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Reductive *N*-Alkylation of Nitroarenes: A Green Approach for the *N*-Alkylation of Natural Products

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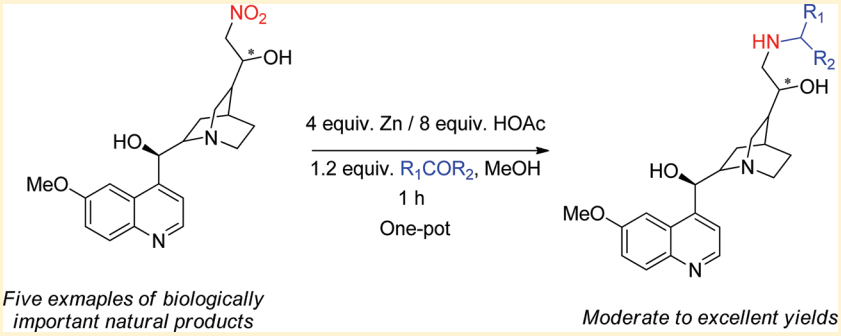
Supporting Information



ABSTRACT: A simple, mild, cost-effective, and green approach for the reductive mono-*N*-alkylation of nitroarenes has been developed. HOAc/Zn are utilized as the reducing system together with a carbonyl compound as an alkyl source in methanol. Excellent yields were obtained with stoichiometric control of mono- over dialkylated products. Application to five complex natural products demonstrated the practical utility of the method.

INTRODUCTION

One-pot reactions are those in which two or more chemical transformations take place under the same reaction conditions without purification of intermediates and avoiding protection/deprotection steps.[1] Because of this advantage, one-pot reactions are highly practical in organic process development and in the field of total synthesis of complex natural products.[2] Indeed, the value of such reactions is maximized if they maintain the green chemistry principles such as waste prevention, atom economy, safer solvents, and catalysis selectivity.[3] Simple and gentle chemical modifications are a key element for lead optimization studies where the pharmacological properties of leads must be altered through synthesis or semisynthesis. Nitration of aromatic and heterocyclic compounds is a simple and useful reaction for introduction of a stable nitro group onto a natural product skeleton. The benefit of introducing the nitro group is the ease of conversion to the corresponding amine that can be further alkylated to create primary and secondary aromatic amines. These alkylated amines are important building blocks for drug candidates.

During our detailed structure−activity relationship (SAR) and lead optimization studies of manzamine A against malaria and neuroinflammation,[4] we introduced a nitro group at C-6 and C-8 of the β-carboline moiety. These nitromanzamines are stable, while the corresponding amines are not.[4b] This instability was the inspiration for development of our one-pot reductive amidation method using Zn/HOAc as the reducing system and acyl chloride/Et_3N as the acylating agent in DMF.[5] The same challenges occurred when attempting to *N*-alkylate aminomanzamines by direct and reductive alkylation methods. As a result, we explored the utility of our previously used reducing system (Zn/HOAc) to accomplish an effective one-pot reductive *N*-alkylation of nitroarenes with carbonyl compounds as the alkyl source.

Several examples of one-pot reductive mono-*N*-alkylations of nitroarenes with different reducing systems using carbonyl compounds as the alkyl source have been reported. Bae et al. used decaborane and 10% Pd/C[6] in methanol as a reducing system with a carbonyl compound as the alkyl source. Although this method showed high yields (~90%) of the mono-*N*-alkyl products, it has several drawbacks. Addition of the reducing agent in one batch resulted in an incomplete reaction because of the formation of the corresponding ether through reductive etherification. Another report used hydrogen over 10% Pd/C as reducing system and aldehydes as an alkyl source.[7] This method is not selective and not applicable to natural products modification since H_2/10% Pd/C will reduce isolated double bonds. In a similar reaction, ammonium formate was used as in situ hydrogen donor with 5% Pd/C as a reducing system in addition to aldehydes as alkyl source.[8] Xiang et al. reported the use of aqueous MeOH as an in situ source of H_2 over an Au−Pd/Al_2O_3 catalyst for the conversion of nitroarenes into the

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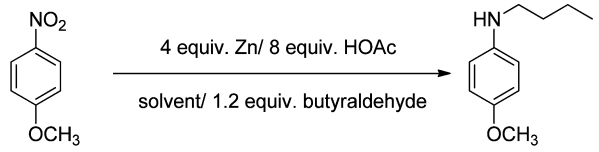
corresponding imines.[9] Nitriles have also been used as alkylating agents. Hudson et al. have used nitriles and ammonium formate with 5% Pd/C as reducing agent in methanol.[10] This approach gave relatively low yields with nitroarenes bearing electron-withdrawing groups. Polymethylhydrosiloxane was also used as reducing agent in the presence of $Pd(OH)_2/C$ as catalyst and nitriles as alkylating agents.[11] These two methods have the drawbacks of a long reaction time in the first method and an expensive reducing agent in the second method. Other reductive alkylation methods have been reported, including allylic amination of cyclohexene by nitroarenes catalyzed by ruthenium complexes,[12] electrochemical reduction,[13] addition of functionalized arylmagnesium compounds to nitroarenes,[14] the palladium catalyzed coupling of allyl carbonate,[15] the addition of allymagnesium chloride to nitroarenes followed by reduction with LAH,[16] and the zinc promoted reductive alkylation utilizing alkyl halides as the alkyl source.[17]

Apparently, none of the previously reported one-pot reductive *N*-alkylation methods of nitroarenes is suitable for drug development, because of either selectivity problems or the use of costly or toxic reagents (i.e., a deviation from green chemistry principles). Moreover, they all lack the application to a real drug lead or natural products. Herein, we report the development of a one-pot reductive *N*-alkylation of nitroarenes using inexpensive zinc metal with acetic acid as a selective reducing system (alkenes are stable under these conditions)[18] and carbonyl compounds as alkyl source with an application to five natural product scaffolds.

RESULTS AND DISCUSSION

Solvent optimization using 4-nitroanisole as a model reaction revealed that methanol was the solvent of choice with quantitative yield of the mono-*N*-alkyl product (Table 1). We

Table 1. Solvent Optimization for the Reductive Mono-*N*-Alkylation of Nitroarenes



4-nitroanisole **1a**

entry	solvent	time (min)	yield (%)[a]
1	DCM	30	94
2	MeOH	30	quant.
3	DMF	30	91
4	Toluene	30	86
5	THF	30	87

[a]Isolated yield. All reactions were done using 1 mmol of 4-nitroanisole.

then optimized the reaction conditions using simple nitroarenes and several carbonyl compounds. Mono-*N*-alkyl products were obtained in high yields when one mole of carbonyl compound was used. (Table 2). Addition of 2 equiv or more of carbonyl compound resulted in the formation of tertiary amines in excellent yields in an atom-economical approach.

