The Asymmetric Synthesis of (2*R*,3*R*)- and (2*R*,3*S*)-3-Methyl-aspartates via an Enantiodiscrimination Strategy

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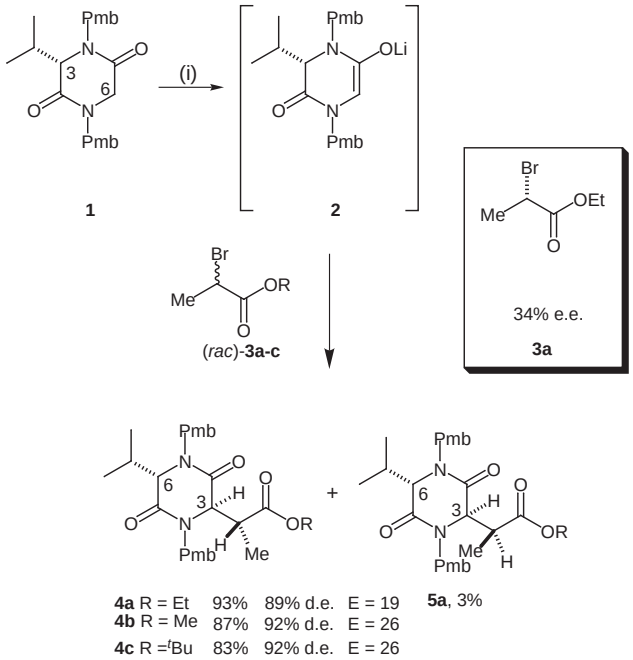
Abstract: The enolate of (*S*)-*N*,*N*'-*bis*-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione exhibits high levels of enantiodiscrimination towards racemic 2-bromo-propionate esters to afford adducts containing two new stereogenic centres which may be deprotected to afford (2*R*,3*R*)-3-methyl-aspartates or epimerised and then deprotected to afford (2*R*,3*S*)-3-methyl-aspartates as single diastereoisomers in high e.e.

Key words: enantiodiscrimination, diketopiperazine auxiliary, 3-alkylaspartates, asymmetric synthesis

(2*R*,3*S*)-3-Methyl-aspartic acid is an α-amino acid which occurs as a component of certain members of the highly toxic microcystin and nodularin families of natural products, cyclic peptides which are known to be potent inhibitors of many serine and threonine phosphatases.[1] Indeed, the pharmacological activity of related β-alkyl-aspartate fragments has been recognised by medicinal chemists for the preparation of potential drug candidates directed towards a wide range of therapeutic areas.[2] As a consequence, much attention has been directed towards the development of new methodology for the synthesis of homochiral β-alkyl-aspartates.[3] We now wish to report herein a novel chiral recognition strategy towards this class of α-amino acid which relies on the capacity of the enolate **2** of glycine equivalent **1** to discriminate between the enantiomers of racemic 2-bromopropionate esters to afford masked 3-methyl-aspartate derivatives containing two new stereocentres in high d.e.

We have recently reported that the *bis*-*N*,*N*'-protected diketopiperazine (*S*)-**1** may be employed as a chiral glycine enolate equivalent for the asymmetric synthesis of homochiral (*R*)-α-amino acids.[4] Given the high facial selectivity observed in the alkylation of the enolate derived from **1** with a wide range of haloalkyl electrophiles, we wished to investigate whether enolate **2** had the capacity to resolve racemic electrophiles such as α-bromo-propionate esters **3a-c**.[5] Thus, treatment of enolate **2** with ten equivalents of racemic ethyl 2-bromopropionate **3a** in THF at -78 °C afforded a 94.5: 5.5 mixture of diastereoisomers **4a** and **5a**,[6] which after chromatographic purification (1:1 ether:hexane) gave ethyl (3*R*,6*S*,2'*R*)-2'-[*N*,*N*'-*bis*-*p*-methoxybenzyl-6-*iso*-propylpiperazine-2-5-dion-3-yl]propionoate **4a** {$[\alpha]^{23}_D$ = -13.1, (*c* 1.0 in $CHCl_3$)}, and ethyl (3*R*,6*S*,2'*S*)-2'-[*N*,*N*'-*bis*-*p*-methoxybenzyl-6-*iso*-propylpiperazine-2-5-dion-3-yl]propionoate **5a** {$[\alpha]^{23}_D$ = +62.4, (*c* 1.0 in $CHCl_3$)}, in 93% and 3% isolated yields respectively (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) LHMDS, THF, -78 °C.

