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Synthesis of Withasomnines and Their Non-natural Analogues from Aldehydes and 4-Nitro-1-butanol in Three Steps

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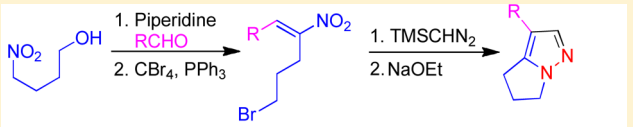
Supporting Information

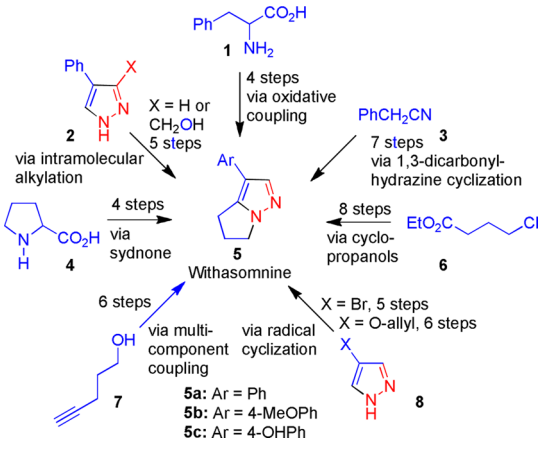
ABSTRACT: Total synthesis of all three pyrazole-based withasomnine alkaloids and selected examples of their non-natural analogs has been achieved from readily available aldehydes and 4-nitro-1-butanol in three steps. Since 4-nitro-1-butanol in turn is prepared in two steps via Michael addition of nitromethane to acrylate followed by borane reduction of the ester group and the key 1,3-dipolar cycloaddition step is carried out with commercially available $TMSCHN_2$, this approach is a very convenient and economical one.



6 Examples, including 3 natural products (withasomnines: R = Ph, 4-MeOPh, 4-HO-Ph), overall yields for 5 steps from ethyl acrylate and CH_3NO_2: 19-26%

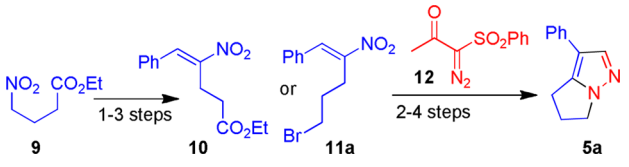
Withasomnine **5a**, isolated from the roots of the Indian medicinal plant *Withania somnifera,* belonging to the Solanaceae family,[1] has been used in traditional Ayurvedic medicine for the treatment of enlarged spleen, migraines, and many infections and as an aphrodisiac. The analgesic as well as CNS and circulatory system depressant properties of withasomnine **5a** and its analogues **5b,c**, isolated from similar plant sources, are described in more recent literature.[2] These biological properties of withasomnines **5a−c** motivated many research groups to pursue their synthesis. Most of the approaches targeted withasomnine **5a** and involved reactions such as intramolecular alkylation,[3] oxidative coupling,[4] sydnone cycloaddition,[5,6] hydrazine-1,3-dicarbonyl cyclization,[7] conversion of cyclopropanols to pyrazoles,[8] radical cyclization,[9] multicomponent coupling,[10] and Claisen rearrangement[11] as the key steps (Scheme 1). A diverse array of starting materials (e.g., **1**−**4** and **6**−**8**), and conditions were employed in those schemes which often required complex reagents and numerous synthetic operations.

Scheme 1



As part of our efforts to develop novel and efficient methodologies for the synthesis of functionalized and fused pyrazoles,[12,13] we recently reported a novel approach for the synthesis of withasomnine **5a** based on base-mediated 1,3-dipolar cycloaddition of nitroester **10** or bromonitroalkene **11a** with diazosulfone **12** (Scheme 2).[13] However, this required

Scheme 2



diazosulfone **12** to be prepared in two steps from commercially available chloroacetone, and the sulfonyl group had to be removed in the final step. Second, possible generalization of our methodology to synthesis of other natural and non-natural analogues of withasomnine **5a** was not investigated. In fact, there is only one report on the total synthesis of withasomnine analogs **5b,c** in the literature which is based on 1,3-dipolar cycloaddition of sydnones with acetylenes (Schemes 1, **4** to **5**).[6]

Against the above background, we report here the total synthesis of all three withasomnine natural products **5a−c** and their three other non-natural analogues through a general and highly efficient strategy from commercially available starting materials in five steps. Our retrosynthetic analysis suggested that withasomnine **5a** could be synthesized from pyrazole **13a** via intramolecular alkylation of **13a** in which X is a good leaving group (Scheme 3). Pyrazole **13a** in turn would be accessible via 1,3-dipolar cycloaddition of nitroalkene **11** with a diazoalkane **14**.[14] Nitroalkene **11** would arise from condensation of benzaldehyde **15a** with a suitable aliphatic nitro compound **16**.

