

## **Chemoenzymatic preparation of optically active 3-(1*H*-imidazol-1-yl)cyclohexanol-based ionic liquids: Application in organocatalysis and toxicity studies**

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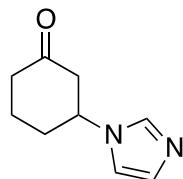
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## 1. General Information

*Candida antarctica* lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novozymes. *Pseudomonas cepacia* lipase PCL-C I (1638 U/g) was purchased from Sigma-Aldrich and *Burkholderia cepacia* lipases PCL SD (24700 U/g) and PCL IM (943 U/g) were purchased from Amano Enzyme Inc. Alcohol dehydrogenase from *Ralstonia sp.* was generously given by Prof. Wolfgang Kroutil (University of Graz, Austria). All commercially obtained reagents were used as received unless otherwise noted. Solvents were distilled over an appropriate desiccant under nitrogen. Thin-layer chromatography (TLC) was conducted with Merck Silica Gel 60 F<sub>254</sub> precoated plates and visualized with UV and potassium permanganate stain. Column chromatography was performed using Merck Silica Gel 60 (230-400 mesh). NMR spectra were recorded on a Bruker DPX-300 or NAV-300 spectrometer at 300 (<sup>1</sup>H), 282 (<sup>19</sup>F) and 75 (<sup>13</sup>C) MHz. Chemical shifts are reported in parts per million (ppm) relative to Me<sub>4</sub>Si ( $\delta$  0.00) using deuterated solvent (CD<sub>3</sub>OD or CDCl<sub>3</sub>) as an internal standard. Data is reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ap = apparent; coupling constant(s) ( $J$ ) in Hz; integration. IR spectra were recorded as thin films on NaCl plates or as KBr pellets on a Perkin-Elmer Spectrum 100 FT-IR and are reported in frequency of absorption (cm<sup>-1</sup>). Mass spectra were obtained by positive or negative electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Hewlett-Packard 1100 chromatograph mass detector. High-resolution mass spectra (HRMS) were obtained on a Bruker MicroTofQ by ESI<sup>+</sup>. Microwave reactions were carried out with a CEM Discover system S-Class microwave; conditions for all microwave reactions are as follows: temperature at 150 °C, power at 200 W and pressure at 250 psi with medium to high stirring. Melting points were obtained on a Gallenkamp apparatus and are reported uncorrected. High pressure liquid chromatography (HPLC) was performed using a Hewlett-Packard 1100 with chiral columns Daicel Chiralcel OB-H, OJ-H and Chiraldex AS (25 cm x 4.6 mm) using mixtures of 2-propanol / hexanes as eluent and UV detection at 210, 215 and 254 nm. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter, values are reported in 10<sup>-1</sup> cm<sup>2</sup> x degree x g<sup>-1</sup> (concentration, solvent).

## 2. Experimental procedures

### 3-(1*H*-Imidazol-1-yl)cyclohexanone (3)



Imidazole (1.362 g, 20.0 mmol) was dissolved in acetonitrile (10 mL) in a microwave vessel and cyclohex-2-en-1-one (3.872 mL, 40.0 mmol) was added. After 2 h and 30 min of microwave reaction, the solution mixture was transferred to a round bottom flask, the solvent was evaporated under reduced pressure and the yellow oil was left under high vacuum. The resulting solid was crushed to a powder and washed with Et<sub>2</sub>O (3 x 10 mL) to obtain a beige fine powder (3.145 g, 96%). *R*<sub>f</sub> (10% MeOH / CH<sub>2</sub>Cl<sub>2</sub>): 0.49; mp: 80-82 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.57 (s, 1H), 7.07 (s, 1H), 6.96 (s, 1H), 4.37 (ap tt, *J* = 10.7, 4.4 Hz, 1H), 2.84 (ap ddt, *J* = 14.1, 4.8, 1.6 Hz, 1H), 2.71 (dd, *J* = 14.1, 11.0 Hz, 1H), 2.51-2.28 (m, 3H), 2.15-2.00 (m, 2H), 1.81-1.65 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 206.8, 135.4, 129.9, 116.8, 55.7, 48.9, 40.6, 32.6, 22.0; IR (KBr) ν 3305, 3052, 2943, 2864, 2785, 2622, 1713, 1631, 1502, 1285, 1154, 1074, 925, 664 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 187 [(M+Na)<sup>+</sup>, 100%]; HRMS (ESI<sup>+</sup>) *m/z* calculated for C<sub>9</sub>H<sub>13</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 165.1022, found: 165.1019.

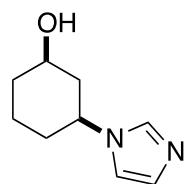
### Bioreductions with racemic ketone (±)-3 employing *Candida parapsilosis* ADH (CPADH), *Lactobacillus brevis* ADH (LBADH), *Thermoanaerobacter* sp. ADH (ADH-T) and *Rhodococcus ruber* ADH (ADH-A)

In a 1.5 mL Eppendorf vial, CPADH, LBADH, *E. coli*/ADH-T or *E. coli*/ADH-A (3U) was added in Tris.HCl buffer [600 μL, 50 mM, pH 7.5, 1 mM NADPH for LBADH or ADH-T, 1 mM NADH for ADH-A or CPADH and 1 mM MgCl<sub>2</sub> for LBADH] and mixed with 2-propanol (32 μL, 5% v v<sup>-1</sup>) and ketone **3** (20 mM). Reactions were shaken at 30 °C and 120 rpm for 24 h and stopped by extraction with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na<sub>2</sub>SO<sub>4</sub>. Conversions and diastereomeric excess of the corresponding alcohols were determined by HPLC.

### Bioreductions with racemic ketone ( $\pm$ )-3 employing *Ralstonia* sp. ADH (RasADH) and *Lactobacillus kefir* ADH (LKADH)

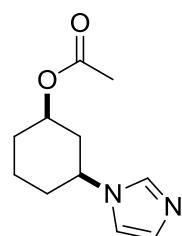
In a 1.5 mL Eppendorf vial, *E. coli*/RasADH or LKADH (3U) was added in Tris.HCl buffer (600  $\mu$ L, 50 mM, pH 7.5, 1 mM NADPH) and mixed with 5 U of GDH and glucose (40 mM) with ketone 3 (20 mM). Reactions were shaken at 30 °C and 120 rpm for 24 h and stopped by extraction with ethyl acetate (2 x 0.5 mL). The organic layer was separated by centrifugation (2 min, 13000 rpm) and dried over Na<sub>2</sub>SO<sub>4</sub>. Conversions and diastereomeric excess of the corresponding alcohols were determined by HPLC.

#### ( $\pm$ )-*cis*-3-(1*H*-Imidazol-1-yl)cyclohexanol [( $\pm$ )-*cis*-4]



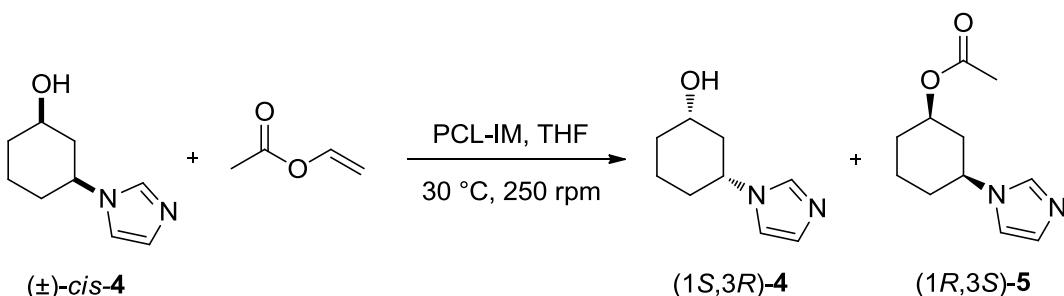
A solution of the ketone (6.50 g, 39.6 mmol) dissolved in anhydrous MeOH (12 mL) was cooled to -78 °C and NaBH<sub>4</sub> (1.05 g, 27.7 mmol) was added. The reaction mixture was stirred at this temperature for 15 h, then left to warm at room temperature and quenched with 1 N HCl (5 mL). The solvent was then evaporated, the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the pure product as a white powder (6.42 g, 98%) with a *cis/trans* ratio of 95:5 (90% *dr*) measured by <sup>1</sup>H NMR. After recrystallisation from CH<sub>2</sub>Cl<sub>2</sub>, the desired racemic *cis* diastereomer was obtained pure as white solid crystals (>99% *dr*, 4.69 g, 74%). *R*<sub>f</sub> (10% MeOH / CH<sub>2</sub>Cl<sub>2</sub>): 0.30; mp: 141-142 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  7.73 (s, 1H), 7.20 (d, *J* = 1.2 Hz, 1H), 6.97 (d, *J* = 1.1 Hz, 1H), 4.15 (ap tt, *J* = 12.2, 3.8 Hz, 1H), 3.70 (ap tt, *J* = 11.0, 4.2 Hz, 1H), 2.32 (ap dtt, *J* = 11.6, 3.9, 2.0 Hz, 1H), 2.04-1.99 (m, 2H), 1.92 (ap dtt, *J* = 13.1, 3.4, 3.1 Hz, 1H), 1.72-1.56 (m, 2H), 1.47 (ap ddt, *J* = 13.0, 12.5, 3.4 Hz, 1H), 1.29 (dddd, *J* = 12.9, 12.6, 11.0, 3.8 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.7, 128.8, 118.6, 69.8, 56.3, 44.0, 35.3, 34.3, 23.1; IR (KBr)  $\nu$  3192, 2935, 2920, 2858, 1665, 1505, 1222, 1055, 732 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 189 [M<sup>+</sup>, 100%], 190 [(M+H)<sup>+</sup>, 11%]; HRMS (ESI<sup>+</sup>) *m/z* calculated for C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>ONa (M+Na)<sup>+</sup>: 189.0998, found: 189.0990.

**( $\pm$ )-*cis*-3-(1*H*-Imidazol-1-yl)cyclohexyl acetate [ $(\pm)$ -*cis*-5]**



DMAP (14.7 mg, 0.12 mmol) and Ac<sub>2</sub>O (228  $\mu$ L, 2.41 mmol) were dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (15 mL), and the alcohol ( $\pm$ )-*cis*-4 (200 mg, 1.20 mmol) and NEt<sub>3</sub> (507  $\mu$ L, 3.61 mmol) were added. The reaction mixture was stirred for 30 min, the solvent was then evaporated and the crude was purified by flash column chromatography (5% MeOH / CH<sub>2</sub>Cl<sub>2</sub>), affording the pure product (237 mg, 95%) as a clear yellow oil.  $R_f$  (10% MeOH / CH<sub>2</sub>Cl<sub>2</sub>): 0.60; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.48 (s, 1H), 6.95 (s, 1H), 6.87 (s, 1H), 4.77-4.67 (m, 1H), 4.05-3.86 (m, 1H), 2.35-2.31 (m, 1H), 2.04-1.95 (m, 5H), 1.90-1.85 (m, 1H), 1.68-1.56 (m, 1H), 1.53-1.22 (m, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  170.2, 135.1, 128.9, 116.8, 70.8, 54.5, 39.3, 33.0, 30.6, 21.7, 21.1; IR (NaCl)  $\nu$  3385, 3113, 2946, 2867, 1734, 1647, 1500, 1365, 1245, 1046, 665 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 209 [M<sup>+</sup>, 100%], 210 [(M+H)<sup>+</sup>, 15%]; HRMS (ESI<sup>+</sup>) *m/z* calculated for C<sub>11</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 209.1285; found: 209.1279.

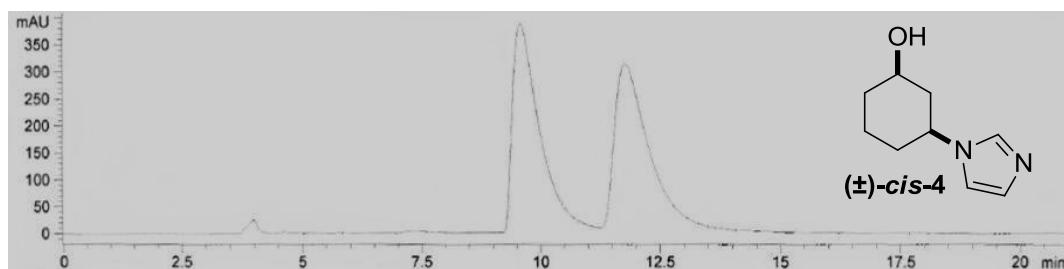
**Enzymatic resolution of ( $\pm$ )-*cis*-3-(1*H*-imidazol-1-yl)cyclohexanol [ $(\pm)$ -*cis*-4]**



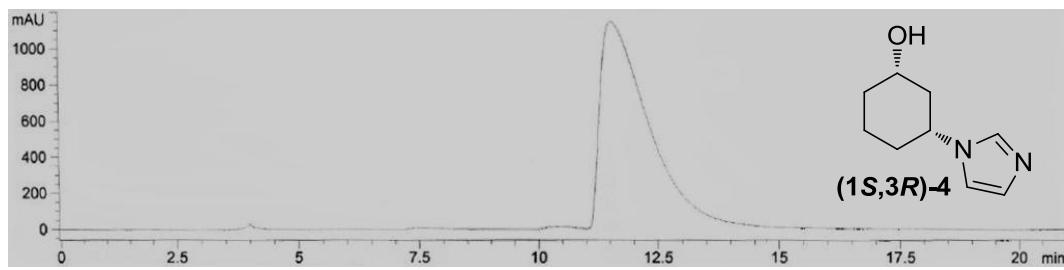
To a solution of the alcohol ( $\pm$ )-*cis*-4 (1.0 g, 6.0 mmol) and PCL IM (1.0 g) in anhydrous THF (60 mL), vinyl acetate (1.664 mL, 18.0 mmol) was added and the reaction mixture was left in an orbital shaker at 250 rpm and 30 °C. The reaction was followed by taking aliquots at regular intervals and analysed by HPLC. After 23 h, 50% conversion was obtained and the reaction was stopped by filtering the enzyme out and washing it with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The solvent was then evaporated under reduced pressure and the crude was purified by flash chromatography (5-10% MeOH / CH<sub>2</sub>Cl<sub>2</sub>), obtaining the alcohol (1*S*,3*R*)-4 (492 mg, 98%,  $[\alpha]_D^{20} = -3.0$  (*c* 1.0, MeOH), 99% *ee*) as a pure white powder and the acetate (1*R*,3*S*)-5 (614 mg, 98%,  $[\alpha]_D^{20} = +56.0$  (*c* 1.0, CHCl<sub>3</sub>), 97% *ee*) as a clear yellow liquid. The acetate

(1*R*,3*S*)-**5** (2.50 g, 12.0 mmol) was further hydrolysed with  $\text{K}_2\text{CO}_3$  (4.976 g, 36.0 mmol) in MeOH (12 mL) overnight at room temperature. The solvent was then evaporated and the crude was purified by flash column chromatography (10% MeOH /  $\text{CH}_2\text{Cl}_2$ ) to obtain the alcohol (1*R*,3*S*)-**4** as a pure white powder (1.95 g, 98%, 97% *ee*).

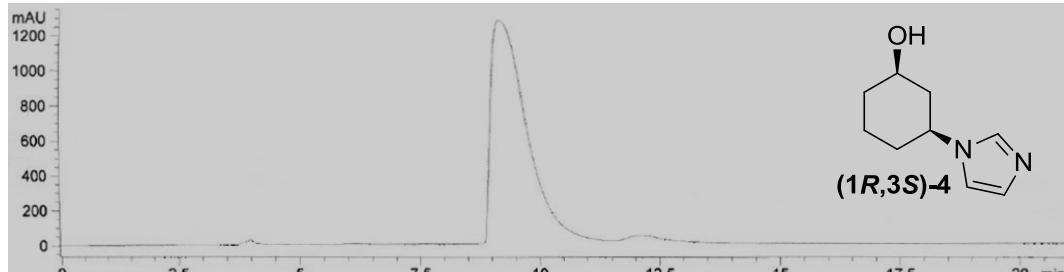
HPLC separation: Chiralcel OB-H column, 20% 2-propanol / hexanes, 25 °C, 0.8 mL/min.



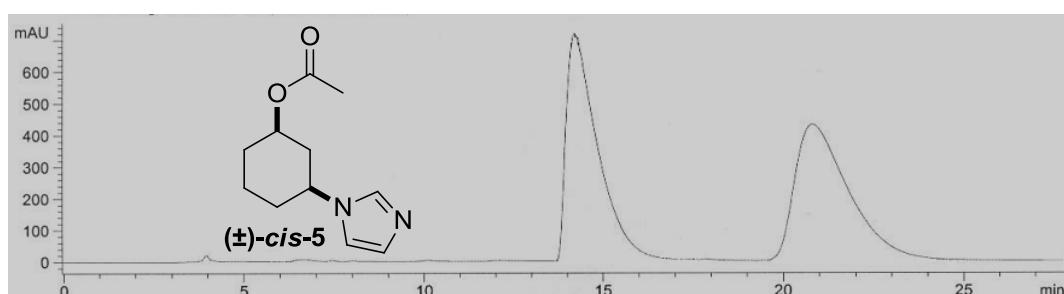
Alcohol (±)-*cis*-**4**:  $t_{\text{R}}$  (1*R*,3*S*): 9.4 min,  $t_{\text{R}}$  (1*S*,3*R*): 11.6 min



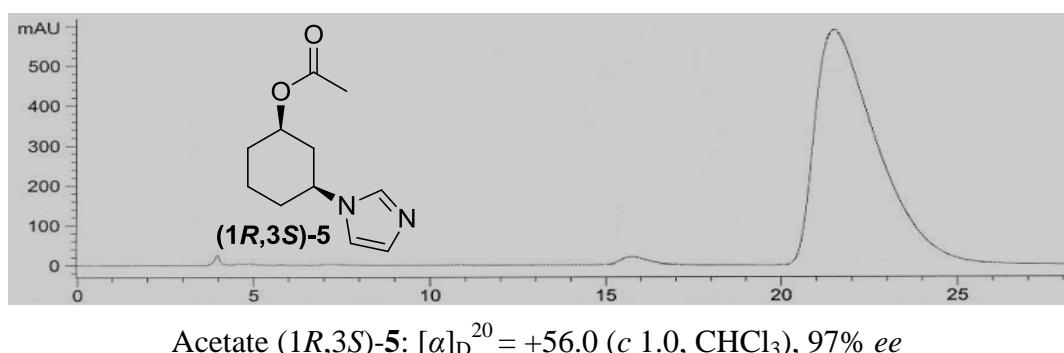
Alcohol (1*S*,3*R*)-**4**:  $[\alpha]_D^{20} = -3.0$  (*c* 1.0, MeOH), 99% *ee*



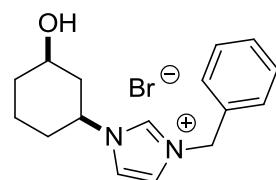
Alcohol (1*R*,3*S*)-**4**: 97% *ee* (obtained by chemical hydrolysis of acetate (1*R*,3*S*)-**5**)



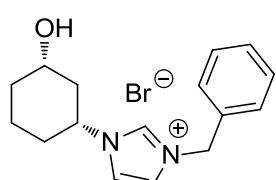
Acetate (±)-*cis*-**5**:  $t_{\text{R}}$  (1*S*,3*R*): 14.1 min,  $t_{\text{R}}$  (1*R*,3*S*): 20.8 min



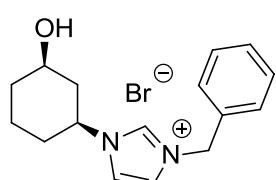
**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [ $(\pm)$ -*cis*-IM-OH-Bn-Br]**



The alcohol ( $\pm$ )-*cis*-4 (200 mg, 1.20 mmol) was dissolved in acetonitrile (1 mL) and benzyl bromide (172  $\mu$ L, 1.44 mmol) was added. The reaction mixture was stirred at 70 °C in a sealed tube in a sand bath for 2 h 30 min and then cooled to room temperature. Et<sub>2</sub>O (5 mL) was added and the resulting white solid precipitate was further washed with Et<sub>2</sub>O (3 x 10 mL) to remove the excess of benzyl bromide thus obtaining the bromide salt ( $\pm$ )-*cis*-IM-OH-Bn-Br (398.2 mg, 98%) as a pure white powder. mp: 173-175 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.27 (s, 1H), 7.79 (s, 1H), 7.64 (s, 1H), 7.48-7.38 (m, 5H), 5.45 (s, 2H), 4.43 (ap tt, *J* = 12.1, 3.8 Hz, 1H), 3.73 (ap tt, *J* = 10.9, 4.2 Hz, 1H), 2.46-2.38 (m, 1H), 2.15 (ap d, *J* = 12.0 Hz, 1H), 2.03-1.90 (m, 2H), 1.77-1.63 (m, 2H), 1.58-1.42 (m, 1H), 1.37-1.24 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.2, 135.3, 130.4, 130.3, 129.7, 123.7, 122.4, 69.3, 59.4, 54.2, 42.7, 34.9, 33.3, 22.7; IR (KBr)  $\nu$  3333, 3064, 2951, 2925, 2860, 1656, 1554, 1154, 1066, 711 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 20%]; HRMS (ESI<sup>+</sup>) *m/z* calculated for C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O (M)<sup>+</sup>: 257.1648, found: 257.1655.



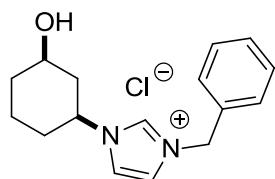
The synthesis of 3-benzyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [(1*S*,3*R*)-IM-OH-Bn-Br] was carried out using the same procedure starting with the enantiopure alcohol (1*S*,3*R*)-*cis*-4:  $[\alpha]_D^{20} = -1.0$  (*c* 1.0, MeOH).



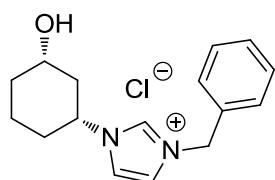
The synthesis of 3-benzyl-1-((1*R*,3*S*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [(1*R*,3*S*)-IM-OH-Bn-Br] was carried out

using the same procedure starting with the enantiopure alcohol (*1R,3S*)-*cis*-4.

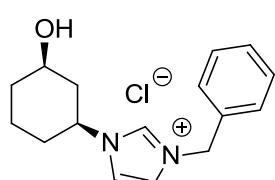
**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [ $(\pm)$ -*cis*-IM-OH-Bn-Cl]**



To a solution of the alcohol ( $\pm$ )-*cis*-4 (200 mg, 1.20 mmol) in acetonitrile (1 mL) was added benzyl chloride (1.384 mL, 12.0 mmol). The reaction mixture was stirred at 70 °C in a sealed tube in a sand bath for 7 h and then cooled to room temperature. Et<sub>2</sub>O (5 mL) was added and the resulting white solid precipitate was further washed with Et<sub>2</sub>O (3 x 10 mL) to obtain the chloride salt ( $\pm$ )-*cis*-IM-OH-Bn-Cl (352.2 mg, 98%) as a pure white powder. mp: 121-123 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 9.23 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.44 (s, 5H), 5.43 (s, 2H), 4.39 (ap tt, *J* = 12.1, 3.8 Hz, 1H), 3.77-3.67 (m, 1H), 2.43 (ap d, *J* = 11.3 Hz, 1H), 2.15 (ap d, *J* = 11.9 Hz, 1H), 2.03-1.92 (m, 2H), 1.76-1.62 (m, 2H), 1.56-1.43 (m, 1H), 1.37-1.25 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD) δ 136.2, 135.3, 130.43, 130.37, 129.6, 123.8, 122.5, 69.3, 59.4, 54.2, 42.7, 34.9, 33.3, 22.7; IR (NaCl) ν 3317, 3045, 2947, 2857, 1650, 1555, 1158, 1066, 711 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 21%]; HRMS (ESI<sup>+</sup>) *m/z* calculated for C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 257.1648, found: 257.1636.



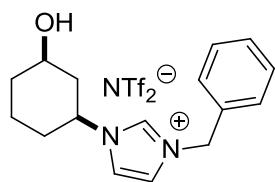
The synthesis of 3-benzyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [(1*S*,3*R*)-IM-OH-Bn-Cl] was carried out using the same procedure starting with the enantiopure alcohol (1*S*,3*R*)-*cis*-4: [α]<sub>D</sub><sup>20</sup> = -1.3 (c 1.0, MeOH).



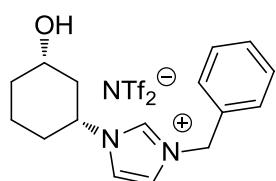
The synthesis of 3-benzyl-1-((1*R*,3*S*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [(1*R*,3*S*)-IM-OH-Bn-Cl] was carried out using the same procedure starting with the enantiopure alcohol (1*R*,3*S*)-*cis*-4.

**(±)-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium sulfonimide [±-*cis*-IM-OH-Bn-NTf<sub>2</sub>]**

trifluoromethane

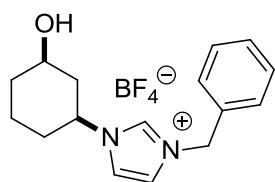


To a solution of the bromide salt (±)-*cis*-IM-OH-Bn-Br (100 mg, 0.297 mmol) in MeOH (7.0 mL) was added a solution of lithium bis(trifluoromethanesulfonimide) (LiNTf<sub>2</sub>) (128 mg, 0.445 mmol) in H<sub>2</sub>O (300  $\mu$ L) and the reaction mixture was stirred for 24 h at room temperature. The solvent was then evaporated under reduced pressure and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the trifluoromethane sulfonimide salt (±)-*cis*-IM-OH-Bn-NTf<sub>2</sub> (152.1 mg, 95%) as a clear yellow oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.06 (s, 1H), 7.71 (s, 1H), 7.56 (s, 1H), 7.42 (s, 5H), 5.39 (s, 2H), 4.37 (ap tt, *J* = 12.2, 3.8 Hz, 1H), 3.71 (ap tt, *J* = 10.9, 4.1 Hz, 1H), 2.44-2.38 (m, 1H), 2.14 (ap d, *J* = 12.0 Hz, 1H), 2.02-1.90 (m, 2H), 1.74-1.61 (m, 2H), 1.55-1.40 (m, 1H), 1.36-1.23 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.0, 135.1, 130.4, 130.3, 129.6, 127.5, 123.7, 123.3, 122.4, 119.1, 114.8, 69.3, 59.4, 54.2, 42.6, 34.9, 33.2, 22.6; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)  $\delta$  -81.48 (NTf<sub>2</sub>); IR (NaCl)  $\nu$  3535, 3149, 2948, 2870, 1647, 1557, 1456, 1351, 1196, 1138, 1059, 958, 791, 741, 711 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 20%]; MS (ESI<sup>-</sup>, *m/z*): 280 [NTf<sub>2</sub><sup>-</sup>, M<sup>-</sup>, 100%].



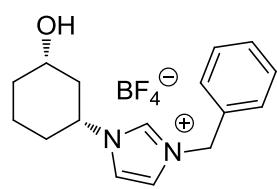
The synthesis of 3-benzyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium trifluoromethane sulfonimide [(1*S*,3*R*)-IM-OH-Bn-NTf<sub>2</sub>] was carried out using the same procedure starting with the enantiopure bromide salt (1*S*,3*R*)-*cis*-IM-OH-Bn-Br:  $[\alpha]_D^{20} = -0.9$  (*c* 1.0, MeOH).

**(±)-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate [±-*cis*-IM-OH-Bn-BF<sub>4</sub>]**



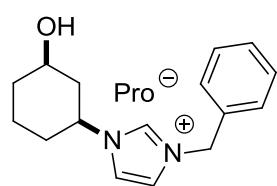
To a solution of the bromide salt (±)-*cis*-IM-OH-Bn-Br (100 mg, 0.297 mmol) in MeOH (7.0 mL) was added a solution of sodium tetrafluoroborate (NaBF<sub>4</sub>) (49 mg, 0.445 mmol) in H<sub>2</sub>O (300  $\mu$ L) and the reaction mixture was stirred for 24 h at room temperature. The solvent was then evaporated under reduced pressure and the product was dissolved in minimal amounts of 10% MeOH / MeCN. The remaining precipitated white salt was filtered

out with a short pipette cotton plug and the solvent was evaporated under reduced pressure to afford the tetrafluoroborate salt ( $\pm$ )-*cis*-IM-OH-Bn-BF<sub>4</sub> (87 mg, 85%) as a white semi-solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.10 (s, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 7.43 (s, 5H), 5.40 (s, 2H), 4.42-4.34 (m, 1H), 3.75-3.68 (m, 1H), 2.43-2.39 (m, 1H), 2.14 (ap d,  $J$  = 12.0 Hz, 1H), 2.01-1.91 (m, 2H), 1.75-1.61 (m, 2H), 1.55-1.41 (m, 1H), 1.36-1.23 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  135.2, 130.4, 130.3, 129.7, 123.6, 122.3, 69.3, 59.3, 54.1, 42.6, 34.9, 33.2, 22.6; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)  $\delta$  -155.03 (<sup>10</sup>BF<sub>4</sub>), -155.08 (<sup>11</sup>BF<sub>4</sub>); IR (NaCl)  $\nu$  3419, 2945, 2866, 1645, 1557, 1531, 1455, 1361, 1164, 1063, 959 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 20%]; MS (ESI<sup>-</sup>, *m/z*): 86 [<sup>10</sup>BF<sub>4</sub><sup>-</sup>, 25%], 87 [<sup>11</sup>BF<sub>4</sub><sup>-</sup>, 100%].



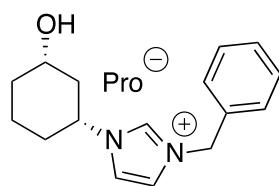
The synthesis of 3-benzyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate [(1*S*,3*R*)-IM-OH-Bn-BF<sub>4</sub>] was carried out using the same procedure starting with the enantiopure bromide salt (1*S*,3*R*)-IM-OH-Bn-Br:  $[\alpha]_D^{20}$  = -1.5 (c 1.0, MeOH).

**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate  
[( $\pm$ )-*cis*-IM-OH-Bn-Pro]**



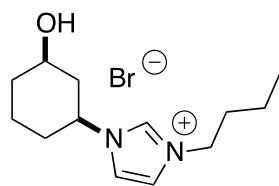
To a solution of the chloride salt ( $\pm$ )-*cis*-IM-OH-Bn-Cl (150 mg, 0.512 mmol) in distilled H<sub>2</sub>O (5.0 mL) were added two scoops of Amberlite IRA-440-OH resin (previously washed with distilled water and methanol).<sup>1</sup> The mixture was stirred for 5 min, then the resin was filtered out and proline (70.8 mg, 0.615 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the oil was left to dry under high vacuum. The oil was then dissolved in minimal amounts of 10% MeOH / MeCN and the resulting precipitate observed was filtered out with a short pipette cotton plug, thus removing any excess of L-proline. The solvent was evaporated and the product was left to dry under high vacuum for 48 h, obtaining ( $\pm$ )-*cis*-IM-OH-Bn-Pro as a clear light yellow oil (157 mg, 82%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.22 (s, 1H), 7.78 (d,  $J$  = 2.1 Hz, 1H), 7.64 (d,  $J$  = 2.0 Hz, 1H), 7.48-7.38 (m, 5H), 5.42 (s, 2H), 4.38 (ap tt,  $J$  = 12.2, 3.9 Hz, 1H), 3.71 (ap tt,  $J$  = 10.9, 4.1 Hz, 1H), 3.56 (dd,  $J$  = 8.5, 6.1 Hz, 1H), 3.14 (dt,  $J$  = 10.9, 6.4 Hz, 1H), 2.83 (dt,  $J$  = 10.7, 6.9 Hz, 1H), 2.41 (ap ddq,  $J$  = 9.6, 3.9, 2.0 Hz, 1H), 2.17-2.08 (m, 2H), 2.03-1.81 (m, 3H), 1.78-1.61 (m, 4H), 1.48 (ap ddt,  $J$  = 13.3, 12.9, 3.3 Hz, 1H), 1.31 (ap ddt,  $J$  = 13.2, 11.1, 3.7 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$

207.9, 180.0, 135.3, 130.44, 130.38, 129.6, 123.7, 122.4, 69.3, 63.2, 59.4, 54.2, 47.6, 42.7, 35.0, 33.3, 32.1, 26.6, 22.7; IR (NaCl)  $\nu$  3310, 3130, 3051, 2942, 2863, 1649, 1565, 1454, 1382, 1158, 1071, 1037, 958, 764  $\text{cm}^{-1}$ ; MS (ESI $^+$ ,  $m/z$ ): 257 [ $\text{M}^+$ , 100%], 258 [ $(\text{M}+\text{H})^+$ , 26%]; MS (ESI $^-$ ,  $m/z$ ): 114 [L-Proline,  $\text{M}^-$ , 100%].

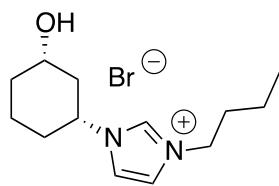


The synthesis of 3-benzyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate [(1*S*,3*R*)-IM-OH-Bn-Pro] was carried out using the same procedure starting with the enantiopure chloride salt (1*S*,3*R*)-IM-OH-Bn-Cl:  $[\alpha]_D^{20} = -29.1$  (*c* 1.0, MeOH).

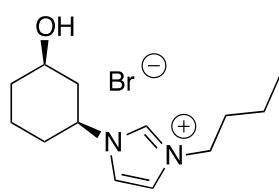
**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [ $(\pm)$ -*cis*-IM-OH-Bu-Br]**



To a solution of the alcohol ( $\pm$ )-*cis*-4 (200 mg, 1.20 mmol) in acetonitrile (1 mL) was added butyl bromide (155  $\mu\text{L}$ , 1.44 mmol). The reaction mixture was stirred at 100  $^\circ\text{C}$  in a sealed tube in a sand bath for 24 h and then cooled to room temperature. Alternatively, the same reaction was done using microwave conditions in 30 min.  $\text{Et}_2\text{O}$  (5 mL) was added and the resulting white solid precipitate was further washed with  $\text{Et}_2\text{O}$  (3 x 10 mL) to remove the excess of butyl bromide and obtain the bromide salt ( $\pm$ )-*cis*-IM-OH-Bu-Br (359 mg, 98%) as a pure white powder. mp: 127-129  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.16 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 4.41 (ap tt,  $J = 12.2, 3.8$  Hz, 1H), 4.24 (t,  $J = 7.4$  Hz, 2H), 3.73 (ap tt,  $J = 10.9, 4.1$  Hz, 1H), 2.44 (ap d,  $J = 11.4$  Hz, 1H), 2.16 (ap d,  $J = 12.0$  Hz, 1H), 2.04-1.84 (m, 4H), 1.77-1.63 (m, 2H), 1.59-1.44 (m, 1H), 1.43-1.24 (m, 3H), 0.99 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  136.0, 123.7, 122.2, 69.3, 59.3, 50.8, 42.8, 35.0, 33.3, 33.1, 22.7, 20.5, 13.8; IR (KBr)  $\nu$  3402, 3137, 3086, 2939, 2866, 1641, 1561, 1467, 1369, 1164, 1068, 958, 756  $\text{cm}^{-1}$ ; MS (ESI $^+$ ,  $m/z$ ): 223 [ $\text{M}^+$ , 100%], 224 [ $(\text{M}+\text{H})^+$ , 20%].

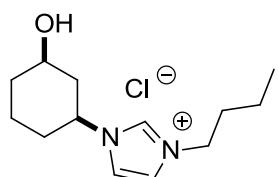


The synthesis of 3-butyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [(1*S*,3*R*)-IM-OH-Bu-Br] was carried out using the same procedure starting with the enantiopure alcohol (1*S*,3*R*)-4:  $[\alpha]_D^{20} = -7.8$  (*c* 1.0, MeOH).

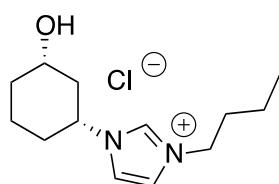


The synthesis of 3-butyl-1-((1*R*,3*S*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [(1*R*,3*S*)-IM-OH-Bu-Br] was carried out using the same procedure starting with the enantiopure alcohol (1*R*,3*S*)-4.

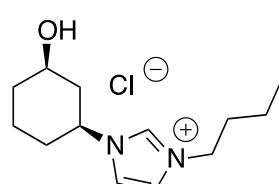
**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [ $(\pm)$ -*cis*-IM-OH-Bu-Cl]**



To a solution of the alcohol (450 mg, 2.71 mmol) in acetonitrile (2 mL) was added butyl chloride (2.848 mL, 27.1 mmol). The reaction was done using microwave conditions in 1 h. Et<sub>2</sub>O (5 mL) was added and the resulting clear colourless oil was further washed with Et<sub>2</sub>O (3 x 10 mL) to remove the excess of butyl chloride and obtain the chloride salt ( $\pm$ )-*cis*-IM-OH-Bu-Cl (418 mg, 90%) as a clear colourless oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.14 (s, 1H), 7.77 (s, 1H), 7.68 (s, 1H), 4.39 (ap tt, *J* = 12.2, 3.9 Hz, 1H), 4.23 (t, *J* = 7.4 Hz, 3H), 3.73 (ap tt, *J* = 10.9, 4.2 Hz, 1H), 2.44 (ap ddq, *J* = 9.6, 3.9, 2.0 Hz, 1H), 2.15 (ap d, *J* = 11.9 Hz, 1H), 2.05-1.84 (m, 4H), 1.76-1.62 (m, 2H), 1.58-1.44 (m, 1H), 1.42-1.19 (m, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.0, 123.8, 122.2, 69.3, 59.3, 50.7, 42.7, 35.0, 33.3, 33.1, 22.7, 20.5, 13.7; IR (NaCl)  $\nu$  3385, 3136, 3083, 2939, 2865, 1642, 1562, 1467, 1368, 1165, 1068, 958, 756 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 223 [M<sup>+</sup>, 100%], 224 [(M+H)<sup>+</sup>, 15%].

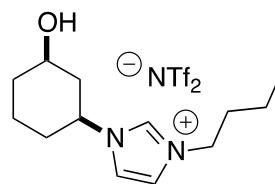


The synthesis of 3-butyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [(1*S*,3*R*)-IM-OH-Bu-Cl] was carried out using the same procedure starting with the enantiopure alcohol (1*S*,3*R*)-4:  $[\alpha]_D^{20} = -7.2$  (*c* 1.0, MeOH).



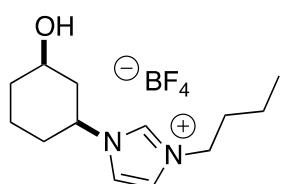
The synthesis of 3-butyl-1-((1*R*,3*S*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [(1*R*,3*S*)-IM-OH-Bu-Cl] was carried out using the same procedure starting with the enantiopure alcohol (1*R*,3*S*)-4.

**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium trifluoromethane sulfonimide [ $(\pm)$ -*cis*-IM-OH-Bu-NTf<sub>2</sub>]**



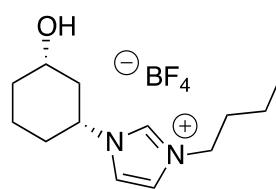
To a solution of the bromide salt ( $(\pm)$ -*cis*-IM-OH-Bu-Br (50 mg, 0.165 mmol) in MeOH (4.0 mL) was added a solution of LiNTf<sub>2</sub> (70.9 mg, 0.247 mmol) in H<sub>2</sub>O (171  $\mu$ L) and the reaction mixture was stirred for 24 h at room temperature. The solvent was then evaporated under reduced pressure and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the trifluoromethane sulfonimide salt ( $(\pm)$ -*cis*-IM-OH-Bu-NTf<sub>2</sub> (76.9 mg, 93%) as a clear yellow oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  8.99 (s, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 4.36 (ap tt, *J* = 12.2, 3.8 Hz, 1H), 4.21 (t, *J* = 7.4 Hz, 2H), 3.72 (ap tt, *J* = 10.9, 4.1 Hz, 1H), 2.43 (ap d, *J* = 11.4 Hz, 1H), 2.13 (ap d, *J* = 11.9 Hz, 1H), 2.03-1.83 (m, 4H), 1.75-1.61 (m, 2H), 1.57-1.44 (m, 1H), 1.43-1.24 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 2H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  135.8, 127.5, 123.7, 123.3, 122.1, 119.1, 114.8, 69.3, 59.3, 50.7, 42.7, 34.9, 33.2, 33.0, 22.6, 20.4, 13.7; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)  $\delta$  -81.53 (NTf<sub>2</sub><sup>-</sup>); IR (NaCl)  $\nu$  3535, 3417, 3149, 2943, 2872, 1562, 1456, 1352, 1196, 1138, 1059, 958, 792, 741 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 223 [M<sup>+</sup>, 100%], 224 [(M+H)<sup>+</sup>, 16%]; MS (ESI<sup>-</sup>, *m/z*): 280 [NTf<sub>2</sub><sup>-</sup>, 100%].

