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Efficient Synthesis of a 5-HT$_{2C}$ Receptor Agonist Precursor

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Abstract:

A short, scaleable, synthetic approach toward the tricyclic indole derivative 2, an intermediate in the synthesis of the 5-HT$_{2C}$ agonist 1, is described. The synthesis started with Williamson etherification of inexpensive 4-nitro-3-methylphenol (11) followed by reduction to the corresponding aniline 13 and subsequent Boc protection. Acylation of the methyl group in 14 via lithiation furnished γ-chloroketone 16, which was subjected to acid promoted indole formation to afford 17. In the final step, NaOH induced hydrolytic cleavage of the Boc protecting group followed by direct intramolecular nucleophilic substitution gave rise to target molecule 2 in an overall yield of 65% over six steps.

Introduction

5-Hydroxytryptamine (5-HT or serotonin) is a key neurotransmitter that is involved in a variety of sensory, motor, and behavioral processes.[1] The various effects of this neurotransmitter are related to the extensive projections of serotonergic neurons throughout the brain and the large number of distinct serotonin receptor subtypes.

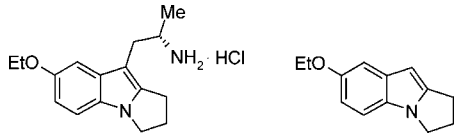
The 5-HT$_2$ subfamily of serotonin receptors is composed of three subtypes, the 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptors. The scarcity of selective pharmacological agents makes it difficult to determine the contribution of these receptors to specific actions of serotonin. However, gene-targeting techniques have shown that 5-HT$_{2C}$ receptors are implicated in the regulation of food intake and anxiety.[2]

Clarification of the functional roles of these receptors entails the development of human 5-HT$_{2C}$ receptor agonists, which have good selectivity over other human 5-HT receptors. Indole[3] derivative **1** was found to be an interesting compound for further studies to find a drug candidate that would have weight-loss-inducing properties (Figure 1). Our target molecule **2** is a key intermediate toward **1**.

Results and Discussion

A compound closely related to our target molecule **2** had already been synthesized by former Syntex chemists (Scheme 1). Clark et al. reported an elegant route to tricycle **10** that is based on a modified Madelung−Houlihan[4]-type indole synthesis starting with the suitably substituted aniline derivative **3**, which was first Boc protected and then dilithiated using *s*-butyllithium in THF at low temperature.[5]

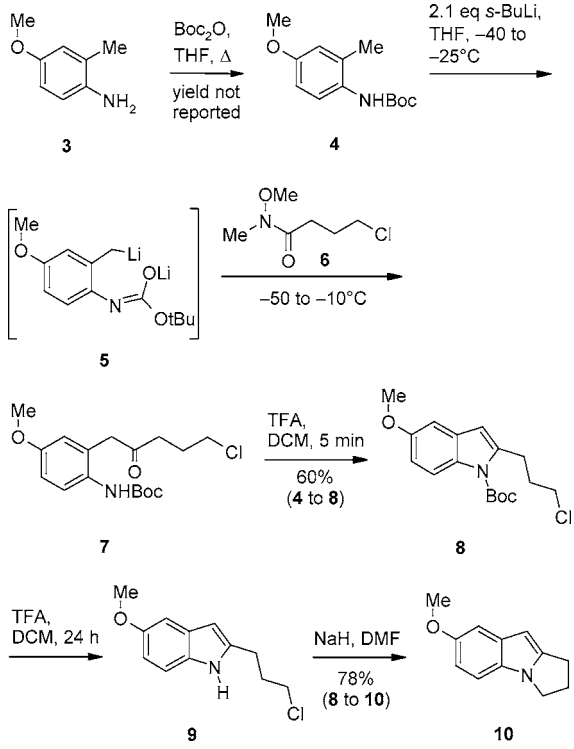
Carbanion **5** was trapped by Weinreb amide[6] **6**, bearing a chloro substituent at the γ-position. This trapping reaction is chemoselective in a double sense: not only with regard to Hauser's rule[7] predicting the more basic and nucleophilic carbanion to react exclusively with the electrophile in the



