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Supporting Information

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Organocatalytic Asymmetric Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides

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General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. NMR NOE experiments were recorded at 600 MHz. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$). Coupling constants are given in Hz. Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. X-ray structure analysis was carried out at the Department of Organic Chemistry *"A. Mangini"* X-ray Crystallography facility. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent).

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2]
β-keto esters **1a-b** and **1d-f** and β-diketones **1h-i** were purchased from Aldrich or Lancaster and used as received. β-keto esters **1c**[3] and **1g**[4] were prepared following the literature procedures.
Maleimides **2a-d** were purchased from Aldrich and used as received.
Natural cinchona alkaloids quinine **Q** and quinidine **QD** were purchased from Aldrich and used as received. Benzoylquinine (**BQ**) was prepared according to standard literature procedures (quinine / Et_3N / benzoylchloride /DCM/ overnight, RT).[5] Bifunctional organocatalysts **A**,[6] **B**[7] and **C**[8] were prepared following the literature procedures.

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Chiralcel OD-H with i-PrOH/hexane as the eluent were used.

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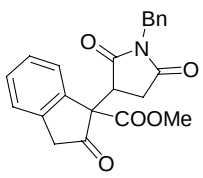
[1] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[2] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
[3] K. Van Emelen, T. De Wit, G. J. Hoornaert, F. Compernolle, *Tetrahedron* **2002**, *58*, 4225.
[4] A. G. M. Barrett, H. G. Sheth, *J. Org. Chem.* **1983**, *48*, 5017.
[5] S. France, H. Wack, A. E. Taggi, A. M. Hafez, T. R. Wagerle, M. H. Shah, C. L. Dusich, T. Lectka, *J. Am. Chem. Soc.* **2004**, *126*, 4245.
[6] H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.
[7] B. Vakulya, Sz. Varga, A. Csámpai, T. Soos, *Org. Lett.* **2005**, *7*, 1967.
[8] Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219.

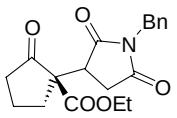
HPLC traces were compared to racemic samples prepared with equimolar amount of quinine and quinidine or by using Et_3N as the catalyst.

Experimental Procedures.

General Procedure for the Natural Cinchona Alkaloids-catalyzed Asymmetric Conjugate Addition of 1,3-Dicarbonyl Compounds to *N*-Benzylmaleimide. All the reactions were carried out in undistilled solvent without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, quinine **Q** or quinidine **QD** (0.02 mmol) was dissolved in 0.4 mL of DCM. After addition of the 1,3-dicarbonyl compound (0.2 mmol), the tube was closed with a rubber stopper and the mixture was stirred at the indicated temperature for 10 minutes. Then *N*-benzylmaleimide **2d** (0.24 mmol) was added in one portion and stirring was continued until GC and TLC analysis showed disappearance of the 1,3-dicarbonyl compound. Then the crude reaction mixture was diluted with hexane (2 mL) and flushed through a plug of silica, using hexane/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography (FC) to yield the desired 1,4-adduct.

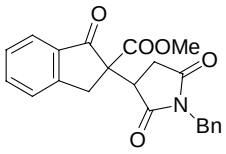


3d – The reaction was carried out at –20°C for 24 h using 10 mol% of **Q** to furnish the crude product [dr = 94:6, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.63 ppm, δ_{minor} 2.66 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a white solid (melting point: 57-62 °C) in 97% yield (dr = 95:5, confirmed by relative areas of HPLC analysis) and 92% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (92% ee): τ_{major} = 15.6 min, τ_{minor} = 18.2 min; minor diastereomer (5% ee): τ_{major} = 22.5 min, τ_{minor} = 24.6 min;]. $[\alpha]^{rt}_D$= -9.6° (*c* = 1.0, $CHCl_3$, 92% ee). HRMS: *m/z* calcd for $C_{22}H_{19}NO_5$: 377.12632; found: 377.12601. ^{1}H NMR ($CDCl_3$): δ = 2.54 (dd, *J* = 6.0, 18.0, 1H), 2.92 (dd, *J* = 9.2, 18.0, 1H), 3.59 (AB, *J* = 22.8, 2H), 3.73 (s, 3H), 3.98 (dd, *J* = 6.0, 9.2, 1H), 4.59 (AB, *J* = 14.0, 2H), 7.08-7.38 (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 32.1 (CH_2), 42.5 (CH_2), 43.1 (CH_2), 44.6(CH), 53.4 (CH_3), 64.8 (C), 124.5 (CH), 125.1 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH, 2C), 128.7 (CH, 2C), 129.3 (CH), 135.3 (C), 137.1 (C), 137.5 (C), 168.3 (C), 174.7 (C), 175.9 (C), 209.6 (C).

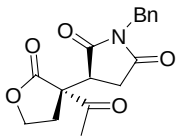


4b – The reaction was carried out at –60°C for 40 h using 10 mol% of **QD** to furnish the crude product [dr = 87:13, determined by integration of one set of ^{1}H NMR signal (δ_{major} 4.20-4.25 ppm, δ_{minor} 4.10-4.14 ppm)]. The title compound was isolated by column chromatography (hexane/AcOEt = 8/2) as a colourless foam in 99% yield (dr = 87:13, confirmed by relative areas of HPLC analysis) and 98% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214; (R*,S*)-major diastereomer (98% ee): τ_{minor} = 14.4 min, τ_{major} = 16.2 min; (R*,R*)-minor diastereomer (24% ee): τ_{minor} = 18.0 min, τ_{major} = 19.1 min]. $[\alpha]^{rt}_D$= - 11.8° (*c* = 1.04, $CHCl_3$, 98% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_5$: 343.14197; found 343.14184. ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.2, 3H), 1.97-2.07 (m, 2H), 2.14-2.24 (m, 1H), 2.38-2.56 (m, 3H), 2.68 (dd, *J* = 6.0, 18.0, 1H), 2.87 (dd, *J* = 9.2, 18.0, 1H), 3.50 (dd, *J* = 6.0, 9.2, 1H), 4.22 (q, *J* = 7.2, 2H), 4.62 (AB, *J* = 14.2, 2H), 7.24-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 19.1 (CH_2), 31.6 (CH_2), 32.6 (CH_2), 37.9 (CH_2), 42.1 (CH), 42.2 (CH_2), 60.6 (C), 62.0 (CH_2), 127.7 (CH), 128.3 (CH, 2C), 128.5 (CH, 2C), 135.4 (C), 169.5 (C), 175.0 (C), 177.0 (C), 213.5 (C).

The relative configuration (R*, S*) of the major diastereomer of (-)-4b was determined by extensive NMR NOE studies.

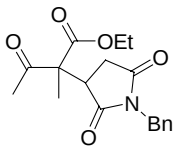


4c – The reaction was carried out at –60°C for 38 h using 10 mol% of **Q** to furnish the crude product [dr = 91:9, determined by integration of one set of ^{1}H NMR signal (δ_{major} 3.75 ppm, δ_{minor} 3.57 ppm - s)]. The title compound was isolated by column chromatography (hexane/AcOEt = 7/3) as a white solid (melting point: 57-60 °C) in 98% yield (dr = 91:9, confirmed by relative areas of HPLC analysis) and 94% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (94% ee): τ_{major} = 19.9 min, τ_{minor} = 31.0 min; minor diastereomer (27% ee): τ_{major} = 23.2 min, τ_{minor} = 28.3 min]. $[\alpha]^{rt}_D$= - 47.1° (*c* = 1.87, $CHCl_3$, 94% ee). HRMS: *m/z* calcd for $C_{19}H_{21}NO_5$: 377.12632; found: 377.12659. ^{1}H NMR ($CDCl_3$): δ = 2.38 (dd, *J* = 6.0, 18.4, 1H), 2.88 (dd, *J* = 9.2, 18.4, 1H), 3.43 (AB, *J* = 17.6, 2H), 3.75 (s, 3H), 4.06 (dd, *J* = 6.0, 9.2, 1H), 4.60 (AB, *J* = 14.4, 2H), 7.25-7.30 (m, 5H), 7.37-7.41 (m, 1H), 7.45-7.48 (m, 1H), 7.61-7.66 (m, 1H), 7.69-7.72 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 31.4 (CH_2), 34.0 (CH_2), 42.5 (CH_2), 43.1 (CH), 53.4 (CH_3), 60.5 (C), 124.9 (CH), 126.4 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH, 4C), 134.8 (C), 135.4 (C), 136.1 (CH), 152.8 (C), 169.2 (C), 174.8 (C), 176.6 (C), 199.5 (C).



