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SYNTHESIS OF INDOLO[1,2-*b*]INDAZOLE DERIVATIVES

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Abstract- New methods to synthesize indolo[1,2-*b*]indazole derivatives as an extension of available methods and thiol reduction of ketone to methylene peculiar to this skeleton were presented.

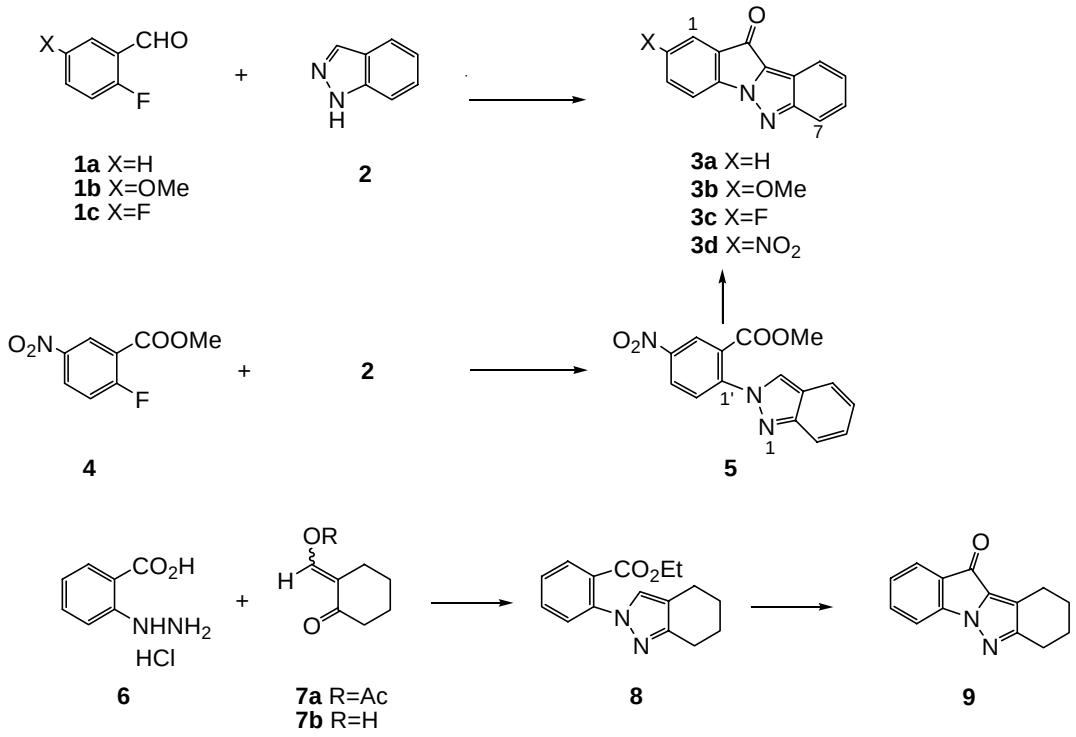
INTRODUCTION

We have been involved in the studies of anti-cancer activities of pyrazolo[1,5-*a*]indole derivatives.[1] As an extension of this research we have figured out the structure of indolo[1,2-*b*]indazole as a next target, and reported a new method to construct this skeleton by intramolecular amination of hydrazine derivatives.[2] Even combining a few available methods[3] including this new method, known methods are not good enough to synthesize the potential anti-cancer agents with the nucleus of indolo[1,2-*b*]indazole due to laborious preparation of the starting materials and troubles in introducing a variety of functional groups such as nitro- and halogeno-groups. Also the chemistry of indolo[1,2-*b*]indazole is totally unexplored. In this report we provide a few supplemental methods to fulfill such kind of shorthand in the synthesis of indolo[1,2-*b*]indazole derivatives.

RESULTS AND DISCUSSION

Simplest method reported for the construction of indolo[1,2-*b*]indazole is a reaction of indazole (**2)** with 2-fluorobenzaldehyde (**1a)** in the presence of K_2CO_3 in DMF at 110°C, and 11-oxo-11*H*-indolo[1,2-*b*]indazole (**3a)** was obtained in 20% yield based on consumed indazole.[3] Reaction mechanism may involve substitution, base-catalyzed cyclization and air-oxidation of alcoholic

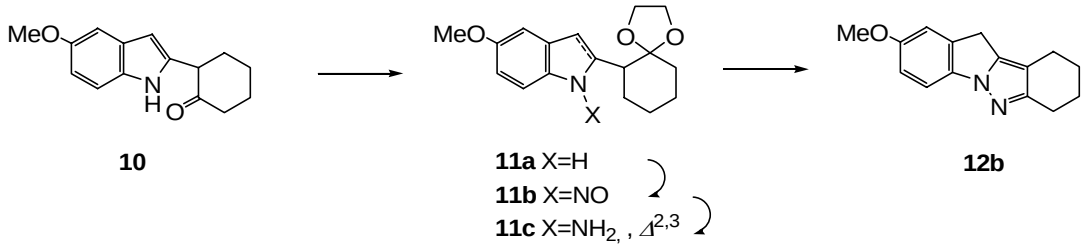
Scheme 1



product. Addition of NaF did not improve the yield of **3a**. Although yield was low, the reaction was straightforward, so the scope of this reaction was investigated by using substituted 2-fluorobenzaldehydes. When 5-methoxy-2-fluorobenzaldehyde (**1b)** was employed, **3b** was obtained in low yield (12%), and 2,5-difluorobenzaldehyde (**1c)** gave **3c** in poor yield (7%). Other 2-fluorobenzaldehyde derivatives with 5-Cl, Br and NO_2 substituents were intact in this reaction. 5-Nitro derivative (**3d**) was synthesized by an alternative method, starting with methyl 5-nitro-2-fluorobenzoate (**4)**. Substitution product (**5**) obtained by the reaction of lithium salt of **2** with **4** was cyclized by the treatment with LDA, and **3d** was obtained in 51.4% isolated yield. Structure of **3d** was confirmed by comparing the spectra with those of **3a** and **3b**. Similar cyclization was also effected with indazole derivative (**8**). Compound (**8**) was prepared by coupling

reaction of 2-carboxyphenylhydrazine (**6**) with masked 1,3-dicarbonyl compound (**7a**) and following esterification reaction. Cyclization of **8** with LDA gave 7,8,9,10-tetrahydro-11*H*-indolo[1,2-*b*]indazole (**9**) in 41% yield. Similar coupling reaction with unprotected 1,3-dicarbonyl compound (**7b**)[4] did not give **8** but its regioisomer, 1-(2-ethoxycarbonylphenyl)-4,5,6,7-tetrahydroindazole (65%). The structure of this regioisomer was supported by the observation of NOE between 7'-H and 6-H in ^{1}H NMR spectrum. These results suggest that hydrazone formation was regioselective and depended upon a species of 1,3-dicarbonyl compound.

