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An efficient synthesis of (7*S*,10*R*)-2-bromo-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole: application in the preparation and structural confirmation of a potent 5-HT$_6$ antagonist

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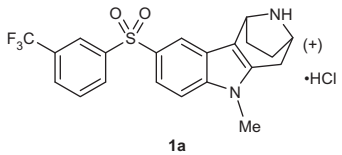
ABSTRACT

(7*S*,10*R*)-5-Methyl-2-((3-(trifluoromethyl)phenyl)sulfonyl)-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole **1a** is a potent 5-HT$_6$ antagonist (h5-HT$_6$ K_i = 1.5 nM) which is derived from an epiminocyclohept[*b*]indole scaffold. In order to synthesize **1a** on a multi-gram scale to support advanced biological testing, an efficient chiral resolution of the intermediate *tert*-butyl 2-bromo-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate **2** was developed. After derivatizing **2** with (1*R*)-(−)-menthyl chloroformate it was found that a single diastereomer **7a** could be isolated by selective precipitation from *n*-hexane. The absolute stereochemistry of **7a** was determined by X-ray crystallography and the structure was confirmed as (7*S*,10*R*)-*tert*-butyl 2-bromo-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate. Removal of the chiral auxiliary under basic conditions afforded intermediate **2a** in >99% enantiomeric purity and with 80% yield based on recovery from the racemic compound **2**. Intermediate **2a** was used successfully to synthesize 5-HT$_6$ antagonist **1a** on a multi-gram scale.

1. Introduction

The 5-HT$_6$ receptor is a G-protein coupled receptor (GPCR) which is localized primarily in the central nervous system.[1] The 5-HT$_6$ receptor is expressed in areas of the brain known to be involved in learning and memory.[2] Antagonism of the 5-HT$_6$ receptor has been demonstrated to induce beneficial effects in treating cognitive deficits associated with conditions such as Alzheimer's disease and schizophrenia.[3] An advanced 5-HT$_6$ antagonist SB-742457 is currently in Phase II trials for treating cognitive deficits associated with Alzheimer's disease.[4] In addition, 5-HT$_6$ modulators have shown promising signs of efficacy in pre-clinical animal models for anxiety and depression,[5] epilepsy,[6] and pain.[7] Moreover, 5-HT$_6$ modulators, in particular antagonists, have also been pursued and studied as potential therapeutic agents for the treatment of obesity. Modulation of the 5-HT$_6$ receptor has been shown to produce significant weight loss in rodent models of obesity.[8]

We have recently reported the discovery and structure activity relationship (SAR) development of a new series of 5-HT$_6$ antagonists.[9] The rational design and employment of 5-HT$_6$ ligand-receptor pharmacophore models led us to successfully identify arylsulfone-substituted epiminocyclo-hepta[*b*]indoles as a potent lead series with a tractable SAR. Taking into account the chiral nature of the epiminocyclo-hepta[*b*]indole ring system and possible differences in the biological activity in vivo, high importance was also placed on profiling compounds of interest as individual enantiomers during optimization studies. Through this work compound **1a** (Fig. 1), characterized as the (+)-enantiomer with unknown stereochemistry, was identified as a potent 5-HT$_6$ antagonist with a favorable in vitro profile. Compound **1a** was selected as an advanced lead, which was suitable for further in vivo profiling. In or-



1a
h5-HT$_6$ K_i = 1.5 nM

Figure 1. Formula of 5-HT$_6$ antagonist **1**.

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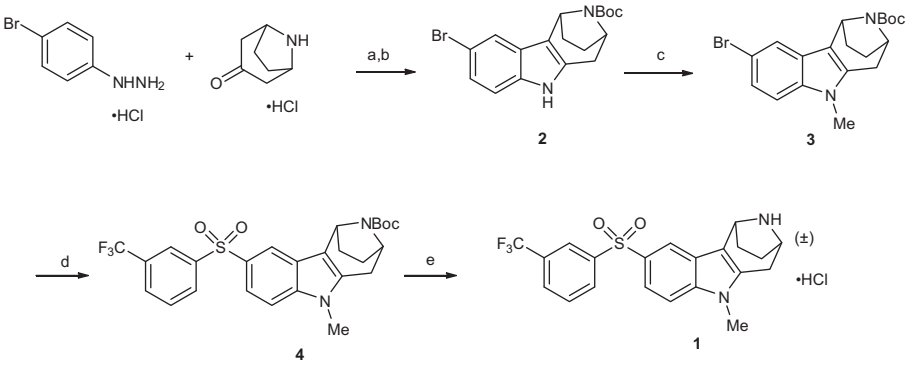
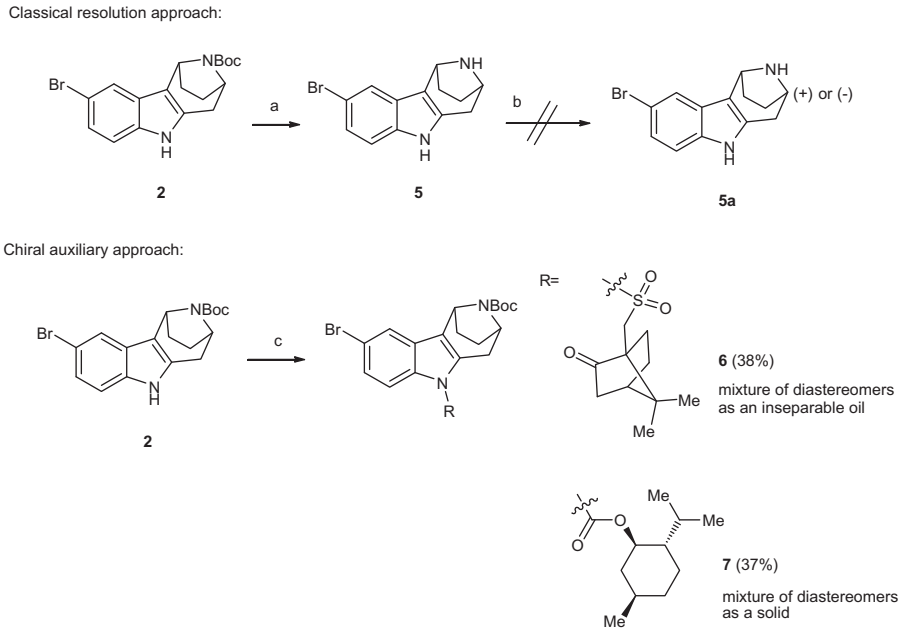
der to synthesize the multi-gram quantities of material needed for these studies, a viable synthetic route to access (+)-**1a** was required. A method for the determination of the absolute stereochemistry of **1a** was also desirable.