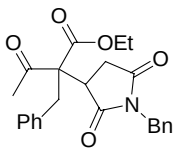
4d – The reaction was carried out at –60°C for 40 h using 15 mol% of **QD** to furnish the crude product [dr = >98:2, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.80-2.90 ppm, δ_{minor} 2.98-3.08 ppm)]. The title compound was isolated by column chromatography (DCM/AcOEt = 95/5) as a white solid (melting point: 120-124 °C) in 91% yield (dr = >98:2, confirmed by relative areas of HPLC analysis) and 93% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 8/2 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (93% ee): τ_{major} = 26.4 min, τ_{minor} = 29.6 min; minor diastereomer (54% ee): τ_{minor} = 19.3 min, τ_{major} = 23.4 min]. $[\alpha]^{rt}_D$= -19.1° (*c* = 0.98, $CHCl_3$, 93% ee). HRMS: *m/z* calcd for $C_{17}H_{17}NO_5$: 315.11067; found: 315.11064. ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 2.43-2.51 (m, 1H), 2.53 (dd, *J* = 6.4, 18.4, 1H), 2.73-2.78 (m, 1H), 2.83 (dd, *J* = 9.2, 18.4, 1H), 3.39 (dd, *J* = 6.4, 9.2, 1H), 4.32-4.38 (m, 2H), 4.68 (AB, *J* = 14.4, 2H), 7.27-7.34 (m, 3H), 7.37-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 25.9 (CH_3), 28.7 (CH_2), 31.7 (CH_2), 42.1 (CH), 42.6 (CH_2), 61.6 (C), 65.9 (CH_2), 127.9 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 135.3 (C), 173.6 (C), 174.4 (C), 176.1 (C), 200.7 (C).
Single crystallization from a mixture of EtOH/Et_2O afforded the optically pure product as a single steroisomer.

The relative configuration (R*, S*) of the major diastereomer of 4d was determined by X-ray crystallographic analysis of (-)-4d.

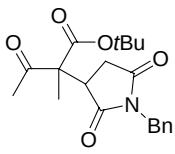


4e – The reaction was carried out at –15°C for 50 h using 20 mol% of **QD** to furnish the crude product [dr = 93/7, determined by integration of two sets of ^{1}H NMR signal (δ_{major} 2.24 ppm, δ_{minor} 2.27 ppm - singlet; δ_{major} 3.37 ppm, δ_{minor} 3.43 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 8/2) as a white foam in 52% yield (dr = 93:7, confirmed by relative areas of HPLC analysis) and 85% ee (major diastereomer) [HPLC analysis on a Chiralpak AS-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (85% ee): τ_{major} = 20.3 min, τ_{minor} = 27.3 min; minor diastereomer (11% ee): τ_{major} = 30.0 min, τ_{minor} = 41.2 min]. $[\alpha]^{rt}_D$= -21.2° (*c* = 0.98, $CHCl_3$, 85% ee). HRMS: *m/z* calcd for $C_{18}H_{21}NO_5$: 331.14197; found: 331.14175. ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.2, 3H), 1.50 (s, 3H), 2.24 (s, 3H), 2.44 (dd, *J* = 6.0, 18.4, 1H), 2.85 (dd, *J* = 9.2, 18.4, 1H), 3.37 (dd, *J* = 6.0, 9.2, 1H), 4.18 (q, *J* = 7.2, 2H), 4.64 (AB, *J* = 14.0, 2H), 7.23-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 18.9 (CH_3), 26.8 (CH_3), 32.4 (CH_2), 42.4 (CH_2), 44.9(CH), 61.2 (C), 62.2 (CH_2), 127.8 (CH), 128.5 (CH, 2C),

128.7 (CH, 2C), 135.6 (C), 170.7 (C), 175.2 (C), 177.0 (C), 204.2 (C).

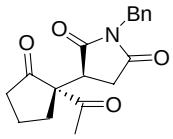


4f – The reaction was carried out at –15°C for 88 h using 20 mol% of **QD** to furnish the crude product [dr = 77/23, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.64 ppm, δ_{minor} 2.82 ppm - dd)]. The title compound was isolated by column chromatography (DCM/AcOEt = 99/1) as a white foam in 63% yield (dr = 78:22, confirmed by relative areas of HPLC analysis) and 85% ee (major diastereomer) [HPLC analysis on a Chiralcel OD-H column: 85/15 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (85% ee): τ_{major} = 25.7 min, τ_{minor} = 50.4 min; minor diastereomer (24% ee): τ_{major} = 44.7 min, τ_{minor} = 32.2 min]. $[\alpha]^{rt}_{D}$= - 16.2° (*c* = 1.0, $CHCl_3$, 85% ee). HRMS: *m/z* calcd for $C_{24}H_{25}NO_5$: 407.17327; found: 407.17361. ^{1}H NMR (600MHz, $CDCl_3$): major diastereomer: *δ* = 1.16 (t, *J* = 7.2, 3H), 2.27 (dd, *J* = 6.6, 18.6, 1H), 2.33 (s, 3H), 2.64 (dd, *J* = 9.6, 18.6, 1H), 3.33 (dd, *J* = 6.6, 9.6, 1H), 3.49 (s, 2H), 4.14 (q, *J* = 7.2, 2H), 4.60 (AB, *J* = 14.4, 2H), 7.18-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$): *δ* = 13.8 (CH_3), 28.5 (CH_3), 33.8 (CH_2), 39.9 (CH_2), 42.3 (CH_2), 42.5 (CH), 62.0 (CH_2), 66.9 (C), 127.6 (CH), 127.7 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 128.7 (CH, 2C), 130.3 (CH, 2C), 135.0 (C), 135.6 (C), 169.9 (C), 175.6 (C), 177.6 (C), 204.5 (C); minor diastereomer (selected signals): *δ* = 1.07 (t, *J* = 7.2, 3H), 2.29 (s, 3H), 2.42 (dd, *J* = 5.4, 18.6, 1H), 2.82 (dd, *J* = 6.4, 18.6, 1H), 3.37 (d, *J* = 13.8, 1H), 3.83 (d, *J* = 13.8, 1H), 3.90 (m, 1H), 4.04 (m, 1H).



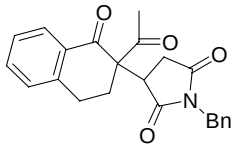
4g – The reaction was carried out at RT for 72 h using 20 mol% of **Q** to furnish the crude product [dr = 92:8, determined by integration of two sets of ^{1}H NMR signal (δ_{major} 1.47 ppm, δ_{minor} 1.48 ppm – s; δ_{major} 2.24 ppm, δ_{minor} 2.26 ppm – s)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a white foam in 75% yield (dr = 92:8, confirmed by relative areas of HPLC analysis) and 92% ee (major diastereomer) [HPLC analysis on a Chiralpak AS-H column: 9/1 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (92% ee): τ_{major} = 30.4 min, τ_{minor} = 22.0 min; minor diastereomer (9% ee): τ_{major} = 42.0 min, τ_{minor} = 33.5 min]. $[\alpha]^{rt}_{D}$= + 26.8° (*c* = 1.0, $CHCl_3$, 92% ee). HRMS: *m/z* calcd for $C_{20}H_{25}NO_5$: 359,17327; found: 359.17341. ^{1}H NMR ($CDCl_3$): *δ* = 1.47 (s, 9H), 1.51 (s, 3H), 2.26 (s, 3H), 2.49 (dd, *J* = 6.4, 18.4, 1H), 2.84 (dd, *J* =

9.2, 18.4, 1H), 3.29 (dd, *J* = 6.4, 9.2, 1H), 4.65 (AB, *J* = 14.4, 2H), 7.27-7.33 (m, 3H), 7.35-7.38 (m, 2H); δ = 19.2 (CH_3), 26.9 (CH_3), 27.7 (CH_3, 3C), 32.6 (CH_2), 42.3 (CH_2), 45.0 (CH), 61.8 (C), 83.4 (C), 127.8 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 135.6 (C), 169.7 (C), 175.4 (C), 177.1 (C), 204.6 (C).



