Stereoselective Synthesis of Functionalized γ-Amino Esters: Azetidinium Salts and Epoxy Esters

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SPECTROSCOPIC DATA OF COMPOUNDS 3

(+)-(2*S*,3*S*)-1,1-Dibenzyl-3-ethoxycarbonylmethyl-3-hydroxy-2-methylazetidinium chloride (3a): $[\alpha]^{20}_{D}$ = +24.2 (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79-7.77 (2 H, m), 7.56-7.39 (8 H, m), 6.89 (1 H, s), 5.27 (1 H, d, *J* = 12.7), 5.19 (1 H, q, *J* = 6.8), 4.87 (1 H, d, *J* = 13.1), 4.77 (1 H, d, *J* = 12.7), 4.62 (1 H, d, *J* = 12.2), 4.52 (1 H, d, *J* = 13.1), 4.28 (1 H, d, *J* = 12.2), 3.93 (2 H, q, *J* = 7.1), 2.66 (2 H, s), 1.53 (3 H, d, *J* = 6.8), 1.10 (3 H, t, *J* = 7.1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0 (C), 132.9, 132.6, 130.5, 130.2, and 129.3 (5 x CH), 128.2 (C), 127.6 (C), 77.2 (CH), 70.0 (C), 66.6 (CH_2), 61.6 (CH_2), 60.6 (CH_2), 58.7 (CH_2), 41.6 (CH_2), 13.9 (CH_3), 8.9 (CH_3); IR (KBr) 3391, 1729. Anal. Calcd for $C_{22}H_{28}ClNO_3$: C, 67.77; H, 7.24; N, 3.59. Found: C, 67.85; H, 7.20; N, 3.57.

(+)-(2*S*,3*S*)-1,1-Dibenzyl-3-ethoxycarbonylmethyl-3-hydroxy-2-(2-methylpropyl)azetidinium chloride (3b): $[\alpha]^{20}_{D}$ = +40.2 (*c* 0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79-7.76 (2 H, m), 7.56-7.43 (8 H, m), 7.14 (1 H, s), 5.32 (1 H, d, *J* = 12.6), 5.14-5.10 (1 H, m), 4.85-4.79 (2 H, m), 4.56 (1 H, d, *J* = 13.1), 4.45 (1 H, d, *J* = 12.6), 4.32 (1 H, d, *J* = 11.8), 3.95 (2 H, q, *J* = 7.0), 2.82 (2 H, AB syst., *J* = 15.9), 2.36-2.27 (2 H, m), 1.60-1.52 (1 H, m), 1.14 (3 H, t, *J* = 7.0), 0.87 (3 H, d, *J* = 6.5), 0.81 (3 H, d, *J* = 6.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3 (C), 132.9, 132.6, 130.3, 129.8, and 129.0 (5 x CH), 127.8 (C), 127.6 (C), 77.2 (CH), 70.0 (C), 65.8 (CH_2), 61.6 (CH_2), 60.4 (CH_2), 58.8 (CH_2), 41.9 (CH_2), 30.9 (CH_2), 24.2 (CH), 23.6 (CH_3), 20.9 (CH_3), 13.6 (CH_3); IR (KBr) 3389, 1729. Anal. Calcd for $C_{25}H_{34}ClNO_3$: C, 69.51; H, 7.93; N, 3.24. Found: C, 69.45; H, 7.83; N, 3.23.