2. Results and discussion

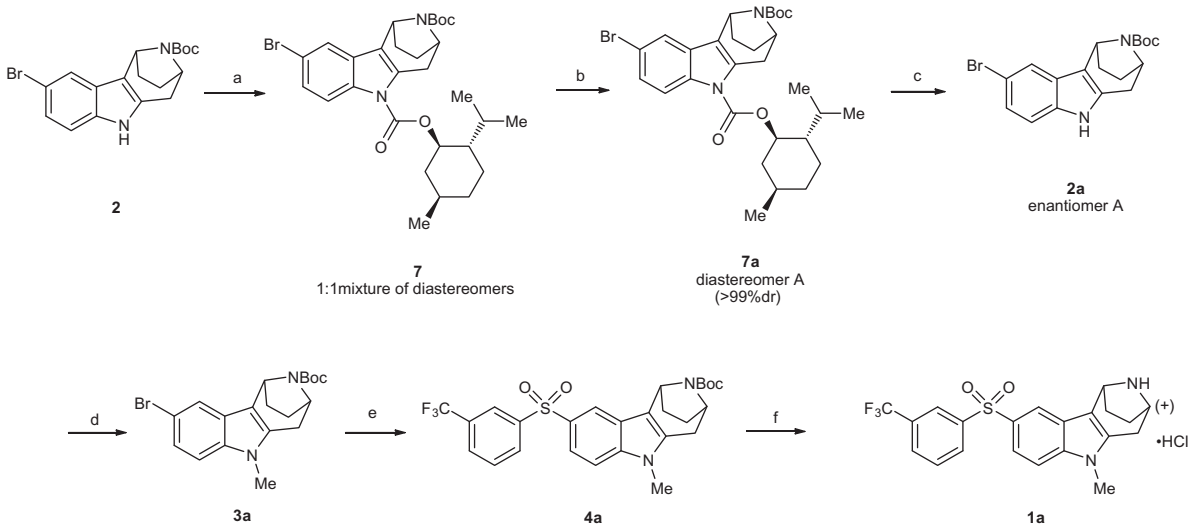
At the onset of the work, a convenient route to the desired epiminocyclo-hepta[*b*]indoles in racemic form was available. The target compounds could be synthesized in 5 steps from commercially available 4-bromophenylhydrazine and nortropinone using a Fisher-indole reaction as the key step (Scheme 1).[10] For initial studies the (+)-enantiomer **1a** was obtained by means of chiral phase preparative HPLC of the racemate **1**. The large scale synthesis of **1a** using this method was precluded due to the relatively poor solubility of **1** and its precursors in the chiral column mobile phase. Attention was therefore focused on a non-chromatographic method to resolve **1** or preferably an intermediate, which could also be utilized in the synthesis of other analogues, which were also of interest for development. The resolution of the epiminocyclo-hepta[*b*]indole scaffold has been reported by classical means using the fractional crystallization of tartrate salts.[11] We reasoned that a similar method could be applied to the resolution of the deprotected analogue of **2**. Compound **2** was the key intermediate in the synthesis since it could be obtained in multi-gram quantities by in situ Boc-protection during the Fisher-indole step. The introduction of the Boc group at this point had the added benefit of enabling the isolation of substantially pure product **2** without the need for chromatographic purification. In order to access the required free base for the resolution, compound **2** was deprotected with 2 M HCl in diethyl ether to afford **5** in modest yield after purification (Scheme 2). Treatment of a solution of **5** in hot ethanol with aqueous L-tartaric acid afforded diastereomeric salts, which could be filtered from the reaction mixture after cooling to 5 °C. However, upon conversion to the free base the enantiomeric ratio of reclaimed compound **5a** was determined to be only 45:55 by



Scheme 1. Synthesis of racemate **1**. Reagents and conditions: (a) EtOH, HCl, reflux, 65 h; (b) Boc_2O, K_2CO_3, *i*-PrOH, H_2O, 0 °C to room temperature, 6 h, 25–30% over two steps; (c) NaH, MeI, DMF, 0 °C to room temperature, 2 h, 80–90%; (d) $ArSO_2Na$, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, toluene, reflux, 4 h, 55%; (e) (i) HCl, THF, 0 °C to room temperature, overnight; (ii) HCl in MeOH, CH_2Cl_2, room temperature, 5 min, 84% over two steps.



