A divergent strategy to the withasomnines†

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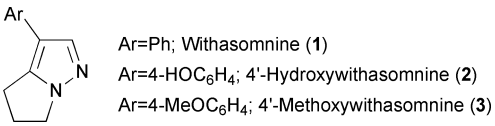
A concise synthesis of three members of the withasomnine family of natural products is reported. The synthesis features a regioselective sydnone–alkynylboronate cycloaddition followed by Suzuki cross coupling and silyl group removal, and marks the first divergent approach to this family of pyrazole based natural products.

Introduction

The withasomnine alkaloids are a rare class of pyrazole based natural products isolated from the roots of *Withania somnifer* (*Solanaceae*),[1] *Newbouldia laevis*,[2] the shrub *Elytraria acaulis*,[3] and recently from the stem bark of *Discopodium penninervium*.[4] Withasomnine **1** displays both CNS and circulatory system depressant properties as well as being a mild analgesic.[2]



Owing to these attributes, these natural products are ideal candidates for the demonstration of new pyrazole based synthetic methodologies. Indeed, several syntheses of the parent molecule (**1**) have been reported. Some examples include, tin mediated radical cyclisations of selenium containing substrates,[5] conversion of functionalised cyclopropanols to pyrazoles,[6] intramolecular alkylation,[7] oxidative coupling of diamines[8] and cycloadditions of sydnones with alkynes.[9] In general, all of the approaches thus far reported are not amenable for efficient and rapid divergency to all three of the natural withasomnine congeners (**1**, **2** and **3**). We envisaged that such a strategy could serve as a basis for the discovery of more potent unnatural analogues. Herein we report the realisation of this goal as demonstrated by a short, regioselective and divergent approach to withasomnine **1**, 4′ hydroxywithasomnine **2** and 4′ methoxywithasomnine **3**.

Results and discussion

Within the last decade we have developed a series of alkynylboronate cycloadditions[10] to access a range of (hetero)aromatic boronic esters. Specifically relevant to this case is the cycloaddition of alkynylboronates with sydnones for the synthesis of functionalisable pyrazoles.[10i–k] With this methodology in mind, retrosynthetic analysis of the withasomnines hinged upon the regioselective cycloaddition of the known proline derived sydnone **4** with alkyne **5** (Fig. 1).[11] Previous studies on the cycloaddition

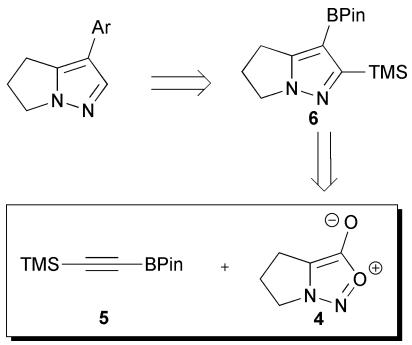


Fig. 1 Divergent synthetic strategy to the withasomnines.

of this particular mesoionic heterocycle have shown that the trimethylsilyl substituted alkynylboronate **5** would deliver the desired regiochemistry.[10k] Moreover, the employment of this alkyne would append a removable group at the 3-position of the pyrazole product.

In general, we have found that *C*-4 substituted sydnone substrates typically require more forcing conditions for cycloaddition with alkynylboronates (typically 48 hours at 180 °C).[10k] However, Nikitenko *et al*. have demonstrated that sydnone **4** is thermally unstable, showing a large exotherm at 180 °C, presumed to be due to the loss of carbon dioxide.[11] Indeed, our previously reported studies on this particular regioselective cycloaddition support this data, yielding only 21% of decarboxylated cycloadduct (**6**) after 72 hours at 160 °C.[10k] Accordingly, preliminary investigations were geared towards promoting cycloaddition over degradation of the sydnone; our results are shown in Table 1. Increasing the reaction temperature to 210 °C (Table 1, entry 4) gave only trace amounts of product and confirmed our suspicions of the thermal instability of sydnone **4**. Changing the solvent to *ortho*-dichlorobenzene (*o*-DCB) and reducing the reaction temperature to 180 °C (Table 1, entry 5) demonstrated that a 19% yield of the cycloadduct was attainable within a quarter of the reaction time. Interestingly, analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed that the alkynylboronate had undergone degradation. With this in mind, addition of a further 2 equivalents of alkyne and further heating for another 24 hours gave the product in greatly increased yield (Table 1, entry 6). Finally, it was discovered that starting the reaction with 4 equivalents of alkynylboronate and heating for 24 hours at 180 °C delivers the desired pyrazole boronic ester in 66% yield as a single regioisomer (Table 1, entry 7).[12]

