Preparation and cycloaddition chemistry of 1-amino substituted isobenzofurans

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Dedicated to Professor Branko Stanovnik on the occasion of his 65th anniversary

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Abstract

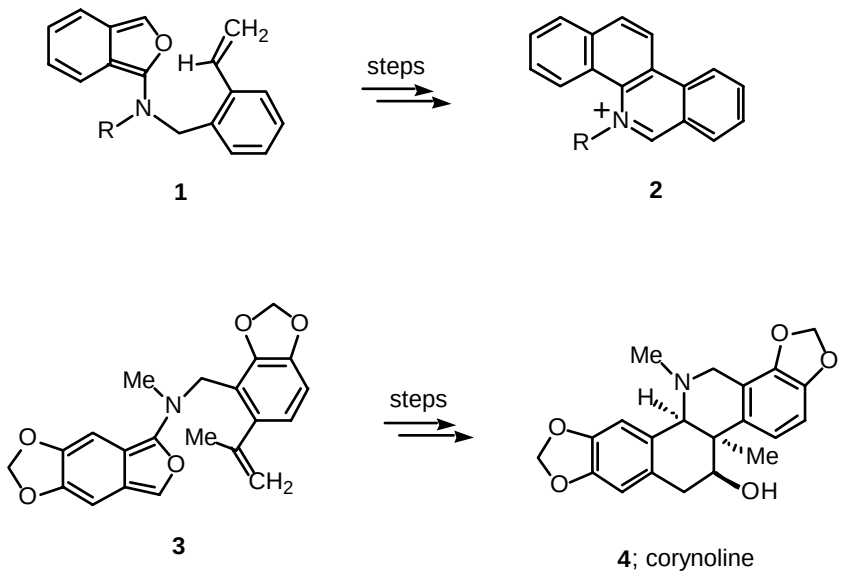
A new strategy for the synthesis of the core skeleton of the benzophenanthridine alkaloid corynoline has been developed which is based on an intramolecular [4+2]-cycloaddition of an amino substituted isobenzofuran derivative.

Keywords: 1-Amino substituted isobenzofuran, intramolecular, Diels-Alder, cycloaddition

Introduction

Isobenzofurans represent versatile intermediates for organic synthesis and have attracted a great deal of attention for the high reactivity they exhibit.[1,2] The isobenzofuran nucleus contains 10π-electrons and is traditionally grouped with other Hückel aromatic species such as naphthalene and isoindole. However, this molecule exhibits greater reactivity than these related compounds. Highly reactive at the 1- and 3-positions, the isobenzofuran ring readily participates in various transformations that allow for the regeneration of the aromaticity of the benzene ring. The most important of these reactions is the Diels-Alder reaction.[3,4] Most isobenzofurans are transient species; only those with exocyclic conjugation are stable enough to be isolated and characterized.[5] Since these heteroaromatic ring systems are highly reactive as Diels-Alder dienes, they are commonly generated in the presence of a dienophilic trap. While examples of 1-alkyl and 1-aryl substituted isobenzofurans are common[6,7] there are only a few citations in the literature that involve amino-substituted isobenzofurans.[8-10]

Our interest in preparing various benzo[*c*]phenanthridinium salts (**2**) as antitumor agents[11] as well as the benzophenanthridine alkaloid corynoline (**4**)[12] led us to explore their syntheses *via* the intramolecular Diels-Alder reaction of an amino substituted isobenzofuran[13] as illustrated in Scheme 1. The [4+2]-cycloaddition reaction should lead to a Diels-Alder cycloadduct that would eventually be converted to the desired systems (*i.e.* **2** and **4**).

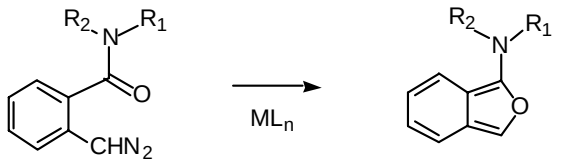


Scheme 1

In this paper, we describe the synthesis of several 1-amino substituted isobenzofurans by the deprotonation of cyclic imidate salts and a study of their subsequent [4+2]-cycloaddition behavior.

Results and Discussion

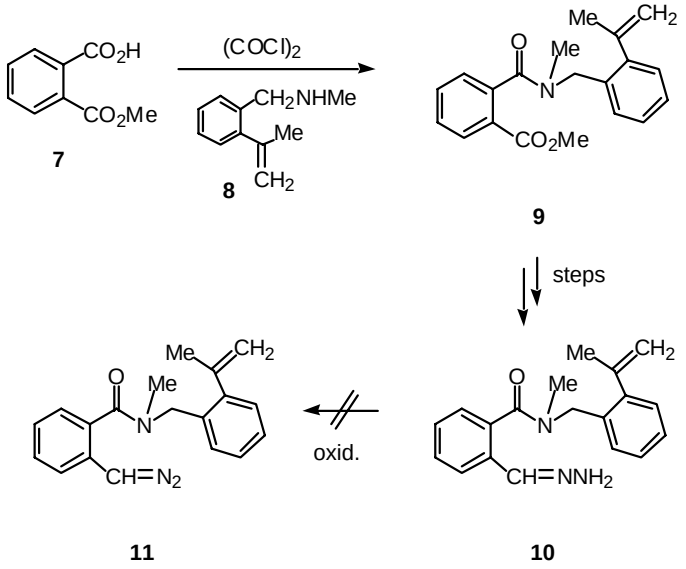
AM1 calculations indicate that the placement of an electron donating heteroatom at the 1-position of isobenzofuran raises the HOMO level and decreases the HOMO-LUMO gap in a "normal electron demand" Diels-Alder reaction. These predictions suggest that 1-(dialkylamino) substituted isobenzofuran should be more reactive than the parent system and show higher regio and stereoselectivity.[14] Before starting our planned synthesis of corynoline (**4**), we decided to first investigate the inter- and intramolecular Diels-Alder behavior of several simpler amino-isobenzofurans in order to probe the viability of our approach. Of the three reported methods for generating 1-amino isobenzofurans,[8] we first chose to explore the metal-induced decomposition of a 2-diazomethyl benzamide derivative such as **11**. This approach toward amino-substituted isobenzofurans is an extension of some earlier work carried out by Ibata and Hamaguchi[15] as well as Contreras and MacLean.[16] As outlined in Scheme 2, these amino substituted isobenzofurans *(i.e.* **6**) were generated by a metal catalyzed cyclization of the *o*-diazomethyl substituted benzamide **5**.



