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An Efficient and Scalable Synthesis of *tert*-butyl (3a*R*,6a*S*)-5-oxohexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: A Pharmacologically Important Intermediate[#]

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ABSTRACT

Hexahydrocyclopentapyrrolone derivatives constitute an important class of bicycles and it represents an essential pharmacophore for diversified pharmacological activities. A highly efficient process for the synthesis of *tert*-butyl(3a*R*,6a*S*)-5-oxohexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate **1** has been developed. The improved process involves transformation of isoindole **4** to diacid **5**, using an inexpensive $KMnO_4$ mediated oxidative cleavage as a key-step. The developed process demonstrated cost effective, high yielding, kilogram scalable and commercially viable synthesis of **1**.

KEYWORDS

Hexahydrocyclopentapyrrolone, synthesis, Pauson-Khand cyclocarbonylation, tert-butyl (3aR,6aS)-5-oxohexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate, $KMnO_4$, oxidative cleavage.

INTRODUCTION

Carbocyclic or heterocyclic scaffolds constitute the basic skeleton of numerous bioactive compounds and pharmaceutical products.[1] Hexahydrocyclopentapyrrolone (Figure 1) derivatives represent an essential pharmacophore for diversified pharmacological activities such as antibacterial agents,[1] autotaxin inhibitors,[2] α4β2 inhibitors,[3] CCR5 antagonist,[4] DPP-IV inhibitors,[5] FAAH inhibitors,[6] Glutamate receptor modulators,[7] HSP90 inhibitors,[8] JAK inhibitor,[9] c-MET protein kinase inhibitors,[10] Retinol binding protein-4 antagonist[11] and Type-1 glycine transporter (GlyT1) inhibitors.[12]

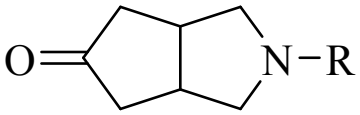


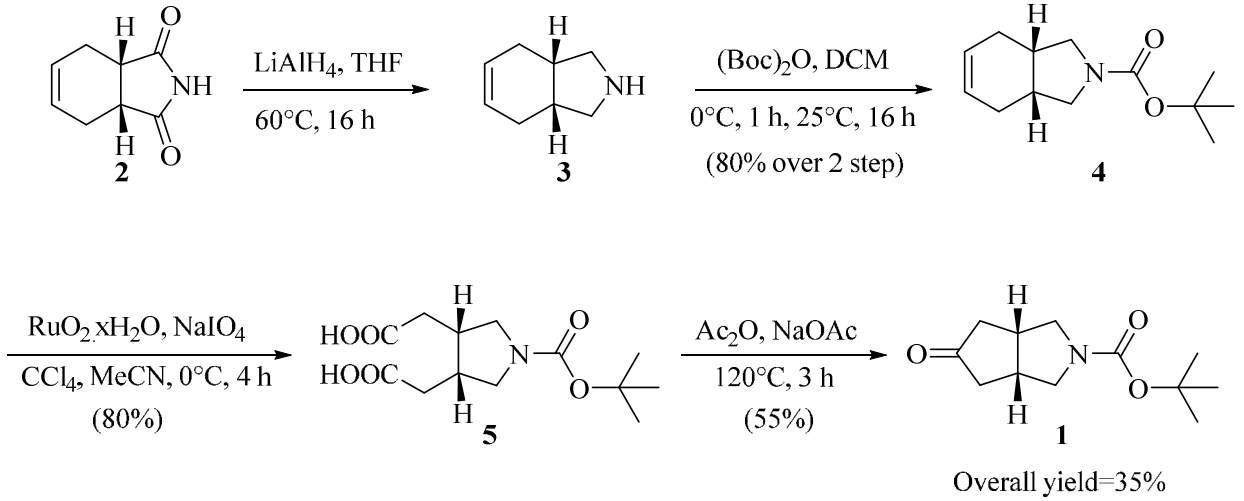
Figure 1. Hexahydrocyclopentapyrrolone

An interesting structure of hexahydrocyclopentapyrrolone derivatives as well as their pharmacological potential generated tremendous interest in these compounds. Thus, various routes for the synthesis of hexahydrocyclopentapyrrolone derivatives have been documented in literature.[13-21] Reported procedures include the synthesis of hexahydrocyclopentapyrrolone derivatives mainly from tetrahydroisoindoledione[13-16] or, a reductive Pauson-Khand cyclocarbonylation of *tert*-butyl allyl(2-propynyl)carbamate or an asymmetric cyclocarbonylation.[17-21]