1 **2**

Figure 1. **5-HT$_{2C}$ receptor agonist 1 and its synthetic precursor 2.**

Scheme 1. **Syntex synthesis of indole tricycle 10**



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presence of the deprotonated carbamate moiety but also regarding the chloro atom, which was not attacked under these conditions. Cyclization to an indole was accomplished by short treatment of ketone **7** with trifluoroacetic acid in dichloromethane yielding indole **8** in 60% yield over two steps (acylation and cyclization). Boc deprotection of indole **8** was subsequently accomplished using the same reaction conditions (TFA in DCM) again, but requiring extended reaction time (24 to 48 h). The ultimate cyclization was finally achieved by intramolecular nucleophilic displacement of the chloro substituent, furnishing **10** in 78% yield over the last two steps.

Although this synthesis seemed appropriate for our purposes, several aspects had to be reinvestigated and improved to provide the basis for a future large-scale route. The following questions were addressed:

(1) Is *s*-BuLi absolutely necessary for the dilithiation of **4**?

(2) Due to the high costs of MeNHOMe·HCl, is there a substitute for Weinreb amide **6**, which is less expensive to prepare?

(3) Is the isolation of Boc-protected indole **8** necessary?

(4) Is it feasible to replace sodium hydride in DMF by a safer base/solvent combination for the final intramolecular substitution step?

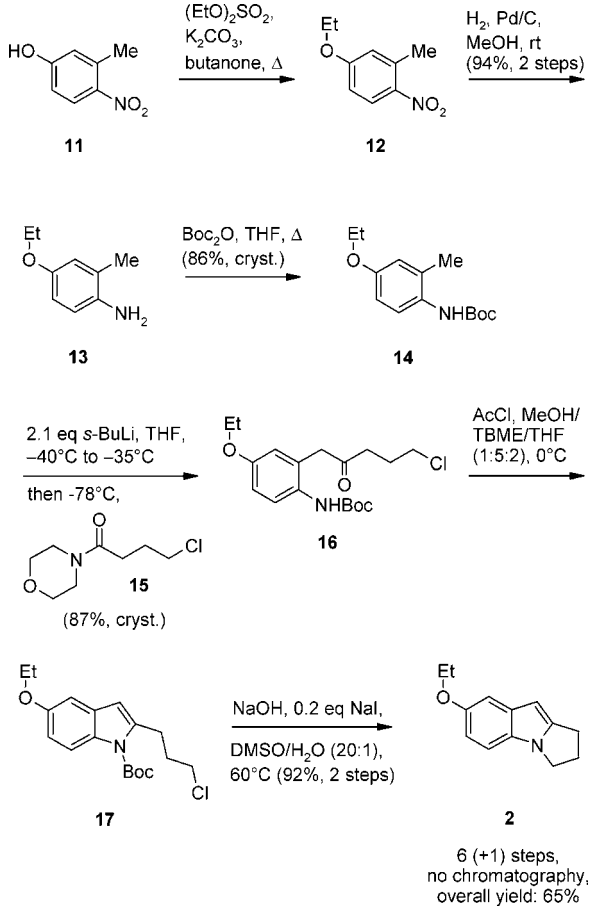
(5) Can the column chromatographies during product isolation be avoided?

As the homologous ethoxy derivative of Syntex starting material **3** is not commercially available, we started with inexpensive 3-methyl-4-nitrophenol (**11**, Fluka: ca. 55 USD/500 g). The phenol group was alkylated in quantitative yield with diethyl sulfate in refluxing 2-butanone using potassium carbonate as base (Scheme 2). Due to its high toxicity, diethyl sulfate was used in only slight excess, and the remaining reagent was quenched efficiently by treatment with aqueous ammonia.

