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Synthesis of dihydrobenzoimidazo[2,1-*a*]isoquinolines

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ABSTRACT

A one-pot protocol toward several substituted 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolines **1** starting with 2-allylbenzaldehydes **2** was described. The process was carried out the one-pot condensation/hydroamination reaction of substituted 2-allylbenzaldehydes **2** with 1,2-diaminobenzenes **3** in refluxing toluene in good yields. Skeleton **2** was prepared via one-pot ortho-metalative $PhBCl_2$-mediated double alkylation of hydroxybenzaldehyde **4** with LDA in moderate yields.

Introduction

Dihydroimidazoisoquinoline and its derivatives are very important compounds due to their pharmacological and biological activities.[1] For example, skeleton **A** is a potent phosphodiesterase (PDE10A) inhibitor with excellent selectivity compared to other enzymes,[2,3] and skeleton **B** has been identified as a platelet-activating factor (PAF) antagonist (Fig. 1). Functionalized benzimidazo[2,1-*a*]isoquinolines **C** are prevalent scaffolds that serve as crucial building blocks for numerous syntheses.[4–6] There are a number of processes available to generate skeleton **C**, but generally, they are described as in Figure 2: (1) $Pd(OAc)_2$-catalysed intermolecular tandem cyclization of 2-bromoarylaldehydes with terminal alkynes and 1,2-diaminobenzene under the microwave-accelerated irradiation condition,[5a] (2) CuI-catalysed the intramolecular cyclocondensation reaction of 2-bromoarylamidines with 1,2-diaminobenzene in refluxing MeCN,[5b] (3) the nucleophilic substitution of 3-fluoro-4-nitrophenol with tetrahydroisoquinoline followed by the intramolecular cyclodehydration of the resulting N-oxides with PCl_3.[5c]

While a great number of benzimidazo[2,1-*a*]isoquinolines and their derivatives with this specific substitution pattern have been developed, new methods for their preparation are needed.[6] Because the procedures are almost transition metal-mediated cyclization or microwave enhanced irradiation condition, we want to explore a one-pot method for preparing tetracyclic skeleton **1** by the treatment of 2-allylbenzaldehyde **2** with 1,2-diaminobenzene **3** via tandem condensation, followed by an intramolecular metal-free hydroamination of the corresponding benzimidazole. Metal-mediated hydroamination of alkenes with amines which had been developed, was done well.[7,8] However, there have been few investigations of the metal-free hydroamination approach.

In comparison with two excellent one-pot methods (Ohno and Yanada),[5a,6d] two major differences for preparing skeleton **1** are starting the benzaldehydes with the ortho-alkynyl group and the metal-promoted reaction condition. In previous studies, we have explored one efficient synthetic application of 2-allylbenzaldehyde to generate the tricyclic structure of 1-indanonyl oxepanes and benzodioxpanes via one-pot and facile $PhBCl_2$-mediated double alkylation of hydroxybenzaldehyde analogues with LDA in moderate yields (see Scheme 1).[9] Furthermore, we utilized the one-pot and convenient protocol to prepare the tetracyclic skeleton of 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolines **1**.

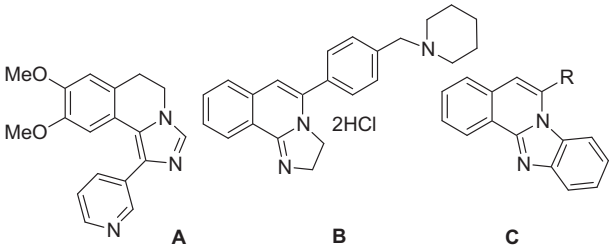

Figure 1. Structures of dihydroimidazoisoquinolines.

