# Divergent Synthesis and Evaluation of Inhibitory Activities against Cyclooxygenases-1 and -2 of Natural Withasomnines and Analogues

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**The divergent synthesis of natural withasomnines and analogues was achieved from 4-hydroxypyrazoles, which was prepared *via* alkaline hydrolysis of the Baeyer–Villiger oxidation products from 4-formylpyrazoles. Key steps of this synthesis are regioselective Claisen rearrangement of 4-allyloxypyrazoles and the Suzuki–Miyaura coupling of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl trifluoromethanesulfonate and commercially available arylboronic acids. The Suzuki–Miyaura coupling at the final step of this strategy enabled facile access to natural withasomnines and their analogues. The biological activities of the twelve synthesized compounds against cyclooxygenases-1 and -2 (COX-1 and COX-2) were evaluated.**

**Key words** 4-hydroxy-1*H*-pyrazole; withasomnine; Claisen rearrangement; Suzuki–Miyaura coupling; microwave; cyclooxygenase inhibitory activity

Pyrazoles are important heterocyclic compounds that exhibit various biological activities, and extensive studies of the synthesis of substituted or functionalized pyrazoles have been conducted.[1,2] Of the many available methods for the synthesis of the pyrazole ring, the reaction of hydrazines with 1,3-dicarbonyl compounds is probably the most general and versatile.[3–7] In contrast, synthetic methods using the direct functionalization of pyrazoles have been little reported.

A binuclear platinum complex bearing C-4 alkylpyrazole ligands was reported to exhibit remarkable anticancer activities against cisplatin-resistant human cancer cell lines.[8,9] This has inspired us to examine the direct functionalization at the C-4 position of pyrazoles. We recently reported the synthesis of 4-substituted pyrazoles *via* the Kumada–Tamao coupling,[10] the Suzuki–Miyaura coupling,[11] the Heck reaction,[12] as well as the synthesis of 2*H*-indazoles *via* a double Sonogashira coupling followed by Bergmann–Masamune cycloaromatization reaction.[13]

4-Hydroxypyrazoles possess important and interesting biological activities, including the inhibition of several kinds of cytochrome P450 (CYP) enzymes and the induction of CYP2E1.[14–18] It has been reported that 4-hydroxypyrazole is a metabolite of pyrazole in mouse hepatic microsomes. However, as far as we know, there are almost no reports of the synthesis of 4-hydroxypyrazoles. Therefore, our interest was directed to the development of a new method for the synthesis of 4-hydroxy-1*H*-pyrazoles. Further, the synthesis of 4-hydroxypyrazoles may lead to find novel biologically active substances.

Although the isolation of natural pyrazole alkaloids from higher plants has been rarely reported, withasomnine (**1a**) shown in Fig. 1 was originally isolated in 1966 from the root bark of *Withania somnifera* (Solanaceae),[19] which is widely distributed in India and Africa. The plant is also known as Achwagandha in Sanskrit or Indian ginseng and used as folk medicine in India. In the 1990s, withasomnines **1b** and **1c** along with **1a** from the root bark of *Newbouldia laevis* Seem (Bignoniaceae) were reported.[20–22] The isolation of withasomnines from *Elytraria acaulis* (Acanthaceae)[23] and *Discopodium penninervium* (Solanaceae)[24] was also reported in 2001 and 2008, respectively. Withasomnine **1a** exhibited central nervous and circulatory system depressions, mild analgesic activity,[25,26] and $TBL_4$, cyclooxygenase-1 (COX-1), and COX-2 inhibitory activities.[24] Because of these interesting biological activities, several reports of the synthesis of **1a** were disclosed.[27–36] In the course of our synthetic studies of small natural products and their analogues,[37–42] we recently reported the divergent synthesis of withasomnines **1a**–**c** and their analogues *via* 4-hydroxypyrazole intermediates in a preliminary communication.[43] We herein describe the details of the divergent synthesis of natural **1a**–**c** as well as nine withasomnine analogues **1d**–**l**, which were easily prepared by the Suzuki–Miyaura coupling of key intermediate **16**. In this work, we focused on the use of 4-hydroxypyrazole intermediates followed by the Claisen rearrangement of their 4-*O*-allyl ethers. Furthermore, the inhibitory activities of **1a**–**l** against COX-1 and COX-2 were tested.

## Results and Discussion

4-Iodo-1-trityl-1*H*-pyrazole (**4a**) was prepared from commercially available pyrazole (**2**) *via* 4-iodo-1*H*-pyrazole (**3**) following our previous work[10,12,13] (Chart 1). Compound **4a** was treated with isopropylmagnesium chloride for halogen–metal exchange and after 1 h, *N*,*N*-dimethylformamide (DMF)

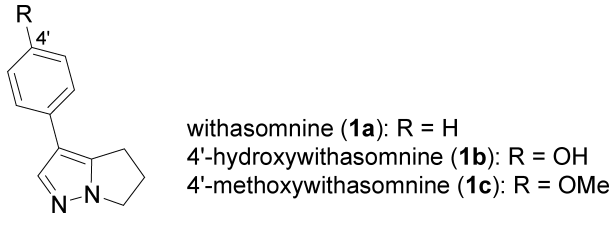


Fig. 1. Structures of Natural Withasomnines **1a**–**c**

The authors declare no conflict of interest.

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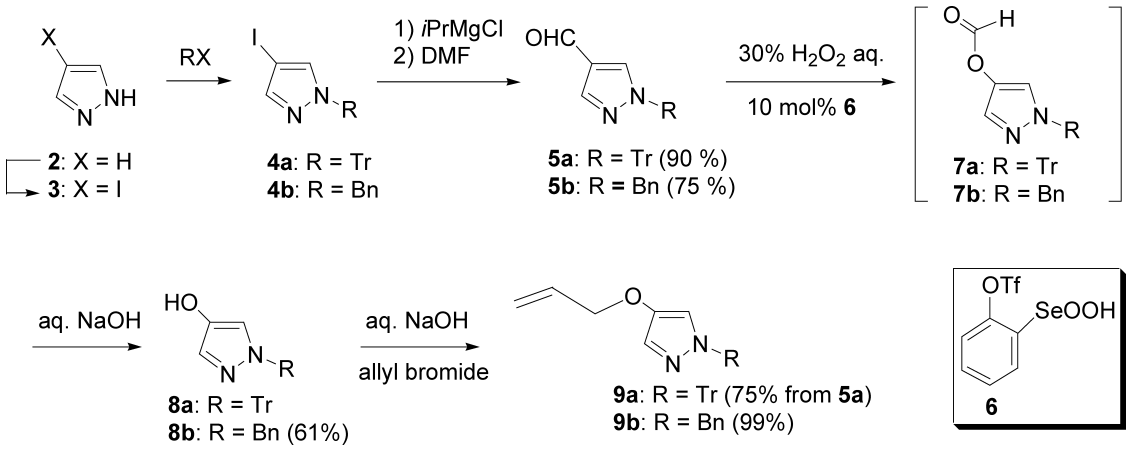



Chart 1. Synthesis of 4-Hydroxypyrazoles

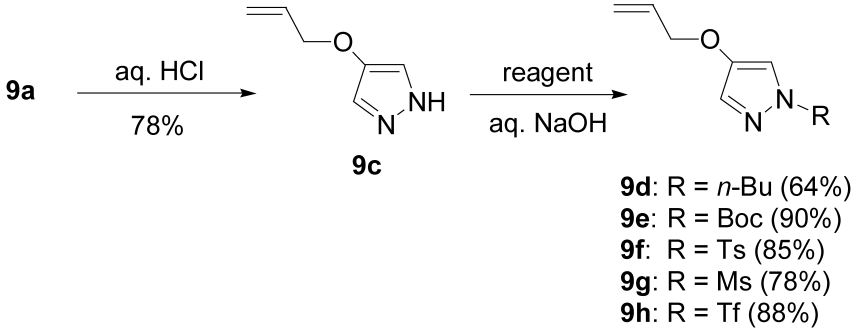



Chart 2. Preparation of 1-Substituted-4-allyloxy-1*H*-pyrazoles **9c**–**h**

was added to afford 4-formylpyrazole **5a**.[44] Aldehyde **5a** was subsequently converted into allyl ether **9a** *via* the following three steps in a simple one-pot procedure: 1) The Baeyer–Villiger oxidation of **5a** with 30% aq. hydrogen peroxide using catalytic 2-trifluoromethane-sulfonyloxyphenylselenic acid (**6**), which was developed in our previous work,[45] providing formate **7a**. 2) Alkaline hydrolysis of **7a** with aq. NaOH under reflux afforded desired 4-hydroxy-1-trityl-1*H*-pyrazole (**8a**). 3) Reaction of **8a** with allyl bromide gave corresponding allyl ether **9a** (75% overall yield from **5a**), which could be used immediately for the following Claisen rearrangement. Similarly, 1-benzyl-4-hydroxy-1*H*-pyrazole (**8b**) and allyl ether **9b** were obtained in good yields from **5b**.

The next crucial step in the total synthesis of **1** is the regioselective Claisen rearrangement of 4-allyloxy-1*H*-pyrazoles (**9**). The Claisen rearrangement of 3-substituted-5-allyloxypyrazoles was reported by Hori and colleagues[46] and Hwang *et al.*[47] independently, in which the allyl group was rearranged toward C-4 exclusively resulting from the structure of the substrate, 3-substituted-5-allyloxypyrazoles. However, allyl ethers **9** offer two possible routes for the Claisen rearrangement. Thus, the Claisen rearrangement of **9** having various N-1 protecting groups with control of regioselectivities is useful for the synthesis of withasomnine. In order to examine the directionality of the rearrangement, five additional 4-allyloxy-1*H*-pyrazoles **9d**–**h** were prepared from **9c** as shown in Chart 2.