We utilized our optimized conditions for the synthesis of several *N*-alkyl analogues of biologically active natural product scaffolds. Five natural products were nitrated to generate starting nitro materials (Scheme 1). Manzamine F (**2**), selected as an example of manzamine alkaloids, yielded upon nitration three nitro products: 7-nitromanzamine F (**3**), 5-nitromanzamine F (**4**), and 5,7-dinitromanzamine F (**5**). The regiochemistry of the nitro group in **3** was assigned on the basis of the strong HMBC correlations of H-5 (δ_H 7.91) to C-4a (δ_C 131.4) and C-4b (δ_C 129.1). Nitration of harmane (**6**),[5] a β-carboline alkaloid, with sodium nitrite gave two nitro products: 8-nitroharmane (**7**) and 6-nitroharmane (**8**). Recently, several β-carboline related alkaloids identified as prototypes to potent and orally efficient antimalarial leads were synthesized via similar reductive amination chemistry.[19] This supports our use of β-carbolines as model compounds. Nitration of the steroid, estradiol (**9**), led to simultaneous nitration of the phenol moiety and oxidation of the C-17 hydroxy functionality to afford 2-nitroestrone (**10**) and the 2,4-dinitro analogue (**11**). Nitration of quinine (**12**) resulted in an interesting hydroxynitration of the terminal double bond, which led to the formation of compound **13** in moderate yield. The ^{1}H and ^{13}C NMR of **13** revealed the absence of the olefinic resonances and the presence of a disubstituted quinoline ring (^{1}H NMR: δ 8.95, 1H, d, J = 4.4 Hz; 8.25, 1H, d, J = 7.7; 8.14, 1H, d, J = 10.9; 7.74, 1H, d, J = 10.0 Hz and 7.61, 1H, s), which indicated that the double bond was nitrated instead of the quinoline ring. This could be attributed to the deactivation of the quinoline ring by TFA. The molecular formula of **13** was determined as $C_{20}H_{26}N_3O_5$ $(M + H)^+$ from HRESIMS (m/z 388.1872) and the NMR data, which confirmed the addition of a hydroxy group and a nitro group in the molecule. The presence of the methylene resonance at δ 79.2 as well as the oxygenated methine resonance at δ 68.5 in the ^{13}C NMR spectra confirmed the regiochemistry of the nitro and the hydroxy groups to be at C-11 and C-10, respectively. Nitration of curcudiol (**14**) gave the mononitro (**15**) and dinitro products (**16**). The nitro group in **15** was assigned at C4 on the basis of the presence of the two singlet resonances at δ 7.51 and 6.31 in the ^{1}H NMR spectra.

The optimized reductive *N*-alkylation conditions applied to the nitrated natural products gave moderate to excellent yields (Table 3). 7-Nitromanzamine F gave a high yield (91%) of the corresponding 7-*N*-ethylaminomanzamine F (**17**) when 1 equiv of acetaldehyde was used. The nitroquinine product **13** gave a moderate yield of 47% of the *N*-ethylamino product **18**. Moreover, nitrocurcudiol **15** gave 64% yield of the *N*-ethylamino analogue **19**. A high yield of the 6-*N*-butylaminoharmane (**20**, 97%) was obtained from the reductive alkylation of 6-nitroharmane (**8**). Moreover, a high yield (88%) of the *N*,*N*-dimethylamino analogue **21** was obtained in the case of 2-nitroestrone when reacted with 2 equiv of formaldehyde.

CONCLUSION

In conclusion, a practical, mild, cost-effective and environmentally benign green method for the one-pot reductive mono-*N*-alkylation of nitroarenes has been developed. This method gives excellent yields with our model compounds with high selectivity for the mono-*N*-alkyl over the dialkylated product in an atom economical approach with easy workup step (no hazardous waste). The reaction conditions were well tolerated by a variety of natural product models and afforded moderate to excellent yields. The major advantage of our method is the use of inexpensive zinc metal and acetic acid as a mild and selective reducing system to nitro group, which makes our method greener. When taken in conjunction with the mild

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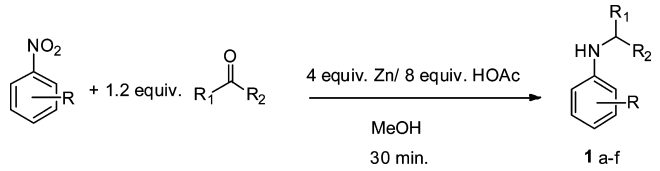
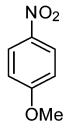
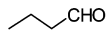
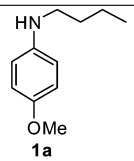
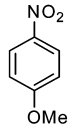
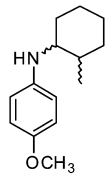
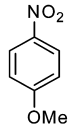
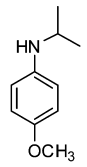
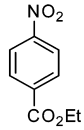
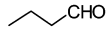
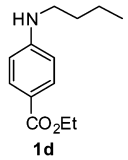
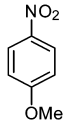
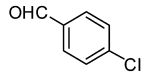
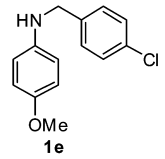
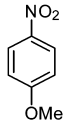
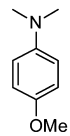
Table 2. Screening of Simple Nitroarenes under Optimized Conditions



Entry	Nitro compounds	Carbonyl compounds	*N*-alkyl products	Yield (%)[a]
1			 **1a**	Quant.
2			 **1b**	96
3			 **1c**	95
4			 **1d**	Quant.
5			 **1e**	97
6		HCHO	 **1f**	96[b]

[a]Isolated yields. All reactions were done using 1.0 mmol of starting material. [b]2.2 equiv of HCHO, 10 equiv of Zn, and 20 equiv of HOAc were used. The reaction time was 1 h.

reaction conditions, this method may well find applications in drug development.

EXPERIMENTAL SECTION

General Experimental Procedures. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, methanol-d_4, or acetone-d_6 on NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shift (δ) values are expressed in parts per million (ppm) and are referenced to the residual solvent signals of the solvent used. High resolution ESI-MS spectra were measured using electrospray ionization mass spectrometer. TLC analysis was carried out on precoated silica gel G254 aluminum plates. Reagents were purchased from commercial sources and used without further purification. Reactions were carried out in oven-dried glassware.

General Procedure for the Mono-*N*-Alkylation of Nitroarenes. Carbonyl compound (1.2 equiv), zinc dust (4 equiv), and acetic acid glacial (8 equiv) were added to a solution of the nitroarene (1 mmol) in MeOH (2 mL). The mixture was stirred at room temperature for 30 min. Water (5 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum.

