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Metal-Free Synthetic Shortcut to Octahydro-Dipyrroloquinoline Skeletons from 2,5-Cyclohexadienone Derivatives and L-Proline

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Cite This: J. Org. Chem. 2021, 86, 10397−10406 Read Online

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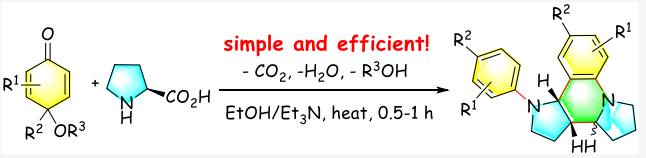
ABSTRACT: The tandem decarboxylative condensation−dimerization reaction of L-proline with 2,5-cyclohexadienones including *p*-quinone monoacetals, *p*-quinol ethers, and *p*-quinols is reported to provide a concise and rapid synthesis of octahydro-dipyrroloquinoline compounds. The reaction features the use of cost-effective and readily available starting materials, high efficiency, metal-free and green reaction conditions. The reaction is applied to the synthesis of incargranine B aglycone. The discovery of this reaction may suggest a biosynthetic pathway from 2,5-cyclohexadienones and proline for natural ingredients containing pyrroloquinoline moieties.



INTRODUCTION

The concise and rapid synthesis of complex azacyclic compounds is of high importance in organic synthesis because of their abundance in valuable artificial and natural substances including pharmaceutical compounds, therapeutic agents, and natural products (Figure 1A).[1] The octahydro-dipyrroloquinoline is among a new structurally interesting azatetracyclic scaffold that has received increasing attention since it has been identified in natural products of incargranine B and seneciobipyrrolidine.[2,3] The total synthesis and structure revision of incargranine B were first reported by Lawrence using a biomimetic strategy in 2013.[4] Several other protocols toward this core structure have also been described in literature (Figure 1B).[5−8] For example, the Fustero group has already shown a Au-catalyzed intramolecular hydroamination and formal aza-Diels−Alder reaction sequence of propargylic amino esters to access similar azatetracyclic compounds in 2012.[5] Dong and Liu reported the Au-catalyzed cyclization reactions of homopropargylic amines[6a] and further contributed to a diastereo- and enantioselective variant of the reaction enabled by a chiral silver phosphate catalyst.[6b] Recently, the Schneider group reported an impressive modular synthesis of stereodiverse dipyrroloquinoline derivatives via a one-pot multicomponent reaction of arylamines, aldehydes, and bis-(silyl) dienediolates.[7] Despite these excellent contributions, new concise and efficacious methods toward these structurally interesting skeletons still remain desirable, particularly in the context of green and sustainable chemistry of current interest.

Herein we report an alternative new synthesis of octahydro-dipyrroloquinoline products via a tandem decarboxylative condensation−dimerization reaction of 2,5-cyclohexadienone derivatives with L-proline (Figure 1C). This new method has advantages such as high efficiency, operational simplicity, totally metal-free conditions, and the use of a green solvent. The starting materials for the reaction are easily available, for example, 2,5-cyclohexadienone derivatives such as *p*-quinone monoacetals (*p*-QMAs), *p*-quinol ethers, and *p*-quinols, are all versatile synthetic intermediates with wide utilities in organic synthesis[9,10] and can be facilely obtained via oxidation of the cheap and abundant arenols,[11] not mention to the naturally abundant and renewable L-proline. While the reaction enables a highly efficient assemble of these common building blocks to construct the complex core structure from a synthetic perspective, we further note that the discovery of this transformation may also imply a possible biosynthetic origin of natural ingredients bearing pyrroloquinoline moieties from 2,5-cyclohexadienone derivatives and proline in biosynthetic scenarios. It is a truth that a large number of natural products show structural motifs derived from 2,5-cyclohexadienone derivatives biosynthetically, and many feature such structural moieties in their final structural framework.[9c,d]

RESULTS AND DISCUSSION

The reaction was discovered during a recent project on the utilities of *p*-QMAs as arylation reagents for the synthesis of nitrogen- and phosphorus-functionalized aromatics.[12] Previously, we unexpectedly observed the formation of the octahydro-dipyrroloquinoline compounds as byproducts from the three-component reaction of *p*-QMA, L-proline, and naphthol.[12f] The subsequent study showed that *p*-QMA **1a** indeed coupled with L-proline (**2a**) to give octahydro-dipyrroloquinolines **3a** and **3b** in moderate to good yields,

Received: May 9, 2021
Published: July 20, 2021

https://doi.org/10.1021/acs.joc.1c01083
J. Org. Chem. 2021, 86, 10397−10406

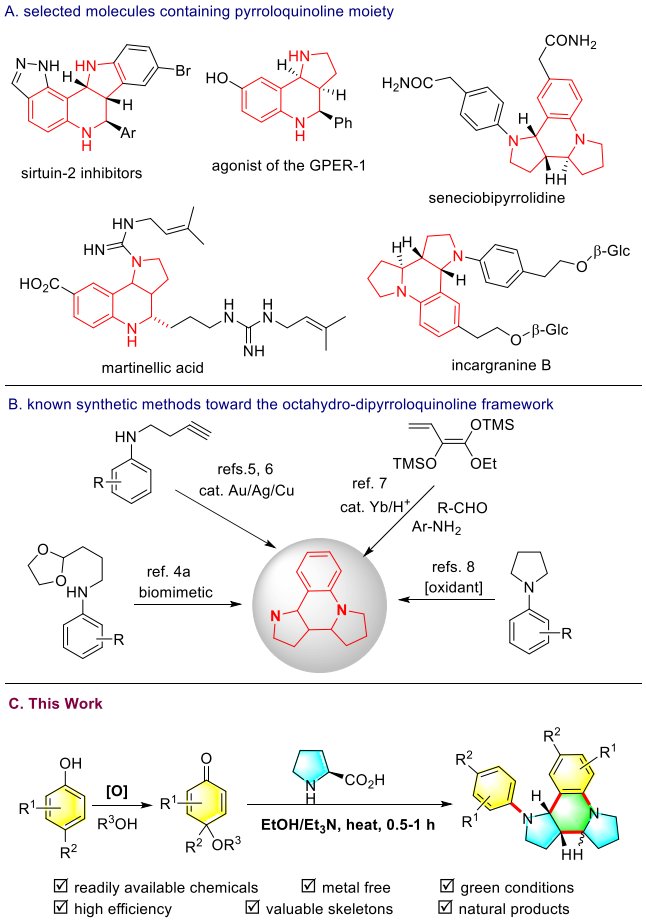
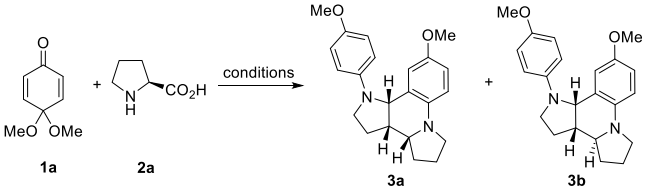


Figure 1. Bioactive azacyclic agents and natural products containing a pyrroloquinoline moiety and synthetic approaches for the octahydro-dipyrroloquinoline framework.

and the detailed survey on the reaction parameters for the improvement of the reaction is present in Table 1. The reactions completed in 2 h in the presence of HOAc and $Ph_2P(O)OH$, but the product yields were not improved (Table 1, entries 2 and 3). The use of CF_3CO_2H resulted in the decomposition of starting materials under the reaction conditions (Table 1, entry 4). The presence of $ZnCl_2$ also led to a decreased yield (Table 1, entry 5), and no product was detected when $Zn(OTf)_2$ or $Sc(OTf)_3$ was added (Table 1, entries 6 and 7). It was found that the solvents have a significant effect on the outcome of the reaction. THF, toluene, and (trifluoromethyl)benzene all gave the products in poor yields (Table 1, entries 9–11). No reaction took place in hexane because of the poor solubility of **2a** (Table 1, entry 12). In contrast, the reaction took place more efficiently in protic solvents such as EtOH and ^{t}BuOH (Table 1, entries 13 and 14). The reactions in these solvents were completed within 0.5 h at 100 °C in a closed Schlenk tube. EtOH gave a much better yield (72%), which was similar to that achieved using MeCN as a solvent in 4 h (Table 1, entry 1 vs entry 13). However, the use of hexafluoropropan-2-ol, water, or HOAc as the solvent led to the decomposition of starting materials, and the product was not formed (Table 1, entries 15–17). The reaction performed in EtOH at 120 °C gave the product in a slightly low yield (Table 1, entry 18). When conducted at 80 °C, the reaction turned out to be a little slower and completed in 1 h to give the products in 68% yield (Table 1, entry 19). The influence of some bases was also examined. The presence of