Claisen rearrangements using 4-allyloxypyrazoles **9** were performed in *N*,*N*-diethylaniline (DEA) as solvent under microwave (MW) irradiation to afford 1-substituted 3-allyl-4-hydroxy-1*H*-pyrazole (**10**) and 1-substituted 5-allyl-4-hydroxy-1*H*-pyrazole (**11**) (The numbering in the text was tentatively derived from that of **9**). As summarized in Table 1, the results indicated a highly regioselective rearrangement at C5 to give **11** as the major product. The structures of all the rearranged products were determined by nuclear Overhauser effect spectroscopy (NOESY) analyses. Key NOESY correlations were observed in **10a** and **11a** as representative compounds (Fig. 2). Positive effect of MW irradiation could not be observed in this reaction (entries 1, 2) since entry 1 was carried out in a sealed tube with heating similarly to entry 2 in a sealed vessel for MW reaction. It was interesting that only in the case of *N*-benzylpyrazole **9b** (entry 3) was a very small amount of 3,5-diallyl-2-benzyl-4-hydroxy-2*H*-pyrazole (**12**, 2%) obtained along with major product **11b** (92%). However the separation of **11b** and **12** was troublesome. Claisen rearrangement of *N*-tosylpyrazole **9f** (R=Ts) provided a significant amount of minor rearranged product **10f** (20%) along with **11f** (65%) (entry 5). Entries on **9e** (R=Boc) or **9h** (R=Tf) are not presented in Table 1 because desired products **10** or **11** could not be obtained. Boc group was removed thermolytically during MW reaction in case of **9e**.

Although understanding of the rearrangement direction of **9** arising from various N-protecting groups remains incomplete, electron-donating groups at N-1 tended to show preference for the desired C5-rearrangements (entries 1−4).

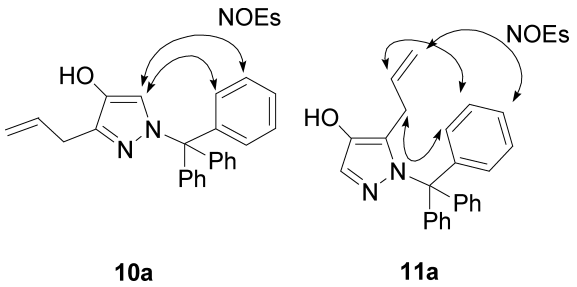



Fig. 2. Selected NOEs in **10a** and **11a**

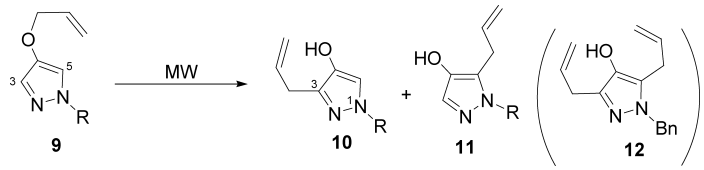
The preference for **11** in the Claisen rearrangement could be explained by the relative stabilities of two intermediates (**IMs**), **IM1** for **11** and **IM2** for **10**, as shown in Fig. 3. **IM1** had opposite electric charges ($\delta^+$ and $\delta^-$) lying side by side at C4 and C5. Meanwhile, **IM2** seemed less stable than **IM1** because the partially negative charge ($\delta^-$) on C3 neighbored the negative charge on N2 in **IM2**, causing a mismatch of the charge balance. In addition, electrons on the *O*-allyl group as well as all $\pi$ electrons on the pyrazole ring could be forced to participate in the rearrangement into **10**.

N1-Tritylated pyrazole **11a** (R=Tr) possessing an allylic side chain at C5 was selected as the key intermediate for the total synthesis of withasomnines owing to the easy removal of the trityl group in the acidic condition. Thus, the MW-assisted Claisen rearrangement of **9a** was further examined under various conditions (Table 1, entries 7–13). (Reaction time of entries 1–7 was determined by TLC monitoring consumption of **9**.) Use of 1,2-dimethoxyethane (DME) as the solvent under MW condition (200°C, 30 min) afforded the desirable rearrangement product **11a** in 65% yield with recovery of the staring **9a** (23%), contaminating **10a** (1.4%) (entry 9). In addition, the MW reaction in DME or EtOH tended to suppress formation of unfavorable **10a** (entries 7–12), while the use of $CH_3CN$ contrarily provided only a small amount of **10a** (16%) (entry 13). The reaction solutions of **9** in DEA or $CH_3CN$ were turned red under MW irradiations, but they were kept colorless in DME or EtOH. The color change in DEA or $CH_3CN$ may be allowed to presume the decomposition of the reaction contents.

The transformation of **11a** into 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl trifluoromethanesulfonate (**16**) is summarized in Chart 3.[48] The 4-hydroxyl group of **11a** was converted into triflate **13** (87%) using triflic anhydride as the functional group for the subsequent Suzuki–Miyaura coupling. The hydroboration–oxidation sequence of **13** with borane–dimethylsulfide complex resulted in desired alcohol **14** in 27–40% yields under various reaction conditions. Alternatively, the use of 9-BBN improved the yield of **14** to 87%. Alcohol **14** was subsequently treated with *p*-toluenesulfonyl chloride and triethylamine to give tosylate **15** in 93% yield. Detritylation of **15** under reflux in hydrochloric acid induced a spontaneous intramolecular $S_N2$ reaction to furnish intermediate **16** in 40% yield.

The final step in the total synthesis of withasomnine **1a** is the Suzuki–Miyaura coupling of triflate **16** and phenylboronic acid. Various reaction conditions in DME–$H_2O$ to form **1a** were examined as shown in Table 2. MW irradiation shortened the reaction time remarkably (entry 2) compared to conventional reflux conditions (entry 1), affording **1a** in the similar low yields along with undesired **17**. Changing ratio of DME–$H_2O$ from 1 : 1 to 9 : 1 depressed the production of **17** (entry 3). Although the DME–$H_2O$ solvent system was effective for the reaction as reported in the literature,[35] the sole use of DME did not give **1a** (entry 5). In an investigation of the effects of phase transfer catalyst on the reaction, we found that the addition of 2 eq of tetra-*n*-butylammonium bromide (TBAB) gave a slightly better yield (54%) (entry 7), whereas the addition of only one drop of trioctylmethylammonium

Table 1. Claisen Rearrangement of 4-Allyloxy-1*H*-pyrazoles




| Entry[a] | Substrate | Solvent | Temp. (°C) | Time (min) | Product yield[b] (%) | | | Recovery of **9** |
|---|---|---|---|---|---|---|---|---|
| | | | | | **10** | **11** | **12** | |
| 1[c] | **9a** (R=Tr) | DEA | 190 | 60 | 3 | 59 | 0 | |
| 2 | **9a** | DEA | 190 | 60 | 3 | 61 | 0 | |
| 3 | **9b** (R=Bn) | DEA | 190 | 30 | 0 | 92 | 2 | |
| 4 | **9d** (R=*n*-Bu) | DEA | 190 | 60 | 2 | 84 | 0 | |
| 5 | **9f** (R=Ts) | DEA | 190 | 30 | 20 | 65 | 0 | |
| 6 | **9g** (R=Ms) | DEA | 190 | 60 | Trace[d] | 68 | 0 | |
| 7 | **9a** | DME | 200 | 10 | ND[e] | 53 | 0 | 35 |
| 8 | **9a** | DME | 200 | 20 | ND | 53 | 0 | 40 |
| 9 | **9a** | DME | 200 | 30 | 1.4 | 65 | 0 | 23 |
| 10 | **9a** | DME | 200 | 60 | 1.5 | 59 | 0 | 27 |
| 11 | **9a** | DME | 150 | 60 | 0 | 13 | 0 | 84 |
| 12 | **9a** | EtOH | 180 | 30 | 2 | 51 | 0 | 43 |
| 13 | **9a** | $CH_3CN$ | 200 | 30 | 16 | 0 | 0 | 0 |

*a*) All entries except 1 were carried out under MW irradiation. *b*) Isolated yield. *c*) Conventional heating in a sealed tube. *d*) Not isolated but observed in the crude $^1$H-NMR spectrum. *e*) ND: not detected.

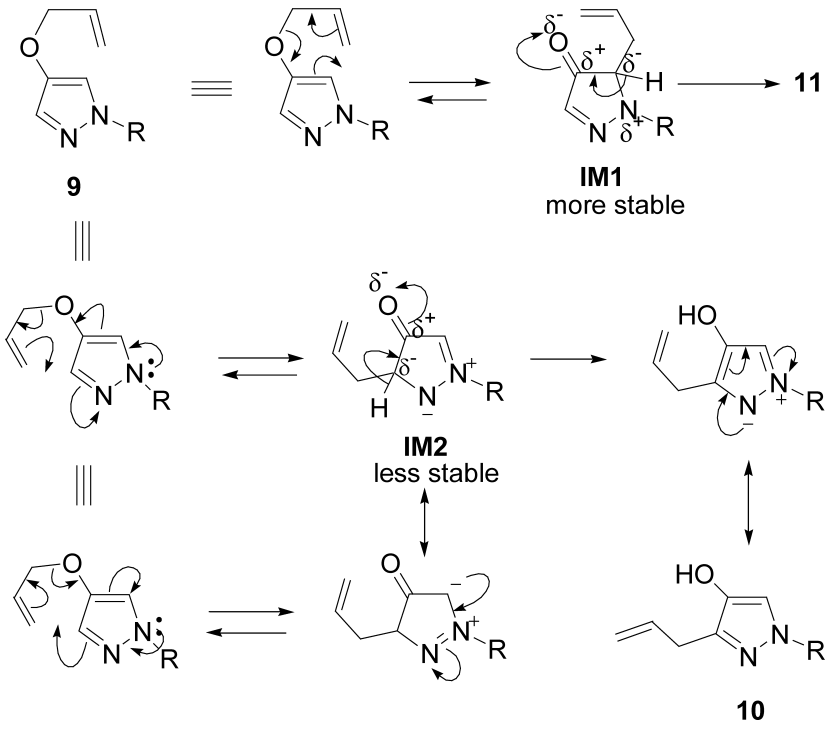



Fig. 3. Mechanism of Claisen Rearrangement from **9** to **10** and **11**

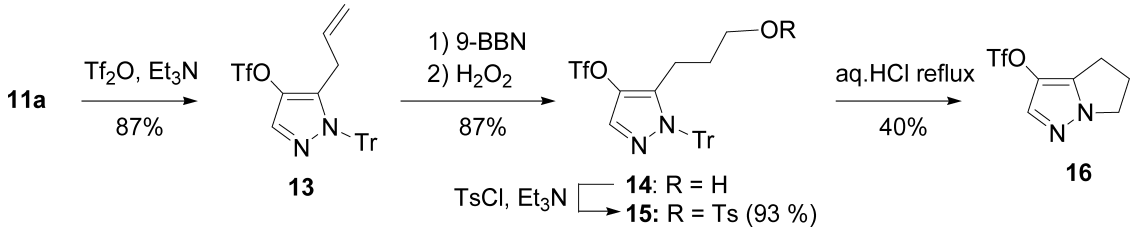



Chart 3. Transformation of **11a** into **16**

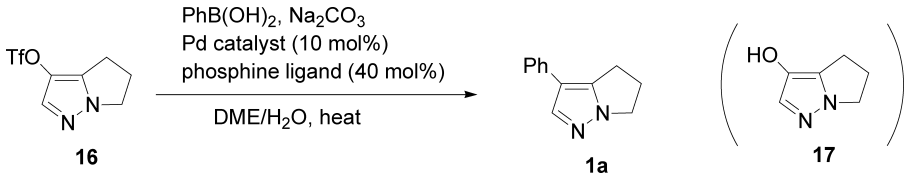
chloride (TOMAC) showed a remarkable improvement, giving target compound **1a** in 90% yield (entry 8). From entries 8–10, the optimum reaction time for the Suzuki–Miyaura coupling under MW irradiation was determined to be 30 min (entry 10). Indeed, the reaction condition in entry 10 was applied to the synthesis of other natural withasomnines and withasomnine derivatives.