5 **6**

Scheme 2

Preparation of the desired diazomethyl benzamide **11** required the initial synthesis of 2-hydrazonomethyl-*N*-(2-isopropenylbenzyl)-*N*-methylbenzamide (**10**). This hydrazone could be prepared in good overall yield from mono-methyl phthalate (**7**) by treating the corresponding acid chloride with 2-(isopropenylbenzyl)methylamine (**8**). Conversion of the ester functionality to the aldehyde followed by treatment with hydrazine hydrate gave hydrazone **10** in 70% overall yield (Scheme 3). Unfortunately, oxidation of hydrazone **10** led to extensive decomposition producing a myriad of products and we ultimately had to abandon this approach. Our attempts at oxidation involved changing the oxidant (NiO_2, $Pb(OAc)_4$, MnO_4, Ag_2O, and HgO), the solvent, the base and the dehydrating agent. Sonication also failed to produce a sample of the desired diazo compound **11**.

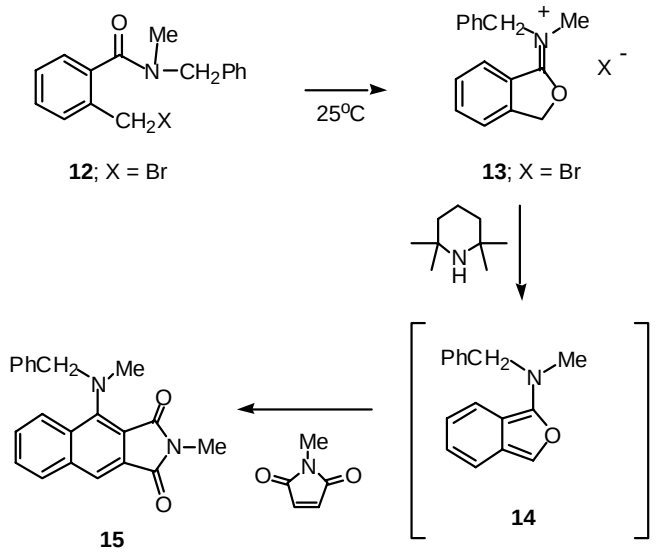


7 **8** **9** **11** **10**

Scheme 3

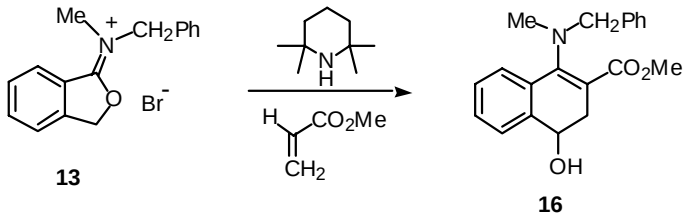
At this point in time, we decided to prepare a representative amino isobenzofuran using an alternative method which involves a base-induced 1,4-elimination of a cyclic precursor such as an iminium salt.[17] We were able to generate iminium salt **13** by allowing *N*-benzyl-2-bromomethyl-*N*-methylbenzamide (**12**) to stand for 10 min at ambient temperature (Scheme 4). The

solid that precipitated was insoluble in ether and the structure was assigned on the basis of ^{1}H and ^{13}C NMR and IR spectroscopy. When **13** was treated with 2,2,6,6-tetramethylpiperidine in the presence of *N*-methylmaleimide, naphthalene **15** was obtained in 90% yield as a crystalline solid. We tried several additional bases and found that diazobicycloundecane (DBU) nicely promoted the formation of product **15** in excellent yield.



Scheme 4

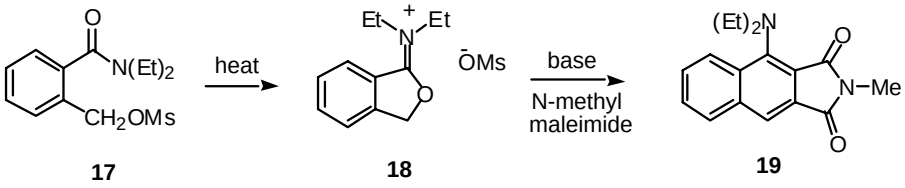
Treatment of salt **13** with methyl acrylate and base also gave rise to a cycloadduct (*i.e.* **16**) in 68% yield (Scheme 5). We were not able to detect the presumed isobenzofuran intermediate **14** by carrying out the reaction in the absence of a trapping agent. The only material that was obtained corresponded to a dark oil which resisted all of our efforts at purification.



Scheme 5

We were curious to know whether the nature of the leaving group at the benzylic carbon would influence the cyclization reaction. With this in mind, we prepared mesylate **17**. Instead of spontaneously cyclizing to form the salt as was encountered with bromide **12**, mesylate **17** had to be heated at reflux in THF for 1 h in order for the cyclization to occur. However, the yield of the

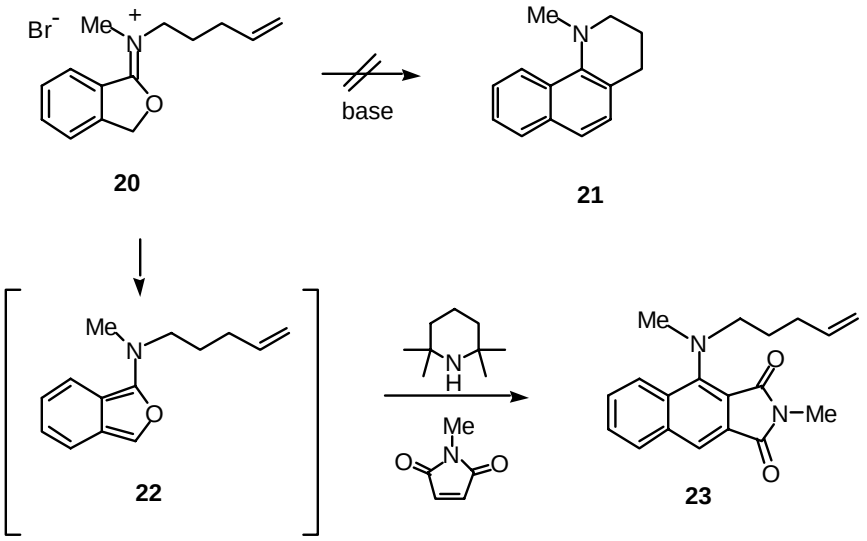
resulting mesylate salt **18** was high (78%) and the base induced cycloaddition proceeded in excellent yield to give **19** (Scheme 6).