Table 1. Optimization of Reaction Conditions for the Reaction of 1a and 2a[a]



entry	solvent	additive	temp (°C)	time (h)	yield (%)[b]	ratio of 3a/3b[c]
1	MeCN		100	4	70	69:31
2	MeCN	HOAc[d]	100	2	55	59:41
3	MeCN	$Ph_2P(O)OH$[d]	100	2	32	55:45
4	MeCN	CF_3CO_2H[d]	100	1	decomp[e]	
5	MeCN	$ZnCl_2$[d]	100	2	36	56:44
6	MeCN	$Zn(OTf)_2$[d]	100	2	decomp[e]	
7	MeCN	$Sc(OTf)_3$[d]	100	2	decomp[e]	
8	DMF		100	4	54	51:49
9	THF		100	4	10	nd[f]
10	toluene		100	4	26	63:37
11	$PhCF_3$		100	4	34	57:43
12	hexane		100	4	NR[g]	
13	EtOH		100	0.5	72	62:38
14	^{t}BuOH		100	0.5	48	70:30
15	$(CF_3)CHOH$		100	0.5	decomp[e]	
16	H_2O		100	1	decomp[e]	
17	HOAc		100	1	decomp[e]	
18	EtOH		120	0.5	64	61:39
19	EtOH		80	1	68	50:50
20	EtOH	Et_3N[h]	100	0.5	77	60:40
21	EtOH	pyridine[h]	100	0.5	69	54:46
22	EtOH	K_2CO_3[i]	100	0.5	18	nd[f]
23	EtOH	NaOH[i]	100	0.5	trace	nd[f]

[a]Unless otherwise noted, a mixture of **1a** (0.2 mmol), **2a** (0.24 mmol), and the solvent (2 mL) charged to a 10 mL screw-capped Schlenk tube under dry nitrogen was heated to 80–120 °C for a specific time. [b]Combined yields. [c]Deduced from ^{1}H NMR. [d]30 mol%. [e]**1a** was decomposed. [f]Not determined. [g]No reaction. [h]0.5 mL. [i]0.24 mL.

Et_3N appears to be beneficial for the improvement of the reaction, giving the products in 77% yield with 60:40 dr (Table 1, entry 20). The presence of pyridine did not foster a better result (Table 1, entry 21), whereas the use of inorganic bases (e.g., K_2CO_3 and NaOH) led to very poor yields due to the

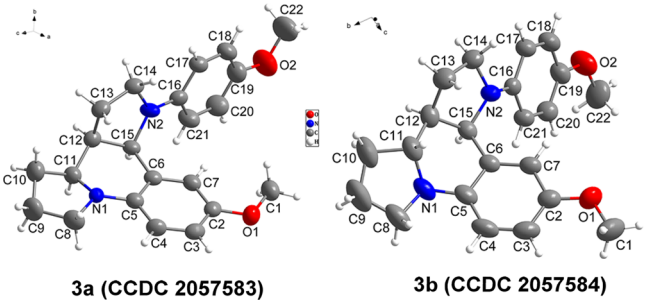


Figure 2. Molecular structures of octahydro-dipyrroloquinolines **3a** and **3b**. (Ellipsoids shown at 50% probability level.)

https://doi.org/10.1021/acs.joc.1c01083
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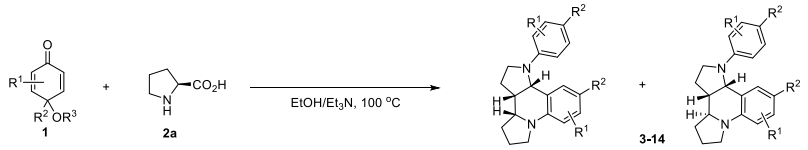
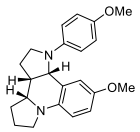
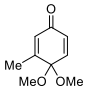
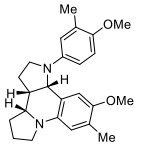
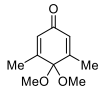
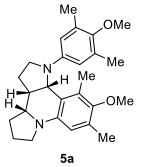
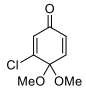
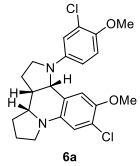
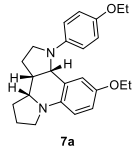
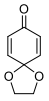
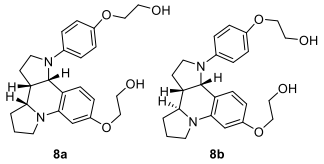
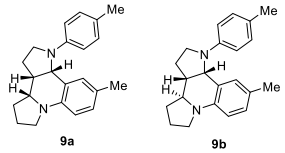
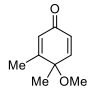
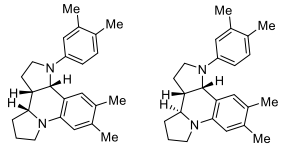
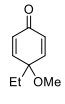
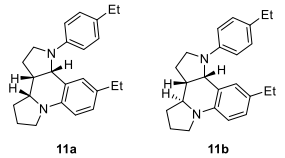
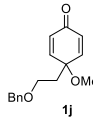
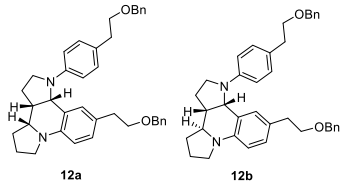
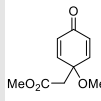
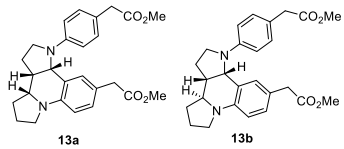
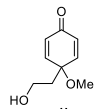
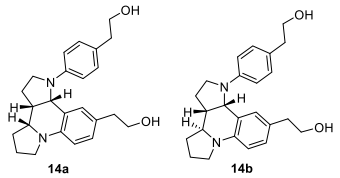
Table 2. Synthesis of Octahydro-Dipyrroloquinolines from QMAs and L-Proline[a]



entry	substrate	products	yield (dr)[b]
1	 1a	 3a, 3b	77% (59/41) 68% (53/47)[c]
2	 1b	 4a, 4b	70% (54/46)
3	 1c	 5a, 5b	74% (91/9)
4	 1d	 6a, 6b	41% (74/26)[d,e]
5	 1e	 7a, 7b	65% (55/45)[e]
6	 1f	 8a, 8b	53% (67/33)[d]
7	 1g	 9a, 9b	82% (53/47)[e]
8	 1h	 10a, 10b	61% (56/44)[e]
9	 1i	 11a, 11b	65% (59/41)
10	 1j	 12a, 12b	45% (51/49)[e] 40% (53/47)[f]
11	 1k	 13a, 13b	55% (67/33)[d,e]
12	 1l	 14a, 14b	63% (60/40)[d, g]

[a]Unless otherwise noted, a mixture of **1** (0.2 mmol), **2a** (1.2 equiv), EtOH (2 mL), and Et_3N (0.5 mL) in a screw-capped Schlenk tube was heated to 100 °C under dry nitrogen for 0.5−1 h. [b]Combined yields. Unless otherwise noted, the value of diastereo ratio (dr) was calculated based on the isolated yields of the diastereoisomers. [c]6 mmol scale. [d]Determined from ^1H NMR. [e]0.5 mmol scale. [f]2 mmol scale. [g]1 mmol scale.

partial decomposition of the substrates (Table 1, entries 22 and 23).

The stereostructures of **3a** and **3b** were further determined by the single-crystal X-ray diffraction analysis (Figure 2).

