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An Improved Large-Scale Synthesis of Benz[*cd*]indol-2(1*H*)-one and 5-Methylbenz[*cd*]indol-2(1*H*)-one

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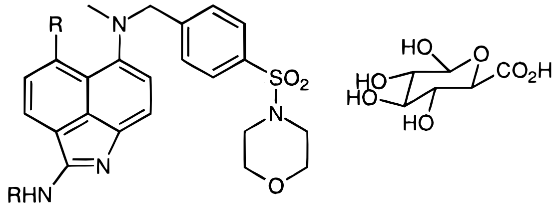
Abstract:

An improved synthesis of benz[*cd*]indol-2(1*H*)-one (3) and a novel synthesis of 5-methylbenz[*cd*]indol-2(1*H*)-one (4) utilizing analogous methodology is reported. Starting from 1,8-naphthoic anhydride and 4-nitro-1,8-naphthoic anhydride, an appropriately substituted *N*-(2,4-dinitrophenoxy)naphthalimide is prepared. Subjecting these intermediates to improved Lossen rearrangement conditions yields 3 and 5-nitrobenz[*cd*]indol-2(1*H*)-one (11). 11 is converted to 5-iodobenz[*cd*]indol-2(1*H*)-one (13) by standard reduction and diazonium chemistry. 13 is converted to 4 by palladium(II)-catalyzed coupling of the aryl iodide with methyl-Grignard.

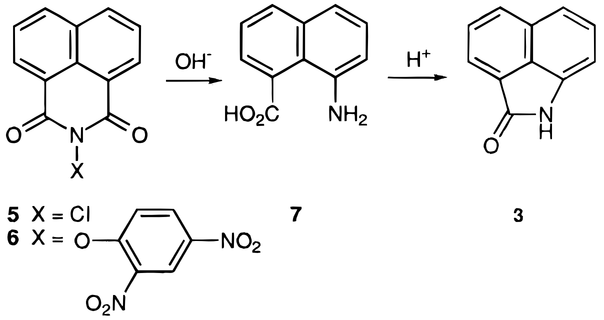
5,6-Disubstituted benz[*cd*]indoles, such as AG331 (**1**) and AG341 (**2**), have been shown to be effective inhibitors of the enzyme thymidylate synthase (TS), and hence potential anticancer therapies.[1] More recently, substituted 6-(methylthio)benz[*cd*]indol-2(1*H*)-ones have been demonstrated to be active hypotensive agents.[2] Syntheses of both classes of compounds utilize either benz[*cd*]indol-2(1*H*)-one (**3**) or 5-methylbenz[*cd*]indol-2(1*H*)-one (**4**) as starting material, neither of which is available on a commercial scale. Successful preclinical evaluation and subsequent clinical testing of AG331 and AG341 required a reliable and scalable synthesis of these compounds.



1 R = H (AG331)
2 R = CH_3 (AG341)

Compound **3** has been prepared by base-induced rearrangement of either *N*-chloro-1,8-naphthalimide (**5**)[3] or *N*-(2,4-dinitrophenoxy)naphthalimide (**6**).[4] Acid-catalyzed cyclization of the intermediate 1-amino-8-carboxynaphthalene (**7**) yields the desired **3**.

Both of these published procedures suffer from processing shortcomings that make scaleup as-is undesirable. Rearrangement of **5** releases nitrogen trichloride, an explosive gas, and requires fickle crystallization procedures to yield a product uncontaminated with side products.[3] The Lossen rearrangement of **6**, as published, requires dilute reaction conditions, difficult filtrations, and chromatographic purification of the desired product.[4] We report a substantially improved procedure for the Lossen rearrangement of **6** that yields **3** in >67% theoretical yield starting from 1,8-naphthoic anhydride. By extension of this procedure to 4-nitro-1,8-naphthoic anhydride (**8**), we have also developed a novel route to **4**.



