Supporting Information

Stereoselective organocatalysed reactions in deep eutectic solvents: highly tunable and biorenewable reaction media for sustainable organic synthesis

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General Methods

Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Melting point were determined with Branstead Electrothermal 9100 capillary melting point apparatus. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{19}F NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282 MHz. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Optical rotations were obtained on a polarimeter at 589 nm using 5 mL or 1 mL cell 1 dm long. Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Microwaves assisted reactions were performed in MW instrument CEM Discover S.

Materials

Commercial grade reagents and solvents were used without further purifications. Quinine (anhydrous, technical grade 98%), *trans*-β-nitrostyrene (technical grade 97%), trifluoroacetic acid (99%), were purchased from Sigma-Aldrich. Silica (Apex Prepsil Silica Media 8 μm) was purchased from Grace.

Trans-ethyl-3-nitrobut-2-enoate[1] was prepared according to published procedures.
Isobutyraldehyde, was purified by distillation under atmospheric pressure and under nitrogen atmosphere before use. Cyclohexanone and was purified by distillation under reduced pressure before use.
4-Hydroxycoumarin was recrystallized from EtOAc before use; benzalacetone was recrystallized from hexane before use.

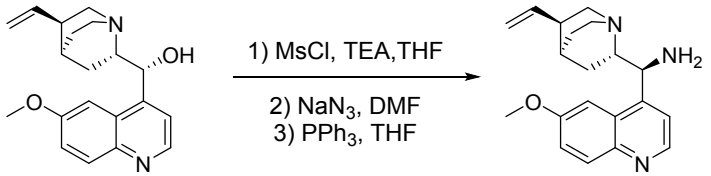
DES Preparation

The employed Deep Eutectic Solvents (*DESs*)[2] [*DES* **A** choline chloride/urea 1/2; *DES* **B** choline chloride fructose/water 1/1/1; *DES* **C** choline chloride /glycerol 1/2)] were prepared by gentle heating under stirring at 70 °C for 15 min the corresponding individual components until a clear solution was obtained.

Determination of DES B density

Density of *DES* **B** was determined to be 1.21 g/mL.
For this determination, the *DES* (1.21 g) was weighted directly in a 1 mL volumetric flask.

Synthesis of catalyst Q



Quinine **Q**

9-Amino-(9-deoxy)-*epi*-quinine **Q** is known[3] and it was prepared according to the published procedure.[4] Anhydrous quinine (3.08 mmol, 1 g) was dissolved in dry THF (30 mL) under nitrogen atmosphere, then dry triethylamine (15.4 mmol) was added. The solution was cooled to 0 °C with an ice-water bath and after 10 minutes of stirring, methanesulfonyl chloride (9.3 mmol) was added dropwise. After 5 minutes, the mixture was warmed to room temperature and it was stirred for 5 hours. After reaction time, $NaHCO_3$ (10 mL, saturated solution) was added. The organic layer was separated, and then the aqueous phase was extracted three times with CH_2Cl_2 (20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The mesylate derivative, obtained as a pale yellow solid, was dissolved in dimethylformamide (30 mL) and NaN_3 (6.2 mmol) was subsequently added. The mixture was stirred at 70 °C for 18 hours; after this period, the solvent was removed under reduced pressure. The crude was dissolved in CH_2Cl_2 (15 mL) and water was added (8 mL). The organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2 (8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, affording the product as a brownish solid.

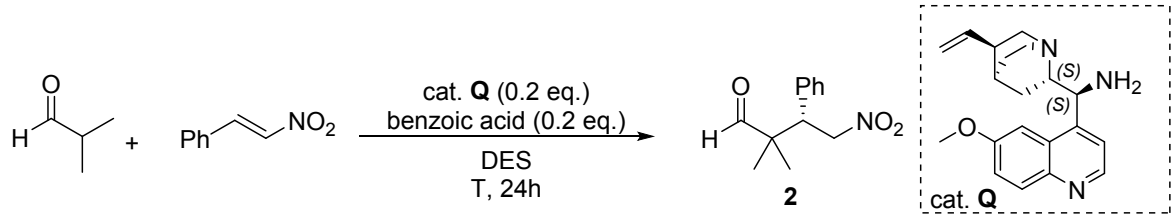
The azide derivative was dissolved in dry THF (25 mL) under nitrogen atmosphere and heated to 50 °C. A solution of PPh_3 (4.6 mmol) in dry THF (6 mL) was slowly added and the mixture was stirred at 50 °C for 4 hours. After this period, the mixture was cooled to room temperature and water (1 mL) was added. After 15 hours of stirring, the solvent was evaportaed under vacuum, the crude product was diluted in CH_2Cl_2 (20 mL) and HCl (5 mL, 10 % wt. solution) was added up to pH 4. The organic layer was washed twice with CH_2Cl_2 (12 mL); subsequently, NH_4OH (5 mL, 33% wt solution) was added up to pH 8. The organic phase was extracetd three times with CH_2Cl_2 (15 mL) and the combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum affording a yellowish solid. The crude product was purified by flash column chromatography on silica-gel (eluent: CH_2Cl_2/MeOH/NH_4OH = 98/2/1 to 95/5/1) yielding to amine **Q** as a white-off solid (2.2 mmol, 73 % yield).

TLC R_f = 0.22 (CH_2Cl_2/MeOH = 9/1, stained orange with ninhydrin)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.71 (d, 1H), 7.99 (d, 1H), 7.65 (bs, 1H), 7.42 8d, 1H), 7.34-7.38 (dd, 1H), 5.72-5.84 (m, 1H), 4.96 (d, 1H), 4.93 (d, 1H), 4.55 (d, 1H), 3.94 (s, 3H), 3.19-3.30 (m, 2H), 3.05 (q, 1H), 2.76-2.82 (m, 2H), 2.26 (bs, 1H), 1.51-1.61 (m, 3H), 1.41 (bt, 1H), 0.72-0.78 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.8, 148.5, 148.4, 145.1, 142.1, 131.5, 130.1, 123.4, 115.4, 102.8, 63.0, 56.5, 56.3, 41.7, 40.4, 28.7, 28.1, 26.6, 24.3

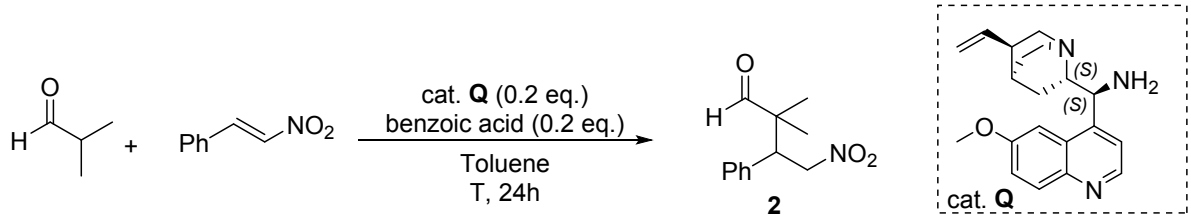
Addition of a carbonyl compound to nitrostyrene: substrate activation *via* enamine



