Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Exploiting neighboring group interactions for the self-selection of a catalytic unit

Giulio Gasparini, Leonard J. Prins, Paolo Scrimin**

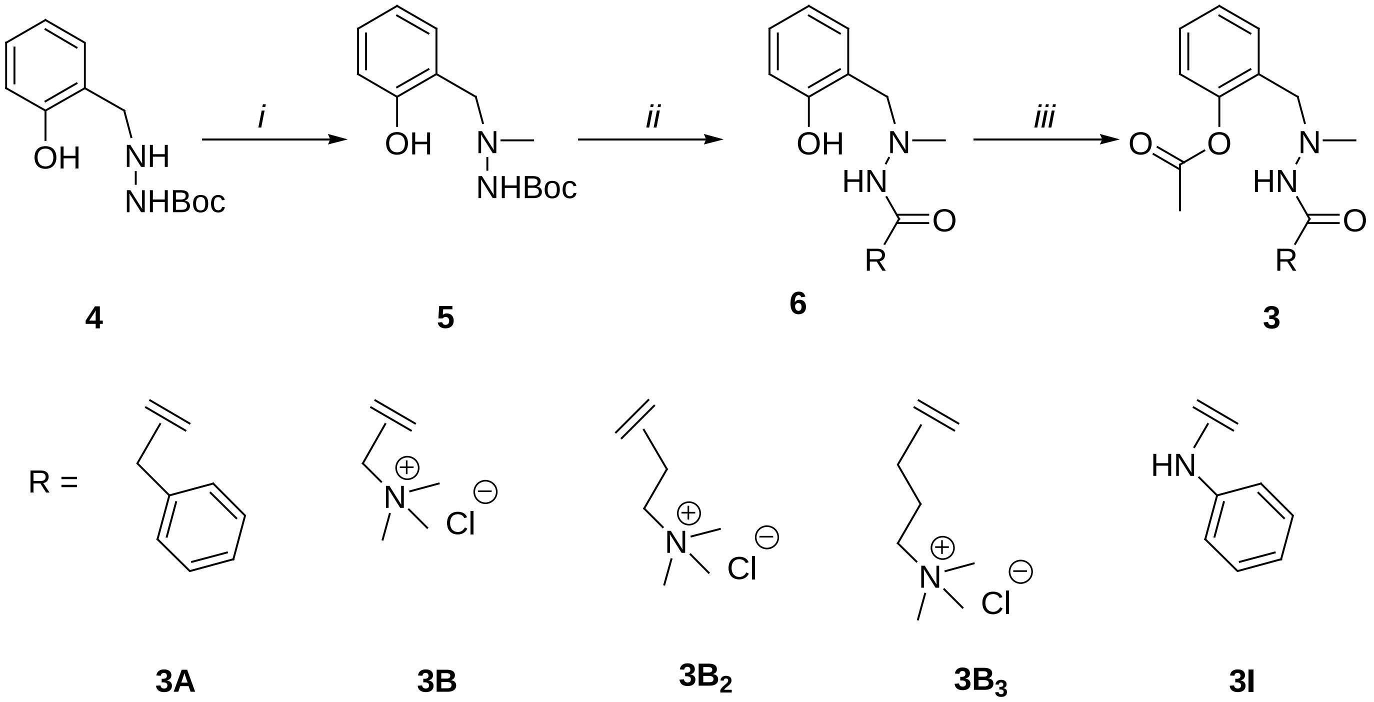
Department of Chemical Sciences, University of Padova
and CNR ITM, Padova Section
Padova, Italy
Via Marzolo 1, 3513 Padova, Italy
Fax: (+39) 0498265239
E-mail: leonard.prins@unipd.it; paolo.scrimin@unipd.it

Contents:

1. Synthesis and characterization of compounds **3A, 3B, $3B_2$, $3B_3$ and 3I**. SI-2
2. Synthesis and characterization of hydrazide **B_3** SI-7
3. HSQC spectra of scaffolds **1** and **2** with hydrazide library **A-I**. SI-8
4. Fingerprint parts of the ^{1}H NMR spectra used for determination of the amplification. SI-10
5. Plot of log k_{obs} vs pH for the hydrolysis of compounds **3A** and **3B**. SI-12
6. Methanolysis of compounds **3B**, **$3B_2$**, and **$3B_3$** SI-13
7. Methanolysis of compound **3B** at different concentrations SI-14

1. Synthesis and characterization of compounds 3A, 3B, $3B_2$, $3B_3$ and 3I.

A synthetic scheme was used that allows a very facile access to compounds **3** via the common intermediate **5**.



Scheme SI-1. (i) CH_3I, 60°C, CH_3CN, (ii) *1.* HCl,MeOH. *2.* HOBT, EDC, R-COOH, CH_3CN, (iii) acetic anhydride, CH_3CN.

Compound 5. Compound **4**[1] (1.1g, 4.61mmol) was dissolved in CH_3CN and the resulting clear solution was transferred in a pyrex bottle with a screw cap. After addition of methyl iodide (3.5 ml, 56.2 mmol) the solution was stirred at 60 °C for 5h, after which the solvent was evaporated under reduced pressure. The resulting solid was crystallized (EtOAc) to give **5** as a white solid (541mg, 47% yield).

^{1}H-NMR (250 MHz, CD_3CN) δ (ppm): 10.34-9.94 (m, 2H), 7.09 (dd, *J* = 8.18, 3.42 Hz, 1H), 6.95 (t, *J* = 7.50, 7.50 Hz, 1H), 4.67 (s, 2H), 3.20 (s, 3H), 1.36 (s, 9H).
^{13}C-NMR (62.5 MHz, CD_3CN) δ (ppm): 157.25, 133.78, 132.92, 121.22, 116.50, 85.26, 60.87, 46.47, 27.98, 25.48.
ESI-MS(+) MeOH+0.1%HCOOH: $[M+H]^+$ 253m/z
HPLC (Jupiter Proteo 4u 250x4.60x4u, flow=0.8ml/min, 0-15min 10-90% ACN+0.1%TFA, 15-25min 90%ACN+0.1%TFA, λ=226nm): 18.8 min

---

[1] H. Zhao, N. Neamati, S. Sunder, H. Hong; S. Wang, G. W. A. Milne, Y. Pommier, T. R. Burke, Jr.. *J. Med. Chem*, **1997**, *40,* 937-941.

General procedure for the synthesis of compounds 6

Compound **5** (300 mg, 1.19mmol) was dissolved in 25ml of a 1.75 M solution of HCl in MeOH. After one night the solvent was evaporated, which yielded BOC-deprotected **5** in quantitative yield, which was used as such.