Compound **6** was prepared starting from readily available 1,8-naphthoic anhydride. Reaction of 1,8-naphthoic anhydride with hydroxylamine hydrochloride in hot water buffered with sodium acetate yielded *N*-hydroxynaphthalimide in nearly quantitative yield.[4] The product was isolated by filtration, and the wet filter cake was carried into the next reaction with no further manipulation. The wet *N*-hydroxynaphthalimide was mixed with a slight excess of 2,4-dinitro-1-chlorobenzene and sodium carbonate, heated to 80−90 °C, and held there for 90 min. Caution had to be exercised to control foaming during the heating period due to the heterogeneous nature of the reaction mixture and the inherent formation of carbon dioxide as a reaction byproduct. Too rapid heating would result in substantial growth in the volume of the reactor contents. Addition of Dow Corning Antifoam 2210 to the reaction mixture prior to heating alleviated this problem. The product was isolated by filtration of the cooled reaction mixture, washed with water, reslurried in hot methanol to remove excess 1-chloro-2,4-dinitrobenzene, and dried in vacuum to yield **6** in 89% theoretical yield.

Conversion of **6** to **3** was accomplished in a two-step process. First, **6** was subjected to a base-induced rearrangement in an ethanol/water mixture, yielding the intermediate aminocarboxylic acid **7**, which was isolated after acidification of the reaction mixture. The concentration of the reaction mixture and the ethanol/water ratio were critical to the success of the rearrangement. Too dilute a solution (20:1 vol/wt) or too high an ethanol/water ratio (70/30) resulted

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[1] Varney, M. D.; Marzoni, G. P.; Palmer, C. L.; Deal, J. D.; Weber, S.; Welsh, K. M.; Bacquet, R. J.; Bartlett, C. A.; Morse, C. A.; Booth, C. L. J.; Herrmann, S. M.; Howland, E. F.; Ward, R. W.; White, J. *J. Med. Chem.* **1992**, *35*, 663.

[2] Newman, H.; Sassiver, M. L.; Tomcufrik, A. S. US Patent 5,229,411, 1993; *Chem. Abstr.* **1993**, *119*, 270998t.

[3] Arndt, O.; Papenfuhs, T. US Patent 4,824,962, 1989; *Chem. Abstr.* **1987**, *107*, 58850w.

[4] Plakidin, V. L.; Vostrova, V. N.; Gnatyuk, P. P.; Zadorozhnyi, N. M. *Zh. Org. Khim.* **1977**, *13*, 2194.

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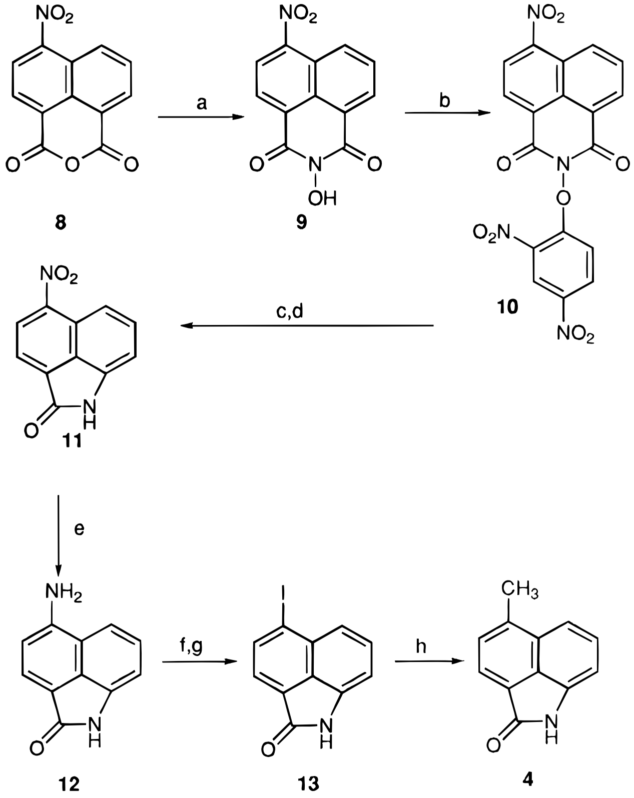
Scheme 1[a]