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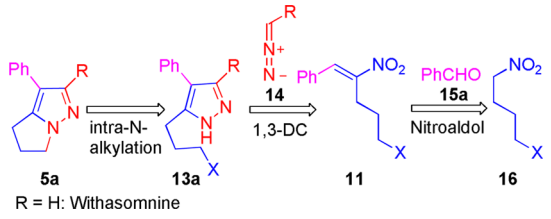
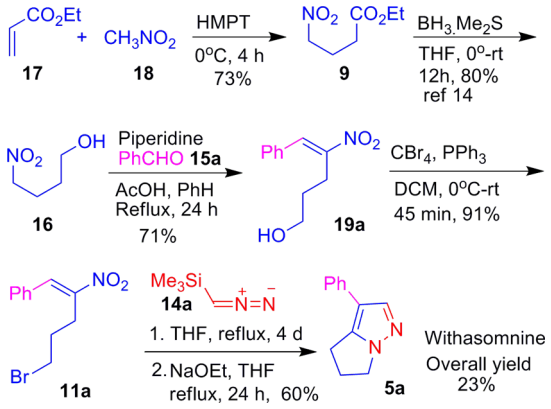
Scheme 3



In practice, we prepared nitroester **9** in 73% yield following a known procedure via HMPT-mediated Michael addition of nitromethane **18** to ethyl acrylate **17** (Scheme 4).[15] Reduction

Scheme 4

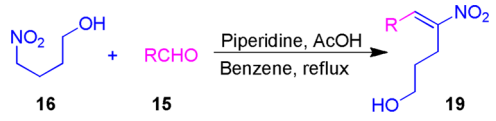


of nitroester **9** with $BH_3{\cdot}Me_2S$ in THF afforded nitrobutanol **16** in 80% yield.[15] Henry condensation of nitrobutanol **16** with benzaldehyde **15a** proceeded well to provide nitroalkenol **19a** in 71% yield. It appeared prudent to convert the OH group in **19a** to a better leaving group Br at this stage. Thus, **19a** was converted to bromonitroalkene **11a** in excellent yield (91%) under mild conditions using CBr_4 and Ph_3P. The key step in our synthetic sequence, i.e., 1,3-dipolar cycloaddition of bromide **11a**, was performed using commercially available $TMSCHN_2$ **14a**. Although this reaction took 4 days for completion, our attempts to carry out the intramolecular alkylation in the same pot by treating the intermediate pyrazole **13a** (R = H, X = Br) with NaOEt under reflux met with success, and we were pleased to isolate withasomnine **5a** in 60% yield (for two steps).

The good overall yield of the above sequence involving practically five steps starting from ethyl acrylate **17** and nitromethane **18** prompted us to pursue the synthesis of other natural and non-natural analogues of withasomnine **5a** and generalize our methodology. Thus, various commercially available aldehydes **15b–g** were condensed with nitrobutanol **16** to afford the nitroalkenols **19b–g** in good yield (64–74%, Table 1). Aldehydes with strong electron-donating groups **15b** and **15c** as well as those with weakly and strongly deactivating groups **15d** and **15g**, respectively, afforded corresponding nitroalkenols **19b**, **19c**, **19d**, and **19g** in good yield (64–74%, entries 1–3 and 6). Representative heteroaromatic aldehyde **15e** and aliphatic aldehyde **15f** also underwent smooth Henry condensation with nitrobutanol **16** to provide nitroalkenols **19e** and **19f**, respectively, in good yields (65–68%, entries 4 and 5).

The nitroalkenols **19b–g** were subsequently converted to bromides **11b–g** in excellent yield (80–94%) using CBr_4 and Ph_3P (Table 2). The yields were particularly high (92–93%) in

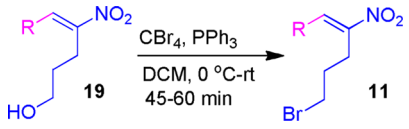
Table 1. Preparation of Nitroalkenols 19



entry	15, R	time (h)	19, % yield[a]
1	**15b**, 4-OMePh	34	**19b**, 73
2	**15c**, 4-OHPh	34	**19c**, 64
3	**15d**, 4-ClPh	36	**19d**, 74
4	**15e**, 2-furyl	36	**19e**, 68
5	**15f**, cyclohexyl	48	**19f**, 65
6	**15g**, 4-NO_2Ph	21	**19g**, 65

[a]Isolated yield after purification by silica gel column chromatography.

