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Supporting Information for

Faster and cleaner dynamic kinetic resolution *via* mechanochemistry

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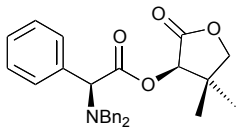
Table of contents

General:

All reagents were purchased from Sigma-Aldrich and used without further purification. The milling treatments were carried out in a Retsch Mixer Mill 200 at 30 Hz in a 10 mL stainless steel reactor with one 10 mm diameter ball. η ratio is defined as the ratio of the added water volume to the sum of the mass of reactants and is expressed in µL mg^{-1}.[1] ^{1}H NMR spectra were recorded on a Bruker Avance DPX 300 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as s = singlet, d = doublet, t = triplet, m = multiplet; coupling constant in Hz; integration. ^{13}C NMR spectra were recorded on a Bruker Avance AM 75 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). Mass spectra were obtained by LC-MS with ESI using a Water Alliance 2695 as LC, coupled to a Waters ZQ spectrometer with electrospray source, a simple quadrupole analyzer and a UV Waters 2489 detector. Diastereomeric excess was measured using 300 MHz ^{1}H NMR spectra.

General procedures:

2-(*S*)-(Dibenzylamino)-phenylacetatic acid (*R*)-pantolactone ester 2a:[2]



Reactions in solvent with magnetic stirring:

Reaction in THF with Et_3N as base (Table 1, entry 1 in the manuscript):[2]

(*R*,*S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (100.0 mg, 0.306 mmol, 1.0 eq), Et_3N (85 µL, 0.611 mmol, 2.0 eq) and TBAI (22.6 mg, 0.061 mmol, 0.2 eq) were introduced in a round-bottom flask equipped with a magnetic stirrer and dissolved in anhydrous THF (1.53 mL). After 15 min of vigorous stirring, dibenzylamine (71 µL, 0.367 mmol, 1.2 eq) was added to the reaction mixture and the latter was stirred until complete conversion of the starting material (5 h). The reaction medium was diluted with deionised water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with 10% aqueous $KHSO_4$ solution and with deionised water. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified on silica gel (cyclohexane/EtOAc) to afford 80.0 mg of the desired product **2a** as an oil (59% yield) with a diastereomeric ratio superior to 98:2 as determined by 300 MHz ^{1}H NMR spectrum of the crude.

Reaction in water and $NaHCO_3$ as base (Table 1, entry 2 in the manuscript):

(*R*,*S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (25.0 mg, 0.076 mmol, 1.0 eq), $NaHCO_3$ (7.5 mg, 0.089 mmol, 1.2 eq) and TBAI (5.5 mg, 0.015 mmol, 0.2 eq) were introduced in a test tube equipped with a magnetic stirrer and dissolved in a minimum of water (0.5 mL) allowing for efficient stirring of the reaction mixture. After 15 min of vigorous stirring, dibenzylamine (17.5 µL, 0.091 mmol, 1.2 eq) was added and the reaction mixture was stirred during 6 h. EtOAc was added to the reaction media, the organic phase was washed with an aqueous 10% $KHSO_4$ solution, water, dried over $MgSO_4$, filtered, concentrated and purified on column chromatography on silica gel (cyclohexane/EtOAc) to afford 19.6 mg of a 50:50 mol:mol mixture of the desired product **2a** and the starting material **1** (34% yield, 50% brsm). The diastereomeric ratio of **2a** could be determined as 87:13 by 300 MHz ^{1}H NMR spectrum of the crude.

Reactions in EtOAc, DMF and $NaHCO_3$ as base (Table 1, entries 3 and 6 in the manuscript):

(*R*,*S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (50.0 mg, 0.153 mmol, 1.0 eq), $NaHCO_3$ (15.4 mg, 0.183 mmol, 1.2 eq) and TBAI (11.3 mg, 0.031 mmol, 0.2 eq) were introduced in a test tube equipped with a magnetic stirrer and dissolved in a minimum of solvent (1.0 mL) allowing for efficient stirring of the reaction mixture. After 15 min of vigorous stirring, dibenzylamine (35 µL, 0.183 mmol, 1.2 eq) was added to the reaction mixture which was stirred until complete conversion of the substrate. Deionised water was added to the reaction media, and phases were separated. Aqueous phase was extracted with EtOAc and the combined organic phases were washed with an aqueous 10% $KHSO_4$ solution, water, dried over $MgSO_4$, filtered, concentrated and purified on column chromatography on silica gel

(cyclohexane/EtOAc) to afford the desired product **2a** as a yellow oil with the following yields and diastereomeric ratios: EtOAc : 73%, dr > 98:2; DMF : 55%, dr > 98:2.

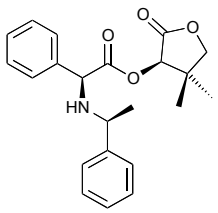
Reaction in the ball-mill (Table 1, entries 7, 8 and 9 in the manuscript):

(*R*,*S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (84.2 mg, 0.257 mmol, 1.0 eq), $NaHCO_3$ (25.9 mg, 0.309 mmol, 1.2 eq), TBAI (19.0 mg, 0.051 mmol, 0.2 eq) and the corresponding amount of water (no water for η ratio = 0 µL mg^{-1}; 190 µL for η ratio = 1 µL mg^{-1} and 380 µL for η ratio = 2 µL mg^{-1})[1] were placed in a 10 mL jar with one 10 mm diameter ball. After 15 minutes of mechanical stirring at 30 Hz, dibenzylamine (59.3 µL, 0.309 mmol, 1.2 eq) was added and the reaction medium was stirred in the ball-mill during 1 hour at 30 Hz. Conversion of the substrate was determined by HPLC analysis of the reaction mixture during the course of the reaction. The reaction medium was recovered with EtOAc and the organic phase was washed with an aqueous 10% $KHSO_4$ solution, water, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford the desired product **2a** as a colorless oil with the following yields and diastereomeric ratios:

- η = 0, 62% yield, dr>98:2
- η = 1, 94% yield, dr>98:2
- η = 2, 96% yield, dr>98:2.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48-7.18 (m, 15H), 5.58 (s, 1H), 4.76 (s, 1H), 4.06 (s, 2H), 3.82 (ABq, 4H, *J* 13.9 Hz), 1.20 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 171.4, 139.7, 136.9, 129.4, 129.1, 128.9, 128.7, 128.5, 127.5, 76.3, 75.1, 65.6, 54.1, 39.9, 22.9, 19.8. MS (ESI): *m/z* 444.2 $[M+H]^+$

2-(*S*)-[(*S*)-α-methylbenzylamine]-phenylacetatic acid (*R*)-pantolactone ester 3:[2]

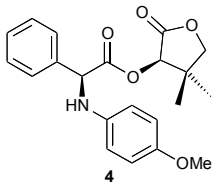


3

(*R*,*S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (96.0 mg, 0.294 mmol, 1.0 eq), $NaHCO_3$ (29.6 mg, 0.352 mmol, 1.2 eq), TBAI (21.7 mg, 0.059 mmol, 0.2 eq) and water (380 µL for η ratio = 2 µL mg^{-1})[1] were placed in a 10 mL jar with one 10 mm diameter ball. After 15 minutes of mechanical stirring at 30 Hz, (*S*)-(−)-α-methylbenzylamine (45.4 µL, 0.352 mmol, 1.2 eq) was added and the reaction medium was stirred in the ball-mill during 30 min at 30 Hz. The reaction medium was recovered with EtOAc and the organic phase was washed with water, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford the desired product **3** as a yellow oil (86 mg, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.17 (m, 10H), 5.36 (s, 1H), 4.32 (s, 1H), 3.91 (s, 2H), 3.87 (q, 1H, *J* 6.5 Hz), 2.30 (s large, 1H), 1.36 (d, 3H, *J* 6.5 Hz), 0.95 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 172.0, 144.6, 138.3, 128.9, 128.7, 128.3, 127.4, 127.2, 76.2, 75.4, 63.0, 56.6, 40.4, 24.6, 22.9, 19.5. MS (ESI): *m/z* 367.9 $[M+H]^+$

2-(*S*)-(4-Methoxyphenylamino)phenylacetatic acid (*R*)-pantolactone ester 4:[2]

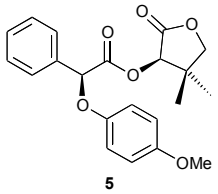


4

(*R*,*S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (50.4 mg, 0.154 mmol, 1.0 eq), $NaHCO_3$ (15.5 mg, 0.185 mmol, 1.2 eq), TBAI (11.4 mg, 0.031 mmol, 0.2 eq), water (300 µL, η ratio = 3 µL mg^{-1}) were placed in a 10 mL jar with one 10 mm diameter ball. After 15 minutes of mechanical stirring at 30 Hz, *p*-anisidine (22.8 mg, 0.185 mmol, 1.2 eq) was added and the reaction medium was stirred in the ball-mill during 6 h at 30 Hz. The reaction medium was recovered with EtOAc and the organic phase was washed with an aqueous 10% $KHSO_4$ solution, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford 36.3 mg of the desired product **4** as a yellow oil (64% yield) with a diastereomeric ratio of 88:12 determined by 300 MHz ^{1}H NMR spectrum of the crude.

