JOC The Journal of Organic Chemistry

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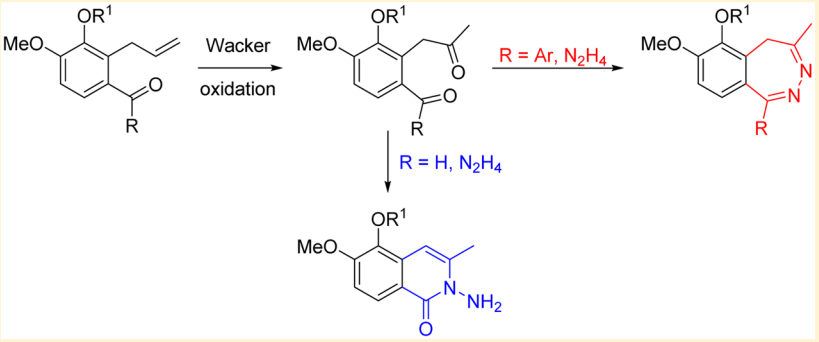
# Synthesis of Substituted 2,3-Benzodiazepines

Chieh-Kai Chan, Yu-Lin Tsai, Yi-Ling Chan, and Meng-Yang Chang*

Department of Medicinal and Applied Chemistry and General Research Centers of R&D Office, Kaohsiung Medical University, Kaohsiung 807, Taiwan

Supporting Information




**ABSTRACT:** A new, four-step synthetic route for substituted 2,3-benzodiazepines **1**, starting from aldehyde **4**, was developed with excellent overall yields. This route included the 1,2-addition of various aromatic Grignard reagents to **4**, PCC oxidation, and aerobic Wacker-type oxidation of the olefinic group of **6**, followed by condensation of the resulting 1,5-dicarbonyl **7** with $N_2H_4$. Isoquinolones **9** were obtained when an aldehyde group was used instead of a ketone. The key structures were confirmed by X-ray single-crystal diffraction analysis.

## INTRODUCTION

The benzodiazepine moiety is considered a prominent skeleton in medicinal chemistry, and many biologically active compounds, such as those with anti-inflammatory, anticonvulsant, antianxiety, antidepressive, sedative, psychoactive, and hypnotic activities, possess this important core.[1] Among them, substituted 2,3-benzodiazepines **1** act as tranquilizing agents and constitute the partial molecules of meaningful scaffolds known as noncompetitive 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptor antagonists, which exert anticonvulsant and neuroprotective activities.[2] In addition, tofisopam, which is the most activated derivative, was found to be a highly active nonsedative, anxiolytic in humans.[3] Other representative 2,3-benzodiazepines, such as girisopam and nerisopam, are biologically active (Figure 1). Some synthetic routes for the synthesis of the 2,3-benzodiazepine skeleton, such as the four-step formation starting from arylethanols or arylacetones,[4] base-mediated reaction of arynes with $\beta$-diketones,[5] and acid-promoted transformation from 2-benzopyrylium salts,[6] have been reported. Herein, a facile synthetic route starting from commercially available materials with higher isolated yields is reported.

## RESULTS AND DISCUSSION

Recently, we developed a series of synthetic routes toward benzofused compounds, such as 1-azahomoisotwistanes,[7] benzodioxepanes,[8] benzo[*g*]indazoles,[9] benzo[*g*]chrysenes,[10] 2-naphthols,[11] isochromenes,[12] and isoquinolines,[13] by using commercially available isovanillin (**2a**) as a starting material. All of the compounds were derived from the versatile 2-allylbenzaldehyde (**4**), which was easily prepared via a three-step synthesis with moderate overall yields by a reaction procedure of O-allylation and Claisen rearrangement followed by O-alkylation. We established the synthetic procedures for substituted benzazepines, including dihydro-1-benzazepines[14] and tetrahydro-3-benzazepines, via the facile, efficient, and high-yield synthetic routes.[15] On the basis of these results, the synthesis of dinitrogen-containing, heterocyclic 2,3-benzodiazepines **1** skeletons from 2-allylbenzaldehyde **2** was our goal (Scheme 1).

Allylbenzenes are well-known molecules with naturally occurring scaffolds that are mainly isolated from plants.[16] Among them, generalized allylbenzenes, such as 2-propenylbenzenes and 1-propenylbenzenes, are widely used in the pharmaceutical, materials chemistry, fragrance, and cosmetic industries and are also important intermediates for the construction of complicated compounds in organic chemistry.[17]

On the basis of our successful experiments, including Grignard addition of aldehydes, PCC oxidation of secondary alcohols, and aerobic Wacker-type oxidation of the resulting terminal olefins,[11] we believed that it may be possible to develop a synthetic route for 1,5-dicarbonyl skeleton **7**, which can condense with $N_2H_4$ to afford 2,3-benzodiazepines. As shown in Table 1, an efficient five-step synthetic route was employed to build **6** from isovanillin (**2a**) and 2-hydrox-

**Received:** August 10, 2016
**Published:** October 7, 2016





DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836−9847

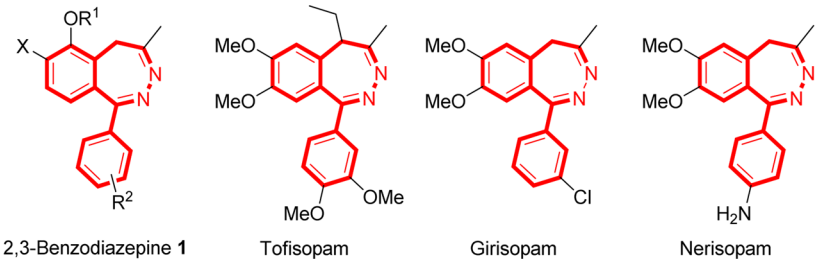
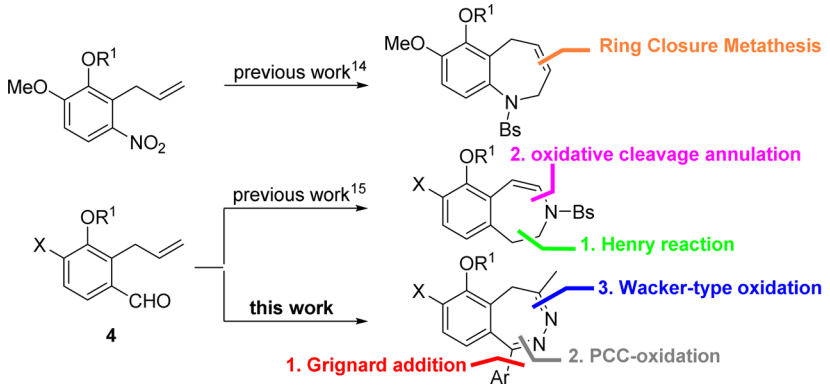



**Figure 1.** Bioactive 2,3-benzodiazepines.

**Scheme 1. Synthesis of Benzofused Nitrogen-Containing Compounds**




ybenzaldehyde (**2b**) via (i) O-allylation with allyl or *trans*-crotyl bromide (R = H or Me), (ii) Claisen rearrangement with decalin, (iii) O-alkylation or O-benzylation of **3** with alkyl or benzyl bromide, (iv) Grignard 1,2-addition with arylmagnesium bromide ($R_2$ = 4-$OMeC_6H_4$, 4-$FC_6H_4$, 4-$MeC_6H_4$, 2-$MeC_6H_4$, or $C_6H_5$), and (v) oxidation with pyridinium chlorochromate (PCC).

Next, for the aerobic Wacker reaction of **6** with a terminal olefin moiety, **6a** was selected as the model substrate in a $Pd^{II}$/$Cu^{II}$ system-catalyzed oxidation. Then, the condensation reaction of in situ-generated **7** with $N_2H_4$ took place. As shown in Table 2, after screening different Wacker-type oxidative conditions and considering our previous work,[11,18] we still believed that the $PdCl_2$/$CuCl_2$ system-mediated Wacker-type oxidation by $O_2$ was better than that with other oxidants such as CAN, DDQ, IBX, Oxone, *t*-$BuO_2H$, and TBHP, which all gave lower yields (entries 1−6, respectively). When molecular oxygen was used as the oxidant, the isolated yield increased to 91% (entry 7). No apparent yield was isolated when the amounts of $PdCl_2$ and $CuCl_2$ were increased (entries 8−10). Changing the Pd(II) catalyst from $PdCl_2$ to $Pd(OAc)_2$, $PdBr_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, or $Pd_2(dba)_3$ gave a similar yield of the desired 1,5-dicarbonyl **7a** as shown in entries 11−15. Without molecular oxygen, **7a** was isolated in only 15% yield, with **6a** recovered in a yield of 80% (entry 16).

The results described above show that **7a** was isolated in high yield (Table 2, entry 7). An efficient synthetic route for substituted 2,3-benzodiazepines **1** from **6** was created. On the basis of the results, **6a** was selected as the model substrate to test the feasibility of a one-pot method with $N_2H_4$. Accordingly, desired product **1a** was obtained in good yield, and the overall two-step yield was 87% (Scheme 2).

On the basis of the optimal conditions (Scheme 2), we further examined the substrate scope and generality of the reaction. The electron-donating group ($R^2$ = 4-OMe) and various aryl substituents on **6**, including an electron-withdrawing group ($R^2$ = 4-F) and electron-neutral groups ($R^2$ = 4-Me, 2-Me, or H), were all also suitable for the synthesis of **1b**−**1e**. Changing the $R^1$ substituents of **6** to isopropyl, *n*-butyl, cyclopentyl, and benzyl groups was well tolerated, providing desired products **1f**−**1y**. Accordingly, **1z** (X = OMe; R = Me) and **1aa** (X = H; R = H) were also synthesized in this transformation. Consequently, **6a**−**6aa** were synthesized in this successive procedure, which included a Wacker-type oxidation and condensation with $N_2H_4$ to synthesize 2,3-benzodiazepines **1a**−**1aa** in high yields ranging from 79 to 90%. All of the compound structures and corresponding isolated yields for **1a**−**1aa** are listed in Table 3. The structures of **1a**, **1c**, **1p**, and **7y** were determined by single-crystal X-ray crystallography.[19]

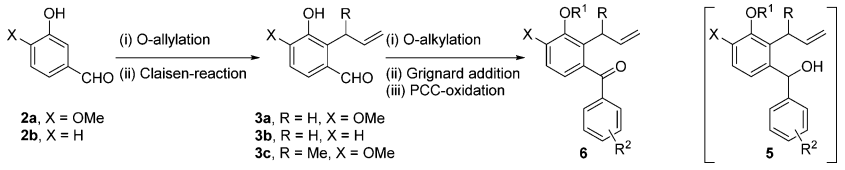
Isoquinolone is an important molecular framework in alkaloidal natural products, and compounds that contain this skeleton show distinct bioactivities.[20] Because of their chemical stability, isoquinolones are frequently used as building blocks.[21] Among them, functionalized isoquinolin-1(2*H*)-ones appear in numerous natural products and drugs.[22] Although a number of methods for the synthesis of isoquinolin-1(2*H*)-ones and their derivatives are available, the development of efficient approaches for the synthesis of the isoquinolin-1(2*H*)-one skeleton is of interest.[23] Starting material **6** when changed to **4**, which has an H atom instead of the Ar substituent group (ketone → aldehyde), and a Wacker-type oxidation afforded compound **8**. Then, **8** reacted with $N_2H_4$ under optimized conditions. Intriguingly, the desired 2,3-benzodiazepine was not observed, but the substituted isoquinolones **9a**−**9d** were isolated in good yields (Scheme 3). The structure of **9a** was confirmed by single-crystal X-ray crystallography (see the Supporting Information).[19]

The possible mechanism for the synthesis of **9a** is shown in Scheme 4. First, pathway intermediate **I** should form via the condensation of **4a** with $N_2H_4$. With an intramolecular aldol-



DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836−9847

**Table 1. Five-Step Synthesis of 6**[a]

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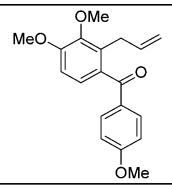
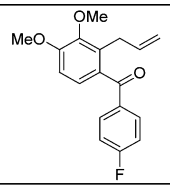
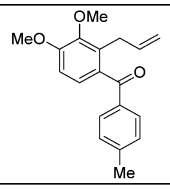
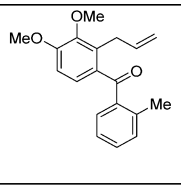
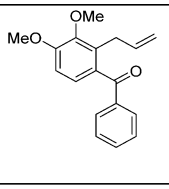
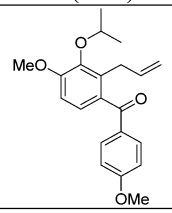
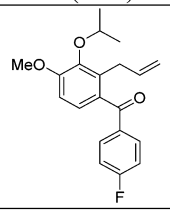
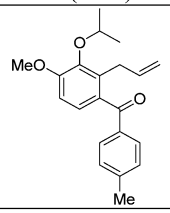
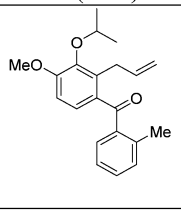
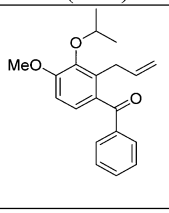
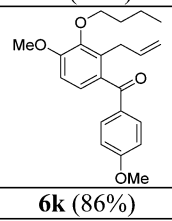
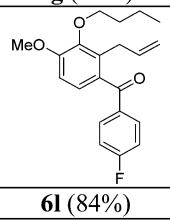
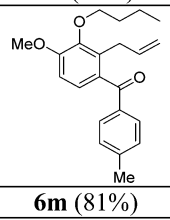
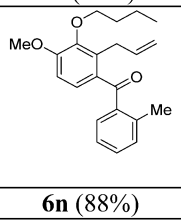
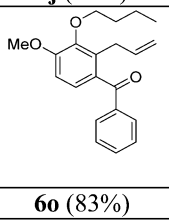
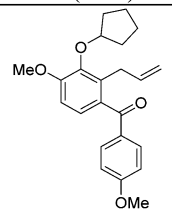
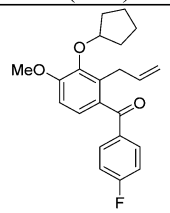
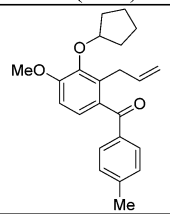
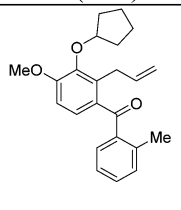
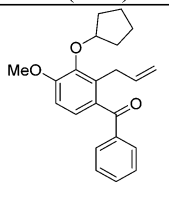
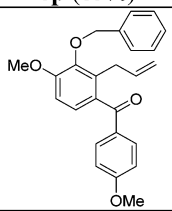
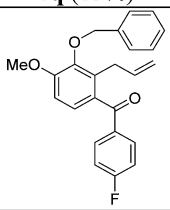
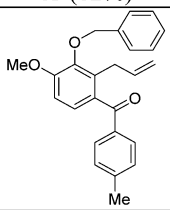
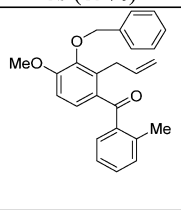
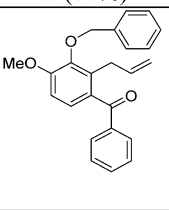
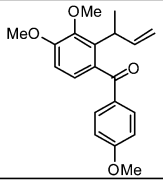
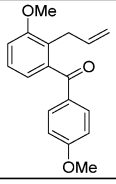
|  |  |  |  |  |
| **6a** (90%) | **6b** (83%) | **6c** (85%) | **6d** (86%) | **6e** (88%) |
|  |  |  |  |  |
| **6f** (86%) | **6g** (87%) | **6h** (84%) | **6i** (89%) | **6j** (87%) |
|  |  |  |  |  |
| **6k** (86%) | **6l** (84%) | **6m** (81%) | **6n** (88%) | **6o** (83%) |
|  |  |  |  |  |
| **6p** (85%) | **6q** (83%) | **6r** (82%) | **6s** (89%) | **6t** (87%) |
|  |  |  |  |  |
| **6u** (85%) | **6v** (83%) | **6w** (81%) | **6x** (90%) | **6y** (86%) |
|  | |  | | |
| **6z** (84%) | | **6aa** (78%) | | |

[a]The reactions were conducted on a 1.0 mmol scale with **2**. Isolated products **6a**–**6aa** were >95% pure as determined by $^1$H NMR analysis.

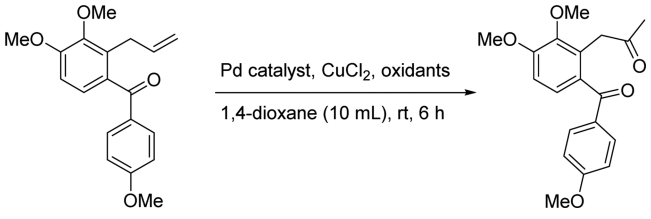
type condensation of **I**, **IV** was formed from the hydrated reaction of **II** and dehydration of **III** (path a). In another route (path b), the deprotonative elimination of hydroxyl anion from **III** to install the alkene is likely to compete with the cleavage of the C–N bond, leading to formation of an enol **I-1**, which will reverse to **I** by tautomerization. Then, in situ hydration generated **IV** to produce **V**. Finally, the oxygen-catalyzed oxidation of **V** was conducted to form **9a**.

The differential behavior of **7** and **8** with $N_2H_4$ is discussed in Scheme 5. For the construction of 2,3-benzodiazepines **1**, we think that $N_2H_4$ first preferred to interact with the C5 position of **7** via intermolecular condensation (carbonyl reactivity: C5 > C1). Subsequently, the formal (5+2) annulation was achieved



DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836–9847

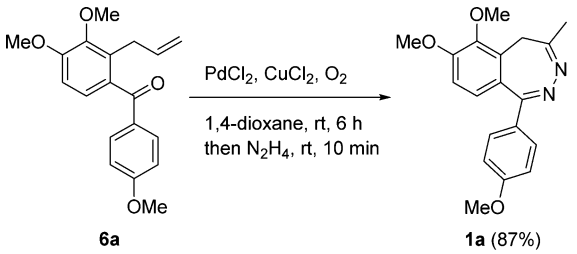
**Table 2. Reaction Conditions of 6a**[a,b]




| entry | $Pd^{II}$ (mol %) | $CuCl_2$ (equiv) | oxidant (equiv) | yield (%)[b] |
|---|---|---|---|---|
| 1 | $PdCl_2$ (5.8) | 1.5 | CAN (1.0) | 20[c] |
| 2 | $PdCl_2$ (5.8) | 1.5 | DDQ (1.0) | 18[c] |
| 3 | $PdCl_2$ (5.8) | 1.5 | IBX (1.0) | 15[c] |
| 4 | $PdCl_2$ (5.8) | 1.5 | Oxone (1.0) | 16[c] |
| 5 | $PdCl_2$ (5.8) | 1.5 | *t*-$BuO_2H$ (1.0) | 19[c] |
| 6 | $PdCl_2$ (5.8) | 1.5 | TBHP (1.0) | 14[c] |
| 7 | **$PdCl_2$ (5.8)** | 1.5 | **$O_2$** | **91**[d] |
| 8 | $PdCl_2$ (11.6) | 1.5 | $O_2$ | 85[d] |
| 9 | $PdCl_2$ (5.8) | 3.0 | $O_2$ | 83[d] |
| 10 | $PdCl_2$ (11.6) | 3.0 | $O_2$ | 84[d] |
| 11 | $Pd(OAc)_2$ (5.8) | 1.5 | $O_2$ | 85[d] |
| 12 | $PdBr_2$ (5.8) | 1.5 | $O_2$ | 86[d] |
| 13 | $PdCl_2(ACN)_2$ (5.8) | 1.5 | $O_2$ | 85[d] |
| 14 | $PdCl_2(PPh_3)_2$ (5.8) | 1.5 | $O_2$ | 83[d] |
| 15 | $Pd_2(dba)_3$ (5.8) | 1.5 | $O_2$ | 83[d] |
| 16 | $PdCl_2$ (5.8) | 1.5 | air | 15[e] |

[a]The reactions were conducted on a 1.0 mmol scale with **6a**. [b]**7a** was >95% pure as determined by $^1H$ NMR analysis. [c]Unknown products were obtained (entry 1, 5%; entry 2, 6%; entry 3, 6%; entry 4, 5%; entry 5, 7%; entry 6, 5%). [d]Trace amounts (<5%) of unknown products were obtained. [e]The starting material **6a** was recovered in 80% yield.

**Scheme 2. One-Pot Synthetic Route for 1a from 6a**




by intramolecular condensation between the primary amine and benzylic ketone (eq 1). Compared with the formation of isoquinolin-1(2*H*)-ones **9**, the formyl group (C1) of aldehydes **8** was favored for reaction with $N_2H_4$ versus the C5 carbonyl position by intermolecular condensation. In the following intramolecular process, the formal (5+1) annulation of the tertiary amine with ketone was conducted because of the ring closure tendency (six-membered > seven-membered), as shown in eq 2. Therefore, $N_2H_4$ played a key condensation role in the construction of bicycles **1** and **9** via the intermolecular and intramolecular routes.

On the basis of our successful synthesis of substituted quinoxalines,[24] we changed the dinitrogen source from $N_2H_4$ ($H_2N-NH_2$) to 1,2-diaminobenzene ($H_2N-C-C-NH_2$). **8a** was transformed into benzimidazo[2,1-*a*]isoquinoline **10** in high yield (Scheme 6).

In summary, we have presented a facile synthetic route for the synthesis of substituted 2,3-benzodiazepines via Grignard addition, PCC oxidation, aerobic Wacker-type oxidation, and the condensation with $N_2H_4$ in high yields. Changing the functional group from allylketone to allylaldehyde, a one-pot procedure of Wacker-type oxidation/$N_2H_4$, or 1,2-diaminobenzene condensation provided the functionalized isoquinolin-1(2*H*)-ones and benzimidazo[2,1-*a*]isoquinoline in good to excellent yields under optimal conditions. This protocol started from simple starting materials and reagents and provided a new synthetic route toward the skeleton of 2,3-benzodiazepines. The structural frameworks of key products were confirmed by single-crystal X-ray diffraction analysis. Further investigation of synthetic applications of 2-allylbenzaldehyde and bioactive applications of 2,3-benzodiazepines will be conducted and the results published in due course.

## EXPERIMENTAL SECTION

**General.** All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely performed under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Purity was determined by NMR and melting point. Melting points were determined with an SMP3 melting apparatus. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts ($\delta$) are reported in parts per million, and coupling constants ($J$) are given in hertz. High-resolution mass spectrometry (HRMS) spectra were recorded with a mass spectrometer microTOF-Q by ESI using a hybrid ion trap. X-ray crystal structures were obtained with a diffractometer (CAD4, Kappa CCD).

**General Synthetic Procedure for the Synthesis of 6a–6aa.** A solution of a Grignard reagent (1.0 M in THF, 1.5 mL, 1.5 mmol) was added to a stirred solution of skeleton **4** (1.0 mmol) in THF (10 mL) in an ice bath. The reaction mixture was stirred at rt for 5 h. Water (5 mL) was added to the reaction mixture, and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford different crude products under reduced pressure. Without further purification, a solution of the resulting secondary alcohol **5** in DCM (10 mL) was added to a mixture of pyridinium chlorochromate (430 mg, 2.0 mmol) and Celite (500 mg) in DCM (20 mL). After being stirred at rt for 3 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to yield the crude compound. Purification on silica gel (6/1 to 3/1 hexanes/EtOAc) afforded **6a–6aa**.

*(2-Allyl-3,4-dimethoxyphenyl)(4-methoxyphenyl)methanone (**6a**).*[13a] Yield 90% (281 mg); colorless gum; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J$ = 8.8 Hz, 2H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.84 (d, $J$ = 8.8 Hz, 2H), 6.74 (d, $J$ = 8.4 Hz, 1H), 5.89–5.79 (m, 1H), 4.86–4.79 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.51 (dt, $J$ = 1.2, 6.0 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 195.8, 163.1, 154.0, 147.3, 136.9, 133.3, 132.2 (2×), 132.0, 130.7, 125.1, 115.0, 113.2 (2×), 108.7, 60.4, 55.4, 55.1, 30.4; HRMS (ESI, $M^+$ + Na) calcd for $C_{19}H_{20}O_4Na$ 335.1259, found 335.1252.

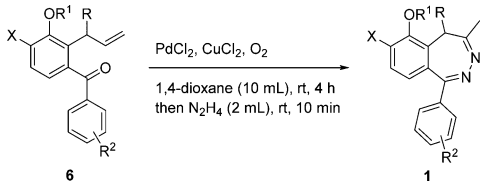
*(2-Allyl-3,4-dimethoxyphenyl)(4-fluorophenyl)methanone (**6b**).*[13a] Yield 83% (249 mg); colorless gum; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.81–7.77 (m, 2H), 7.13–7.07 (m, 2H), 7.04 (d, $J$ = 8.4 Hz, 1H), 6.80 (d, $J$ = 8.4 Hz, 1H), 5.93–5.83 (m, 1H), 4.90–4.84 (m, 2H), 3.92 (s, 3H), 3.85 (s, 3H), 3.58 (dt, $J$ = 1.6, 6.0 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 195.9, 165.5 (d, $J$ = 253.2 Hz), 154.7, 147.8, 137.1, 134.7 (d, $J$ = 3.1 Hz), 134.1, 132.8 (d, $J$ = 9.1 Hz, 2×), 131.6, 125.9, 115.4, 115.3 (d, $J$ = 21.9 Hz, 2×), 108.9, 60.9, 55.7, 30.5; HRMS (ESI, $M^+$ + H) calcd for $C_{18}H_{18}FO_3$ 301.1240, found 301.1244.