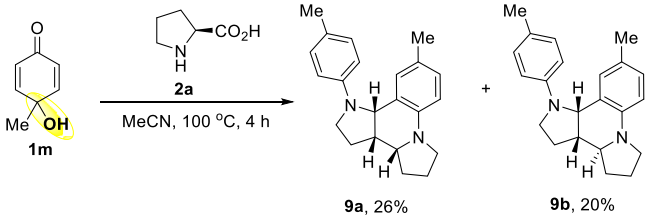
Table 2 shows the representative examples of octahydro-dipyrroloquinolines prepared from different substituted 2,5-cyclohexadienones **1** and L-proline (**2a**) by taking advantage of the present method. Thus, 3-methyl-substituted *p*-QMA **1b** reacted with **2a** to give **4a** and **4b** in high yields (Table 2, entry 2). Notably, 3,3′-dimethyl-substituted *p*-QMA **1c** gave **5a** and **5b** in a combined yield of 74%, and the reaction demonstrated remarkably high diastereoselectivity up to 91:9 in favor of the formation of **5a** (Table 2, entry 3). The 3-halide-substituted *p*-QMA **1d** was allowed to produce the corresponding products **6a** and **6b**, albeit in a lower yield (Table 2, entry 4). The ethanol-derived QMA **1e** participated similarly in the reaction to furnish the desired products **7a** and **7b** in a combined yield of 65% with 55:45 dr (Table 2, entry 5). The glycol-derived *p*-QMA **1f** could also be used to produce **8a** and **8b** in 53% yield with a dr value of 69:31 (Table 2, entry 6). In addition, common *p*-quinol ethers **1g**−**1h** all reacted smoothly with **2a** to give the corresponding products in good yields (Table 2, entries 7−9). Remarkably, *p*-quinol ethers that bear a benzyloxyl, an ester, and even a free hydroxyl group were proved suitable for the present reaction to

https://doi.org/10.1021/acs.joc.1c01083
J. Org. Chem. 2021, 86, 10397−10406

deliver the expected products in good yields (Table 2, entries 10−12). It is worth mentioning that the diastereoisomers of products **3**, **4**, **5**, **7**, and **9**−**12** were separable by common flash chromatography and well-characterized. The products **6**, **8**, **13**, and **14** were obtained as diastero mixtures due to the similar polarity of the compounds. In addition, the reaction of **1a** and **2a** on a 6 mmol scale was performed to afford **3a** and **3b** in 36% and 32% yields, respectively (total: 68%; dr: 53:47).

The present transformation was also found to take place between *p*-quinol **1m** and L-proline (**2a**) (Scheme 1). MeCN

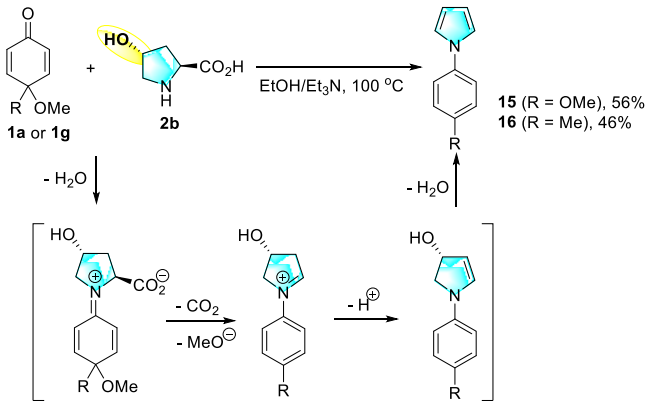
Scheme 1. Reaction of *p*-Quinol 1m and L-Proline



was a better solvent for choice, and the reaction cleanly gave products **9a** and **9b** in 26% and 20% yields, respectively. In contrast, the reaction in EtOH gave slightly low yields (38%−40% total yield) in 0.5 h, and the formation of unidentified byproducts was observed.

Furthermore, the reactions of other cyclic amino acids were investigated but did not give similar products. For example, the reactions of 4-hydroxyl-proline (**2b**) with *p*-QMA **1a** and *p*-quinol ether **1g** both took place smoothly to give *N*-arylated pyrroles **15** and **16** in moderate yields (Scheme 2). The results can be rationalized by a cascade process involving condensation, decarboxylation, demethoxylation, and dehydration (Scheme 2).

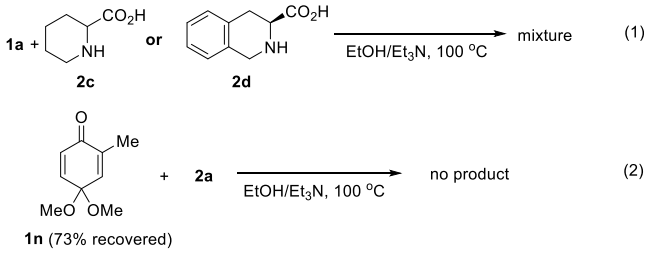
Scheme 2. Reactions of 4-Hydroxyl-Proline with QMAs to Afford *N*-Arylated Pyrroles



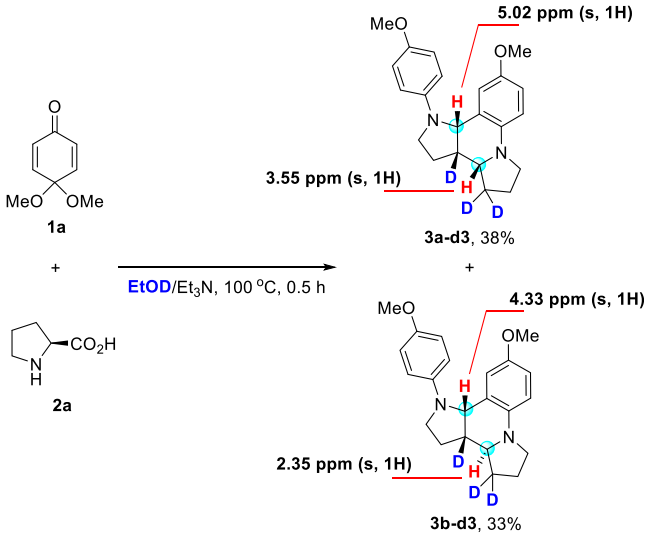
On the other hand, the reactions of the six-membered piperidine-2-carboxylic acid (**2c**) and (*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**2d**) with **1a** failed to give any identifiable product (Scheme 3, eq 1). In addition, 2-methyl-substituted QMA **1n** did not react with **2a** to give any product, indicative of the steric hindering effect retarding the condensation step (Scheme 3, eq 2).

The reaction of **1a** and **2a** in a deuterium-labeling solvent (EtOD) was performed to better understand the reaction mechanism (Scheme 4). The reaction took place smoothly to

Scheme 3. Failed Substrates for the Reaction



Scheme 4. Deuterium-Labeling Experiment



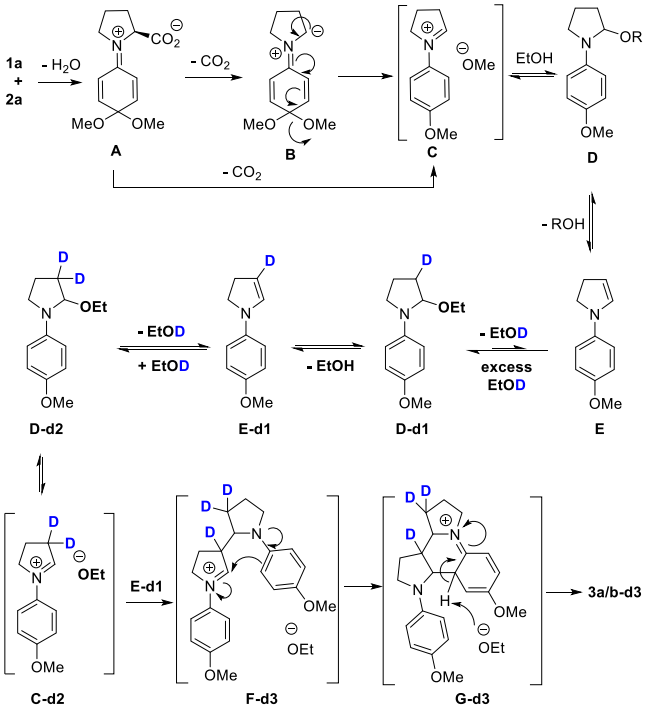
provide the deuterium-labeled products **3a-d3** and **3b-d3** in 38% and 33% yields, respectively. It is interesting to observe that approximately three hydrogen atoms were replaced by deuterium atoms in the products **3a-d3** and **3b-d3** as indicated from their ^{1}H NMR spectra (Scheme 4). Particularly, it is clearly observed that the coupling splitting disappeared with respect to the hydrogens (as highlighted in red in Scheme 4) attached to the tertiary carbon atoms adjacent to the nitrogen atoms.

