Supporting Information

C−H Amination Reactions inside α-Cyclodextrin Supramolecular Capsule

Ivan Barvík,[b] Ivana Císařová,[c] Juraj Dian,[d,e] Oksana Holovko-Kamoshenkova,[a,f] Martin Štícha,[a] Zdeněk Tošner,[a] Jindřich Jindřich*[a] and Radim Hrdina *[a]

Contents

1. General information

NMR spectra were recorded on Bruker 400 or 600 MHz spectrometers at room temperature (25 °C) unless otherwise stated. ^{1}H-NMR chemical shifts are given in ppm relative to Me_4Si with the solvent resonance used as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C-NMR (101 or 150 MHz) chemical shifts are given in ppm relative to Me_4Si with the solvent resonance used as the internal standard ($CDCl_3$ = 77.16 ppm). IR spectra were recorded using an ATR sampler (Thermo Nicolet - Avatar 370 5T-IR) and are reported in wave numbers (cm^{-1}). Melting points (m.p.) were measured in open capillary tubes and are uncorrected. All reactions involving air sensitive compounds were carried out under anhydrous and inert atmosphere (N_2 or argon) by means of an inert gas/vacuum double manifold line and standard Schlenk techniques. High resolution mass spectra were recorded with Bruker Micro TOF LC.

2. Experimental procedures

2.1 Preparation of 2-adamantyl carbonazidate

Adamantan-2-ol (1 g, 6.6 mmol) and sodium azide (0.86 g, 13.2 mmol) were charged into a dry Schlenk tube and dissolved in pyridine (66 ml) and the mixture was cooled down to -15 °C. A prepared of solution of $(Cl_3CO)_2CO$ (0.98 g ,3.3 mmol) in DCM (3.3 ml) was added dropwise under vigorous stirring and left stirring at -15 °C for an additional 10 minutes. The reaction mixture was then left to warm up to room temperature, stirred for 1h and then transferred to a heating bath and heated to 50 °C stirring overnight. The reaction mixture was allowed to cool down to room temperature and partitioned between Et_2O and brine. The organic phase was washed 2x with distilled water and the combined aqueous phases were extracted with Et_2O (30 ml). The combined organic layers were washed with brine, dried over anh. $MgSO_4$ and the solvent was removed under reduced pressure. The product 2-adamantyl carbonazidate was purified by silica gel column chromatography eluting with pure DCM and obtained as a white crystalline solid in a yield of 95% (1.39 g).

R_f : 0.6 (DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 – 4.89 (m, 1H), 2.08 (s, 2H), 2.03 – 1.95 (m, 2H), 1.90 – 1.80 (m, 4H), 1.79 – 1.70 (m, 4H), 1.60 – 1.53 (m, 2H).

Analytical data are in accordance with those published in literature. Lee, J.; Lee, J.; Jung, H.; Kim, D.; Park, J.; Chang, S. Versatile Cp*Co(III)(LX) Catalyst System for Selective Intramolecular C–H Amidation Reactions. *J. Am. Chem. Soc.* **2020**, *142*, 12324–12332.

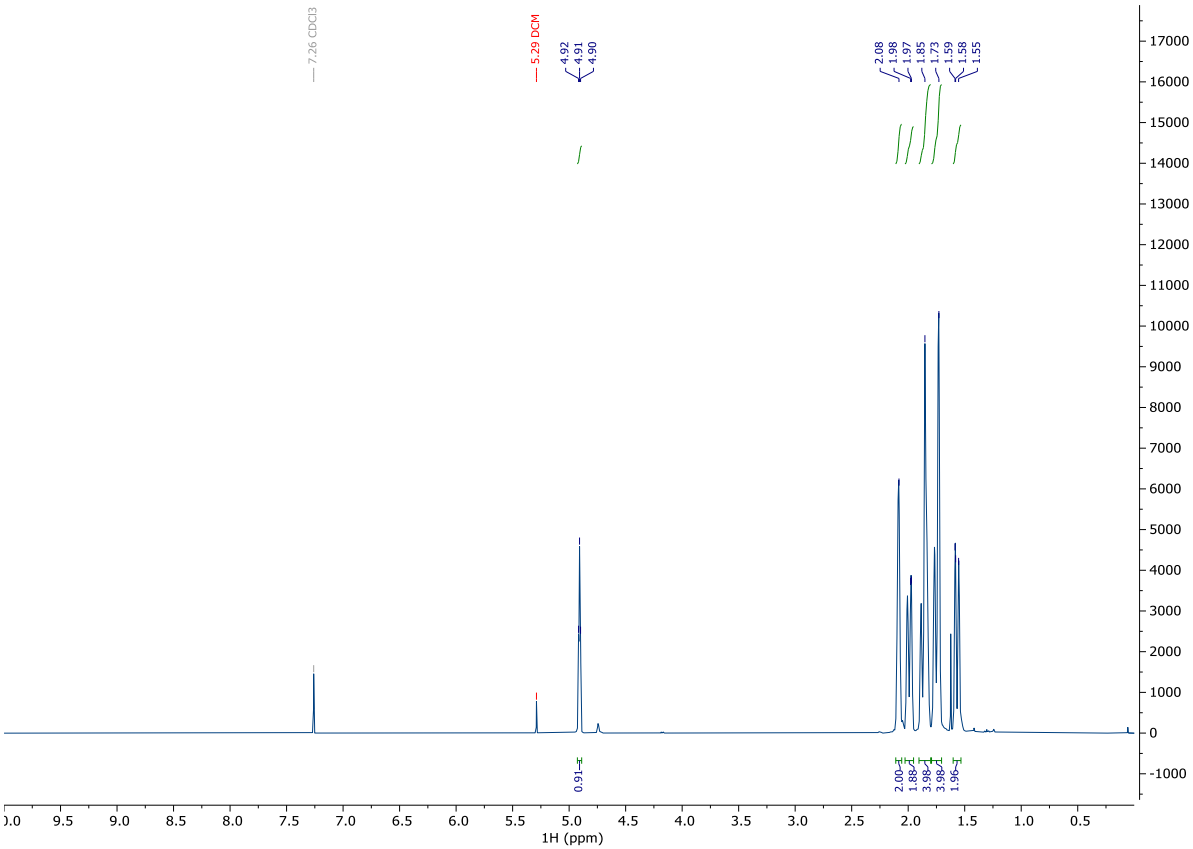


Figure 1. ^{1}H NMR spectrum of 2-adamantyl carbonazidate (Larmor frequency 400 MHz, solvent $CDCl_3$, temperature 25°C)

2.2 Preparation of carbamate *rac*-**3**

Starting material, 2-adamantyl carbonazidate, (1 g, 4.5 mmol) was loaded into a pressure vessel under a stream of nitrogen and dissolved in dry DCE (26 ml). The pressure vessel was sealed, transferred to an oil bath and the reaction mixture was heated to 130 °C and left stirring overnight. The reaction mixture was allowed to cool down to room temperature. The pressure vessel was cooled down in an ice bath and carefully opened. The solvent was evaporated under reduced pressure and the product *rac*-**3** purified by silica gel column chromatography (30% EtOAc:DCM) to give a white crystalline solid in a yield of 73% (633 mg).