4h – The reaction was carried out at –60°C for 40 h using 15 mol% of **QD** to furnish the crude product [dr = 92:8, determined by integration of one set of ^{1}H NMR signal (δ_{major} 2.74 ppm, δ_{minor} 2.85 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a white foam in 99% yield (dr = 92:8, confirmed by relative areas of HPLC analysis) and 91% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (91% ee): τ_{major} = 14.5 min, τ_{minor} = 14.9 min; minor diastereomer (88% ee): τ_{major} = 13.2 min, τ_{minor} = 13.5 min]. $[\alpha]^{rt}_D$= + 24.5° (*c* = 1.0, $CHCl_3$, 91% ee). HRMS: *m/z* calcd for $C_{18}H_{19}NO_4$: 313.13141; found: 313.13133. ^{1}H NMR ($CDCl_3$): δ = 1.80-2.00 (m, 3H), 2.17 (s, 3H), 2.34 (dd, *J* = 6.4, 18.4, 1H), 2.40-2.56 (m, 3H), 2.74 (dd, *J* = 9.2, 18.4, 1H), 3.54 (dd, *J* = 6.4, 9.2, 1H), 4.63 (AB, *J* = 14.0, 2H), 7.24-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 19.4 (CH_2), 26.2 (CH_3), 28.8 (CH_2), 31.8 (CH_2), 38.4 (CH_2), 42.5 (CH_2), 43.6 (CH), 68.7 (C), 128.0 (CH), 128.6 (CH, 2C), 128.7 (CH, 2C), 135.4 (C), 174.7 (C), 176.5 (C), 202.0 (C), 213.4 (C).

The relative configuration (S*, S*) of the major diastereomer of (+)-4h was determined by extensive NMR NOE studies.

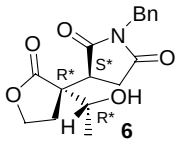


4i – The reaction was carried out at –30°C for 66 h using 20 mol% of **QD** to furnish the crude product [dr = 95:5, determined by integration of one set of ^{1}H NMR signal (δ_{major} 3.30 ppm, δ_{minor} 3.37 ppm - dd)]. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a solid (melting point = 184-189 °C) in 75% yield (dr = 95:5, confirmed by relative areas of HPLC analysis) and 84% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (84% ee): τ_{major} = 22.7 min, τ_{minor} = 19.8 min; minor diastereomer (26% ee): τ_{major} = 23.9 min, τ_{minor} = 19.0 min]. $[\alpha]^{rt}_D$= + 44.4° (*c* = 0.99, $CHCl_3$, 84% ee). HRMS: *m/z* calcd for $C_{23}H_{21}NO_4$: 375.14706; found: 375.14641. ^{1}H NMR ($CDCl_3$, T = 50 °C): δ = 2.19 (s,

3H), 2.40-2.56 (m, 3H), 2.65 (dd, *J* = 6.0, 18.4, 1H), 2.98-3.03 (m, 2H), 3.30 (dd, *J* = 6.0, 9.2, 1H), 4.73 (AB, *J* = 14.4, 2H), 7.23-7.38 (m, 5H), 7.39-7.45 (m, 2H), 7.53 (t, *J* = 7.6, 9.2, 1H), 8.07 (d, *J* = 7.6, 9.2, 1H); ^{13}C NMR ($CDCl_3$, T = 50 °C): δ = 25.6 (CH_2), 29.1 (CH_3), 31.1 (CH_2), 31.9 (CH_2), 42.6 (CH_2), 44.2 (CH), 65.5 (C), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.5 (CH, 2C), 128.6 (CH, 2C), 129.0 (CH), 132.1 (CH), 134.4 (C), 135.9 (C), 142.9 (C), 175.0 (C), 177.1 (C), 196.1 (C), 205.6 (C).

Gram-scale experiment and synthesis of (-)-6.

In an ordinary 50mL round-bottom flask equipped with a magnetic stirring bar, quinidine **QD** (1.5 mmol, 486 mg) was dissolved in 20 mL of DCM. After addition of the 1,3-dicarbonyl compound (10 mmol, 1.08 mL), the flask was closed with a rubber stopper and the mixture was stirred at −60 °C for 10 minutes. Then *N*-benzylmaleimide **2d** (11 mmol, 2.057 g) was added in one portion and stirring was continued for 48h. Then the crude reaction mixture was concentrated to 3 mL and directly charged on the chromatography column and purified on silica, using DCM/AcOEt 95/5 as the eluent. **4d** was isolated as a white solid in quantitative yield (3.12 g) and dr = >98:2 (confirmed by relative areas of HPLC analysis) and 94% ee (major diastereomer). Single crystallization from a mixture of EtOH/Et_2O afforded the optically pure product as a single steroisomer.



6

Enantiomerically pure (-)-**4d** (2 mmol, 630 mg) was dissolved in MeOH (20 mL) and stirred at −78 °C for 5 minutes. Then, $NaBH_4$ (1.5 equiv., 3 mmol) was added in one portion and stirring continued for 3 hours, at which time the reaction mixture was quenched with brine, extracted with AcOEt (3 times) and dried over anhydrous $MgSO_4$. NMR analysis of the crude mixture showed that the reduction proceeded with complete chemoselectivity and high stereocontrol (d.r. 93/7, determined by integration of two sets of ^{1}H NMR signal (δ_{major} 2.98 ppm, δ_{minor} 2.89 ppm – dd / δ_{major} 3.63 ppm, δ_{minor} 3.32 ppm – dd). The title compound **6** was isolated by column chromatography (DCM/AcOEt = 75/25) as a white foam in 93% yield (dr = 93:7, confirmed by relative areas of HPLC analysis) and >99% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254; major diastereomer (>99% ee): τ_{major} = 16.9 min, τ_{minor} = 14.4 min; minor diastereomer (>99% ee): τ_{major} = 11.5 min, τ_{minor} = 10.7 min]. $[\alpha]^{rt}_D$= -2.7 (*c* = 1.1, $CHCl_3$, 99% ee). HRMS: *m/z* calcd for $C_{17}H_{19}NO_5$: 317.12632; found: 317.12665. ^{1}H NMR ($CDCl_3$): δ = 1.26 (d, *J* = 6.4, 3H), 1.80-1.88 (m, 1H), 2.02-2.08 (m, 1H), 2.49 (dd, *J* = 6.4,

18.4, 1H), 2.50 (br s, 1H), 2.98 (dd, J = 9.6, 18.4, 1H), 3.63 (dd, J = 6.4, 9.6, 1H), 3.82-3.89 (m, 1H), 4.17-4.28 (m, 2H), 4.65 (s, 2H), 7.27-7.32 (m, 3H), 7.35-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 18.5 (CH_3), 26.8 (CH_2), 31.6 (CH_2), 42.6 (CH_2), 43.9 (CH), 52.3 (C), 65.7 (CH_2), 70.0 (CH), 128.1 (CH), 128.7 (CH, 2C), 128.8 (CH, 2C), 135.5 (C), 174.9 (C), 177.3 (C), 178.7 (C).

The relative configuration (R*, R*, S*) of the major diastereomer of (-)-6 was determined by extensive NMR NOE studies.

X-Ray Structure Analysis.

Determination of Absolute and Relative Configurations of 5.

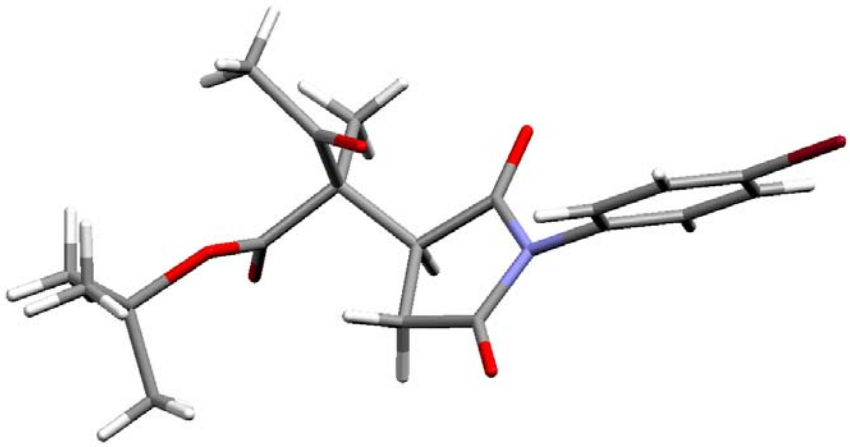
The absolute and relative configurations of compound **5** (Eq. 1) were assigned by X-ray crystallographic analysis. CCDC-296418 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif .

(*R*, *S*) - **5**

Compound **5** was prepared following the general procedure by mixing **1g** (1 equiv) and *N*-4-bromo-phenylmaleimide (1.2 equiv) in DCM (0.5 M) at RT in the presence of quinine **Q** (20 mol%) as the catalyst. The title compound was isolated after 72h by column chromatography (hexane/AcOEt = 80/20) as a white solid (melting point: 135-140°C) in 65% yield (dr = 96:4, determined by integration of one set of ^{1}H NMR signal: δ_{major} 2.28 ppm, δ_{minor} 2.30 ppm - s) and 85% ee (major diastereomer) [HPLC analysis on a Chiralpak AD-H column: 75/25 hexane/*i*-PrOH, flow rate 0.75 mL/min, λ = 214, 254 nm; major diastereomer (85% ee): τ_{major} = 18.0 min, τ_{minor} = 20.5 min]. $[\alpha]^{rt}_D$= + 13.7° (*c* = 1.1, $CHCl_3$, 85% ee). HRMS: *m/z* calcd for $C_{19}H_{22}NO_5Br$: 423.06813; found: 423.06824. ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 9H), 1.65 (s, 3H), 2.28 (s, 3H), 2.66 (dd, J = 6.4, 18.4, 1H), 2.98 (dd, J = 9.2, 18.4, 1H), 3.39 (dd, J = 6.4, 9.2, 1H), 7.21 (d, J = 8.8, 2H),

7.59 (d, J = 8.8, 2H); δ = 19.9 (CH_3), 27.2 (CH_3), 27.8 (CH_3, 3C), 32.9 (CH_2), 45.1 (CH), 62.5 (C), 83.7 (C), 122.5 (C), 128.1 (CH, 2C), 130.9 (C), 132.3 (CH, 2C), 169.8 (C), 174.5 (C), 176.4 (C), 205.1 (C).

Crystallization from a mixture of hexane/Et_2O afforded a single enantiopure stereoisomer (confirmed by HPLC analysis of the very same crystal used for X-ray analysis) as fine colourless needles suitable for X-ray diffraction measurements with the configuration as shown in Equation 1.



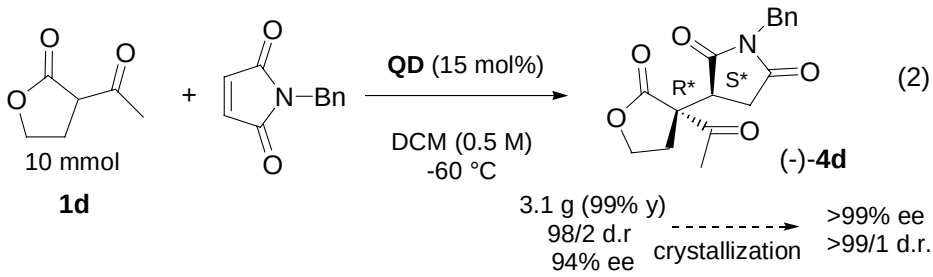
Molecular formula: $C_{19}H_{22}BrNO_5$, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.486(1), b = 15.479(2), c = 19.892(3) Å, V = 1997.1(5) Å^3, T = 298(2) K, Z = 4, ρ_c = 1.411 g cm^{-3}, F(000) = 872, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 2.086 mm^{-1}, colourless needle (0.50 × 0.15 × 0.10 mm^3), empirical absorption correction with SADABS (transmission factors: 0.6804 – 0.2862), 2400 frames, exposure time 20 s, 1.67 ≤ θ ≤ 28.70, −8 ≤ h ≤ 8, −20 ≤ k ≤ 20, −26 ≤ l ≤ 26, 22454 reflections collected, 4834 independent reflections (R_{int} = 0.0548), 3195 reflections with $I > 2\sigma(I)$ (R_σ = 0.0482), solution by direct methods (SHELXS) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (XSHELL), hydrogen atoms refined with a riding model, data / parameters = 4834 / 241, $S(F^2)$ = 1.008, $R(F)$ = 0.0800 and $wR(F^2)$ = 0.1251 on all data, $R(F)$ = 0.0440 and $wR(F^2)$ = 0.1096 for reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0603P)^2 + 0.000P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference between peak and hole 0.692 and −0.409 e Å^{-3}, Flack parameter[9] 0.000(12). The absolute structure has been also confirmed by comparison of the structural refinements of the two enantiomorphs. Crystallographic data (excluding structure factors)

[9] H. D. Flack, *Acta Crystallogr., Sect. A* **1983**, *39*, 876.

have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-296418. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Determination of Relative Configuration of (-)-4d.

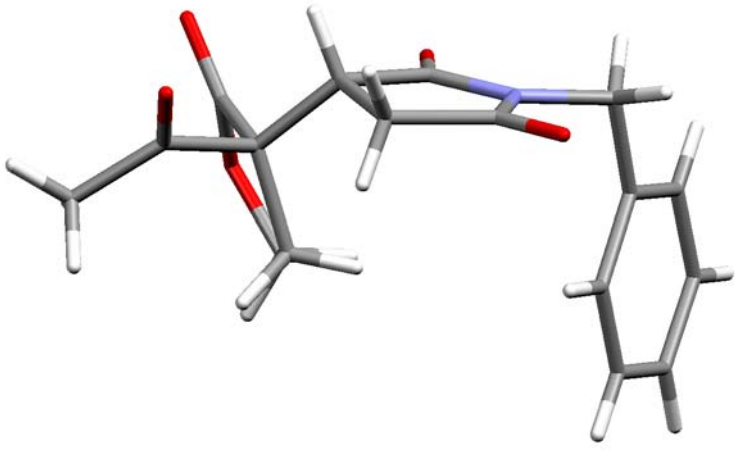
The relative configuration of compound (-)-**4d** was assigned by X-ray crystallographic analysis. Crystallization from a mixture of EtOH/Et_2O afforded a single enantiopure stereoisomer (confirmed by HPLC analysis) as fine colourless needles suitable for X-ray diffraction measurements with the relative configuration as shown in Equation 2.



(2)

Compound **4d** lacks of a sufficiently heavy atom to allow the determination of the absolute configuration.

Figure 1: X-ray data for compound (R*, S*)-(-)-**4d**



Molecular formula: $C_{17}H_{17}NO_5$, M_r = 315.32, monoclinic, space group $P2_1$ (No. 4), a = 11.6945(7), b = 5.7763(4) Å, c = 12.6299(8) Å, β =114.5060(8), V = 776.31(9) $Å^3$, T = 298(2) K, Z = 2, ρ_c = 1.015 g cm^{-3}, $F(000)$ = 332, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073

Å), μ ($Mo_{K\alpha}$) = 0.100 mm^{-1}, colourless needle (0.5 × 0.2 × 0.2 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9517 – 0.9803), 2400 frames, exposure time 15 s, 1.77 ≤ θ ≤ 28.51, −15 ≤ *h* ≤ 15, −7 ≤ *k* ≤ 7, −16 ≤ *l* ≤ 16, 8940 reflections collected, 3609 independent reflections (R_{int} = 0.0137), solution by direct methods (SHELXS97[a]) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97 [a]), hydrogen atoms refined with a riding model, data / parameters = 3609 / 209, $S(F^2)$ = 1.055, $R(F)$ = 0.0387 and $wR(F^2)$ = 0.1047 on all data, $R(F)$ = 0.0379 and $wR(F^2)$ = 0.1038 for 3494 reflections with $I > 2\sigma(I)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0736P)^2 + 0.0544P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.232 and −0.267 e $Å^{-3}$; Flack parameter: 0.1(8). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-605040. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

NMR NOE Analysis.

The relative configurations of compounds **4b**, **4h** and **6** were deduced from extensive NMR NOE analysis of both the major and the minor diastereomers. Diasteroisomeric separation was achieved by means of semipreparative HPLC (Waters Novapak, silica 6 um, 8x300 mm, hexane/iPrOH) for compounds **4b** and **6**, and by flash chromatography on silica gel for compound **4h**.

All the ^{1}H and ^{13}C NMR signals of the two diastereomers were recorded at 600 MHz and previously assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. NOE spectra were obtained using the DPFGSE-NOE sequence,[10] with a mixing time of 1.00-2.00 s and two "rsnob" 30-50 Hz wide selective pulses. Zero-Quantum Coherence effects were reduced according to the method proposed by Keeler.[11] As an example of the method, the NOE spectrum of **6**, obtained on irradiation of the carbinolic CH, is shown in Figure 2.