Accordingly to the above results, we proposed a reaction mechanism as shown in Scheme 5. Iminium zwitterion intermediate **A** may be generated from the condensation reaction of **1a** and **2a** at first. After decarboxylation, **A** is converted to the iminium intermediate **C** through a conjugated azomethine ylide intermediate **B**. An alternative straightforward pathway is also possible for the generation of **C** from **A** after decarboxylation. An equilibrium between the intermediate **C** and the *N*,*O*-acetal species **D** should be present.[13,14] Elimination of one molecule of MeOH from the intermediates **C** and/or **D** leads to an enamine intermediate **E**. As indicated from the results of the deuterium-labeling experiment, the conversion between intermediates **D** and **E** should be reversible. Thus, when EtOD was used as a solvent, the formation of deuterium-labeled intermediates **D-d1**, **E-d1**, **C-d2**, and **D-d2** were dominated. The reaction of **C-d2** and **E-d1** forms the intermediate **F-d3**. Finally, an intramolecular Pictet−Spengler-type reaction[15] takes place to give the products **3a**/**b-d3**.

At last, we applied the present reaction to the synthesis of the aglycone of incargranine B. As described above, the aglycone of incargranine B could be obtained from the reaction of **1l** and **2a** but as a diastereo mixture of **14a** and **14b**. The separation of the two diastereoisomers usually required preparative HPLC.[4a] This

https://doi.org/10.1021/acs.joc.1c01083
J. Org. Chem. 2021, 86, 10397−10406

Scheme 5. Proposed Reaction Mechanism

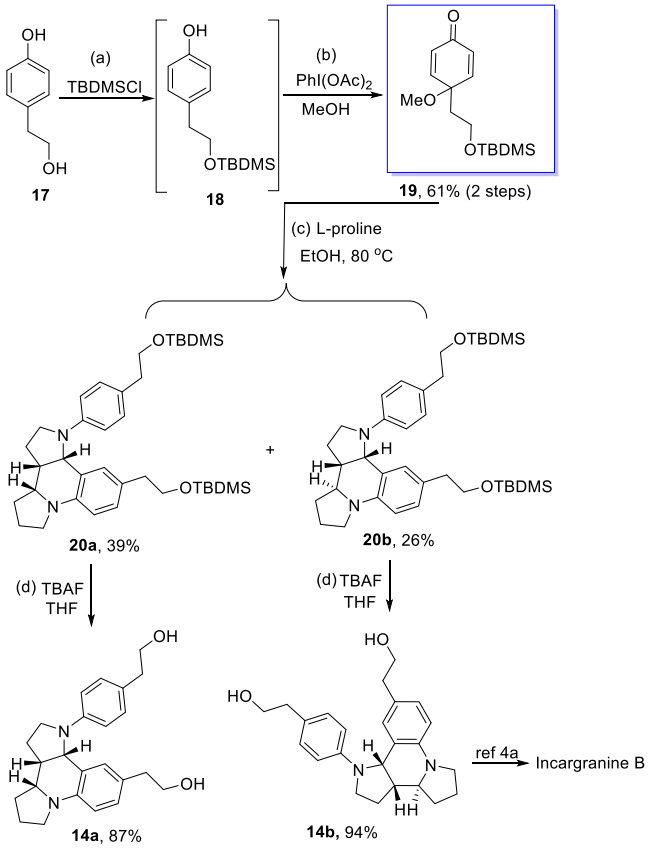


may limit the practical application of the methods. Fortunately, we found that the *tert*-butyldimethylsilyl (TBDMS)-protected ethers could be easily separated by common flash chromatography. Accordingly, a modified route starting from tyrosol (**17**) was successfully executed by using the present reaction (Scheme 6). First, the selective silylation of **17** with *tert*-butyldimethylsilyl chloride (TBDMSCl) afforded the protected precursor **18**, which was used without further purification for the next step. The treatment of the crude **18** with $PhI(OAc)_2$ in MeOH then gave the desired *p*-quinol ether **19** in 61% yield over two steps. The reaction of **19** and L-proline in EtOH under reflux provided the products **20a** and **20b** in 39% and 26% yields, which were facilely separated by the mean of flash column chromatography on silica. Finally, the removal of the TBDMS groups by treatment of tetrabutylammonium fluoride (TBAF) in THF at 0 °C gave the pure products **14a** and **14b** in high yields, respectively (for details, see Experimental Section).

CONCLUSION

In conclusion, we have reported a simple method for the synthesis of complex azacyclic compounds featuring the octahydro-dipyrroloquinoline skeleton via the decarboxylative condensation−dimerization reaction of 2,5-cyclohexadienone derivatives with L-proline. The reaction would be synthetically useful because of the simplicity of starting chemicals, high reaction efficiency, and the green reaction conditions. The metal-free synthetic route toward the aglycone of incargranine B was also developed by using the present method. Given the wide occurrence of the 2,5-cyclohexadienone motif in a natural source, we suppose that the identification of the reaction may imply a potential biosynthetic pathway for the origins of natural products containing pyrroloquinolines from cyclohexadienones and amino acids. Conclusive proofs are still required for biological chemistry.

Scheme 6. Synthesis of Incargranine B Aglycone and Analogue



EXPERIMENTAL SECTION

General Information. All reactions were performed in sealable Schlenk flasks with Teflon plug valves. The solvents used were distilled prior to use using the appropriate drying agents. Flash chromatography was performed on silica gel using petroleum ether and EtOAc as an eluent. Melting points were measured with a Shanghai Jingke WRS-2A digital melting point apparatus instrument and were uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were acquired on a Bruker Ascend 400 spectrometer at 400 and 100 MHz, respectively. HRMS analysis was performed on an Agilent 6540 UHD accurate-mass quadrupole time-of-flight (Q-TOF) mass spectrometer in the electrospray ionization mode (positive mode). The X-ray crystallographic analysis of products **3a** and **3b** was performed on a Bruker SMART APEX II CCD diffractometer using graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation. The starting materials **1a**,[16a] **1b**,[16a] **1c**,[16a] **1d**,[16b] **1e**,[16a] **1f**,[16c] **1g**,[16d] **1h**,[16d] **1i**,[16e] **1l**,[16e] **1m**,[16f] and **1n**[16d] were synthesized by known methods in literatures. Compounds **1j** and **1k** were new compounds, and the synthetic procedures and characterization data were given as below.

Synthesis of *p*-Quinol Ether 1j. To a stirred solution of 4-(2-(benzyloxy)ethyl)phenol (1.140 g, 5.0 mmol) in MeOH (10 mL) at 0 °C was added phenyliodonium diacetate (1.770 g, 5.5 mmol) portionwise. The mixture was stirred at 0 °C for 45 min, warmed to room temperature, and kept stirring for another 8 h. The reaction was slowly quenched with aq $NaHCO_3$ solution (20 mL). The mixture was then extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using PE/EtOAc (6:1 v/v) as an eluent to afford 4-(2-(benzyloxy)ethyl)-4-methoxycyclohexa-2,5-dien-1-one (**1j**) (1.150 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36−7.26 (m, 5H), 6.79 (d, J = 10.4 Hz, 2H), 6.35 (d, J = 10.4 Hz, 2H), 4.43 (s, 2H), 3.53 (t, J = 6.4

https://doi.org/10.1021/acs.joc.1c01083
J. Org. Chem. 2021, 86, 10397−10406

Hz, 2H), 3.19 (s, 3H), 2.05 (t, J = 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 185.4, 150.9, 138.0, 131.1, 128.4, 127.7, 127.6, 74.4, 73.0, 65.1, 52.9, 39.7. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{19}O_3$, 259.1334; found, 259.1335.

Synthesis of *p*-Quinol Ether 1k. Following a similar procedure for the synthesis of **1j**, the reaction of methyl 2-(4-hydroxyphenyl)acetate (0.841 g, 5.0 mmol) and phenyliodonium diacetate (2.420 g, 7.5 mmol) (conditions: 10 mL of MeOH, 0 °C, 45 min; room temperature: 24 h) afforded methyl 2-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)acetate (**1k**) (0.721 g, 73%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.89 (d, J = 10.4 Hz, 2H), 6.35 (d, J = 10.4 Hz, 2H), 3.64 (s, 3H), 3.16 (s, 3H), 2.68 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 184.8, 168.8, 149.0, 131.6, 72.7, 53.0, 52.0, 44.3. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{13}O_4$, 197.0814; found, 197.0817.

General Procedure for the Synthesis of Octahydro-Dipyrroloquinolines. To an oven-dried Schlenk tube (10 mL) were added *p*-QMA or *p*-quinol ether **1** (0.2 mmol), L-proline (**2a**) (1.2 equiv), EtOH (2 mL), and Et_3N (0.5 mL) under an atmosphere of dry nitrogen. The tube was sealed, and the mixture was stirred and heated to 100 °C in an oil bath for 0.5−1 h. After the reaction was cooled down to room temperature, silica gel (ca. 200 mg) was added, and the volatiles were removed in vacuo to afford a dry powder. The residue was purified by column chromatography on silica (pretreated with 1%−5% Et_3N) using PE/EtOAc as an eluent to afford the pure products or a diastereo mixture.