^{1}H-NMR (250 MHz, CD_3CN) δ (ppm): 7.70-7.06 (m, 2H), 6.95-6.82 (m, 2H), 4.30 (s, 2H), 2.84 (s, 3H)

^{13}C-NMR (62.5 MHz, CD_3CN) δ (ppm): 157.71, 133.62, 132.53, 120.93, 117.73, 116.40, 60.32, 44.72

ESI-MS(+) MeOH+0.1%HCOOH: $[M+H]^+$ 153m/z

The commercial (except for **7** and **9**, see below) carboxylic acid (1.5 eq.) was dissolved in anhydrous CH_3CN and HOBT (2eq) was added. After stirring the resulting suspension for 20 minutes in an ice bath, EDC (2 eq) was added. Stirring was continued for 15 minutes at 0 ºC and at room temperature for 15 minutes. After renewed cooling to 0 °C, a solution of the BOC-deprotected **5** (1 eq) and Et_3N (6eq) in CH_3CN was added dropwise. The reaction mixture was stirred at 0 °C for 4h and one night at room temperature. Subsequently, the solvent was removed under reduced pressure and the residue was purified by chromatography.

Compound 6A

^{1}H-NMR (250 MHz, CD_3CN) δ (ppm): 7.37-7.15 (m, 6H), 7.12-7.01 (m, 1H), 6.84-6.73 (m, 2H), 3.96 (s, 2H), 3.44 (s, 2H), 2.55 (s, 3H)

^{13}C-NMR (62.5 MHz, CD_3CN) δ (ppm): 170.47, 158.15, 135.90, 131.04, 130.69, 130.05, 129.46, 127.83, 121.80, 120.20, 117.15, 62.39, 43.15, 41.29

ESI-MS(+) MeOH+0.1%HCOOH: $[M+H]^+$ 271 m/z, $[M+Na]^+$ 293 m/z,

HPLC (Jupiter Proteo 4u 250x4.60x4u, flow=0.8ml/min, 0-15min 10-90% ACN+0.1%TFA, λ=280nm): 16.11 min

Compound 6B

^{1}H-NMR first isomer (60%) (250 MHz, CD_3OD) δ (ppm): 7.18-7.14 (m, 2H), 6.89-6.80 (m, 2H), 4.26 and 4.07 (ABq, ^{2}J = 16.8 Hz, 2H), 3.90 and 3.63 (ABq, ^{2}J = 11.7 Hz, 2H), 3.06 (s, 9H), 2.64 (s, 3H).

^{1}H-NMR second isomer (40%) (250 MHz, CD_3OD) δ (ppm): 7.18-7.14 (m, 2H), 6.89-6.80 (m, 2H), 3.97 (s, 2H), 3.32 (s, 2H), 3.20 (s, 9H), 2.63 (s, 3H).

^{13}C-NMR first isomer (60%) (75 MHz, CD_3OD) δ (ppm): 167.74, 157.87, 133.95, 130.91, 123.92, 120.72, 116.50, 64.85, 60.71, 54.86, 45.94

^{13}C-NMR second isomer (40%) (75 MHz, CD_3OD) δ (ppm): 163.19, 157.57, 131.79, 130.58, 122.84, 117.11, 116.50, 63.93, 59.92, 54.50, 44.21

ESI-MS(+) MeOH+0.1%HCOOH: $[M]^+$ 252.0 m/z

HPLC (Jupiter Proteo 4μ 250x4.60x4u, flow=0.8ml/min, 0-15min 10-90% ACN+0.1%TFA, λ=280nm): 11.12 min

Compound $6B_2$

^{1}H-NMR first isomer (60%) (250 MHz, CD_3OD) δ (ppm): 7.18-7.15 (m, 2H), 6.86-6.78 (m, 2H), 4.03 (s, 2H), 3.63 (t, J=7.5 Hz, 2H), 3.07 (s, 9H), 2.71 (t, t, J=7.2Hz, 2H), 2.68 (s, 3H)

^{1}H-NMR second isomer (40%) (250 MHz, CD_3OD) δ (ppm):): 7.18-7.15 (m, 2H), 6.86-6.78 (m, 2H), 4.03 (s, 2H), 3.63 (t, J=7.5 Hz, 2H), 3.07 (s, 9H), 2.72 (t, t, J=7.2Hz, 2H), 2.66(s, 3H)

^{13}C-NMR first isomer (60%) (62.5 MHz, CD_3OD) δ (ppm): 168.72, 157.58, 133.99, 130.76, 124.45, 120.65, 116.53, 63.10 (t, J_{CN} = 3.3 Hz), 59.75, 53.67 (t, J_{CN} = 3.3 Hz), 44.10, 26.86.

^{13}C-NMR second isomer (40%) (62.5 MHz, CD_3OD) δ (ppm): 168.70, 158.06, 133.99, 130.76, 124.45, 120.70, 117.10, 62.84 (t, J_{CN} = 3.3 Hz), 61.06, 53.49 (t, J_{CN} = 3.3 Hz), 43.55, 28.65.
ESI-MS(+) H_2O: $[M]^+$ 266.1 m/z
HPLC (Jupiter Proteo 4μ 250x4.60x4u, flow=0.8ml/min, 0-15min 10-90% ACN+0.1%TFA, λ = 280nm): 11.55 min

Compound 6B$_3$
^{1}H-NMR first isomer (85%) (300 MHz, CD_3OD) δ (ppm): 7.23-7.12 (m, 2H), 6.87-6.78 (m, 2H), 4.07 (s, 2H), 3.28-3.22 (m, 2H), 3.11 (s, 9H), 2.69 (s, 3H), 2.26 (t, *J*=7.2Hz, 2H), 2.08-2.00 (m, 2H)
^{1}H-NMR second isomer (15%) (300 MHz, CD_3OD) δ (ppm): 7.23-7.12 (m, 2H), 6.87-6.78 (m, 2H), 4.07 (s, 2H), 3.28-3.22 (m, 2H), 3.08 (s, 9H), 2.63 (s, 3H), 2.34 (t, *J*=7.2Hz, 2H), 2.08-2.00 (m, 2H)
^{13}C-NMR first isomer (85%) (75 MHz, CD_3OD) δ (ppm): 168.86, 155.57, 130.91, 129.20. 128.31, 118.05, 114.49, 64.17, 58.72, 50.98, 41.31, 27.86, 16.86.
^{13}C-NMR second isomer (15%) (75 MHz, CD_3OD) δ (ppm): 168.86, 154.92, 130.91, 129.20. 128.31, 117.81, 113.78, 64.51, 56.93, 50.98, 41.20, 25.90, 16.12.
ESI-MS(+) H_2O MeOH: $[M]^+$ 280.2 m/z
HPLC (Jupiter Proteo 4μ 250x4.60x4u, flow=0.8ml/min, 0-30min 10-60% ACN+0.1%TFA, λ=280nm): 12.80 min