The Suzuki–Miyaura coupling toward them was carried out. Results are summarized in Table 3. Remaining two natural **1b** and **1c** could be prepared in good yields using 4-hydroxyphenyl- and 4-methoxyphenylboronic acids, respectively (entries 2, 3). Further applications to unnatural withasomnine analogues **1d**–**l** were also demonstrated *via* the reaction between **16** and various arylboronic acids (entries 4–12). The easy access to these analogues from the common intermediate **16** proved to be an advantage of our synthetic method compared to recent approaches by other research groups,[35,36] since all arylboronic acids appearing in Table 3 are commercially available.

Since **1a** was reported to exhibit minor inhibitory activity against COX-1 and COX-2 in the literature,[24] synthesized withasomnines **1a**–**l** were applied to the preliminary inhibitory assay against those enzymes. Among them, natural compound **1b** (Ar=4-hydroxyphenyl) and unnatural **1d** (Ar=3-hydroxyphenyl) and **1g** (Ar=3-aminophenyl) showed potent inhibitory activities against COX-1 and COX-2. Then the $IC_{50}$ values of them were determined by further experiments using aspirin as the positive control and results are summarized in Table 4. Worth mentioning is that the COX-1 and COX-2 inhibitory activities of **1g** were stronger than those of aspirin. The presence of an amino group in **1g** increased its potency by one order of magnitude for COX-1 and two orders for COX-2 compared to **1b** and **1d**, both of which possess a hydroxyl group. The COX-2 inhibitory activity ($IC_{50}$: $2.7\times10^{-6}$ M) of **1g** was almost four times as effective as its COX-1 inhibitory activity ($IC_{50}$: $1.0\times10^{-5}$ M). Compounds **1b** and **1d** exhibited nearly two-fold higher selectivity for COX-1 than COX-2, being similar to the selectivity of aspirin. Meanwhile, the other nine compounds showed much lower inhibitory activities ($IC_{50}>10^{-3}$ M) against both enzymes.

The results suggested that the presence of the groups, which are capable of hydrogen bonding, on the aromatic ring of synthesized withasomnines increased their inhibitory activities against COX-1 and COX-2.[49] These findings may stimulate the design of COX inhibiting drugs based on withasomnine derivatives.

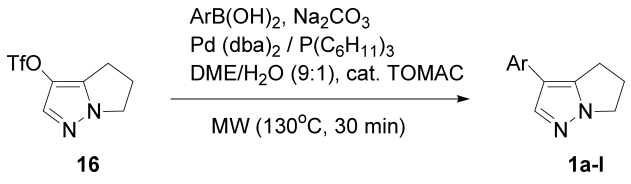
Table 2. Suzuki–Miyaura Coupling of **16** and Phenylboronic Acid to Withasomnine **1a**




| Entry | Catalyst/Ligand | DME/$H_2O$ | Additive | Condition | **1a** (yield, %) | **17** (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2/PPh_3$ | 1/1 | No | Reflux, 24 h | 20 | 77 |
| 2 | $Pd(OAc)_2/PPh_3$ | 1/1 | No | MW, 130°C, 1 h | 24 | 71 |
| 3 | $Pd(OAc)_2/PPh_3$ | 9/1 | No | MW, 130°C, 1 h | 29 | 0 |
| 4 | $Pd(dba)_2/PPh_3$ | 9/1 | No | MW, 130°C, 1 h | 42 | 0 |
| 5 | $Pd(OAc)_2/PPh_3$ | 1/0 | No | MW, 130°C, 1 h | 0 | 0 |
| 6 | $Pd(dba)_2/P(o\text{-tol})_3$ | 9/1 | No | MW, 130°C, 1 h | 51 | 0 |
| 7 | $Pd(dba)_2/P(C_6H_{11})_3$ | 9/1 | TBAB (2 eq) | MW, 130°C, 1 h | 54 | 0 |
| 8 | $Pd(dba)_2/P(C_6H_{11})_3$ | 9/1 | TOMAC (1 drop) | MW, 130°C, 1 h | 90 | 0 |
| 9 | $Pd(dba)_2/P(C_6H_{11})_3$ | 9/1 | TOMAC (1 drop) | MW, 130°C, 10 min | 37[a)] | 0 |
| 10 | $Pd(dba)_2/P(C_6H_{11})_3$ | 9/1 | TOMAC (1 drop) | MW, 130°C, 30 min | 88 | 0 |

*a*) Starting material **16** was recovered in 55%.

Table 3. Suzuki–Miyaura Coupling of **16** and Arylboronic Acid to Withasomnines **1a–l**




| Entry | $ArB(OH)_2$: Ar = | Product (yield, %) |
|---|---|---|
| 1[a)] | Phenyl | **1a** (88) |
| 2 | 4-Hydroxyphenyl | **1b** (84) |
| 3 | 4-Methoxyphenyl | **1c** (82) |
| 4 | 3-Hydroxyphenyl | **1d** (71) |
| 5 | 2-Methylphenyl | **1e** (88) |
| 6 | 3-Nitrophenyl | **1f** (70) |
| 7 | 3-Aminophenyl | **1g** (76) |
| 8 | 3,4-Methylenedioxyphenyl | **1h** (83) |
| 9 | 4-Fluorophenyl | **1i** (80) |
| 10 | 2-Thiophenyl | **1j** (83) |
| 11 | 3-Thiophenyl | **1k** (92) |
| 12 | 2-Furyl | **1l** (82) |

*a*) The same reaction appeared in entry 10 in Table 2.

Table 4. Inhibitory Activities of Selected Withasomnines **1b**, **1d**, and **1g** against COX-1 and COX-2

| Compound | $IC_{50}$ (M) | |
|---|---|---|
| | COX-1 | COX-2 |
| **1b** | $1.1\times10^{-4}$ | $2.4\times10^{-4}$ |
| **1d** | $1.1\times10^{-4}$ | $2.3\times10^{-4}$ |
| **1g** | $1.0\times10^{-5}$ | $2.7\times10^{-6}$ |
| Aspirin | $4.6\times10^{-5}$ | $8.4\times10^{-5}$ |

## Conclusion

We have developed a novel method for the synthesis of 4-hydroxy-1*H*-pyrazoles **8**, which utilizes our previously developed Baeyer–Villiger oxidation reaction.

We also found that the Claisen rearrangement of *O*-allyl derivatives **9** gave 5-allyl-4-hydroxy-2*H*-pyrazoles in good yields with high regioselectivities. Our divergent synthesis was completed with the Suzuki–Miyaura coupling of triflate ester of 4-hydroxypyrazole derivative **16** and various arylboronic acids, affording various natural and synthetic withasomnines **1a–l**. Diverging from intermediate **16** realized easy access to various withasomnines. The COX-1 and COX-2 inhibitory activities of the synthesized compounds **1a–l** were evaluated. Among them, **1b**, **1d**, and **1g** showed significant inhibitory activities against both enzymes. Of particular interest was that **1g** exhibited the most potent activities against COX-1 and COX-2.

## Experimental

**General** IR spectra were obtained with a JASCO FT/IR-680 Plus spectrometer. High resolution (HR)-MS were determined using a JEOL JMS-700 (2) mass spectrometer. NMR spectra were recorded at 27°C on Varian UNITY INOVA-500 and Mercury-3000 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as the internal reference. Melting points were determined on a Yanagimoto micromelting point apparatus MD-S3 and are uncorrected. Liquid column chromatography was conducted over silica gel (SILICYCLE, Silia Flash F60, mesh 230–400). Analytical TLC was performed on precoated Merck glass plates (DC-Alufolien Kieselgel 60 $F_{254}$) and compounds were visualized by spraying plates with an ethanol solution of phosphomolybdic acid followed by heating. Dry tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl under nitrogen atmosphere. Microwave reactions were carried out with a Biotage Initiator®. A COX Fluorescent Activity Assay Kit was purchased from Cayman Chemical (Ann Arbor, MI, U.S.A.).

**4-Formyl-1-trityl-1*H*-pyrazole 5a** To a solution of **4a** (22.8 g, 52.3 mmol) in $Et_2O$ (120 mL) and THF (240 mL) was added 2.0 M isopropylmagnesium chloride in THF (31.5 mL, 52.3 mmol) at 0°C under nitrogen atmosphere. After stirring for 1 h, *N*,*N*-dimethylformamide (DMF) (14 mL, 160 mmol) was added and the reaction mixture was stirred for another hour at room temperature (rt). After the reaction was quenched

by the addition of water, extraction was carried out with $CH_2Cl_2$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by recrystallization to afford **5a** (16.0 g, 90%). **5a**: Colorless needles ($CH_2Cl_2$); mp 208–210°C; IR (KBr) $\nu_{max}$ 1686 (C=O), 1546 (C=C), 1491 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 7.12–7.16 (m, 6H, Tr-H), 7.31–7.36 (m, 9H, Tr-H), 7.97 (s, 1H, pyrazole-H), 8.12 (s, 1H, pyrazole-H), 9.83 (s, 1H, CHO); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 79.7, 122.8, 127.8, 128.0, 130.0, 135.9, 140.6, 142.0, 184.3; HR-MS *m/z* Calcd for $C_{23}H_{19}N_2O$ ($[M+H]^+$) 339.1498, Found 339.1503.