*Synthesis of Octahydro-Dipyrroloquinolines **3a** and **3b**.* Following the general procedure, the reaction of **1a** (30.9 mg, 0.2 mmol) and **2a** (28.1 mg, 0.24 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 0.5 h afforded **3a** (15.7 mg, 45% yield) and **3b** (11.1 mg, 32% yield), which were purified by column chromatography on silica (pretreated with 1% Et_3N) using PE/EtOAc (50:1 v/v) as an eluent. Total yield: 77%.

Compound **3a**: white solid. Mp: 144−145 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.97 (s, 1H), 6.88 (d, J = 7.2 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 8.8 Hz, 1H), 5.03 (d, J = 6.8 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.57−3.55 (m, 1H), 3.45−3.37 (m, 2H), 3.23−3.13 (m, 2H), 2.56−2.50 (m, 1H), 2.10−2.05 (m, 1H), 2.03−1.87 (m, 4H), 1.75−1.65 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 150.9, 150.8, 143.9, 138.4, 125.2, 115.2, 115.0, 113.5, 112.3, 111.3, 58.4, 57.2, 56.0, 55.7, 48.2, 47.1, 40.6, 29.9, 23.3, 23.0. This compound has been reported in a previous publication.[12f] The structure was further confirmed by a single-crystal X-ray diffraction study.

Compound **3b**: white solid. Mp: 102−103 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.84 (d, J = 8.8 Hz, 2H), 6.73−6.72 (m, 2H), 6.65−6.61 (m, 3H), 4.33 (d, J = 9.2 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.64−3.61 (m, 1H), 3.43 (td, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.28−3.22 (m, 1H), 2.81−2.66 (m, 2H), 2.39−2.33 (m, 1H), 2.27−2.14 (m, 4H), 2.12−1.93 (m, 1H), 1.78−1.73 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 153.0, 151.6, 143.9, 141.2, 130.2, 114.7, 114.0, 113.8, 112.5, 111.6, 65.3, 60.5, 55.8, 55.5, 50.0, 48.0, 47.7, 31.6, 30.4, 22.3. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_2$, 351.2073; found, 351.2075. The structure was further confirmed by a single-crystal X-ray diffraction study.

Procedure for the Gram-Scale Reaction for the Synthesis of 3a and 3b. To an oven-dried Schlenk tube (50 mL) were added *p*-QMA **1a** (926.1 mg, 6 mmol), L-proline (**2a**) (830.1 mg, 7.2 mmol), EtOH (24 mL), and Et_3N (6 mL) under an atmosphere of dry nitrogen. The tube was sealed, and the resulting mixture was stirred and heated to 100 °C in an oil bath for 0.5 h. After the reaction was cooled down to room temperature, the volatiles were removed in vacuo. The residue was purified by column chromatography on silica (pretreated with 1% Et_3N) using PE/EtOAc (50:1) as an eluent to afford the pure products **3a** (382.2 mg, 36%) and **3b** (339.1 mg, 32%). Total yield: 68%.

*Synthesis of Octahydro-Dipyrroloquinolines **4a** and **4b**.* Following the general procedure, the reaction of **1b** (34.1 mg, 0.2 mmol) and **2a** (28.2 mg, 0.24 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 1 h afforded **4a** (14.3 mg, 38% yield) and **4b** (12.1 mg, 32%), which were purified by column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (50:1 v/v) as an eluent. Total yield: 70%.

Compounds **4a**: white solid. Mp: 126−127 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.92 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 2.8 Hz, 1H), 6.62 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.26 (s, 1H), 5.03 (d, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.52 (s, 3H), 3.52−3.48 (m, 1H), 3.46−3.39 (m, 2H), 3.22−3.10 (m, 2H), 2.56−2.49 (m, 1H), 2.24 (s, 3H), 2.16 (s, 3H), 2.10−1.87 (m, 4H), 1.74−1.64 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 149.3, 149.1, 143.7, 138.0, 127.5, 126.3, 122.0, 114.7, 113.5, 112.2, 112.1, 109.2, 58.4, 57.4, 56.3, 56.0, 48.0, 47.0, 40.6, 29.8, 23.2, 22.9, 16.6, 16.1. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_2$, 379.2386; found, 379.2388.

Compound **4b**: oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.78 (d, J = 8.8 Hz, 1H), 6.69 (s, 1H), 6.62 (d, J = 2.8 Hz, 1H), 6.56−6.54 (m, 2H), 4.31 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 3.66−3.61 (m, 1H), 3.61 (s, 3H), 3.46 (td, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.30−3.24 (m, 1H), 2.86−2.80 (m, 1H), 2.71−2.63 (m, 1H), 2.46−2.39 (m, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.19−2.11 (m, 3H), 2.03−1.95 (m, 1H), 1.84−1.68 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 150.9, 150.1, 143.9, 140.6, 127.1, 126.9, 124.8, 116.6, 114.8, 111.5, 111.4, 111.1, 65.1, 60.7, 56.1, 56.0, 50.3, 47.80, 47.76, 31.6, 30.3, 22.4, 16.5, 16.1. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_2$, 379.2386; found, 379.2387.

*Synthesis of Octahydro-Dipyrroloquinolines **5a** and **5b**.* Following the general procedure, the reaction of **1c** (37.4 mg, 0.2 mmol) and **2a** (28.4 mg, 0.24 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 1 h afforded **5a** (27.4 mg, 67% yield) and **5b** (2.7 mg, 7% yield), which were purified by column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (100:1 v/v) as an eluent. Total yield: 74%.

Compound **5a**: white solid. Mp: 75−77 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.53 (s, 2H), 6.20 (s, 1H), 4.99 (d, J = 7.6 Hz, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.48−3.43 (m, 1H), 3.37−3.27 (m, 2H), 3.19−3.12 (m, 1H), 3.01−2.95 (m, 1H), 2.72−2.67 (m, 1H), 2.26 (s, 3H), 2.25 (s, 6H), 2.05 (s, 3H), 1.96−1.84 (m, 4H), 1.71−1.62 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 149.6, 148.6, 147.1, 143.9, 132.2, 130.7, 129.5, 121.5, 116.1, 111.1, 60.0, 59.9, 59.6, 59.2, 50.8, 47.8, 40.2, 29.7, 24.1, 22.9, 16.5, 16.4, 13.3. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_2$, 407.2699; found, 407.2705.

Compound **5b**: oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.26 (s, 2H), 6.23 (s, 1H), 3.90 (d, J = 4.0 Hz, 1H), 3.73−3.70 (m, 1H), 3.61 (s, 3H), 3.52 (s, 3H), 3.48−3.46 (m, 1H), 3.43−3.29 (m, 2H), 3.22−3.16 (m, 1H), 2.29 (s, 3H), 2.23−2.19 (m, 1H), 2.08 (s, 6H), 1.98−1.88 (m, 1H), 1.72−1.62 (m, 3H), 1.53 (s, 3H), 1.48−1.41 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 151.3, 147.3, 143.9, 141.0, 132.6, 130.8, 129.8, 120.1, 116.3, 110.0, 62.0, 60.1, 59.9, 58.0, 47.9, 46.9, 39.4, 31.7, 26.0, 23.8, 16.6, 16.3, 12.4. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_2$, 407.2699; found, 407.2704.

*Synthesis of Octahydro-Dipyrroloquinolines **6a** and **6b**.* Following the general procedure, the reaction of **1d** (94.7 mg, 0.5 mmol) and **2a** (69.6 mg, 0.6 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 1 h afforded **6a** and **6b** as a mixture (total amount: 44.3 mg, total yield: 41%, dr: 74:26), which were obtained after column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (30:1 v/v) as an eluent. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.93−6.92 (m, 1.1H), 6.90 (s, 0.3H), 6.85−6.83 (m, 1.0H), 6.77 (d, J = 3.2 Hz, 0.3H), 6.70 (s, 0.2H), 6.68−6.64 (m, 1.1H), 6.51 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 0.3H), 6.42 (s, 0.7H), 4.96 (d, J = 7.2 Hz, 0.74H), 4.23 (d, J = 9.2 Hz, 0.26H), 3.85−3.84 (m, 3.0H), 3.65 (s, 0.7H), 3.62−3.58 (m, 3.0H), 3.39−3.29 (m, 1.6H), 3.21−3.15 (m, 1.5H), 2.81 (q, J = 8.8 Hz, 0.3H), 2.73−2.64 (m, 0.3H), 2.57−2.50 (m, 0.7H), 2.46−2.40 (m, 0.3H), 2.28−2.18 (m, 0.6H), 2.13−1.65 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.0, 147.3, 146.1, 146.0, 144.3, 144.1, 141.6, 138.8, 123.8, 123.3, 122.5, 122.4, 122.2, 120.9, 115.5, 114.7, 114.3, 114.0, 113.9, 113.3, 113.0, 112.8, 112.0, 110.3, 64.7, 60.6, 58.0, 57.3, 57.1, 57.0, 56.9, 56.8, 50.1, 47.8, 47.7, 47.6, 47.0, 40.3, 31.8, 30.2, 30.0, 23.22, 23.15, 22.4. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}Cl_2N_2O_2$, 419.1293; found, 419.1296.