^{1}H NMR (300 MHz, $CDCl_3$): δ =7.54 (d, 2H, *J* 6.5 Hz), 7.40-7.32 (m, 3H), 6.73 (d, 2H, *J* 8.9 Hz), 6.64 (d, minor dia, *J* 9.2 Hz), 6.57 (d, 2H, *J* 8.9 Hz), 5.37 (s, 1H), 5.31 (s, minor dia), 5.19 (s, 1H), 4.61 (s large, 1H), 3.94 (s, 2H), 3.74 (s, minor dia), 3.71 (s, 3H), 1.14 (s, 0.12H, minor dia), 1.05 (s, 0.12H, minor dia) 0.91 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 171.6, 173.4 (min dia), 152.8, 140.1, 137.8, 136.7 (min dia), 129.1, 129.0 (min dia), 128.8, 128.7 (min dia), 127.6, 127.3 (min dia), 115.4 (min dia), 115.0, 114.9 (min dia), 114.8, 76.3, 76.2 (min dia), 75.9, 61.9 (min dia), 61.8, 55.8, 40.5, 40.4 (min dia), 23.1 (min dia), 22.7, 19.9 (min dia), 19.3. MS (ESI): *m/z* 370.2 $[M+H]^+$

2-(*S*)-(*p*-Anisyloxy)phenylacetatic acid (*R*)-pantolactone ester 5:[3]



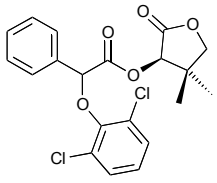
5

(*R*,*S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (50.3 mg, 0.154 mmol, 1.0 eq), $NaHCO_3$ (15.5 mg, 0.184 mmol, 1.2 eq), TBAI (11.4 mg, 0.031 mmol, 0.2 eq) and water (200 µL, η ratio = 2 µL mg^{-1}) were placed in a 10 mL jar with one 10 mm diameter ball. After 15 minutes of mechanical stirring at 30 Hz, 4-methoxyphenol (22.9 mg, 0.184 mmol, 1.2 eq) was added and the reaction medium was stirred in the ball-mill during 2 h at 30 Hz. The reaction medium was recovered with EtOAc and the organic phase was washed with an aqueous 0.1 N NaOH solution, water, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford 49.0 mg of the desired product **5** as a yellow oil (86% yield and 72:28 dr determined by 300 MHz ^{1}H NMR spectrum of the crude).

^{1}H NMR (300 MHz, $CDCl_3$): δ =7.62-7.59 (m, 2H), 7.39-7.26 (m, 3H), 6.93 (d, 2H, *J* 9.1 Hz), 6.81 (d, 2H, *J* 9.1 Hz), 5.70 and 5.69 (s, 1H, **5** and minor dia), 5.39 and 5.30 (s, 1H, **5** and minor dia), 3.95 (s, 2H), 1.13 (. ^{13}C NMR (75 MHz, $CDCl_3$, 2 diastereoisomers): δ = 172.0, 171.5 (min dia), 169.5, 155.2 (min dia), 155.0, 151.5 (min dia), 151.4, 135.6, 135.3 (min dia), 129.6, 129.4 (min dia), 129.2, 129.0 (min dia), 127.7, 127.2 (min dia), 117.7 (min dia), 116.9, 115.0, 114.9 (min dia), 80.1 (min dia), 79.2, 76.3 (min dia), 76.3, 76.1

(min dia), 75.7, 55.9, 40.7, 40.6 (min dia), 23.3 (min dia), 22.9, 20.0 (min dia), 19.5. MS (ESI): *m/z* 388.2 $[M+NH_4]^+$

2-(2,6-dichlorophenoxy)phenylacetatic acid (*R*)-pantolactone ester 6:[4]

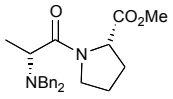


6

(*R,S*)-2-Bromo-2-phenylacetic acid (*R*)-pantolactone ester (**1**)[2] (89.1 mg, 0.272 mmol, 1.0 eq), $NaHCO_3$ (27.5 mg, 0.327 mmol, 1.2 eq), TBAI (20.1 mg, 0.054 mmol, 0.2 eq) and water (380 µL for η ratio = 2 µL mg^{-1})[1] were placed in a 10 mL jar with one 10 mm diameter ball. After 15 minutes of mechanical stirring at 30 Hz, 2,6-dichlorophenol (53.3 mg, 0.327 mmol, 1.2 eq) was added and the reaction medium was stirred in the ball-mill during 1 h 30 at 30 Hz. The reaction medium was recovered with EtOAc and the organic phase was washed twice with aqueous saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford the desired product **6** as a colorless oil (86 mg, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$, 2 diastereoisomers): δ = 7.68-7.58 (m, 2H), 7.42-7.39 (m, 3H), 7.30 (d, 1.12H, *J* 2.4 Hz), 7.28 (d, 0.88H, *J* 2.0 Hz), 7.04-6.96 (m, 1H), 6.00 (s, 0.56H), 5.98 (s, 0.44H), 5.48 (s, 0.56H), 5.39 (s, 0.44H), 4.07-3.99 (m, 2H), 1.19 (s, 1.32H), 1.06 (s, 1.32H), 1.06 (s, 1.68H), 0.75 (s, 1.68H). ^{13}C NMR (75 MHz, $CDCl_3$, 2 diastereoisomers): δ = 171.8, 171.2, 168.5, 168.4, 150.0, 149.9, 134.9, 134.4, 129.8, 129.6, 129.4, 129.3, 129.2, 128.7, 128.6, 128.5, 128.1, 125.6, 125.5, 82.7, 82.4, 76.2, 76.1, 75.9, 75.6, 40.6, 40.4, 23.1, 23.0, 19.8, 19.4. MS (ESI): *m/z* 426.1 $[M+NH_4]^+$

***N,N*-Dibenzyl-*D*-alanyl-*L*-proline methyl ester 8:**[5, 6]

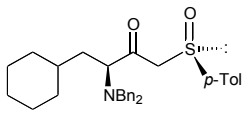


8

1-(2-Bromo-1-oxopropyl)-*L*-proline methyl ester (**7**)[7] (39.1 mg, 0.148 mmol, 1.0 eq), $NaHCO_3$ (14.9 mg, 0.178 mmol, 1.2 eq), TBAI (10.9 mg, 0.030 mmol, 0.2 eq) and water (200 µL, η ratio = 2 µL mg^{-1}) were placed in a 10 mL jar with one 10 mm diameter ball. After 15 minutes of mechanical stirring, dibenzylamine (34.2 µL, 0.178 mmol, 1.2 eq) was added and the reaction medium was stirred in a ball-mill during 12 hours at 30 Hz. Dibenzylamine was added (27.3 µL, 0.142 mmol, 0.96 eq) and the reaction medium was stirred during 1 hour to reach complete conversion of the substrate. The reaction medium was recovered with EtOAc and the organic phase was washed with an aqueous 10% $KHSO_4$ solution, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford 42.3 mg of product **8** as a yellow oil (75% yield) with a dr > 98:2 determined by 300 MHz ^{1}H NMR spectrum of the crude.

^{1}H NMR (300 MHz, $CDCl_3$, *trans* conformer): δ =7.39-7.23 (m, 10H), 4.46-4.42 (m, 1H), 3.78 (d, 2H, *J* 13.4 Hz), 3.78-3.70 (m, 1H), 3.62 (s, 3H), 3.58 (d, 2H, *J* 13.4 Hz), 3.45-3.38 (m, 1H), 2.90-2.82 (m, 1H), 2.16-1.72 (m, 4H), 1.28 (d, 3H, *J* 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, *trans* conformer): δ =173.0, 172.7, 140.0, 129.5, 128.3, 127.1, 59.2, 54.8, 54.2, 52.2, 46.8, 29.2, 25.2, 10.1. MS (ESI): *m/z* 381.3 $[M+H]^+$

(*S*)-4-Cyclohexyl-3-(dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2- one 10:[8]

