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Synthesis of N-BOC-3-Azabicyclo[3.3.0]octan-7-one via Reductive Pauson-Khand Cyclization and Subsequent Conversion to a Novel Diazatricyclic Ring System

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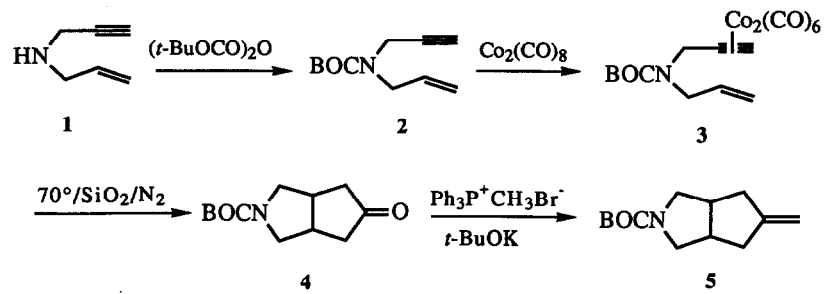
Abstract: *An intramolecular reductive Pauson-Khand reaction of the hexacarbonyldicobalt complex of N-(tert-butyloxycarbonyl)allylpropargylamine under dry-state adsorption conditions directly afforded the saturated N-BOC-3-azabicyclo[3.3.0]octan-7-one when the reaction was performed under an inert atmosphere. This bicyclic ketone was converted in several steps to the novel octahydro-1-azeto[2',3':3,4]cyclopenta[1,2-C]pyrrole ring system as confirmed by single crystal X-ray analysis.*

Pauson has described[1] a detailed study of Pauson-Khand[2] cyclizations of N-protected allylpropargylamines under a variety of experimental conditions in which the expected unsaturated 3-azabicyclo[3.3.0]oct-1-en-7-one products were obtained along with varying amounts of saturated ketone product. In these studies Pauson found that Smit-Caple dry-state adsorption conditions (DSAC)[3] in the presence of oxygen gave the greatest amounts of saturated 3-azabicyclo[3.3.0]octan-7-one, but a mixture is obtained even under these conditions.[4] Another Pauson-Khand approach to the synthesis of 3-azabicyclo[3.3.0]oct-1-en-7-ones was reported by Jeong, who utilized a Nicholas Reaction with amidic nitrogen nucleophiles followed by Pauson-Khand cyclization to synthesize the expected unsaturated enones.[5]

As part of our ongoing research in the preparation of novel serotonergic agents[6] we have explored the chemistry of 3-azabicyclo[3.3.0]octan-7-ones and have developed an efficient synthesis of the versatile intermediate N-(tert-butyloxycarbonyl)-3-azabicyclo[3.3.0]octan-7-one **4** utilizing a *reductive* Pauson-Khand cyclization based on a modification of Pauson's[1] approach. Specifically, we have discovered that the Pauson-Khand cyclization of N-BOC-allylpropargylamine yields exclusively the saturated ketone **4** when the reaction is performed under DSAC conditions *under an inert atmosphere.*[7] This reaction is general for other allylpropargylamines when the nitrogen is protected as the acetyl, Cbz, tosyl or benzoyl derivatives.[7]

Additionally, we have converted the ketone **4** into the novel,[8] rigid tricyclic diamine **10**, as conformationally restricted diamines are interesting as potentially pharmacologically active agents[9] and pharmaceutical intermediates.

