Supporting Information

Synthesis of the Marine Sponge Derived β_2-Adrenoceptor Agonist S1319

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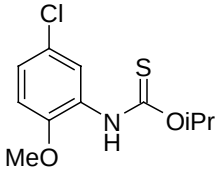
Contents; Experimental for the preparation and cyclisation reactions with DMF, for **3**, **6** and **9**. Experimental and nmr spectra for the preparation of **12** and **2**.

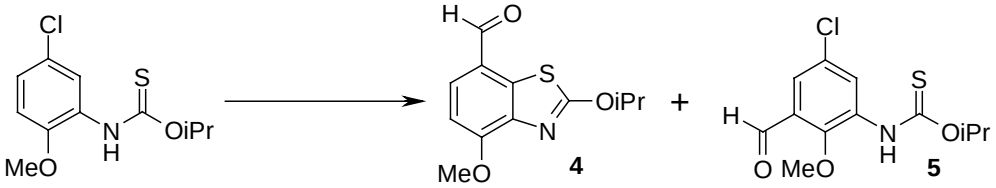
General procedures; Reagents and solvents were purchased from commercial suppliers and used as received. All reactions were carried out under an atmosphere of argon unless otherwise stated. TLC was performed on Merck Kieselgel 60 F254 plates and column chromatography was conducted on Merck Kieselgel 60 (230-400 mesh). Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were recorded neat with a Nicolet Avatar 360 E.S.P. instrument. NMR analyses were performed on Bruker ARX/AV 400 MHz spectrometers at room temperature unless otherwise stated. Chemical shifts (δ) are expressed in ppm relative to residual proton signals in solvent. ^{13}C resonances are assigned from DEPT and ^{1}H-^{13}C correlation experiments as methyl (q), methylene (t), methyne (d) and quaternary (s). High resolution mass spectrometry was performed with a Micromass Time-of-Flight LCT instrument. Elemental analyses were performed on a LECO CHNS 932 instrument for carbon, hydrogen, nitrogen and sulphur, and by argentometric titration for fluorine content.

Preparation of *O*-isopropyl 5-chloro-2-methoxy-phenylthiocarbamate 3;

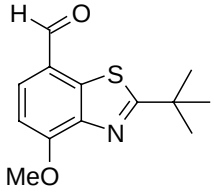


Prepared following the procedure of Hodgkins *et al* from 1-methoy-4-chloro-2-phenylisothiocyanate (81.1 g, 406 mmol).[13] Purification by flash column chromatography, eluent 20:1 hexanes-ethyl acetate, gave **3** as a clear yellow solid (99.2 g, 94% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, br, 1H), 7.74 (s, br, 1H), 7.03 (dd, J = 2 and 8 Hz, 1H), 6.77 (d, J = 8 Hz), 5.66 (septet, J = 6 Hz, 1H), 3.84 (s, 3H), 1.43 (d, br, J = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 187.8 (s, br), 147.0 (s, br), 128.2 (s), 126.0 (s), 124.4 (d), 121.2 (d), 111.5 (d), 77.7 (s, br), 56.5 (q), 22.1 (q).

Cyclisation of 3 and trapping with DMF;