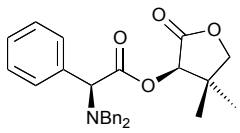


10

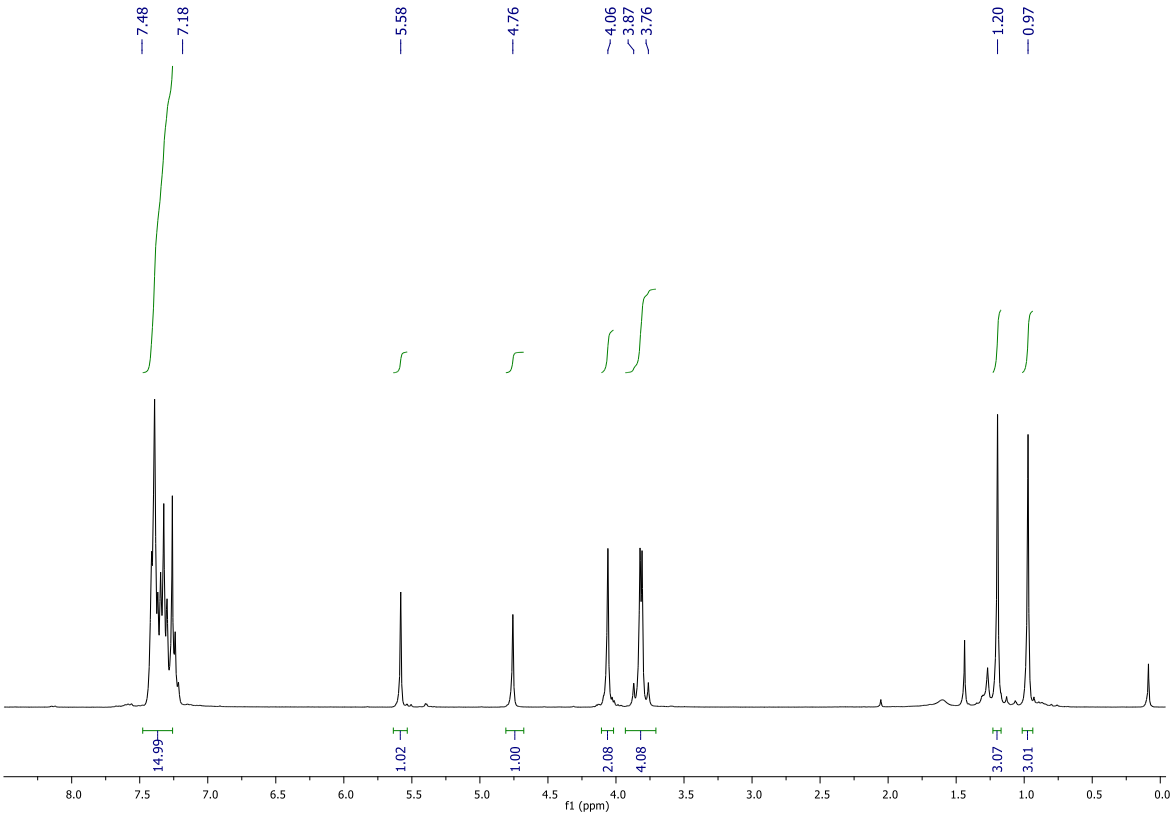
3-Bromo-4-cyclohexyl-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one (**9**)[8] (75.2 mg, 0.203 mmol, 1.0 eq), TBAI (15.0 mg, 0.041 mmol, 0.2 eq) and water (380 µL, η ratio = 2 µL mg^{-1}) were placed in a 10 mL jar with one 10 mm diameter ball. After 15 minutes of mechanical agitation, dibenzylamine (98 µL, 0.506 mmol, 2.5 eq) was added and the reaction medium was stirred in a ball-mill during 7 hours at 30 Hz. The reaction medium was recovered with EtOAc and the organic phase was washed with an aqueous 10% $KHSO_4$ solution, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (cyclohexane/EtOAc) to afford 70.4 mg of the desired product **10** as a yellow oil (71% yield) and a diastereomeric ratio superior to 98:2 as determined by 300 MHz ^{1}H NMR spectrum of the crude.

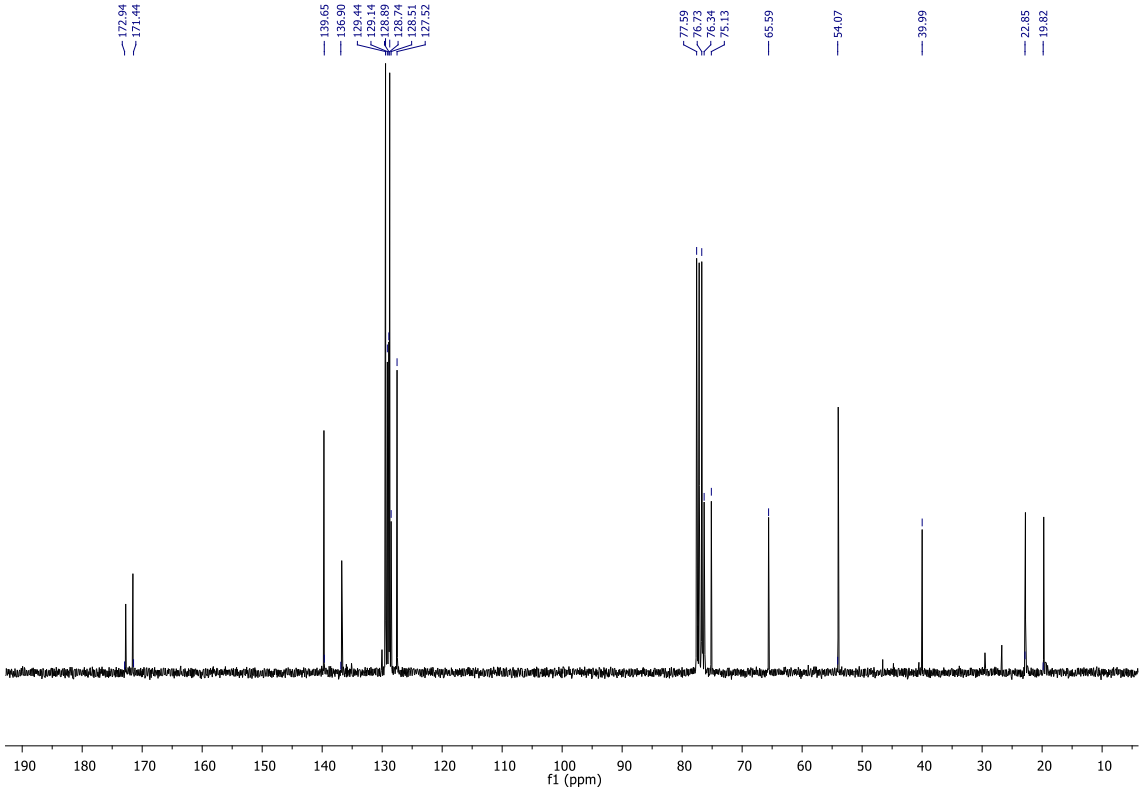
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.25 (m, 12H), 7.11 (d, 2H, *J* 8.0 Hz), 4.21 (d, 1H, *J* 13.2 Hz), 4.09 (d, 1H, *J* 13.2 Hz), 3.60 (d, 2H, *J* 13.1 Hz), 3.32 (d, 2H, *J* 13.4 Hz), 2.75-2.72 (m, 1H), 2.33 (s, 3H), 1.65-0.54 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 142.7, 140.4, 139.3, 130.4, 129.7, 129.0, 128.0, 125.3, 66.5, 65.3, 54.8, 34.4, 34.1, 32.4, 28.7, 26.8, 26.2, 26.0, 21.2. MS (ESI): *m/z* 488.3 $[M+H]^+$

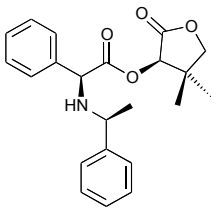
^{1}H and ^{13}C spectra:



2a



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O
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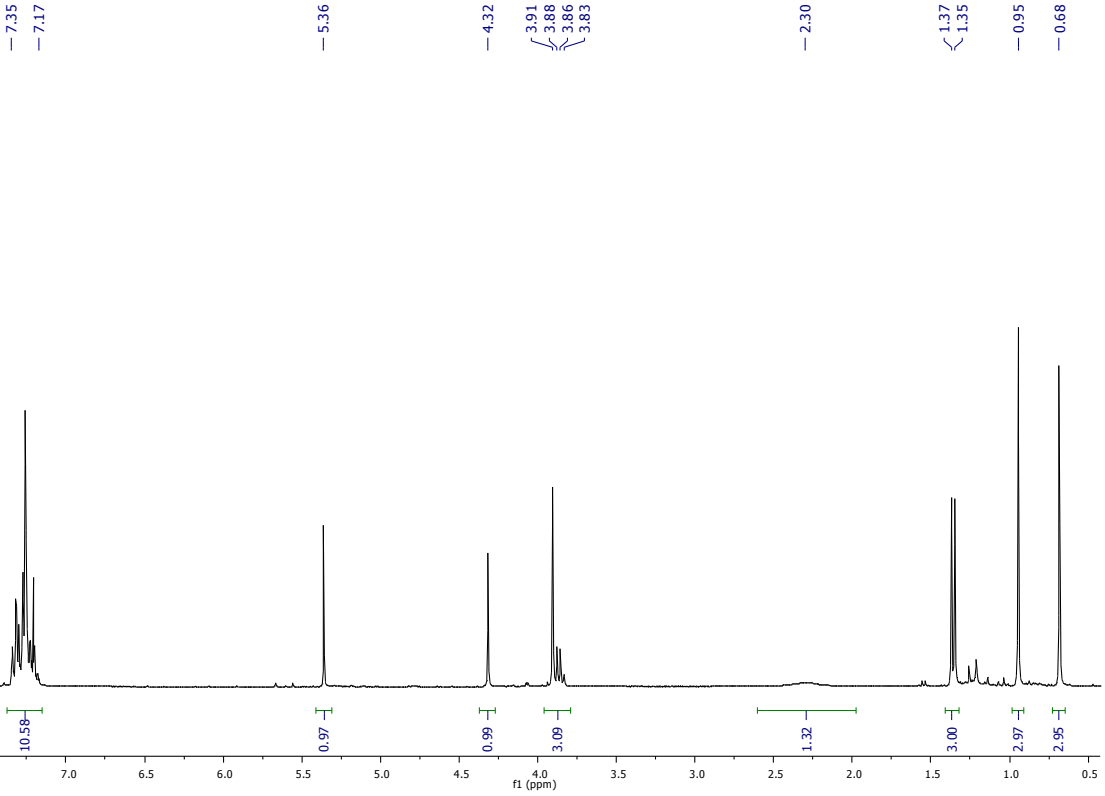
HN

