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Enantioselective Synthesis of Indoloquinolizidines via Asymmetric Catalytic Hydrogenation/Lactamization of Imino Diesters

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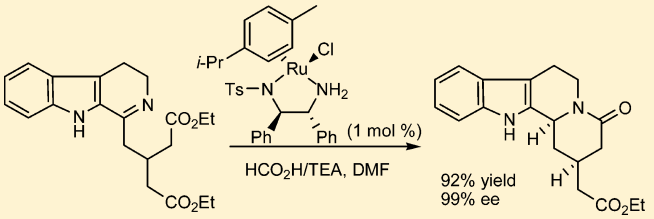
Supporting Information

ABSTRACT: We have developed a highly efficient cascade sequence for asymmetric synthesis of indoloquinolizidines with absolute control of *cis*-H2/H12b relative geometry in good to excellent yields and excellent enantioselectivities. This cascade was triggered by the Ru(II)−TsDPEN-catalyzed asymmetric transfer hydrogenation of imino diesters, with subsequent spontaneous lactamization with discrimination between the two diastereotopic 2-alkoxy-2-oxoethyl groups. The synthetic utility of this strategy was demonstrated by the asymmetric preparation of dihydrocorynantheol, geissoschizol, and isogeissoschizol.



INTRODUCTION

Corynantheine alkaloids with a tetracyclic indole[2,3-*a*]-quinolizidine motif are of great significance and interest to both the pharmaceutical and chemical communities[1] due to their broad bioactivity profile, such as analgesic,[2] anti-inflammatory,[3] antiarthritic,[4] antiallergic,[5] antibacterial,[6] and antiviral activities.[7] In the past few decades, numerous efforts have been invested in the total synthesis of these alkaloids, and particularly dihydrocorynantheol (**1**) has been the most studied target for the development of novel synthetic strategies designed for total synthesis of alkaloids featuring a indolo-[2,3-*a*]quinolizidine framework.[8] In contrast to dihydrocorynantheol (**1**), geissoschizol, bearing an (*E*)-ethylidenyl group at C(3), has been far less targeted and only five total syntheses have been reported,[9] probably due to the difficulty in installing the (*E*)-ethylidene side chain as well as controlling the C2/C12b relative stereochemistry; the latter is on top of the challenges encountered in the synthesis of indoloquiolizidine alkaloids (Figure 1).

Recently, the Franzén group and our group have described an organocatalytic cascade sequence between active methylene compounds tethered with electron-rich nucleophiles and α,β-unsaturated enals to afford complex multiheterocycles, including indolo[2,3-*a*]quinolizidine.[10,11] In our cases, this cascade led to *trans*-H2/H12b-cyclized products exclusively in good to excellent yields and excellent enantioselectivities. However, both *cis*- and *trans*-H2/H12 indoloquinolizidine could be obtained as major isomers via adjustment of the reaction conditions in Franzén's research.

In our search for a highly efficient methodology for the asymmetric synthesis of indoloquinolizidines with absolute control of the *cis*-H2/H12b relative geometry, we speculated

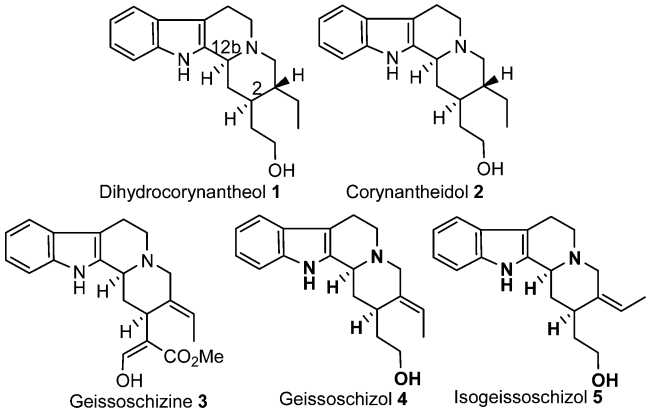


Figure 1. Examples of corynantheine alkaloids.

that imine **6** could be converted into the desired cyclized product **8** via a sequence of asymmetric catalytic hydrogenation of the imino functionality and subsequent spontaneous intramolecular lactamization with differentiation of two 2-alkoxy-2-oxoethyl groups (Scheme 1).[12] It could be anticipated that lactamization would occur via a chairlike transition state in which the 2-alkoxy-2-oxoethyl group that did not undergo cyclization would adopt equatorial placement. On the basis of our previous observation while working with a similar lactamization, we predicted that the cascade sequence would proceed with high *cis*-H2/H12b diastereoselectivity.[13] Herein we report our new findings on this cascade sequence and the

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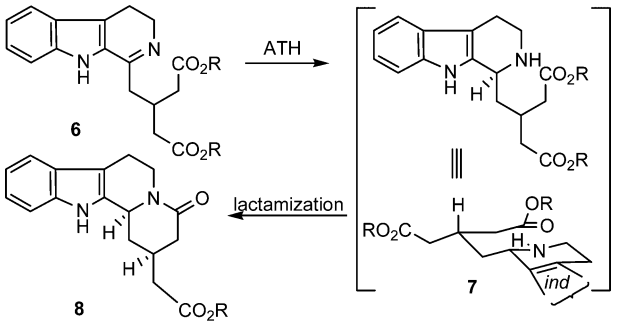
Scheme 1. Working Concept of ATH/Lactamization Cascade Sequence



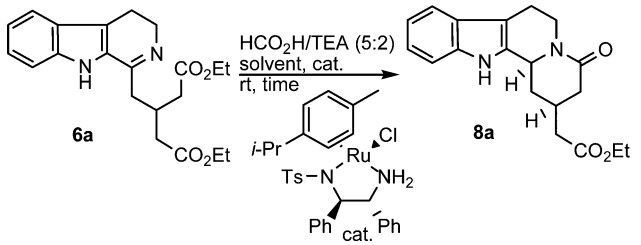
application of this methodology to the total synthesis of (−)-dihydrocoryantheol, (−)-geissoschizol, and (--)-isogeissoschizol.

RESULTS AND DISCUSSION

The requisite cyclic imino diester **6a** was conveniently prepared from tryptamine via condensation with acid diester in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) followed by Bischler−Napieralski cyclization promoted by phosphorus oxychloride (Scheme 2). The acid diester **10** was readily prepared through Wittig olefination of diethyl acetone-1,3-dicarboxylate with *tert*-butyl ester phosphorus ylide, hydrogenation of the newly formed double bond and TFA-promoted cleavage of the *tert*-butyl ester. Similarly, a set of imino diesters (**6b−g**) with different substitution patterns were prepared in moderate overall yields.