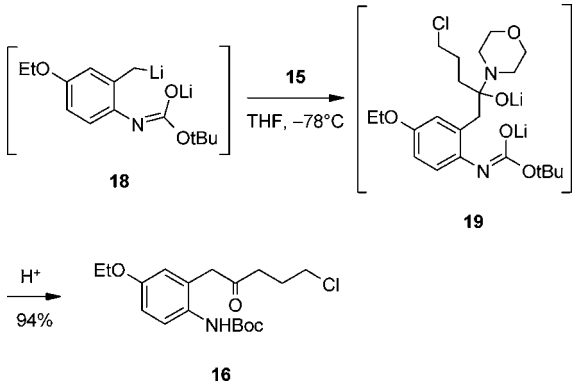
Aryl ether **12** was isolated as a solid, after filtration of the reaction mixture, thus allowing separation from the solid base and subsequent evaporation of solvent. The nitro group was then reduced to the amino functionality using 1.1 atm of hydrogen in methanol over palladium on charcoal. Filtration of the heterogeneous catalyst and subsequent aqueous workup gave rise to the oily aniline **13**, which was then Boc protected using modified literature conditions.[8] No base was required for this transformation. Replacement of the originally employed saturated aqueous citric acid for workup by saturated aqueous ammonium chloride increased the yield by up to 20%. Recrystallization of the crude product **14** from TBME/hexane provided pale-brown crystals, while the mother liquid contained the excess Boc_2O.

The stage was now set to investigate the dilithiation of **14** followed by acylation of the carbanion generated. We found that, by employing *s*-butyllithium, dilithiation proceeded very smoothly in THF at −40 °C. Dilithiation is complete within 30 min under these conditions as demonstrated by complete conversion of **14** after addition of electrophiles **6** or **15**. In our first experiments, dianion **18**

Scheme 2. **Practical synthesis of 5-HT_{2C} receptor agonist precursor 2**



Scheme 3. **Chemoselective electrophilic trapping of dianion 18 with morpholine amide 15**



was trapped by Weinreb amide **6**. This was later replaced by morpholine amide **15**[9,10] as it was much less expensive to prepare. Both electrophiles react with carbon nucleophile **18** within seconds, even at −78 °C, in a completely chemoselective manner. Since chloro atom substitution was never observed, it was assumed that the postulated tetrahedral intermediate lithium *N*,*O*-semiacetal **19** (Scheme 3) is not reactive enough to displace the leaving group in the γ position.

To find a substitute for *s*-BuLi, additional conditions were tested; with lithiumdiisopropyl amide (LDA) as a base in

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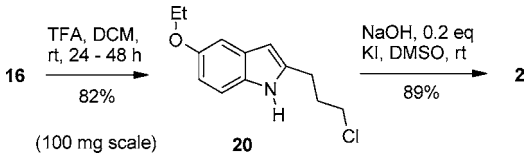
Scheme 4. **Synthesis of 2 via cyclization of the deprotected indole 20**



ethereal solvents such as diethyl ether or THF at temperatures ranging from −78 to +20 °C, only starting material was reisolated. Using two equivalents of *n*-butyllithium in THF at −20 °C for 30 min resulted in the formation of only 18% product **16** next to recovered starting material. Extension of the metalation time to 90 min in the presence of TMEDA as cosolvent led to the formation of product **16** in 30% yield. Raising the temperature to 0 °C for 4.5 h furnished 78% product **16**, 14% starting material **14**, and several unidentified side products. In comparison, the reaction was much smoother with *s*-butyllithium, which requires the same handling precautions as *n*-butyllithium from a safety point of view. Since the price difference is small (for 1000 kg: *n*-BuLi ca. 33 Euro/kg active material; *s*-BuLi ca. 49 Euro/kg), further experiments were abandoned.