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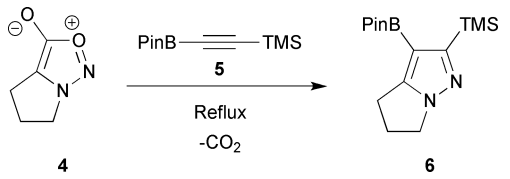
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **1–3**, **6–9**; ^{1}H spectrum of pyrazole isolates from cycloaddition of sydnone **4** and alkyne **10**. See DOI: 10.1039/b910632d

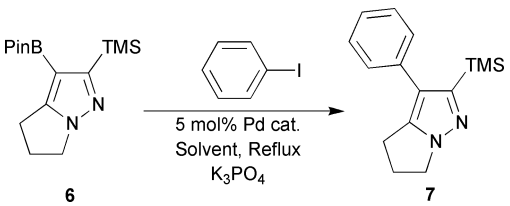
Table 1 Optimisation of the cycloaddition reaction



Entry	Solvent[a]	Equiv. **5**	Time (h)	Yield (%)
1	Xylenes (140)	2	64	9
2	Mesitylene (160)	2	48	14
3	Mesitylene (160)	2	72	21
4	Nitrobenzene (210)	2	18	Trace
5	*o*-Dichlorobenzene (180)	2	18	19
6	*o*-Dichlorobenzene (180)	4[b]	42[b]	52
7	*o-Dichlorobenzene (180)*	*4*	*24*	*66*

[a] Reaction temperature (°C) in parentheses. [b] Reaction started with 2 equiv. of **5**, with a further 2 equiv. added after 18 h.

Table 2 Optimisation of the coupling reaction



Entry	Pd cat.	Solvent	Time (hrs)	Yield (%)
1	$Pd(dppf)Cl_2$	1,4-dioxane[a]	20	0
2	$Pd(dppf)Cl_2$	1,4-dioxane	24	Trace
3	Pd_2dba_3, $^tBu_3P{\cdot}HBF_4$	MeCN	72	81
4	$PdCl_2(PPh_3)_2$	DME/H_2O (1:1)	18	78

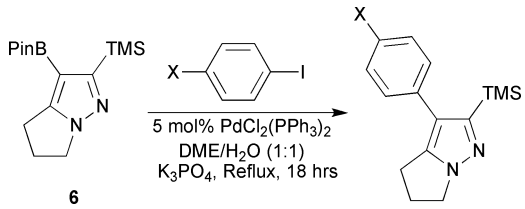
[a] Reaction conducted at 85 °C.

With the required boronic ester in hand, the Suzuki–Miyaura cross coupling reaction was assessed. Preliminary studies were conducted towards withasomnine **1**, by employing iodobenzene as the coupling partner.

Attempts to make use of some previously successful conditions for the coupling of pyrazolyl-4-boronic esters failed to yield any biaryl compound **7** (Table 2, entry 1).[10i] Increasing the reaction temperature to the solvent boiling point appeared to deliver minimal amounts of the product (Table 2, entry 2). Switching to an alternative set of catalyst conditions, Pd_2dba_3, $^tBu_3P{\cdot}HBF_4$ developed by Fu and Netherton[13] was found to furnish 3-trimethylsilylwithasomnine **7** in 81% yield. Disappointingly however, this reaction required 72 hours for complete consumption of the boronic ester (Table 2, entry 3). In order to circumvent this prolonged reaction time we opted to assess alternative conditions. Pleasingly, switching to a DME/H_2O solvent system allowed us to generate the product in 78% yield using a relatively simple Pd(II) pre-catalyst (Table 2, entry 4).

Using these optimal conditions, the palladium mediated couplings towards the other natural analogues were studied. Within 18 hours both the *para*-iodophenol (65%) and the *para*-iodoanisole (74%) had successfully coupled in good yield (Table 3, entries 2 and 3). Moreover, these reactions could also be conducted in a microwave reactor and were complete within 1 hour.

