

CLAISEN REARRANGEMENT OF 4-ALLYLOXY-1-*p*-METHOXY-BENZYLPIRAZOLE AND SYNTHESIS OF PYRAZOLE-FUSED 7-MEMBERED LACTONES

Hayato Ichikawa,* Hiroki Takashima, and Shoichi Shimizu

College of Industrial Technology, Nihon University, 1-2-1 Izumicho Narashino, Chiba 275-8575, Japan. e-mail:ichikawa.hayato64@nihon-u.ac.jp

This manuscript is in celebration of Professor Yasuyuki Kita's 77th birthday.

Abstract – Allyl 4-pyrazolyl ethers were subjected to the Claisen rearrangement that involved heating under microwave condition to prepare the corresponding products with regioselective allylation at 5-position of the pyrazoles in good yields. The rearrangement products were converted into 7-membered pyrazololactones having an oxygen atom at 4-position of pyrazole, via a hydroesterification reaction with Pd(OAc)₂ and DPE-phos as ligand under 40 atm of CO/H₂ (6:34) in moderate to excellent yields.

INTRODUCTION

Pyrazole derivatives are employed in various applications in medicinal chemistry, agrochemical science, and materials science.^{1,2} A number of pyrazole derivatives have been prepared and investigated for potential use as anti-inflammatory, antipyretic, and analgesic agents.³ For example, celecoxib is a selective inhibitor of COX-2⁴ and rimonabant is a selective cannabinoid-1 receptor (CB1) blocker that has been shown to reduce body weight and improve cardiovascular risk factors in obese patients (Figure 1).⁵ Razaxaban, an orally active factor Xa inhibitor that is used for the treatment of venous thromboembolism, shows antithrombotic effect in the rabbit arterio-venous shunt thrombosis model.⁶

Many pyrazololactones prepared by the condensation of pyrazole and lactone are bioactive. As such, much effort has been concentrated on the development of their synthetic methods.⁷ As examples, **I** has antiplatelet activity⁸ and **II** is a GABA receptor (Figure 1).⁹ However, only a few methods for the synthesis of pyrazololactones are available.¹⁰