**1-Benzyl-4-formyl-1*H*-pyrazole (5b)** Compound **5b** was prepared from **4b** similarly except for purification procedure (by column chromatography) in 75% yield. **5b**: Oil; IR (liquid film) $\nu_{max}$ 1685 (C=O), 1543 (C=C), 1489 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 5.34 (s, 2H, ArC$\underline{H}_2$Ph), 7.26–7.29 (2H, m, Ph-H), 7.36–7.41 (3H, m, Ph-H), 7.88 (1H, s, pyrazole-H), 8.01 (1H, s, pyrazole-H), 9.84 (1H, s, CHO); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 56.6, 128.2, 128.7, 129.1, 132.5, 134.7, 139.4, 141.0, 184.0; HR-MS *m/z* Calcd for $C_{11}H_{11}N_2O$ ($[M+H]^+$) 187.0872, Found 187.0868.

**1-Benzyl-4-hydroxy-1*H*-pyrazole (8b)** To a solution of **5b** (200 mg, 1.1 mmol) in $CH_2Cl_2$ (6 mL) were added 30% $H_2O_2$ aq. (0.7 mL, 6.2 mmol) and 2-trifluoro-methanesulfonyl-phenylselenic acid (**6**) (46 mg, 0.1 mmol) at rt. After stirring for 24 h, 10% NaOH aq. (0.7 mL) was added to the reaction mixture containing 1-benzylpyrazol-4-yl formate (**7b**). The reaction mixture was warmed at 50°C for 1.5 h. After the reaction was quenched with $NH_4Cl$ aq., extraction was carried out with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=1 : 1) to afford **8b** (93 mg, 61% in 2 steps). **8b**: Colorless crystals ($CH_2Cl_2$); mp 84–86°C; IR (KBr) $\nu_{max}$ 3735 (OH), 1584 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 5.05 (2H, s, PhC$\underline{H}_2$Ar), 6.90 (1H, s, pyrazole-H), 7.07–7.09 (2H, m, Ph-H), 7.08 (1H, s, pyrazole-H), 7.22–7.25 (3 H, m, Ph-H), 8.80 (1H, br s, OH); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 56.1, 116.8, 127.4, 128.0, 128.2, 128.7, 136.2, 141.8; HR-MS *m/z* Calcd for $C_{10}H_{10}N_2O$ ($M^+$) 174.0788, Found 174.0787.

**4-Allyloxy-1-benzyl-1*H*-pyrazole (9b)** To a solution of **8b** (89 mg, 0.5 mmol) in 10% NaOH aq. (0.4 mL, 1 mmol) was added allyl bromide (52 $\mu$L, 0.6 mmol) at rt and the reaction mixture was stirred for 2 h. After the reaction was quenched with $NH_4Cl$ aq., extraction was carried out with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=4 : 1) to afford **9b** (107 mg, 99%). **9b**: Yellow oil; IR (liquid film) $\nu_{max}$ 3032 (C–H), 1649 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 4.36 (2H, ddd, *J*=5.4, 1.6, 1.5 Hz, –OC$\underline{H}_2$CH=), 5.18 (2H, s, ArC$\underline{H}_2$Ph), 5.24 (1H, dtd, *J*=10.5, 1.5, 1.5 Hz, –CH=C$\underline{H}$H), 5.35 (1H, dtd, *J*=17.3, 1.6, 1.5 Hz, –CH=CH$\underline{H}$), 5.98 (1H, ddt, *J*=17.3, 10.5, 5.4 Hz, –$CH_2$C$\underline{H}$=$CH_2$), 7.04 (1H, d, *J*=0.6 Hz, pyrazole-H), 7.18 (2H, m, Ph-H), 7.26–7.36 (4H, m, Ph-H, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 56.5, 72.4, 115.0, 117.8, 127.4, 127.4, 127.9, 128.7, 133.2, 136.6, 145.6; HR-MS *m/z* Calcd for $C_{13}H_{14}N_2O$ ($M^+$) 214.1106, Found 214.1104.

**4-Allyloxy-1-trityl-1*H*-pyrazole (9a)** To a solution of **5a** (7.2 g, 21 mmol) in $CH_2Cl_2$ (107 mL) were added 30% $H_2O_2$ aq. (10.7 mL, 94 mmol) and **6** (746 mg, 2.1 mmol) at rt. After stirring for 24 h, 10% NaOH aq. (1.7 mL) was added and the reaction mixture was warmed at 50°C for 1.5 h. Then, allyl bromide (2.5 mL, 26 mmol) was added at rt and the reaction mixture was stirred for 2 h. After quenching the reaction with $NH_4Cl$ aq., extraction was carried out with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=3 : 1) to afford **9a** (5.9 g, 75% in 3 steps). **9a**: White powder; mp 123–125°C; IR (KBr) $\nu_{max}$ 1649, 1570, 1492 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 4.34 (2H, ddd, *J*=5.6, 1.4, 1.6 Hz, –OC$\underline{H}_2$CH=), 5.23 (1H, ddt, *J*=10.6, 1.4, 1.4 Hz, –CH=C$\underline{H}_{cis}$H), 5.32 (1H, ddt, *J*=17.2, 1.6, 1.4 Hz, –CH=C$\underline{H}_{trans}$H), 5.97 (1H, ddt, *J*=17.2, 10.6, 5.6 Hz, –C$\underline{H}$=$CH_2$), 7.03 (1H, s, pyrazole-H), 7.13–7.17 (6H, m, Tr-H), 7.27–7.32 (9H, m, Tr-H), 7.42 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 72.4, 78.6, 117.9, 118.4, 127.6, 127.9, 128.1, 130.1, 133.2, 143.1, 144.1; HR-MS *m/z* Calcd for $C_{25}H_{22}N_2O$ ($M^+$) 366.1732, Found 366.1727.

**1-Tritylpyrazol-4-yl Formate (7a)** Colorless crystals ($CH_2Cl_2$); mp 130–131°C; IR (KBr) $\nu_{max}$ 1741 (C=O), 1577 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 7.12–7.17 (6H, m, Tr-H), 7.28–7.33 (9H, m, Tr-H), 7.55 (1H, d, *J*=0.7 Hz, pyrazole-H), 7.67 (1H, d, *J*=0.7 Hz, pyrazole-H), 8.15 (1H, s, –OCO$\underline{H}$); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 79.2, 123.2, 127.6, 127.8, 127.9, 130.1, 130.8, 142.7, 157.4; HR-MS *m/z* Calcd for $C_{23}H_{18}N_2O_2$ ($M^+$) 354.1368, Found 354.1364.

**4-Hydroxy-1-trityl-1*H*-pyrazole (8a)** Colorless crystals (EtOAc); mp >300°C; IR (KBr) $\nu_{max}$ 3137 (OH), 1608 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 7.06 (1H, d, *J*=0.9 Hz, pyrazole-H), 7.13–7.17 (6H, m, Tr-H), 7.28–7.32 (9H, m, Tr-H), 7.37 (1H, d, *J*=0.9 Hz, pyrazole-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 76.5 (s), 119.9 (d), 127.6 (d), 129.5 (d), 130.1 (d), 139.6 (s), 143.1 (s) (one of a doublet signal should be overlapped); HR-MS *m/z* Calcd for $C_{22}H_{18}N_2O$ ($M^+$) 326.1219, Found 326.1412.

**4-Allyloxy-1*H*-pyrazole (9c)** To a solution of **9a** (183 mg, 0.5 mmol) in acetone (1 mL) was added 1 N HCl aq. (2 mL, 2 mmol). After stirring at 50°C for 30 min, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=3 : 1) to afford **9c** (48 mg, 78%). **9c**: White powder; mp 40−42°C; IR (KBr) $\nu_{max}$ 3308 (NH) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 4.42 (2H, ddd, *J*=5.6, 1.5, 1.2 Hz, –OC$\underline{H}_2$CH=), 5.27 (1H, ddt, *J*=10.5, 1.5, 1.2 Hz, –CH=C$\underline{H}$H), 5.38 (1H, dq, *J*=17.4, 1.5 Hz, –CH=CH$\underline{H}$), 6.02 (1H, ddt, *J*=17.4, 10.5, 5.6 Hz, –OC$H_2$C$\underline{H}$=$CH_2$), 7.30 (2H, s, pyrazole-H), 11.10 (1H, br s, NH); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 72.6, 117.9, 120.8, 120.8, 133.2, 145.0; HR-MS *m/z* Calcd for $C_6H_8N_2O$ ($M^+$) 124.0637, Found 124.0634.

**Synthesis of 4-Allyloxy-1*H*-pyrazoles (9d–9h) General** To a solution of **9c** (62 mg, 0.5 mmol) in 10% NaOH aq. (0.4 mL, 1 mmol) was added *n*-butylbromide (110 $\mu$L, 1 mmol) at rt and the reaction mixture was stirred for 12 h. After the reaction was quenched with $NH_4Cl$ aq., extraction was carried out with EtOAc. The organic layer was washed with brine,

dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=4 : 1) to afford **9d** (118 mg, 85%).