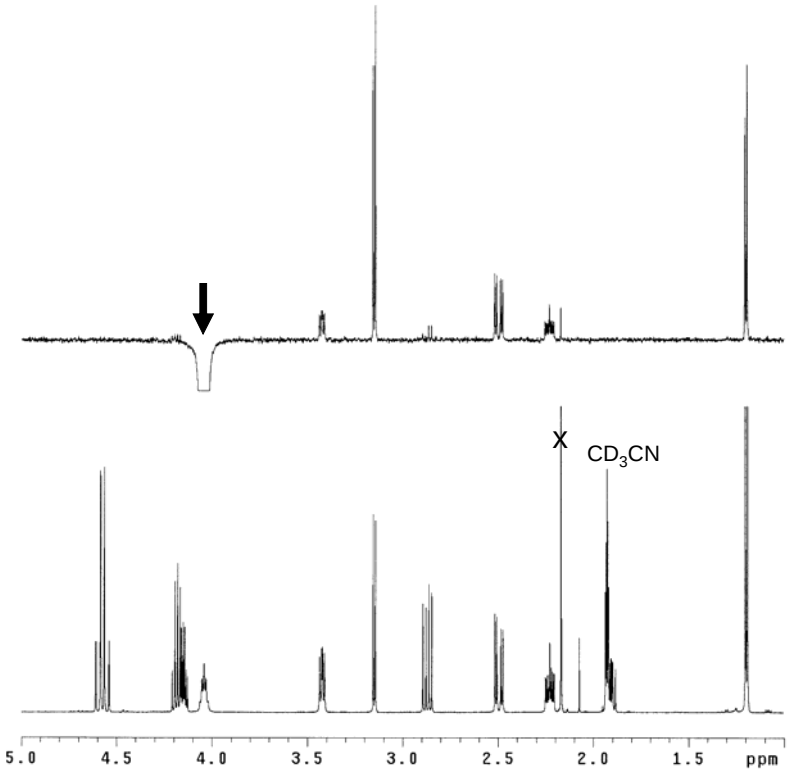


Figure 2. Bottom: ^{1}H-NMR spectrum (600 MHz in CD_3CN) of the major diastereoisomer of compound **6**. Top: DPFGSE-NOE spectrum obtained on saturation of the carbinolic CH (indicated by the arrow).

[10] (a) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J .Am. Chem. Soc.* **1994**, *116*, 6037. (b) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (c) Stott, K.; Keeler, J.; Van, Q.N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302.

Determination of the Relative Configuration of (+)-**4h.**

The two diastereomers of compound **4h**, obtained by the **QD**-catalyzed reaction (92/8 d.r. 91% ee major diastereomer), were previously isolated by flash chromatography on silica gel (hexane/AcOEt 75/25; R_f^{minor}= 0.3 - R_f^{major}= 0.2).

In the case of the minor isomer of **4h**, selective saturation of the CH signal shows positive NOEs on the syn hydrogen of the maleimmide moiety, (Figure 3, NOE n° 5), on the COMe signal (NOE n° 8), and on both the diastereotopic hydrogens of the CH_2 near to the quaternary carbon of the cyclic ketone (NOE n° 4 and n° 6). Selective saturation of the hydrogen of maleimmide syn to the CH shows positive NOEs on the CH (NOE n° 5), on the hydrogen anti to the CH (NOE n° 1) and solely one hydrogen of the CH_2 near to the quaternary carbon of the cyclic ketone (NOE n° 3).

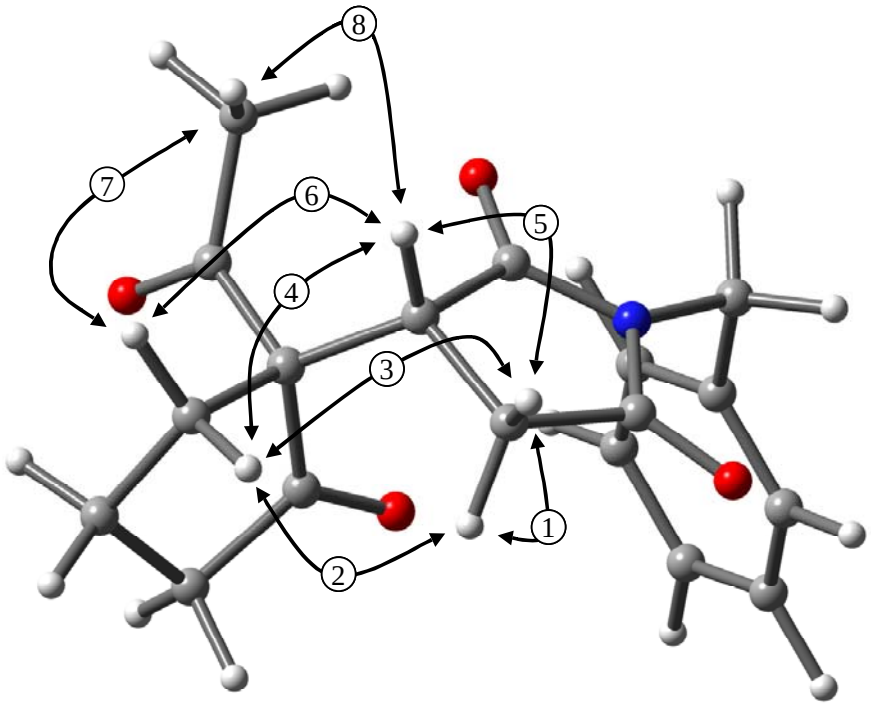
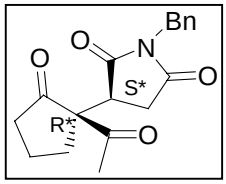


Figure 3 - minor diastereoisomer of **4h** (8%, R*S* configuration)

Selective saturation of the hydrogen of maleimmide anti to the CH shows positive NOE on the other portion of the AB system (NOE n° 1) and on the same hydrogen of the alfa-quaternary CH_2 mentioned before (NOE n° 2). Finally, saturation of the COMe signal yields a very strong effect on the CH (NOE n° 8), on one of the hydrogens of the

[11] Thrippleton, M.J.; Keeler, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 3938-3941

CH_2 near to the quaternary carbon of the cyclic ketone (NOE n° 7) and a very weak effect on the hydrogen syn to the CH. (not shown in Figure 3).



All the constrains agree very well with the structure in which the two chiral centers have opposite descriptors (so R*S*).

In the case of the major isomer of **4h** (Figure 4), selective saturation of the maleimidic CH signal shows positive NOEs on the syn hydrogen of the maleimmidic CH_2 (NOE n° 2), on the COMe signal (NOE n°3) and on one of the hydrogens in β-CO position of the cyclic ketone (NOE n° 5).

Selective saturation of the maleimmidic hydrogen syn to the CH shows positive NOEs on the CH (NOE n° 2), on the other diastereotopic hydrogen (NOE n° 1) and on the COMe signal (NOE n° 6). Selective saturation of the hydrogen of maleimmide anti to the CH shows positive NOE only on the other diastereotopic hydrogen of the AB system (NOE n° 1). Finally, saturation of the COMe signal yields a very strong positive NOE on the CH (NOE n° 3), on one of the hydrogens near to the quaternary carbon of the cyclic ketone (NOE n° 4) and a weak effect on the hydrogen syn to the CH (NOE n° 6). In this case all the constrains agree very well with the structure in which the two chiral centres have the same descriptor (so R*R*).