Compound 6I
^{1}H-NMR (250 MHz, CD_3OD) δ (ppm): 7.42-7.29 (m, 2H), 7.27-7.17 (m, 2H), 7.16-7.05 (m, 2H), 7.01-6.93 (m, 1H), 6.85-6.72 (m, 2H), 3.82 (s, 2H), 2.56 (m, 3H)
^{13}C-NMR (62.5 MHz, CD_3OD) δ (ppm): 158.67, 157.57, 140.23, 133.08, 130.54, 129.80, 124.34, 123. 88, 120.65, 120.53, 116.42, 61.54, 44.92
ESI-MS(+) MeOH+0.1%HCOOH: $[M+H]^+$ 272 m/z, $[M+Na]^+$ 294 m/z

General procedure for the synthesis of compounds 3

Compound **6** was dissolved in anhydrous CH_3CN and acetic anhydride (2eq) was added. The mixture was stirred for 8h, after which the solvent was evaporated under reduced pressure. The final compounds **3A**, **3B**, **3B$_2$**, **3B$_3$** were purified by preparative HPLC. Compound **3I** was purified by recrystallization from ethyl acetate.

Compound 3A
^{1}H-NMR first isomer (75%) (300 MHz, CD_3CN) δ (ppm): 7.29-6.82 (m, 9H), 4.11 (s, 2H), 3.37 (s, 2H), 2.83 (s, 3H), 2.28 (s, 3H).
^{1}H-NMR second isomer (25%) (300 MHz, CD_3CN) δ (ppm): 7.29-6.82 (m, 9H), 4.01 (s, 2H), 3.44 (s, 2H), 2.53 (s, 3H), 2.31 (s, 3H).
^{13}C-NMR first isomer (75%) (62.5 MHz, $CDCl_3$) δ (ppm): 170.42, 169.37, 149.91, 135.27, 132,03, 129.52, 129.30, 128.88, 128.50, 127.21, 126.74, 126.34, 126.33, 122.85, 56.03, 44.43, 38.94, 21.01
^{13}C-NMR second isomer (25%) (62.5 MHz, $CDCl_3$) δ (ppm): 170.09, 169.31, 149.85, 134.50, 131.75, 129.50, 129.48, 129.13, 128.59, 127.22, 126.75, 126.36, 126.35, 122.97, 59.13, 46.56, 42.54, 21.10
ESI-MS(+) MeOH+0.1%HCOOH: $[M+H]^+$ 313 m/z, $[M+Na]^+$ 335 m/z, $[M+K]^+$ 351 m/z.
HPLC (Agilent Eclipse XDB-C18, 5μm 150x4.60mm, flow=0.8ml/min, 0-15min 10-90% ACN+0.1%TFA, 15-25min 90%ACN+0.1%TFA, λ=280nm): 11.83 min

Compound 3B

^{1}H-NMR first isomer (80%) (300 MHz, CD_3OD) δ (ppm): 7.46-7.18 (m, 4H), 4.09 and 3.44 (Abq, ^2J = 12.5 Hz, 2H), 3.98 and 3.66 (ABq, ^2J = 16.8 Hz, 2H), 2.96 (s, 9H), 2.72 (s, 3H), 2.37 (s, 3H).

^{1}H-NMR second isomer (20%) (300 MHz, CD_3OD) δ (ppm): 7.61 (dd, ^3J = 7.5 Hz, ^4J = 1.8 Hz, 1H), 7.33-7.23 (m, 2H), 7.04 (dd, ^3J = 7.9 Hz, ^4J = 1.4 Hz, 1H), 3.87 (s, 2H), 3.85 (s, 2H), 3.10 (s, 9H), 2.68 (s, 3H), 2.35 (s, 3H).

^{13}C-NMR first isomer (80%) (75 MHz, CD_3OD) δ (ppm): 169.24, 165.19, 148.71, 131.28, 128.09, 127.30, 124.62, 122.02, 60.68, 56.17, 51.74, 44.88, 19.00

^{13}C-NMR second isomer (20%) (75 MHz, CD_3OD) δ (ppm): 169.24, 165.19, 148.69, 129.90, 128.09, 127.28, 124.43, 121.23, 62.45, 55.05, 52.10,42.92, 18.92

ESI-MS(+) MeOH+0.1%HCOOH: $[M]^+$ 294.2 m/z

HPLC (Jupiter Proteo 4u 250x4.60x4u, flow=0.8ml/min, 0-15min 10-90% ACN, 15-25min 90%ACN, λ=280nm): 21.4 min.

Compound 3B$_2$

^{1}H-NMR first isomer (70%) (300 MHz, CD_3OD) δ (ppm): 7.46-7.18 (m, 4H), 4.24 and 4.11 (ABq, ^2J = 12.9 Hz, 2H), 3.51 and 3.26 (ABq, ^2J = 7.0 Hz, 2H), 3.00 (s, 3H), 2.87 (s, 9H), 2.74 (s, 3H), 2.66 (m, 2H)

^{1}H-NMR second isomer (30%) (300 MHz, CD_3OD) δ (ppm): 7.46-7.18 (m, 4H), 4.34 and 4.06 (ABq, ^2J = 13.2 Hz, 2H), 3.86 (s, 2H), 2.98 (s, 3H), 2.92 (s, 9H), 2.76 (s, 3H), 2.61 (m, 2H)

^{13}C-NMR first isomer (70%) (75 MHz, CD_3OD) δ (ppm): 167.74, 167.52, 147.38, 129.44, 126.71, 123.17, 123.13, 120.46, 58.97, 55.01, 49.50, 41.22, 24.93, 18.86

^{13}C-NMR second isomer (30%) (75 MHz, CD_3OD) δ (ppm): 167.70, 167.06, 147.21, 129.15, 126.51, 125.74, 123.20, 119.64, 58.80, 53.64, 49.51, 38.96. 24.90, 19.16

ESI-MS(+) MeOH+0.1%HCOOH: $[M]^+$ 308.2 m/z

HPLC (Jupiter Proteo 4u 250x4.60x4u, flow=0.8ml/min, 0-15min 10-90% ACN, 15-25min 90%ACN, λ=280nm): 22.4 min.

Compound 3B$_3$

^{1}H-NMR first isomer (55%) (300 MHz, CD_3OD) δ (ppm): 7.39-7.22 (m, 4H), 4.28 and 4.10 (ABq, ^2J = 13.1 Hz, 2H), 3.93 (m, 1H), 3.54 (m, 1H), 3.02 (s, 9H), 2.70 (s, 3H), 2.34 (s, 3H), 2.11 (t, ^3J = 6.6 Hz, 2H), 1.92-1.88 (m, 2H).