(–)-(2*S*,3*S*)-1,1,2-Tribenzyl-3-ethoxycarbonylmethyl-3-hydroxyazetidinium chloride (3c): $[\alpha]^{20}_{D}$ = –15.8 (*c* 0.69, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88-7.86 (2 H, m), 7.53-7.34 (9 H, m), 7.20-7.11 (5 H, m), 5.57 (1 H, d, *J* = 12.5), 5.15 (1 H, d, *J* = 13.1), 4.92-4.83 (3 H, m), 4.19 (1 H, d, *J* = 12.0), 4.14 (1 H, d, *J* = 13.1), 3.71 (2 H, q, *J* = 7.1), 3.57 (1 H, t, *J* = 12.0), 3.30 (1 H, dd, *J* = 12.4, 3.3), 2.09 (2 H, AB syst., *J* = 16.2), 0.94 (3 H, t, *J* = 7.1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2 (C), 134.0 (C), 133.0, 132.6, 130.3, 129.9, 129.4, 128.9, and 128.3 (7 x CH), 127.8 (C), 127.5 (C), 126.8 (CH), 78.1 (CH), 69.6 (C), 65.0 (CH_2), 61.6 (CH_2), 60.2 (CH_2), 60.0 (CH_2), 41.7 (CH_2), 28.6 (CH_2), 13.5 (CH_3); IR (KBr) 3388, 1730. Anal. Calcd for $C_{28}H_{32}ClNO_3$: C, 72.17; H, 6.92; N, 3.01. Found: C, 72.27; H, 6.78; N, 2.89.

(2*S*,3*S*,2'*S*)-1,1-Dibenzyl-3-[1'-ethoxycarbonyl-2'-(phenyl)ethyl]-3-hydroxy-2-methylazetidinium chloride (3d): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.86 (2 H, m), 7.39-7.01 (14 H, m), 5.31 (1 H, d, *J* = 12.5), 5.15-5.11 (2 H, m), 4.83 (1 H, q, *J* = 7.8), 4.60 (1 H, d, *J* = 11.7), 4.00 (1 H, d, *J* = 13.1), 3.85-3.64 (3 H, m), 2.90-2.68 (2 H, m), 2.56-2.52 (1 H, m), 1.64 (3 H, d, *J* = 7.8), 0.90 (3 H, t, *J* = 7.1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 138.1, 133.2, 132.9, 130.3, 130.0, 129.1, 129.0, 128.9, 128.0, 127.6, 126.2, 75.8, 72.0, 63.8, 61.3, 60.6, 59.8, 53.3, 32.2, 13.6, 8.8; IR (KBr) 3393, 1731. Anal. Calcd for $C_{29}H_{34}ClNO_3$: C, 72.56; H, 7.14; N, 2.92. Found: C, 72.37; H, 7.18; N, 2.89.

SPECTROSCOPIC DATA OF COMPOUNDS 4

Ethyl (+)-(3*R*,1'*S*)-3-[1'-(Dibenzylamino)ethyl]-3,4-epoxybutanoate (4a): R_f = 0.35 (hexane/ethyl acetate 5/1); $[\alpha]^{20}_{D}$ = +29.6 (*c* 1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41-7.26 (10 H, m), 3.98 (2 H, q, *J* = 7.2), 3.63 (2 x 2 H, AB syst., *J* = 13.6), 3.36 (1 H, q, *J* = 6.8), 2.87 (2 H, AB syst., *J* = 4.4), 2.82 (2 H, AB syst., *J* = 15.6), 1.16 (3 H, t, *J* = 7.2), 1.32 (3 H, d, *J* = 6.8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

169.9 (C), 139.4 (C), 128.6, 128.2, and 126.9 (3 x CH), 60.3 (CH_2), 57.5 (C), 54.7 (CH), 54.3 (CH_2), 48.7 (CH_2), 39.0 (CH_2), 13.9 (CH_3), 5.0 (CH_3); IR (neat) 1732; MS, *m/z* 353 (M^+, 1), 224 (86), 91(100); HRMS Calcd for $C_{22}H_{27}NO_3$: 353.1991, found: 353.1995.