3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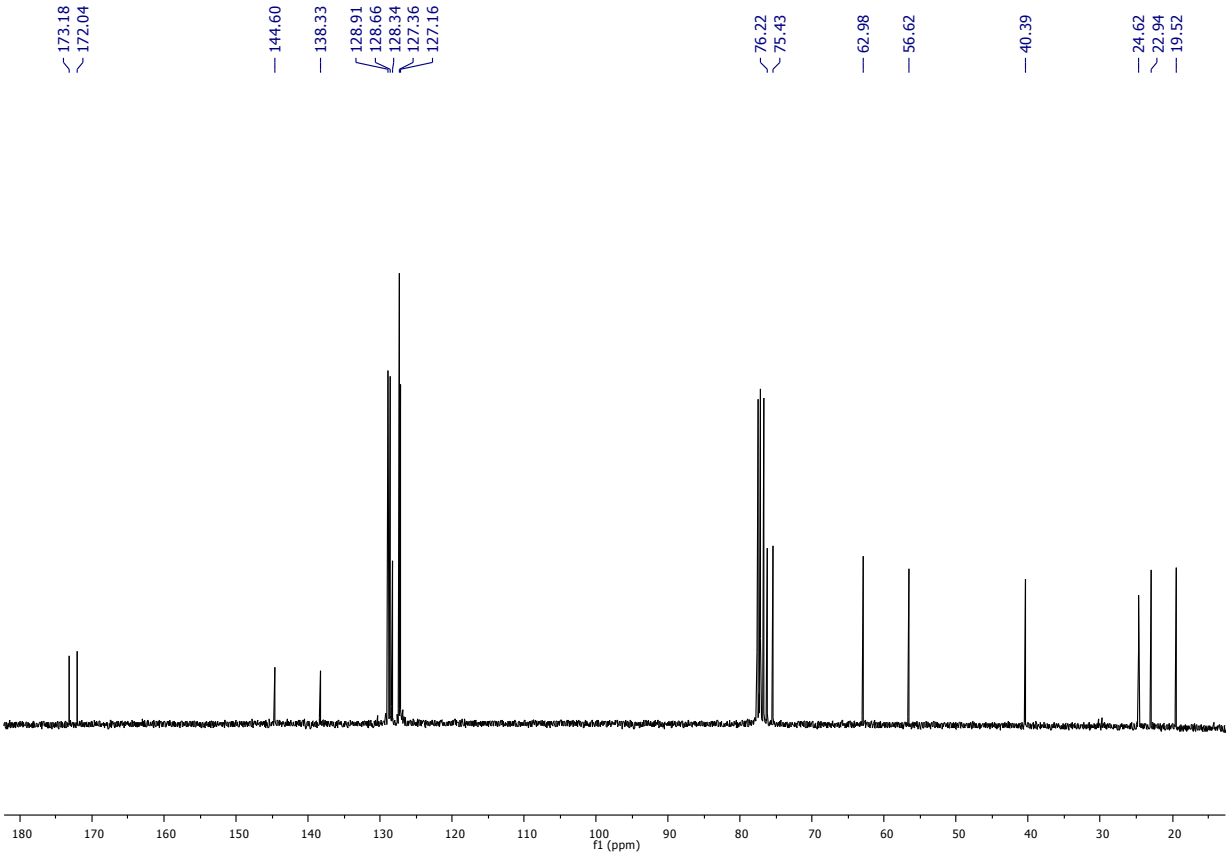
2.95
f1 (ppm)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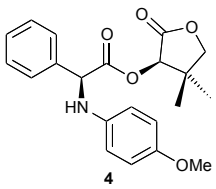
f1 (ppm)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OMe

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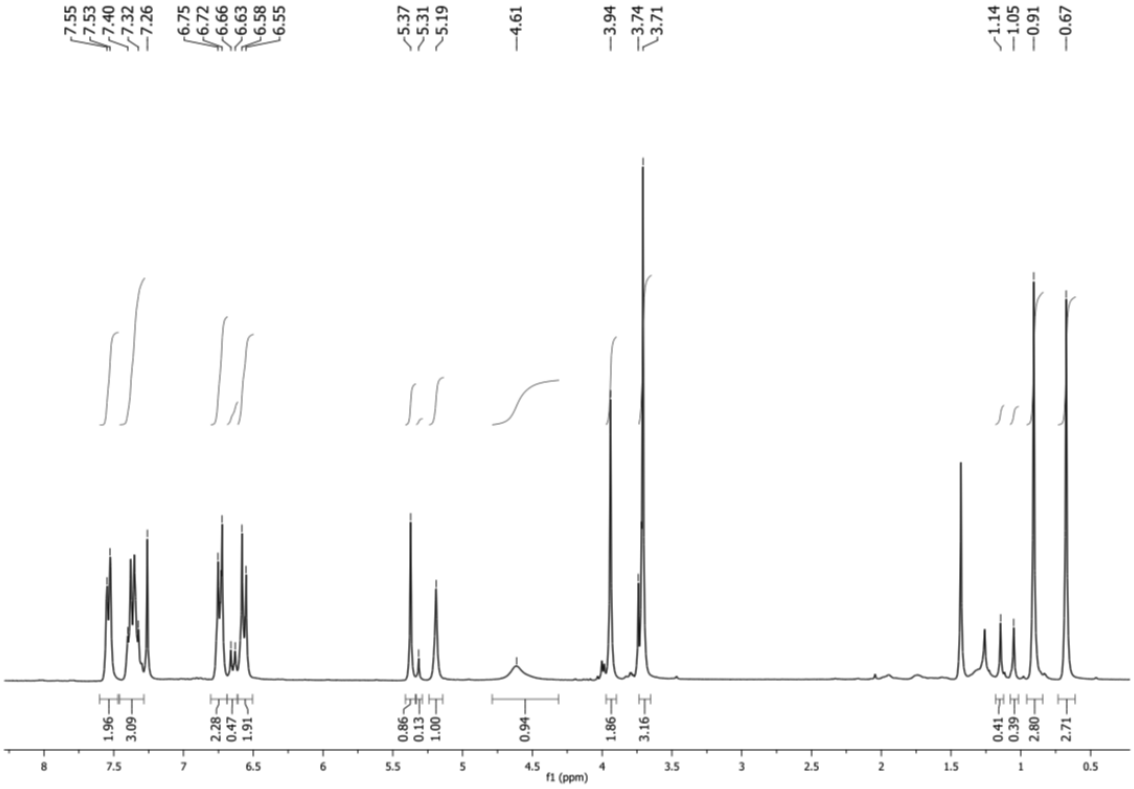
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1.05
0.91
0.67
1.96
3.09
2.28
0.47
1.91
0.86
0.13
1.00
0.94
1.86
3.16
0.41
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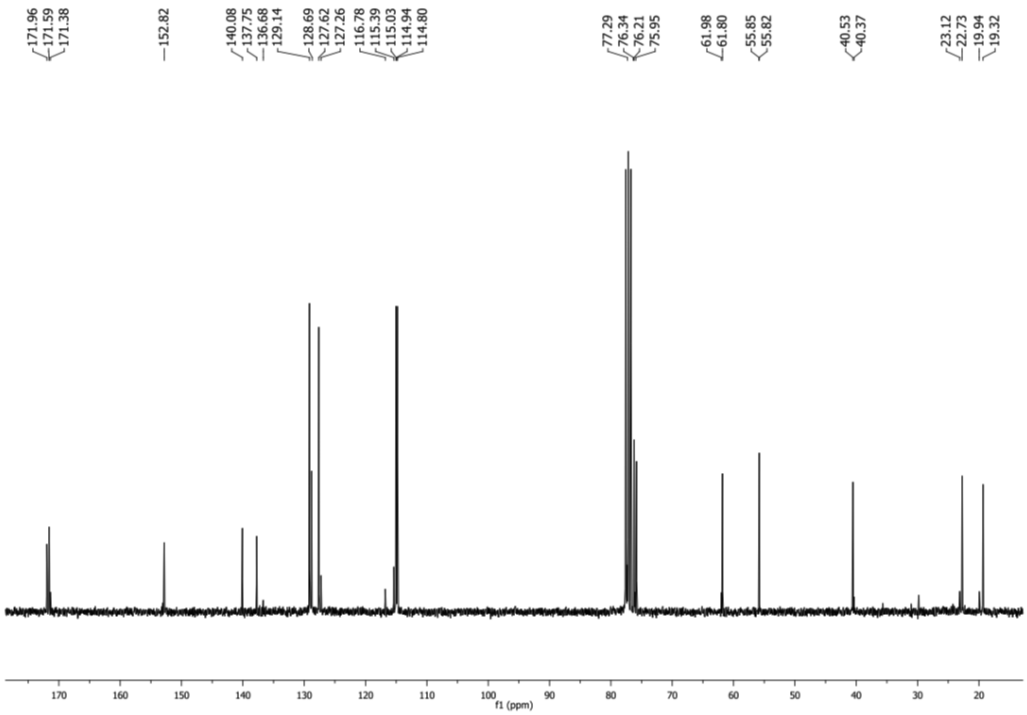
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114.94
114.80
77.29
76.34
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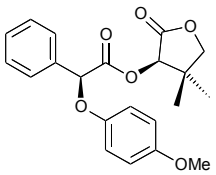
f1 (ppm)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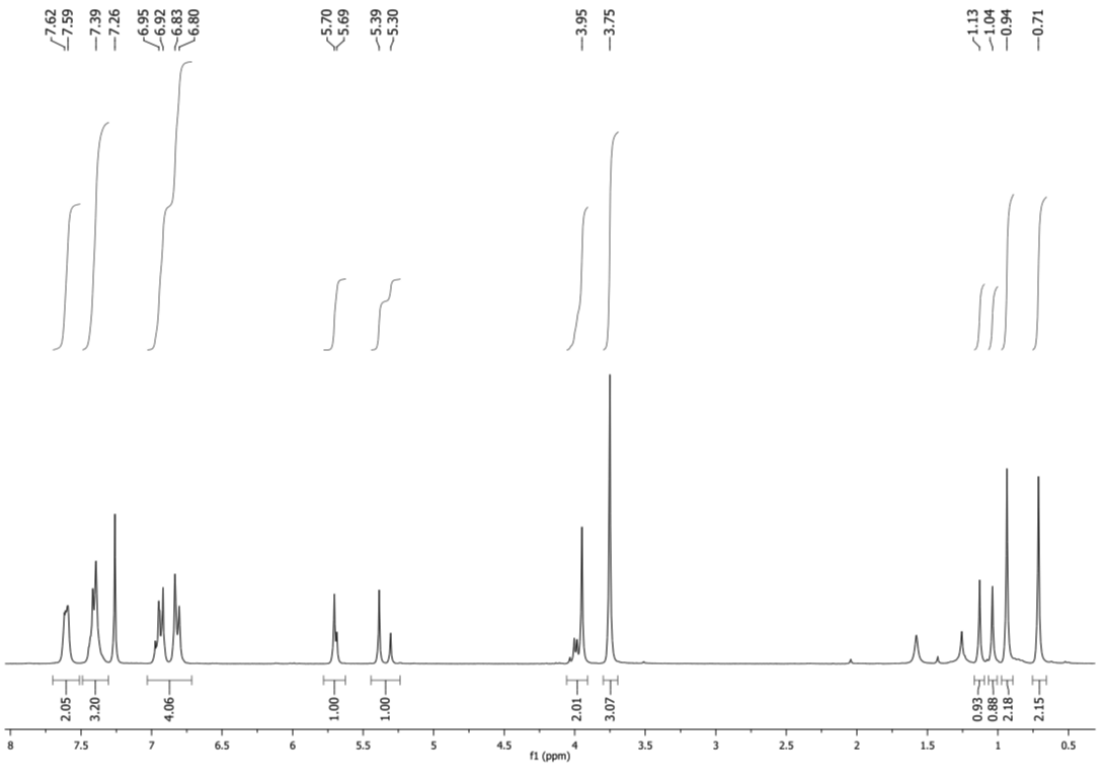
O
O
O
O
OMe