*(2-Allyl-3,4-dimethoxyphenyl)(p-tolyl)methanone (**6c**).* Yield 85% (252 mg); colorless solid; mp 59–60 °C (recrystallized from hexanes

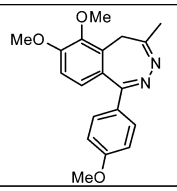
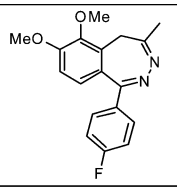
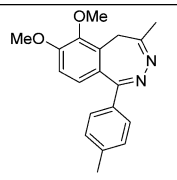
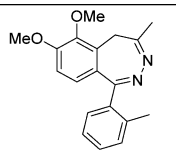
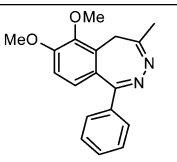
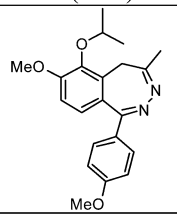
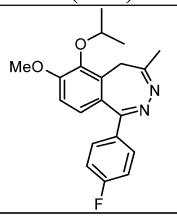
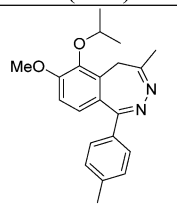
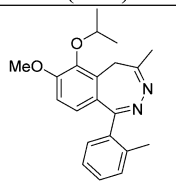
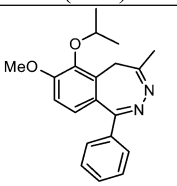
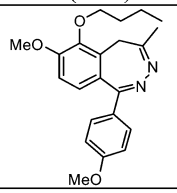
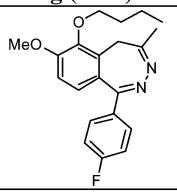
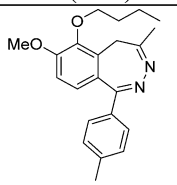
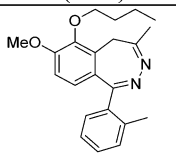
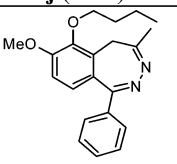
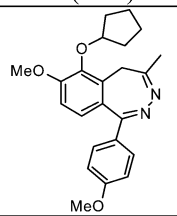
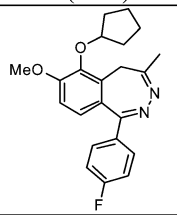
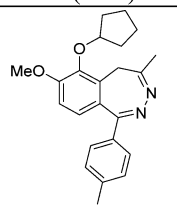
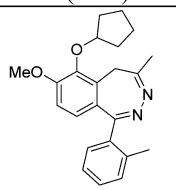
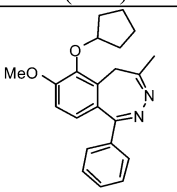
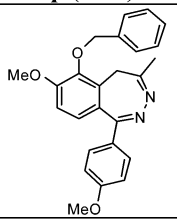
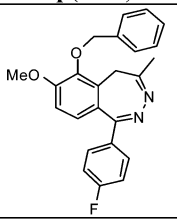
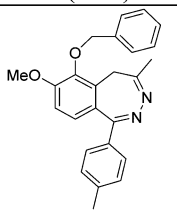
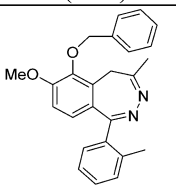
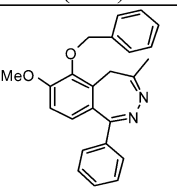
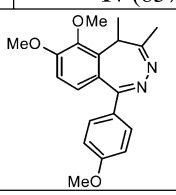
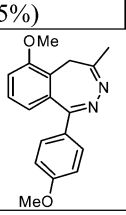


DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836–9847

**Table 3. Synthesis of 1**[a]




6 1

| | | | | |
|---|---|---|---|---|
|  |  |  |  |  |
| **1a** (87%) | **1b** (88%) | **1c** (83%) | **1d** (86%) | **1e** (90%) |
|  |  |  |  |  |
| **1f** (89%) | **1g** (82%) | **1h** (81%) | **1i** (86%) | **1j** (88%) |
|  |  |  |  |  |
| **1k** (89%) | **1l** (85%) | **1m** (82%) | **1n** (86%) | **1o** (88%) |
|  |  |  |  |  |
| **1p** (90%) | **1q** (85%) | **1r** (84%) | **1s** (84%) | **1t** (85%) |
|  |  |  |  |  |
| **1u** (89%) | **1v** (83%) | **1w** (81%) | **1x** (85%) | **1y** (84%) |
|  | |  | | |
| **1z** (85%) | | **1aa** (79%) | | |

[a]Optimal reaction conditions: (i) compound **6** (1.0 mmol), $PdCl_2$ (10 mg, 5.8 mol %), $CuCl_2$ (200 mg, 1.5 mmol), $O_2$ (bubbled), dioxane (10 mL), rt, 10 h; (ii) $N_2H_4$ (2 mL), rt, 10 min. Isolated products **1a**−**1aa** were >95% pure as determined by $^1H$ NMR analysis.

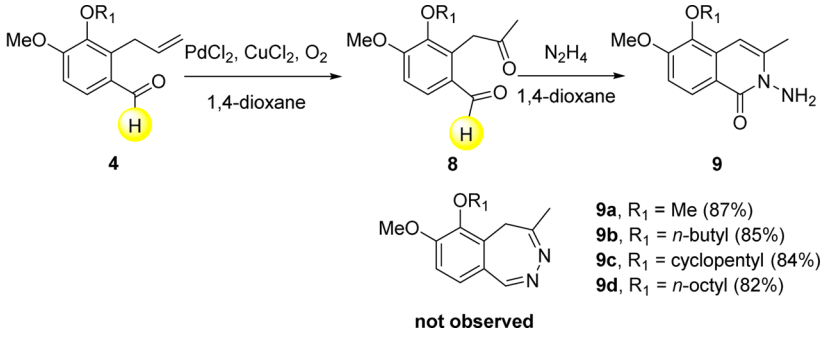
and EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (d, $J$ = 8.4 Hz, 2H), 7.23 (d, $J$ = 8.4 Hz, 2H), 7.06 (d, $J$ = 8.4 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 5.94−5.84 (m, 1H), 4.91−4.85 (m, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 3.58 (dt, $J$ = 1.6, 6.0 Hz, 2H), 2.42 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 154.5, 147.7, 143.6, 137.2, 135.8, 134.0, 132.2, 130.4 (2×), 128.9 (2×), 125.9, 115.3, 108.9, 60.8, 55.7, 30.6, 21.6; HRMS (ESI, $M^+$ + H) calcd for $C_{19}H_{21}O_3$ 297.1491, found 297.1493.

*(2-Allyl-3,4-dimethoxyphenyl)(o-tolyl)methanone* (***6d***).[13a] Yield 86% (255 mg); colorless gum; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.15 (m, 4H), 7.06 (d, $J$ = 8.4 Hz, 1H), 6.73 (d, $J$ = 8.4 Hz, 1H),

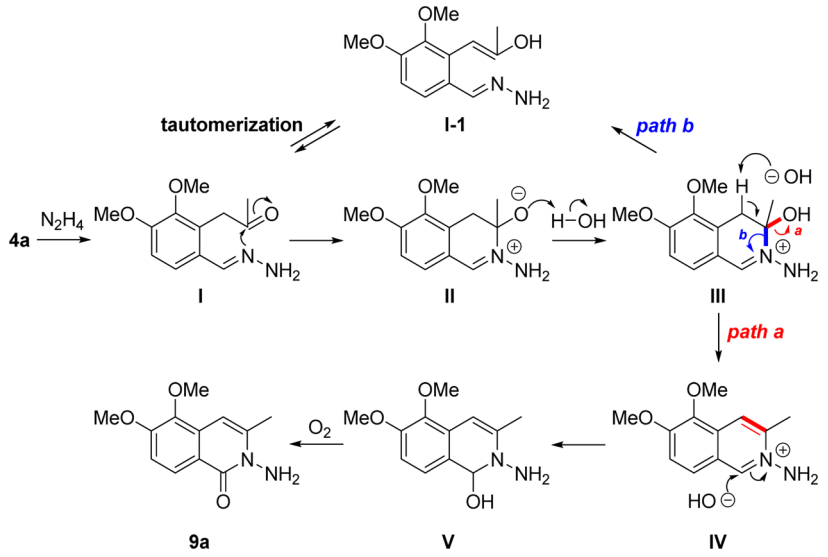


DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836−9847

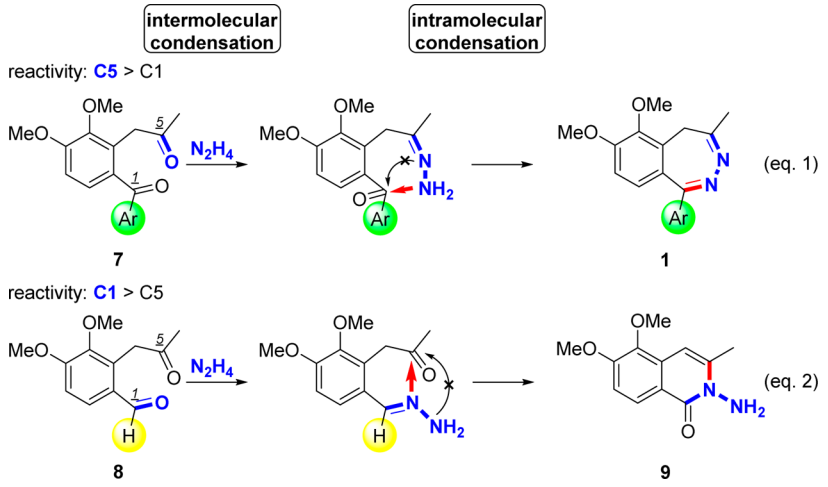
**Scheme 3. Synthesis of 1 and 9**




**Scheme 4. Possible Mechanism**




**Scheme 5. Differential Behavior of 7 and 8 with $N_2H_4$**




6.05–5.95 (m, 1H), 5.00–4.94 (m, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.77 (dt, $J$ = 1.6, 6.4 Hz, 2H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.3, 155.4, 147.7, 139.7, 137.6, 137.3, 135.1, 132.0, 131.0, 130.5, 129.8, 128.4, 125.1, 115.1, 108.7, 60.8, 55.6, 30.3, 20.3; HRMS (ESI, $M^+$ + H) calcd for $C_{19}H_{21}O_3$ 297.1491, found 297.1496.

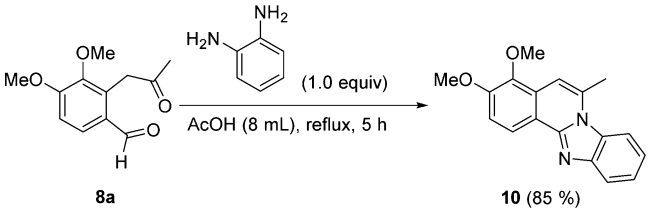
*(2-Allyl-3,4-dimethoxyphenyl)(phenyl)methanone* ***(6e)***.[13a] Yield 88% (248 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78–7.75 (m, 2H), 7.57–7.52 (m, 1H), 7.44–7.40 (m, 2H), 7.07 (d, $J$ = 8.4 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 5.95–5.86 (m, 1H), 4.92–4.89 (m, 1H), 4.88–4.86 (m, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.60 (dt, $J$ = 1.6, 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 154.6, 147.7, 138.4, 137.1, 134.2, 132.6, 131.7, 130.1 (2×), 128.1 (2×), 126.2, 115.3, 108.8, 60.8, 55.7, 30.5; HRMS (ESI, $M^+$ + Na) calcd for $C_{18}H_{18}O_3Na$ 305.1154, found 305.1146.

