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Synthetic study of perophoramidine: construction of pentacyclic core structure via SmI_2-mediated reductive cyclization

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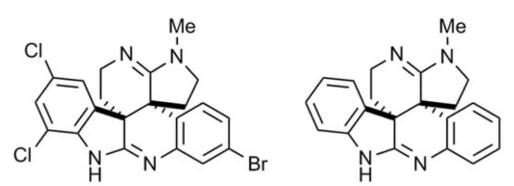
ABSTRACT

An intramolecular SmI_2-mediated reductive cyclization of carbodiimides and unsaturated lactams was applied to functionalized substrates bearing tetrasubstituted olefins. The reaction afforded arylated spiro-2-iminoindolines in high yield. Although the stereochemistry of the product was different from the desired one, the optimized palladium-catalyzed aryl amidination realized the isomerization and C–N bond formation in a single step and resulted in efficient construction of pentacyclic core of perophoramidine synthetically equivalent to the Rainier's intermediate.

1. Introduction

Natural products isolated from ascidians, as represented by a kind of ecteinascidins,[1] possess unique structures and biological, especially antitumor, activities that intrigue synthetic chemists as well as pharmaceutical scientists. Perophoramidine (**1**, Fig. 1), whose isolation, structural determination, and biological activities were reported in 2002,[2] is one of this class of natural products. Ireland and co-workers isolated this alkaloid from an extract of Philippine ascidian *perophora namei*. They revealed its highly complex polycyclic structure using spectrometry, including 2D INADEQUATE, and discovered that this natural product induces apoptosis via PARP cleavage and exhibits cytotoxicity toward the HCT116 colon carcinoma cell line, with an IC_{50} of 60 μM. Its structure was validated by the total synthesis of (±)-perophoramidine reported by Funk in 2004, and its absolute configuration was confirmed by the total synthesis of (+)-perophoramidine by Qin in 2010.[3] These syntheses were achieved by taking advantage of Diels–Alder reactions of indoles and *ortho*-quinone methide imines, the biosynthetic pathway proposed independently by Stoltz and by Funk in 2003.[4] To date, much effort has been devoted to its synthetic studies,[5] represented by a synthesis of (±)-dehaloperophoramidine **2** by Rainier in 2006.[5b] Since Funk, Qin, and Rainier utilized indoles and their oxidized intermediates at the late stages of the syntheses for the construction of 2-iminoindoline moiety, we planned a distinct synthetic strategy based on the assembly of 3,3-disubstituted 2-iminoindolines at the initial stage.



perophoramidine (**1**) dehaloperophoramidine (**2**)

Fig. 1. Perophoramidine and the related compound.

Indole or indoline derivatives that are nitrogenated at a 2-position, including 2-aminoindolines and 2-iminoindolines, are universal and fundamental structures often found in natural products as well as in pharmaceutical ingredients that exhibit important biological activities.[6] Recently we reported a reductive cyclization, mediated by samarium diiodide (SmI_2) that transforms carbodiimides **3** bearing unsaturated carbonyl moieties into 2-iminoindolines **4** with all-carbon quaternary centers at a 3-position (Scheme 1).[7] Later we successfully applied this reaction to a more highly functionalized substrate and converted the resultant product into a pentacyclic amidine by palladium-catalyzed aryl amidination. Herein we describe the construction of the pentacyclic core of perophoramidine in detail.

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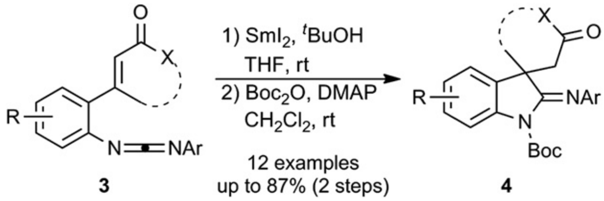
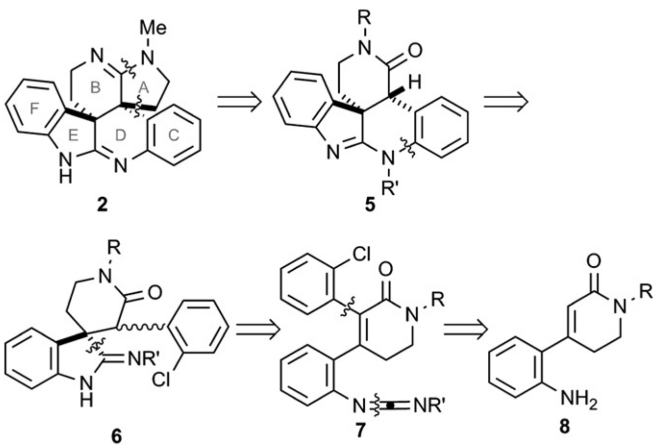


Scheme 1. SmI_2-mediated reductive cyclization.