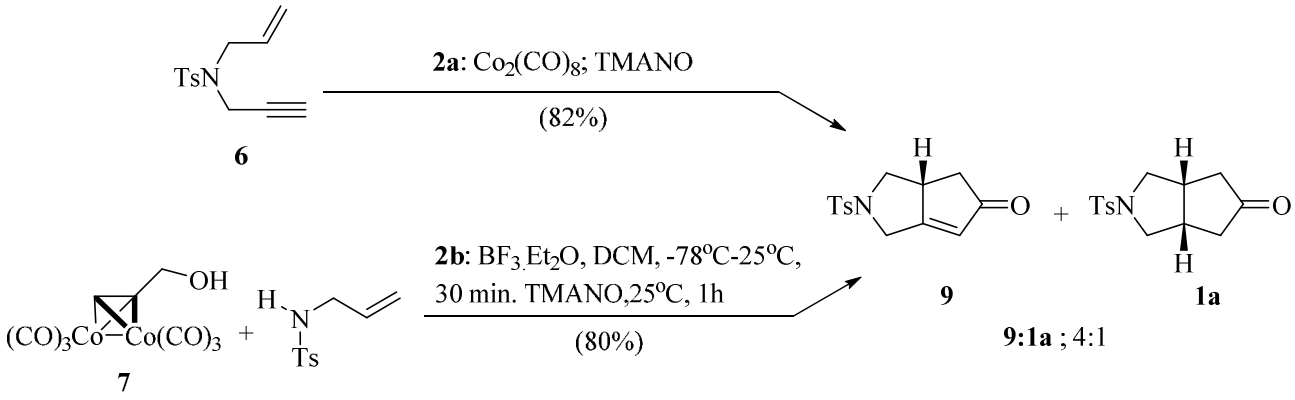
A patent from Vertex Phamaceuticals[14] reported synthesis of *tert*-butyl 5-oxohexahydrocyclopenta[*c*]pyrrole -2(1*H*)-carboxylate **1,** with overall 35% yield (Route 1, Scheme 1). The process involved expensive ruthenium (IV) oxide (RuO_2) as an oxidizing agent for the transformation of isoindole **4** to diacid **5**, which makes the process commercially non-viable. The synthesis of *N*-Cbz protected compound **1** is reported using potassium permanganate ($KMnO_4$) mediated oxidative cleavage of *N*-Cbz protected compound **4** to corresponding diacid **5**, with 39% overall yield.[16] Alternatively, cocyclization of alkynes with alkenes and carbon monoxide by dicobalt octacarbonyl, under Pauson-Khand reaction conditions led to the formation of compound **1** (Route 2 and 3, Scheme 1). [17-21]

Scheme 1. Reported Synthesis of *tert*-butyl 5-oxohexahydrocyclopenta[*c*]pyrrole -2(1*H*)-carboxylate (**1**)

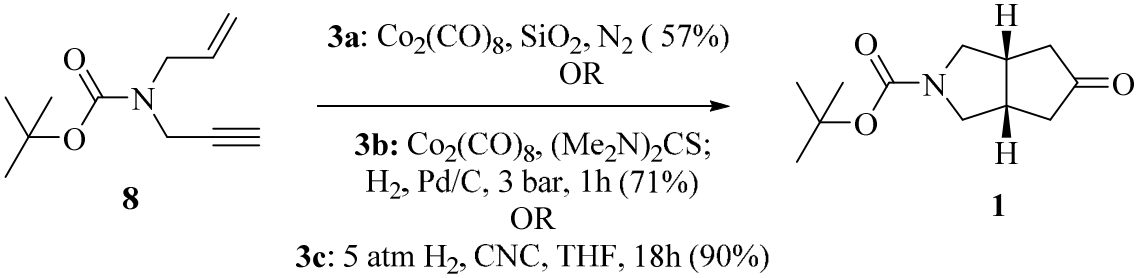
Route-1:



Route-2a-b:



Route-3a-c:



Based on this concept, Jeong et al., reported an improved process for the synthesis of tosyl protected compound **1** (2-tosylhexahydrocyclopenta[*c*]pyrrol-5(1*H*)-one **1a**), via intramolecular Pauson-Khand cyclization of *N*-(tosyl)allylpropargylamine **6**, accelerated by trimethylamine *N*-oxide (TMANO), under inert atmosphere (Route 2a, Scheme 1).[18] Same group also reported synthesis of **1a**, using cobalt-propagyl alcohol complex **7** and allyl tosylamide, via Nicholas reaction, in presence of boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$), followed by Pauson-Khand cyclization (Route 2b, Scheme 1).[19] Under both the conditions, 2-tosylhexahydrocyclopenta[*c*]pyrrol-5(1*H*)-one **9** was obtained as major product, while the desired compound **1a** (16% overall yield) as a minor product (Route 2a-b, Scheme 1).

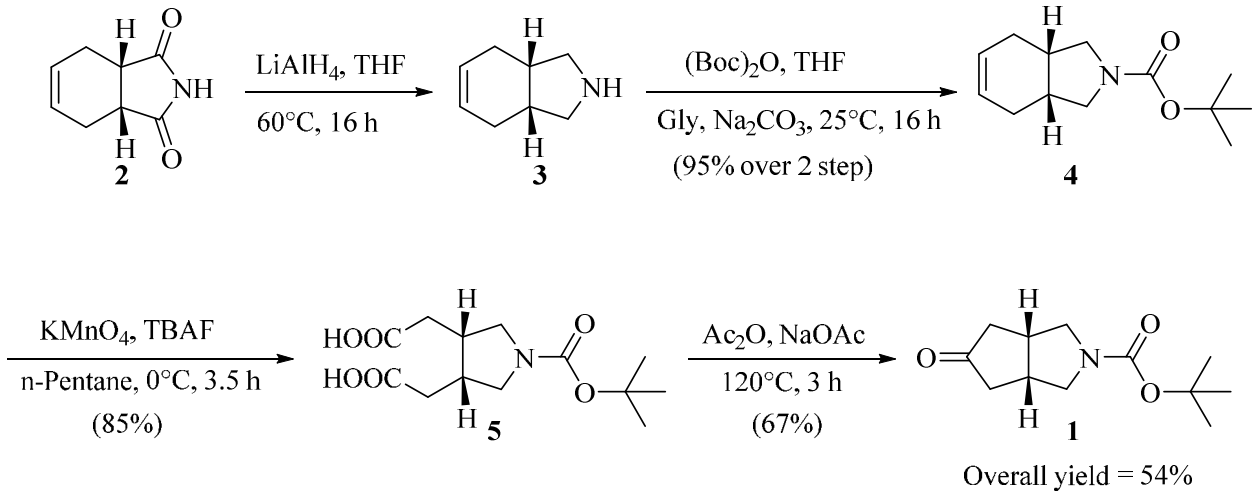
Becker et al.[20] reported a synthesis of compound **1,** with 57% yield, without contamination by the corresponding unsaturated enone **9**, via intramolecular reductive Pauson-Khand reaction of the hexacarbonyldicobalt complex of *N*-(*tert*-butyloxycarbonyl)allylpropargylamine **8**, under dry-state adsorption conditions (Route 3a, Scheme 1). Guillemont et al.[17] reported an efficient synthesis of compound **1** (overall 71% yield), via intramolecular reductive Pauson-Khand reaction of the compound **8** with 1,1,3,3-tetramethyl-2-thiourea, under pressure of carbon monoxide (3 bar), in an autoclave, followed by hydrogenation (Route 3b, Scheme 1). Chung et al.[21] reported one pot Cobalt Nanoparticles on Charcoal (CNC) catalyzed carbonylative cycloaddition of alkyne and carbon monoxide, followed by hydrogenation and the reductive Pauson-Khand reaction to get compound **1**(Route 3c, Scheme 1). However, Pauson-Khand reaction requires high temperature and long reaction time due to slow decarbonylation and expensive reagents.