**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate [ $(\pm)$ -*cis*-IM-OH-Bu-BF<sub>4</sub>]**



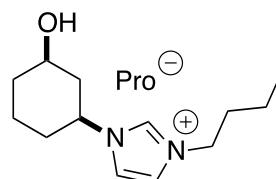
To a solution of the bromide salt ( $(\pm)$ -*cis*-IM-OH-Bu-Br (50 mg, 0.165 mmol) in MeOH (4.0 mL) was added a solution of NaBF<sub>4</sub> (27.1 mg, 0.247 mmol) in H<sub>2</sub>O (171  $\mu$ L) and the reaction mixture was stirred for 24 h at room temperature. The solvent was then evaporated under reduced pressure and the product was dissolved in minimal amounts of 10% MeOH / MeCN. The remaining precipitated white solid was filtered out with a short pipette cotton plug and the solvent was evaporated under reduced pressure to afford the tetrafluoroborate salt ( $(\pm)$ -*cis*-IM-OH-Bu-BF<sub>4</sub> (37.9 mg, 74%) as a white semi-solid oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.08 (s, 1H), 7.75 (s, 1H), 7.66 (s, 1H), 4.39 (ap tt, *J* = 12.2, 3.8 Hz, 1H), 4.23 (t, *J* = 7.4 Hz, 2H), 3.73 (ap tt, *J* = 10.9, 4.1 Hz, 1H), 2.44 (ap d, *J* = 11.4 Hz, 1H), 2.15 (ap d, *J* = 11.9 Hz, 1H), 2.04-1.84 (m, 4H), 1.76-1.62 (m, 2H), 1.58-1.44 (m, 1H), 1.42-1.24 (m, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.0, 123.7, 122.1, 69.3, 59.3, 50.7, 42.7, 35.0,

33.3, 33.1, 22.7, 20.5, 13.7;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  -155.09 ( $^{10}\text{BF}_4$ ), -155.14 ( $^{11}\text{BF}_4$ ); IR (NaCl)  $\nu$  3390, 3156, 3094, 2936, 2865, 1642, 1564, 1455, 1368, 1164, 1066, 958, 758  $\text{cm}^{-1}$ ; MS (ESI $^+$ ,  $m/z$ ): 223 [ $\text{M}^+$ , 100%], 224 [ $(\text{M}+\text{H})^+$ , 18%]; MS (ESI $^-$ ,  $m/z$ ): 86 [ $^{10}\text{BF}_4^-$ , 25%], 87 [ $^{11}\text{BF}_4^-$ , 100%].

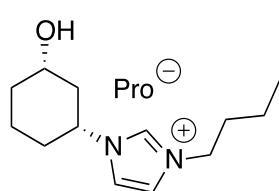


The synthesis of 3-butyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate [(1*S*,3*R*)-IM-OH-Bu-BF<sub>4</sub>] was carried out using the same procedure starting with the enantiopure bromide salt (1*S*,3*R*)-IM-OH-Bu-Br:  $[\alpha]_D^{20} = -3.1$  ( $c$  1.0, MeOH)

**(±)-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate  
[(±)-*cis*-IM-OH-Bu-Pro]**



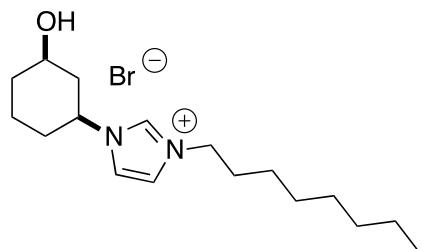
To a solution of the chloride salt (±)-*cis*-IM-OH-Bu-Cl (200 mg, 0.775 mmol) in distilled  $\text{H}_2\text{O}$  (5.0 mL) were added two scoops of Amberlite IRA-440-OH resin (previously washed with distilled water and methanol). The mixture was stirred for 5 min, then the resin was filtered out and proline (98.1 mg, 0.853 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated *under reduced pressure* and the oil was left to dry under high vacuum. The oil was then dissolved in minimal amounts of 10% MeOH / MeCN and the resulting precipitate was filtered out with a short pipette cotton plug, thus removing any excess of L-proline. The solvent was evaporated and the product was dried under high vacuum for 48 h, obtaining (±)-*cis*-IM-OH-Bu-Pro as a clear light yellow oil (237.6 mg, 91%),  $[\alpha]_D^{20} = -32.0$  ( $c$  1.0, MeOH).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.11 (s, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 4.37 (ap tt,  $J$  = 12.2, 3.9 Hz, 1H), 4.22 (t,  $J$  = 7.4 Hz, 2H), 3.72 (ap tt,  $J$  = 10.9, 4.2 Hz, 1H), 3.56 (dd,  $J$  = 8.5, 6.1 Hz, 1H), 3.15 (dt,  $J$  = 10.9, 6.4 Hz, 1H), 2.82 (dt,  $J$  = 10.7, 6.9 Hz, 1H), 2.43 (ap ddt,  $J$  = 9.4, 3.7, 2.0 Hz, 1H), 2.20-2.08 (m, 2H), 2.03-1.61 (m, 9H), 1.58-1.44 (m, 1H), 1.43-1.24 (m, 3H), 1.00 (t,  $J$  = 7.4 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  179.6, 123.7, 122.2, 69.3, 63.2, 59.3, 50.7, 47.6, 42.7, 35.0, 33.3, 33.1, 32.0, 26.5; IR (NaCl)  $\nu$  3290, 3133, 3082, 2939, 2867, 1589, 1454, 1383, 1168, 1076, 1037, 959, 763  $\text{cm}^{-1}$ ; MS (ESI $^+$ ,  $m/z$ ): 223 [ $\text{M}^+$ , 100%], 224 [ $(\text{M}+\text{H})^+$ , 25%]; MS (ESI $^-$ ,  $m/z$ ): 114 [L-Proline,  $\text{M}^-$ , 100%].



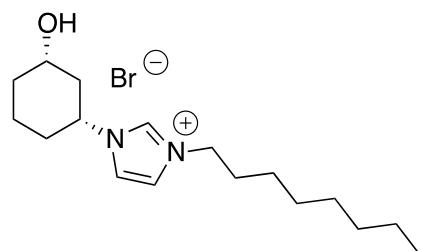
1.0, MeOH).

The synthesis of 3-butyl-1-((1*S*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate [(1*S*,3*R*)-IM-OH-Bu-Pro] was carried out using the same procedure starting with the enantiopure chloride salt (1*S*,3*R*)-IM-OH-Bu-Cl:  $[\alpha]_D^{20} = -40.7$  (c

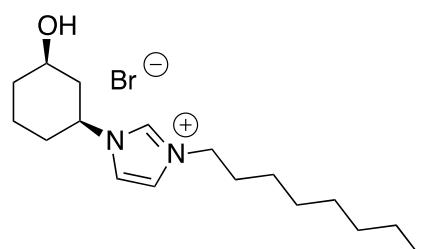
**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium bromide [ $(\pm)$ -*cis*-IM-OH-Oct-Br]**



To a solution of the alcohol ( $\pm$ )-**4** (200 mg, 1.20 mmol) in acetonitrile (1 mL) was added octyl bromide (251.2  $\mu$ L, 1.44 mmol). The reaction mixture was stirred at 70 °C in a sealed tube in a sand bath for 24 h and then cooled to room temperature. Alternatively, the same reaction was done using microwave conditions in 1 h. Et<sub>2</sub>O (5 mL) was added and the resulting clear colourless oil was further washed with Et<sub>2</sub>O (3 x 10 mL) to remove the excess of octyl bromide and obtain the bromide salt ( $\pm$ )-*cis*-IM-OH-Oct-Br (421.7 mg, 98%) as a clear colourless oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.15 (s, 1H), 7.77 (s, 1H), 7.68 (s, 1H), 4.40 (ap tt, *J* = 12.2, 3.8 Hz, 1H), 4.23 (t, *J* = 7.4 Hz, 2H), 3.73 (ap tt, *J* = 10.9, 4.1 Hz, 1H), 2.44 (ap d, *J* = 11.4 Hz, 1H), 2.16 (ap d, *J* = 12.0 Hz, 1H), 2.04-1.89 (m, 4H), 1.76-1.62 (m, 2H), 1.51 (ap ddt, *J* = 13.1, 9.9, 3.2 Hz, 1H), 1.37-1.25 (m, 11H), 0.90 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.0, 123.7, 122.2, 69.3, 59.3, 51.0, 42.8, 35.0, 33.4, 32.9, 31.1, 30.2, 30.0, 27.3, 23.7, 22.7, 14.4; IR (NaCl)  $\nu$  3371, 3131, 3073, 2931, 2858, 1644, 1563, 1466, 1368, 1163, 1070, 958, 757 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 279 [M<sup>+</sup>, 100%], 280 [(M+H)<sup>+</sup>, 20%].



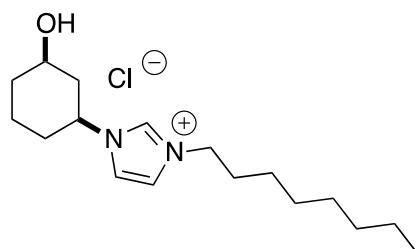
The synthesis of 1-((1*S*,3*R*)-3-hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium bromide [(1*S*,3*R*)-IM-OH-Oct-Br] was carried out using the same procedure starting with the enantiopure alcohol (1*S*,3*R*)-**4**:  $[\alpha]_D^{20} = -2.5$  (c 1.0, MeOH).



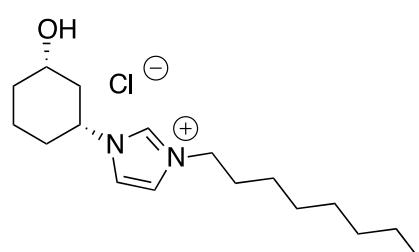
The synthesis of 1-((1*R*,3*S*)-3-hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium bromide [(1*R*,3*S*)-IM-OH-Oct-Br] was carried out using the same procedure starting with the enantiopure alcohol (1*R*,3*S*)-**4**:  $[\alpha]_D^{20} = 2.5$  (c 1.0, MeOH).

Br] was carried out using the same procedure starting with the enantiopure alcohol (*1R,3S*)-*cis*-4.

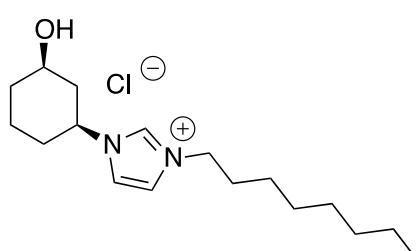
**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium chloride [ $(\pm)$ -*cis*-IM-OH-Oct-Cl]**



To a solution of the alcohol ( $\pm$ )-*cis*-4 (100 mg, 0.602 mmol) in acetonitrile (1.2 mL) was added octyl chloride (1.022 mL, 6.0 mmol). The reaction was done using microwave conditions in 1 h. Et<sub>2</sub>O (5 mL) was added and the resulting clear colourless oil was further washed with Et<sub>2</sub>O (3 x 10 mL) to remove the excess of octyl chloride and obtain the chloride salt ( $\pm$ )-*cis*-IM-OH-Oct-Cl (155.4 mg, 82%) as a clear colourless oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.13 (s, 1H), 7.77 (s, 1H), 7.68 (s, 1H), 4.39 (ap tt,  $J$  = 12.1, 3.8 Hz, 1H), 4.22 (t,  $J$  = 7.4 Hz, 2H), 3.73 (ap tt,  $J$  = 10.9, 4.1 Hz, 1H), 2.43 (ap ddt,  $J$  = 7.5, 3.7, 1.8 Hz, 1H), 2.15 (ap d,  $J$  = 11.8 Hz, 1H), 2.04-1.88 (m, 4H), 1.76-1.62 (m, 2H), 1.51 (ap ddt,  $J$  = 13.2, 11.4, 3.3 Hz, 2H), 1.36-1.25 (m, 11H), 0.90 (t,  $J$  = 7.4 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.0, 123.7, 122.2, 69.3, 59.3, 51.0, 42.8, 35.0, 33.4, 32.9, 31.1, 30.2, 30.0, 27.3, 23.7, 22.7, 14.4; IR (NaCl)  $\nu$  3376, 3140, 3081, 2931, 2858, 1645, 1563, 1467, 1368, 1164, 1070, 959, 756 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 279 [M<sup>+</sup>, 100%], 280 [(M+H)<sup>+</sup>, 18%].

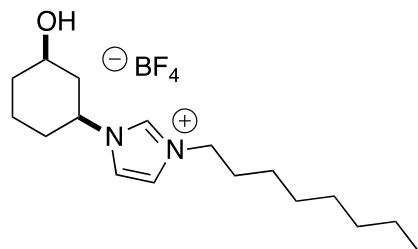


The synthesis of 1-((1*S*,3*R*)-3-hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium chloride [(1*S*,3*R*)-IM-OH-Oct-Cl] was carried out using the same procedure starting with the enantiopure alcohol (1*S*,3*R*)-*cis*-4:  $[\alpha]_D^{20} = -5.7$  (*c* 1.0, MeOH).

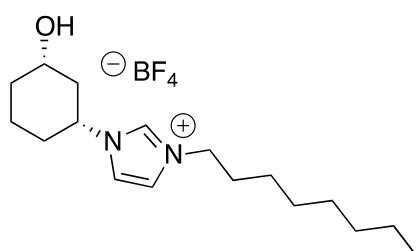


The synthesis of 1-((1*R*,3*S*)-3-hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium chloride [(1*R*,3*S*)-IM-OH-Oct-Cl] was carried out using the same procedure starting with the enantiopure alcohol (1*R*,3*S*)-*cis*-4.

**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium tetrafluoroborate [ $(\pm)$ -*cis*-IM-OH-Oct-BF<sub>4</sub>]**

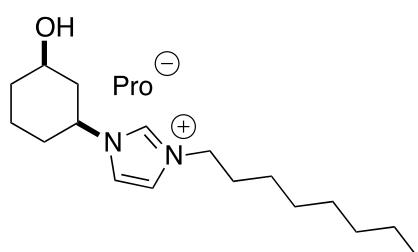


To a solution of the bromide salt ( $\pm$ )-*cis*-IM-OH-Oct-Br (100 mg, 0.278 mmol) in MeOH (7 mL) was added a solution of NaBF<sub>4</sub> (45.8 mg, 0.417 mmol) in H<sub>2</sub>O (200  $\mu$ L) and the reaction mixture was stirred for 24 h at room temperature. The solvent was then evaporated *under reduced pressure* and the product was dissolved in minimal amounts of 10% MeOH / MeCN. The remaining precipitated white salt was filtered out with a short pipette cotton plug and the solvent was evaporated under reduced pressure to afford the tetrafluoroborate salt ( $\pm$ )-*cis*-IM-OH-Oct-BF<sub>4</sub> (101.8 mg, 98%) as a white semi-solid oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.03 (s, 1H), 7.74 (s, 1H), 7.65 (s, 1H), 4.37 (ap tt,  $J$  = 12.2, 3.8 Hz, 1H), 4.21 (t,  $J$  = 7.4 Hz, 2H), 3.72 (ap tt,  $J$  = 10.8, 4.1 Hz, 1H), 2.43 (ap d,  $J$  = 11.4 Hz, 1H), 2.14 (ap d,  $J$  = 12.0 Hz, 1H), 2.03-1.87 (m, 4H), 1.75-1.61 (m, 2H), 1.56-1.42 (m, 1H), 1.35-1.31 (m, 11H), 0.90 (t,  $J$  = 7.4 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  135.9, 123.7, 122.1, 69.3, 59.3, 51.0, 42.7, 35.0, 33.3, 32.9, 31.1, 30.2, 30.0, 27.3, 23.7, 22.7, 14.4; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)  $\delta$  -154.19 (<sup>10</sup>BF<sub>4</sub>), -154.24 (<sup>11</sup>BF<sub>4</sub>); IR (NaCl)  $\nu$  3543, 3383, 3152, 2932, 2860, 1634, 1563, 1469, 1369, 1164, 1066, 958, 763 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 279 [M<sup>+</sup>, 100%], 280 [(M+H)<sup>+</sup>, 15%]; MS (ESI<sup>-</sup>, *m/z*): 86 [<sup>10</sup>BF<sub>4</sub><sup>-</sup>, 25%], 87 [<sup>11</sup>BF<sub>4</sub><sup>-</sup>, 100%].



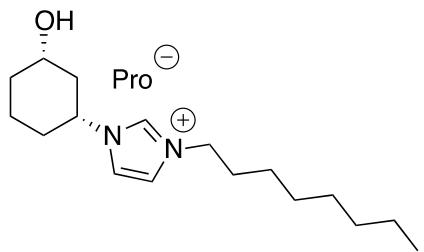
The synthesis of 1-((1*S*,3*R*)-3-hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium tetrafluoroborate [(1*S*,3*R*)-IM-OH-Oct-BF<sub>4</sub>] was carried out using the same procedure starting with the enantiopure alcohol (1*S*,3*R*)-**4**:  $[\alpha]_D^{20}$  = -4.1 (c 1.0, MeOH).

**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate [ $(\pm)$ -*cis*-IM-OH-Oct-Pro]**



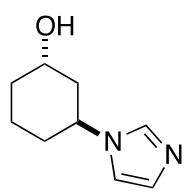
To a solution of the chloride salt ( $\pm$ )-*cis*-IM-OH-Oct-Cl (80 mg, 0.255 mmol) in distilled H<sub>2</sub>O (5.0 mL) was added one scoop of Amberlite IRA-440-OH resin (previously

washed with distilled water and methanol). The mixture was stirred for 5 min, then the resin was filtered out and L-proline (32.2 mg, 0.280 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the oil was left to dry under high vacuum. The oil was then dissolved in minimal amounts of 10% MeOH / MeCN and the resulting precipitate observed was filtered out with a short pipette cotton plug, thus removing any excess of L-proline. The solvent was evaporated and the product was dried under high vacuum for 48 h, obtaining  $(\pm)$ -*cis*-IM-OH-Oct-Pro as a clear light yellow oil (98.1 mg, 98%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  9.11 (s, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 4.36 (ap tt,  $J$  = 12.2, 3.8 Hz, 1H), 4.21 (t,  $J$  = 7.4 Hz, 2H), 3.77-3.67 (m, 1H), 3.61 (dd,  $J$  = 8.3, 6.4 Hz, 1H), 3.22-3.12 (m, 1H), 2.87 (ap dt,  $J$  = 10.8, 7.0 Hz, 1H), 2.43 (ap d,  $J$  = 11.4 Hz, 1H), 2.19-2.10 (m, 2H), 2.04-1.96 (m, 5H), 1.83-1.61 (m, 5H), 1.56-1.42 (m, 1H), 1.35-1.31 (m, 1H), 0.90 (t,  $J$  = 6.5 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  179.3, 123.7, 122.2, 69.3, 63.1, 59.3, 51.0, 47.5, 42.7, 35.0, 33.4, 32.9, 31.9, 31.1, 30.2, 30.0, 27.3, 26.4, 23.7, 22.7, 14.4; IR (NaCl)  $\nu$  3291, 3136, 3087, 2932, 2860, 1593, 1382, 1166, 1077, 959, 772  $\text{cm}^{-1}$ ; MS (ESI $^+$ ,  $m/z$ ): 279 [ $\text{M}^+$ , 100%], 280 [ $(\text{M}+\text{H})^+$ , 25%]; MS (ESI $^-$ ,  $m/z$ ): 114 [L-Proline,  $\text{M}^-$ , 100%].



The synthesis of  $1-((1S,3R)\text{-}3\text{-hydroxycyclohexyl})\text{-}3\text{-octyl-1H-imidazol-3-iun}$  pyrrolidine-2-carboxylate [ $(1S,3R)\text{-IM-OH-Oct-Pro}$ ] was carried out using the same procedure starting with the enantiopure chloride salt  $(1S,3R)\text{-IM-OH-Oct-Cl}$ :  $[\alpha]_D^{20} = -39.2$  ( $c$  1.0, MeOH).

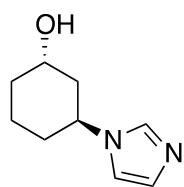
#### $(\pm)$ -*trans*-3-(1H-Imidazol-1-yl)cyclohexanol [ $(\pm)$ -*trans*-4]



To a solution of the alcohol  $(\pm)$ -*cis*-4 (500 mg, 3.01 mmol) in anhydrous THF (15 mL) were added *para*-nitrobenzoic acid (1.005 g, 6.02 mmol) and triphenylphosphine (1.578 g, 6.02 mmol). Diethyl azodicarboxylate (DEAD) (1.084 mL, 6.02 mmol) was added dropwise leaving a clear yellow solution.

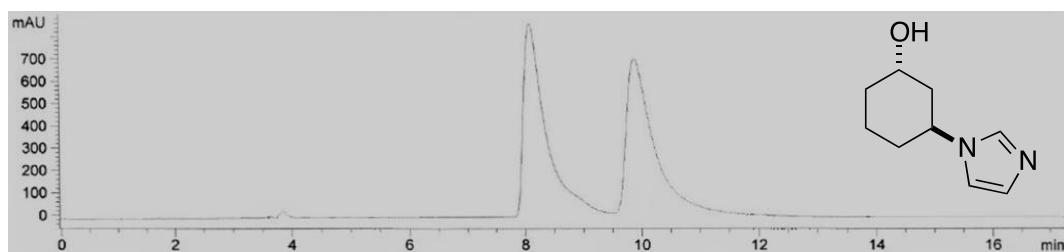
The reaction mixture was stirred at room temperature for 2 h. Then, the solvent was evaporated and a solution of NaOMe (15 mL) was added. The reaction was stirred at room temperature for 2 h. Afterwards, the solvent was evaporated and the crude was purified by column chromatography (5% MeOH /  $\text{CH}_2\text{Cl}_2$ ), affording the pure product (255 mg, 51%) as a white powder. mp: 127-129 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.70 (s, 1H), 7.17 (s, 1H),

6.95 (s, 1H), 4.45 (ap tt,  $J$  = 11.7, 3.9 Hz, 1H), 4.22-4.20 (m, 1H), 2.15-2.01 (m, 2H), 1.98-1.84 (m, 2H), 1.80-1.64 (m, 3H), 1.55 (ap tt,  $J$  = 13.2, 3.1 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  136.7, 128.8, 118.7, 67.2, 53.4, 41.2, 34.9, 32.4, 20.6; IR (KBr)  $\nu$  3154, 3104, 2941, 2924, 2880, 1651, 1611, 1497, 1222, 1094, 985, 808, 764, 660  $\text{cm}^{-1}$ ; MS (ESI $^+$ ,  $m/z$ ): 167 [M $^+$ , 100%], 189 [(M+Na $^+$ ), 85%]; HRMS (ESI $^+$ )  $m/z$  calculated for  $\text{C}_9\text{H}_{15}\text{N}_2\text{O}$  (M+H) $^+$ : 167.1179, found: 167.1173.

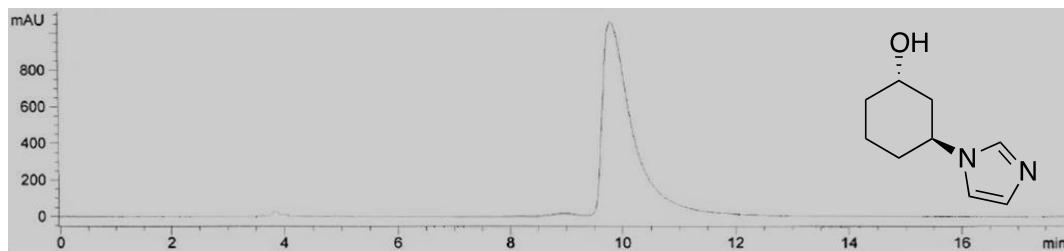


The enzymatic resolution of the racemic *trans* compound was carried using lipases, however high enantiomeric excess was not achieved. Therefore, the synthesis of the (1*R*,3*R*)-3-(1*H*-imidazol-1-yl)cyclohexanol [(1*R*,3*R*)-4] was carried out using the same Mitsunobu reaction and hydrolysis protocol starting with the enantiopure alcohol (1*S*,3*R*)-4:  $[\alpha]_D^{20} = -11.6$  ( $c$  1.0, MeOH).

HPLC separation: Chiralcel AS column, 15% 2-propanol / hexanes, 25 °C, 0.8 mL/min.

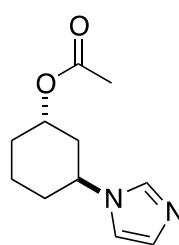


Alcohol ( $\pm$ )-*trans*-4:  $t_R$  (1*S*,3*S*): 8.0 min,  $t_R$  (1*R*,3*R*): 9.8 min



Alcohol (1*R*,3*R*)-4:  $t_R$  (1*R*,3*R*): 9.8 min,  $[\alpha]_D^{20} = -11.6$  ( $c$  1.0, MeOH), 99% ee

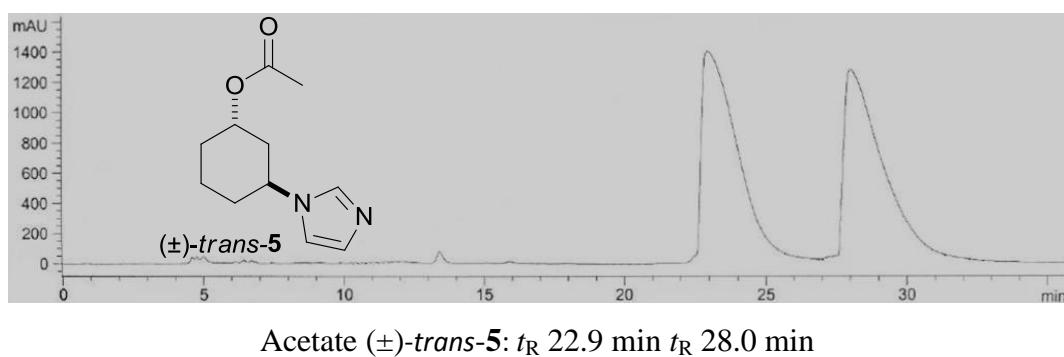
### ( $\pm$ )-*trans*-3-(1*H*-Imidazol-1-yl)cyclohexyl acetate [( $\pm$ )-*trans*-5]



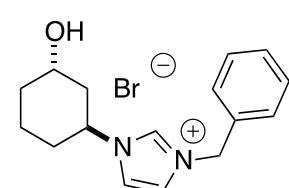
DMAP (1.5 mg, 0.012 mmol) and  $\text{Ac}_2\text{O}$  (22.8  $\mu\text{L}$ , 0.24 mmol) were dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (1.5 mL) and the alcohol ( $\pm$ )-*trans*-9 (20 mg, 0.12 mmol) and  $\text{NEt}_3$  (50.6  $\mu\text{L}$ , 0.36 mmol) were added. The reaction mixture was stirred at room temperature for 30 min. The solvent was then evaporated under reduced pressure, and the crude mixture was purified by

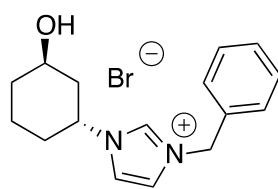
column (5-10% MeOH / CH<sub>2</sub>Cl<sub>2</sub>), to afford the acetate ( $\pm$ )-*trans*-5 (24 mg, 96%) as a clear yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 (s, 1H), 7.04 (s, 1H), 6.94 (s, 1H), 5.24 (m, 1H), 4.33-4.22 (m, 1H), 2.29-2.21 (m, 1H), 2.16-2.10 (m, 1H), 2.09 (s, 3H), 1.96-1.81 (m, 2H), 1.79-1.61 (m, 3H), 1.96-1.45 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  170.3, 135.5, 129.3, 116.9, 69.5, 52.2, 37.7, 33.7, 29.0, 21.4, 20.0; IR (KBr)  $\nu$  3154, 3104, 2941, 2924, 2880, 1651, 1611, 1497, 1222, 1094, 985, 808, 764, 660 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 209 [M<sup>+</sup>, 100%], 210 [(M+H)<sup>+</sup>, 15%].

HPLC separation: Chiralcel OJ-H column, 10% 2-propanol / hexanes, 25 °C, 0.8 mL/min.



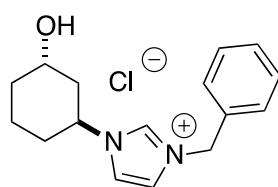
**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [ $(\pm)$ -*trans*-IM-OH-Bn-Br]**

 To a solution of alcohol ( $\pm$ )-*trans*-4 (100 mg, 0.60 mmol) in MeCN (0.5 mL) was added benzyl bromide (72.2  $\mu$ L, 0.61 mmol) in a sealed tube and the reaction mixture was stirred at 60 °C in a sand bath for 48 h and cooled to room temperature. Et<sub>2</sub>O (5 mL) was then added to the oily mixture and the resulting white solid was further washed with Et<sub>2</sub>O (3 x 5 mL) to obtain the bromide salt ( $\pm$ )-*trans*-IM-OH-Bn-Br (157.4 mg, 97%) as a pure white powder. mp: 120-122 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.24 (s, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.44 (m, 5H), 5.43 (s, 2H), 4.68 (ap tt, *J* = 11.8, 3.8 Hz, 1H), 4.25 (m, 1H), 2.25-2.16 (m, 2H), 2.05-1.90 (m, 2H), 1.90-1.69 (m, 3H), 1.63-1.52 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.2, 135.3, 130.4, 130.3, 129.7, 123.8, 122.5, 66.7, 57.2, 54.2, 40.2, 34.0, 32.1, 20.2; IR (KBr):  $\nu$  3333, 3064, 2951, 2925, 2860, 1656, 1554, 1154, 1066 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 25%]; HRMS (ESI<sup>+</sup>) *m/z* calculated for C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 257.1648, found: 257.1665.

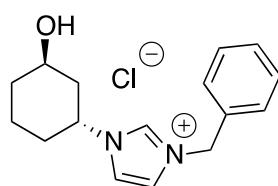


The synthesis of the bromide salt 3-benzyl-1-((1*R*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide [(1*R*,3*R*)-IM-OH-Bn-Br] was carried out using the same procedure starting with the enantiopure alcohol (1*R*,3*R*)-4:  $[\alpha]_D^{20} = -11.0$  (*c* 1.0, MeOH).

**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [ $(\pm)$ -*trans*-IM-OH-Bn-Cl]**

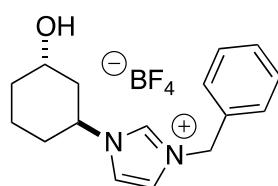


To a solution of alcohol ( $\pm$ )-*trans*-IM-OH-Bn-Cl (50 mg, 0.30 mmol) in MeCN (0.5 mL) was added benzyl chloride (173.2  $\mu$ L, 1.51 mmol) in a sealed tube and the reaction mixture was stirred at 60 °C in a sand bath for 24 h and cooled to room temperature. Et<sub>2</sub>O (5 mL) was then added to the oily mixture and the resulting white solid was further washed with Et<sub>2</sub>O (3 x 5 mL) to obtain the chloride salt ( $\pm$ )-*trans*-IM-OH-Bn-Cl (79.9 mg, 91%) as a pure white powder. mp: 144-146 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.26 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 7.45 (m, 5H), 5.44 (s, 2H), 4.69 (ap tt, *J* = 11.8, 3.8 Hz, 1H), 4.28-4.26 (m, 1H), 2.27-2.17 (m, 2H), 2.06-1.93 (m, 2H), 1.87-1.71 (m, 3H), 1.64-1.53 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.2, 135.3, 130.4, 130.3, 129.6, 123.8, 122.5, 66.7, 57.2, 54.2, 40.2, 34.0, 32.1, 20.2 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H<sup>+</sup>), 28%]; HRMS (ESI<sup>+</sup>) *m/z* calculated for C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O (M+H)<sup>+</sup>: 257.1648, found: 257.1658.



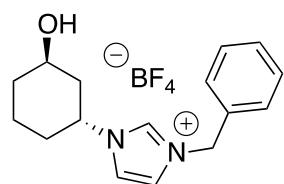
The synthesis of the chloride salt 3-benzyl-1-((1*R*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [(1*R*,3*R*)-IM-OH-Bn-Cl] was carried out using the same procedure starting with the enantiopure alcohol (1*R*,3*R*)-4:  $[\alpha]_D^{20} = -10.6$  (*c* 1.0, MeOH).

**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate [ $(\pm)$ -*trans*-IM-OH-Bn-BF<sub>4</sub>]**



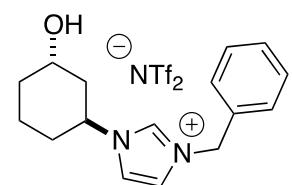
To a solution of the bromide salt ( $\pm$ )-*trans*-IM-OH-Bn-Br (50 mg, 0.148 mmol) in MeOH (4 mL) was added a solution of NaBF<sub>4</sub> (24.4 mg, 0.22 mmol) in H<sub>2</sub>O (100  $\mu$ L) and the reaction mixture was stirred for 24 h at room temperature. The solvent was then evaporated under reduced pressure and the product was dissolved in minimal amounts of 10% MeOH / MeCN.

The remaining precipitated white salt was filtered out with a short pipette cotton plug and the solvent was evaporated under reduced pressure to afford the tetrafluoroborate salt  $(\pm)$ -*trans*-IM-OH-Bn-BF<sub>4</sub> (49.8 mg, 98%) as a white semi-solid oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.23 (s, 1H), 7.76 (s, 1H), 7.62 (s, 1H), 7.44 (m, 5H), 5.44 (s, 2H), 4.68 (ap tt,  $J$  = 11.8, 3.8 Hz, 1H), 4.25 (m, 1H), 2.26-2.16 (m, 2H), 2.06-1.87 (m, 2H), 1.86-1.68 (m, 3H), 1.63-1.52 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.2, 135.3, 130.4, 130.3, 129.7, 123.7, 122.4, 66.7, 57.2, 54.1, 40.2, 34.0, 32.0, 20.2; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)  $\delta$  -154.78 (<sup>10</sup>BF<sub>4</sub>), -154.84 (<sup>11</sup>BF<sub>4</sub>); IR (NaCl):  $\nu$  3425, 2945, 1645, 1531, 1455, 1288, 1030 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 20%]; MS (ESI<sup>-</sup>, *m/z*): 86 [<sup>10</sup>BF<sub>4</sub><sup>-</sup>, 25%], 87 [<sup>11</sup>BF<sub>4</sub><sup>-</sup>, 100%].

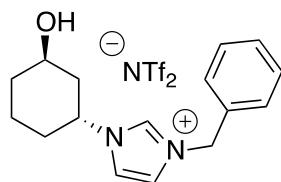


The synthesis of the tetrafluoroborate salt 3-benzyl-1-((1*R*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate [(1*R*,3*R*)-IM-OH-Bn-BF<sub>4</sub>] was carried out using the same procedure starting with the enantiopure bromide salt (1*R*,3*R*)-IM-OH-Bn-Br:  
[ $\alpha$ ]<sub>D</sub><sup>20</sup> = -10.5 (*c* 1.0, MeOH).

**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium trifluoromethane sulfonimide [ $(\pm)$ -*trans*-IM-OH-Bn-NTf<sub>2</sub>]**



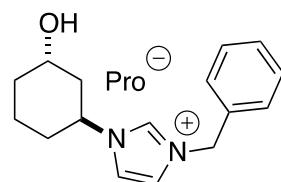
To a solution of the bromide salt ( $\pm$ )-*trans*-IM-OH-Bn-Br (50 mg, 0.148 mmol) in MeOH (4 mL) was added a solution of LiNTf<sub>2</sub> (63.7 mg, 0.22 mmol) in H<sub>2</sub>O (100  $\mu$ L) and the reaction mixture was stirred for 24 h at room temperature. The solvent was then evaporated under reduced pressure and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the trifluoromethane sulfonimide salt ( $\pm$ )-*trans*-IM-OH-Bn-NTf<sub>2</sub> (74.3 mg, 93%) as a clear yellow oil. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.09 (s, 1H), 7.71 (d,  $J$  = 1.9 Hz, 1H), 7.58 (d,  $J$  = 1.9 Hz, 1H), 7.42 (m, 5H), 5.39 (s, 2H), 4.66 (ap tt,  $J$  = 11.8, 3.8 Hz, 1H), 4.25 (m, 1H), 2.24-2.15 (m, 2H), 2.03-1.87 (m, 2H), 1.85-1.68 (m, 3H), 1.62-1.51 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  136.0, 135.1, 130.4, 130.3, 129.6, 127.6, 123.8, 123.7, 123.3, 122.4, 119.1, 114.8, 66.7, 57.2, 54.2, 40.1, 33.9, 32.0, 20.1; <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)  $\delta$  -81.53 (NTf<sub>2</sub>); IR (NaCl):  $\nu$  3535, 3149, 2948, 2870, 1647, 1557, 1456, 1351, 1196, 1059 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 20%]; MS (ESI<sup>-</sup>, *m/z*): 280 [NTf<sub>2</sub><sup>-</sup>, 100%].



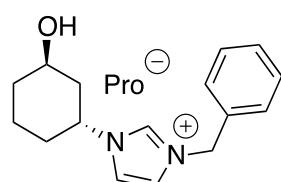
The synthesis of the trifluoromethane sulfonimide salt 3-benzyl-1-((1*R*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium trifluoromethane sulfonimide [(1*R*,3*R*)-IM-OH-Bn-NTf<sub>2</sub>] was carried out using the same procedure starting with the enantiopure bromide salt (1*R*,3*R*)-IM-OH-Bn-Br:  $[\alpha]_D^{20} = -6.3$  (*c* 1.0, MeOH).

**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium carboxylate [ $(\pm)$ -*trans*-IM-OH-Bn-Pro]**

pyrrolidine-2-

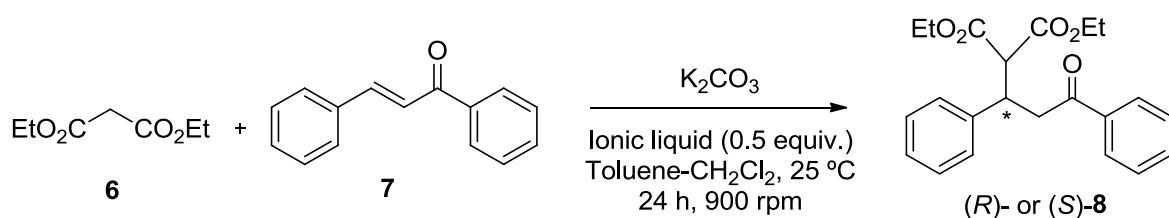


To a solution of the chloride salt ( $\pm$ )-*trans*-IM-OH-Bn-Cl (200 mg, 0.775 mmol) in distilled H<sub>2</sub>O (5.0 mL) were added two scoops of Amberlite IRA-440-OH resin (previously washed with distilled water and methanol). The mixture was stirred for 5 min, then the resin was filtered out and L-proline (98.1 mg, 0.853 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the oil was left to dry under high vacuum. The oil was then dissolved in minimal amounts of 10% MeOH / MeCN and the resulting precipitate observed was filtered out with a short pipette cotton plug, thus removing any excess of L-proline. The solvent was evaporated and the product was dried under high vacuum for 48 h, obtaining ( $\pm$ )-*trans*-IM-OH-Bn-Pro as a pure clear light yellow oil (237.6 mg, 91%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.21 (s, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.43 (m, 5H), 5.41 (s, 2H), 4.68 (ap tt, *J* = 11.8, 3.7 Hz, 1H), 4.25 (s, 1H), 3.70-3.65 (m, 1H), 3.24-3.17 (m, 1H), 2.98-2.90 (m, 1H), 2.24-2.12 (m, 3H), 2.03-1.89 (m, 3H), 1.84-1.69 (m, 5H), 1.62-1.51 (m, 1H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  178.4, 135.3, 130.44, 130.36, 129.6, 123.8, 122.4, 66.7, 63.1, 57.2, 54.2, 47.4, 40.2, 34.0, 32.1, 31.7, 26.2, 20.2; IR (NaCl)  $\nu$  3308, 3131, 3051, 2941, 2863, 1648, 1566, 1454, 1382, 1168, 1070, 1048, 958, 762 cm<sup>-1</sup>; MS (ESI<sup>+</sup>, *m/z*): 257 [M<sup>+</sup>, 100%], 258 [(M+H)<sup>+</sup>, 25%]; MS (ESI<sup>-</sup>, *m/z*): 114 [L-Proline, M<sup>-</sup>, 100%].



The synthesis of 3-benzyl-1-((1*R*,3*R*)-3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate [(1*R*,3*R*)-IM-OH-Bn-Pro] was carried out using the same procedure starting with the enantiopure chloride salt (1*R*,3*R*)-IM-OH-Bn-Cl:  $[\alpha]_D^{20} = -52.6$  (*c* 2.0, MeOH).

### 3. Organocatalysis



The Michael addition of diethylmalonate **6** (1.2 equiv) to *trans*-chalcone **7** (1 equiv) was performed in a toluene- $\text{CH}_2\text{Cl}_2$  (300  $\mu\text{L}$  + 60  $\mu\text{L}$ ) mixture in an eppendorf tube, with dry  $\text{K}_2\text{CO}_3$  (3 equiv) and the corresponding imidazole derivative (0.5 equiv) at 25 °C at 900 rpm for 24 h. Afterwards, the reaction was stopped by filtering the crude in a short cotton plug pipette and evaporating the solvent. The crude was analysed by  $^1\text{H}$  NMR for conversion and by HPLC (AS column) for the determination of the enantiomeric excess of the product **8** as previously done in our research group.<sup>2</sup>

The absolute configuration of the product **8** was demonstrated by comparison of its optical rotation value with the already described in the literature:  $[\alpha]_D^{20} = -0.5$  (*c* 1.0,  $\text{CHCl}_3$ ) taken from the reactions with (1*S*,3*R*)-(-)-*cis*-IM-OH-Bu-Cl, (1*S*,3*R*)-(-)-*cis*-IM-OH-Oct-Br, (1*S*,3*R*)-(-)-*cis*-IM-OH-Oct-Cl, 6% *ee* and conversions values over 95%.<sup>3</sup>

#### 4. Toxicity tests

The agar diffusion tests were performed as previously described in the literature.<sup>4</sup>

Individual Tables S1-S4 have been prepared to explain the influence of different parameters in the toxicity of the imidazolium derivatives:

**Table S1. Anion dependence**

Entry	Compound	Amount of compound (μmol)	Size of inhibition zone (mm)	Normalised inhibition zone (mm/μmol)
3	(±)- <i>trans</i> -OH-Bn-Br	0.0152	4.5	296
13	(±)- <i>trans</i> -OH-Bn-Cl	0.0114	4.5	395
17	(±)- <i>trans</i> -OH-Bn-BF <sub>4</sub>	0.0257	6.5	253
21	(±)- <i>trans</i> -OH-Bn-NTf <sub>2</sub>	0.0067	5	746
24	(±)- <i>trans</i> -OH-Bn-Pro	0.0051	1	196
4	(±)- <i>cis</i> -OH-Bn-Br	0.0170	3	176
14	(±)- <i>cis</i> -OH-Bn-Cl	0.0256	5	195
18	(±)- <i>cis</i> -OH-Bn-BF <sub>4</sub>	0.0081	1.25	154
22	(±)- <i>cis</i> -OH-Bn-NTf <sub>2</sub>	0.0085	2	235
25	(±)- <i>cis</i> -OH-Bn-Pro	0.0142	2.25	158
7	(±)- <i>cis</i> -OH-Bu-Br	0.0300	2	67
15	(±)- <i>cis</i> -OH-Bu-Cl	0.0213	2	94
19	(±)- <i>cis</i> -OH-Bu-BF <sub>4</sub>	0.0190	1.75	92
23	(±)- <i>cis</i> -OH-Bu-NTf <sub>2</sub>	0.0117	2.5	214
26	(±)- <i>cis</i> -OH-Bu-Pro	0.0226	2	88
10	(±)- <i>cis</i> -OH-Oct-Br	0.0171	11.5	673
16	(±)- <i>cis</i> -OH-Oct-Cl	0.0130	12.2	938
20	(±)- <i>cis</i> -OH-Oct-BF <sub>4</sub>	0.0131	12.5	954
27	(±)- <i>cis</i> -OH-Oct-Pro	0.0133	10.5	798

Clearly NTf<sub>2</sub> species are the more toxic derivatives.