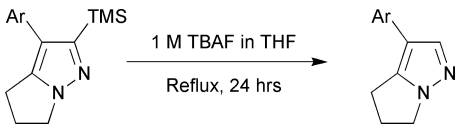
Table 3 Couplings towards the other natural product precursors



Entry	X	Yield (%)[a]
1	H (**7**)	78 (76)
2	OH (**8**)	65 (50)
3	OMe (**9**)	74 (54)

[a] Numbers in parentheses represent yields when reaction conducted in a microwave reactor at 130 °C for 1 h

Table 4 Desilylation to the withasomnines



Entry	Ar	Yield (%)
1	Ph (**1**)	70
2	4-HO-Ph (**2**)	55
3	4-MeO-Ph (**3**)	83

Finally we turned our attention to the desilylation step. Interestingly, previous studies from our laboratory have found the pyrazolyl-3-trimethylsilyl group to be surprisingly resistant to removal. For example, K_2CO_3 in MeOH, 1M $HCl_{(aq)}$ in refluxing ether and trifluoroacetic acid in DCM (1:1) all failed to produce even a trace of desilylated pyrazole. Pleasingly however, switching to TBAF and heating the reaction mixture for 24 hours at reflux in THF facilitated the required desilylation, furnishing the three natural withasomine congeners in good yields (Table 4).

Having confirmed that the alkynylboronate cycloaddition approach could be exploited in the synthesis of the withasomnines, we felt that it was important to compare this approach with the potentially simpler aryl-substituted alkyne cycloaddition reactions. In this context, Ranganathan and Bamezai have previously reported the synthesis of withasomnine through a cycloaddition of phenylacetylene and the proline derived sydnone **4**.[9] Unfortunately, this cycloaddition delivers the reverse isomer as the major product (approximately 3:1 in favour of the 3-phenyl-4*H*-pyrazole analogue, **12**) giving the natural product in just 18% yield. Employing our optimal cycloaddition conditions we were able to verify that indeed iso-withasomnine **12** is obtained as the major product from this cycloaddition. Nonetheless, it could be argued that phenyl trimethylsilyl acetylene **10** could potentially offer improved regiocontrol (Fig. 2). Accordingly, we conducted the cycloaddition of alkyne **10** with sydnone **4** and found it to be non-selective and significantly slower than the reaction of the alkynylboronate, delivering a 1:1 mixture of the 3- and 4- trimethylsilyl substituted pyrazole isomers **7** and **11** in modest yield. Moreover, this sample was contaminated by a significant amount of *iso*-withasomnine.

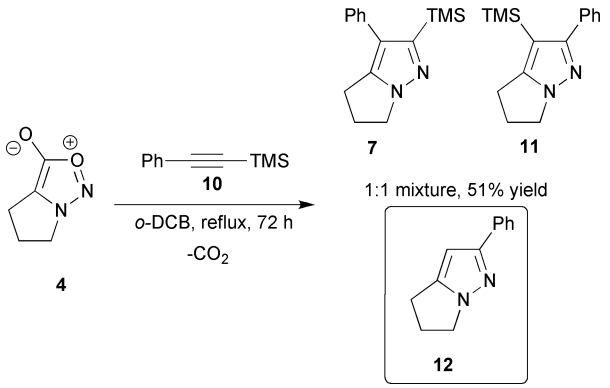


Fig. 2 Cycloaddition of phenyl trimethylsilyl acetylene.

Lastly, we investigated the possibility of the combined removal of the silyl group and cross coupling of the boronate (*i.e.* **6**→**1**). We have previously reported a tactic for isoxazole desilylation in the presence of a boronic ester employing caesium fluoride.[10d]

However, a CsF promoted Suzuki coupling reaction on similar pyrazole structures has proven unsuccessful for silyl group removal.[14] Palladium catalysed cross-coupling reactions in the presence of TBAF are known in the literature.[15] We were pleased to find that on heating our optimal coupling reaction in the presence of 2 equivalents of TBAF we could successfully isolate withasomnine **1** in 50% yield after 72 hours. We have also demonstrated that this process can be carried out in a sealed tube giving an improved 68% yield at 140 °C for 20 hours.[16]

Conclusions

In conclusion we have developed an efficient, regioselective and divergent strategy for the synthesis of all three withasomnine natural products from the key intermediate **6**. We have also highlighted the potential of alkynylboronates to offer improved regioselectivity and reactivity over alternative 1,2-disubstituted alkynes. Finally, we envisage that the discovery of a tandem regioselective cycloaddition/one pot desilylative Suzuki reaction protocol provides the opportunity to rapidly generate a series of novel pyrazole libraries.