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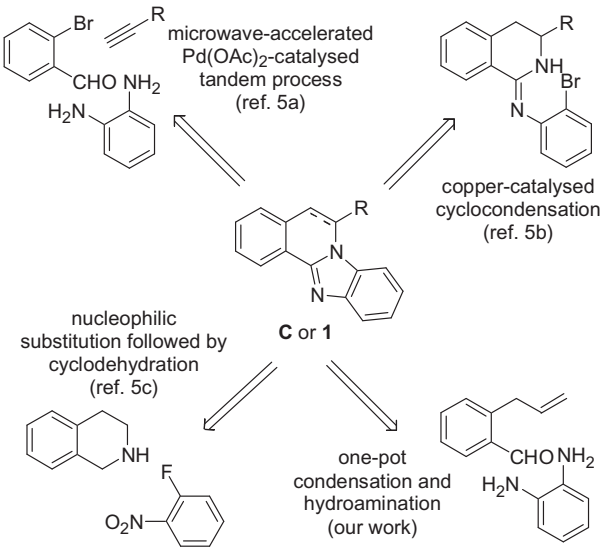
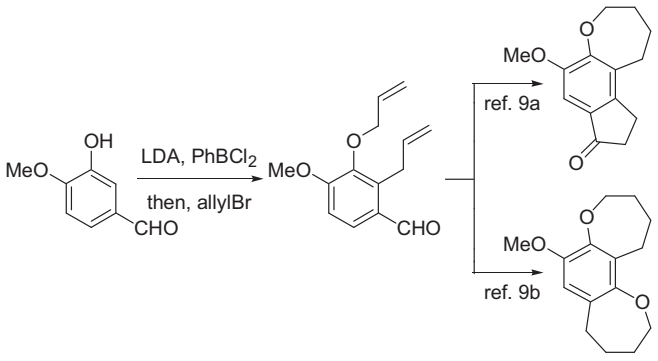
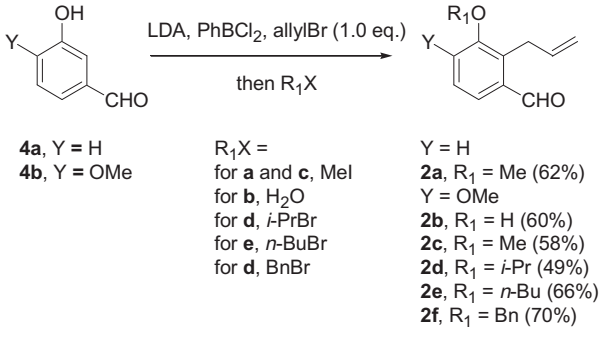


Figure 2. Synthetic strategies toward skeleton **1**.



Scheme 1. $PhBCl_2$-mediated syntheses of 1-indanonyl oxepane and benzodioxpanes.

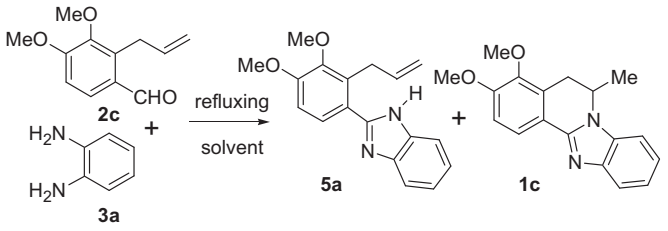


Scheme 2. Synthesis of 2-allylbenzaldehyde **2**.

Results and discussion

As the starting materials, substituted 2-allylbenzaldehydes **2a**–**2f** were prepared from commercially available 3-hydroxybenzaldehyde (**4a**) and isovanillin (**4b**) in one step, according to the known procedure with the sequence of C-allylation followed by the *O*-alkylation.[9b] As shown in Scheme 2, the treatment of **4a** or **4b** with $PhBCl_2$ and LDA afforded the dianion intermediate under the metalation condition. After the ordinal addition of allyl bromide and alkyl halide (R_1X), **2a**–**2f** were yielded with 49–70% yields.

Table 1
Reaction of compound **2c** with **3a**



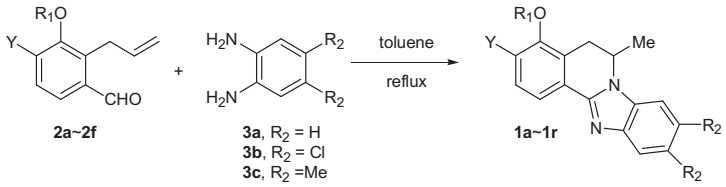
Entry	Solvent (mL), temp, time (h)	**5a**/**1c**, yield[a,b] (%)
1	Toluene (5), reflux, 2	67/22
2	Toluene (1), reflux, 2	40/46
3	Toluene (1), reflux, 3	~8/75
4	Toluene (1), reflux, 4	—/88
5	DMF (1), reflux, 4	Trace/80
6	Declain (1), reflux, 4	Trace/76
7	DME (1), reflux, 4	Trace/70
8	CH_2Cl_2 (10), reflux, 6	89/—