2. Synthetic plan

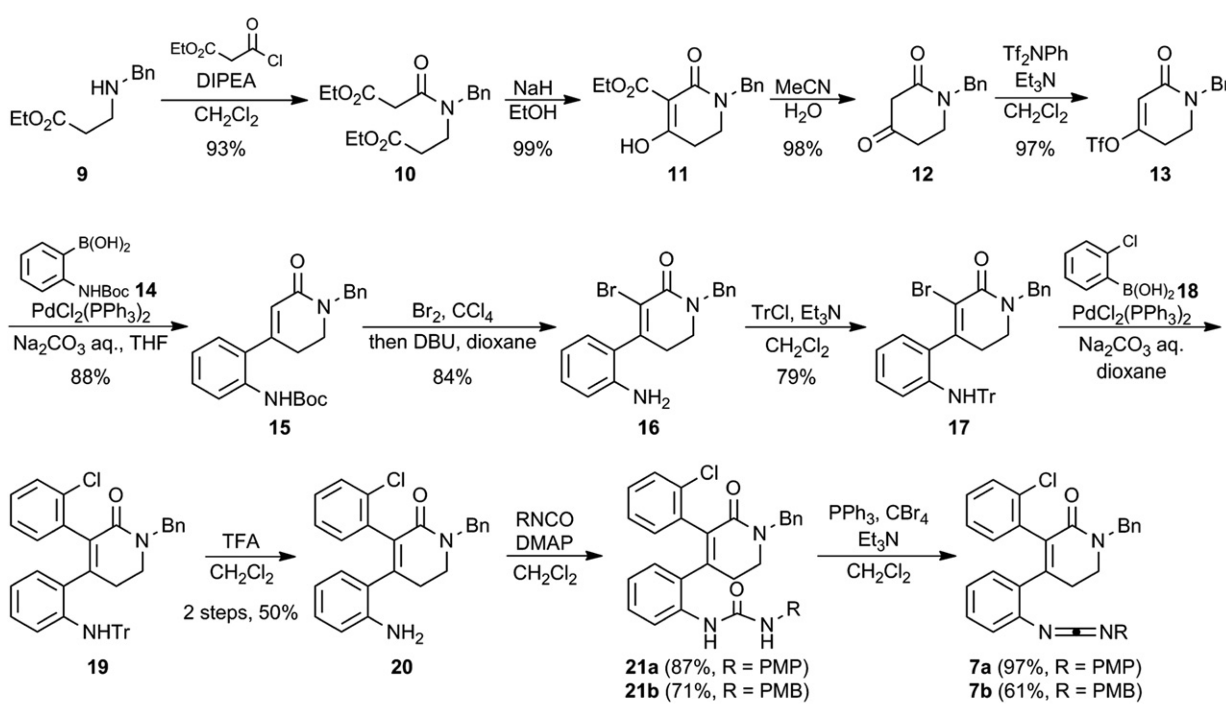
Our synthetic plan in this study is illustrated in Scheme 2. We expected that the formation of the A ring of **2** could be achieved from pentacyclic compound **5** by the established procedure.[5b] The D ring of compound **5** was planned to be constructed via transition-metal-catalyzed intramolecular C–N bond formation between an amidine nitrogen and a haloarene moiety in spiro-2-iminoindoline **6**. The synthesis of spiro-2-iminoindoline **6** would be achieved by the SmI_2-mediated reductive cyclization of carbodiimide **7** bearing an electron-deficient tetrasubstituted olefin. Carbodiimide of substrate **7** was expected to be obtained from the corresponding aniline, and the tetrasubstituted olefin would be synthesized via the α-bromination and coupling reaction of β-aryl-α,β-unsaturated lactam **8**.



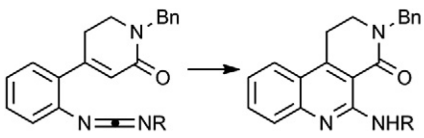
Scheme 2. Synthetic plan in this study.

3. Results and discussion

Synthesis of carbodiimides **7**, based on the synthetic plan described above, is presented in Scheme 3. Commercially available ethyl *N*-benzylaminopropionate **9** was acylated with ethyl malonyl chloride to give amide **10** in 93% yield. The following Dieckmann condensation of the product afforded lactam **11**, which was hydrolyzed and subsequently decarboxylated to β-ketolactam **12** by heating in refluxing aqueous acetonitrile in 88% yield from **9**. Treatment of **12** with *N*-phenyl trifluoromethanesulfonimide (Tf_2NPh)[8] provided vinyl triflate **13** in 97% yield. The Suzuki coupling reaction of triflate **13** and boronic acid **14**[9] gave Boc-protected aniline **15** in 88% yield, and successive treatment of the coupling product with bromine and with DBU resulted in α-bromination to produce lactam **16** in 84% yield, the *N*-Boc group of which was removed in the course of the sequence. Since direct cross coupling of lactam **16** and 2-chlorophenyl boronic acid **18** was unsuccessful due to the intramolecular C–N bond formation between the aniline and α-position of the lactam in **16**, the aniline **16** was converted into corresponding tritylated aniline **17** in 79% yield. Then the protected aniline **17** was subjected to the Suzuki coupling with the boronic acid **18** and the crude material including the product **19** was treated with trifluoroacetic acid to provide aniline **20** in 50% yield from **17**. Treatment of the product **20** with *para*-methoxyphenyl (PMP)[10] and *para*-methoxybenzyl (PMB) isocyanates afforded *N*-PMP urea **21a** in 87% yield and *N*-PMB urea **21b** in 71% yield, respectively. Urea **21a** and **21b** were transformed into carbodiimides **7a** and **7b**, respectively, by dehydration using triphenylphosphine and carbon tetrabromide.[11] These substrates were rather stable at ambient temperature, while carbodiimides **22** without α-substituents of α,β-unsaturated lactams were consumed via 6π electrocyclic reaction, providing 2-aminoquinolines,[12] such as **23** in a gradual manner under the same condition (Scheme 4).



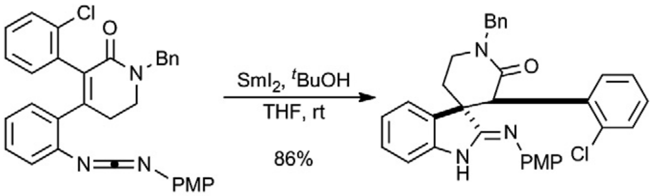
Scheme 3. Synthesis of carbodiimides **7**.



22 23

Scheme 4. Thermal 6π electrocyclic reaction.

After we had obtained carbodiimides bearing tetrasubstituted olefins, we applied SmI_2-mediated reductive cyclization to these substrates. When *N*-PMP carbodiimide **7a** was treated with SmI_2 (2.8 equiv) in the presence of *tert*-butyl alcohol (10 equiv) at ambient temperature, the desired cyclization proceeded and spiro-2-iminoindoline **6a** was obtained in 86% yield (Scheme 5). While the product **6a** was observed as a mixture of two isomers at a ratio of 4:1 in $CDCl_3$ on the ^1H NMR spectrum, we reasoned they were amidine-tautomers of a single diastereomer, based on the observation that the ratio was decreased to 2:1 by changing the solvent to pyridine-d_5. A single crystal of iminoindoline **6a** was obtained via crystallization from Et_2O, and X-ray crystallographic analysis of **6a** revealed two aryl groups on a 2-piperidinone ring with a cis configuration (Fig. 2).[13]



7a 6a

Scheme 5. Reductive cyclization of carbodiimide **7a**.