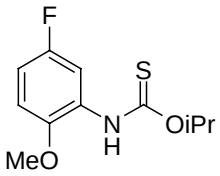


To a solution of **3** (259 mg, 1.0 mmol) in THF (5 ml) cooled at -78 °C ($CO_{2(s)}$ / acetone bath) was added dropwise a solution of *tert*.butyl lithium in pentanes (1.6 ml of 1.7 M solution, 2.8 mmol). The reaction mixture was warmed to -10 °C over 120 minutes then recooled to -78 °C before the addition of DMF (0.4 ml, 5.0 mmol). The reaction mixture was warmed to -10 °C over 60 minutes, $NH_4Cl_{(aq)}$ added, extracted 3-times with chloroform, dried over $MgSO_4$, and evaporated to give the crude reaction mixture as a clear yellow oil. Purification by flash column chromatography on silica gel eluting with chloroform gave three predominant fractions:
Higher running fraction of recovered starting material **3** (*Rf* 0.40) as a clear yellow oil (73 mg, 28% yield).
Intermediate running fraction of *O*-isopropyl 5-chloro-3-formyl-2-methoxy-phenylthiocarbamate **5** (*Rf* 0.28) as a waxy yellow / white solid (75 mg, 26% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.23 (s, 1H), 8.44 (s, br, 1H), 7.55 (d, *J* = 3 Hz, 1H), 5.67 (septet, *J* = 6 Hz, 1H), 3.94 (s, 3H), 1.45 (d, *J* = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 188.0 (d), 185.9 (s, br), 151.5 (s, br), 133.2 (s, br), 130.8 (s), 130.0 (s), 128.0 (d, br), 124.3 (d, br), 75.0 (d, br), 65.0 (q), 22.0 (q).
Lower running fraction of 7-formyl-2-isopropoxy-4-methoxybenzothiazole **4** (*Rf* 0.20) as a white crystalline solid (63 mg, 25% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.92 (s, 1H), 7.65 (d, *J* = 8 Hz, 1H), 6.93 (d, *J* = 8 Hz, 1H), 5.46 (septet, *J* = 6 Hz, 1H), 4.03 (s, 3H), 1.39 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 189.5 (d), 175.8 (s), 156.6 (s), 140.5 (s), 131.7 (d), 131.4 (s), 124.4 (s), 107.6 (d), 76.6 (d), 56.9 (q), 22.3 (q); HRMS calculated for $C_{12}H_{13}NO_3S$ (M^+) 251.0616, found 251.0550.

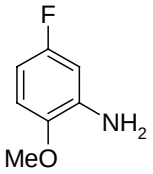


Increasing the *tert*.buyl lithium excess to 3.0 and 3.5 equivalents in the above reaction gave increasing amounts of 7-formyl-4-methoxy-2-*tert*-butyl-benzothiazole as a clear glass; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.94 (s, 1H), 7.76 (d, *J* = 7 Hz, 1H), 6.98 (d, *J* = 7 Hz, 1H), 4.10 (s, 3H), 1.51 (s, 9H).

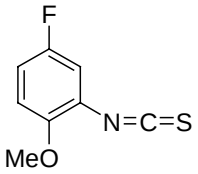
Preparation of *O*-isopropyl 5-fluoro-2-methoxy-phenylthiocarbamate 6;



The title compound **6** was prepared in 3 steps as described below;



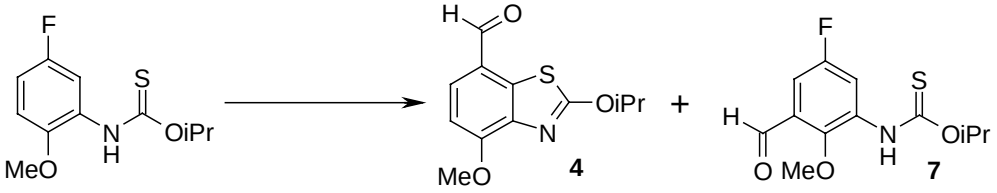
A suspension of platinum (IV) oxide (1 g) in a solution of 4-fluoro-2-nitroanisole (49.1 g, 287 mmol), in methanol (500 ml) was stirred under an atmosphere of hydrogen for 16 hours. Filtration and evaporation gave 5-fluoro-2-methoxyaniline as a clear orange oil (39.9 g, 99%) which was used directly in the next reaction; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.65 (dd, J = 5 and 9 Hz, 1H), 6.44-6.31 (m, 2H), 3.81 (s, br, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.2 (s, J_{C-F} = 231 Hz), 143.8 (s), 137.9 (s, J_{C-F} = 10 Hz), 111.2 (d, J_{C-F} = 10 Hz), 103.7 (d, J_{C-F} = 23 Hz), 102.4 (d, J_{C-F} = 27 Hz), 56.4 (s).