The use of oxometal reagents may lead to an excess of residual heavy metal in the final product. Second, these methods involve high manufacturing costs, due to the application of expensive raw materials and reagents. Moreover, these processes often involve cumbersome reaction work up and chromatography. Herein, we report an efficient, scalable and commercially viable process for the plant scale manufacturing of *tert*-butyl (3a*R*,6a*S*)- 5-oxohexahydrocyclopenta[*c*]pyrrole -2(1*H*)-carboxylate **1**, starting from readily available inexpensive reagents, with an excellent overall yield.

RESULTS AND DISCUSSION

As depicted in Scheme 2, synthesis of compound **1** was carried out starting from a commercially available (3a*R*,7a*S*)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2*H*)-dione **2**. Lithium aluminum hydride facilitated reduction of compound **2** afforded corresponding amine (**3**)[22] almost in quantitative yield, which without further purification was immediately transformed to its Boc protected derivative (**4**) in high yields (95% yield over 2 steps). Importantly, this two-step reaction sequence was carried out in common solvent (THF). Workup protocol was optimized and instead of column chromatography, treatment of crude reaction mixture with glycine and sodium carbonate (to remove excess of Boc anhydride, as Boc-Gly-OH), followed by extraction with a nonpolar solvent (hexane), afforded compound **4**, with improved yield (95%) and high purity (94% by GC).

Scheme 2. Improved synthesis of compound **1**



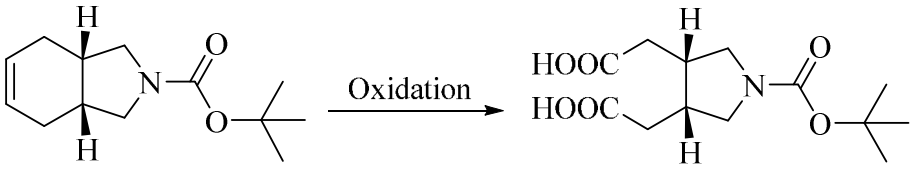
With the readily available compound **4**, we further investigated the oxidative cleavage to diacid **5** using various oxometal reagents (Table 1). Ruthenium (IV) oxide is known for the conversion of compound **4** to **5**.[14] However, this reaction condition not only required expensive ruthenium catalyst, but also needs chromatographic purifications, due to presence of traces of ruthenium, periodate and iodate, in the crude reaction mixture. Hydrogen peroxide (H_2O_2), sodium hypochlorite (NaOCl), and osmium tetroxide (OsO_4), although frequently used for such oxidative cleavage reaction,[23] did not lead to significant amount of product (Table 1, entries 2-4).

Next, use of $KMnO_4$ was investigated. In literature, synthesis of adipic acid is reported by direct oxidation of cyclohexene, using $KMnO_4$.[24] A recent patent from Mnemosyne Pharmaceuticals[16] described the conversion of *N*-Cbz derivative of compound **4** to its corresponding diacid **5** using $KMnO_4$, albeit with lower yield and purity. Our succeeding investigations found that $KMnO_4$ was the most effective agent for the transformation of compound **4** to **5**. Treatment of compound **4** with $KMnO_4$ (3 equivalent) and tetrabutyl ammonium bromide (TBAB, 0.15 equivalent), in *n*-pentane, at 0 °C afforded crude compound **5**. The work up protocol was altered and the purification of crude product via solvent treatment (Hexane/EtOAc, 2:1) delivered the best yield (85%), with excellent 94% purity (entry 5). The heavy metal content analysis results of compound **5** confirmed absence of manganese traces. Further, replacing the solvent from *n*-pentane to *n*-hexane or *n*-heptane resulted in similar yields (refer Supporting Information, Table S1). However, a lower yield was found at room temperature (entry 6, Table S1).

To ensure a safe implementation of the reaction conditions, a safety evaluation of the process was carried out by performing a reaction calorimetry (RC). The reaction calorimetry data established low severity (9 ^{o}C rise in adiabatic temperature during *n*-pentane addition to compound **4** and 6 ^{o}C rise during $KMnO_4$ mediated oxidative cleavage of compound **4** to **5**). Since, *n*-pentane, a class-2 solvent is usually a less preferred solvent for the large scale manufacturing (highly flammable, explosive and causes dizziness, headache and skin irritation), we recommend appropriate safety measures, such as closed delivery system, proper air ventilation (including breathing protection), explosion-proof electrical equipments and protective gloves should be used while handling *n*-pentane on a large scale.

