82-7.78 (m, 2H); 7.53-7.48 (m, 1H); 7.46-7.41 (m, 2H); 7.35-7.31 (m, 2H); 7.26-7.21 (m, 2H); 2.64 (dd, 1H, *J*=9.0 Hz and *J*=6.8 Hz); 2.32-2.24 (m, 1H); 2.21-2.12 (m, 5H); 1.92-1.86 (m, 1H); 1.85-1.78 (m, 1H); 1.51-1.42 (m, 1H) 1.32 (dd, 1H, *J*=6.8 Hz and *J*=5.1 Hz) 0.66 (t, 6H, *J*=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 202.0; 137.4; 135.7; 132.8; 132.1; 130.3; 128.8; 128.6; 128.5; 50.4; 46.7; 37.0; 29.6; 28.5; 15.9; 11.0. HRMS (Ion Mode: FAB^+) calcd for $C_{22}H_{26}ONCl$ (M^++1): 356.1781, found: 356.1794.

Stereochemical assignment of compound 4 *via NOESY* and *NOE* spectroscopy

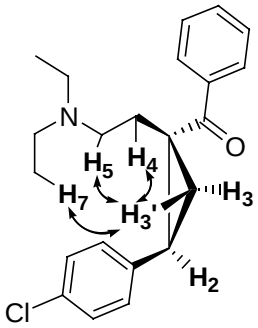
The *anti/syn* stereochemistry was determined by *NOESY*/*NOE* experiments on pure **4** (see figure below). The identity of proton $\mathbf{H_3}$ was determined through a *NOESY* experiment, by a correlation peak with $\mathbf{H_2}$ (strong *NOE*-correlation $\mathbf{H_2}\rightarrow\mathbf{H_3}$ and weak *NOE*-correlation $\mathbf{H_2}\rightarrow\mathbf{H_{3'}}$). Further *NOE*-correlations were observed between $\mathbf{H_{3'}}\rightarrow\mathbf{H_4}$, $\mathbf{H_{3'}}\rightarrow\mathbf{H_5}$ and $\mathbf{H_{3'}}\rightarrow\mathbf{H_7}$.

Anti stereoisomer

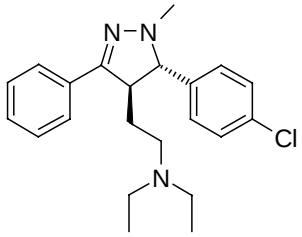
NOESY-correlation of H_2



NOE-correlation of anti-$H_{3'}$



***anti/syn*-5-(4-Chloro-phenyl)-4-(2-diethylamino-ethyl)-1-methyl-3-phenyl-4,5-dihydro-1*H*-pyrazole (5a/5b)**



In a 20 mL vial, at room temperature, methyl-hydrazine (268 µL; 230 mg; 5.0 mmol; 5.0 eq.) and $InCl_3$ (88 mg; 0.4 mmol; 0.4 eq.) were added to a solution of **2** (341 mg; 1.0 mmol; 1.0 eq.) in absolute EtOH (10.0 mL). The resulting mixture was vigorously shaken for 10 h at 80 ºC and then quenched with a saturated aqueous $NaHCO_3$ solution (3 mL), extracted with EtOAc (15 mL) and washed with brine (3 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The corresponding crude reaction product was purified by flash chromatography on silica gel

(CH_2Cl_2+MeOH 4%→6%) to give a 85:15 mixture of a *anti/syn* mixture of substituted dihydro-pyrazoles **5a**/**5b** (264 mg; 72% yield) as an oil.