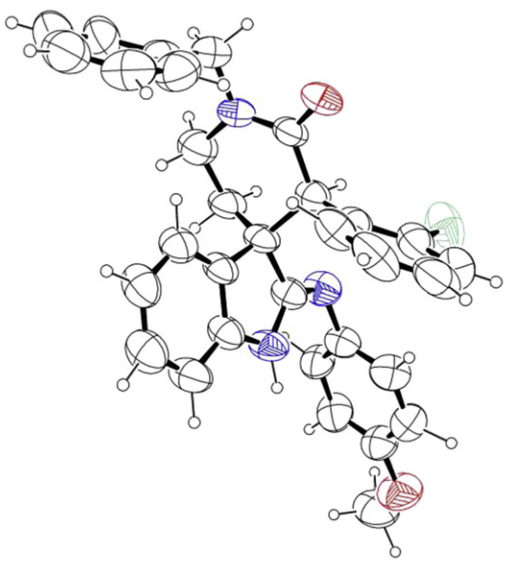
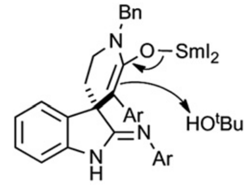


Fig. 2. X-ray structure of **6a**.

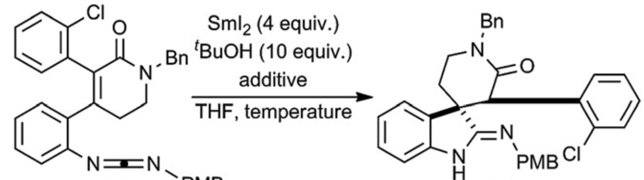
This result can be explained by stereoselective protonation of samarium enolate **24** from a side of the ring that is less sterically hindered (Fig. 3). We also attempted reductive cyclization of *N*-PMB carbodiimide **7b** (Table 1). Interestingly, the usual reaction conditions resulted in complete recovery of the starting material (entry 1), even when the reaction mixture was heated to 60 °C (entry 2). The addition of HMPA as a co-solvent, generally utilized to increase the reduction potential of SmI_2,[14] had a dramatic effect on the reaction, and the desired cyclization proceeded at ambient temperature to afford iminoindoline **6b** in 90% yield (entry 3).



24

Fig. 3. Protonation of samarium enolate **24**.

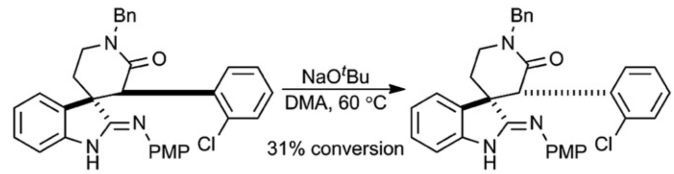
Table 1
Reductive cyclization of carbodiimide **7b**



7b 6b

Entry	Additives	Temperature	Results
1	None	rt	No reaction
2	None	60 °C	No reaction
3	HMPA (10%vol)	rt	90%

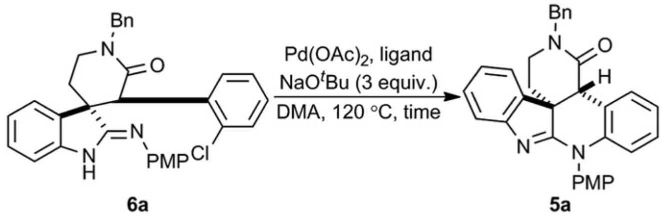
Toward the construction of a pentacyclic core of perophoramidine, we planned intramolecular palladium-catalyzed aryl amidination[15] of the spiro-2-iminoindoline **6a** and **6b**. Since direct aryl amidination of diastereomers **6a** and **6b** was expected to result in a rather strained pentacyclic species, the ideal cyclization in this case would involve stereochemical inversion of the α-position of the lactam in advance of the desired amidination. To examine the isomerization conditions, spiro-2-iminoindoline **6a** was treated with 3 equiv of sodium *tert*-butoxide in DMA. No reaction occurred at ambient temperature, however, 31% conversion of **6a** to the stereoisomer **6c** was observed after heating to 60 °C for 2 h by ^1H NMR analysis (Scheme 6). Surprisingly, when the reaction mixture was heated to 120 °C for 24 h, another product was obtained that proved to be the desired pentacyclic compound **5a** (Table 2, entry 1).[16] On examination of the effects of palladium catalysts and phosphine ligands, we first added 10 mol % of palladium acetate and 20 mol % of alkylphosphine ligands (entries 2–6). All of the conditions tested contributed to the improvement of product yields, but their degrees of enhancement were different. While the condition using cataCXium® A[17] resulted in a slight increase in yield (entry 2), tri-*tert*-butylphosphine,[18] CyclehexylJohnPhos,[19] DavePhos,[20] and tricyclohexylphosphine (Cy_3P)[21] showed greatly improved yields (entries 3–6). The reaction rate enhancement by Cy_3P was especially notable, and the reaction was completed in 17 h to afford product **5a** in 78% yield (entry 6). Decreased amounts of palladium catalyst and ligand increased the yield to 86% (entry 7). The stereochemistry of pentacycle **5a** was determined by NOESY, which showed the proton at α-position of lactam has correlation to two different protons on the aromatic rings (Fig. 4). Unfortunately,



6a 6c

Scheme 6. Isomerization of iminoindoline **6a**.

Table 2
Intramolecular aryl amidination of iminoindoline **6a**



Entry	$Pd(OAc)_2$	Ligand (mol %)	Time	Yield
1	None	None	24 h	27%
2	10 mol %	cataCXium® A (20)	24 h	31%
3	10 mol %	$^tBu_3P\cdot HBF_4$ (20)	24 h	63%
4	10 mol %	CyclohexylJohnPhos (20)	24 h	66%
5	10 mol %	Davephos (20)	24 h	70%
6	10 mol %	$Cy_3P\cdot HBF_4$ (20)	17 h	78%
7	5 mol %	$Cy_3P\cdot HBF_4$ (10)	17 h	86%

these optimized conditions did not work at all in the case of *N*-PMB-protected iminoindoline **6b**, resulting in the recovery of the starting material. The difference in reactivity was probably derived from the electronic property of amidines bearing different substituents. However the precise mechanism that encumbers the desired reaction remained unclear. The pentacyclic compound **5a** thus obtained was comparable to Rainier's pentacycle,[5b] which led to dehaloperophoramidine via further transformations.