5-fluoro-2-methoxyaniline (39.4 g, 279 mmol) was converted to the corresponding isothiocyanate following the procedure of Hodgkins *et al*.[13] Purification by flash column chromatography, eluent 20:1 hexanes-ethyl acetate, gave 5-fluoro-2-methoxyisothocyanate as a clear pale yellow oil (48.3 g, 95% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93 (dt, J = 8 and 3 Hz, 1H), 6.86-6.78 (m, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 156.6 (s, J_{C-F} = 239 Hz), 153.1 (s), 142.3 (s), 121.9 (s, J_{C-F} = 19 Hz), 114.7 (d, J_{C-F} = 30 Hz), 112.9 (d, J_{C-F} = 29 Hz), 112.3 (d, J_{C-F} = 10 Hz), 56.9 (q).

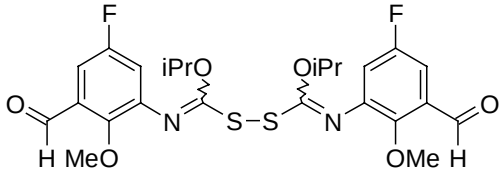
5-fluoro-2-methoxyisothocyanate was converted to **6** by the procedure of Stanetty *et al*.[9] Purification by flash column chromatography, eluent 10:1 hexanes-ethyl acetate, gave **6** as an amorphous orange solid (61.0 g, 90% yield). Recrystallisation of a sample from hexanes gave white prisms; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, br, 1H), 7.40 (s, br, 1H), 6.74-6.59 (m, 2H), 5.57 (septet, br, J = 6 Hz, 1H), 3.73 (s, 3H), 1.35 (s, br, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 187.8 (s, br), 157.9 (s, J_{C-F} = 238 Hz), 144.4 (s, br), 128.0 (s, br), 111.1 (d, J_{C-F} = 9 Hz), 110.3 (d, J_{C-F} = 19 Hz), 108.6 (d, J_{C-F} = 20 Hz), 77.8 (d, br), 56.6 (q), 22.1 (q); HRMS calculated for $C_{11}H_{15}FNO_2S$ (M+H) 244.0808, found 244.0821; Analysis Calculated for $C_{11}H_{14}FNO_2S$: C, 54.30; H, 5.80; N, 5.76; S 13.18. Found: C, 54.52; H, 5.87; N, 5.80; S, 13.01.

Cyclisation of 6 and trapping with DMF;



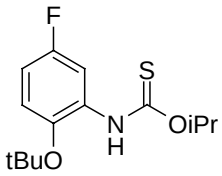
To a solution of **6** (670 mg, 2.75 mmol) in THF (14 ml) cooled at -78 °C ($CO_{2(s)}$ / acetone bath) was added dropwise a solution of *tert*.butyl lithium in pentanes (4.5 ml of 1.7 M solution, 7.70 mmol). The reaction mixture was warmed to -20 °C over 90 minutes then recooled to -78 °C before the addition of DMF (0.5 ml, 6.7 mmol). The reaction mixture was warmed to 10 °C over 90 minutes, $NH_4Cl_{(aq)}$ added, extracted 3-times with dichloromethane, dried over $MgSO_4$, and evaporated to give the crude product mixture as a clear orange oil. Purification by flash column chromatography on silica gel eluting (isocratic) with 33% dichloromethane in hexanes gave three predominant fractions:
Higher running fraction of recovered starting material **6** (*Rf* 0.51) as a clear pale yellow oil (161 mg, 24% yield).
Intermediate running fraction of *O*-isopropyl 5-fluoro-3-formyl-2-methoxy-phenylthiocarbamate **7** (*Rf* 0.33) as a clear yellow oil (129 mg, 17% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.18 (s, 1H), 8.75 (s, br, 1H), 7.22 (d, *J* = 6 Hz, 1H), 5.10 (septet, *J* = 6Hz, 1H), 3.86 (s, 3H), 1.39 (d, *J* = 6Hz, 6H); HRMS calculated for $C_{12}H_{15}FNO_3S$ (M+H) 272.0757, found 272.0763.
Lower running fraction of 7-formyl-2-isopropoxy-4-methoxybenzothiazole **4** (*Rf* 0.20) as an off-white solid (198 mg, 29% yield).