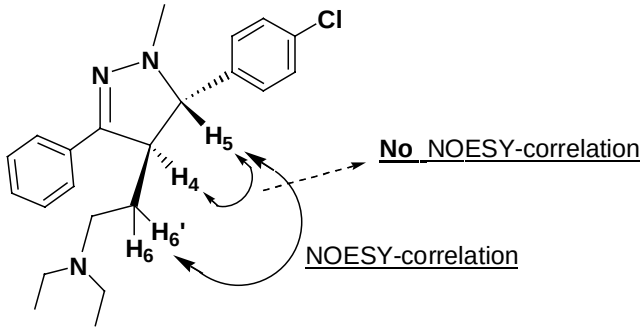
Data for the *anti/syn* mixture of dihydropyrazoles **5a/5b**: R_f : 0.31 (silica gel, CH_2Cl_2+MeOH 5%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.75-7.69 (m, 2H, *syn*); 7.59-7.56 (m, 2H, *anti*); 7.37-7.24 (m, 14H); 4.17 (d, 1H, *J*=9.4 Hz, *syn*); 3.98 (d, 1H, *J*=10.2 Hz, *anti*); 3.59-3.50 (m, 2H); 2.79 (s, 3H, *syn*); 2.78 (s, 3H, *anti*); 2.49-2.31 (m, 6H, *anti*); 2.28-2.21 (m, 2H, *syn*); 2.18-2.09 (m, 2H, *syn*); 2.01-1.86 (m, 2H); 1.81-1.72 (m, 2H); 1.61-1.52 (m, 1H, *syn*); 1.38-1.29 (m, 1H, *syn*); 0.87 (t, 6H, *J*=7.2 Hz, *anti*); 0.77 (t, 6H, *J*=7.2 Hz, *syn*). ^{13}C NMR (100 MHz, $CDCl_3$) 155.4 (*syn*); 151.9 (*anti*); 139.8; 135.4; 133.8; 133.6; 133.1; 132.4; 129.8; 129.3; 129.1; 128.9; 128.8; 128.7; 128.5; 127.9; 126.6; 126.3; 77.5 (*anti*); 76.2 (*syn*); 54.1 (*anti*); 50.4 (*syn*); 50.1 (*2C*); 48.2 (*syn*); 46.9 (*anti*); 46.7 (*syn*); 41.6 (*syn*); 40.8 (*anti*); 28.5 (*anti*); 23.9 (*syn*); 11.7 (*anti*). HRMS (Ion Mode: FAB^+) calcd for $C_{22}H_{28}ClN_3$ (M^++1): 370.2050, found: 369.2041.

Stereochemical assignment of compounds 5a/5b *via NOESY* spectroscopy

The *anti*/*syn* stereochemistry was determined by *NOESY* experiments on a 3:1 mixture of both stereoisomers **5a** (major) and **5b** (minor) (see figure below). In the major isomer (*anti*) strong *NOESY* correlations were observed between $\mathbf{H_5}$→$\mathbf{H_6}$ and $\mathbf{H_5}$→$\mathbf{H_6}$', furthermore **No** *NOESY* correlations were observed between $\mathbf{H_4}$→$\mathbf{H_5}$. In the minor isomer (*syn*) strong *NOESY* correlations were observed between $\mathbf{H_4}$→$\mathbf{H_5}$**,** but **No** *NOESY* correlations were observed between $\mathbf{H_5}$→$\mathbf{H_6}$ and $\mathbf{H_5}$→$\mathbf{H_6}$'.

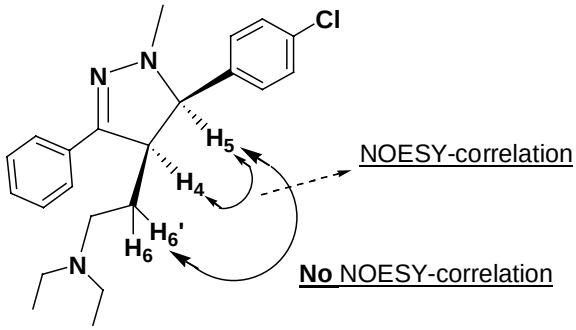
***Anti* stereoisomer**

(major)

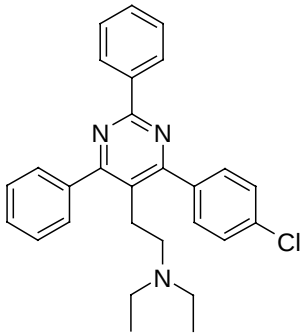


***Syn* stereoisomer**

(minor)



4-(4-Chloro-phenyl)-5-(2-diethylamino-ethyl)-2,6-diphenyl-pyrimidine (6)