*(2-Allyl-3-isopropoxy-4-methoxyphenyl)(4-methoxyphenyl)-methanone* ***(6f)***. Yield 86% (293 mg); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$ = 8.8 Hz, 2H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.88 (d, $J$ = 8.8 Hz, 2H), 6.76 (d, $J$ = 8.8 Hz, 1H), 5.84–5.74 (m, 1H), 4.83–4.78 (m, 2H), 4.58–4.51 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.59 (dt, $J$ = 1.6, 6.4 Hz, 2H), 1.29 (d, $J$ = 6.4 Hz, 6H); $^{13}$C NMR (100



DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836–9847

**Scheme 6. Synthesis of 10**




**8a** **10** (85 %)

MHz, $CDCl_3$) $\delta$ 196.3, 163.2, 154.2, 145.1, 136.6, 133.8, 132.9, 132.4 (2×), 131.1, 124.8, 115.2, 113.3 (2×), 108.6, 74.7, 55.5, 55.3, 30.8, 22.5 (2×); HRMS (ESI, $M^+$ + Na) calcd for $C_{21}H_{24}O_4Na$ 363.1572, found 363.1566.

*(2-Allyl-3-isopropoxy-4-methoxyphenyl)(4-fluorophenyl)-methanone (**6g**).* Yield 87% (285 mg); colorless solid; mp 46−47 °C (recrystallized from hexanes and EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 8.8 Hz, 1H), 7.74 (d, $J$ = 8.8 Hz, 1H), 7.07−7.02 (m, 2H), 6.96 (d, $J$ = 8.4 Hz, 1H), 6.75 (d, $J$ = 8.4 Hz, 1H), 5.83−5.73 (m, 1H), 4.81−4.76 (m, 2H), 4.57−4.51 (m, 1H), 3.83 (s, 3H), 3.61 (dt, $J$ = 1.6, 6.0 Hz, 2H), 1.27 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 195.9, 165.3 (d, $J$ = 252.5 Hz), 154.6, 145.2, 136.6, 134.6 (d, $J$ = 3.0 Hz), 134.2, 132.5 (d, $J$ = 9.1 Hz, 2×), 131.5, 125.2, 115.3, 115.1 (d, $J$ = 21.2 Hz, 2×), 108.6, 74.7, 55.4, 30.5, 22.4 (2×); HRMS (ESI, $M^+$ + Na) calcd for $C_{20}H_{21}FO_3Na$ 351.1372, found 351.1366.

*(2-Allyl-3-isopropoxy-4-methoxyphenyl)(p-tolyl)methanone (**6h**).* Yield 84% (272 mg); colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.0 Hz, 2H), 7.22 (d, $J$ = 8.0 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 1H), 5.86−5.76 (m, 1H), 4.85−4.80 (m, 2H), 4.58−4.52 (m, 1H), 3.88 (s, 3H), 3.62 (dt, $J$ = 1.6, 6.4 Hz, 2H), 2.41 (s, 3H), 1.31 (d, $J$ = 6.4 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 154.5, 145.2, 143.4, 136.8, 135.9, 134.3, 132.3, 130.3 (2×), 128.9 (2×), 125.4, 115.4, 108.6, 74.9, 55.6, 30.8, 22.6 (2×), 21.6; HRMS (ESI, $M^+$ + H) calcd for $C_{21}H_{25}O_3Na$ 325.1804, found 325.1809.

*(2-Allyl-3-isopropoxy-4-methoxyphenyl)(o-tolyl)methanone (**6i**).* Yield 89% (289 mg); colorless gum; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.32 (m, 1H), 7.28−7.23 (m, 2H), 7.19−7.15 (m, 1H), 7.03 (d, $J$ = 8.4 Hz, 1H), 6.71 (d, $J$ = 8.4 Hz, 1H), 5.96−5.86 (m, 1H), 4.95−4.90 (m, 2H), 4.58−4.52 (m, 1H), 3.86 (s, 3H), 3.79 (dt, $J$ = 1.6, 6.4 Hz, 2H), 2.39 (s, 3H), 1.31 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.5, 155.4, 145.3, 139.7, 137.8, 137.0, 135.5, 132.3, 131.1, 130.5, 129.9, 127.8, 125.1, 115.2, 108.5, 74.8, 55.5, 30.5, 22.5 (2×), 20.4; HRMS (ESI, $M^+$ + Na) calcd for $C_{21}H_{24}O_3Na$ 347.1623, found 347.1617.

*(2-Allyl-3-isopropoxy-4-methoxyphenyl)(phenyl)methanone (**6j**).* Yield 87% (270 mg); colorless gum; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.77−7.74 (m, 2H), 7.57−7.53 (m, 1H), 7.45−7.41 (m, 2H), 7.03 (d, $J$ = 8.4 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 1H), 5.87−5.77 (m, 1H), 4.86−4.83 (m, 1H), 4.82−4.80 (m, 1H), 4.59−4.53 (m, 1H), 3.88 (s, 3H), 3.64 (dt, $J$ = 1.6, 6.4 Hz, 2H), 1.31 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 154.8, 145.3, 138.5, 136.8, 134.6, 132.6, 130.5, 130.2 (2×), 128.2 (2×), 125.8, 115.4, 108.6, 74.9, 55.6, 30.7, 22.6 (2×); HRMS (ESI, $M^+$ + Na) calcd for $C_{20}H_{22}O_3Na$ 333.1467, found 333.1460.

*(2-Allyl-3-butoxy-4-methoxyphenyl)(4-methoxyphenyl)-methanone (**6k**).* Yield 86% (305 mg); colorless solid; mp 59−60 °C (recrystallized from hexanes and EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.8 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 1H), 6.89 (d, $J$ = 8.8 Hz, 2H), 6.77 (d, $J$ = 8.4 Hz, 1H), 5.91−5.81 (m, 1H), 4.86−4.82 (m, 2H), 3.96 (t, $J$ = 7.2 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.56 (d, $J$ = 1.6, 6.0 Hz, 2H), 1.81−1.74 (m, 2H), 1.55−1.46 (m, 2H), 0.97 (t, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 196.2, 163.3, 154.3, 146.8, 137.1, 133.6, 132.5 (2×), 132.3, 131.1, 125.2, 115.1, 113.3 (2×), 108.8, 72.9, 55.6, 55.3, 32.3, 30.6, 19.1, 13.8; HRMS (ESI, $M^+$ + Na) calcd for $C_{22}H_{26}O_4Na$ 377.1729, found 377.1722.

*(2-Allyl-3-butoxy-4-methoxyphenyl)(4-fluorophenyl)methanone (**6l**).* Yield 84% (287 mg); colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (d, $J$ = 8.8 Hz, 1H), 7.76 (d, $J$ = 8.8 Hz, 1H), 7.10−7.04 (m, 2H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 1H), 5.91−5.81 (m, 1H), 4.85−4.80 (m, 2H), 3.96 (t, $J$ = 6.4 Hz, 2H), 3.87 (s, 3H), 3.58 (dt, $J$ = 1.6, 6.0 Hz, 2H), 1.80−1.73 (m, 2H), 1.55−1.46 (m, 2H), 0.96 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 195.8, 165.4 (d, $J$ = 253.2 Hz), 154.7, 146.9, 137.0, 134.7 (d, $J$ = 3.0 Hz), 134.1, 132.6 (d, $J$ = 9.1 Hz, 2×), 131.4, 125.7, 115.2 (d, $J$ = 22.0 Hz, 2×), 115.2, 108.8, 72.9, 55.6, 32.3, 30.4, 19.1, 13.8; HRMS (ESI, $M^+$ + Na) calcd for $C_{21}H_{23}FO_3Na$ 365.1529, found 365.1525.

*(2-Allyl-3-butoxy-4-methoxyphenyl)(p-tolyl)methanone (**6m**).* Yield 81% (274 mg); colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (d, $J$ = 8.0 Hz, 2H), 7.22 (d, $J$ = 8.0 Hz, 2H), 7.04 (d, $J$ = 8.4 Hz, 1H), 6.78 (d, $J$ = 8.4 Hz, 1H), 5.93−5.83 (m, 1H), 4.89−4.83 (m, 2H), 3.97 (t, $J$ = 6.4 Hz, 2H), 3.89 (s, 3H), 3.59 (dt, $J$ = 1.6, 6.4 Hz, 2H), 2.41 (s, 3H), 1.82−1.75 (m, 2H), 1.57−1.47 (m, 2H), 0.98 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.3, 154.6, 146.9, 143.5, 137.2, 135.8, 134.1, 132.1, 130.4 (2×), 128.9 (2×), 125.7, 115.2, 108.8, 73.0, 55.7, 32.3, 30.6, 21.6, 19.2, 13.9; HRMS (ESI, $M^+$ + H) calcd for $C_{22}H_{27}O_3$ 339.1960, found 339.1965.

*(2-Allyl-3-butoxy-4-methoxyphenyl)(o-tolyl)methanone (**6n**).* Yield 88% (342 mg); colorless gum; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.33 (m, 1H), 7.27−7.23 (m, 2H), 7.20−7.16 (m, 1H), 7.05 (d, $J$ = 8.4 Hz, 1H), 6.71 (d, $J$ = 8.4 Hz, 1H), 6.03−5.93 (m, 1H), 4.98−4.92 (m, 2H), 3.96 (t, $J$ = 6.4 Hz, 2H), 3.88 (s, 3H), 3.77 (dt, $J$ = 1.6, 6.0 Hz, 2H), 2.38 (s, 3H), 1.83−1.76 (m, 2H), 1.57−1.48 (m, 2H), 0.99 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.5, 155.5, 147.0, 139.8, 137.7, 137.4, 135.3, 132.1, 131.1, 130.5, 129.9, 128.3, 125.2, 115.1, 108.7, 73.1, 55.6, 32.3, 30.4, 20.4, 19.2, 13.9; HRMS (ESI, $M^+$ + Na) calcd for $C_{22}H_{26}O_3Na$ 361.1780, found 361.1775.

*(2-Allyl-3-butoxy-4-methoxyphenyl)(phenyl)methanone (**6o**).* Yield 83% (269 mg); colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.77−7.74 (m, 2H), 7.55−7.50 (m, 1H), 7.42−7.39 (m, 2H), 7.04 (d, $J$ = 8.4 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 1H), 5.94−5.84 (m, 1H), 4.90−4.84 (m, 2H), 3.98 (t, $J$ = 6.4 Hz, 2H), 3.87 (s, 3H), 3.63 (dt, $J$ = 1.6, 6.4 Hz, 2H), 1.82−1.75 (m, 2H), 1.57−1.47 (m, 2H), 0.98 (t, $J$ = 7.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 154.7, 146.9, 138.4, 137.1, 134.2, 132.5, 131.6, 130.1 (2×), 128.1 (2×), 126.0, 115.1, 108.7, 72.9, 55.6, 32.3, 30.5, 19.1, 13.8; HRMS (ESI, $M^+$ + Na) calcd for $C_{21}H_{24}O_3Na$ 347.1623, found 347.1619.

*[2-Allyl-3-(cyclopentyloxy)-4-methoxyphenyl](4-methoxyphenyl)-methanone (**6p**).* Yield 85% (311 mg); colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.8 Hz, 2H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.89 (d, $J$ = 8.8 Hz, 2H), 6.77 (d, $J$ = 8.4 Hz, 1H), 5.85−5.75 (m, 1H), 4.91−4.86 (m, 1H), 4.83−4.77 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.56 (dt, $J$ = 1.6, 6.0 Hz, 2H), 1.93−1.71 (m, 6H), 1.61−1.57 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 196.4 163.3, 154.1, 145.5, 136.7, 133.8, 132.4 (2×), 132.4, 131.1, 124.7, 115.2, 113.3 (2×), 108.8, 84.6, 55.5, 55.4, 32.8 (2×), 30.7, 23.6 (2×); HRMS (ESI, $M^+$ + H) calcd for $C_{23}H_{27}O_4$ 367.1909, found 367.1904.

*[2-Allyl-3-(cyclopentyloxy)-4-methoxyphenyl](4-fluorophenyl)-methanone (**6q**).* Yield 83% (294 mg); colorless solid; mp 70−71 °C (recrystallized from hexanes and EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (d, $J$ = 8.8 Hz, 1H), 7.77 (d, $J$ = 8.8 Hz, 1H), 7.11−7.05 (m, 2H), 6.97 (d, $J$ = 8.4 Hz, 1H), 6.77 (d, $J$ = 8.4 Hz, 1H), 5.85−5.75 (m, 1H), 4.91−4.82 (m, 1H), 4.82−4.77 (m, 2H), 3.88 (s, 3H), 3.59 (dt, $J$ = 1.6, 6.0 Hz, 2H), 1.93−1.70 (m, 6H), 1.62−1.57 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 196.1, 165.4 (d, $J$ = 253.2 Hz), 154.5, 145.7, 136.7, 134.7 (d, $J$ = 3.0 Hz), 134.2, 132.7 (d, $J$ = 9.1 Hz, 2×), 131.6, 125.2, 115.3, 115.2 (d, $J$ = 21.2 Hz, 2×), 108.8, 84.7, 55.6, 32.8 (2×), 30.6, 23.6 (2×); HRMS (ESI, $M^+$ + Na) calcd for $C_{22}H_{23}FO_3Na$ 377.1529, found 377.1523.