Variable amounts of an additional product (*Rf* 0.30), assigned as the disulphide derivative of **7**, shown below, were isolated in runs of this reaction (ranging from less than 5% to *ca.* 10% in the crude reaction mixture). The factors controlling the formation of this byproduct were not investigated further.

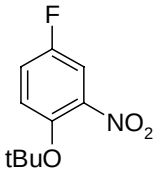


Viscous clear pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.36 (d, *J* = 1 Hz, 2H), 7.22-7.15 (m, 2H), 6.83-6.76 (m, 2H), 5.27 (septet, *J* = 6 Hz, 2H), 3.77 (s, 6H), 1.37 (d, *J* = 6 Hz, 12H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 188.8 (d), 158.7 (s, J_{CF} = 247 Hz), 155.2 (s), 151.3 (s, J_{CF} = 3 Hz), 141.8 (s, J_{CF} = 10 Hz), 130.6 (s, J_{CF} = 8 Hz), 116.2 (d, J_{CF} = 25 Hz), 109.1 (d, J_{CF} = 23 Hz), 74.7 (d), 62.1 (q), 21.6 (q); HRMS calculated for $C_{24}H_{27}F_2N_2O_6S_2$ (M+H) 541.1279, found 541.1319.

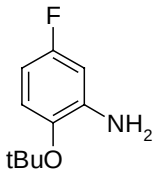
Preparation of *O*-isopropyl 2-*tert*-butoxy-5-fluoro-phenylthiocarbamate 9;



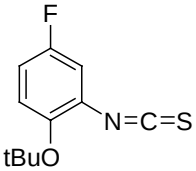
The title compound **9** was prepared in 4 steps as described below;



1-*tert*-Butoxy-4-fluoro-2-nitrobenzene **8** was prepared following procedure of Woiwode *et al* from 2,5-difluoronitrobenzene (18.4 g, 116 mmol).[14] Purification by flash column chromatography, eluent 9:1 hexanes-ethyl acetate, gave **8** as a clear pale yellow oil (22.0 g, 89% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (dd, J = 2 and 8 Hz, 1H), 7.16-7.10 (m, 2H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 157.4 (s, J_{CF} = 253 Hz), 150.0 (s), 145.8 (s, J_{CF} = 10 Hz), 126.8 (d, J_{CF} = 10 Hz), 120.3 (d, J_{CF} = 31 Hz), 112.5 (d, J_{CF} = 31 Hz), 83.5 (s), 29.1 (q).



A solution of **8** (22.0 g, 103 mmol) in methanol (150 ml) was hydrogenated over platinum oxide (1.5 g) under 1 atmosphere of hydrogen for 18 hours at room temperature. Removal of the catalyst by filtration and evaporation gave 2-*tert*-butoxy-5-fluoroaniline as a brown oil (18.07 g, 96% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78 (dd, J = 5 and 9 Hz, 1H), 6.35 (dd, J = 3 and 9 Hz, 1H), 6.23 (ddd, J = 3, 9 and 9 Hz, 1H), 3.80 (s, br, D_2O exchangeable, 2H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 159.8 (s, J_{CF} = 232 Hz), 142.9 (s, J_{CF} = 20 Hz), 139.1 (s, J_{CF} = 9 Hz), 124.0 (d, J_{CF} = 12 Hz), 104.0 (d, J_{CF} = 31 Hz), 102.7 (d, J_{CF} = 31 Hz), 80.2 (s), 29.2 (q).

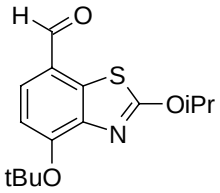


1-*tert*-Butoxy-4-fluorophenylisothiocyanate was prepared from 2-*tert*-butoxy-5-fluoroaniline (6.88 g, 37.60 mmol) following the procedure of Hodgkins *et al*.[13] Purification by flash column chromatography, eluent hexanes, gave the product as a clear pale yellow oil (7.05 g, 83% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (dd, J = 3 and 8 Hz, 1H), 7.03-6.83 (m, 2H), 1.45 (s, 9H).