The stereochemistry of the major diastereoisomer **4a** was assigned as (3*R*,6*S*,2'*R*) according to the following arguments. The configuration of the newly formed stereogenic centre at C_3 of **4a** was assigned as *R* according to extensive literature precedent since it is known that alkylation of enolate **2** with electrophiles affords *trans*-alkylated products in high d.e.[4] Furthermore, comparison of the sign and value of the specific rotation of the unreacted electrophile recovered from the reaction of enolate **2** and 1.5 equivalents of ethyl 2-bromopropionate **3a** {recovered yield 16%, $[\alpha]^{23}_D$ = -11.1, (*c* 1.1 in $CHCl_3$)}, with the specific rotation previously described for homochiral ethyl (*R*)-(+)-2-bromo-propionate **3a** {$[\alpha]^{23}_D$ +32.4, (*c* 3.9 in $CHCl_3$)},[7] revealed that it was enantiomerically enriched in the *S*-enantiomer. While the 34% e.e. obtained for the recovered electrophile ethyl (*S*)-(–)-2-bromopropionate **3a** is lower than the value which would have been expected from consideration of the previously obtained 94.5: 5.5 ratio of (3*R*,6*S*,2'*R*)-**4a** : (3*R*,6*S*,2'*S*)-**5a**, this discrepancy may be explained by the known propensity of bromide anions to catalyse racemisation of homochiral ethyl 2-bromo-propionate **3a** via a S_N2 process.[5a,8] Thus, it follows that since the recovered sample of ethyl 2-bromopropi-

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onate **3a** (34% e.e.) was enriched in the *S*-enantiomer, enolate **2** must have reacted preferentially with the *R*-enantiomer of α-bromoester **3a** via a S_N2 type process to afford the major diastereoisomer **4a** with a (2'*R*) stereocentre. Changing the ester functionality of the racemic 2-bromopropionate electrophile did not affect the enantiodiscriminating ability of enolate **2** towards this class of electrophile since alkylation with (*rac*)-methyl 2-bromopropionate **3b** gave (3*R*,6*S*,2'*R*)-**4b** in 92% d.e., which after chromatographic purification gave diastereomerically pure (3*R*,6*S*,2'*R*)-**4b** {$[\alpha]^{23}_D$ = -10.4, (*c* 1.0 in $CHCl_3$)}, in 87% yield. Similarly, alkylation of enolate **2** with *tert*-butyl 2-bromopropionate **3c** gave (3*R*,6*S*,2'*R*)-**4c** {$[\alpha]^{23}_D$ = -10.3, (*c* 1.0 in $CHCl_3$)}, in 92% d.e, which after chromatographic purification gave diastereomerically pure (3*R*,6*S*,2'*R*)-**4c** in 83% yield.

The capacity of enolate **2** to discriminate between the enantiomers of racemic 2-bromopropionate esters **3a-c** to afford (3*R*,6*S*,2'*R*)-**4a-c** as major diastereomers in high d.e. may be explained by invoking a chelated transition state in which the carbonyl group of the *R*-enantiomer of the α-bromo ester is coordinated to the lithium counterion of the oxygen atom of the enolate fragment, with its small C_2-H substituent directed towards the enolate fragment on the *Re*- face of the enolate (Figure 1). This transition state is more favoured than the alternative reaction manifold in which enolate **2** reacts with the *S*-enantiomer of 2-bromopropionate esters **3a-c** because a similar chelated transition state would result in severe steric interactions between the C_2-methyl group of the incipient electrophile and the ring of enolate **2** (Figure 2).