*[2-Allyl-3-(cyclopentyloxy)-4-methoxyphenyl](p-tolyl)methanone (**6r**).* Yield 82% (287 mg); colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.0 Hz, 2H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.76 (d, $J$ = 8.4 Hz, 1H), 5.87−5.77 (m, 1H), 4.91−4.87 (m, 1H), 4.85−4.80 (m, 2H), 3.87 (s, 3H), 3.60 (dt, $J$ = 1.6, 6.0 Hz, 2H), 2.40 (s, 3H), 1.94−1.72 (m, 6H), 1.62−1.56 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.3, 154.3, 145.5, 143.4, 136.7, 135.8, 134.1, 132.1, 130.3 (2×), 128.8 (2×), 125.2, 115.2, 108.7, 84.6, 55.5, 32.8 (2×),



DOI: 10.1021/acs.joc.6b01935
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30.6, 23.6 (2×), 21.5; HRMS (ESI, $M^+$ + H) calcd for $C_{23}H_{27}O_3$ 351.1960, found 351.1965.

*[2-Allyl-3-(cyclopentyloxy)-4-methoxyphenyl](o-tolyl)methanone (**6s**).* Yield 89% (312 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.33 (m, 1H), 7.28−7.23 (m, 2H), 7.19−7.15 (m, 1H), 7.02 (d, $J$ = 8.8 Hz, 1H), 6.71 (d, $J$ = 8.8 Hz, 1H), 5.96−5.86 (m, 1H), 4.94−4.85 (m, 3H), 3.87 (s, 3H), 3.76 (dt, $J$ = 1.6, 6.4 Hz, 2H), 2.39 (s, 3H), 1.94−1.81 (m, 4H), 1.79−1.72 (m, 2H), 1.64−1.58 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.6, 155.3, 145.7, 139.7, 137.8, 137.0, 135.3, 132.3, 131.1, 130.5, 129.9, 127.7, 125.1, 115.2, 108.7, 84.7, 55.6, 32.8 (2×), 30.4, 23.6 (2×), 20.4; HRMS (ESI, $M^+$ + Na) calcd for $C_{23}H_{26}O_3Na$ 373.1780, found 373.1773.

*[2-Allyl-3-(cyclopentyloxy)-4-methoxyphenyl](phenyl)methanone (**6t**).* Yield 87% (292 mg); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76−7.73 (m, 2H), 7.54−7.49 (m, 1H), 7.41−7.37 (m, 2H), 7.01 (d, $J$ = 8.4 Hz, 1H), 6.76 (d, $J$ = 8.4 Hz, 1H), 5.88−5.78 (m, 1H), 4.91−4.88 (m, 1H), 4.85−4.80 (m, 2H), 3.86 (s, 3H), 3.62 (dt, $J$ = 1.6, 6.4 Hz, 2H), 1.94−1.70 (m, 6H), 1.64−1.53 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 154.4, 145.5, 138.4, 136.7, 134.2, 132.5, 131.7, 130.0 (2×), 128.0 (2×), 125.5, 115.2, 108.7, 84.5, 55.5, 32.7 (2×), 30.5, 23.5 (2×); HRMS (ESI, $M^+$ + Na) calcd for $C_{22}H_{24}O_3Na$ 359.1623, found 359.1619.

*[2-Allyl-3-(benzyloxy)-4-methoxyphenyl](4-methoxyphenyl)-methanone (**6u**).* Yield 85% (330 mg); colorless solid; mp 65−66 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.77 (d, $J$ = 8.8 Hz, 2H), 7.51 (d, $J$ = 7.2 Hz, 2H), 7.42−7.38 (m, 2H), 7.36−7.32 (m, 1H), 7.09 (d, $J$ = 8.4 Hz, 1H), 6.92 (d, $J$ = 8.8 Hz, 2H), 6.85 (d, $J$ = 8.4 Hz, 1H), 5.93−5.83 (m, 1H), 5.07 (s, 2H), 4.88−4.83 (m, 2H), 3.93 (s, 3H), 3.85 (s, 3H), 3.57 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.1, 163.3, 154.3, 146.2, 137.6, 136.9, 133.8, 132.4 (2×), 132.4, 131.0, 128.2 (2×), 127.9 (2×), 127.8, 125.4, 115.3, 113.4 (2×), 109.0, 74.5, 55.6, 55.3, 30.8; HRMS (ESI, $M^+$ + Na) calcd for $C_{25}H_{24}O_4Na$ 411.1572, found 411.1567.

*[2-Allyl-3-(benzyloxy)-4-methoxyphenyl](4-fluorophenyl)-methanone (**6v**).* Yield 83% (312 mg); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.81−7.76 (m, 2H), 7.50 (d, $J$ = 8.8 Hz, 2H), 7.42−7.32 (m, 3H), 7.13−7.09 (m, 2H), 7.08 (d, $J$ = 8.4 Hz, 1H), 6.85 (d, $J$ = 8.4 Hz, 1H), 5.90−5.80 (m, 1H), 5.05 (s, 2H), 4.88−4.80 (m, 2H), 3.94 (s, 3H), 3.57 (dt, $J$ = 1.6, 6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 195.8, 165.5 (d, $J$ = 253.2 Hz), 154.8, 146.4, 137.6, 136.9, 134.7 (d, $J$ = 3.1 Hz), 134.4, 132.7 (d, $J$ = 9.1 Hz, 2×), 131.6, 128.4 (2×), 128.0 (2×), 127.9, 126.0, 115.4 (d, $J$ = 22.0 Hz, 2×), 115.2, 109.0, 74.7, 55.7, 30.7; HRMS (ESI, $M^+$ + H) calcd for $C_{24}H_{22}FO_3$ 377.1553, found 377.1558.

*[2-Allyl-3-(benzyloxy)-4-methoxyphenyl](p-tolyl)methanone (**6w**).* Yield 81% (301 mg); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$ = 8.4 Hz, 2H), 7.54 (d, $J$ = 8.4 Hz, 2H), 7.43−7.39 (m, 2H), 7.37−7.33 (m, 1H), 7.25 (d, $J$ = 8.4 Hz, 2H), 7.12 (d, $J$ = 8.4 Hz, 1H), 6.85 (d, $J$ = 8.4 Hz, 1H), 5.97−5.88 (m, 1H), 5.09 (s, 2H), 4.93−4.87 (m, 2H), 3.93 (s, 3H), 3.64 (dt, $J$ = 1.6, 6.4 Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 154.9, 146.7, 143.9, 138.0, 137.4, 136.1, 134.5, 132.5, 130.6 (2×), 129.2 (2×), 128.6 (2×), 128.3 (2×), 128.2, 126.4, 115.7, 109.3, 74.9, 56.0, 31.1, 21.9; HRMS (ESI, $M^+$ + H) calcd for $C_{25}H_{25}O_3$ 373.1804, found 373.1812.

*[2-Allyl-3-(benzyloxy)-4-methoxyphenyl](o-tolyl)methanone (**6x**).* Yield 90% (335 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 7.2 Hz, 2H), 7.43−7.33 (m, 4H), 7.29−7.25 (m, 2H), 7.21−7.18 (m, 1H), 7.11 (d, $J$ = 8.4 Hz, 1H), 6.78 (d, $J$ = 8.4 Hz, 1H), 6.03−5.94 (m, 1H), 5.05 (s, 2H), 4.97−4.92 (m, 2H), 3.93 (s, 3H), 3.77 (d, $J$ = 6.0 Hz, 2H), 2.41 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.3, 155.5, 146.5, 139.7, 137.7, 137.6, 137.3, 135.4, 132.2, 131.1, 130.5, 129.8, 128.5, 128.3 (2×), 127.9 (2×), 127.9, 125.2, 115.2, 108.8, 74.7, 55.7, 30.5, 20.4; HRMS (ESI, $M^+$ + Na) calcd for $C_{25}H_{24}O_3$ 395.1623, found 395.1616.

*[2-Allyl-3-(benzyloxy)-4-methoxyphenyl](phenyl)methanone (**6y**).* Yield 86% (308 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.77−7.74 (m, 2H), 7.58−7.32 (m, 8H), 7.11 (d, $J$ = 8.4 Hz, 1H), 6.84 (d, $J$ = 8.4 Hz, 1H), 5.92−5.82 (m, 1H), 5.05 (s, 2H), 4.88−4.81 (m, 2H), 3.94 (s, 3H), 3.58 (dt, $J$ = 1.6, 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 154.8, 146.4, 138.4, 137.7, 137.1, 134.5, 132.7, 130.2 (2×), 128.4 (2×), 128.2 (2×), 128.0 (2×), 127.9 (2×), 126.4, 115.4, 108.9, 74.7, 55.8, 30.8; HRMS (ESI, $M^+$ + Na) calcd for $C_{24}H_{22}O_3Na$ 381.1467, found 381.1460.

*[2-(But-3-en-2-yl)-3,4-dimethoxyphenyl](4-methoxyphenyl)-methanone (**6z**).*[13a] Yield 84% (274 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (d, $J$ = 8.8 Hz, 2H), 6.93−6.89 (m, 3H), 6.80 (d, $J$ = 8.4 Hz, 1H), 6.14 (ddd, $J$ = 6.4, 10.8, 17.2 Hz, 1H), 4.90−4.85 (m, 2H), 3.90 (s, 3H), 3.87 (s, 6H), 3.69−3.62 (m, 1H), 1.38 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.1, 163.6, 154.1, 148.0, 152.5, 138.2, 132.9, 132.6 (2×), 131.2, 123.7, 113.5 (2×), 113.4, 109.5, 60.6, 55.7, 55.5, 38.7, 19.6; HRMS (ESI, $M^+$ + H) calcd for $C_{20}H_{23}O_4$ 327.1596, found 327.1600.

*(2-Allyl-3-methoxyphenyl)(4-methoxyphenyl)methanone (**6aa**).* Yield 78% (220 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (d, $J$ = 8.8 Hz, 2H), 7.24 (t, $J$ = 7.6 Hz, 1H), 6.97 (d, $J$ = 8.0 Hz, 1H), 6.90 (d, $J$ = 9.2 Hz, 2H), 6.86 (d, $J$ = 7.6 Hz, 1H), 5.91−5.81 (m, 1H), 4.86−4.80 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.39 (d, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.8, 163.7, 157.8, 140.8, 136.4, 132.6 (2×), 130.5, 126.7, 126.6, 119.9, 115.0, 113.5 (2×), 111.7, 55.7, 55.4, 31.0; HRMS (ESI, $M^+$ + H) calcd for $C_{18}H_{19}O_3$ 283.1334, found 283.1337.

**General Synthetic Procedure for the Synthesis of 1a−1aa and 9a−9d.** A representative synthetic procedure for skeleton **1** or **9** is as follows. $PdCl_2$ (10 mg, 5.8 mol %) and $CuCl_2$ (200 mg, 1.5 mmol) were added to a solution of skeleton **6** or **4** (1.0 mmol) in dioxane (10 mL) at rt. Then oxygen was bubbled into the mixture for 2 h, and the mixture was stirred at rt for 4 h. $N_2H_4$ (2 mL) was added to the reaction mixture at rt. The reaction mixture was stirred at rt for 10 min. The residue was diluted with water (2 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product. Purification on a silica gel (5/1 to 3/1 hexanes/EtOAc) afforded skeletons **1a−1aa** and **9a−9d**.

*6,7-Dimethoxy-1-(4-methoxyphenyl)-4-methyl-5H-benzo[d][1,2]-diazepine (**1a**).* Yield 87% (282 mg); colorless solid; mp 196−197 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 8.8 Hz, 2H), 7.02 (d, $J$ = 8.8 Hz, 1H), 6.89 (d, $J$ = 8.8 Hz, 2H), 6.86 (d, $J$ = 8.8 Hz, 1H), 3.91 (s, 3H), 3.90 (d, $J$ = 12.0 Hz, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 2.73 (d, $J$ = 12.0 Hz, 1H), 2.13 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.9, 157.8, 155.6, 154.5, 144.0, 133.6, 131.5, 130.9 (2×), 126.5, 124.0, 113.4 (2×), 110.4, 61.3, 55.7, 55.2, 30.6, 23.3; HRMS (ESI, $M^+$ + H) calcd for $C_{19}H_{21}N_2O_3$ 325.1552, found 325.1546. For the single-crystal X-ray diagram, a crystal of **1a** was grown by slow diffusion of EtOAc into a solution of **1a** in $CH_2Cl_2$ to yield colorless prisms. The compound crystallizes in the monoclinic crystal system in space group $P21/n$: $a$ = 8.1616(6) Å, $b$ = 8.6757(7) Å, $c$ = 22.6247(19) Å, $V$ = 1601.9(2) Å$^3$, $Z$ = 4, $d_{calcd}$ = 1.345 g/cm$^3$, $F(000)$ = 688, 2$\theta$ range of 1.80−26.47°, $R$ indices (all data) $R_1$ = 0.0418 and $wR_2$ = 0.1152.