Little difference was observed for other anions although bromide and proline derivatives led to lower toxicity values.

**Table S2. Cation alkyl chain length dependence**

Entry	Compound	Amount of compound (μmol)	Size of inhibition zone (mm)	Normalised inhibition zone (mm/μmol)
4	(±)- <i>cis</i> -OH-Bn-Br	0.0170	3	176
7	(±)- <i>cis</i> -OH-Bu-Br	0.0300	2	67
10	(±)- <i>cis</i> -OH-Oct-Br	0.0171	11.5	673
14	(±)- <i>cis</i> -OH-Bn-Cl	0.0256	5	195
15	(±)- <i>cis</i> -OH-Bu-Cl	0.0213	2	94
16	(±)- <i>cis</i> -OH-Oct-Cl	0.0130	12.2	938
18	(±)- <i>cis</i> -OH-Bn-BF <sub>4</sub>	0.0081	1.25	154
19	(±)- <i>cis</i> -OH-Bu-BF <sub>4</sub>	0.0190	1.75	92
20	(±)- <i>cis</i> -OH-Oct-BF <sub>4</sub>	0.0131	12.5	954
22	(±)- <i>cis</i> -OH-Bn-NTf <sub>2</sub>	0.0085	2	235
23	(±)- <i>cis</i> -OH-Bu-NTf <sub>2</sub>	0.0117	2.5	214
25	(±)- <i>cis</i> -OH-Bn-Pro	0.0142	2.25	158
26	(±)- <i>cis</i> -OH-Bu-Pro	0.0226	2	88
27	(±)- <i>cis</i> -OH-Oct-Pro	0.0133	10.5	798

Larger cation alkyl chain lengths led to higher toxicity values: Oct >> Bn > Bu.

**Table S3. *cis/trans* Stereochemistry in the cyclohexyl ring**

Entry	Compound	Amount of compound (μmol)	Size of inhibition zone (mm)	Normalised inhibition zone (mm/μmol)
3	( $\pm$ )- <i>trans</i> -OH-Bn-Br	0.0152	4.5	296
4	( $\pm$ )- <i>cis</i> -OH-Bn-Br	0.0170	3	176
13	( $\pm$ )- <i>trans</i> -OH-Bn-Cl	0.0114	4.5	395
14	( $\pm$ )- <i>cis</i> -OH-Bn-Cl	0.0256	5	195
17	( $\pm$ )- <i>trans</i> -OH-Bn-BF <sub>4</sub>	0.0257	6.5	253
18	( $\pm$ )- <i>cis</i> -OH-Bn-BF <sub>4</sub>	0.0081	1.25	154
21	( $\pm$ )- <i>trans</i> -OH-Bn-NTf <sub>2</sub>	0.0067	5	746
22	( $\pm$ )- <i>cis</i> -OH-Bn-NTf <sub>2</sub>	0.0085	2	235
24	( $\pm$ )- <i>trans</i> -OH-Bn-Pro	0.0051	1	196
25	( $\pm$ )- <i>cis</i> -OH-Bn-Pro	0.0142	2.25	158

The *cis*-isomers clearly behave as the more benign derivatives.

**Table S4. Chirality dependence**

Entry	Compound	Amount of compound (μmol)	Size of inhibition zone (mm)	Normalised inhibition zone (mm/μmol)
4	( $\pm$ )- <i>cis</i> -IM-OH-Bn-Br	0.0170	3	176
5	( $-$ )- <i>cis</i> -(1 <i>S</i> ,3 <i>R</i> )-IM-OH-Bn-Br	0.0246	8	325
6	( $+$ )- <i>cis</i> -(1 <i>R</i> ,3 <i>S</i> )-IM-OH-Bn-Br	0.0187	14	749
7	( $\pm$ )- <i>cis</i> -IM-OH-Bu-Br	0.0300	2	67
8	( $-$ )- <i>cis</i> -(1 <i>S</i> ,3 <i>R</i> )-IM-OH-Bu-Br	0.0284	2	71
9	( $+$ )- <i>cis</i> -(1 <i>R</i> ,3 <i>S</i> )-IM-OH-Bu-Br	0.0330	2	61
10	( $\pm$ )- <i>cis</i> -IM-OH-Oct-Br	0.0171	11.5	673
11	( $-$ )- <i>cis</i> -(1 <i>S</i> ,3 <i>R</i> )-IM-OH-Oct-Br	0.0053	4	757
12	( $+$ )- <i>cis</i> -(1 <i>R</i> ,3 <i>S</i> )-IM-OH-Oct-Br	0.0206	5.5	267

In all cases the opposite enantiomer shows significant different toxicities but a clear correlation was not observed.

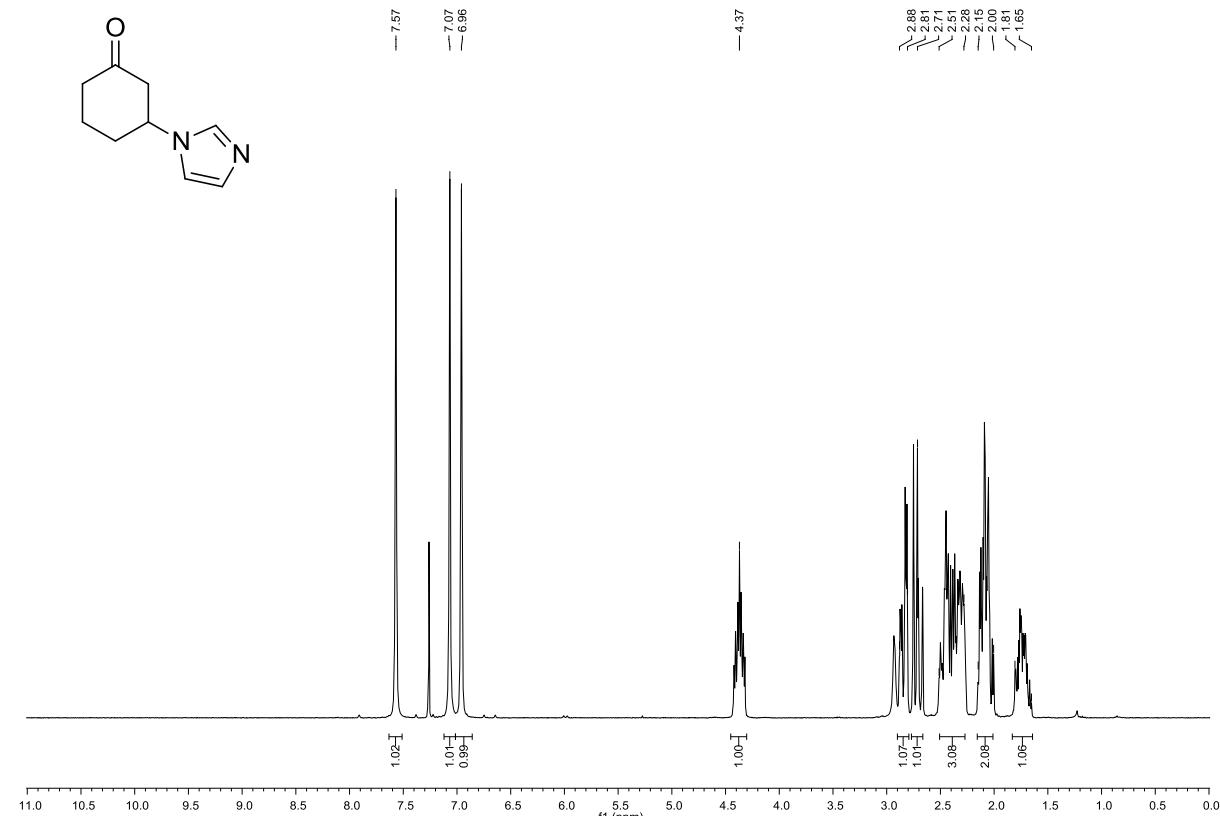
## 5. References

1. K. Fukumoto, M. Yoshizawa and H. Ohno, *J. Am. Chem. Soc.*, 2005, **127**, 2398-2399.
2. N. Ríos-Lombardía, R. Porcar, E. Bustos, I. Alfonso, J. Montejo-Bernardo, S. García-Granda, V. Gotor, S. V. Luis, E. García-Verdugo and V. Gotor-Fernández, *ChemCatChem*, 2011, **3**, 1921-1928.
3.  $[\alpha]_D^{20} = -23.2$  (*c* 0.68, CHCl<sub>3</sub>) for (*R*)-**21** in 99% *ee* in: D. Chen, Z. Chen, X. Xiao, Z. Yang, L. Lin, X. Liu and X. Feng, *Chem. Eur. J.*, 2009, **15**, 6807-6810.
4. M. Rebros, H. Q. N. Gunaratne, J. Ferguson, K. R. Seddon and G. Stephens, *Green Chem.*, 2009, **11**, 402-408.

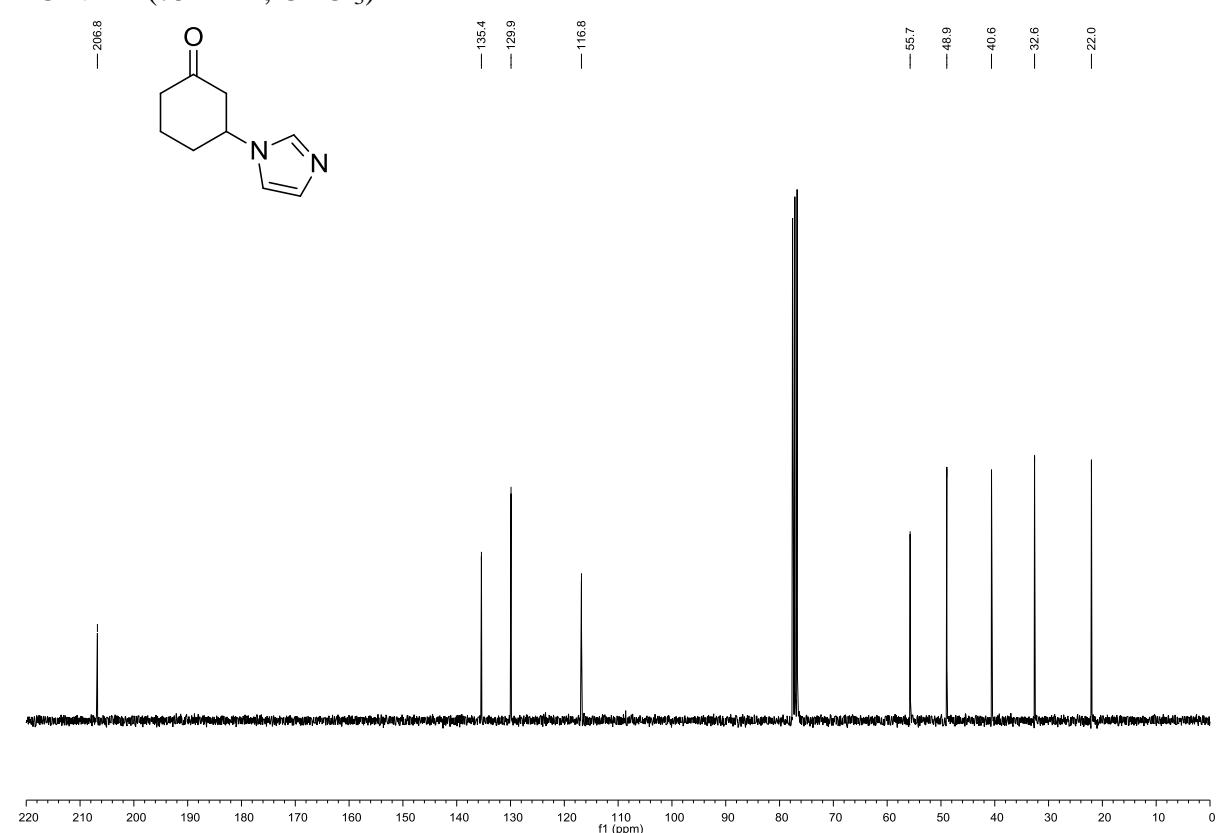
## 6. Spectral data

### 3-(1*H*-Imidazol-1-yl)cyclohexanone (3)

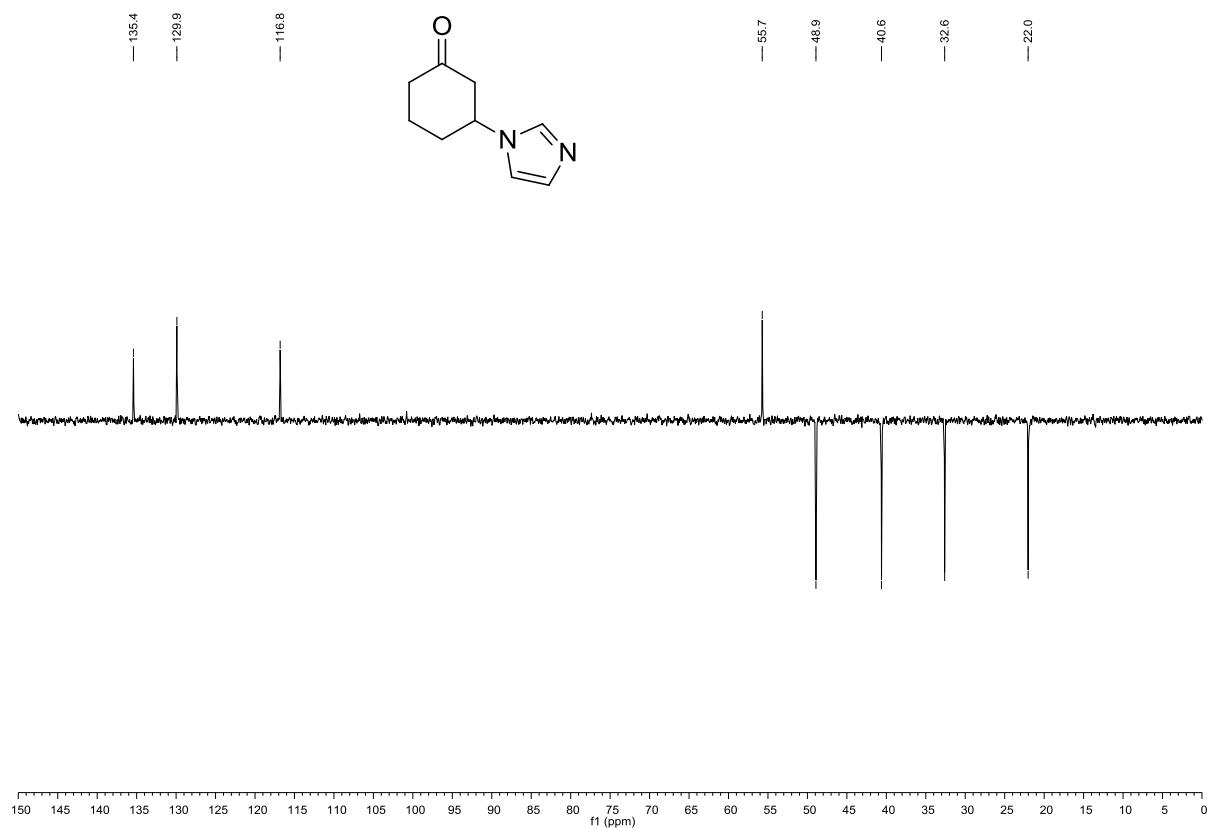
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



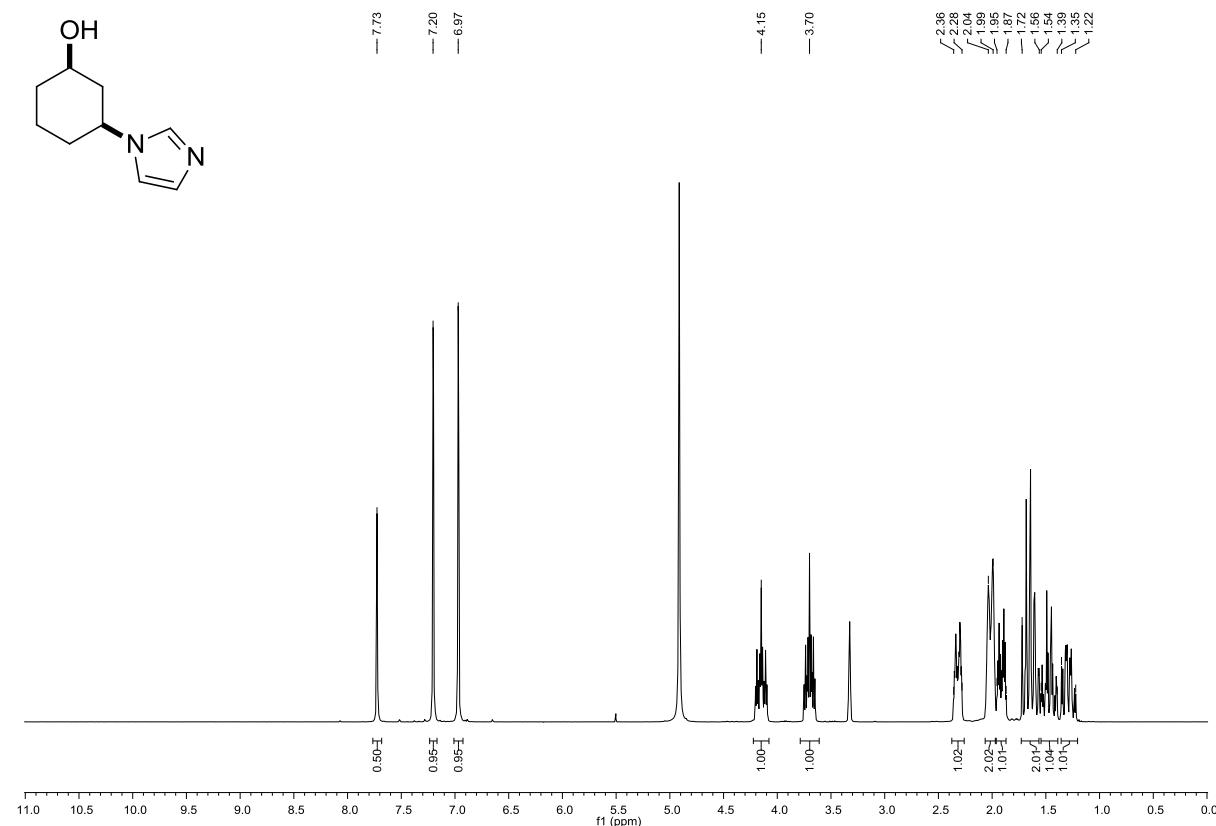
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )



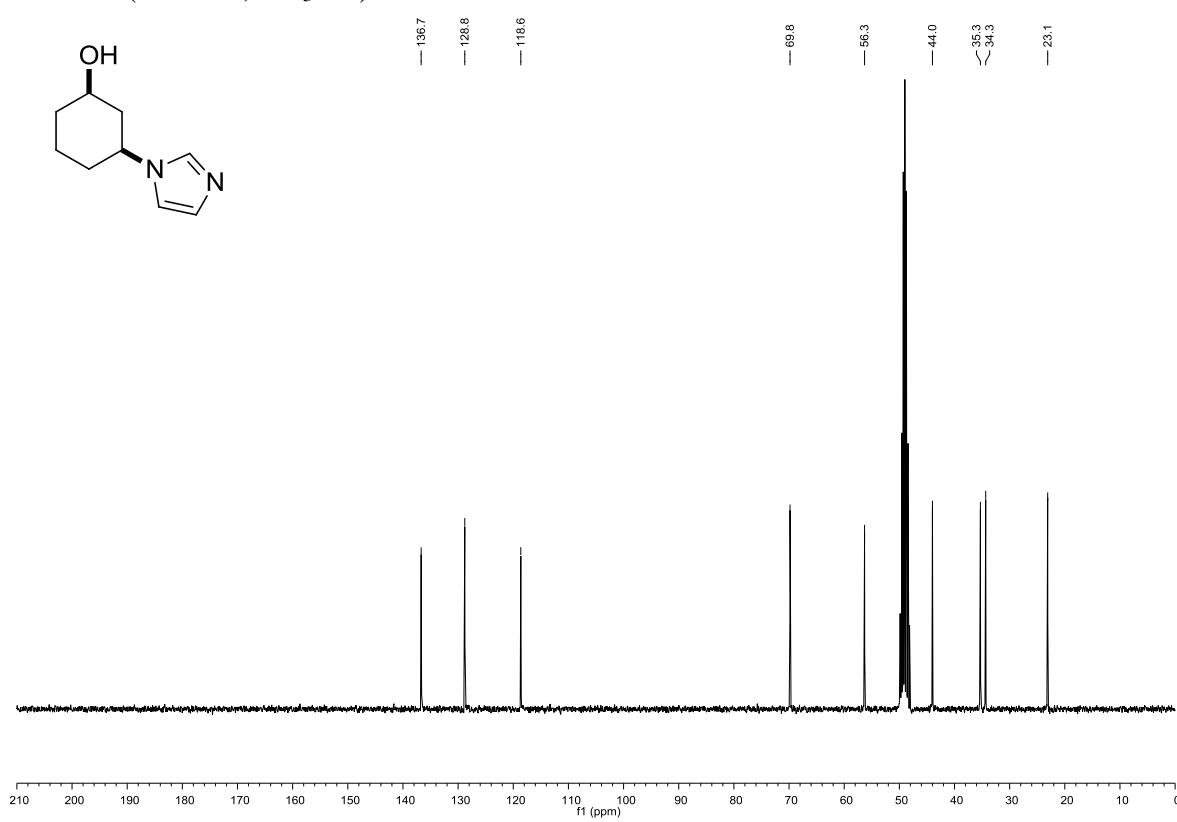
DEPT-135 NMR (75 MHz, CDCl<sub>3</sub>)



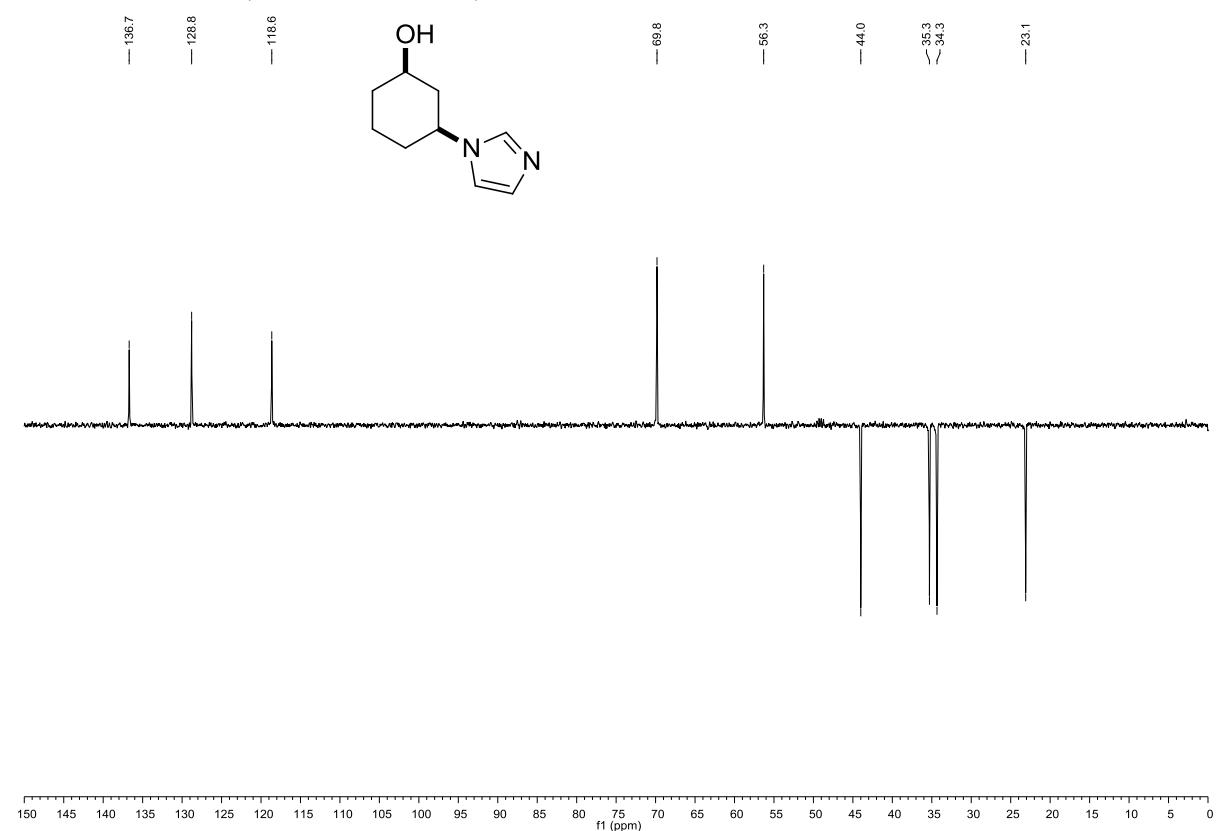
**( $\pm$ )-*cis*-3-(1*H*-Imidazol-1-yl)cyclohexanol [ $(\pm)$ -*cis*-4]**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



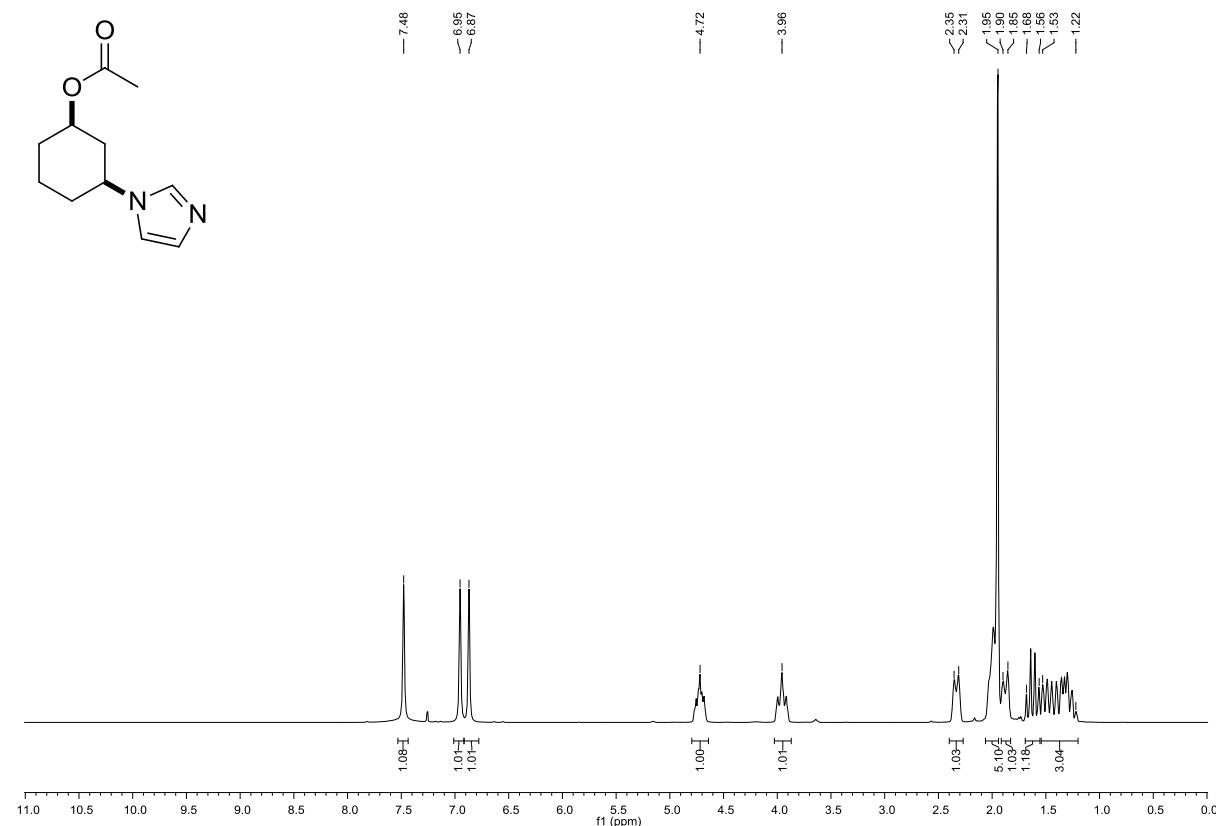
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



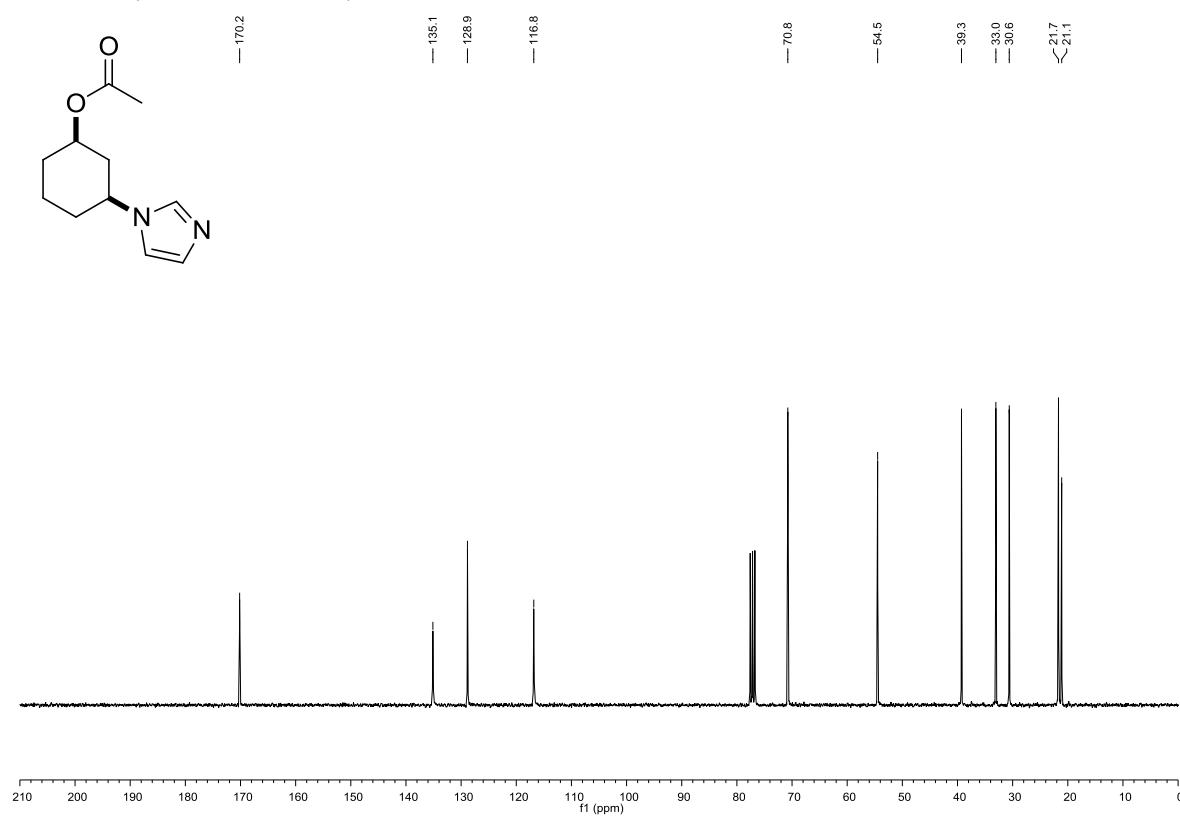
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



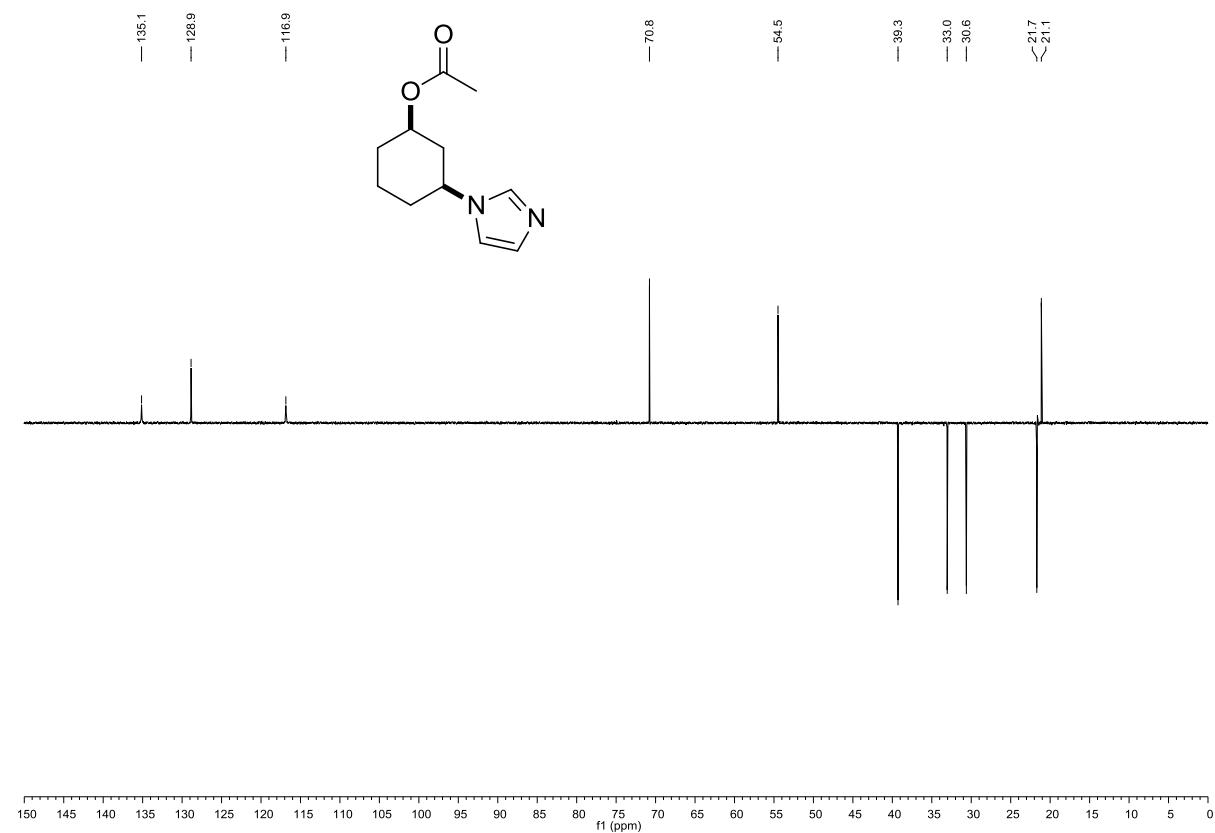
**( $\pm$ )-*cis*-3-(1*H*-Imidazol-1-yl)cyclohexyl acetate [ $(\pm)$ -*cis*-5]**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )



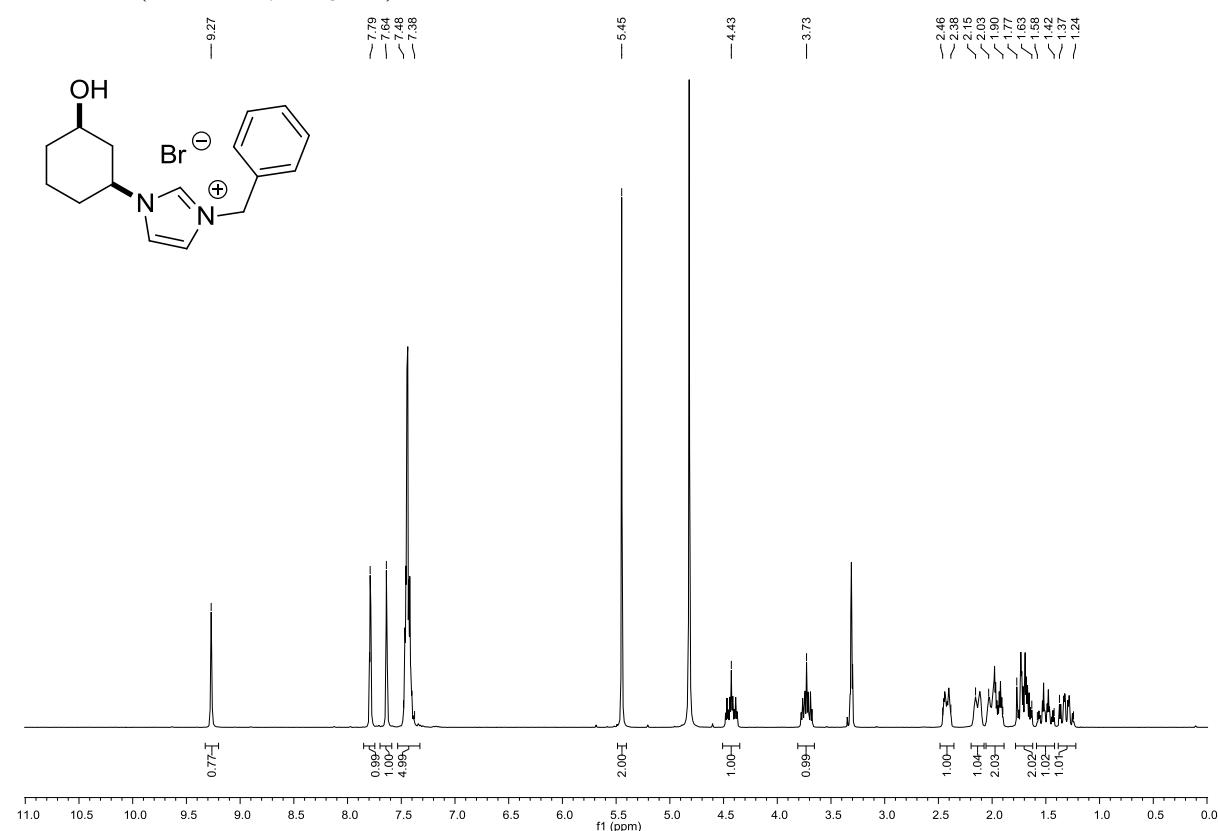
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )



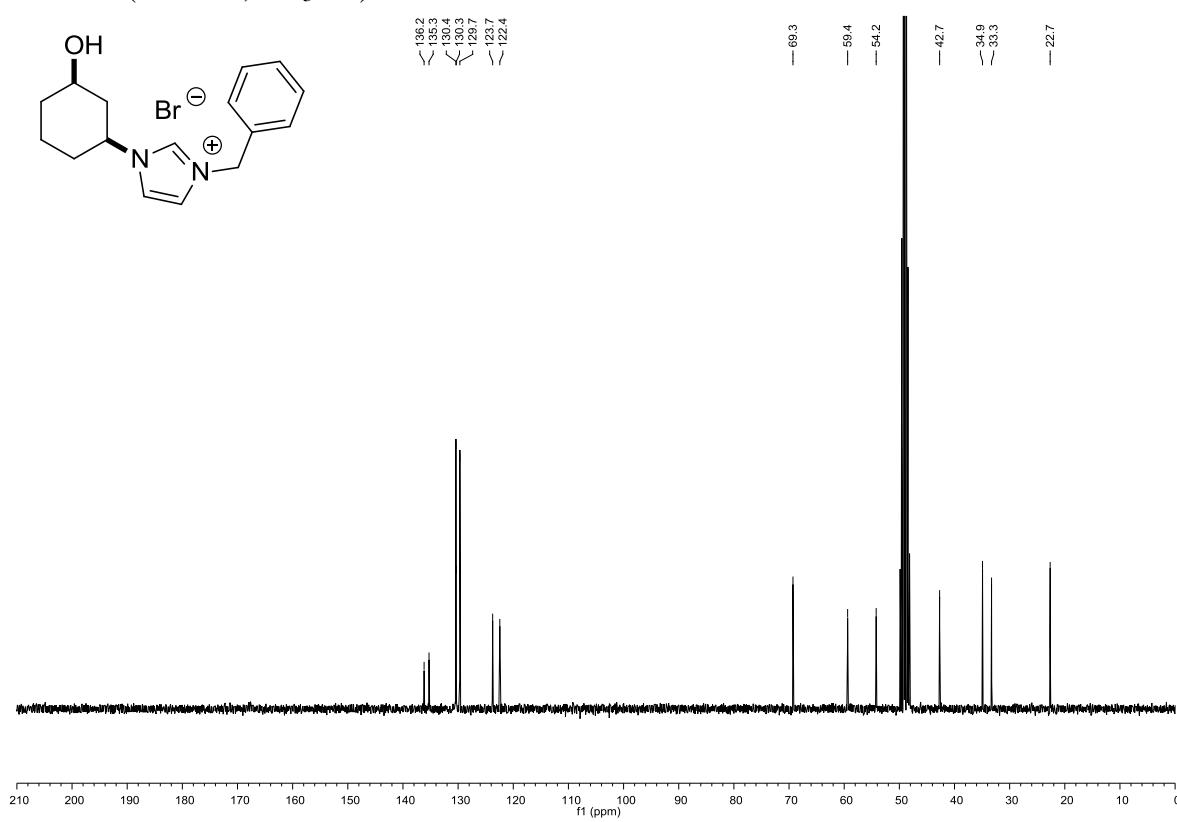
DEPT-135 NMR (75 MHz,  $\text{CDCl}_3$ )