5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6.80
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3.95
3.75
1.13
1.04
0.94
0.71
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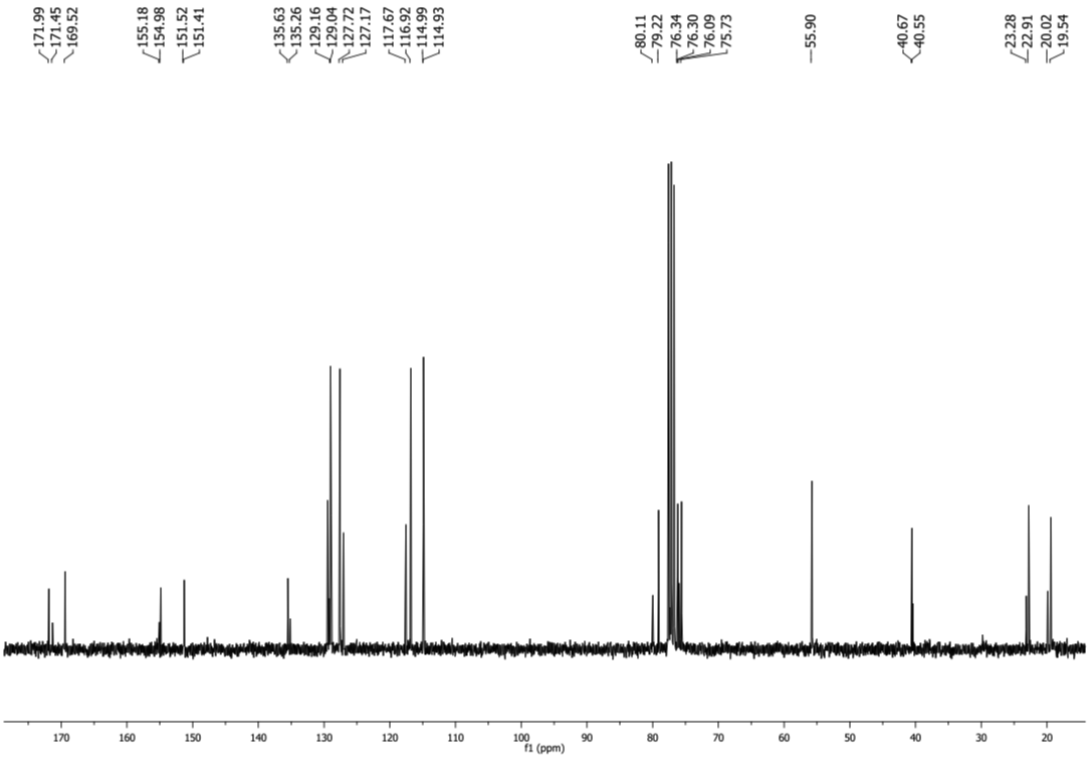
f1 (ppm)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117.67
116.92
114.99
114.93
80.11
79.22
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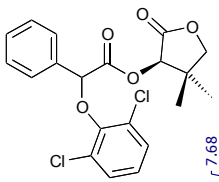
f1 (ppm)