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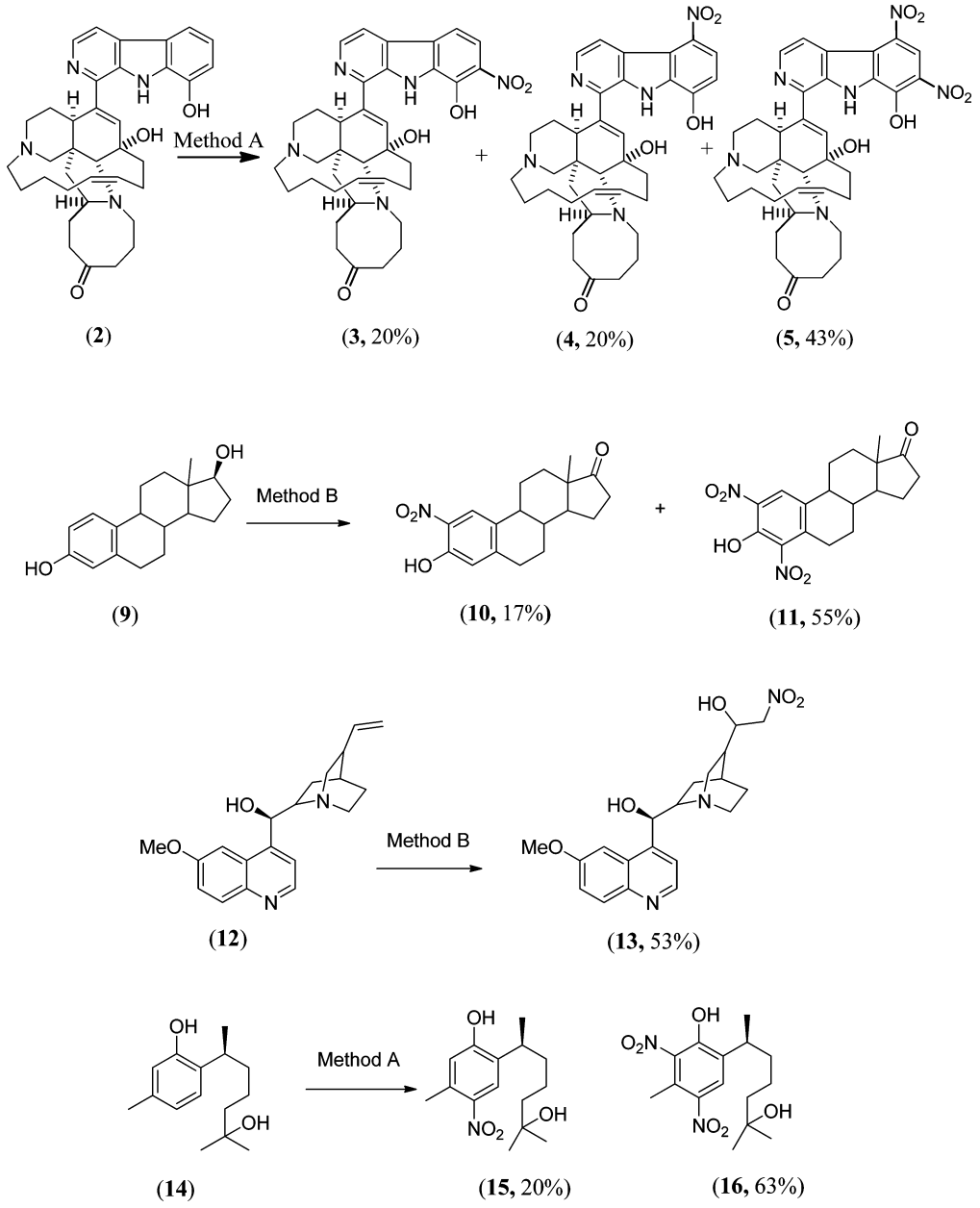
Scheme 1. Nitration of Natural Product Scaffolds[a]



(2) (3, 20%) (4, 20%) (5, 43%)

(9) (10, 17%) (11, 55%)

(12) (13, 53%)

(14) (15, 20%) (16, 63%)

[a]Method A: 1 equiv of natural product dissolved in TFA, 1.1 equiv of $NaNO_2$, 0 °C to rt, 1.5 h. Method B: 1 equiv of natural product dissolved in HOAc, 3 equiv of HNO_3, 0 °C to rt, 1 h.

The crude products were purified by silica column using 98:2 *n*-hexane/acetone.

4-*N*(*n*-Butylamino)anisole (1a).[20] Data: (179 mg, quant.); yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.84 (2H, d, J = 9.1 Hz), 6.63 (2H, d, J = 9.0 Hz), 3.77 (3H, s), 3.09 (2H, t, J = 7.6 Hz), 1.61 (2H, t, J = 7.5 Hz), 1.47 (2H, m), 1.00 (3H, t, J = 7.5 Hz); HRESIMS m/z calcd for $C_{11}H_{18}NO$ $(M + H)^+$ 180.1388, found 180.1394.

4-*N*(2-Methylcyclohexylamino)anisole (1b).[21] Data: (212 mg, 96%); yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.77 (2H, d, J = 8.7 Hz), 6.67 (2H, d, J = 8.9 Hz), 3.76 (3H, s), 1.4–2.2 (2H, m), 1.08 (3H, d, J = 7.1 Hz); HRESIMS m/z calcd for $C_{14}H_{22}NO$ $(M + H)^+$ 220.1701, found 220.1687.

4-*N*(Isopropylamino)anisole (1c).[22] Data: (157 mg, 95%); yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.78 (2H, d, J = 8.7 Hz), 6.60 (2H, d, J = 8.9 Hz), 3.77 (3H, s), 3.56 (1H, m), 1.2 (6H, d, J = 7.1 Hz); HRESIMS m/z calcd for $C_{10}H_{16}NO$ $(M + H)^+$ 166.1232, found 166.1197.

4-*N*(*n*-Butylamino)ethyl benzoate (1d).[23] Data: (221 mg, quant.); yellowish solid (mp 134); ^{1}H NMR ($CDCl_3$) δ 7.84 (2H, d, J = 8.9 Hz), 6.55 (2H, d, J = 8.7 Hz), 4.29 (2H, q, J = 7.4 Hz), 3.12 (2H, q, J = 7.1 Hz), 1.58 (2H, m), 1.41 (2H, m), 1.33 (3H, t, J = 7.0 Hz), 0.93 (3H, t, J = 7.0 Hz); HRESIMS m/z calcd for $C_{13}H_{20}NO_2$ $(M + H)^+$ 222.1494, found 222.1510.

4-(*p*-Chlorobenzylamino)anisole (1e).[24] Data: (240 mg, 97%); yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.22 (2H, d, J = 8.6 Hz), 7.07 (2H, d, J = 8.9 Hz), 6.74 (2H, d, J = 8.9 Hz), 6.52 (2H, d, J = 8.9 Hz) 4.42 (1H, brs), 3.72 (3H, s); ^{13}C NMR ($CDCl_3$) 152.8 (C), 140.7 (C), 140.2 (C), 138.7 (C), 133.3 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 115.7 (CH), 115.7 (CH), 115.0 (CH), 114.9 (CH), 64.6 (CH_2), 55.7 (CH_3); HRESIMS m/z calcd for $C_{14}H_{15}ClNO$ $(M + H)^+$ 248.0842, found 248.0857.