*1-(4-Fluorophenyl)-6,7-dimethoxy-4-methyl-5H-benzo[d][1,2]-diazepine (**1b**).* Yield 88% (275 mg); colorless solid; mp 150−151 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 (d, $J$ = 8.8 Hz, 2H), 7.07 (t, $J$ = 8.8 Hz, 2H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 3.95 (d, $J$ = 12.0 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 2.73 (d, $J$ = 12.0 Hz, 1H), 2.16 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.9 (d, $J$ = 248.7 Hz), 157.6, 156.0, 154.9, 144.3, 135.1 (d, $J$ = 3.0 Hz), 133.7, 131.5 (d, $J$ = 8.3 Hz, 2×), 126.4, 123.9, 115.1 (d, $J$ = 22.0 Hz, 2×), 110.7, 61.4, 55.8, 30.7, 23.4; HRMS (ESI, $M^+$ + H) calcd for $C_{18}H_{18}FN_2O_2$ 313.1352, found 313.1347.

*6,7-Dimethoxy-4-methyl-1-p-tolyl-5H-benzo[d][1,2]diazepine (**1c**).* Yield 83% (256 mg); colorless solid; mp 155−156 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 8.0 Hz, 2H), 7.18 (d, $J$ = 8.0 Hz, 2H), 7.01 (d, $J$ = 8.8 Hz, 1H), 6.86 (d, $J$ = 8.8 Hz, 1H), 3.91 (d, $J$ = 12.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.73 (d, $J$ = 12.0 Hz, 1H), 2.37 (s, 3H), 2.14 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.2, 155.5, 154.5, 144.0, 139.7, 136.2, 133.6, 129.4 (2×), 128.7 (2×), 126.4, 124.1, 110.4, 61.3, 55.7, 30.6, 23.3, 21.2; HRMS (ESI, $M^+$ + H) calcd for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1596. For the single-crystal X-ray diagram, a



DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836−9847

crystal of **1c** was grown by slow diffusion of EtOAc into a solution of **1c** in $CH_2Cl_2$ to yield colorless prisms. The compound crystallizes in the monoclinic crystal system in space group $P21/c$: $a$ = 7.1877(5) Å, $b$ = 25.1688(16) Å, $c$ = 9.8090(6) Å, $V$ = 1664.46(19) Å$^3$, $Z$ = 4, $d_{calcd}$ = 1.231 g/cm$^3$, $F(000)$ = 656, $2\theta$ range of 1.62−26.41°, $R$ indices (all data) $R_1$ = 0.0649 and $wR_2$ = 0.1299.

*6,7-Dimethoxy-4-methyl-1-o-tolyl-5H-benzo[d][1,2]diazepine (**1d**).* Yield 86% (265 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 7.2 Hz, 1H), 7.32−7.22 (m, 2H), 7.18 (d, $J$ = 7.2 Hz, 1H), 6.80 (d, $J$ = 8.8 Hz, 1H), 6.75 (d, $J$ = 8.8 Hz, 1H), 4.01 (d, $J$ = 12.0 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 2.80 (d, $J$ = 12.0 Hz, 1H), 2.20 (s, 3H), 2.04 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.8, 155.4, 154.7, 144.2, 139.3, 137.0, 132.6, 130.5, 130.4, 129.1, 125.9, 125.7, 125.6, 110.9, 61.5, 55.8, 30.6, 23.6, 20.2; HRMS (ESI, M$^+$ + H) calcd for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1599.

*6,7-Dimethoxy-4-methyl-1-phenyl-5H-benzo[d][1,2]diazepine (**1e**).* Yield 90% (265 mg); colorless solid; mp 131−132 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.63 (d, $J$ = 8.0 Hz, 2H), 7.37−7.32 (m, 3H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.85 (d, $J$ = 8.4 Hz, 1H), 3.91 (d, $J$ = 12.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.71 (d, $J$ = 12.0 Hz, 1H), 2.13 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.3, 155.4, 154.5, 143.9, 138.9, 133.5, 129.5, 129.4 (2×), 127.9 (2×), 126.3, 123.9, 110.5, 61.2, 55.6, 30.5, 23.2; HRMS (ESI, M$^+$ + H) calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1441.

*6-Isopropoxy-7-methoxy-1-(4-methoxyphenyl)-4-methyl-5H-benzo[d][1,2]diazepine (**1f**).* Yield 89% (313 mg); colorless solid; mp 158−159 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (d, $J$ = 8.8 Hz, 2H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.91 (d, $J$ = 8.8 Hz, 2H), 6.85 (d, $J$ = 8.4 Hz, 1H), 4.54−4.48 (m, 1H), 3.95 (d, $J$ = 12.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.74 (d, $J$ = 12.0 Hz, 1H), 2.12 (s, 3H), 1.42 (d, $J$ = 6.0 Hz, 3H), 1.25 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.9, 158.1, 156.1, 154.8, 141.9, 134.7, 131.7, 131.0 (2×), 126.1, 124.1, 113.4 (2×), 110.3, 75.4, 55.7, 55.3, 31.2, 23.4, 22.9, 22.1; HRMS (ESI, M$^+$ + H) calcd for $C_{21}H_{25}N_2O_3$ 353.1865, found 353.1860.

*1-(4-Fluorophenyl)-6-isopropoxy-7-methoxy-4-methyl-5H-benzo[d][1,2]diazepine (**1g**).* Yield 82% (279 mg); colorless solid; mp 189−190 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 9.2 Hz, 1H), 7.64 (d, $J$ = 8.8 Hz, 1H), 7.09−7.03 (m, 2H), 6.96 (d, $J$ = 8.8 Hz, 1H), 6.86 (d, $J$ = 8.8 Hz, 1H), 4.55−4.49 (m, 1H), 3.97 (d, $J$ = 12.0 Hz, 1H), 3.88 (s, 3H), 2.72 (d, $J$ = 12.0 Hz, 1H), 2.13 (s, 3H), 1.43 (d, $J$ = 6.0 Hz, 3H), 1.25 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.8 (d, $J$ = 247.9 Hz), 157.6, 156.0, 155.0, 142.0, 135.3 (d, $J$ = 3.0 Hz), 134.7, 131.4 (d, $J$ = 8.4 Hz, 2×), 125.9, 123.8, 115.0 (d, $J$ = 21.2 Hz, 2×), 110.4, 75.4, 55.7, 31.2, 23.4, 22.9, 22.1; HRMS (ESI, M$^+$ + H) calcd for $C_{20}H_{22}FN_2O_2$ 341.1665, found 341.1660.

*6-Isopropoxy-7-methoxy-4-methyl-1-p-tolyl-5H-benzo[d][1,2]-diazepine (**1h**).* Yield 81% (272 mg); colorless solid; mp 115−116 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 8.0 Hz, 2H), 7.19 (d, $J$ = 8.0 Hz, 2H), 6.99 (d, $J$ = 8.4 Hz, 1H), 6.85 (d, $J$ = 8.4 Hz, 1H), 4.54−4.48 (m, 1H), 3.95 (d, $J$ = 12.0 Hz, 1H), 3.88 (s, 3H), 2.74 (d, $J$ = 12.0 Hz, 1H), 2.38 (s, 3H), 2.13 (s, 3H), 1.43 (d, $J$ = 6.0 Hz, 3H), 1.25 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.6, 156.1, 154.8, 141.9, 139.8, 136.3, 134.7, 129.5 (2×), 128.8 (2×), 126.1, 124.1, 110.3, 75.4, 55.7, 31.2, 23.4, 22.9, 22.1, 21.3; HRMS (ESI, M$^+$ + H) calcd for $C_{21}H_{25}N_2O_2$ 337.1916, found 337.1909.

*6-Isopropoxy-7-methoxy-4-methyl-1-o-tolyl-5H-benzo[d][1,2]-diazepine (**1i**).* Yield 86% (289 mg); colorless solid; mp 135−136 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 7.2 Hz, 1H), 7.30−7.22 (m, 2H), 7.15 (d, $J$ = 7.2 Hz, 1H), 6.77 (d, $J$ = 8.8 Hz, 1H), 6.71 (d, $J$ = 8.8 Hz, 1H), 4.58−4.52 (m, 1H), 4.03 (d, $J$ = 12.0 Hz, 1H), 3.84 (s, 3H), 2.79 (d, $J$ = 12.0 Hz, 1H), 2.16 (s, 3H), 1.99 (s, 3H), 1.42 (d, $J$ = 6.4 Hz, 3H), 1.22 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.9, 155.5, 154.8, 141.8, 139.5, 136.8, 133.8, 130.5, 130.2, 128.9, 125.8, 125.5, 125.2, 110.7, 75.0, 55.7, 31.0, 23.6, 22.8, 22.0, 20.0; HRMS (ESI, M$^+$ + H) calcd for $C_{21}H_{25}N_2O_2$ 337.1916, found 337.1911.

*6-Isopropoxy-7-methoxy-4-methyl-1-phenyl-5H-benzo[d][1,2]-diazepine (**1j**).* Yield 88% (284 mg); colorless solid; mp 133−134 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.0 Hz, 2H), 7.39−7.37 (m, 3H), 6.98 (d, $J$ = 8.8 Hz, 1H), 6.85 (d, $J$ = 8.8 Hz, 1H), 4.55−4.48 (m, 1H), 3.96 (d, $J$ = 12.0 Hz, 1H), 3.87 (s, 3H), 2.73 (d, $J$ = 12.0 Hz, 1H), 2.13 (s, 3H), 1.42 (d, $J$ = 6.0 Hz, 3H), 1.25 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.6, 155.9, 154.8, 141.8, 139.1, 134.7, 129.6, 129.5 (2×), 128.0 (2×), 126.0, 123.9, 110.3, 75.3, 55.7, 31.1, 23.4, 22.8, 22.1; HRMS (ESI, M$^+$ + H) calcd for $C_{20}H_{23}N_2O_2$ 323.1760, found 323.1755.

*6-Butoxy-7-methoxy-1-(4-methoxyphenyl)-4-methyl-5H-benzo-[d][1,2]diazepine (**1k**).* Yield 89% (326 mg); colorless solid; mp 166−167 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 8.8 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 1H), 6.90 (d, $J$ = 8.8 Hz, 2H), 6.86 (d, $J$ = 8.4 Hz, 1H), 4.07−3.98 (m, 2H), 3.92 (d, $J$ = 11.6 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.74 (d, $J$ = 11.6 Hz, 1H), 2.14 (s, 3H), 1.87−1.79 (m, 2H), 1.61−1.52 (m, 2H), 1.01 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.9, 157.9, 155.7, 154.7, 143.4, 133.9, 131.7, 131.0 (2×), 126.3, 124.1, 113.4 (2×), 110.4, 73.7, 55.7, 55.3, 32.3, 30.8, 23.3, 19.2, 13.9; HRMS (ESI, M$^+$ + H) calcd for $C_{22}H_{27}N_2O_3$ 367.2022, found 367.2017.

*6-Butoxy-1-(4-fluorophenyl)-7-methoxy-4-methyl-5H-benzo[d]-[1,2]diazepine (**1l**).* Yield 85% (301 mg); colorless solid; mp 142−143 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 (d, $J$ = 8.8 Hz, 1H), 7.63 (d, $J$ = 8.8 Hz, 1H), 7.08−7.02 (m, 2H), 6.97 (d, $J$ = 8.8 Hz, 1H), 6.87 (d, $J$ = 8.8 Hz, 1H), 4.08−3.98 (m, 2H), 3.94 (d, $J$ = 12.0 Hz, 1H), 3.89 (s, 3H), 2.71 (d, $J$ = 12.0 Hz, 1H), 2.14 (s, 3H), 1.87−1.79 (m, 2H), 1.61−1.52 (m, 2H), 1.01 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.8 (d, $J$ = 247.9 Hz), 157.4, 155.7, 154.9, 143.5, 135.2 (d, $J$ = 3.0 Hz), 133.9, 131.4 (d, $J$ = 8.3 Hz, 2×), 126.1, 123.8, 115.0 (d, $J$ = 21.2 Hz, 2×), 110.6, 73.7, 55.7, 32.3, 30.8, 23.4, 19.2, 13.9; HRMS (ESI, M$^+$ + H) calcd for $C_{21}H_{24}FN_2O_2$ 355.1822, found 355.1818.