Ethyl (+)-(3*R*,1'*S*)-3-[1'-(dibenzylamino)-3'-(methyl)butyl]-3,4-epoxybutanoate (4b): R_f = 0.43 (hexane/ethyl acetate 5/1); $[\alpha]^{20}_D$ = +13.0 (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.21 (10 H, m), 3.95 (2 H, q, *J* = 7.1), 3.65 (2 x 2 H, AB syst., *J* = 13.5), 3.28 (1 H, dd, *J* = 8.0, 4.6), 2.80 (2 H, AB syst., *J* = 15.9), 2.79 (2 H, AB syst., *J* = 4.4), 1.85-1.71 (1 H, m), 1.44-1.35 (1 H, m), 1.14 (3 H, t, *J* = 7.1), 1.17-1.01 (1 H, m), 0.91 (3 H, d, *J* = 6.8), 0.84 (3 H, d, *J* = 6.8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0 (C), 139.8 (C), 128.9, 128.1, and 126.8 (3 x CH), 60.4 (CH_2), 57.2 (C), 54.6 (CH), 54.5 (CH_2), 49.0 (CH_2), 39.4 (CH_2), 32.4 (CH_2), 26.0 (CH), 23.2 (CH_3), 22.6 (CH_3), 13.9 (CH_3); IR (neat) 1736; MS, *m/z* 395 (M^+, 8), 338 (28), 266 (100), 250 (99), 174 (40), 131 (52), 119 (53), 91(62); HRMS Calcd for $C_{25}H_{33}NO_3$ 395.2460, found 395.2460.

Ethyl (–)-(3*R*,1'*S*)-3-[1'-(dibenzylamino)-2'-(phenyl)ethyl]-3,4-epoxybutanoate (4c): R_f = 0.39 (hexane/ethyl acetate 5/1); $[\alpha]^{20}_D$ = −5.0 (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.20 (15 H, m), 3.96 (2 H, q, *J* = 7.0), 3.72 (1 H, dd, *J* = 7.4, 4.8), 3.70 (2 x 2 H, AB syst., *J* = 13.5), 2.93 (1 H, dd, *J* = 14.4, 7.4), 2.88 (2 H, AB syst., *J* = 4.4), 2.84 (2 H, AB syst., *J* = 15.7), 2.73 (1 H, dd, *J* = 14.4, 4.8), 1.16 (3 H, t, *J* = 7.0); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8 (C), 140.8 (C), 139.2 (C), 129.3, 128.7, 128.2, 128.0, 126.8, and 125.8 (6 x CH), 61.0 (CH), 60.3 (CH_2), 57.1 (C), 54.5 (CH_2), 49.0 (CH_2), 39.1 (CH_2), 29.4 (CH_2), 13.8 (CH_3); IR (neat) 1731; MS, *m/z* 429 (M^+, <1), 338 (100), 299 (90), 208 (46), 91(82); HRMS Calcd for $C_{28}H_{31}NO_3$ 429.2304, found 429.2308.

Ethyl (+)-(3*R*,1'*S*)-3-[1'-(Dibenzylamino)ethyl]-3,4-epoxy-2,2-dimethylbutanoate (4e): R_f = 0.34 (hexane/ethyl acetate 10/1); $[\alpha]^{20}_D$ = +26.9 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.42-7.23 (10 H, m), 4.11-3.73 (2 H, m), 3.66 (2 x 2 H, AB syst., *J* = 13.8), 3.51 (1 H, q, *J* = 6.9), 3.03 (2 H, AB syst., *J* = 4.4), 1.08 (3 H, t, *J* = 7.2), 1.03 (3 H, s), 1.00 (3 H, d, *J* = 6.9), 0.97 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6 (C), 138.9 (C), 128.9, 128.0, and 126.7 (3 x CH), 61.4 (C), 60.4 (CH_2), 54.1 (CH_2), 52.6 (CH), 46.8 (CH_2), 44.9 (C), 23.2 (CH_3), 20.9 (CH_3), 13.7 (CH_3), 5.4 (CH_3); IR (neat) 1731; HRMS Calcd for $C_{24}H_{31}NO_3$ 381.2304, found 381.2267.