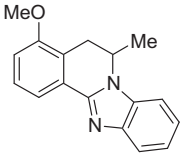
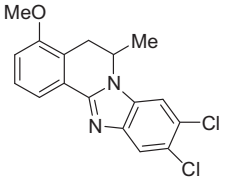
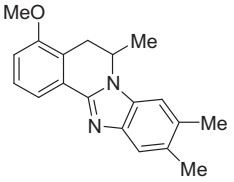
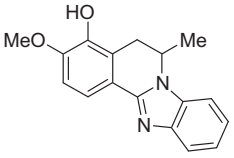
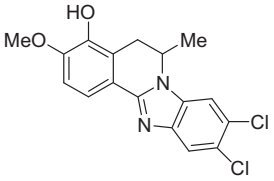
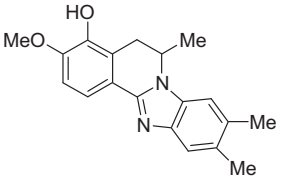
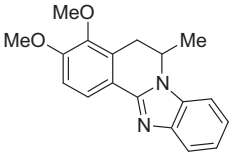
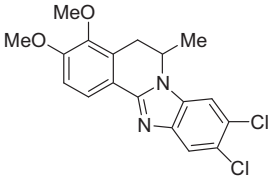
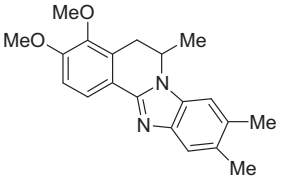
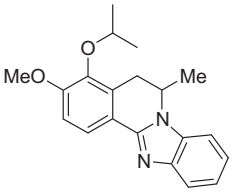
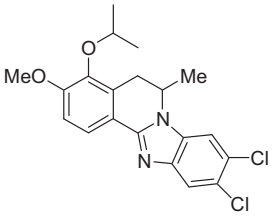
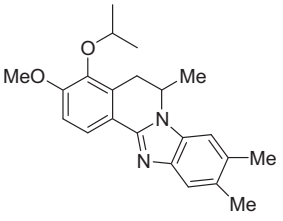
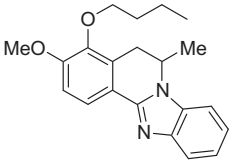
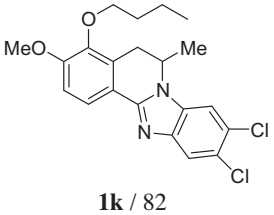
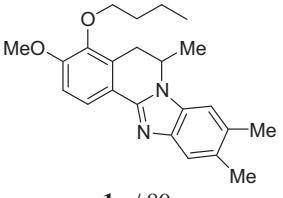
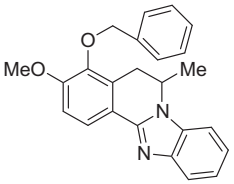
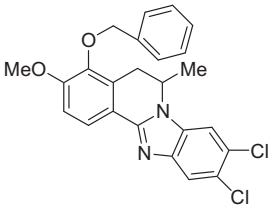
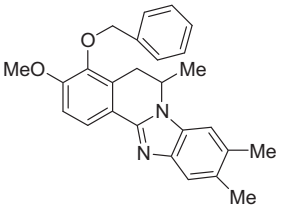
[a] The reactions were run on a 0.5 mmol scale with **2c**.
[b] The products were >95% pure as determined by ^1H NMR analysis.