Experimental

General methods

All cycloaddition reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry nitrogen. Flash chromatography was performed on silica gel (Fluorochem Silicagel LC60A4–63 micron). Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}) which were developed using standard visualizing agents: Ultra Violet light or potassium permanganate. ^{1}H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or AMX-400 (400 MHz) supported by an Aspect 3000 data system, unless otherwise stated. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.27 ppm) unless otherwise stated. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (*J*) in Hz. ^{13}C NMR spectra were recorded on a Bruker AC-250 (62.9 MHz), AMX-400 (100.6 MHz) or DRX-500 (500 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm) unless otherwise stated. Infrared (FTIR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Samples were recorded as thin films using sodium chloride plates, as a DCM solution. Low resolution mass spectra were recorded on Micromass Autospec, operating in E.I., C.I. or FAB mode; or a Perkin-Elmer Turbomass Benchtop GC-MS operating in either E.I. or C.I mode. High-resolution mass spectroscopy recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES$^+$) or a MicroMass Prospec operating in either FAB (FAB$^+$), EI (EI$^+$) or CI (CI$^+$) mode. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Microwave reactions were performed on a Biotage Initiator Sixty supplied with built in temperature/pressure probes and associated software.

Synthesis of 5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]oxadiazol-3-ol 4[11]. To L-proline (5.00 g, 43.4 mmol) and sodium nitrite (4.10 g, 59.5 mmol) in water (50 mL) was added concentrated hydrochloric acid (3.70 mL) at 0 °C. The resulting slurry was stirred for 16 hours at room temperature. The crude reaction mixture was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude nitrosamine as a white solid (3.65 g, 25.3 mmol). This solid (caution: this material is a suspected carcinogen) was taken to the next step without further purification. To the nitrosamine (3.65 g, 25.3 mmol) in THF (50 mL) was added TFAA (3.60 mL, 50.7 mmol) at 0 °C. The resulting reaction mixture was stirred under nitrogen for 16 hours at room temperature. The solvent was removed *in vacuo* to give the crude product. Further purification by flash chromatography on silica gel (25% EtOAc in PE) gave product **4** (1.71 g, 54%) as a yellow solid. M.p. 31–33 °C. (Lit. m.p. 33–38 °C[11]). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 4.40 (2H, t, J = 7.5 Hz, CH_2), 2.92–2.71 (4H, m, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 165.3, 110.6, 50.5, 26.0, 21.0; FTIR (CH_2Cl_2): 2970 (w), 2878 (w), 1727 (s), 1507 (m), 1452 (m) cm^{-1}.

Synthesis of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole 6. A solution of sydnone **4** (530 mg, 4.21 mmol) and alkyne **5** (3.77 g, 16.83 mmol) in *o*-DCB (10 mL) was stirred under nitrogen at reflux for 24 hours. The solvent was removed *in vacuo* to give the crude product. Further purification by flash chromatography on silica gel (20% EtOAc in PE) gave product **6** (850 mg, 66%) as a yellow solid. M.p. 110–112 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 4.15 (2H, t, J = 7.0 Hz, CH_2), 2.96 (2H, t, J = 7.0 Hz, CH_2), 2.67–2.55 (2H, m, CH_2), 1.29 (12H, s, CH_3), 0.33 (9H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 156.3, 154.1, 83.1, 47.6, 27.2, 25.4, 23.6, 0.4; FTIR (CH_2Cl_2): 2973 (s), 1541 (s), 1406 (s), 1370 (m) 1311 (m), 1243 (s), 1149 (s), 1044 (s), 842 (s) cm^{-1}; HRMS (EI): *m/z* [M]$^+$ calcd for $C_{15}H_{27}BN_2O_2Si$: 306.1935, found: 306.1927.