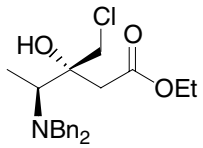
Ethyl (–)-(3*R*,1'*S*)-3-[1'-(dibenzylamino)-3'-(methyl)butyl]-3,4-epoxy-2,2-dimethylbutanoate (4f): R_f = 0.43 (hexane/ethyl acetate 10/1); $[\alpha]^{20}_D$ = −6.6 (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.39-7.18 (10 H, m), 4.07 (2 H, q, *J* = 7.2), 3.87 (2 x 2 H, AB syst., *J* = 14.1), 3.30 (1 H, dd, *J* = 9.5, 4.6), 2.83 (2 H, AB syst., *J* = 4.0), 2.12-1.98 (1 H, m), 1.75-1.62 (2 H, m), 1.24 (3 H, t, *J* = 7.2), 1.13 (6 H, s), 0.99 (3 H, d, *J* = 6.7), 0.80 (3 H, d, *J* = 6.7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3 (C), 140.6 (C), 128.8, 127.9, and 126.5 (3 x CH), 65.9 (C), 60.5 (CH_2), 53.5 (CH), 53.4 (CH_2), 47.9 (CH_2), 46.3 (C), 39.0 (CH_2), 24.6 (CH), 23.7 (CH_3), 22.1 (CH_3), 21.7 (CH_3), 13.8 (CH_3); IR (neat) 1731; HRMS Calcd for $C_{27}H_{37}NO_3$ 423.2773, found 423.2792.

Ethyl (+)-(2*R*,1'*S*)-1-{2-[1'-(dibenzylamino)ethyl]oxiranyl}cyclohexanecarboxylate (4g): R_f = 0.42 (hexane/ethyl acetate 10/1); $[\alpha]^{20}_D$ = +23.0 (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44-7.22 (10 H, m), 4.06 (1 H, dq, *J* = 10.8, 7.1), 3.92 (1 H, dq, *J* = 10.8, 7.1), 3.59 (2 x 2 H, AB syst., *J* = 14.0), 3.50 (1 H, q, *J* = 6.8), 3.04 (2 H, AB syst., *J* = 4.3), 1.98-1.06 (10 H, m), 1.14 (3 H, t, *J* = 7.1), 0.98 (3 H, d, *J* = 6.8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (C), 139.2 (C), 128.8, 128.1, and 126.8 (3 x CH), 63.1 (C), 60.2 (CH_2), 54.2 (CH_2), 52.5 (CH), 50.2 (C), 47.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 25.2 (CH_2), 23.0 (CH_2), 14.0 (CH_3), 7.3 (CH_3); IR (neat) 1732; HRMS Calcd for $C_{26}H_{32}NO_3$ (M^+ – CH_3) 406.2382, found 406.2362.

SPECTROSCOPIC DATA OF COMPOUND 5a

(+)-(2*S*,3*S*)-1-Benzyl-3-ethoxycarbonylmethyl-2-methylazetidin-3-ol (5a): R_f = 0.10 (hexane/ethyl acetate 1/1); $[\alpha]^{20}_D$ = +28.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36-7.24 (5 H, m), 4.16 (2 H, q, *J* = 7.2), 3.64 (2 H, AB syst., *J* = 12.7), 3.17 (1 H, q, *J* = 6.4), 3.16 (2 H, AB syst., *J* = 8.5), 2.64 (2 H, s), 1.27 (3 H, t, *J* = 7.2), 1.06 (3 H, d, *J* = 6.4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2 (C), 137.2 (C), 128.9, 128.0, and 127.0 (3 x CH), 71.0 (C), 69.4 (CH), 63.8 (CH_2), 61.0 (CH_2), 60.4 (CH_2), 43.6 (CH_2), 14.0 (CH_3), 13.1 (CH_3); IR (neat) 3452, 3063, 3029, 1729; HRMS Calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1514.