R_f : 0.4 (30% EtOAc:DCM)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 1H), 4.14 – 4.10 (m, 1H), 2.44 – 2.38 (m, 1H), 2.15 – 2.09 (m, 1H), 2.06 – 2.00 (m, 1H), 1.97 – 1.91 (m, 1H), 1.90 – 1.79 (m, 4H), 1.78 – 1.54 (m, 5H).

Analytical data are in accordance with those published in literature. Lee, J.; Lee, J.; Jung, H.; Kim, D.; Park, J.; Chang, S. Versatile Cp*Co(III)(LX) Catalyst System for Selective Intramolecular C–H Amidation Reactions. *J. Am. Chem. Soc.* **2020**, *142*, 12324–12332.

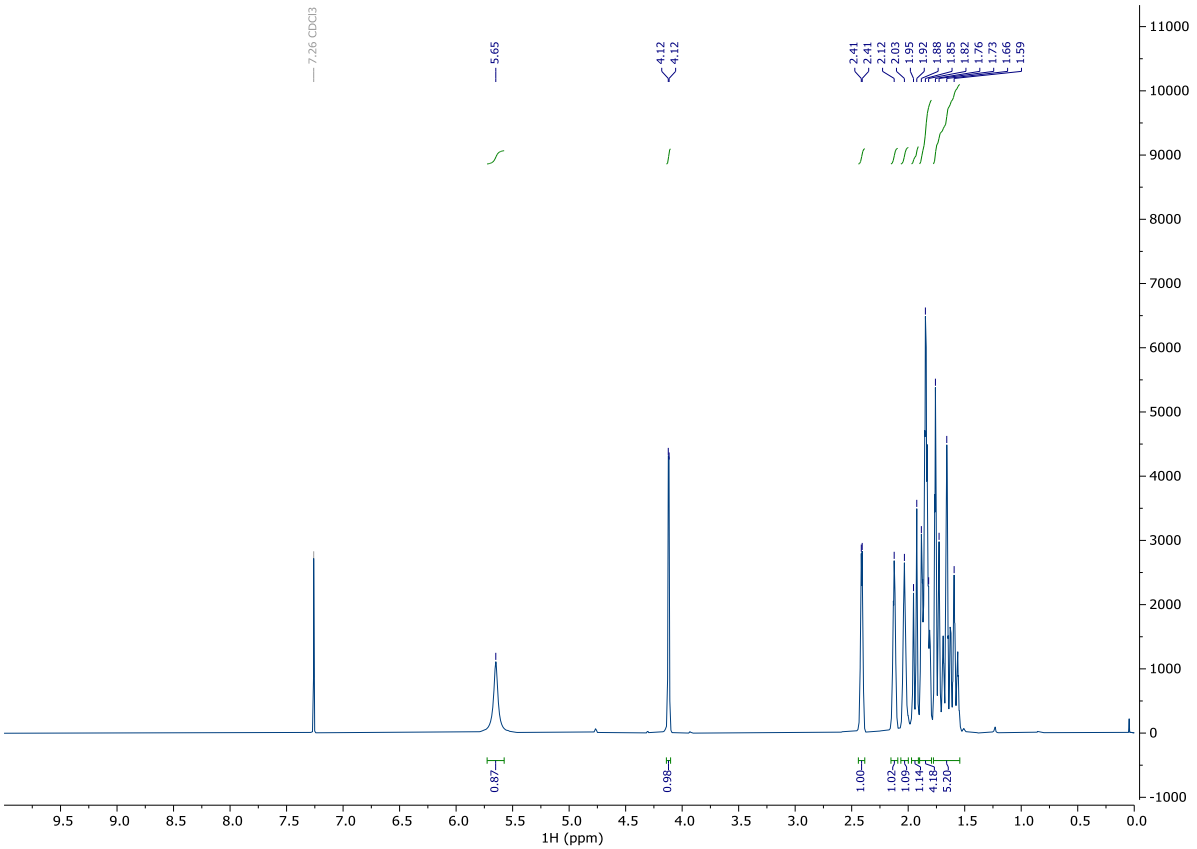
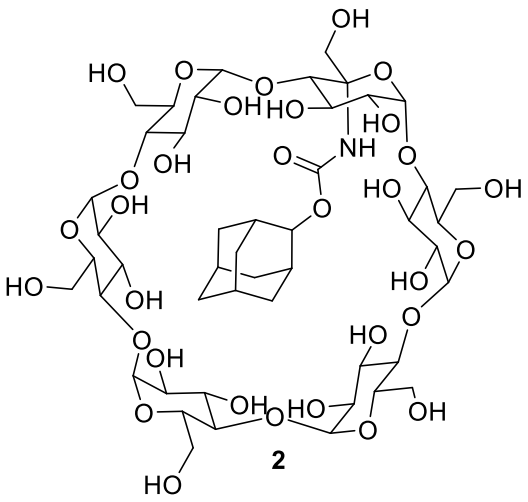


Figure 2. ^{1}H NMR spectrum of carbamate *rac*-**3** (Larmor frequency 400 MHz, solvent $CDCl_3$, temperature 25°C).

2.3 Co-crystallisation of 2-adamantylcarbonazidate with α-cyclodextrin to assembly **1**.

2-Adamantylcarbonazidate (221 mg, 1 mmol) was dissolved in 40 mL of EtOH and added to hot solution of α-cyclodextrin (1.94 g, 2 mmol) in 50 mL H_2O. The solution was heated to dissolve all material and then let crystallise at 60 °C for 16h. (The temperature must be maintained for the whole crystallisation process). The yield of assembly **1** was 1.6 g, 82 %.
It is important to note that without guest molecule (adamantyl carbonazidate) the α-cyclodextrin does not form a dimer that could cocrystallise together.
Crystalls of **1** were filtered off and used directly for the next experiment (UV irradiation) or subjected to X-ray analysis and IR analysis.

2.4 UV light irradiation of assembly **1** and isolation of derivatised α-cyclodextrin, compound **2**.



2

Assembly **1** was irradiated with UV (254 nm) either in solid phase or in hexane suspension for 2h. UV irradiation was performed using a 254 nm line from UV lamp (p-lab, 2 x 4 W). Intensity at 254 nm was 500 μW/cm^2 (15 cm), actual distance was about 6-7 cm, corresponding intensity for 6 cm was ~3 mW/cm^2. The suspension was then filtered off, solid material **2c** was dissolved in pyridine and compound **2** was separated on silica gel using 1-propanol: H_2O: toluene: ammonia in water (6:3:1:1) mixture as mobile phase. Compound **2** was obtained in 75 % yield.

m.p.: (crystallised from MeOH) 181.2-182.0 °C
HRMS: m/z = 1188.4172 ([M+Na$^+$]; calculated for $C_{47}H_{75}NO_{32}Na^+$, m/z = 1188.4164).