4-(*N*,*N*-Dimethylamino)anisole (1f).[25] Data: (145 mg, 96%); yellowish white oil; ^{1}H NMR ($CDCl_3$) δ 6.84 (2H, d, J = 8.6 Hz), 6.75

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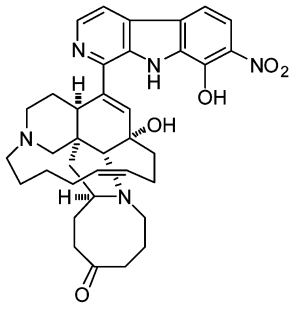
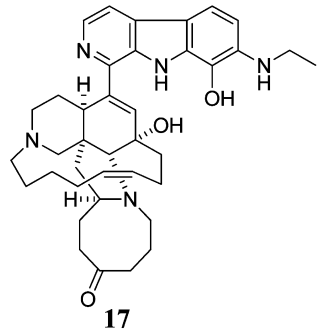
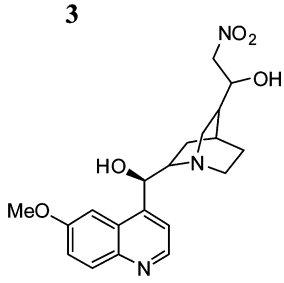
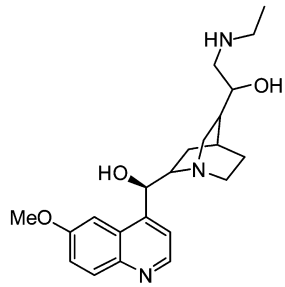
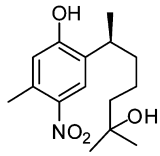
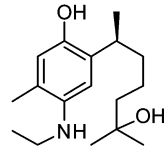
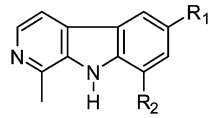
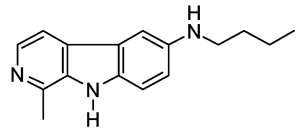
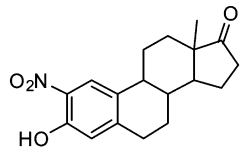
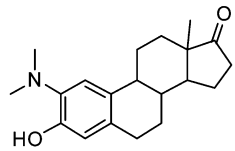
Table 3. Reductive *N*-Alkylation of Nitrated Natural Products

Entry	Nitro products	*N*-alkyl products	Yield (%)[a]
1	 **3**	 **17**	91
2	 **13**	 **18**	47
3	 **15**	 **19**	64
4	 R_1=R_2=H: Harmane (**6**) R_1=H, R_2=NO_2: 8-nitroharmane (**7**) R_1=NO_2, R_2=H: 6-nitroharmane (**8**)	 **20**	97
5	 **10**	 **21**	88[b]

[a]Isolated yields. 1.2 equiv of aldehydes were used. Reaction time was 1 h. [b]2.2 equiv of HCHO, 10 equiv of Zn, and 20 equiv of HOAc were used.

(2H, d, J = 8.9 Hz), 2.86 (6H, s), 3.76 (3H, s); HRESIMS m/z calcd for $C_9H_{14}NO$ $(M + H)^+$ 152.1075, found 152.1102.

General Methods for the Nitration of Natural Products. *Method A.* One equivalent of natural product was dissolved in TFA (3 mL) and stirred for 10 min at 0 °C. $NaNO_2$ (1.1 equiv) was added at once, and the reaction mixture was stirred at 0 °C for 1 h and then for 30 min at room temperature. The reaction mixture was poured into water and neutralized by ammonium hydroxide, producing a precipitate that was filtered and dried. If no precipitate was formed, the aqueous mixture was extracted with DCM (3 × 10 mL), and the organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum.

Method B. One equivalent of natural product was dissolved in glacial acetic acid (3 mL) and nitric acid (2 equiv) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C then for another 30 min at room temperature. The reaction mixture was poured into water

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and neutralized by ammonium hydroxide producing a precipitate that was filtered and dried. If no precipitate was formed, the aqueous mixture was extracted with DCM (3 × 10 mL), and the organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum.

Nitration of Manzamine F (2). Manzamine F (100 mg, 0.172 mmol) and $NaNO_2$ (13 mg, 0.188 mmol) were reacted by method A. After workup, the crude nitromanzamine F products were purified by silica column chromatography using *n*-hexane/acetone (9:1). Further purification was carried out on a Phenomenex Luna C8 250 × 10 mm, 5 μm Luna reverse-phase HPLC column using gradient CH_3CN (0.1% TFA)/water (0.1% TFA) with flow rate of 6 mL/min to give the pure nitro analogues.

Manzamine F (2). Data: ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d, J = 7.6 Hz), 7.88 (1H, d, J = 7.5 Hz), 7.63 (1H, d, J = 7.6 Hz), 7.61 (1H, d, J = 7.6 Hz), 7.12 (1H, d, J = 7.6 Hz), 6.66 (1H, s), 5.60 (2H, m), 3.70 (1H, s), 3.11 (m), 2.92 (m), 2.57 (m), 2.38 (m), 2.10 (m); ^{13}C NMR ($CDCl_3$) δ 211.0 (C), 143.7 (C), 143.1 (C), 141.3(C), 138.3 (CH), 137.7 (CH), 133.3 (C), 132.6 (C), 130.1 (C), 128.0 (CH), 123.4 (C), 121.1 (CH), 113.8 (CH), 112.2 (CH), 82.1 (CH), 69.6 (C), 63.5 (CH), 53.2 (CH_2), 49.8 (CH_2), 47.6 (C), 46.7 (CH_2), 46.1 (CH_2), 45.1 (CH_2), 42.5 (CH), 39.9 (CH_2), 38.9 (CH_2), 34.2 (CH_2), 32.7 (CH_2), 26.9 (CH_2), 25.7 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 21.5 (CH_2).