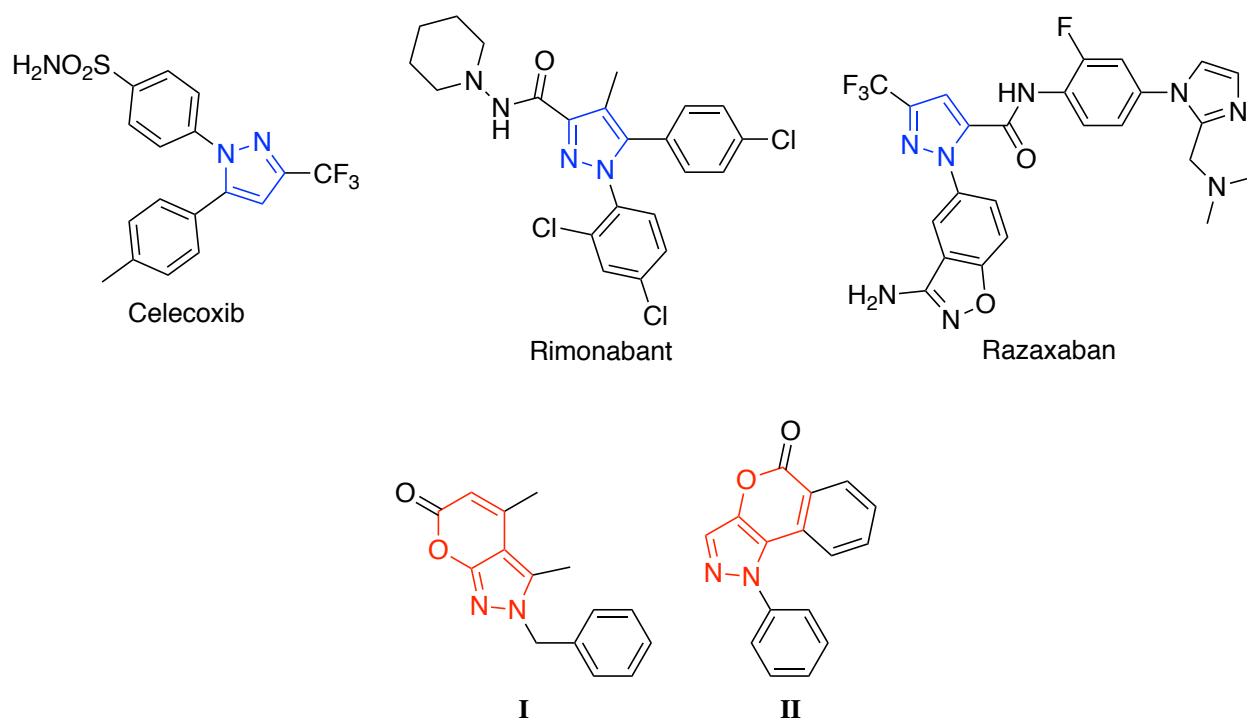


Figure 1. Bioactive pyrazole derivatives

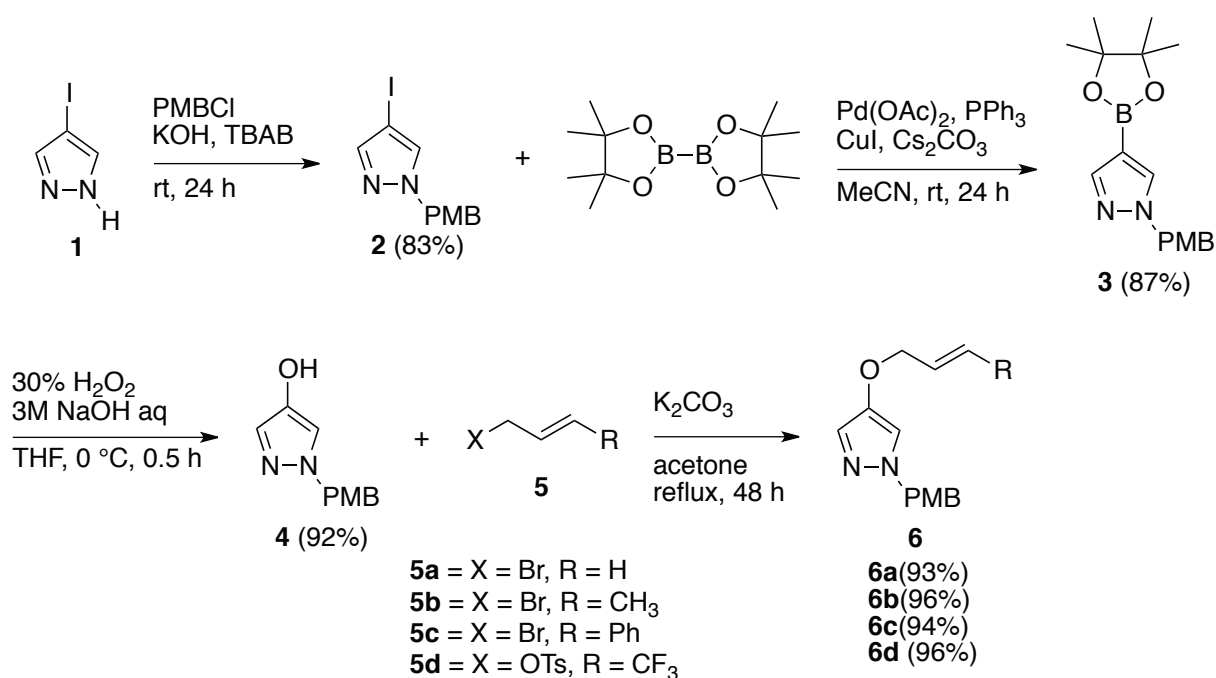
In this regard, methods for the facile preparation and functionalization of these compounds would have significant value. However, synthetic approaches to these pyrazole derivatives are complicated and often result in the formation of an isomeric mixture. We have reported the synthesis of some pyrazole derivatives, which is based on substitution and cross coupling reactions on the pyrazole ring,¹¹ including the synthesis of withasomnines and their derivatives.¹² It appears that the regioselective Claisen rearrangement of 4-allyloxy pyrazole takes place by heating.

On the other hand, ϵ -caprolactones are representative raw materials of polyester¹³ and are synthesized by the Baeyer-Villiger oxidation of cyclohexanone,¹⁴ alkene metathesis,¹⁵ and intramolecular esterification.¹⁶ One of the more common lactone synthesis methods is the hydroesterification of hydroxyalkene with CO/H₂ in the presence of palladium catalyst.¹⁷ Hydroesterification, a carbonylation reaction, has been intensively studied because ester is a multipurpose functional group that is derived from a catalytic reaction and synthesized from commercially available reagents.

Herein we report that the hydroesterification of 5-allyl-4-hydroxy-1-*p*-methoxybenzylpyrazole derived from the Claisen rearrangement of 4-allyloxy-1-*p*-methoxybenzylpyrazole with CO/H₂ in the presence of palladium catalyst selectively generates a pyrazole-fused 7-membered lactone. This is the first example of the synthesis of a pyrazole-fused 7-membered lactone that includes an oxygen atom at 4-position of pyrazole, although there are a few reports of the synthesis of pyrazole-fused lactones. We found that the excellent regioselectivity of the Claisen rearrangement of 4-allyloxy-1-*p*-methoxybenzylpyrazole resulted in the generation of only the 5-allyl-4-hydroxy-1-*p*-methoxybenzylpyrazole.

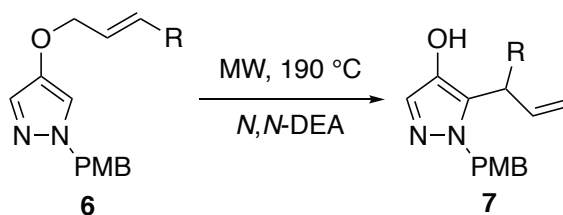
RESULTS AND DISCUSSION

Iodopyrazole **1** was reacted with *p*-methoxybenzyl chloride in the presence of KOH and tetrabutylammonium chloride without solvent for 24 h at room temperature to obtain 4-iodo-1-*p*-methoxybenzylpyrazole in 83% yield (Scheme 1).¹⁸ To a solution of **2** in acetonitrile were added bis(pinacolato)diboron, palladium acetate, triphenyl phosphine, copper iodide(I), and cesium carbonate, and the reaction mixture was stirred for 24 h at room temperature to produce **3** in 87% yield.^{19,20} To induce oxidation, 30% hydrogen peroxide solution and 3M sodium hydroxide solution were added to a solution of **3** in THF, and the reaction mixture was stirred for 30 min at 0 °C to generate 4-hydroxy-1-*p*-methoxybenzylpyrazole (**4**) in 92% yield. The yield of the 4-hydroxypyrazole derivative was higher than that in a previous report of the synthesis of withasommines.¹² Hydroxypyrazole **4** was reacted with various allylic reagents **5a–d** containing methyl, dimethyl, phenyl, and trifluoromethyl groups, respectively, to produce corresponding ethers **6** in good yields.



Scheme 1. Synthesis of allylic ether **6**

Allylpyrazole ethers **6** having hydrogen (**6a**), methyl (**6b**), and phenyl (**6c**) groups were each heated by microwave irradiation for 1 h at 190 °C in *N,N*-diethylaniline to generate 5-allyl-4-hydroxy-1-*p*-methoxybenzylpyrazoles **7a–c** in good yields with excellent regioselectivity (Table 1, Entries 1–3). The Claisen rearrangement of pyrazole allylic ether **6d**, which has a trifluoromethyl group, required a higher temperature than the reactions of the other compounds, and corresponding rearrangement product **7d** was obtained in 79% yield (Entry 4). 3-Allyl-4-hydroxy-1-*p*-methoxybenzylpyrazole was not produced under these conditions.