Scheme 2. Synthetic approaches to the resolution of **2**. Reagents and conditions: (a) 2 N HCl in Et_2O, $CHCl_3$, 23%; (b) (i) L-tartaric acid, EtOH, H_2O, 70 °C, 1 h; (ii) cool to 5 °C, 14 h; (iii) filter then NH_4OH, CH_2Cl_2; (c) (i) NaH, THF, room temperature, 20 min; (ii) (1*S*)-(+)-10-camphorsulfonyl chloride or (1*R*)-(−)-menthyl chloroformate, 2 h.



Scheme 3. Synthesis of **1a**. Reagents and conditions: (a) (1*R*)-(−) menthyl chloroformate, NaOH, *n*-Bu_4NHSO_4, CH_2Cl_2, water, room temperature, 4 h, >95%; (b) Precipitation from *n*-hexane (×2), 72 h, 87%; (c) LiOH·H_2O, THF, MeOH, H_2O, room temperature, 2.5 h, 92%; (d) NaH, MeI, DMF, 0 °C to room temperature, 2 h, 84%; (e) $ArSO_2Na$, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, toluene, reflux, 4 h, 55%; (f) (i) HCl, THF, 0 °C to room temperature, overnight; (ii) HCl in MeOH, CH_2Cl_2, room temperature, 5 min, 84% over two steps.

chiral HPLC analysis (Chiralcel OD column). Another two recrystallizations of this material were unsuccessful in significantly improving the diasteromeric purity; furthermore the overall recovery of the product was low and not suitable for scale up synthesis.

As an alternative approach we next considered whether we could perform a chiral resolution directly on the key intermediate **2**, we thus turned our attention to chiral auxiliary based approaches, which would derivatize the unsubstituted indole nitrogen. We evaluated two inexpensive chiral derivatizing agents, (1*S*)-(+)-10-camphorsulfonyl chloride and (1*R*)-(−)-menthyl chloroformate by preparing the corresponding intermediates **6** and **7**. Both compounds **6** and **7** were obtained in moderate yields as inseparable mixtures of diasteromers after column chromatography. Camphorsulfonyl derivative **6** had the physical characteristics of an oil, which made it difficult to perform a fractional crystallization in order to separate the diasteromers. In contrast menthol carbamate **7** was an amorphous solid and various solvents were screened to identify a suitable medium for crystallization. For the re-synthesis of **7**, intermediate **2** was reacted with (1*R*)-(−)-menthyl chloroformate under alternative phase transfer conditions to obtain **7** as a 1:1 mixture of diastereomers with improved yield (Scheme 3). Screening of potential crystallization solvents revealed neat *n*-hexane to be advantageous for this purpose. The diastereomeric mixture **7** was appreciably soluble in *n*-hexane upon warming, but upon cooling slow and preferential precipitation of a single compound **7a** (diastereomer A) was observed. The diastereomeric ratio of a sample of **7a** was determined by removal of the chiral auxiliary under basic conditions to afford **2a** (enantiomer A). Analysis of **2a** in comparison with racemate **2** (Chiralcel OD HPLC column) indicated that **7a** had been isolated in a diasteromeric ratio of 9:1. In order to further purify **7a**, the material was re-suspended in *n*-hexane and the precipitation process repeated. The partially purified diasteromer **7a** displayed a much reduced solubility in this process and only fractionally dissolved at 60 °C under vigorous stirring. This partial solubility did not affect the further purification of **7a** by this method since after cooling and filtration the isolated compound **7a** was found to be pure diastereomer A (>99%) as determined by chiral phase HPLC. Conversion of the whole batch of **7a**–**2a** was achieved under mild conditions and in high yield by cleavage of the chiral auxiliary with lithium hydroxide. The overall recovery of **2a** from racemic intermediate **2** using this three step process was 80%. This provided an efficient and scalable method for the preparation of **2a** in enantiomerically pure form to support compound development on the 5-HT_6 medicinal chemistry program.

With **2a** in hand, the synthesis was advanced toward the preparation of the single enantiomer of the 5-HT_6 antagonist **1**. At this stage, it was unknown as to whether intermediate **2a** would lead to the desired enantiomer **1a**. N-methylation of the indole was achieved under standard conditions to produce compound **3a**. This was subjected to a palladium-catalyzed aryl sulfonylation[12] using 3-trifluoromethylbenzenesulfinate sodium salt, which could be prepared in a single step from the sulfonyl chloride[13] generating **4a**. Removal of the Boc group under acidic conditions afforded a single enantiomer of **1** as the hydrochloride salt. Polarimetry anal-

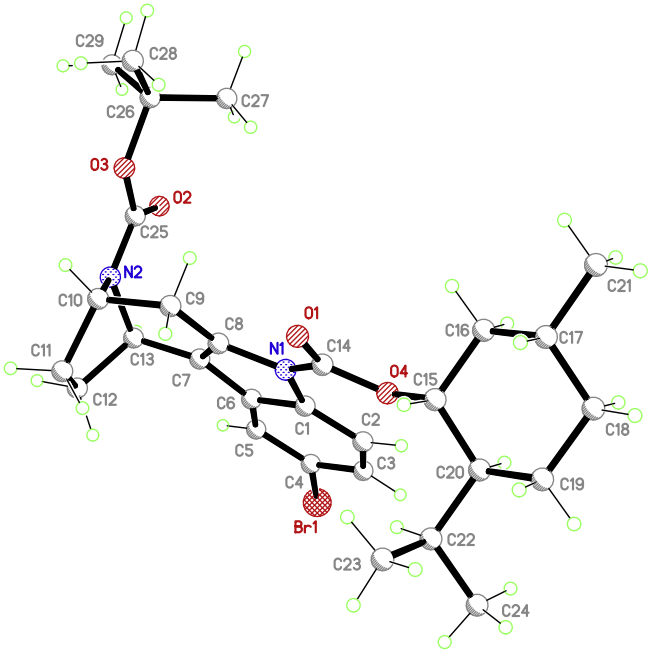
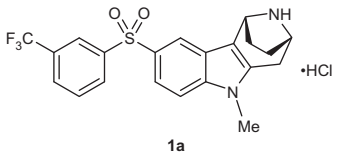