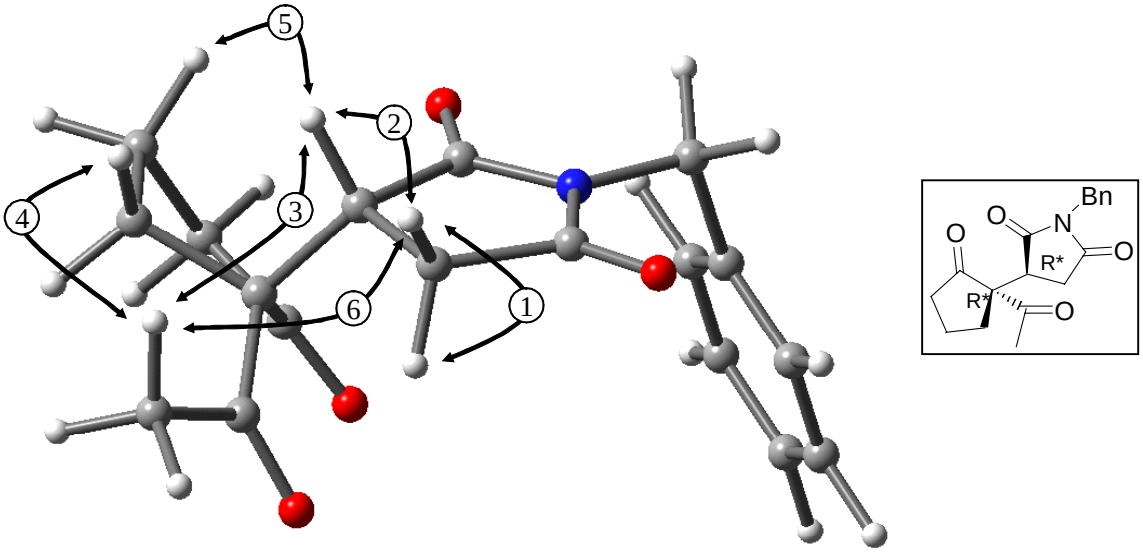


Figure 4 - major diastereoisomer of **4h** (92%, R*R* configuration).

Thus, in the mayor diastereoisomer of **4h**, the main differences lie in the absence of any NOE between the maleimmidic hydrogens and the hydrogens of the cyclopentanone ring. In both isomers relevant NOE effects are visible between the methyl group and the maleimmidic CH.

Compound 4b

The two diastereomers of compound **4b**, obtained by the **QD**-catalyzed reaction (87/13 d.r. 98% ee major diastereomer), were previously isolated by semi preparative HPLC (Waters Novapak, silica, 6 μm, 7.8x300 mm, hexane/*i*PrOH 98/2).

In the case of **4b**, NOE spectra show the same trend of **4h**. In Figures 5 and 6 are reported the structure derived. In this case the NOE spectra assign the R*S* configuration to the major diastereoisomer, and the R*R* configuration to the minor. It is important to note that the change in the configuration is due to the different priority of the COOEt substituent with respect to the COMe group. In other words, the two major diastereoisomers of **4b** and **4h** have the same structure, but one of the two chiral centres has changed its descriptor.

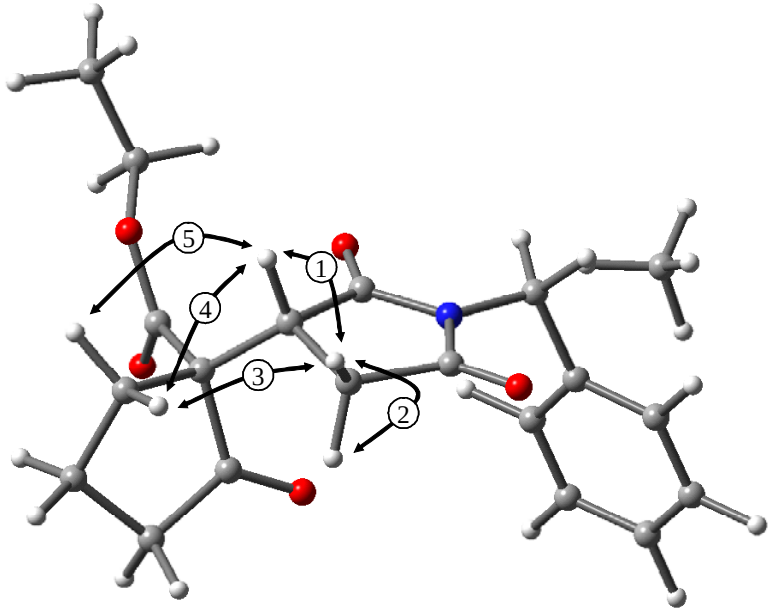


Figure 5 - minor diastereoisomer of **4b** (13%, R*R* configuration)

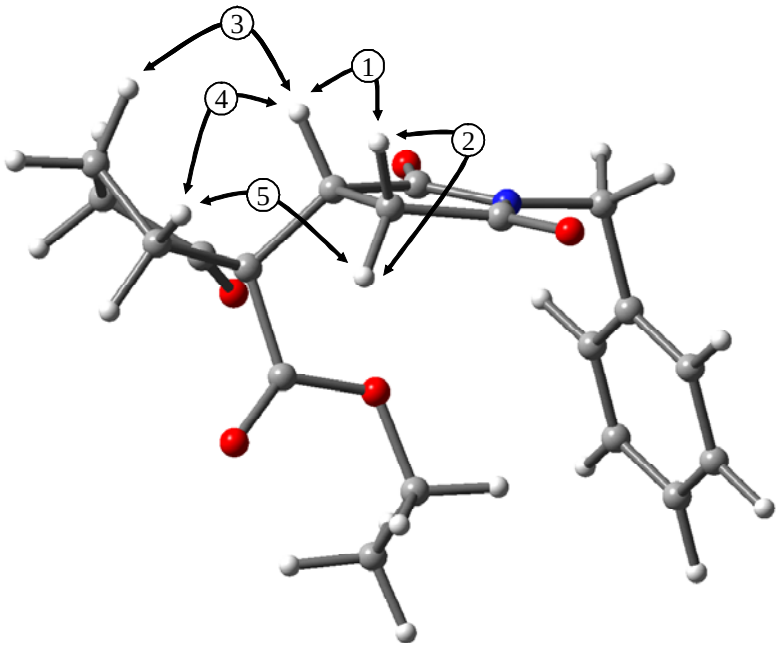
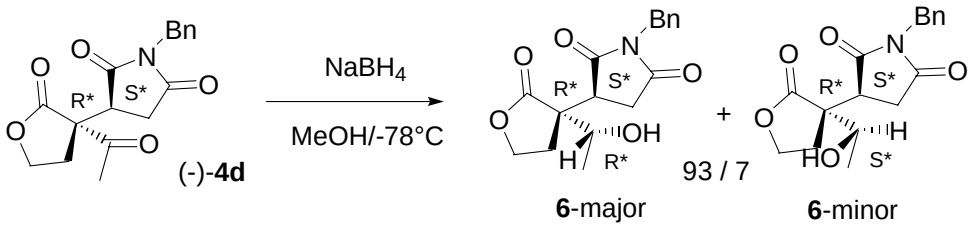


Figure 6 - major diastereoisomer of **4b** (87%, R*S* configuration).

Determination of the Relative Configuration of (-)-6.

A mixture 60/40 of compound **6** was prepared by reduction of **4d** at -30 °C in DCM as the solvent, using BH_3.THF as the reducing agent in the presence of a stoichiometric amount of $TiCl_4$. The two diastereomers were separated by HPLC (Waters Novapak, silica, 6 μm, 7.8x300 mm, hexane/*i*PrOH 80/20).



All the ^{1}H and ^{13}C NMR signals of the two diastereomers were previously assigned as reported above. NOE spectra were obtained using the DPFGSE-NOE sequence,[10] with a mixing time of 1.50-2.00 s and two "rsnob" 30-50 Hz wide selective pulses. Zero-Quantum Coherence effects were reduced according to the method proposed by Keeler.[11]

The X-ray structural analysis of the precursor of **6** (i.e. **4d**) was available (see Figure 1, X-ray section), so the relative R*S* stereochemistry of two out of the three chiral centres of **6** was

known (compound **4d** lacks of a sufficiently heavy atom to allow the determination of the absolute configuration).
In this case the NOE analysis is complicated by the presence of the two identical chiral centres that make the NOE constraints between the hydrogens of the two cycles almost indistinguishable (NOE constraints from 1 to 8 in Figures 7 and 8). Thus the NOE analysis has to be focused on the effects revealed when the methyl group and the carbinolic CH are saturated. In both diastereoisomers, selective saturation of the CH shows NOE effects on the three maleimmidic CH (NOE n° 6, 7, 9) and on one hydrogen of the lactone (NOE n° 4). These results indicate that in both cases the CH is located more or less in the same position (see Figure 2 for the NOE spectrum of the major diastereoisomer).

On the other hand, in the case of the major stereoisomer, selective saturation of the methyl group yields two strong NOE effects on two hydrogens of the lactone (NOE n° 11 and 12 in Figure 7), while in the case of the minor stereoisomer the saturation of the methyl group shows NOE effect on the maleimmidic CH (NOE n°11 of Figure 8), whereas NOE effects are not observed on the hydrogen of the lactone. Finally, although a NOE effect obtained on saturation of an hydroxyl group is never completely sound, the NOE effect is observable on the maleimmidic CH in the case of the major diastereoisomer, while in the minor diastereoisomer NOE is observed on one hydrogen of the lactone. These convergent results show that the predominant stereoisomer of **6** has the R*S*S* configuration, while the minor has the R*S*R* configuration.