7-Nitromanzamine F (3). Data: (21 mg, 20%); $[\alpha]_D^{25}$ +11.5 (*c* 0.05, MeOH); yellow solid; (R_f = 0.6, 9:1 DCM/MeOH); IR 3534 (br), 3211, 3050, 2959, 2924, 2852, 1711, 1650, 1574, 1507, 1457, 1421, 1260, 1072, 1024, 911, 802, 729 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.55 (1H, d, J = 7.6 Hz), 8.38 (1H, d, J = 7.5 Hz), 8.18 (1H, d, J = 7.6 Hz), 7.91 (1H, d, J = 7.6 Hz), 6.71 (1H, s), 5.65 (2H, m), 3.70 (1H, s), 3.44 (m), 3.29 (m), 3.14 (m), 2.92 (m), 2.72 (m), 2.53 (m), 2.34 (m), 2.24 (m) 2.08 (s), 2.03 (m), 1.96 (m), 1.74 (m), 1.48 (m); ^{13}C NMR (acetone-d_6) δ 211.0 (C), 150.9 (C), 139.6 (C), 136.1 (CH), 135.2 (CH), 133.7 (CH), 132.6 (C), 131.4, 129.1 (CH), 122.3 (C), 121.7 (C), 121.6 (C), 119.6 (C), 115.4 (CH), 113.3 (CH), 79.8 (CH), 70.6 (C), 69.2 (CH_2), 58.8 (CH_2), 55.7 (CH), 51.1 (CH_2), 47.3 (CH_2), 45.6 (CH_2), 41.6 (CH_2), 36.6 (CH_2), 36.3 (CH_2), 34.7 (CH_2), 28.1 (CH_2), 25.1 (CH_2), 24.3 (CH_2), 22.9 (CH_2), 20.7 (CH_2); HRESIMS m/z calcd for $C_{36}H_{44}N_5O_5$ $(M + H)^+$ 626.3342, found 626.3335.

5-Nitromanzamine F (4). Data: (21 mg, 20%); $[\alpha]_D^{25}$ +12.1 (*c* 0.05, MeOH); pale orange solid; (R_f = 0.50, 9:1 DCM/MeOH); IR 3194 (br), 3090, 2964, 2930, 2854, 2802, 1710, 1671, 1649, 1560, 1456, 1417, 1335, 1202, 1194, 1073, 1026, 911, 820, 805, 729 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.70 (1H, d, J = 7.6 Hz), 8.53 (1H, d, J = 7.5 Hz), 8.12 (1H, d, J = 7.6 Hz), 7.12 (1H, d, J = 7.6 Hz), 6.99 (1H, s), 5.65 (2H, m), 3.70 (1H, s), 3.44 (m), 3.29 (m), 3.14 (m), 2.92 (m), 2.72 (m), 2.53 (m), 2.34 (m), 2.24 (m) 2.08 (s), 2.03 (m), 1.96 (m), 1.74 (m), 1.48 (m); ^{13}C NMR (acetone-d_6) δ 211.0 (C), 149.3 (C), 141.7 (C), 141.0 (C), 136.0 (CH), 135.1 (C), 132.5 (CH), 131.9 (CH), 129.4 (C), 122.5 (C), 121.7 (C), 118.0 (CH), 117.1 (CH), 115.2 (CH), 114.0 (CH), 79.0 (CH), 72.0 (CH_2), 67.5 (CH_2), 56.6 (CH_2), 56.3 (CH), 53.5(CH_2), 52.2 (CH_2), 49.3 (CH_2), 46.3(CH_2), 42.4 (CH), 36.8(CH_2), 36.6 (CH_2), 33.4 (CH_2), 30.6 (CH_2), 29.6 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 25.2 (CH_2), 22.1 (CH_2), 20.0 (CH_2); HRESIMS m/z calcd for $C_{36}H_{44}N_5O_5$ $(M + H)^+$ 626.3342, found 626.3335.

5,7-Dinitromanzamine F (5). Data: (46 mg, 43%); $[\alpha]_D^{25}$ +18.5 (*c* 0.1, MeOH); orange solid; (R_f = 0.4, 9:1 DCM/MeOH); IR 3239 (br), 3050, 2932, 2854, 2797, 1693, 1562, 1446, 1418, 1365, 1330, 1271, 1245, 1112, 1075, 823, 789 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 8.59 (1H, d, J = 7.6 Hz), 8.21 (1H, d, J = 7.5 Hz), 8.20 (1H, s), 6.52 (1H, s), 5.36 (2H, m), 3.70 (1H, s), 3.44 (m), 3.29 (m), 3.14 (m), 2.92 (m), 2.72 (m), 2.53 (m), 2.34 (m), 2.24 (m) 2.08 (s), 2.03 (m), 1.96 (m), 1.74 (m), 1.48 (m); ^{13}C NMR (acetone-d_6) δ 212.0 (C), 151.1 (C), 143.6 (C), 141.5 (C), 138.4 (CH), 137.7 (CH), 136.9 (C), 133.5 (C), 131.8 (CH), 130.2 (CH), 128.3 (C), 124.1 (C), 120.2 (C), 114.3 (CH), 109.3 (CH), 80.5 (CH), 70.1 (CH_2), 69.9 (CH_2), 57.1 (CH_2), 55.7 (CH_2), 53.9 (CH), 51.4 (CH_2), 46.8 (CH_2), 43.3 (CH), 39.7 (CH_2), 36.6 (CH_2), 36.4 (CH_2), 34.6 (CH_2), 32.7 (CH_2), 27.3 (CH_2), 25.2 (CH_2), 24.3 (CH_2), 22.1 (CH_2), 21.0 (CH_2); HRESIMS m/z calcd for $C_{36}H_{43}N_6O_7$ $(M + H)^+$ 671.3193, found 671.3207.

Nitration of Harmane (6). Harmane (100 mg, 0.440 mmol) and $NaNO_2$ (33.4 mg, 0.480 mmol) were reacted by method A. After workup, the crude nitro products of harmane were loaded onto a column packed with 15 g of silica gel. 8-Nitroharmane (**7**) was eluted first with 99:1 DCM/MeOH, followed by 6-nitroharmane (**8**) after the mobile polarity was increased with 95:5 DCM/MeOH.

8-Nitroharmane (7).[26] Data: (54 mg, 43%); yellow powder (mp 211−212 °C; lit. 209−210 °C); (R_f = 0.8, 9:1 DCM/MeOH); IR 3087, 3044, 2974, 2865, 2784, 1660, 1640, 1530,1491, 1339, 1288, 1202, 1184, 1131, 833 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.87 (s, brd), 8.44 (1H, d, J = 5.6 Hz), 8.40 (1H, d, J=8.0 Hz), 8.37 (1H, d, J = 8.0 Hz), 7.78 (1H, d, J = 5.6 Hz), 7.33 (1H, t, J = 8.0 Hz), 2.86 (s); ^{13}C NMR ($CDCl_3$) δ 143.3 (C), 140.6 (CH), 134.8 (C), 134.0 (C), 133.7 (C), 127.4 (CH), 127.6 (C), 126.4 (C), 124.2 (CH), 119.4 (CH), 112.6 (CH), 20.2 (CH_3); HRESIMS m/z calcd for $C_{12}H_{10}N_3O_2$ $(M + H)^+$ 228.0773, found 228.0770.