^{13}C NMR SPECTRA



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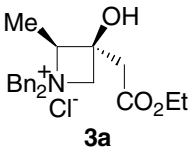

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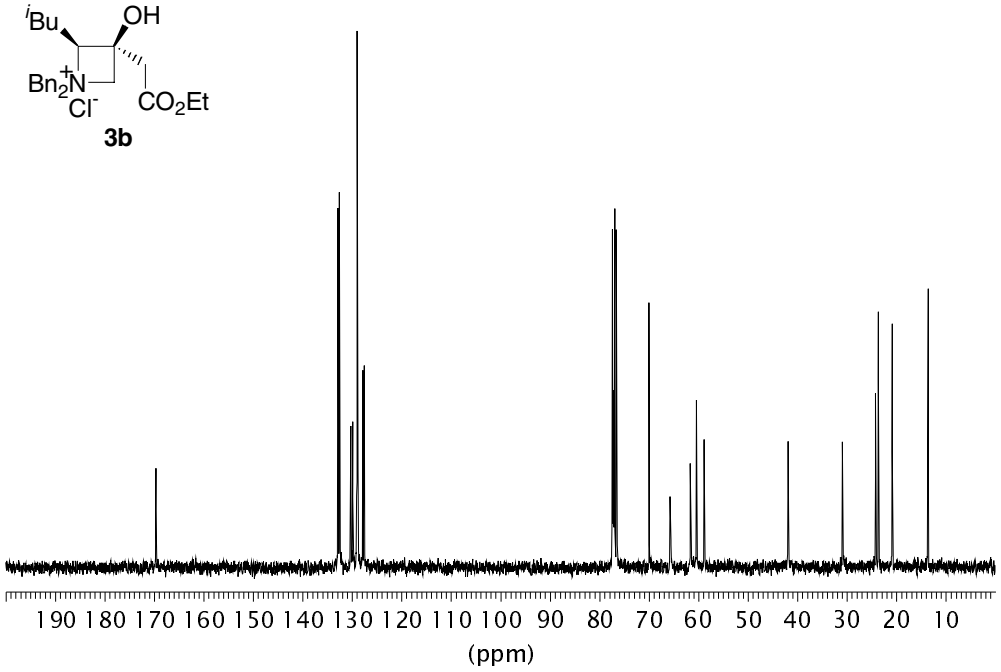
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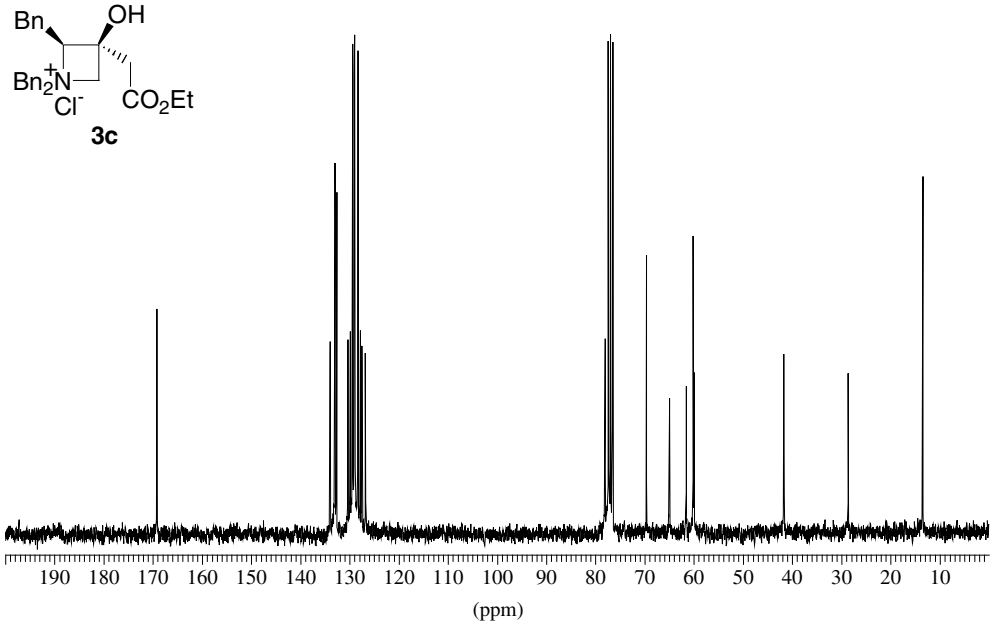