17 **18** **19**

Scheme 6

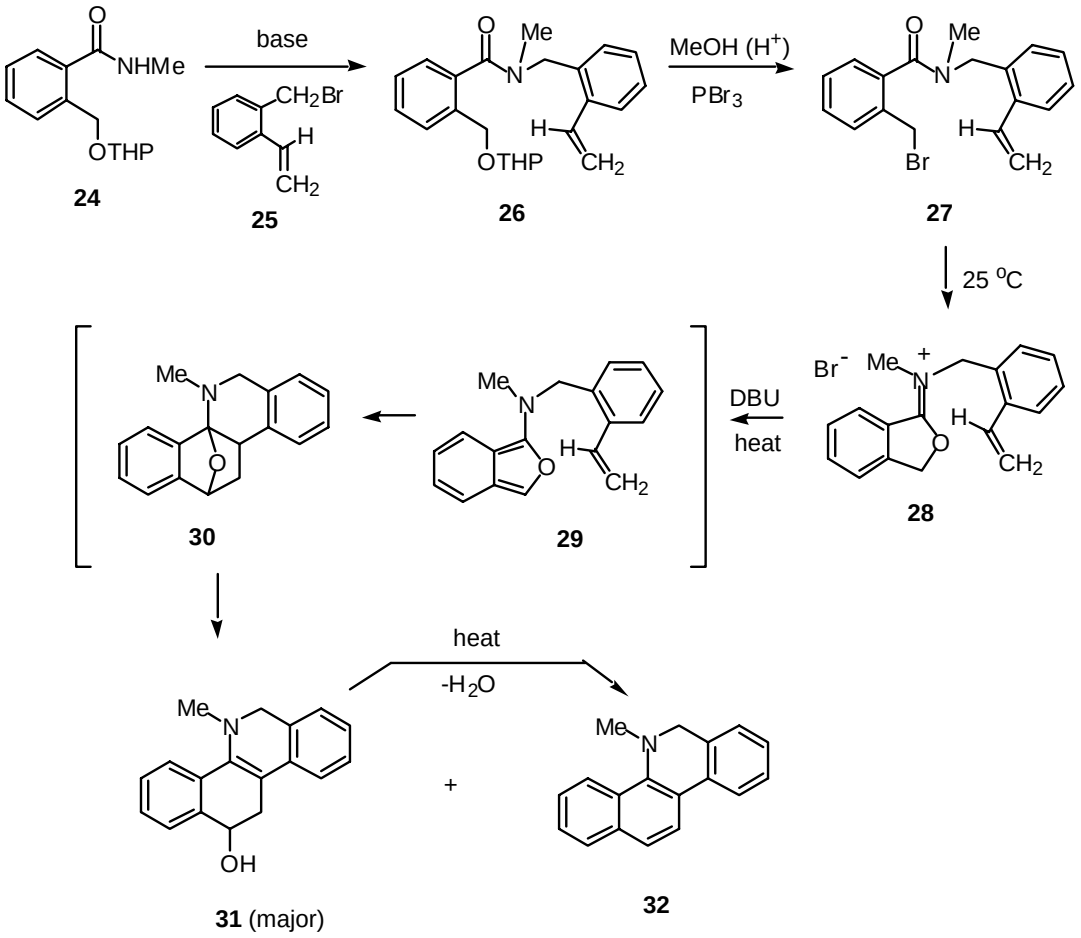
We also examined the base promoted reaction of the related 4-pentenyl substituted iminium salt **20** using similar conditions. Under no circumstances, however, were we able to detect any of the expected tetrahydrobenzo[*b*]quinoline **21** which would have been produced from an intramolecular Diels-Alder reaction of a transient isobenzofuran followed by elimination of water. Treatment of **20** with tetramethylpiperidine in the presence of *N*-methylmaleimide did give rise to naphthalene **23** in 89% yield (Scheme 7). Evidently, the π-bond present on the tethered alkene is not sufficiently activated to allow the intramolecular [4+2]-cycloaddition to occur. Use of a dienophile with a much lower lying LUMO is seemingly necessary in order for the [4+2]-cycloaddition of amino-isobenzofuran **22** to occur.



Scheme 7

At this stage of our investigations, we decided to turn our attention toward a study of the intramolecular [4+2]-cycloaddition of an amino substituted isobenzofuran that contained a more activated π-bond. Attachment of an aryl group on an olefinic π-bond is known to lower its

LUMO energy level thereby facilitating [4+2]-cycloaddition chemistry. With an eventual synthesis of corynoline (**4**) in mind, we set out to prepare 2-bromomethyl-*N*-methyl-*N*-(2-vinylbenzyl)benzamide (**27**). Our intention was to convert **27** into the corresponding iminium salt **28** which should give rise to the desired amino substituted isobenzofuran **29** upon treatment with base. A subsequent Diels-Alder reaction across the styryl activated π-bond was expected to lead to the skeletal framework of corynoline (**4**). A sample of bromide **27** was easily prepared according to the sequence of reactions outlined in Scheme 8. Once formed, bromide **27** slowly underwent cyclization upon standing to furnish the desired salt **28** in good yield.



Scheme 8

In this case, tetramethylpiperidine was not particularly useful for the generation of the desired amino isobenzofuran **29**. Consequently, the less nucleophilic DBU was employed as the base. When the bromide salt **28** was heated at reflux with DBU, alcohol **31** was formed in 54% yield together with 5-methyl-5,6-dihydro-benzo[*c*]phenanthridine (**32**) in 15% yield. We suspect that both products are derived from cycloadduct **30** which undergoes spontaneous ring opening to give **31** and this is followed by a subsequent dehydration to give **32**.

In summary, a new strategy for the synthesis of the core skeleton of the benzophenanthridine alkaloid corynoline (**4**) has been developed which is based on an intramolecular [4+2]-cycloaddition of an amino substituted isobenzofuran derivative. This approach is particularly attractive as the starting 2-bromomethylbenzamide can be prepared efficiently on a large-scale, and the cyclization/cycloaddition sequence proceeds in good yield. We are currently investigating the application of the methodology toward corynoline (**4**) and related alkaloids.

Experimental Section

General Procedures. Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data.

(2-Isopropenylbenzyl)-methylamine (8). To a solution containing 4.1 g (28.1 mmol) of 2-isopropenyl benzaldehyde[18] in 30 mL of MeOH was added 3.1 mL (40 mmol) of methylamine at rt. The yellow solution was stirred for 30 min and 0.5 g (14 mmol) of sodium borohydride was added in portions. After the reaction subsided, the mixture was stirred for an additional 90 min, H_2O was added and the mixture was extracted with CH_2Cl_2. The solvent was removed under reduced pressure affording 4.1 g (91%) of the titled compound as a yellow oil; IR (neat) 3324, 3068, 2968, 2840, 2783, 1637, and 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (brs, 1H), 2.08-2.09 (m, 3H), 2.46 (s, 3H), 3.77 (s, 2H), 4.89-4.91 (m, 1H), 5.22-5.23 (m, 1H), 7.14-7.16 (m, 1H), 7.20-7.28 (m, 2H), and 7.39-7.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 36.3, 53.4, 115.0, 126.7, 127.0, 128.1, 128.9, 136.7, 143.6, and 145.3; HRMS Calcd. for $C_{11}H_{15}N$: 161.1204. Found: 161.1211.