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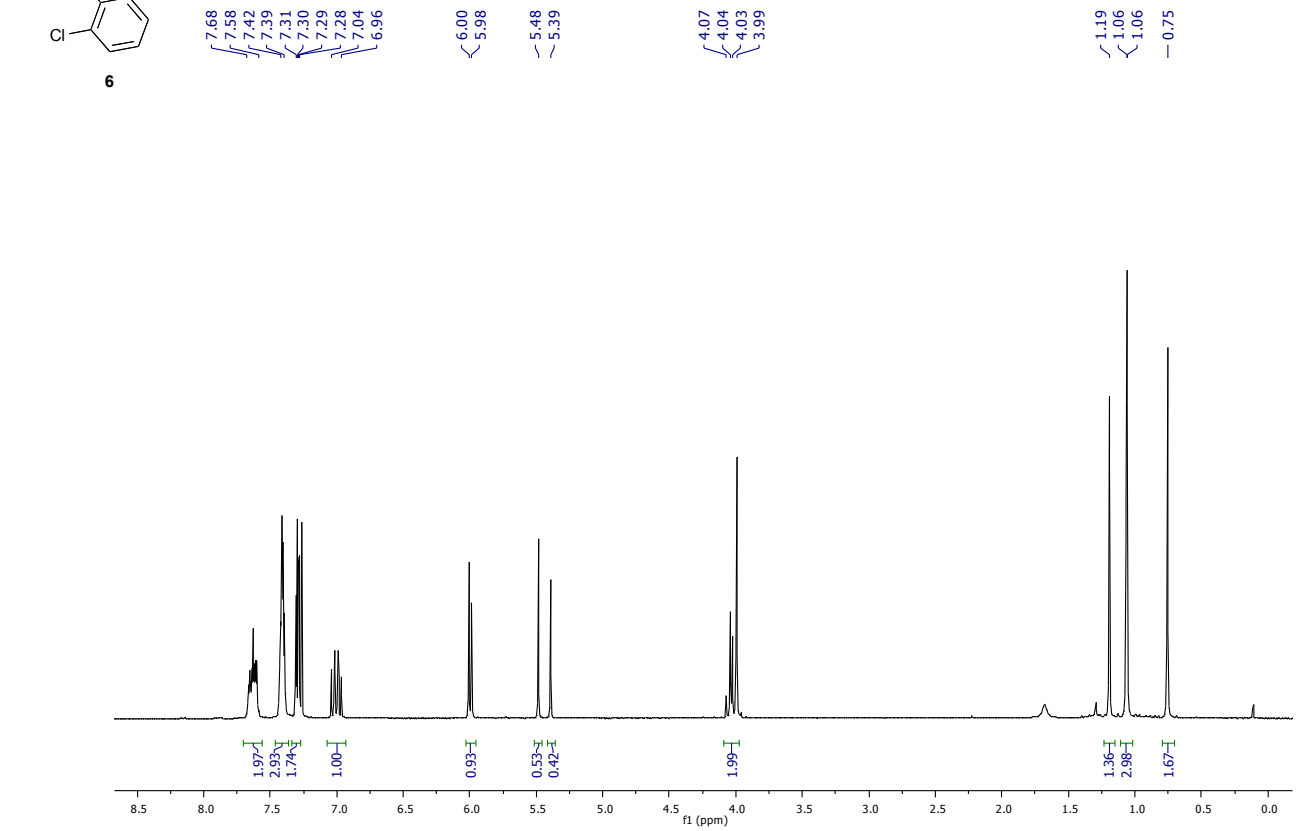
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5.48
5.39
4.07
4.04
4.03
3.99
1.19
1.06
1.06
0.75
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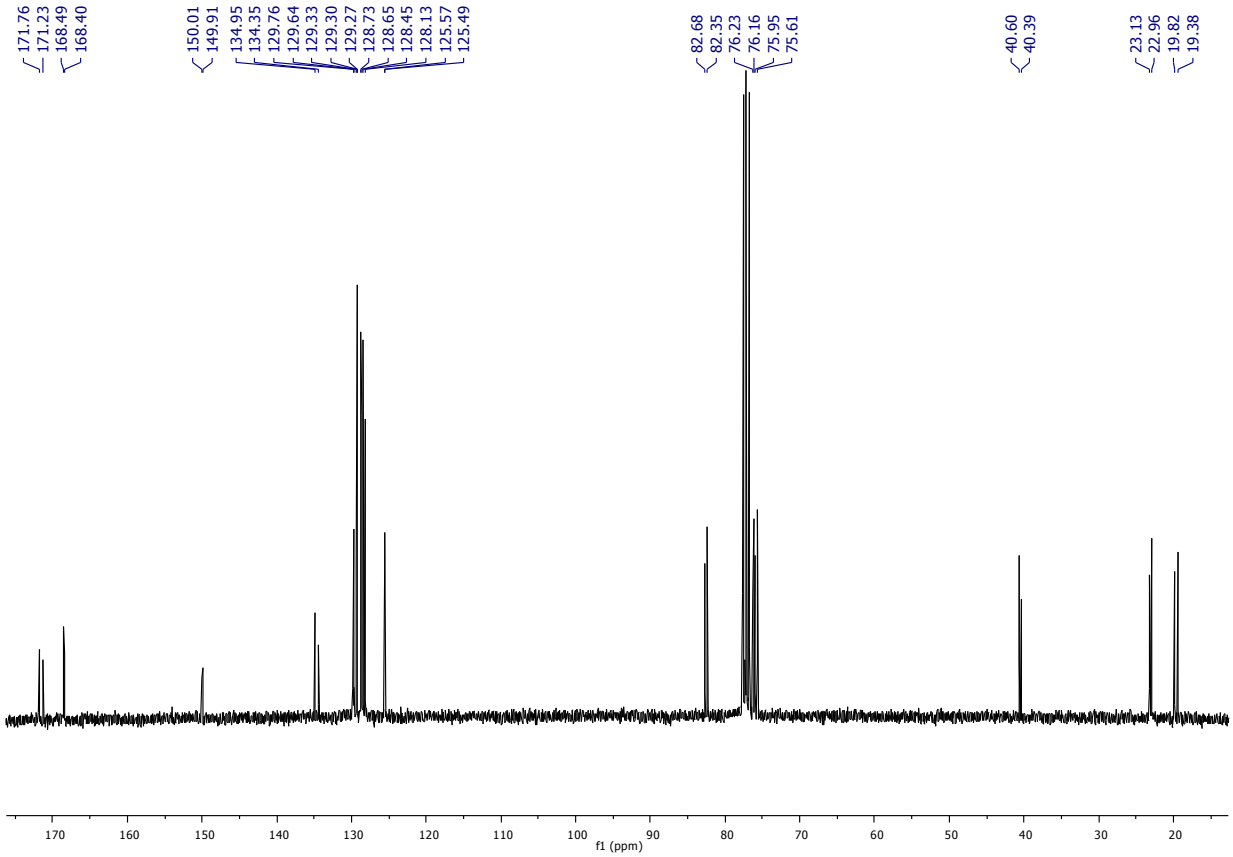
f1 (ppm)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128.13
125.57
125.49
82.68
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23.13
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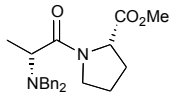
19.38
f1 (ppm)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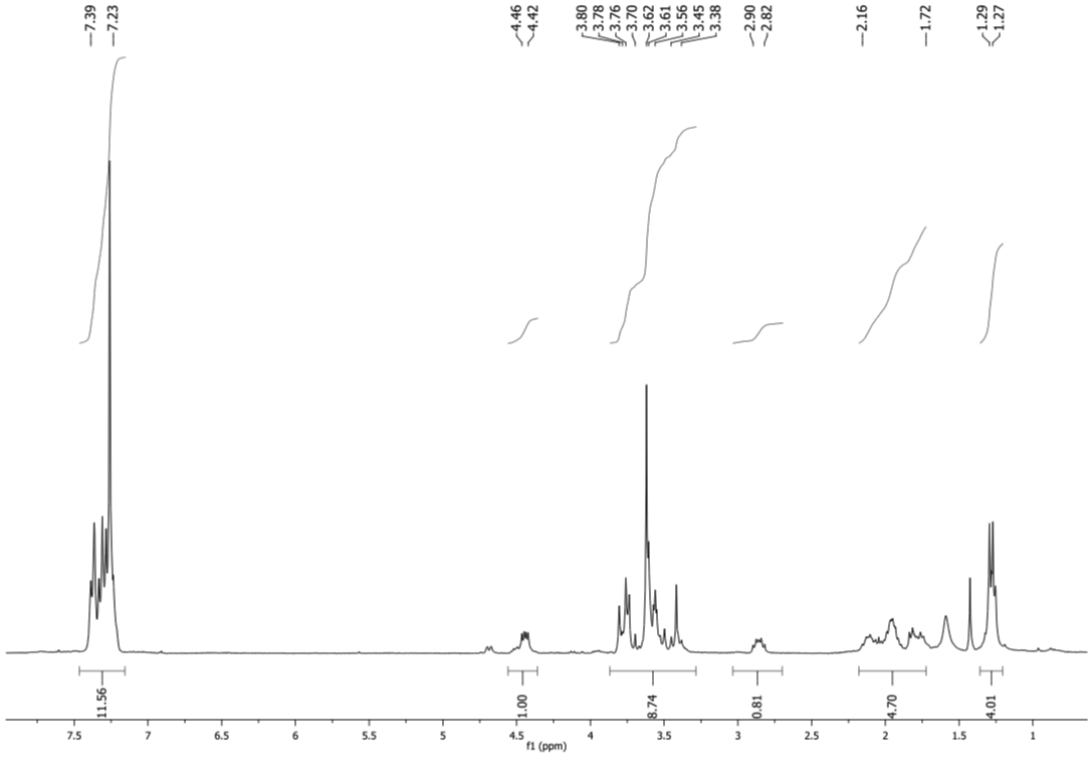
N
NBn2

8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2.90
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0.81
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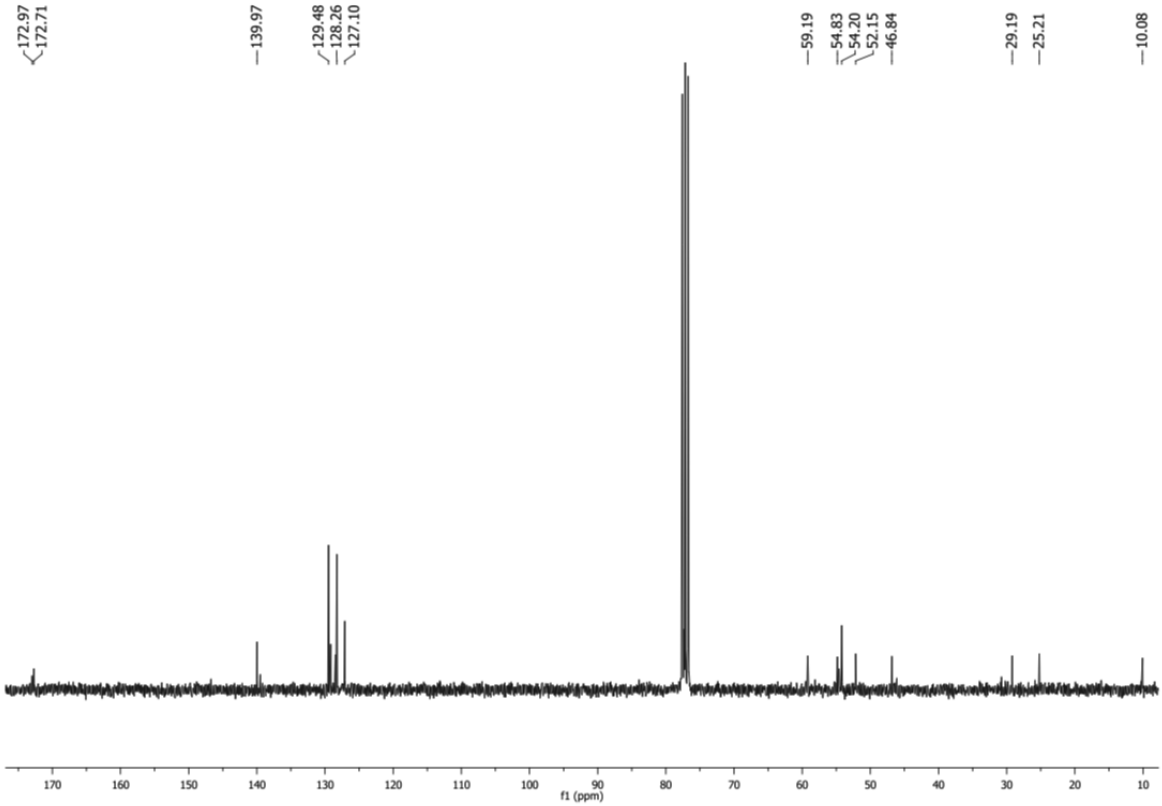
f1 (ppm)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29.19
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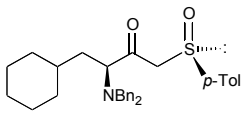
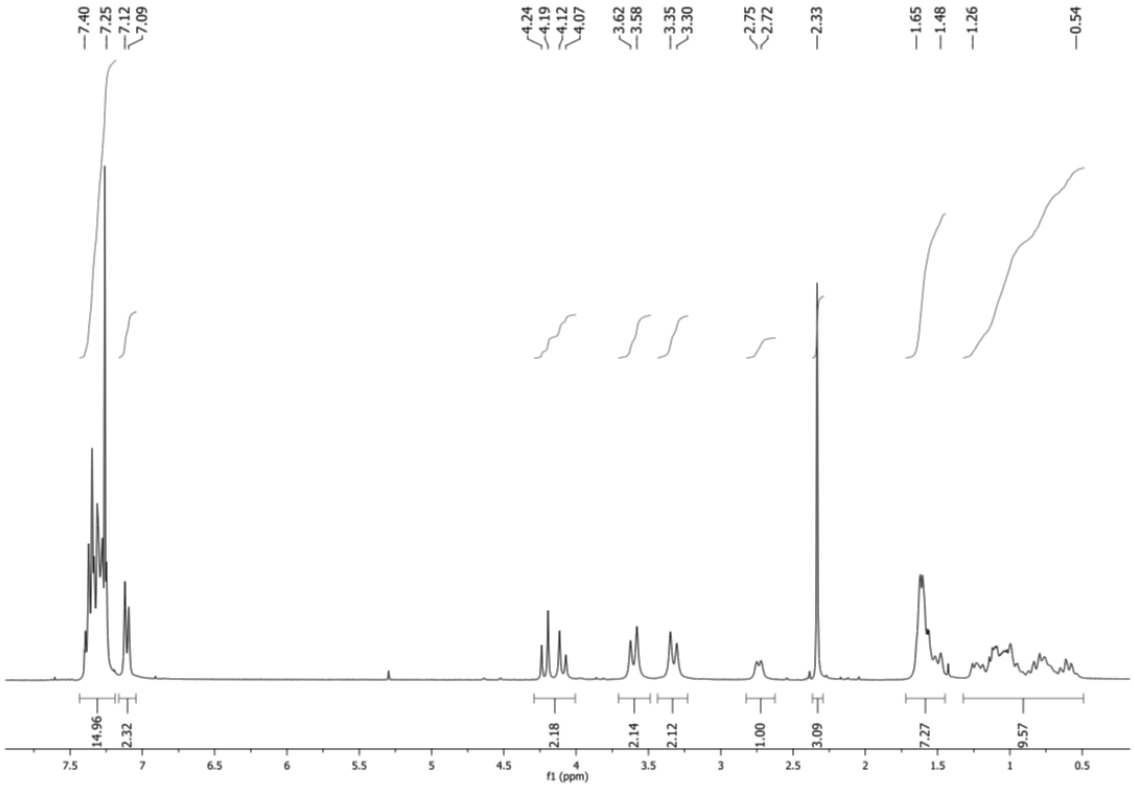
f1 (ppm)