It has also to be noted that the major isomer is a viscous and soluble liquid, while the minor is a almost insoluble powder in apolar solvents like chloroform. This unusual behaviour can be explained by inspection of the two structures of **6**: in the case of the major isomer the OH is involved in a intra-molecular hydrogen bond (indicated by the dotted line in Figure 7) with the carbonyl of the lactone. In the other stereoisomer, on the contrary, the hydroxyl group is free for an inter-molecular hydrogen bond, thus accounting for the solid appearance of the compound.

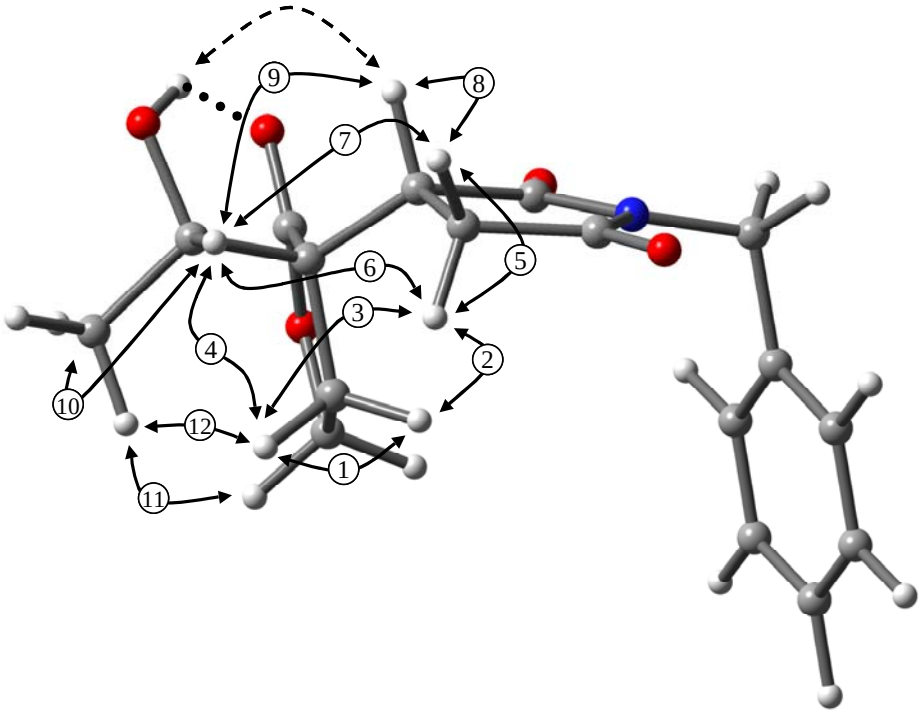


Figure 7 – major reaction product (93%, R*S*S* configuration) of compound **6**

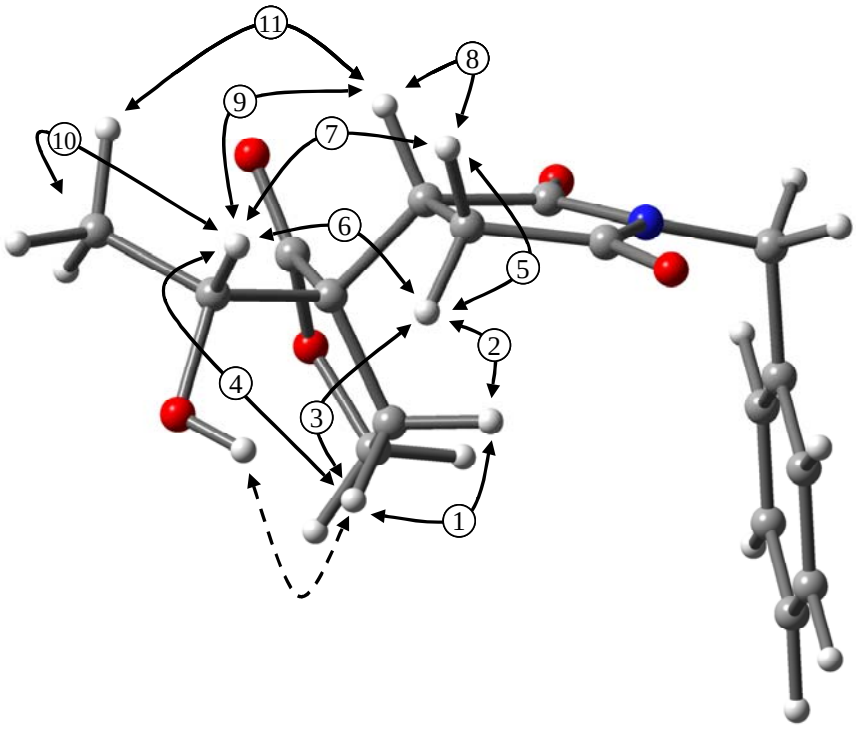
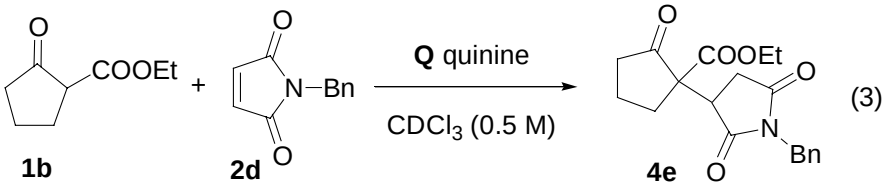


Figure 8 – minor reaction product (7%, R*S*R* configuration) of compound **6**

Kinetic Studies.

The kinetic parameters of the reaction depicted in Eq. 3 were determined by *in situ* monitoring of the consumption of ethyl 2-oxocyclopentane carboxylate **1b** (triplet at 3.14 ppm) and *N*-benzylmaleimide **2d** (singlet at 6.71 ppm) by using ^{1}H NMR spectroscopy.



(3)

Order in ethyl 2-oxocyclopentane carboxylate **1b** was established by using a large excess of *N*-benzylmaleimide **2d** (5 equiv) and 10 mol% **Q**. Plotting in ln[**1b**] versus time gave a straight line (R^2 = 0.9993, Figure 8), thus establishing a first-order dependence on **1b**.

Order in *N*-benzylmaleimide **2d** was established by using a large excess of ethyl 2-oxocyclopentane carboxylate **1b** (5 equiv) and 10 mol% quinine as the catalyst. Plotting in ln[**2d**] versus time gave a straight line (R^2 = 0.9987, Figure 10), thus establishing a first-order dependence on maleimide (**2d**).

The reaction order in catalyst was established by determining the kinetic rate constants at various catalyst concentrations (equimolar amounts of *N*-benzylmaleimide **2d** and ethyl 2-oxocyclopentane carboxylate **1b**). A plot of the rate constants k_{obs} vs the catalyst concentration gave a straight line for quinine (R^2 = 0.9808, Figure 12). The reaction displays first-order dependence on catalyst.

General procedure for kinetic studies.

In an ordinary NMR tube, *N*-benzylmaleimide **2d** (65.5 mg, 0.35 mmol) and quinine (11.3 mg, 0.035 mmol) were dissolved in 0.7 mL of $CDCl_3$ (0.5 M solution in nucleophile). Then in a period as short as possible ethyl 2-oxocyclopentane carboxylate **1b** (52 µL, 0.35 mmol) was introduced in one portion via a syringe and the resulting mixture was shaken well. The first ^{1}H NMR acquisition was collected after 3 minutes, and the resulting reaction mixture was monitored every 60 seconds for 20-40 minutes.

Figure 8. Determination of the order of the ketoester **1b**: the linear relationship between ln[**1b**] and time indicates that the reaction is first order on **1b**.