***N*-(2-Isopropenylbenzyl)-*N*-methylphthalamic acid methyl ester (9).** To a solution containing 4.6 g (26 mmol) of mono-methyl phthalate (**7**) in 45 mL of CH_2Cl_2 was added 2 drops of DMF followed by 4.5 mL (52 mmol) of oxalyl chloride at rt. The reaction was stirred for 2 h and was concentrated under reduced pressure. To the residue was added 45 mL of CH_2Cl_2, 6.3 g (51 mmol) of DMAP, and 4.1 g (26 mmol) of amine **8**, and the mixture was stirred at rt for 18 h. A saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. Silica gel chromatography of the crude reaction mixture afforded 6.5 g (79%) of **9** as a white solid which consisted of a mixture of rotamers: mp 95-97 °C; IR (CH_2Cl_2) 2947, 1723, 1637, and 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) major rotamer (60%) δ 2.08 (s, 3H), 2.63 (s, 3H), 3.91 (s, 3H), 4.89 (brs, 3H), 5.26 (s, 1H), 7.06-7.62 (m, 7H), and 8.00-8.05 (m, 1H); minor rotamer (40%) δ 1.83 (s, 3H), 3.06 (s, 3H), 3.92 (s, 3H), 4.32 (s, 2H), 4.57 (brs, 1H), 5.01 (brs, 1H), 7.06-7.62 (m, 7H), and 8.00-8.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.0, 25.4, 33.1, 36.1, 47.4, 52.0, 52.7,

77.4, 115.8, 115.9, 126.8, 126.9, 127.0, 127.1, 127.2, 127.3, 127.4, 127.5, 128.0, 128.2, 128.3, 128.7, 130.6, 130.7, 132.8, 133.0, 133.4, 138.8, 139.2, 143.2, 143.9, 144.7, 166.1, 171.3, and 171.6; Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.55; N, 4.33. Found: C, 74.03; H, 6.45; N, 4.32.

2-Hydroxy-*N*-(2-isopropenylbenzyl)-*N*-methylbenzamide. To a refluxing solution containing 4.5 g (14 mmol) of ester **9** and 1.6 g (41 mmol) of $NaBH_4$ in 50 mL of *t*-BuOH was added 10 mL of MeOH slowly over a period of 1 h. After the addition, the reaction was heated at reflux for an additional 1 h. Water was added and the mixture was extracted with CH_2Cl_2. Silica gel chromatography of the crude reaction mixture afforded 2.8 g (69%) of the titled compound as a colorless oil which consisted of a mixture of rotamers; IR (neat) 3388, 2968, 1630, and 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) major rotamer (57%) δ 2.09 (s, 3H), 2.78 (s, 3H), 3.77 (brs, 1H), 4.61 (brs, 2H), 4.89 (brs, 3H), 5.28 (t, 1H, *J* = 1.8 Hz), and 7.11-7.48 (m, 8H); minor rotamer (43%) δ 1.86 (s, 3H), 3.06 (s, 3H),3.77 (brs, 1H), 4.53 (s, 2H), 4.58 (s, 2H), 4.62 (brs, 1H), 5.12 (t, 1H, *J* = 1.6 Hz), and 7.11-7.48 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 25.0, 33.3, 36.6, 47.4, 52.4, 63.3, 63.4, 115.8, 126.0, 126.2, 126.3, 127.1, 127.2, 127.3, 127.4, 127.5, 128.2, 128.3, 129.4, 129.5, 129.6, 129.7, 132.6, 132.8, 134.7, 135.1, 138.8, 139.1, 143.1, 143.7, 143.8, 144.5, 171.9, and 172.4; HRMS Calcd. for $C_{19}H_{21}NO_2$ $[M-H_2O]^+$: 277.1467. Found: 277.1465.

2-Formyl-*N*-(2-isopropenylbenzyl)-*N*-methylbenzamide. To a solution containing 0.17 g (0.6 mmol) of the above alcohol in 40 mL of $CHCl_3$ was added 1.2 g (14 mmol) of MnO_2 and the mixture was stirred at rt for 24 h. The reaction mixture was filtered through Celite and the solid was washed with $CHCl_3$ and EtOH. The solvent was removed under reduced pressure affording 0.17 g (99%) of the titled compound as a colorless oil which consisted of a mixture of rotamers; IR (neat) 3060, 2968, 2854, 2747, 1694, 1630, and 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) major rotamer (57%) δ 2.09 (s, 3H), 2.63 (s, 3H), 4.88-4.89 (m, 1H), 4.93 (s, 2H), 5.08-5.09 (m, 1H), 7.18 (d, 1H, *J* = 7.4 Hz), 7.23-7.96 (m, 7H), and 10.12 (s, 1H); minor rotamer (43%) δ 1.82 (s, 3H), 3.09 (s, 3H), 4.34 (s, 2H), 4.55-4.56 (m, 1H), 5.27-5.28 (m, 1H), 7.08 (d, 1H, *J* = 7.2 Hz), 7.23-7.96 (m, 7H), and 10.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) d 24.9, 25.3, 33.3, 36.1, 47.5, 52.1, 115.9, 126.5, 127.1, 127.2, 127.3, 127.5, 127.6, 127.8, 128.2, 128.4, 129.4, 130.7, 130.8, 132.4, 132.7, 132.9, 134.1, 134.3, 138.3, 138.7, 143.2, 143.7, 143.9, 144.6, 169.8, 170.0, 190.6, and 190.7; HRMS Calcd. for $C_{19}H_{19}NO_2$: 293.1416. Found: 293.1413.

2-Hydrazonomethyl-*N*-(2-isopropenylbenzyl)-*N*-methylbenzamide (10). To a solution containing 0.18 mL (6 mmol) of hydrazine hydrate and 2 drops of pyridine in 15 mL of Et_2O was added 0.17 g (0.6 mmol) of the above aldehyde as an ether solution (2 mL). The reaction mixture was stirred at rt for 18 h and extracted into EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Silica gel chromatography of the crude reaction mixture afforded 0.12 g (70%) of **10** as a yellow oil which consisted of a mixture of rotamers; IR (neat) 3388, 3203, 3060, 2918, and 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) major rotamer (56%) δ 2.07 (s, 3H), 2.64 (s, 3H), 4.87-4.88 (m, 3H), 5.25-5.26 (m, 1H), 5.63 (s, 2H), 7.05-7.42 (m, 7H), and 7.76-7.81 (m, 2H); minor rotamer (44%) δ 1.80 (s, 3H), 3.03 (s, 3H), 4.35 (s, 2H), 4.56-4.57 (m, 1H), 5.08-5.09 (m, 1H), 5.67 (s, 2H), 7.05-7.42 (m, 7H), and 7.76-7.81 (m, 2H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 24.9, 25.2, 33.1, 36.4, 47.4, 52.1, 116.0, 126.2, 126.3, 126.4, 126.5, 126.6, 127.3, 127.4, 127.5, 127.6, 127.9, 128.3, 128.4, 128.5, 129.1, 129.2, 131.9, 132.1, 132.9, 133.3, 134.7, 135.1, 139.8, 139.9, 143.3, 143.9, 144.1, 144.7, 171.2, and 171.6; HRMS Calcd. for $C_{19}H_{21}N_3O$: 307.1685. Found: 307.1691.