O-isopropyl 2-*tert*-butoxy-5-fluoro-phenylthiocarbamate **9** was prepared following the procedure of Stanetty *et al* from 1-*tert*-butoxy-4-fluorophenylisothiocyanate (7.05

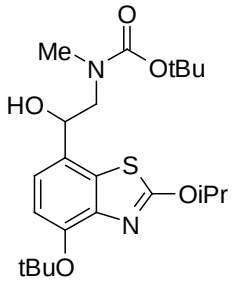
g, 31.20 mmol).[9] Purification by flash column chromatography, eluent 9:1 hexanes-ethyl acetate gave **9** as a viscous pale yellow oil (8.88 g, 80% yield). Recrystallisation of a sample from hexanes gave white plates; mp 65.4-66.2 °C; IR 3314 (br), 2974, 1600, 1516, 1465, 1210, 1142; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.60 (br, s, 1H), 7.38 (br, s, 1H), 7.01 (dd, J = 5 and 9 Hz, 1H), 6.73 (ddd, J = 3, 9 and 9 Hz, 1H), 5.58 (septet, J = 6 Hz, 1H), 1.43-1.32 (m, 6H), 1.32-1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 187.6 (s, br), 158.6 (s, J_{CF} = 241 Hz), 140.7 (s, br), 133.3 (s, br), 123.7 (d, J_{CF} = 9 Hz), 110.5 (d, J_{CF} = 23 Hz), 108.8 (d, J_{CF} = 29 Hz), 81.6 (s), 77.7 (d, br), 29.1 (q), 22.1 (q); Analysis Calculated for $C_{14}H_{20}FNO_2S$: C, 58.92; H, 7.06; N, 4.91; S 11.24. Found: C, 58.84; H, 6.86; N, 4.88; S, 11.43.

Cyclisation of 9 to prepare 7-formyl-2-isopropoxy-4-*tert*-butoxybenzothiazole 10;



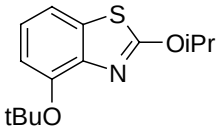
To a solution of **9** (1.42g, 5.0 mmol) in THF (25 ml) cooled at -78 °C ($CO_{2(s)}$ / acetone bath) was added dropwise a solution of *tert*.butyl lithium in pentanes (8.2 ml of 1.7 M solution, 14.0 mmol). The reaction mixture was warmed to -10 °C over 90 minutes then recooled to -78 °C before the addition of DMF (3.9 ml, 50 mmol). The reaction mixture was warmed to 0 °C over 60 minutes, $NH_4Cl_{(aq)}$ added, extracted 3-times with ethyl acetate, the combined organic layers dried over $MgSO_4$, and evaporated. Purification by flash column chromatography on silica gel eluting with dichloromethane gave the product **10** as a clear pale yellow oil (1.14 g, 78% yield); IR 2978, 1679, 1561, 1532, 1236; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.55 (s, 1H), 7.58 (d, J = 7 Hz, 1H), 7.10 (d, J = 7 Hz, 1H), 5.38 (septet, J = 6 Hz, 1H), 1.43 (s, 9H), 1.30 (d, J = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 189.5 (d), 174.8 (s), 153.3 (s), 146.0 (s), 131.5 (s), 129.9 (d), 125.6 (s), 120.2 (d), 82.3 (s), 76.2 (d), 29.1 (q), 21.8 (q); HRMS calculated for $C_{15}H_{20}NO_3S$ (M+H) 294.1156, found 294.1164.