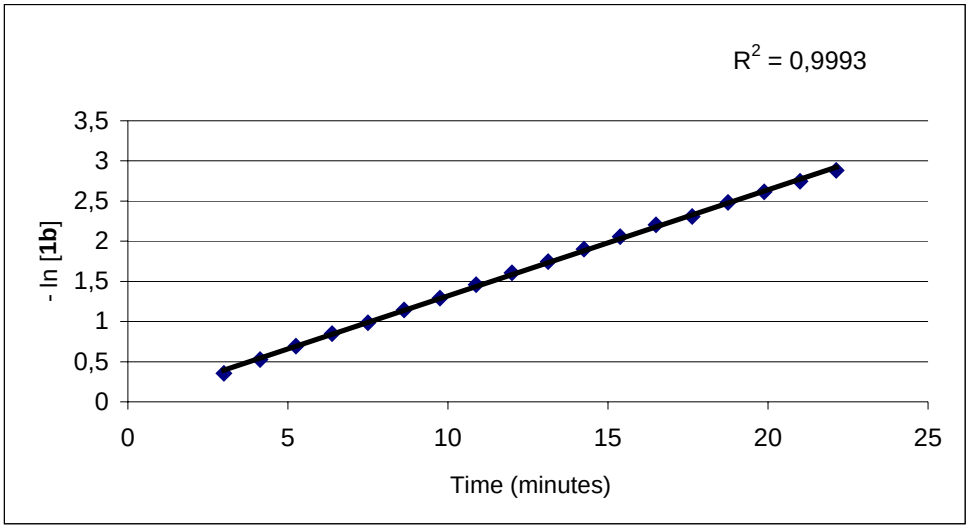


Figure 9. Determination of the order of the ketoester **1b**: the non-linear relationship between 1/[**1b**] and time clearly indicates that the reaction is not second order on **1b**.

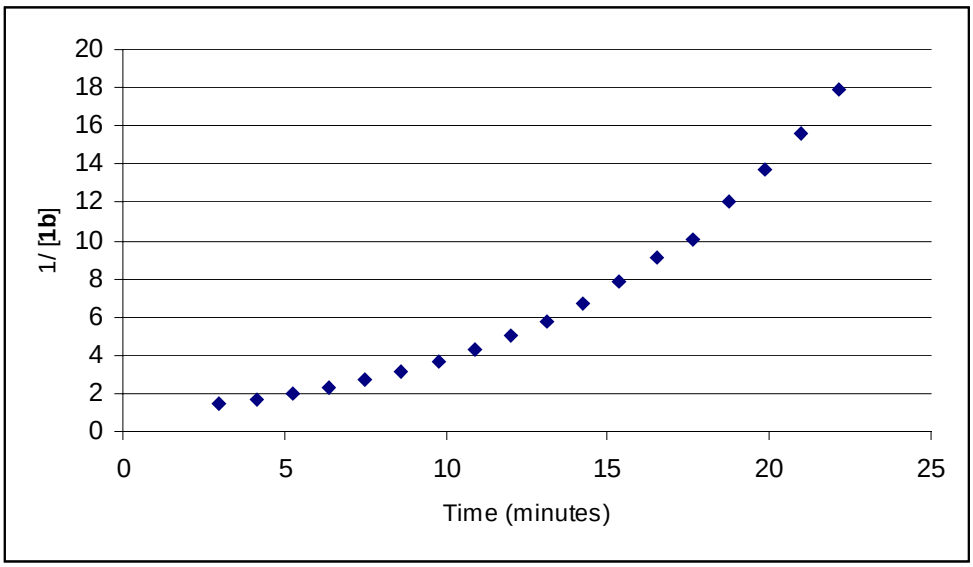


Figure 10. Determination of the order of the maleimide **2d**: the linear relationship between ln[**2d**] and time indicates that the reaction is first order on **2d**.

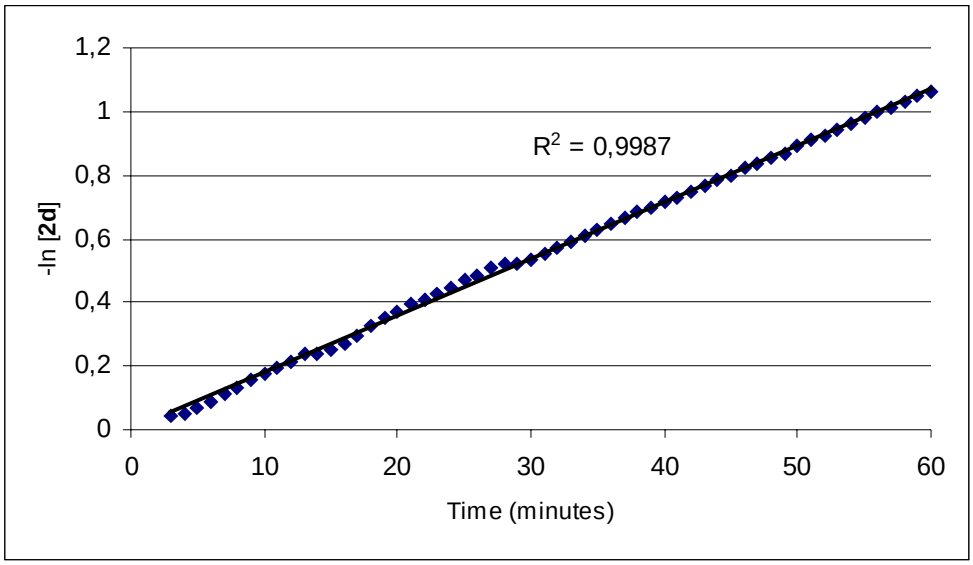
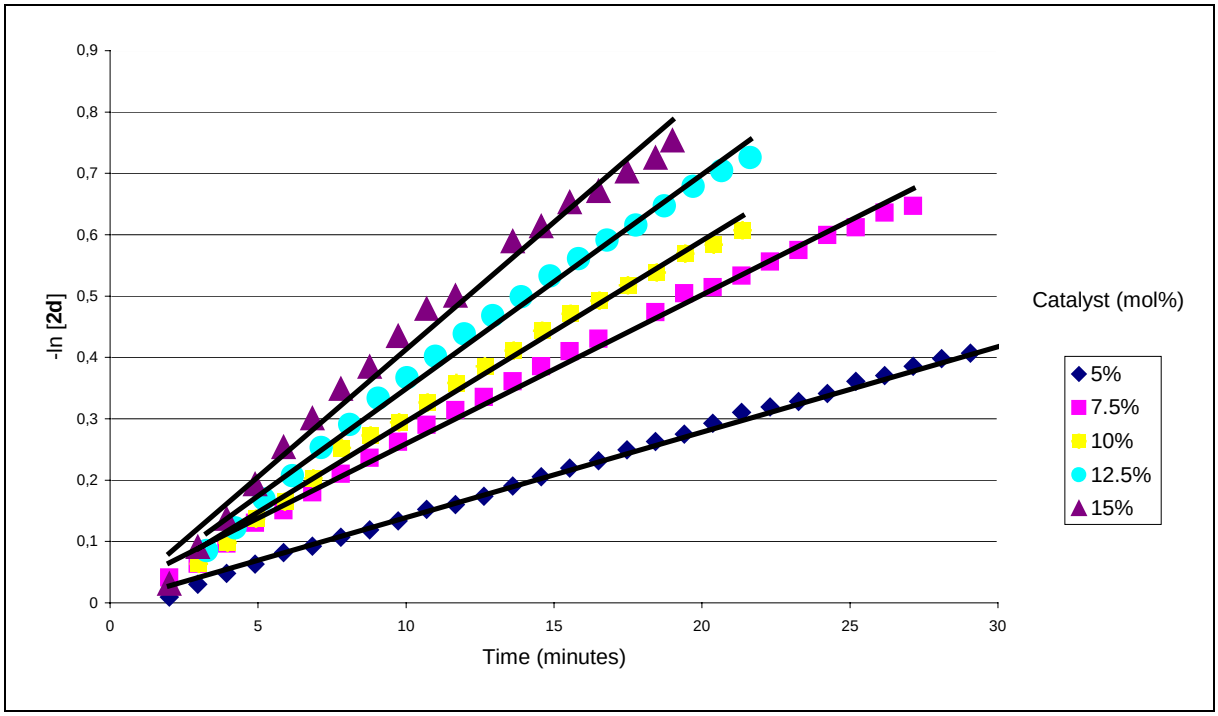


Figure 11. kinetic profiles for the catalyst quinine **Q**



Catalyst [mol%]	k_{obs}	R^2
5	2,322 E-04	0.9980
7.5	4,044 E-04	0.9946
10	4,919 E-04	0.9935
12.5	5,816 E-04	0.9932
15	6,870 E-04	0.9846

Figure 12. Kinetic rate constant (k_{obs}) at different concentration of quinine **Q**