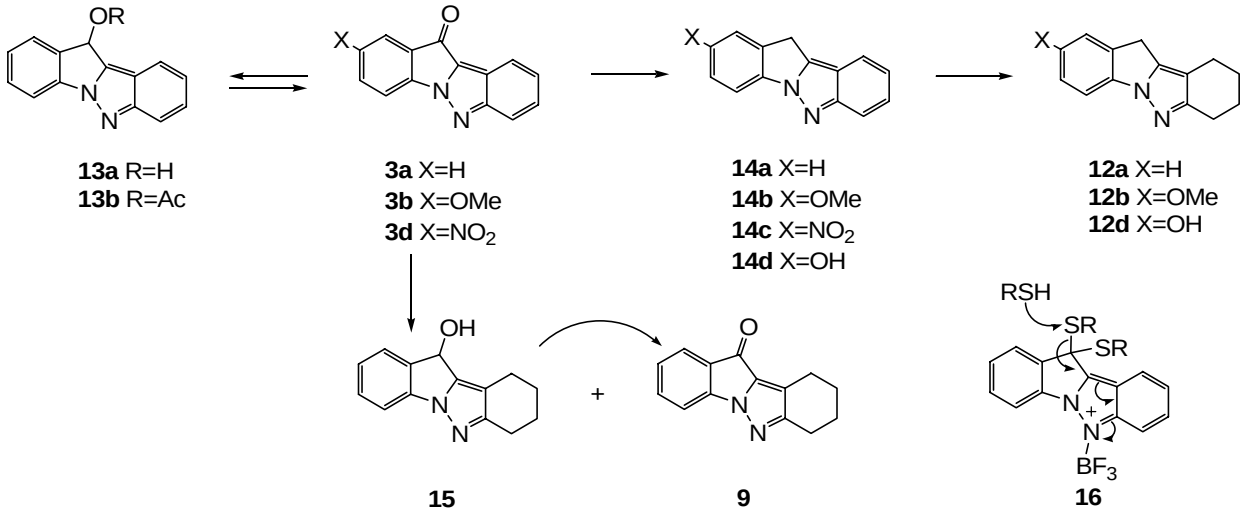
Scheme 2



An alternative route to synthesize 7,8,9,10-tetrahydro derivative was also developed (Scheme 2). Starting material (**10**) was prepared according to the procedure reported for 5-unsbustituted compound[5] starting with 5-methoxy-2-nitrophenyl acetic acid.[6] Carbonyl group of **10** was transferred to acetal, and reduced to indoline (**11a**) by $NaBH_3CN$ in a mixture of HOAc and MeCN. Treatment of **11a** with nitrous acid, reduction of product (**11b**) with $LiAlH_4$, and subsequent treatment of N-amino product with silica gel in CH_2Cl_2 overnight permitted air-oxidation to give 1-aminoindole (**11c**) in 58% overall yield. Deacetallization and cyclization were effected in 80% acetic acid, and **12b** was obtained in 91% yield.

Reduction of keto group of **3a** to methylene faced with a few difficulties. Reductions by conventional Wolff-Kishner (hydrazine/NaOH) and modified method (tosylhydrazone/$NaBH_3CN$)[7] failed. 11-Ketone (**3a**) was readily reduced by sodium borohydride to alcohol (**13a**). In extraction of **13a**, it was critical to use ethyl acetate, since **13a** was quite susceptible to air-oxidation. **13a** was oxidized to **3a** in 84% after 12 h in$CDCl_3$ when monitored by ^{1}H NMR spectrum. No notable oxidation was detected in CD_3OD after 24 h of leaving. [8] Acetate (**13b**) was stable in these conditions. Since **13a** was sparingly soluble in CH_2Cl_2,

Scheme 3



13a R=H
13b R=Ac

3a X=H
3b X=OMe
3d X=NO_2

14a X=H
14b X=OMe
14c X=NO_2
14d X=OH

12a X=H
12b X=OMe
12d X=OH

15 **9** **16**

crude **13a** was readily purified by brief washing with cold CH_2Cl_2. Deoxygenation of alcohol (**13a**) to **14a** did not succeed with $PdCl_2/NaBH_4$[9] and $HSiEt_3/CF_3COOH$.[10] In order to use Mozzingo reduction, ketone (**3a**) was treated with ethanedithiol and BF_3 etherate. Thioacetalization was slow (TLC), so that the solution was refluxed to complete reaction (TLC analysis). The product was not thioacetal, but reduction product (**14a**) in quantitative yield. There are two isomers possible for reduction product, 11*H*-isomer (**14a**) and 6*H*-isomer. Calculation (MOPAC AM1) revealed that 11*H*-isomer is 6.695 Kcal/mol more stable than 6*H*-isomer. Hydrogen sulfide is known to reduce carbonyl to methylene group, [11] but thiol reduction observed above has no precedence,[12] thus the scope of this novel reduction was further investigated and result is summarized in Table 1.

Thiol reduction of keto group in **3a** to methylene group in **14a** was effected by a variety of thiol. In typical procedure a solution of ketone in 20 times mole of thiol was refluxed in the presence of 5 equivalent of BF_3 etherate for 6 h. After cooling upper layer (thiol) was removed by decantation and lower layer was washed with hexane to remove thiol. Work-up with aqueous alkaline solution, and chromatography of crude product yielded odorless reduction product. This reduction was ineffective in the absence of Lewis acid, and in BuSH/KSBu. 9-Fluorenone and 4-oxo-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole in above condition resisted to reduction, but yielded dithioacetals. These observations conclude that above thiol reduction is

Table 1. Thiol reduction of **3a** to **14a** *a)*

Entry	RSH	Yield (%)
1	*n*-BuSH	98
2	*n*-PrSH	95
3	$PhCH_2SH$	54
4	4-Me C_6H_4SH	60
5	4-ClC_6H_4SH	90*b)*
6	$HS(CH_2)_2SH$	100
7	$HS(CH_2)_3SH$	98
8	Dihydrolipoic acid*c)*	81
9	Lawesson reagent*d)*	100

a) Reaction procedure in text.