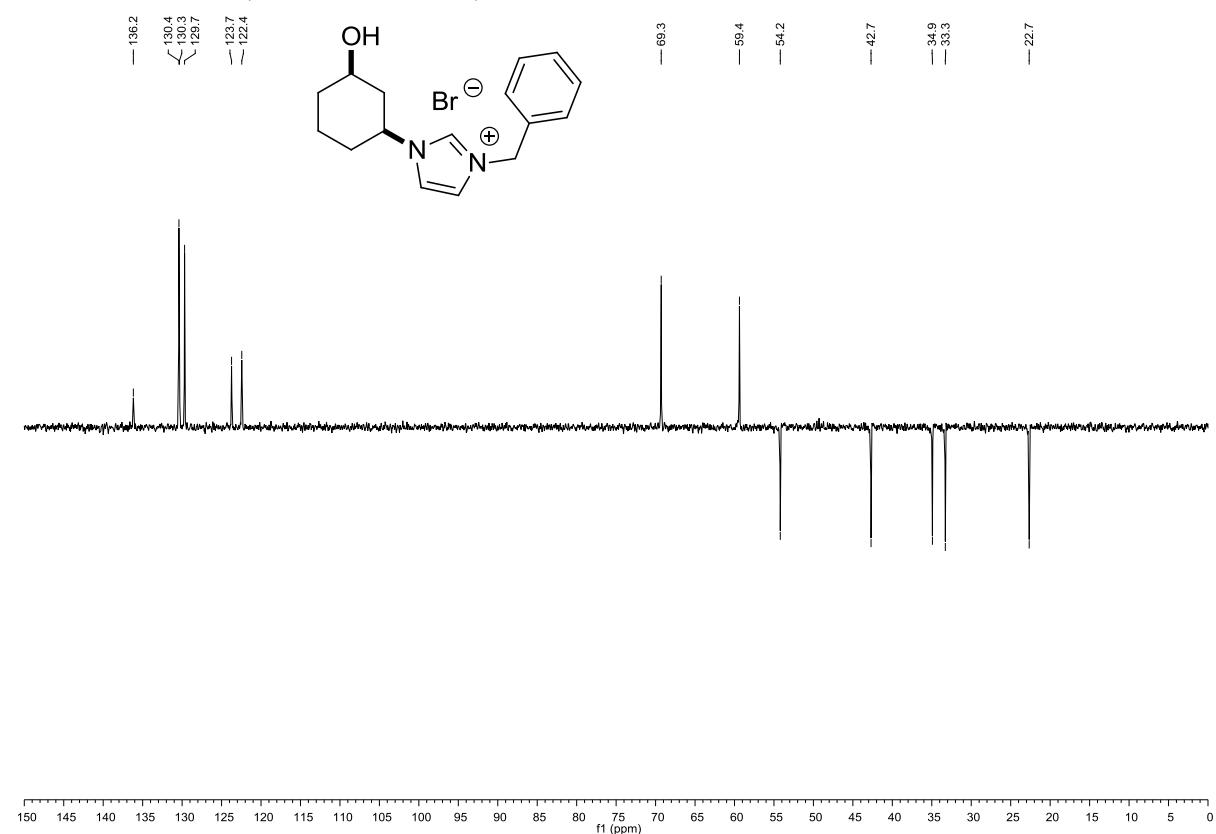
**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



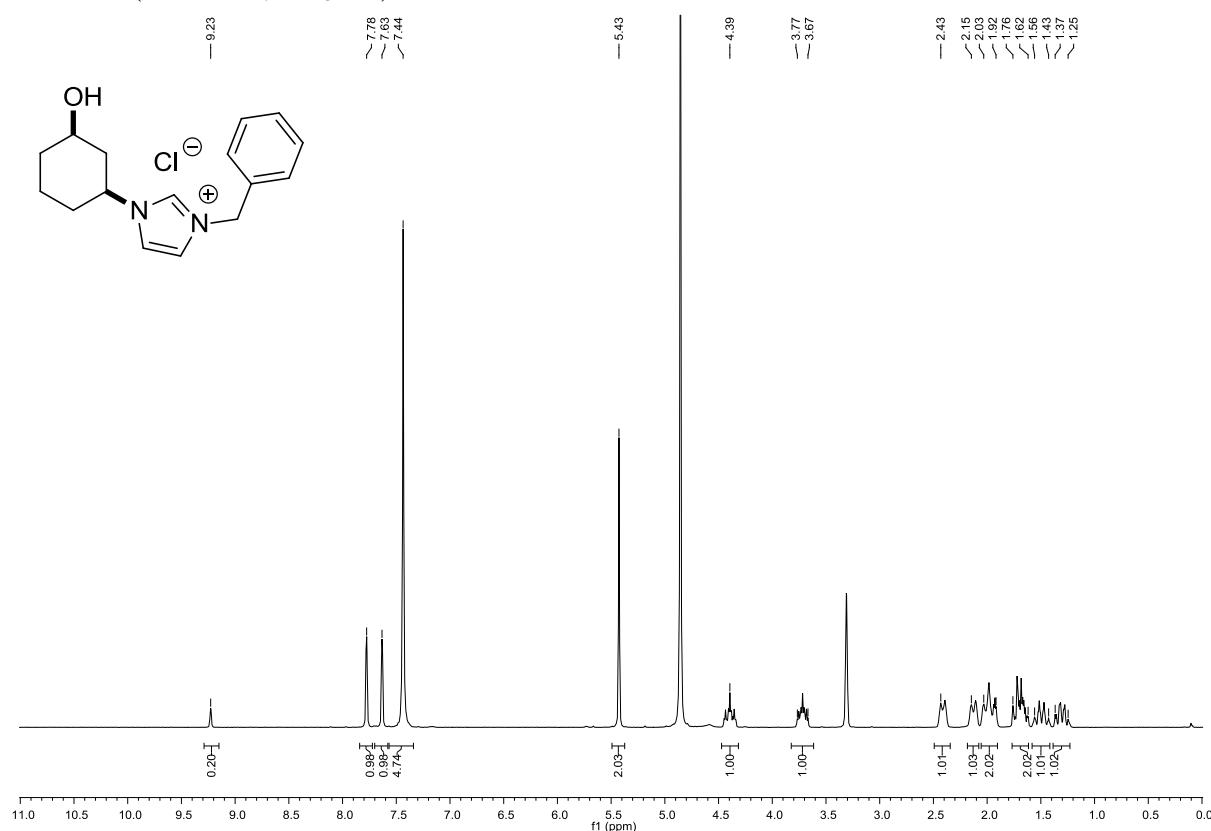
<sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)



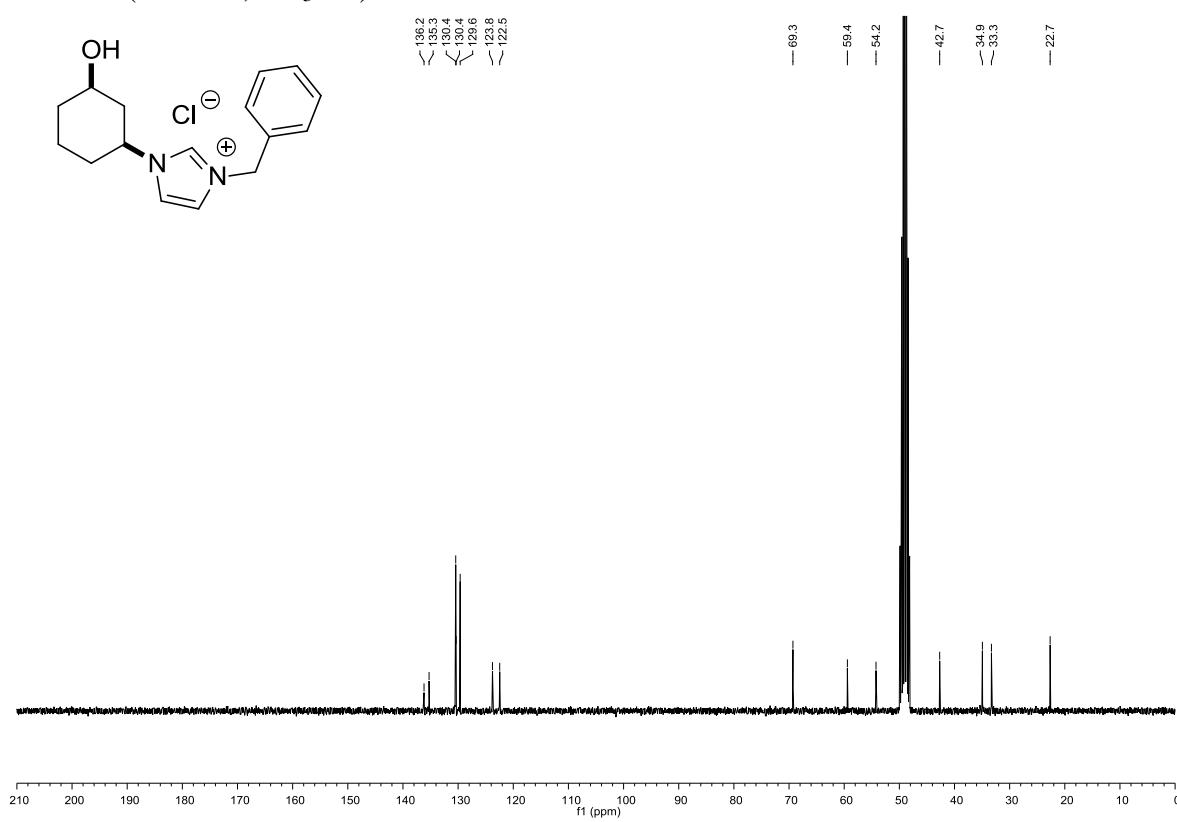
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



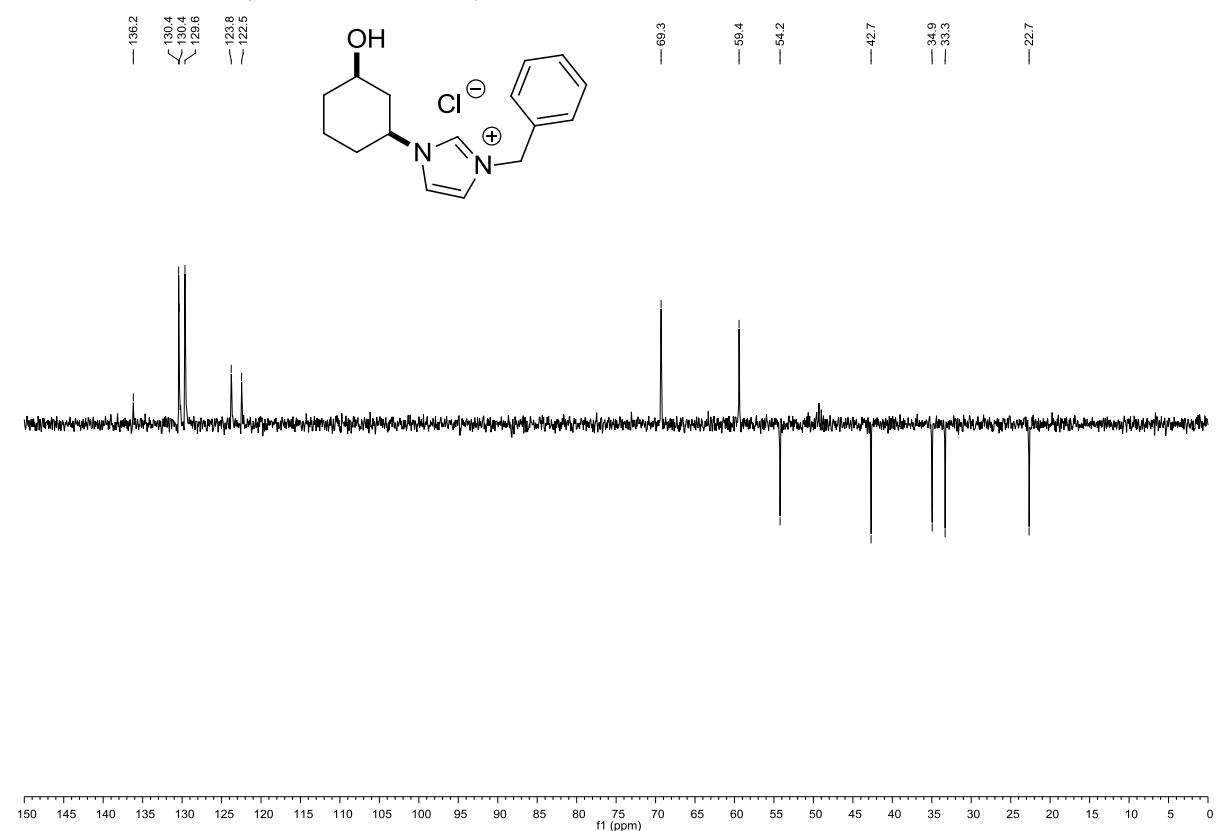
**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride**  
 $^1\text{H}$  NMR (300 MHz, CD<sub>3</sub>OD)



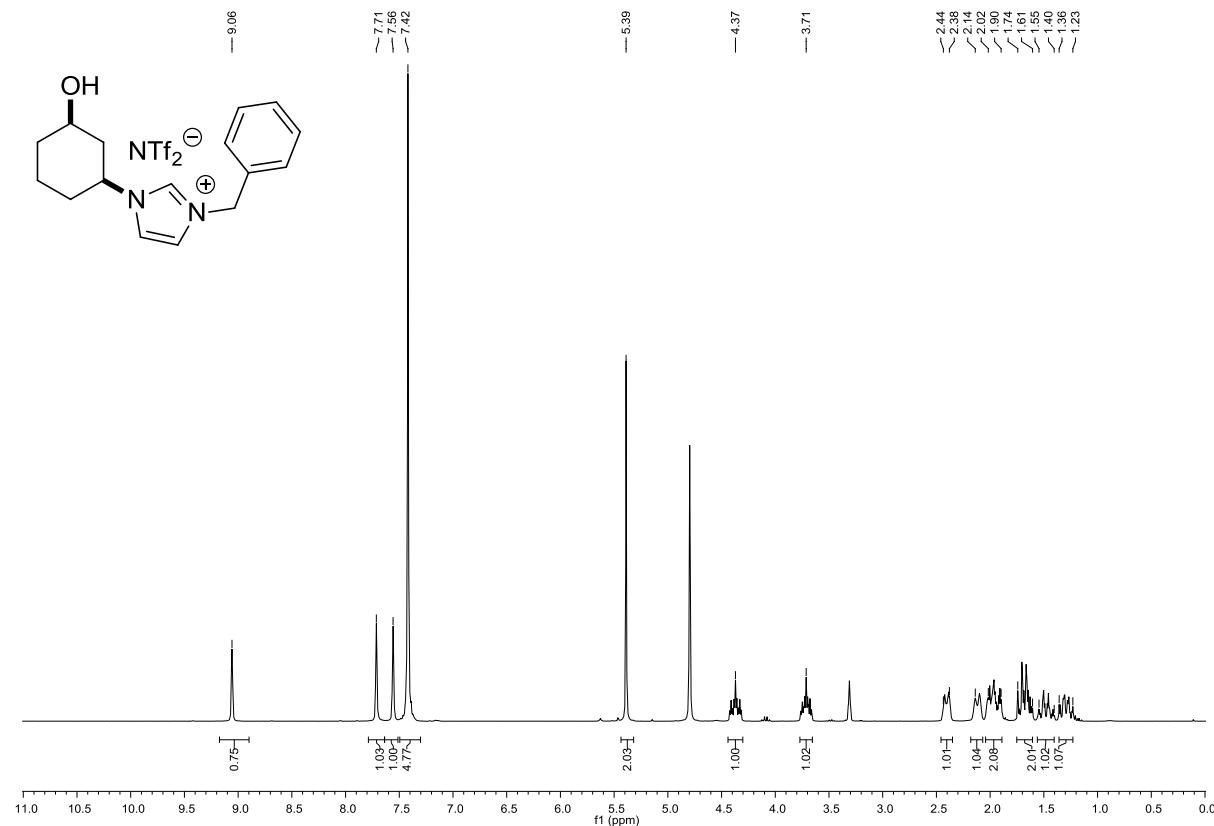
<sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)



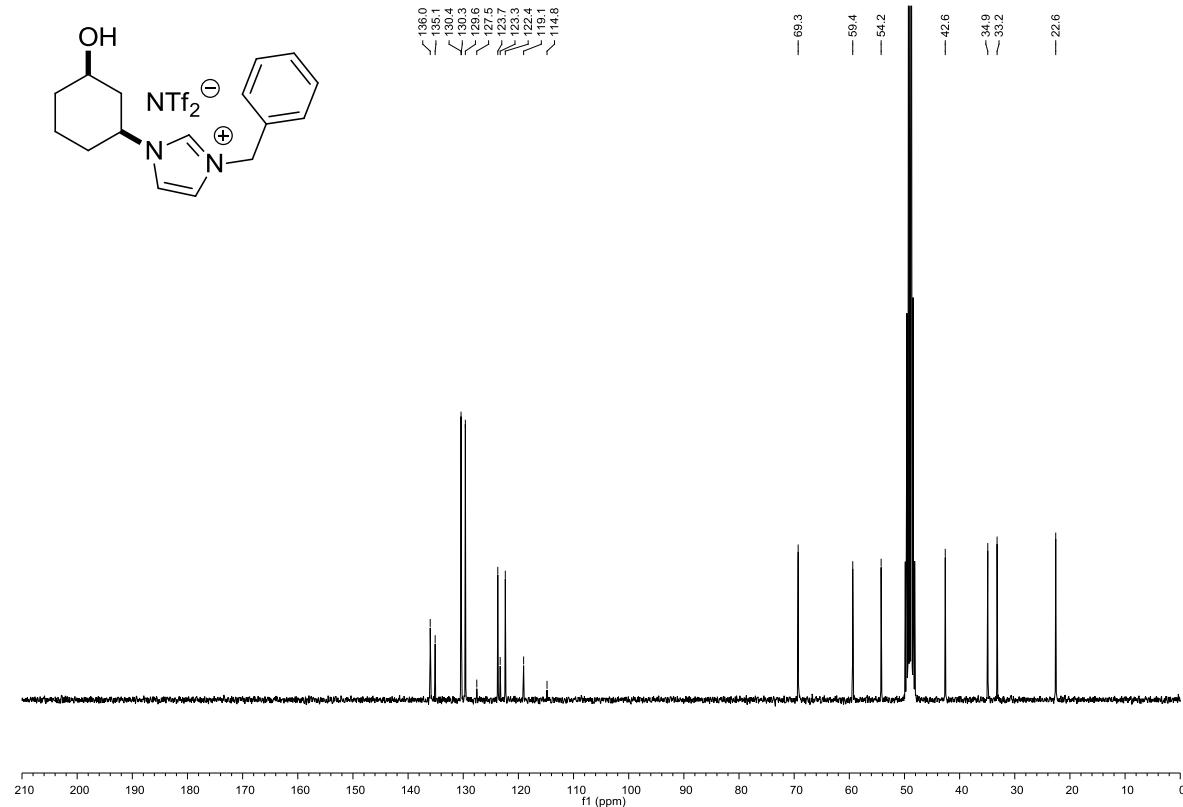
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



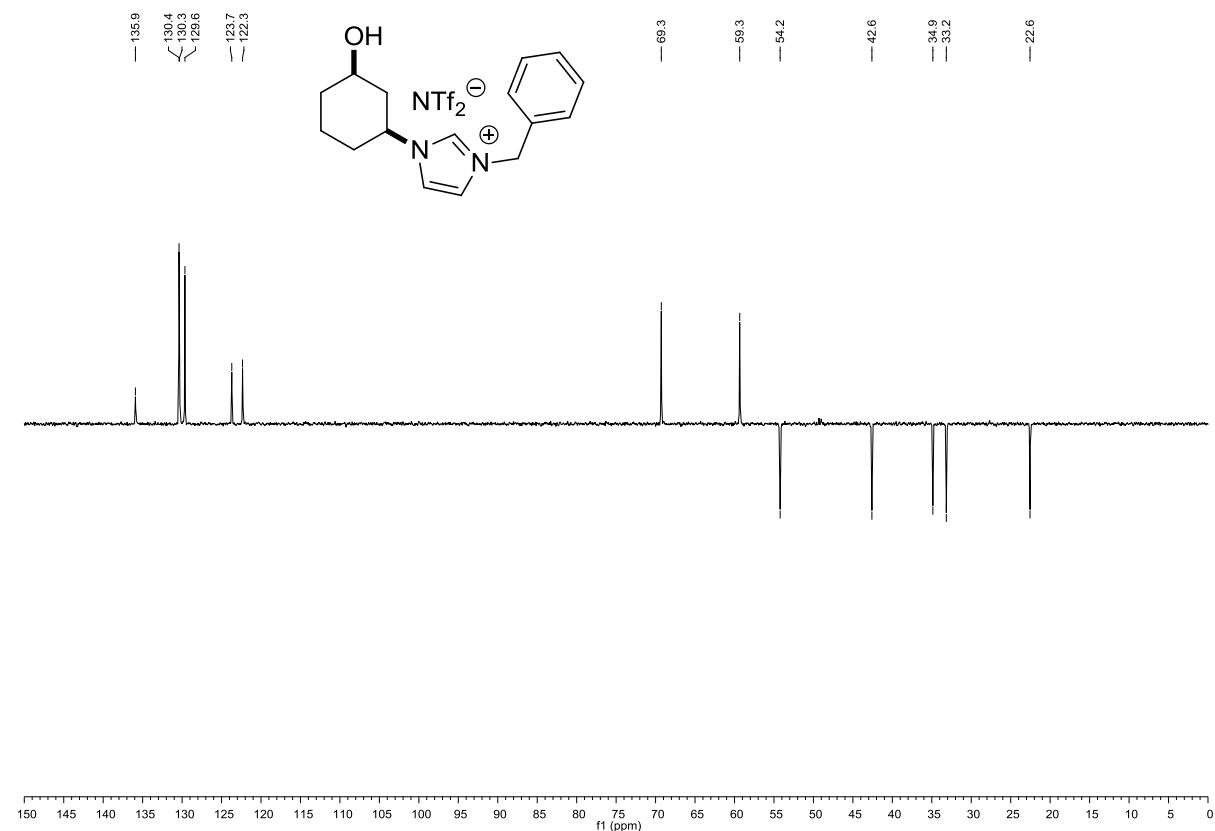
**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium sulfonimide**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



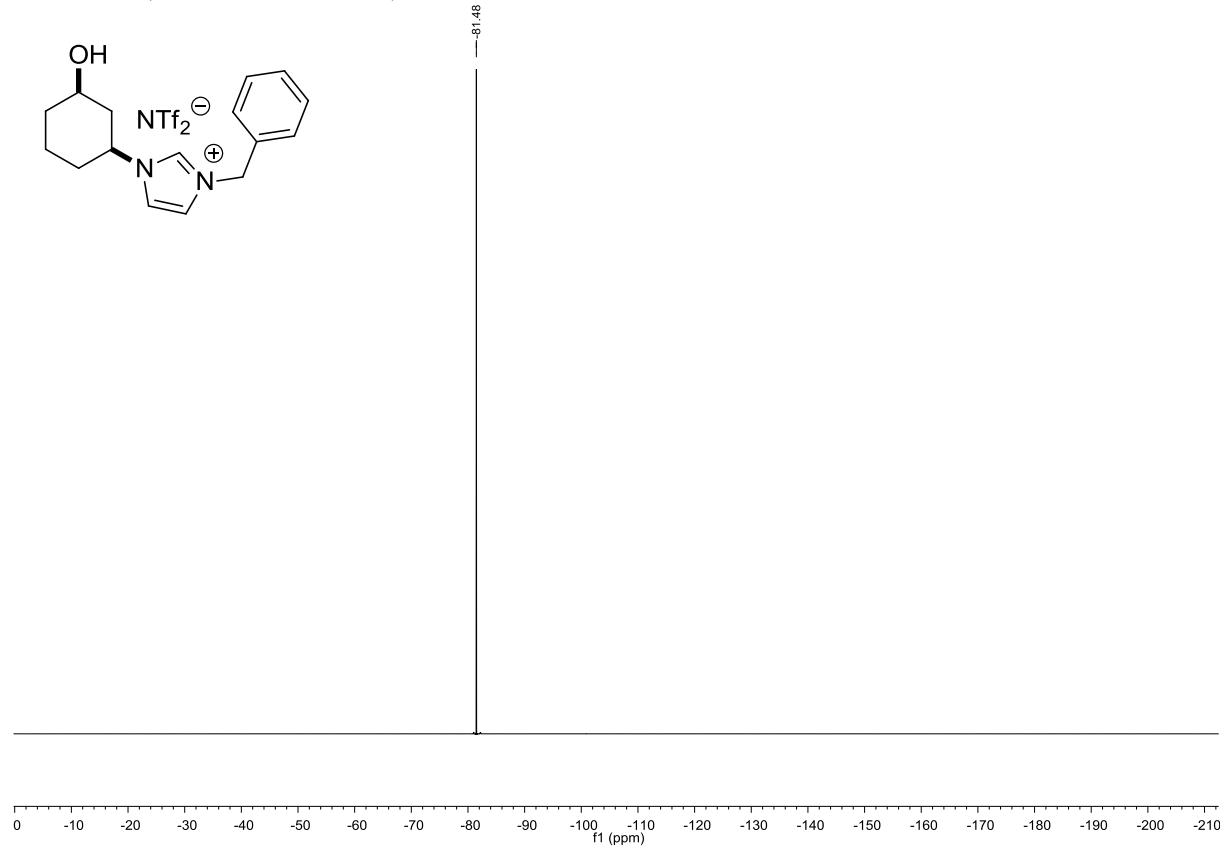
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



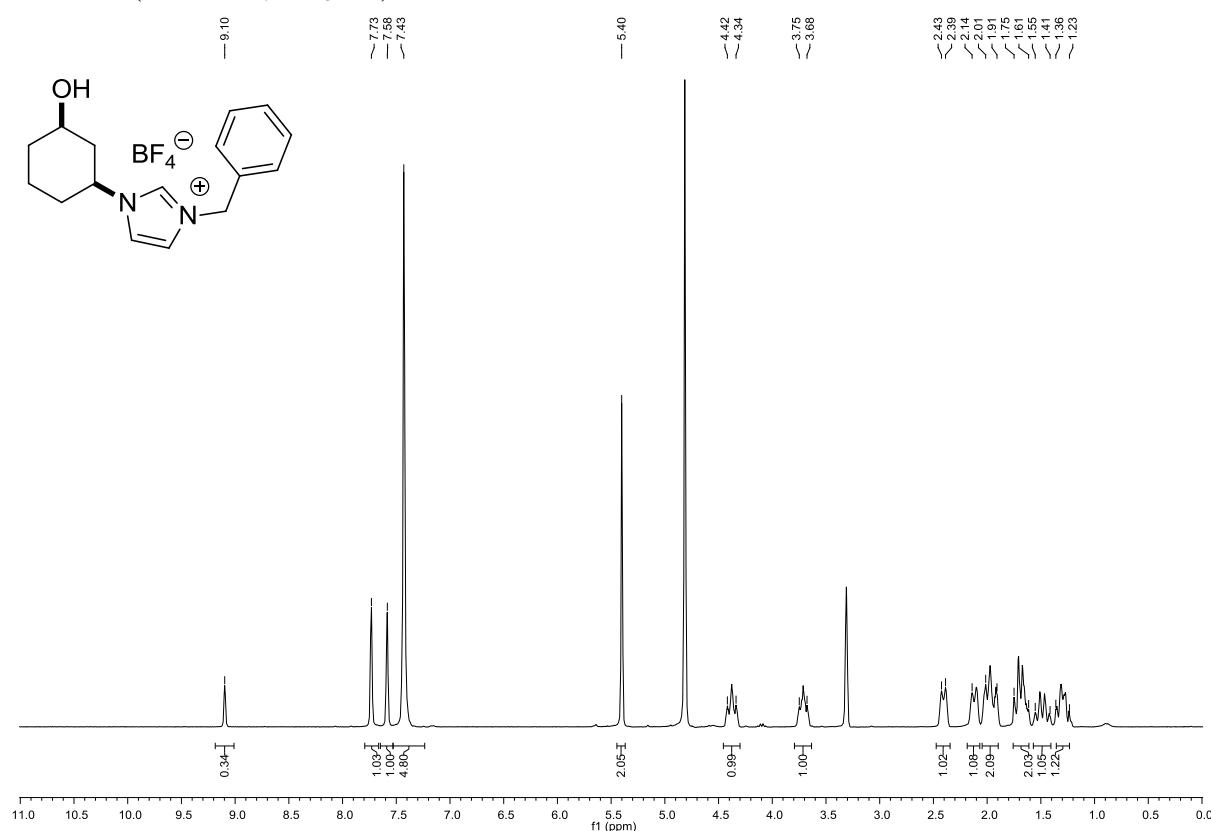
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



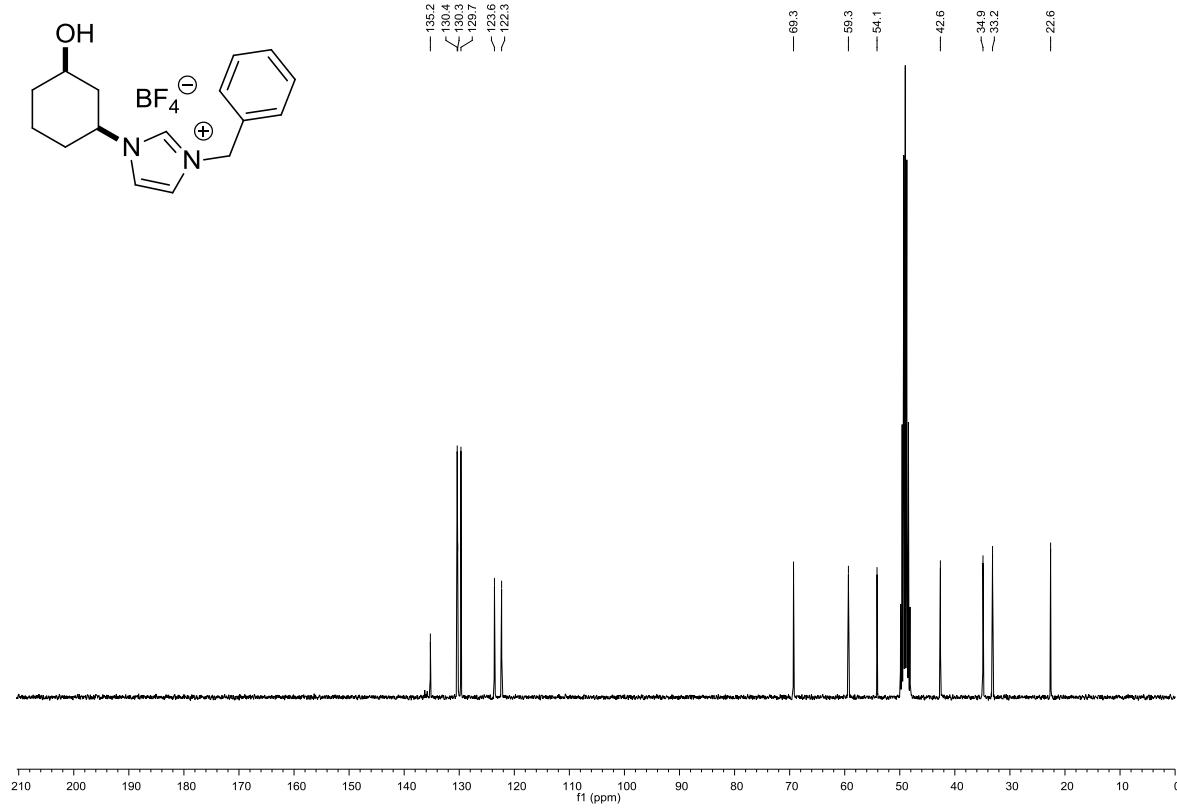
<sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)



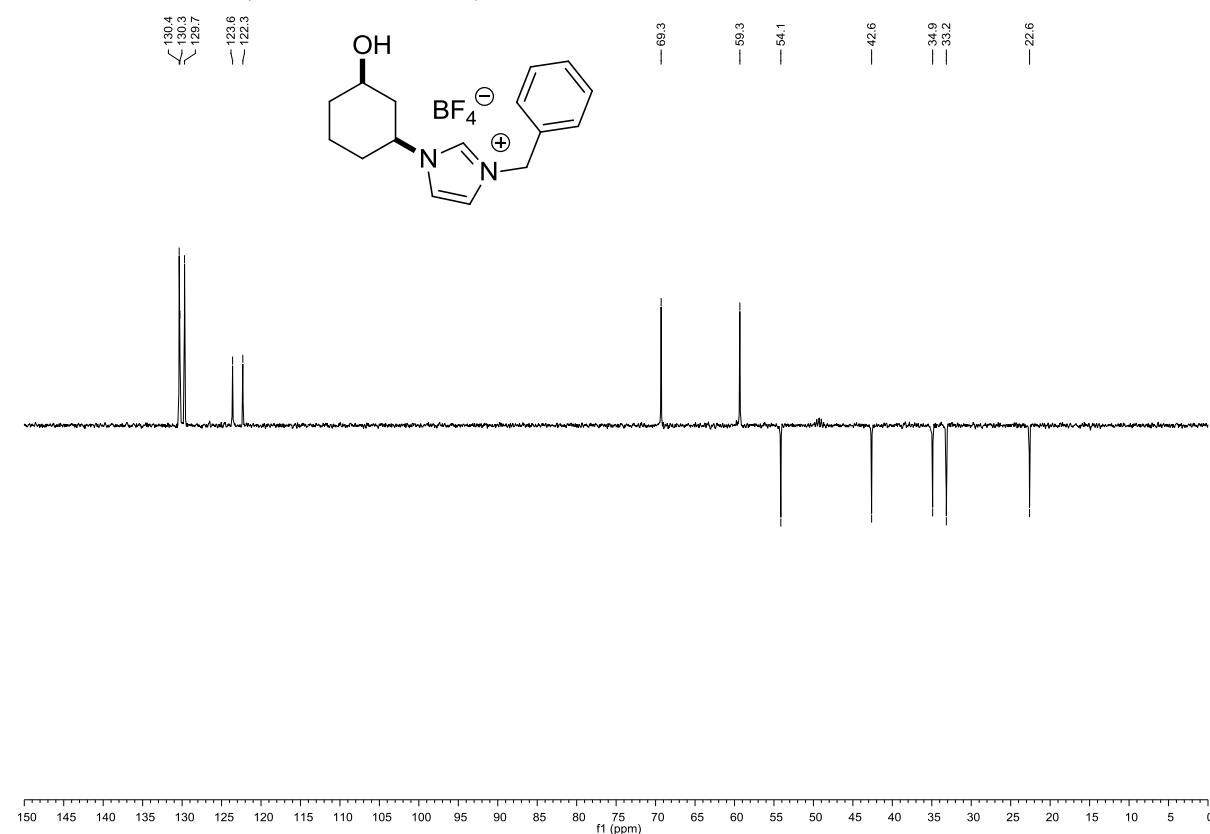
**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



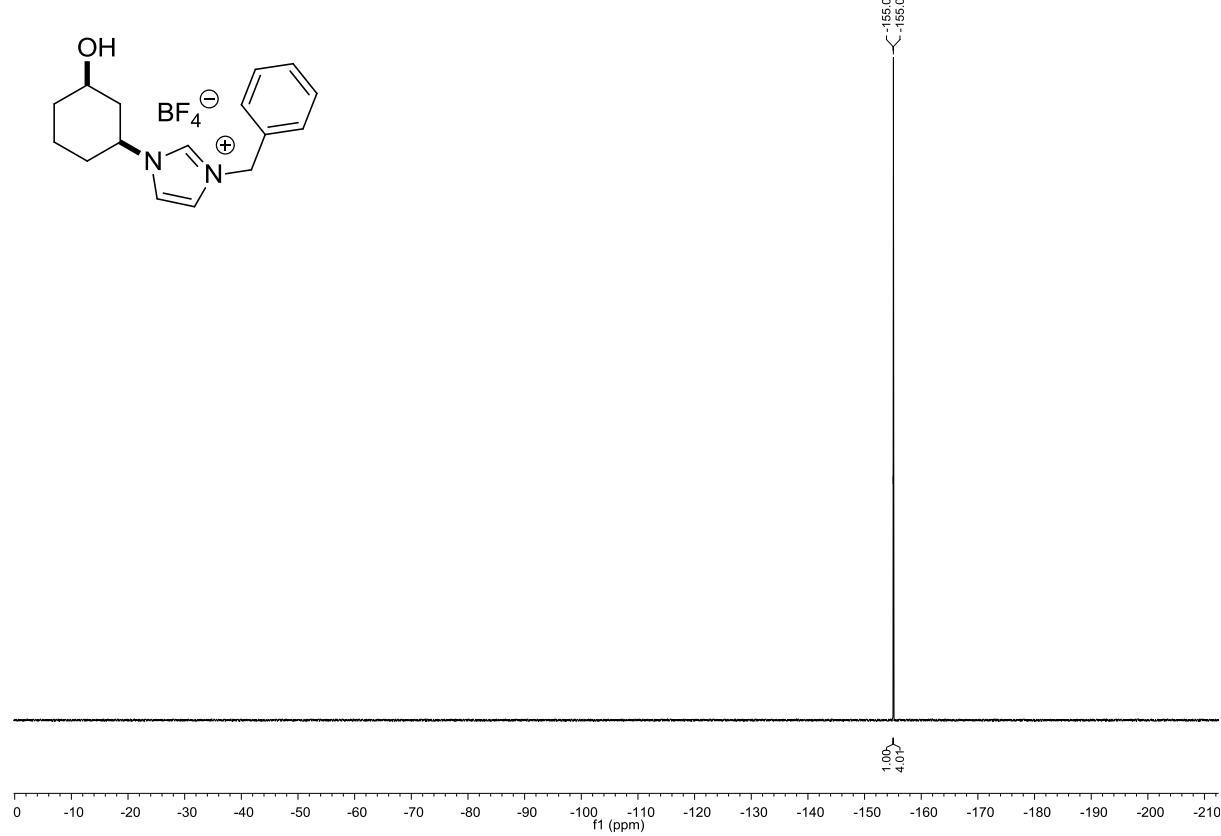
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



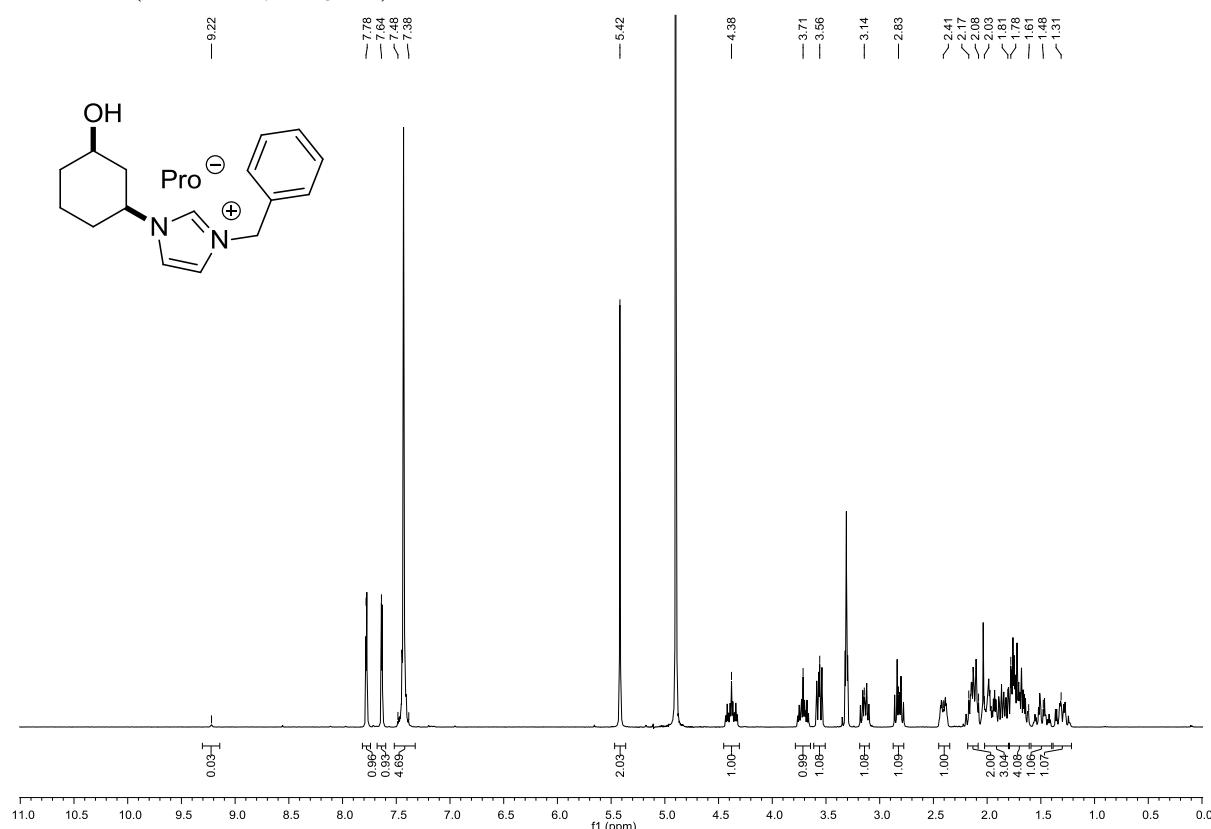
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