*6-Butoxy-7-methoxy-4-methyl-1-p-tolyl-5H-benzo[d][1,2]-diazepine (**1m**).* Yield 82% (287 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.0 Hz, 2H), 7.20 (d, $J$ = 8.0 Hz, 2H), 7.02 (d, $J$ = 8.4 Hz, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 4.09−3.98 (m, 2H), 3.94 (d, $J$ = 12.0 Hz, 1H), 3.90 (s, 3H), 2.75 (d, $J$ = 12.0 Hz, 1H), 2.39 (s, 3H), 2.16 (s, 3H), 1.88−1.80 (m, 2H), 1.63−1.51 (m, 2H), 1.02 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.6, 156.0, 154.8, 143.4, 139.9, 136.3, 133.9, 129.6 (2×), 128.8 (2×), 126.4, 124.2, 110.5, 73.8, 55.8, 32.4, 30.9, 23.4, 21.3, 19.3, 13.9; HRMS (ESI, M$^+$ + H) calcd for $C_{22}H_{27}N_2O_2$ 351.2073, found 351.2066.

*6-Butoxy-7-methoxy-4-methyl-1-o-tolyl-5H-benzo[d][1,2]-diazepine (**1n**).* Yield 86% (301 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 7.2 Hz, 1H), 7.31−7.22 (m, 2H), 7.16 (d, $J$ = 7.2 Hz, 1H), 6.78 (d, $J$ = 8.8 Hz, 1H), 6.73 (d, $J$ = 8.8 Hz, 1H), 4.06−4.01 (m, 2H), 4.01 (d, $J$ = 12.0 Hz, 1H), 3.86 (s, 3H), 2.80 (d, $J$ = 12.0 Hz, 1H), 2.19 (s, 3H), 2.02 (s, 3H), 1.88−1.80 (m, 2H), 1.63−1.53 (m, 2H), 1.02 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.8, 155.2, 154.7, 143.4, 139.5, 136.9, 132.9, 130.5, 130.4, 129.0, 125.9, 125.6, 125.4, 110.8, 73.8, 55.7, 32.3, 30.7, 23.6, 20.1, 19.2, 13.9; HRMS (ESI, M$^+$ + H) calcd for $C_{22}H_{27}N_2O_2$ 351.2073, found 351.2065.

*6-Butoxy-7-methoxy-4-methyl-1-phenyl-5H-benzo[d][1,2]-diazepine (**1o**).* Yield 88% (296 mg); colorless solid; mp 89−90 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (d, $J$ = 8.0 Hz, 2H), 7.39−7.33 (m, 3H), 6.98 (d, $J$ = 8.8 Hz, 1H), 6.85 (d, $J$ = 8.8 Hz, 1H), 4.08−3.98 (m, 2H), 3.94 (d, $J$ = 12.0 Hz, 1H), 3.87 (s, 3H), 2.72 (d, $J$ = 12.0 Hz, 1H), 2.14 (s, 3H), 1.87−1.79 (m, 2H), 1.59−1.53 (m, 2H), 1.01 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.4, 155.5, 154.7, 143.3, 139.0, 133.8, 129.5, 129.5 (2×), 127.9 (2×), 126.2, 123.9, 110.4, 73.6, 55.6, 32.2, 30.7, 23.3, 19.1, 13.8; HRMS (ESI, M$^+$ + H) calcd for $C_{21}H_{25}N_2O_2$ 337.1916, found 337.1908.

*6-(Cyclopentyloxy)-7-methoxy-1-(4-methoxyphenyl)-4-methyl-5H-benzo[d][1,2]diazepine (**1p**).* Yield 90% (340 mg); colorless solid; mp 156−157 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 9.2 Hz, 2H), 6.97 (d, $J$ = 8.4 Hz,



DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836−9847

1H), 6.88 (d, $J$ = 9.2 Hz, 2H), 6.83 (d, $J$ = 8.4 Hz, 1H), 4.87−4.83 (m, 1H), 3.87 (d, $J$ = 11.6 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.72 (d, $J$ = 11.6 Hz, 1H), 2.09 (s, 3H), 2.04−1.60 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.8, 157.9, 155.8, 154.6, 142.0, 134.4, 131.6, 130.9 (2×), 125.8, 123.9, 113.3 (2×), 110.3, 85.0, 55.6, 55.1, 33.2, 32.1, 30.9, 23.6, 23.4, 23.2; HRMS (ESI, $M^+$ + H) calcd for $C_{23}H_{27}N_2O_3$ 379.2022, found 379.2018. For the single-crystal X-ray diagram, a crystal of **1p** was grown by slow diffusion of EtOAc into a solution of **1p** in $CH_2Cl_2$ to yield colorless prisms. The compound crystallizes in the triclinic crystal system in space group $P\bar{1}$: $a$ = 8.4384(6) Å, $b$ = 11.0458(8) Å, $c$ = 12.1243(8) Å, $V$ = 1041.25(13) Å$^3$, $Z$ = 2, $d_{calcd}$ = 1.207 g/cm$^3$, $F(000)$ = 404, 2$\theta$ range of 1.82−26.51°, $R$ indices (all data) $R_1$ = 0.0071 and $wR_2$ = 0.1461.

*6-(Cyclopentyloxy)-1-(4-fluorophenyl)-7-methoxy-4-methyl-5H-benzo[d][1,2]diazepine (**1q**).* Yield 85% (311 mg); colorless solid; mp 153−154 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.8 Hz, 1H), 7.65 (d, $J$ = 8.8 Hz, 1H), 7.09−7.03 (m, 2H), 6.95 (d, $J$ = 8.8 Hz, 1H), 6.86 (d, $J$ = 8.8 Hz, 1H), 4.90−4.86 (m, 1H), 3.92 (d, $J$ = 12.0 Hz, 1H), 3.88 (s, 3H), 3.72 (d, $J$ = 12.0 Hz, 1H), 2.12 (s, 3H), 2.07−2.01 (m, 1H), 1.97−1.77 (m, 4H), 1.73−1.61 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.8 (d, $J$ = 248.6 Hz), 157.5, 155.9, 154.8, 142.3, 135.2 (d, $J$ = 3.0 Hz), 134.5, 131.4 (d, $J$ = 8.4 Hz, 2×), 125.7, 123.8, 115.0 (d, $J$ = 21.2 Hz, 2×), 110.6, 85.2, 55.7, 33.4, 32.2, 31.1, 23.7, 23.5, 23.3; HRMS (ESI, $M^+$ + H) calcd for $C_{22}H_{24}FN_2O_2$ 367.1822, found 367.1817.

*6-(Cyclopentyloxy)-7-methoxy-4-methyl-1-p-tolyl-5H-benzo[d][1,2]diazepine (**1r**).* Yield 84% (304 mg); colorless solid; mp 156−157 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.0 Hz, 2H), 7.18 (d, $J$ = 8.0 Hz, 2H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.84 (d, $J$ = 8.4 Hz, 1H), 4.89−4.85 (m, 1H), 3.90 (d, $J$ = 11.6 Hz, 1H), 3.87 (s, 3H), 2.73 (d, $J$ = 11.6 Hz, 1H), 2.37 (s, 3H), 2.11 (s, 3H), 2.07−2.01 (m, 1H), 1.96−1.77 (m, 4H), 1.70−1.61 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.5, 155.8, 154.6, 142.1, 139.7, 136.3, 134.5, 129.5 (2×), 128.7 (2×), 125.9, 124.0, 110.4, 85.1, 55.6, 33.3, 32.1, 31.0, 23.6, 23.5, 23.3, 21.2; HRMS (ESI, $M^+$ + H) calcd for $C_{23}H_{27}N_2O_2$ 363.2073, found 363.2068.

*6-(Cyclopentyloxy)-7-methoxy-4-methyl-1-o-tolyl-5H-benzo[d][1,2]diazepine (**1s**).* Yield 84% (304 mg); colorless solid; mp 104−105 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 7.2 Hz, 1H), 7.31−7.22 (m, 2H), 7.16 (d, $J$ = 7.2 Hz, 1H), 6.78 (d, $J$ = 8.4 Hz, 1H), 6.71 (d, $J$ = 8.4 Hz, 1H), 4.92−4.89 (m, 1H), 3.98 (d, $J$ = 12.0 Hz, 1H), 3.85 (s, 3H), 2.80 (d, $J$ = 12.0 Hz, 1H), 2.16 (s, 3H), 2.02 (s, 3H), 2.00−1.75 (m, 5H), 1.72−1.64 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.9, 155.4, 154.6, 142.1, 139.5, 136.9, 133.7, 130.5, 130.3, 128.9, 125.9, 125.6, 125.1, 110.8, 84.9, 55.7, 33.3, 32.1, 30.9, 23.7, 23.6, 23.6, 20.1; HRMS (ESI, $M^+$ + H) calcd for $C_{23}H_{27}N_2O_2$ 363.2073, found 363.2067.

*6-(Cyclopentyloxy)-7-methoxy-4-methyl-1-phenyl-5H-benzo[d][1,2]diazepine (**1t**).* Yield 85% (296 mg); colorless solid; mp 154−155 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (d, $J$ = 8.0 Hz, 2H), 7.43−7.36 (m, 3H), 6.99 (d, $J$ = 8.8 Hz, 1H), 6.86 (d, $J$ = 8.8 Hz, 1H), 4.90−4.86 (m, 1H), 3.92 (d, $J$ = 11.6 Hz, 1H), 3.89 (s, 3H), 2.74 (d, $J$ = 11.6 Hz, 1H), 2.13 (s, 3H), 2.07−2.02 (m, 1H), 1.97−1.78 (m, 4H), 1.71−1.62 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.7, 156.0, 154.8, 142.2, 139.1, 134.6, 129.65, 129.62 (2×), 128.0 (2×), 126.0, 124.1, 110.5, 85.2, 55.7, 33.4, 32.2, 31.1, 23.7, 23.5, 23.4; HRMS (ESI, $M^+$ + H) calcd for $C_{22}H_{25}N_2O_2$ 349.1916, found 349.1910.

*6-(Benzyloxy)-7-methoxy-1-(4-methoxyphenyl)-4-methyl-5H-benzo[d][1,2]diazepine (**1u**).* Yield 89% (356 mg); colorless solid; mp 152−153 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 8.4 Hz, 2H), 7.48 (d, $J$ = 8.4 Hz, 2H), 7.41−7.31 (m, 3H), 7.05 (d, $J$ = 8.8 Hz, 1H), 6.93−6.90 (m, 3H), 5.12 (d, $J$ = 11.2 Hz, 1H), 5.08 (d, $J$ = 11.2 Hz, 1H), 3.92 (s, 3H), 3.85 (d, $J$ = 12.0 Hz, 1H), 3.82 (s, 3H), 2.61 (d, $J$ = 12.0 Hz, 1H), 2.07 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.8, 157.8, 155.6, 154.5, 142.6, 137.1, 134.1, 131.5, 130.9 (2×), 128.3 (2×), 128.0, 127.9 (2×), 126.5, 124.0, 113.3 (2×), 110.4, 75.3, 55.7, 55.1, 30.7, 23.2; HRMS (ESI, $M^+$ + H) calcd for $C_{25}H_{25}N_2O_3$ 401.1865, found 401.1858.

*6-(Benzyloxy)-1-(4-fluorophenyl)-7-methoxy-4-methyl-5H-benzo[d][1,2]diazepine (**1v**).* Yield 83% (322 mg); colorless solid; mp 198−199 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66−7.62 (m, 2H), 7.49−7.47 (m, 2H), 7.42−7.35 (m, 3H), 7.10−7.06 (m, 2H), 7.02 (d, $J$ = 8.4 Hz, 1H), 6.93 (d, $J$ = 8.4 Hz, 1H), 5.13 (d, $J$ = 11.2 Hz, 1H), 5.09 (d, $J$ = 11.2 Hz, 1H), 3.95 (s, 3H), 3.88 (d, $J$ = 12.0 Hz, 1H), 2.59 (d, $J$ = 12.0 Hz, 1H), 2.08 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.8 (d, $J$ = 248.6 Hz), 157.4, 155.8, 154.8, 142.8, 137.1, 135.2 (d, $J$ = 3.0 Hz), 134.2, 131.4 (d, $J$ = 8.3 Hz, 2×), 128.4 (2×), 128.15, 128.05 (2×), 126.4, 123.8, 115.0 (d, $J$ = 22.0 Hz, 2×), 110.6, 75.4, 55.8, 30.8, 23.3; HRMS (ESI, $M^+$ + H) calcd for $C_{24}H_{22}FN_2O_2$ 389.1665, found 389.1658.