Table 2. Preparation of Bromonitroalkenes 11



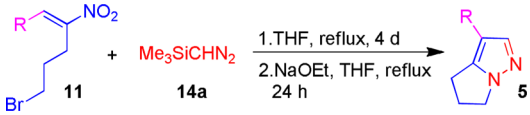
entry	19, R	11, % yield[a]
1	**19b**, 4-OMePh	**11b**, 93
2	**19c**, 4-OHPh	**11c**, 82
3	**19d**, 4-ClPh	**11d**, 92
4	**19e**, 2-furyl	**11e**, 94
5	**19f**, cyclohexyl	**11f**, 92
6	**19g**, 4-NO_2Ph	**11g**, 80

[a]Isolated yield after purification by silica gel column chromatography.

the conversion of nitroalkenols **19b,d–f** to bromonitroalkenes **11b,d–f**, respectively (entries 1, 3–5). Slightly lower yields (80–82%) were encountered in the preparation of bromides **11c** and **11g** from alcohols **19c** and **19g**, respectively.

Having prepared a variety of bromonitroalkenes **11b–g** in two steps from commercially available aldehydes **15b–g** and easily accessible nitrobutanol **16**, we proceeded to execute the one-pot 1,3-dipolar cycloaddition–elimination–intramolecular alkylation protocol to accomplish the synthesis of withasomnine analogues **5b–g** (Table 3). Thus, bromonitroalkenes **11b–g** were refluxed with $TMSCHN_2$ **14a** in THF for 4 days during which time the 1,3-dipolar cycloaddition and aromatization via elimination were complete. The reaction mixture was then refluxed with NaOEt in THF for 24 h for the cyclization via intramolecular alkylation to take place. We were gratified to

Table 3. Synthesis of Withasomnine Analogues 5



entry	11, R	5, % yield[a]	overall % yield for five steps[b]
1	**11b**, 4-OMePh	**5b**, 64	25
2	**11c**, 4-OHPh	**5c**, 60	18
3	**11d**, 4-ClPh	**5d**, 66	26
4	**11e**, 2-furyl	**5e**, 65	25
5	**11f**, cyclohexyl	**5f**, 55	19
6	**11g**, 4-NO_2Ph	**5g**, –[c]	

[a]Isolated yield after purification by silica gel column chromatography. [b]Starting from ethyl acrylate **17** and nitromethane **18**. [c]Complex mixture.

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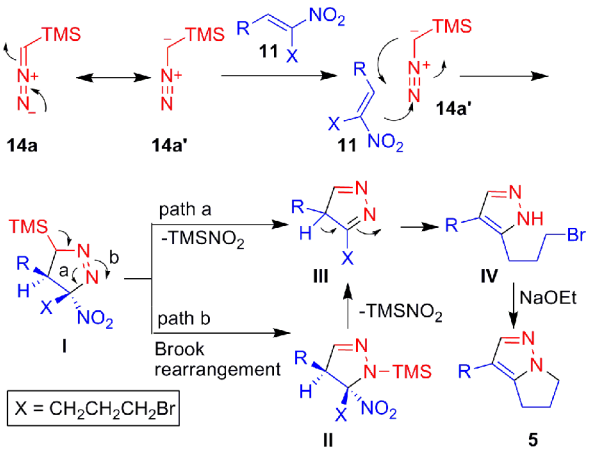
note the formation of withasomnine analogues **5b–f** in 55–66% yield (for two steps, entries 1–5). Unfortunately, bromonitroalkene **11g** afforded only a complex mixture (entry 6). In fact, the yields are in the range of 60–65% for bromonitroalkenes **11b–e** with a variety of R groups, viz., an aromatic ring with strongly electron-donating groups **11b** and **11c** (entries 1 and 2), weakly deactivating aromatic ring **11d** (entry 3), and a heteroaromatic ring **11e** (entry 4). A slightly lower yield (55%) was encountered only when R was aliphatic (cyclohexyl, entry 5).

The proposed mechanism involves regio- and presumably stereoselective 1,3-dipolar cycloaddition of $TMSCHN_2$ **14a** with bromonitroalkene **11** to form the initial cycloadduct **I** (Scheme 5). Elimination of $TMSNO_2$ directly (path a) or after

Scheme 5



a Brook rearrangement (path b) would provide intermediate **III**. Tautomerization of **III** gives **IV** which in the presence of NaOEt cyclizes to afford withasomnine **5**.