At first, imino diester **6a** was used as a probe to test the feasibility of the ATH/lactamization sequence. Noyori ATH of cyclic imines using *p*-cymene−Ru(II) complexes of certain chiral 1,2-diamines as catalysts has been well documented and successfully applied to the synthesis of quite a number of alkaloids.[14] In our study, hydrogenation of imino diester **6a** with commercially available (*R*,*R*)-Ru^{II}−TsDPEN would lead to an *S* configuration according to the general model proposed by Noyori.[14a] To our delight, when **6a** was treated with (*R*,*R*)-Ru^{II}−TsDPEN (1 mol %) in DMF and a HCOOH/Et_3N mixture (5/2) at room temperature for 4 h, the desired tetracyclic indoloquinolizidine **8a** was obtained with complete control of *cis*-H2/H12b relative stereochemistry in 92% yield and 99% ee. Within the limits of detection, no formation of *trans* isomer was observed (Table 1, entry 1). Dichloromethane and acetonitrile were also suitable solvents in reported procedures;[14a,f] however in our case, when **6a** was subjected to ATH in dichloromethane or acetonitrile, the reaction

Table 1. Screening Studies of Cascade Reaction Conditions[a]



entry	cat. loading (mol %)	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	1	DMF	4	92	98
2	1	CH_2Cl_2	24	24	7
3	1	MeCN	24	21	92
4	0.3	DMF	21	60	98
5	0.1	DMF	50	40	94

[a]Reagents and conditions: **6a** (0.5 mmol), cat. (1 mol %), and HCO_2H/TEA (5/2, 70 uL) in solvent (1 mL) at room temperature. [b]Yield referred to isolated pure product. [c]Enantiomeric excess of **8a** was determined by HPLC analysis on a chiral stationary phase.

proceeded sluggishly to give the desired product in poor yield even after a prolonged reaction time. ATH of imino diester **6a** in acetonitrile afforded **8a** with 92% ee, while in dichloromethane it led to almost racemic product (Table 1, entries 2 and 3). Lowering the catalyst loading resulted in a substantial decrease in yield (Table 1, entries 4 and 5).

With the optimized conditions established (Table 1, entry 1), this sequence was then extended to other imino diesters. The performance of various substrates with a substituent at the indolyl C5 was first explored (Table 2, entries 1−4). All the reactions proceeded well to afford the cyclization products in good to excellent yields and excellent enantioselectivities. Methyl esters **6e,f** were also suitable substrates for this cascade sequence, providing products with excellent ee values in good yields (entries 5 and 6). In all cases, only *cis* diastereoisomers were observed in the reaction mixture. Furthermore, cyclic imine **6g** derived from 3,4-dimethoxyphenethylamine also worked well under the reaction conditions, affording the benzoquinolizidine product **8g** in 81% yield, with 98% ee (entry 7).

The relative configurations of the isolated diastereomers were assigned on the basis of NMR studies of compound **8a**. An NOE correlation was observed between H2 and H12b; thus, **8a** was determined to have a *cis*-H2/H12b relative stereochemistry. The absolute stereochemistry of **8a** was confirmed by spectroscopic comparison of its $LiAlH_4$ reduced derivative (2-epidevinylantirhine, **11**) with 12b-epidevinylantirhine (*ent*-**11**) previously reported in the literature (Scheme

Scheme 2. Syntheses of Imine Diesters

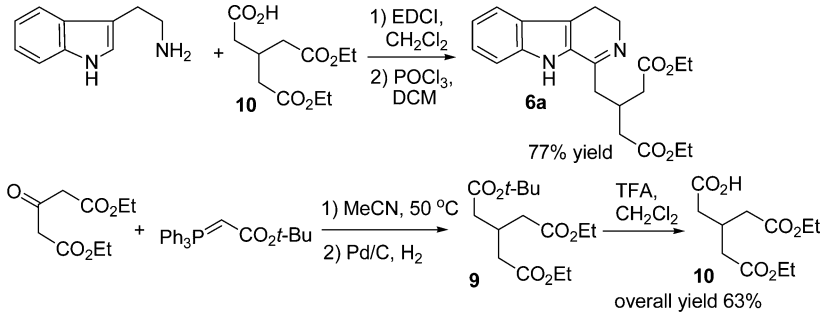


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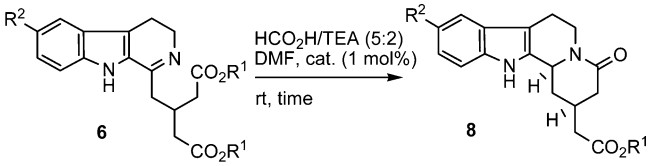
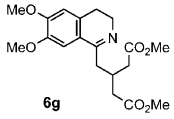
Table 2. Expanding the Substrate Scope



entry	R^1, R^2, **6**	**8**	time	yield (%)[b]	ee (%)[c]
1	Et, H, **6a**	**8a**	4 h	92	98
2	Et, Me, **6b**	**8b**	4 h	68	99
3	Et, MeO, **6c**	**8c**	7 h	70	99
4	Et, Br, **6d**	**8d**	4 h	82	98
5	Me, Br, **6e**	**8e**	3 h	74	99
6	Me, MeO, **6f**	**8f**	3 h	73	98
7		**8g**	6 h	81	98

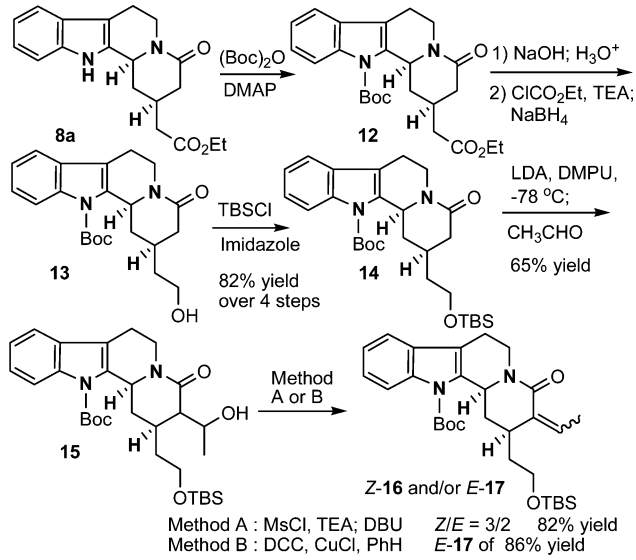
[a]Yield referred to isolated pure product. [b]Enantiomeric excess of **8** was determined by HPLC analysis on a chiral stationary phase.

3).[15] The ^{1}H NMR data of **11** matched those of previously reported 12b-epidevinylantirhine, while the optical rotation of **11** was opposite in sign to that of 12b-epidevinylantirhine.[15a] Thus, the absolute configuration of **8a** was determined to be 2*S*,12b*S*.

To demonstrate the synthetic utility of present methodology in the synthesis of corynantheine alkaloids, dihydocorynantheol (**1**), geissoschizol (**4**), and isogeissoschizol (**5**) were chosen as our targets.[16] Our synthesis of these alkaloids commenced with conversion of **8a** to **14** through a four-step sequence (Scheme 4). The indolyl nitrogen in **8a** was first protected with a Boc group to furnish **12**, and then the ester in **12** was saponified and the crude acid was used directly in the next step; the crude carboxylic acid reacted with ethyl chloroformate to afford a mixed anhydride which was reduced with $NaBH_4$ to furnish alcohol **13**, silylation of which delivered silyl ether **14** in an overall yield of 82% from **8a**.