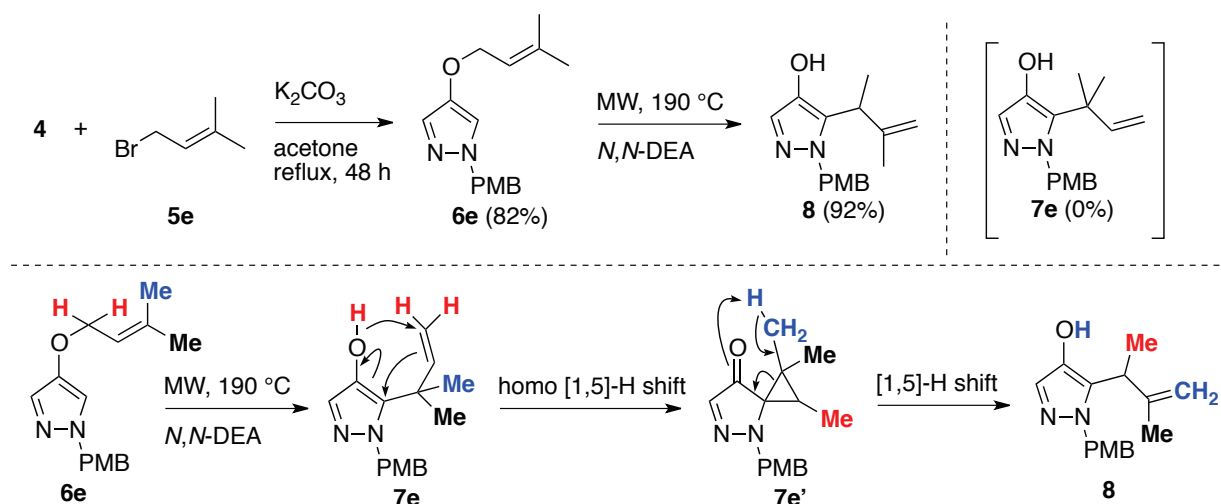


Entry	Substrate (R)	Temp. (°C)	Yield (%)
1	6a : R = H	190	98
2	6b : R = Me	190	93
3	6c : R = Ph	190	81
4	6d : R = CF ₃	250	79

MW = microwave; *N,N*-DEA = *N,N*-Diethylaniline

Table 1. Claisen rearrangement of **6**

On the other hand, the Claisen rearrangement of prenyl pyrazole ether **6e**, which is obtained from **4** and **5e**, under the same conditions generated **8**, from rearrangement product **7e**.

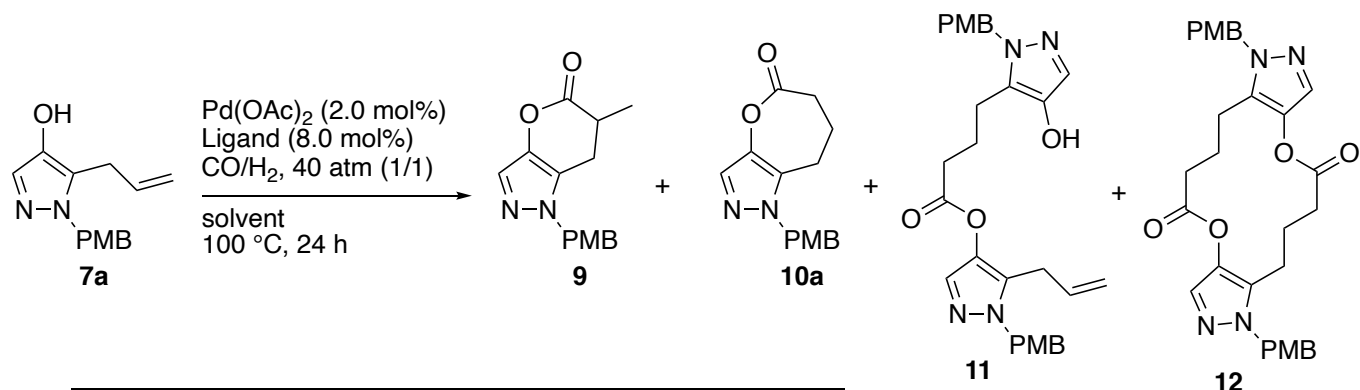


Scheme 2. Synthesis of prenyl pyrazole ether **6e** and rearrangement

The generation of **8** was a result of three consecutive processes: Claisen rearrangement product **7e** underwent homo[1,5]-hydride shift to produce **7e'**, and **7e'** in turn underwent [1,5]-hydrogen shift to yield **8**. An abnormal Claisen rearrangement was first reported in 1936.²¹ The excellent regioselectivity of the Claisen rearrangement of **6** was explained in a previous report.²² The regioselective rearrangement products were assigned to **7** on the basis of the NOESY spectra of the methylene of the *p*-methoxybenzyl group and the methine of the allyl group.

Rearrangement product **7a** was used as the substrate in a hydroesterification reaction that involved a palladium complex and dppb as ligand, with CO/H₂ in 1:1 ratio at 40 atm pressure (Table 2).²³ The hydroesterification proceeded in CH₂Cl₂ to furnish a 7-membered lactone in 59% yield as well as an

intermolecular hydroesterification dimer as the byproduct (Entries 1–4). The hydroesterification of **7a** was affected by the ligand. Triphenylphosphine, which is a monodentate ligand, and palladium catalyst accelerated the reaction in low yields (Entry 6). Whereas such bidentate ligands as dppe, dppp, dppf, and xantphos failed to promote the hydroesterification, a regioselective reaction took place with DPE-phos to produce pyrazole-fused 7-membered lactone **10a** in good yield (Entries 7–11).



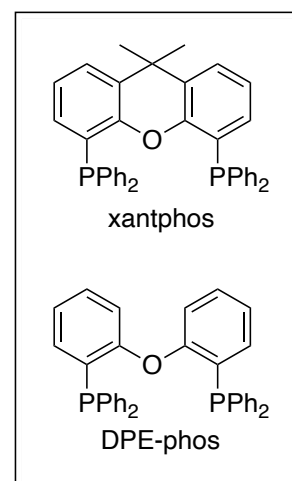
Entry	Solvent	Ligand	Yield(%)			
			9	10a	11^b	12
1	toluene	dppb	1	0	24	0
2	CH ₂ Cl ₂	dppb	12	59	12	11
3	MeCN	dppb	–	–	–	–
4	THF	dppb	1	3 ^a	30	0
5	CH ₂ Cl ₂	PPh ₃ (8 mol%)	0	trace	13	0
6	CH ₂ Cl ₂	PPh ₃ (20 mol%)	3	27	16	0
7	CH ₂ Cl ₂	dppe	–	–	–	–
8	CH ₂ Cl ₂	dppp	–	–	–	–
9	CH ₂ Cl ₂	dppf	0	0	7	0
10	CH ₂ Cl ₂	xantphos	–	–	–	–
11	CH ₂ Cl ₂	DPE-phos	7	89	0	4
12	CH ₂ Cl ₂	–	–	–	–	–

^a ¹H-NMR ratio, ^b crude yield.