General procedure for stereoselective organocatalyzed conjugate addition in *DES*

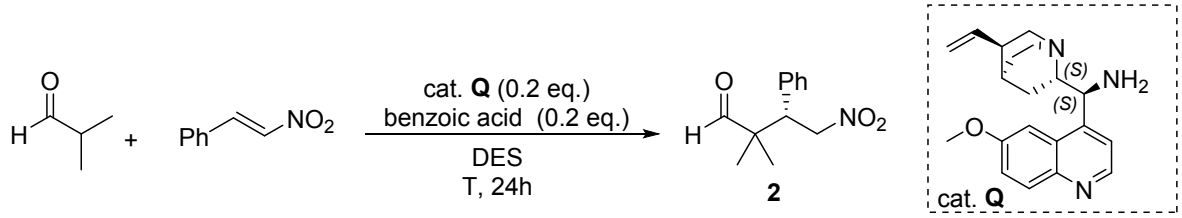
Catalyst **Q** (17 mg, 0.053 mmol, 20 mol%) and benzoic acid (0.053 mmol 20 mol%; while investigating reaction conditions, it was observed that the desired product is formed even in the absence of the benzoic acid – see Table 2) were dissolved in the desired *DES* (353.3 mg – for optimization studies about reaction concentration in *DES* see Table 3) and kept under stirring; after 5 minutes, freshly distilled isobutyraldehyde (1.325 mmol, 5 eq) was added and the reaction mixture was kept under stirring for further 5 minutes. Nitrostyrene (0.265 mmol, 1 eq) was finally added and the reaction mixture was stirred for the reported time at the desired temperature (see Table 2 and 3). After this period, the mixture was treated with water and the desired product was extracted with Et_2O. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.
When the reaction was subjected to microwave irradiation, it was run in proper MW vial.

General procedure for stereoselective organocatalyzed conjugate addition in toluene



Catalyst **Q** (10 mg, 0.031 mmol, 20 mol%) and benzoic acid (0.031 mmol, 20 mol%; while investigating reaction conditions, it was observed that the desired product is formed even in the absence of the benzoic acid – see Table 2) were dissolved in toluene (0.17 mL); after 5 minutes, freshly distilled isobutyraldehyde (0.77 mmol, 5 eq) was added and stirred for further 5 minutes. After this period, nitrostyrene (0.155 mmol, 1 eq) was added. The reaction mixture was kept under constant stirring for 24 hours at the desired temperature (see Table 2) and finally quenched with HCl (10% aqueous solution) (2 mL). The product was extracted with EtOAC. The collected organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

General procedure for recycle experiments

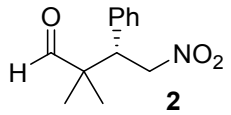


Catalyst **Q** (43 mg, 0.133 mmol, 20 mol%) and benzoic acid (0.133 mmol, 20 mol%) were dissolved in the desired *DES* (886.7 mg) and kept under stirring; after 5 minutes freshly distilled isobutyraldehyde (3.325 mmol, 5 eq) was added and the reaction mixture was kept under stirring for further 5 minutes. Nitrostyrene (0.665 mmol, 1 eq) was finally added and the reaction mixture was stirred for the reported time at room temperature (see Table 4). After this period, hexane/iPr$_2$O 7/3 (1 mL) was added and the mixture stirred for further 2 minutes. The stirring was stopped to allow phase separation. The organic layer was removed through settling and the solvent was removed under reduced pressure; this procedure was repeated twice.

The desired product, extracted through this procedure in the organic phase, was purified by flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

The catalytic system (i.e. catalyst and acidic co-catalyst) was regenerated by benzoic acid addition (20 mol%), in the *DES* phase, where catalyst **Q** was still dissolved. Thus, a further reaction was performed within this *DES*, where isobutyraldehyde (5 eq.) and *trans*-β-nitrostyrene (1 eq.) were added. This reaction mixture was subjected to the above described procedure and further reaction cycles were repeated within the same *DES* phase.

Characterization of product 2



2

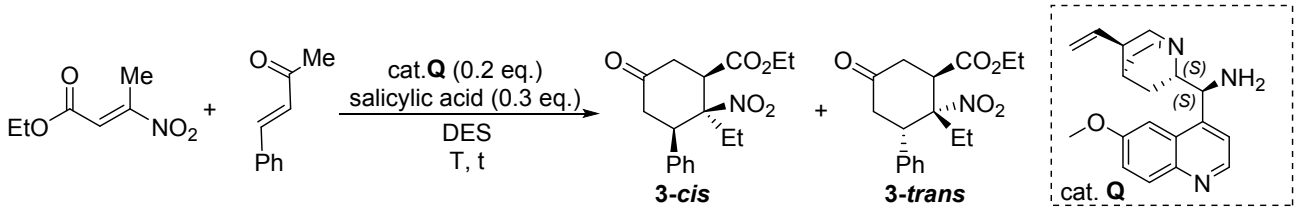
Compound **2** was purified by flash column chromatography on silica gel (eluent: Hexane/EtOAC = 9/1) to afford a colorless oil; analytical data are in agreement with the reported ones[5].

TLC R_f = 0.27 (Hexane/EtOAC = 9/1, stained blue with phosphomolibdic acid)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.35-7.20 (m, 5H), 4.88 (dd, J=12.9, 11.3 Hz, 1H), δ 4.72 (dd, J=13.0, 4.3 Hz, 1H), 3.81 (dd, J=11.2, 4.3 Hz, 1H), 1.15 (s, 3H), 1.03 (s, 3H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent hexane/*i*PrOH = 8/2, flow rate 0.8 mL/min, λ=210 nm, τ_{minor}=12.5 min, τ_{major}=17.2 min.