***N*-Benzyl-2-hydroxymethyl-*N*-methylbenzamide.** To 13 g (100 mmol) of aluminum chloride in 40 mL of 1,2-dichloroethane at 0 °C was added slowly a solution containing 25 mL (194 mmol) of *N*-benzyl-methylamine in 20 mL of 1,2-dichloroethane so that the internal temperature remained below 20 °C. After the addition was complete, the solution was warmed to rt and 10 g (77 mmol) of phthalide was added in one portion and the mixture was stirred for 18 h. The solution was quenched with 100 mL of ice water and was stirred for 0.5 h. The suspension was filtered through Celite, and the aqueous phase was extracted with 1,2-dichloroethane. The organic phases were combined, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by silica gel chromatography to provide 18 g (96%) of the title compound as a yellow oil which consisted of a mixture of rotamers; IR (neat) 3399, 2925, 1620, 1397, 1257, and 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) major rotamer δ 2.82 (s, 3H), 3.75 (brs, 1H), 4.56 (s, 2H), 4.78 (s, 2H), 7.12 (d, 1H, *J* = 7.2 Hz), and 7.28 - 7.46 (m, 8H); minor rotamer δ 3.06 (s, 3H), 3.75 (brs, 1H), 4.47 (s, 2H), 4.56 (s, 2H), 7.12 (d, 1H, *J* = 7.2 Hz), and 7.28 - 7.46 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.2, 36.9, 50.8, 55.4, 64.1, 64.2, 126.5, 126.7, 127.1, 127.6, 127.7, 127.8, 127.9, 128.4, 128.9, 129.0, 130.0, 130.1, 130.2, 130.3, 135.3, 135.5, 136.3, 136.9, 139.2, 139.4, 171.9, and 172.5; HRMS Calcd. for $C_{16}H_{17}NO_2$: 255.1259. Found: 255.1249.

Benzyl-(3*H*-isobenzofuran-1-ylidene)methyl-ammonium bromide (13). To a solution containing 18 g (74 mmol) of the above alcohol in 500 mL of CH_2Cl_2 was added 8 mL (88 mmol) of phosphorus tribromide and the reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The solvent was removed under reduced pressure affording 19 g (96%) of *N*-benzyl-2-bromomethyl-*N*-methylbenzamide (**12**) as a colorless oil which consisted of a mixture of rotamers; IR (neat) 3057, 30.27, 2919, 1629, 1490, 1444, 1398, 1260, and 1060 cm^{-1}. Upon standing, benzylic bromide **12** was converted to salt **13** which was obtained as a white solid: mp 124-125 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.89 (s, 3H), 5.22 (s, 2H), 6.12 (s, 2H), 7.39 - 7.42 (m, 5H), 7.69 - 7.73 (m, 1H), 7.85-7.87 (m, 2H), and 8.33 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.7, 58.8, 79.1, 123.6, 127.1, 128.5, 129.1, 129.5, 129.6, 130.8, 132.0, 136.8, 148.2, and 173.4; Anal. Calcd. for $C_{16}H_{16}BrNO$: C, 60.56; H, 5.09; N, 4.42. Found: C, 60.49; H, 5.13; N, 4.35.

4-(Benzylmethylamino)-2-methylbenzo[*f*]isoindole-1,3-dione (15). To a solution of 0.08 g (0.7 mmol) of *N*-methylmaleimide and 0.1 mL (0.8 mmol) of 2,2,6,6-tetramethyl-piperidine in 30 mL of THF at reflux was added 0.2 g (0.6 mmol) of salt **13** in 1 mL CH_2Cl_2. After stirring for 20 min, the suspension was allowed to cool to rt and was filtered through a pad of silica gel. The solvent was removed under reduced pressure and chromatography on silica gel gave 0.2 g (90%) of cycloadduct **15** as a yellow solid: mp 133-135 °C; IR (neat) 3062, 3032, 2939, 1757, 1705, 1582, 1511, 1429, 1378, and 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.99 (s, 3H), 3.22 (s,

3H), 4.61 (s, 2H), 7.24 - 7.28 (m, 1H), 7.32 - 7.35 (m, 2H), 7.41 - 7.43 (m, 2H), 7.63 - 7.69 (m, 2H), 7.95 - 7.97 (m, 1H), 8.07 (s, 1H), and 8.53-8.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 41.6, 60.8, 119.6, 121.1, 127.0, 127.3, 128.5, 128.8, 129.2, 129.5, 130.7, 134.9, 136.8, 139.6, 150.3, 167.4, and 168.3; Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.18; H, 5.73; N, 8.20.

1-(Benzylmethylamino)-4-hydroxy-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (16). To a solution of 2 mL (18 mmol) of methyl acrylate and 0.3 mL (1.5 mmol) of 2,2,6,6-tetramethylpiperidine in 6 mL THF at reflux was added 0.4 g (1.3 mmol) of salt **13** in 1 mL of CH_2Cl_2. After stirring for 30 min, the suspension was allowed to cool to rt and was filtered through a pad of silica gel. The solvent was removed under reduced pressure and chromatography on silica gel gave 0.3 g (68%) of cycloadduct **16** as a yellow oil; IR (neat) 3421, 3062, 2945, 1695, 1603, 1557, 1434, 1244, and 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (brs, 1H), 2.67 (s, 3H), 2.77 - 2.78 (m, 2H), 3.78 (s, 3H), 4.12 (s, 2H), 4.75 (t, 1H, *J* = 6.2 Hz), 7.27 - 7.32 (m, 1H), 7.33 - 7.39 (m, 6H), 7.48 - 7.50 (m, 1H), and 7.66 - 7.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.0, 39.8, 51.7, 59.7, 67.5, 108.5, 126.3, 126.9, 127.4, 128.0, 128.5, 129.0, 129.7, 132.1, 139.1, 141.5, 153.5, and 169.7; Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.55; N, 4.33. Found: C, 74.09; H, 6.32; N, 4.30.