O
O
S
NBn2
p-Tol

10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4.07
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3.58
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3.30
2.75
2.72
2.33
1.65
1.48
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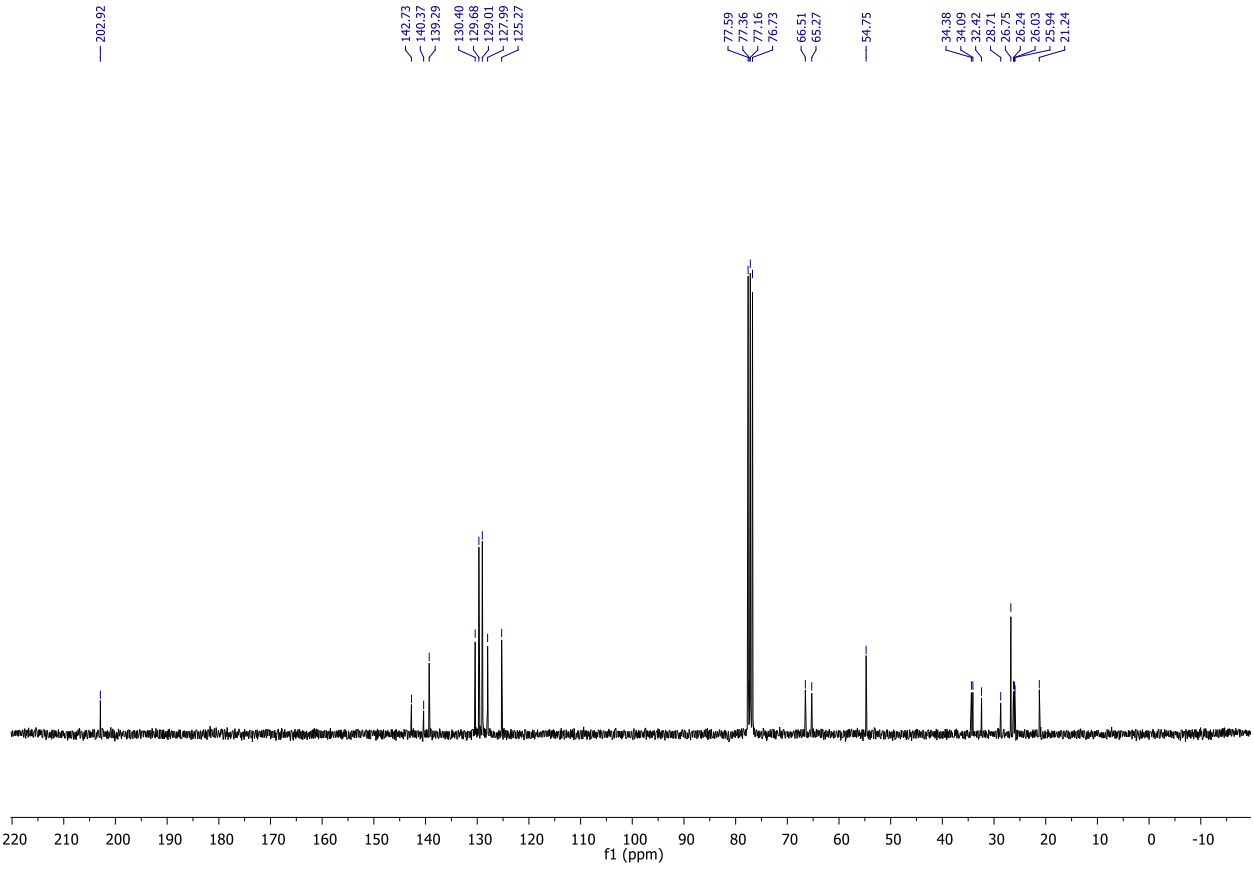
f1 (ppm)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76.73
66.51
65.27
54.75
34.38
34.09
32.42
28.71
26.75
26.24
26.03
25.94
21.24
f1 (ppm)

EcoScale calculation:[9]

For all reactions, the EcoScale evaluation has been done for the production of 10 mmoles of the product starting from the corresponding substrate.

For reactions of dibenzylamine on (*R*,*S*)-2-bromo-2-phenylacetic acid (*R*)-pantolactone ester (Table 1 of the manuscript):

Parameters	**Penalty points**						
Homogenization technique	Magnetic stirrer	Magnetic stirrer	Magnetic stirrer	Magnetic stirrer	Ball-mill	Ball-mill	Ball-mill
Solvent	THF	Water	EtOAc	DMF	Solvent-free	Water (η = 1)	Water (η = 2)
Base	Et_3N	$NaHCO_3$	$NaHCO_3$	$NaHCO_3$	$NaHCO_3$	$NaHCO_3$	$NaHCO_3$
1. Yield (%)	59	44[a]	73	55	62	94	96
Penalty points	20,5	28	13,5	22,5	19	3	2
2. Reaction components							
Compound **1** (not commercially available)	3	3	3	3	3	3	3
Bn_2NH (96,60USD for 500g)	0	0	0	0	0	0	0
TBAI (230USD for 500g)	0	0	0	0	0	0	0
Et_3N (94,30USD for 1L)	0	-	-	-	-	-	-
$NaHCO_3$ (64,10USD for 1kg)	-	0	0	0	0	0	0
3. Safety							
Compound **1**	0	0	0	0	0	0	0
Bn_2NH	0	0	0	0	0	0	0
TBAI	0	0	0	0	0	0	0
$NaHCO_3$	-	0	0	0	0	0	0
Et_3N: T, F	10	-	-	-	-	-	-
THF: T, F	10	-	-	-	-	-	-
Water	-	0	-	-	-	0	0
EtOAc : F	-	-	5	-	-	-	-
DMF : T, F	-	-	-	10	-	-	-
4. Technical setup							
Magnetic stirrer	0	0	0	0	-	-	-
Ball-mill	-	-	-	-	2	2	2
5. Temperature/ Time							
Room temperature	1	2	3	1	0	0	0
6. Workup and purification							
Adding solvent	0	0	0	0	0	0	0
Liquid-Liquid extraction	3	3	3	3	3	3	3
Classical chromatography	10	10	10	10	10	10	10
Total	57,5	46	37,5	49,5	37	21	20
Ecoscale score	**42,5**	**54**	**62,5**	**50,5**	**63**	**79**	**80**
Ranking of reaction	Inadequate synthesis	Acceptable Synthesis	Acceptable Synthesis	Acceptable Synthesis	Acceptable Synthesis	**Excellent Synthesis**	**Excellent Synthesis**

[a] yield of pure diastereoisomer based on 50% yield based on recovered material and a diastereomeric ratio of 87:13

For reaction of (*S*)-(−)-α-methylbenzylamine on (*R*,*S*)-2-bromo-2-phenylacetic acid (*R*)-pantolactone ester:

Parameters					**Penalty points**	
Homogenization technique					Magnetic stirrer	Ball-mill
Solvent					THF	Water
Base					Et_3N	$NaHCO_3$
1. Yield (%)[a]					84,0	80,0
Penalty points					8,0	10,0
2. Reaction components	**Eq.**	**M**	**Price/g (Sigma-Aldrich)**	**Price to get 10mmol of product**		
Compound **1** (not commercially available)	1,00	-	-	-	3	3
(*S*)-(−)-α-Methylbenzylamine (146USD for 100g)	1,05	121,18	1,46	2,21	0	-
(*S*)-(−)-α-Methylbenzylamine (146USD for 100g)	1,20	121,18	1,46	2,65	-	0
THAI (96,60USD for 10g)	0,20	481,58	9,66	11,08	3	-
TBAI (230USD for 500g)	0,20	369,37	0,46	0,42	-	0
Et_3N (94,30USD for 1L)	2,00	101,19	0,13	0,31	0	-
$NaHCO_3$ (64,10USD for 1kg)	1,20	84,01	0,06	0,08	-	0
3. Safety						
Compound **1**					0	0
(*S*)-(−)-α-Methylbenzylamine					0	0
THAI					0	-
TBAI					-	0
Et_3N: T, F					10	-
$NaHCO_3$					-	0
THF: T, F					10	-
Water					-	0
4. Technical setup						
Magnetic stirrer					0	-
Ball-mill					-	2
5. Temperature/ Time						
Room temperature					1	0
6. Workup and purification						
Adding solvent					0	0
Liquid-Liquid extraction					3	3
Classical chromatography					10	10
Total					48,0	28,0
Ecoscale score					**52,0**	**72,0**
Ranking of reaction					Acceptable Synthesis	Acceptable Synthesis