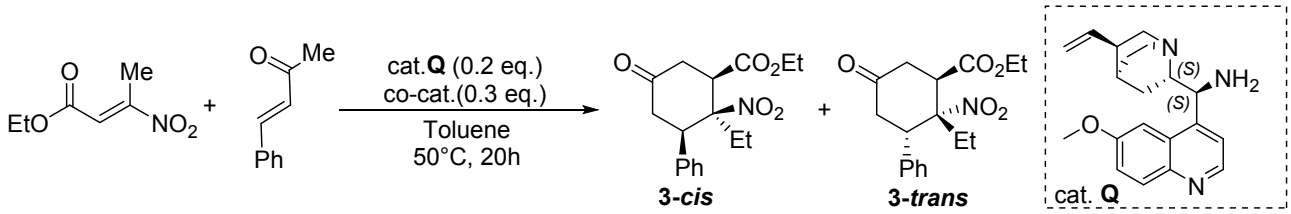
Addition of nitroacrylate to benzalacetone: substrate activation *via* dienamine



General procedure for stereoselective organocatalyzed conjugate addition in *DES*

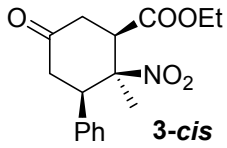
Catalyst **Q** (20 mg, 0.063 mmol, 20 mol%), salicylic acid (0.094 mmol, 30 mol%) and *trans*-ethyl-3-nitrobut-2-enoate (0.314 mmol, 1 eq) were dissolved in the desired *DES* (314 mg) and stirred for 10 minutes; benzalacetone (0.628 mmol, 2 eq) was finally added. The reaction mixture was stirred at the desired temperature for the reported time (see Table 5) and after this period was treated with water. The desired product was extracted with Et_2O. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.
When the reaction was subjected to microwave irradiation, it was run in proper MW vial.[6]

General procedure for stereoselective organocatalyzed conjugate addition in toluene



Catalyst **Q** (12 mg, 0.038 mmol, 20 mol%), salycilic acid (0.057 mmol, 30 mol%) and *trans*-ethyl-3-nitrobut-2-enoate (0.19 mmol, 1 eq) were dissolved in dry toluene (0.19 mL) under N_2 atmosphere and stirred for 10 minutes. After this period, benzalacetone (0.38 mmol, 2 eq) was added. The reaction mixture was stirred at the desired temperature for 20 hours, after which solvent was removed under reduced pressure. The desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 90/10 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

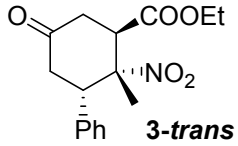
Characterization of products 3



3-*cis*

Compound **3-*cis*** was purified by flash column chromatography on silica gel (eluent: hexane/EtOAC = 90/10) to afford a white-off solid; analytical data are in agreement with the reported ones.[7]

TLC R_f = 0.09 (Hexane/EtOAC = 8/2)
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 7.10-7.07 (m, 2H), 4.23-4.20 (m, 2H), 3.53-3.43 (m, 1H+1H), 3.25-3.16 (m, 1H+1H), 2.84 (ddd, J=15.5, 5.6, 1.7 Hz, 1H), 2.63 (ddd, J=15.5, 4.5, 1.8 Hz, 1H), 1.58 (s, 6H), 1.29 (t, J=7.1 Hz, 4H).
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent Hexane/*i*PrOH = 8/2, flow rate 0.8 mL/min, λ=210 nm, τ_{minor}=21.5 min, τ_{major}=40.7 min.



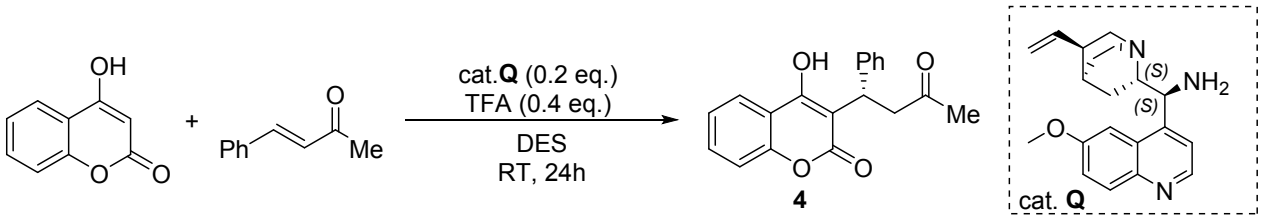
3-*trans*

Compound **3-*trans*** was purified by flash column chromatography on silica gel (eluent: hexane/EtOAC = 90/10) to afford a white-off solid; analytical data are in agreement with the reported ones.[7]

TLC R_f = 0.14 (Hexane/EtOAC = 8/2)
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34-7.28 (m, 4H), 7.10 (d, J=2.5 Hz, 2H), 4.25-4.18 (m, 2H), 3.87 (dd, J=9.8, 4.8 Hz, 1H), 3.65 (dd, J=9.3, 4.5 Hz, 1H), 3.25 (dd, J =16.4, 9.7 Hz, 1H), 3.10 (dd, J=17.2, 5.1 Hz, 1H), 2.73 (dd, J=15.2, 9.8 Hz, 1H), 2.69-2.61 (m, 1H), 1.83 (s, 3H), 1.29 (d, J=1.2 Hz, 7H).
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralpack AD column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=210 nm, τ_{major}=27.9 min, τ_{minor}=33.5 min.

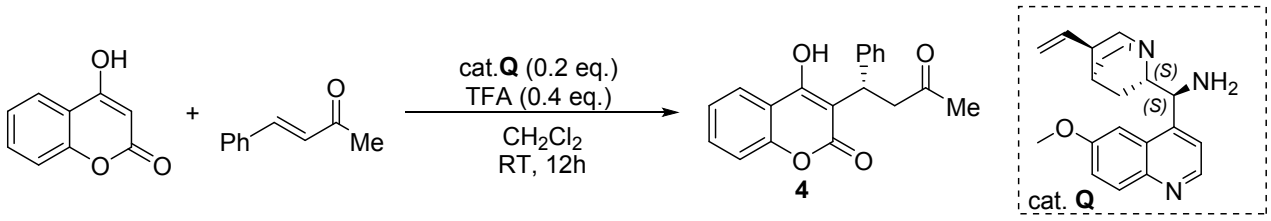
Addition of 4-hydroxycoumarin to benzalacetone (synthesis of (*S*)-Warfarin): substrate activation *via* iminium ion

General procedure for stereoselective organocatalyzed conjugate addition in DES



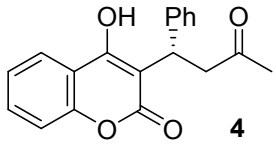
Catalyst **Q** (10 mg 0.031 mmol, 20 mol%), benzalacetone (0.31 mmol, 2 eq) 4-hydroxycoumarin (0.155 mmol, 1 eq) and trifluoroacetic acid (0.062 mmol, 40 mol%) were dissolved in the desired *DES* (155 mg). The reaction mixture kept under constant stirring for 24 hours at room temperature. After this period, the reaction mixture was treated with water and the desired product was extracted with Et_2O. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified by flash column chromatography on silica gel using the mixture hexane/EtOAC 70/30 as eluent. The enantiomeric excess was determined byHPLC analysis on chiral stationary phase.