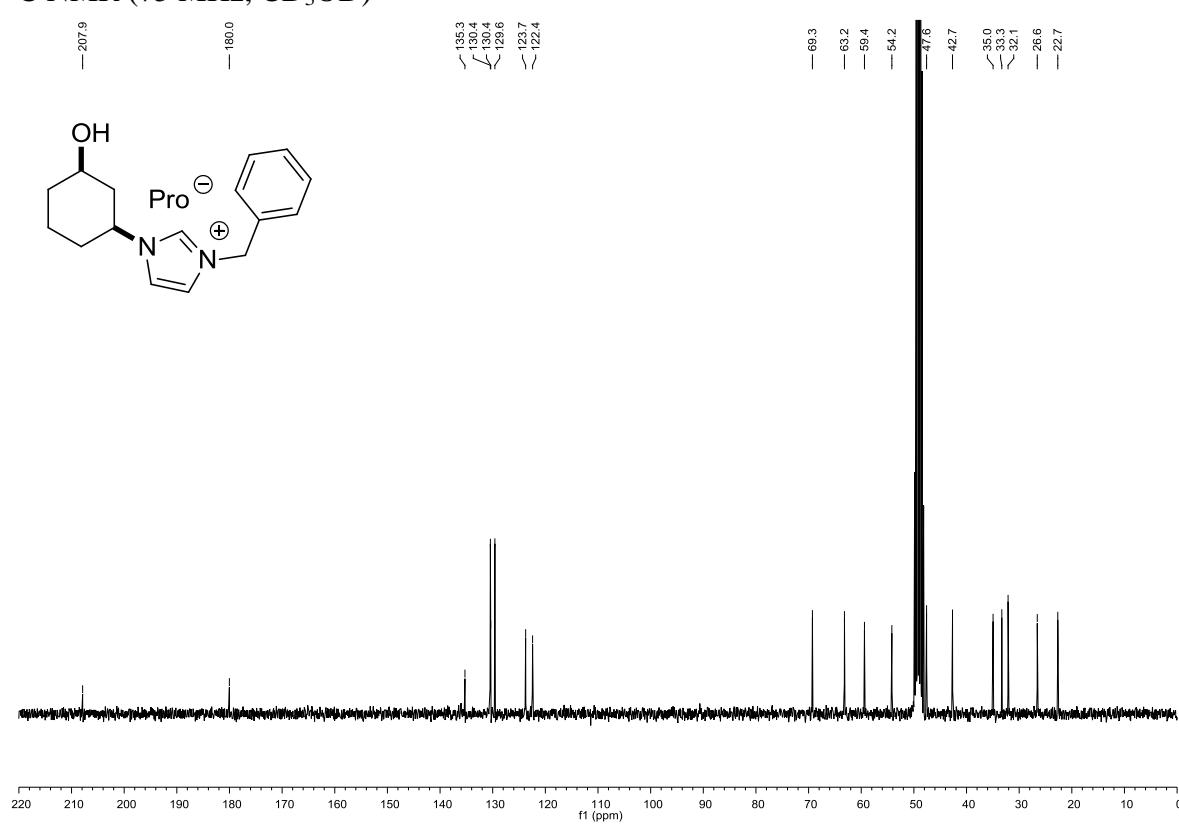
<sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)



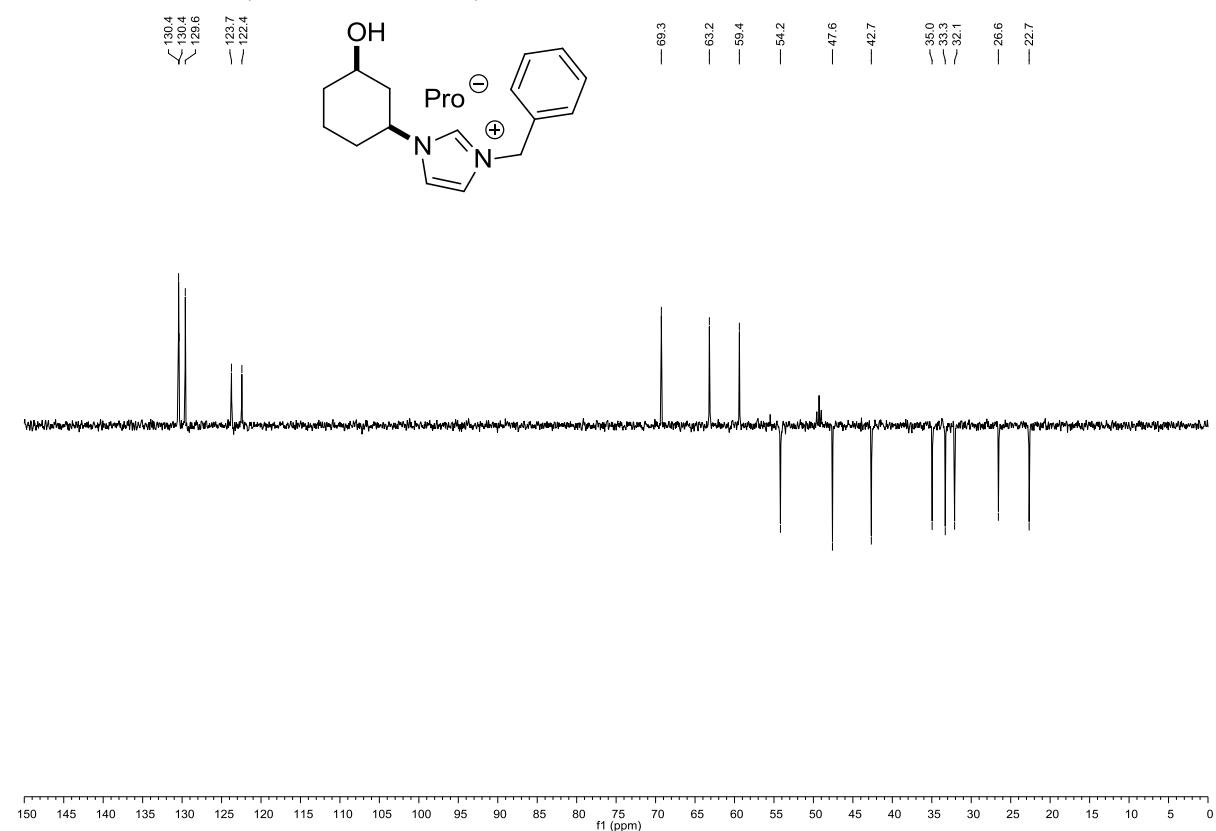
**( $\pm$ )-*cis*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



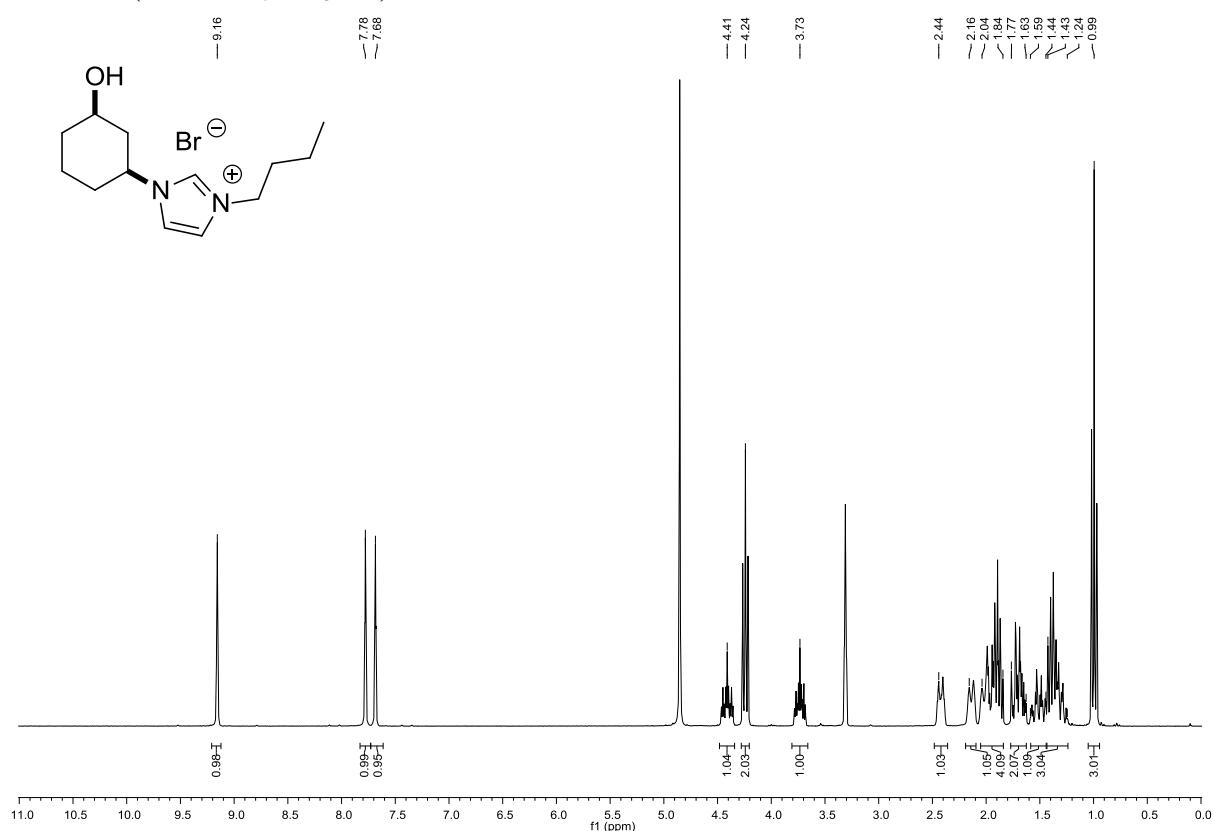
<sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)



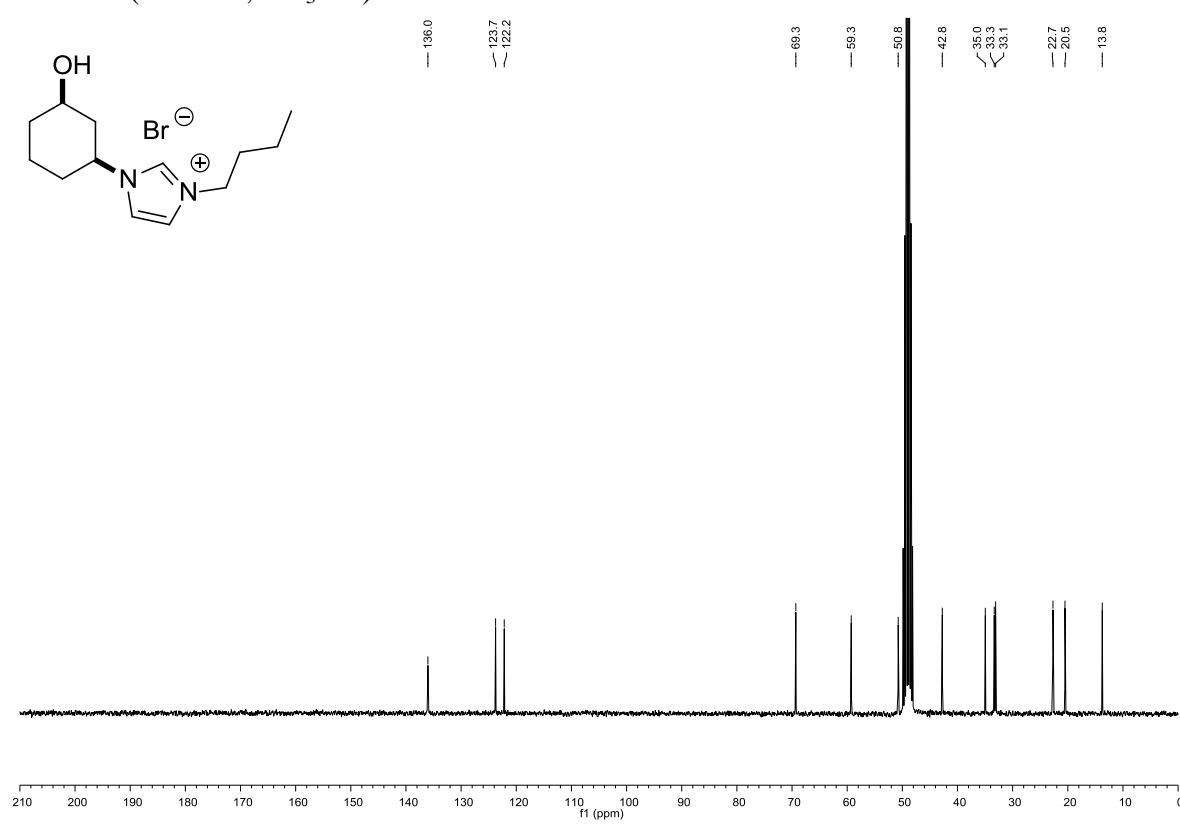
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



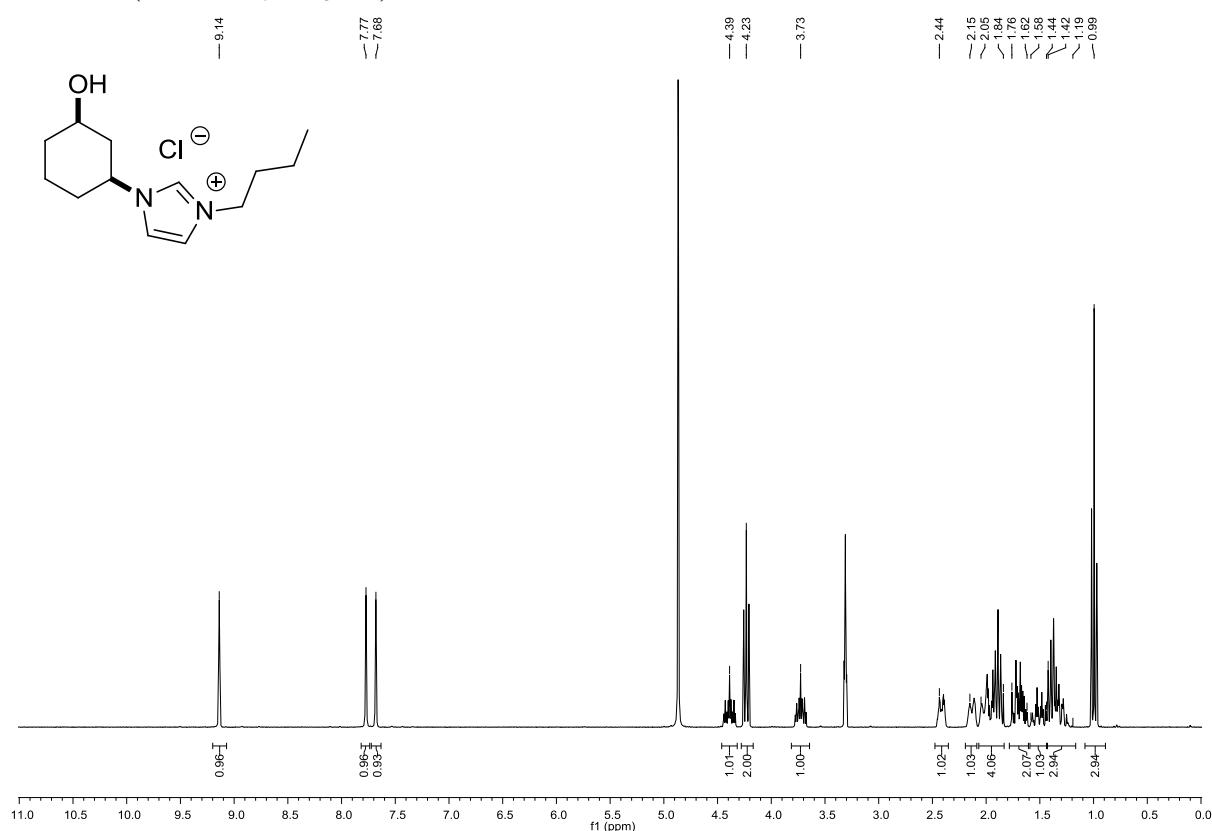
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



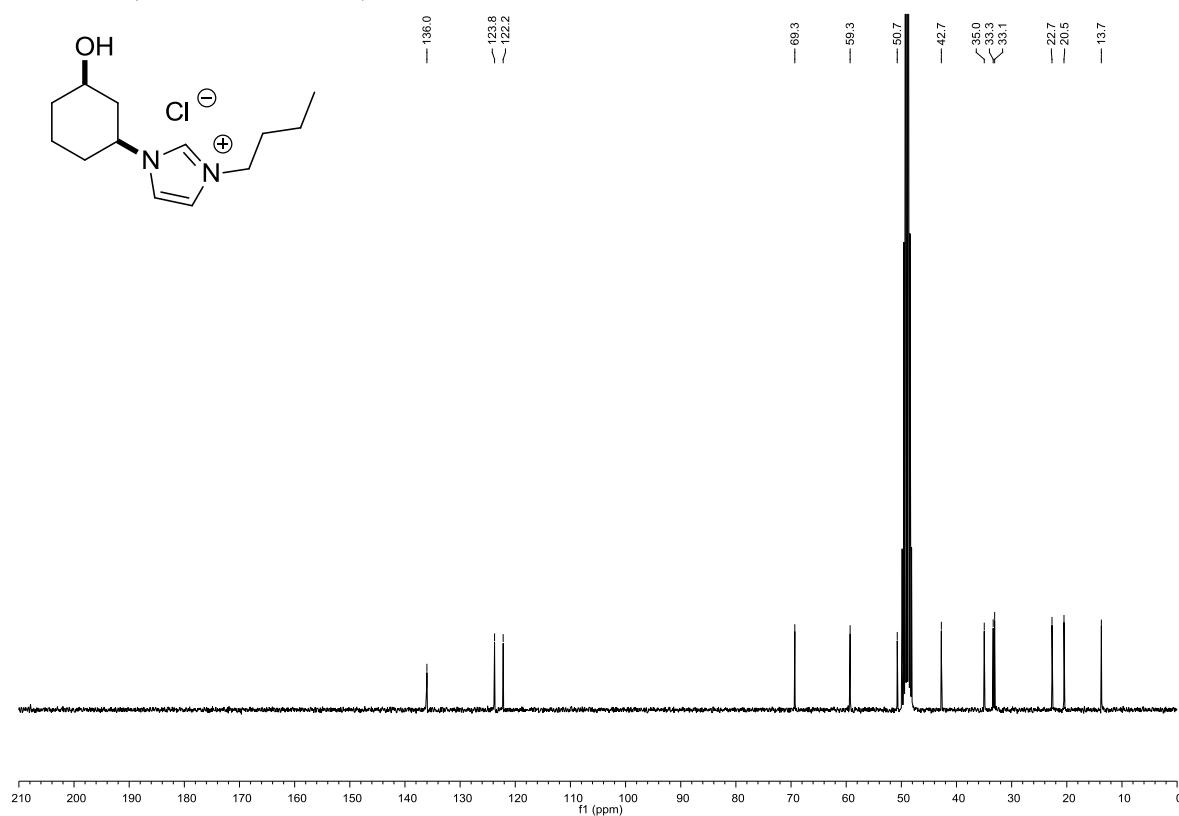
### DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



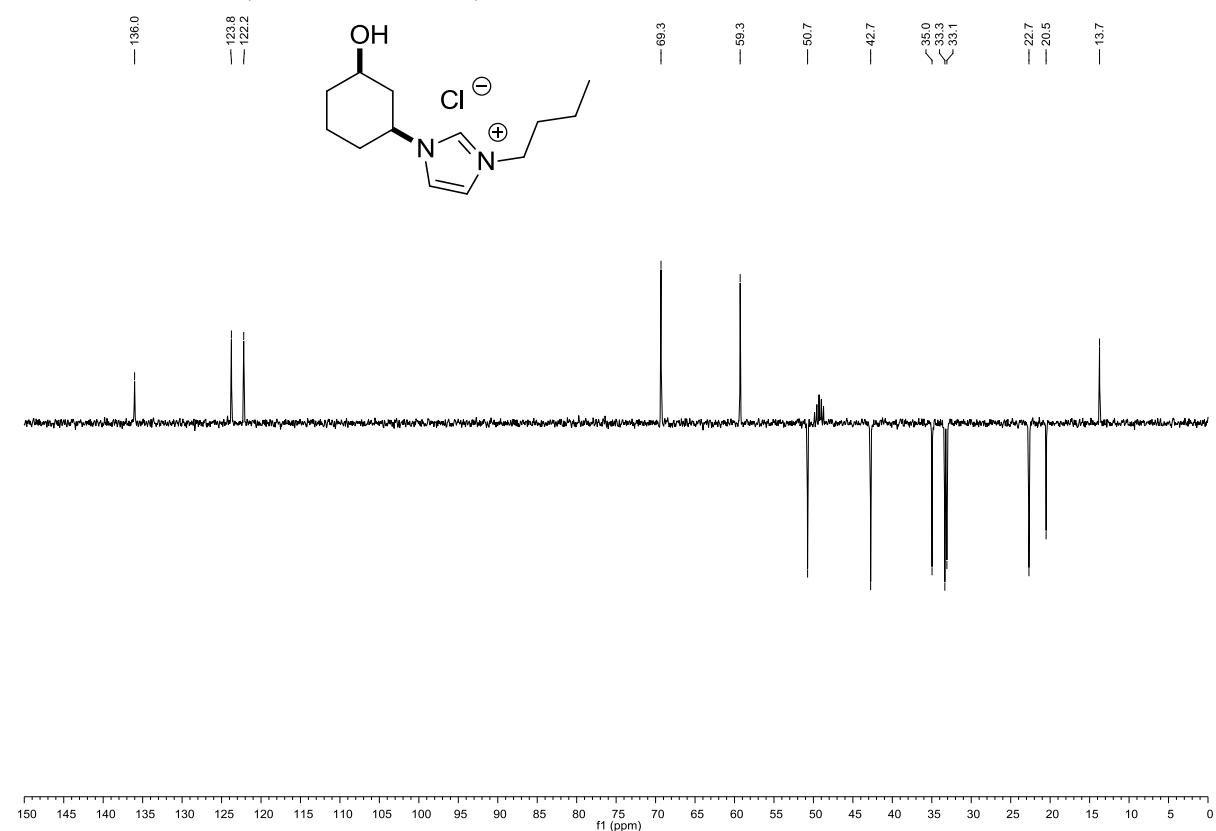
**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )

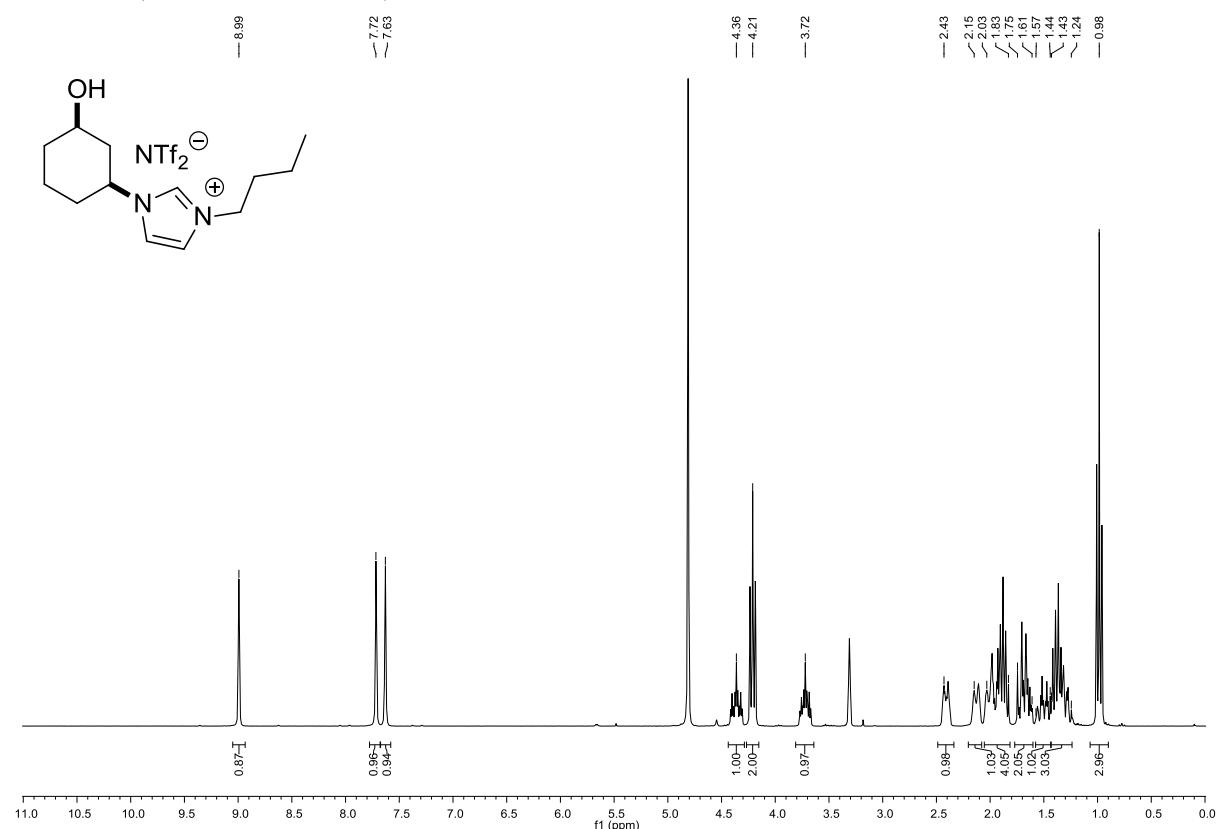


DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)

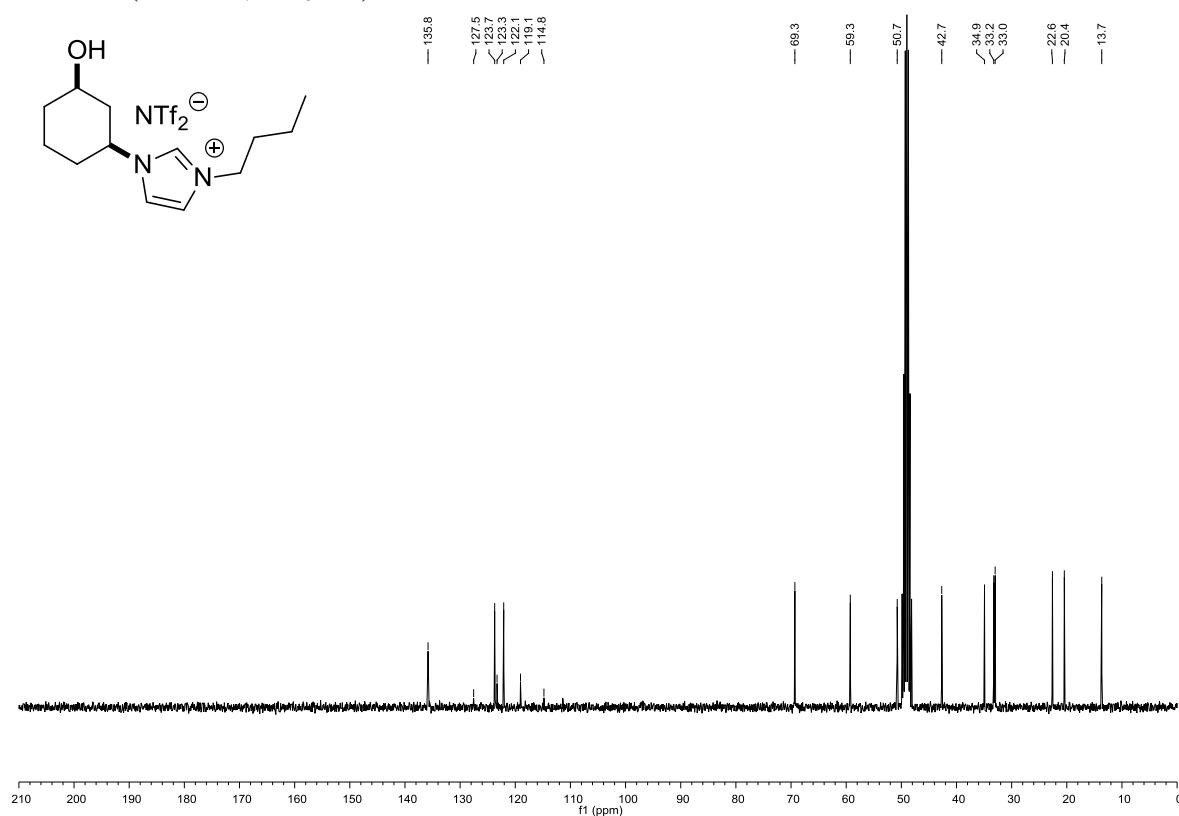


**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium trifluoromethane sulfonimide**

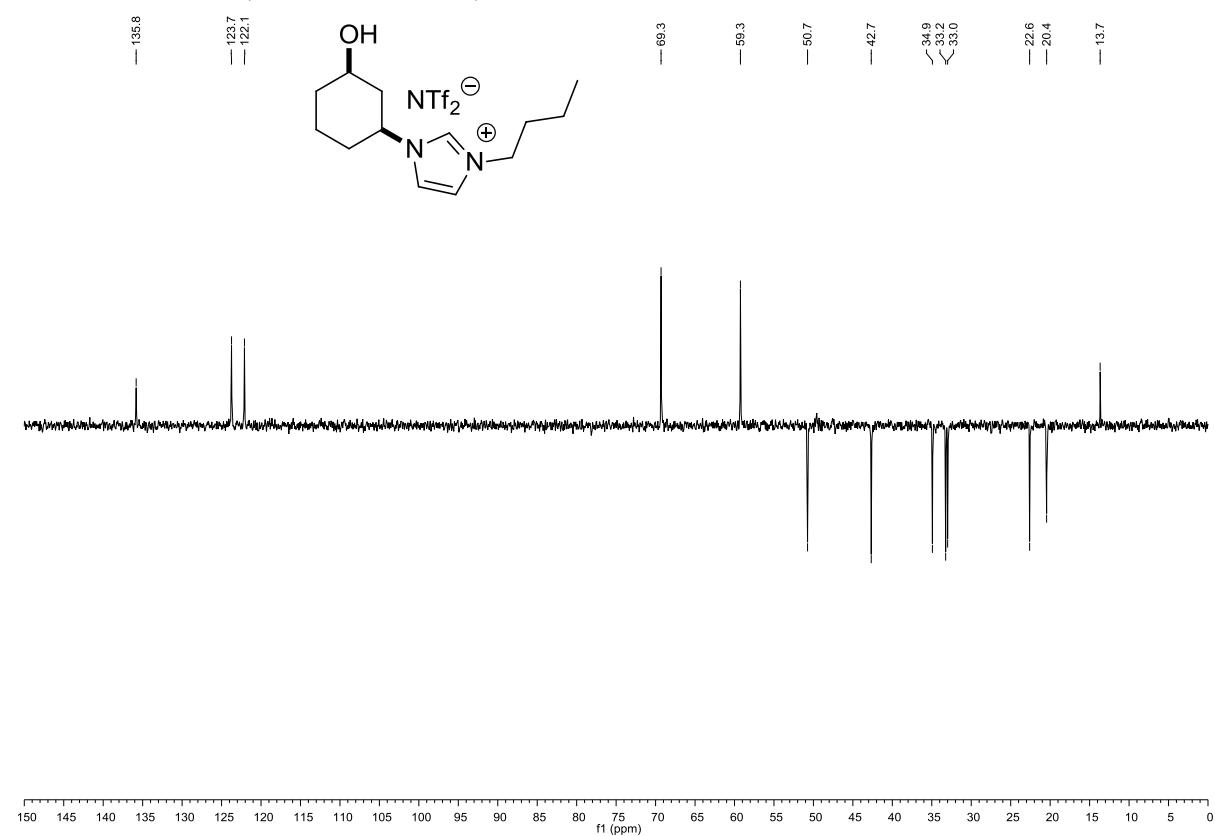
$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



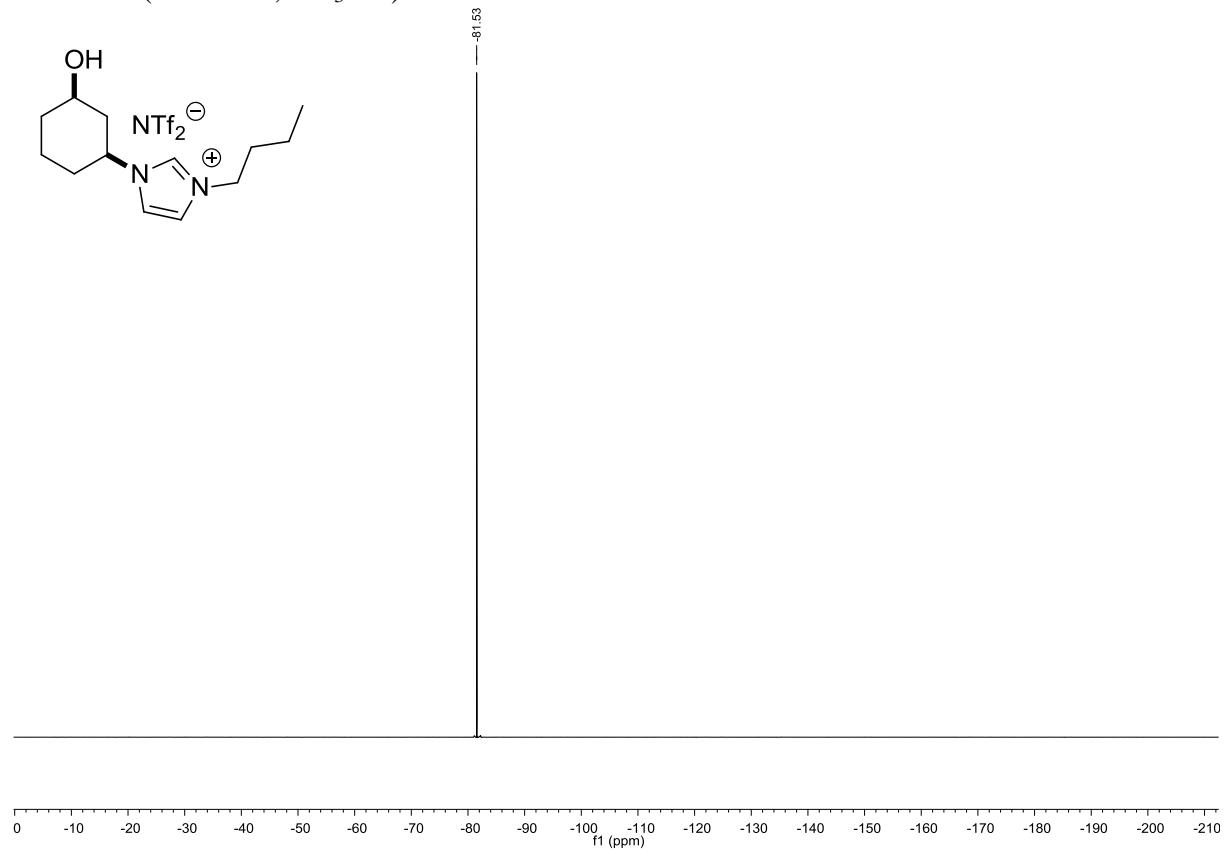
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



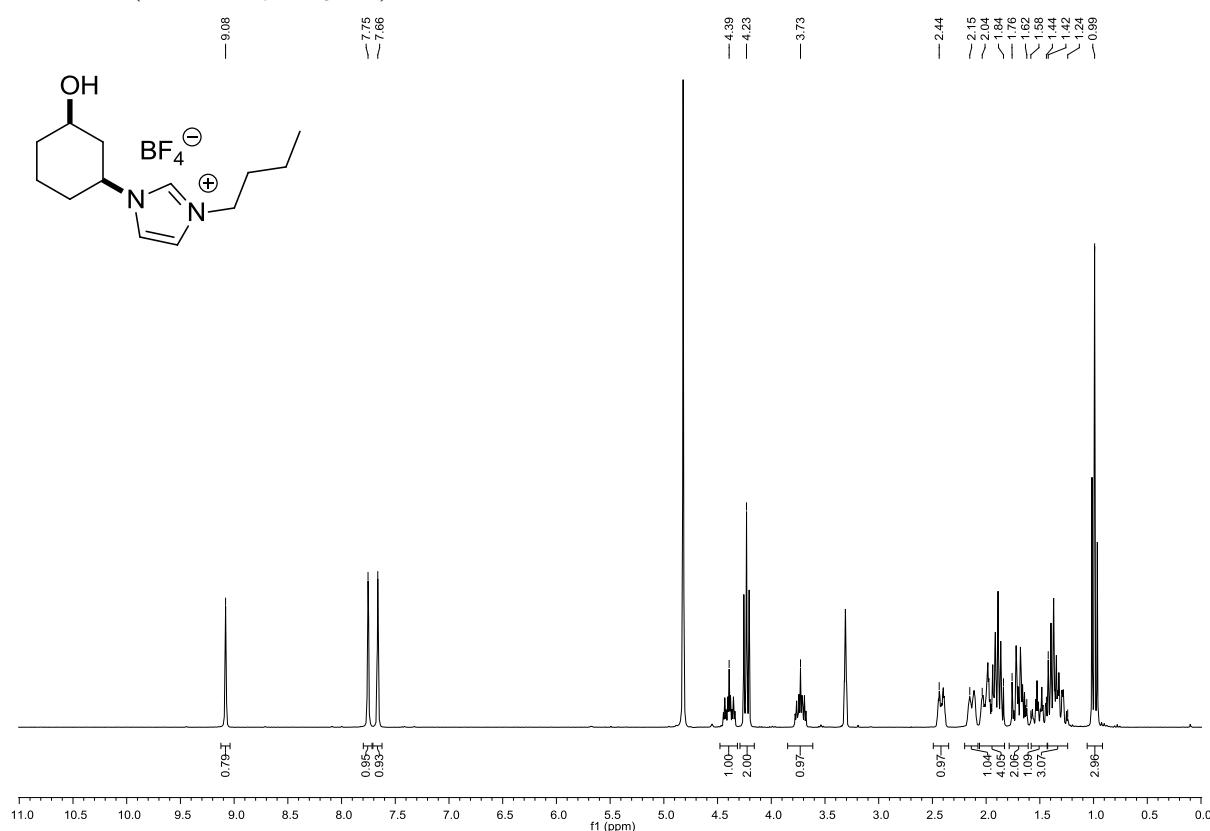
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



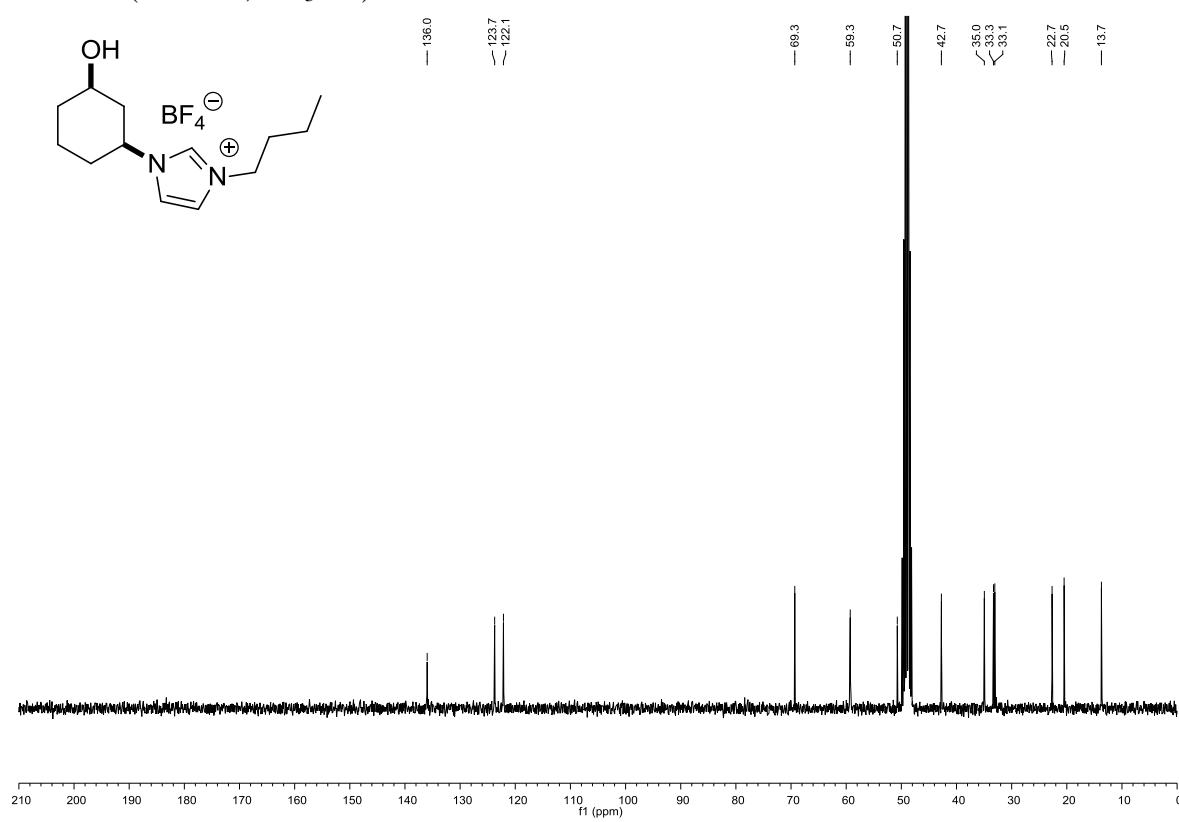
<sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)