To initiate the synthetic work of skeleton **1**, one-pot condensation/hydroamination reaction of **2c** (R_1 = Me, Y = OMe) with 1,2-diaminobenzene **3a** in different solvent was examined. After screening four kinds of boiling solvents (toluene, DMF, decalin or DME), we found that **1c** was isolated with the similar yields (88%, 80%, 76% or 70%) by the reaction of **2c** (0.5 mmol) with **3a** (0.55 mmol) for 4 h. Some experimental conditions and results were shown in Table 1. Therefore, this reaction must be controlled in nearly solvent-free condition (1 mL of toluene); otherwise, benzimidazole **5a** was isolated as the major component among the product mixture (entry 1).[10] Toluene was chosen as the reaction solvent due to it possessing the appropriate boiling point and better operation convenience for the nearly solvent-free condition among these solvents. When CH_2Cl_2 was chosen as the solvent under this reaction condition, only **5a** was isolated (entry 8). Based on the above mentioned phenomenon, we envisioned that the nearly solvent-free condition should be the key factor affecting the distribution of hydroamination product. Compounds **1a**–**1r** were obtained by the domino condensation/hydroamination reaction of six substituted 2-allylbenzaldehydes **2** with three 1,2-diaminobenzenes **3** in refluxing toluene for 4 h; they are summarized in Table 2.[11]

According to the facile one-pot procedure, skeleton **1** with different functionalized group was also synthesized with 70–88% yields. In comparison with the isolated yields of products with different substituents, it was found that the skeleton **1** with hydroxyl group (entries 2, 8 and 14) or isopropyl group (entries 4, 10 and 16) was slightly poorer than the other analogues. Attempts to extend this one-pot reaction to 2-aminophenol or 2-aminobenzenethiol were unsuccessful. Only benzooxazole or benzothiazole skeleton was isolated. The formation of eighteen cycloadducts was confirmed through spectral analysis. For example, the ^1H NMR spectrum of **1c** exhibited a doublet of doublet δ 3.38 (J = 1.6, and 16.0 Hz) and 3.21 (J = 6.4 and 16.0 Hz) for the CH_2 protons. The methyl proton exhibited a singlet at δ 1.28 (J = 6.4 Hz) and the CH proton appeared a multiplet at the range of δ 4.89 and 4.82.[12] Finally, **1c** was confirmed by high resolution mass spectrometry, which showed a peak at m/z 295.1439 [M^++1]. Further, five compounds **1c**, **1i**, **1m**, **1n** and **1o** were determined by the single-crystal X-ray crystallography. Structure **1c** was shown in Figure 3.[13]

Table 2
Synthesis of substituted 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolines **1**[a,b]



Entry	Reactants 2/3	Product 1/yield (%)	Entry	Reactants 2/3	Product 1/yield (%)	Entry	Reactants 2/3	Product 1/yield (%)
1	**2a/3a**	 **1a** / 84	7	**2a/3b**	 **1g** / 80	13	**2a/3c**	 **1m** / 83
2	**2b/3a**	 **1b** / 73	8	**2b/3b**	 **1h** / 70	14	**2b/3c**	 **1n** / 74
3	**2c/3a**	 **1c** / 88	9	**2c/3b**	 **1i** / 86	15	**2c/3c**	 **1o** / 82
4	**2d/3a**	 **1d** / 73	10	**2d/3b**	 **1j** / 72	16	**2d/3c**	 **1p** / 71
5	**2e/3a**	 **1e** / 85	11	**2e/3b**	 **1k** / 82	17	**2e/3c**	 **1q** / 80
6	**2f/3a**	 **1f** / 80	12	**2f/3b**	 **1l** / 82	18	**2f/3c**	 **1r** / 79

[a] For the best one-pot reaction conditions: skeleton **2** (0.5 mmol), skeleton **3** (0.55 mmol), toluene (1 mL), reflux, 4 h.
[b] The isolated products were >95% pure as determined by ^{1}H NMR analysis.