6-Nitroharmane (8).[26] Data: (56 mg, 45%); yellow powder (mp 297−299 °C; lit. 299−300 °C); (R_f = 0.7, 9:1 DCM/MeOH); IR 3305, 3086, 2869, 1673, 1640, 1531, 14942, 1434, 1338, 1201, 1138, 832 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.83 (1H, d, J = 2.4 Hz), 8.13 (1H, d, J = 2.4 Hz), 8.11 (1H, d, J=2.4 Hz), 8.08 (1H, d, J = 6.8 Hz), 7.96 (1H, d, J = 6.8 Hz), 7.38 (1H, d, J = 8.0 Hz), 2.87 (s); ^{13}C NMR ($CDCl_3$) δ 150.0 (C), 144.2 (C), 137.0 (C), 134.8 (CH), 129.6 (CH), 123.8 (CH), 119.7 (CH), 119.4 (CH), 117.0 (CH), 19.6 (CH_3); HRESIMS m/z calcd for $C_{12}H_{10}N_3O_2$ $(M + H)^+$ 228.0773, found 228.0770.

Nitration of β-Estradiol (9). β-Estradiol (100 mg, 0.36 mmol) was nitrated with method B. After workup, the crude nitro products were purified with silica column eluted with DCM/MeOH (95:5). The hydroxy group was oxidized under these conditions.

2-Nitroestrone (10).[27] Data: (19.8 mg, 17%); $[\alpha]_D^{25}$ +96.2 (*c* 0.1, DCM); yellow powder (mp 178−179 °C; lit. 178−180 °C); (R_f = 0.56, 100% DCM); IR 3078, 2928, 2857, 1736, 1631, 1525, 1479, 1433, 1374, 1310, 1263, 1053, 897, 734, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.99 (1H,s), 6.88 (1H,s), 2.97 (2H, m), 2.53 (1H, dd, J = 17.0, 8.3 Hz), 2.46 (1H, m), 2.31−1.97 (6H, m), 1.75−1.40 (8H, m), 0.91 (3H,s); ^{13}C NMR ($CDCl_3$) δ 220.1 (C), 153.0 (C), 148.9 (C), 133.2 (C), 131.7 (C), 121.7 (CH), 119.1 (CH), 50.5 (CH), 48.0 (C), 43.6 (CH), 37.8 (CH), 35.9 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 21.7 (CH_2), 13.9 (CH_3); HRESIMS m/z calcd for $C_{18}H_{22}NO_4$ $(M + H)^+$ 316.1549, found 316.1552.

2,4-Dinitroestrone (11).[27] Data: (64 mg, 55%); $[\alpha]_D^{25}$ +90.1 (*c* 0.1, DCM); yellow powder (mp 186−188 °C; lit. 185−188 °C); (R_f = 0.4, 100% DCM); IR 3350, 3008, 2987, 1734, 1631, 1532, 1345, 1308, 1259, 1061, 897 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.14 (1H,s), 2.88 (2H, m), 2.53 (1H, dd, J = 17.0, 8.3 Hz), 2.46 (1H, m), 2.31−1.97 (6H, m), 1.75−1.40 (8H, m), 0.91 (3H,s); ^{13}C NMR ($CDCl_3$) δ 220.1 (C), 144.8 (C), 141.7 (C), 139.2 (C), 133.6 (C), 132.1 (C), 122.7 (CH), 50.0 (CH), 47.7 (C), 43.5 (CH), 37.0 (CH), 35.7 (CH_2), 31.2 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 24.9 (CH_2), 24.8, 21.5 (CH_2), 13.7 (CH_3); HRESIMS m/z calcd for $C_{18}H_{21}N_2O_6$ $(M + H)^+$ 361.1399, found 361.1402.

Nitration of Quinine (12). Quinine (100 mg, 0.31 mmol) was nitrated by method B. After workup, the crude product was fractionated using solid phase extraction (SPE-C18), and the fraction eluted with H_2O/MeOH (80:20) was further purified on a Phenomenex Luna C8 250 × 22 mm, 5 μm Luna reverse-phase HPLC column using gradient CH_3CN (0.1% TFA)/water (0.1% TFA) with flow rate of 20 mL/min to give the pure nitro analogue.

Quinine (12). Data: ^{1}H NMR (methanol-d_4) δ 8.61 (1H, d, J = 8.0 Hz), 7.90 (1H, d, J = 8.0 Hz), 7.65 (1H, d, J = 4.0 Hz), 7.36 (1H, s), 7.33 (1H, s), 6.23 (1H, d, J = 4.0 Hz), 5.65 (1H, m), 5.56 (1H, m), 4.82 (1H, m), 3.92 (3H, s), 3.65 (1H, m), 3.07 (2H, m), 2.63 (2H, m), 2.26 (1H, m), 1.82 (2H, m), 1.70 (1H, m), 1.52 (1H, m), 1.36 (1H, m); ^{13}C NMR (methanol-d_4) δ 159.5 (C), 150.6 (C), 148.0 (CH), 144.7 (C), 142.7 (CH), 131.4 (CH), 131.3, 128.0 (C), 123.2 (CH), 120.0 (CH), 119.9, 114.9 (CH_2), 102.3 (CH), 72.2 (CH), 60.1 (CH), 57.7 (CH_2), 56.4 (CH_3), 44.1 (CH_2), 40.1 (CH), 29.2 (CH), 28.2 (CH_2), 21.6 (CH_2).

11-Nitro-10-hydroxyquinine (13). Data: (63 mg, 53%); $[\alpha]_D^{25}$ +133.0 (*c* 1, MeOH); yellow-orange powder mp 167−170 °C); (R_f =

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0.5, 100% DCM); IR 3368, 3007, 2971, 2839, 1672, 1621, 1556, 1510, 1473, 1242, 1229, 1133, 1027, 834, 799 cm^{-1}; ^1H NMR (methanol-d_4) δ 8.95 (1H, d, J = 4.4 Hz), 8.25 (1H, d, J = 7.7 Hz), 8.14 (1H, d, J = 10.9 Hz), 7.74 (1H, d, J = 10.0 Hz), 7.61 (1H, s), 6.23 (1H, m), 4.50 (2H, t, J = 9.8 Hz), 4.29 (1H, m), 4.04 (3H, s), 3.88 (1H, m), 3.49 (1H, m), 3.25 (1H, m), 2.33−1.50 (6H, m); ^{13}C NMR (methanol-d_4) δ 162.9 (C), 162.5 (C), 162.3 (C), 157.0 (C), 142.4 (CH), 135.8 (C), 129.0 (C), 128.8 (CH), 124.7 (CH), 121.3 (CH), 119.3 (CH), 102.8 (CH), 98.9 (C), 89.0 (C), 81.5 (C), 79.2 (CH_2), 68.5 (CH), 67.1 (CH), 61.0 (CH), 57.4 (CH), 53.6 (CH_2), 53.4 (CH_2), 45.5 (CH_2), 38.3 (C), 38.1 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 20.0 (CH_2); HRESIMS m/z calcd for $C_{20}H_{26}N_3O_5$ $(M + H)^+$ 388.1872, found 388.1859.