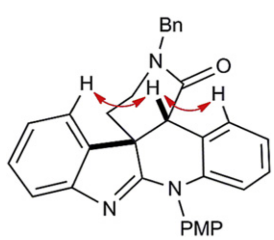


Fig. 4. NOESY correlation of pentacycle **5a**.

4. Conclusion

In summary, an intramolecular SmI_2-mediated reductive cyclization between carbodiimide moieties and unsaturated amides was successfully developed and applied to functionalized substrates bearing tetrasubstituted olefins. The reaction afforded arylated spiro-2-iminoindolines in high yield, and the structure of the product was determined by X-ray crystallography. Although the stereochemistry of the product was different from the desired one, the optimized palladium-catalyzed aryl amidination realized the isomerization of α-stereochemistry of the lactam and C–N bond formation in a single step, resulting in the efficient construction of a pentacyclic core of perophoramidine synthetically equivalent to Rainier's pentacyclic amidine.[5b]

5. Experimental section

5.1. General methods

Unless otherwise noted, all reactions were performed under nitrogen or argon atmosphere. Tetrahydrofuran was distilled from metal sodium and benzophenone. Samarium diiodide (0.1 M in THF) was prepared from metal samarium and diiodoethane.[22] Analytical thin-layer chromatography was performed with Merck Silica gel 60 and Merck 25 DC-Alufolein. Flash silica gel column chromatography was performed with Kanto Silica gel 60 (spherical, 63–210 μm), Kanto Silica gel 60 N (spherical, neutral, 40–100 μm) or Fuji Silysia BW silica gel. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JEOL JNM-ECA500 KP at 500 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); dd (double doublet); dt (double triplet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-ECA500 KP at 125 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on FT/IR-4100 (JASCO). Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on SHIMADZU PARVUM 2 mass spectrometer.

5.2. Ethyl 3-[Benzyl(3-ethoxy-3-oxopropyl)amino]-3-oxopropanoate (10)

To a stirred solution of ethyl 3-(*N*-benzylamino)propionate **9** (414 mg, 2.00 mmol) and ethyldiisopropylamine (342 μL, 2.00 mmol) in 4 mL of CH_2Cl_2 at 0 °C, was added ethyl malonyl chloride (303 μL, 2.40 mmol). The reaction mixture was warmed to ambient temperature and stirred for 10 min. H_2O was added at 0 °C and the separated aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution and with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to give the titled compound (598 mg, 93%) as a viscous colorless oil. ^1H NMR ($CDCl_3$, δ); 7.32–7.27 (m, 5H), 4.65 (s, 2H), 4.61* (s, 2H), 4.25–4.08 (m, 4H), 3.65 (t, 2H, *J*=6.9 Hz), 3.56* (t, 2H, *J*=6.9 Hz), 3.44 (s, 2H), 2.65 (t, 2H, *J*=6.9 Hz), 2.54* (t, 2H, *J*=6.9 Hz), 1.31–1.22 (m, 6H); ^{13}C NMR ($CDCl_3$, δ) 171.9, 170.9*, 167.6*, 167.4, 166.7, 166.5*, 136.7*, 136.2, 129.0, 128.6*, 127.81, 127.77*, 127.4*, 126.3, 61.5*, 61.4, 61.0*, 60.5, 52.7, 47.9*, 43.1*, 43.0, 41.4, 41.1*, 33.1*, 32.5, 14.09*, 14.06, 14.0; IR (ATR) 1736, 1654 cm^{-1}; Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.68; H, 7.29; N, 4.39. HRMS (MH^+) calcd for $C_{17}H_{24}NO_5$: 322.1654. Found: 322.1654 (major:minor=57:43, *peaks of minor conformer).

5.3. Ethyl 1-benzyl-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (11)

To a stirred solution of NaH (60% wt, 708 mg, 17.7 mmol) in 80 mL of EtOH at 0 °C, was added a solution of amide **10** (5.18 g, 16.1 mmol) in 20 mL of EtOH dropwise over 10 min. The reaction mixture was warmed to ambient temperature and stirred for 12 h. A 2 M aqueous HCl solution was added and the resultant solution was evaporated. The residue was dissolved in H_2O and extracted with $CHCl_3$ three times (pH of the aqueous layer$<$2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/AcOEt=6/4 to 4/6) to give the titled compound (4.03 g, 91%) as a viscous oil. ^1H NMR ($CDCl_3$, δ); 7.34–7.27 (m, 5H), 4.64 (s, 2H), 4.41 (q, 2H, *J*=7.2 Hz), 3.32 (t, 2H, *J*=6.9 Hz), 2.54 (t, 2H, *J*=6.9 Hz), 1.42 (t, 2H, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$, δ) 182.9, 172.0, 162.4, 137.7, 128.6, 128.0, 127.4, 98.2, 61.8, 49.4, 41.5, 29.6, 14.2; IR ($CHCl_3$) 1729, 1658 cm^{-1}; HRMS (MH^+) calcd for $C_{15}H_{18}NO_4$: 276.1236. Found: 276.1244.

5.4. 1-Benzylpiperidine-2,4-dione (12)

A solution of lactam **11** (3.78 g, 13.7 mmol) and 0.1 mL of H_2O in 100 mL of MeCN was heated to reflux for 3.5 h. The reaction mixture was evaporated and purified by silica gel column chromatography ($CHCl_3$/MeOH=98/2 to 95/5) to give the titled compound (2.73 g, 98%) as colorless solids. Mp 59–60 °C; ^1H NMR ($CDCl_3$, δ);

7.34–7.26 (m, 5H), 4.69 (s, 2H), 3.49 (t, 2H, *J*=6.3 Hz), 3.43 (s, 2H), 2.54 (t, 2H, *J*=6.3 Hz). ^{13}C NMR ($CDCl_3$, δ) 203.4, 166.3, 136.2, 128.8, 128.0, 127.9, 50.0, 48.9, 42.3, 38.6; IR (ATR) 1715, 1651 cm^{-1}; MS (FAB$^+$) *m*/*z*=204 (MH^+); Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.78; H, 6.48; N, 6.85.