[a] (a)$H_2NOH \cdot HCl$, H_2O, >99%; (b) 1-chloro-2,4-dinitrobenzene, H_2O, Na_2CO_3, 93%; (c) EtOH, H_2O, NaOH; (d) H_2SO_4, 81%; (e) H_2/Pd/C, THF, 67%; (f) $NaNO_2$, HCl; (g) KI, 85%; (h) CH_3MgBr, $Pd(PhP_3)_2Cl_2$, THF, 58%.

in successful reaction, but a low yield (42−45%). Too low an ethanol/water ratio (30/70) gave a solid mass prior to acidification that could not be stirred. Optimal solvent conditions were found to be a 14/1 vol/wt concentration of a 50/50 ethanol/water mixture. This yielded a thick, but stirrable, reaction mixture that gave a high yield of **7** on acidification and isolation. Suspension of **7** in hot water acidified to a pH of 2−3 with concentrated sulfuric acid yielded on filtration **3** contaminated with 2,4-dinitrophenol. This contaminant was easily removed by reslurrying the crude product cake in hot water. On drying, **3** was obtained in 71−76% yield from **6**. This procedure as described has subsequently been run at a 40-kg scale to yield **3** in 79% theoretical yield from 1,8-naphthoic anhydride (94% theoretical yield of **6** from 1,8-naphthoic anhydride, 84% theoretical yield of **3** from **6**).

Our previous method for preparing **4** used quite harsh conditions, and the procedure was not amenable to scaleup. It required heating 5-methylnaphthoyl isocyanate with BCl_3 at 115 °C in a sealed tube.[1] Subsequently, we have discovered that compound **4** can be prepared from 5-nitrobenz[*cd*]indol-2(1*H*)-one (**11**) (Scheme 1). **11** was synthesized from 4-nitronaphthoic anhydride in an analogous manner to **3** with minor variations to the published procedure.[1] Reduction of **11** to 5-aminobenz[*cd*]indol-2(1*H*)-one (**12**) was accomplished under an hydrogen atmosphere using Pd/C as reduction catalyst. Diazotization of **12** with sodium nitrite in sulfuric acid followed by the addition of potassium iodide yielded 5-iodobenz[*cd*]indol-2(1*H*)-one (**13**) in high yield.

Conversion of **13** into **4** was first accomplished using tetramethyltin in DMF in the presence of 10 mol % bis(triphenylphosphine)palladium(II) chloride.[5] The need for an extractive workup and a chromatographic removal of tin byproducts and the only moderate yield (51%) of **4** made it clear that a more easily conducted procedure was needed. Since the coupling of aryl halides with Grignard reagents catalyzed by palladium(II) species had been reported,[6] the use of methyl-Grignard in place of tetramethyltin seemed a rational alternative. Subsequent experiments demonstrated this to be the case. Reaction of **13** with excess methyl-Grignard in THF catalyzed by 1 mol % bis(triphenylphosphine)palladium(II) chloride gave **4** in moderate yield. Workup of the reaction and isolation of the product were substantially easier than with the Stille reaction. After quenching of the excess methyl-Grignard with aqueous ammonium chloride, the reaction mixture was filtered, concentrated, and quenched into water. The precipitated product was collected and dried. The dried product was recrystallized from chlorobenzene, yielding pure **4** in 58% theoretical yield. Overall, **4** was prepared on a 22-L scale in seven chemical steps from readily available 4-nitronaphthoic anhydride in 26% theoretical yield.