In conclusion, a simple, highly efficient, and general method for the synthesis of all three withasomnine alkaloids and their selected non-natural analogues has been developed for the first time. The key step in the synthesis is a 1,3-dipolar cycloaddition of α-bromopropyl nitroalkenes with commercially available $TMSCHN_2$. The bromonitroalkenes in turn are prepared via nitroaldol (Henry) condensation of commercially available aldehydes with 4-nitro-1-butanol. An overall yield of 18–26% for five steps was observed for the six examples reported here, making this approach a very attractive one.

EXPERIMENTAL SECTION

General Methods. The melting points recorded are uncorrected. The ^1H NMR spectra were recorded at 400 MHz, and the ^1H decoupled ^{13}C NMR spectra were recorded at 100 or 75 MHz with TMS as the internal standard. The coupling constants (J values) are given in Hz. The high-resolution mass spectra were recorded under ESI Q-TOF conditions. $TMSCHN_2$ was commercially available.

General Procedure for the Preparation of Nitroalkenols 19. To a stirred solution of nitrobutanol **16** (1.2 g, 10 mmol) and aldehyde (11 mmol) in benzene (80 mL) were added piperidine (1.71 g, 20.08 mmol) and acetic acid (6 mL). The reaction mixture was refluxed overnight under Dean–Stark conditions. After completion of the reaction (monitored by TLC), the mixture was diluted with water (10 mL), and the aqueous layer was extracted with EtOAc (5 × 20 mL) and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude residue was purified by silica gel column chromatography (60–120 mesh, 70/30 pet ether/ethyl acetate) to afford pure product.

(E)-4-Nitro-5-phenylpent-4-en-1-ol ***(19a)***:[13] yellow liquid; yield 71% (1.470 g); IR (neat, cm^{-1}) 3378 (m), 2934 (w), 1652 (w), 1518 (s), 1450 (w), 1325 (s), 1217 (w), 1063 (m), 761 (m); ^1H NMR (400 MHz, $CDCl_3$) 1.88–1.95 (m, 2H), 2.09 (br s, 1H), 2.97 (t, J = 7.6 Hz, 2H), 3.74 (t, J = 3.1 Hz, 2H), 7.43–7.47 (m, 5H), 8.08 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 30.8, 62.0, 129.2, 130.0, 130.3, 132.3, 134.2, 151.7. Consistent with literature data.[13]

(E)-5-(4-Methoxyphenyl)-4-nitropent-4-en-1-ol ***(19b)***: yellow solid; yield 73% (1.730 g); mp 75–76 °C; IR (KBr, cm^{-1}) 3324 (m), 3247 (m), 2942 (m), 2876 (w), 1640 (m), 1604 (s), 1518 (s), 1500 (m), 1440 (w), 1306 (vs), 1262 (vs), 1179 (s), 1061 (m), 1034 (m), 830 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (br s, 1H), 1.88–1.96 (m, 2H), 3.02 (t, J = 7.8 Hz, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 30.6, 55.5, 61.9, 114.7, 124.4, 132.2, 134.2, 149.4, 161.4; MS (ES+) m/z (rel intensity) 260 (MNa^+, 90), 238 (MH^+, 91), 192 (100); HRMS (ES+) calcd for $C_{12}H_{16}NO_4$ (MH^+) 238.1079, found 238.1070.

(E)-4-(5-Hydroxy-2-nitropent-1-enyl)phenol ***(19c)***: yellow solid; yield 64% (1.427 g); mp 124–125 °C; IR (KBr, cm^{-1}) 3434 (br m), 2929 (m), 1603 (s), 1519 (m), 1445 (w), 1375 (w), 1314 (w), 1279 (m), 1174 (m), 1022 (m); ^1H NMR (400 MHz, CD_3OD) δ 1.79–1.86 (m, 2H), 2.93–2.98 (m, 2H), 3.66 (t, J = 6.2 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.99 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 23.8, 30.3, 61.0, 115.7, 123.1, 132.3, 133.7, 148.8, 159.8; MS (ES+) m/z (rel intensity) 246 (MNa^+, 95), 224 (MH^+, 48), 214 (35), 206 (50), 178 (100); HRMS (ES+) calcd for $C_{11}H_{14}NO_4$ (MH^+) 224.0923, found 224.0931.