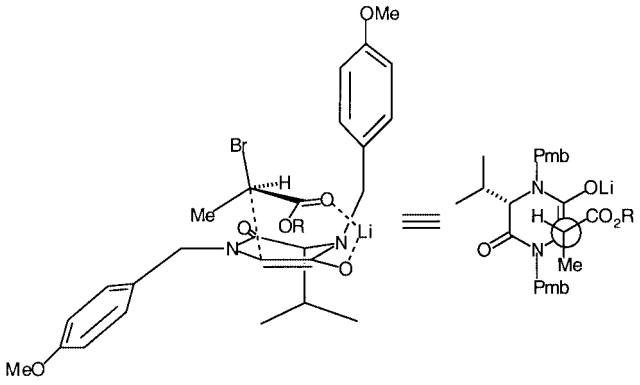


Figure 1 Reaction of enolate **2** with *(R)*-α-bromopropionate esters **3a-c**.

Treatment of the crude reaction product containing (3*R*,6*S*,2'*R*)-**4a** and (3*R*,6*S*,2'*S*)-**5a** in a 94.5: 5.5 ratio with lithium ethoxide in ethanol, in the presence of methyl iodide as a scavenger, resulted in selective side chain epimerisation to afford a 20: 80 mixture of (3*R*,6*S*,2'*R*)-**4a** and (3*R*,6*S*,2'*S*)-**5a**. Highly crystalline (3*R*,6*S*,2'*S*)-**5a** was easily isolated as a single diastereoisomer in 66% yield via simple fractional recrystallisation (Scheme 2).

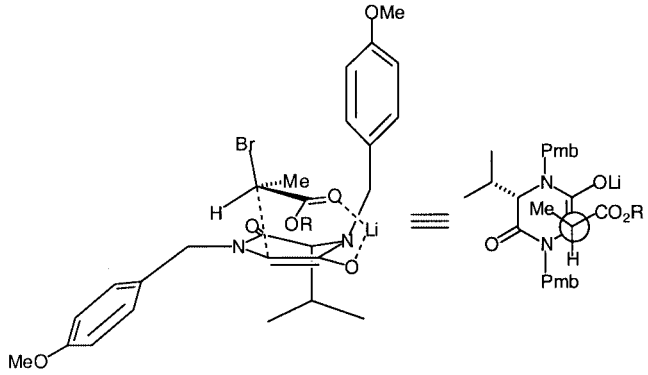
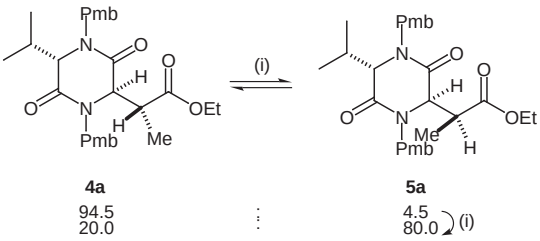


Figure 2 Reaction of enolate **2** with *(S)*-α-bromopropionate esters **3a-c**.



Scheme 2 *Reagents and conditions:* (i) Lithium ethoxide, methyl iodide, ethanol, rt.

N,*N*'-Deprotection of (3*R*,6*S*,2'*R*)-**4a** was achieved via treatment with refluxing trifluoroacetic acid to afford ethyl (3*R*,6*S*,2'*R*)-2'-[6-*iso*-propylpiperazine-2-5-dion-3-yl]propionoate **6** in 60% yield. Methylation of (3*R*,6*S*,2'*R*)-**6** with Me_3OBF_4 under novel reaction conditions using the ionic liquid *N*-butyl-*N*'-methyl-imidazolium tetrafluoroborate (bmim. BF_4)[9] as solvent, afforded the (3*R*,6*S*,2'*R*)-*bis*-lactim ether **7** cleanly in 95% yield.[10] Hydrolysis of *bis*-lactim ether **7** was achieved via treatment with 0.5 M TFA at room temperature to afford a mixture of 4-ethyl, 1-methyl (2*R*,3*R*)-3-methyl aspartate **8** and L-valine methyl ester as their trifluoroacetate salts, which were converted to their free amines and separated by fractional distillation[11] to afford (2*R*,3*R*)-3-methyl-aspartate-*bis*-ester **8** {$[\alpha]^{23}_D$ = -8.6, (*c* 0.7 in $CHCl_3$)} in >95% d.e., and in >98% e.e. as determined from ^{19}F NMR spectroscopic analysis of its Mosher's amide derivative (Scheme 3).[12] A similar strategy was employed for deprotection of (3*R*,6*S*,2'*S*)-**5a** which afforded (2*R*,3*S*)-3-methyl-aspartate-*bis*-ester **9** ($[\alpha]^{23}_D$ = -6.8, *c* 1.1 in $CHCl_3$) in >95% d.e., and in >98% e.e. as determined by ^{19}F NMR spectroscopic analysis of its Mosher's amide derivative. Thus, both of the diastereoisomers **8** and **9** are available from alkylation of the enolate derived from **1** with the *R*-enantiomer of ethyl 2-bromopropionate **3a**.