Nitration of Curcudiol (14). Curcudiol (100 mg, 0.423 mmol) and $NaNO_2$ (32 mg, 0.463 mmol) were reacted by method A. After workup, the crude products were purified by silica column eluted with *n*-hexane/acetone (85:15).

Curcudiol (14). Data: ^1H NMR ($CDCl_3$) δ 7.04 (1H, d, J = 8.0 Hz), 6.70 (1H, d, J = 8.0 Hz), 3.14 (1H,t, J = 7.2 Hz), 2.25 (3H, s), 1.64−1.20 1.20 (8H, m), 1.20−1.18 (9H, m); ^{13}C NMR ($CDCl_3$) δ 153.8 (C), 136.6 (C), 131.2 (C), 127.2 (CH), 121.7 (CH), 116.8 (CH), 72.2 (C), 43.9 (CH_2), 38.2 (CH_2), 31.6, 31.3 (CH), 29.9 (CH_3), 29.1 (CH_3), 22.6 (CH_2), 21.6 (CH_3).

4-Nitrocurcudiol (15). Data: (24 mg, 20%); $[\alpha]_D^{25}$ +8.3 (c 0.2, MeOH); yellow powder (mp 103 °C); (R_f = 0.6, 7:3 hexane/EtOAc); IR 3365, 3177, 3067, 2919, 2850, 2793, 2298, 1776, 1714, 1638, 1602, 1571, 1443, 1370, 1216, 1151, 1134, 1030, 997, 851, 814, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (1H, s), 6.31 (1H, s), 3.00 (1H,m), 2.17 (3H, s), 1.6−1.2 (12H, m), 1.20 (6H, s), 1.12 (3H, d, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 187.4 (C), 150.8 (C), 148.3 (C), 146.1 (C), 129.6 (C), 119.5 (CH), 89.4 (C), 40.4 (CH_2), 36.3 (CH_2), 31.5 (CH), 29.9 (CH_3), 25.7 (CH_3), 21.9 (CH_3), 19.9 (CH_2), 17.2 (CH_3); HRESIMS m/z calcd for $C_{15}H_{22}NO_4$ $(M - H)^-$ 280.1548, found 280.1541.

2,4-Dinitrocurcudiol (16). Data: (24 mg, 20%); $[\alpha]_D^{25}$ +10.1 (c 0.1, MeOH); yellow powder (mp 125 °C); (R_f = 0.3, 7:3 hexane/EtOAc); IR 3329, 3013, 2928, 2863, 1705, 1618, 1585, 1518, 1453, 1420, 1374, 1288, 1228, 1150, 1108, 944, 909, 859, 775, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (1H, s), 2.95 (1H,m), 2.12 (3H, s), 1.6−1.2 (12H, m), 1.16 (6H, s), 1.07 (3H, d, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 186.5 (C), 152.1 (C), 149.9 (C), 148.4 (C), 129.2 (C), 119.1 (C), 71.6 (C), 43.6 (CH_2), 36.6 (CH_2), 31.5 (CH), 29.1 (CH_3), 25.7 (CH_3), 21.9 (CH_2), 19.9 (CH_3), 17.0 (CH_3); HRESIMS m/z calcd for $C_{15}H_{21}N_2O_6$ $(M - H)^-$ 325.1399, found 325.1392.

Reductive *N*-Alkylation of Natural Products Scaffolds. *7-N-Ethylaminomanzamine F (17).* 7-Nitromanzamine F (**3,** 21 mg, 0.034 mmol) and acetaldehyde (2.0 μL, 0.040 mmol) were reacted by the general reductive alkylation method (0.2 mL of DCM was added as a cosolvent). The reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The crude product was purified on a Phenomenex Luna C8 250 × 10 mm, 5 μm Luna reverse-phase HPLC column using gradient CH_3CN (0.1% TFA)/water (0.1% TFA) with flow rate of 6 mL/min to give the pure *N*-ethylamino analogue. 7-*N*-Ethylaminomanzamine F: (19 mg, 91%); $[\alpha]_D^{25}$ +17.2 (c 0.1, MeOH); pale yellow powder; (R_f = 0.5, 9:1 DCM/MeOH); IR 3239, 3210, 3050, 2932, 2854, 2797, 1693, 1562, 1446, 1418, 1365, 1330, 1271, 1245, 1112, 1075, 823, 789 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (1H, d, J = 7.6 Hz), 7.71 (1H, d, J = 7.5 Hz), 7.35 (1H, d, J = 7.6 Hz), 7.03 (1H, d, J = 7.6 Hz), 6.50 (1H, s), 5.53 (2H, m), 3.50 (1H, s), 3.44 (m), 3.01 (m), 2.60 (m), 2.40 (m), 2.35 (m), 2.34 (m), 1.70 (m), 1.56 (m), 1.35 (3H, t, J = 10 Hz); ^{13}C NMR ($CDCl_3$) δ 211.0 (C), 142.2 (C), 140.6 (C), 137.1 (CH), 137.7 (CH), 135.9 (C), 132.2 (CH), 131.9 (CH), 130.3 (C), 129.4 (C), 126.5 (C), 121.4 (C), 115.1 (CH), 112.4 (CH), 111.9 (CH), 109.4 (CH), 81.5 (CH), 70.1 (CH_2), 63.2 (CH_2), 55.9 (CH), 55.0 (CH_2), 51.1 (CH_2), 44.8 (CH), 38.2 (CH_2), 35.8 (CH_2), 35.6 (CH_2), 34.7 (CH_2), 27.3 (CH_2), 26.0 (CH_2), 25.3 (CH_2), 23.5 (CH_2), 20.8 (CH_2), 14.1 (CH_3); HRESIMS m/z calcd for $C_{38}H_{50}N_5O_3$ $(M + H)^+$ 624.3913, found 624.3932.