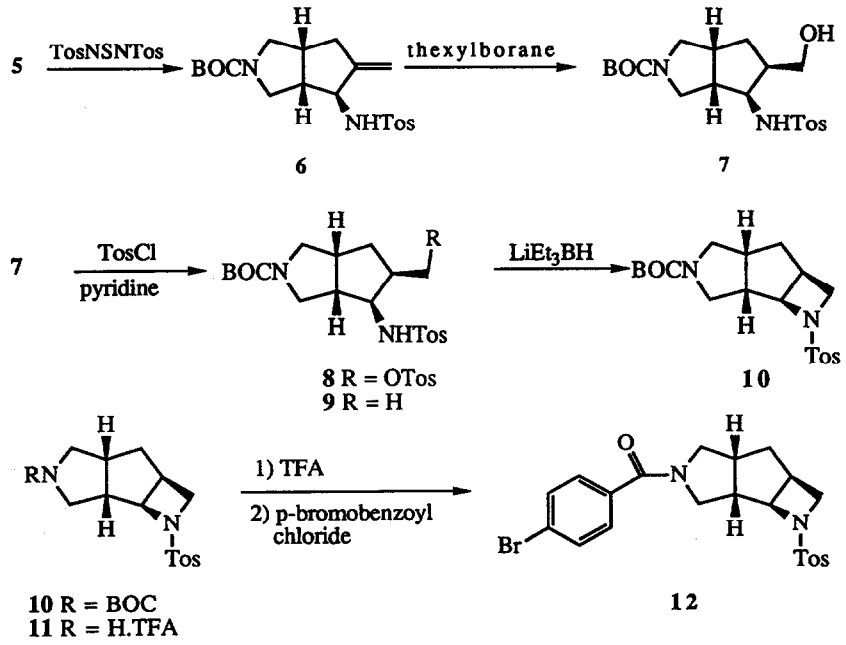
Scheme 1 describes the rapid assembly of 3-azabicyclo[3.3.0]octan-7-one **4** utilizing the reductive Pauson-Khand cyclization reaction under DSAC conditions under nitrogen and subsequent conversion to the corresponding exocyclic methylene compound **5**. Allylpropargylamine[10] **1** was protected as the *t*-butylcarbamate derivative **2** in 95% distilled yield and subsequently converted to the hexacarbonyldicobalt complex **3** (77%) by exposure to octacarbonyldicobalt.[11] Adsorption of cobalt complex **3** onto silica gel followed by heating at 70°C under nitrogen for 2.5 h cleanly gave the in-situ reduced ketone **4** in 85% without contamination by the corresponding unsaturated enone. We have observed that the in-situ reduction giving rise to 3-azabicyclo[3.3.0]octan-7-one is optimal when the DSAC Pauson-Khand cyclization is performed under an inert atmosphere,[7] rather than in air according to standard DSAC protocol.[1,3] Wittig methylenation of **4** (Scheme 2) utilizing potassium t-butoxide[12] gave the exocyclic methylene compound **5** in 82% yield.



Scheme 1

The exo-p-toluenesulfonamide **6** (Scheme 2) was prepared stereoselectively from olefin **5** in 81% yield[13] with the Sharpless allylic amination procedure utilizing bis(p-toluenesulfonyl)sulfodiimide.[14] The epimeric (endo) tosylamide was not detected in the reaction mixture. Hydroboration with thexylborane followed by an oxidative workup gave an epimeric mixture of alcohols which were separated by flash chromatography to give the desired exo alcohol **7** in 44% yield and the epimeric endo alcohol in 38% yield. Rhodium-catalyzed hydroboration[15] utilizing an excess of catecholborane and Wilkinson's catalyst gave a 1.23:1 mixture of **7** and the endo isomer by HPLC, but the reaction was extremely slow. Tosylation of **7** with p-toluenesulfonyl chloride in pyridine gave the tosylate **8** and subsequent treatment with lithium triethylborohydride gave rise to a visible effervescence and clean formation of the azetidine compound **10** in quantitative yield from alcohol **7**. None of the reduced exo-methyl compound **9** was observed. The structural assignment of **10** was made based on proton and ^{13}C NMR, IR, high resolution MS, and combustion analysis. To confirm the unusual azetidine-containing tricyclic structure of **10** we sought to obtain a crystal structure. Crystals of **10** were unsuitable for crystallography, so the BOC group was removed with trifluoroacetic acid and the resulting amine **11** was

acylated with p-bromobenzoyl chloride to give the amide **12** (86% from **10**), which gave suitable crystals from ethyl acetate. The crystal structure of **12** is shown in Figure 1[16] confirming the novel ring system.