5.5. 1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (13)

To a solution of ketolactam **12** (6.09 g, 30.0 mmol) and Et_3N (8.35 mL, 60.0 mmol) in 100 mL of CH_2Cl_2 at 0 °C, was added *N*-phenyl trifluoromethanesulfonimide (12.9 g, 36.0 mmol). After 60 min, the reaction mixture was warmed to ambient temperature and stirred for 2 h. A 0.1 M aqueous HCl was added to the mixture at 0 °C and a separated aqueous layer was extracted with $CHCl_3$. The combined organic layers were successively washed with a 0.1 M aqueous HCl solution, brine, a saturated aqueous $NaHCO_3$ solution, and brine. The resultant solution was dried over Na_2SO_4 and concentrated under reduced pressure. This crude material was purified by silica gel column chromatography (hexane/AcOEt=9/1 to 8/2) to give the titled compound (9.81 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$, δ); 7.35–7.28 (m, 5H), 6.06 (s, 1H), 4.62 (s, 2H), 3.44 (t, 2H, *J*=7.2 Hz), 2.69 (t, 2H, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$, δ) 162.7, 157.5, 136.3, 128.7, 127.9, 127.7, 118.3 (q, *J*=320.7 Hz), 114.2, 49.3, 43.3, 27.1; IR (ATR) 1680, 1366, 1219 cm^{-1}; MS (FAB$^+$) *m*/*z*=336 (MH^+); Anal. Calcd for $C_{13}H_{12}F_3NO_4S$: C, 46.57; H, 3.61; N, 4.18. Found: C, 46.52; H, 3.61; N, 4.28.

5.6. *tert*-Butyl [2-(1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl)phenyl]carbamate (15)

A solution of vinyl triflate **13** (19.2 g, 57.3 mmol), boronic acid **14**[9] (16.3 g, 68.8 mmol), and $PdCl_2(PPh_3)_2$ (2.01 g, 2.87 mmol) in 150 mL of THF and 150 mL of a 2.0 M aqueous Na_2CO_3 solution was heated to reflux for 60 min. The reaction mixture was gradually cooled to ambient temperature. The separated aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/AcOEt=8/2 to 4/6) to give the titled compound (19.0 g, 88%) as colorless solids. Mp 171–172 °C; ^{1}H NMR ($CDCl_3$, δ); 7.84 (d, 1H, *J*=8.6 Hz), 7.34–7.32 (m, 6H), 7.14–7.08 (m, 2H), 6.49 (s, 1H), 6.09 (s, 1H), 4.69 (s, 2H), 3.47 (t, 2H, *J*=7.0 Hz), 2.63 (t, 2H, *J*=7.0 Hz), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, δ) 164.3, 152.9, 149.4, 137.2, 134.3, 130.8, 129.3, 128.7, 128.2, 127.6, 127.5, 124.0, 123.8, 122.0, 80.9, 49.7, 44.8, 29.1, 28.3; IR (ATR) 3160, 1709, 1656 cm^{-1}; HRMS (MH^+) calcd for $C_{23}H_{27}N_2O_3$: 379.2022. Found: 379.2020.

5.7. 4-(2-Aminophenyl)-1-benzyl-3-bromo-5,6-dihydropyridin-2(1*H*)-one (16)

To a solution of *N*-Boc aniline **15** (567 mg, 1.50 mmol) in 10 mL of CCl_4, was added bromine (84.6 μL, 1.65 mmol) dropwise at 0 °C. After 10 min, the reaction mixture was directly evaporated and this residue was dissolved in 10 mL of dioxane. DBU (447 μL, 3.00 mmol) was added at 0 °C in a dropwise manner. After 20 min, a saturated aqueous NH_4Cl solution was added and the separated aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/AcOEt=8/2 to 6/4) to give the titled compound (450 mg, 84%) as brown solids. Mp 66–68 °C; ^{1}H NMR ($CDCl_3$, δ); 7.37–7.28 (m, 5H), 7.16 (m, 1H), 6.95 (dd, 1H, *J*=7.5, 1.5 Hz), 6.80 (m, 1H), 6.75 (d, 1H, *J*=8.0 Hz), 4.76 (d, 1H, *J*=14.3 Hz), 4.67 (d, 1H, *J*=14.3 Hz), 3.66 (br s, 2H), 3.47 (t, 2H, *J*=6.9 Hz), 2.70–2.59 (m, 2H). ^{13}C NMR ($CDCl_3$, δ) 160.4, 149.0, 141.7, 136.8, 129.6, 128.7, 128.2, 127.7, 127.3, 125.9, 118.7, 118.4, 116.2, 51.3, 44.4, 31.4; IR (ATR) 3420, 3342, 1635 cm^{-1}; HRMS (MH^+) calcd for $C_{18}H_{18}{}^{79}BrN_2O$: 357.0603. Found: 357.0601.