General procedure for stereoselective organocatalyzed conjugate addition in CH_2Cl_2



Catalyst **Q** (0.02 mmol, 20 mol%), 4-hydroxycoumarin (0.1 mmol, 1eq), benzalacetone (0.15 mmol, 2 eq) and trifluoroacetic acid (0.04 mmol, 40 mol%) were dissolved in CH_2Cl_2 (2 mL) for 12 hours at room temperature. After this period, the reaction mixture was quenched by adding 1M HCl (0.5 mL). After this period, the reaction mixture was treated with water and the desired product was extracted with EtOAC. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure; the desired product was purified through flash column chromatography on silica gel using the mixture hexane/EtOAC 70/30 as eluent. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

Characterization of products 4

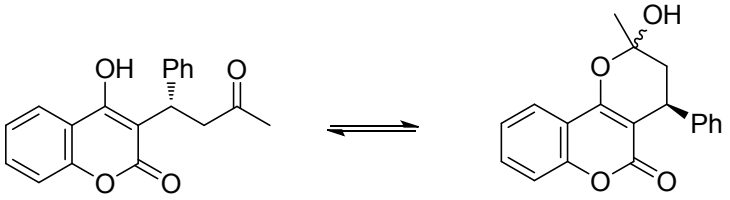


4

Compound **4** was purified by flash column chromatography on silica gel (eluent: hexane/EtOAC = 70/30) to afford a white-off solid; analytical data are in agreement with the reported ones.[8]

TLC R_f = 0.28 (Hexane/EtOAC = 70/30, stained yellow with $KMnO_4$)

Compound **4** was found to exist in rapid equilibrium with hemiketal form in solution. The equilibrium is rapid enough so that the two forms are not observed during HPLC analysis using the mixture of hexane/*i*PrOH containing 0.1% TFA as eluent; however, both forms are visible in the ^{1}H NMR spectrum.[i]

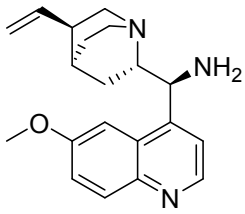


mixture diastereoisomers

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 0.14H), 7.92 (d, *J* = 7.9 Hz, 0.37H), 7.84 (d, *J* =8.0 Hz, 0.42H), 7.61-7.50 (m, 1.13H), 7.39-7.21 (m, 7.38H), 4.73(d, *J* = 10.0 Hz, 0.17H), 4.32 (dd, *J* =6.4, 2.8 Hz, 0.45H), 4.22-4.11 (m, 0.70H), 3.89 (dd, *J* = 19.6, 10.2 Hz, 0.20H), 3.37(s, 0.12H), 3.27 (d, *J* =21.8 Hz, 0.77H), 2.55-2.41 (m, 1.55H), 2.05(dd, *J*= 17.3, 7.7 Hz, 0.98H), 1.74 (s, 1.53), 1.70 (s, 1.40H).

The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralpack AD column: eluent hexane/*i*PrOH = 8/2 +0.1% TFA, flow rate 0.8 mL/min, λ=280 nm, τ_{minor}=7.7, τ_{major}=18.8 min

^{1}H NMR spectra



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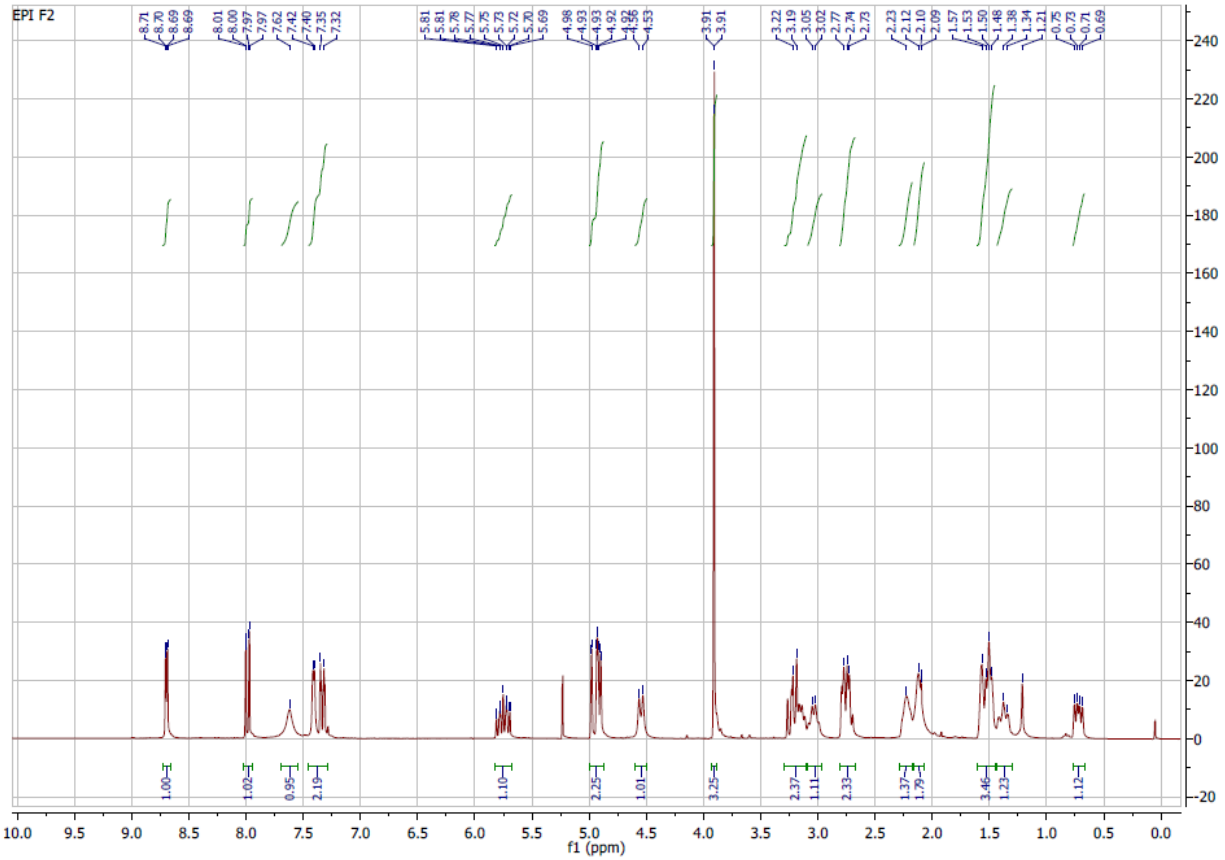