Cyclization to form **17** was accomplished by treating ketone **16** with acid. Interestingly, the Boc protecting group of indole **17** proved extremely stable against strong acids such as hydrogen chloride, sulfuric acid, or *p*-toluenesulfonic acid. This can be explained by the marked nucleophilicity/basicity of the indole's (enamine-like) 3-position leading to its complete protonation, thus deactivating further protonation of the Boc group, which is essential for deprotection. While with strong acids the reaction stopped at the stage of Boc-protected indole **17**, treatment with weaker acids such as trifluoroacetic acid (TFA) furnished mixtures of **17** and deprotected **20** due to incomplete indole protonation, thus facilitating deprotection (Scheme 4). Applying the conditions reported by Syntex on **17** (TFA in dichloromethane)[5] proved preparatively not a very useful step due to scale-up problems. Although indole formation and Boc cleavage both occurred smoothly on a 100-mg scale within 24 h, the reaction sequence became increasingly sluggish on larger scale. A reaction time exceeding 24 h resulted in decomposition of product **20** prior to complete conversion.

The best conditions for conversion of indole **20** into target molecule **2** were found to be NaOH (2.0 equiv)/KI (0.2 equiv) in DMSO at room-temperature resulting in a very smooth formation of **2** in high yield.

Due to the above-mentioned scale-up problem for the formation of **20** in combination with the air sensitivity of indole **20** and its oily consistency, we developed a direct transformation of **16** into **2** avoiding the isolation of **20**. Taking into account that Boc-protected indole **17** is generated almost quantitatively on treatment of **16** with strong acids, it appeared tempting to produce this nonsensitive, solid material first followed by a basic hydrolytic cleavage of the Boc protecting group with subsequent cyclization, directly providing target molecule **2**.

The transformation **16** → **17** was optimized in terms of acid and solvent systems. The most selective conversion was observed with HCl, in situ generated from methanol/acetyl chloride in a THF/TBME mixture (Scheme 2). H_2SO_4 and *p*-TsOH gave similar results, but larger amounts of unidentified side products were formed. THF was found essential to hold the starting material in solution at 0 °C and TBME to ensure a high solubility of HCl. Cyclization with HCl in ethyl acetate/methanol led to precipitation of large amounts of starting material on a 20-g scale when cooling the solution down to 0 °C. The solvent system dioxane/MeOH was slightly inferior compared to TBME/THF/MeOH (5:2:1) concerning yield and purity. In the latter system, conversion was complete within 5 min; however, even after 30−60 min, only very little Boc deprotection was detected. One equivalent of HCl was required to obtain full conversion. When only 0.1 equiv of HCl was used, the reaction stopped after about 10% conversion, but interestingly, under these conditions we also observed Boc-deprotected indole **20** in almost equal amounts as determined by HPLC.

The Boc group was found to be hydrolyzed with NaOH followed by direct cyclization to **2**. The aza anion thus generated in situ was trapped by an intramolecular nucleophilic substitution, yielding target molecule **2** in a cascade reaction. Using a mixture of NaOH and catalytic amounts of NaI in refluxing ethanol resulted in the formation of a mixture of target molecule **2** and a product resulting from an intermolecular nucleophilic displacement of chloride by ethoxide. Changing to the less nucleophilic polar aprotic solvent DMSO yielded tricyclic product **2**, however, in moderate, non-reproducible and scale-dependent yield containing several unidentified impurities. Addition of water as cosolvent (DMSO/H_2O = 20:1) rendered the reaction mixture more homogeneous allowing a decrease of temperature from 80 to 60 °C, thus furnishing target molecule **2**, which after precipitation by addition of an excess of water still contained salt impurities and included DMSO. Purification of crude **2** was easily achieved by redissolving in ethyl acetate and a subsequent aqueous workup. This two-step sequence (indole formation/tricyclization) worked equally well on a 100-mg as on a 10-g scale and gave access to **2** in excellent yield (92% over two steps).

In conclusion, the presented optimized synthesis of tricyclic heterocycle **2** works remarkably efficiently using inexpensive starting material and reagents. The synthesis does not require any chromatographic purification and provides an overall yield of 65% over 6 (+1) steps (average yield per step is 93%).