Deprotonation of lactam **14** and addition of the resulting enolate to acetaldehyde gave aldol adduct **15** in 65% yield (Scheme 4). No further attempt was made to confirm the absolute stereochemistry of **15**, as the secondary alcohol at the side chain was to be eliminated to afford α,β-unsaturated lactamide in a subsequent dehydration. A close examination of

Scheme 4. Synthesis of *Z*-16 and *E*-17

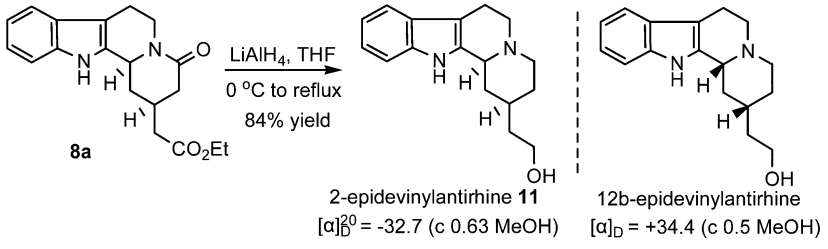


the literature revealed that dehydration of β-hydroxyl lactams similar to **15** furnished the *exo* ethylidenyl side chain in various *Z*/*E* ratios.[17] In our study, an antielimination[18] sequence (CH_3SO_2Cl, DBU) led to the two separable isomers *Z*-**16** and *E*-**17** in an approximate ratio of 3/2; on the other hand, although the unambiguous stereochemical assignment for the aldol adduct **15** was not yet available, if the *syn* elimination[19] procedure was carried out by treatment with DCC and CuCl in benzene, the *E* isomer was obtained exclusively. The olefinic protons in *Z*-**16** and *E*-**17** were distinguishable by ^{1}H NMR. The olefinic proton of *Z*-**16** appeared at 5.89 ppm, while the olefinic proton of *E*-**17** was shifted downfield to 6.67 ppm. This pattern is in line with reports of NMR spectroscopic data of geometrical isomers of similar indolo[2,3-*a*]quinolizidines.[20]

With *Z*-**16** and *E*-**17** bearing the frameworks of isogeissoschizol and geissoschizol, respectively, in hand, reduction of the lactam group became our focus. To our delight, when it was subjected to reduction with DIBAL-H, *Z*-**16** was readily reduced to amine **18** in a yield of 83% (Scheme 5). Cleavage of the silyl ether by treating **18** with TBAF and subsequent removal of the Boc group by K_2CO_3 in refluxing methanol afforded isogeissoschizol (**5**) with a (*Z*)-ethylidenyl group at C3. To the best of our knowledge, this is the first synthesis of isogeissoschizol ever since its isolation from *Aspidosperna marcgrarianum* by Jousselin et al.[16] ^{1}H NMR spectra and optical rotation of our synthetic isogessoschizol (**5**) matched well those reported for the natural product.

In sharp contrast, in the case of *E*-**17**, no reduction product was observed when it was subjected to DIBAL-H under cryogenic conditions, and it resulted in an unidentified mixture

Scheme 3. Conversion of 8a to 2-Epidevinylantirhine (11)



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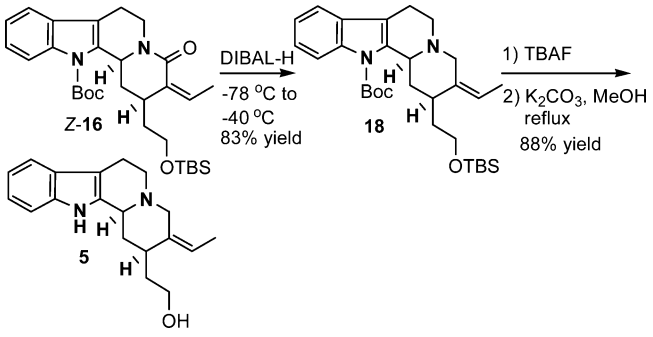
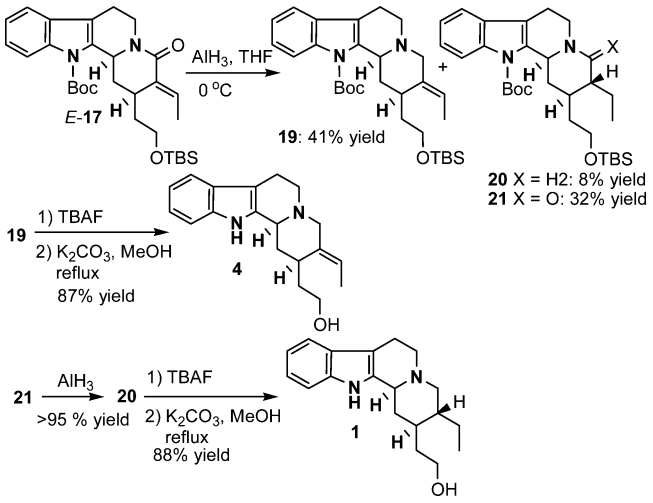
Scheme 5. Synthesis of Isogeissoschizol (5)



at elevated temperatures (0 °C to room temperature). After many attempts, it was finally found that *E*-**17** reacted smoothly with freshly prepared alane solution in THF to afford the amines **19** and **20**, together with amide **21**, in a ratio of 5/1/4 (Scheme 6). Both **19** and **20** could be used in alkaloid

Scheme 6. Synthesis of Dihydrocorynantheol (1) and Geissoschizol (4)



synthesis, while amide **21** could be readily coverted to amine **20** quantitatively. Amines **19** and **20** were deprotected following prior procedures to furnish geissoschizol (**4**) and dihydrocorynantheol (**1**) in overall yields of 87% and 88%, respectively. The spectral data and optical rotation of our synthetic geissoschizol (**4**) and dihydrocorynantheol (**1**) were in accordance with those reported in the literature.[8i,r−t,9c]

CONCLUSION

We have developed a highly efficient cascade sequence for the asymmetric synthesis of indoloquinolizidines with complete control of *cis*-H2/H12b relative geometry in good to excellent yields and excellent enantioselectivities. This cascade was initiated through Noyori ATH of imino diester substrates using Ru^{II}−TsDPEN as the catalyst, followed by spontaneous lactamization with discrimination of two diastereotopic 2-alkoxy-2-oxoethyl chains. The synthetic utility of this strategy was demonstrated by asymmetric synthesis of dihydrocorynantheol (**1**), geissoschizol (**4**), and isogeissoschizol (**5**).