**9d**: White powder; mp 120°C; IR (KBr) $\nu_{max}$ 1648 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 0.93 (3H, t, $J$=7.4 Hz, $-NCH_2CH_2CH_2C\underline{H}_3$), 1.31 (2H, tq, $J$=7.4, 7.5 Hz, $-OCH_2CH_2C\underline{H}_2CH_3$), 1.80 (2H, tt $J$=7.5, 7.4 Hz, $-NCH_2C\underline{H}_2CH_2CH_3$), 4.01 (2H, t, $J$=7.4 Hz, $-NC\underline{H}_2CH_2-$), 4.40 (2H, ddd, $J$=5.6, 1.6, 1.4 Hz, $-OC\underline{H}_2CH=CH_2$), 5.27 (1H, ddt, $J$=10.5, 1.5, 1.4 Hz, $-CH=C\underline{H}_{cis}H$), 5.38 (1H, ddt, $J$=17.3, 1.6, 1.5 Hz, $-CH=C\underline{H}_{trans}H$), 6.02 (1H, ddt, $J$=17.3, 10.5, 5.6 Hz, $-CH_2C\underline{H}=CH_2$), 7.07 (1H, s, pyrazole-H), 7.23 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 13.6, 19.8, 32.3, 52.5, 72.6, 114.9, 117.9, 126.8, 133.4, 145.1; HR-MS *m/z* Calcd for $C_{10}H_{16}N_2O$ ($M^+$) 180.1263, Found 180.1264.

**9e**: Oil; IR (liquid film) $\nu_{max}$ 1595 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.64 (9H, s, –O–*t*-Bu), 4.44 (2H, d, $J$=5.4 Hz, $-OC\underline{H}_2CH=$), 5.31 (1H, d, $J$=10.7 Hz, $-CH=C\underline{H}H$), 5.41 (1H, d, $J$=17.3 Hz, $-CH=C\underline{H}H$), 6.01 (1H, ddt, $J$=17.3, 10.7, 5.4 Hz, $-CH_2C\underline{H}=CH_2$), 7.52 (1H, s, pyrazole-H), 7.63 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 27.1, 27.6, 72.0, 84.8, 112.6, 118.0, 132.2, 134.9, 146.5; HRMS *m/z* Calcd for $C_{11}H_{16}N_2O_3$ ($M^+$) 224.1161, Found 224.1166.

**9f**: Oil; IR (liquid film) $\nu_{max}$ 1589 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.42 (3H, s, $ArC\underline{H}_3$), 4.40 (2H, d, $J$=5.4 Hz, $-OC\underline{H}_2CH=$), 5.31 (1H, dd, $J$=10.4, 1.4 Hz, $-CH=C\underline{H}H$) 5.38 (1H, dd, $J$=17.3, 1.4 Hz, $-CH=C\underline{H}H$), 5.96 (1H, ddt, $J$=17.3, 10.4, 5.4 Hz, $-CH_2C\underline{H}=CH_2$), 7.32 (2H, d, $J$=8.3 Hz, Ph-H), 7.52 (1H, s, pyrazole-H), 7.64 (1H, s, pyrazole-H), 7.85 (2H, d, $J$=8.3 Hz, Ph-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 21.6, 72.3, 113.6, 118.6, 127.8, 129.9, 132.0, 133.9, 136.8, 145.6, 146.9; HR-MS *m/z* Calcd for $C_{13}H_{14}N_2O_3S$ ($M^+$) 278.0725, Found 278.0719.

**9g**: Oil; IR (liquid film) $\nu_{max}$ 1590 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.26 (3H, s, $-SO_2C\underline{H}_3$), 4.45 (2H, ddd, $J$=5.4, 1.4, 1.3 Hz, $-OC\underline{H}_2CH=$), 5.34 (1H, ddt, $J$=10.5, 1.4, 1.3 Hz, $-CH=C\underline{H}H$), 5.42 (1H, ddt, $J$=17.4, 1.4, 1.3 Hz, $-CH=C\underline{H}H$), 6.00 (1H, ddt, $J$=17.4, 10.5, 5.4 Hz, $-CH_2C\underline{H}=CH_2$), 7.59 (1H, s, pyrazole-H), 7.63 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 40.9, 72.5, 113.4, 118.8, 132.1, 136.8, 146.7; HR-MS *m/z* Calcd for $C_7H_{10}N_2O_3S$ ($M^+$) 202.0412, Found 202.0414.

**9h**: Oil; IR (liquid film) $\nu_{max}$ 1644 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 4.49 (2H, ddd, $J$=5.7, 1.5, 1.4 Hz, $-OC\underline{H}_2CH=$), 5.37 (1H, dtd, $J$=10.4, 1.4, 1.3 Hz, $-CH=C\underline{H}H$), 5.43 (1H, dtd, $J$=17.3, 1.5, 1.3 Hz, $-CH=C\underline{H}H$), 5.99 (1H, ddt, $J$=17.3, 10.4, 5.7 Hz, $-CH_2C\underline{H}=CH_2$), 7.55 (1H, s, pyrazole-H), 7.81 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 72.6, 112.5, 114.4, 119.0 (q, $J_{C-F}$=323.6 Hz), 119.1, 131.4, 141.1, 148.2; HR-MS *m/z* Calcd for $C_7H_7F_3N_2O_3S$ ($M^+$) 256.0129, Found 256.0120.

**Claisen Rearrangement of 4-Allyloxy-1*H*-pyrazoles 9 General Procedure under Microwave Irradiation (Table 1 Entry 3)** A sealed vial containing a solution of **9b** (214 mg, 1.0 mmol) in DEA (2.0 mL) was heated at 190°C for 30 min under microwave irradiation. After the reaction was quenched with $NH_4Cl$ aq., extraction was carried out with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=2 : 1) to afford **11b** (197 mg, 92%) and **12** (4.0 mg, 2%).

**10a**: White powder; mp 88–90°C; IR (KBr) $\nu_{max}$ 3031 (OH), 1638, 1584 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 3.43 (2H, ddd, $J$=6.4, 1.7, 1.4 Hz, $ArC\underline{H}_2CH=$), 5.13 (1H, ddt, $J$=10.1, 1.8, 1.4 Hz, $-CH=C\underline{H}H$), 5.18 (1H, ddt, $J$=17.2, 1.8, 1.7 Hz, $-CH=C\underline{H}H$), 6.02 (1H, ddt, $J$=17.2, 10.1, 6.4 Hz, $-CH_2C\underline{H}=CH_2$), 6.95 (1H, s, pyrazole-H), 7.14–7.18 (6H, m, Tr-H), 7.27–7.30 (9H, m, Tr-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 30.5 (t), 78.1 (s), 116.3 (t), 120.5 (d), 127.5 (d), 127.6 (d), 130.1(d), 135.8 (d), 138.0 (s), 138.3 (s), 143.3 (s); HR-MS *m/z* Calcd for $C_{25}H_{22}N_2O$ ($M^+$) 366.1732, Found 366.1728.

**11a**: White powder; mp 120–121°C; IR (KBr) $\nu_{max}$ 3436 (OH), 1644, 1597 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 2.84 (2H, br d, $J$=6.3 Hz, Ar-$C\underline{H}_2CH=$), 4.07 (1H, br s, OH), 4.94 (1H, dd, $J$=10.5, 1.4 Hz, $-CH=C\underline{H}H$), 4.97 (1H, dd, $J$=17.2, 1.4 Hz, $-CH=C\underline{H}H$), 5.07 (1H, ddt, $J$=17.2, 10.5, 6.3 Hz, $-CH_2C\underline{H}=CH_2$), 7.13–7.15 (6H, m, Tr-H), 7.28 (1H, s, pyrazole-H), 7.26–7.31 (9H, m, Tr-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 31.5 (t), 78.4 (s), 117.2 (t), 125.9 (s), 127.3 (d), 127.6 (d), 130.0 (d), 132.9 (d), 141.2 (s), 143.0 (s); HR-MS *m/z* Calcd for $C_{25}H_{22}N_2O$ ($M^+$) 366.1732, Found 366.1729.

**11b**: Yellow powder; mp 75–78°C; IR (KBr) $\nu_{max}$ 3111 (OH), 1637 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 3.23 (2H, ddd, $J$=5.9, 1.6, 1.4 Hz, $-OC\underline{H}_2CH=$), 4.96 (1H, ddt, $J$=17.1, 1.6 Hz, $-CH=C\underline{H}H$), 5.02 (1H, ddt, $J$=10.3, 1.6, 1.4 Hz, $-CH=C\underline{H}H$), 5.17 (2H, s, $ArC\underline{H}_2Ph$) 5.72 (1H, ddt, $J$=10.3, 17.1, 5.9 Hz, $-CH_2C\underline{H}=CH_2$), 6.99–7.02 (2H, m, Ph-H), 7.14 (1H, s, pyrazole-3-H), 7.20–7.27 (3H, m, Ph-H), 7.68 (1H, br s, OH); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 27.0 (t), 53.6 (t), 116.5 (t), 126.6 (d), 127.6 (d), 127.9 (d), 128.6 (d), 133.5 (d), 136.9 (s), 139.1 (s) (a singlet carbon should be overlapped with a benzyl methine at 126.6 ppm since a signal at 126.6 ppm correlated with $C\underline{H}_2$ at 3.23 ppm in the HMBC spectrum); HR-MS *m/z* Calcd for $C_{13}H_{14}N_2O$ ($M^+$) 214.1106, Found 214.1100.

**3,5-Diallyl-2-benzyl-4-hydroxy-2*H*-pyrazole (12)** White powder; mp 55–58°C; IR (KBr) $\nu_{max}$ 3079 (OH), 1639 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 3.23 (2H, dt, $J$=6.0, 1.6 Hz, $-OC\underline{H}_2CH=$), 3.44 (2H, dt, $J$=6.4, 1.6 Hz, $-OC\underline{H}_2CH=$), 3.84 (1H, br s, OH), 5.03 (1H, ddt, $J$=17.1, 1.7, 1.6 Hz, $-CH=C\underline{H}H$), 5.08 (1H, ddt, $J$=10.1, 1.7, 1.6 Hz, $-CH=C\underline{H}H$), 5.15 (1H, ddt, $J$=10.1, 1.8, 1.6 Hz, $-CH=C\underline{H}H$), 5.18 (2H, s, $ArC\underline{H}_2Ph$), 5.22 (1H, ddt, $J$=17.2, 1.8, 1.6 Hz, $-CH=C\underline{H}H$), 5.77 (1H, ddt, $J$=17.1, 10.1, 6.0 Hz, $-CH_2C\underline{H}=CH_2$), 6.06 (1H, ddt, $J$=17.2, 10.1, 6.4 Hz, $-CH_2C\underline{H}=CH_2$), 7.02–7.05 (2H, m, Ph-H), 7.23–7.31 (3H, m, Ph-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 27.5 (t), 30.5 (t), 53.6 (t), 116.3 (t), 116.8 (t), 126.5 (d), 127.5 (d), 127.9, 128.6 (d), 133.4 (d), 135.6 (d), 136.6 (s), 137.3 (s), 137.5(s); HR-MS *m/z* Calcd for $C_{16}H_{18}N_2O$ ($M^+$) 254.1419, Found 254.1418.