Subsequently, treatment of 2,2'-(1-(*tert*-butoxycarbonyl)pyrrolidine-3,4-diyl)diacetic acid (**5**) with acetic anhydride and sodium acetate under Dieckmann-Condensation reaction conditions afforded compound **1** with an improved yield (67%). Notably, compound **1** was purified by reprecipitation from cyclohexane, thereby, eliminating column chromatographic purification.

Table 1. Optimization of oxidative cleavage reaction



4 **5**

entry	oxidizing agents	yield of **5**	purity of **5**[d]
1	RuO_2 & $NaIO_4$	80%[a or c]	65%
2	OsO_4	12%[b]	93%
3	H_2O_2 & $Na_2WO_4 \cdot 2H_2O$	19%[a]	92%
4	NaOCl & TMCAC	23%[a]	90%
5	$KMnO_4$ (3 eq.), TBAB, 0 °C	85%[c]	94%
6	$KMnO_4$ (3 eq.), TBAB, rt	62%[c]	65%

a) % yield after column chromatography; b) crude yield; c) % yield after solvent treatment; d) Purity by HPLC.

Compared with the reported synthesis, the overall yield was improved from 35% to 54%, mainly due to improvement in yield from 80% to 95% for intermediate **4**, 80% to 85% for intermediate **5** and 55% to 67% in the final step. All the steps were run on kilogram scale and no chromatography was needed. From a process stand point, column chromatographic purification of advanced intermediates may not be considered as an efficient strategy due to the loss of a significant component of the API, which can contribute to higher costs. Thus, improved process using commercially available isoindole **2** to **1** was significantly optimized with high yields and easy workup.

Additionally, we mapped our improved process for the total solvent consumption, considering as a parameter for green chemistry. Data analysis of the solvent consumption comparison for one kilogram synthesis of compound **1**, adopting Scheme 1(Route 1) or Scheme 2 (Figure 2) revealed 77% reduction (4.4 fold, from 1518 L to 347 L) in the total solvent consumption with our improved process. In addition, this improved process also resulted in significant reduction in raw material cost (RMC). For example, as per the literature process (Scheme 1, Route 1), RMC of **1** would be approximately $3950/kg, whereas with the newly developed process, the RMC comes

to around $1439/kg (64% of cost reduction, see supporting information, Table S2 for raw material costing).

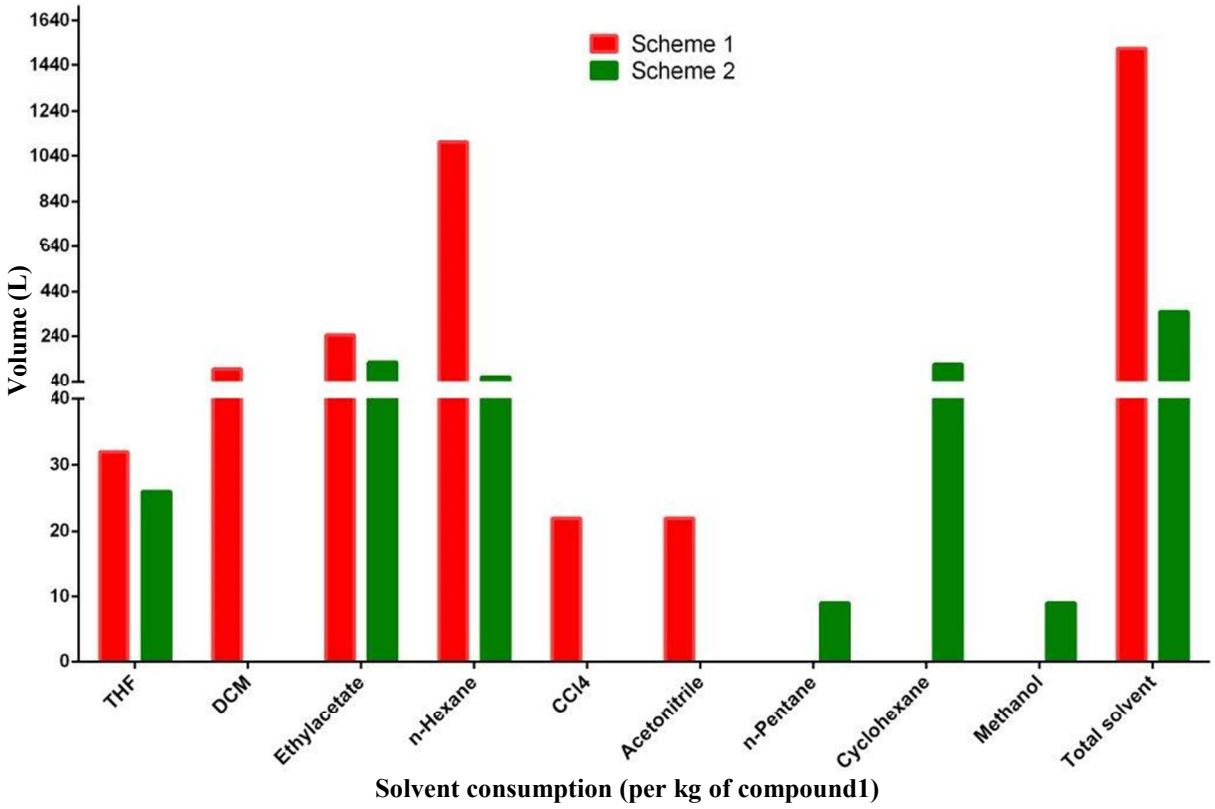
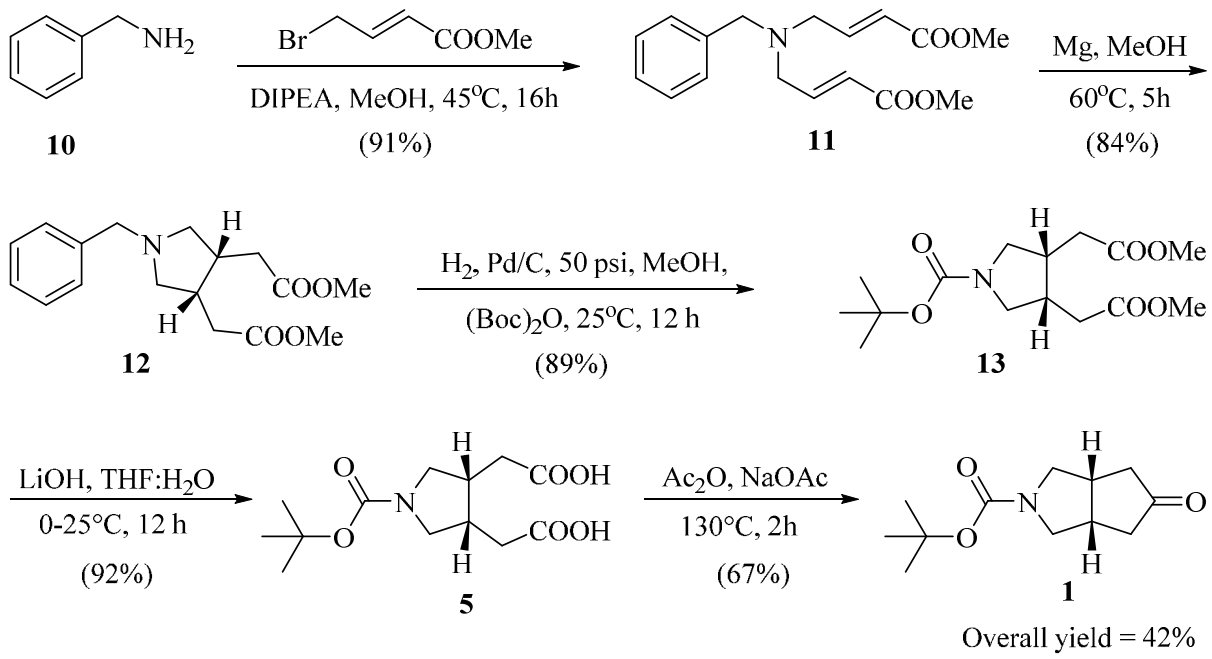