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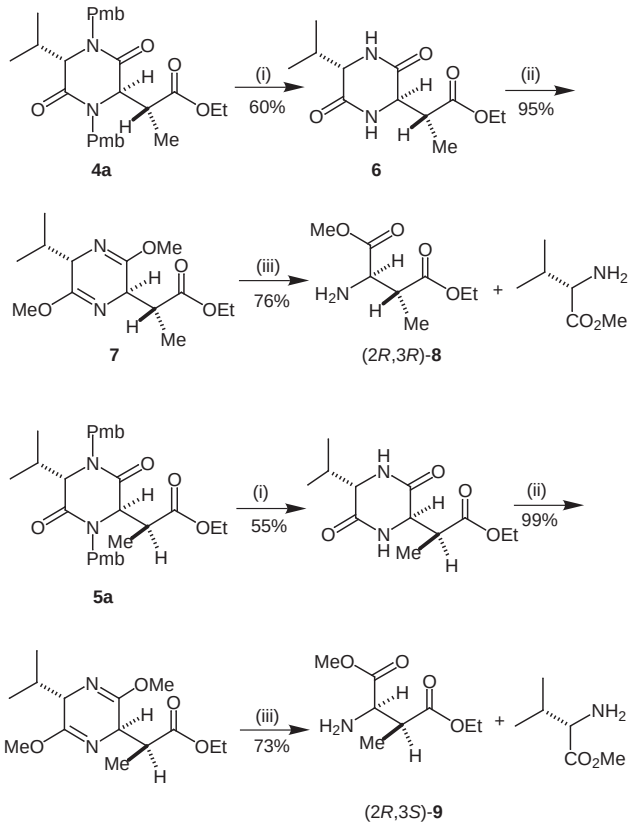

Scheme 3 *Reagents and conditions:* (i) TFA, Δ; (ii) 4 eq. Me_3OBF_4, bmim.BF_4; (iii) 0.5M aqueous TFA.

In conclusion, the enolate derived from **1** exhibits a high degree of enantiodiscrimination towards a range of racemic α-bromo-esters **3a-c** to afford *trans*-alkylated products (3*R*,6*S*,2'*R*)-**4a-c** in high d.e. It has been shown that (3*R*,6*S*,2'*R*)-**4a** may be deprotected to afford either diastereoisomer (2*R*,3*R*)-**8** or (2*R*,3*S*)-**9** of 3-methyl-aspartic acid, 4-ethyl, 1-methyl diester in homochiral form. Since the *R*-enantiomer of **1** is also readily available from D-valine, this methodology constitutes a versatile approach towards the asymmetric synthesis of all four possible stereoisomers of homochiral 3-methyl-aspartates in high d.e. and e.e.

