



Supporting Information

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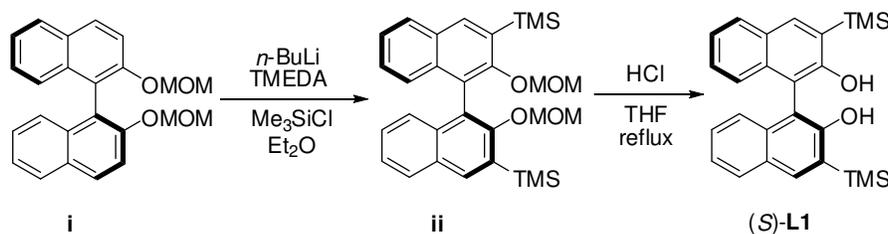
69451 Weinheim, Germany

Catalytic Enantioselective Reformatsky Reaction with Aldehydes

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General Procedures: Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Visualization of the chromatogram was performed by UV and phosphomolibdic acid staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890; MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on a AEI-MS-902 mass spectrometer. ¹H- and ¹³C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using CDCl₃ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl₃: δ 7.26 for ¹H, δ 77.0 for ¹³C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). Absolute configurations were determined by comparison of optical rotation of compounds previously published. Enantioselectivities were determined by capillary GC analysis using flame ionization detector (in comparison with racemic products). HPLC analysis was carried out on a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. Et₂O was dried with sodium/benzophenone and distilled. All aldehydes were purchased and used without purification. Me₂Zn 2M in toluene (Fluka) was used for all the reactions. All racemic β-hydroxyesters were prepared adding all reagents under air. The ligands (S)-L2 and (S)-L3 were synthesized following the procedure described in the literature.¹

Synthesis of (S)-3,3'-bis(trimethylsilyl)1,1'-binaphthyl-2,2'-diol [(S)-L1]¹



Binol diether **i** (2g, 5.34 mmol) was dissolved in Et₂O (100 mL) followed by addition at room temperature of TMEDA (4.32 mL, 28.05 mmol) and *n*-BuLi (14.71 mL, 1.6M, 23.55 mmol). The resulting suspension was stirred at 35 °C for 30 min. The mixture was cooled to room temperature, chlorotrimethylsilane (4.53 mL, 34.90 mmol) was added followed by stirring for 16 h. The reaction was quenched by addition of sat. aq. NH₄Cl, then extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and the solvent evaporated under reduced pressure to give a yellow oil. The product was purified by flash column chromatography (pentane:Et₂O 45:1) to yield the product as a white solid. Aq. HCl (6M) (90 mL) was added to a solution of **ii** (5.34 mmol) in THF (90 mL). The resulting solution was heated at 60 °C for 21 h. The reaction mixture was cooled down to room temperature. The product was extracted with Et₂O and the organic phases were dried over MgSO₄, filtered and the solvent evaporated under reduced pressure. The product was purified by flash column chromatography (pentane) to give (S)-L1 as white solid in 85% yield (two steps).

[α]_D = -148 (c = 1.0, THF). Lit.¹ (R) [α]_D = +143 (c = 0.98, THF).

¹H-NMR δ 0.41 (s, 18H), 5.22 (s, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.23-7.38 (m, 4H), 7.89 (d, *J* = 7.9 Hz, 2H), 8.07 (s, 2H).

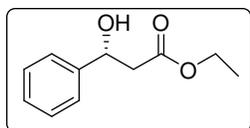
General procedure for the Enantioselective Reformatsky Reaction: In a two neck 100 mL round bottom flask² equipped with a CaCl₂ tube, was added at room temperature, Et₂O (5 mL), (S)-L1 (0.025 mmol, 20 mol%) and ethyl iodoacetate (0.5 mmol, 2 equiv). Me₂Zn (1 mmol, 4 equiv, 2M solution in toluene) was added and immediately the addition over 10 min of a solution of aldehyde (0.25 mmol) in Et₂O (1 mL) was started using a syringe pump.³ At the same time that the addition of aldehyde started, again Me₂Zn (1 mmol, 4 equiv, 2M solution in toluene) was added. The resulting solution was stirred for 1 h and quenched with aq. HCl (1M). The organic phase was separated, and the aqueous phase extracted with Et₂O (5 mL). The combined organic phases were dried over MgSO₄ and the solvent evaporated under reduced pressure to give an oil. The product was purified by flash chromatography.