Figure 2. X-ray crystal structure of intermediate **7a** (CCDC 908732).

ysis identified this enantiomer as (+)-enantiomer **1a** which was consistent with the previously purified batches. This confirmed that the initially chosen (−)-enantiomer of menthyl chloroformate was a suitable chiral auxiliary for the preparation of the desired enantiomer **1a**. The process was reproduced reliably in multiple batches and could be easily scaled up to prepare multi-gram batches of **2a**. In a parallel process the alternate enantiomer to **2a** (i.e., **2b**, enantiomer B) could be successfully obtained by employing (1*S*)-(+)-menthol chloroformate as the chiral derivatizing agent in the initial step.

With the successful asymmetric synthesis of **1a** complete, the question with regard to the relative stereochemistry of the bicyclic ring system remained. Compound **7a** provided a useful handle to provide this answer in that it was readily amenable to X-ray crystallographic analysis. X-ray quality crystals of **7a** were produced by crystallization from 2-propanol and submitted for structural determination. From this study, it was confirmed that the epiminocyclo-hepta[*b*]indole ring had a (7*S*,10*R*) geometry (Figs. 2 and 3).



1a

Figure 3. Absolute configuration of 5-HT_6 antagonist **1a**.

3. Conclusion

In conclusion, an efficient 7-step method for the asymmetric synthesis of epiminocyclo-hepta[*b*]indole derived 5-HT_6 antagonists has been developed. Functionalization of the racemic indole derivative **2** with (1*R*)-(−)-menthol chloroformate enabled the separation of (7*S*,10*R*)-*tert*-butyl 2-bromo-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate **2a** in 81% recovery. Homochiral derivative **2a** was utilized to prepare the scaled-up quantities of target compound (+)-**1a** to support biological studies of this compound. X-Ray crystallography confirmed the absolute configuration of **2a**, which in turn enabled the structural assignment of the target compounds derived from this intermediate by the reaction sequence established. Thus, the potent 5-HT_6 antagonist **1a** was assigned as (7*S*,10*R*)-5-methyl-2-((3-(trifluoromethyl)phenyl)sulfonyl)-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole hydrochloride.

4. Experimental

4.1. General

All reactions were conducted under an argon atmosphere unless otherwise noted. Silica gel coated aluminum plates from M/s Merck were used for TLC. Flash chromatography was performed with SiliCyle silica gel (SDS, 40–63 μm, 230–400 mesh) or with a Teledyne Isco CombiFlash system with commercially prepacked Silica RediSep cartridges. ^{1}H and ^{13}C NMR spectra were recorded on Bruker UltraShield 300/400 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as an internal standard or by calibration on the solvent resonance peak. Coupling constants (J) are reported in Hertz (Hz). Sample purity was measured with a Shimadzu Prominence HPLC system equipped with a Phenomenex Luna C18(2) 100 Å 5 μm 250 × 4.60 mm column. Chiral purity was measured with a Shimadzu Prominence HPLC (SIL–20A) system equipped with a Chiralcel OD 5 μm 250 × 4.60 mm column or a Chiralpak AD 5 μm 250 × 4.60 mm column. Optical rotations were measured on an Optical Activity polAAr31 auto polarimeter. Melting points were recorded on a Mel-Temp electro thermal apparatus.

4.2. Experimental procedures for the preparation of 1a

4.2.1. *tert*-Butyl 2-bromo-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate 2

A slurry of 4-bromophenyl hydrazine hydrochloride (124.0 g, 554.8 mmol) and nortropinone hydrochloride (89.7 g, 554.8 mmol) in ethanol (900 mL) was heated at reflux for 4 h. The reaction mixture was cooled to room temperature and concentrated hydrochloric acid (650 mL) was added; again the reaction mixture was refluxed for a further 65 h. The reaction mixture was concentrated in vacuo to give a brown oil, which was diluted with 2-propanol (900 mL), water (450 mL), basified with potassium carbonate (214 g, 1.5 mol) at 0 °C prior to the addition of di-*tert*-butyl dicarbonate (181.6 g, 832.0 mmol). The reaction mixture was stirred at 0 °C for 6 h then diluted with water (1.5 L) and extracted with dichloromethane (2 × 2 L). The extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was diluted with dichloromethane, stored overnight in a refrigerator and filtered. The filter cake was rinsed with cold dichloromethane, and dried in vacuo to afford **2** (55.4 g, 26%) as a gray solid. Mp 230–232 °C; IR (KBr): υ_{max} (cm^{-1}) 3347, 2970, 1683, 1461, 1385, 1173, 1108, 980, 813, 684; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.03 (s, 1H), 7.66 (d, J = 1.5 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.09 (dd, J = 1.8, 8.7 Hz, 1H), 5.11 (d, J = 5.1 Hz, 1H), 4.45 (br s, 1H), 3.17–3.32 (m, 1H), 2.48–2.62 (m, 1H), 2.20 (br s, 1H), 1.98–2.13 (m, 1H), 1.73–1.87 (m, 1H), 1.53–1.67 (m, 1H), 1.35 (br s, 9H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 152.7, 134.1, 132.6, 126.0, 122.4, 119.2, 114.5, 112.8, 111.1, 78.4, 51.8, 51.0, 35.1, 31.5, 29.1, 27.9; HRMS (ESI): (m/z) calcd for $C_{18}H_{22}BrN_2O_2$ [M+H]$^+$: 377.0865, found: 377.0847.