^{1}H-NMR second isomer (45%) (300 MHz, CD_3OD) δ (ppm): 7.39-7.22 (m, 4H), 3.82 (s, 2H), 3.12-3.14 (m, 2H), 3.01 (s, 9H), 2.68 (s, 3H), 2.35 (s, 3H), 2.11 (t, ^3J = 6.6 Hz, 2H), 1.92-1.88 (m, 2H).

^{13}C-NMR first isomer (55%) (75 MHz, CD_3OD) δ (ppm): 167.56, 167.21, 147.26, 129.58, 128.95, 125.63, 123.01, 119.70, 62.88, 53.64, 49.53, 41.78, 27.09, 18.88, 15.72.

^{13}C-NMR second isomer (45%) (75 MHz, CD_3OD) δ (ppm): 167.41, 167.18, 146.94, 129.60, 128.33, 126.64, 123.30, 120.22, 62.71, 54.99, 49.55, 38.90, 22.99, 16.87, 14.93.

ESI-MS(+) MeOH+0.1%HCOOH: $[M]^+$ 322.2 m/z

HPLC (Jupiter Proteo 4u 250x4.60x4u, flow=0.8ml/min, 0-15min 10-90% ACN, 15-25min 90%ACN, λ=280nm): 23.0 min.

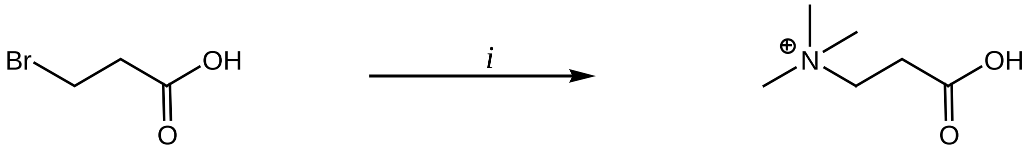
Compound 3I

^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 7.95 (s, 1H), 7.44-6.91 (m, 9H), 5.34 (s, 1H), 3.75 (s, 2H), 2.63 (s, 3H), 2.33 (s, 3H)

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ (ppm): 169.90, 155.38, 149.74, 138.45 131.86, 129.67, 128.69, 128.05, 126.39, 122.83, 122.74, 119.15, 59.57, 46.54, 30.94

ESI-MS(+) MeOH+0,1%HCOOH: $[M+Na]^+$ 336 m/z

Synthesis of carboxylic acids 7 and 8.

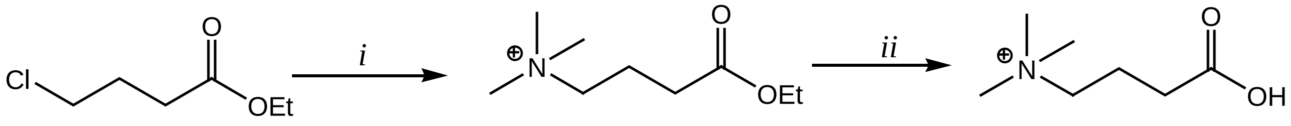


7

Scheme SI-2. *i)* $N(CH_3)_3$, CH_3CH_2OH.

To a solution of commercially available 3-bromopropionic acid (2.04 g, 13.3 mmol) in ethanol (10 ml) was added a 4.2 N solution of trimethylamine in ethanol (28 ml, 120 mmol, 9 equiv.) and the mixture was stirred for 3 days at room temperature. Excess of trimethylamine was removed by flushing air through the reaction mixture, after which the solvent was removed under reduced pressure. Compound **7** was obtained as a white solid (2.8 g, 74%).

^{1}H-NMR (250 MHz, CD_3OD) δ (ppm): 3.66 (t, J= 7.5 Hz, 2H), 3.17 (s, 9H), 2.79 (t, J = 7.3 Hz, 2H).
^{13}C-NMR (62.5 MHz, CD_3OD) δ (ppm): 174.45, 64.46, 53.78 (t, J_{NC} = 3.4 Hz), 30.84.
ESI-MS(+) MeOH: $[M]^+$ 132.0 m/z.



8 **9**

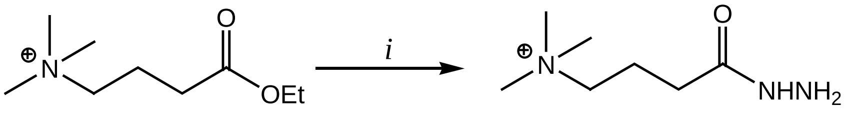
Scheme SI-3. *i)* $N(CH_3)_3$, CH_3CH_2OH, *ii)* 1N HCl in H_2O.

Compound 8. A solution of trimethylamine in ethanol (4.2 N, 40 ml, 9 equiv.) was added to a solution of ethyl 4-chlorobutyrate (2.7 g, 18 mmol) in ethanol (10 ml) and the mixture was stirred at room temperature for 3 days. The addition of diethyl ether resulted in the precipitation of compound **8**, which was collected by filtration and dried under high vacuum. Compound **8** (300 mg, 10%) was obtained as a white solid.
^{1}H-NMR (300.13 MHz, CD_3OD) δ (ppm): 4.16 (q, J = 7.2 Hz, 2H), 3.42-3.36 (m, 2H), 3.17 (s, 9H), 2.47 (t, J = 6.9 Hz, 2H), 2.11-2.06 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H).
^{13}C-NMR (75.00 MHz, CD_3OD) δ (ppm): 171.01, 64.14, 59.31, 51.02, 28.48, 16.80, 11.89.
ESI-MS(+) H_2O: $[M]^+$ 174.1 m/z.

Compound 9. Compound **8** (100 mg, 0.47 mmol) was dissolved in a solution of HCl in H_2O (1N) and stirred at room temperature over night. Lyophilization yielded compound **9** as a white solid (84 mg, 97%).

^{1}H-NMR (250 MHz, CD_3OD) δ (ppm): 3.42-3.35 (m, 2H), 3.16 (s, 9H), 2.45 (t, J=6.9 Hz, 2H), 2.13-2,00 (m, 2H)
^{13}C-NMR (62.5 MHz, CD_3OD) δ (ppm): 174.11, 66.77 (t, J_{NC} = 3.2 Hz), 53.59 (t, J_{NC} = 4.0 Hz), 30.82 (t, J_{NC} = 1.9 Hz), 19.42.
ESI-MS(+) H_2O : $[M]^+$ 146.0 m/z.

2. Synthesis of hydrazide B_3



8 **B_3**

Scheme SI-4. *i*) $NH_2NH_2.H_2O$, EtOH.