*6-(Benzyloxy)-7-methoxy-4-methyl-1-p-tolyl-5H-benzo[d][1,2]diazepine (**1w**).* Yield 81% (311 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 8.0 Hz, 2H), 7.48 (d, $J$ = 8.4 Hz, 2H), 7.42−7.33 (m, 3H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.05 (d, $J$ = 8.4 Hz, 1H), 6.92 (d, $J$ = 8.4 Hz, 1H), 5.13 (d, $J$ = 11.2 Hz, 1H), 5.09 (d, $J$ = 11.2 Hz, 1H), 3.95 (s, 3H), 3.86 (d, $J$ = 12.0 Hz, 1H), 2.61 (d, $J$ = 12.0 Hz, 1H), 2.40 (s, 3H), 2.08 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.4, 155.8, 154.7, 142.8, 139.8, 137.2, 136.3, 134.3, 129.6 (2×), 128.8 (2×), 128.5 (2×), 128.2, 128.1 (2×), 126.7, 124.2, 110.5, 75.5, 55.8, 30.9, 23.3, 21.3; HRMS (ESI, $M^+$ + H) calcd for $C_{25}H_{25}N_2O_2$ 385.1916, found 385.1909.

*6-(Benzyloxy)-7-methoxy-4-methyl-1-o-tolyl-5H-benzo[d][1,2]diazepine (**1x**).* Yield 85% (327 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48−7.27 (m, 7H), 7.25−7.23 (m, 1H), 7.17−7.15 (m, 1H), 6.83 (d, $J$ = 8.4 Hz, 1H), 6.76 (d, $J$ = 8.4 Hz, 1H), 5.14 (d, $J$ = 11.2 Hz, 1H), 5.10 (d, $J$ = 11.2 Hz, 1H), 3.92 (s, 3H), 3.86 (d, $J$ = 12.0 Hz, 1H), 2.57 (d, $J$ = 12.0 Hz, 1H), 2.11 (s, 3H), 1.92 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.8, 155.5, 154.7, 142.4, 139.4, 136.9, 136.9, 133.4, 130.5, 130.3, 129.1, 128.4 (4×), 128.3, 125.8, 125.8, 125.6, 110.9, 75.3, 55.8, 30.8, 23.5, 20.2; HRMS (ESI, $M^+$ + H) calcd for $C_{25}H_{25}N_2O_2$ 385.1916, found 385.1909.

*6-(Benzyloxy)-7-methoxy-4-methyl-1-phenyl-5H-benzo[d][1,2]diazepine (**1y**).* Yield 84% (311 mg); colorless solid; mp 157−158 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.0 Hz, 2H), 7.49 (d, $J$ = 8.0 Hz, 2H), 7.41−7.32 (m, 6H), 7.03 (d, $J$ = 8.8 Hz, 1H), 6.91 (d, $J$ = 8.8 Hz, 1H), 5.13 (d, $J$ = 11.2 Hz, 1H), 5.10 (d, $J$ = 11.2 Hz, 1H), 3.92 (s, 3H), 3.88 (d, $J$ = 11.6 Hz, 1H), 2.61 (d, $J$ = 11.6 Hz, 1H), 2.08 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.2, 155.4, 154.5, 142.5, 138.9, 137.0, 134.0, 129.44, 129.36 (2×), 128.2 (2×), 127.9, 127.9 (2×), 127.8 (2×), 126.4, 123.8, 110.4, 75.2, 55.6, 30.6, 23.1; HRMS (ESI, $M^+$ + H) calcd for $C_{24}H_{23}N_2O_2$ 371.1760, found 371.1752.

*6,7-Dimethoxy-1-(4-methoxyphenyl)-4,5-dimethyl-5H-benzo[d][1,2]diazepine (**1z**).* Yield 85% (287 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.8 Hz, 2H), 7.03 (d, $J$ = 8.8 Hz, 1H), 6.91 (d, $J$ = 8.8 Hz, 2H), 6.88 (d, $J$ = 8.8 Hz, 1H), 4.39 (q, $J$ = 7.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 2.15 (s, 3H), 1.17 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.9, 158.6, 157.0, 154.6, 144.3, 139.0, 132.4, 131.0, 130.9 (2×), 128.0, 122.9, 113.5 (2×), 110.6, 61.7, 55.8, 55.3, 35.9, 25.2; HRMS (ESI, $M^+$ + H) calcd for $C_{20}H_{23}N_2O_3$ 339.1709, found 339.1702.

*6-Methoxy-1-(4-methoxyphenyl)-4-methyl-5H-benzo[d][1,2]diazepine (**1aa**).* Yield 79% (232 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, $J$ = 9.2 Hz, 2H), 7.25 (t, $J$ = 8.0 Hz, 1H), 7.04 (d, $J$ = 8.0 Hz, 1H), 6.93−6.89 (m, 3H), 4.00 (d, $J$ = 12.0 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 2.62 (d, $J$ = 12.0 Hz, 1H), 2.13 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.0, 158.4, 156.0, 155.0, 131.4, 131.3, 130.9 (2×), 128.3, 127.0, 122.1, 113.5 (2×), 112.1, 55.9, 55.3, 29.8, 23.4; HRMS (ESI, $M^+$ + H) calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1439.

*2-Amino-5,6-dimethoxy-3-methylisoquinolin-1(2H)-one (**9a**).* Yield 87% (204 mg); colorless solid; mp 181−182 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J$ = 8.8 Hz, 1H), 7.06 (d, $J$ = 8.8 Hz, 1H), 6.58 (s, 1H), 4.89 (br s, 2H), 3.95 (s, 3H), 3.87 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.7, 154.3, 141.3, 140.9, 131.5, 124.4, 118.2, 111.6, 98.4, 61.0, 56.0, 19.8; HRMS (ESI, $M^+$ + Na) calcd for $C_{12}H_{14}N_2O_3Na$ 257.0902, found 257.0897.



DOI: 10.1021/acs.joc.6b01935
J. Org. Chem. 2016, 81, 9836−9847

*2-Amino-5-butoxy-6-methoxy-3-methylisoquinolin-1(2H)-one (**9b**).* Yield 85% (235 mg); colorless gum; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J$ = 8.8 Hz, 1H), 7.07 (d, $J$ = 8.8 Hz, 1H), 6.62 (s, 1H), 4.94 (br s, 2H), 4.01 (t, $J$ = 6.8 Hz, 2H), 3.94 (s, 3H), 2.48 (s, 3H), 1.83−1.76 (m, 2H), 1.59−1.49 (m, 2H), 0.99 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.8, 154.4, 140.7, 140.6, 131.9, 124.2, 118.2, 111.7, 98.8, 73.4, 56.0, 32.3, 19.9, 19.2, 13.9; HRMS (ESI, $M^+$ + H) calcd for $C_{15}H_{21}N_2O_3$ 277.1552, found 277.1548.

*2-Amino-5-(cyclopentyloxy)-6-methoxy-3-methylisoquinolin-1(2H)-one (**9c**).* Yield 84% (242 mg); colorless solid; mp 55−56 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.08 (d, $J$ = 8.8 Hz, 1H), 7.07 (d, $J$ = 8.8 Hz, 1H), 6.60 (s, 1H), 4.93−4.90 (m, 3H), 3.94 (s, 3H), 2.48 (s, 3H), 1.93−1.84 (m, 4H), 1.77−1.60 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.8, 154.3, 140.3, 139.4, 132.6, 123.8, 118.2, 111.7, 99.2, 84.7, 56.0, 32.7 (2×), 23.7 (2×), 19.9; HRMS (ESI, $M^+$ + H) calcd for $C_{16}H_{21}N_2O_3$ 289.1552, found 289.1548.

*2-Amino-6-methoxy-3-methyl-5-(octyloxy)isoquinolin-1(2H)-one (**9d**).* Yield 82% (272 mg); colorless solid; mp 77−78 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J$ = 8.8 Hz, 1H), 7.07 (d, $J$ = 8.8 Hz, 1H), 6.62 (s, 1H), 4.94 (br s, 2H), 4.00 (t, $J$ = 6.8 Hz, 2H), 3.95 (s, 3H), 2.49 (s, 3H), 1.85−1.77 (m, 2H), 1.52−1.46 (m, 2H), 1.39−1.23 (m, 8H), 0.89 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.8, 154.4, 140.7, 131.9, 124.2, 111.7, 98.8, 73.7, 56.0, 31.8, 30.2 (2×), 29.7, 29.4, 29.3, 26.0, 22.6, 19.9, 14.1; HRMS (ESI, $M^+$ + H) calcd for $C_{19}H_{29}N_2O_3$ 333.2178, found 333.2174.

**General Synthetic Procedure for the Synthesis of 8a and 8b.** A representative synthetic procedure of skeleton **8** is as follows. $PdCl_2$ (10 mg, 5.6 mol %) and $CuCl_2$ (200 mg, 1.5 mmol) were added to a solution of skeleton **4** (1.0 mmol) in dioxane (10 mL) at rt. Then oxygen was bubbled into the mixture for 2 h, and the mixture was stirred at rt for 13 h. The residue was diluted with water (2 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product. Purification on silica gel (10/1 to 6/1 hexanes/EtOAc) afforded skeleton **8**.

*3,4-Dimethoxy-2-(2-oxopropyl)benzaldehyde (**8a**).*[11] Yield 90% (200 mg); colorless solid; mp 72−73 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.80 (s, 1H), 7.51 (d, $J$ = 8.4 Hz, 1H), 6.96 (d, $J$ = 8.4 Hz, 1H), 4.23 (s, 2H), 3.92 (s, 3H), 3.75 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 205.6, 191.9, 157.2, 148.0, 133.3, 130.3, 128.0, 110.1, 60.8, 55.8, 40.5, 30.0; HRMS (ESI, $M^+$ + H) calcd for $C_{12}H_{15}O_4$ 223.0970, found 223.0977.

*3-Butoxy-4-methoxy-2-(2-oxopropyl)benzaldehyde (**8b**).*[11] Yield 86% (227 mg); colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.81 (s, 1H), 7.52 (d, $J$ = 8.8 Hz, 1H), 6.96 (d, $J$ = 8.8 Hz, 1H), 4.25 (s, 2H), 3.92 (s, 3H), 3.87 (t, $J$ = 6.8 Hz, 2H), 2.32 (s, 3H), 1.74−1.66 (m, 2H), 1.49−1.43 (m, 2H), 0.95 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 205.7, 192.0, 157.4, 147.4, 133.2, 130.3, 128.0, 110.0, 73.3, 55.8, 40.7, 32.2, 30.0 19.1, 13.8; HRMS (ESI, $M^+$ + H) calcd for $C_{15}H_{21}O_4$ 265.1440, found 265.1446.

*3,4-Dimethoxy-6-methylbenzo[4,5]imidazo[2,1-a]isoquinoline (**10**).* 1,2-Diaminobenzene (108 mg, 1.0 mmol) was added to a solution of skeleton **8a** (1.0 mmol) in AcOH (8 mL) at rt. The mixture was stirred at reflux for 5 h. The residue was diluted with aqueous $NaHCO_3$ (95%, 10 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product. Purification on silica gel (10/1 to 6/1 hexanes/EtOAc) afforded compound **10**: yield 85% (248 mg); colorless solid; mp 141−142 °C (recrystallized from hexanes and EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.57 (d, $J$ = 8.8 Hz, 1H), 8.07 (d, $J$ = 8.4 Hz, 1H), 7.98 (d, $J$ = 8.4 Hz, 1H), 7.49−7.45 (m, 1H), 7.34−7.30 (m, 1H), 7.28 (d, $J$ = 8.8 Hz, 1H), 7.10 (s, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.04 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.9, 148.3, 144.0, 142.4, 135.1, 131.3, 127.1, 124.1, 121.6, 121.4, 119.4, 116.5, 113.8, 113.1, 104.9, 61.3, 56.1, 21.5; HRMS (ESI, $M^+$ + Na) calcd for $C_{18}H_{16}N_2O_2Na$ 315.1110, found 315.1114.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01935.

X-ray analysis data of **1a** (CIF)
X-ray analysis data of **1c** (CIF)
X-ray analysis data of **1p** (CIF)
X-ray analysis data of **7y** (CIF)
X-ray analysis data of **9a** (CIF)
Spectroscopic data for all compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: mychang@kmu.edu.tw.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors thank the Ministry of Science and Technology of the Republic of China for financial support (MOST 105-2113-M-037-001). This study is supported partially by Kaohsiung Medical University "Aim for the Top Universities Grant, Grant KMU-TP104PR15".

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DOI: 10.1021/acs.joc.6b01935
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DOI: 10.1021/acs.joc.6b01935
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