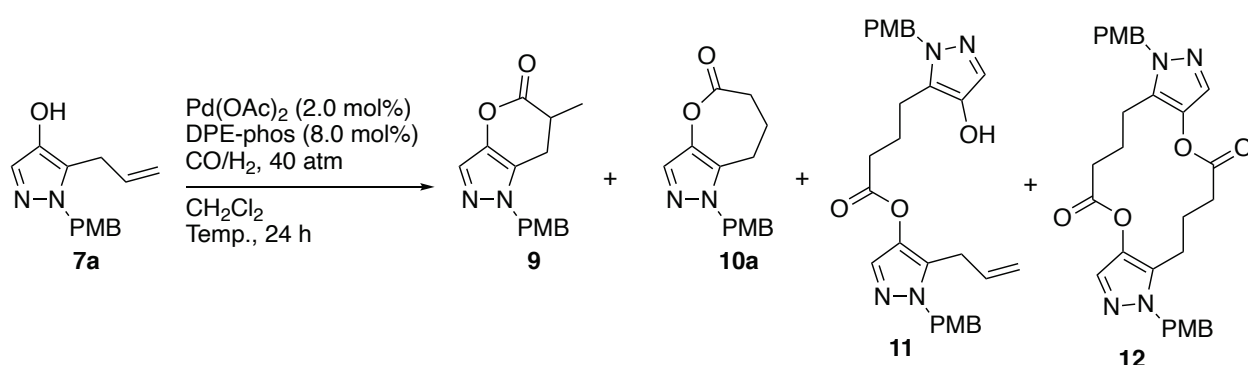
Table 2. Optimization of solvents and ligands used in hydroesterification

As shown in Table 2, the best reactivity and regioselectivity of the intramolecular reaction were achieved when DPE-phos was used as the ligand. However, it appeared that a more flexible ligand would improve the reactivity because xantphos palladium catalyst did not promote the hydroesterification. Regarding regioselectivity, as DPE-phos can form a palladium carbonyl complex as a tridentate ligand,²⁴ it is possible that the regioselectivity of the intramolecular hydroesterification would be improved. Interestingly, an intermolecular hydroesterification of 5-allyl-4-hydroxypyrazole **7a** took place to form 14-membered dilactone **12** although the intermolecular cyclization of *o*-allylphenol has not been reported. This dimer synthesis from a pyrazole substrate is a unique reaction.

The reaction temperature and the CO/H₂ ratio were investigated under the optimized catalytic conditions



(Table 3). The reaction did not proceed at 80 °C and the product yield was reduced at 120 °C because of isomerization of the double bond to form **13** (Entries 1–3). When the CO/H₂ ratio was increased, intermolecular hydroesterification proceeded to yield dimer **11** (Entries 4 and 5). The CO/H₂ ratio of 6:34 promoted the intramolecular hydroesterification selectively (Entry 7). The results suggest that a high hydrogen to carbon monoxide ratio is effective for the intramolecular cyclization of allylic hydroxypyrazole **7a** although a 5-membered lactonization is favorable on a hydroesterification of *o*-allylphenol derivatives as reported by Alper because of the isomerization of the double bond followed by the hydroesterification.²³

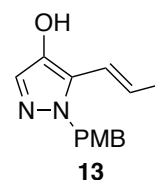


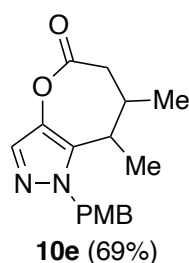
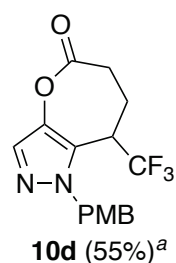
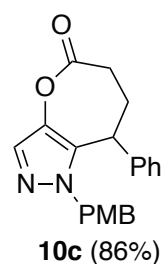
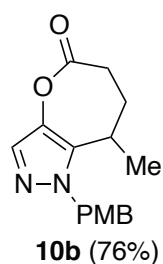
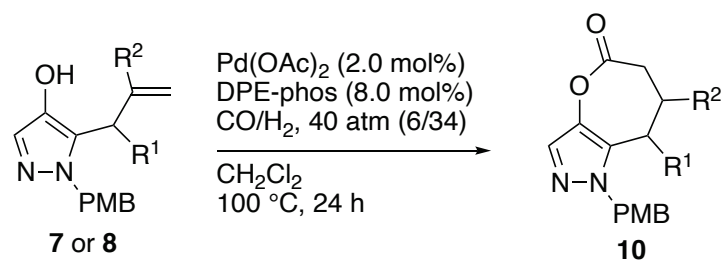
Entry	CO/H ₂	atm	Temp. (°C)	Yield(%)			
				9	10a	11^b	12
1	1/1	40	100	7	89	0	4
2	1/1	40	80	–	–	–	–
3	1/1	40	120	0	54 ^{a, c}	0	0
4	27/13	40	100	0	19 ^a	21	0
5	34/6	40	100	0	3 ^a	35	0
6	1/1	20	100	10	74	0	0
7	6/34	40	100	4	85	0	0

^a ¹H-NMR ratio, ^b crude yield, ^c mixture of **13**.

Table 3. Optimization of temperature and CO/H₂ ratio

With the optimized conditions in hand, we next explored other Claisen rearrangement products and the results are summarized in Table 4. Pyrazole-fused 7-membered lactones **10b–e** were obtained in moderate to good yields.

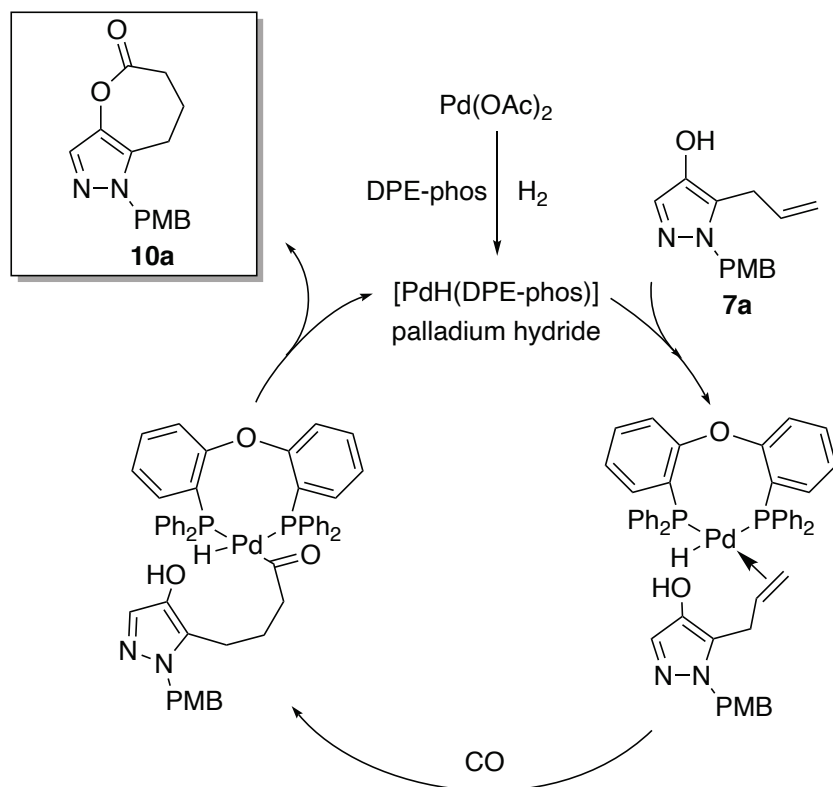




^a ¹H-NMR ratio.