Hydrazide B_3 . Compound **8** (100 mg, 0.5 mmol) was dissolved in EtOH (1 ml) and $NH_2NH_2.H_2O$ (0.5 ml) and stirred over night at 50 ºC. Addition of diethyl ether resulted in the precipitation of hydrazide **B_3**, which was obtained as a white solid (90 mg, 92%).
^{1}H-NMR (250 MHz, CD_3OD) δ (ppm): 3.39-3.30 (m, 2H), 3.15 (s, 9H), 2.28 (t, J = 6.8 Hz, 2H), 2.14-2.08 (m, 2H), 1.93 and 1.89 (s, 1H, two isomers).
^{13}C-NMR (62.5 MHz, CD_3CN) δ (ppm): 173.08, 67.00 (t, J_{NC} = 2.8 Hz), 53.70 (t, J_{NC} = 3.7 Hz), 30.86, 20.07.
ESI-MS(+) MeOH: $[M]^+$ 160.0 m/z.

3. HSQC spectra of scaffolds 1 and 2 with hydrazide libraries A-I

HSQC spectra were recorded on a Bruker Avance 300. Samples were prepared by adding either scaffold **1** or **2** (5 mM) to a mixture of hydrazides **A-I** (7.5 mM each) in MeOD and subsequent equilibration at 50 ºC. Fingerprint parts of the resulting spectra are shown in Figures SI-1 and SI-2 for scaffolds **1** and **2**, respectively. All hydrazones could be identified by comparison with the ^{1}H and ^{13}C spectra of the pure hydrazones. In some cases, the total amount of hydrazone was calculated based on correction of a single isomer peak with the known isomer distribution. The resulting concentrations (relative to the concentration of hydrazone **1A** or **2A**, respectively) are shown in Figure SI-3. To illustrate the excellent correlation, also the relative concentrations for the competition experiments of each separate hydrazine against hydrazide **A** are given. Division of the numbers for each separate hydrazone gives the amplification factors shown in Figure 1 of the main text.

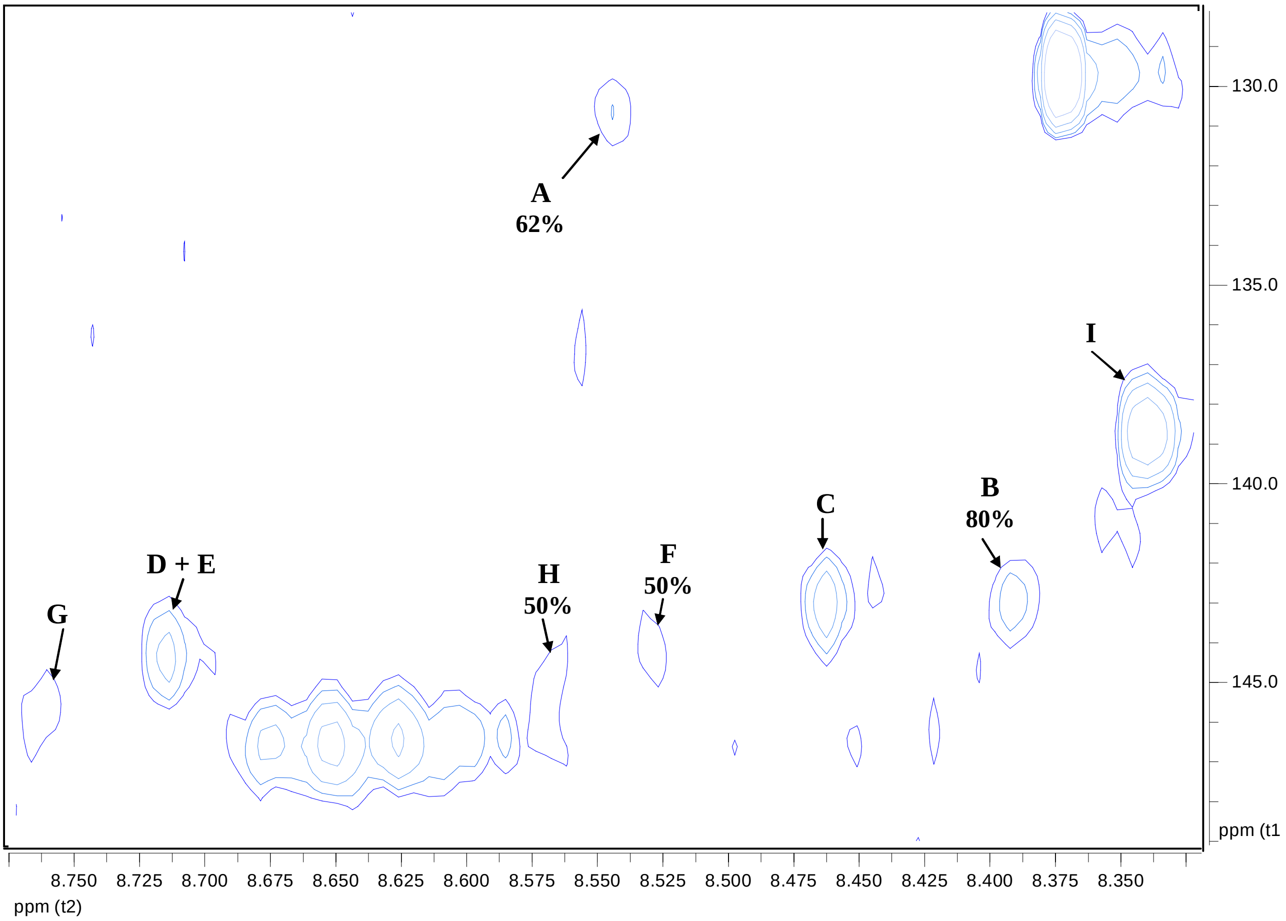


Figure SI-1. Fingerprint part of the HSQC spectrum of the library **2A-2I** in MeOD (300 MHz, 50 ºC).