Experimental Section

All chemicals were used as purchased. Reactions were run under a nitrogen atmosphere, except for aqueous-based reactions. Reagents used were ACS grade when available. Solvents were used as received, except as otherwise specified. ^{1}H-NMR spectra were collected using a GE QE300 300 MHz spectrometer. Chemical shifts are reported in parts per million (δ) with setting of the references such that in $CDCl_3$ the $CHCl_3$ peak is at 7.26 ppm and in DMSO-d_6 the DMSO peak is at 2.49 ppm. Standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; brs, broad singlet; brd, broad doublet; br, broad signal; m, multiplet. Mass spectra were determined at the University of California Riverside Mass Spectrometry Center. Elemental microanalyses were performed by Atlantic Microlab Inc. (Norcross, GA) and gave results for the elements stated within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was performed on precoated sheets of 60 F_{254} (Merck Art. 5719). Melting points were determined on a Mel-Temp apparatus and are uncorrected. Antifoam 2210 was obtained from Dow Corning Corp. (Midland, MI). An authentic standard of benz[*cd*]indol-2(1*H*)-one was obtained from Aldrich Chemical Co. (Milwaukee, WI). Other authentic standards used were synthesized in these laboratories and have been reported previously.[1]

***N*-(2,4-Dinitrophenoxy)naphthalimide (6).** To a clean, dry, three-necked, 22-L flask were added 1,8-naphthoic anhydride (1001 g, 5.05 mol), hydroxylamine hydrochloride (422 g, 5.986 mol, 1.18 equiv), sodium acetate (497 g, 5.777 mol, 1.14 equiv), and 10 L of deionized water. The mixture was heated with agitation to 70−80 °C and maintained at that temperature for 4 h. Progress of the reaction was monitored by TLC (9/1 $CHCl_3$/MeOH). The flask contents were cooled to below 30 °C, and the intermediate product,

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(5) Milstein, D.; Stille, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
(6) Seriya, A.; Ishikawa, N. J. *Organomet. Chem.* **1976**, *118*, 349.

N-hydroxynaphthalimide, was collected by filtration and washed with 2 L of deionized water. The wet filter cake was transferred back to the 22-L flask, and sodium carbonate, anhydrous (309 g, 2.915 mol, 1.15 equiv), 1-chloro-2,4-dinitrobenzene (1094 g, 5.428 mol, 1.07 equiv), and 11 L of deionized water were added. To this agitated mix was added 110 g of Antifoam 2210 (10% active). The resulting slurry was heated to 85−95 °C slowly and carefully to avoid overheating. The reaction mixture was maintained at 85−95 °C for 90 min and then allowed to cool to below 30 °C. The product was collected by filtration, washed with 2 L of deionized water and returned to the 22-L flask. The wet cake was mixed with 9.52 L of methanol and heated to reflux. The mixture was cooled, filtered, washed with 1500 mL of methanol, and dried in vacuum at 60−70 °C to yield 1705.7 g (89.1% theoretical yield) of **6**. Mp: 246−248 °C. ^{1}H-NMR(DMSO-d_6) δ (ppm): 7.95 (t, 2H, $J = 6.7$ Hz); 8.05 (d, 1H, $J = 10$ Hz); 8.39 (dd, 1H, $J = 3.3$ Hz, 10 Hz); 8.57 (t, 4H, $J = 6.7$ Hz); 8.94 (d, 1H, $J = 3.3$ Hz). Anal. Calcd for C, H, N: C, 57.00; H, 2.39; N, 11.08. Found: C, 56.84; H, 2.43; N, 11.08.