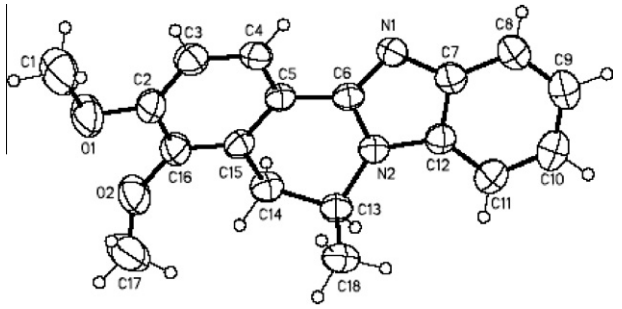
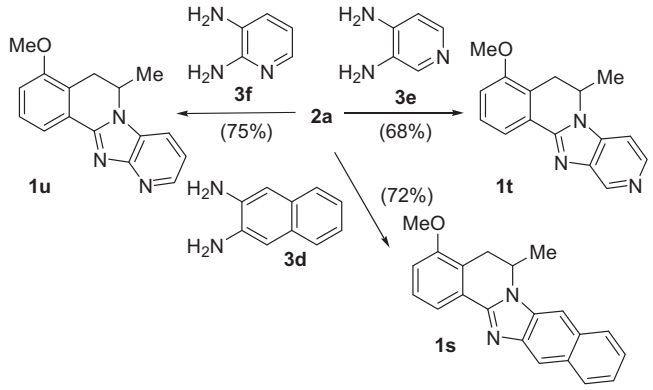


Figure 3. X-ray structure of **1c**.



Scheme 3. Reactions of **2a** with **3d**, **3e** and **3f**.

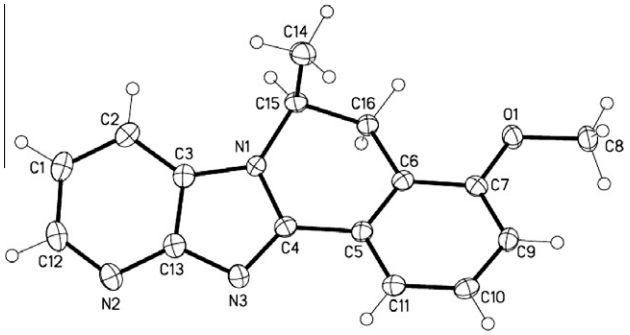


Figure 4. X-ray structure of **1u**.

To increase the synthetic application, diamine **3d** was also examined by the facile one-pot methodology (Scheme 3). Compound **1s** was provided via a reaction of **2a** with **3d** in 72% yield. Compound **1s** with a pentacyclic skeleton was constructed. When the one-pot reaction of **2a** was treated with 3,4-diaminopyridine **3e** or 2,3-diaminopyridine **3f**, only one isomer **1t** or **1u** was isolated in 75% or 68% yield. The plausible reason should be the electronic repulsion effect between the nitrogen lone pair of pyridine ring and terminal olefin. Following the previous literatures, two proton NMR spectral data of **1t** and **1u** were similar to those reported by the Maes group.[14,15] The structural skeleton of **1u** was determined by single-crystal X-ray crystallography (Fig. 4).[13] This present methodology is the metal-free, simplest and perhaps quickest synthesis of triaza-benzo[*a*]fluorene derivatives for the whole synthetic procedure.

Conclusion

A synthetic methodology for producing substituted 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinolines **1** has been successfully presented from the one-pot facile tandem condensation/hydroamination reaction of substituted 2-allylbenzaldehydes **2** with 1,2-diaminobenzenes **3** in refluxing toluene in good yields under the nearly solvent-free condition. The starting skeleton **2** was prepared via one-pot ortho-metalative $PhBCl_2$-mediated double alkylation of 3-hydroxybenzaldehyde **4** with LDA in moderate yields. Further investigation is required regarding the structure-activity relationship of the tetracyclic benzimidazo[2,1-*a*]isoquinoline analogues.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedure and scanned photocopies of ^1H and ^{13}C NMR ($CDCl_3$) spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.132.