(E)-5-(4-Chlorophenyl)-4-nitropent-4-en-1-ol ***(19d)***: light yellow solid; yield 74% (1.783 g); mp 78–79 °C; IR (KBr, cm^{-1}) 3550 (m), 3251 (br vs), 2939 (m), 2873 (m), 1648 (s), 1590 (m), 1506 (s), 1489 (s), 1451 (m), 1316 (s), 1278 (m), 1089 (s), 1066 (s), 1023 (m), 840 (m), 817 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.86–1.94 (m, 2H), 2.95–2.99 (m, 2H), 3.75 (t, J = 5.8 Hz, 2H), 7.41–7.46 (m, 4H), 8.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 30.5, 61.7, 129.4, 130.6, 131.2, 132.8, 136.3, 151.9; MS (ES+) m/z (rel intensity) 244 ([MH +2]$^+$, 20), 242 (MH^+, 60), 226 (33), 224 (100); HRMS (ES+) calcd for $C_{11}H_{13}NO_3Cl$ (MH^+) 242.0584, found 242.0580.

(E)-5-(Furan-2-yl)-4-nitropent-4-en-1-ol ***(19e)***: yellow liquid; yield 68% (1.340 g); IR (neat, cm^{-1}) 3432 (br m), 2945 (m), 1647 (m), 1510 (s), 1472 (m), 1315 (vs), 1065 (m), 1024 (s), 757 (s); ^1H NMR (400 MHz, $CDCl_3$) 1.79 (br s, 1H), 1.85–1.94 (m, 2H), 3.14–3.18 (td, J = 7.5, 1.0 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 6.59 (dd, J = 3.5, 1.8 Hz, 1H), 6.91 (d, J = 3.5 Hz, 1H), 7.65–7.66 (m, 1H), 7.87 (d, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 30.8, 61.9, 113.1, 119.8, 121.0, 146.6, 147.7, 148.0; MS (ES+, Ar) m/z (rel intensity) 220 (MNa^+, 21), 198 (MH^+, 42), 180 (100), 152 (25); HRMS (ES+, Ar) calcd for $C_9H_{12}NO_4$ (MH^+) 198.0766, found 198.0766.

(E)-5-Cyclohexyl-4-nitropent-4-en-1-ol ***(19f)***: yellow liquid; yield 65% (1.385 g); IR (neat, cm^{-1}) 3417 (br s), 2932 (vs), 2855 (m), 1551 (m), 1519 (vs), 1449 (m), 1333 (s), 1267 (m), 1061 (m), 738 (vs); ^1H NMR (400 MHz, $CDCl_3$) 1.16–1.42 (m, 6H), 1.66–1.95 (m, 6H), 2.22–2.37 (m, 2H), 2.61–2.73 (m, 2H), 3.67 (t, J = 6.1 Hz, 2H), 6.97 (d, J = 10.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 25.2, 25.6, 31.1, 32.0, 37.5, 61.6, 141.8, 149.9; MS (ES+, Ar) m/z (rel intensity) 215 ([MH + 1]$^+$, 14), 214 (MH^+, 100), 213 (5), 212 (23); HRMS (ES+, Ar) calcd for $C_{11}H_{20}NO_3$ (MH^+) 214.1443, found 214.1434.

(E)-4-Nitro-5-(4-nitrophenyl)pent-4-en-1-ol ***(19g)***: light yellow solid; yield 65% (1.638 g); mp 94–95 °C; IR (KBr, cm^{-1}) 3557 (m), 3308 (m), 2934 (w), 2876 (w), 1651 (w), 1597 (w), 1516 (vs), 1492 (m), 1449 (w), 1344 (s), 1305 (m), 1061 (m); ^1H NMR (400 MHz, $CDCl_3$) 1.84–1.93 (m, 2H), 2.96 (t, J = 7.8 Hz, 2H), 3.73 (t, J = 5.8 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 8.04 (s, 1H), 8.29 (d, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 30.6, 61.7, 124.3, 130.6, 131.3, 138.8, 148.3, 154.3; MS (ES+, Ar) m/z (rel intensity) 253 (MH^+, 55), 251 (70), 249 (100); HRMS (ES+, Ar) calcd for $C_{11}H_{13}N_2O_5$ (MH^+) 253.0824, found 253.0834.

General Procedure for the Preparation of Bromides 11. To a stirred solution of alcohol **19** (2 mmol) and CBr_4 (1.658 g, 5 mmol) in

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CH_2Cl_2 (20 mL) was added PPh_3 (1.310 g, 5 mmol) solution in CH_2Cl_2 (5 mL) at 0 °C. Then the reaction mixture was stirred until complete consumption of starting material (~45 min). The solvent was evaporated and the crude residue was purified by silica gel column chromatography (60−120 mesh, 95/5 petroleum ether/ethyl acetate) to get pure bromides **11**.