Scheme 2

In conclusion, we have employed a *reductive* Pauson-Khand cyclization to rapidly assemble the versatile intermediate N-(tert-butyloxycarbonyl)-3-azabicyclo[3.3.0]octan-7-one **4** without contamination by the usual enone product. Cobalt presumably functions as the reducing agent and silica gel as the proton source in the reduction. Compound **4** was then converted in good yield to tricycle **10**, which contains a novel, fused-azetidine ring system. In addition, the generality[7] of the reductive Pauson-Khand reaction should increase the utility of this already very useful reaction.

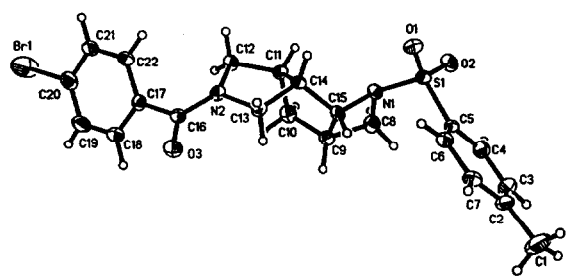


Figure 1: ORTEP drawing of 12

EXPERIMENTAL SECTION

General. All reactions were performed under an atmosphere of argon. Chemicals were purchased from Aldrich Chemical Co. and used without further purification. p-Bromobenzoyl chloride was recrystallized from n-pentane prior to use. THF was distilled from sodium benzophenone ketyl immediately prior to use. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Merck Kieselgel 60 F254 DC-Fertigplatten (0.25 mm, Art. 5719) were used for TLC. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. MIR refers to multiple internal reflectance infrared spectroscopy. ^{1}H NMR spectra were recorded at 300 MHz with TMS as an internal reference. Noise-decoupled and APT ^{13}C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer. IR spectra were recorded on a Perkin Elmer 685 spectrophotometer. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Elemental analyses were conducted on a Control Equipment CEC240-XA instrument. Compounds obtained as hydrates are indicated as such with the molecular formula.

N-(tert-Butyloxycarbonyl)-allylpropargylamine 2

To a solution of amine **1**[10] (14.3 g, 0.15 mol) in dry THF (150 mL) was added solid di-tert-butyl dicarbonate (32.7 g, 0.15 mol) in portions over 10 min, which gave rise to a vigorous effervescence. After continued stirring at rt for 5 d, the solvent was removed on the rotary evaporator, and the residue was distilled to give the desired carbamate **2** (28.3 g, 97%) as a colorless oil: bp 62-64°C (0.05 mm Hg); IR (neat) ν 3301, 3253, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1 H, ddt, J = 16, 10, 6 Hz), 5.18 (1 H, d, J = 16 Hz), 5.16 (1 H, d, J = 10 Hz), 4.02 (2 H, br s), 3.94 (2 H, d, J = 6 Hz), 2.18 (1 H, t, J = 2 Hz), 1.47 (9 H, s); ^{13}C NMR (100 MHz, $CDCl_3$; doubling observed due to rotamers) δ 154.7, 146.6, 133.2, 116.9 (br), 85.1, 80.2, 77.3, 71.2, 48.4, 35.2, 28.3, 27.3. Anal calcd for $C_{11}H_{17}NO_2 \cdot 0.2H_2O$: C, 66.43; H, 8.82; N, 7.04. Found: C, 66.37; H, 8.83; N, 6.82.

N-(tert-Butyloxycarbonyl)-allylpropargylamine Hexacarbonyldicobalt Complex 3

To BOC-allylpropargyl amine **2** (0.39 g, 2.00 mmol) in ether (10 mL) was added solid dicobalt octacarbonyl (684 mg, 2.00 mmol) in one portion which gave rise to a vigorous evolution of carbon monoxide (CAUTION). After stirring under argon for 19 h, the solvent was removed in vacuo and the residue was applied to a bed of silica gel (19 g) and eluted with ether/n-pentane (5/95). A fast green-brown band [$Co_4(CO)_{12}$] was followed by a blood-red band which was collected and concentrated to give the cobalt complex **3** (0.70 g, 73%) as a thick red oil: IR ($CHCl_3$) ν 3008, 2081, 2048, 2022, 1992, 1681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$; doubling observed due to rotamers) δ 6.06 (1 H, s), 5.80 (1 H, br m), 5.28-5.09 (2 H, br m), 4.55 (2 H, s), 4.02-3.86 (2 H, br m), 1.49 & 1.45 (9 H, 2 br s). Anal calcd for $C_{17}H_{17}NO_8Co_2$: C, 42.43; H, 3.56; N, 2.91. Found: C, 42.34; H, 3.56; N, 2.92.