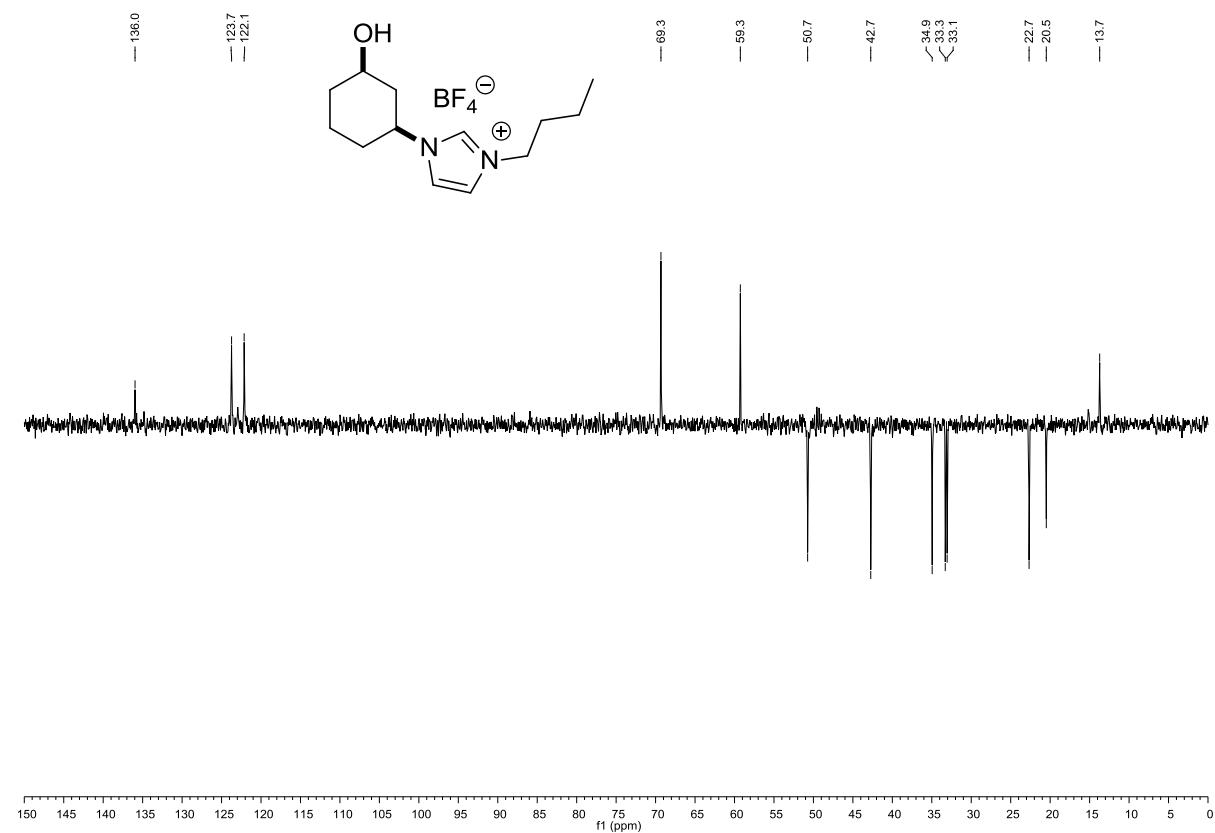
**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



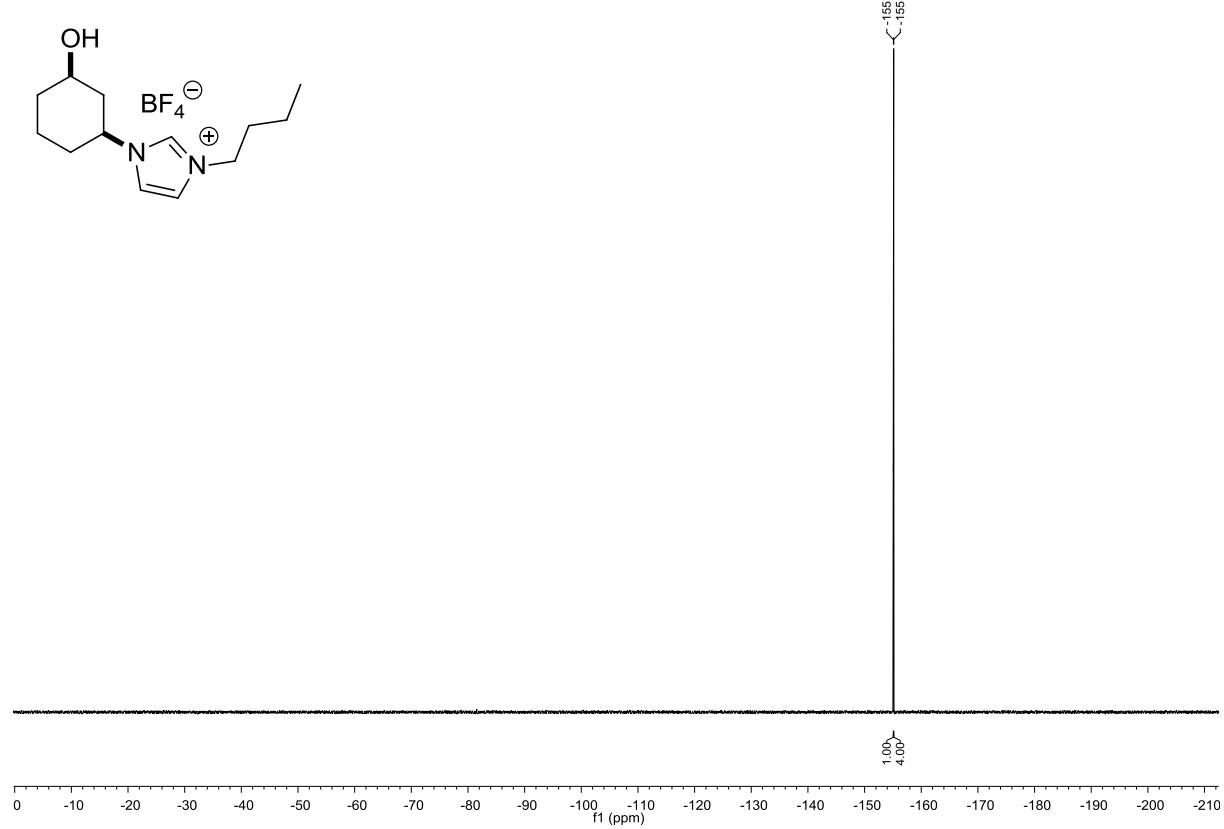
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



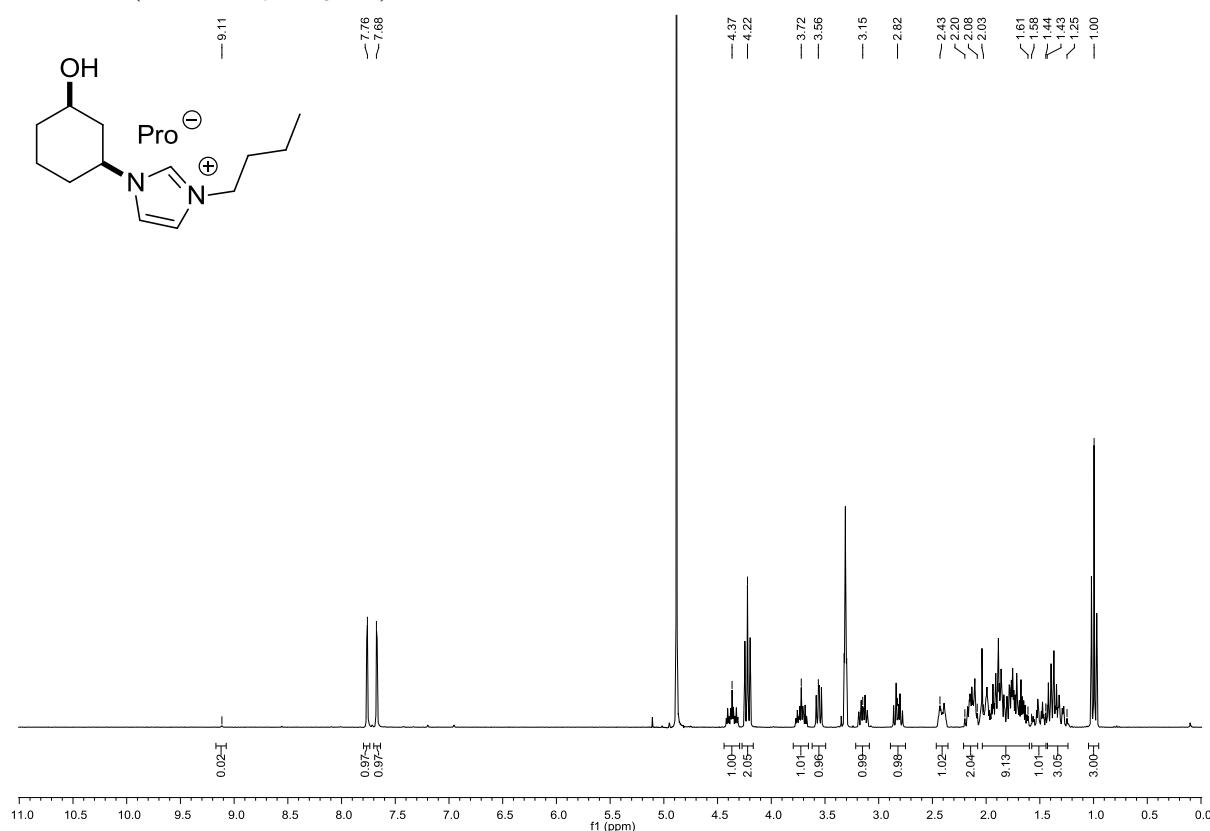
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



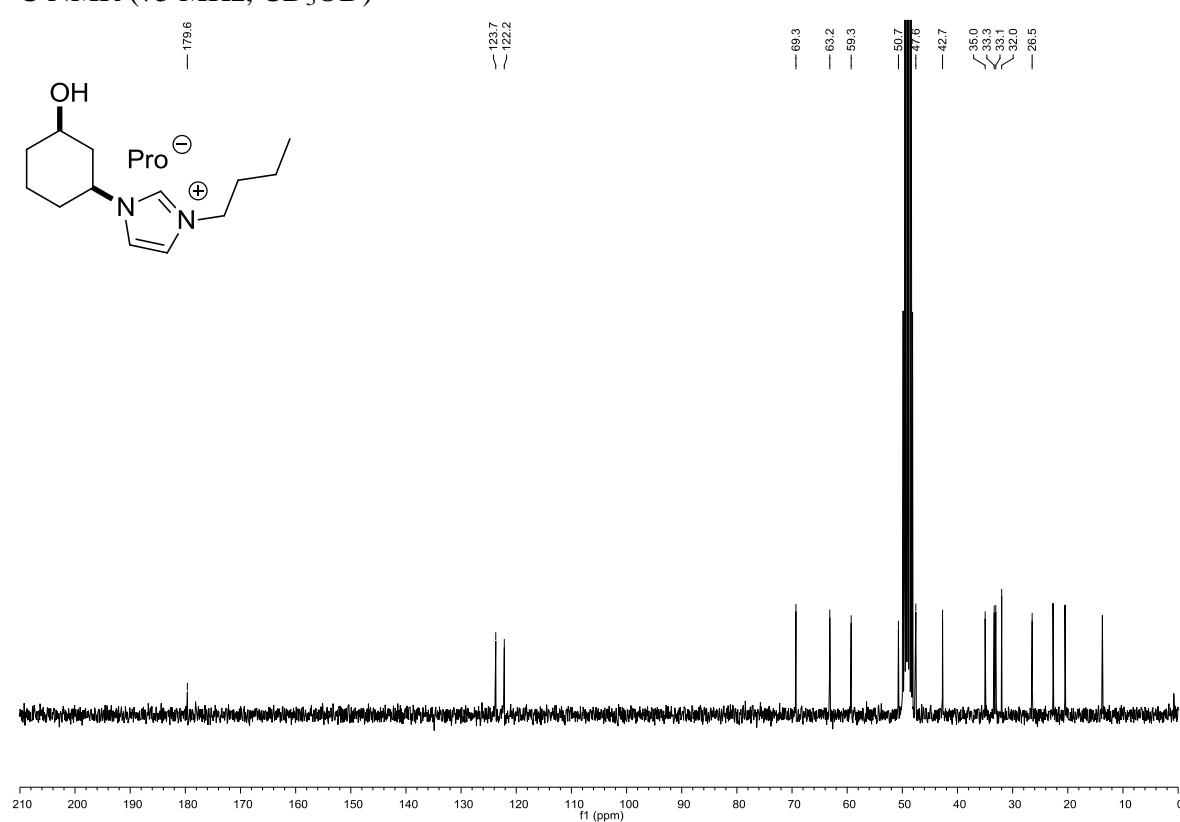
<sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)



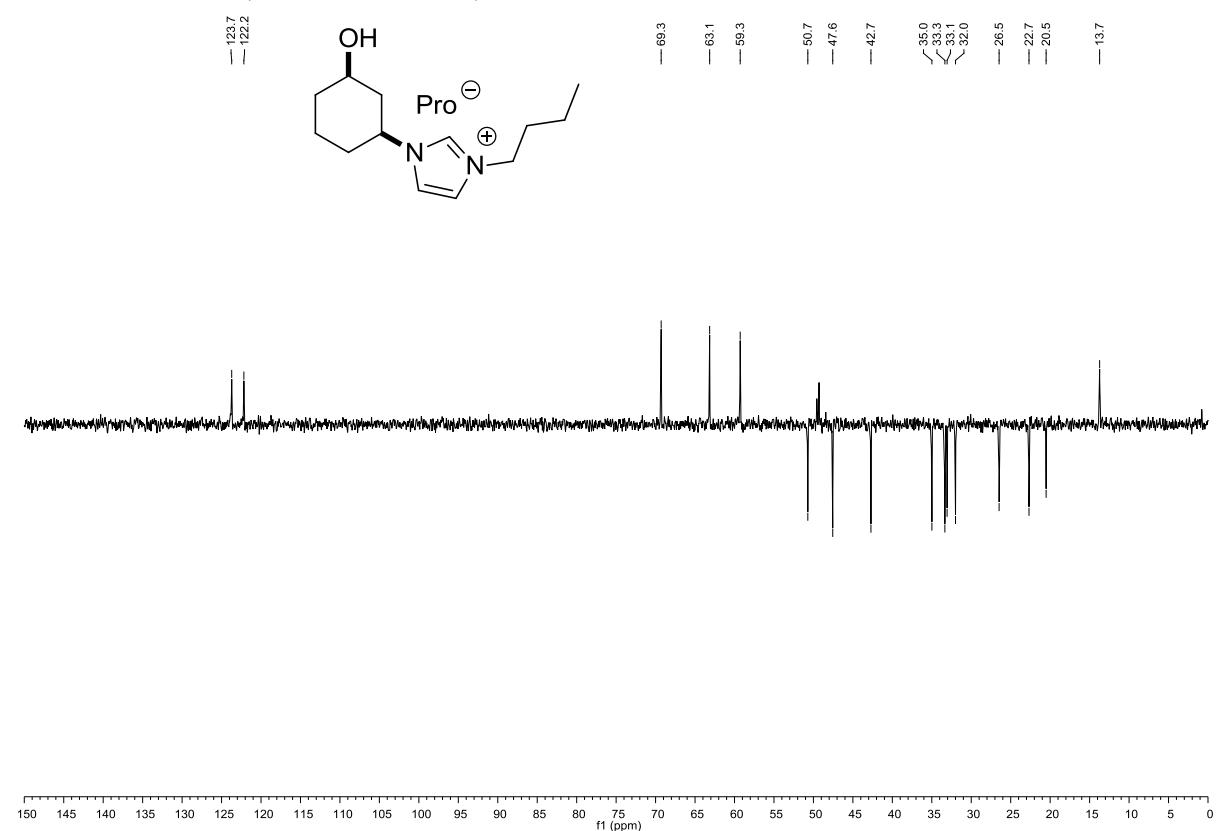
**( $\pm$ )-*cis*-3-Butyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



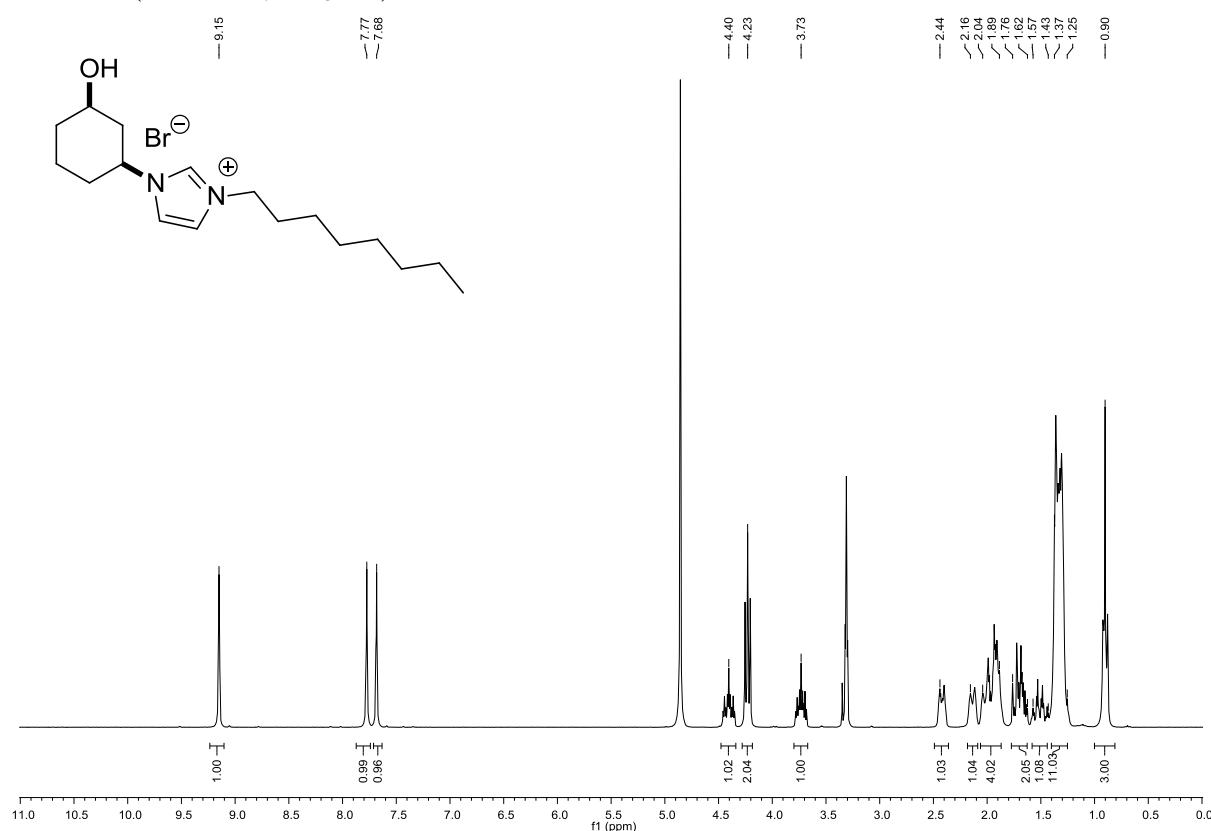
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



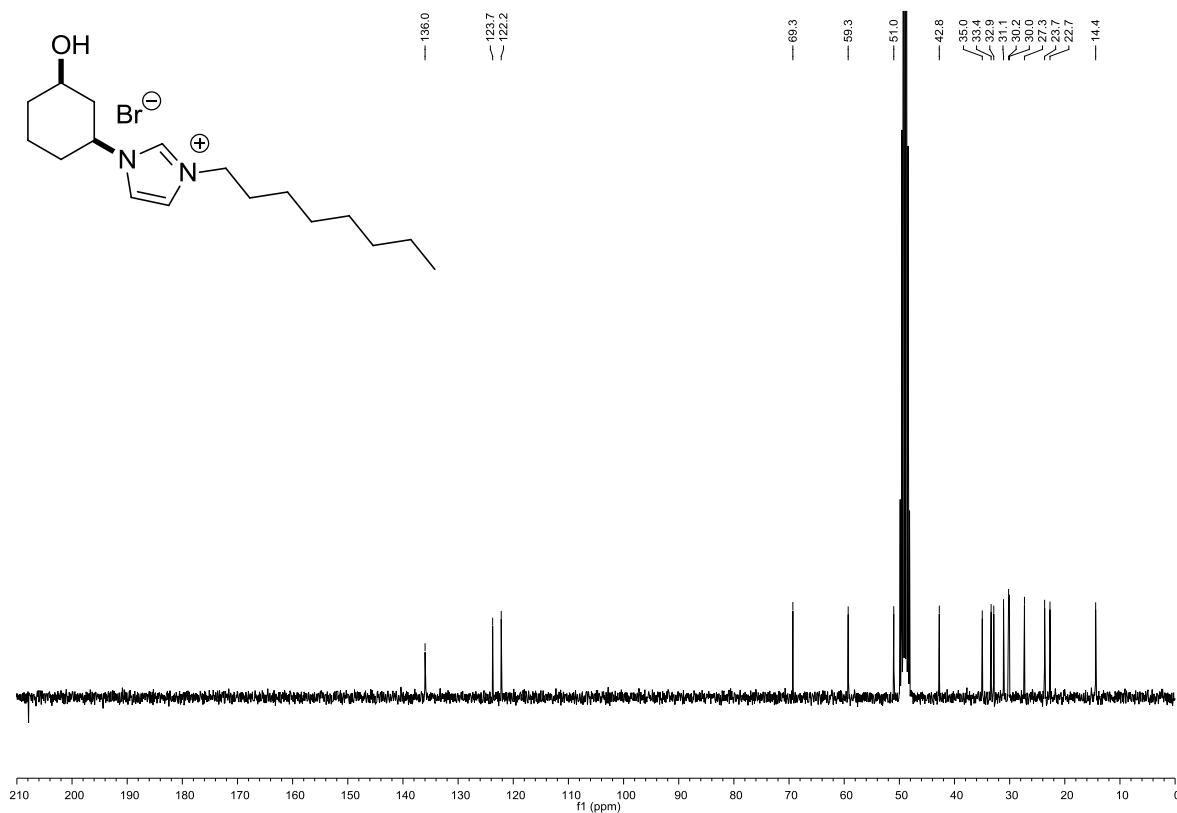
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



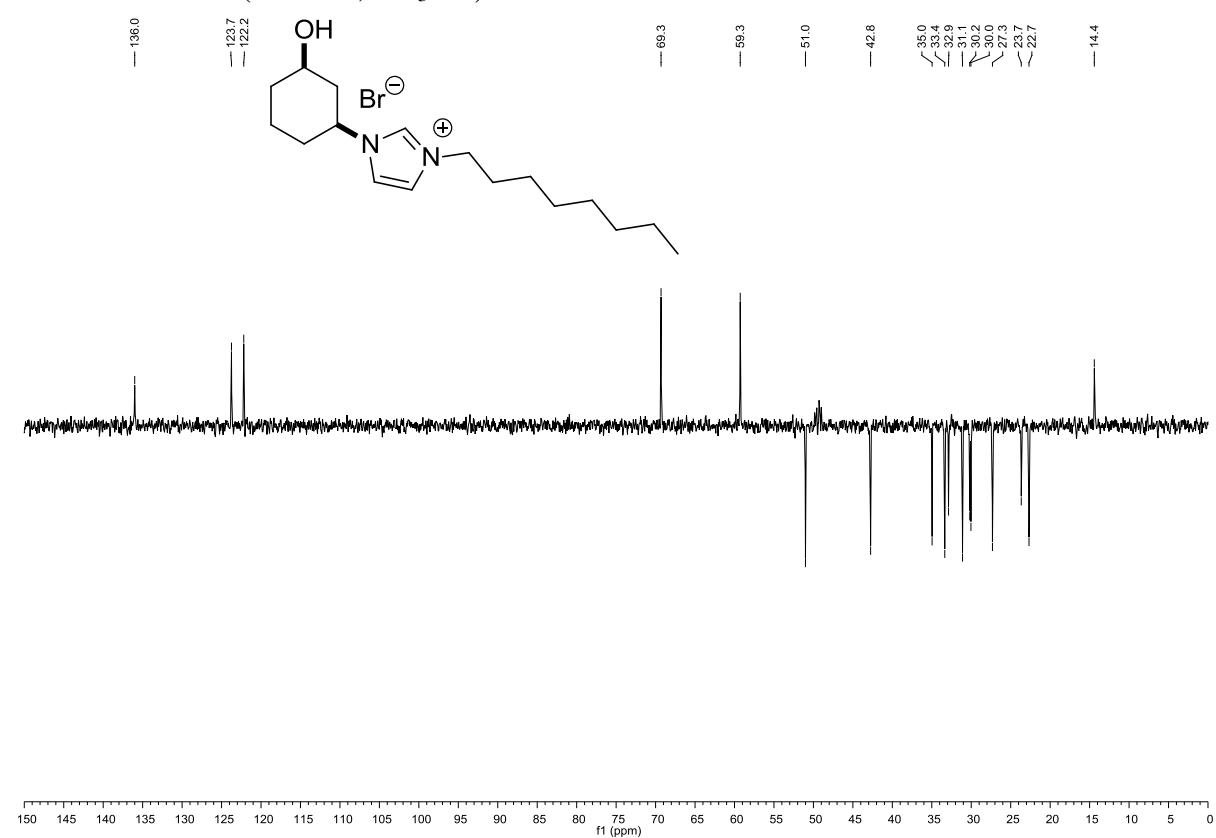
**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium bromide**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



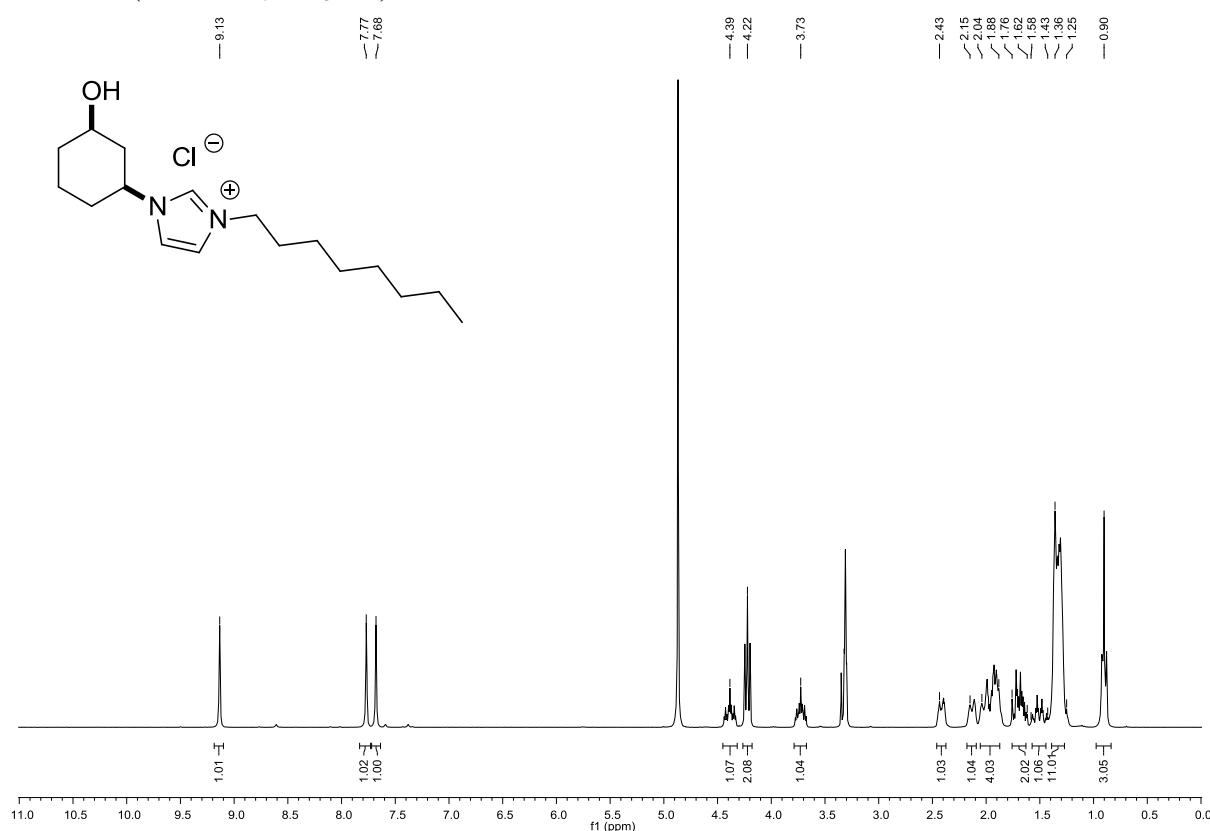
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



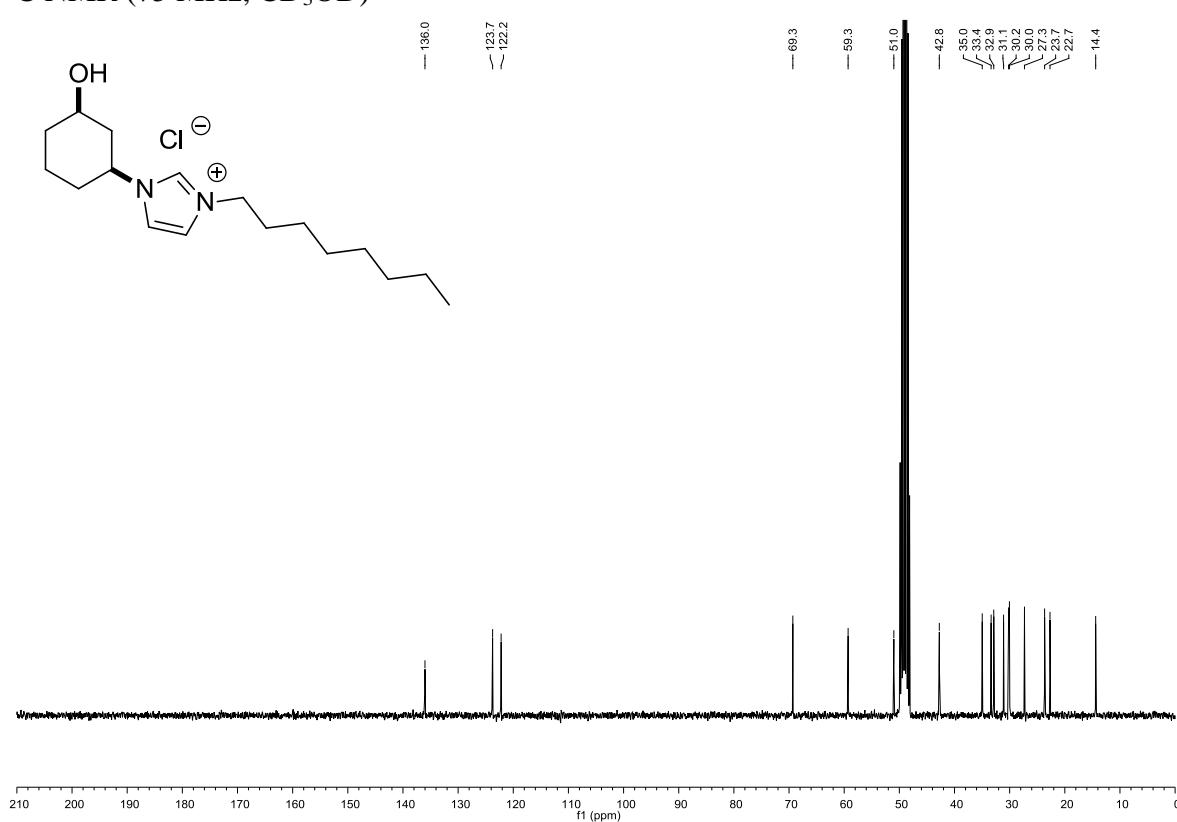
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



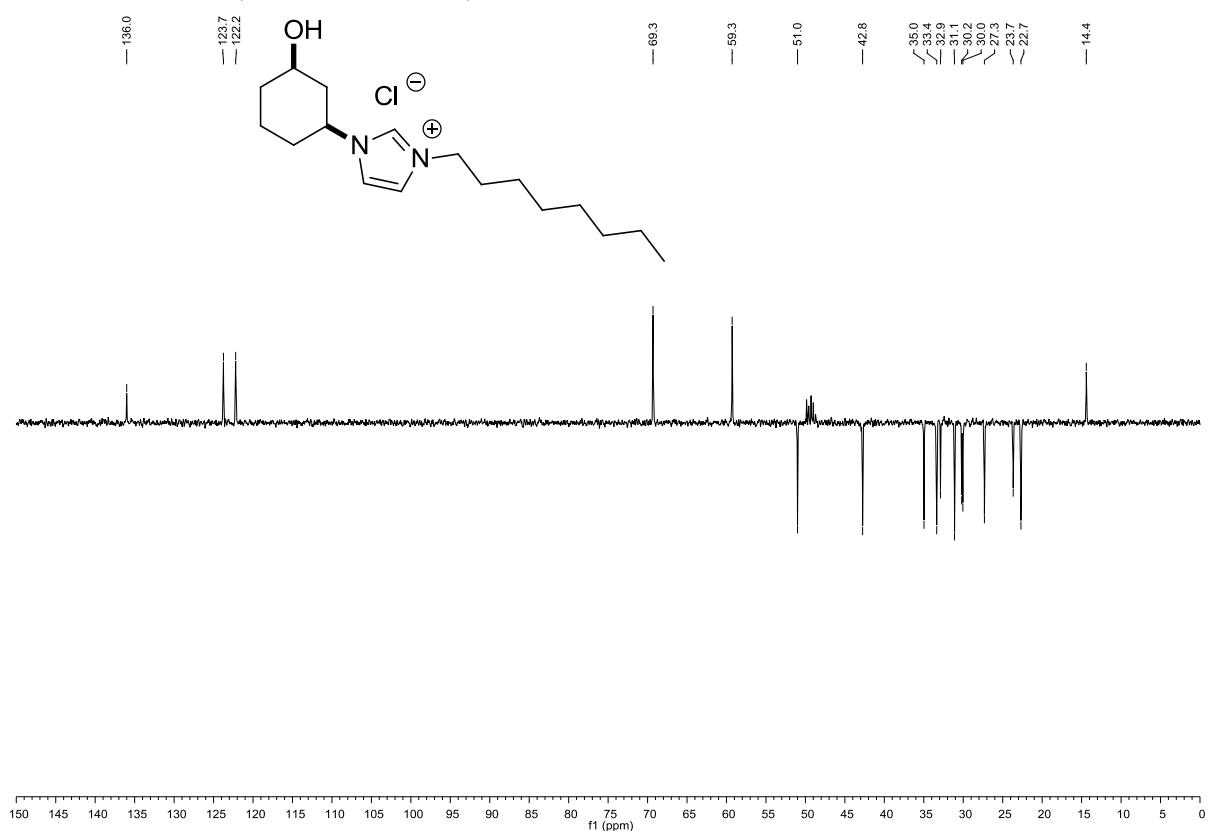
**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium chloride**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



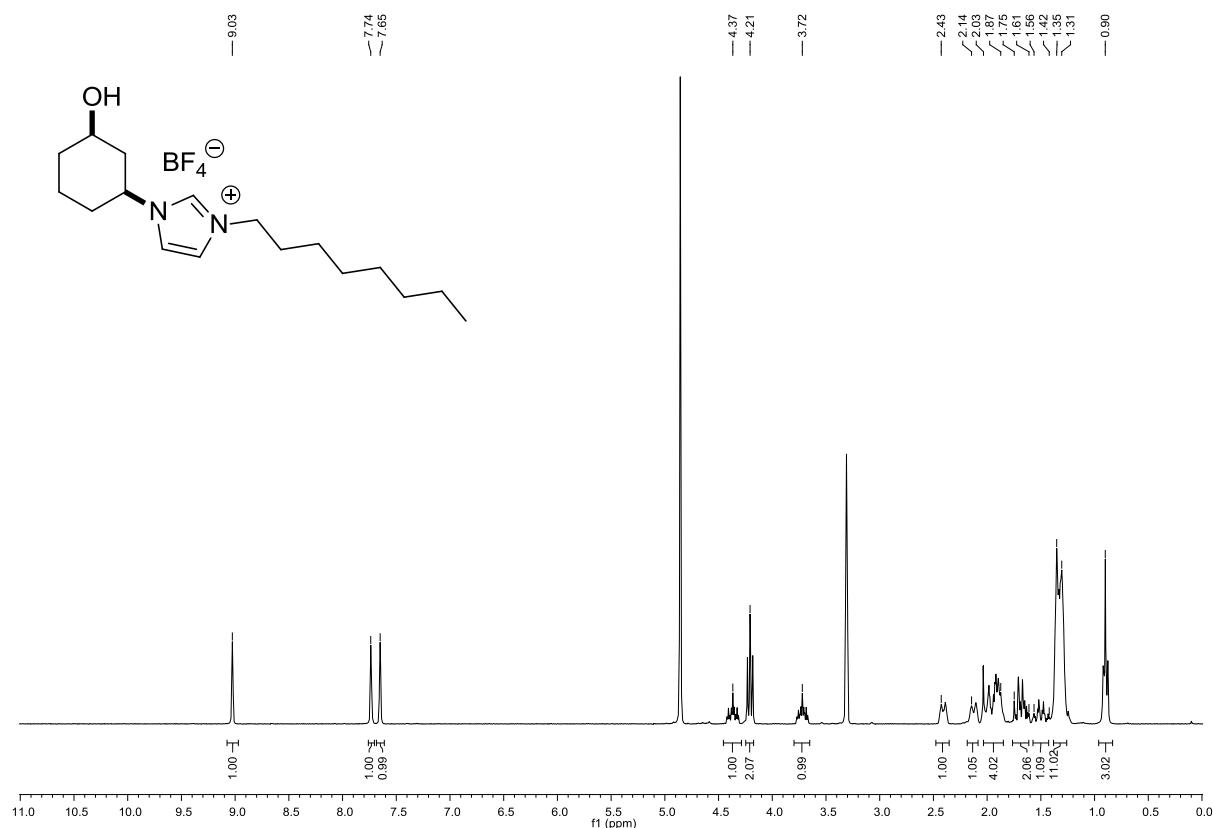
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



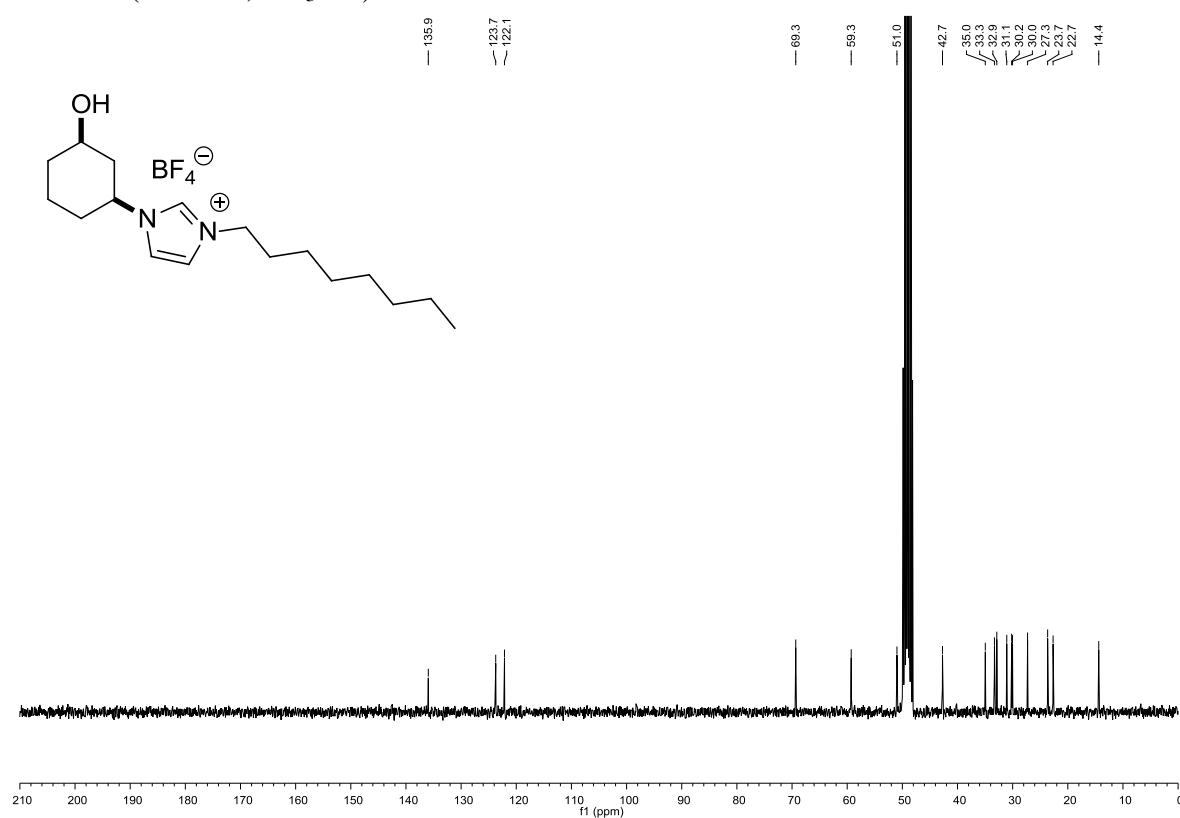
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