4.2.2. (7*S*,10*R*)-11-*tert*-Butyl 5-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2-bromo-7,8,9,10-tetrahydro-7,10-epiminocyclohepta[*b*]indole-5,11(6*H*)-dicarboxylate 7a

To a suspension of powdered NaOH (45.4 g, 1.13 mol) and water (40 mL) in CH_2Cl_2 (1.5 L) at room temperature was added compound **2** (95.0 g, 251.9 mmol), followed by (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate (77.2 g, 352.8 mmol) and n-Bu_4NHSO_4 (3.4 g, 10.0 mmol). The mixture was stirred vigorously for 4 h, quenched with aqueous saturated NH_4Cl solution (750 mL) and extracted with CH_2Cl_2 (2 × 400 mL). The combined extracts were dried (Na_2SO_4), filtered and the solvent evaporated to give an oil, which was purified by column chromatography (SiO_2, hexane/ethyl acetate, 95:5) to afford a mixture of diastereomers **7**, which was dissolved directly in hexane (2.5 L) at room temperature. The solution was then stored at -5 °C for 72 h. The resulting precipitate was filtered, washed with chilled hexane (200 mL) and dried to give 69.0 g of a pinkish solid. The solid was crushed to a fine powder, suspended in hexane (1.4 L) and heated at 60 °C for 40 min with vigorous stirring. The resulting slurry was cooled to room temperature and stored at −5 °C for 72 h. The solid was filtered, washed with chilled hexane (250 mL) and dried to give pure diastereomer **7a** (61.0 g, 87%) as a light-pink solid. Mp 187–189 °C; $[\alpha]_D^{20} = -100.0$ (c 1.0, $CHCl_3$); IR (KBr): υ_{max} (cm^{-1}) 2950, 2868, 1732, 1693, 1458, 1387, 1164, 1125, 982, 866, 801, 758; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 1.6 Hz, 1H), 7.35 (dd, J = 1.6, 8.8 Hz, 1H), 5.12 (br s, 1H), 4.92 (dt, J = 4.4, 10.8 Hz, 1H), 4.45–4.80 (m, 1H), 3.42–3.62 (m, 1H), 2.81 (d, J = 17.6 Hz, 1H), 2.10–2.38 (m, 3H), 1.90–2.03 (m, 2H), 1.51–1.82 (m, 5H), 1.42 (s, 9H), 1.08–1.22 (m, 2H), 0.88–1.01 (m, 1H), 0.94 (t, J = 6.4 Hz, 6H), 0.80 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 151.1, 134.5, 133.6, 128.6, 126.5, 121.6, 120.1,

117.1, 116.3, 79.8, 77.8, 52.3, 51.7, 47.3, 41.2, 35.2, 34.1, 31.5, 29.8, 28.4 26.3, 23.3, 21.9, 20.9, 16.2; HRMS (ESI): (*m*/*z*) calcd for $C_{29}H_{40}BrN_2O_4$ $[M+H]^+$: 559.2171, found: 559.2172.

4.2.3. (7*S*,10*R*)-*tert*-Butyl 2-bromo-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate 2a

To a solution of compound **7a** (55.0 g, 98.3 mmol) in tetrahydrofuran (600 mL) and MeOH (300 mL) was added $LiOH{\cdot}H_2O$ (12.4 g, 294.8 mmol) dissolved in water (90 mL) at room temperature. The mixture was stirred vigorously for 2.5 h, quenched with aqueous saturated NH_4Cl solution (500 mL), and extracted with ethyl acetate (2 × 750 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 7:3) to afford the pure enantiomer **2a** (34.0 g, 92%) as a white solid. Mp 230–232 °C; enantiomeric purity >99%, Retention time (t_r): 16.9 min, HPLC conditions: chiralcel OD, 22 °C, 250 nm, heptane/ethanol = 98/2, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = -104.4$ (*c* 0.9, DMSO); IR (KBr): υ_{max} (cm^{-1}) 3343, 2972, 1680, 1463, 1365, 1152, 1101, 978, 811, 682; ^1H NMR (DMSO-d_6, 400 MHz): δ 11.04 (s, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.09 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.11 (d, *J* = 5.2 Hz, 1H), 4.45 (br s, 1H), 3.18–3.33 (m, 1H), 2.47–2.61 (m, 1H), 2.22 (br s, 1H), 1.99–2.12 (m, 1H), 1.73–1.85 (m, 1H), 1.53–1.65 (m, 1H), 1.35 (s, 5H), 1.27 (s, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.7, 134.2, 132.5, 126.1, 122.4, 119.1, 114.5, 112.8, 111.6, 78.5, 51.9, 51.0, 35.1, 31.5, 29.1, 28.0; HRMS (ESI): (*m*/*z*) calcd for $C_{18}H_{22}BrN_2O_2$ $[M+H]^+$: 377.0865, found: 377.0877.