EXPERIMENTAL SECTION

General Information. Thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) or iodine. Flash column chromatography was performed on silica gel H (10−40 μm). ^{1}H NMR spectras were recorded at 500 MHz, and ^{13}C NMR spectras were recorded at 125 MHz. Chemical shifts (δ) are given in ppm relative to TMS, with coupling constants (J) in Hz. High-resolution mass spectra were recorded by FTMS. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

Synthesis of 5-Ethoxy-3-(2-ethoxy-2-oxoethyl)-5-oxopentanoic Acid (10). Dimethyl acetone-1,3-dicarboxylate (4.04 g, 20 mmol, 1.0 equiv) was added to a solution of *tert*-butyl ester phosphorus ylide (11.3 g, 30 mmol, 1.5 equiv) in 45 mL acetonitrile. The solution was heated to 55 °C overnight. After the mixture was cooled to room temperature, the acetonitrile was removed in vacuo and the residue was diluted with Et_2O. The solution was filtered through a silica plug and eluted with additional Et_2O. Purification of the crude oil by silica chromatography (1/2 EA/hexane) yielded the olefin triester (5.3 g, 17.7 mmol) as a yellow oil. A portion of 5% Pd/C (500 mg) was added to a solution of olefin triester (5.3 g, 17.7 mmol, 1.0 equiv) in 20 mL of MeOH. The flask was evacuated and purged with H_2, and then the contents were stirred in an atmosphere of H_2 at room temperature overnight. The Pd/C was removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo to yield triester **9** as a clear oil which was used directly in the next step. Triester **9** was dissolved in dichloromethane (30 mL) followed by slow addition of 5 mL of TFA via a syringe over 20 min. After complete comsumption of triester as followed by TLC, the reaction was quenched by a solution of 5.4 g of NaOAc in 30 mL of water. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford pure acid diester **10** (3.1 g, 12.6 mmol) as a light yellow oil in a yield of 63% over three steps.

*Diethyl 3-(2-tert-butoxy-2-oxoethyl)pentanedioate (**9**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 4H), 2.73 (s, 1H), 2.45 (d, J = 6.7 Hz, 4H), 2.36 (d, J = 6.7 Hz, 2H), 1.44 (s, 9H), 1.25 (t, J = 7.1 Hz, 6H).

*5-Ethoxy-3-(2-ethoxy-2-oxoethyl)-5-oxopentanoic acid (**10**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (q, J = 7.1 Hz, 4H), 2.81−2.72 (m, 1H), 2.54 (d, J = 6.6 Hz, 2H), 2.48 (d, J = 6.7 Hz, 4H), 1.25 (t, J = 8.6 Hz, 5.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 171.9, 60.5, 37.6, 37.4, 28.5, 14.1; HRMS (ESI) calcd for $(C_{11}H_{18}NaO_6)^+$ 269.0996, found 269.0991.

General Procedure for Preparation of Imine Diester Derivatives 6. To a solution of tryptamine (0.65 g, 4.1 mmol) and acid diester **9** (1.0 g, 4.0 mmol) in dichloromethane (30 mL) at 0 °C was added EDCI (0.86 g, 4.5 mmol). The reaction mixture was stirred at room temperature for 5 h and then washed with 5% aqueous HCl (15 mL), 5% aqueous $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the pure amide diester (1.25 g, 3.22 mmol) as a white solid (79% yield).

To a stirred solution of amide diester (1.25 g, 3.22 mmol) in dichloromethane (50 mL) was added phosphoryl chloride (3.0 mL, 32 mmol) at room temperature. The resulting pale yellow solution was heated to reflux overnignt. After it was cooled to room temperature, the reaction mixture was concentrated by evaporation under reduced pressure. The residue was diluted with dichloromethane, poured into saturated aqueous $NaHCO_3$, and extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford pure amide diester **6a** (1.15 g, 3.11 mmol) as a yellow solid in an overall yield of 77%.

*Diethyl 3-((4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl)-pentanedioate (**6a**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.25 (s, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.51−7.46 (m, 1H),

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7.23 (t, J = 7.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 4H), 4.02 (m, 2H), 3.27 (t, J = 8.9 Hz, 2H), 3.18 (d, J = 6.1 Hz, 2H), 2.84 (d, J = 6.0 Hz, 1H), 2.65 (m, 4H), 1.27 (dt, J = 12.0 Hz, 5.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 167.7, 141.2, 129.1, 125 0.7, 124.5, 124.3, 121.9, 121.5, 113.6, 61.2, 42.5, 38.1, 36.7, 31.3, 19.2, 14.0; HRMS (ESI) calcd for $(C_{21}H_{27}N_2O_4)^+$ 371.1965, found 371.1973.

*Diethyl 3-((6-methyl-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-methyl)pentanedioate (**6b**):* This compound was prepared according to the general procedure and isolated as a yellow solid (0.892 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.39−7.34 (m, 2H), 7.16 (d, J = 8.3 Hz, 1H), 4.16 (dd, J = 14.0 Hz, 6.9 Hz, 4H), 3.90 (t, J = 8.6 Hz, 2H), 2.94 (t, J = 8.6 Hz, 2H), 2.89−2.69 (m, 3H), 2.61−2.47 (m, 4H), 2.42 (d, J = 14.8 Hz, 3H), 1.25 (d, J = 4.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 136.7, 129.9, 128.0, 127.5, 125.1, 119.6, 112.4, 61.0, 46.1, 39.0, 37.8, 30.3, 29.7, 29.5, 19.2, 14.2; HRMS (ESI) calcd for $(C_{22}H_{29}N_2O_4)^+$ 385.2122, found 385.2114.

*Diethyl 3-((6-methoxy-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-methyl)pentanedioate (**6c**):* This compound was prepared according to the general procedure and isolated as a yellow solid (1.036 g, 81%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.16 (s, 1H), 7.43 (d, J = 9.1 Hz, 1H), 7.15 (dd, J = 9.1 Hz, 2.3 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 4.23−4.14 (m, 4H), 4.02 (t, J = 8.4 Hz, 2H), 3.87 (s, 3H), 3.26 (d, J = 6.2 Hz, 2H), 3.21 (t, J = 8.9 Hz, 2H), 2.82 (d, J = 7.1 Hz, 1H), 2.66 (m, 4H), 1.28 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 168.0, 154.3, 133.6, 131.2, 127.2, 112.2, 111.6, 109.3, 100.4, 60.7, 55.9, 39.9, 38.3, 34.9, 28.2, 20.9, 14.2; HRMS (ESI) calcd for $(C_{22}H_{29}N_2O_5)^+$ 401.2071, found 401.2065.

*Diethyl 3-((6-bromo-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-methyl)pentanedioate (**6d**):* This compound was prepared according to the general procedure and isolated as a yellow solid (0.954 g, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.74 (s, 1H), 7.76 (s, 1H), 7.51−7.43 (m, 2H), 4.18−4.06 (m, 4H), 4.00 (t, J = 8.7 Hz, 2H), 3.25 (d, J = 6.1 Hz, 2H), 3.18 (t, J = 8.8 Hz, 2H), 2.90−2.78 (m, 1H), 2.64 (m, 4H), 1.27−1.17 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 168.2, 139.4, 132.0, 125.5, 125.7, 123.8, 122.8, 121.4, 115.2, 61.3, 42.4, 38.2, 36.6, 31.1, 19.0, 14.0; HRMS (ESI) calcd for $(C_{21}H_{26}BrN_2O_4)^+$ 449.1070, found 449.1083.