¹ K. Maruoka, T. Itoh, Y. Araki, T. Shirasaka, H. Yamamoto. *Bull. Chem. Soc. Jpn.*, **1988**, *61*, 2975-2976.

² It is necessary to use a relative large size flask in order to have a good contact between oxygen and dimethylzinc.

³ It is necessary to start the addition of aldehyde as soon as possible after the first addition of dimethylzinc.

(3*R*) Ethyl 3-hydroxy-3-phenylpropanoate (**1a**)⁴



1a was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (72% yield, 84% *ee*).

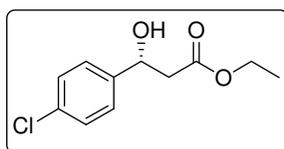
[α]_D = +40 (c = 0.8, CHCl₃). Lit.⁴ (*R*) [α]_D = +44 (c = 1.4, CHCl₃), optical purity > 99%.

¹H-NMR δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.68-2.79 (m, 2H), 3.39 (br, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.13 (m, 1H), 7.27-7.39 (m, 5H).

¹³C-NMR δ 14.3, 43.5, 61.1, 70.5, 125.9, 128.0, 128.7, 142.7, 172.6.

Ee determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane:*i*-PrOH 90:10, retention times: 13.8 min (*S*), 15.6 min (*R*).

(3*R*) Ethyl 3-(4-chlorophenyl)-3-hydroxypropanoate (**1b**)⁵



1b was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (75% yield, 80% *ee*).

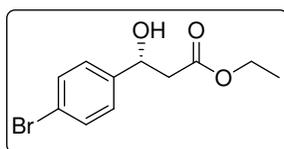
[α]_D = +29 (c = 2.0, CHCl₃). Lit.⁵ (*S*) [α]_D = -55 (c = 1.0, CHCl₃), optical purity 97%.

¹H-NMR δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.63-2.73 (m, 2H), 3.49 (d, *J* = 3.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.09 (m, 1H), 7.23 (m, 2H), 7.45 (m, 2H).

¹³C-NMR δ 14.3, 43.4, 61.2, 69.8, 127.3, 128.8, 133.6, 141.2, 172.4.

Ee determination by chiral HPLC analysis, Chiralpack AS column, Heptane:*i*-PrOH 98:2, retention times: 14.4 min (*R*), 17.8 min (*S*).

(3*R*) Ethyl 3-(4-bromophenyl)-3-hydroxypropanoate (**1c**)⁵



1c was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (70% yield, 80% *ee*).

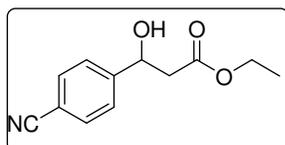
[α]_D = +27 (c = 2.3, CHCl₃). Lit.⁵ (*S*) [α]_D = -57 (c = 1.1, CHCl₃), optical purity 95%.

¹H-NMR δ 1.24 (t, *J* = 7.1 Hz, 3H), 2.63-2.72 (m, 2H), 3.50 (d, *J* = 3.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 5.06 (m, 1H), 7.25-7.32 (m, 4H).

¹³C-NMR δ 14.3, 43.3, 61.2, 69.8, 121.7, 127.6, 131.8, 141.7, 172.4.

Ee determination by chiral HPLC analysis, Chiralpack AS column, Heptane:*i*-PrOH 98:2, retention times: 16.8 min (*R*), 21.1 min (*S*).

Ethyl 3-(4-cyanophenyl)-3-hydroxypropanoate (**1d**)



1d was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 1:1), as a colorless oil (72% yield, 76% *ee*).

[α]_D = +26 (c = 1.9, CHCl₃).

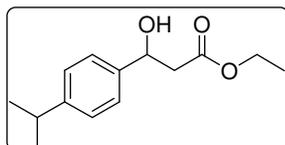
¹H-NMR δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.64-2.73 (m, 2H), 3.61 (br, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.17 (m, 1H), 7.49 (m, 2H), 7.64 (m, 2H).

¹³C-NMR δ 14.3, 43.1, 61.4, 69.7, 111.7, 118.9, 126.6, 132.6, 147.9, 172.2.

MS (CI) *m/z*: 219 (M⁺, 58), 130 (100); HRMS calcd for C₁₂H₁₃NO₃ (M⁺): 229.0895; found: 219.0890.