Acknowledgement

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(12) Experimental Procedure for the Preparation of **4a**; To a stirred solution of **1** (200 mg, 0.5 mmol) in degassed anhydrous THF (10mL) at −78 °C was added a solution of LHMDS in THF (0.55 mL, 1 molL^{-1}, 0.55 mmol). The resultant solution was allowed to stir at −78 °C for 1 h prior to the addition of ethyl α-bromopropionate (0.64 mL, 5 mmol). The mixture was stirred at −78°C for 12 h then allowed to warm to room temperature when saturated NH_4Cl was added. This mixture was partitioned between ethyl acetate and water. The aqueous phase extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product from which excess of α-bromo ester was removed under high vacuum (1 mm of Hg, ambient temperature). Column chromatography (silica, 1:1 ether:hexane) gave **(3*R*,6*S*,2'*R*)-*N*,*N*'-di(*p*-methoxybenzyl)-3-isopropyl-6-ethylpropanoate-piperazine-2,5-dione 4a** as the first eluting compound (230 mg, 93%); mp 112-114 °C (ether); $[\alpha]^{23}_D$ = -13.3 (*c* 0.98 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1730 (ester), 1646 (amide); δ_H(400 MHz, $CDCl_3$) 0.77 (d, 3H, *J* 6.9 Hz), 1.13 (d, 3H, *J* 6.9 Hz), 1.14 (d, 3H, *J* 7.2 Hz), 1.15 (t, 3H, *J* 7.2), 2.30 (m, 1H), 3.48 (dq, 1H, *J* 8.0, 8.0, 8.0, 1.6 Hz), 3.69 (d, 1H, *J* 15.2 Hz) 3.77 (d, 1H, *J* 3.3 Hz), 3.79 (s, 3H), 3.80 (s, 3H), 3.89 (d, 1H, *J* 14.7 Hz), 3.95 (m, 1H), 4.14 (m, 1H), 4.57 (d, 1H, *J* 15.2 Hz), 5.28 (d, 1H, *J* 15.2 Hz), 5.34 (d, 1H, *J* 14.7 Hz), 6.84 (m, 4H), 7.18 (m, 4H); δ_C (100 MHz, $CDCl_3$) 11.8, 14.0, 16.4, 19.8, 31.3, 42.4, 46.0, 47.1, 55.2, 61.2, 113.9, 114.2, 127.4, 127.7, 129.4, 129.9, 159.1, 159.3, 165.7, 165.8, 173.7; m/z (APCI) 497 (MH^+, 50%), 121 (100); (Found: MH^+ 497.2652,. $C_{28}H_{37}N_2O_6$ requires 497.2645). Further elution

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provided **(3*R*,6*S*,*2'S*)-*N*,*N'*-di(*p*-methoxybenzyl)-3-isopropyl-6-ethylpropanoate-piperazine-2,5-dione 5a** (15 mg, 3%). mp 136 °C (ethyl acetate / hexane); (Found: C, 67.7; H, 7.3; N, 5.6. $C_{28}H_{36}N_2O_6$ requires C, 67.7; H, 7.3; N, 5.6%); $[\alpha]^{23}_D$ = +62.4 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2984, 2933, 1739 (ester), 1640 (amide); δ_H(400 MHz, $CDCl_3$) 0.83 (d, 3H, *J* 6.9 Hz), 0.98 (d, 3H, *J* 6.9 Hz), 1.10 (d, 3H, *J* 7.0 Hz), 1.26 (t, 3H, *J* 7.1), 2.30 (m, 1H), 3.10 (dq, 1H, *J* 3.0, 6.9, 6.9, 6.9 Hz), 3.778 (d, 1H, *J* 3.1 Hz) 3.782 (d, 1H, *J* 14.6 Hz), 3.81 (s, 6H), 3.99 (d, 1H, *J* 14.9 Hz), 4.14-4.38 (m, 2H), 4.70 (d, 1H, *J* 3.2 Hz), 5.27 (d, 1H, *J* 14.9 Hz), 5.43 (d, 1H, *J* 14.7 Hz), 6.86-6.88 (m, 4H), 7.14-7.27 (m, 4H); δ_C (100 MHz, $CDCl_3$) 8.64, 11.8, 14.1, 31.7, 40.0, 46.1 46.2, 55.23, 55.26, 60.0, 60.8, 62.2, 114.0, 114.2, 126.9, 127.3, 130.0, 130.2, 159.3, 159.4, 164.4, 165.8, 172.0; m/z (APCI) 497 (MH^+, 10%), 121 (100).