Table 4. Hydroesterification of allylhydroxypyrazoles

A plausible catalytic cycle is shown in Scheme 3. As mentioned above, according to the intramolecular hydroesterification of *o*-allylphenol by Alper,²³ although the use of excess H₂ in the mixture generates a high concentration of a palladium hydride species, [Pd-H], which can catalyze efficient double bond isomerization,²⁵ the corresponding seven-membered ring lactone obtained in excellent yield with perfect selectivity in this esterification (Table 3). In addition, the hydroesterification in the absence of H₂ gave only traces of lactones. Our results are in good agreement with the Alper's report. When the hydroesterification of **7a** with dppb as a ligand proceeded isomerization of double bond to obtain **13**. However, the dimer **11** generated in the esterification with DPE-phos ligand, instead of the double bond isomer. It seems that the palladium hydride species take part in this hydroesterification.



Scheme 3. Catalytic cycle of hydroesterification

CONCLUSION

In summary, we have developed an improvement of the synthesis of 4-hydroxypyrazole via pyrazole pinacolborate derivatives instead of the Baeyer-Villiger oxidation of 4-formylpyrazole and hydroxylation. The Claisen rearrangement of allyl 4-pyrazolyl ethers occurred with heating under microwave condition to furnish the corresponding rearrangement products with regioselective allylation at 5-position of the pyrazoles in good yields. Substrate **6e** having dimethyl groups on the allyl group gave **8** instead of **7e** in excellent yield after the abnormal Claisen rearrangement. These results indicated that the substituent on the allyl group has no effect and the allylation takes place at 5-position of pyrazole. The rearrangement products were converted into 7-membered pyrazololactones having an oxygen atom at 4-position of pyrazole, through a hydroesterification with $\text{Pd}(\text{OAc})_2$ and DPE-phos as ligand under 40 atm of CO/H_2 (6:34) in moderate to excellent yields. In these reactions, 14-membered dilactone was detected and its analogue was not obtained when *o*-allylphenol derivative was used under the same conditions. Intramolecular hydroesterification proceeded selectively by increasing the hydrogen ratio to prepare 7-membered pyrazololactone **10**. This method is more tolerant than the previous synthesis method of pyrazololactone. Because it has been reported that pyrazololactones have bioactivity, 7-membered pyrazololactones containing oxygen at 4-position have accumulated interest in medical and agricultural fields.

EXPERIMENTAL

General Experimental Methods

Microwave reaction was carried out using a Biotage Initiator⁺ (2.45 GHz, 300–900 rpm). NMR spectra were recorded at 27 °C on a Bruker Avance III 500 MHz in CDCl₃ with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a JASCO FT/IR-4200. Melting points were determined with Yazawa Micromelting Point BY-1 and were uncorrected. Liquid column chromatography was conducted over silica gel (Kanto Chemical 60 spherical, 40–50 μm). Analytical TLC was performed on precoated Merck glass plates (TLC Silicagel 60 F₂₅₄), and compounds were detected by spraying an ethanol solution of phosphomolybdic acid, followed by heating. Dry THF and diethyl ether were distilled over sodium benzophenone ketyl under argon atmosphere. Dry acetonitrile was dried over molecular sieves 3A and DMF and dichloromethane were dried over molecular sieves 4A.

Synthesis of 4-iodo-1-*p*-methoxybenzylpyrazole (**2**)

Into a 500-mL three-necked flask was added pyrazole (6.81 g, 100 mmol) in 200 mL of dry MeCN in argon. Then, iodine (15.23 g, 60 mmol) and ammonium cerium(IV) nitrate (CAN) (32.89 g, 60 mmol) were added and the reaction mixture was stirred for 1 h at room temperature. The end of the reaction was checked by TLC and the reaction was quenched by adding sodium hydrogen sulfite solution. The resulting mixture was extracted with EtOAc and the organic layer was washed with brine and dried over MgSO₄. The solvent was removed by a rotary evaporator. Purification of the residue by recrystallization from EtOAc and hexane gave 4-iodopyrazole (**1**) (16.29 g, 84 mmol) in 84% yield. Into a 500-mL round-bottom flask was added 4-iodopyrazole (**1**) (9.698 g, 50 mmol). Then, aqueous KOH solution (4.2 mL, 75 mmol) and tetrabutylammonium bromide (TBAB) (806 mg, 2.5 mmol) were added at 0 °C. *p*-Methoxybenzyl chloride (8.2 mL, 60 mmol) was dropped into the reaction mixture and the reaction temperature was increased to room temperature. After stirring for 24 h, the end of the reaction was checked by TLC and the resulting mixture was extracted with CH₂Cl₂. The organic layer was washed with brine and dried over MgSO₄. The solvent was removed by a rotary evaporator. Purification of the residue by column chromatography on silica gel (hexane/EtOAc = 4:1 as eluent) gave 4-iodo-1-*p*-methoxybenzylpyrazole (**2**) (13.03 g, 41.5 mmol) in 83% yield.

2: White solid: ¹H-NMR (500 MHz, CDCl₃) δ 3.80 (s, 3H, OCH₃), 5.23 (s, 2H, CH₂), 6.88 (dt, *J* = 8.5 Hz, *J* = 2.5 Hz, 2H, Ar-*H*), 7.19 (dt, *J* = 8.5 Hz, *J* = 2.5 Hz, 2H, Ar-*H*), 7.35 (s, 1H, pyrazole), 7.52 (s, 1H, pyrazole).

Synthesis of 4-hydroxy-1-*p*-methoxybenzylpyrazole (**4**)

Into a 200-mL round-bottom flask was added 4-iodo-1-*p*-methoxybenzylpyrazole (**2**) (15.706 g, 50

mmol) in 160 mL of MeCN. Then, Pd(OAc)₂ (225 mg, 1.0 mmol), Cs₂CO₃ (262 mg, 1.0 mmol), and bis(pinacolato)diboron (19.046 g, 75 mmol) were added and the reaction mixture was stirred for 24 h at room temperature. The end of the reaction was checked by TLC and the mixture was filtered through Celite. The filtrate was washed with water and brine, and dried over MgSO₄. The solvent was removed by a rotary evaporator. Purification of the residue by column chromatography on silica gel (hexane/EtOAc = 4:1 as eluent) gave **3** (13.67 g, 43.5 mmol) in 87% yield.