N-(tert-Butyloxycarbonyl)-3-Azabicyclo[3.3.0]octan-7-one 4

To a slurry of silica gel (31 g, 10g/mmol) in ether was added a solution of hexacarbonyldicobalt complex **3** (1.50 g, 3.12 mmol) and the suspension was concentrated on a rotary evaporator at rt. The free-flowing pink

powder in the same flask was then thoroughly purged with nitrogen (7 X house vacuum alternating with nitrogen). With a slow flow of nitrogen through the rotary evaporator the rotating flask was then immersed in a 70°C water bath for 3 h. The silica, which then had a blue-gray color, was allowed to cool and then loaded onto a frit and rinsed with ethyl acetate (3 X 100 mL). Concentration of the eluent in vacuo gave a residue which was chromatographed on silica gel eluting with 30/70 ethyl acetate/hexane to give the desired azabicyclic ketone **4** (547 mg, 78%) as a colorless oil which solidifies on standing: mp 68-70.5°C; bp 120°C at 0.15 mm Hg [CAUTION: Compound **4** should *not* be distilled from the crude mixture containing cobalt-residues, as we have observed a violent thermal decomposition when attempting to distill the crude product when prepared in this manner. The chromatographed ketone may be distilled without incident.]; IR (MIR) ν 1737, 1680, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (2 H, br m), 3.22 (2 H, br dd, J = 19, 8 Hz), 2.93 (2 H, m), 2.49 (2 H, dd, J = 19, 8 Hz), 2.16 (2 H, dd, J = 19, 5 Hz), 1.46 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, doubling observed due to rotamers) δ 217.2, 154.2, 79.2, 50.5 (br), 42.1, 39.2, 38.3, 28.2. HRMS calcd for $C_{12}H_{19}NO_3$ m/z 225.1365, found 225.1360. Anal calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.69; H, 8.50; N, 6.16.

Exocyclic Methylene Derivative 5

To a suspension of potassium tert-butoxide (278 mg, 2.48 mmol) in dry THF (5 mL) at rt was added solid methyltriphenylphosphonium bromide (886 mg, 2.48 mmol; freshly dried at 61°C at 1 mm Hg for 16 h). The yellow suspension was warmed to 35°C for 30 min, then cooled to rt and the ketone **4** (542 mg, 2.41 mmol) was added as a solution in THF (3 mL). The reaction was heated to 40°C for 45 min, cooled to rt, and quenched with water (15 mL). The mixture was extracted with ether (3 X 25 mL), washed with water and brine, and dried (Na_2SO_4). Concentration gave a residue (1.107 g) which was applied to a bed of silica gel using CH_2Cl_2 (2 mL) to effect complete solubilization of the residue, and eluted with 20/80 ethyl acetate/hexane to give the desired olefin **5** (442 mg, 82%) as a colorless oil which solidified on standing: IR (KBr) ν 3420 (br), 1690, 1388, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88, (2 H, br s), 3.52 (2 H, m), 3.16 (1 H, d, J = 10 Hz), 3.07 (1 H, d, J = 10 Hz) ,2.67 (2 H, m), 2.56 (2 H, dd, J = 16, 6 Hz), 2.19 (2 H, d, J = 16 Hz) 1.45 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, doubling observed due to rotamers) δ 154.6, 151.1, 107.1, 79.0, 51.1, 50.8, 43.0, 42.2, 37.4, 28.5. HRMS calcd for $C_{13}H_{21}NO_2$ m/z 223.1572, found 223.1578. Anal calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.03; H, 9.47; N, 6.20.