General method A: Suzuki cross-coupling of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole 4 with aryliodides. To **6** (1 eq.),

aryliodide (2 eq.) and tripotassium phosphate (2 eq.) in 50% DME in water (0.1–0.2 M) was added dichlorobis(triphenylphosphine)palladium(II) (5 mol%). The resulting reaction mixture was stirred at reflux for 18 hours. The crude reaction mixture was extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. Further purification by flash chromatography on silica gel (20% EtOAc in PE) gave products **7–9**.

General method B: Microwave assisted Suzuki cross-coupling of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole 4 with aryliodide. To **6** (1 eq.), aryliodide (2 eq.) and tripotassium phosphate (2 eq.) in 50% DME in water (0.1–0.2 M) was added dichlorobis(triphenylphosphine)palladium(II) (5 mol%). The resulting reaction mixture was heated at 130 °C for 1 hour in a sealed microwave vessel in a microwave reactor. The crude reaction mixture was extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. Further purification by flash chromatography on silica gel (20% EtOAc in PE) gave products **7–9**.

General method C: Synthesis of withasomnine natural products 1–3. A solution of pyrazole **7**, **8** or **9** (1 eq.) in TBAF (1M in THF) (10 eq.) was heated at reflux for 24 hours. The crude reaction mixture was extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. Further purification by flash chromatography on silica gel (100% Et_2O) gave products **1–3**.

Synthesis of 3-phenyl-2-trimethylsilanyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole 7. Using general method A: Boronic ester **6** (100 mg, 0.33 mmol), iodobenzene (13 mg, 0.65 mmol), tripotassium phosphate (140 mg, 0.65 mmol), dichlorobis(triphenylphosphine)palladium(II) (12 mg, 0.02 mmol) and 50% DME in water (2 mL), gave product **7** (65 mg, 78%) as a yellow solid. M.p. 118–120 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.33–7.16 (5H, m, Ar), 4.16 (2H, t, J = 7.0 Hz, CH_2), 2.84 (2H, t, J = 7.0 Hz, CH_2), 2.65–2.54 (2H, m, CH_2), 0.15 (9H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 156.1, 145.0, 135.6, 129.2, 128.5, 126.6, 123.1, 48.0, 27.3, 22.7, 0.2; FTIR (CH_2Cl_2): 2966 (w), 1602 (m), 1540 (w), 1498 (w), 1434 (w), 1247 (s), 987 (m), 842 (s), 756 (s) cm^{-1}; HRMS (ES): m/z [MH]$^+$ calcd. for $C_{15}H_{20}N_2Si$ 256.1396, found 256.1384.

Using general method B: boronic ester **6** (50 mg, 0.16 mmol), iodobenzene (3.6 mg, 0.33 mmol), tripotassium phosphate (70 mg, 0.33 mmol), dichlorobis(triphenylphosphine)palladium(II) (6 mg, 0.01 mmol) and 50% DME in water (2 mL), gave product **7** (32 mg, 76%) as a yellow solid.

Synthesis of 4-(2-trimethylsilanyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)-phenol 8. Using general method A: Boronic ester **6** (50 mg, 0.16 mmol), 4-iodophenol (72 mg, 0.33 mmol), tripotassium phosphate (70 mg, 0.33 mmol), dichlorobis(triphenylphosphine)palladium(II) (6 mg, 0.01 mmol) and 50% DME in water (2 mL), gave product **8** (29 mg, 65%) as a yellow solid. M.p. 198–202 °C; ^{1}H NMR (250 MHz, $CDCl_3$:CD_3OD (1:1)): δ_H 6.83 (2H, d, J = 8.0 Hz, Ar), 6.53 (2H, d, J = 8.0 Hz, Ar), 3.88 (2H, t, J = 7.0 Hz, CH_2), 3.05 (1H, s, OH), 2.57 (2H, t, J = 7.0 Hz, CH_2), 2.41–2.37 (2H, m, CH_2), 0.13 (9H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$:CD_3OD (1:1)): δ_C 155.5 (2 C), 144.8, 130.0, 125.9, 122.8, 114.8, 47.2, 26.7, 21.8, 0.8; FTIR (CH_2Cl_2): 3117 (s), 2923 (w), 1610 (w), 1541 (m), 1506 (w), 1428 (w), 1269 (m), 1199 (w), 994 (w), 841 (m), 750 (w) cm^{-1}; HRMS (ES): m/z [MH]$^+$ calcd. for $C_{15}H_{20}ON_2Si$ 272.1345, found 272.1334.