4.2.4. (7*S*,10*R*)-*tert*-Butyl 2-bromo-5-methyl-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate 3a

To a solution of compound **2a** (34.0 g, 90.4 mmol) in DMF (250 mL) under an argon atmosphere was added NaH (60% dispersion in mineral oil) (5.4 g, 135.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h before the addition of iodomethane (7.0 mL, 113.0 mmol). Stirring was continued for an additional 1 h before the reaction mixture was quenched with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, dried over sodium sulfate and concentrated in vacuo to give **3a** (30.0 g, 84%) as a yellow solid. Mp 199–201 °C; $[\alpha]_D^{20} = +121.8$ (*c* 1.1, $CHCl_3$); IR (KBr): υ_{max} (cm^{-1}) 2968, 2927, 1688, 1470, 1389, 1163, 1096, 975, 865, 792; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.61 (d, *J* = 1.5 Hz, 1H), 7.20 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 5.15 (br s, 1H), 4.68 (br s, 1H), 3.55 (s, 3H), 3.23–3.49 (m, 1H), 2.47 (d, *J* = 16.2 Hz, 1H), 2.08–2.37 (m, 2H), 1.85–1.97 (m, 1H), 1.53–1.68 (m, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.9, 135.3, 133.9, 125.9, 123.2, 119.8, 114.9, 112.4, 110.2, 79.5, 52.3, 51.4, 36.0, 30.8, 29.3, 29.2, 28.4; HRMS (ESI): (*m*/*z*) calcd for $C_{19}H_{24}BrN_2O_2$ $[M+H]^+$: 391.1021, found: 391.1021.

4.2.5. (7*S*,10*R*)-*tert*-Butyl 5-methyl-2-((3-(trifluoromethyl)phenyl)-sulfonyl)-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate 4a

A mixture of compound **3a** (10.0 g, 25.5 mmol), sodium 3-(trifluoromethyl)benzenesulfinate (7.4 g, 31.9 mmol), di-palladium-tris(dibenzylideneacetone) (1.17 g, 1.27 mmol), cesium carbonate (12.5 g, 38.3 mmol), and xantphos (1.4 g, 2.5 mmol), was taken up in anhydrous toluene (150.0 mL). The reaction flask was purged with argon and refluxed at 120 °C for 4 h. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate (250 mL) and filtered through a Celite bed. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (SiO_2, 7:3 hexane/ethyl acetate) to afford compound **4a** (7.3 g, 55%) as a light-yellow solid. Mp 189–191 °C; $[\alpha]_D^{20} = -64.6$ (*c* 1.3, $CHCl_3$); IR (KBr): υ_{max} (cm^{-1}) 2975, 1681, 1406, 1322, 1136, 1098, 867, 801, 723; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16–8.25 (m, 2H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.57–7.64 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 5.26 (br s, 1H), 4.58–4.80 (m, 1H), 3.60 (s, 3H), 3.22–3.50 (m, 1H), 2.51 (d, *J* = 16.0 Hz, 1H), 2.15–2.40 (m, 2H), 1.88–1.98 (m, 1H), 1.56–1.68 (m, 1H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.9, 144.4, 138.7, 136.0, 131.71 (q, *J* = 33.2 Hz), 130.6, 130.5, 129.9, 129.1 (q, *J* = 3.4 Hz), 124.2 (q, *J* = 3.6 Hz), 123.2 (CF_3, q, *J* = 271.3 Hz), 119.7, 118.5, 117.1, 109.8, 79.8, 52.2, 51.4, 36.0, 30.9, 29.6, 29.2, 28.3; HRMS (ESI): (*m*/*z*) calcd for $C_{26}H_{28}F_3N_2O_4S$ $[M+H]^+$: 521.1722, found: 521.1741.

4.2.6. (7*S*,10*R*)-5-Methyl-2-((3-(trifluoromethyl)phenyl)sulfonyl)-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole hydrochloride 1a

To a solution of compound **4a** (7.2 g, 13.8 mmol) in tetrahydrofuran (83.4 mL) was added concentrated HCl (16.6 mL) at 0 °C. The reaction mixture was slowly allowed to reach room temperature. After stirring overnight at room temperature the reaction mixture was quenched with 10% sodium bicarbonate solution (300 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 9:1 dichloromethane/methanol) to give the free base of compound **1a** which was converted directly to the hydrochloride salt by dissolving it in dichloromethane and then treating it with 1.25 M HCl in methanol. The reaction mixture was concentrated in vacuo to afford compound **1a** (5.3 g, 84%) as a white solid. Mp 291–293 °C; enantiomeric purity >99%, retention time (t_r): 34.9 min, HPLC conditions: chiralpak AD, 22 °C, 250 nm, heptane/2-propanol = 80/20, flow rate = 1.0 mL/min.; $[\alpha]_D^{20} = +36.6$ (*c* 0.8, MeOH); IR (KBr): υ_{max} (cm^{-1}) 2719, 2522, 1598, 1481, 1305, 1139, 1098, 963, 826, 722, 670; ^1H NMR (DMSO-d_6, 400 MHz): δ 9.65 (br s, 2H), 8.48 (d, *J* = 1.6 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.82–7.89 (m, 1H), 7.75 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 5.35 (d, *J* = 5.2 Hz, 1H), 4.41–4.52 (m, 1H), 3.68 (s, 3H), 3.32–3.47 (m, 1H), 3.00 (d, *J* = 16.8 Hz, 1H), 2.22–2.39 (m, 2H), 2.12–2.03 (m, 1H), 1.73–1.83 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 143.9, 138.7, 134.9, 131.2, 131.1, 130.4, 130.0 (q, *J* = 32.5 Hz), 129.8 (q, *J* = 3.4 Hz), 123.2 (CF_3, q, *J* = 271.3 Hz), 123.1 (q, *J* = 5.5 Hz), 119.8, 119.0, 111.1, 111.0, 52.6, 51.8, 34.3, 29.8, 29.6, 26.8; Purity (HPLC): 99.2% (t_R = 21.5 min); HRMS (ESI): (*m*/*z*) calcd for $C_{21}H_{20}F_3N_2O_2S$ $[M+H]^+$: 421.1198, found: 421.1200.