*Synthesis of Octahydro-Dipyrroloquinolines **7a** and **7b**.* Following the general procedure, the reaction of **1e** (91.7 mg, 0.5 mmol) and **2a** (69.4 mg, 0.6 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 1 h afforded **7a** (34.1 mg, 36% yield) and **7b** (27.9 mg, 29% yield),

https://doi.org/10.1021/acs.joc.1c01083
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which were purified by column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (150:1 v/v) as an eluent. Total yield: 65%.

Compound **7a**: white solid. Mp: 112−114 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.94 (d, J = 2.8 Hz, 1H), 6.87 (d, J = 9.2 Hz, 2H), 6.74 (d, J = 9.2 Hz, 2H), 6.69 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.34 (d, J = 8.8 Hz, 1H), 5.01 (d, J = 7.2 Hz, 1H), 4.00 (d, J = 6.8 Hz, 2H), 3.78 (d, J = 6.8 Hz, 2H), 3.59−3.54 (m, 1H), 3.44−3.36 (m, 2H), 3.22−3.12 (m, 2H), 2.54−2.47 (m, 1H), 2.10−2.05 (m, 1H), 1.99−1.86 (m, 4H), 1.73−1.66 (m, 1H), 1.39 (t, J = 6.8 Hz, 3H), 1.26 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 150.2, 149.9, 143.9, 138.3, 125.1, 116.1, 115.6, 114.4, 112.2, 111.2, 64.4, 63.9, 58.4, 57.2, 48.2, 47.0, 40.5, 29.9, 23.3, 23.0, 15.1, 15.0. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_2$, 379.2386; found, 379.2390.

Compound **7b**: oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.84 (d, J = 8.8 Hz, 2H), 6.74−6.72 (m, 2H), 6.64−6.61 (m, 3H), 4.34 (d, J = 9.2 Hz, 1H), 3.99 (q, J = 7.2 Hz, 2H), 3.90−3.81 (m, 2H), 3.65−3.61 (m, 1H), 3.43 (td, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.29−3.22 (m, 1H), 2.81−2.68 (m, 2H), 2.39−2.33 (m, 1H), 2.27−2.09 (m, 3H), 1.99−1.94 (m, 1H), 1.78−1.68 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 152.4, 150.9, 144.1, 141.2, 130.4, 115.7, 114.5, 114.0, 112.6, 112.6, 65.4, 64.2, 63.8, 60.7, 50.1, 48.1, 47.8, 31.7, 30.5, 22.4, 15.1, 15.0. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_2$, 379.2386; found, 379.2389.

*Synthesis of Octahydro-Dipyrroloquinolines **8a** and **8b**.* Following the general procedure, the reaction of **1f** (31.1 mg, 0.2 mmol) and **2a** (28.1 mg, 0.24 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 0.5 h afforded **8a** and **8b** as a mixture (total amount: 22.1 mg, yield: 53%, dr: 67:33), which were obtained after column chromatography (pretreated with 5% Et_3N) using PE/EtOAc (1:1 v/v) as an eluent. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.92−6.84 (m, 2.9H), 6.74−6.61 (m, 3.5H), 6.33 (d, J = 8.4 Hz, 0.6H), 5.00 (d, J = 6.0 Hz, 0.67H), 4.31 (d, J = 8.8 Hz, 0.33H), 4.04−3.80 (m, 8.0H), 3.60−3.57 (m, 1.0H), 3.42−3.37 (m, 1.2H), 3.19−3.15 (m, 1.4H), 2.81−2.69 (m, 0.7H), 2.51 (s, 0.8H), 2.37−1.66 (m, 8.9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 152.0, 150.6, 149.8, 149.7, 144.4, 144.2, 141.7, 138.7, 130.2, 125.0, 116.3, 115.8, 114.7, 114.3, 114.1, 112.65, 112.58, 112.3, 111.2, 70.3, 70.1, 69.7, 69.6, 65.3, 61.75, 61.70, 61.58, 61.55, 60.7, 58.4, 57.1, 50.1, 48.2, 48.0, 47.8, 47.1, 40.5, 31.7, 30.5, 30.0, 23.3, 23.1, 22.4. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_4$, 411.2284; found, 411.2288.

*Synthesis of Octahydro-Dipyrroloquinolines **9a** and **9b**.* Following the general procedure, the reaction of **1g** (69.4 mg, 0.5 mmol) and **2a** (69.3 mg, 0.6 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 1 h afforded **9a** (34.5 mg, 44% yield) and **9b** (30.5 mg, 38% yield), which were purified by column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (30:1 v/v) as an eluent. Total yield: 82%.

Compound **9a**: white solid. Mp: 144−145 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.14 (s, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.33 (d, J = 8.0 Hz, 1H), 5.02 (d, J = 7.2 Hz, 1H), 3.66−3.63 (m, 1H), 3.47 (t, J = 8.4 Hz, 1H), 3.41−3.35 (m, 1H), 3.26−3.19 (m, 2H), 2.49−2.45 (m, 1H), 2.30 (s, 3H), 2.13 (s, 3H), 2.08−1.84 (m, 5H), 1.74−1.64 (m, 1H). The data above is in agreement with that which has been previously reported.[17a]

Compound **9b**: oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.06 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.62 (d, J = 8.0 Hz, 3H), 4.38 (d, J = 9.2 Hz, 1H), 3.65 (t, J = 8.4 Hz, 1H), 3.45 (t, J = 8.0 Hz, 1H), 3.32−3.26 (m, 1H), 2.83−2.69 (m, 2H), 2.41−2.35 (m, 1H), 2.29 (s, 3H), 2.21−2.12 (m, 6H), 2.02−1.94 (m, 1H), 1.83−1.69 (m, 2H). The data above is in agreement with that which has been previously reported.[17b]

*Synthesis of Octahydro-Dipyrroloquinolines **10a** and **10b**.* Following the general procedure, the reaction of **1h** (76.3 mg, 0.5 mmol) and **2a** (69.8 mg, 0.6 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 1 h afforded **10a** (29.5 mg, 34% yield) and **10b** (23.4 mg, 27% yield), which were purified by column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (30:1 v/v) as an eluent. Total yield: 61%.

Compound **10a**: white solid. Mp: 149−151 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.10 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 6.60 (dd, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 2H), 6.24 (s, 1H), 4.99 (d, J = 6.4 Hz, 1H), 3.62−3.58 (m, 1H), 3.46 (t, J = 8.4 Hz, 1H), 3.41−3.35 (m, 1H), 3.24−3.17 (m, 2H), 2.45−2.40 (m, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.04 (s, 3H), 1.98−1.85 (m, 5H), 1.72−1.65 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.8, 141.5, 137.2, 136.1, 130.4, 130.1, 123.9, 123.3, 121.3, 112.9, 112.1, 108.8, 57.9, 56.8, 48.2, 46.7, 40.4, 30.1, 23.3, 23.1, 20.5, 19.9, 18.9, 18.6. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2$, 347.2487; found, 347.2490.

Compound **10b**: oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.0 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.55 (d, J = 2.8 Hz, 1H), 6.53 (s, 1H), 6.47 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1H), 4.38 (d, J = 9.2 Hz, 1H), 3.65 (t, J = 8.0 Hz, 1H), 3.45 (td, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.32−3.25 (m, 1H), 2.85−2.78 (m, 1H), 2.73−2.65 (m, 1H), 2.42−2.36 (m, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.21−2.01 (m, 3H), 2.21 (s, 3H), 2.13 (s, 3H), 2.02−1.92 (m, 1H), 1.83−1.68 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.1, 145.2, 137.1, 135.0, 130.2, 128.3, 126.8, 126.4, 124.4, 114.3, 113.8, 110.4, 65.1, 59.8, 49.7, 48.1, 47.6, 31.9, 30.6, 22.3, 20.3, 19.9, 19.0, 18.6. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2$, 347.2487; found, 347.2489.