**10d**: Oil; IR (liquid film) $\nu_{max}$ 3081 (OH), 1639 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 0.88 (3H, t, $J$=7.6 Hz, $-NCH_2CH_2CH_2C\underline{H}_3$), 1.27 (2H, tq, $J$=7.7, 7.6 Hz, $-NCH_2CH_2C\underline{H}_2CH_3$), 1.71 (2H, tt, $J$=7.7, 7.6 Hz, $-NCH_2C\underline{H}_2CH_2CH_3$), 3.38 (2H, dt, $J$=6.0, 1.6 Hz, $ArC\underline{H}_2CH=$), 3.91 (2H, t, $J$=7.6 Hz, $NC\underline{H}_2CH_2CH_2CH_3$), 5.02 (1H, ddt, $J$=17.3, 1.6 Hz, $-CH=C\underline{H}H$), 5.08 (1H, ddt, $J$=10.0, 1.6 Hz, $-CH=C\underline{H}H$), 5.85 (1H, ddt, $J$=17.3, 10.0, 6.0 Hz, $-CH_2C\underline{H}=CH_2$), 7.07 (1H, s, pyrazole-3-H), 8.23 (1H, br s, OH); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 13.6 (q), 19.8 (t), 27.0 (t), 32.3 (t), 49.3 (t), 116.2 (t), 126.1 (s), 127.2 (d), 133.9 (d), 138.5

(s); HR-MS *m/z* Calcd for $C_{10}H_{16}N_2O$ ($M^+$) 180.1262, Found 180.1260.

**11d**: Oil; IR (liquid film) $\nu_{max}$ 3340 (OH) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 0.92 (3H, t, $J$=7.6 Hz, $-NCH_2CH_2CH_2C\underline{H}_3$), 1.31 (2H, tq, $J$=7.6, 7.6 Hz, $-NCH_2CH_2C\underline{H}_2CH_3$), 1.76 (2H, tt, $J$=7.6, 7.3 Hz, $-NCH_2C\underline{H}_2CH_2CH_3$) 3.41 (2H, ddd, $J$=6.5, 1.6, 1.4 Hz, $ArC\underline{H}_2CH=$), 3.94 (2H, t, $J$=7.3 Hz, $NC\underline{H}_2CH_2CH_2CH_3$), 5.15 (1H, ddt, $J$=10.1, 1.8, 1.4 Hz, $-CH=C\underline{H}H$), 5.21 (1H, ddt, $J$=17.2, 1.8, 1.6 Hz, $-CH=C\underline{H}H$), 6.04 (1H, ddt, $J$=17.2, 10.1, 6.5 Hz, $-CH_2C\underline{H}=CH_2$), 7.03 (1H, s, pyrazole-5-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 13.6 (q), 19.8 (t), 30.3(t), 32.5 (t), 52.2 (t), 116.4 (t), 116.9 (d), 135.6 (d), 137.0 (s), 138.5 (s); HR-MS *m/z* Calcd for $C_{10}H_{16}N_2O$ ($M^+$) 180.1262, Found 180.1258.

**10f**: Brown powder; mp 120–122°C; IR (KBr) $\nu_{max}$ 1643 (C=C), 3133 (OH) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 2.40 (3H, s, $ArC\underline{H}_3$), 3.72 (2H, d, $J$=6.3 Hz, $ArC\underline{H}_2CH=$), 5.09 (1H, dd, $J$=17.2, 1.4 Hz, $-CH=C\underline{H}H$), 5.11 (1H, dd, $J$=10.3, 1.4 Hz, $-CH=C\underline{H}H$), 5.93 (1H, ddt, $J$=17.2, 10.3, 6.3 Hz, $-CH_2C\underline{H}=CH_2$), 7.27 (2H, d, $J$=8.4 Hz, Ph-H), 7.42 (1H, s, pyrazole-H), 7.77 (2H, d, $J$=8.4 Hz, Ph-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 21.6, 28.0, 117.4, 127.8, 128.4, 129.9, 133.2, 134.5, 136.6, 141.2, 145.5; HR-MS *m/z* Calcd for $C_{13}H_{14}N_2O_3S$ ($M^+$) 278.0725, Found 278.0720.

**11f**: White powder; mp 138–139°C; IR (KBr) $\nu_{max}$ 3133 (OH), 1644, 1598 (C=C) $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 2.41 (3H, s, $ArC\underline{H}_3$), 3.39 (2H, ddd, $J$=6.6, 1.5, 1.4 Hz, $ArC\underline{H}_2CH=$), 5.13 (1H, ddt, $J$=17.4, 1.5 Hz, $-CH=C\underline{H}H$), 5.14 (1H, ddt, $J$=9.8, 1.5, 1.4 Hz, $-CH=C\underline{H}H$), 5.93 (1H, ddt, $J$=17.4, 9.8, 6.6 Hz, $-CH_2C\underline{H}=CH_2$), 7.29 (2H, br d, $J$=8.5 Hz, Ph-H), 7.60 (1H, s, pyrazole-5-H), 7.82 (2H, br d, $J$=8.5 Hz, Ph-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 21.7 (q), 30.4 (t), 116.6 (t), 117.7 (d), 127.8 (d), 130.0 (d), 133.5 (d), 134.2 (s), 141.8 (s), 145.4 (s), 147.7 (s); HR-MS *m/z* Calcd for $C_{13}H_{14}N_2O_3S$ ($M^+$) 278.0725, Found 278.0722.

**11g**: Oil; IR (liquid film) $\nu_{max}$ 3375 (OH), 1642, 1595 (C=C), $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 3.13 (3H, s, $-SO_2C\underline{H}_3$), 3.48 (2H, ddd, $J$=6.5, 1.5, 1.4 Hz, $ArC\underline{H}_2CH=$), 5.20 (1H, ddt, $J$=10.7, 1.7, 1.5 Hz, $-CH=C\underline{H}H$), 5.23 (1H, ddt, $J$=17.2, 1.7, 1.4 Hz, $-CH=C\underline{H}H$), 5.96 (1H, ddt, $J$=17.2, 10.7, 6.5 Hz, $-CH_2C\underline{H}=CH_2$), 7.61 (1H, s, pyrazole-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 28.4, 36.6, 117.6, 127.1, 130.4, 133.2, 137.5; HR-MS *m/z* Calcd for $C_7H_{10}N_2O_3S$ ($M^+$) 202.0412, Found 202.0414.

**Procedure for Heating in a Sealed Tube (Table 1 Entry 1)** A sealed tube containing a solution of **9a** (4.0 g, 11 mmol) in DEA (44 mL) was heated at 190°C for 1 h in an oil bath. After the reaction was quenched with $NH_4Cl$ aq., extraction was carried out with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=2 : 1) to afford 3-allyl-4-hydroxy-2-trityl-2*H*-pyrazole (**11a**) (2.36 g, 59%) and 3-allyl-4-hydroxy-1-trityl-1*H*-pyrazole (**10a**) (120 mg, 3%).

**3-Allyl-4-trifluoromethanesulfonyloxy-2-trityl-2*H*-pyrazole (13)** To a solution of **11a** (183 mg, 0.5 mmol) in $CH_2Cl_2$ (2 mL) with triethylamine (90 $\mu$L, 0.6 mmol) was added trifluoromethanesulfonic anhydride (100 $\mu$L, 0.6 mmol) at −20°C. After stirring for 30 min at that temperature, the reaction was quenched with $NH_4Cl$ aq. and extraction was carried out with $CH_2Cl_2$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=6 : 1) to afford **13** (217 mg, 87%). **13**: White powder; mp 58–59°C; IR (KBr) $\nu_{max}$ 1648 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.43 (2H, ddd, $J$=6.4, 1.6, 1.6 Hz, $ArCH_2$–), 5.07 (1H, ddt, $J$=10.3, 1.6, 1.6 Hz, –C=C$\underline{H}$H), 5.08 (1H, ddt, $J$=16.9, 1.6, 1.6 Hz, –C=CH$\underline{H}$), 5.91 (1H, ddt, $J$=16.9, 10.3, 6.4 Hz, –C$\underline{H}$=C), 7.11–7.15 (6H, m, Tr-H), 7.29–7.34 (9H, m, Tr-H), 7.35 (1H, s, pyrazole-5-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 29.7 (t), 79.4 (s), 116.6 (t), 118.6 (q, $^1J_{C-F}$=321.2 Hz), 125.1 (d), 127.8 (d), 128.0 (d), 130.0 (d), 130.4 (s), 133.7 (d), 142.1 (s), 142.3 (s); HR-MS *m/z* Calcd for $C_{26}H_{21}F_3N_2O_3S$ ($M^+$) 498.1225, Found 498.1224.

**3-(3-Hydroxy)propyl-4-trifluoromethanesulfonyloxy-2-trityl-2*H*-pyrazole (14)** To a solution of **13** (498 mg, 1 mmol) in THF (1 mL) was added 9-BBN (244 mg, 1 mmol) at 0°C. After stirring for 2 h at rt, MeOH (5 mL) was added at 0°C to quench the reaction. Then, 10% NaOH aq. (0.4 mL, 1 mmol) and 30% $H_2O_2$ aq. (0.42 mL, 3.7 mmol) were added at 0°C. After stirring at rt for 20 h, the reaction was quenched with $NH_4Cl$ aq. and extraction was carried out with $CH_2Cl_2$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=3 : 1) to afford **14** (449 mg, 87%). **14**: Colorless oil; IR (liquid film) $\nu_{max}$ 3376 (OH), 1495 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.85 (2H, tt, $J$=6.2, 6.9 Hz, $-CH_2CH_2CH_2OH$), 2.75 (2H, t, $J$=6.9 Hz, $-CH_2CH_2CH_2OH$), 3.52 (2H, t, $J$=6.2 Hz, $-CH_2CH_2C\underline{H}_2OH$), 7.10–7.13 (6H, m, Tr-H), 7.28–7.33 (9H, m, Tr-H), 7.40 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 21.5, 30.3, 61.6, 79.5, 118.5 (q, $J_{C-F}$=321.3 Hz), 125.0, 127.9, 128.0, 129.9, 130.1, 142.1, 143.7; HR-MS *m/z* Calcd for $C_{26}H_{23}F_3N_2O_4S$ ($M^+$) 516.1331, Found 516.1334.