3: ¹H-NMR (500 MHz, CDCl₃) δ 1.29 (s, 12H, CH₃), 3.79 (s, 3H, OCH₃), 5.23 (s, 2H, CH₂), 6.86 (dt, *J* = 8.5, 2.5 Hz, 2H, Ar-*H*), 7.19 (dt, *J* = 8.5, 2.5 Hz, 2H, Ar-*H*), 7.62 (s, 1H, pyrazole), 7.80 (s, 1H, pyrazole); ¹¹B-NMR (160 MHz, CDCl₃) δ 29.78; IR (KBr): 1556, 1518, 1401, 1372, 1255, 1246, 1146, 995, 985, 859, 693 cm⁻¹.

To a solution of boronate **3** (3.14 g, 10.0 mmol) in THF (25 mL) in a 100-mL round-bottom flask were added 3M aqueous NaOH solution (33.3 mL) and 30% H₂O₂ (10.5 mL) at 0 °C for 30 min. The end of the reaction was checked by TLC and the reaction was quenched by adding 0.5 M sodium thiosulfate solution. The resulting mixture was extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄. The solvent was removed by a rotary evaporator. Purification of the residue by recrystallization from CHCl₃ and hexane gave 4-hydroxy-1-*p*-methoxybenzylpyrazole (**4**) (1.88 g, 9.2 mmol) in 92% yield.

4: ¹H-NMR (500 MHz, CDCl₃) δ 3.79 (s, 3H, OCH₃), 4.24 (br, 3H, OH), 5.26 (s, 2H, CH₂), 6.86 (dt, *J* = 8.5, 2.5 Hz, 2H, Ar-*H*), 7.02 (s, 1H, pyrazole), 7.16 (dt, *J* = 8.5, 2.5 Hz, 2H, Ar-*H*), 7.22 (s, 1H, pyrazole).

Synthesis of 4,4,4-trifluoro-1-tosyloxy-2-butene (**5d**)²⁶

Into a 100-mL three-necked flask after drying were added AlCl₃ (2.00 g, 15 mmol) and 15 mL of dry Et₂O at 0 °C. Then, LiAlH₄ (1.14 g, 30 mmol) was added in argon and the reaction mixture was stirred for 30 min at 0 °C to prepare AlH₃. A 10-mL dry Et₂O solution of ethyl 4,4,4-trifluorocrotonate (3 mL, 20 mmol) was dropped into the AlH₃ solution and the reaction mixture was stirred at 0 °C for 2 h. The end of the reaction was checked by TLC and the reaction was quenched by adding saturated NH₄Cl solution. After filtration through Celite, the filtrate was extracted with Et₂O and the organic layer was washed with brine and dried over MgSO₄. The solvent was removed by a rotary evaporator. Purification of the residue by column chromatography on silica gel (Et₂O as eluent) gave 4,4,4-trifluoro-2-butenol (17.2 mmol) in 86% yield. Into a 300-mL round-bottom flask were added 4,4,4-trifluoro-2-butenol and Et₃N (3.59 mL, 25.8 mmol) in 100 mL of CH₂Cl₂. Then, TsCl (4.89 g, 25.8 mmol) was added at 0 °C and the reaction mixture was stirred for 4 h. The end of the reaction was checked by TLC and the reaction was quenched by adding saturated NH₄Cl solution. The resulting mixture was extracted with CH₂Cl₂ and the organic

layer washed with brine and dried over MgSO_4 . The solvent was removed by a rotary evaporator. Purification of the residue by column chromatography on silica gel (hexane/EtOAc = 6:4 as eluent) gave 4,4,4-trifluoro-1-tosyloxy-2-butene (**5d**) (2.37 g, 8.5 mmol) in 49% yield.

5d: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 2.44 (s, 3H, OCH_3), 4.14–4.19 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCF}_3$), 4.54–4.59 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCF}_3$), 5.83–5.88 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCF}_3$), 6.30–6.35 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCF}_3$), 7.36 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.62 (d, $J = 8.5$ Hz, 2H, Ar-H).

General synthesis of allyl pyrazolyl ether (**6**)

Into a 200-mL round-bottom flask was added hydroxypyrazole **4** (2.00 mmol) in acetone (100 mL). Then, allylation reagents **5** (2.2 mmol) were dropped and the reaction mixture was refluxed for 48 h. The end of the reaction was checked by TLC and the reaction mixture was filtered to remove potassium carbonate. The filtrate was extracted with EtOAc. The organic layer was washed with brine and dried over MgSO_4 . The solvent was removed by a rotary evaporator. Purification of the residue by column chromatography on silica gel (hexane/EtOAc = 4:1 as eluent) gave allyl pyrazolyl ether (**6**) in 82–96% yield as shown in Table 1 and Scheme 2.

6a: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 3.79 (s, 3H, OCH_3), 4.36 (dt, $J = 5.5, 1.5$ Hz, m, 2H, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.12 (s, 2H, CH_2), 5.25 (dq, $J = 11.5, 1.3$ Hz, 1H, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.98 (tt, $J = 17, 5.5$ Hz, 1H, $\text{OCH}_2\text{CH}=\text{CH}_2$), 6.44–6.49 (dq, $J = 17, 1.7$ Hz, $\text{OCH}_2\text{CH}=\text{CH}_2$), 6.86 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.01 (d, 1H, $J = 1.0$ Hz, pyrazole), 7.16 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.26 (s, 1H, pyrazole).

6b: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 1.73 (d, $J = 8.5$ Hz, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.28 (dt, $J = 6.5, 1$ Hz, 2H, $\text{OCH}_2\text{CH}=\text{CHCH}_3$), 5.12 (s, 2H, CH_2), 5.63–5.69 (m, 1H, $\text{OCH}_2\text{CH}=\text{CHCH}_3$), 5.77–5.82 (m, 1H, $\text{OCH}_2\text{CH}=\text{CHCH}_3$), 6.86 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.14 (s, 1H, pyrazole), 7.15 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.30 (s, 1H, pyrazole); IR (KBr): 3117, 1613, 1573, 1515, 1458, 1408, 1332, 1305, 1246, 1175, 1027, 836 cm^{-1} .