p-Toluenesolfonamide 6

To exocyclic olefin **5** (1.57 g, 7.02 mmol) in dry CH_2Cl_2 (8 mL) at 0°C under argon was added a solution of bis-(toluenesulfonyl)sulfodiimide[17] (2.73 g, 7.37 mmol) in dry CH_2Cl_2 (15 mL). After 1 h at 0°C, the reaction was allowed to warm to rt. and stirred for 16 h. Concentration then gave a yellow foam to which was added 50 mL of a K_2CO_3 stock solution prepared from 30 g K_2CO_3/150 mL MeOH/100 mL H_2O) and the resulting solution was stirred for 5 h. After 4 h an additional 15 mL of K_2CO_3 solution was added. Concentration in vacuo gave a slurry to which was added 1 N NaOH/brine (2:1, 100 mL) and the mixture was extracted with 2:1 ether/chloroform (3 X 75 mL). The combined organic extractions were washed successively with 2:1 NaOH/brine (2 X 50 mL, to remove residual p-toluenesulfonamide), brine, and dried (Na_2SO_4). Concentration

gave the desired allylic tosylamide **6** (2.74 g, 86%) as a crystalline solid: mp 166.5-168°C; IR (KBr) ν 3110 (br), 1661, 1408, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (2 H, d, J = 8 Hz), 7.52 (2 H, d, J = 8 Hz), 5.06-4.62 (3 H, m), 3.82 (1 H, t, J = 6 Hz), 3.51 (1 H, m), 3.36 (1 H, dd, J = 12, 7 Hz), 3.27 (1 H, m), 3.05 (1 H, m), 2.75-2.55 (2 H, m), 2.54-2.45 (1 H, m), 2.44 (3 H, s), 2.18 (1 H, d, J = 15 Hz), 1.45 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 143.4, 137.8, 129.6, 126.9, 109.9, 79.2, 61.0, 51.0, 48.8, 39.6, 38.6, 35.0, 28.4, 21.4; MS m/e calcd for $C_{20}H_{28}N_2O_4S$ 392, found 392. Anal calcd for $C_{20}H_{28}N_2O_4S.1/4H_2O$: C, 60.50; H, 7.24; N, 7.06; S, 8.08. Found: C, 60.42; H, 7.10; N, 6.98; S, 8.24.

Alcohol 7

To borane-THF complex (42.1 mL of a 1 M solution in THF, 42.1 mmol) at 0°C was added 2,3-dimethyl-2-butene (42.1 mL of a 1 M solution in THF, 42.1 mmol) over 45 min. After stirring for 3.5 h at 0°C, a solution of olefin **6** (4.59 g, 11.4 mmol) in dry THF (70 mL) was added via cannula. After the addition was complete the reaction was allowed to warm to rt and then stirred for 16 h. The solution was then recooled to 0°C and 10% aqueous NaOH (21.5 mL, 53.8 mmol) was slowly and carefully added (effervescence) followed by the slow addition of 30% H_2O_2 (17.9 mL, 158 mmol; exotherm). Stirring was continued for 1 h at 0°C, then 2 h at rt Concentration gave a white slurry which was extracted with ether (5 X 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a colorless foam (5.18 g). Chromatography on silica gel eluting with ethanol/CH_2Cl_2 (1.5/98.5) gave the exo alcohol **7** (2.11 g, 44%) as a colorless foam: mp 47-57°C; IR (KBr) ν 3430 (br), 3250 (br), 1689, 1663, 1409, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (2 H, d, J = 8 Hz), 7.32 (2 H, d, J = 8 Hz), 5.50 (1 H, br s), 3.73 (1 H, m), 3.66 (1 H, m), 3.54-3.42 (2 H, m), 3.31 (1 H, t, J = 10 Hz), 3.09 (2 H, br m), 2.72 (1 H, m), 2.56-2.38 (1 H, m), 2.44 (3 H, s), 2.30 (1 H, br m), 2.16 (1 H, br m), 1.77 (1 H, dt, J = 13, 9 Hz), 1.54 (1 H, m), 1.42 (9 H, s); HRMS m/z calcd for $C_{20}H_{30}N_2O_5S$ 353.1171, found 353.1171. Anal calcd for $C_{20}H_{30}N_2O_5S{\cdot}0.1H_2O$: C, 58.26; H, 7.38; N, 6.79; S, 7.78. Found: C, 57.95; H, 7.38; N, 6.84; S, 7.89.