Cyclisation of 9 to prepare *O*-*tert*-butyl *N*-[2-(4-*tert*-butoxy-2-isopropoxybenzothiazol-7-yl)-2-hydroxyethyl]-*N*-methyl-carbamate 12;



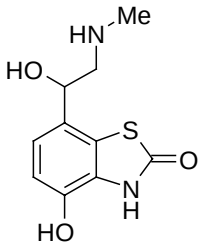
To a solution of **9** (1.04 g, 3.63 mmol) in THF (34 ml) cooled at -78 °C ($CO_{2(s)}$ / acetone bath) was added dropwise a solution of *tert*.butyl lithium in pentanes (6.8 ml of 1.5 M solution, 10.2 mmol). The reaction mixture was warmed to -10 °C over 90

minutes then recooled to -78 °C before the addition of a solution of *O-tert*-butyl *N*-methyl-*N*-(2-oxo-ethyl)-carbamate **11** (756 mg, 4.36 mmol) in THF (2 ml).[15] The reaction mixture was warmed to 0 °C over 60 minutes, $NH_4Cl_{(aq)}$ added, extracted three-times with ethyl acetate, the combined organic layers dried over $MgSO_4$, and evaporated. Purification by flash column chromatography on silica gel eluting with a gradient from 10% to 25% ethyl acetate in hexanes gave two predominant fractions: Higher running minor component consistent with the 7-protonated 2-isopropoxy-4-*tert*-butoxybenzothiazole, shown below, as an off-white waxy solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (dd, *J* = 1 and 8 Hz, 1H), 7.13 (t, *J* = 8 Hz, 1H), 7.02 (dd, *J* = 1 and 8 Hz, 1H), 5.49 (septet, *J* = 6 Hz, 1H), 1.47 (d, *J* = 6 Hz, 6H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.2 (s), 147.9 (s), 146.0 (s), 133.7 (s), 123.7 (d), 122.3 (d), 116.9 (d), 81.0 (s), 76.2 (d), 29.41 (q), 22.2 (q); HRMS calculated for $C_{14}H_{20}NO_2S$ (M+H) 266.1215, found 266.1222.



Lower running major component of the product **12** as a viscous clear pale yellow / green oil (1.17 g, 74% yield); ^{1}H NMR (d_6-DMSO, recorded at 500 MHz with a Bruker AVANCE DRX500 instrument at 398 K) δ 7.05 (d, *J* = 8 Hz, 1H), 6.96 (d, *J* = 8 Hz, 1H), 5.31 (septet, *J* = 6 Hz, 1H), 4.93-4.85 (m, 1H), 3.50-3.38 (m, 2H), 2.75 (s, 3H), 1.44 (d, *J* = 6 Hz, 6H), 1.39 (s, 9H), 1.33 (s, 9H); ^{13}C NMR (d_6-DMSO, recorded at 126 MHz with a Bruker AVANCE DRX500 instrument at 363 K) δ 179.0 (s), 155.3 (s), 146.9 (s), 145.7 (s), 132.6 (s), 129.9 (s), 121.4 (d), 121.3 (d), 80.0 (s), 78.8 (s), 76.1 (d), 71.1 (d), 54.7 (t), 35.7 (q), 29.2 (q), 28.4 (q), 21.9 (q); HRMS calculated for $C_{22}H_{35}N_2O_5S$ (M+H) 439.2267, found 439.2273.