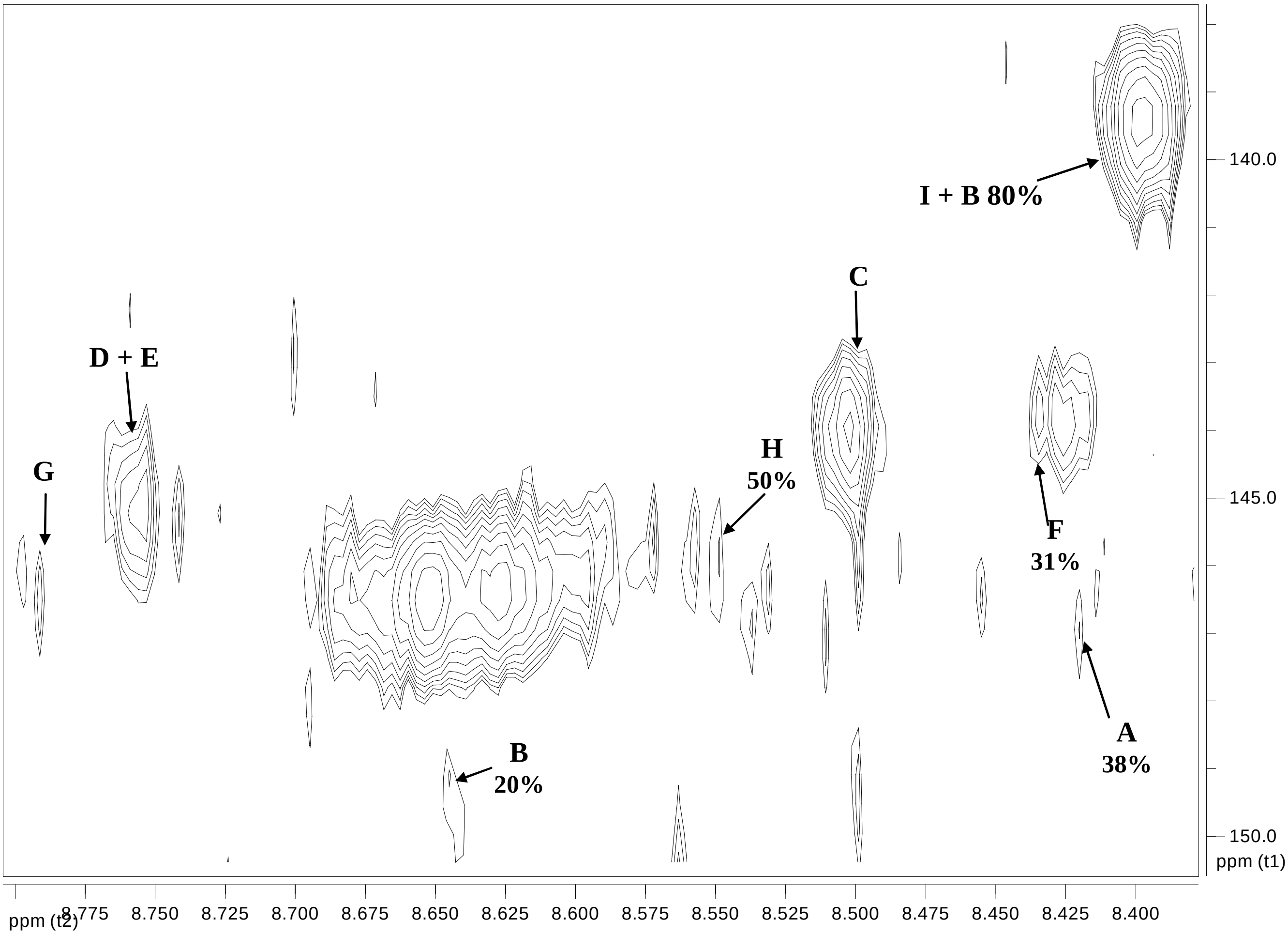


Figure SI-2. Fingerprint part of the HSQC spectrum of the library **1A-1I** in MeOD (300 MHz, 50 ºC).

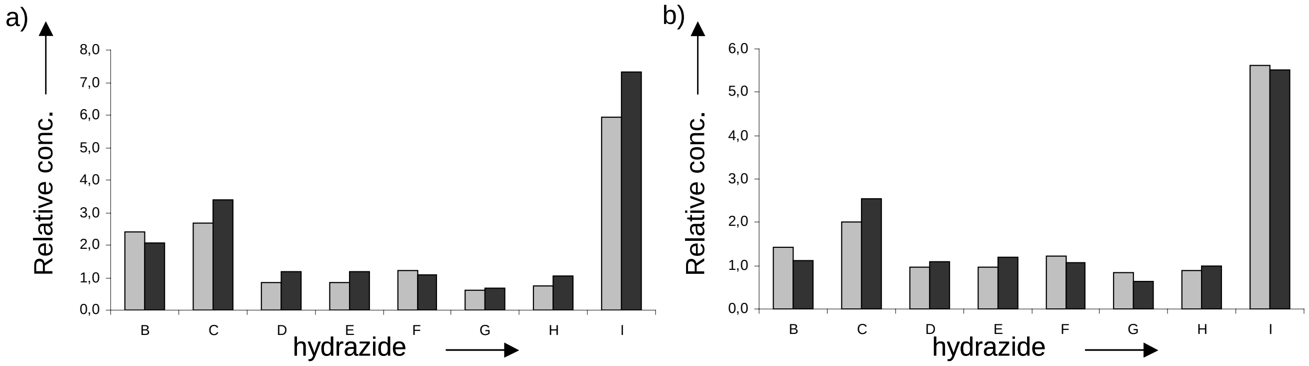


Figure SI-3. Relative concentrations of each hydrazone (a) **1B-1I** and (b) **2B-2I** with respect to hydrazone **1A** or **2A**, respectively, obtained from the HSQC-spectra (░) or direct competition experiments (■).

4. Fingerprint parts of the ^{1}H NMR spectra used for determination of the amplification.

Hydrazone formation between scaffolds **1** and **2** and hydrazides **A** and **B** is extensively discussed (including all experimental details) in a previous communication (*Chem.Commun.* **2007**, 1340-1342). In Figure SI-4 fingerprint parts of the ^{1}H NMR spectra are shown of the competition experiments between hydrazide **A** and either one of the library members **C-I** and $\mathbf{B}_3$ using either scaffold **1** (left) or scaffold **2** (right). The spectrum of hydrazones **1A** and **1B** is shown as a reference (Figure SI-4, a, peaks are indicated in the other spectra with □). In cases where assignment of signals was not entirely clear due to overlap, the spectrum of the pure hydrazone was used for unambiguous assignment. Some hydrazones are present as two isomers due to *E*,*Z*-isomerism around the NH-C(O) bond based on related studies in the literature (F.V. Bagrov, T.V. Vasil'eva *Russ. J. Org, Chem.* 2002, **38**, 1309-1313.). Hydrazone ratios were determined by integrating the corresponding signals (occasionally using deconvolution) and are reported in Table SI-1.

Table SI-1. Amplification factors obtained from the NMR competition experiments.[a]

hydrazide	Scaffold **1**			Scaffold **2**			Amplif.
	1X (%)	**1A** (%)	$K_{\mathbf{1},target}$	**2X** (%)	**2A** (%)	$K_{\mathbf{2},ref}$	
B[b]	67	33	2.1	53	47	1.1	1.8
$\mathbf{B}_3$	62	38	1.6	52	48	1.1	1.5
C	77	23	3.4	72	28	2.6	1.3
D	54	46	1.2	52	48	1.1	1.1
E	54	46	1.2	55	45	1.2	1.0
F	52	48	1.1	52	48	1.1	1.0
G	41	59	0.7	39	61	0.6	1.1
H	51	49	1.1	50	50	1.0	1.1
I	88	12	7.3	85	15	5.5	1.3

(a) All spectra obtained in CD_3OD (300 MHz). (b) From a previous communication (*Chem.Commun.* **2007**, 1340-1342).