Tosylate 8

To a solution of exo alcohol **7** (100 mg, 0.244 mmol) in pyridine (1 mL) at 0°C was added p-toluenesulfonyl chloride (139 mg, 0.73 mmol). After complete dissolution was effected with stirring, the pale yellow solution was allowed to stand at 0°C for 60 h. Ice (2 g) was then added and the solution was extracted with Et_2O (5 X 3 mL). The combined extracts were washed consecutively with H_2O (5 X 10 mL) and brine and then dried over Na_2SO_4. Concentration gave the desired tosylate **8** (141 mg, 100%) as a colorless solid: mp 64-66°C; IR (MIR) ν 3288 (br), 1691, 1660, 1361, 1173, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2 H, d, J = 8 Hz), 7.72 (2 H, d, J = 8 Hz), 7.37 (2 H, d, J = 8 Hz), 7.30 (2 H, d, J = 8 Hz), 5.08 (1 H, br s), 4.11-3.94 (2 H, br m), 3.50-3.35 (2 H, m), 3.19 (1 H, dd, J = 11, 8 Hz), 3.10-2.37 (2 H, br m), 2.67 (1 H, m), 2.46 (3 H, s), 2.43 (3 H, s), 1.83 (1 H, dq, J = 9, 7 Hz), 1.62 (1 H, m), 1.40 (9 H, s); Anal calcd for $C_{27}H_{36}N_2O_7S_2{\cdot}0.6H_2O$: C, 56.34; H, 6.52; N, 4.87; S, 11.14. Found: C, 56.37; H, 6.38; N, 4.68; S, 10.86.

Diazatricycle 10

To a solution of tosylate **8** (85 mg, 0.15 mmol) in dry THF (1.5 mL) at 0°C was added lithium triethylborohydride (0.20 mL of a 1 M solution in THF, 0.20 mmol), which gave rise to a vigorous effervescence. The solution was then warmed to rt over 2 h and then quenched with the addition of 2N NaOH (2 mL) and extracted with Et_2O (3 X 5 mL). The combined extracts were washed successively with H_2O and brine and dried over Na_2SO_4. Concentration gave a residue (80 mg) which was purified by chromatography on silica gel eluting with 1.5/98.5 EtOH/CH_2Cl_2 to give the tricyclic compound **10** (59 mg, 100%) as a colorless solid: mp 160-163°C; IR (KBr) 3420 (br), 1694, 1401, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (2 H, d, J = 8 Hz), 7.37 (2 H, d, J = 8 Hz), 4.26 (1 H, d, J = 6 Hz) 3.77 (1 H, q, J = 8 Hz), 3.52 - 3.32 (4 H, m), 3.18 (1 H, br m), 2.91 (1 H, dd, J = 10, 6 Hz), 2.80 (1 H, br m), 2.67 (1 H, q, J = 10 Hz), 2.46 (4 H, br s), 1.98 (1 H, m), 1.50 (1 H, m), 1.44 (9 H, s). ^{13}C NMR (125 MHz, DMSO-d_6, doubling observed due to rotamers) δ 153.7, 143.6, 132.2, 129.8, 127.8, 78.2, 70.6, 70.5, 53.7, 50.1, 49.8, 49.8, 48.8, 45.6, 45.4, 42.1, 41.2, 34.5, 33.6, 28.1, 21.0 ppm. HRMS *m/z* calcd for $C_{20}H_{28}N_2O_4S$: 392.1770, Found: 392.1781. Anal calcd for $C_{20}H_{28}N_2O_4S \cdot 0.8H_2O$: C, 59.03; H, 7.33; N, 6.88; S, 7.88. Found: C, 59.22; H, 7.15; N, 6.50; S, 7.18.