*Synthesis of Octahydro-Dipyrroloquinolines **11a** and **11b**.* Following the general procedure, the reaction of **1i** (30.5 mg, 0.2 mmol) and **2a** (27.7 mg, 0.24 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 1 h afforded **11a** (13.1 mg, 38% yield) and **11b** (9.5 mg, 27% yield), which were purified by column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (30:1 v/v) as an eluent. Total yield: 65%.

Compound **11a**: white solid. Mp: 114−115 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.18 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.95 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 6.37 (d, J = 8.0 Hz, 1H), 5.05 (d, J = 6.8 Hz, 1H), 3.68−3.63 (m, 1H), 3.46 (t, J = 8.4 Hz, 1H), 3.40−3.36 (m, 1H), 3.27−3.21 (m, 2H), 2.61 (q, J = 7.2 Hz, 2H), 2.51−2.41 (m, 3H), 2.13−1.87 (m, 5H), 1.75−1.65 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.5, 141.4, 131.7, 131.2, 128.6, 128.5, 127.2, 123.6, 111.3, 110.5, 58.2, 56.8, 48.1, 46.2, 40.3, 30.2, 28.0, 27.9, 23.3, 23.2, 16.1, 16.0. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2$, 347.2487; found, 347.2488.

Compound **11b**: oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.09 (d, J = 8.4 Hz, 2H), 7.03 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 6.98 (s, 1H), 6.67−6.64 (m, 3H), 4.38 (d, J = 9.2 Hz, 1H), 3.67 (t, J = 8.0 Hz, 1H), 3.46 (td, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 3.35−3.28 (m, 1H), 2.87−2.80 (m, 1H), 2.77−2.68 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 2.52 (q, J = 7.2 Hz, 2H), 2.46−2.40 (m, 1H), 2.29−2.09 (m, 3H), 2.03−1.92 (m, 1H), 1.85−1.70 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H), 1.14 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.7, 145.1, 134.8, 132.4, 128.7, 128.4, 126.9, 126.1, 113.0, 111.9, 64.9, 60.3, 49.7, 48.3, 47.5, 31.9, 30.6, 28.4, 27.9, 22.4, 16.1, 16.0. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2$, 347.2487; found, 347.2489.

*Synthesis of Octahydro-Dipyrroloquinolines **12a** and **12b**.* Following the general procedure, the reaction of **1j** (129.1 mg, 0.5 mmol) and **2a** (69.1 mg, 0.6 mmol) in EtOH (4 mL) and Et_3N (1 mL) at 100 °C for 1 h afforded **12a** (32.1 mg, 23%) and **12b** (30.8 mg, 22%), which were purified by column chromatography (pretreated with 1% Et_3N) using PE/EtOAc (30:1 v/v) as an eluent. Total yield: 45%.

*Procedure for 2 mmol Scale Reaction for the Synthesis of **12a** and **12b**.* To an oven-dried Schlenk tube (25 mL) were added **1j** (517.0 mg, 2 mmol), L-proline (**2a**) (277.1 mg, 2.4 mmol), EtOH (8 mL), and Et_3N (2 mL) under an atmosphere of dry nitrogen. The tube was sealed, and the resulting mixture was stirred and heated to 100 °C in an oil bath for 1 h. After the reaction was cooled down to room temperature, the volatiles were removed in vacuo. The residue was purified by column chromatography on silica (pretreated with 1%−5% Et_3N) using PE/EtOAc (50:1) as an eluent to afford the pure products **12a** (120.1 mg, 21%) and **12b** (103.7 mg, 19%). Total yield: 40%.

Compound **12a**: white solid. Mp: 107−108 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.34 (d, J = 4.4 Hz, 4H), 7.31−7.24 (m, 6H), 7.14 (s, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.8 Hz, 2H), 6.34 (d, J = 8.0 Hz, 1H), 5.01 (d, J = 6.8 Hz, 1H), 4.55 (s, 2H), 4.44 (s, 2H), 3.69−3.64 (m, 3H), 3.56−3.52 (m, 2H), 3.45−3.32 (m, 2H), 3.25−3.18 (m, 2H),2.87 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.49−2.42 (m, 1H), 2.11−2.04 (m, 1H), 2.00−1.81 (m, 4H),

https://doi.org/10.1021/acs.joc.1c01083
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1.72−1.65 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.8, 141.8, 138.6, 138.6, 129.8, 129.3, 128.5, 128.4, 128.3, 127.7, 127.7, 127.5, 127.4, 125.9, 125.5, 123.4, 111.3, 110.5, 73.0, 72.8, 72.0, 71.8, 58.1, 56.6, 47.9, 46.7, 40.2, 35.4, 35.4, 30.2, 23.3, 23.2. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{38}H_{43}N_2O_2$, 559.3325; found, 559.3327.

Compound **12b**: oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33−7.24 (m, 10H), 7.07−7.03 (m, 3H), 6.96 (s, 1H), 6.63−6.58 (m, 3H), 4.53 (s, 2H), 4.43 (s, 2H), 4.35 (d, J = 9.2 Hz, 1H), 3.67−3.61 (m, 3H), 3.58−3.54 (m, 2H), 3.44 (td, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 3.31−3.25 (m, 1H), 2.87−2.76 (m, 5H), 2.73−2.67 (m, 1H), 2.44−2.38 (m, 1H), 2.27−2.08 (m, 3H), 2.00−1.92 (m, 1H), 1.81−1.67 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.0, 145.6, 138.6, 138.6, 129.8, 129.2, 128.6, 128.4, 128.3, 127.7, 127.7, 127.6, 127.6, 127.5, 127.4, 126.7, 112.9, 112.0, 73.0, 72.8, 71.9, 71.8, 64.8, 60.1, 49.5, 48.3, 47.5, 35.8, 35.4, 32.0, 30.6, 22.4. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{38}H_{43}N_2O_2$, 559.3325; found, 559.3328.

*Synthesis of Octahydro-Dipyrroloquinolines **13a** and **13b**.* Following the general procedure, the reaction of **1k** (98.1 mg, 0.5 mmol) and **2a** (69.4 mg, 0.6 mmol) in EtOH (4 mL) and Et_3N (1 mL) at 100 °C for 1 h afforded **13a** and **13b** as a mixture (total amount: 59.5 mg, yield: 55%, dr: 67:33), which were obtained after column chromatography (pretreated with 5% Et_3N) using PE/EtOAc (6:1 v/v) as an eluent. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.20−7.09 (m, 3H), 7.02−6.99 (m, 1H), 6.77 (d, J = 8.8 Hz, 1.33H), 6.68−6.62 (m, 1H), 6.37 (d, J = 8.4 Hz, 0.67H), 5.05 (d, J = 6.8 Hz, 0.67H), 4.38 (d, J = 9.2 Hz, 0.33H), 3.72−3.22 (m, 15 H), 2.88−2.69 (m, 0.76H), 2.51−2.42 (m, 1H), 2.26−1.66 (m, 5.33H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 172.96, 172.87, 172.8, 172.6, 148.5, 148.2, 146.2, 142.3, 130.1, 129.9, 129.6, 128.8, 128.5, 127.94, 127.92, 124.3, 123.1, 121.8, 121.0, 120.7, 112.9, 112.3, 111.4, 110.6, 64.6, 59.9, 57.9, 56.5, 52.0, 51.9, 51.85, 51.79, 49.4, 48.3, 47.8, 47.3, 46.7, 40.7, 40.38, 40.32, 40.28, 40.1, 32.0, 30.5, 30.2, 23.3, 22.4. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{31}N_2O_4$, 435.2284; found, 435.2289.

*Synthesis of Octahydro-Dipyrroloquinolines **14a** and **14b**.* Following the general procedure, the reaction of **1l** (168.2 mg, 1.0 mmol) and **2a** (139.1 mg, 1.2 mmol) in EtOH (8 mL) and Et_3N (2 mL) at 100 °C for 1 h afforded **14a** and **14b** as a mixture (total amount: 119.1 mg, yield: 63%, dr: 60:40), after column chromatography (pretreated with 5% Et_3N) using PE/EtOAc (1:1 v/v) as an eluent.