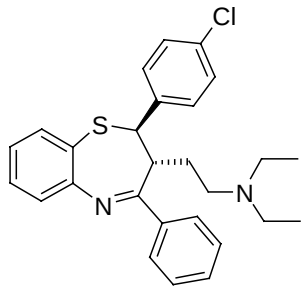


In a 20 mL vial, at room temperature, benzamidine (720 mg; 6.0 mmol; 6.0 eq.) was added to a solution of **2** (341 mg; 1.0 mmol; 1.0 eq.) in DMF (10.0 mL). The resulting mixture was vigorously shaken for 12h at 100 ºC under air atmosphere. The reaction was then quenched with few drops of water and the mixture was washed with a saturated aqueous $NaHCO_3$ solution (3 mL), brine (3 mL) and extracted with EtOAc (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The corresponding crude reaction product was purified by flash chromatography on silica

gel (CH_2Cl_2+MeOH 3%) to afford the substituted pyrimidine **6** (236 mg; 53% yield) as a solid.

Data for **6**: M.p.= 90.5-92.3 ºC (uncryst.); R_f: 0.33 (silica gel, CH_2Cl_2+MeOH 5%); ^{1}H NMR (400 MHz, $CDCl_3$) 8.53-8.45 (m, 2H); 7.66-7.59 (m, 4H); 7.53-7.48 (m, 5H); 7.46-7.42 (m, 3H); 2.98-2.92 (m, 2H); 2.25-2.18 (m, 2H); 2.14 (q, 4H, *J*=7.2 Hz); 0.59 (t, 6H, *J*=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 168.2; 166.7; 161.7; 139.3; 138.1; 137.9; 137.7; 135.3; 130.6; 130.5; 129.2; 128.9; 128.8; 128.7; 128.6; 128.5; 51.5; 46.9; 25.2; 11.8. HRMS (Ion Mode: FAB$^+$) calcd for $C_{28}H_{28}ClN_3$ (M^++1): 442.2050, found: 442.2046.

***anti*-2-(4-Chloro-phenyl)-3-(2-diethylamino-ethyl)-4-phenyl-2,3-dihydro-benzo-[*b*]-[1,4]-thiazepine (7)**



In a 20 mL vial, at room temperature, 2-aminothiophenol (534 µL; 625 mg; 5.0 mmol; 5.0 eq.) and p-toluenesulfonic acid monohydrate (190 mg; 1.0 mmol; 1.0 eq.) were added to a solution of **2** (341 mg; 1.0 mmol; 1.0 eq.) in toluene (10.0 mL) in the presence of 4Å molecular sieves. The resulting mixture was refluxed for 24h and then quenched with saturated aqueous $NaHCO_3$ solution (3 mL), extracted with EtOAc (15 mL) and washed with brine (3 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The corresponding crude reaction product was purified by flash chromatography on silica gel (CH_2Cl_2+MeOH 1% to 3%) to give one diastereoisomer of the substituted dihydro-benzothiazepine **7** (201 mg; 45% yield) as an oil.

Data for **7**: R_f: 0.38 (silica gel, CH_2Cl_2+MeOH 5%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.88-7.83 (m, 2H); 7.54-7.44 (m, 5H); 7.37-7.31 (m, 1H); 7.28-7.22 (m, 2H); 7.14-7.08 (m, 3H); 4.88 (d, 1H, *J*=11.5 Hz); 3.46-3.38 (m, 1H); 2.18-2.08 (m, 2H); 2.06-1.91 (m, 4H); 1.76-1.66 (m, 1H); 1.24-1.14 (m, 1H); 0.68 (t, 6H, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 175.0; 152.1; 142.1; 139.3; 135.4; 133.7; 130.4; 130.0; 129.2;

128.7; 127.9; 127.8; 125.3; 124.7; 121.9; 65.4; 50.6; 47.6; 46.8; 28.3; 11.8. HRMS (Ion Mode: FAB^+) calcd for $C_{27}H_{29}ClN_2S$ (M^++1): 449.1818, found: 449.1819.

Stereochemical assignment of compounds 7 *via NOESY* spectroscopy

The *anti*/*syn* stereochemistry was determined by NOESY experiments on the pure diastereoisomer **7** (see figure below). Strong *NOESY* correlations were observed between **H_2→H_4/$H_{4'}$;** furthermore **No** *NOESY* correlations were observed between **H_2→H_3**.