Ee determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane:*i*-PrOH 97:3, retention times: 69.4 min (*minor*), 72.6 min (*major*).

Ethyl 3-hydroxy-3-(4-isopropylphenyl)propanoate (**1e**)



1e was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (87% yield, 80% *ee*).

[α]_D = +33 (c = 2.5, CHCl₃).

¹H-NMR δ 1.23 (m, 9H), 2.68 (dd, *J* = 3.7 and 16.2 Hz, 1H), 2.77 (dd, *J* = 9.2 and 16.2 Hz, 1H), 2.91 (sep, *J* = 6.9 Hz, 1H), 3.31 (d, *J* = 3.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 5.09 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 2H),

7.29 (d, *J* = 8.1 Hz, 2H).

¹³C-NMR δ 14.3, 24.2, 34.0, 43.5, 61.0, 70.4, 125.9, 126.8, 140.2, 148.7, 172.6.

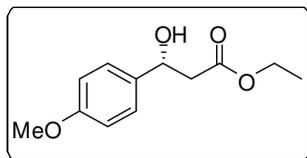
MS (CI) *m/z*: 236 (M⁺, 30), 149 (100); HRMS calcd for C₁₄H₂₀O₃ (M⁺): 236.1412; found: 236.1423.

Ee determination by chiral HPLC analysis, Chiralpack AS-H column, Heptane:*i*-PrOH 99:1, retention times: 20.6 min (*major*), 22.3 min (*minor*).

⁴ C. Xu, C. Yuan, *Tetrahedron* **2005**, *61*, 2169-2186.

⁵ Q. Xu, X. Gu, S. Liu, Q. Dou, M. Shi, *J. Org. Chem.* **2007**, *72*, 2240-2242.

(3*R*)-Ethyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (**1f**)⁴



1f was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (73% yield, 80% *ee*).

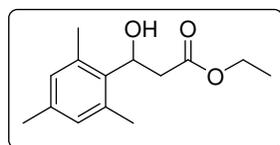
[α]_D = +34 (c = 2.0, CHCl₃). Lit.⁴ (*R*) [α]_D = +26.5 (c = 1.5, CHCl₃), optical purity 86%.

¹H-NMR δ 1.25 (t, *J* = 7.0 Hz, 3H), 2.70 (m, 2H), 3.27 (br s, 1H), 3.78 (s, 3H), 4.16 (q, *J* = 7.0 Hz, 2H), 5.07 (m, 1H), 6.86 (m, 2H), 7.27 (m, 2H).

¹³C-NMR δ 14.1, 43.3, 55.2, 60.7, 69.9, 113.8, 126.9, 134.7, 1259.1, 172.3.

Ee determination by chiral HPLC analysis, Chiralpack AS column, Heptane:*i*-PrOH 95:5, retention times: 13.9 min (*R*), 20.9 min (*S*).

Ethyl 3-hydroxy-3-mesitylpropanoate (**1g**)



1g was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (72% yield, 76% *ee*).

[α]_D = +18 (c = 2.1, CHCl₃).

¹H-NMR δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.56 (s, 3H), 2.43 (s, 6H), 2.55 (dd, *J* = 3.1 and 16.4 Hz, 1H), 2.90 (br, 1H), 3.05 (dd, *J* = 10.0 and 16.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 5.60 (dd, *J* = 3.1 and 10.5 Hz, 1H), 6.82 (s,

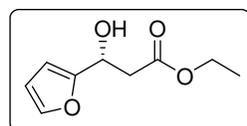
2H).

¹³C-NMR δ 14.4, 20.9, 40.3, 61.1, 67.7, 130.3, 134.9, 136.3, 137.1, 172.8.

MS (CI) *m/z*: 236 (M⁺, 4), 218 (M⁺-18, 31), 149 (100); HRMS calcd for C₁₄H₂₀O₃ (M⁺): 236.1412; found: 236.1417.

Ee determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane:*i*-PrOH 95:5, retention times: 16.3 min (*minor*), 18.9 min (*major*).

(3*R*) Ethyl 3-(2-furyl)-3-hydroxypropanoate (**1h**)⁴



1h was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (75% yield, 54% *ee*).

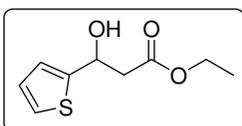
[α]_D = +18 (c = 1.6, CHCl₃). Lit.⁴ (*R*) [α]_D = +15.0 (c = 0.9, CHCl₃), optical purity 75%.