[a] Calculated yield of pure major diastereoisomer

For reaction of *p*-anisidine on (*R*,*S*)-2-bromo-2-phenylacetic acid (*R*)-pantolactone ester:

Parameters					**Penalty points**	
Homogenization technique					Magnetic stirrer	Ball-mill
Solvent					THF	Water
Base					Et_3N	$NaHCO_3$
1. Yield (%)[a]					75,0	56,0
Penalty points					12,5	22,0
2. Reaction components	**Eq.**	**M**	**Price/g (Sigma-Aldrich)**	**Price to get 10mmol of product**		
Compound **1** (not commercially available)	1,00	-	-	-	3	3
p-Anisidine (119USD for 1kg)	1,05	123,15	0,12	0,21	0	-
p-Anisidine (119USD for 1kg)	1,20	123,15	0,12	0,31	-	0
THAI (96,60USD for 10g)	0,20	481,58	9,66	12,41	3	-
TBAI (230USD for 500g)	0,20	369,37	0,46	0,61	-	0
Et_3N (94,30USD for 1L)	2,00	101,19	0,13	0,35	0	-
$NaHCO_3$ (64,10USD for 1kg)	1,20	84,01	0,06	0,12	-	0
3. Safety						
Compound **1**					0	0
p-Anisidine : T					5	5
THAI					0	-
TBAI					-	0
Et_3N: T, F					10	-
$NaHCO_3$					-	0
THF: T, F					10	-
Water					-	0
4. Technical setup						
Magnetic stirrer					0	-
Ball-mill					-	2
5. Temperature/ Time						
Room temperature					3	1
6. Workup and purification						
Adding solvent					0	0
Liquid-Liquid extraction					3	3
Classical chromatography					10	10
Total					59,5	46,0
Ecoscale score					**40,5**	**54,0**
Ranking of reaction					Inadequate synthesis	Acceptable Synthesis

[a] Calculated yield of pure major diastereoisomer

For reaction of *p*-methoxyphenol on (*R*,*S*)-2-bromo-2-phenylacetic acid (*R*)-pantolactone ester:

Parameters					**Penalty points**	
Homogenization technique					Magnetic stirrer	Ball-mill
Solvent					THF	Water
Base					NaH	$NaHCO_3$
1. Yield (%)[a]					70,0	62,0
Penalty points					15,0	19,0
2. Reaction components	**Eq.**	**M**	**Price/g (Sigma-Aldrich)**	**Price to get 10mmol of product**		
Compound **1** (not commercially available)	1,00	-	-	-	3	3
p-MeOPhenol (88.40USD for 1kg)	1,20	124,14	0,09	0,19	0	-
p-MeOPhenol (88.40USD for 1kg)	1,20	124,14	0,09	0,21	-	0
THAI (96,60USD for 10g)	0,20	481,58	9,66	13,29	3	-
TBAI (230USD for 500g)	0,20	369,37	0,46	0,55	-	0
NaH (2075USD for 1kg)	1,10	24,00	2,08	0,78	0	-
$NaHCO_3$ (64,10USD for 1kg)	1,20	84,01	0,06	0,10	-	0
3. Safety						
Compound **1**					0	0
p-MeOPhenol					0	0
THAI					0	-
TBAI					-	0
NaH: Corrosive, F					10	-
$NaHCO_3$					-	0
THF: T, F					10	-
Water					-	0
4. Technical setup						
Magnetic stirrer					0	-
Ball-mill					-	2
5. Temperature/ Time						
Cooling, <0°C					5	-
Room temperature					-	1
6. Workup and purification						
Adding solvent					0	0
Liquid-Liquid extraction					3	3
Classical chromatography					10	10
Total					59	38,0
Ecoscale score					**41**	**62**
Ranking of reaction					Inadequate synthesis	Acceptable Synthesis

[a] Calculated yield of pure major diastereoisomer

For reaction of 2,6-dichlorophenol on (*R*,*S*)-2-bromo-2-phenylacetic acid (*R*)-pantolactone ester:

Parameters					**Penalty points**	
Homogenization technique					Magnetic stirrer	Ball-mill
Solvent					THF	Water
Base					NaH	$NaHCO_3$
1. Yield (%)[a]					39,0	43,0
Penalty points					30,5	28,5
2. Reaction components	**Eq.**	**M**	**Price/g (Sigma-Aldrich)**	**Price to get 10mmol of product**		
Compound **1** (not commercially available)	1,00	-	-	-	3	3
2,6-Dichlorophenol (73.80USD for 100g)	1,30	163,00	0,74	4,01	0	-
2,6-Dichlorophenol (73.80USD for 100g)	1,20	163,00	0,74	3,36	-	0
TPAI (165,00USD for 100g)	0,20	425,49	1,65	3,60	0	-
TBAI (230USD for 500g)	0,20	369,37	0,46	0,79	-	0
NaH (2075USD for 1kg)	1,10	24,00	2,08	1,40	0	-
$NaHCO_3$ (64,10USD for 1kg)	1,20	84,01	0,06	0,15	-	0
3. Safety						
Compound **1**					0	0
2,6-Dichlorophenol: Dangerous for environment					5	5
TPAI					0	-
TBAI					-	0
NaH: Corrosive, F					10	-
$NaHCO_3$					-	0
THF: T, F					10	-
Water					-	0
4. Technical setup						
Magnetic stirrer					0	-
Ball-mill					-	2
5. Temperature/ Time						
Cooling, <0°C					5	-
Room temperature					-	1
6. Workup and purification						
Adding solvent					0	0
Liquid-Liquid extraction					3	3
Classical chromatography					10	10
Total					76,5	52,5
Ecoscale score					**23,5**	**47,5**
Ranking of reaction					Inadequate synthesis	Inadequate synthesis

[a] Calculated yield of pure major diastereoisomer

For reaction of dibenzylamine on 1-(2-bromo-1-oxopropyl)-L-proline methyl ester:

Parameters					**Penalty points**	
Homogenization technique					Magnetic stirrer	Ball-mill
Solvent					DCM	Water
Base					Et_3N	$NaHCO_3$
1. Yield (%)					70,0	75,0
Penalty points					15,0	12,5
2. Reaction components	**Eq.**	**M**	**Price/g (Sigma-Aldrich)**	**Price to get 10mmol of product**		
Compound **7** (not commercially available)	1,00	-	-	-	3	3
Bn_2NH (96,60USD for 500g)	1,05	197,28	0,19	0,57	0	-
Bn_2NH (96,60USD for 500g)	2,16	197,28	0,19	1,10	-	0
TBAI (230USD for 500g)	1,00	369,37	0,46	2,43	0	-
TBAI (230USD for 500g)	0,20	369,37	0,46	0,45	-	0
Et_3N (94,30USD for 1L)	1,00	101,19	0,13	0,19	0	-
$NaHCO_3$ (64,10USD for 1kg)	1,20	84,01	0,06	0,09	-	0
3. Safety						
Compound **7**					0	0
Bn_2NH					0	0
TBAI					0	0
Et_3N: T, F					10	-
$NaHCO_3$					-	0
Water					-	0
DCM : T					5	-
4. Technical setup						
Magnetic stirrer					0	-
Ball-mill					-	2
5. Temperature/ Time						
Room temperature					3	1
6. Workup and purification						
Adding solvent					0	0
Liquid-Liquid extraction					3	3
Classical chromatography					10	10
Total					49,0	31,5
Ecoscale score					**51,0**	**68,5**
Ranking of reaction					Acceptable Synthesis	Acceptable Synthesis

For reaction of dibenzylamine on 3-bromo-4-cyclohexyl-1-[(*R*)-*p*-tolylsulfinyl]butan-2-one:

Parameters					**Penalty points**	
Homogenization technique					Magnetic stirrer	Ball-mill
Solvent					THF	Water
Base					Bn_2NH	Bn_2NH
1. Yield (%)					74,0	71,0
Penalty points					13,0	14,5
2. Reaction components	**Eq.**	**M**	**Price/g (Sigma-Aldrich)**	**Price to get 10mmol of product**		
Compound **9** (not commercially available)	1,00	-	-	-	3	3
Bn_2NH (96,60USD for 500g)	2,50	197,28	0,19	1,29	0	-
TBAI (230USD for 500g)	0,20	369,37	0,46	0,48	-	0
3. Safety						
Compound **9**					0	0
Bn_2NH					0	0
TBAI					-	0
Water					-	0
THF : T, F					10	-
4. Technical setup						
Magnetic stirrer					0	-
Ball-mill					-	2
5. Temperature/ Time						
Room temperature					3	1
6. Workup and purification						
Adding solvent					0	0
Liquid-Liquid extraction					3	3
Classical chromatography					10	10
Total					42,0	33,5
Ecoscale score					**58,0**	**66,5**
Ranking of reaction					Acceptable Synthesis	Acceptable Synthesis

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