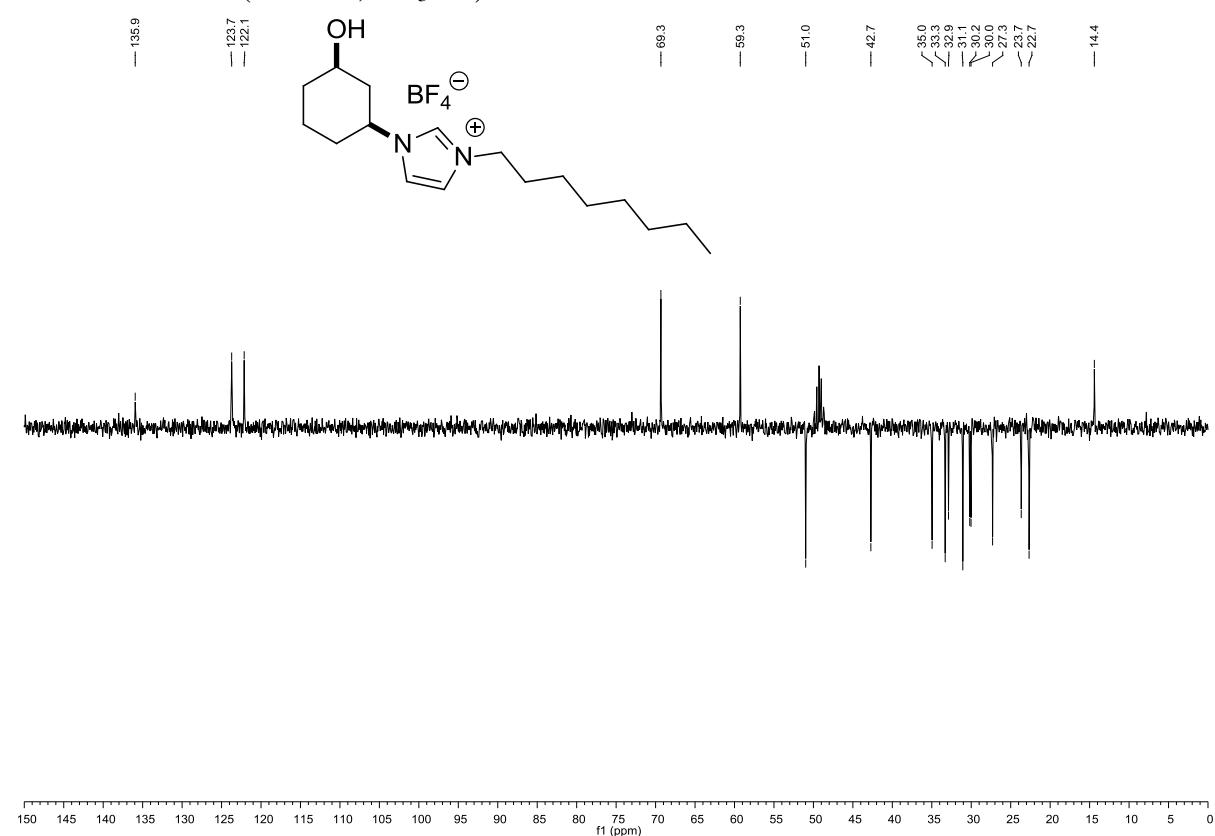
**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium tetrafluoroborate**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



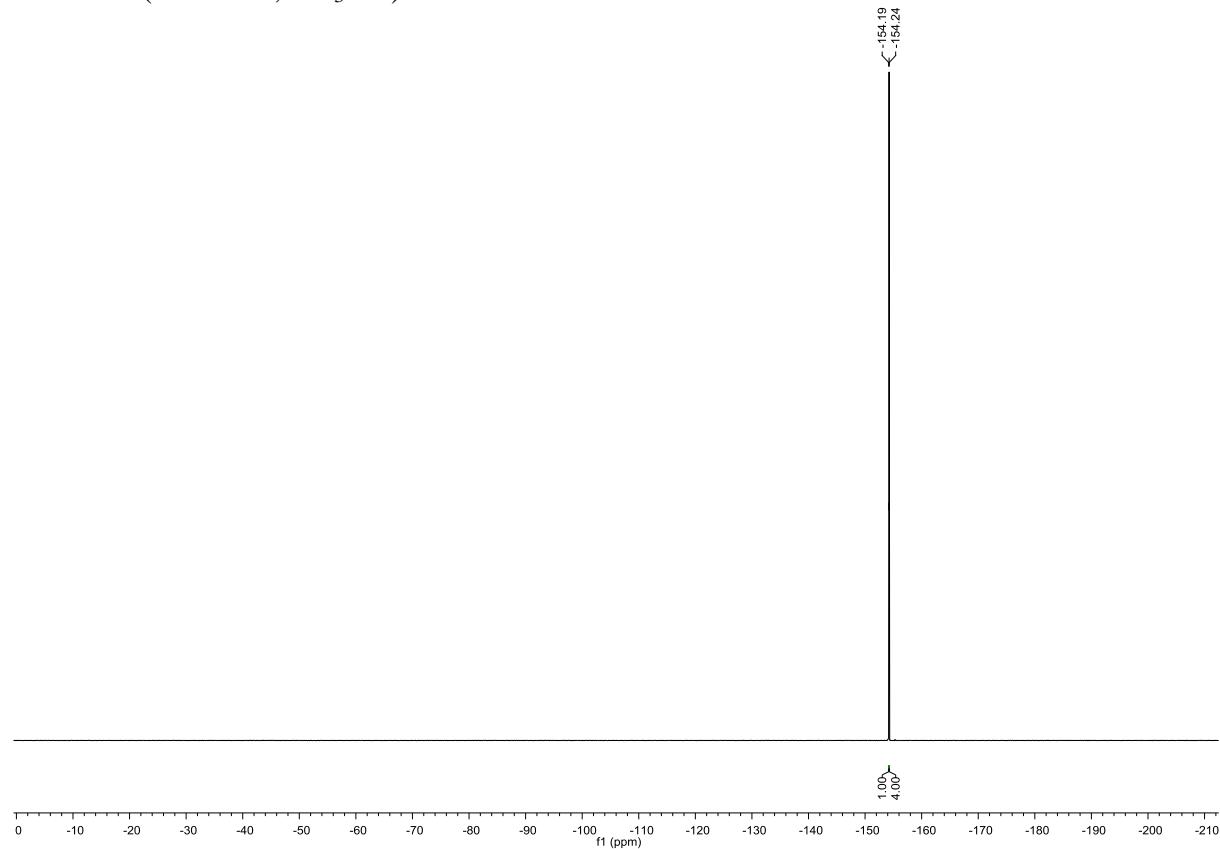
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



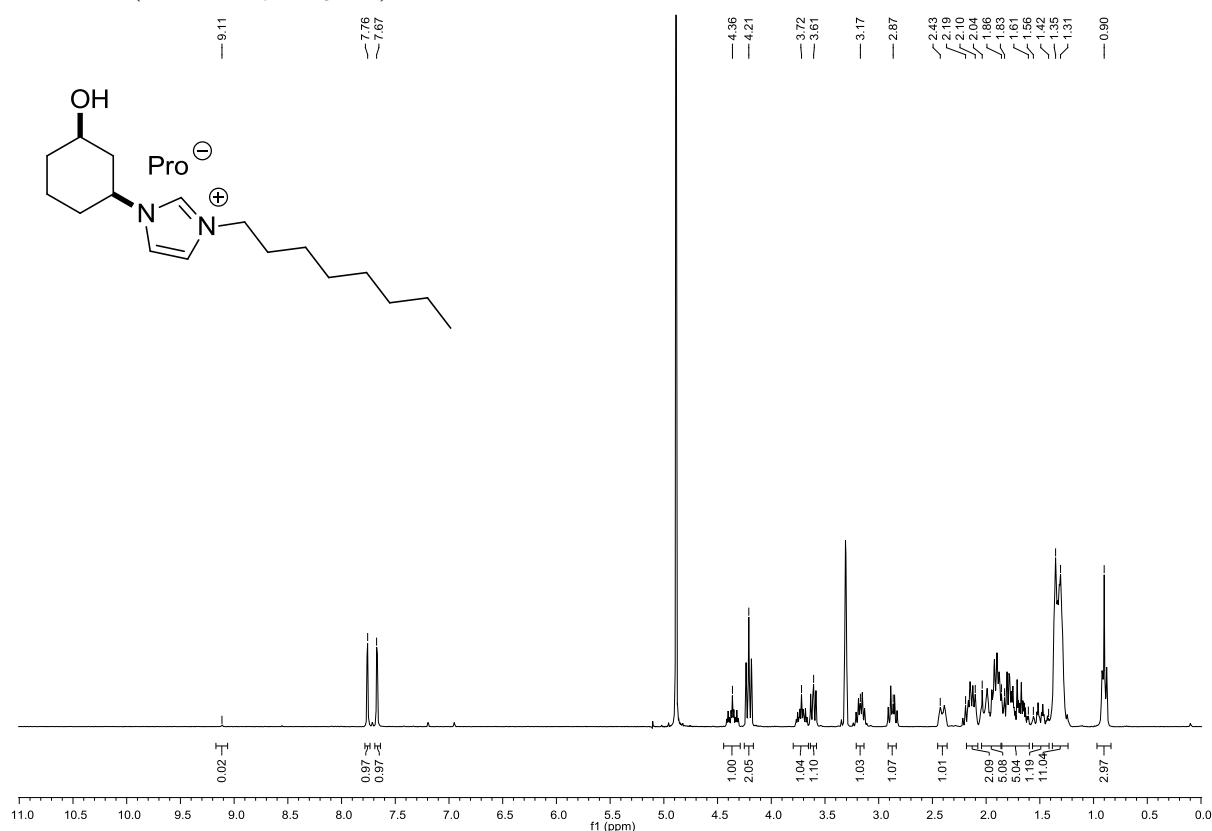
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



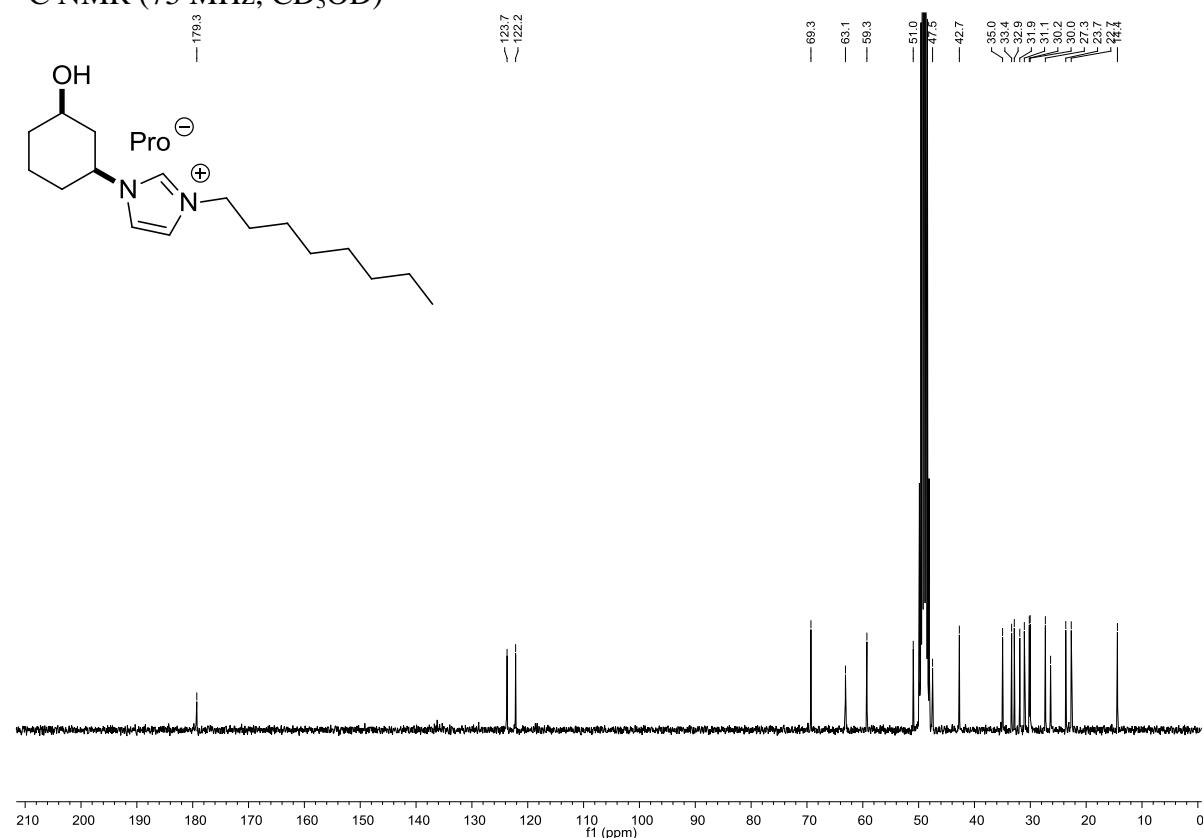
<sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)



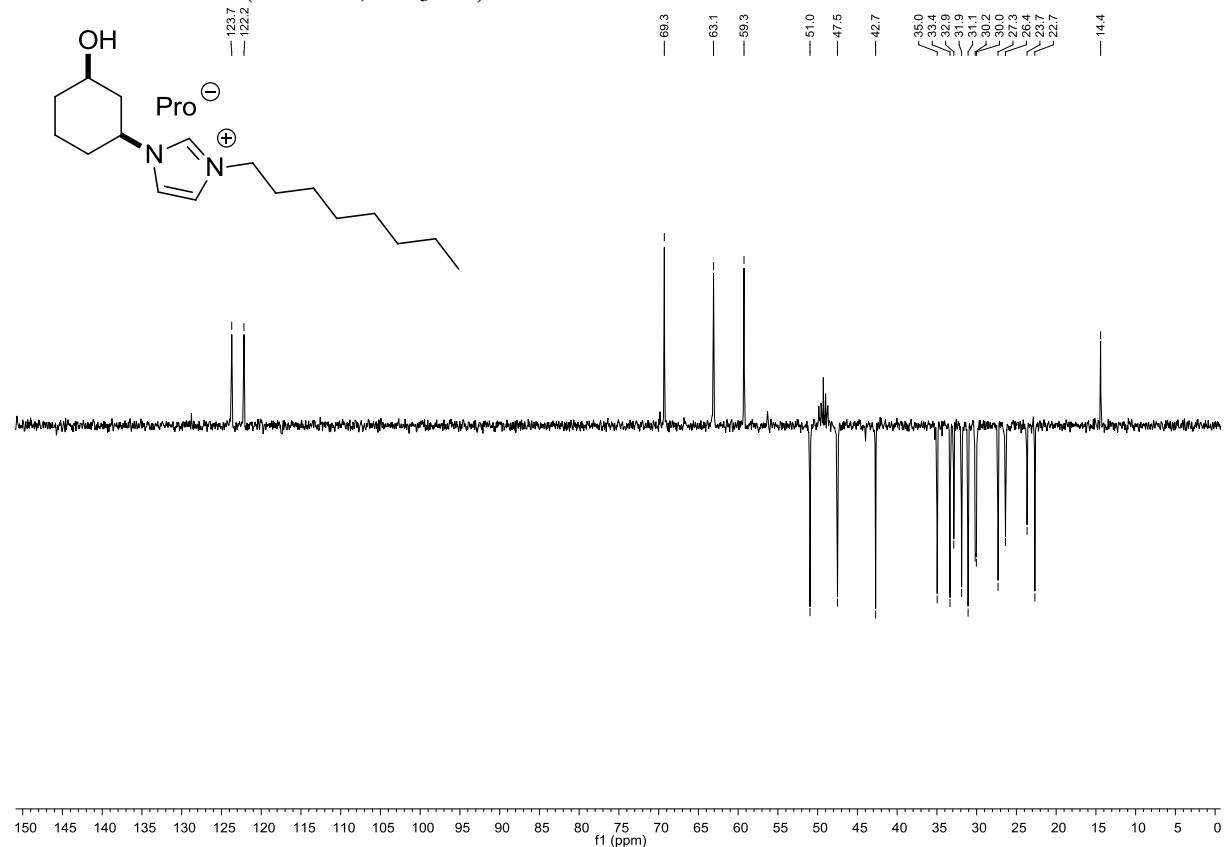
**( $\pm$ )-*cis*-1-(3-Hydroxycyclohexyl)-3-octyl-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



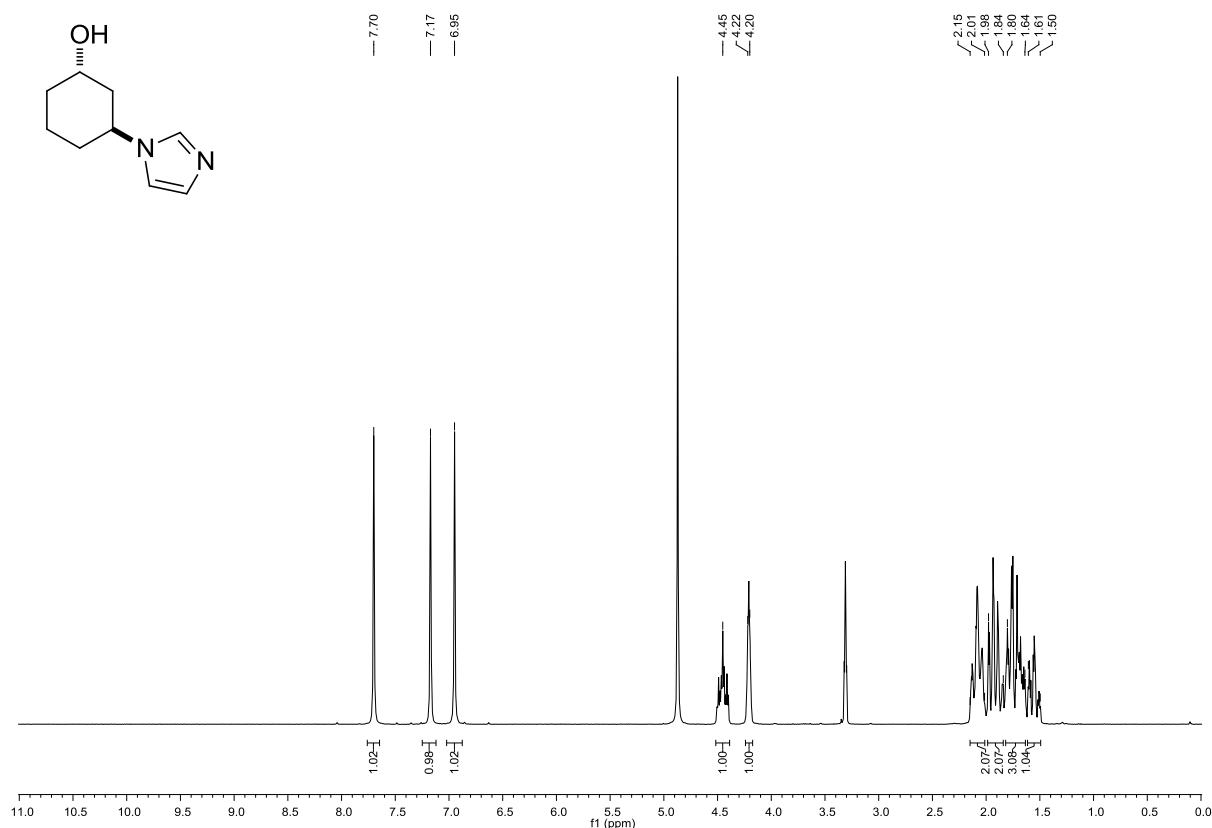
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



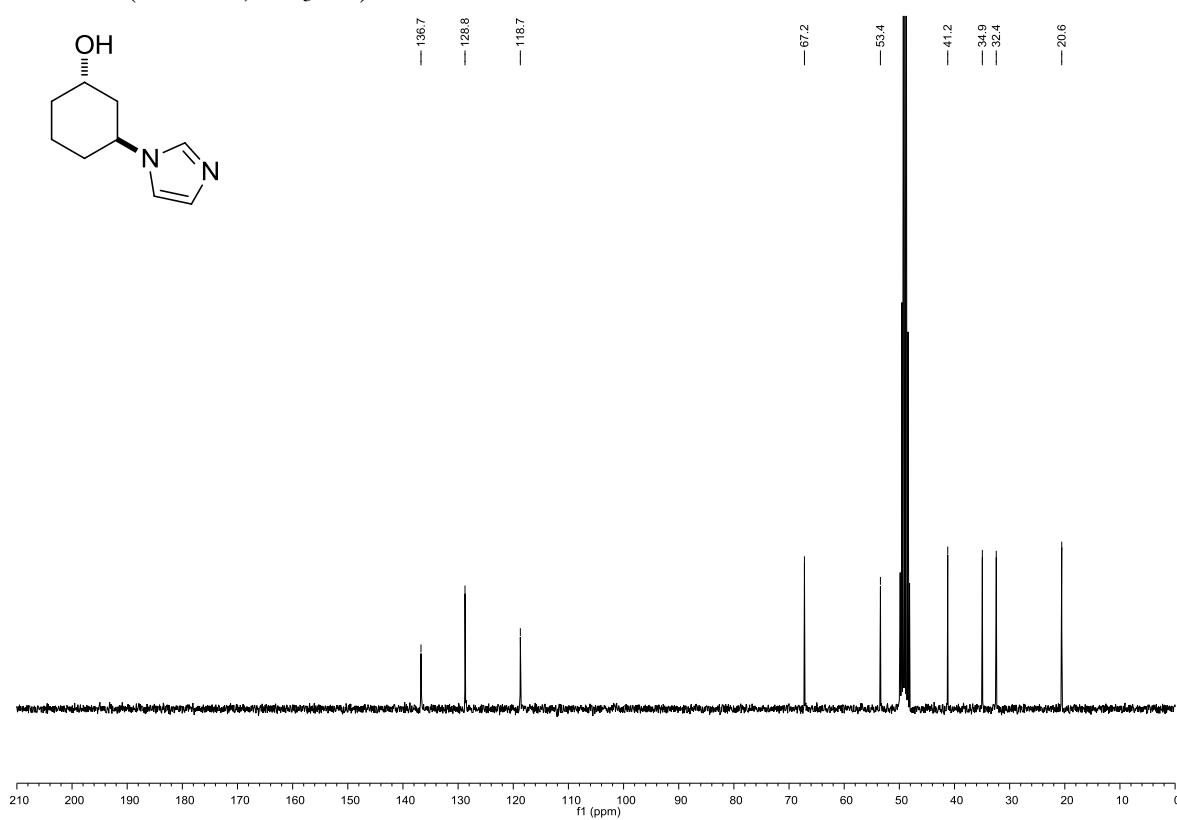
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



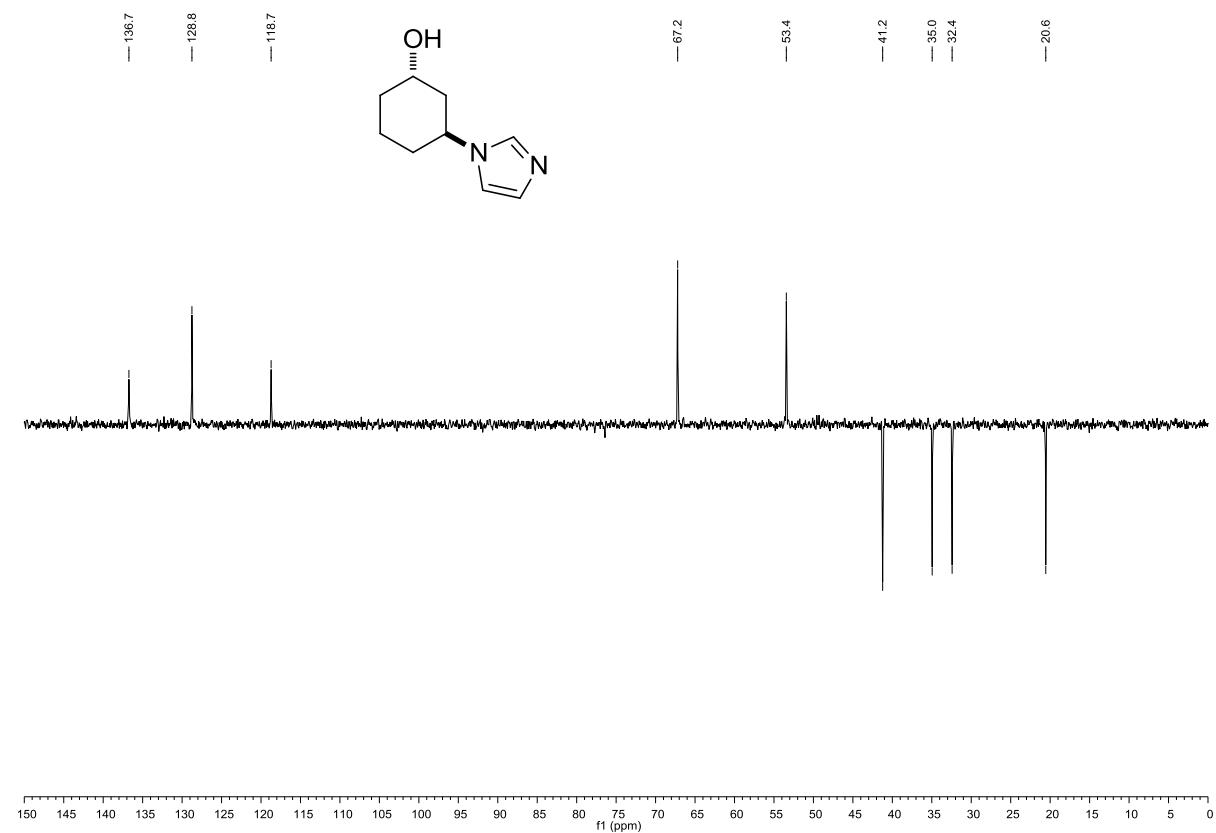
**( $\pm$ )-*trans*-3-(1*H*-Imidazol-1-yl)cyclohexanol [ $(\pm)$ -*trans*-4]**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



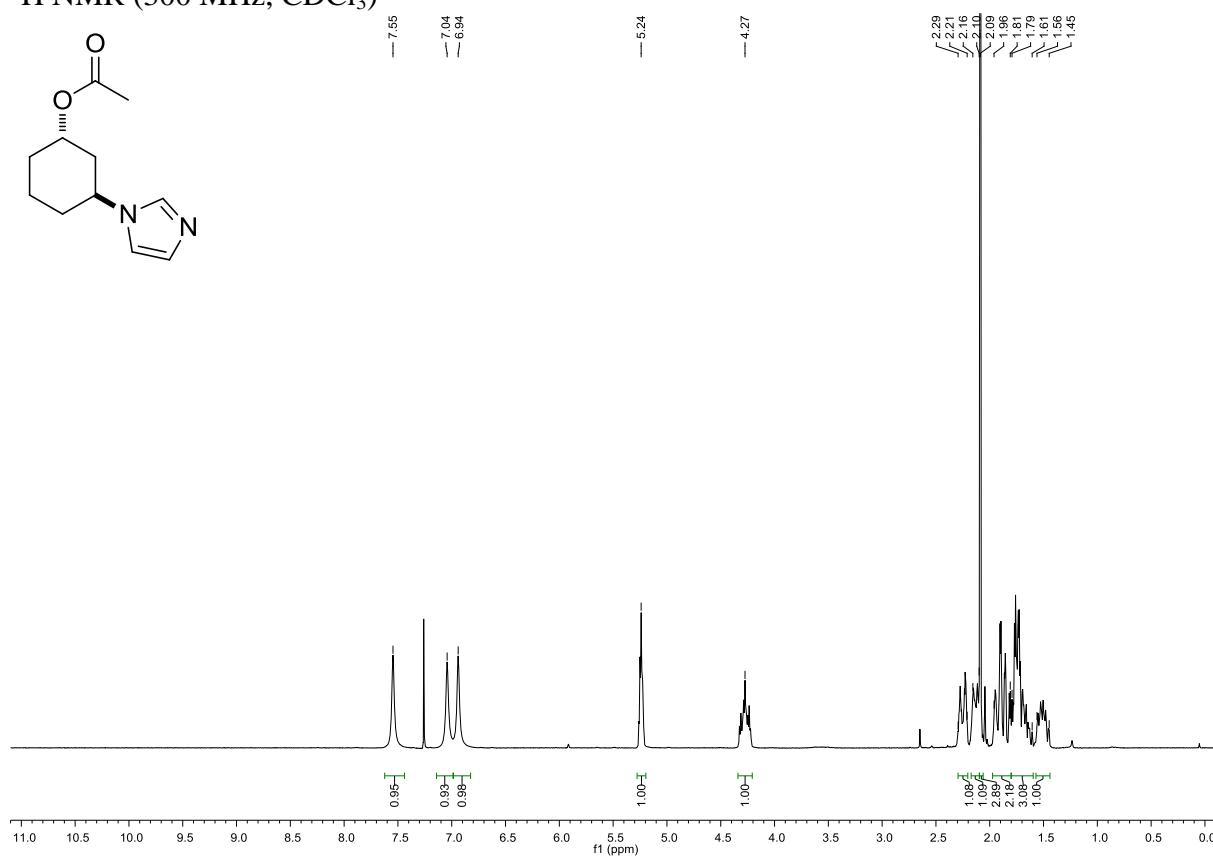
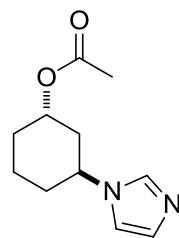
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )**



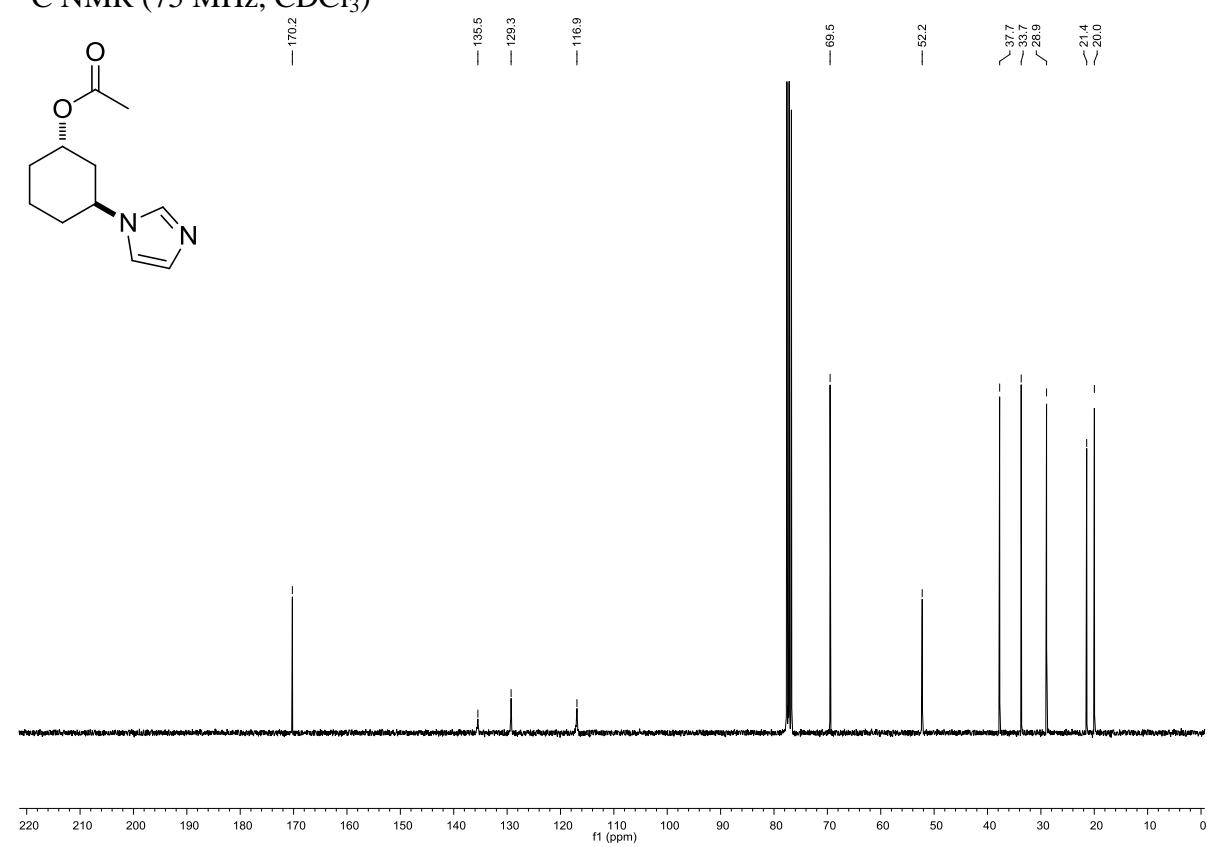
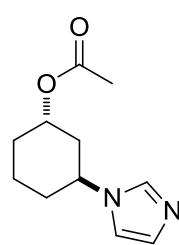
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



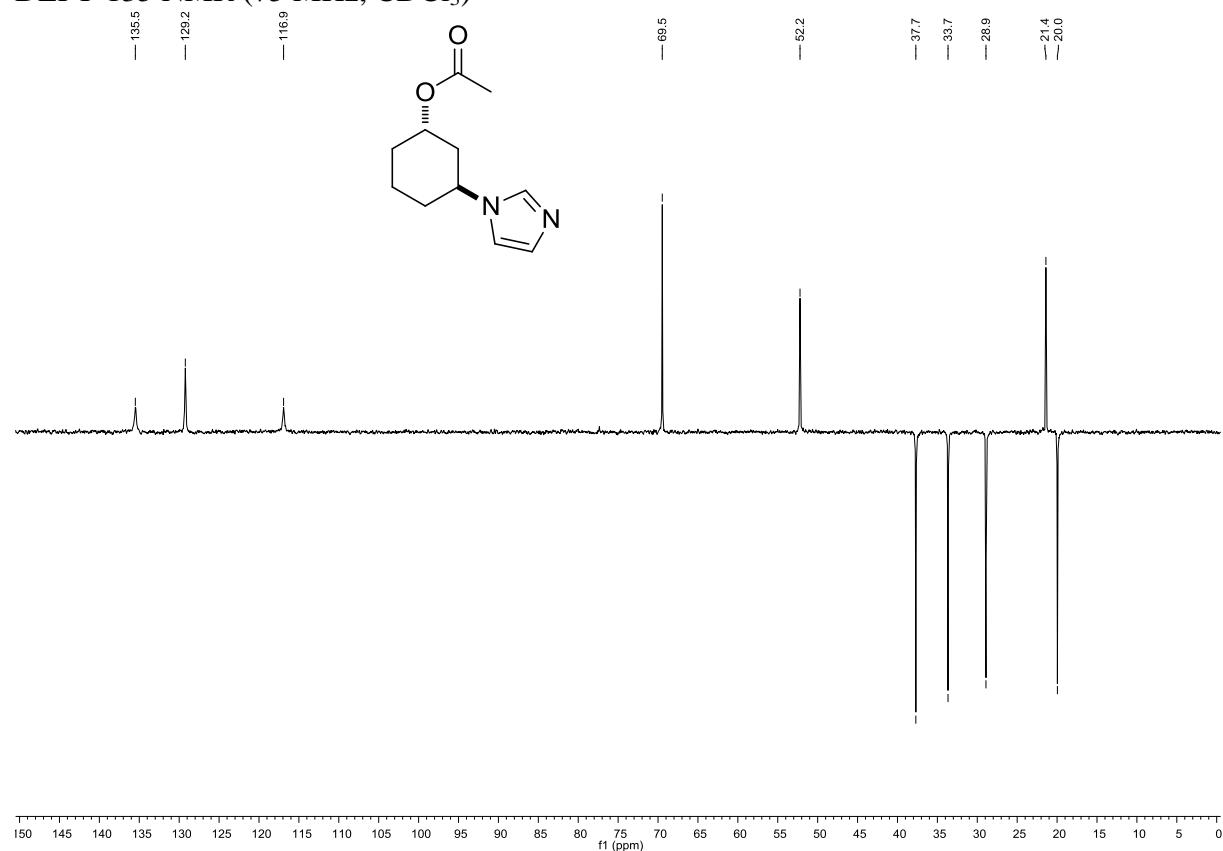
**( $\pm$ )-*trans*-3-(1H-Imidazol-1-yl)cyclohexyl acetate [ $(\pm)$ -*trans*-5]**



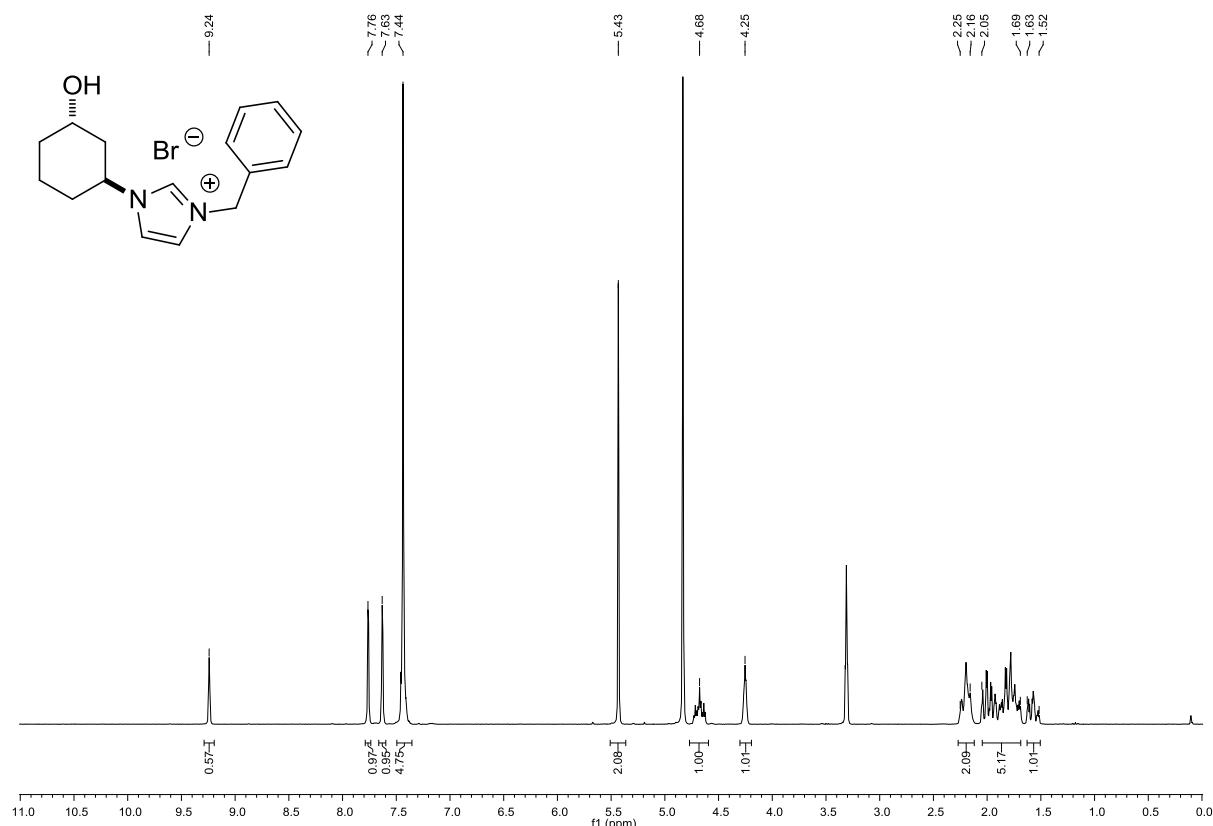
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)



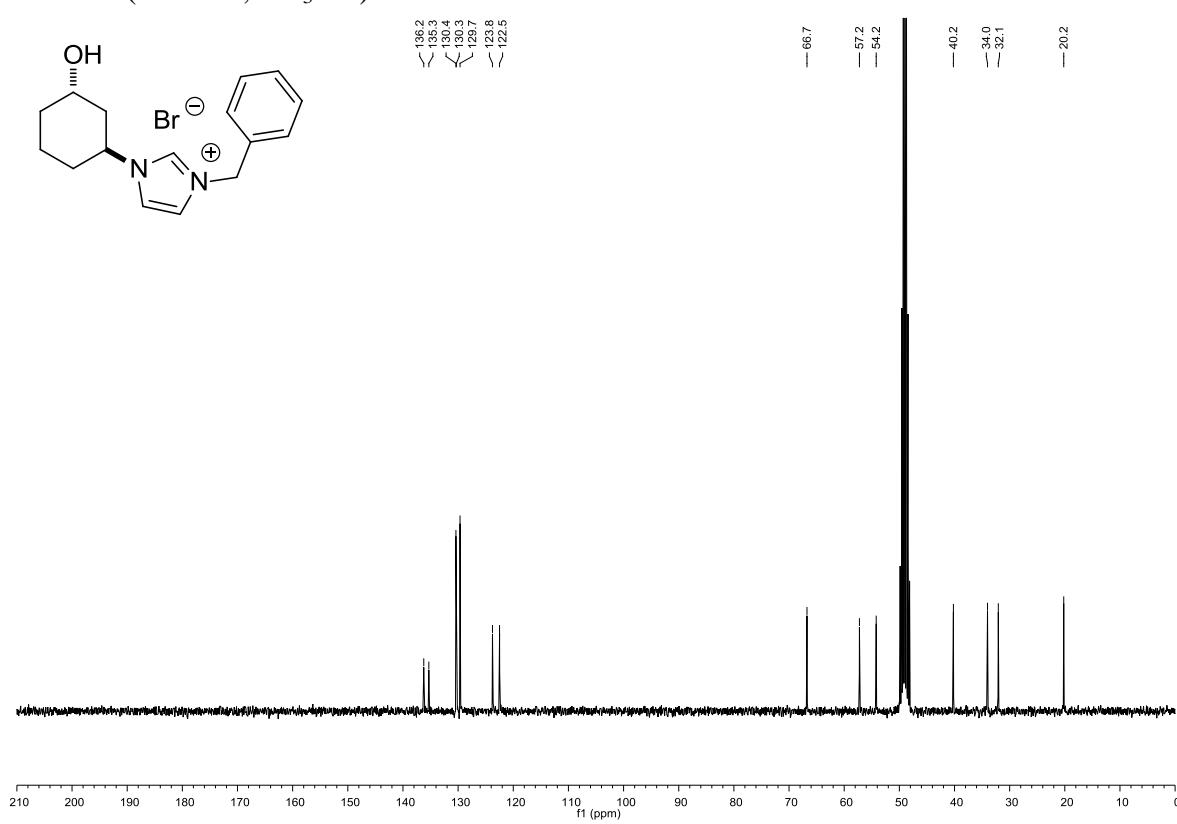
DEPT-135 NMR (75 MHz,  $\text{CDCl}_3$ )



**( $\pm$ )-trans-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium bromide**  
 $^1\text{H}$  NMR (300 MHz, CD<sub>3</sub>OD)