*Dimethyl 3-((6-bromo-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-methyl)pentanedioate (**6e**):* This compound was prepared according to the general procedure and isolated as a yellow solid (0.914 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.97 (s, 1H), 7.75 (s, 1H), 7.48 (q, J = 8.6 Hz, 2H), 3.99 (s, 2H), 3.62 (d, J = 12.3 Hz, 6H), 3.20 (d, J = 7.2 Hz, 4H), 2.87 (s, 1H), 2.74−2.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 168.7, 139.7, 132.1, 125.6, 125.7, 123.7, 123.0, 115.4, 115.2, 52.1, 42.6, 38.0, 37.0, 31.2, 19.0; HRMS (ESI) calcd for $(C_{19}H_{22}BrN_2O_4)^+$ 421.0757, found 421.0764.

*Dimethyl 3-((6-methoxy-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-methyl)pentanedioate (**6f**):* This compound was prepared according to the general procedure and isolated as a yellow solid (0.558 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.50 (s, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.36(s, 1H), 7.26 (t, J = 4.3 Hz, 1H), 3.96 (t, J = 7.8 Hz, 2H), 3.63 (s, 6H), 3.19 (dd, J = 10.3 Hz, 6.9 Hz, 4H), 2.85 (d, J = 6.6 Hz, 1H), 2.63 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 167.7, 140.1, 131.8, 131.6, 125.7, 124.6, 123.9, 120.3, 113.4, 52.1, 42.5, 37.9, 36.7, 31.3, 21.4, 19.3; HRMS (ESI) calcd for $(C_{20}H_{25}N_2O_5)^+$ 373.1758, found 373.1764.

*Dimethyl 3-((6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)methyl)-pentanedioate (**6g**):* This compound was prepared according to the general procedure and isolated as a yellow solid (0.544 g, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.67 (s, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.63 (s, 6H), 3.62 (d, J = 7.7 Hz, 2H), 2.85−2.74 (m, 3H), 2.60 (t, J = 8.06 Hz, 2H), 2.48−2.40 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 165.3, 150.8, 147.7, 131.3, 121.4, 110.4, 109.4, 56.4, 55.9, 51.5, 46.8, 40.6, 37.9, 30.1, 25.7; HRMS (ESI) calcd for $(C_{19}H_{26}NO_6)^+$ 364.1755, found 364.1746.

General Procedure for Asymmetric Catalyzed Hydrogenation/Lactamization. To a stirred solution of the imine **6a** (185 mg, 0.5 mmol) in DMF (1 mL) at room temperature was added a HCOOH/Et_3N mixture (5/2, 70 μL) followed by (*R*,*R*)-TsDPEN−Ru^{II} catalyst (3.2 mg, 0.005 mmol). The reaction mixture was stirred for 4 h and quenched with saturated aqueous Na_2CO_3 (10 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with a petroleum ether and ethyl acetate mixture as eluent to afford the pure product **8a** as a light green solid (149 mg, 0.457 mmol) in a yield of 92% with 99% ee.

*Ethyl 2-((2S,12bS)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**8a**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 5.22−5.09 (m, 1H), 4.84−4.79 (m, 1H), 4.22−4.13 (m, 2H), 2.91−2.73 (m, 3H), 2.72−2.65 (m, 1H), 2.62−2.57 (m, 1H), 2.53−2.44 (m, 1H), 2.40 (dd, J = 15.9 Hz, 5.6 Hz, 1H), 2.30 (dd, J = 15.9 Hz, 8.0 Hz, 1H), 2.13 (dd, J = 17.3 Hz, 12.2 Hz, 1H), 1.50 (q, J = 12.2 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 168.2, 136.3, 132.9, 126.7, 122.1, 119.7, 118.3, 111.0, 109.1, 60.8, 53.8, 39.9, 38.3, 34.9, 28.3, 21.0, 14.2; HRMS (ESI) calcd for $(C_{19}H_{23}N_2O_3)^+$ 327.1703, found 327.1714; $[\alpha]^{25}_D$ −60.25° (c 0.33, $CHCl_3$); HPLC (phenomenex amylose-2, hexane/2-propanol 9/1, flow rate 1.0 mL/min, λ 220 nm) t_R = 17.675 min (minor enantiomer), t_R = 15.834 min (major enantiomer).

*Ethyl 2-((2S,12bS)-9-methyl-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**8b**):* This compound was prepared according to the general procedure from **6b** (0.192 g, 0.5 mmol), and isolated as a light green solid (0.115 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.28 (s, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 5.19−5.10 (m, 1H), 4.83−4.76 (m, 1H), 4.20−4.13 (m, 2H), 2.88−2.64 (m, 4H), 2.60−2.53 (m, 1H), 2.51- 2.45 (m, 1H); 2.44 (s, 3H), 2.38 (dd, J = 15.8 Hz, 5.8 Hz, 1H), 2.29 (dd, J = 15.8 Hz, 8.1 Hz, 1H), 2.12 (dd, J = 17.3 Hz, 12.2 Hz, 1H), 1.48 (q, J = 12.2 Hz, 1H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 168.1, 134.6, 133.0, 129.1, 127.0, 123.7, 118.1, 110.6, 108.8, 60.7, 53.8, 39.9, 38.7, 34.9, 28.3, 21.4, 21.0, 14.2; $[\alpha]^{25}_D$ −31.50° (c 0.27, $CHCl_3$); HRMS (ESI) calcd for $(C_{20}H_{25}N_2O_3)^+$ 341.1860, found 341.1868; HPLC (phenomenex amylose-2, hexane/2-propanol 19/1, flow rate 1.0 mL/min, λ 220 nm) t_R = 16.475 min (minor enantiomer), t_R = 13.999 min (major enantiomer).

*Ethyl 2-((2S,12bS)-9-methoxy-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**8c**):* This compound was prepared according to the general procedure from **6c** (0.200 g, 0.5 mmol), and isolated as a light green solid (0.125 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 5.19−5.10 (m, 1H), 4.83−4.76 (m, 1H), 4.21−4.12 (m, 2H), 3.85 (s, 3H), 2.90−2.63 (m, 4H), 2.59−2.52 (m, 1H), 2.50−2.43 (m, 1H), 2.40 (dd, J = 15.8 Hz, 5.6 Hz, 1H), 2.29 (dd, J = 15.8 Hz, 8.2 Hz, 1H), 2.12 (dd, J = 17.3 Hz, 12.2 Hz, 1H), 1.50 (q, J = 12.2 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 168.0, 154.3, 133.6, 131.2, 127.2, 112.2, 111.6, 109.3, 100.4, 65.7, 60.7, 55.9, 53.8, 39.9, 38.3, 34.9, 28.2, 21.0, 14.2; $[\alpha]^{25}_D$ −6.25° (c 0.48, $CHCl_3$); HRMS (ESI) calcd for $(C_{20}H_{25}N_2O_4)^+$ 357.1809, found 357.1822; HPLC (phenomenex cellulose-1, hexane/2-propanol 19/1, flow rate 1.0 mL/min, λ 220 nm) t_R = 20.235 min (minor enantiomer), t_R = 18.552 min (major enantiomer).