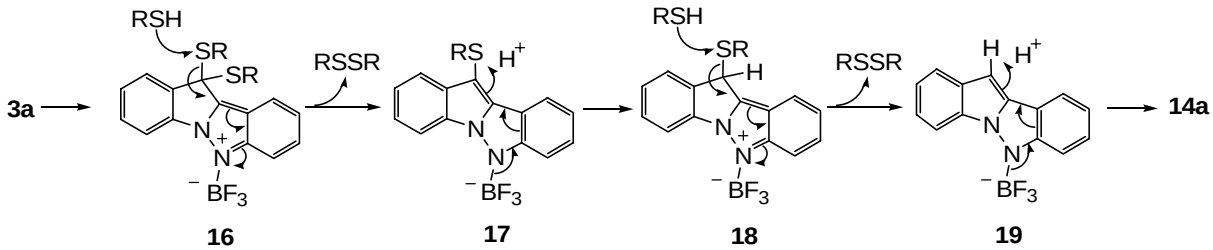
b) 10 Equiv. of BF_3 etherate and 24 h period were employed.

c) $HS(CH_2)_2CH(SH)(CH_2)_2COOH$

d) 2.2 Equiv. of reagent in refluxing toluene for 1 h.

peculiar to the ring system of **3a**, and its novelty can be interpreted by the participation of the reduction mechanism shown in Scheme 4. The first stage of reduction represented by **16** yields **17** as reduction product and disulfide as oxidation product.[13] Following protonation to **17**, reduction of **18** in a similar manner, and second protonation to **19** eventually yield methylene product **14a**. Reduction of thioacetal by thiol is a reported procedure,[12,14a] and plays a key role in reductive activation of 7-(*N*-mercaptoalkyl)mitomycins.[14b] But the observed reduction of keto group to methylene group by thiol has no precedence.

Scheme 4

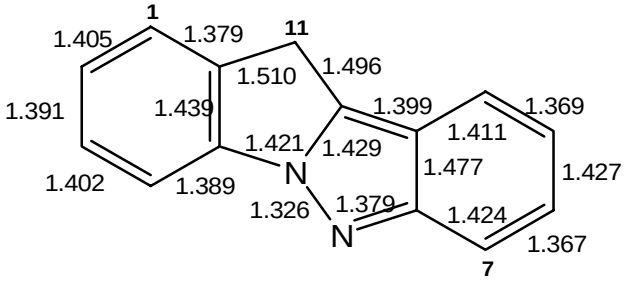


Reduction with dihydrolipoic acid is noteworthy on the standpoint of odorless procedure. In search of

odorless method,[14c] we found that a combination of $LiAlH_4$ and $AlCl_3$[15] was quite effective in reduction of **3a**, and **14a** was obtained in 71% yield. Since a combination of thiol with BF_3 is known to effect in cleaving ether linkage,[16] reduction of **3b** in above reaction condition yielded a mixture of **14b** and demethylated product (**14d**). Demethylation of **14b** to **14d** in 55% yield was also effected with LiI in refluxing collidine.[17] Also nitro ketone (**3c**) was reduced to **14c** with intact nitro group in moderate yield. Although above thiol reduction uses thiol of unpleasant odor and is tedious to obtain odorless product, there is no alternative method to reduce 11-keto group in **3c** to methylene group in **14c** without touching reduction-sensitive nitro group.

Hydrogenation of **3a** as in the case of 4-oxopyrazolo[1,5-*a*]indole derivatives[18] was carried out by 10%Pd-C/H_2 in ethyl acetate, and alcohol (**15**) with saturated D-ring was obtained in 78% yield. Similar reduction in methanol containing acetic acid (30%) yielded **15** (42.3%), **12a** (20.5%), and **9** (10.7%). Reduction in acetic acid under pressured hydrogen did not increase a yield of **12a**. Catalytic hydrogenation of **14a** on 10%Pd on charcoal gave **12a** and PCC oxidation of **15** in the presence of Celite[19] yielded ketone (**9**). Similarly **14b** afforded **12b** in good yield. 2-Phenylindazole was readily hydrogenated to 4,5,6,7-tetrahydro-2-phenylindazole in the similar reaction condition. These chemical behaviors of D-ring in hydrogenation reaction are supported from calculation results (MOPAC AM1). The bond lengths between C-7 and C-8 and between C-9 and C-10 (1.37 Å) are found to be shorter than that of benzene double bond (1.39 Å)(Figure 1). Contrary to ease in hydrogenation, dehydrogenation of **12b** to **14b** resisted to various reaction conditions (10%Pd-C in xylene at refluxing temperature; oxidation with MnO_2).

Figure 1
Bond Length (Angstrom) by MOPAC AM1 Calculation



In summary we have provided various pathways to fulfill the methods in synthesizing a variety of indolo[1,2-*b*]indazole derivatives. Also spatial chemical behaviors due to the skeleton of indolo[1,2-*b*]indazole are presented.

AKNOWLEGEMENT

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EXPERIMENTAL

Unless otherwise noted, following procedures were employed; chromatography by silica gel; usual work-up by consecutive procedures of washing (saturated brine thrice), drying (Na_2SO_4), filtration and evaporation in vacuo; IR spectrum in KBr pellet with cm^{-1}; chemical shift of NMR spectra (400 MHz) by δ (ppm) in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise noted; MS spectra by EI ionization. Assignments of NMR spectra were carried out by using COSY, HOHAHA, PNOESY, CHSHF, and LRCHSHF spectra.