Using general method B: boronic ester **4** (50 mg, 0.16 mmol), 4-iodophenol (72 mg, 0.33 mmol), tripotassium phosphate (70 mg, 0.33 mmol), dichlorobis(triphenylphosphine)palladium(II) (6 mg, 0.01 mmol) and 50% DME in water (2 mL), gave product **8** (22 mg, 50%) as a yellow solid.

Synthesis of 3-(4-methoxy-phenyl)-2-trimethylsilanyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole 9. Using general method A: Boronic ester **6** (50 mg, 0.16 mmol), 4-iodoanisole (75 mg, 0.33 mmol), tripotassium phosphate (70 mg, 0.33 mmol), dichlorobis(triphenylphosphine)palladium(II) (6 mg, 0.01 mmol) and 50% DME in water (2 mL), gave product **9** (35 mg, 74%) as a yellow solid. M.p. 86–88 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.25–7.22 (2H, m, Ar), 6.93–6.89 (2H, m, Ar), 4.22 (2H, t, J = 7.0 Hz, CH_2), 3.84 (3H, s, CH_3), 2.88 (2H, t, J = 7.0 Hz, CH_2), 2.71–2.60 (2H, m, CH_2), 0.21 (9H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 158.5, 156.1, 144.8, 130.4, 127.9, 122.7, 113.9, 55.7, 48.0, 27.3, 22.6, 0.2; FTIR (CH_2Cl_2): 2955 (w), 1556 (w), 1506 (m), 1246 (s), 1175 (w), 990 (w), 838 (s), 758 (w) cm^{-1}; HRMS (ES): m/z [MH]$^+$ calcd. for $C_{16}H_{22}ON_2Si$ 286.1501, found 286.1504.

Using general method B: boronic ester **6** (50 mg, 0.16 mmol), 4-iodoanisole (75 mg, 0.33 mmol), tripotassium phosphate (70 mg, 0.33 mmol), dichlorobis(triphenylphosphine)palladium(II) (6 mg, 0.01 mmol) and 50% DME in water (2 mL), gave product **9** (25 mg, 54%) as a yellow solid.

Synthesis of withasomnine 1. Using general method C: Pyrazole **7** (30 mg, 0.12 mmol) and TBAF (1 M in THF) (1.2 mL, 1.17 mmol), gave product **1** (15 mg, 70%) as a colourless solid. M.p. 114–116 °C. This sample of withasomnine **1** showed identical analytical data (^{1}H, ^{13}C, HRMS) to that reported.[2a,c] ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.82 (1H, s, Ar), 7.47–7.16 (5H, m, Ar) 4.18 (2H, t, J = 7.0 Hz, CH_2), 3.10 (2H, t, J = 7.0 Hz, CH_2) 2.69 (2H, m, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 142.6, 140.9, 133.4, 128.8, 125.6, 125.0, 115.3, 47.5, 26.4, 23.8; HRMS (ES): m/z [MH]$^+$ calcd. for $C_{12}H_{12}N_2$ 184.1006, found 184.1000.

Synthesis of 4′-hydroxywithasomnine 2. Using general method C: Pyrazole **8** (28 mg, 0.10 mmol) and TBAF (1 M in THF) (1.0 mL, 1.00 mmol), gave product **2** (11 mg, 55%) as a colourless solid. M.p. 232–234 °C. This sample of 4′-hydroxywithasomnine **2** showed identical analytical data (^{1}H, ^{13}C, HRMS) to that reported.[2a,b,3] ^{1}H NMR (250 MHz, $CDCl_3$:CD_3OD (1:1)): δ_H 7.51 (1H, s, Ar), 7.10 (2H, d, J = 8.0 Hz, Ar), 6.66 (2H, d, J = 8.0 Hz, Ar), 3.96 (2H, t, J = 7.0 Hz, CH_2), 3.17 (1H, s, OH), 2.89 (2H, t, J = 7.5 Hz, CH_2) 2.52 (2H, m, CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$:CD_3OD (1:1)): δ_C 154.9, 142.1, 139.7, 126.0, 124.2, 115.3, 115.3, 47.0, 26.0, 23.2. HRMS (ES): m/z [MH]$^+$ calcd. for $C_{12}H_{12}N_2O$ 200.0956, found 200.0950.