TFA Salt 11

The BOC amine **10** (21 mg, 0.053 mmol) was dissolved in freshly distilled TFA (5 mL) and then concentrated in vacuo to give the TFA salt **11** (23 mg, 100%) as a colorless solid: IR (MIR) 1673, 1340, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (2 H, d, J = 8 Hz), 7.47 (2 H, d, J = 8 Hz), 4.37 (1 H, d, J = 6 Hz), 3.76 (1 H, t, J = 9 Hz), 3.57-3.35 (4 H, m), 3.29 (1 H, m), 3.05 (1 H, dt, J = 7, 10 Hz), 2.86 (1 H, m), 2.75 (1 H, t, J = 11 Hz), 2.46 (3 H, s), 2.13 (1 H, dd, J = 14, 8 Hz), 1.59 (1 H, dt, J = 14, 10 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 145.9, 133.7, 131.1, 129.3, 71.8, 55.4, 52.3, 51.3, 46.4, 44.7, 35.7, 35.6, 21.6. HRMS *m/z* (M+1) calcd for $C_{15}H_{21}N_2O_2S$: 293.1324, Found: 293.1317.

p-Bromobenzamide 12

The TFA salt **11** (20 mg, 0.049 mmol) was treated with 20% K_2CO_3 (1 mL) and extracted with $CHCl_3$ (3 X 5 mL). The combined extracts were washed successively with H_2O and brine and dried over Na_2SO_4. Concentration gave the free amine (17 mg, 100%) as an oil. To a solution of the amine in dry $CHCl_3$ (0.4 mL) was added Et_3N (10 mg, 0.098 mmol) followed by solid p-bromobenzoyl chloride (13 mg, 0.059 mmol). After 48 h at rt the reaction was concentrated in vacuo to give a residue which was purified by chromatography on silica gel eluting with 60/30/10 EtOAc/hexane/CH_2Cl_2 to give the desired p-bromobenzamide **12** (20 mg, 86%) as a colorless solid: mp 163-166°C (EtOAc); IR (MIR) ν 1622, 1589, 1414, 1337, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, doubling observed due to rotamers) δ 7.74 (0.6 H, d, J = 8 Hz), 7.68 (0.4 H, d, J = 8 Hz), 7.54 (2 H, br d, J = 8 Hz), 7.42-7.30 (4 H, m), 4.31 (0.6 H, d, J = 6 Hz), 4.18 (0.4 H, d, J = 6 Hz), 3.83-3.66 (3 H, m), 3.57-3.20 (3 H, m), 3.13-2.94 (2 H, m), 2.81 (1 H, m), 2.47 (1.8 H, s), 2.45 (1.2 H, s), 2.09 (0.4 H, dd, J = 14, 8 Hz), 1.93 (0.6 H, dd, J = 14, 8 Hz), 1.56 (0.4 H, m), 1.37 (0.6 H, m); ^{13}C NMR (75 MHz,

CD_3OD, doubling observed due to rotamers) δ 169.1, 144.0, 135.2, 132.6, 131.6, 129.8, 128.9, 128.7, 128.0, 127.9, 124.5, 71.0, 70.3, 54.1, 53.7, 50.74, 50.71, 49.2, 48.8, 46.3, 43.1, 41.3, 35.2, 34.5, 34.2, 29.7, 21.6.

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16. Crystal data for compound **12**: $C_{22}H_{23}BrN_2O_3S$, M = 475.4, monoclinic, space group $P2_1/c$, a = 15.408(7) Å, b = 9.890(3) Å, c = 14.713(4) Å, b = 107.49(3)°, V = 2138.6(8) $Å^3$, D_c = 1.476 Mg/m^3 for Z = 4 (at 173K), l = 0.71073 Å, absorption coefficient = 2.045 mm^{-1}. A list of refined coordinates and e.s.d.'s has been deposited at the Cambridge Crystallographic Data Centre.
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