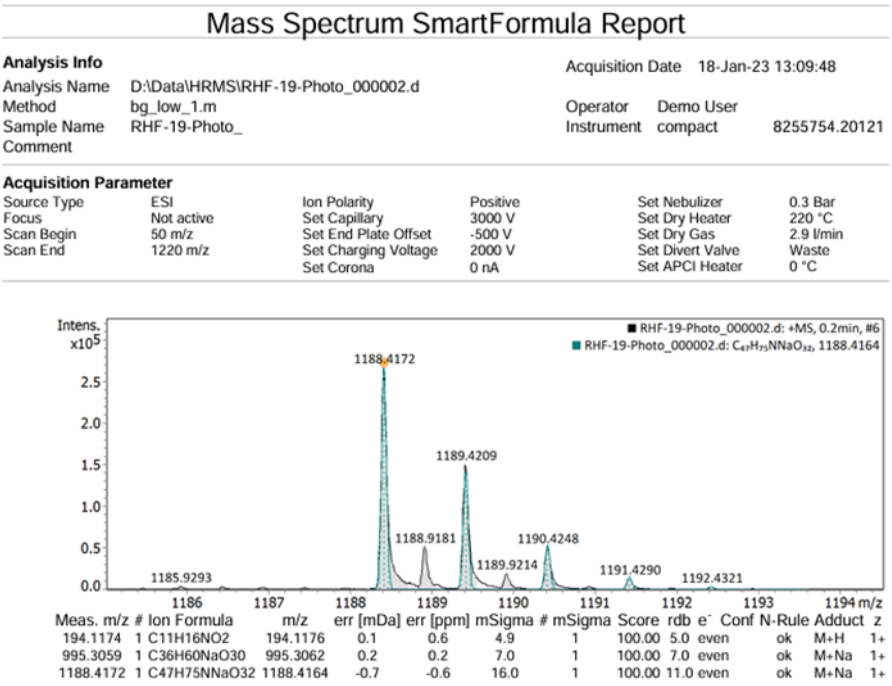
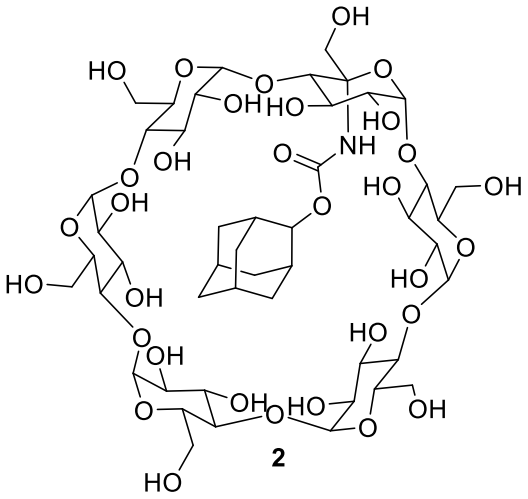


Fig. 3. High resolution mass spectrum of compound **2**.

IR spectrum of isolated compound **2**

IR (neat): $\tilde{\nu}$ /cm^{-1} = 3244, 2924, 2858, 1707, 1662, 1635, 1512, 1489, 1450, 1410, 1375, 1363, 1329, 1292, 1149, 1099, 1076, 1024, 949, 933, 860, 752, 696.



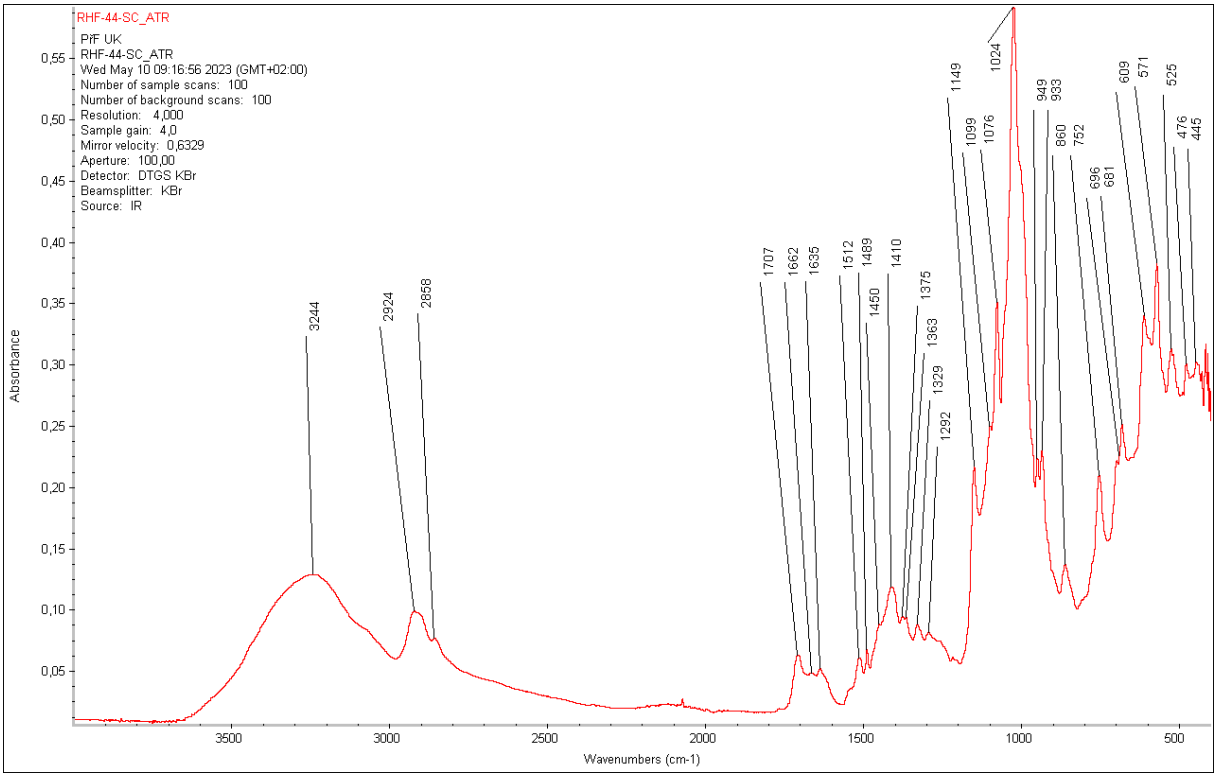


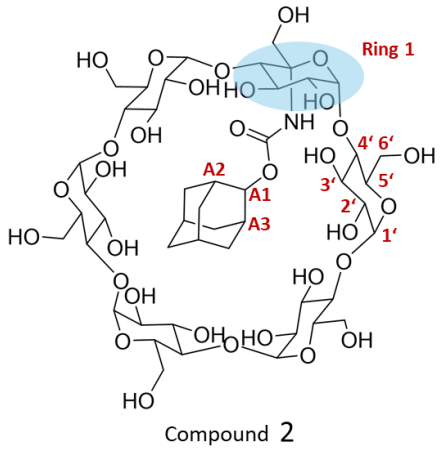
Figure 4. IR spectrum of compound **2.**

3. NMR analysis of compound 2

NMR spectra were measured in deuterated pyridine at 90 °C.