¹H-NMR δ 1.27 (t, *J* = 7.1 Hz, 3H), 2.83 (dd, *J* = 4.1 and 16.4 Hz, 1H), 2.90 (dd, *J* = 8.4 and 16.4 Hz, 1H), 3.23 (br, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.14 (dd, *J* = 4.1 and 8.4 Hz, 1H), 6.27-6.33 (m, 2H), 7.37 (m, 1H).

¹³C-NMR δ 14.3, 39.9, 61.1, 64.4, 106.5, 110.4, 142.4, 154.9, 172.1.

Ee determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane:*i*-PrOH 90:10, retention times: 14.2 min (*S*), 26.4 min (*R*).

Ethyl 3-hydroxy-3-(2-thienyl)propanoate (**1i**)



1i was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (69% yield, 84% *ee*).

[α]_D = +19 (c = 1.7, CHCl₃).

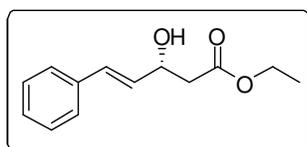
¹H-NMR δ 1.26 (t, *J* = 7.1 Hz, 3H), 2.79-2.90 (m, 2H), 3.50 (br, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 5.36 (m, 1H), 6.96 (m, 2H), 7.24 (m, 1H).

¹³C-NMR δ 14.3, 43.4, 61.2, 66.8, 123.8, 125.0, 126.9, 146.5, 172.1.

MS (CI) *m/z*: 200 (M⁺, 54), 113 (100); HRMS calcd for C₉H₁₂O₃S (M⁺): 200.0507; found: 200.0517.

Ee determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane:*i*-PrOH 90:10, retention times: 14.6 min (*minor*), 22.3 min (*major*).

(3*R*)-(E)-Ethyl 3-hydroxy-5-phenylpent-4-enoate (**1j**)⁶



1j was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (82% yield, 42% *ee*).

[α]_D = +2 (c = 2.2, CHCl₃). Lit.⁶ (*S*) [α]_D = -2.6 (c = 2.7, CHCl₃), optical purity 99%.

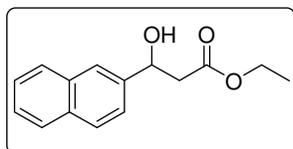
¹H-NMR δ 1.27 (t, *J* = 7.0 Hz, 3H), 2.63 (m, 2H), 3.20 (br s, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.72 (m, 1H), 6.23 (dd, *J* = 6.0 and 15.7 Hz, 1H), 6.65 (d, *J* = 15.7 Hz, 1H), 7.21-7.38 (m, 5H).

¹³C-NMR δ 14.1, 41.5, 60.8, 68.8, 126.5, 127.7, 128.5, 130.0, 130.6, 136.4, 172.1.

Ee determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane:*i*-PrOH 95:5, retention times: 28.5 min (*S*), 36.5 min (*R*).

⁶ S. K. Padhi, A. Chadha, *Tetrahedron: Asymmetry* **2005**, *16*, 2790-2798.

Ethyl 3-hydroxy-3-(2-naphthyl)propanoate (**1k**)



1k was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (61% yield, 80% *ee*).

$[\alpha]_D = +32$ ($c = 1.8$, CHCl₃).

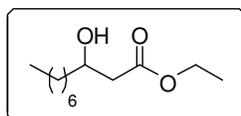
¹H-NMR δ 1.26 (t, $J = 7.1$ Hz, 3H), 2.76-2.87 (m, 2H), 3.47 (d, $J = 3.4$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 5.30 (m, 1H), 7.47 (m, 3H), 7.83 (m, 4H).

¹³C-NMR δ 14.3, 43.5, 61.1, 70.6, 123.9, 124.7, 126.2, 126.4, 127.9, 128.2, 128.6, 133.2, 133.4, 140.1, 172.6.

MS (CI) m/z : 244 (M⁺, 71), 157 (96), 129 (100); HRMS calcd for C₁₅H₁₆O₃ (M⁺): 244.1099; found: 244.1094.

Ee determination by chiral HPLC analysis, Chiralpak AS column, Heptane:*i*-PrOH 99.5:0.5, retention times: 50.69 min (*major*), 59.2 min (*minor*).