*Ethyl 2-((2S,12bS)-9-bromo-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**8d**):* This compound was prepared according to the general procedure from **6d** (0.224 g, 0.5 mmol), and isolated as a light green solid (0.166 g, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.24 (dd, J = 8.6 Hz, 1.4 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 5.18−5.11 (m, 1H), 4.84−4.77 (m, 1H), 4.22−4.06 (m, 2H), 2.90−2.64 (m, 4H), 2.63−2.56 (m, 1H), 2.52−2.43 (m, 1H), 2.40 (dd, J = 15.8 Hz, 5.6 Hz, 1H), 2.29 (dd, J = 15.8 Hz, 8.2 Hz, 1H), 2.13 (dd, J = 17.3 Hz, 12.2 Hz, 1H), 1.50 (q, J = 12.2 Hz, 1H), 1.26 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 168.1, 134.9, 134.2, 128.5, 124.9, 121.1, 112.9, 112.4, 109.1, 60.8, 53.7, 39.85, 39.80, 38.3, 34.8, 28.2, 20.8, 14.2; $[\alpha]^{25}_D$ −8.3° (c 0.50, $CHCl_3$); HRMS (ESI) calcd for $(C_{19}H_{22}BrN_2O_3)^+$ 405.0808, found 405.0812; HPLC (phenomenex amylose-2, hexane/2-propanol 19/1, flow rate 1.0 mL/min, λ 220 nm)

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t_R = 12.882 min (minor enantiomer), t_R = 5.825 min (major enantiomer).

*Methyl 2-((2S,12bS)-9-bromo-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**8e**):* This compound was prepared according to the general procedure from **6e** (0.210 g, 0.5 mmol) and isolated as a light green solid (0.144 g, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.60 (d, J = 1.7 Hz, 1H), 7.23 (dd, J = 8.6 Hz, 1.8 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 5.19−5.09 (m, 1H), 4.83−4.78 (m, 1H), 3.70 (s, 3H), 2.90−2.74 (m, 2H), 2.74−2.65 (m, 2H), 2.63−2.57 (m, 1H), 2.52−2.44 (m, 1H), 2.41 (dd, J = 15.7 Hz, 5.5 Hz, 1H), 2.30 (dd, J = 15.7 Hz, 8.1 Hz, 1H), 2.18−2.08 (dd, J = 17 Hz, 12.1 Hz, 1H), 1.50 (q, J = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 168.1, 134.9, 134.2, 128.5, 124.9, 121.1, 112.9, 112.4, 109.0, 53.7, 51.8, 39.8, 39.5, 38.3, 34.7, 28.2, 20.8; $[\alpha]^{25}_D$ −31.50 (c 0.27, $CHCl_3$); HRMS (ESI) calcd for $(C_{18}H_{20}BrN_2O_3)^+$ 391.0652, found 391.0660; HPLC (phenomenex amylose-2, hexane/2-propanol 19/1, flow rate 1.0 mL/min, λ 220 nm) t_R = 6.297 min (minor enantiomer), t_R = 11.275 min (major enantiomer).

*Methyl 2-((2S,12bS)-9-methoxy-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**8f**):* This compound was prepared according to the general procedure from **6f** (0.186 g, 0.5 mmol), and isolated as a light green solid (0.124 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.28 (s, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.00 (dd, J = 8.2 Hz, 1.2 Hz, 1H), 5.18−5.09 (m, 1H), 4.82−4.76 (m, 1H), 3.71 (s, 3H), 2.89−2.70 (m, 3H), 2.70−2.63 (m, 1H), 2.62−2.52 (m, 1H), 2.50−2.44 (m, 1H), 2.43 (s, 3H), 2.42−2.36 (m, 1H), 2.30 (dd, J = 15.7 Hz, 8.2 Hz, 1H), 2.12 (dd, J = 17.3 Hz, 12.1 Hz, 1H), 1.48 (q, J = 12.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 168.0, 134.5, 132.9, 129.1, 127.0, 123.7, 118.1, 110.6, 108.9, 53.8, 51.7, 39.9, 39.6, 38.3, 34.9, 28.3, 21.4, 21.0; $[\alpha]^{25}_D$ −41.5° (c 0.47, $CHCl_3$); HRMS (ESI) calcd for $(C_{19}H_{23}N_2O_4)^+$ 343.1652, found 343.1661; HPLC (phenomenex cellulose-1, hexane/2-propanol 19/1, flow rate 1.0 mL/min, λ 220 nm): t_R = 16.53 min (minor enantiomer), t_R = 8.30 min (major enantiomer).

*Methyl 2-((2R,11bR)-9,10-dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate (**8g**):* This compound was prepared according to the general procedure from **6g** (0.182 g, 0.5 mmol), and isolated as a light green solid (0.134 g, 81%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.58 (s, 1H), 4.84−4.81(m, 1H), 4.65 (dd, J = 11.3 Hz, 4.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.68 (s, 3H), 2.88−2.75 (m, 2H), 2.65−2.54 (m, 3H), 2.47−2.40 (m, 1H), 2.34 (d, J = 6.8 Hz, 2H), 2.05 (dd, J = 16.8 Hz, 12.7 Hz, 1H), 1.48 (q, J = 12.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 168.1, 147.8, 147.7, 128.6, 127.1, 111.5, 108.2, 56.2, 56.1, 55.9, 51.7, 39.9, 39.5, 38.1, 37.0, 28.5; $[\alpha]^{25}_D$ −48.3° (c 0.60, $CHCl_3$); HRMS (ESI) calcd for $(C_{18}H_{24}NO_5)^+$ 334.1649, found 334.1657; HPLC (phenomenex amylose-2, hexane/2-propanol 19/1, flow rate 1.0 mL/min, λ 220 nm) t_R = 16.53 min (minor enantiomer), t_R = 8.30 min (major enantiomer).

Synthesis of 2-Epidevinylantirhine (11). To a solution of **8a** (100 mg, 0.30 mmol) in dry THF (8 mL) at 0 °C was added $LiAlH_4$ (76 mg, 2 mmol) in portions. The solution was warmed to reflux and followed by TLC. After 12 h, the reaction mixture was cooled to 0 °C and quenched with successive addition of 76 μL of H_2O, 76 μL of 15% NaOH solution, and 222 μL of H_2O. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford **11** (71 mg, 0.263 mmol) as a pale yellow solid in a yield of 84%.

*2-Epidevinylantirhine (**11**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 3.69 (t, J = 6.5 Hz, 1H), 3.57 (d, J = 12.5 Hz, 1H), 3.18−3.10 (m, 1H), 3.09−2.95 (m, 2H), 2.77−2.62 (m, 2H), 2.54−2.47 (m, 1H), 2.44−2.37 (m, 1H), 1.87−1.73 (m, 2H), 1.61−1.54 (m, 2H), 1.50−1.39 (m, 2H), 1.23 (t, J = 8.0 Hz, 1H); $[\alpha]^{25}_D$ −32.7° (c 0.63, MeOH).