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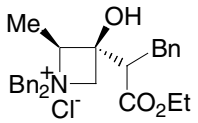
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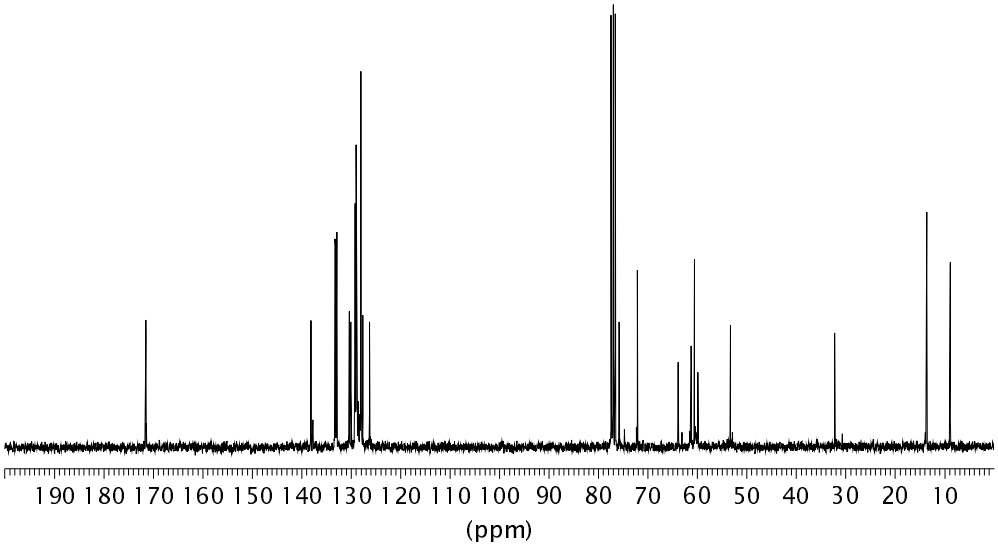
3d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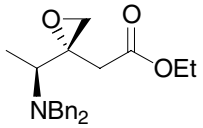
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4a