**3-(3-Toluenesulfonyloxy)propyl-4-trifluoromethanesulfonyloxy-2-trityl-2*H*-pyrazole (15)** To a solution of **14** (124 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) with triethylamine (70 $\mu$L, 0.48 mmol) was added *p*-toluenesulfonylchloride (97 mg, 0.48 mmol) at rt. After stirring for 24 h, the reaction was quenched with $NH_4Cl$ aq. and extraction was carried out with $CH_2Cl_2$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=3 : 1) to afford **15** (150 mg, 93%). **15**: Colorless needles ($CH_2Cl_2$); mp 66–70°C; IR (KBr) $\nu_{max}$ 1598 (C=C), 1492 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.00 (2H, tt, $J$=6.8, 7.1 Hz, $-CH_2C\underline{H}_2CH_2OTs$), 2.40 (3H, s, $ArC\underline{H}_3$), 2.66 (2H, t, $J$=7.1 Hz, $-C\underline{H}_2CH_2CH_2OTs$), 4.03 (2H, t, $J$=6.8 Hz, $-CH_2CH_2C\underline{H}_2OTs$), 7.05–7.12 (6H, m, Ar-H), 7.25–7.36 (12H, m, Ar-H), 7.72–7.75 (2H, m, Ar-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 20.8, 21.5, 26.9, 69.5, 79.4, 118.5 (q, $^1J_{C-F}$=321.3 Hz), 125.0, 125.1, 127.1, 127.7, 127.75, 127.80, 128.0, 129.7, 129.9, 133.0, 142.16, 142.23, 144.6; HR-MS *m/z* Calcd for $C_{33}H_{29}F_3N_2O_6S_2$ ($M^+$) 670.1419, Found 670.1417.

**5,6-Dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl Trifluoromethanesulfonate (16)** To a solution of **15** (150 mg, 0.22 mmol) in EtOH (2 mL) was added 1 N HCl aq. (4 mL, 4 mmol). After stirring for 18 h at 80°C, the reaction was quenched with $NaHCO_3$ aq. and extraction was carried out

with $CH_2Cl_2$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography ($CH_2Cl_2$) to afford **16** (23 mg, 40%). **16**: Colorless oil; IR (liquid film) $\nu_{max}$ 1541 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.65 (2H, tt, $J$=7.7, 7.4 Hz, $-CH_2-$), 3.00 (2H, t, $J$=7.7 Hz, $-CH_2-$), 4.17 (2H, t, $J$=7.4 Hz, $-CH_2-$), 7.45 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 22.4, 25.6, 48.7, 118.5 (q, $^1J_{C-F}$=321.3 Hz), 127.3, 134.6, 136.7; HR-MS $m/z$ Calcd for $C_7H_7F_3N_2O_3S$ ($M^+$) 256.0129, Found 256.0132.

**Suzuki–Miyaura Coupling of 16 and Arylboronic Acids into Withasomnines 1a–l**

**Suzuki–Miyaura Coupling by Conventional Heating (Table 2 Entry 1)** To a solution of **16** (48 mg, 0.19 mmol) in 1,2-diethoxyethane (DME) (1.0 mL) and $H_2O$ (1.0 mL) were added phenylboronic acid (46 mg, 0.38 mmol), $Pd(dba)_2$ (3.0 mg, 10 mol%), tricyclohexylphosphine (20 mg, 40 mol%), and $NaCO_3$ (40 mg, 0.38 mmol). The reaction mixture was heated at 100°C for 24 h with stirring. Then, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography ($CH_2Cl_2$–$Et_2O$=1 : 1) to afford **1a** (7.0 mg, 20%).

**General Procedure for Suzuki–Miyaura Coupling under Microwave Irradiation (Table 2 Entry 10=Table 3 Entry 1)** To a solution of **16** (10.3 mg, 0.04 mmol) in DME (1.8 mL) and $H_2O$ (0.2 mL) in a vial for microwave irradiator were added phenylboronic acid (9.8 mg, 0.08 mmol), $Pd(dba)_2$ (2.3 mg, 10 mol%), tricyclohexylphosphine (4.6 mg, 40 mol%), $Na_2CO_3$ (9.5 mg, 0.086 mmol), and TOMAC (1 drop, 8 mg). The reaction vial was filled with nitrogen gas, sealed, and then heated at 130°C for 30 min under microwave irradiation. After cooling, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography ($CH_2Cl_2$–$Et_2O$=1 : 1) to afford **1a** (6.5 mg, 88%).

**1a**: Colorless crystals ($CH_2Cl_2$); mp 112–113°C (lit.[1b] 117–118°C); IR (KBr) $\nu_{max}$ 1606 (C=C), 1501 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.69 (2H, tt, $J$=7.7, 7.2 Hz, $-CH_2-$), 3.10 (2H, t, $J$=7.7 Hz, $ArCH_2CH_2-$), 4.18 (2H, t, $J$=7.2 Hz, $-NCH_2CH_2-$), 7.16–7.47 (5H, m, Ph-H), 7.82 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.8, 26.4, 47.6, 115.3, 125.0, 125.6, 128.8, 133.4, 140.9, 142.6; HR-MS $m/z$ Calcd for $C_{12}H_{12}N_2$ ($M^+$) 184.1000, Found 184.0998.

**1b**: Colorless crystals ($CH_2Cl_2$); mp 225–229°C; IR (KBr) $\nu_{max}$ 3401 (OH), 1570 (C=C), 1515 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$–$CD_3OD$=1 : 1) $\delta$: 2.53 (2H, tt, $J$=7.5, 7.2 Hz, $-CH_2-$), 2.90 (2H, t, $J$=7.2 Hz, $ArCH_2CH_2-$), 3.16 (1H, br s, –OH), 3.96 (2H, t, $J$=7.5 Hz, $-NCH_2CH_2-$), 6.65 (2H, d, $J$=8.3 Hz, Ph-H), 7.12 (2H, d, $J$=8.3 Hz, Ph-H), 7.51 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$–$CD_3OD$=1 : 1) $\delta$: 22.9, 25.7, 46.7, 115.0, 115.0, 124.0, 125.7, 139.4, 141.9, 154.7; HR-MS $m/z$ Calcd for $C_{12}H_{12}N_2O$ ($M^+$) 200.0949, Found 200.0955.

**1c**: Colorless crystals ($CH_2Cl_2$); mp 124–128°C; IR (KBr) $\nu_{max}$ 1577 (C=C), 1565 (C=C), 1509 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.68 (2H, tt, $J$=7.7, 7.2 Hz, $-CH_2CH_2CH_2-$), 3.07 (2H, t, $J$=7.7 Hz, $ArCH_2CH_2-$), 3.82 (3H, s, $-OCH_3$), 4.17 (2H, t, $J$=7.2 Hz, $-NCH_2CH_2-$), 6.92 (2H, d, $J$=8.4 Hz, Ph-H), 7.37 (2H, d, $J$=8.4 Hz, Ph-H), 7.74 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.7, 26.4, 47.5, 55.3, 114.3, 115.0, 126.1, 126.2, 140.6, 141.9, 157.7; HR-MS $m/z$ Calcd for $C_{13}H_{14}N_2O$ ($M^+$) 214.1106, Found 214.1106.

**1d**: Colorless crystals ($CH_2Cl_2$); mp 162–165°C; IR (KBr) $\nu_{max}$ 3079 (OH), 1593 (C=C), 1504 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CD_3OD$) $\delta$: 2.71 (2H, quint, $J$=7.2 Hz, $-CH_2CH_2CH_2-$), 3.11 (2H, t, $J$=7.2 Hz, $ArCH_2CH_2-$), 4.14 (2H, t, $J$=7.5 Hz, $-NCH_2CH_2-$), 4.73 (1H, s, –OH), 6.68 (1H, br d, $J$=7.8 Hz, Ph-H), 6.94 (1H, s, Ph-H), 6.65 (1H, d, $J$=7.8 Hz, Ph-H), 7.19 (1H, t, $J$=7.8 Hz, Ph-H), 7.76 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CD_3OD$) $\delta$: 23.0, 25.6, 46.7, 111.1, 112.2, 114.9, 115.8, 129, 133.7, 139.8, 142.7, 156.7; HR-MS $m/z$ Calcd for $C_{12}H_{12}N_2O$ ($M^+$) 200.0949, Found 200.0947.

**1e**: Colorless crystals ($CH_2Cl_2$); mp 84–85°C; IR (KBr) $\nu_{max}$ 1551 (C=C), 1484 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.37 (3H, s, $ArCH_3$), 2.66 (2H, tt, $J$=7.4, 7.2 Hz, $-CH_2CH_2CH_2-$), 2.93 (2H, t, $J$=7.4 Hz, $ArCH_2CH_2-$), 4.21 (2H, t, $J$=7.2 Hz, $-NCH_2CH_2-$), 7.15–7.28 (4H, m, Ph-H), 7.60 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 20.9, 23.6, 26.5, 47.7, 115.1, 125.8, 126.5, 129.3, 130.5, 132.8, 135.6, 143.1, 143.7; HR-MS $m/z$ Calcd for $C_{13}H_{14}N_2$ ($M^+$) 198.1157, Found 198.1153.