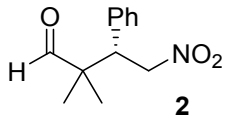

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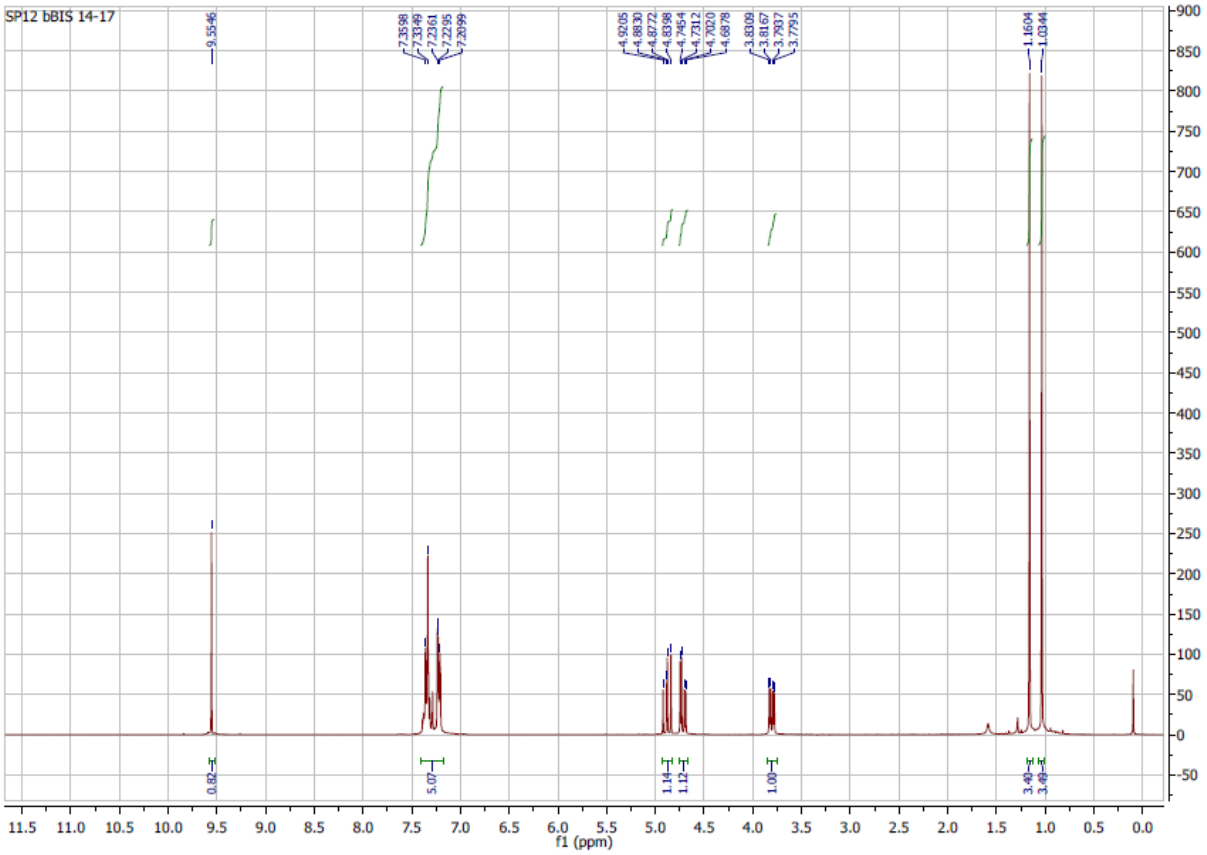
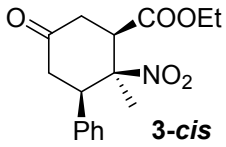
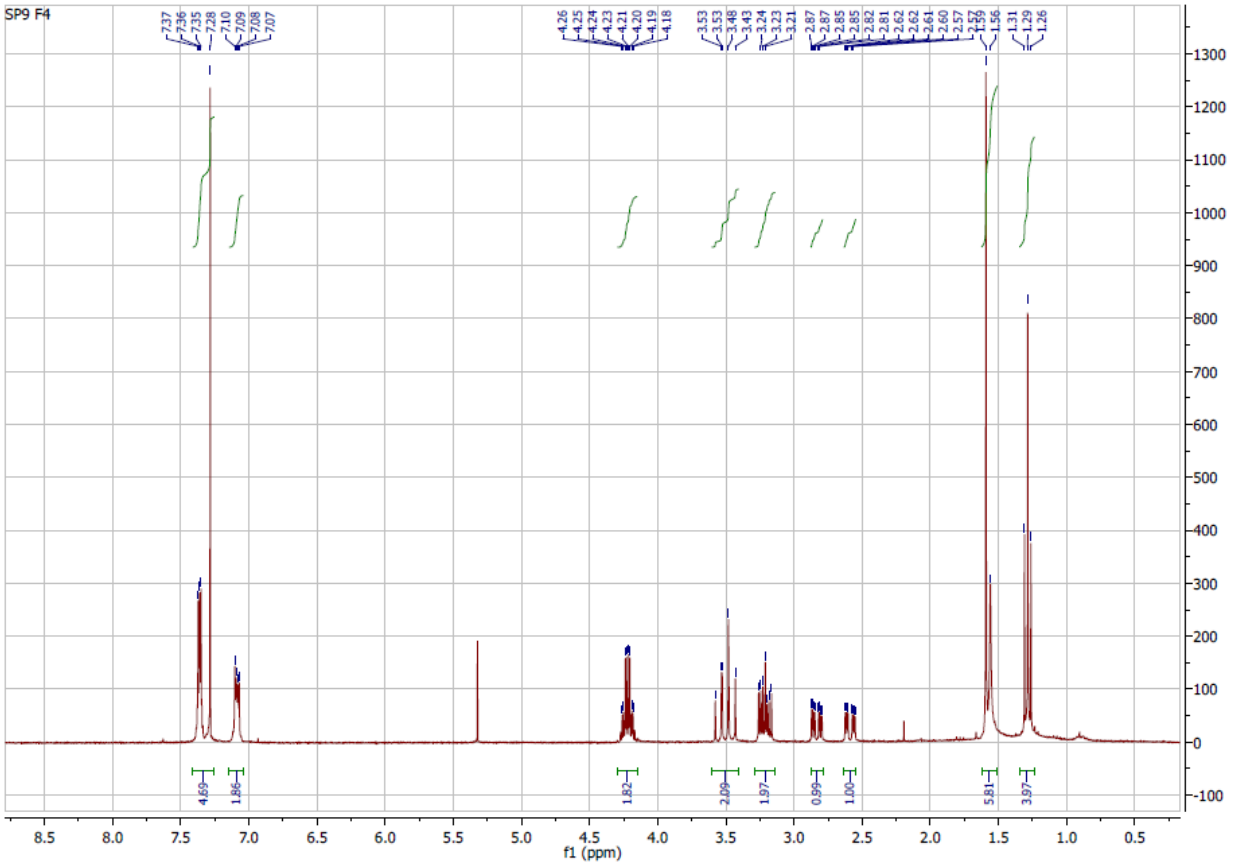
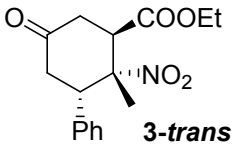