Figure 2: Solvent consumption comparison for per kg synthesis of compound **1**, adopting **Scheme 1** (Route 1) and **Scheme 2**.

We also explored an alternative novel route for the gram scale synthesis of compound **1**, starting from readily available benzyl amine (Scheme 3). Benzyl protected pyrrolidine diester **12** was obtained *via* 2-steps reported procedure, starting from benzyl amine.[25] Debenzylation of **12** under hydrogenation conditions followed by protection with Boc group afforded compound **13** in 89% yield, on gram scale. Hydrolysis of **13** with sodium hydroxide, followed by cyclization using acetic anhydride afforded compound **1** in 5-steps, with 42% overall yield.

Scheme 3. Novel route for the synthesis of compound **1**



CONCLUSION

In conclusion, we have developed an efficient synthesis of *tert*-butyl 5-oxohexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate **1**, a pharmacologically important intermediate. The process involves an inexpensive $KMnO_4$ mediated oxidative cleavage of isoindole **4** to diacid **5**, as a key-step. This approach afforded compound **1** in 4-steps with 54% overall yield, in kilogram scale. Major highlights of our improved process include (i) simplified reaction workup; (ii) no usage of chromatography; (iii) optimal solvent consumption; (iv) an economical synthetic sequence; and (v) higher overall yield. Taken together, this developed process demonstrated cost effective, high yielding, and commercially viable synthesis of **1** and has the potential for large scale manufacturing. Additionally, an alternative novel route afforded compound **1**, in gram scale, in 5-steps, with 42% overall yield, starting from benzyl amine.

EXPERIMENTAL SECTION

General Methods

Melting points were recorded on a scientific melting point apparatus and are uncorrected. IR spectra were recorded as neat (for oils) or on KBr pellet (for solid) on FT-IR 8300 Shimadzu and

are reported in wavenumbers ν (cm^{-1}). NMR spectra were measured on a Varian Unity 400 (^1H at 400 MHz, ^{13}C at 100 MHz), magnetic resonance spectrometer. Spectra were taken in the indicated solvent at ambient temperature. Chemical shifts (δ) are given in parts per million (ppm) with tetramethylsilane as an internal standard. Multiplicities are recorded as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. Coupling constants (J values) are given in Hz. Mass spectra are recorded on Perkin-Elmer Sciex API 3000. ESI-Q-TOF-MS measurements were performed with a micrOTOF-Q II (Bruker Daltonics) mass spectrometer. HPLC analysis were carried out at λ_{max} 220 nm using column ODS C-18, 150 mm x 4.6 mm x 4 µm on AGILENT 1100 series. Reactions were monitored using thin layer silica gel chromatography (TLC) using 0.25 mm silica gel 60F plates from Merck. Plates were visualized by treatment with UV, acidic *p*-anisaldehyde stain, $KMnO_4$ stain with gentle heating. Products were purified by column chromatography using silica gel 100-200 mesh and the solvent systems indicated.