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11. A representative procedure of skeleton **1** is as follows: A solution of skeleton **3** (0.55 mmol) was added to a solution of skeleton **2** (0.5 mmol) in toluene (1 mL). The reaction mixture was stirred at reflux. The reaction mixture was cooled to rt and the solvent was concentrated. The residue was diluted with water (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 yield crude compound. Purification on silica gel (hexanes/EtOAc = 4/1–1/1) afforded skeleton **1**. For compound **1c**: Yield 88% (130 mg); Brown solid; mp = 126–127 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) Calcd for $C_{18}H_{19}N_2O_2$ 295.1447. Found 295.1439; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.8 Hz, 1H), 7.80–7.76 (m, 1H), 7.36–7.32 (m, 1H), 7.28–7.22 (m, 2H), 6.96 (d, J = 8.4 Hz, 1H), 4.89–4.82 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.38 (dd, J = 1.6, 16.0 Hz, 1H), 3.21 (d, J = 6.4, 16.0 Hz, 1H), 1.28 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.35, 148.10, 146.69, 144.00, 133.63, 126.93, 122.18, 122.16, 122.90, 119.39, 119.30, 110.97, 108.80, 60.60, 55.69, 46.88, 28.12, 19.47; Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.69; H, 6.32; N, 9.80. Single-crystal X-Ray diagram: crystal of compound **1c** was grown by slow diffusion of EtOAc into a solution of compound **1c** in CH_2Cl_2 to yield a prism. The compound crystallizes in the monoclinic crystal system, space group P 1 21 1, a = 6.7204(9) Å, b = 8.6319(11) Å, c = 13.1308(17) Å, V = 761.71(17) Å^3, Z = 2, d_{Calcd} = 1.283 g/cm^3, F(000) = 312, 2θ range 1.55–26.40°, R indices (all data) R1 = 0.0470, wR2 = 0.0958. For compound **1i**: Yield = 86% (156 mg); Brown solid; M.p. = 232–233 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) Calcd for $C_{18}H_{17}Cl_2N_2O_2$ 363.0667, found 363.0670; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 7.44 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.81–4.77 (m, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.41 (dd, J = 1.6, 16.0 Hz, 1H), 3.22 (dd, J = 6.4, 16.0 Hz, 1H), 1.28 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.02, 149.98, 146.76, 143.08, 132.89, 126.95, 126.23, 126.08, 122.39, 120.22, 118.33, 111.17, 110.22, 60.68, 55.78, 47.44, 28.02, 19.47; Anal. Calcd for $C_{18}H_{16}Cl_2N_2O_2$: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.69; H, 4.58; N, 7.53. Single-crystal X-Ray diagram: crystal of compound **1i** was grown by slow diffusion of EtOAc into a solution of compound **1i** in CH_2Cl_2 to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group P 1 21/c 1, a = 6.7316(2) Å, b = 8.8114(2) Å, c = 28.6531(7) Å, V = 1698.03(8) Å^3, Z = 4, d_{Calcd} = 1.421 g/cm^3, F(000) = 752, 2θ range 1.42–26.38°, R indices (all data) R1 = 0.0769, wR2 = 0.1538. For compound **1o**: Yield = 82% (132 mg); Brown solid; mp = 187–188 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) Calcd for $C_{20}H_{23}N_2O_2$ 323.1760. Found 323.1765; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.11 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.83-4.76 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.36 (dd, J = 1.6, 16.0 Hz, 1H), 3.19 (dd, J = 6.4, 16.0 Hz, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.06, 147.31, 146.65, 142.49, 132.11, 131.29, 130.98, 126.71, 121.65, 119.68, 119.40, 110.91, 109.15, 60.59, 55.68, 46.82. 28.16, 20.50, 20.28, 19.46; Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.69; H, 7.03; N, 8.87. Single-crystal X-Ray diagram: crystal of compound **1o** was grown by slow diffusion of EtOAc into a solution of compound **1o** in CH_2Cl_2 to yield a prism. The compound crystallizes in the monoclinic crystal system, space group P 1 21/c 1, a = 6.8421(2) Å, b = 8.7801(3) Å, c = 28.6827(9) Å, V = 1720.56(9) Å^3, Z = 2, d_{Calcd} = 1.245 g/cm^3, F(000) = 688, 2θ range 2.43–26.41°, R indices (all data) R1 = 0.0851, wR2 = 0.1315.

12. The representative procedure and spectral analysis of skeleton **1** were described in supplementary material. The series of skeleton **1** should be formed as a mixture of two diastereomers. However, the related resolutions of diastereomers had been not observed from the NMR spectrum.
13. CCDC 870780 (**1c**), 870782 (**1i**), 875929 (**1m**), 875928 (**1n**), 875930 (**1o**), 876964 (**1u**), and 870781 (**5a**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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