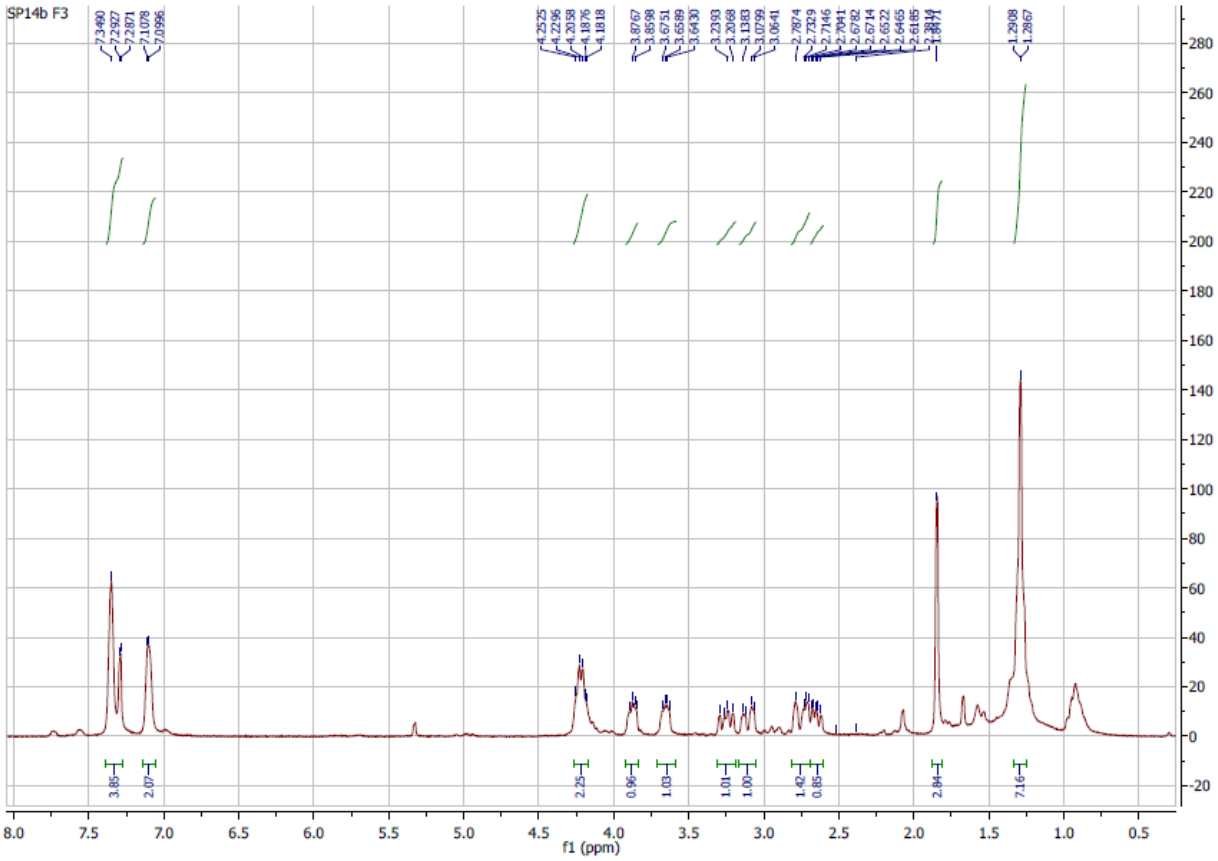


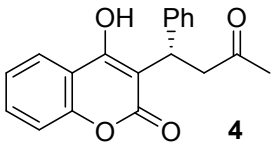
3-*cis*





3-*trans*





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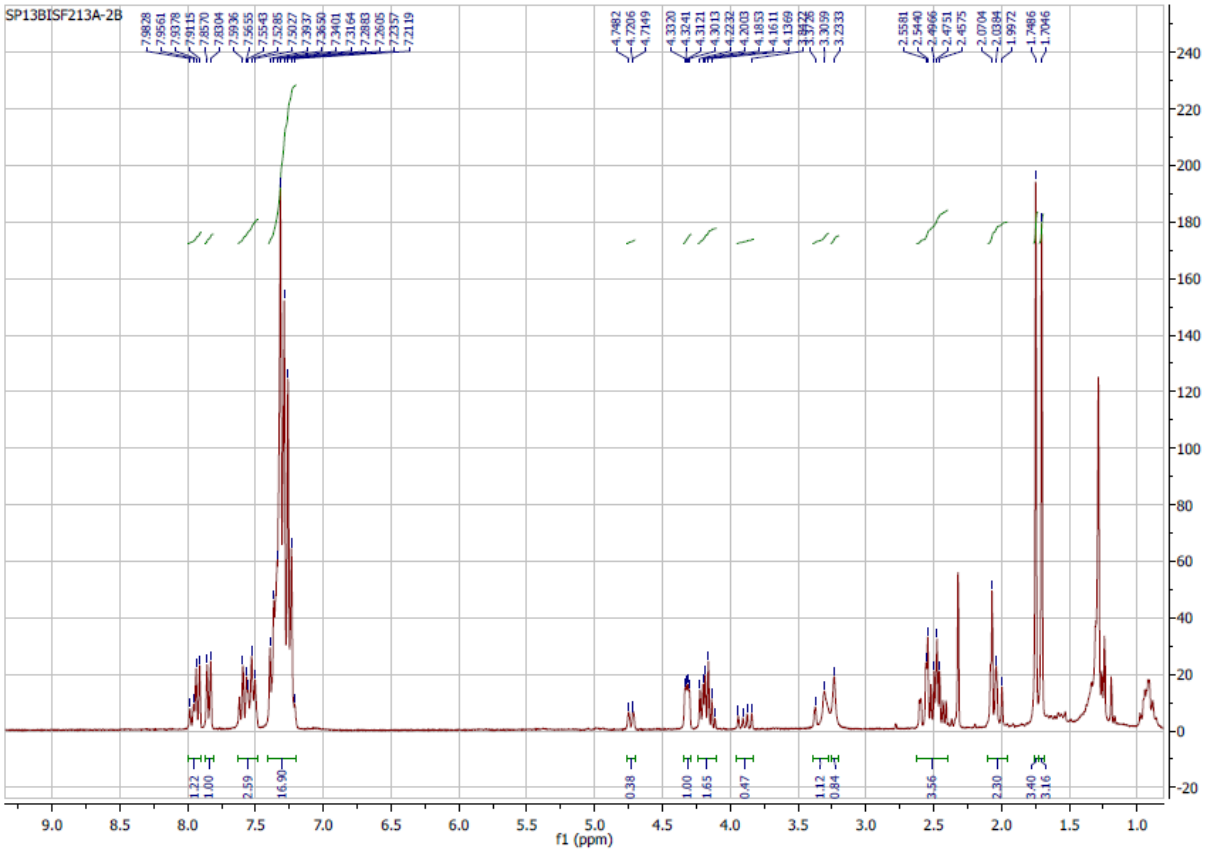
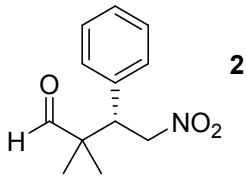
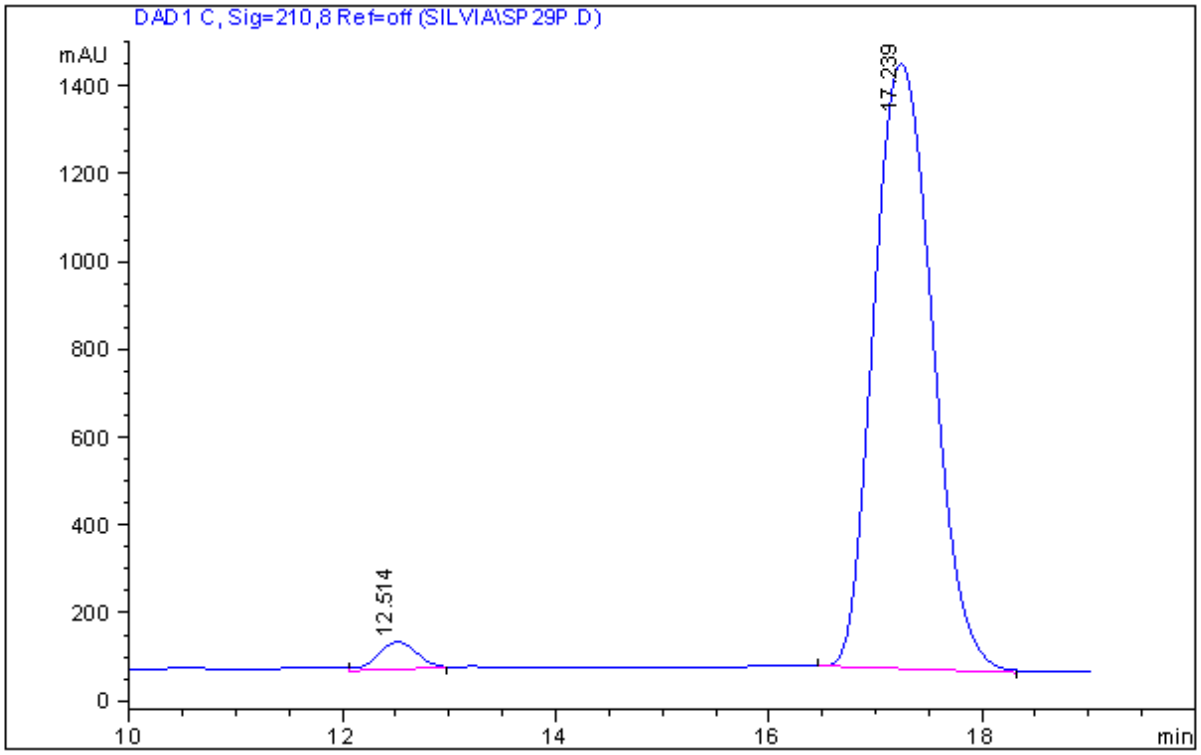