All reactions involving air or moisture sensitive compounds were performed under nitrogen atmosphere in flame dried glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium/ benzophenone under nitrogen atmosphere. Other solvents used for reactions were purified according to standard procedures. Starting reagents were purchased from commercial suppliers and used without further purification unless otherwise specified.

Synthesis of *tert*-butyl 5-oxohexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (1)

2,3,3a,4,7,7a-hexahydro-1H-isoindole (3).

In a 100 L fixed glass assembly, THF (23 L) was charged and cooled externally with dry ice to -5 to 0 °C. Lithium aluminum hydride powder (1.0 kg, 26.3 mol) was added portion wise, over a period of 1.5 hour, while maintaining internal temperature below 5 °C. Tetrahydrophthalimide (**2**) (1.53 kg, 10.13 mol) was added portion wise, over a period of 1 hour, maintaining an internal temperature below 5 °C. Reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then heated at 66 - 67 °C for 16 h. Reaction mixture was cooled to room temperature and subsequently up to -10 °C with dry ice. The reaction mixture was quenched with dropwise addition of ice water (750 mL), while maintaining internal temperature below 5 °C. Upon completion of water addition, the reaction mixture turned to thick slurry. Additional THF (6 L) and solid sodium sulfate (~1.5 kg) were added followed by dropwise addition of KOH solution (15%; 180 g KOH dissolved in 1.2 L of water), over a period of 1 h,

while maintaining an internal temperature below 5 °C. Additional water (1 L) and solid sodium sulfate (2 kg) were added and the reaction mixture was slowly warmed to room temperature. At room temperature it was stirred for another 30 minutes and the solid inorganic material was filtered off through HyFlo SuperCel bed. Inorganic solid impurity was washed twice with THF (2 x 1.5 L), combined THF layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to yield compound **3** as oil (1.589 kg, contains 20% THF), which was used in next the reaction, without any further purification.

***tert*-butyl 3a,4,7,7a-tetrahydro-1H-isoindole-2(3*H*)-carboxylate (4).**

50 L SS reactor was charged with compound **3 (**1.589 kg, 10.12 mol, contains 20% THF), dissolved in THF (23 L) and cooled up to 0 to -5 °C. Boc-anhydride (2.793 kg, 2.94 L, 12.65 mol) was added drop wise, while maintaining an internal temperature between 0-5 °C, over a period of 30 minutes. The reaction mixture was warmed to room temperature and stirred at room temperature for 16 h. A solution of glycine (0.60 kg, 7.99 mol) and sodium carbonate (1.80 kg, 16.98 mol) in water (12 L) was added to the reaction mixture at room temperature and stirred for additional 20 h. The reaction mixture was concentrated under reduced pressure to remove THF and dried under vacuum. The n-Hexane (25 L) and additional water (8 L) were added and stirred at room temperature for 15 minutes. The reaction mixture was filtered through HyFlo SuperCel and the layers were separated. Aqueous layer was extracted with n-hexane (2 x 20 L) and the combined organic layer was washed with water (2 x 20 L) and brine (20 L). Hexane layer was stirred with activated charcoal (~500 g), for 1 hour at room temperature, filtered through HyFlo SuperCel. Combined hexane was dried over sodium sulfate, filtered, concentrated *in vacuo* to afford compound **4** (2.15 kg, 95%) as a brown oil. % Purity: 93.72% (GC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 9H), 1.89-194 (m, 2H), 2.20-2.33 (m, 4H), 3.08 (dd, J_1 = 6.2 Hz, J_2 = 10.2 Hz, 1H), 3.17 (dd, J_1 = 4.8 Hz, J_2 = 10.4 Hz, 1H), 3.37-3.43 (m, 2H), 5.65 (s, 2H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.63, 24.68, 28.49, 33.35, 34.23, 50.86, 50.92, 78.88, 124.19, 124.50, 155.22; IR ($CHCl_3$): ν = 756, 1128, 1170, 1217, 1411, 1685, 2937, 2978, 3009 cm^{-1}; TOFMS: [$C_{13}H_{21}NO_2 + H^+$]: calculated 224.1645, found 168.0958 (M-*tBu* + H)$^+$ (100%), 246.1382 (M + Na)$^+$ (5%).

2,2'-(1-(*tert*-butoxycarbonyl)pyrrolidine-3,4-diyl)diacetic acid (5).

A 200 L glass liner reactor (equipped with a condenser and a thermometer pocket) was charged with a solution of compound **4** (2.0 kg, 8.969 mol), dissolved in *n*-pentane (10.0 L) and cooled externally to 0 °C. Freshly prepared solution of potassium permanganate (4.248 kg, 26.906 mol) and tetrabutylammonium bromide (0.431 kg, 1.781 mol) dissolved in water (80 L) was added to reaction mixture at 0-5 °C, in 2.5 h. Reaction mixture was further stirred at 0-5 °C for 1 h.