5.8. 1-Benzyl-3-bromo-4-[2-(tritylamino)phenyl]-5,6-dihydropyridin-2(1*H*)-one (17)

To a solution of α-bromolactam **16** (4.64 g, 13.0 mmol) and triethylamine (18.1 mL, 130 mmol) in 100 mL of CH_2Cl_2, was added triphenylmethyl chloride (21.7 g, 78.0 mmol) in two portions at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 5 h. Then a saturated aqueous $NaHCO_3$ solution was added and the separated organic layer was washed with water and a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/AcOEt=9/1 to 7/3) to give the titled compound (6.16 g, 79%) as colorless solids. Mp 201–203 °C; ^{1}H NMR ($CDCl_3$, δ); 7.35–7.19 (m, 20H), 6.89 (dd, 1H, *J*=7.4, 1.7 Hz), 6.77 (m, 1H), 6.63 (m, 1H), 6.14 (d, 1H, *J*=8.0 Hz), 4.91 (s, 1H), 4.73 (d, 1H, *J*=14.3 Hz), 4.67 (d, 1H, *J*=14.3 Hz), 3.46–3.33 (m, 2H), 2.68–2.67 (m, 2H). ^{13}C NMR ($CDCl_3$, δ) 160.3, 149.2, 140.9, 136.8, 128.8, 128.7, 128.2, 128.1, 128.0, 127.9, 127.7, 127.1, 127.0, 126.4, 119.9, 117.2, 116.0, 71.0, 51.2, 44.5, 31.5; IR (ATR) 3431, 1651 cm^{-1}; HRMS (MH^+) calcd for $C_{37}H_{32}{}^{81}BrN_2O$: 601.1678. Found: 601.1677.

5.9. 4-(2-Aminophenyl)-1-benzyl-3-(2-chlorophenyl)-5,6-dihydropyridin-2(1*H*)-one (20)

A solution of *N*-trityl aniline **18** (300 mg, 0.500 mmol), 2-chlorophenyl boronic acid (235 mg, 1.50 mmol), and $PdCl_2(PPh_3)_2$ (17.5 mg, 25.0 μmol) in 10 mL of dioxane and 10 mL of a 2.0 M aqueous Na_2CO_3 solution was heated to reflux for 60 min. The reaction mixture was gradually cooled to ambient temperature. The separated aqueous layer was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. This material was dissolved in 9.5 mL of CH_2Cl_2 and the resultant solution was cooled to 0 °C. To the solution was added 0.5 mL of TFA. After 5 min, a saturated aqueous $NaHCO_3$ solution was added and the separated aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/AcOEt=8/2 to 5/5) to give the titled compound (96.6 mg, two steps 50%) as a yellow amorphous. ^{1}H NMR ($CDCl_3$, δ); 7.38–7.35 (m, 4H), 7.30–7.28 (m, 2H), 7.11–7.04 (m, 3H), 6.94–6.90 (m, 2H), 6.56 (br, 2H), 4.83 (d, 1H, *J*=14.9 Hz), 4.66 (d, 1H, *J*=14.9 Hz), 3.68–3.59 (m, 3H), 3.41–3.39 (m, 1H), 2.88 (br, 1H), 2.55 (br, 1H). ^{13}C NMR ($CDCl_3$, δ) 163.6, 147.3, 142.2, 137.2, 134.8, 132.6, 130.6, 128.5, 128.43, 128.39, 128.34, 128.1, 127.9, 127.4, 127.2, 125.9, 124.4, 117.5, 115.5, 50.0, 44.4, 29.7; IR (ATR) 3450, 2247, 1649 cm^{-1}; HRMS (MH^+) calcd for $C_{24}H_{22}{}^{35}ClN_2O$: 389.1421. Found: 389.1421.

5.10. 1-{2-[1-Benzyl-5-(2-chlorophenyl)-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]phenyl}-3-(4-methoxyphenyl)urea (21a)

To a solution of diaryllactam **20** (335 mg, 861 μmol) in 5 mL of CH_2Cl_2, were added 4-methoxyphenyl isocyanate (123 μL, 947 μmol) and DMAP (10.0 mg, 81.9 μmol) at ambient temperature. The reaction mixture was stirred for 2 h. Et_2O 10 mL was added to the reaction mixture and colorless precipitate was observed. The precipitate was filtered, washed with CH_2Cl_2, and dried in vacuo to give the titled compound (405 mg, 87%) as colorless solids. Mp 225–227 °C; ^{1}H NMR (DMSO-d_6, δ); 8.91 (s, 1H), 7.88 (s, 1H), 7.73 (d, 1H, *J*=8.3 Hz), 7.35–7.29 (m, 9H), 7.15–7.13 (m, 1H), 7.11–7.07 (m, 3H), 6.89–6.83 (m, 2H), 6.76 (d, 1H, *J*=3.4 Hz), 4.95 (d, 1H, *J*=14.6 Hz), 4.41 (d, 1H, *J*=14.6 Hz), 3.72 (s, 3H), 3.55–3.54 (m, 2H), 3.00–2.91 (m, 1H), 2.49–2.37 (m, 2H). ^{13}C NMR (DMSO-d_6, δ) 163.0, 154.5, 152.5, 147.3, 146.2, 137.5, 136.2, 135.4, 133.5, 132.6, 131.4, 130.9, 128.9, 128.5, 128.4, 128.0, 127.7, 127.3, 127.2, 126.5, 122.4, 121.7, 120.0, 114.1, 55.2, 49.5, 44.7, 29.0; IR (ATR) 3338, 1702, 1641 cm^{-1}; HRMS (MH$^+$) calcd for $C_{32}H_{29}{}^{35}ClN_3O_3$: 538.1897. Found: 538.1896.

5.11. 1-{2-[1-Benzyl-5-(2-chlorophenyl)-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]phenyl}-3-(4-methoxybenzyl)urea (21b)

To a solution of diaryllactam **20** (93.0 mg, 239 μmol) in 1 mL of CH_2Cl_2, were added 4-methoxybenzyl isocyanate (40.5 μL, 263 μmol) and DMAP (9.6 mg, 78.6 μmol) at ambient temperature. The reaction mixture was heated to 40 °C and stirred for 24 h. After gradual cooling to ambient temperature, the reaction mixture was directly subjected to silica gel column chromatography (hexane/AcOEt=9/1 to 5/5) to give the titled compound (94.2 mg, 71%) as colorless solids. Mp 192–193 °C; ^{1}H NMR (CDCl$_3$, δ); 7.79–7.65 (br, 1H), 7.31–7.06 (m, 12H), 6.82–6.78 (br, 3H), 6.65–6.55 (br, 2H), 6.35–6.16 (br, 1H), 5.58–4.62 (m, 1H), 4.24–4.19 (br, 2H), 4.01–3.98 (br, 1H), 3.76 (s, 3H), 3.62–3.59 (br, 1H), 3.24–2.91 (br, 2H), 2.38–2.27 (br, 1H). ^{13}C NMR (CDCl$_3$, δ) 164.8, 158.5, 155.8, 148.4, 135.9, 135.7, 135.1, 133.5, 133.0, 132.0, 131.9, 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 127.4, 126.2, 122.5, 113.8, 113.7, 55.2, 51.0, 45.4, 43.0, 29.0 (The peaks on ^{1}H and ^{13}C spectra were highly broadened.); IR (ATR) 3366, 1640 cm^{-1}; HRMS (MH$^+$) calcd for $C_{33}H_{31}{}^{35}ClN_3O_3$: 552.2054. Found: 552.2059.