*(E)-(5-Bromo-2-nitropent-1-enyl)benzene (**11a**):*[13] yellow liquid; yield 91% (491 mg); IR (neat, cm^{-1}) 3060 (w), 2926 (m), 2852 (w), 1651 (m), 1521 (vs), 1449 (m), 1325 (vs), 1255 (m), 1216 (m), 700 (m); ^1H NMR (400 MHz, $CDCl_3$) 2.18−2.25 (m, 2H), 3.01−3.05 (m, 2H), 3.50 (t, J = 6.1 Hz, 2H), 7.45−7.48 (m, 5H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 30.7, 33.0, 129.3, 130.0, 130.5, 132.0, 134.9, 150.5. Consistent with literature data.[13]

*(E)-1-(5-Bromo-2-nitropent-1-enyl)-4-methoxybenzene (**11b**):* yellow solid; yield 93% (558 mg); mp 67−68 °C; IR (KBr, cm^{-1}) 2969 (m), 2940 (m), 2840 (w), 1643 (w), 1605 (s), 1519 (m), 1501 (vs), 1446 (m), 1430 (m), 1311 (vs), 1265 (m), 1251 (m), 1181 (m), 1027 (s), 838 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 2.18−2.27 (m, 2H), 3.03−3.07 (m, 2H), 3.54 (t, J = 6.2 Hz, 2H), 3.86 (s, 3H), 6.98 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 30.5, 33.3, 55.6, 114.8, 124.1, 132.3, 134.9, 148.2, 161.6; MS (ES+) m/z (rel intensity) 302 ([MH + 2]$^+$, 100), 300 (MH$^+$, 100); HRMS (ES+) calcd for $C_{12}H_{15}NO_3Br$ (MH$^+$) 300.0235, found 300.0240.

*(E)-4-(5-Bromo-2-nitropent-1-enyl)phenol (**11c**):* light yellow solid; yield 82% (469 mg); mp 104−105 °C; IR (KBr, cm^{-1}) 3391 (br m), 1640 (w), 1605 (vs), 1585 (m), 1518 (s), 1504 (s), 1446 (m), 1380 (w), 1317 (m), 1279 (m), 1218 (m), 1174 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 2.18−2.25 (m, 2H), 3.03−3.08 (m, 2H), 3.53 (t, J = 6.2 Hz, 2H), 6.17 (br s, 1H), 6.95 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 30.5, 33.3, 116.5, 124.2, 132.6, 135.3, 148.2, 158.2; MS (ES+) m/z (rel intensity) 288 ([MH + 2]$^+$, 23), 286 (MH$^+$, 22), 174 (35), 123 (100); HRMS (ES+) calcd for $C_{11}H_{13}NO_3Br$ (MH$^+$) 286.0079, found 286.0090.

*(E)-1-(5-Bromo-2-nitropent-1-enyl)-4-chlorobenzene (**11d**):* light yellow solid; yield 92% (560 mg); mp 74−75 °C; IR (KBr, cm^{-1}) 2924 (w), 1644 (m), 1590 (m), 1514 (vs), 1492 (s), 1450 (m), 1314 (vs), 1092 (m), 828 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.18−2.24 (m, 2H), 3.00−3.04 (m, 2H), 3.51 (t, J = 6.2 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 30.6, 33.0, 129.6, 130.4, 131.2, 133.6, 136.7, 150.9; MS (ES+) m/z (rel intensity) 226 ([M + 2]$^+$, 33), 224 (100, M$^+$), 179 (20), 177 (45); HRMS (ES+) calcd for $C_{11}H_{11}NO_2Cl$ (M$^+$) 224.0478, found 224.0481.

*(E)-2-(5-Bromo-2-nitropent-1-enyl)furan (**11e**):* yellow liquid; yield 94% (488 mg); IR (neat, cm^{-1}) 2929 (m), 2857 (w), 1648 (s), 1513 (m), 1310 (m), 750 (vs); ^1H NMR (400 MHz, $CDCl_3$) 2.15−2.22 (m, 2H), 3.19−3.52 (m, 2H), 4.44 (t, J = 6.8 Hz, 2H), 6.60 (dd, J = 3.5, 1.8 Hz, 1H), 6.91 (d, J = 3.5 Hz, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 31.0, 32.9, 113.2, 120.3, 121.4, 146.8, 146.9, 147.5; MS (ES+, Ar) m/z (rel intensity) 262 ([M + 2]H$^+$, 45), 260 (MH$^+$, 45), 241 (63), 167 (25), 149 (63), 97 (100); HRMS (ES+, Ar) calcd for $C_9H_{11}NO_3Br$ (MH$^+$) 259.9922, found 259.9925.