The reaction mixture was filtered through HyFlo SuperCel, residual solid was slurry washed with water (2 x 8 L). The combined filtrate was washed with ethyl acetate (12 L) and the organic layer was separated. The aqueous layer was acidified with 1N HCl solution (pH ~ 3) and extracted with ethyl acetate (3 x 40 L). The combined ethyl acetate layer was washed with brine (28 L), treated with activated charcoal (900 g) and filtered through HyFlo SuperCel. The organic solvent was distilled under vacuum to afford title compound (2.55 kg) as off white solid, which was purified by solvent treatment. Ethyl acetate (3.825 L) was added and the solid was stirred for 30 minutes, at room temperature, slowly n-hexane (7.65 L) was added and stirred for 90 minutes. Solid product was filtered *in vacuo* and washed with 30% ethyl acetate in n-hexane (1 x 2.5 L). Product was dried for 2 h to yield compound **5** (2.187 kg, 85%) as a white solid. MP: 162-163 ^{o}C, % purity: 94.09% (HPLC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.38 (s, 9H), 2.10-2.18 (m, 2H), 2.28-2.32 (m, 2H), 2.49-2.50 (m, 2H, merged with DMSO peak), 2.97-3.03 (m, 2H), 3.33-3.40 (m, 2H). 12.23 (bs, 2H); ^{1}H NMR (CD_3OD, 400 MHz) δ: 1.46 (s, 9H), 2.26 (ddd, J_1 = 2.8 Hz, J_2 = 9.2 Hz, J_3 = 16.0 Hz, 2H), 2.43 (dd, J_1 = 5.2 Hz, J_2 = 16.0 Hz, 2H), 2.69 (m, 2H), 3.16 (dd, J_1 = 5.2 Hz, J_2 = 10.8 Hz, 2H), 3.49-3.54 (m, 2H).; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 28.49, 32.97, 36.49, 37.31, 50.10, 50.20, 78.67, 154.05, 173.96; IR (KBr): ν = 871, 933, 1143, 1166, 1292, 1411, 1689, 1708, 2881, 2929, 2980, 3001 cm^{-1}; TOFMS: [$C_{13}H_{21}NO_6$ - H^+]: calculated 286.1296, found 286.1031(100%).

***tert*-butyl (3a*R*,6a*S*)-5-oxohexahydrocyclopenta[c]pyrrole-2(1*H*)-carboxylate (1).**

A 50L glass assembly (equipped with a double surface condenser and a thermometer pocket) was charged with acetic anhydride (10.42 kg, 9.65 L, 102.09), followed by slow addition of compound **5** (2.0 kg, 6.968 mol). The reaction mixture was heated at 135 °C for 45 minutes. Sodium acetate (0.486 kg, 5.924 mol) was added to the reaction mixture portion wise, over a period of 30 minutes and additionally, the mixture was stirred at 135 °C for 30 minutes. The

reaction mixture was cooled up to 5-10 °C, MeOH (10 L) was added dropwise, while maintaining an internal temperature between 10 -15 °C, addition of methanol was completed within 2 h and the reaction mixture was cooled up to -5 °C. The reaction mixture was poured into 10 L ice water and slowly solid sodium carbonate (~12 kg, pH ~10) was added, followed by cyclohexane addition (~50 L). The reaction mixture was stirred for 15 minutes and filtered through HyFlo SuperCel to remove solid inorganic waste and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with cyclohexane (2 x 40 L). The combined organic solvent was dried over sodium sulfate and concentrated *in vacuo* to afford crude product (~ 1.44 kg).

The crude product was purified by recrystallization from cyclohexane. The crude product was dissolved in cyclohexane (6 L) at 60 °C. Allowed it to cool gradually to room temperature and then cooled up to 5-10 °C in an ice bath, for 1 hour. The off white colored solid product was filtered and dried *in vacuo* to afford pure compound **1** (1.051 kg, 67%) as a white solid. MP: 70-71 ^{o}C (uncorrected); $[\alpha]^{25}_{D}$ +0.40° (c 1.00 $CHCl_3$); % purity: 98.5% (HPLC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.46 (s, 9H), 2.15 (dd, J_1 = 4.8 Hz, J_2 = 19.6 Hz, 2H), 2.47 (dd, J_1 = 7.4 Hz, J_2 = 19.6 Hz, 2H), 2.93 (bs, 2H), 3.16-3.28 (m, 2H), 3.65-3.67 (m, 2H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 38.49, 39.36, 42.32, 50.51, 50.77, 79.49, 154.39, 217.65; IR (KBr): ν = 638, 771, 877, 1118, 1166, 1247, 1367, 1402, 1691, 1741, 2877, 2910, 2958, 2976, 3005 cm^{-1}; TOFMS: $[C_{12}H_{19}NO_3 + H^+]$: calculated 226.1438, found 152.0663 $(M\text{-}OtBu)^+$ (100%), 170.0755 $(M\text{-}tBu + H)^+$ (40%), 248.1166 $(M+Na)^+$ (5%). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.89; H, 8.27; N, 5.97.

Dimethyl 4,4'-(benzylazanediyl)(2*E*,2'*E*)-bis(but-2-enoate) (11).

To a stirred solution of benzyl amine **10** (100 g, 0.933 mol) and DIPEA (386 g, 2.99 mol), in dry MeOH (2 L), at room temperature under inert atmosphere, in a 5 L 4-neck round bottom flask (equipped with a condenser and a thermometer pocket) was added (*E*)-methyl 4-bromobut-2-enoate (418 g, 3.80 mol) in a single portion. Reaction mixture was heated to 45 °C and stirred for 16 h. Reaction mixture was then evaporated under reduced pressure to give crude product.

Crude product was purified by column chromatography over silica gel with 10% EtOAc/n-hexane as eluent to furnish compound **11**, (258 g, 91% yield) as yellow oil. % purity: 93.4% (UPLC); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.23 (dd, J_1 = 1.6 Hz, J_2 = 6.0 Hz, 4H), 3.62 (s, 2H),

3.75 (s, 6H), 6.07 (dt, J_1 = 1.6 Hz, J_2 = 16.0 Hz, 2H), 6.97 (dt, J_1 = 6.0 Hz, J_2 = 16.0 Hz, 2H), 7.25-7.34 (m, 5H-merged with $CDCl_3$ proton).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 51.53, 53.42, 58.37, 122.66, 127.28, 128.41, 128.55, 128.76, 138.24, 145.84, 166.58; IR ($CHCl_3$): ν = 758, 1215, 1278, 1437, 1660, 1720, 2806, 2953, 3020, 3421 cm^{-1}; TOFMS: [$C_{17}H_{21}NO_4$ + H^+]: calculated 304.1543, found 304.1703(100%).