5.12. 1-Benzyl-3-(2-chlorophenyl)-4-[2-(4-methoxyphenyliminomethyleneamino)phenyl]-5,6-dihydropyridin-2(1*H*)-one (7a)

To a stirred solution of urea **21a** (404 mg, 0.751 mmol), PPh_3 (295 mg, 1.13 mmol), and Et_3N (230 μL, 1.65 mmol) in 10 mL of CH_2Cl_2, was added CBr_4 (299 mg, 901 μmol) at 0 °C. The reaction mixture was stirred for 60 min and warmed to ambient temperature. Then additional PPh_3 (300 mg, 1.14 mmol) was added in three portions and the reaction mixture was stirred for additional 5 h and directly evaporated. The resultant residue was purified by silica gel column chromatography (hexane/AcOEt=8/2 to 7/3) to give the titled compound (379 mg, 97%) as a colorless oil. ^{1}H NMR (CDCl$_3$, δ); 7.40–7.38 (m, 2H), 7.36–7.33 (m, 2H), 7.30–7.27 (m, 2H), 7.13–7.00 (m, 7H), 6.94–6.84 (m, 4H), 4.83 (d, 1H, J=14.9 Hz), 4.66 (d, 1H, J=14.9 Hz), 3.79 (s, 3H), 3.68–3.66 (m, 1H), 3.48–3.43 (m, 1H), 3.07 (br, 1H), 2.60 (br, 1H). ^{13}C NMR (CDCl$_3$, δ) 163.9, 157.5, 147.4, 137.5, 135.9, 135.6, 134.3, 134.2, 134.1, 132.4, 131.8, 130.3, 128.9, 128.8, 128.56, 128.55, 128.53, 128.2, 127.3, 126.1, 125.12, 125.05, 124.8, 114.8, 55.5, 50.3, 44.5, 30.2; IR (ATR) 2129, 1654 cm^{-1}; HRMS (MH$^+$) calcd for $C_{37}H_{27}{}^{35}ClN_3O_2$: 520.1792. Found: 520.1800.

5.13. 1-Benzyl-3-(2-chlorophenyl)-4-[2-(4-methoxybenzyl)iminomethyleneaminophenyl]-5,6-dihydropyridin-2(1*H*)-one (7b)

To a stirred solution of urea **21b** (167 mg, 0.303 mmol), PPh_3 (119 mg, 454 μmol), and Et_3N (127 μL, 909 μmol) in 6 mL of CH_2Cl_2, was added CBr_4 (121 mg, 364 μmol) at 0 °C. The reaction mixture was stirred for 60 min and warmed to ambient temperature. The reaction mixture was stirred for 10 h and directly evaporated. The resultant residue was purified by silica gel column chromatography (hexane/AcOEt=8/2 to 6/4) to give the titled compound (98.3 mg, 61%) as a colorless oil. ^{1}H NMR (CDCl$_3$, δ); 7.40–7.33 (m, 4H), 7.28–7.23 (m, 4H), 7.05–6.99 (m, 2H), 6.91–6.80 (m, 7H), 4.81 (d, 1H, J=14.6 Hz), 4.65 (d, 1H, J=14.6 Hz), 4.45 (s, 2H), 3.75 (s, 3H), 3.60–3.58 (m, 1H), 3.40–3.35 (m, 1H), 2.96 (s, 1H), 2.43–2.41 (m, 1H). ^{13}C NMR (CDCl$_3$, δ) 163.9, 159.1, 147.8, 138.7, 137.5, 136.9, 135.8, 135.6, 134.1, 133.9, 131.9, 131.7, 129.8, 128.60, 128.57, 128.5, 128.4, 128.3, 128.2, 127.3, 126.0, 124.3, 124.0, 114.1, 55.2, 50.2, 49.9, 44.4, 29.9; IR (ATR) 2125, 1653 cm^{-1}; HRMS (MH$^+$) calcd for $C_{33}H_{29}{}^{35}ClN_3O_2$: 534.1948. Found: 534.1951.

5.14. (3*RS*,3′*RS*,*Z*)-1′-Benzyl-3′-(2-chlorophenyl)-2-(4-methoxyphenylimino)spiro[indoline-3,4′-piperidin]-2′-one (6a)