2-Methoxy-11*H*-indolo[1,2-*b*]indazol-11-one (**3b)**

A solution of **1b** (2.31 g, 15 mmol), **2** (3.54 g, 30 mmol) and K_2CO_3 (2.76 g, 20 mmol) in DMSO (35 mL) was heated at 110 ^oC for 8 h under extrusion of moisture. Benzaldehyde (**1b**) (2.31 g, 15 mmol) and potassium carbonate (2.27 g, 16.4 mmol) were supplemented, and heating was resumed for another 8 h to complete reaction (TLC). A mixture was poured into ice-water (100 g), neutralized (1N HCl) and extracted with ether (100 mL x 2) and ethyl acetate (100 mL x 2). The crude product was chromatographed (CH_2Cl_2 - Hex 3 : 1), and eluate was recrystallized from C_2H_5OH to give **3b** (0.87 g, 11.6%) as red crystals, mp 202.0-203.0 ^oC (Acetone). MS *m/z*: 250 (M^+, 100%), 235(46.0), 207(8.0), 179(8.4). IR: 1708, 1698, 1610, 1479, 1436, 1303, 1226, 1024, 815. ^1H NMR δ: 3.88 (3H, s), 7.00 (1H, dd, *J*= 2.7, 8.6 Hz), 7.22 (1H, d, *J*=2.7 Hz), 7.30-7.33 (2H, m), 7.52 (1H, d, *J*=8.6 Hz), 7.77-7.84 (2H, m).

^{13}C NMR δ: 56.1, 110.8, 113.1, 118.7, 119.9, 119.9, 119.9, 127.1, 127.7, 130.5, 131.6, 136.5, 154.2, 160.4. 177.9. *Anal.* Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 72.28; H, 3.93; N, 11.19.

2-Fluoro-11*H*-indolo[1,2-*b*]indazol-11-one (**3c**)

A mixture of **2** (0.71 g, 6.0 mmol), **1c** (0.32 mL), K_2CO_3 (1.00 g, 7.2 mmol) and DMSO (7 mL) was heated at 110 °C (bath temperature) for 7 h. **1c** (0.32 mL, mmol), K_2CO_3 (1.00 g, 7.2 mmol) and DMSO (7 mL) were added and reaction was resumed for another 10 h. Work-up, chromatography (CH_2Cl_2-hexane=7 : 1), and recrystallization gave **3c** (100 mg, 7.0%) as pale yellow needles, mp 202.0-203.0 °C (C_2H_5OH). MS *m/z*: 238(M^+, 100), 210(14.4), 182(5.9), 94(6.8). IR: 1704, 1634, 1475, 1211, 821, 800, 743. ^{1}H NMR δ: 7.23(1H, td, $^3J_{H\text{-}F}$=8.5 Hz, $^3J_{H\text{-}H}$ =8.5 Hz, $^4J_{H\text{-}H}$ =2.6 Hz), 7.32-7.35 (1H, m), 7.35(1H, d, *J*=9.6 Hz), 7.38(1H, dd, *J*=6.8, 2.5 Hz), 7.59 (1H, dd, *J*=8.4, 3.9 Hz), 7.78-7.87(2H, m). ^{13}C NMR δ: 112.7($^2J_{C\text{-}F}$=25.5 Hz), 113.3 ($^3J_{C\text{-}F}$=8.1 Hz), 120.0, 120.0, 120.1, 120.5($^2J_{C\text{-}F}$=24.9 Hz), 127.6, 128.1, 130.8($J_{C\text{-}F}$=2.0 Hz), 131.3($J_{C\text{-}F}$=7.4 Hz), 139.4($^4J_{C\text{-}F}$=2.7 Hz), 154.5, 162.6($^1J_{C\text{-}F}$=250.1 Hz), 176.4($^4J_{C\text{-}F}$= 2.0 Hz,).

2-Nitro-11-oxo-11*H*-indolo[1,2-*b*]indazole (3d)

a) To lithium salt prepared by addition of *n*-BuLi (1.64 M, 14.7 mL, 24.2 mmol) to a solution of **2** (2.59 g, 22.0 mmol) in dry THF (25 mL) at 0°C for 30 min in dry nitrogen, a solution of **4** (4.37 g, 22.0 mmol) in dry THF (20 mL) was introduced, and the resulting mixture was kept at the same temperature for 3 h, then warmed up to rt. Quenching with 5% NH_4Cl (5 mL) and extraction with CH_2Cl_2 (200 mL) gave the crude product. Chromatography (CH_2Cl_2-hexane 19 : 1), and recrystallization (CH_2Cl_2-hexane) yielded **5** (3.20 g, 49.0%), mp 159.5-162.0 °C. IR: 3129, 1743, 1589, 1535, 1520, 1347, 1282, 1132, 771, 749. MS *m/z*: 298(M^+ + 1, 100%), 281(4.2), 266(17.6), 251(3.3), 239(32.7), 220(17.8), 193(9.5), 179(3.8), 164(6.1). HRMS Calcd for M^+: 297.0748; Found: 297.0723. ^{1}H NMR δ (DMSO-d_6): 3.68(3H, s, Me), 7.14(1H, dd, *J*=8.3, 6.6 Hz), 7.35(1H, dd, *J*=8.7, 6.6 Hz), 7.68(1H, d, *J*=8.7 Hz), 7.81(1H, d, *J*=8.3 Hz), 8.17(1H, d, *J*=8. 6Hz), 8.55-8.59(2H, m), 9.00(1H, s). ^{13}C NMR δ (DMSO-d_6): 52.7, 117.4, 121.1, 122.4, 122.6, 124.8,

125.0, 126.1, 126.9, 127.5, 128.5, 142.4, 146.4, 149.5, 165.2. *Anal*. Calcd for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.73; N, 14.13. Found: C, 60.43; H, 3.72; N, 14.05.