Experimental Section

General Methods. Unless otherwise noted, solvents and reagents were used as received from commercial suppliers. All reactions were carried out under argon atmosphere, with the exception of the hydrogenation step. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates, 0.25 mm (Merck). Qualitative HPLC was performed on a Hewlett-Packard Series 1050 system with UV detection at a wavelength of 210 nm using Chromolith Performance columns (100 mm × 4.6 mm) with gradient eluent H_2O/MeCN containing 10% of a phosphate buffer at pH 3.0. ^1H

NMR were recorded using tetramethylsilane as internal standard. Spectra are given in ppm (δ), and coupling constants J are reported in Hz. Peaks in IR spectra are reported in cm^{-1}. Low-resolution electron impact mass spectra (EI-MS) were obtained at an ionization voltage of 70 eV. Data are reported in the form of m/z (intensity relative to base = 100).

4-Ethoxy-2-methyl-1-nitro-benzene (12). To a stirred solution of 20.00 g of 4-nitro-3-methylphenol (**11**, 130.6 mmol) in 400 mL of 2-butanone, was added 36.14 g of potassium carbonate (261.2 mmol, 2.00 equiv) under argon followed by 17.96 mL of diethyl sulfate (137.1 mmol, 1.05 equiv). The brown reaction mixture was heated to reflux (oil bath temperature 110 °C). After 2 h, no more starting material **11** was detected by TLC. The mixture was cooled to room temperature and treated with 15 mL of aqueous ammonia (25%). After stirring overnight, the mixture was filtered, and the filter cake was washed with 150 mL of 2-butanone. All volatile compounds of the filtrate were evaporated using a rotary evaporator (55 °C/4 mbar) providing the crude product (24.16 g, 102 wt %) as a yellow-brown solid material. TLC: R_f = 0.68 (Hex/AcOEt = 4:1). Mp: 51 °C. IR (Nujol): ν = 2925, 2854, 1610, 1587, 1507, 1493, 1335, 1263, 1078, 1039, 839, 757, 649, 493. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (m, 1H), 6.79 (d, 1H), 6.76 (s, 1H), 4.10 (q, J = 7.0, 2H), 2.62 (s, 3H), 1.44 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 142.0, 137.0, 127.6, 117.9, 112.2, 64.2, 21.7, 14.6. MS (m/z) = 181.1 (100, M^+), 164.1 (89), 136 (66). MA: $C_9H_{11}NO_3$ (181.191) calcd: C = 59.66; H = 6.12; N = 7.73; found: C = 59.58; H = 5.95; N = 7.61.

4-Ethoxy-2-methyl-phenylamine (13). An autoclave was charged with 2.50 g of Pd/C and 50 mL of methanol. A solution of 24.16 g of 4-ethoxy-2-methyl-1-nitro-benzene (**12**) (133.3 mmol) in 450 mL of methanol was then added. The reactor was closed, and air was exchanged with nitrogen (5 bar gauge). A hydrogen pressure of 1.1 bar gauge was applied. The reaction mixture was stirred at 800 rpm for 1.5 h at room temperature. After completion of hydrogen consumption, the mixture was filtered. Autoclave and catalyst were washed with 100 mL of methanol. TLC showed complete conversion. After evaporation of solvent by rotary evaporation at 50 °C/10 mbar, the residue was dissolved in 300 mL of ethyl acetate. The solution was washed three times with 200 mL of saturated aqueous sodium hydrogen carbonate. The organic phase was dried over 50 g of sodium sulfate (30 min) and filtered. The solid was washed with 100 mL of ethyl acetate. After removal of solvent on a rotary evaporator (50 °C, 5 mbar), the crude product was obtained as a dark-red oil (18.59 g, 122.9 mmol, 92 wt %; over two steps from **11**: 94 wt %). TLC: R_f = 0.32 (Hex/AcOEt = 4:1). IR (film): ν = 3359, 2977, 2929, 2900, 1608, 1503, 1479, 1286, 1236, 1166, 1051, 495. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.66 (d, 1H), 6.61 (s, 1H), 6.60 (d, 1H), 3.95 (q, J = 7.0, 2H), 3.33 (s, 2H), 2.15 (s, 3H), 1.36 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 136.3, 122.1, 115.4, 114.1, 111.1, 62.1, 15.8, 13.1. MS (m/z) = 151.1 (77, M^+), 122.0 (100). MA: $C_9H_{13}NO$ (151.209) calcd: C = 71.49; H = 8.67; N = 9.26; found: C = 71.11; H = 8.93; N = 9.08, 0.25% water.