^{1}H NMR (600 MHz, pyridine-d5) δ 6.74 (s, 1H), 5.5-5.4 (m, 6H), 5.18 (s, 1H), 5.16 (s, 1H), 4.89 (m, 1H), 4.82 (m, 1H), 4.65-4.07 (m, 44H), 4.03-3.86 (m, 6H), 2.38 (s, 1H), 2.29 (s, 1H), 2.20 (s, 2H), 1.9-1.3 (m, 10H).

^{13}C NMR (150 MHz, pyridine-d5) δ 105 (6CH), 90.6 (CH), 84 (6CH), 80.2 (CH), 77-74 (16CH), 72.1 (CH), 65.9 (CH_2), 63.0 ($5CH_2$), 38.8 (CH_2), 37.7 ($2CH_2$), 33.9 ($2CH_2$), 33.5 (2CH), 28.8 (2CH), (C of carbonyl group is not detectable).



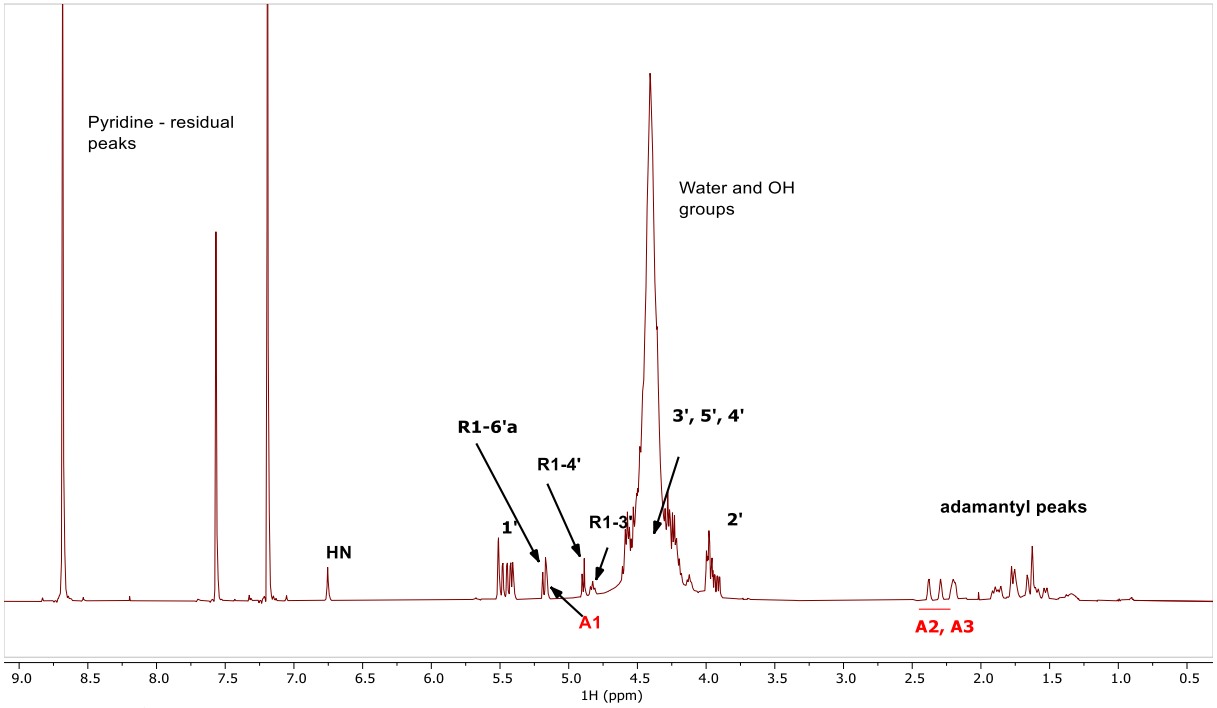


Figure 5. ^{1}H NMR spectrum of compound **2** (Larmor frequency 600 MHz, solvent pyridine-d5, temperature 90°C).

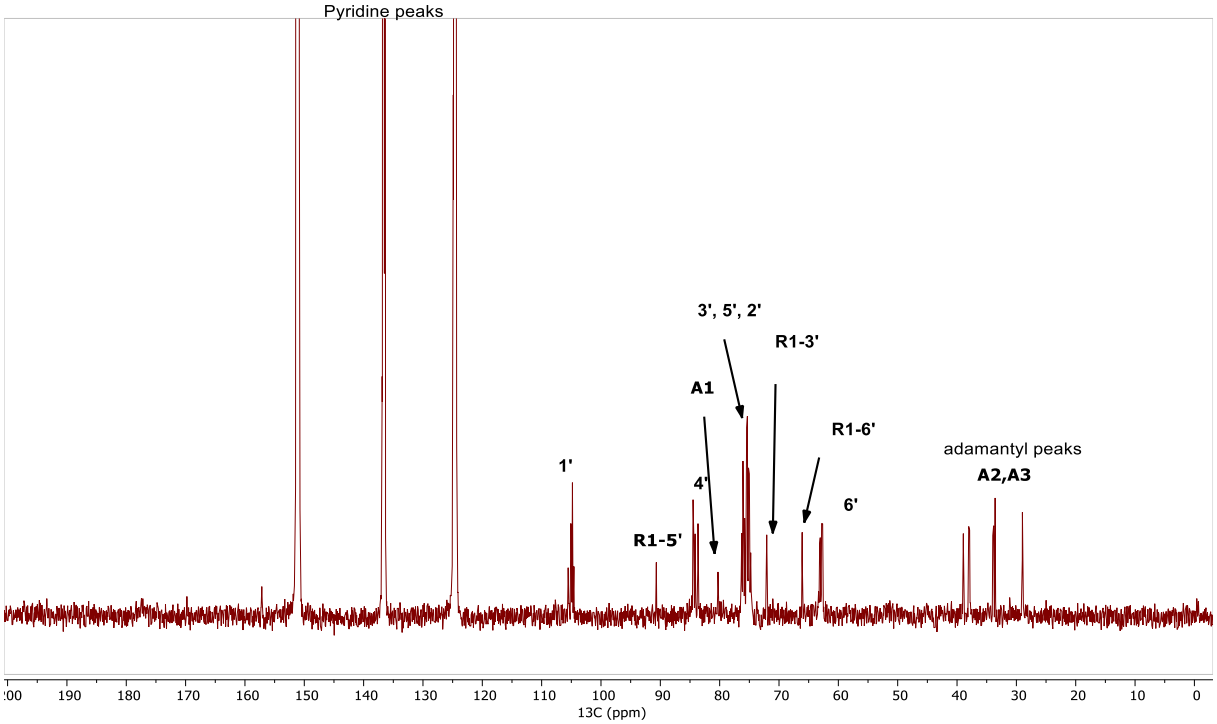


Figure 6. ^{13}C NMR spectrum of compound **2** (Larmor frequency 150 MHz, solvent pyridine-d5, temperature 90°C).