b) A LDA solution (2M in hexane, 1.5 mL, 3 mmol) was added to a solution of **5** (597 mg, 2.0 mmol) in dry THF (50 mL) at –70 °C for 3 min. After 2.5 h of reaction time, the solution (–43 °C) was recooled to –70 °C and another amount of LDA (1.0 mL, 2 mmol) was added. Reaction was completed within 1.5 h, and the mixture was quenched (water and aqueous sodium carbonate), and extracted with CH_2Cl_2 twice. Chromatography (CH_2Cl_2) gave **3d**, (274 mg, 51.4%), as yellow needle, mp 246.0-246.5 °C (EtOAc). MS *m/z*: 265(M^+, 100), 235(13.2), 219(34.2), 191(5.1), 164(14.5), 163. IR: 1716, 1635, 1532, 1343, 1075, 766, 742, 730. ^{1}H NMR δ: 7.38-7.41(2H, m), 7.77(1H, d, *J*=8.1 Hz), 7.79-7.90(2H, m), 8.48-8.52(2H, m). ^{13}C NMR δ: 112.4, 120.2, 120.4, 120.4, 120.5, 128.8, 129.1, 130.7, 131.0, 132.0, 147.0, 148.0, 155.6, 175.0(C-11). *Anal.* Calcd for $C_{14}H_7N_3O_3$: C, 63.40; H, 2.66; N, 15.84. Found: C, 63.60; H, 2.57; N, 16.04.

7,8,9,10-Tetrahydro-11-oxo-11*H*-indolo[1,2-*b*]indazole (9)

a) A solution of **6** (1.89 g, 10.0 mmol) and **7a** (2.02 g, 12.0 mmol) prepared by acetylation of **7b**[4] in ethanol-water (1 : 1, 60 mL) was stirred at 50 °C for 30 min. After addition of 5% sulfuric acid (0.5 mL) , the solution was refluxing for 2 h. Extraction with ethyl acetate and washing of the extracts (brine) gave the crude product, which was esterified by the reaction of DCC (3.5 g, 17.0 mmol) and DMAP (0.3 g, 2.5 mmol) in CH_2Cl_2- C_2H_5OH (40 mL + 2 mL). Solid isolated was removed, and the filtrate was evaporated in vacuo. The residue was chromatographed (hexane-ether) to give 2-(2-ethoxycarbonylphenyl)-4,5,6,7-tetrahydro-2*H*-indazole (**8)** as a colorless oil (1.10 g, 40.6 %). MS *m/z*: 270(100), 241(27.4), 225(37.6), 198(63.9), 170(16.7). ^{1}H NMR δ: 1.17 (3H, t, *J*=7.1 Hz), 1.76-1.86 (4H, m), 2.62 (2H, t, *J*=5.7 Hz), 2.73 (2H, t, *J*=6.3 Hz), 4.21 (2H, q, *J*=7.2 Hz), 7.36 (1H, td, *J*=7.3, 1.3 Hz), 7.37(1H s), 7.46(1H, dd, *J*=7.9, 1.4 Hz), 7.52(1H, td, J=7.3, 1.6 Hz), 7.75(1H, dd, J=7.7, 1.6 Hz). ^{13}C NMR δ: 13.9, 20.7, 23.5, 23.5, 23.5, 61.3, 117.6, 124.7, 126.7, 126.9, 127.7, 130.2, 131.6, 139.6, 151.0, 167.4.

b) A solution of **8** (1.32 g, 4.9 mmol) in THF (5 mL) was added at –78 °C to a solution of LDA (2M in hexane, 2.5 mL, 5.0 mmol) in THF (10 mL) under nitrogen atmosphere, and reaction was continued for 1

h. Quenching (5% NH_4Cl), extraction (CH_2Cl_2, 60 mL), and chromatography (hexane-CH_2Cl_2) of the crude product afforded **9** (0.45 g, 40.9 %) as yellow needle, mp 121.0-121.5 °C (MeOH). MS *m/z*: 224(M^+, 100), 196(64.9), 168(9.5), 130(6.8), 102(5.8). IR: 1709, 1625, 1473, 895, 752. ^{1}H NMR δ: 1.82(4H, m), 2.75(4H, m), 7.13(1H, ddd, *J*=7.6, 7.3, 1.0 Hz), 7.31(1H, d, *J*=7.8 Hz), 7.48(1H, ddd, *J*=7.8, 7.6, 1.2 Hz), 7.56 (1H, d, *J*=7.3 Hz). ^{13}C NMR δ: 21.0, 22.4, 23.7, 109.9, 120.3, 124.6, 125.4, 128.3, 134.2, 135.4, 143.9, 156.5, 178.0.

7,8,9,10-Tetrahydro-2-methoxy-11*H*-indolo[1,2-*b*]indazole (12b)

a) 2-(5-Methoxy-2-nitrophenylacetyl)cyclohexanone (5.85 g, 20.1 mmol) prepared from 5-methoxy-2-nitrophenyl acetic acid[6] was transformed to 2-(5-methoxyindol-2-yl)cyclohexanone (**10)** by a similar method reported for 5-demethoxylated derivative,[5] and a solution of **10** in benzene (150 mL) containig *p*-toluensulfonic acid monohydrate (150 mg) and ethylene glycol (1 mL) was refluxed for 4 h. Dilution with ethyl acetate (200 mL) and usual work-up gave the crude product. Chromatography (hexane-EtOAc 10 : 1) afforded acatal of **10** (3.80 g, 66% overall) as needles, mp 129-130 °C (hexane-EtOAc). MS *m/z*: 287(M^+, 100), 244(11.3), 242(13.8), 215(34.0), 200(11.4), 188(21.9), 186(26.6), 175(35.9), 159(19.1). IR: 3374, 1488, 1455, 1208, 1159, 1092, 1035, 924. ^{1}H NMR δ : 1.38-2.40 (8H, m), 3.01 (1H, dd, *J*=5.0, 10.8 Hz), 3.42-3.47(1H, m), 3.57-3.63(1H, m), 3.80-3.86(2H, m), 3.833(3H, s, OMe), 6.26 (1H, s), 6.78 (1H, dd, *J*=2.5, 8.8 Hz), 7.03 (1H, d, *J*=2.4 Hz), 7.20 (1H, d, *J*=8.8 Hz), 8.40 (1H, br s, NH). ^{13}C NMR δ :23.8, 24.8, 29.7, 35.6, 44.8, 55.9. 64.7, 65.0, 100.6, 102.1, 110.2, 111.0, 128.6, 130.99, 140.2, 153.9. *Anal*. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.88. Found: C, 70.89; H, 7.29; N, 4.82.