10-N-Ethylamino-11-hydroxyquinine (18). 10-Nitro-11-hydroxyquinine (**13,** 50 mg, 0.129 mmol) and acetaldehyde (9.0 μL, 0.155 mmol) were reacted by the general reductive alkylation method. The reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The crude product was purified on a Phenomenex Luna C8 250 × 10 mm, 5 μm Luna reverse-phase HPLC column using gradient CH_3CN (0.1% TFA)/water (0.1% TFA) with flow rate of 6 mL/min to give the pure *N*-ethylamino analogue. 10-*N*-Ethylamino-11-hydroxyquinine: (23 mg, 47%); $[\alpha]_D^{25}$ +140.9 (c 1, DCM); brown powder (mp 156−158 °C); (R_f = 0.3, 100% DCM); IR 3345, 3239, 3156, 3007, 2932, 1620, 1591, 1552, 1509, 1469, 1448, 1430, 1371, 1332, 1324, 1228, 1174, 1136, 1082, 1025, 988, 953, 827, 760 cm^{-1}; ^1H NMR (methanol-d_4) δ 8.95 (1H, d, J = 4.4 Hz), 8.20 (1H, d, J = 7.7 Hz), 8.14 (1H, d, J = 10.9 Hz), 7.74 (1H, d, J = 10.0 Hz), 7.61 (1H, s), 6.27 (1H, m), 4.50 (2H, t, J = 9.8 Hz), 4.29 (1H, m), 4.06 (3H, s), 3.78 (1H, m), 3.49 (1H, m), 3.33 (1H, m), 2.99 (2H, q, J = 10.0 Hz), 2.33−1.50 (6H, m), 1.23 (3H, t, J = 10.0 Hz); ^{13}C NMR (methanol-d_4) δ 162.0 (C), 162.5 (C), 162.3 (C), 157.0 (C), 142.4 (CH), 135.8 (C), 128.9 (CH), 128.8 (C), 124.7 (CH), 121.3 (C), 119.3 (CH), 102.8 (CH), 98.9 (C), 89.0 (C), 81.5 (CH), 70.2 (CH_2), 68.5 (CH), 61.0 (CH), 57.4 (CH_2), 53.6 (CH_2), 53.4 (CH_2), 45.5 (CH_2), 44.0 (CH_2), 38.3 (CH_2), 38.1 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 20.0 (CH_2), 11.1 (CH_3); HRESIMS m/z calcd for $C_{22}H_{32}N_3O_3$ $(M + H)^+$ 386.2443, found 386.2424.

4-N-Ethylaminocurcudiol (19). 4-Nitrocurcudiol (**15**, 20 mg, 0.071 mmol) and acetaldehyde (5.0 μL, 0.085 mmol) were reacted by the general reductive alkylation method. The reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The crude product was purified on a Phenomenex Luna C8 250 × 10 mm, 5 μm Luna reverse-phase HPLC column using gradient CH_3CN (0.1% TFA)/water (0.1% TFA) with flow rate of 6 mL/min to give the pure *N*-ethylamino analogue. 4-*N*-Ethylaminocurcudiol (**19**): (13 mg, 64%); $[\alpha]_D^{25}$ +4.7 (c 0.05, DCM); pale-yellow oil; (R_f = 0.7, 7:3 hexane/EtOAc); IR 3402(brd), 3012, 2960, 2932, 2873, 2359, 2341, 1775, 1705, 1637, 1513, 1420, 1367, 1219, 1164, 1091, 1009, 987, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (1H, s), 6.39 (1H, s),3.14 (2H, q, J = Hz), 3.02 (1H,m), 2.13 (3H, s), 1.79−1.56 (12H, m), 1.47 (6H, s), 1.21 (3H, d, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 155.7 (C), 149.4 (C), 135.6 (C), 133.8 (C), 132.1 (C), 118.1 (CH), 89.4 (C), 43.1 (CH_2), 40.1 (CH_2), 36.8 (CH_2), 31.6 (CH), 29.5 (CH3), 25.4 (CH_3), 22.2 (CH_2), 21.5 (CH_3), 20.6 (CH_3), 16.6 (CH_3), 12.8 (CH_3); HRESIMS m/z calcd for $C_{17}H_{28}NO_2$ $(M - H)^-$ 278.2120, found 278.2131.

6-N-n-Butylaminoharmane (20). 6-Nitroharmane (**8**, 50 mg, 0.220 mmol) and butyraldehyde (24.0 μL, 0.264 mmol) were reacted by the general reductive alkylation method. The reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The crude product was purified on a Phenomenex Luna C8 250 × 10 mm, 5 μm Luna reverse-phase HPLC column using gradient CH_3CN (0.1% TFA)/water (0.1% TFA) with flow rate of 6 mL/min to give the pure *N*-ethylamino analogue. 6-*N*-*n*-Butylaminoharmane: (55 mg, 98%); brownish oil; (R_f = 0.6, 100% DCM); IR 3258, 3012, 2941, 2587, 2079, 1664, 1637, 1534, 1490, 1428, 1402, 1336.93, 1319, 1286, 1266, 1206, 1179, 1131, 1118, 1054, 990, 836, 820, 794, 751, 742, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (1H, d, J = 8.0 Hz), 7.74 (1H, d, J = 7.8 Hz), 7.29 (1H, d, J = 8.0 Hz), 7.25 (1H, d, J = 8.0 Hz), 6.90 (1H, d, J = 8.0), 3.19 (2H, t, J = 7.6 Hz), 2.75 (s), 2.43 (2H, t, J = 7.6 Hz), 1.66 (2H, q, J = 8.0 Hz), 1.43 (2H, p, J = 8.0 Hz), 1.00 (3H, t, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 143.2 (C), 141.7, 136.9 (CH), 135.4 (C), 134.5 (C), 128.4 (C), 122.9 (CH), 118.3 (CH), 113.2 (CH), 112.7 (C), 102.8 (CH), 45.1 (CH_2), 32.0 (CH_2), 20.6 (CH_2), 21.0 (CH_3), 14.2 (CH_3). HRESIMS m/z calcd for $C_{16}H_{20}N_3$ $(M + H)^+$ 254.1657, found 254.1649.

2,2-N,N-Dimethylaminoestrone (21). 2-Nitroestrone (**10**, 20 mg, 0.062 mmol) and formaldehyde (17 μL, 0.140 mmol) were reacted by the general reductive alkylation method (0.2 mL of DCM was added as a cosolvent). The reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The crude product was purified on a Phenomenex Luna C8 250 × 10 mm, 5 μm Luna reverse-phase HPLC column using gradient CH_3CN (0.1% TFA)/water (0.1% TFA) with flow rate of 6 mL/min to give the pure analogue. 2,2-*N*,*N*-

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Dimethylaminoestrone: (17 mg, 88%); $[\alpha]_D^{25}$ +148.8 (*c* 1, DCM); yellow powder (mp 162−165 °C); (R_f = 0.4, 100% DCM); IR 3362, 3016, 2928, 2862, 2784, 1737, 1581, 1502, 1453, 1260, 1081, 801 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07 (1H,s), 6.66 (1H,s), 2.61 (6H, s), 2.53 (1H, dd, J = 17.0, 8.3 Hz), 2.46 (1H, m), 2.31−1.97 (6H, m), 1.59−1.23 (8H, m), 0.89 (3H,s); ^{13}C NMR ($CDCl_3$) δ 221.0 (C), 149.3 (C), 138.3 (C), 134.1 (C), 131.1 (C), 117.4 (CH), 113.8 (CH), 50.4 (CH), 48.0 (C), 45.3 (CH_3), 44.2 (CH_3), 38.3 (CH), 35.8 (CH_2), 31.5 (CH), 29.6 (CH_2), 29.2 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 21.5 (CH_2), 13.8 (CH_3); HRESIMS *m*/*z* calcd for $C_{20}H_{28}NO_2$ $(M + H)^+$ 314.2120, found 314.2101.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of the compounds in Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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