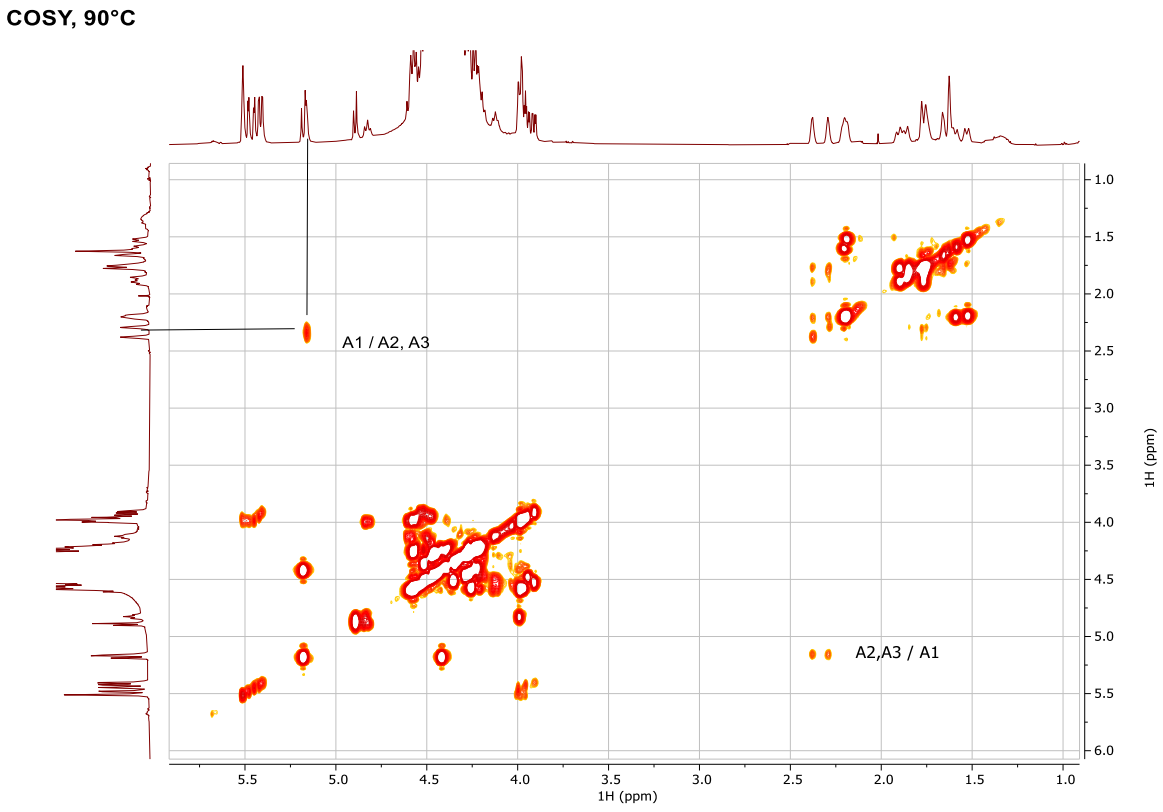


Figure 7. ^{1}H-^{1}H COSY NMR spectrum of compound **2** (Larmor frequency 600 MHz, solvent pyridine-d5, temperature 90°C).

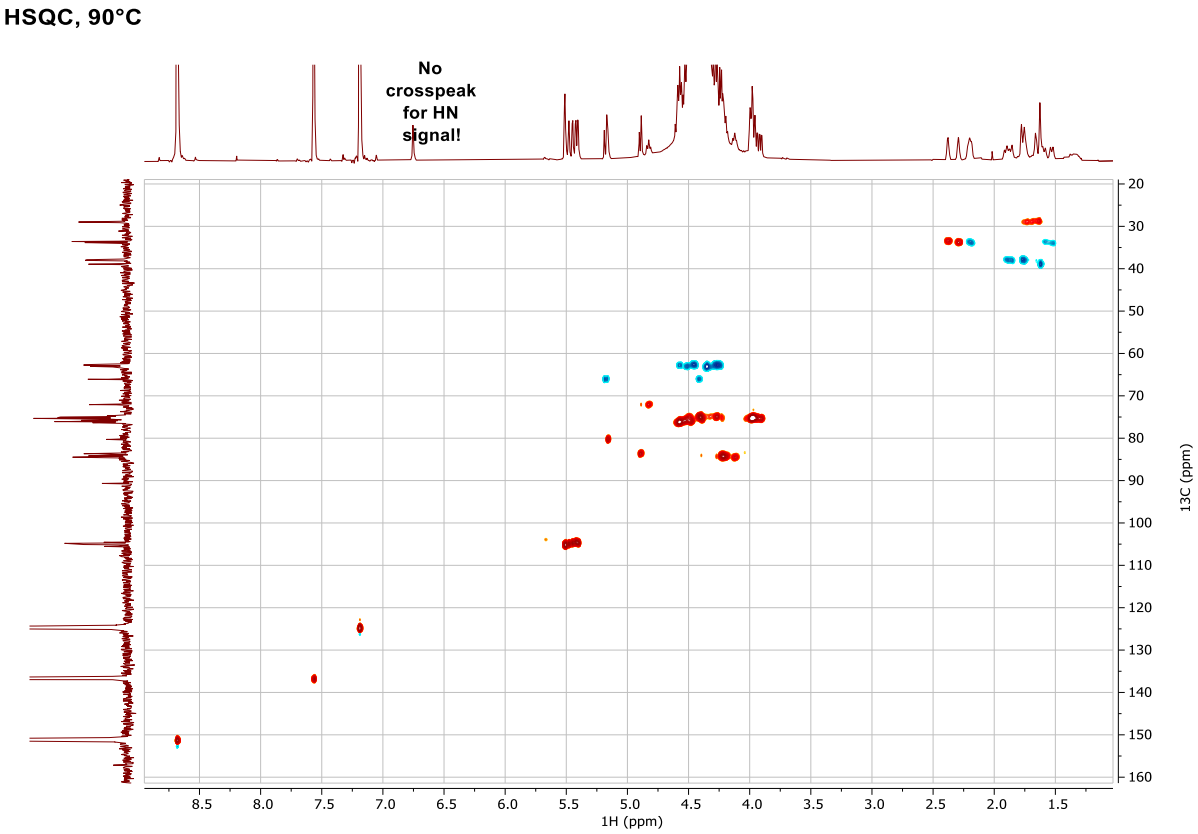


Figure 8. ^{1}H-^{13}C HSQC NMR spectrum with multiplicity editing of compound **2** (Larmor frequency ^{1}H 600 MHz and ^{13}C 150 MHz, solvent pyridine-d5, temperature 90°C). Red peaks correspond to CH or CH_3 groups, blue peaks correspond to CH_2 groups.