Acetal (0.70 g, 2.4 mmol) in HOAc-MeCN (14 + 7 mL) was reduced with $NaBH_3CN$ (0.40 g, 6.4 mmol) at rt for 4 h. Dilution with ether (150 mL) and usual work-up gave the product. Chromatography (hexane - EtOAc 10 : 1) yielded **11a** (0.65g, 92%) as a mixture of isomers, mp 89-91 °C (Hex-EtOAc). MS *m/z*: 289(M^+, 75.0), 244(7.8), 215(14.7), 186(11.5), 175(20.7), 159(13.8), 149(100), 147(100), 133(16.0), 117(13.0), 99(26.3). IR: 3350, 1495, 1231, 1141, 1080, 1034, 924, 809. ^{1}H NMR δ (signals for major isomer): 1.19-1.85 (8H, m), 2.76 (1H, dd, *J*=7.2, 15.1 Hz), 3.15 (1H, dd, *J*=9.5, 16.1 Hz), 3.73 (3H, s),

3.92-4.08(4H, m), 4.235(1H, m), 6.46-6.71 (3H, m). ^{13}C NMR δ (signals for major isomers): 23.8, 23.8, 25.1, 35.0, 35.9, 49.6, 56.0, 57.2, 64.3, 64.6, 108.5, 111.2, 111.3, 112.0, 130.2, 145.7, 152.8.

b) A solution of $NaNO_2$ (0.40 g, 5.8 mmol) in water (4 mL) was dropped slowly to the ice-cooled solution of **11a** (0.75g, 2.6 mmol) in dilute HCl (water: 12 mL + 10% HCl: 3 mL). After 20 min of reaction time, the solution was diluted with ethyl acetate (100 mL) and worked up. The crude **11b** (0.74 g, 90%) was used in the following step without purification.

c) Nitroso compound (**11b**) (0.74 g) in dry ether (20 mL) was gradually added to a suspension of $LiAlH_4$ (95%, 0.74 g, 18.5 mmol) in ether (15 mL), and reaction was continued at rt for 12 h. Excess reagent was decomposed with water. Precipitates were removed by filtration, and washed with ether (60 mL). Crude product was dissolved in CH_2Cl_2 (5 mL), and treated with silica gel (2.0 g) overnight. After filtration the filtrate was evaporated, and residue was chromatographed (hexane-EtOAc 7 : 1) to give **11c** (410 mg, 58%), mp 119-121°C (hexane-EtOAc). MS *m/z*: 302(M^+, 100), 287(44.6), 240(15.0), 215(15.8), 201(10.1), 189(17.9), 175(15.0), 159(15.9). IR: 3430, 3345, 1607, 1481, 1446, 1205, 1157, 1083, 929. ^{1}H NMR δ: 1.37-2.10 (8H, m), 3.15-3.19 (2H, m), 3.29-3.34 (1H, m), 3.69-3.75 (2H, m), 3.83 (3H, s), 4.88 (2H, s), 6.22 (1H, s), 6.84 (1H, dd, *J*=2.4, 8.8 Hz), 6.99 (1H, d, *J*=2.4 Hz), 7.41 (1H, d, *J*=8.8 Hz). ^{13}C NMR δ: 23.9, 25.6, 29.6, 36.8, 42.7, 55.9, 64.7, 65.5, 97.9, 101.8, 110.0, 110.4, 111.1, 125.3, 132.4, 140.9, 154.0.

d) A solution of **11c** (250 mg, 0.83 mmol) in 75% acetic acid (8 mL) was stirred at 70-80 °C for 30 min. The solution was diluted with water and extracted with ethyl acetate (100 mL). The crude product was chromatographed (hexane-EtOAc 10 : 1), and **12b** (180 mg, 91%) was obtained as plates, mp 117-118 °C (C_2H_5OH). MS *m/z*: 240(M^+, 100), 225(28.4), 212(17.6), 183(9.5). IR: 1586, 1488, 1301, 1243, 1130, 1107, 818, 809. ^{1}H NMR δ: 1.77-1.89 (4H, m), 2.58 (2H, t, *J*=6.1 Hz), 2.82 (2H, t, *J*=6.1 Hz), 3.70 (2H, s), 3.82 (3H, s), 6.88 (1H, dd, *J*=2.6, 8.6 Hz), 7.10 (1H, t, *J*= 1.0 Hz), 7.44 (1H, d, *J*=8.5Hz). ^{13}C NMR δ: 20.6, 23.4, 23.5, 24.2, 27.67, 55.8, 109.8, 110.7, 112.3, 113.0, 134.7, 134.9, 140.5, 153.4, 156.6. *Anal*. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.84; H, 6.73; N, 11.61.

11-Hydroxy-11*H*-indolo[1,2-*b*]indazole (13a)