Synthesis of 14. To a solution of **8a** (1.3 g, 4.0 mmol) in anhydrous CH_2Cl_2 (40 mL) were added Boc_2O (1.48 g, 6.8 mmol) and DMAP (97 mg, 0.8 mmol). The resulting mixture was stirred at room temperature for 4 h. Saturated brine (20 mL) was added to quench the reaction. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford the crude product **12** as a yellow solid, which was used directly in the next step.

Crude ester **12** obtained above was dissolved in THF (15 mL). After the mixture was cooled with an ice−water bath for 10 min, a solution of LiOH (0.384 g, 16 mmol) in H_2O (5 mL) was added dropwise, and the resulting mixture was stirred for 4 h at room temperature. The reaction mixture was then acidified with 1 N HCl (pH 3), and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue dried for 12 h under high vacuum to yield the carboxylic acid product as a yellow solid and was used as such without further purification.

The crude acid was dissolved in dry THF (15 mL). After addition of TEA (0.63 mL, 5 mmol), the mixture was cooled with an ice−salt bath for 20 min. A solution of ethyl chloroformate (0.864 g, 8 mmol) in dry THF (5 mL) was added dropwise and stirred for 30 min at room temperature. Then the reaction mixture was cooled with an ice−salt bath again for 20 min. $NaBH_4$ (0.76 g, 20 mmol) was added in one portion followed by dropwise addtition of methanol until the complete consumption of the anhydride. The solution was acidified carefully with 1 N HCl. The mixture was extracted three times with CH_2Cl_2, and the combined extracts were washed with water, 1 N NaOH, and water and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded crude alcohol **13** as a yellow solid, which was used directly in the next step.

Alcohol **13** was dissolved in a minimum amout of dry DMF (6 mL). After the mixture was cooled with an ice−water bath for 10 min, *tert*-butyldimethylchlorosilane (1.2 g, 8 mmol) and imidazole (1.088 g, 16 mmol) were added successively. The reaction mixture was stirred at room temperature and followed by TLC. After complete consumption of alcohol **13**, the solution was diluted with Et_2O. Saturated brine was added, and the organic layer was separated. The aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford pure TBS-ether **14** (1.63 g, 3.27 mmol) as a white solid in an overall yield of 82%.

*(2R,12bS)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-4-oxo-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12(12bH)-carboxylate (**14**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.33−7.28 (m, 1H), 7.25−7.22 (m, 1H), 5.20−5.03 (m, 2H), 3.75−3.60 (m, 2H), 2.87−2.78 (m, 1H), 2.78−2.64 (m, 3H), 2.61 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 2.23−2.12 (m, 1H), 2.07 (dd, J = 17.1 Hz, 11.5 Hz, 1H), 1.68 (s, 9H), 1.62−1.53 (m, 1H), 1.52−1.44 (m, 1H), 1.183 (q, J = 11.5 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 150.1, 136.9, 135.0, 128.6, 124.6, 123.0, 118.36, 118.31, 115.4, 84.2, 59.9, 55.8, 39.4, 38.9, 38.7, 36.6, 28.2, 27.9, 25.9, 21.7, 18.3, −5.2, −5.3; $[\alpha]_D^{18}$ −122.3° (c 0.3, EtOH); HRMS (ESI) calcd for $(C_{28}H_{42}N_2O_4SiNa)^+$ 521.2806, found 521.2810.

Synthesis of 15. TBS-ether **14** (1.0 g, 2 mmol) was dissolved in dry THF (20 mL) and then cooled to −78 °C. Freshly prepared LDA (7 mmol) in mixed solvents of THF and hexane was added dropwise. The mixture was stirred at −78 °C for 30 min. Then dimethylpropyleneurea (DMPU; 0.36 mL, 3 mmol) was added followed by dropwise addition of a solution of acetaldehyde (0.88 g, 20 mmol) in dry THF (5 mL). The reaction mixture was stirred for 3 h at −78 °C. Saturated NH_4Cl (20 mL) was added, and the cold bath was removed. After the reaction mixture was warmed to room temperature, the organic layer was separated and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford alcohol **15** as a white solid (704 mg, 1.3 mmol) in a yield of 65%.

*(2R,12bS)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-(1-hydroxyethyl)-4-oxo-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12(12bH)-carboxylate (**15**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J

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= 8.3 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.35−7.31 (m, 1H), 7.29−7.26 (m, 1H), 5.17−5.11 (m, 2H), 4.07−3.97 (m, 2H), 3.75−3.65 (m, 2H), 2.88−2.82 (m, 1H), 2.80−2.74 (m, 2H), 2.63−2.59 (m, 1H), 2.33−2.30 (m, 1H), 2.14−2.09 (m, 1H), 1.91−1.85 (m, 1H), 1.72 (s, 9H), 1.51−1.44 (m, 1H), 1.42 (d, J = 6.3 Hz, 3H), 1.21−1.14 (m, 1H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 150.1, 136.6, 134.5, 128.5, 124.6, 123.0, 118.3, 117.9, 115.7, 84.3, 70.1, 60.5, 54.2, 54.1, 39.5, 38.9, 37.2, 30.5, 28.2, 25.9, 21.6, 21.3, 18.3, −5.3; HRMS (ESI) calcd for $(C_{30}H_{46}N_2O_5SiNa)^+$ 565.3068, found 565.3077.

Synthesis of *Z*-16 and/or *E*-17. *Method A.* To an ice-cold solution of alcohol **13** (325 mg, 0.60 mmol) in dry CH_2Cl_2 (10 mL) was added TEA (265 uL, 2.1 mmol) followed by methanesulfonyl chloride (138 uL, 1.8 mmol). The mixture was stirred for 4 h at 0 °C. After this time, saturated NH_4Cl (20 mL) was added and the mixture was extracted three times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concetrated in vacuo to afford crude mesylate as a yellow solid, which was used directly in the next step. The residue obtained above was dissolved in dry THF (6 mL), and DBU (438 uL, 3 mmol) was added. Then the mixture was refluxed and followed by TLC. The reaction mixture was cooled, diluted with water, and extracted three times with EA, and the extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford *Z*-**16** (156 mg, 0.298 mmol) and the less polar *E*-**17** (100 mg, 0.190 mmol) as a white solid in a combined yield of 82%.

Method B. To a solution of alcohol **13** (325 mg, 0.60 mmol) in dry toluene (18 mL) were added DCC (618 mg, 3 mmol) and cuprous chloride (588 mg, 6 mmol), and the reaction mixture was heated to reflux overnight. After this time, the mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford *E*-**17** (265 mg, 0.506 mmol) as a white solid in a yield of 86%.