HPLC chromatograms



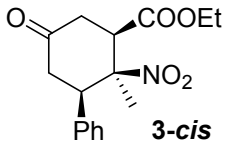
2

Chiralcel OD-H column, eluent Hexane/*i*PrOH = 8/2, flow rate 0.8 mL/min, λ=210 nm



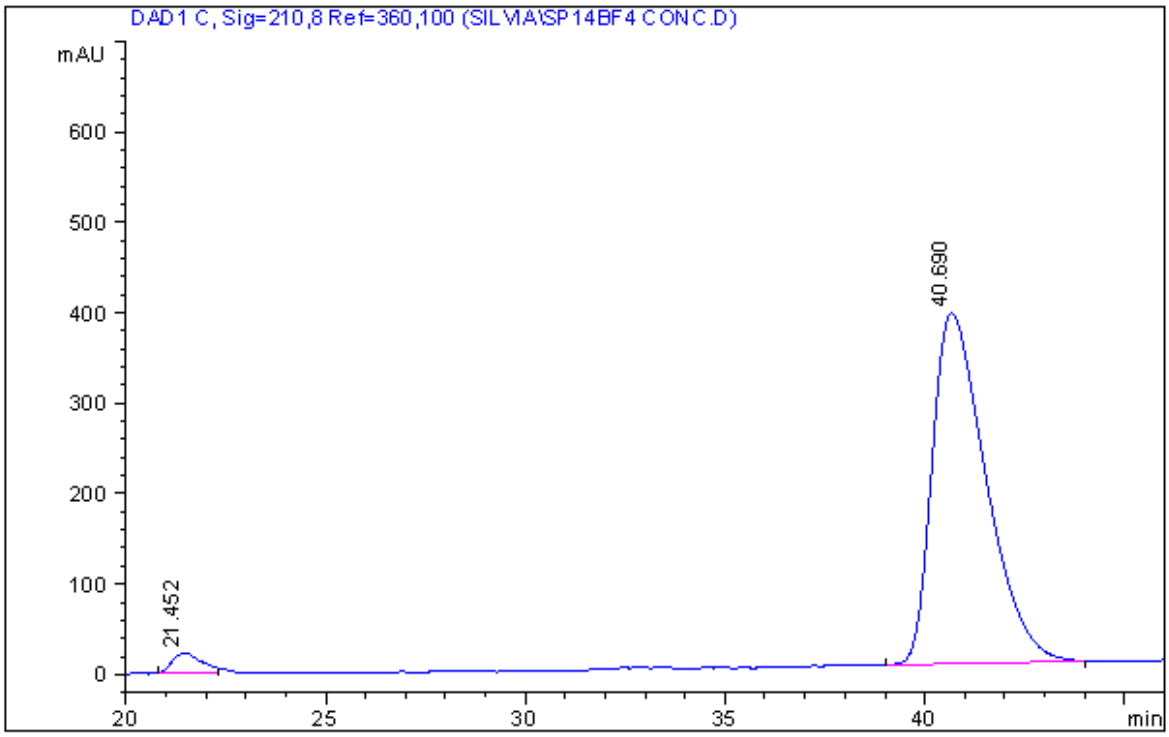
Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	12.514	MM	0.423	1563.251	2.875	
2	17.239	MM	0.640	52814.699	97.125	



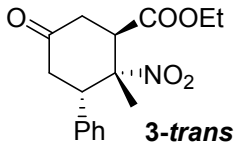
3-*cis*

Chiralcel OD-H column, eluent Hexane/*i*PrOH = 8/2, flow rate 0.8 mL/min, λ=210 nm