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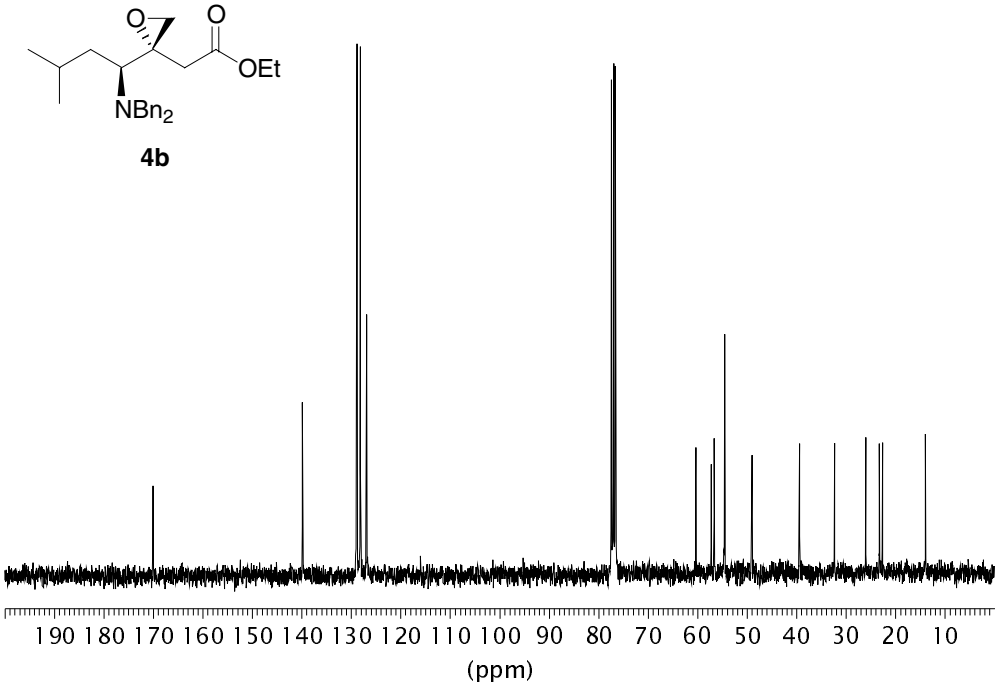
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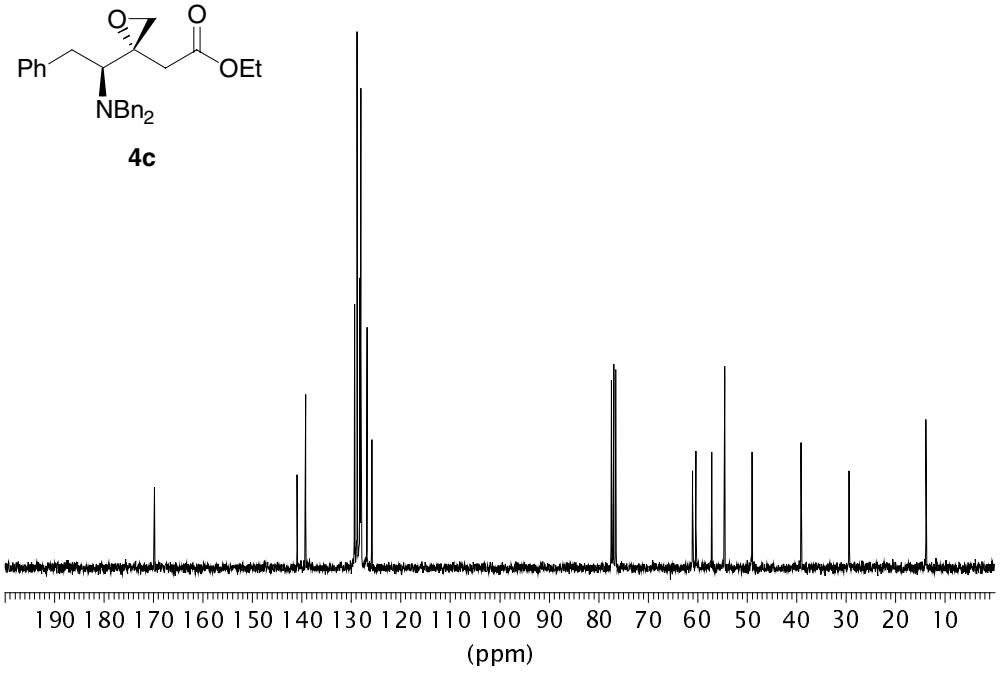
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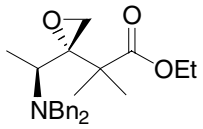
4c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4e

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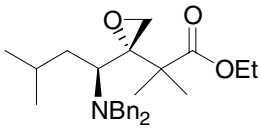
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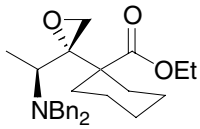
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O
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4g

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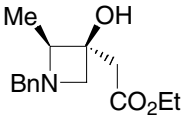
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5a

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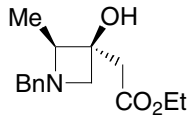
(ppm)

NOESY ^{1}H NMR SPECTRUM



5a