Synthesis of 4′ methoxywithasomnine 3. Using general method C: pyrazole **9** (40 mg, 0.14 mmol) and TBAF (1 M in THF) (1.4 mL, 1.40 mmol), gave product **3** (25 mg, 83%) as a colourless solid. M.p. 123–125 °C. This sample of 4′-methoxywithasomnine **3** showed identical analytical data (^{1}H, ^{13}C, HRMS) to that reported.[2b] ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.74 (1H, s, Ar), 7.37 (2H, d, J = 8.0 Hz, Ar), 6.91 (2H, d, J = 8.0 Hz, Ar), 4.16 (2H, t, J = 7.0 Hz, CH_2), 3.82 (3H, s, CH_3), 3.06 (2H, t,

J = 7.0 Hz, CH_2) 2.67 (2H, m, CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 157.8, 142.1, 140.7, 126.2, 125.1, 115.2, 114.3, 55.3, 47.6, 26.5, 23.7. HRMS (ES): m/z $[MH]^+$ calcd. for $C_{13}H_{14}N_2O$ 214.1113, found 214.1106.

General procedure for a desilylative Suzuki cross-coupling synthesis of withasomnine derivatives demonstrated by the synthesis of withasomnine 1. To **4** (50 mg, 0.16 mmol), iodobenzene (3.6 mg, 0.33 mmol), dichlorobis(triphenylphosphine)palladium(II) (6 mg, 0.01 mmol) and tripotassium phosphate (70 mg, 0.33 mmol) in 50% DME in water (2 mL) was added TBAF in THF (1 M in THF) (0.33 mL, 0.33 mmol). The resulting solution was heated at reflux for 72 hours. The crude reaction mixture was extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. Further purification by flash chromatography on silica gel (100% Et_2O) gave product **1** (15 mg, 50%) as a yellow solid.

Desilylative Suzuki cross-coupling synthesis of withasomnine 1. To **4** (100 mg, 0.33 mmol), iodobenzene (13 mg, 0.65 mmol), dichlorobis(triphenylphosphine)palladium(II) (12 mg, 0.02 mmol) and tripotassium phosphate (140 mg, 0.66 mmol) in 50% DME in water (2 mL) was added TBAF hydrate (853 mg, 3.27 mmol). The reaction mixture was heated in a sealed microwave vessel in a silicone oil bath at reflux for 20 hours. The crude reaction was transferred to a round bottom flask and sodium periodate (210 mg, 0.980 mmol) and 2 M HCl (0.2 mL) were added. The resulting solution was stirred at room temperature for 24 hours. The crude reaction mixture was extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. Further purification by flash chromatography on silica gel (10% acetone in DCM) gave product **1** (41 mg, 68%) as a yellow solid.

Experiment to explore the reactivity and regioselectivity of other disubstituted alkynes. A solution of sydnone **4** (63 mg, 0.5 mmol) and alkyne **10** (350 mg, 2.0 mmol) in *o*-DCB (1.25 mL) was stirred under nitrogen at reflux for 72 hours. The crude reaction mixture was partially resolved by flash chromatography on silica gel (35% EtOAc in PE) to give a mixture of the pyrazole products **7**, **11** and **12** (65 mg, 51%, approximate yield estimated on the basis of the molecular weight of **7** and **11**) as a yellow oil. Crude ^1H NMR (prior to chromatography) gives the same peak ratio as that of the isolated pyrazole products. The peak at 6.30 ppm has been assigned as the pyrazole CH of **12** (as observed by the cycloaddition of phenylacetylene and sydnone **4**). The TMS peaks (at ~ 0.2 ppm) have been assigned to the isomers **7** and **11** in a 1.1:1 ratio. The multiplets at ~ 2.6, 2.95 and 4.15 ppm are ascribed to all three compounds.

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