Ethyl 3-hydroxypentanoate (**1l**)⁷



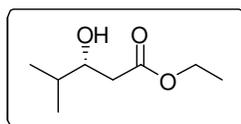
1l was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (56% yield, 7% *ee*).

¹H-NMR δ 0.86 (t, $J = 7.0$ Hz, 3H), 1.19-1.48 (m with t at 1.26, $J = 7.0$ Hz, 15H), 2.38 (dd, $J = 9.2$ and 16.5 Hz, 1H), 2.50 (dd, $J = 3.3$ and 16.5 Hz, 1H), 2.94 (d, 1H), 4.00 (m, 1H), 4.17 (q, $J = 7.0$, 2H).

¹³C-NMR δ 14.3, 14.4, 22.8, 25.7, 29.4, 29.7, 32.0, 36.7, 41.5, 60.9, 68.2, 173.3.

Ee determination by chiral GC analysis, Chirasil Dex CB column (25 m × 0.25 mm × 0.25 μ m). Initial temperature 130 °C for 60 min, then 10 °C/min until 180 °C, retention times: 42.9 min (*major*), 45.0 min (*minor*).

(3*R*)-Ethyl 3-hydroxy-4-methylpentanoate (**1m**)⁸



1m was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (87% yield, 30% *ee*).

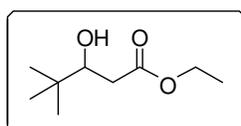
$[\alpha]_D = +5.7$ ($c = 2.0$, CHCl₃). Lit.⁸ (*R*) $[\alpha]_D = +34$ ($c = 0.7$, CHCl₃), optical purity 83%.

¹H-NMR δ 0.86 (t, $J = 7.0$ Hz, 3H), 1.19-1.48 (m with t at 1.26, $J = 7.0$ Hz, 15H), 2.38 (dd, $J = 9.2$ and 16.5 Hz, 1H), 2.50 (dd, $J = 3.3$ and 16.5 Hz, 1H), 2.94 (d, 1H), 4.00 (m, 1H), 4.17 (q, $J = 7.0$ Hz, 2H).

¹³C-NMR δ 14.3, 17.9, 18.5, 33.3, 38.7, 60.9, 72.9, 173.7.

Ee determination by chiral GC analysis, Chirasil Dex CB column (25 m × 0.25 mm × 0.25 μ m). Initial temperature 70 °C for 80 min, then 1 °C/min until 100 °C, then 10 °C/min until 180 °C; retention times: 90.4 min (*R*), 92.8 min (*S*).

Ethyl 3-hydroxy-4,4-dimethylpentanoate (**1n**)⁸



1n was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (70% yield, 50% *ee*).

$[\alpha]_D = +24.9$ ($c = 1.5$, CHCl₃).

¹H-NMR δ 0.90 (s, 9H), 1.26 (t, $J = 7.2$ Hz, 3H), 2.38 (dd, $J = 10.6$ and 16.2 Hz, 1H), 2.50 (dd, $J = 1.8$ and 16.2 Hz, 1H), 2.93 (br s, 1H), 3.69 (m, 1H), 4.14 (q, $J = 7.2$ Hz, 2H).

¹³C-NMR δ 14.1, 25.5, 36.6, 60.7, 75.4, 173.8.

Ee determination by preparation of the corresponding Mosher esters. The reaction with (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride and **1n** under the conditions described in the literature⁹ provided mixture of two diastereoisomers with the following spectra: ¹H-NMR δ 0.88 (s, 6.7H, major) and 0.92 (s, 2.2H, minor), 1.19 (m, 3H), 2.46-2.68 (m, 2H), 3.50 (s, 0.8H, minor) and 3.55 (s, 2.2H, major), 4.07 (m, 2H), 5.35-5.35 (m, 1H), 7.37-7.57 (m, 5H).

⁷ A. Chattopadhyay, A. Salaskar, *Synthesis* **2000**, 461.

⁸ S-i. Fukuzawa, H. Matsuzawa, S-i. Yoshimitsu, *J. Org. Chem.* **2000**, *65*, 1702-1706.

⁹ B. Baskar, N. G. Pandian, K. Priya, A. Chedha, *Tetrahedron: Asymmetry* **2004**, *15*, 3961.

Please note: the peak in ^{13}C around 156 ppm is an artefact.