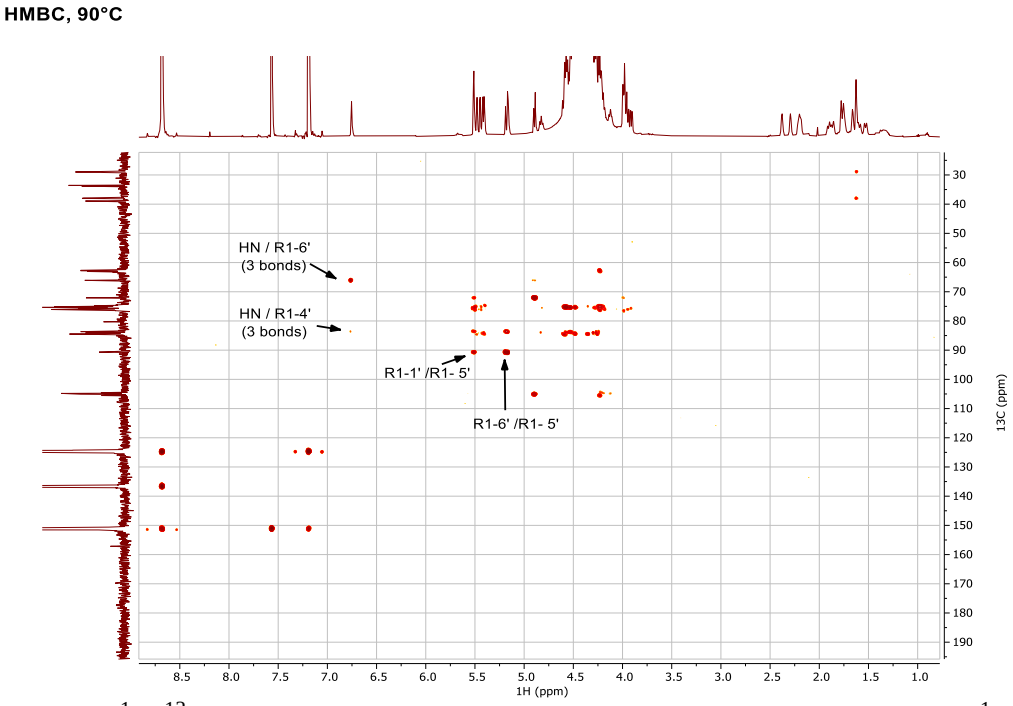


Figure 9. ^{1}H-^{13}C HMBC NMR spectrum of compound **2** (Larmor frequency ^{1}H 600 MHz and ^{13}C 150 MHz, solvent pyridine-d5, temperature 90°C).

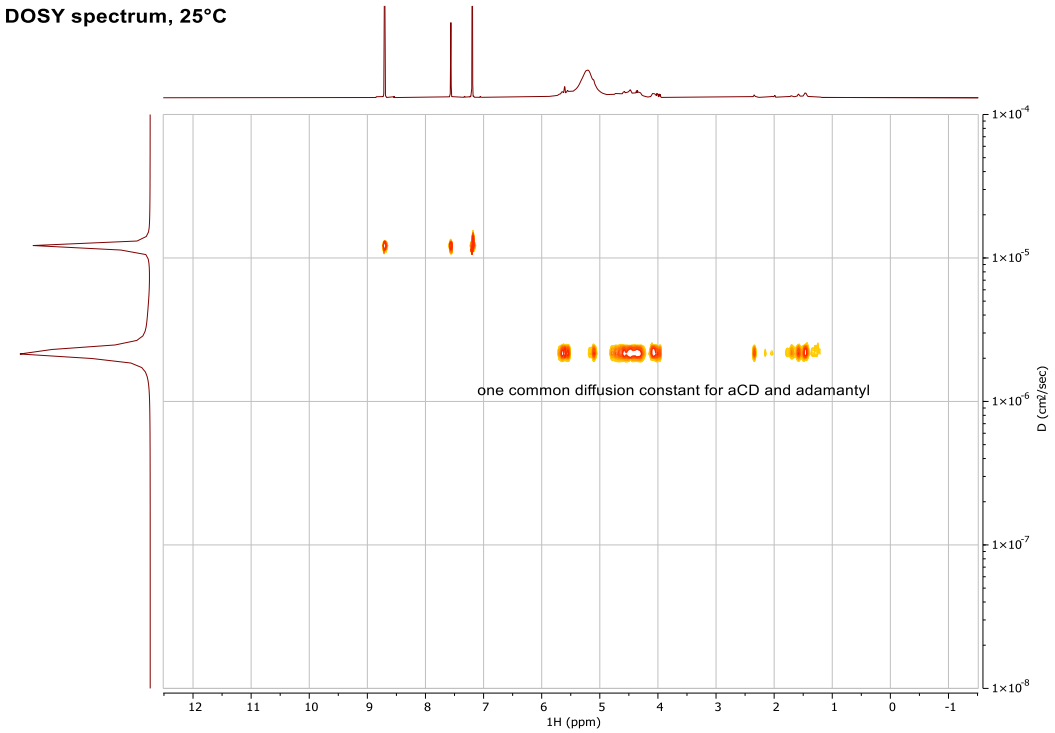


Figure 10. ^{1}H DOSY NMR spectrum of compound **2** (Larmor frequency 600 MHz, solvent pyridine-d5, temperature 25°C). All peaks corresponding to compound-**2** (both cyclodextrin and adamantyl moiety hydrogens) show one common diffusion constant, confirming their chemical bonding.