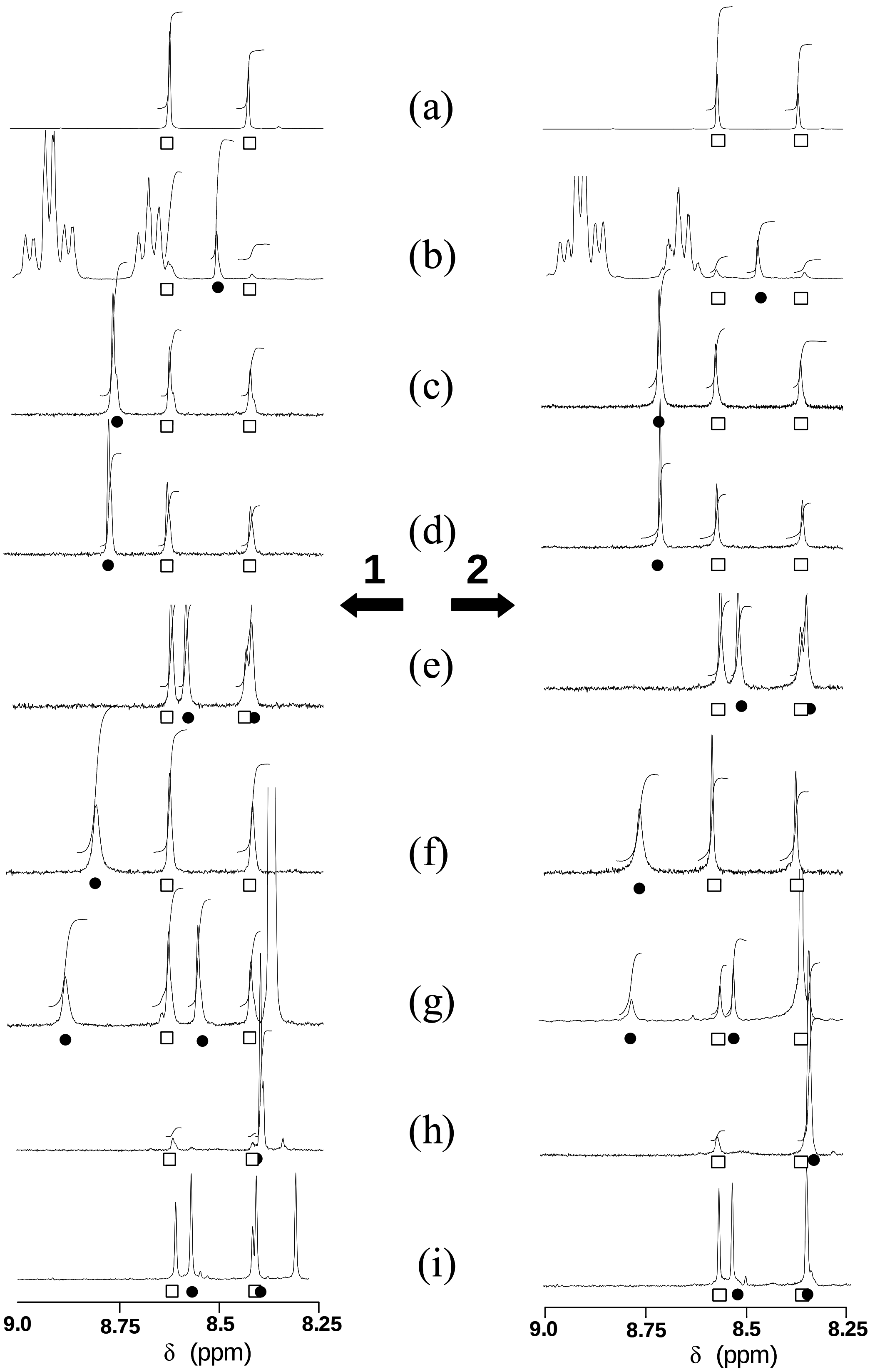


Figure SI-4. Fingerprint parts of the ^{1}H NMR spectra (300 MHz) obtained for the competition experiments between hydrazide **A** (□) and one of the hydrazides **C-I** (b-h,●) and **B_3** (i, ●) using either scaffold **1** (left) or **2** (right).As a reference the spectra of hydrazones **1A** (a, left) and **2A** (a, right) are shown. All spectra were obtained after equilibrating a mixture of **1** or **2** (5mM) and 5 equivalents of both hydrazide **B** and the other hydrazide (**B-I**) in CD_3OD at 50 ºC. Equilibration was continued until no further changes were detected in the ^{1}H NMR spectra.