6c: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 3.80 (s, 3H, OCH_3), 4.53 (dd, $J = 7.5, 1.5$ Hz, 2H, $\text{OCH}_2\text{CH}=\text{CHPh}$), 5.13 (s, 2H, CH_2), 6.35 (dt, $J = 16, 6$ Hz, 1H, $\text{OCH}_2\text{CH}=\text{CHPh}$), 6.67 (d, $J = 16$ Hz, 1H, $\text{OCH}_2\text{CH}=\text{CHPh}$), 6.86 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.04 (s, 1H, pyrazole), 7.15 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.27 (s, 1H, pyrazole), 7.30–7.40 (m, 5H, Ar-H); IR (KBr): 1615, 1576, 1516, 1305, 1251, 1248, 1238, 1175, 1034, 1001, 982, 966, 819, 765, 743 cm^{-1} .

6d: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 3.80 (s, 3H, OCH_3), 4.46–4.49 (m, 2H, $\text{OCH}_2\text{CH}=\text{CHCF}_3$), 5.13 (s, 2H, CH_2), 5.97–6.02 (m, 1H, $\text{OCH}_2\text{CH}=\text{CHCF}_3$), 6.44–6.49 (m, 1H, $\text{OCH}_2\text{CH}=\text{CHCF}_3$), 6.88 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.02 (s, 1H, pyrazole), 7.17 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.30 (s, 1H, pyrazole); IR (KBr): 3120, 1578, 1515, 1316, 1270, 1247, 1122, 1084, 1032, 1024, 956, 831, 811 cm^{-1} .

6e: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 1.68 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.33 (d, $J =$

7.0 Hz, 2H, $\text{OCH}_2\text{CH}=\text{C}(\text{CH}_3)_2$), 5.12 (s, 2H, CH_2), 5.43 (t, $J = 7.0$ Hz, 1H, $\text{OCH}_2\text{CH}=\text{C}(\text{CH}_3)_2$), 6.86 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.99 (d, $J = 1.0$ Hz, 1H, pyrazole), 7.16 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.30 (d, $J = 1.0$ Hz, 1H, pyrazole); IR (KBr): 3114 1613, 1572, 1515, 1458, 1408, 1340, 1323, 1304, 1246, 1175, 1027, 835, 822, 768 cm^{-1} .

General procedure for Claisen rearrangement of **6a–d**

A solution of allylethers **6** in *N,N*-diethylaniline (DEA) (1 mL) in a sealed reactor was irradiated by microwave to 190–250 °C for 1 h. After confirming the end of the reaction by TLC, the reaction mixture was purified by column chromatography on silica gel to give the rearrangement products.

7a: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 3.28 (dt, $J = 6.0, 1.5$ Hz, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.77 (s, 3H, OCH_3), 4.07 (br, 1H, OH), 5.04 (dd, $J = 17, 1.5$ Hz, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.10–5.13 (m, 3H, $\text{CH}_2\text{CH}=\text{CH}_2$, and CH_2Ar), 5.79 (tt, $J = 11.5, 6.0$ Hz, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 6.82 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.02 (d, 2H, $J = 8.5$ Hz, Ar-H), 7.23 (s, 1H, pyrazole).

7b: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 1.26 (d, $J = 8.0$ Hz, 3H, CH_3), 3.55 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 5.06–5.08 (m, 2H, $\text{CH}=\text{CH}_2$), 5.17 (s, 3H, CH_3), 5.94–6.01 (m, 1H, $\text{CH}=\text{CH}_2$), 6.83 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.02 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.22 (d, $J = 5.0$ Hz, 1H, pyrazole); IR (KBr): 2980, 2660, 1615, 1587, 1515, 1348, 1305, 1292, 1249, 1176, 1035, 825, 805 cm^{-1} .

7c: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 3.77 (s, 3H, OCH_3), 3.82 (br, 1H, OH), 4.71 (d, $J = 6.0$ Hz, 1H, CH), 4.93 (dt, $J = 17, 1.5$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.01 (d, $J = 15$ Hz, 1H, CH_2Ar), 5.10 (d, $J = 15$ Hz, 1H, CH_2Ar), 5.31 (dt, $J = 10, 1.2$ Hz, 1H, $\text{CH}=\text{CH}_2$), 6.21–6.28 (m, 1H, $\text{CH}=\text{CH}_2$), 6.80 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.95 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.10 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.25 (s, 1H, pyrazole), 7.28–7.30 (m, 3H, Ar-H); IR (KBr): 2970, 1587, 1514, 1449, 1416, 1359, 1304, 1289, 1244, 1175, 1033, 822, 809 cm^{-1} .

7d: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 3.78 (s, 3H, OCH_3), 4.07 (br, 1H, OH), 4.07 (br, 1H, CH), 4.99 (d, $J = 17$ Hz, H, CH_2Ar), 5.15 (d, $J = 16$ Hz, H, CH_2Ar), 5.30 (t, $J = 14$ Hz, 1H, $\text{CH}=\text{CH}_2$), 6.09 (m, 1H, $\text{CH}=\text{CH}_2$), 6.84 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.00 (d, 2H, $J = 8.5$ Hz, Ar-H), 7.28 (s, 1H, pyrazole); IR (KBr): 2650, 1612, 1515, 1363, 1314, 1254, 1175, 1156, 1107, 932, 823 cm^{-1} .

Abnormal Claisen rearrangement of **6e**

A solution of allylether **6e** (1.00 mmol) in *N,N*-diethylaniline (DEA) (1 mL) in a sealed reactor was irradiated by microwave to 190 °C for 4 h. After confirming the end of the reaction by TLC, the reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc = 4:1 as eluent) to give the rearrangement products **8**.

8: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 1.28 (d, 7.0 Hz, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.42 (q, $J = 7.1$ Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 4.91 (d, $J = 15$ Hz, 2H, $\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)=\text{CH}_2$), 5.14 (s, 2H, CH_2Ar), 6.81 (d,

$J = 8.5$ Hz, 2H, Ar-H), 7.00 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.15 (s, 1H, pyrazole). ^{13}C -NMR (500 MHz, CDCl_3) δ 14.2, 17.1, 21.5, 36.8, 53.3, 55.3, 110.9, 113.9, 114.0, 128.2, 129.4, 139.1, 146.8, 159.1.

General procedure for hydroesterification of 5-allyl-4-hydroxypyrazoles **7** with palladium

A mixture of $\text{Pd}(\text{OAc})_2$, phosphine ligand, and 5-allyl-4-hydroxypyrazoles **7** was dissolved in 15 mL of dry CH_2Cl_2 and placed in an autoclave. The autoclave was purged, pressurized, and heated. The reaction was cooled to room temperature, filtered through Celite, and concentrated by rotary evaporation. Separation and purification of lactones were achieved by silica gel chromatography (hexane/EtOAc = 1:1 to EtOAc as eluent).