Methanesulfonic acid 2-diethylcarbamoylbenzyl ester (17). To a solution of 2.0 g (9.7 mmol) of *N*,*N*-diethyl-2-hydroxymethylbenzamide[19] and 1.6 g (15.5 mmol) of triethylamine in 100 mL of CH_2Cl_2 at 0 °C was added 1.8 g (15.5 mmol) of methane-sulfonyl chloride. After stirring for 1 h, water was added and the aqueous layer was extracted with CH_2Cl_2. The solvent was removed and the residue was chromatographed on silica gel to give 2.4 g (87%) of **17** as a white solid: mp 73-75 °C; IR (neat) 3117, 2989, 1673, 1481, and 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, 3H, *J* = 6.9 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 3.02 (s, 3H), 3.18 (q, 2H, *J* = 7.1 Hz), 3.56-3.58 (m, 2H), 5.25 (s, 2H), 7.27-7.29 (m, 1H), 7.41-7.44 (m, 2H), and 7.49-7.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9, 14.1, 37.8, 39.1, 43.9, 69.5, 126.2, 129.4, 129.5, 130.4, 130.5, 137.4, and 169.5; HRMS Calcd. for $C_{13}H_{19}NO_4S$: 285.1035. Found: 285.1035.

Diethyl-(3*H*-isobenzofuran-1-ylidene)ammonium methanesulfonate (18). A solution of 0.1 g (0.35 mmol) of mesylate **17** in 10 mL THF was heated at reflux. After stirring for 1 h, the suspension was allowed to cool to rt and the solid was collected by filtration, washed with THF, and dried under vacuum to give 0.08 g (78%) of salt **18** as a white solid: mp 128-132 °C; IR (neat) 3082, 2982, 2228, 1666, and 1189 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (t, 3H, *J* = 7.3 Hz), 1.60 (t, 3H, *J* = 7.3 Hz), 2.60 (s, 3H), 4.02 (q, 2H, *J* = 7.3 Hz), 4.29 (q, 2H, *J* = 7.3 Hz), 6.06 (s, 2H), 7.75-7.90 (m, 3H), and 8.16 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3, 12.8, 39.1, 46.6, 48.5, 78.5, 122.1, 123.3, 127.2, 130.4. 136.2, 148.2, and 171.5; Anal. Calcd. for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.72; N, 4.91. Found: C, 54.69; H, 6.62; N, 4.83.

4-Diethylamino-2-methylbenzo[*f*]isoindole-1,3-dione (19). To a solution of 0.03 g (0.3 mmol) of *N*-methylmaleimide and 0.04 g (0.3 mmol) of 2,2,6,6-tetramethylpiperidine in 25 mL THF at reflux was added 0.07 g (0.25 mmol) of salt **18** as a solution in 1 mL of CH_2Cl_2. After 15 min, the suspension was allowed to cool to rt and the solvent was removed. Chromatography on silica

gel gave 0.04 g (56%) of cycloadduct **19** as a yellow solid: mp 98-100 °C; IR (neat) 3068, 2968, 1751, 1702, and 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (t, 6H, *J* = 7.1 Hz), 3.25 (s, 3H), 3.53 (q, 4H, *J* = 7.1 Hz), 7.63-7.67 (m, 2H), 7.95-7.98 (m, 1H), 8.10 (s, 1H), and 8.53-8.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 24.1, 48.2, 120.7, 120.8, 127.4, 128.4, 128.9, 129.3, 130.3, 136.4, 136.6, 148.9, 167.2, and 168.3; Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.43; N, 9.93. Found: C, 72.19; H, 6.46; N, 9.88.

***N*-Methyl-2-(tetrahydropyran-2-yloxymethyl)benzamide.** To 16 g (100 mmol) of 2-hydroxymethyl-*N*-methylbenzamide in 250 mL of CH_2Cl_2 was added 46 mL (504 mmol) of dihydropyran followed by 0.2 g (1 mmol) of *p*-TsOH. The suspension was stirred at rt for 1 h and was poured into a separatory funnel containing 600 mL of Et_2O, 330 mL of H_2O, 165 mL of saturated aqueous NaCl, and 165 mL of saturated aqueous $NaHCO_3$. The Et_2O layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure, and chromatography of the residue on silica gel gave 18 g (71%) of the titled compound as a white solid: mp 77-78 °C; IR (film) 3314, 3063, 2939, 2863, 1644, 1541, 1311, 1116, and 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 - 1.61 (m, 4H), 1.69 - 1.82 (m, 2H), 2.96 (d, 3H, *J* = 4.8 Hz), 3.52 - 3.57 (m, 1H), 3.84 - 3.90 (m, 1H), 4.59 (d, 1H, *J* = 11.6 Hz), 4.71 (t, 1H, *J* = 3.6 Hz), 4.86 (d, 1H, *J* = 11.2 Hz), 7.14 (brs, 1H), 7.33 - 7.40 (m, 3H), and 7.65 - 7.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 25.4, 26.8, 30.8, 62.9, 67.9, 98.4, 128.6, 129.2, 130.4, 130.8, 134.5, 136.8, and 169.5. The spectral data of this compound was identical to that reported in the literature. [20]

***N*-Methyl-*N*-pent-4-enyl-2-(tetrahydropyran-2-yloxymethyl)benzamide.** To a suspension of 0.06 g (2.4 mmol) of NaH in 5 mL DMF at 0 °C was added 0.5 g (2.0 mmol) of the above amide. The suspension was allowed to warm to rt. After 1 hr at rt, 0.36 g (2.4 mmol) of 1-bromo-4-pentene was added as a solution in 5 mL DMF. After stirring for 2 h, water was added and the aqueous layer was extracted with EtOAc. Chromatography of the residue on silica gel gave 0.56 g (93%) of the titled compound as a 1:1 mixture of rotamers as a clear oil; IR (neat) 3068, 2933, 1630, and 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44-1.92 (m, 20H), 2.16 (q, 2H, *J* = 7.7 Hz), 2.82 (s, 2H), 3.08 (s, 4H), 3.49-3.59 (m, 4H), 3.85 - 3.92 (m, 2H), 4.50 - 5.10 (m, 10H), 5.59 - 5.68 (m, 1H), 5.80 - 5.92 (m, 1H), 7.17 - 7.43 (m, 6H), and 7.47 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 19.4, 19.5, 25.2, 25.3, 26.1, 27.1, 30.4, 30.5, 30.6, 31.0, 32.2, 36.9, 46.5, 50.5, 62.0, 62.1, 66.6, 98.1, 98.5, 115.0, 115.2, 125.8, 125.9, 127.4, 127.6, 128.6, 128.7, 128.8, 129.0, 134.7, 134.9, 136.4, 137.0, 137.7, and 170.6; HRMS Calcd. for $C_{19}H_{27}NO_3$: 317.1991. Found: 317.1985.