Benz[*cd*]indol-2(1*H*)-one (3). To a clean, dry, 50-L Morton flask with a bottom stopcock outlet were added 12.675 L of absolute ethanol, 12.675 L of deionized water, and sodium hydroxide (753 g, 18.825 mol, 4.0 equiv). The mixture was stirred until all solids had dissolved, and then **6** (1788 g, 4.727 mol) was added in portions. The progress of the reaction was monitored by TLC (EtOAc). When disappearance of the starting material was complete, the pH of the solution was adjusted to 1−2 with concentrated sulfuric acid. The resultant slurry was filtered, the filter cake rinsed with 50% aqueous ethanol, and the wet cake transferred to a clean, dry, three-necked 22-L flask. The solid was slurried in 10 L of deionized water, and sufficient sulfuric acid was added to lower the pH of the slurry to 2−3. The resultant mixture was heated to 85−90 °C and held at that temperature for 90 min. The mixture was allowed to cool to below 80 °C, and sufficient 5 N NaOH solution was added as a steady stream to raise the pH to 7−8. The reaction mixture was filtered hot (>70 °C) and the product cake rinsed with 4 L of deionized water preheated to 60−65 °C. [If TLC (EtOAc) of the product cake showed remaining dinitrophenol, a hot water reslurry in 10 L of deionized water at 65−70 °C would remove it.] The product cake was dried in vacuum at 50−70 °C to yield 610.7 g of **3** (76.6% theoretical yield). Mp: 181.1−182.5 °C (lit.[7] mp 173−178 °C). Product cospots by TLC (9/1 $CHCl_3$/MeOH) with an authentic standard. ^{1}H NMR (DMSO-d_6) δ (ppm): 6.99 (d, 1H, $J = 6.7$ Hz); 7.49 (t, 1H, $J = 6.7$ Hz); 7.60 (d, 1H, $J = 6.7$ Hz); 7.80 (t, 1H, $J = 10$ Hz); 8.01 (d, 1H, $J = 10$ Hz); 10.78 (brs, 1H).

5-Nitrobenz[*cd*]indol-2(1*H*)-one (11). To a clean, dry, three-necked, 22-L flask were added 4650 mL of deionized water and 10 750 mL of absolute ethanol. To this solution was added sodium hydroxide (236 g, 5.90 mol, 4.04 equiv). The resultant solution was cooled to 10 °C, and *N*-(2,4-dinitrophenoxy)-4-nitronaphthalimide (**10**)[1] (620 g, 1.46 mol, 1.0 equiv) was added. The mixture was stirred for 44 h at ambient temperature until complete by TLC (95/5 $CHCl_3$/MeOH). The pH was adjusted to 3 with 175 mL of concentrated sulfuric acid, and the mixture was cooled to <10 °C and filtered. The wet filter cake was reslurried in 3 L of deionized water and the pH adjusted to 7−8 by the addition of saturated aqueous sodium bicarbonate solution. The mixture was filtered, washed with water and 95% ethanol, and dried under vacuum to yield 254 g (81% theoretical yield) of 5-nitrobenz[*cd*]indol-2(1*H*)-one (**11**). ^{1}H-NMR analysis of the product showed that the product was contaminated with approximately 10% of the regioisomer 6-nitrobenz[*cd*]indol-2(1*H*)-one. This material was carried directly into the subsequent reduction without further purification. ^{1}H-NMR (major isomer) (DMSO-d_6) δ (ppm): 7.1 (d, 1H, $J = 7$ Hz); 7.75 (t, 1H, $J = 4$ Hz); 8.05 (d, 1H, $J = 8$ Hz); 8.17 (d, 1H, $J = 7$ Hz); 8.62 (d, 1H, $J = 7$ Hz); 11.18 (brs, 1H).

5-Aminobenz[*cd*]indol-2(1*H*)-one (12). To a 7.5-L pressure reactor were added 5-nitrobenz[*cd*]indol-2(1*H*)-one (362.8 g, 1.694 mol), 18.0 g of 10% Pd/C, and 5000 mL of THF. The reaction mixture was pressured to 50 psi with hydrogen, and the hydrogenation was conducted at a pressure of 20−50 psi in a temperature range of 22−36 °C for 22 h. TLC (EtOAc) showed complete consumption of starting material. After venting, the catalyst was removed by filtration. The filtrate was evaporated to a pasty solid, 1500 mL of ethyl acetate was added, and the mixture was heated to reflux. After cooling, the product was collected by filtration and dried in vacuum to yield 209 g of **12** that was >95% pure by ^{1}H-NMR (67% theoretical yield) Mp: 266−268 °C (lit.[1] mp 266−269 °C). Product cospots by TLC (EtOAc) with an authentic standard.