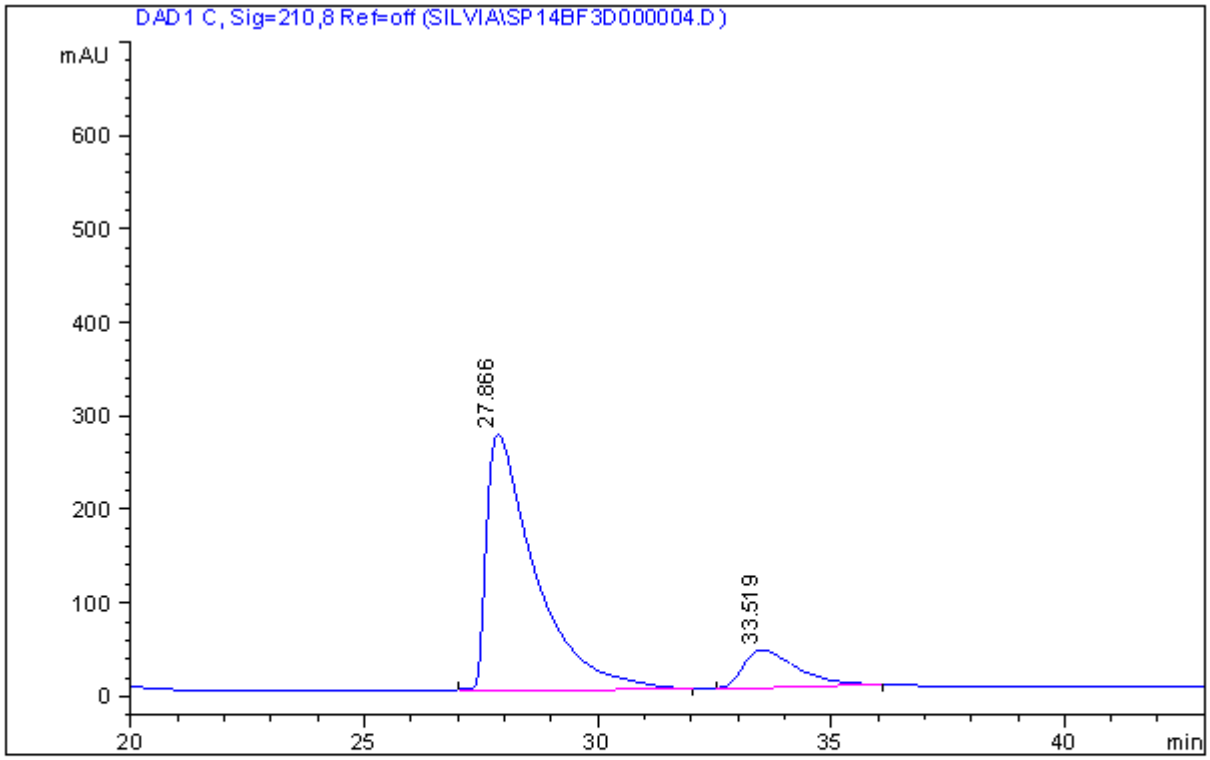
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	21.452	MF	0.857	1115.657	2.986	
2	40.690	MM	1.556	36244.973	97.014	



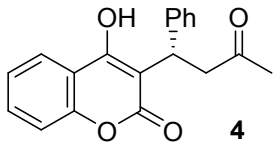
3-*trans*

Chiralcel AD column, eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=210 nm



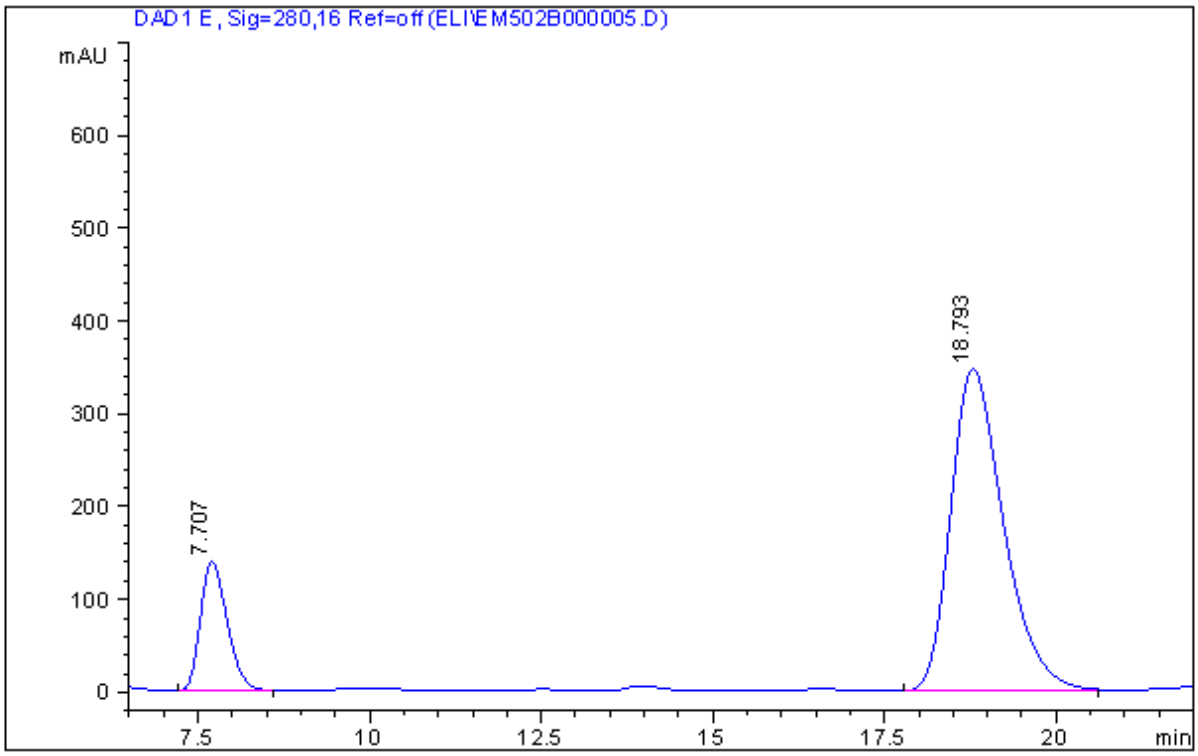
Signal 1: DAD1 C, Sig=210,8 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	27.866	MM	1.215	19944.850	85.973	
2	33.519	MM	0.951	3254.084	14.027	



4

Chiralcel AD column, eluent Hexane/*i*PrOH = 8/2 + 0.1% TFA, flow rate 0.8 mL/min, λ=280 nm



Signal 1: DAD1 E, Sig=280,16 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	7.707	BB	0.419	3758.232	16.841	
2	18.793	BB	0.815	18558.094	83.159	

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