Deprotection of ethyl ester **4a**; Ethyl ester **4a** (400 mg, 0.81 mmol) was stirred in TFA at reflux for 48 h. The mixture was cooled and excess TFA removed in vacuo. Column chromatography (Al_2O_3; ether:hexane, 1:1, followed by ethyl acetate:ethanol, 3:1) afforded diketopiperazinedione **6** as a white solid (124 mg, 60%), mp 204 °C; $[\alpha]^{23}_D$ = (+88.5 *c* 0.99 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1741 (ester), 1673(amide); δ_H(400 MHz, d_4-MeOH) 0.98 (d, 3H, *J* 6.9 Hz), 1.07 (d, 3H, *J* 7.1 Hz), 1.23 (d, 3H, *J* 7.2 Hz), 1.30 (t, 3H, *J* 7.1), 2.32 (m, 1H), 3.23 (dq, 1H, *J* 7.3, 7.3, 7.3, 2.8 Hz), 3.87 (dd, 1H, *J* 3.3, 0.8 Hz), 4.21(m, 2H), 4.50 (dd, 1H, *J* 2.6, 0.8 Hz), 7.18-7.56 (2H, br); δ_C (100 MHz, d_4-MeOH) 11.9, 14.8, 17.4, 19.2, 34.7, 43.7, 57.2, 61.8, 169.5, 170.1, 175.4; m/z (APCI) 257 (MH^+, 40%), 211 (100); (Found: MH^+ 257.1501, $C_{12}H_{21}N_2O_4$ requires 257.1506).

Diketopiperazinedione **6** (100 mg, 0.39 mmol) and trimethyloxonium tetrafluoroborate (230 mg, 1.56 mmol) were stirred in 1-butyl-3-1*H*-methylimidazolium tetrafluoroborate[9] (4 mL) under vacuum (2 mm of Hg) at room temperature for 4 days. The mixture was then poured into saturated $NaHCO_3$ (100 ml) and extracted with ether, the organic phase dried ($MgSO_4$) and the solvent removed under vacuum to provide *bis*-lactim ether **7** as a clear oil (105 mg, 95%); $[\alpha]^{23}_D$ = +27.3 (*c* 0.7 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1738 (ester), 1696 (lactim ether); δ_H(400 MHz, $CDCl_3$) 0.70 (d, 3H, *J* 6.8 Hz), 0.90 (d, 3H, *J* 6.9 Hz), 1.04 (d, 3H, *J* 6.9 Hz), 1.28 (t, 3H, *J* 7.3), 2.25 (m, 1H), 3.05 (dq, 1H, *J* 6.9, 6.9, 6.9, 4.0 Hz), 3.63 (3H, s), 3.71 (3H, s), 3.97 (t, 1H, *J* 3.4, 3.7 Hz), 4.20 (2H, q, *J* 7.4 Hz), 4.57 (t, 1H, *J* 4.0, 3.7 Hz); δ_C (100 MHz, $CDCl_3$) 9.9, 14.2, 16.6, 19.0, 19.6, 30.3, 31.8, 42.2, 52.41, 52.46, 57.3, 60.4, 60.8, 161.9, 164.1, 173.9; m/z (APCI) 285 (MH^+, 100%); (Found: MH^+ 285.1822. $C_{14}H_{25}N_2O_4$ requires 285.1814).

Bis-lactim ether **7** (200 mg, 0.70 mmol) was stirred in 0.5 M aqueous TFA (5 mL) and THF (10 mL) at room temperature for 24 hours then the solvent removed and the resultant oil was loaded onto a short column of silica. Elution (ether : dimethlyethylamine, 20:1) gave a mixture of (2*R*,3*R*)-**8** and L-valine methyl ester which were separated by fractional distillation (0.5 mm, room temperature) to provide (2*R*,3*R*)-3-methyl-aspartic acid, 4-ethyl, 1-methyl diester **8** as an oil (104 mg, 76%). $[\alpha]^{23}_D$ = -8.6 (*c* 0.7 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3391, 2980, 1732 (ester); δ_H(400 MHz, $CDCl_3$) 1.17 (d, 3H, *J* 7.1 Hz), 1.26 (t, 3H, *J* 7.1), 2.96 (1H, m), 3.75 (3H, s), 3.97 (1H, br), 4.17 (2H, q, *J* 7.1 Hz); δ_C (100 MHz, $CDCl_3$) 11.3, 14.1, 42.7, 52.2, 55.8, 60.9, 174.2; m/z (APCI) 190 (MH^+, 100%) 116 (89); (Found: MH^+ 190.1082. $C_8H_{16}NO_4$ requires190.1079). The diastereoisomeric excess (>95%) and enantiomeric excess (>98%) were determined from the ^{19}F NMR spectrum of the Mosher's amide derivative of **8**.

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