*(E)-(5-Bromo-2-nitropent-1-enyl)cyclohexane (**11f**):* yellow liquid; yield 92% (508 mg); IR (neat, cm^{-1}) 3055 (m), 2933 (m), 2987 (w), 2855 (w), 1732 (w), 1552 (w), 1520 (m), 1436 (w), 1422 (w), 1335 (w), 1264 (s), 735 (vs); ^1H NMR (400 MHz, $CDCl_3$) 1.18−1.40 (m, 5H), 1.63−1.81 (m, 5H), 2.04−2.12 (m, 2H), 2.33−2.43 (m, 1H), 2.76−2.80 (m, 2H), 3.43 (t, J = 6.1 Hz, 2H), 7.02 (d, J = 10.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.3, 25.6, 31.0, 32.1, 32.9, 37.7, 142.7, 148.7; MS (ES+, Ar) m/z (rel intensity) 279 ([MH + 3]$^+$, 76), 278 ([MH + 2]$^+$, 100), 276 (14), 262 (23); HRMS (ES+, Ar) calcd for $C_{11}H_{19}NO_2Br$ (MH$^+$) 276.0599, found 276.0600.

*(E)-1-(5-Bromo-2-nitropent-1-enyl)-4-nitrobenzene (**11g**):* light yellow solid; yield 80% (504 mg); mp 85−86 °C; IR (KBr, cm^{-1}) 3122 (w), 2930 (w), 1604 (m), 1539 (s), 1523 (vs), 1347 (vs), 1331 (vs), 1316 (s), 1253 (m), 1046 (w), 929 (w), 839 (w); ^1H NMR (400 MHz, $CDCl_3$) 2.17−2.24 (m, 2H), 3.99−3.03 (m, 2H), 3.49 (t, J = 6.0 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 8.10 (s, 1H), 8.31 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 30.6, 32.8, 124.3, 130.5, 132.2, 138.4, 148.4, 153.0; MS (ES+, Ar) m/z (rel intensity) 235 ([M − Br]H$^+$, 100), 205 (30), 158 (25); HRMS (ES+, Ar) calcd for $C_{11}H_{11}N_2O_4$ ([M − Br]H$^+$) 235.0719, found 235.0712.

General Procedure for the Conversion Bromide 11 to Withasomnine and Its Analogues 5. To a stirred solution of bromide **11** (0.5 mmol) in dry THF (20 mL) was added a 2.0 M solution of trimethylsilyldiazomethane **14a** in hexane (0.5 mL, 1 mmol), and the reaction mixture was refluxed for 2 days. On the third and fourth day, an additional quantity of trimethylsilyldiazomethane **14a** (0.2 mL, 0.4 mmol) was added and reflux continued until complete consumption of **11** (~4 d). NaOEt (272 mg, 4 mmol) was then added, and the reaction mixture was refluxed for another 12 h. The mixture was then concentrated in vacuo, and the crude residue was directly subjected to silica gel column chromatography (60−120 mesh, 70/30 ethyl acetate/petroleum ether) to afford pure withasomnine **5**.

*3-Phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (**5a**):*.[1−11,13] white solid; yield 60% (56 mg); mp 115−116 °C (lit.[6] mp 114−116 °C); IR (KBr, cm^{-1}) 2985 (m), 2912 (m), 1604 (w), 1462 (w), 1411 (s), 1296 (m), 1160 (m), 1075 (m), 862 (m), 695 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 2.61−2.69 (quintet, J = 7.3 Hz, 2H), 3.06 (t, J = 7.3 Hz, 2H), 4.15 (t, J = 7.3 Hz, 2H), 7.16−7.21 (m, 1H), 7.33−7.37 (m, 2H), 7.43−7.46 (m, 2H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.5, 47.6, 115.3, 125.1, 125.7, 128.9, 133.5, 140.9, 142.7. Consistent with literature data.[6]