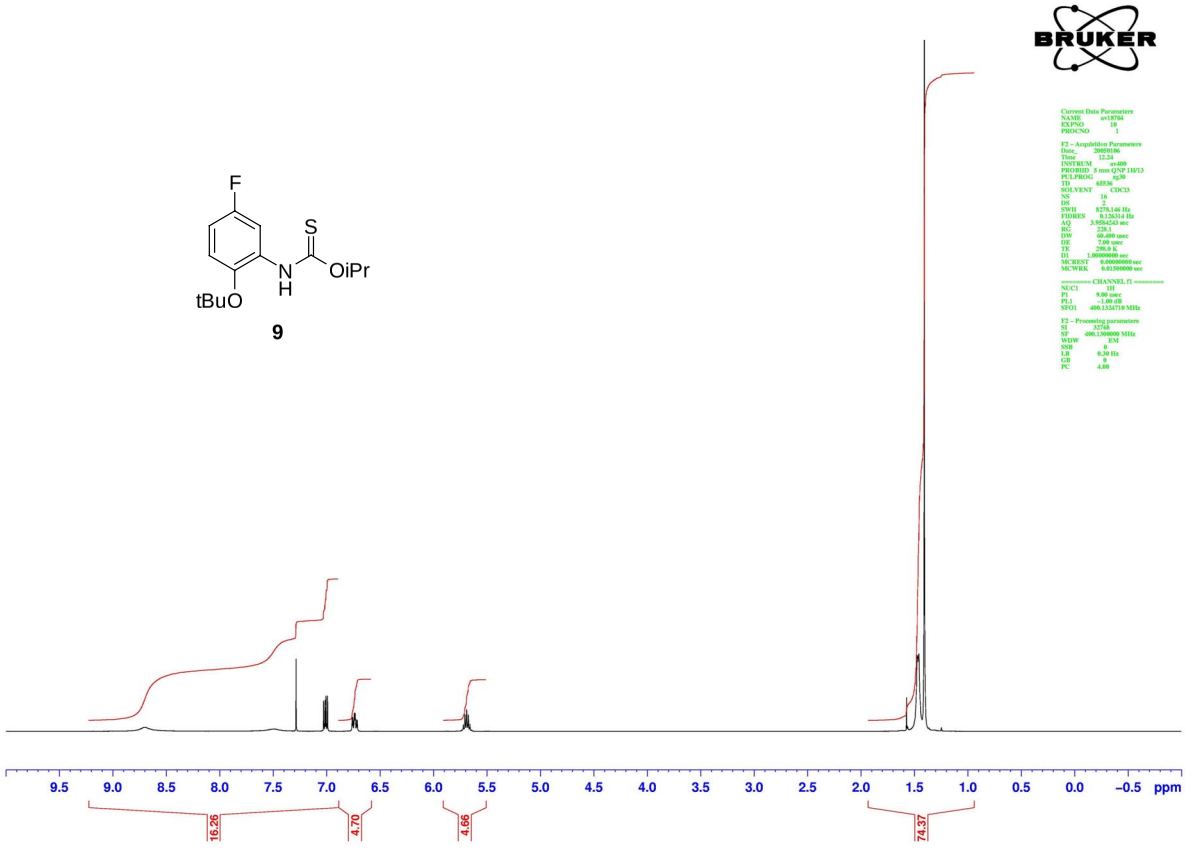
Deprotection of 12 to prepare 4-hydroxy-7-(1-hydroxy-2-methylamino-ethyl)-3*H*-benzothiazol-2-one trifluoroacetate 2;