2-Hydroxymethyl-*N*-methyl-*N*-pent-4-enylbenzamide. To a solution of 0.25 g (0.8 mmol) of the above amide in 3 mL MeOH was added 50 mg of Amberlyst H-15 resin. After stirring for 6 h, the suspension was filtered and the solvent removed to give 0.18 g (98%) of the titled compound as a 1:1 mixture of rotamers as a clear colorless oil; IR (neat) 3395, 3068, 2932, 1766, and 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (p, 2H, *J* = 7.6 Hz), 1.77 (p, 2H, *J* = 7.3 Hz), 1.86 (q, 2H, *J* = 7.1 Hz), 2.14 (q, 2H, *J* = 7.1 Hz), 2.87 (s, 3H), 3.10 (s, 3H), 3.20 (t, 2H, *J* = 7.3), 3.56 (t, 2H, *J* = 7.6 Hz), 4.10 (bs, 2H), 4.50 (s, 4H), 4.86 - 5.30 (m, 4H), 5.54 - 5.67 (m, 1H), 5.80 -

5.93 (m, 1H), 7.20 (d, 2H, *J* = 7.3 Hz), and 7.26 - 7.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 27.0, 30.2, 30.8, 32.4, 37.2, 46.7, 50.6, 63.3, 69.5, 115.1, 115.2, 125.9, 126.0, 127.2, 127.3, 129.3, 129.4, 129.5, 133.9, 135.1, 135.4, 136.7, 137.5, 138.5, 138.6, 171.3, and 171.7; HRMS Calcd. for $C_{14}H_{19}NO_2$: 233.1416. Found: 233.1411.

(3*H*-Isobenzofuran-1-ylidene)-methylpent-4-enylammonium bromide (20). To a solution of 0.18 g (0.8 mmol) of the above alcohol in 8 mL CH_2Cl_2 at 0 °C was added 0.25 g (0.9 mmol) of PBr_3. After stirring for 2 h, water was added and the aqueous layer was extracted with CH_2Cl_2. The solvent was removed to give 0.2 g (89%) of salt **20** as a white solid after 24 h under high vacuum: mp 115-118 °C; IR (neat) 3075, 2932, 2192, 1666, and 912 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (p, 2H, *J* = 7.5Hz), 2.19 (q, 2H, *J* = 6.8 Hz), 3.70 - 4.03 (m, 5H), 5.01 - 5.09 (m, 2H), 5.76 - 5.85 (m, 1H), 6.12 (s, 2H), 7.76 (t, 1H, *J* = 7.7 Hz), 7.90 (t, 1H, *J* = 7.3), 7.96 (d, 1H, *J* = 7.9 Hz), and 8.40 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 30.2, 40.2, 54.8, 78.7, 116.1, 122.6, 123.3, 128.1, 130.3, 135.9, 136.3, 147.6, and 172.0; Anal. Calcd. for $C_{14}H_{18}NOBr$: C, 56.94; H, 6.15; N, 4.75. Found: C, 56.75; H, 6.03; N, 4.72.

2-Methyl-4-(methylpent-4-enylamino)-benzo[*f*]isoindole-1,3-dione (23). To a solution of 0.7 g (0.6 mmol) *N*-methylmaleimide and 0.08 g (0.6 mmol) of 2,2,6,6-tetramethyl-piperidine in 25 mL of THF at reflux was added 0.15 g (0.5 mmol) of salt 20 as a solution in 1 mL of THF. After 15 min, the suspension was allowed to cool to rt and was filtered through Celite. Chromatography of the residue gave 0.14 g (89%) of cycloadduct **23** as a yellow solid: mp 67-69 °C; IR (neat) 3075, 2925, 1751, 1431, 1374, and 763 cm-1; 1H NMR ($CDCl_3$, 300 MHz) δ 1.71 (p, 2H, *J* = 7.1 Hz), 2.05 (q, 2H, *J* = 6.8 Hz), 3.13 (s, 3H), 3.21 (s, 3H), 3.47 (t, 2H, *J* = 7.3 Hz), 4.86-4.94 (m, 2H), 5.68-5.82 (m, 1H), 7.61-7.69 (m, 2H), 7.94-7.98 (m, 1H), 8.05 (s, 1H), and 8.45-8.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 27.8, 31.1, 41.8, 56.0, 114.6, 119.0, 120.4, 126.9, 128.3, 128.9, 129.3, 130.4, 134.9, 136.6, 138.2, 150.1, 166.9, and 168.1; Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 73.99; H, 6.54; N, 9.09. Found: C, 73.87; H, 6.53; N, 9.02.

***N*-Methyl-2-(tetrahydropyran-2-yloxymethyl)-*N*-(2-vinylbenzyl)benzamide (26).** To a solution containing 0.04 g (1.0 mmol) of sodium hydride in 2 mL of DMF was added 0.21 g (0.8 mmol) of *N*-methyl-2-(tetrahydropyran-2-yloxymethyl)-benzamide[20] as a DMF solution (1 mL) at rt. After stirring for 1 h, 0.2 g (1.0 mmol) of 1-bromomethyl-2-vinyl-benzene[21] (**25**) was added as a DMF solution (1 mL). The resulting solution was stirred at rt for 2 h and was quenched with H_2O. The DMF solution was poured into 12 mL of H_2O and extracted with EtOAc. Silica gel chromatography of the crude reaction mixture afforded 0.19 g (61%) of **26** as a yellow oil which consisted of a mixture of rotamers; IR (neat) 3061, 2940, 1766, 1630, and 1396 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) major rotamer (70%) δ 1.49-1.91 (m, 6H), 2.61 (s, 3H), 3.49-3.59 (m, 1H), 3.84-3.95 (m, 1H), 4.40-4.91 (m, 5H), 5.37 (dd, 1H, *J* = 7.7 and 1.4 Hz), 5.70 (dd, 1H, *J* = 17.4 and 1.4 Hz), 7.08-7.15 (m, 1H), and 7.18-7.57 (m, 8H); minor rotamer (30%) δ 1.49-1.91 (m, 6H), 3.02 (s, 3H), 3.49-3.59 (m, 1H), 3.84-3.95 (m, 1H), 4.40-4.91 (m, 5H), 5.25 (dd, 1H, *J* = 10.8 and 1.2 Hz), 5.53 (dd, 1H, *J* = 17.2 and 1.2 Hz), 6.61-6.68 (m, 1H), and 7.18-7.57 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 19.3, 25.2, 30.3, 30.4, 32.5, 35.7, 47.5, 51.9, 61.7, 61.9, 66.4, 66.8, 97.8, 98.2, 116.0, 116.7, 125.3, 125.6, 125.7, 126.1, 126.2, 127.2, 127.5,

127.6, 128.2, 128.3, 128.5, 128.7, 128.8, 129.4, 132.9, 133.0, 133.4, 133.9, 134.7, 135.0, 135.1, 135.7, 136.1, 136.9, 170.0, and 171.1; HRMS Calcd. for $C_{23}H_{27}NO_3$: 365.1991. Found: 365.1986.