Reduction of **3a** (110 mg, 0.5 mmol) with $NaBH_4$ (19 mg, 0.5 mmol) in dry methanol (5 mL) was conducted in nitrogen atmosphere at rt for 10 min. Yellow color faded away, and solution was evaporated in vacuo at 40°C. Product was extracted with ethyl acetate and ice-water, and crystalline product (112 mg) were briefly washed with cold CH_2Cl_2 (2 mL x 2) to give **13a** (97 mg, 87.4%), mp 207-209 °C. IR: 3194, 1518, 1477, 1382, 1057, 747. MS *m/z:* 222(M^+, 100), 221(40), 220(48), 205(42), 194(28). HRMS Calcd for $C_{14}H_{10}N_2O$: 222.0792; Found: 222.0816. ^{1}H NMR (CD_3OD) δ: 6.03(1H, s), 7.18(1H, ddd, *J*=8.5, 6.7, 0.9 Hz), 7.35(1H, ddd, *J*=8.9, 6.7, 1.1 Hz), 7.41(1H, td, *J*=7.5, 1.1 Hz), 7.54(1H, td, *J*=7.7, 1.2 Hz), 7.70(1H, dt, *J*=8.9, 0.9 Hz), 7.72(1H, d, *J*=7.5 Hz), 7.76(1H, d, *J*=7.8 Hz), 7.86(1H, dt, *J*=8.4, 1.1 Hz). ^{13}C NMR (CD_3OD) δ: 68.1, 112.8, 118.9, 119.2, 121.0, 123.9, 127.4, 128.3, 128.4, 131.0, 140.7, 140.8, 141.8, 154.6. Acetate (**13b**) was prepared by the reaction of crude **13a** with complex of Ac_2O-pyridine (0.5 + 0.5 mL) in 73.1% yield. **13b,** mp 177.0-179.0°C (decomp)(hexane). IR: 1742, 1224, 1023, 980, 761, 742. MS *m/z*: 264(M^+, 64), 222(50), 221(54), 205(100). HRMS Calcd for $C_{16}H_{12}N_2O_2$: 264.0899; Found: 264.0934. ^{1}H NMR δ: 6.86(1H, s), 7.16(1H, dd, *J*=8.6, 6.7 Hz), 7.32(1H, ddd, *J*=8.9, 6.8, 1.1 Hz), 7.34(1H, td, *J*=7.6, 1.0 Hz), 7.54(1H, t, *J*=7.8 Hz,), 7.61(1H, d, *J*=7.5 Hz), 7.78(1H, dt, *J*=8.5, 1.1 Hz), 7.79(1H, dt, *J*=8.8, 1.0 Hz), 7.82(1H, d, *J*=7.8 Hz). ^{13}C NMR δ: 20.9, 67.4, 112.4, 118.7, 118.8, 120.5, 123.5, 126.8, 126.9, 127.0, 130.8, 134.5, 135.7, 140.5, 153.6, 171.2.

11*H*-Indolo[1,2-*b*]indazole (14a)

a) Thiol-reduction of 11-keto group to 11-methylene group: *Typical procedure*. A mixture of **3a** (1 mmol), *n*-BuSH (5.4 mL, 20 mmol) and BF_3 etherate (0.63 mL, 5 mmol) was heated at 120°C (bath temperature) for 6 h to complete reaction (TLC analysis). After cooling, upper layer (thiol) was removed, and lower layer was briefly washed with *n*-hexane twice by decantation. Residual material was treated with aqueous 1M NaOH solution and extracted with CH_2Cl_2. Extracts were washed (saturated brine), dried (Na_2SO_4) and evaporated. Column chromatography (CH_2Cl_2) and recrystallization gave **14a**, mp 162.0-164.0°C (isopropyl ether). MS *m/z*: 206(M^+, 100), 178 (15.1), 152 (4.4), 151(4.5), 103(8.3). IR: 3055, 1621, 1478, 1450, 1399, 1369, 1298, 1095, 934, 845, 757, 740. ^{1}H NMR δ: 4.11(2H, s), 7.03(1H,

dd, *J*=8.4, 8.4 Hz), 7.24(2H, m), 7.40(1H, t, *J*=7.8 Hz), 7.48(1H, d, *J*=7.5 Hz), 7.61(1H, d, *J*=8.4 Hz), 7.73(1H, d, *J*=8.9 Hz), 7.82(1H, d, *J*=7.8 Hz). NOE was observed between 10-H_2 and 1-H. ^{13}C NMR δ: 28.6, 112.2, 117.1, 118.5, 119.6, 121.6, 126.0(2xC), 126.4, 128.3, 134.6, 137.2, 140.7, 153.3. *Anal*. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.13; H, 4.78; N, 13.56.

b) Reduction with LAH-$AlCl_3$ complex: A solution of **3a** (200 mg, 0.91 mmoL) in dry ether (20 mL) was introduced to the reagent prepared by adding a solution of $AlCl_3$ (700 mg, 5.25 mmol) in dry ether (10 mL) to a suspension of $LiAH_4$ (300 mg, 7.9 mmol) in dry ether (5 mL). The solution was refluxed for 6 h to complete reduction (TLC analysis). After quenching (C_2H_5OH, 5 mL), the solution was suction-filtered. Inorganics were washed with ether (50 mL). Filtrate and washings were worked up, and chromatography (CH_2Cl_2-Hexane 5 : 1) gave **14a** (133 mg, 71.0%).

2-Nitro-11*H*-indolo[1,2-*b*]indazole (14c)

A mixture of **3d** (376 mg, 1.4 mmol), *n*-BuSH (20 mL, 187 mmol) and BF_3 etherate (0.5 mL, 3.9 mmol) was refluxed for 8 h. Work-up and short column chromatography (CH_2Cl_2 + 5% EtOAc) gave **14c** (153 mg, 43%), mp 240-245 ^{o}C (decomp). MS *m/z*: 251(M^+, 100), 234(14.1), 221(8.7), 205(89.2), 177(10.5), 176(12.1), 151(6.1), 150(5.0). ^{1}H-NMR δ: 4.29(2H, s), 7.16 (1H, ddm, *J*=8.5, 6.7 Hz), 7.37(1H, ddd, *J*=8.9, 6.7, 1.1 Hz), 7.72(1H, dm, *J*=8.5 Hz), 7.80(1H, d, *J*=8.9 Hz), 7.99(1H, d, *J*=9.3 Hz), 8.45 - 8.48(2H, m). ^{13}C NMR δ; 28.9, 112.2, 117.5, 118.8, 119.8, 121.9, 122.8, 125.5, 127.9, 135.7, 139.0, 145.1, 146.1, 154.5. *Anal.* Calcd for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.61; N, 16.73. Found: 66.95; H, 3.63; 16.81.