(4-Ethoxy-2-methyl-phenyl)carbamic Acid *tert*-Butyl Ester (14). To a solution of 18.59 g of **13** (122.9 mmol) in 150 mL of THF was added 29.51 g of di-*tert*-butyldicarbonate (129.3 mmol, 1.05 equiv) under argon. After refluxing the solution (oil bath temperature 80 °C) for 3.5 h, TLC showed complete conversion. The mixture was cooled to room temperature, and the solvent was removed in vacuo (50 °C, 5 mbar). The residue was dissolved in 400 mL of ethyl acetate, and the solution was washed three times with 150 mL of saturated aqueous ammonium chloride and once with 100 mL of saturated aqueous sodium chloride. The organic phase was dried over 20 g of sodium sulfate (30 min) and filtered. The solid was washed with 50 mL of ethyl acetate. After evaporation of solvent on a rotary evaporator (50 °C, 5 mbar), the crude product was obtained as a dark-red oil (34.29 g, 111 wt %), which was dissolved in 35 mL of TBME, and subsequently, 350 mL of of hexane were added at room temperature. To achieve completion of precipitation, the mixture was allowed to stay at −22 °C for 2 days. The pale-brown crystals were filtered from the cold mother liquor, yielding product **14** (26.47 g, 86 wt %). TLC: R_f = 0.47 (Hex/AcOEt = 4:1). Mp: 66 °C. IR (Nujol): ν = 3358, 2925, 2855, 1693, 1619, 1525, 1480, 1465, 1392, 1369, 1288, 1248, 1222, 1163, 1123, 858, 803, 495. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, 1H), 6.67−6.75 (m, 2H), 6.05 (s, 1H), 3.99 (q, J = 7.0, 2H), 2.22 (s, 3H), 1.50 (s, 9H), 1.38 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 153.7, 131.1, 129.0, 124.1, 116.7, 112.2, 80.0, 63.6, 28.4, 18.0, 14.9. MS (m/z) = 251.1 (77, M^+), 122.0 (100). MA: $C_{14}H_{21}NO_3$ (251.326) calcd: C = 66.91; H = 8.42; N = 5.57; found: C = 67.10; H = 8.37; N = 5.62.

4-Chloro-1-morpholin-4-yl-butan-1-one (15). To a solution of 13.1 mL of morpholine (150.0 mmol) in 450 mL of dichloromethane containing 23.1 mL of triethylamine (165.0 mmol, 1.10 equiv) was added 17.2 mL of 4-chlorobutyryl chloride (153.0 mmol, 1.02 equiv) dropwise at 0 °C under argon atmosphere. The mixture was allowed to warm to room temperature and was stirred for another 4 h. The solution was washed twice with 450 mL of saturated aqueous ammonium chloride and once with 450 mL of saturated aqueous sodium hydrogen carbonate and then 450 mL of saturated aqueous sodium chloride. The organic phase was dried over 20 g of sodium sulfate (30 min) and filtered. The solid was washed with 50 mL of dichloromethane. After evaporation of solvent on a rotary evaporator (50 °C, 5 mbar), product **15** was obtained as a yellow liquid (27.45 g, 95 wt %), which should be stored at low temperature (<−20 °C), since it slowly decomposes at room temperature by intramolecular nucleophilic substitution of chloride, thus forming a colorless solid. IR: ν = 2966, 2923, 2859, 1643, 1437, 1362, 1301, 1273, 1236, 1116, 1069, 1031, 849, 513. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.57−3.71 (m, 8H), 3.49 (t, J = 6.4, 2H), 2.50 (t, J = 7.0, 2H), 2.14 (tt, J = 6.4, J = 7.0, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 66.9, 66.6, 45.8, 44.8, 42.0, 29.5, 27.8. MS (m/z) = 191.1 (20, M^+),

156.1 (36), 129.1 (100), 114.0 (25), 105.1 (23), 86.0 (47), 57.2 (41), 41.1 (21). MA: $C_8H_{14}NO_2Cl$ (191.658) calcd: C = 50.14; H = 7.36; N = 7.31; found: C = 50.25; H = 7.43; N = 7.39.