10a: ^1H -NMR (500 MHz, CDCl_3) δ 2.07–2.12 (m, 2H, CH_2), 2.68–2.73 (m, 4H, CH_2), 3.78 (s, 3H, OCH_3), 5.15 (s, 2H, CH_2), 6.85 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.00 (d, $J = 9.0$ Hz, 1H, Ar-H), 7.37 (s, 1H, pyrazole); ^{13}C -NMR (125 Hz, CDCl_3) δ 16.4, 25.3, 33.8, 54.0, 55.3, 114.3, 123.0, 125.1, 128.0, 128.5, 138.1, 159.5, 170.4.

10b: ^1H -NMR (500 MHz, CDCl_3) δ 1.24 (d, $J = 7.0$ Hz, 3H, CH_3), 1.86 (m, 1H, CH_2), 2.25 (m, 1H, CH_2), 2.61 (m, 2H, CH_2), 2.99 (sext, $J = 4.5$ Hz, 1H, CH_2), 3.78 (s, 3H, OCH_3), 5.17 (d, $J = 16$ Hz, 1H, CH_2), 5.27 (d, $J = 16$ Hz, 1H, CH_2), 6.85 (d, $J = 6.5$ Hz, 2H, Ar-H), 7.00 (d, $J = 6.5$ Hz, 1H, Ar-H), 7.38 (s, 1H, pyrazole); ^{13}C -NMR (125 Hz, CDCl_3) δ 20.8, 29.1, 29.4, 31.5, 54.0, 55.3, 114.3, 127.9, 128.6, 128.6, 130.0, 132.9, 135.1, 159.3, 171.7.

10c: ^1H -NMR (500 MHz, CDCl_3) δ 2.04 (m, 1H, CH_2), 2.36 (m, 1H, CH_2), 2.61 (m, 1H, CH_2), 2.77 (m, 1H, CH_2), 3.78 (m, 3H, OCH_3), 3.94 (m, 1H, CH_2), 4.44 (d, $J = 15$ Hz, 1H, CH_2), 4.44 (d, $J = 15$ Hz, 1H, CH_2), 5.01 (d, $J = 15$ Hz, 1H, CH_2), 4.44 (d, $J = 15$ Hz, 1H, CH_2), 6.79–6.82 (m, 4H, Ar-H), 6.82 (d, $J = 3.5$ Hz, 2H, Ar-H), 6.82 (d, $J = 3.5$ Hz, 2H, Ar-H), 7.29–7.37 (m, 3H, Ar-H), 7.48 (s, 1H, pyrazole).

10d: ^1H -NMR (500 MHz, CDCl_3) δ 1.34 (s, 3H, CH_3), 2.27–2.31 (m, 1H, CH_2), 2.37–2.42 (m, 1H, CH_2), 2.55–2.59 (m, 2H, CH_2), 3.66–3.68 (m, $J = 4.5$ Hz, 1H, CH_2), 3.79 (s, 3H, OCH_3), 5.17 (d, $J = 16$ Hz, 1H, CH_2), 5.43 (d, $J = 16$ Hz, 1H, CH_2), 6.87 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.09 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.45 (s, 1H, pyrazole).

10e: ^1H -NMR (500 MHz, CDCl_3) δ 0.97 (d, $J = 7.0$ Hz, 3H, CH_3), 1.20 (d, $J = 7.0$ Hz, 3H, CH_3), 2.13–2.17 (m, 1H, CH_2), 2.44–2.53 (m, 2H, CH_2), 2.65–2.62 (m, 1H, CH_2), 3.78 (s, 3H, OCH_3), 5.15 (d, $J = 16$ Hz, 1H, CH_2), 5.24 (d, $J = 16$ Hz, 1H, CH_2), 6.85 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.00 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.37 (s, 1H, pyrazole); ^{13}C -NMR (125 Hz, CDCl_3) δ 20.7, 22.1, 29.1, 36.1, 37.9, 39.1, 53.8, 54.1, 55.3, 114.1, 128.0, 128.7, 129.3, 133.2, 134.9, 159.4, 171.0.

9: ^1H -NMR (500 MHz, CDCl_3) δ 1.33 (d, $J = 6.5$ Hz, 3H, CH_3), 2.52 (dd, $J = 16$ Hz, $J = 7.0$ Hz, 1H, CH_2), 2.82–2.91 (m, 1H, CH_2), 2.92 (dd, $J = 16$ Hz, $J = 7.0$ Hz, 1H, CH_2), 3.78 (s, 3H, OCH_3), 5.13 (d, $J = 16$ Hz, 1H, CH_2), 5.19 (d, $J = 16$ Hz, 1H, CH_2), 6.86 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.08 (d, $J = 8.0$ Hz, 1H,

Ar-H), 7.28 (s, 1H, pyrazole); ¹³C NMR (125 Hz, CDCl₃) δ 16.4, 25.3, 33.8, 54.0, 55.3, 114.3, 123.0, 125.1, 128.0, 128.5, 138.1, 159.5, 170.4.

11: ¹H-NMR (500 MHz, CDCl₃) δ 1.81 (sext, *J* = 8.0 Hz, 2H, CH₂), 2.42 (t, *J* = 6.5 Hz, 2H, CH₂), 2.61 (t, *J* = 7.2 Hz, 1H, CH₂), 3.20 (d, *J* = 6 Hz, 2H, CH₂), 3.73 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 4.96 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H, CH₂), 5.04 (dd, *J* = 11.5 Hz, *J* = 1.5 Hz, 1H, CH₂), 5.13 (s, 2H, CH₂), 5.19 (s, 2H, CH₂), 5.64-5.72 (m, 2H, CH₂), 6.79 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.99 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.03 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.16 (s, 1H, pyrazole), 7.51 (s, 1H, pyrazole).

12: ¹H-NMR (500 MHz, CDCl₃) δ 1.72 (quin, *J* = 8.0 Hz, 2H, CH₂), 2.35 (t, *J* = 6.0 Hz, 2H, CH₂), 2.70 (t, *J* = 6.7 Hz, 2H, CH₂), 3.78 (s, 3H, OCH₃), 5.20 (s, 2H, CH₂), 6.84 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.04 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.57 (s, 1H, pyrazole); ¹³C NMR (125 Hz, CDCl₃) δ 20.8, 22.3, 30.6, 53.4, 55.3, 114.2, 128.0, 128.8, 130.2, 130.6, 133.8, 159.3, 170.4.

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