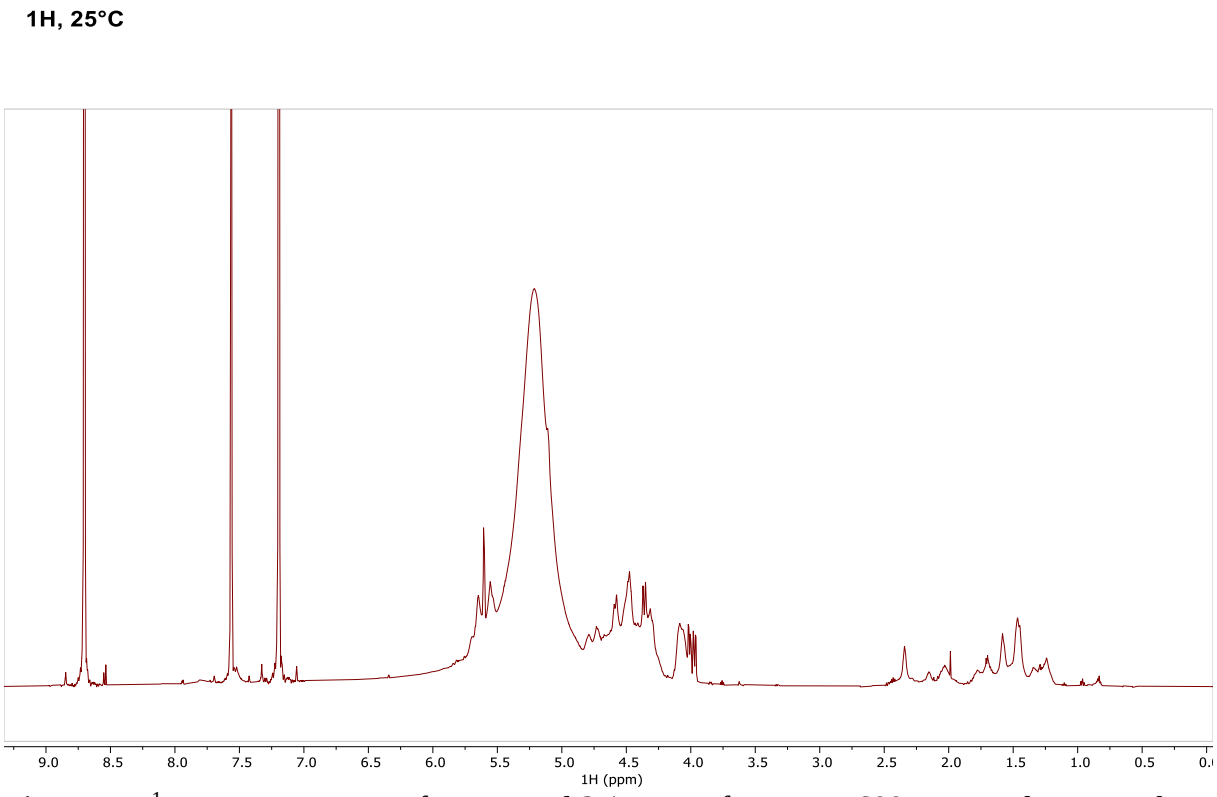


Figure 11. ^{1}H NMR spectrum of compound **2** (Larmor frequency 600 MHz, solvent pyridine-d5, temperature 25°C).

4. HPLC-MS analysis of 3

HP1100+Esquire 3000
Column: Daicel Chiralpak IA (250 x 4.5; 5µm), temp 30 °C
MF (D) heptane/*i*PrOH 8/2
Isocratic elution
Flow: 1 mL/min
Injection: 5 µl
Split: 1:2
Postcolumn MeOH 1 mL/h

Detection:
ESI-positive
Scan: 50-1100 Da
Nebuliser: 15 psi
Dry gas: 5L/min
Temperature: 290 °C
HV capillary: 4000 V

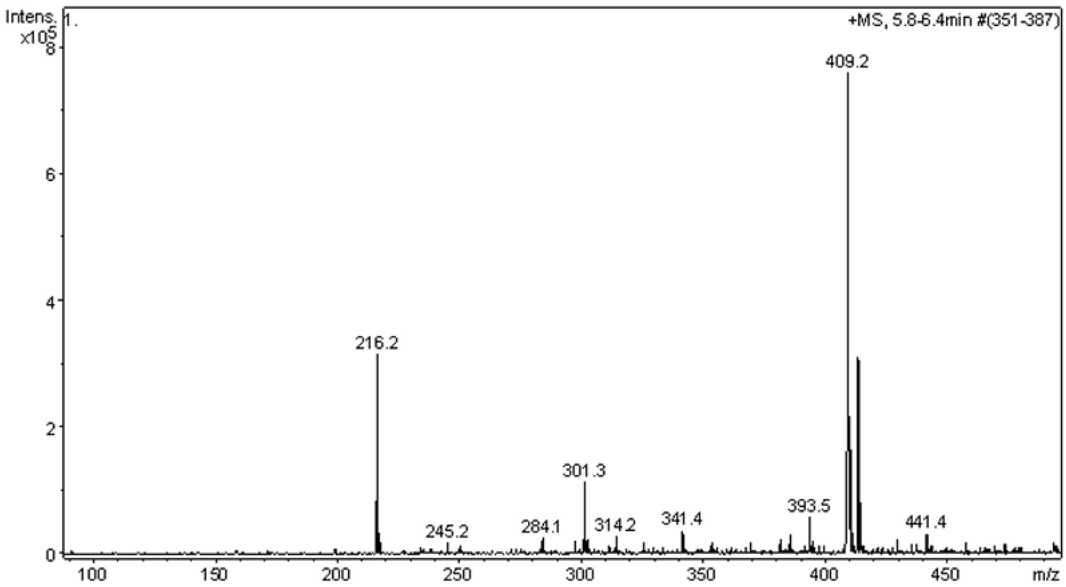
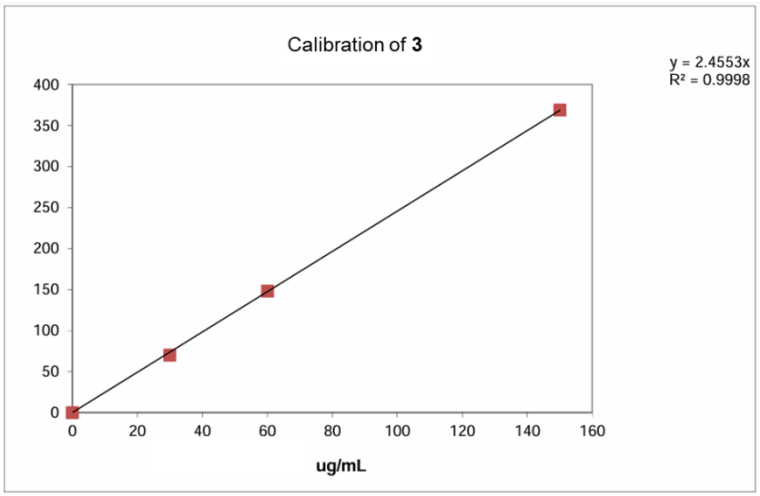


Fig. 12. MS spectrum of compound *rac*-**3.**

konc. ug/ml	I1+I2
0	0
30	70,08
60	148,05
150	368,72

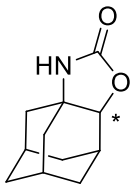
Intensity 41,59
Concentration µg/ml 338,8



	I1			I2					
konc. ug/ml	216	409	216+409	216	409	216+409	I1+I2	1:2	r
0	0	0	0	0	0	0	0		
30	13201584	22519355	35,72094	15270149	19085517	34,35567	70,07661	1,04	
60	16603162	53136887	69,74005	18685749	59623108	78,30886	148,0489	0,89	
150	37753792	1,41E+08	178,7522	33865371	1,56E+08	189,9651	368,7173	0,94	
3	13180706	18617919	31,79863	4528296	5266515	9,794811	41,59344	3,25	20

Fig. 13. Calibration of signal intensity *versus* concentration of compound *rac*-**3**.

Racemic mixture of **3** served as standard.



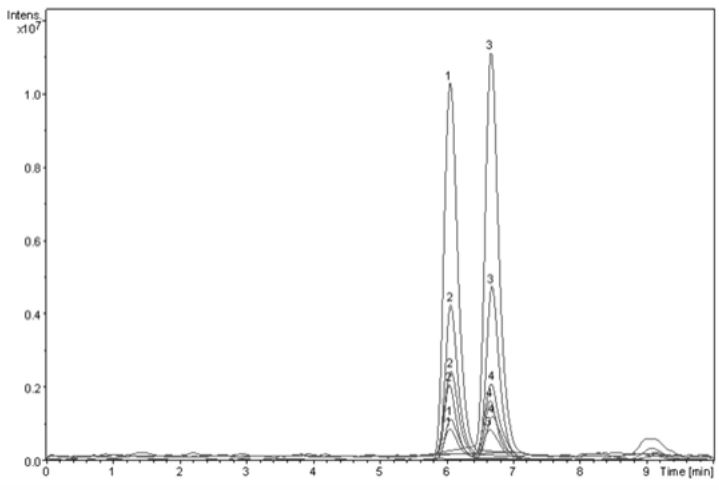
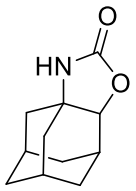


Fig. 14. HPLC-MS spectrum of standard *rac*-**3**.