*3-(4-Methoxyphenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (**5b**):*[6] yellow solid; yield 64% (69 mg); mp 124−126 °C (lit.[6] mp 123−125 °C); IR (KBr, cm^{-1}) 2928 (vs), 2857 (m), 1665 (w), 1564 (w), 1503 (m), 1460 (w), 1257 (m), 1103 (m), 1031 (s), 830 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 2.62 (quint, J = 7.5 Hz, 2H), 3.00 (t, J = 7.5 Hz, 2H), 3.80 (s, 3H), 4.12 (t, J = 7.5 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.5, 47.6, 55.3, 114.3, 115.0, 126.1, 126.2, 140.5, 142.0, 157.7. Consistent with literature data.[6]

*4-(5,6-Dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)phenol (**5c**):*[6] off-white solid; yield 60% (60 mg); mp 230−231 °C (lit.[6] mp 232−234 °C); IR (KBr, cm^{-1}) 3507 (vs), 2951 (m), 2925 (s), 2854 (m), 1656 (vs), 1462 (w), 1267 (m), 764 (m). ^1H NMR (400 MHz, DMSO-d_6) 2.56 (quint, J = 7.2 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 4.03 (t, J = 7.2 Hz, 2H), 4.06 (br s, 1H), 6.73 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.69 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.2, 26.1, 47.0, 114.5, 115.6, 124.2, 125.9, 139.6, 141.4, 155.3; ^1H NMR (400 MHz, $CDCl_3$/CD_3OD, 1:1) δ 2.67 (quint, J = 7.3 Hz, 2H), 3.03 (t, J = 7.3 Hz, 2H), 3.34 (br s, 1H), 4.10 (t, J = 7.3 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD, 1:1) δ 22.9, 25.7, 46.7, 115.0, 115.1, 124.1, 125.7, 139.3, 141.9, 154.8. Consistent with literature data.[6]

*3-(4-Chlorophenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (**5d**):* light yellow solid; yield 66% (72 mg); mp 105−106 °C; IR (KBr, cm^{-1}) 2951 (m), 2923 (s), 2852 (m), 1556 (w), 1490 (w), 1395 (w), 1163 (w), 1093 (m), 825 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 (quint, J = 7.4 Hz, 2H), 3.02 (t, J = 7.4 Hz, 2H), 4.14 (t, J = 7.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.5, 47.7, 114.3, 126.2, 129.0, 131.2, 132.0, 140.8, 142.8; MS (ES+) m/z (rel intensity) 221 ([MH + 2]$^+$, 34), 219 (MH$^+$, 100); HRMS (ES+) calcd for $C_{12}H_{12}N_2Cl$ (MH$^+$) 219.0689, found 219.0679.

*3-(Furan-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (**5e**):* yellow liquid; yield 65% (57 mg); IR (neat, cm^{-1}) 2956 (m), 2928 (m), 1640 (vs), 1546 (w), 1438 (m), 1421 (m), 1338 (m), 1267 (w), 1157 (m), 1019 (m), 736 (s); ^1H NMR (400 MHz, $CDCl_3$) 2.47 (quintet, J = 7.3 Hz, 2H), 3.02 (t, J = 7.3 Hz, 2H), 4.14 (t, J = 7.3 Hz, 2H), 6.20 (d, J = 3.2 Hz, 1H), 6.39−6.40 (m, 1H), 7.34−7.35 (m, 1H), 7.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 26.4, 47.9, 102.7, 107.6, 111.2, 140.1, 140.5, 142.5, 149.0; MS (ES+, Ar) m/z (rel intensity) 176 ([MH + 1]$^+$, 15), 175 (MH$^+$, 100); HRMS (ES+, Ar) calcd for $C_{10}H_{11}N_2O$ (MH$^+$) 175.0871, found 175.0868.

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*3-Cyclohexyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (**5f**):* yellow liquid; yield 55% (52 mg); IR (neat, cm^{-1}) 2923 (vs), 2853 (s), 1720 (m), 1554 (w), 1448 (m), 1415 (m), 1338 (w); ^1H NMR (400 MHz, $CDCl_3$) 1.14−1.38 (m, 5H), 1.66−1.90 (m, 5H), 2.38−2.44 (m, 1H), 2.56 (quint, J = 7.3 Hz, 2H), 2.83 (t, J = 7.3 Hz, 2H), 4.05 (t, J = 7.3 Hz, 2H), 7.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 26.3, 26.5, 26.7, 34.1, 34.5, 47.4, 120.2, 141.6, 142.1; MS (ES+, Ar) m/z (rel intensity) 191 (MH^+, 100); HRMS (ES+, Ar) calcd for $C_{12}H_{19}N_2$ (MH^+) 191.1548, found 191.1543.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all the new compounds. 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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