A solution of carbodiimide **7a** (354 mg, 681 μmol) and ^{t}BuOH (651 μL, 6.81 mmol) in 12 mL of THF was degassed by freeze pump thaw cycles chilled with liquid nitrogen. To the stirred solution at ambient temperature, was added a solution of samarium diiodide (0.1 M in THF, 19 mL) in a dropwise manner over 4.5 h. Then a saturated aqueous NH_4Cl solution was added to the reaction mixture and the organic solvent was removed by evaporation. The resultant mixture was extracted with AcOEt twice and the combined organic layers were washed with a saturated aqueous NH_4Cl solution and dried over Na_2SO_4. The crude solution was concentrated under reduced pressure and dried in vacuo. The crude was subjected to silica gel column chromatography (hexane/AcOEt=8/2 to 6/4) to give the titled compound (307 mg, 86%) as colorless solids. Mp 208–209 °C; ^{1}H NMR (CDCl$_3$, δ) 7.50–7.32 (m, 6H), 7.19–7.13 (m, 3H), 6.94–6.92 (m, 1H), 6.87–6.68 (m, 5H), 6.59–6.53 (m, 3H), 5.03 (s, 1H), 4.97* (d, 1H, J=13.7 Hz), 4.87 (d, 1H, J=14.3 Hz), 4.83* (s, 1H), 4.76 (d, 1H, J=14.3 Hz), 4.66* (d, 1H, J=13.7 Hz), 3.88–3.82 (m, 1H), 3.79 (s, 3H), 3.77* (s, 3H), 3.64–3.62 (m, 1H), 2.58–2.52 (m, 1H), 2.22 (ddd, 1H, J=13.7, 5.7, 5.7 Hz), 2.01–1.98* (m, 1H). ^{13}C NMR (CDCl$_3$, δ) 169.9*, 169.1, 168.2*, 161.4, 156.1*, 155.7, 142.6, 142.2, 136.7, 136.4, 134.6, 134.4*, 133.9*, 132.4*, 132.3*, 130.3*, 130.0, 129.4, 129.3*, 129.2, 129.0*, 128.9*, 128.8, 128.7*, 128.6, 128.5, 128.3, 128.0*, 127.5, 126.1*, 125.9, 124.5, 123.0*, 122.1, 121.6*, 120.9, 118.1*, 114.7, 114.0*, 108.7, 56.8*, 55.4, 51.7, 51.3, 51.0*, 50.8, 49.5*, 43.9*, 43.2, 31.5*, 31.3; IR (ATR) 3246, 1667 cm^{-1}; HRMS (MH$^+$) calcd for $C_{32}H_{29}{}^{35}ClN_3O_2$: 522.1948. Found: 522.1946 (*peaks of minor isomer).

5.15. (3*RS*,3′*RS*,*Z*)-1′-Benzyl-3′-(2-chlorophenyl)-2-(4-methoxybenzylimino)spiro[indoline-3,4′-piperidin]-2′-one (6b)

A solution of carbodiimide **7b** (98.3 mg, 184 μmol) and ^{t}BuOH (176 μL, 1.84 mmol) in 1.8 mL of THF was degassed by freeze pump thaw cycles chilled with liquid nitrogen. To the stirred solution at ambient temperature, was added a solution of samarium diiodide (0.9 M in THF/HMPA=9/1, 8.18 mL) over 2 min. The reaction mixture was stirred for 5 min. Then a saturated aqueous NH_4Cl solution was added to the reaction mixture and the organic solvent was removed by evaporation. The resultant mixture was extracted with AcOEt twice and the combined organic layers were washed with a saturated aqueous LiCl solution twice and dried over Na_2SO_4. The crude solution was concentrated under reduced pressure and dried in vacuo. The crude was subjected to silica gel column chromatography (hexane/AcOEt=8/2 to 4/6) to give the titled compound (88.6 mg, 90%) as colorless amorphous. ^{1}H NMR (CDCl$_3$, δ) 7.44–7.43 (m, 2H), 7.39–7.37 (m, 3H), 7.27–7.27 (m, 1H), 7.24–7.22 (m, 1H), 7.17–7.15 (m, 3H), 7.09–7.05 (m, 1H), 6.85–6.82 (m, 5H), 6.44 (d, 1H, J=8.0 Hz), 4.93–4.89 (m, 2H), 4.64–4.62 (m, 2H), 4.54–4.50 (m, 1H), 4.35–4.32 (m, 1H), 3.81 (s, 3H), 3.77–3.74 (m, 1H), 3.59 (m, 1H), 2.36 (m, 1H), 1.94 (m, 1H). ^{13}C NMR (CDCl$_3$, δ) 173.1, 168.1, 159.0, 155.9, 136.2, 134.5, 134.2, 130.1, 129.6, 129.5, 129.4, 129.3, 129.0, 128.8, 128.7, 128.6, 127.9, 126.2, 123.0, 121.2, 117.3, 113.9, 55.6, 55.2, 50.8, 49.5, 46.4, 43.7, 31.9; IR (ATR) 3433, 1642 cm^{-1}; HRMS (MH$^+$) calcd for $C_{33}H_{31}{}^{35}ClN_3O_2$: 536.2105. Found: 536.2100.

5.16. (4a*RS*,14b*RS*)-2-Benzyl-10-(4-methoxyphenyl)-3,4,10,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-1(2*H*)-one (5a)

A solution of iminoindoline **6a** (52.2 mg, 100 μmol), NaO^{t}Bu (28.8 mg, 300 μmol), $Pd(OAc)_2$ (2.1 mg, 5.09 μmol), and tricyclohexylphosphonium tetrafluoroborate (3.7 mg, 10.0 μmol) in 2 mL of DMA was heated at 120 °C for 17 h. Then the reaction mixture was cooled to ambient temperature and a saturated aqueous NH_4Cl solution was added to it. The mixture was extracted with $CHCl_3$ three times and the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography ($CHCl_3$/AcOEt=10/0 to 9/1) to give the titled compound (41.6 mg, 86%) as colorless solids. Mp 249–250 °C; ^{1}H NMR ($CDCl_3$, δ); 7.69 (d, 1H, J=8.0 Hz), 7.39–7.34 (m, 7H), 7.19–7.08 (m, 6H), 6.85–6.81 (m, 2H), 6.57 (d, 1H, J=8.0 Hz), 4.93 (d, 1H, J=14.3 Hz), 4.74 (d, 1H, J=14.3 Hz), 4.03 (s, 1H), 3.87 (s, 3H), 3.51 (ddd, 1H, J=12.5, 7.0, 6.0 Hz), 3.30 (dd, 1H, J=12.6, 7.0 Hz), 2.56 (ddd, 1H, J=12.5, 7.0, 6.0 Hz), 1.42 (dd, 1H, J=12.6, 6.0 Hz). ^{13}C NMR ($CDCl_3$, δ) 171.8, 167.1, 159.4, 155.0, 140.6, 136.4, 136.1, 131.7, 128.9, 128.8, 128.7, 128.3, 127.9, 127.8, 123.3, 122.3, 122.0, 120.0, 118.8, 117.0, 115.7, 115.5, 55.5, 50.4, 49.2, 45.6, 43.7, 24.8; IR (ATR) 1644, 1548 cm^{-1}; MS (MH$^+$) calcd for $C_{32}H_{28}N_3O_2$: 486.2182. Found: 486.2182.

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