Minor product of UV irradiation experiment of sample **1**. Enantioenriched **3** was isolated using extraction into EtOAc.



(**3**) ratio of enantiomers: 75%:25%

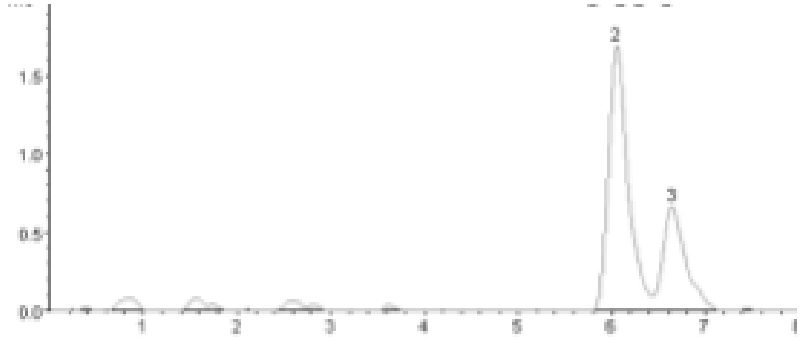


Fig. 15. HPLC-MS spectrum of enantioenriched compound **3**.

5. IR analysis of 1 before and after irradiation

Measurement of reflections IR spectra was performed with FTIR microscope iN10 (Thermo Nicolet). Spectra were measured with both room temperature DTGS and cooled MCT-A detector (128/256 accumulation), aperture 150 x 150 µm/ 400 x 400 µm and spectral resolution 8 cm^{-1}. FTIR reflection spectra were measured against reflectivity of the golden surface.

UV irradiation was performed using a 254 nm line from UV lamp (p-lab, 2 x 4 W). Intensity at 254 nm was 500 $\mu W/cm^2$ (15 cm), actual distance was about 6-7 cm, corresponding intensity for 6 cm was ~3 mW/cm^2. Time of the irradiation was 1 hour.

FTIR reflection spectra of **1** were measured before and after UV irradiation.

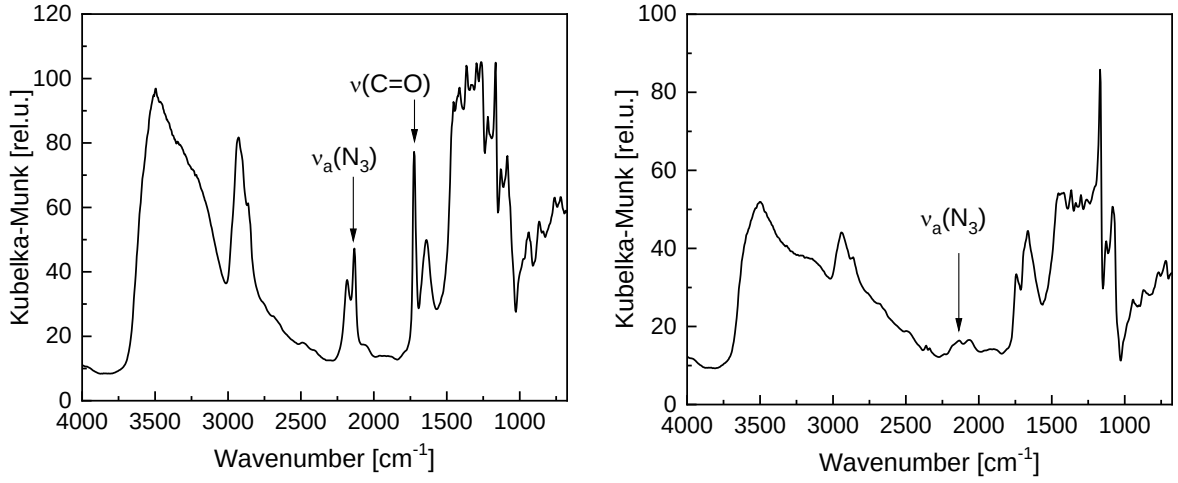


Fig. 16. FTIR reflection spectra of **1** before (A) and after (B) one hour of UV irradiation at 254 nm.

6. Crystallographic data collection and refinement details of assembly 1

The diffraction data of single crystal of assembly **1** sample were obtained on Bruker D8 VENTURE Kappa Duo PHOTONIII by IμS micro-focus sealed tube with CuKα (λ= 1.54178) radiation at temperature of the crystal 150K preserved by Cryostream Cooler 800. The structures were solved by direct methods (XT[39a]) and refined by full matrix least squares based on F^2 (SHELXL2019[39b]). The hydrogen atoms on carbon were fixed into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom). Hydrogen atoms on -O-H moieties were found on difference Fourier map and refined under rigid-body assumption.

Being a α-cyclodextrin compound atoms in the crystal are vastly disordered. Therefore positions of water molecules and many of hydrogen atoms could not be resolved and several restrains have to be applied during refinement. Absolute structure was assigned by known chirality of α-cyclodextrin molecule.

Basic crystallographic data are given in Table 1.

X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC), the deposition numbers are in Table 6.1 and can be obtained free of charge from the Centre via its website (www.ccdc.cam.ac.uk/structures/).

39a. SHELXT: Sheldrick, G.M. (2015). *Acta Cryst*. **A71**, 3-8.

39b. SHELXL: Sheldrick, G.M. (2015). *Acta Cryst.* **C71**, 3-8.

Table 1 Crystal data and structure refinement for complex **1.**

CCDC number	2411472
Empirical formula	$C_{83}H_{123}N_3O_{75.50}$
Formula weight	2370.84
Temperature [K]	150(2)
Crystal system	monoclinic
Space group (number)	$P2_1$ (4)
a [Å]	16.1358(6)
b [Å]	14.0944(6)
c [Å]	24.2566(10)
α [°]	90
β [°]	91.205(2)
γ [°]	90
Volume [Å^3]	5515.3(4)
Z	2
ρ_{calc} [gcm^{-3}]	1.428
μ [mm^{-1}]	1.125
F(000)	2492
Crystal size [mm^3]	0.211×0.234×0.295
Crystal colour	colourless
Crystal shape	prism
Radiation	CuK_α (λ=1.54178 Å)
2θ range [°]	6.52 to 144.53 (0.81 Å)
Index ranges	−19 ≤ h ≤ 19 −17 ≤ k ≤ 17 −29 ≤ l ≤ 29
Reflections collected	132581
Independent reflections	21607 R_{int} = 0.0443 R_{sigma} = 0.0422
Completeness to θ = 67.679°	99.8
Data / Restraints / Parameters	21607 / 55 / 1487
Goodness-of-fit on F^2	1.050
Final *R* indexes [*I*≥2σ(*I*)]	R_1 = 0.0648 wR_2 = 0.1828
Final *R* indexes [all data]	R_1 = 0.0659 wR_2 = 0.1843
Largest peak/hole [eÅ^{-3}]	1.24/−0.45
Flack X parameter	0.00(4)