Dimethyl 2,2'-(1-benzylpyrrolidine-3,4-diyl)diacetate (12).

In a 20 L glass assembly (equipped with a condenser and a thermometer pocket) was charged compound **11** (250 g, 0.825 mol) and dry MeOH (7.5 L) at room temperature, under inert atmosphere. To this mixture was added freshly activated magnesium turnings (198 g, 8.25 mol) and mixture was heated at 70 °C for 6 h. The reaction mixture was cooled up to 5-10 °C, ice cold 2N HCl (2 L) was added slowly, followed by addition of ethyl acetate (5 L). Reaction was stirred for 15 minutes, filtered through HyFlo SuperCel, to remove solid inorganic waste and the ethyl acetate layer was separated from the aqueous layer. The aqueous layer was extracted with ethyl acetate (2 x 3 L). Combined ethyl acetate layer was dried over sodium sulfate and concentrated *in vacuo* to afford compound **12** (212 g, 84%). Product was used for next step without any further purification. % purity: 90.9% (HPLC); ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.25-2.33 (m, 4H), 2.39 (dd, J_1 = 5.6 Hz, J_2 = 15.6 Hz,) 2.74-2.76 (m, 2H), 2.94 (dd, J_1 = 7.0 Hz, J_2 = 9.4 Hz), 3.62 (s, 2H), 3.66 (s, 6H), 7.23-7.27 (m, 1H), 7.30-7.31 (m, 4H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 34.51, 36.16, 51.63, 59.20, 60.23, 126.88, 128.20, 128.55, 139.01, 173.14; IR ($CHCl_3$): ν = 758, 1165, 1217, 1437, 1734, 2796, 2953, 3020, 3448 cm^{-1}; TOFMS: [$C_{17}H_{23}NO_4$ + H^+]: calculated 306.1700, found 306.1865 (100%).

Dimethyl 2,2'-(1-(*tert*-butoxycarbonyl)pyrrolidine-3,4-diyl)diacetate (13).

To a stirred solution of compound **12** (200 g, 0.655 mol) in dry MeOH (2 L), at room temperature, in a hydrogenation vessel was added 10% wet Pd/C (20 g, 0.183 mol, 10% w/w of starting material) and Boc anhydride (171 g, 0.7864 mol). Above reaction was subjected for hydrogenation, at 50 psi for 12 h at 25 ^oC. Reaction mixture was filtered through celite and concentrated to get compound **13** (184 g, 89%) as yellow oil. % purity: 90.15% (HPLC); ^1H NMR ($CDCl_3$, 400 MHz) δ:1.46 (s, 9H), 2.25-2.31 (m, 2H), 2.36-2.43 (m, 2H), 2.72 (m, 2H), 3.08 (dd, J_1 = 5.6 Hz, J_2 = 11.2 Hz, 1H), 3.15 (dd, J_1 = 5.2 Hz, J_2 = 11.2 Hz, 1H), 3.69 (s, 3H),

3.71 (s, 3H).; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.42, 32.81, 49.90, 50.14, 51.78, 79.39, 154.49, 172.30, 172.82; IR ($CHCl_3$): ν = 756, 1166, 1367, 1413, 1685, 1735, 2877, 2955, 2980, 3009 cm^{-1}; TOFMS: [$C_{15}H_{25}NO_6$ + H^+]: calculated 316.1755, found 216.1317(M-Boc + H)$^+$ (100%), 338.1767(M + Na)$^+$ (20%).

2,2'-(1-(*tert*-butoxycarbonyl)pyrrolidine-3,4-diyl)diacetic acid (5).

To a stirred solution of compound **13** (180 g, 0.571 mol), in MeOH (1.8 L) and water (0.9 L), in a 5L four neck round bottom flask, at room temperature was added NaOH (91.38 g, 2.284 mol). Reaction was stirred for 18 h at 25 ^{o}C. The reaction mixture was cooled up to 0 to 5 ^{o}C and acidified using 10% citric acid solution (pH 6). Further, ethyl acetate was added (4 L), stirred for 15 minutes and organic layer was separated from the water layer. The water layer was extracted with ethyl acetate (2 x 1 L). Combined ethyl acetate layer was dried over sodium sulfate and concentrated *in vacuo* to afford compound **5** (151 g, 92%), as white powder. Characterization data for **5** have been reported above. Finally, compound **5** (150 g, 0.522 mol) was converted to compound **1** (79 g, 67%), following the procedure described in Scheme-2.

ASSOCIATED CONTENT

Supporting Information

GC, HPLC, UPLC, TOFMS, ^{1}H & ^{13}C NMR and IR spectra of all new compounds.

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Notes

The authors declare no competing financial interest

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Graphic for Manuscript

An Efficient and Scalable Synthesis of *tert*-butyl (3a*R*,6a*S*)-5-oxohexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate: A Pharmacologically Important Intermediate

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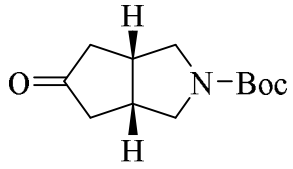
GRAPHICAL ABSTRACT

A highly efficient, improved and cost effective process for the synthesis of hexahydrocyclopentapyrrolone derivatives, *tert*-butyl(3a*R*,6a*S*)-5-oxohexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate **1** has been developed. The process provides commercially viable kilogram scale synthesis of **1**.



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