**1f**: Colorless crystals ($CH_2Cl_2$); mp 130–132°C; IR (KBr) $\nu_{max}$ 1583 (C=C), 1560 (C=C), 1525 ($NO_2$) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.74 (2H, tt, $J$=7.2, 6.9 Hz, $-CH_2CH_2CH_2-$), 3.16 (2H, t, $J$=6.9 Hz, $ArCH_2CH_2-$), 4.22 (2H, t, $J$=7.2 Hz, $-NCH_2CH_2-$), 7.51 (1H, t, $J$=8.1 Hz, Ph-H), 7.75 (1H, ddd, $J$=8.1, 1.5, 0.9 Hz, Ph-H), 7.88 (1H, br s, pyrazole-H), 8.02 (1H, ddd, $J$=8.1, 2.4, 0.9 Hz, Ph-H), 8.25 (1H, dd, $J$=2.4, 1.5 Hz, Ph-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.9, 26.3, 47.7, 113.4, 119.3, 120.2, 129.7, 130.5, 135.2, 141.0, 143.4, 148.7; HR-MS $m/z$ Calcd for $C_{12}H_{11}N_3O_2$ ($M^+$) 229.0851, Found 229.0849.

**1g**: Colorless crystals ($CH_2Cl_2$); mp 145–148°C; IR (KBr) $\nu_{max}$ 3433 ($NH_2$), 1608 (C=C), 1587 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.66 (2H, quint, $J$=7.4 Hz, $-CH_2CH_2CH_2-$), 3.07 (2H, t, $J$=7.4 Hz, $ArCH_2CH_2-$), 4.15 (2H, t, $J$=7.34 Hz, $-NCH_2CH_2-$), 6.54 (1H, br d, $J$=7.8 Hz, Ph-H), 6.78 (1H, br s, Ph-H), 6.85 (1H, br d, $J$=7.8 Hz, Ph-H), 7.14 (1H, t, $J$=7.8 Hz, Ph-H), 7.77 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.8, 26.3, 47.5, 111.6, 112.6, 115.3, 115.6, 129.7, 134.3, 140.9, 142.6, 146.7; HR-MS $m/z$ Calcd for $C_{12}H_{13}N_3$ ($M^+$) 199.1109, Found 199.1113.

**1h**: Colorless crystals ($CH_2Cl_2$); mp 90–93°C; IR (KBr) $\nu_{max}$ 1573 (C=C), 1502 (C=C), 1488 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.67 (2H, quint, $J$=7.2 Hz, $-CH_2CH_2CH_2-$), 3.05 (2H, t, $J$=7.2 Hz, $ArCH_2CH_2-$), 3.82 (3H, s, $-OCH_3$), 4.16 (2H, t, $J$=7.2 Hz, $-NCH_2CH_2-$), 5.95 (2H, s, $-OCH_2O-$), 6.81 (2H, d, $J$=8.1 Hz, Ph-H), 6.90 (1H, d, $J$=8.1 Hz, Ph-H), 6.92 (1H, s, Ph-H), 7.71 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.7, 26.4, 47.5, 100.9, 105.8, 108.7, 115.2, 118.2, 127.6, 140.6, 142.1, 145.5, 148.0; HR-MS $m/z$ Calcd for $C_{13}H_{12}N_2O_2$ ($M^+$) 228.0899, Found 228.0900.

**1i**: Colorless crystals ($CH_2Cl_2$); mp 92–95°C; IR (KBr) $\nu_{max}$ 1567 (C=C), 1508 (C=C), 1509 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.69 (2H, quint, $J$=7.2 Hz, $-CH_2CH_2CH_2-$), 3.07 (2H, t, $J$=7.2 Hz, $ArCH_2CH_2-$), 4.17 (2H, t, $J$=7.2 Hz, $-NCH_2CH_2-$), 7.05 (2H, br t, $J$=8.7 Hz, H-3′,

H-5′), 7.39 (2H, brdd, $J$=8.7, 5.4 Hz, H-2′, H-6′), 7.76 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.7, 26.4, 47.6, 114.5, 115.6 (d, $^2J_{C-F}$=21.8 Hz), 126.4 (d, $^3J_{C-F}$=8.0 Hz), 129.5, 140.8, 142.4, 161.0 (d, $^1J_{C-F}$=244.4 Hz); HR-MS $m/z$ Calcd for $C_{12}H_{11}FN_2$ ($M^+$) 202.0906, Found 202.0908.

**1j**: Colorless crystals ($CH_2Cl_2$); mp 82–85°C; IR (KBr) $\nu_{max}$ 1593 (C=C), 1498 (C=C) cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.68 (2H, tt, $J$=7.7, 7.2 Hz, –$CH_2C\underline{H}_2CH_2$–), 3.03 (2H, t, $J$=7.7 Hz, Ar$C\underline{H}_2CH_2$–), 3.82 (3H, s, –$OC\underline{H}_3$), 4.17 (2H, t, $J$=7.2 Hz, –$NC\underline{H}_2CH_2$–), 6.98–7.04 (2H, m, thienyl-H), 7.14 (1H, dd, $J$=5.1, 1.5 Hz, thienyl-H), 7.71 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.2, 26.3, 47.8, 109.9, 121.3, 122.2, 127.5, 136.0, 140.8, 142.5; HR-MS $m/z$ Calcd for $C_{10}H_{10}N_2S$ ($M^+$) 190.0565, Found 190.0557.

**1k**: Colorless crystals ($CH_2Cl_2$); mp 62–64°C; IR (KBr) $\nu_{max}$ 1595 (C=C), 1493 (C=C) cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.69 (2H, quint, $J$=7.2 Hz, –$CH_2C\underline{H}_2CH_2$–), 3.06 (2H, t, $J$=7.2 Hz, Ar$C\underline{H}_2CH_2$–), 4.17 (2H, t, $J$=7.2 Hz, –$NC\underline{H}_2CH_2$–), 7.14 (1H, dd, $J$=3.0, 1.2 Hz, thienyl-H), 7.21 (1H, dd, $J$=5.1, 1.2 Hz, thienyl-H), 7.35 (1H, dd, $J$=5.1, 3.0 Hz, thienyl-H),7.73 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.3, 26.4, 47.7, 111.3, 117.2, 125.7, 125.9, 134.0, 141.1, 142.6; HR-MS $m/z$ Calcd for $C_{10}H_{10}N_2S$ ($M^+$) 190.0565, Found 190.0559.

**1l**: Oil; IR (liq. film) $\nu_{max}$ 1660 (C=C), 1548 (C=C) cm$^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.66 (2H, m, –$CH_2C\underline{H}_2CH_2$–), 3.04 (2H, m, Ar$C\underline{H}_2CH_2$–), 4.16 (2H, t, $J$=7.2 Hz, –$NC\underline{H}_2CH_2$–), 6.21 (1H, dd, $J$=3.3, 0.9 Hz, furyl-H), 6.41 (1H, dd, $J$=3.3, 1.8 Hz, furyl-H), 7.35 (1H, dd, $J$=1.8, 0.9 Hz, furyl-H), 7.72 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 23.1, 26.3, 47.7, 76.6, 102.5, 111.0, 140.0, 140.3, 142.4, 148.8; HR-MS $m/z$ Calcd for $C_{10}H_{10}N_2O$ ($M^+$) 174.0780, Found 174.0787.

**5,6-Dihydro-5-hydroxy-4*H*-pyrrolo[1,2-*b*]pyrazole (17)** Colorless crystals ($CH_2Cl_2$); mp 137–140°C; IR (KBr) $\nu_{max}$ 3042 (OH), 1604 (C=C) cm$^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$: 2.55 (2H, m, –$CH_2C\underline{H}_2CH_2$–), 2.84 (2H, brt, $J$=7.3 Hz, Ar$C\underline{H}_2CH_2$–), 4.05 (2H, brdd, $J$=7.3, 7.1 Hz, –$NC\underline{H}_2CH_2$–), 7.17 (1H, s, pyrazole-H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$: 21.9 (t), 26.4 (t), 48.1 (t), 131.8 (s), 132.6 (d), 134.4 (s); HR-MS $m/z$ Calcd for $C_6H_8N_2O$ ($M^+$) 124.0637, Found 124.0634.

**Biological Assay**[50] The biological assay for the inhibitory activity of **1a**–**l** against COX-1 and COX-2 was carried out with a COX Fluorescent Activity Assay Kit (Cayman Chemical) following the instructions included in the kit.

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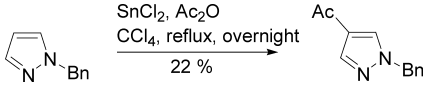
44) Our early effort of the Friedel–Crafts acylation of 1-benzyl-1*H*-pyrazole with acetylchloride or acetic anhydride in the presence of various kinds of metal chloride as Lewis acid catalyst was not successful. One hopeful example was the reaction with acetic anhydride (2.0 eq) carried out in the presence of tin chloride (5.0 eq) under refluxing $CCl_4$ overnight to produce desired 4-acetylated product in 22% yield as shown below. However, this reaction is impractical due to the low chemical yield and the use of a large amount of toxic tin chloride. These disappointing results in our earlier efforts pushed us to examine alternative methods for the synthesis of 4-acylated-1*H*-pyrazoles.




*Experiment*: To a solution of 1-benzyl-1*H*-pyrazole (316 mg, 2.0 mmol) in $CCl_4$ (2.0 mL) were added acetic anhydride (0.95 mL, 10 mmol) and $SnCl_2$ (4.13 g, 10 mmol) at $t_R$. After stirring overnight under reflux, the reaction mixture was treated with water and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude residue that was subsequently purified by column chromatography (hexane–EtOAc=2 : 1) to afford 4-acetyl-1*H*-1-benzylpyrazole (95.0 mg, 22%). 4-Acetyl-1*H*-1-benzylpyrazole: Yellow oil; IR (liquid film) $\nu_{max}$ 1757 (C=O), 1561 (C=C) $cm^{-1}$; $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$: 2.41 (3H, s, $CH_3CO$–), 5.31 (2H, s, $PhCH_2Ar$), 7.24–7.28 (2H, m, Ph-H), 7.34–7.39 (3 H, m, Ph-H), 7.85 (1H, s, pyrazole-H), 7.94 (1H, s, pyrazole-H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$: 20.7, 56.6, 120.0, 127.6, 128.1, 128.7, 130.2, 132.3, 136.0, 167.6; HR-MS *m/z* Calcd for $C_{12}H_{12}N_2O_2$ ($M^+$) 216.0899, Found 216.0894.

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48) The Suzuki–Miyaura coupling of **13** and phenylboronic acid did not give the desired product under various conditions but yielded **11a** in our earlier examination.
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