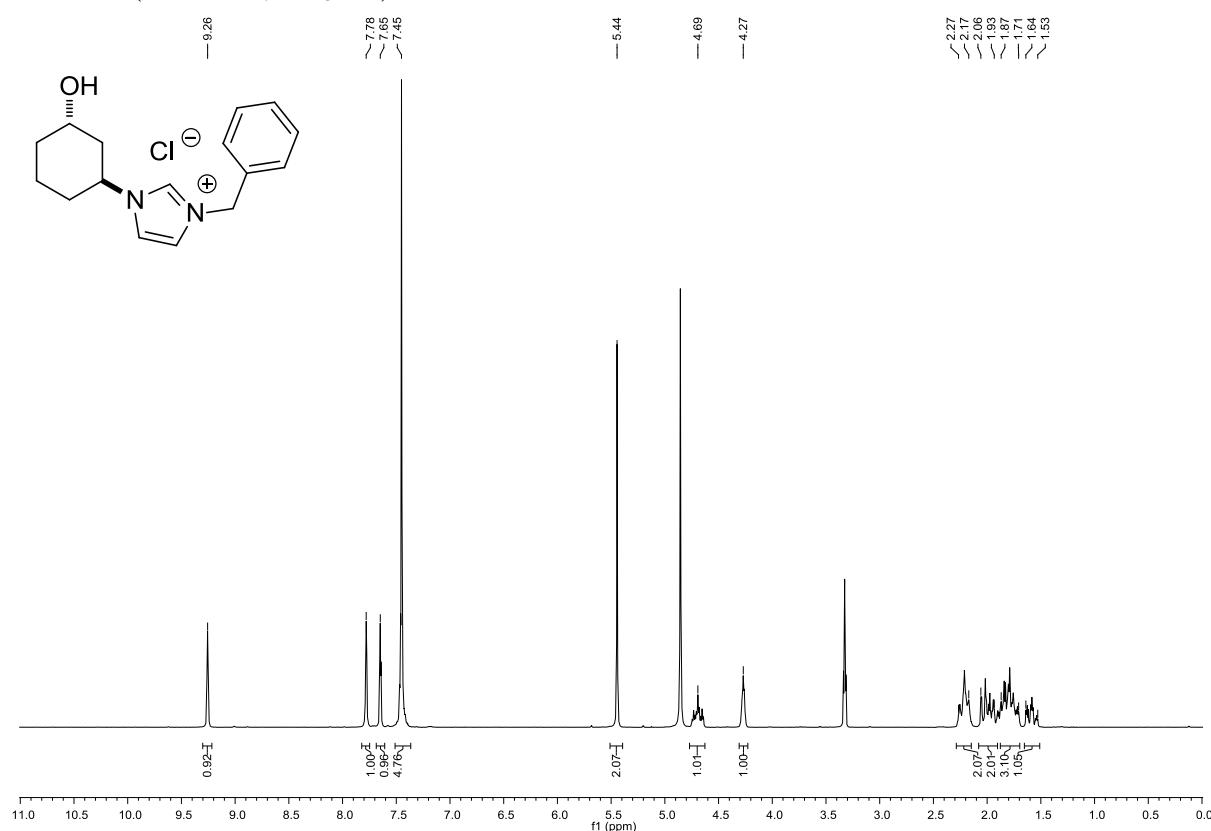
<sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)



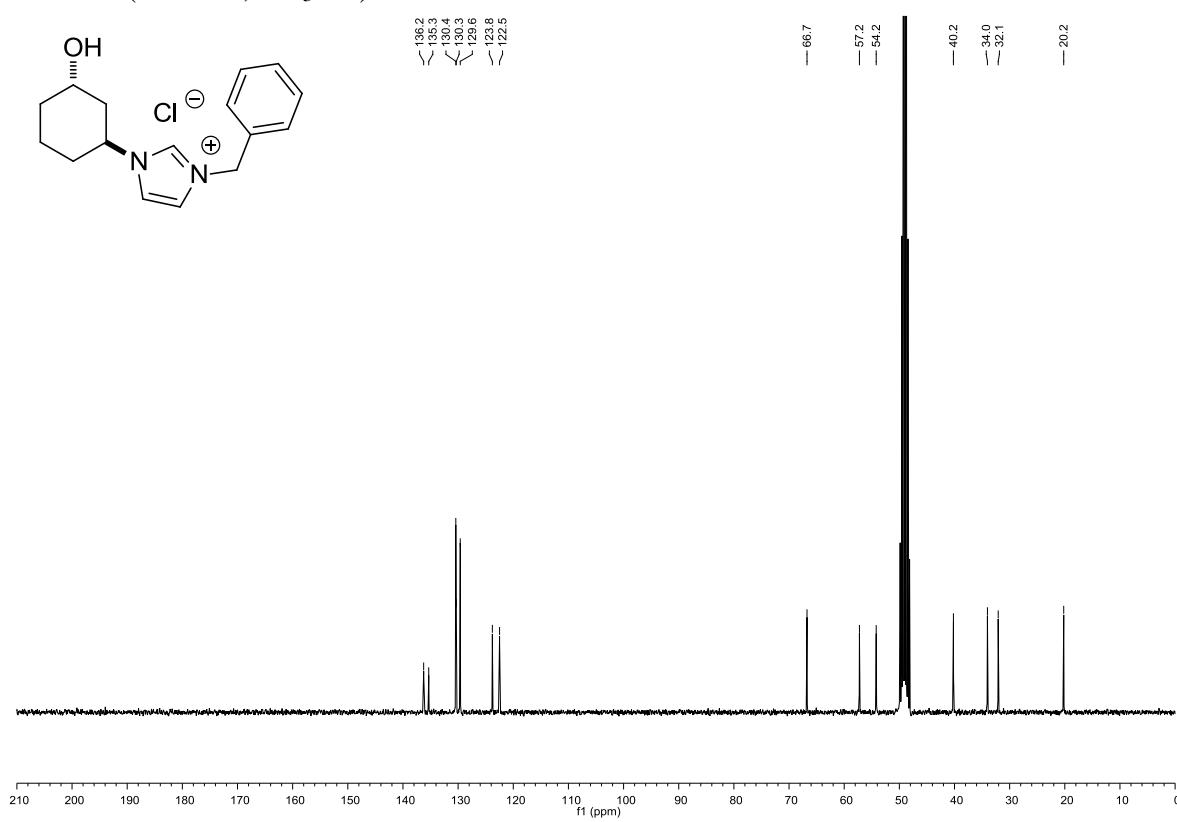
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



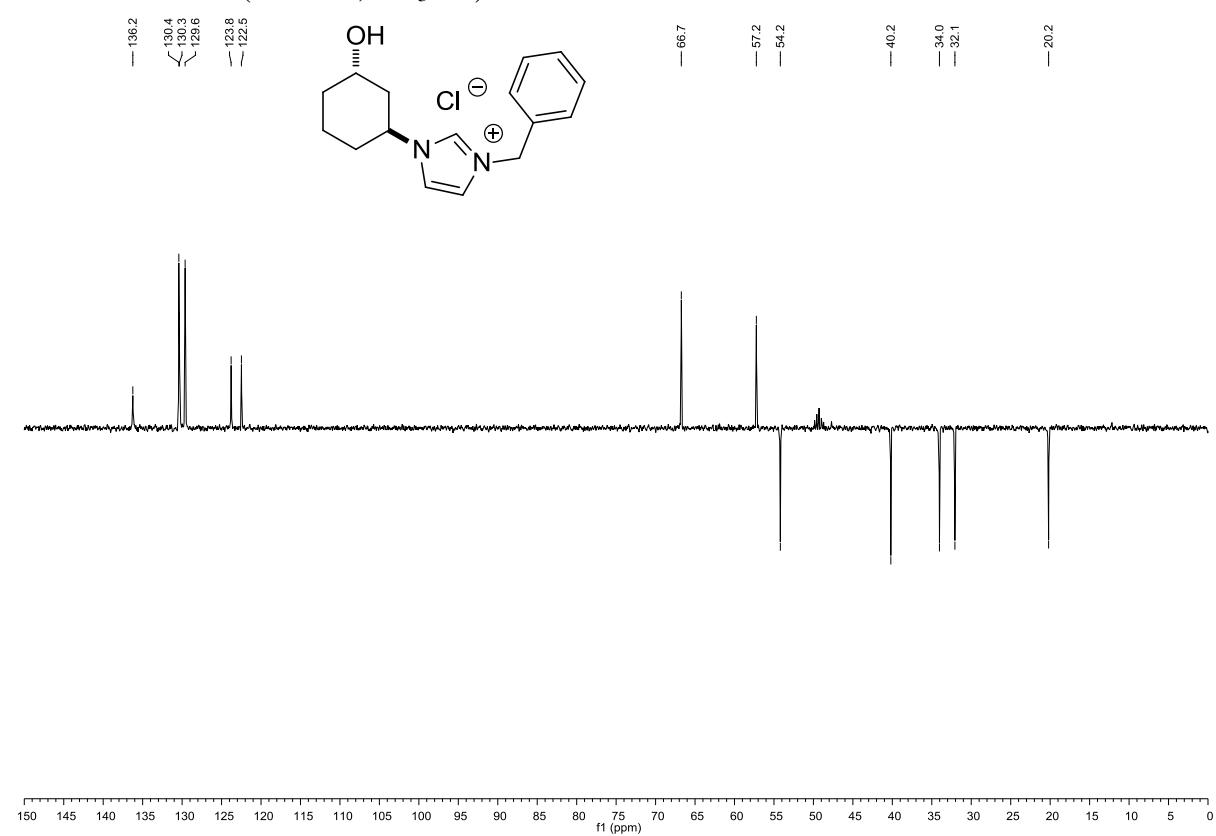
**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



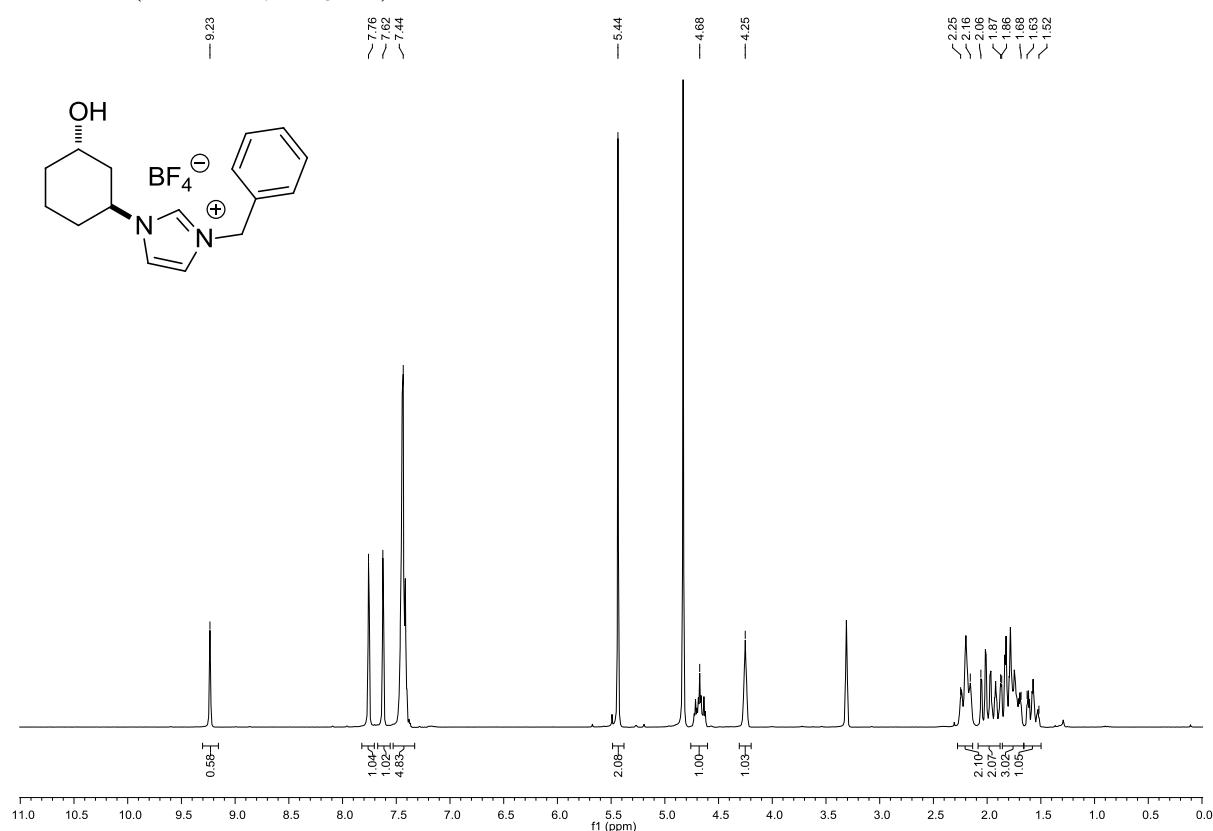
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



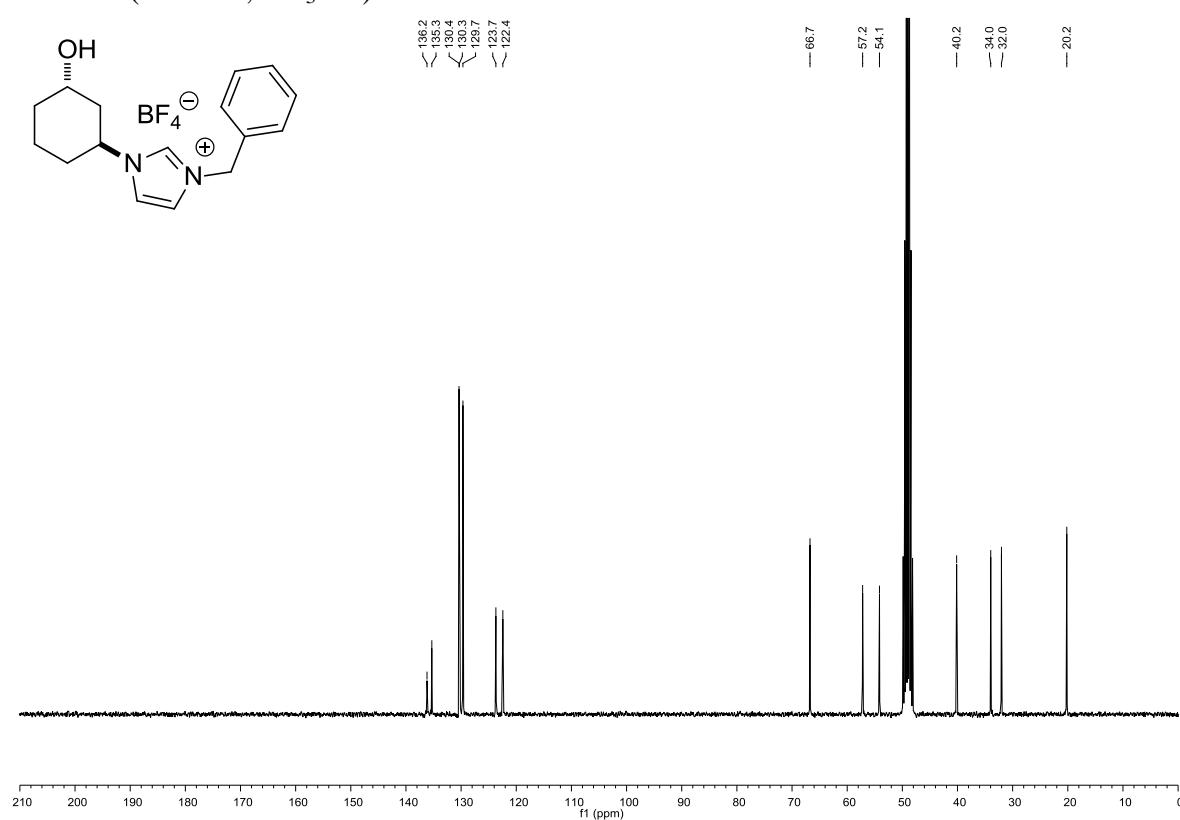
DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)



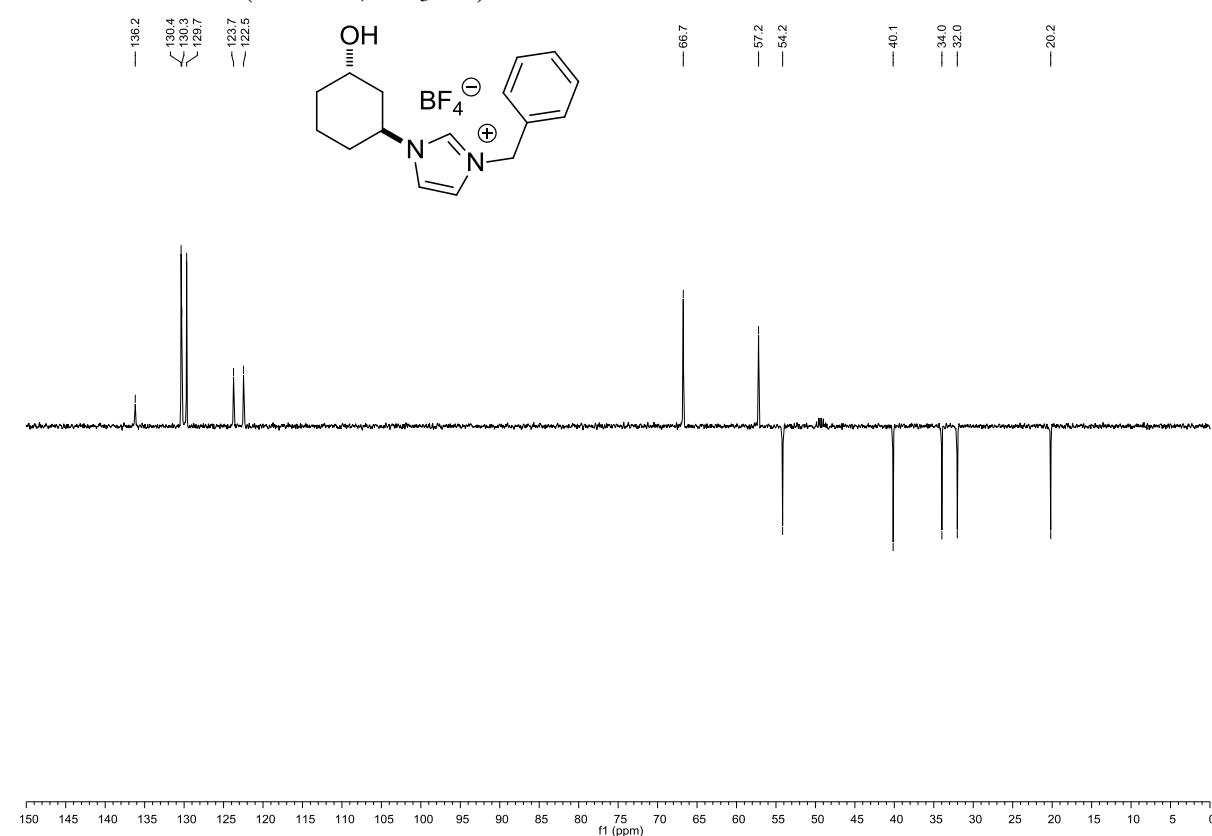
**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium tetrafluoroborate**  
 $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



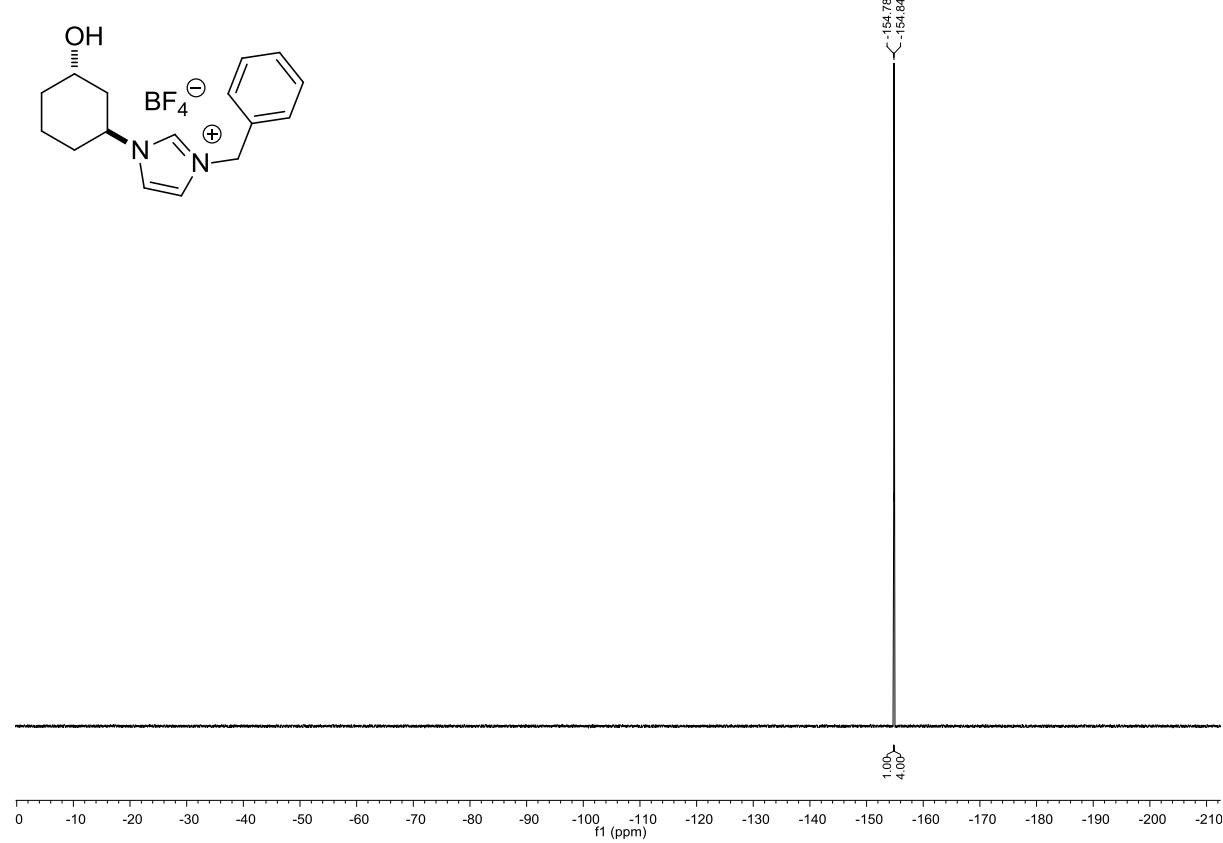
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)

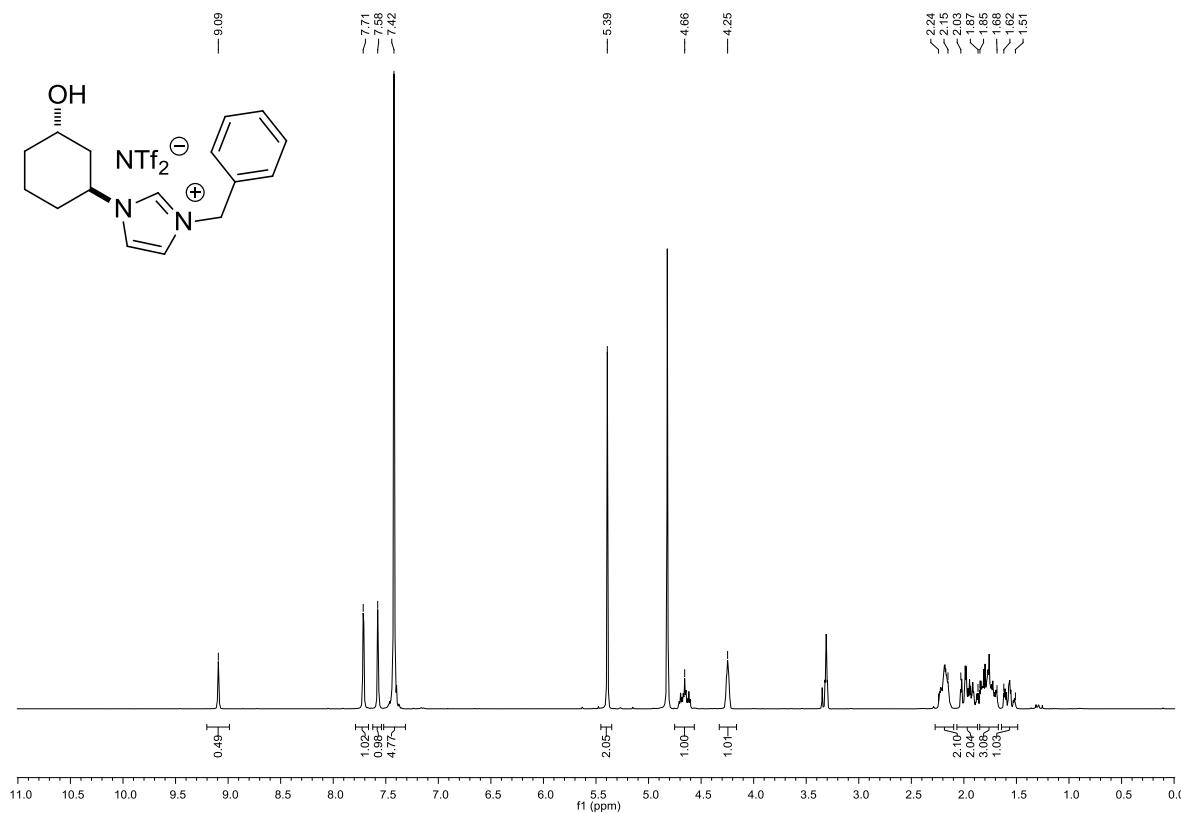


<sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)

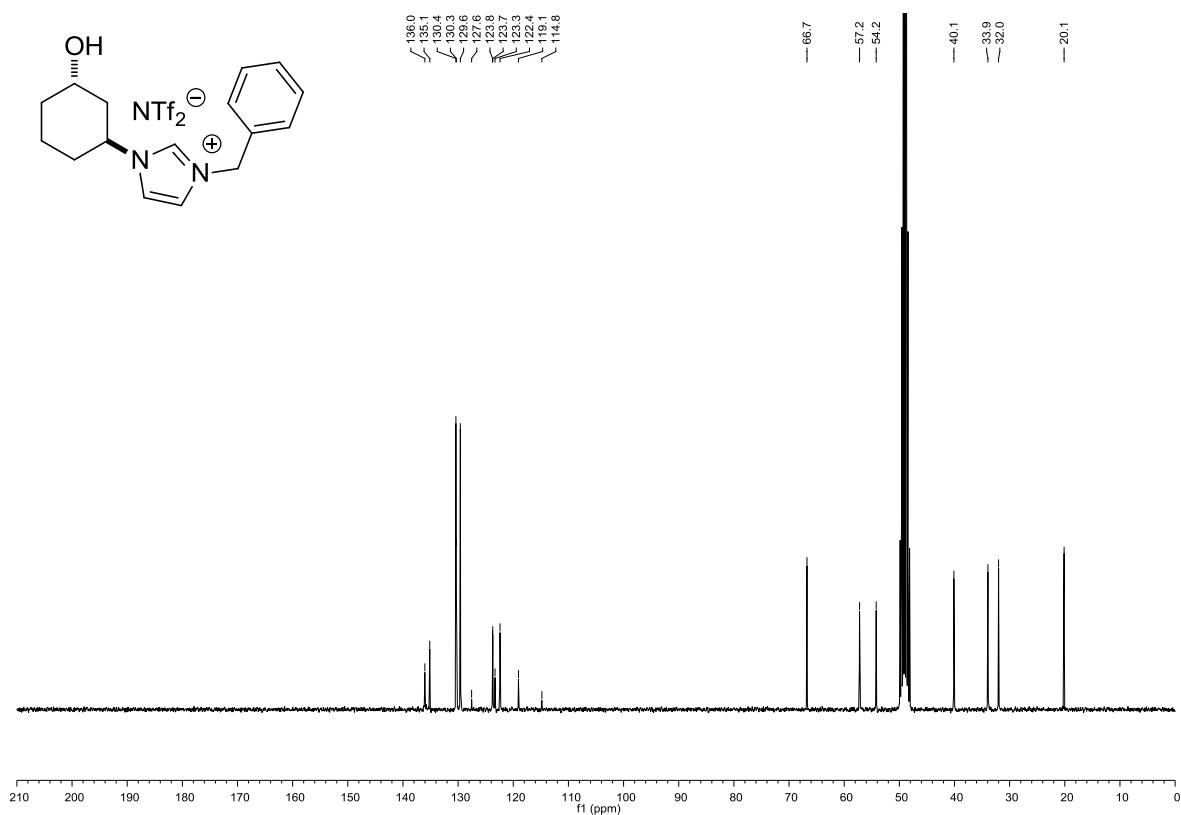


**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium trifluoromethane sulfonimide**

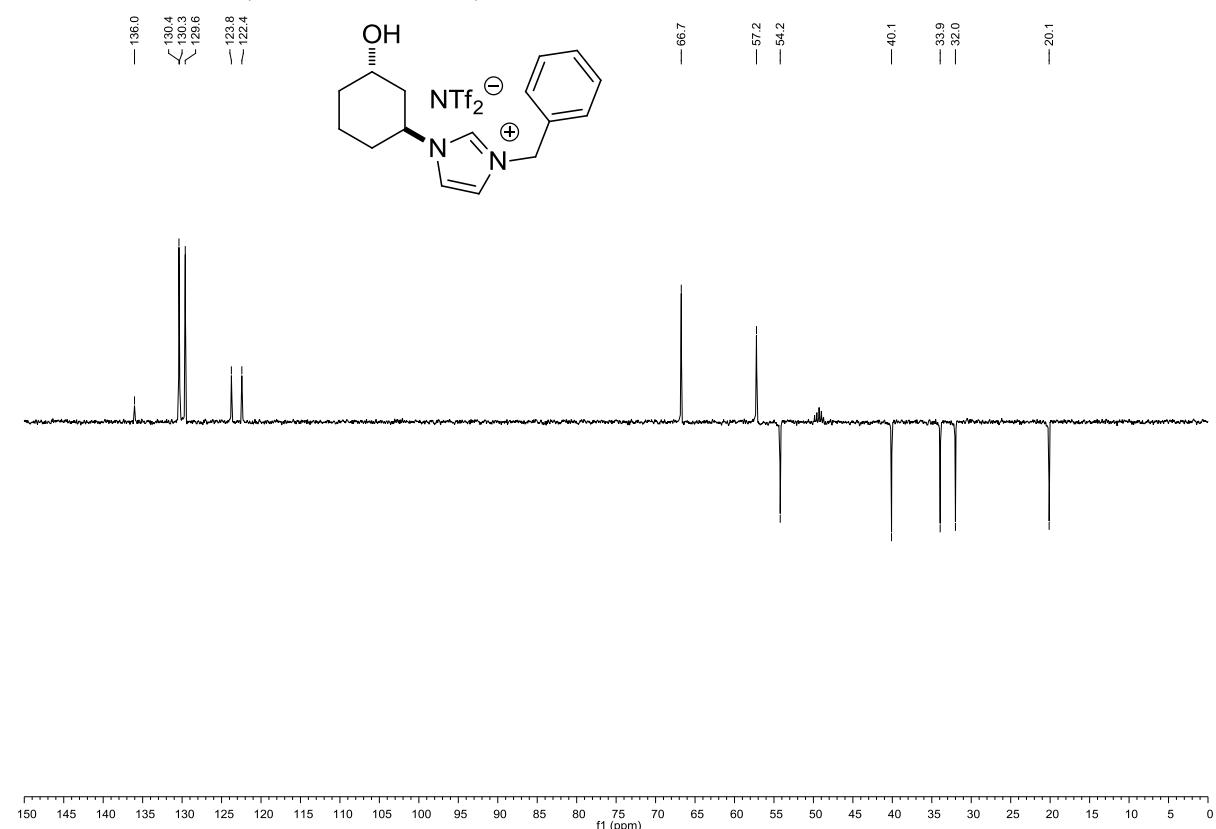
$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



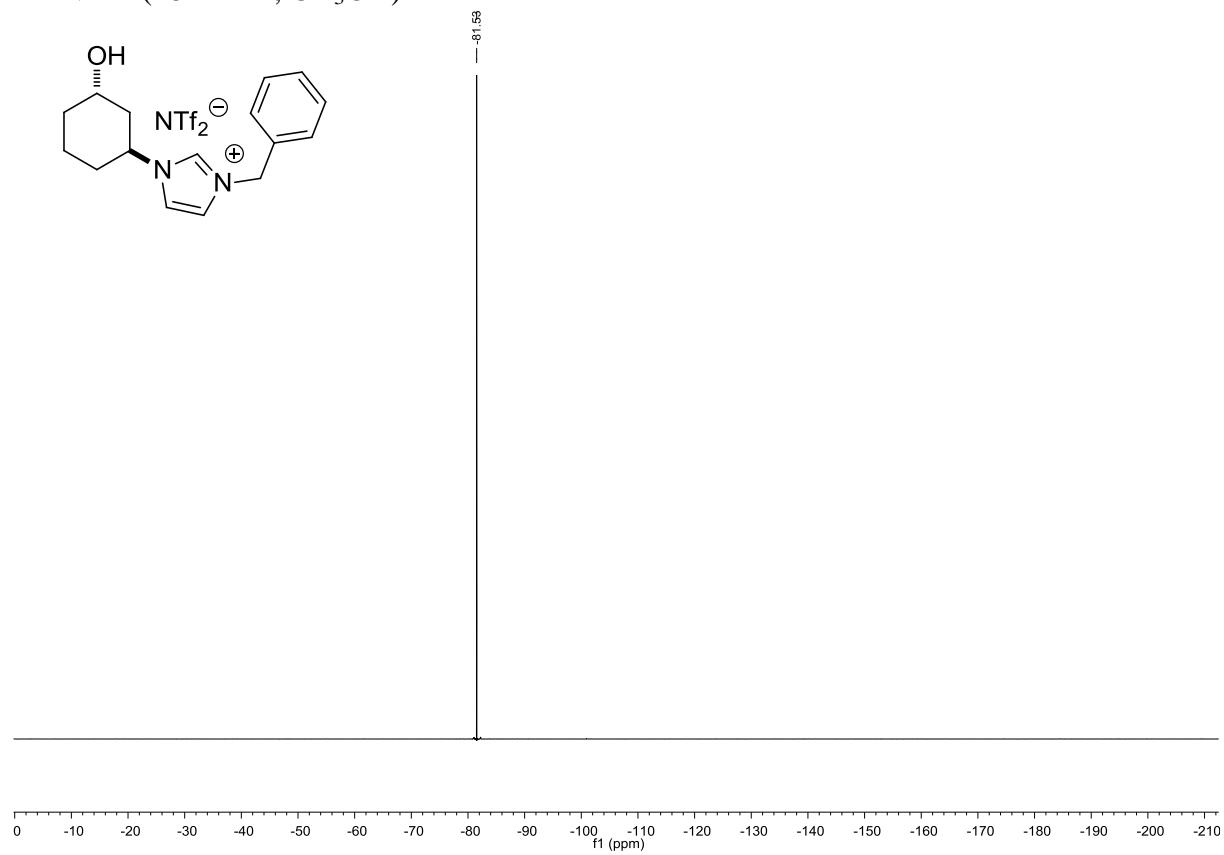
$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)

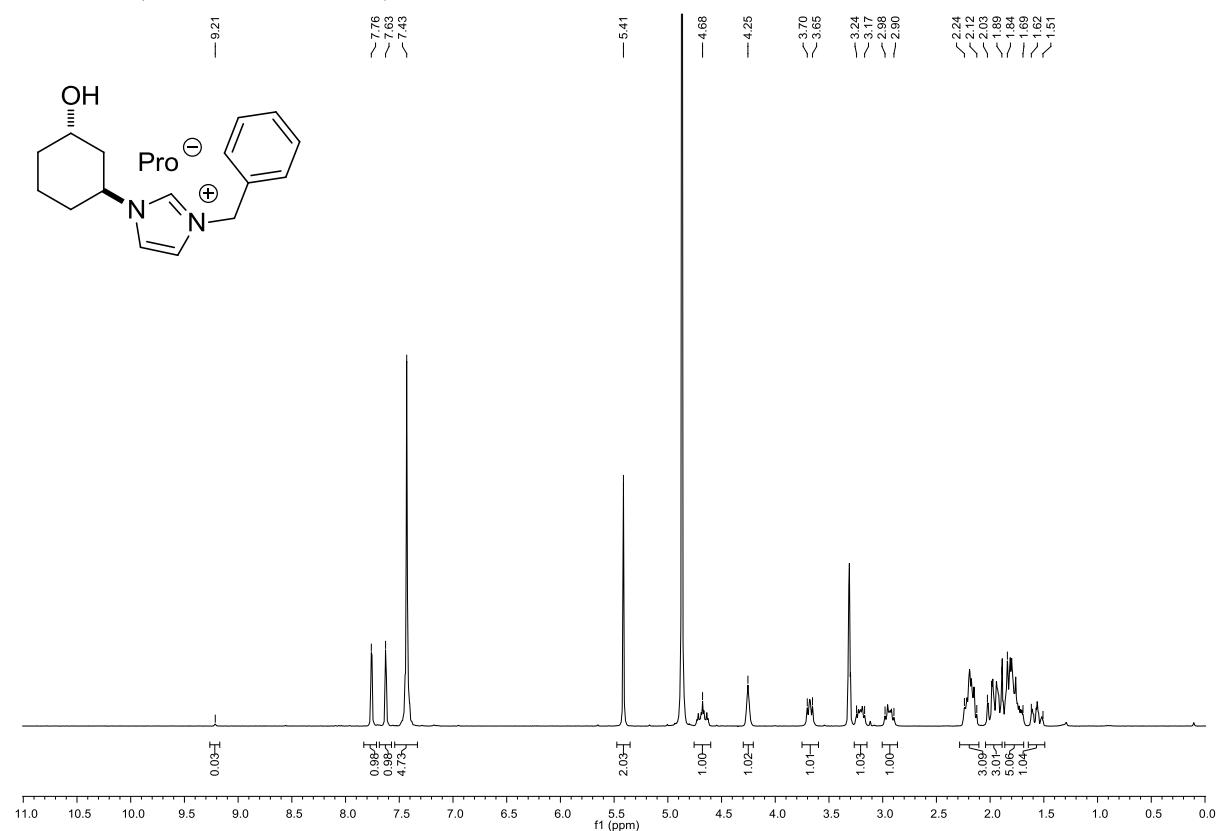


<sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD)

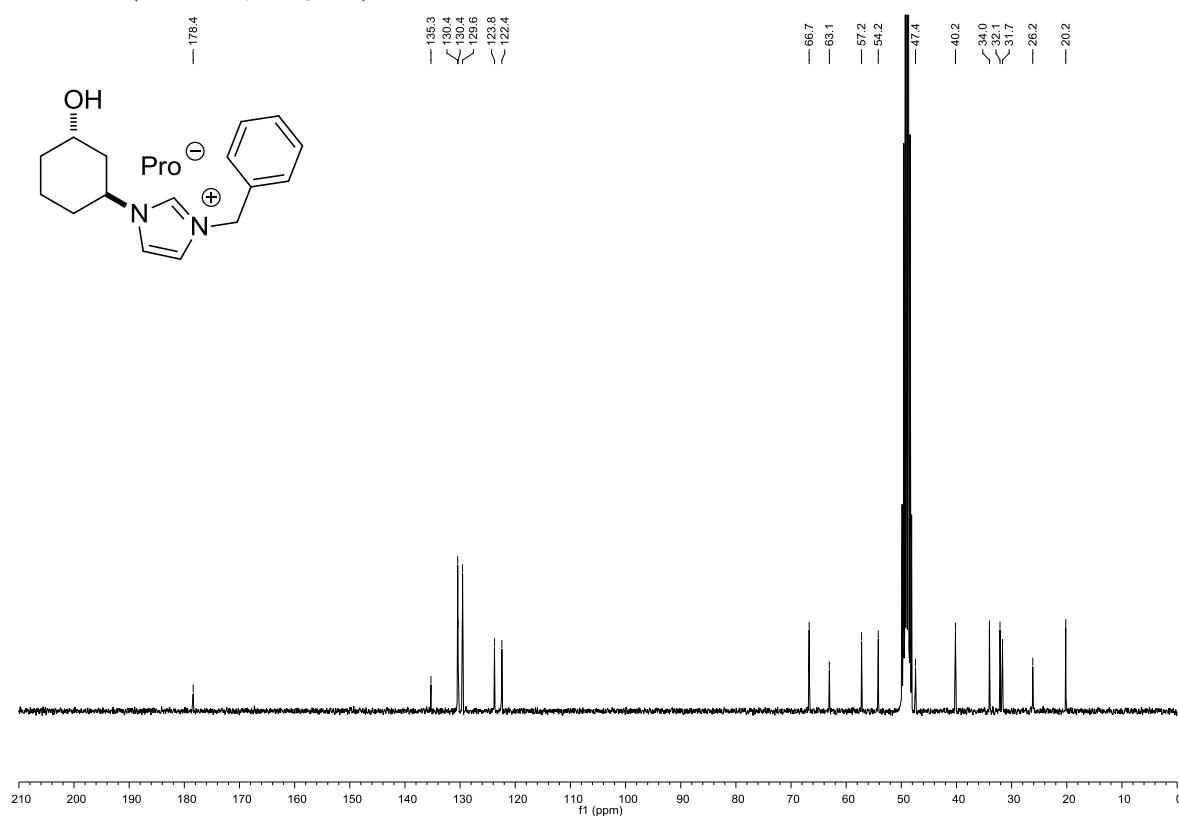


**( $\pm$ )-*trans*-3-Benzyl-1-(3-hydroxycyclohexyl)-1*H*-imidazol-3-ium pyrrolidine-2-carboxylate**

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )



$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )



DEPT-135 NMR (75 MHz, CD<sub>3</sub>OD)