5. Plot of log k_{obs} against pH for the hydrolysis of compounds 3A and 3B.

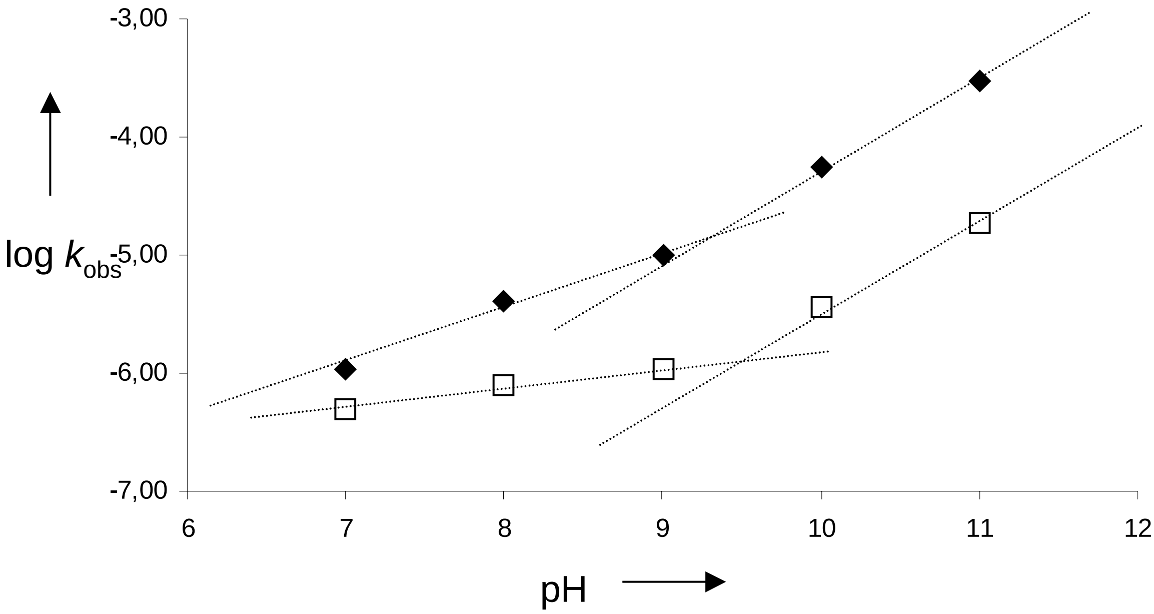


Figure SI-5. Plot of log k_{obs} as a function of pH for the hydrolysis of compounds **3A** (□) and **3B** (■) at different pH. Conditions [**3**] = 0.6 mM, H_2O:CH_3CN = 50:50, 45 °C. The pH was buffered using 60 mM of CAPS (pH 11 and 10), CHES (pH 9), EPPS (pH 8) or HEPES (pH 7). The pH refers to the aqueous component. Kinetics were followed by measuring the increase in absorbance at 280 nm and fitted to a first order exponential.

6. Methanolysis of compounds 3B and $3B_3$

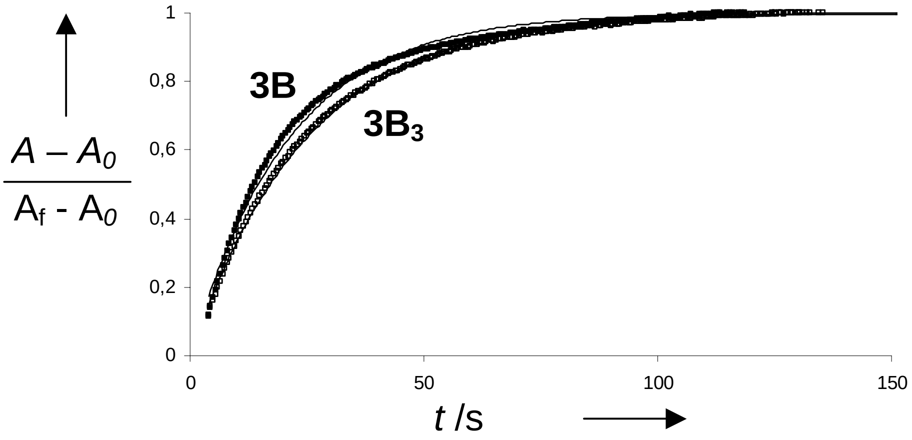


Figure SI-6. Change in the absorbance upon the addition of 12 equiv. of sodium methoxide to a solution of either **3B** or **$3B_3$**. The conditions are identical as to those described in the manuscript.

7. Methanolysis of 3B at different concentrations

The methanolysis of **3B** was performed as described in the experimental section at different concentrations of **3B** ranging from 1.0 mM to 0.1 mM at a constant concentration of sodium methoxide. The concentration boundaries are determined by the upper and lower limits for absorbance. All curves (Figure SI-7) gave excellent fits to a first-order exponential and no significant changes in the observed k_{obs}-values were obtained (Figure SI-8).

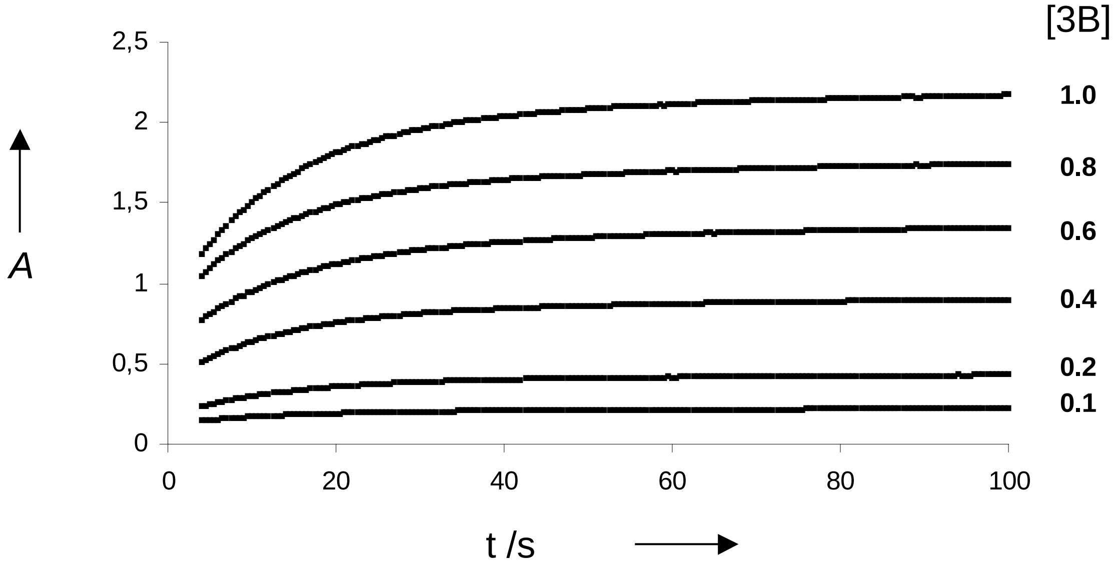


Figure SI-7. Methanolysis of **3B** at different concentrations.

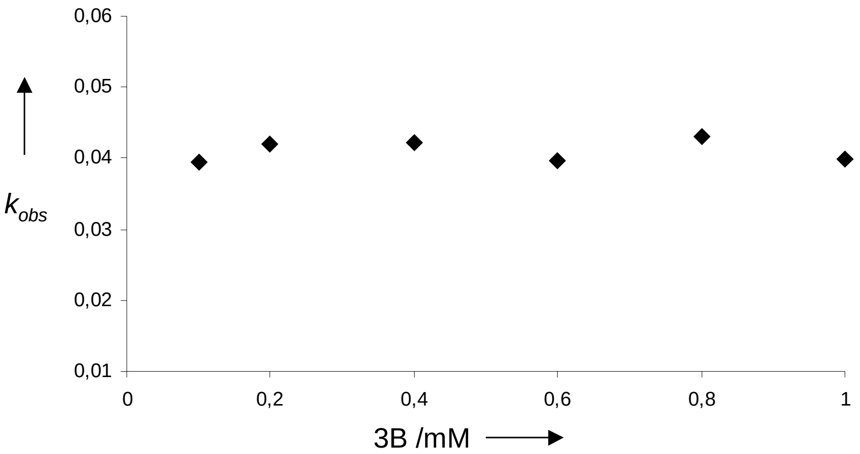


Figure SI-8. Pseudo first order rate constant for the methanolysis of **3B** at different initial concentrations.