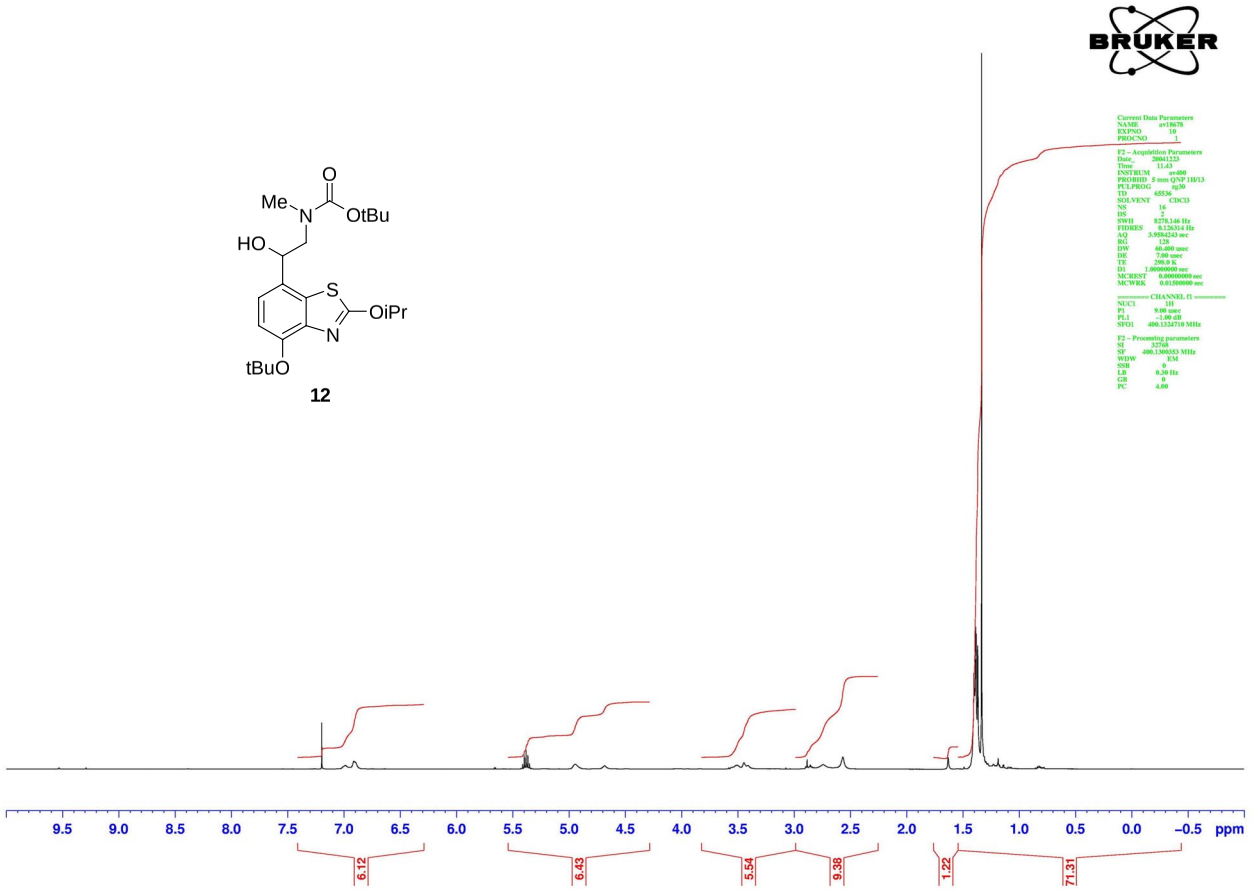
A solution of **12** (1.10 g, 2.51 mmol) in trifluoroacetic acid (12 ml) was stirred at room temperature for 90 minutes then heated at 50 °C for 5 hours (after 90 minutes at room temperature the partially deprotected intermediate lacking the *N*-Boc and 4-*tert*-butoxy protecting groups is formed cleanly, the subsequent heating at 50 °C removes the 2-isopropoxy protecting group). Removal of volatiles followed by repeated evaporation from methanol (3-times 10 ml), stirring in water (20 ml), filtration, evaporation and crystallisation from dichloromethane-methanol (4:1) gave **2** as a white amorphous solid (437 mg, 49% yield); mp 199.5-200.4 °C; ^{1}H NMR (d_4-MeOH, 400 MHz) δ 7.01 (d, *J* = 7 Hz, 1H), 6.68 (d, *J* = 7 Hz, 1H), 5.03-4.95 (m, 1H), 3.23-3.11 (m, 2H), 2.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.5 (s), 163.6 ($CF_3\underline{C}O_2^-$, quartet, $J_{C\text{-}F}$ = 34 Hz), 144.8 (s), 127.5 (s), 126.9 (s), 123.6 (s), 122.6 (d), 118.7 ($\underline{C}F_3CO_2^-$, quartet, $J_{C\text{-}F}$ = 293 Hz), 113.6 (s), 69.9 (d), 55.3 (t), 34.1 (q);

Analysis Calculated for $C_{11}H_{13}F_3N_2O_5S$: C, 40.68; H, 3.70; N, 7.91; S 9.05; F 16.09.
Found: C, 40.54; H, 3.56; N, 7.89; S 9.01; F 16.10.

^{1}H nmr of 9 in $CDCl_3$ at 298K



^{1}H nmr of 12 in $CDCl_3$ at 298K



^{1}H nmr of the trifluoroacetate salt of 2 in d_4-MeOH