2-Hydroxy-*N*-methyl-*N*-(2-vinylbenzyl)benzamide. To a solution containing 1.1 g (3.1 mmol) of the THP-protected alcohol **26** in 15 mL of MeOH was added 0.3 g of Amberlyst 15 ion-exchange resin at rt. After stirring for 18 h, the reaction mixture was filtered to remove the resin and the solvent was removed under reduced pressure. Silica gel chromatography of the crude reaction mixture afforded 0.74 g (85%) of the titled compound as a colorless oil which consisted of a mixture of rotamers; IR (neat) 3395, 3061, 2925, 1758, 1616, 1403, and 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) major rotamer (70%) δ 2.69 (s, 3H), 3.94 (brs, 1H), 4.57 (brs, 2H), 4.90 (s, 2H), 5.38 (dd, 1H, *J* = 11.2 and 1.2 Hz), 5.72 (dd, 1H, *J* = 17.2 and 0.8 Hz), 7.05-7.12 (m, 1H), and 7.22-7.58 (m, 8H); minor rotamer (30%) δ 3.03 (s, 3H), 4.02 (brs, 1H), 4.54 (s, 2H), 4.57 (brs, 2H), 5.26 (d, 1H, *J* = 10.8 Hz), 5.56 (d, 1H, *J* = 17.2 Hz), 6.58-6.65 (m, 1H), and 7.22-7.58 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) d 33.5, 36.7, 48.5, 53.0, 64.2, 64.3, 116.7, 117.4, 126.3, 126.4, 126.7, 126.9, 127.5, 127.8, 128.0, 128.1, 128.3, 128.9, 129.8, 129.9, 130.0, 130.2, 130.3, 133.0, 133.2, 133.5, 134.2, 135.0, 135.5, 136.7, 137.5, 139.1, 139.5, 171.4, and 172.4; HRMS Calcd. for $C_{18}H_{19}NO_2$: 281.1416. Found: 281.1405.

(3*H*-Isobenzofuran-1-ylidene)-methyl-(2-vinylbenzyl)ammonium bromide (28). To a solution containing 0.75 g (2.6 mmol) of the above alcohol in 20 mL of CH_2Cl_2 was added 0.3 mL (3.2 mmol) of phosphorus tribromide and the reaction mixture was stirred for 30 min at 0 °C. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The solvent was removed under reduced pressure to give 0.87 g (95%) of 2-bromo-methyl-*N*-methyl-*N*-(2-vinylbenzyl)-benzamide (**27**) as a colorless oil which consisted of a mixture of rotamers; IR (neat) 3068, 2925, 1766, 1630, 1403, and 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) major rotamer (70%), δ 2.68 (s, 3H), 4.47-5.18 (m, 4H), 5.39 (dd, 1H, *J* = 11.1 and 1.2 Hz), 5.73 (dd, 1H, *J* = 17.4 and 1.2 Hz), 7.07-7.16 (m, 1H), and 7.17-7.61 (m, 8H); minor rotamer (30%) δ 3.10 (s, 3H), 4.47-5.18 (m, 4H), 5.28 (dd, 1H, *J* = 9.9 and 0.9 Hz), 5.56 (dd, 1H, *J* = 17.3 and 0.9 Hz), 6.61-6.71 (m, 1H), and 7.17-7.61 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.8, 31.1, 33.5, 36.7, 48.2, 53.0, 116.6, 117.4, 125.8, 126.1, 126.3, 126.6, 126.7, 127.7, 127.9, 128.0, 128.2, 128.5, 128.8, 129.5, 129.7, 129.8, 131.0, 133.2, 133.6, 134.3, 135.0, 135.1, 136.4, 136.5, 136.9, 137.5, 169.8, and 171.0; HRMS Calcd. for $C_{18}H_{18}BrNO$: 343.0572. Found: 343.0572.

Upon standing, bromide **27** was converted to 0.8 g (94%) of salt **28** which was isolated as a white solid: mp 112-115 °C; IR (film) 3018, 2925, 1659, 1403, and 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H), 5.27-5.31 (m, 3H), 5.58 (d, 1H, *J* = 17.2 Hz), 6.09 (s, 2H), 6.82-6.89 (m, 1H), 7.25-7.89 (m, 7H), and 8.24-8.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.9, 55.9, 79.2, 118.8, 123.3, 123.7, 127.3, 128.4, 128.6, 128.7, 129.9, 130.2, 130.6, 133.2, 136.7, 138.1, 148.2, and 172.7; Anal. Calcd. for $C_{18}H_{18}BrNO$: C, 62.96; H, 5.29; N, 4.08. Found: C, 62.81; H, 5.05; N, 3.91. The salt was immediately used in the next step without further purification.

5-Methyl-5,6,11,12-tetrahydrobenzo[*c*]phenanthridin-12-ol (31). To a refluxing solution containing 0.01 mL (0.07 mmol) of DBU in 3 mL of THF was added 0.046 g (0.14 mmol) of the

bromide salt **28** as a CH_2Cl_2 solution (1 mL). The reaction mixture was heated at reflux for 20 min and after cooling, was filtered through a plug of silica gel. Silica gel chromatography of the crude reaction mixture afforded 0.02 g (54%) of **31** as a pale yellow oil; IR (film) 3402, 3018, 2940, 1595, 1481, 1196, and 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.85 (brd, 1H, *J* = 6.8 Hz), 2.52 (s, 3H), 2.95 (dd, 1H, *J* = 16.2 and 5.0 Hz), 3.11 (dd, 1H, *J* = 16.2 and 6.2 Hz), 4.11-4.20 (m, 2H), 4.87-4.90 (m, 1H), 7.18 (d, 1H, *J* = 7.2 Hz), 7.24-7.48 (m, 6H), and 7.73 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.0, 39.3, 55.1, 68.1, 117.1, 121.9, 125.1, 126.5, 126.9, 127.3, 127.6, 128.1, 128.7, 130.2, 131.4, 133.4, 138.6, and 141.5; Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.09; H, 6.51; N, 5.32. Found: C, 82.03; H, 6.56; N, 5.24.

The minor fraction isolated from the column contained 0.006 g (15%) of 5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (**32**) as a yellow solid; mp 123-124 °C; IR (KBr) 3018, 2940, 1481, 1189, and 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.74 (s, 3H), 4.30 (s, 2H), 7.32-7.62 (m, 5H), 7.72 (d, 1H, *J* = 8.4 Hz), 7.86-7.90 (m, 2H), 7.96 (d, 1H, *J* = 8.4 Hz), and 8.42 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.7, 55.3, 121.9, 122.9, 124.2, 124.7, 125.4, 126.1, 126.2, 126.9, 127.6, 127.8, 128.3, 129.4, 132.1, 132.2, 134.3, and 144.2; Anal. Calcd. for $C_{18}H_{15}N$: C, 88.12; H, 6.17; N, 5.71. Found: C, 88.00; H, 6.24; N, 5.60.

Acknowledgments

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