[2-(5-Chloro-2-oxo-pentyl)-4-ethoxy-phenyl]carbamic Acid *tert*-Butyl Ester (16). A solution of 3.00 g of **14** (11.9 mmol) in 30 mL of THF was cooled to −40 °C under argon atmosphere; 19.9 mL of *s*-BuLi (25.1 mmol, 2.1 equiv) was slowly added so as to maintain a temperature below −35 °C. The shiny, yellow mixture was stirred for 30 min and cooled to −78 °C, and a solution of 2.75 g of **15** (14.3 mmol, 1.2 equiv) in 2.8 mL of THF was added dropwise. The yellow color disappeared immediately after complete addition, and the reaction was quenched after 5 min with 30 mL of saturated aqueous ammonium chloride. Ethyl acetate (180 mL) was added, and the organic phase was washed twice with 180 mL of saturated aqueous ammonium chloride and once with 180 mL of saturated aqueous sodium chloride. The organic phase was dried over 30 g of sodium sulfate (30 min) and filtered. The solid was washed with 60 mL of ethyl acetate. After evaporation of solvent on a rotary evaporator (50 °C, 5 mbar), the crude product was obtained as a slightly pink solid (4.35 g, 102 wt %). The crude product (4.35 g) was dissolved in 12 mL of dichloromethane at 45 °C oil bath temperature. Ketone **16** was precipitated by addition of 120 mL of hexane. To complete precipitation, the mixture was put in a freezer at −22 °C overnight. Slightly pink crystals were filtered from the cold mother liquid, yielding product **16** (3.71, 87 wt %). TLC: R_f = 0.22 (Hex/AcOEt = 4:1). IR (Nujol): ν = 3353, 2925, 2854, 1706, 1690, 1522, 1464, 1446, 1369, 1247, 1234, 1165, 1120, 507. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 2.8, 1H), 6.80 (dd, J = 3.0, J = 8.9, 1H), 6.70 (d, J = 8.5, 1H), 4.00 (q, J = 7.0, 2H), 3.68 (s, 2H), 3.54 (t, J = 6.6, 2H), 2.74 (t, J = 7.0, 2H), 2.03 (tt, J = 6.6, J = 7.0, 2H), 1.50 (s, 9H), 1.39 (t, J = 7.0, 3H). MS (m/z) = 356.3 (23, M^+), 300.3 (57), 256.2 (100). MA: $C_{18}H_{26}ClNO_4$ (355.826) calcd: C = 60.75; H = 7.36; N = 3.94; found: C = 60.97; H = 7.29; N = 4.12.