*Synthesis of 1-(4-Methoxyphenyl)-1H-pyrrole (**15**).* The reaction of **1a** (30.9 mg, 0.2 mmol) and **2b** (32.1 mg, 0.24 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 3 h afforded 1-(4-methoxyphenyl)-1*H*-pyrrole (**15**) (19.4 mg, yield: 56%), which was purified by column chromatography (PE/EtOAc = 60:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (d, J = 8.8 Hz, 2H), 7.02 (t, J = 2.4 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.34 (t, J = 2.4 Hz, 2H), 3.85 (s, 3H). The data above is in agreement with that which has been previously reported.[18a]

*Synthesis of 1-(p-Tolyl)-1H-pyrrole (**16**).* The reaction of **1g** (27.9 mg, 0.2 mmol) and **2b** (32.1 mg, 0.24 mmol) in EtOH (2 mL) and Et_3N (0.5 mL) at 100 °C for 6 h afforded 1-(*p*-tolyl)-1*H*-pyrrole (**16**) (14.6 mg, yield: 46%), which was purified by column chromatography (PE/EtOAc = 60:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.29 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.07 (t, J = 2.0 Hz, 2H), 6.35 (t, J = 2.0 Hz, 2H), 2.38 (s, 3H). The data above is in agreement with that which has been previously reported.[18b]

Synthetic Procedure of Octahydro-Dipyrroloquinolines 14a and 14b from 2 to 4-(2-Hydroxyethyl)phenol 17. To a mixture of 2−4-(2-hydroxyethyl)phenol **17** (1.391 g, 10 mmol) and imidazole (0.824 g, 12 mmol) in dry THF (10 mL) at 0 °C was added dropwise a solution of TBDMSCl (1.823 g, 12 mmol in 5 mL of dry THF) dropwise. The mixture was allowed to stir at 0 °C for 2 h before dilution with Et_2O (50 mL) and aqueous 10% citric acid solution (30 mL). The mixture was partitioned, and the organic layer was collected. The aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. The mixture was filtered, and solvent was removed in vacuo to yield the crude product **18**, which was dissolved in MeOH (20 mL). $PhI(OAc)_2$ (4.25 g, 12 mmol) was added portionwise at 0 °C. The resultant mixture was stirred at 0 °C for 1 h and room temperature for 24 h. The reaction was carefully quenched by the addition of saturated aq $NaHCO_3$ solution and then extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in vacuo to yield an oil, which was purified by chromatography (PE/EtOAc = 10:1) to afford the product **19** as a yellow oil (1.723 g, 61%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.80 (d, J = 10.0 Hz, 2H), 6.32 (d, J = 10.0 Hz, 2H), 3.68 (t, J = 6.4 Hz, 2H), 3.19 (s, 3H), 1.94 (t, J = 6.4 Hz, 2H), 0.85 (s, 9H), 0.00 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 185.5, 151.2, 130.8, 74.4, 57.9, 52.8, 42.9, 25.8, 18.1, −5.5. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{27}O_3Si$, 283.1729; found, 283.1733.

To an oven-dried Schlenk tube (10 mL) were added **19** (282.5 mg, 1.0 mmol), L-proline **2a** (139.5 mg, 1.2 mmol), EtOH (10 mL) and Et_3N (2.5 mL) under an atmosphere. The tube was sealed, and the reaction was heated to 80 °C in an oil bath for 2 h. After the reaction was cooled down to room temperature, the reaction mixture wasconcentratedd to dryness. The residue was purified by column chromatography on silica gel (pretreated with 1% Et_3N) using PE/EtOAc (150:1 v/v) as an eluent to afford **20a** (120.5 mg, yield: 39%) and **20b** (76.0 mg, yield: 26%).

Compound **20a**: white solid. Mp: 84−86 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.14−7.10 (m, 3H), 6.94 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.34 (d, J = 8.4 Hz, 1H), 5.03 (d, J = 6.8 Hz, 1H), 3.80 (t, J = 8.0 Hz, 2H), 3.67−3.63 (m, 3H), 3.46−3.34 (m, 2H), 3.27−3.19 (m, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 2.48−2.43 (m, 1H), 2.14−2.08 (m, 1H), 2.03−1.82 (m, 4H), 1.74−1.66 (m, 1H), 0.93 (s, 9H), 0.86 (s, 9H), 0.062 (s, 3H), 0.058 (s, 3H), −0.024 (s, 3H), −0.027 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.6, 141.7, 130.0, 129.4, 128.6, 125.9, 125.5, 123.4, 111.2, 110.4, 65.4, 65.3, 57.6, 56.6, 47.9, 46.7, 40.2, 38.9, 38.8, 30.2, 26.1, 26.0, 23.3, 23.2, 18.5, 18.4, −5.22, −5.31, −5.33. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{59}N_2O_2Si_2$, 607.4115; found, 607.4118.

Compound **20b**: white solid. Mp: 75−77 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.07 (d, J = 8.4 Hz, 2H), 7.02 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 6.94 (s, 1H), 6.64−6.60 (m, 3H), 4.37 (d, J = 9.2 Hz, 1H), 3.78 (t, J = 7.2 Hz, 2H), 3.72−3.64 (m, 3H), 3.47−3.43 (m, 1H), 3.33−3.26 (m, 1H), 2.84−2.75 (m, 4H), 2.68 (t, J = 7.6 Hz, 2H), 2.42−2.36 (m, 1H), 2.28−2.14 (m, 3H), 2.02−1.94 (m, 1H), 1.82−1.70 (m, 2H), 0.91 (s, 9H), 0.84 (s, 9H), 0.04 (s, 6H), −0.05 (s, 3H), −0.07 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.9, 145.6, 129.7, 129.5, 128.7, 127.8, 127.8, 126.6, 112.7, 112.0, 65.3, 65.1, 65.1, 60.0, 49.6, 48.4, 47.5, 39.1, 38.8, 31.9, 30.7, 26.1, 26.0, 22.4, 18.5, 18.4, −5.2, −5.35, −5.42. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{59}N_2O_2Si_2$, 607.4115; found, 607.4119.

The compound **20a** (40.0 mg, 0.07 mmol) was dissolved in THF (1 mL). Then, a solution of tetrabutylammonium fluoride (0.3 mL, 1 M in THF) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The volatiles were removed in vacuo, and the residue was purified by column chromatography on silica gel (PE/EtOAc = 1:1) to afford **14a** as a white solid (23.1 mg, yield: 87%). Mp: 116−118 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.14 (d, J = 8.4 Hz, 3H), 6.95 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.36 (d, J = 8.4 Hz, 1H), 5.06 (d, J = 6.8 Hz, 1H), 3.85 (t, J = 6.4 Hz, 2H), 3.68−3.63 (m, 2H), 3.42−3.34 (m, 3H), 3.26−3.20 (m, 2H), 2.80 (t, J = 6.4 Hz, 2H), 2.62 (t, J = 6.4 Hz, 2H), 2.56−2.49 (m, 2H), 2.13−2.07 (m, 1H), 2.03−1.83 (m, 5H), 1.74−1.64 (m, 2H). The data above is in agreement with that which has been previously reported.[4a]

The compound **20b** (64.2 mg, 0.11 mmol) was dissolved in THF (1 mL). A solution of tetrabutylammonium fluoride (0.4 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C until TLC analysis indicated complete consumption of the starting material (1 h). The volatiles were removed in vacuo, and the residue was purified by column chromatography on silica gel (PE/EtOAc = 1:1) to afford **14b** as a white solid (39.1 mg, yield: 94%). Mp: 135−137 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.09 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.88 (s, 1H), 6.67−6.63 (m, 3H), 4.32 (d, J = 9.2 Hz, 1H), 3.82 (t, J = 6.0 Hz, 2H), 3.69 (t, J = 6.0 Hz, 2H), 3.64−3.60 (m, 1H), 3.46−3.41 (m, 1H), 3.32−3.26 (m, 1H), 2.90−2.84 (m, 1H), 2.79 (t, J = 6.0 Hz, 2H), 2.70−2.63 (m, 3H), 2.53−2.47 (m, 1H), 2.29−2.19 (m, 2H), 2.16−2.11 (m,

https://doi.org/10.1021/acs.joc.1c01083
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1H), 2.02−1.95 (m, 1H), 1.84−1.68 (m, 4H). The data above is in agreement with that which has been previously reported.[4a]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01083.

X-ray crystallographic structures for compounds **3a** and **3b** and copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for all of the products (PDF)

Accession Codes

CCDC 2057583 and 2057584 contain the crystallographic data of compounds **3a** and **3b** for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Natural Science Foundation of Jiangsu Province (BK20181374), Postgraduate Research & Practice Innovation Program of Jiangsu Province (SJCX20_0361), NSFC (21302095), and Nanjing Tech University is acknowledged.

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