4.3. Experimental procedures for the preparation of 1b

4.3.1. (7*R*,10*S*)-11-*tert*-Butyl 5-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) 2-bromo-7,8,9,10-tetrahydro-7,10-epiminocyclohepta[*b*]indole-5,11(6*H*)-dicarboxylate 7b

Compound **7b** was prepared from **2** (15.0 g, 39.8 mmol) and (1*S*)-(+)-menthyl chloroformate, according to the procedure described for the synthesis of **7a**. Light yellow solid, Yield 9.5 g, 85%; Mp 185–187 °C; $[\alpha]_D^{20} = +105.0$ (*c* 1.2, $CHCl_3$); IR (KBr): υ_{max} (cm^{-1}) 2950, 2868, 1732, 1693, 1458, 1387, 1164, 1125, 982, 866, 801, 758; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 1.6, 8.8 Hz, 1H), 5.12 (br s, 1H), 4.92 (dt, *J* = 4.4, 10.8 Hz, 1H), 4.44–4.77 (m, 1H), 3.42–3.62 (m, 1H), 2.81 (d, *J* = 17.6 Hz, 1H), 2.09–2.37 (m, 3H), 1.90–2.02 (m, 2H), 1.51–1.82 (m, 5H), 1.42 (s, 9H), 1.07–1.22 (m, 2H), 0.89–1.01 (m, 1H), 0.94 (t, *J* = 6.4 Hz, 6H), 0.80 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 151.1, 134.5, 133.6, 128.6, 126.5, 121.6, 120.1, 117.1, 116.2, 79.8, 77.8, 52.3, 51.7, 47.3, 41.2, 35.1, 34.1, 31.5, 29.8, 28.4 26.3, 23.3, 21.9, 20.9, 16.2; HRMS (ESI): (*m*/*z*) calcd for $C_{29}H_{40}BrN_2O_4$ $[M+H]^+$: 559.2171, found: 559.2180.

4.3.2. (7*R*,10*S*)-*tert*-Butyl 2-bromo-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate 2b

Compound **2b** was prepared from **7b** (9.0 g, 16.1 mmol), according to the procedure described for the synthesis of **2a**. White solid, Yield 5.7 g, 95%; Mp 230–232 °C; enantiomeric purity >99%, Retention time (t_r): 19.8 min, HPLC conditions: chiralcel OD, 22 °C, 250 nm, heptane/ethanol = 98/2, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +113.3$ (*c* 1.2, DMSO); IR (KBr): υ_{max} (cm^{-1}) 3341, 2972, 1680, 1464, 1365, 1157, 1102, 982, 813, 658; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.05 (s, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.09 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.11 (d, *J* = 5.6 Hz, 1H), 4.45 (br s, 1H), 3.16–3.32 (m, 1H), 2.48–2.62 (m, 1H), 2.22 (br s, 1H), 2.00–2.12 (m, 1H), 1.73–1.85 (m, 1H), 1.52–1.66 (m, 1H), 1.35 (s, 5H), 1.27 (s, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.7, 134.2, 132.6, 126.1, 122.4, 119.3, 114.5, 112.8, 111.1, 78.5, 51.8, 50.9, 35.1, 31.6, 29.1, 28.0; HRMS (ESI): (*m*/*z*) calcd for $C_{18}H_{22}BrN_2O_2$ $[M+H]^+$: 377.0865, found: 377.0872.

4.3.3. (7*R*,10*S*)-*tert*-Butyl 2-bromo-5-methyl-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole-11-carboxylate 3b

Compound **3b** was prepared from **2b** (5.2 g, 13.8 mmol), according to the procedure described for the synthesis of **3a**. White solid, Yield 5.0 g, 93%; Mp 199–201 °C; $[\alpha]_D^{20} = -120.0$ (*c* 1.4, $CHCl_3$); IR (KBr): υ_{max} (cm^{-1}) 2968, 2927, 1687, 1470, 1389, 1163, 1096, 975, 865, 792; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J* = 1.2 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 5.06–5.30 (m, 1H), 4.52–4.77 (m, 1H), 3.56 (s, 3H), 3.21–3.48 (m, 1H), 2.47 (d, *J* = 16.0 Hz, 1H), 2.10–2.36 (m, 2H), 1.88–1.97 (m, 1H), 1.56–1.66 (m, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.2, 135.3, 134.0, 125.9, 123.2, 119.8, 114.9, 112.4, 110.2, 79.6, 52.4, 51.3, 36.1, 30.8, 29.3, 29.2, 28.4; HRMS (ESI): (*m*/*z*) calcd for $C_{19}H_{24}BrN_2O_2$ $[M+H]^+$: 391.1021, found: 391.1021.