2-(3-Chloro-propyl)-5-ethoxy-indole-1-carboxylic Acid *tert*-Butyl Ester (17). Two milliliters of acetyl chloride (28.3 mmol, 1.02 equiv) was added dropwise to a solution of 25 mL of methanol in 125 mL of TBME at 0 °C. A solution of 9.86 g of **16** (27.7 mmol) in 40 mL of THF was added all at once to this mixture at 0 °C. The reaction was monitored by HPLC. After 30 min at 0 °C (HPLC: < 0.5% area of **16**), the reaction was quenched by addition of 30 mL of saturated aqueous sodium hydrogen carbonate and 350 mL of ethyl acetate. The organic phase was washed with 350 mL of saturated aqueous sodium hydrogen carbonate and subsequently with 350 mL of saturated aqueous sodium chloride, was dried over 40 g of sodium sulfate (30 min), and filtered. The solid was washed with 60 mL of ethyl acetate. After evaporation of solvent on a rotary evaporator (50 °C, 5 mbar), the crude product was obtained as a brown oil, which became a solid when stored in a freezer at −22 °C (9.17 g, 98 wt %). TLC: R_f = 0.76 (Hex/AcOEt = 4:1). Mp: 55 °C. IR (Nujol): ν = 2978, 2925, 2854, 1716, 1594, 1484, 1470, 1449, 1386, 1366, 1346, 1257, 1219, 1189, 1166, 1093, 1048, 873, 804, 767, 484. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 9.0, 1H), 6.92 (d, J = 2.5, 1H), 6.84 (dd, J = 2.6, J = 9.0, 1H), 6.31 (s, 1H), 4.06 (q, J = 7.0, 2H), 3.61 (t, J = 6.6, 2H), 3.16 (t, J = 7.2, 2H), 2.17 (tt, J = 6.6, J = 7.2, 2H), 1.68 (s, 9H), 1.42 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 150.4, 140.8, 131.3, 130.0, 116.4, 112.5, 107.9, 103.5, 83.8, 63.9, 44.3, 31.6, 28.3, 27.3, 15.0. MS (m/z) = 337.1 (26, M^+), 281.1 (100), 237.2 (13), 218.1 (13), 208.1 (9), 175.1 (17), 146.1 (5), 57.1 (9). MA: $C_{18}H_{24}ClNO_3$ (337.847) calcd: C = 63.99; H = 7.16; N = 4.15; found: C = 64.13; H = 7.24; N = 4.07.

6-Ethoxy-2,3-dihydro-1H-3a-aza-cyclopenta[*a*]indene (2). To a solution of 9.17 g of **17** (27.1 mmol) in 92 mL of DMSO and 4.6 mL of water were added 5.60 g of sodium hydroxide (135.7 mmol, 5.0 equiv) and 814 mg of sodium iodide (5.4 mmol, 0.2 equiv). The vigorously stirred reaction mixture was heated to 60 °C overnight under an argon atmosphere. The reaction was monitored by HPLC. After cooling to room temperature (HPLC: < 0.2% area of **17**), tricycle **2** was precipitated by addition of 365 mL of water and filtered. The solid was dissolved in 250 mL of ethyl acetate. The solution was washed with 250 mL of saturated aqueous ammonium chloride and then with 250 mL of saturated aqueous sodium chloride, was dried over 30 g of sodium sulfate (30 min), and filtered. The solid was washed with 50 mL of ethyl acetate. After evaporation of solvent on a rotary evaporator (50 °C, 5 mbar), product **2** was obtained as an off-white solid (5.12 g, 94 wt %).[11] TLC: R_f = 0.58 (Hex/AcOEt = 4:1). Mp: 109 °C. IR (Nujol): ν = 2924, 2854, 1573, 1490, 1470, 1420, 1395, 1310, 1239, 1179, 1129, 1113, 1043, 848, 797, 767, 736, 502. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, J = 8.8, 1H), 7.06 (d, J = 2.0, 1H), 6.80 (dd, J = 2.0, J = 8.8, 1H), 6.10 (s, 1H), 4.09 (q, J = 7.0, 2H), 4.02 (t, J = 6.8, 2H), 3.00 (t, J = 7.2, 2H), 2.60 (tt, J = 6.8, J = 7.2, 2H), 1.45 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 145.2, 133.7, 128.2, 110.7, 109.9, 103.9, 92.0, 64.3, 43.8, 27.8, 24.5, 15.1. MS (m/z) = 201.1 (97, M^+), 172.0 (100), 144.0 (54), 115.9 (12), 29.4 (18). MA: $C_{13}H_{15}NO$ (201.269) calcd: C = 77.58; H = 7.51; N = 6.96; found: C = 77.48; H = 7.57; N = 6.99.

(11) Evaporation to dryness was necessary at this stage of the development to calculate the yield. On larger scale, however, this isolation procedure will be replaced.

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