5-Iodobenz[*cd*]indol-2(1*H*)-one (13). To a 22-L three-necked flask were added **12** (206 g, 1.118 mol, 1.0 equiv) and 3000 mL of deionized water. To this mixture was added concentrated sulfuric acid (137 mL, 2.46 mol, 4.4 equiv). The reaction mixture was cooled to below 10 °C, and a solution of sodium nitrite (78.7 g, 1.141 mol, 1.02 equiv) in 250 mL of deionized water was added at such a rate as to maintain the temperature below 10 °C. After complete addition, the mixture was stirred for 30 min at 10 °C, and then a solution of potassium iodide (193.1 g, 1.163 mol, 1.04 equiv) was added at such a rate as to control foaming. The reaction mixture was stirred overnight at ambient temperature. The product was collected by filtration and reslurried in 3 L of deionized water. The slurry was treated with an aqueous solution of sodium thiosulfate until no more iodine could be detected by potassium iodide/starch paper. The product was once again isolated by filtration, washed with deionized water and methanol, and dried under vacuum to yield 281 g of **13** (85% theoretical yield). An analytically pure sample was prepared by flash chromatography on silica (Merck, silica gel 60, 230−400 mesh) using a CH_2Cl_2/THF gradient. Pure fractions were evaporated, slurried in hot methanol, cooled, and dried in vacuum. Mp: 266−268 °C. ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.02 (d, 1H, $J = 7$ Hz); 7.38 (d, 1H, $J = 10$ Hz); 7.60 (m, 1H); 7.75 (d, 1H, $J = 7$ Hz); 8.30 (d, 1H, $J = 7$ Hz); 10.93 (brs, 1H). Anal. Calcd for C, H, N, I: C, 44.77; H, 2.05; N, 4.75; I, 43.01. Found: C, 44.82; H, 2.05; N, 4.77; I, 42.92.

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(7) *Aldrich Catalog Handbook of Fine Chemicals*; Aldrich Chemical Co.: Milwaukee, WI, 1994−1995; pg 137.

5-Methylbenz[*cd*]indol-2(1*H*)-one (4). To an oven-dried, 12-L, three-necked flask were added 583 g of **13** (1.976 mol, 1.0 equiv), 14.0 g of bis(triphenylphosphine)-palladium(II) chloride (0.02 mol, 0.01 equiv), and 5600 mL of THF dried over 4-Å molecular sieves. This mixture was maintained under a nitrogen atmosphere while 3200 mL of 1.4 M CH_3MgBr in THF/toluene (1/3) was added in a steady stream. Addition required 90 min. The temperature of the reaction rose from 26 °C to near reflux. After an additional 30 min, TLC (EtOAc/petroleum ether) of an aliquot quenched into a THF/saturated aqueous ammonium chloride solution showed complete reaction. The mixture was cooled to below 30 °C, and the reaction was quenched with saturated aqueous ammonium chloride. The mixture was filtered, the filtrate evaporated, and the residue suspended in 2000 mL of refluxing methanol. This mixture was quenched into 12 L of deionized water. The product was collected by filtration and dried in vacuum at 60−70 °C to yield 364.5 g of crude product. The crude product was recrystallized from chlorobenzene to yield 209 g of pure **4** (57.7% theoretical yield). Mp: 218−219.5 °C (lit.[1] mp 215−217 °C). Product cospots by TLC (EtOAc/petroleum ether) with an authentic standard. An analytical sample was recrystallized from acetic acid. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.77 (s, 3H); 6.97 (d, 1H, $J = 3$ Hz); 7.50 (t, 1H, $J = 3$ Hz); 7.60 (dd, 2H, $J = 3$ Hz); 7.87 (d, 1H, $J = 3$ Hz); 10.65 (brs, 1H). Anal. Calcd for C, H, N (as a 0.3 hydrate): C, 76.82; H, 4.62; N, 7.47. Found: C, 76.81; H, 4.83; N, 7.49.

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