4.3.4. (7*R*,10*S*)-*tert*-Butyl 5-methyl-2-((3-(trifluoromethyl)phenyl)-sulfonyl)-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]-indole-11-carboxylate 4b

Compound **4b** was prepared from **3b** (1.2 g, 3.0 mmol), according to the procedure described for the synthesis of **4a**. White solid, Yield 890 mg, 56%; Mp 189–191 °C; $[\alpha]_D^{20} = +64.0$ (*c* 1.0, $CHCl_3$); IR (KBr): υ_{max} (cm^{-1}) 2977, 1691, 1406, 1323, 1135, 1100, 868, 813, 723; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17–8.26 (m, 2H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.64–7.72 (m, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 5.24 (br s, 1H), 4.55–4.81 (m, 1H), 3.61 (s, 3H), 3.20–3.50 (m, 1H), 2.50 (d, *J* = 16.0 Hz, 1H), 2.14–2.40 (m, 2H), 1.89–1.99 (m, 1H), 1.54–1.66 (m, 1H), 1.35 (br s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 144.4, 138.7, 135.5, 131.7 (q, *J* = 32.9 Hz), 130.5, 130.4, 129.9, 129.1(q, *J* = 3.4 Hz), 124.1(q, *J* = 3.6 Hz), 123.2 (CF_3, q, *J* = 271.2 Hz), 119.6, 118.5, 117.1, 109.8, 79.7, 52.1, 51.5, 36.0, 30.8, 29.6, 29.2, 28.3; HRMS (ESI): (*m*/*z*) calcd for $C_{26}H_{28}F_3N_2O_4S$ $[M+H]^+$: 521.1722, found: 521.1727.

4.3.5. (7*R*,10*S*)-5-Methyl-2-((3-(trifluoromethyl)phenyl)sulfonyl)-5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta[*b*]indole hydrochloride 1b

Compound **1b** was prepared from **4b** (550 mg, 1.0 mmol), according to the procedure described for the synthesis of **1a**. White solid, Yield 306 mg, 64%; Mp 291–293 °C; enantiomeric purity >99%, Retention time (t_r): 30.8 min, HPLC conditions: chiralpak AD, 22 °C, 250 nm, heptane/2-propanol = 80/20, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = -36.0$ (*c* 1.0, MeOH); IR (KBr): υ_{max} (cm^{-1}) 2732, 2522, 1598, 1481, 1305, 1146, 1098, 963, 832, 722, 670; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.85 (br s, 1H), 9.22 (br s, 1H), 8.47 (d, *J* = 1.6 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.21 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.81–7.89 (m, 1H), 7.75 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 5.35 (d, *J* = 4.8 Hz, 1H), 4.42–4.50 (m, 1H), 3.68 (s, 3H), 3.34–3.44 (m, 1H), 3.00 (d, *J* = 16.8 Hz, 1H), 2.21–2.38 (m, 2H), 2.02–2.12 (m, 1H), 1.73–1.85 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 143.8, 138.6, 134.8, 131.2, 131.0, 130.4, 130.0 (q, *J* = 32.6 Hz), 129.7 (q, *J* = 3.4 Hz), 123.2 (CF_3, q, *J* = 271.3 Hz), 123.1 (q, *J* = 5.1 Hz), 119.7, 119.0, 111.1, 110.9, 52.5, 51.7, 34.2, 29.7, 29.5, 26.8; Purity (HPLC): 99.2% (t_R = 21.5 min); HRMS (ESI): (*m*/*z*) calcd for $C_{21}H_{20}F_3N_2O_2S$ $[M+H]^+$: 421.1198, found: 421.1198.

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References

1. Hamon, M.; Doucet, E.; Lefevre, K.; Miquel, M.-C.; Lanfumey, L.; Insauti, R.; Frechilla, D.; Del Rio, J.; Verge, D. *Neuropsychopharmacology* **1999**, *21*, 68S–76S.
2. Sleight, A. J.; Boess, F. G.; Bos, M.; Levit-Trafit, B.; Bourson, A. *Expert Opin. Ther. Pat.* **1998**, *8*, 1217.
3. (a) King, M. V.; Marsden, C. A.; Fone, K. C. F. *Trends Pharmacol. Sci.* **2008**, *29*, 482; (b) Rosse, G.; Schaffhauser, H. *Curr. Top. Med. Chem.* **2010**, *10*, 207.
4. Maher-Edwards, G.; Zvartau-Hind, M.; Hunter, A. J.; Gold, M.; Hopton, G.; Jacobs, G.; Davy, M.; Williams, P. *Curr. Alzheimer Res.* **2010**, *7*, 374.
5. Wesolowska, A.; Nikiforuk, A. *Neuropharmacology* **2007**, *52*, 1274.
6. Routledge, C.; Bromidge, S. M.; Moss, S. F.; Price, G. W.; Hirst, W.; Newman, H.; Riley, G.; Gager, T.; Stean, T.; Upton, N.; Clarke, S. E.; Brown, A. M.; Middlemiss, D. M. *Br. J. Pharmacol.* **2000**, *130*, 1606.
7. Finn, D. P.; Fone, K. C.; Beckett, S. R.; Baxter, J. A.; Ansell, L.; Marsden, C. A.; Chapman, V. *Eur. J. Pharmacol.* **2007**, *569*, 59.
8. (a) Heal, D. J.; Smith, S. L.; Fisas, A.; Codony, X.; Buschmann, H. *Pharmacol. Ther.* **2008**, *117*, 207; (b) Sargent, B. J.; Henderson, A. J. *Curr. Opin. Pharmacol.* **2011**, *11*, 52.
9. Henderson, A. J.; Guzzo, P. R.; Ghosh, A.; Kaur, J.; Koo, J.-M.; Nacro, K.; Panduga, S.; Pathak, R.; Shimpukade, B.; Tan, V.; Xiang, K.; Wierschke, J. D.; Isherwood, M. L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1494.
10. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
11. Mewshaw, R. E.; Abreu, M. E.; Silverman, L. S.; Mathew, R. M.; Tiffany, C. W.; Bailey, M. A.; Karbon, E. W.; Ferkany, J. W.; Kaiser, C. *J. Med. Chem.* **1993**, *36*, 3073.
12. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parsi, L.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608.
13. Field, L.; Clark, R. D. *Org. Synth.* **1958**, *38*, 62.