2-Methoxy- and 2-hydroxy-11*H*-indolo[1,2-*b*]indazol-11-one, (14b) and (14d)

a) A mixture of **3b** (500 mg, 2 mmol) in *n*-butanethiol (12 ml) and BF_3 etherate (2.5 ml, 19.7 mmol) was refluxed for 6 h. Crude product was recrystallized from methanol, and crystalline product was chromatographed (CH_2Cl_2-CH_3COCH_3 10 : 1) to give **14b** (240 mg, 51%), mp 213-214 ^{o}C. (CH_2Cl_2-CH_3COCH_3). MS *m/z*: 236(M^+, 100), 221(20.1), 193(19.3), 165(19.5). HRMS Calcd for $C_{15}H_{12}N_2O$: 236.0950; Found: 236.0925. IR: 1603, 1485, 1435, 1264, 1246, 825, 742. ^{1}H NMR δ: 3.88 (3H, s), 4.13

(2H, s), 7.01 (1H, dd, *J*=2.3, 8.6 Hz), 7.11 (1H, t, *J*=7.6 Hz), 7.16 (1H, d, *J*=2.1 Hz), 7.31 (1H, ddd, *J*=1.1, 6.7, 8.8 Hz), 7.70 (1H, d, *J*=8.4 Hz), 7.80 (1H, d, *J*=8.9 Hz), 7.81 (1H, d, *J*=8.9 Hz). ^{13}CNMR δ: 28.9, 55.9, 112.6, 112.8, 113.1, 117.3, 118.3, 119.3, 121.4, 126.0, 134.5, 136.3, 136.5, 153.0, 158.6. The mother liquor of above recrystallization was evaporated and the residue was crystallized from HOAc to give **14d** (160 mg, 36%), mp 270°C (decomp). MS *m/z*: 222(100, M^+), 194(9.2), 165(17.0). IR: 3046, 1602, 1476, 1270, 1254, 827, 748. HRMS Calcd for $C_{14}H_{10}N_2O$: 222.0793; Found: 222.07861. H ^{1}H NMR δ(DMSO-d_6): 4.24(2H, s), 6.90(1H, dd, *J*=2.3, 8.4 Hz), 7.08(1H, t, *J*=7.6 Hz), 7.12(1H, d, *J*=2.4 Hz), 7.27(1H, ddd, *J*=1.2, 6.7, 8.2 Hz), 7.64(1H, d, *J*=8.4 Hz), 7.68(1H, d, *J*=8.7 Hz), 7.77(1H, d, *J*=8.3 Hz). ^{13}C NMR δ(DMSO-d_6): 28.5, 112.2, 113.8, 114.3, 116.8, 117.6, 119.8, 120.6, 125.4, 132.3, 136.4, 136.9, 151.9, 156.3.

b) A mixture of **14b** (118 mg, 0.47 mmol), and LiI (236 mg, 1.0 mmol) in collidine (5 mL) was refluxed for 10 h. After cooling solution was treated with aqueous 3N HCl (10 mL), and extracted with ethyl acetate to give **14d** (55 mg, 50%).

Catalytic hydrogenation of ketone (3a).

a) 10%Pd-C/H_2/EtOAc. Reduction of **3a** (50 mg) in ethyl acetate (15 mL) with H_2/10%Pd-C (17 mg), and chromatography of the crude product gave 11-hydroxy-11*H*-indolo[2,3-*b*]indazole (**15a**) (39 mg, 76%), colorless rod, mp 209.0-210.0 °C (EtOAc). MS *m/z*: 226(M^+, 100), 209(11.1), 198(12.8), 197(18.1), 181(6.0), 170(8.5), 121(7.3). IR: 3195, 1622, 1485, 1354, 1051, 756. ^{1}H NMR δ (DMSO-d_6): 1.75(4H, m), 2.63(4H, m), 5.63(1H, d, *J*=7.6 Hz, 11-H. Singlet after D_2O addition), 5.96(1H, d, *J*=7.6 Hz, OH), 7.14(1H, td-like m), 7.34(1H, m), 7.35(1H, dd, *J*=6.8, 1.2 Hz), 7.51(1H, d, *J*=7.3 Hz). ^{13}C NMR δ (DMSO-d_6): 19.8, 22.7(2 x C), 23.6, 65.4, 108.8, 112.5, 123.9, 125.9, 129.1, 138.0, 139.2, 143.8, 153.3.

b) 10%Pd-C/H_2/MeOH-HOAc. A solution of **3a** (46 mg) and 10% Pd-C (20 mg) in HOAc-MeOH(7 + 3 mL) was hydrogenated. Chromatography (CH_2Cl_2 + 5%, 8%, 10%, 50% EtOAc) gave **9** (5 mg, 10.7%), **12a** (9 mg, 20.5%), **15** (20 mg, 42.3%).

7,8,9,10-Tetrahydro-11*H*-indolo[1,2-b]indazole (12a)

A solution of **14a** (42.6 mg) in ethyl acetate (20 mL) was reduced with hydrogen over 10% Pd-C (18.9 mg) for 1 d. Crystallization of the crude product gave **12a** (27 mg) as colorless plate, mp 113.0-114.5 ^{o}C (EtOAc). MS *m/z*: 210(M^{+}, 100), 206(18.4), 195(16.8), 183(21.4), 182(24.2), 181(25.5), 169(17.7), 160(9.2), 153(24.4), 142(17.6), 141(20.4). HRMS Calcd for $C_{14}H_{14}N_2$: 210.1157; Found: 210.1188. IR: 3058, 1623, 1603, 1486, 747. ^{1}H NMR δ: 1.83(4H, m), 2.58(2H, t-like m), 2.82(2H, t-like m), 3.71(2H, s), 7.11(1H, td, *J*=7.4, 1.0 Hz), 7.343(1H, t, *J*=7.8 Hz), 7.40(1H, d, *J*=7.8 Hz), 7.54(1H, d, *J*=7.8 Hz). ^{13}C NMR δ: 20.6, 23.4, 23.4, 24.2, 27.4, 109.7, 110.8, 123.4, 126.0, 127.9, 133.1, 140.7, 141.10, 154.2.

Oxidation of 15 to 9

Alcohol (**15**) (45 mg, 0.20 mmol) was oxidized with a mixture of PCC (99 mg, 0.46 mmol) and Celite (122 mg) suspended in CH_2Cl_2 (20 mL) for 3.5 h at rt.[18] Dilution with ether, filtration *via* Florisil pad, washing of Florisil with ether, and evaporation of the filtrate and washings gave yellow residue (45 mg). Chromatography (CH_2Cl_2) and recrystallization of yellow crystals (37 mg, 83%) from methanol yielded **9** (22 mg).

Catalytic hydrogenation of 14b to 12b

A solution of **14b** (30 mg) and 10% Pd-C (10 mg) in ethyl acetate (4 mL) was stirred in hydrogen atmosphere for 12 h. Catalyst was removed and the filtrate was evaporated. Chromatography of the product (CH_2Cl_2) gave **12b** (26 mg).

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