*(2R,12bS,Z)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-ethylidene-4-oxo-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12-(12bH)-carboxylate (Z-**16**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.2 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H), 7.32−7.24 (m, 2H), 5.89 (q, J = 6.7 Hz, 1H), 5.06 (d, J = 9.8 Hz, 1H), 4.98 (dd, J = 12.7 Hz, 4.1 Hz, 1H), 3.65−3.54 (m, 2H), 2.94−2.82 (m, 3H), 2.76−2.63 (m, 2H), 2.04 (d, J = 6.7 Hz, 3H), 1.68 (s, 9H), 1.61−1.66 (m, 1H), 1.56−1.51 (m, 1H), 1.26−1.20 (m, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 150.0, 136.6, 134.6, 134.4, 133.7, 128.5, 124.5, 122.9, 118.2, 117.3, 115.7, 84.3, 60.1, 52.7, 39.9, 38.2, 37.9, 35.2, 28.2, 25.9, 20.9, 18.2, 15.3, −5.2, −5.3; $[\alpha]_D^{18}$ −129.3° (c 1.25, EtOH); HRMS (ESI) calcd for $(C_{30}H_{45}N_2O_4Si)^+$ 525.3143, found 525.3146.

*(2R,12bS,E)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-ethylidene-4-oxo-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12-(12bH)-carboxylate (E-**17**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.37−7.24 (m, 2H), 6.67 (q, J = 7.1 Hz, 1H), 5.06−4.96 (m, 2H), 3.65−3.61 (m, 1H), 3.58−3.54 (m, 1H), 3.35−3.27 (m, 1H), 2.95−2.83 (m, 2H), 2.73−2.68 (m, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.85−1.78 (m, 1H), 1.71 (s, 9H), 1.45−1.39 (m, 1H), 1.36−1.29(m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 150.0, 136.5, 135.9, 134.4, 133.6, 128.5, 124.5, 123.0, 118.2, 117.3, 115.8, 84.3, 59.9, 52.1, 39.7, 38.3, 38.1, 29.3, 28.2, 25.9, 20.9, 18.2, 13.8, −5.3; $[\alpha]_D^{18}$ −86.4° (c 1.07, EtOH); HRMS (ESI) calcd for $(C_{30}H_{45}N_2O_4Si)^+$ 525.3143, found 525.3146.

Synthesis of 18. To a solution of *Z*-**16** (156 mg, 0.30 mmol) in dry DME (12 mL) at −78 °C was added DIBAL-H (1 M, toluene, 1.5 mL) dropwise. The solution was warmed slowly to −40 °C over 1.5 h. The reaction was quenched with a small amount of saturated Na_2SO_4 and warmed to room temperature. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford **18** (125 mg, 0.245 mmol) as a pale yellow solid in a yield of 83%.

*(2R,12bS,Z)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-ethylidene-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12-(12bH)-carboxylate (**18**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.29−7.26 (m, 1H), 7.24−7.21 (m, 1H), 5.42 (q, J = 6.7 Hz, 1H), 4.60 (d, J = 10.5 Hz, 1H), 3.99 (d, J = 13.8 Hz, 1H), 3.75−3.71 (m, 2H), 3.35 (d, J = 13.8 Hz, 1H), 3.11−3.05 (m, 1H), 2.91−2.82 (m, 1H), 2.79−2.74 (m, 2H), 2.46−2.36 (m, 1H), 2.23−2.19 (m, 1H), 1.99−1.94 (m, 1H), 1.74 (d, J = 6.7 Hz, 3H), 1.70 (s, 9H), 1.51−1.41 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 136.9, 136.5, 136.0, 129.3, 123.8, 122.6, 117.9, 116.3, 115.7, 114.7, 83.6, 61.3, 57.5, 55.4, 44.3, 38.2, 35.8, 35.0, 28.3, 26.0, 21.9, 18.4, 12.9, −5.2; $[\alpha]_D^{22.3}$ −59.2° (c 0.24, $CHCl_3$); HRMS (ESI) calcd for $(C_{30}H_{47}N_2O_3Si)^+$ 511.3350, found 511.3354.

Synthesis of Isogeissoschizol (5). To a solution of **16** (120 mg, 0.235 mmol) in dry THF (5 mL) at room temperature was added TBAF (1 M in THF, 0.7 mL, 0.7 mmol). The reaction mixture was stirred at room temperature and followed by TLC. After complete consumption of **16**, the reaction was quenched with water. The resulting mixture was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was dissovlved in a mixed MeOH/H_2O solvent (3/1, 4 mL). To the resulting mixture was added K_2CO_3 (2.3 mmol), and the mixture was refluxed overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine and dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with CH_2Cl_2/MeOH (20/1) as eluent to afford isogeissoschizol (**5**; 61 mg, 0.206 mmol) as a pale yellow solid in a yield of 88% over two steps.

*Isogeissoschizol **5**:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (br, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.17−7.13 (m, 1H), 7.11−7.08 (m, 1H), 5.35 (q, J = 6.6 Hz, 1H), 3.92 (d, J = 12.1 Hz, 1H), 3.85−3.82 (m, 2H), 3.49 (d, J = 10.9 Hz, 1H), 3.19−3.15 (m, 1H), 3.06−2.99 (m, 1H), 2.76 (d, J = 12.9 Hz, 2H), 2.73−2.67 (m, 1H), 2.45−2.35 (m, 1H), 2.28−2.24 (m, 1H), 2.11−2.05 (m, 1H), 1.74 (d, J = 6.6 Hz, 3H), 1.73−1.66 (m, 1H), 1.62−1.55 (m, 1H),1.37 (q, J = 11.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 136.1, 134.6, 127.4, 121.3, 119.3, 118.1, 116.3, 110.8, 108.1, 60.6, 59.8, 55.7, 52.7, 37.8, 36.6, 34.3, 21.6, 13.1; $[\alpha]_D^{16.5}$ −27.9° (c 0.33, MeOH); HRMS (ESI) calcd for $(C_{19}H_{25}N_2O)^+$ 297.1961, found 297.1960.

Synthesis of 19−21. A flame-dried round-bottomed flask was charged with $AlCl_3$ (40 mg, 0.30 mmol) and dry THF (3.0 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C, and $LiAlH_4$ (0.9 mmol) was added. After the mixture was stirred for 30 min at 0 °C, a solution of lactam *E*-**15** (315 mg, 0.60 mmol) in dry THF (6 mL) was added via syringe. The reaction mixture was stirred for 45 min at 0 °C, quenched by the addition of saturated aqueous NH_4Cl (10 mL), and extracted three times with ethyl acetate; the combined organic phases were washed with brine and dried with $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford **19** (125 mg, 0.245 mmol), **20** (25 mg, 0.049 mmol), and **21** (101 mg, 0.192 mmol) in a combined yield of 81%.

*(2R,12bS,E)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-ethylidene-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12-(12bH)-carboxylate (**19**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.29−7.26 (m, 1H), 7.25−7.22 (m, 1H), 5.51 (q, J = 7.0 Hz, 1H), 4.60 (d, J = 9.9 Hz, 1H), 3.65−3.61 (m, 2H), 3.48 (d, J = 12.1 Hz, 1H), 3.36 (d, J = 12.1 Hz, 1H), 3.03−2.97 (m, 1H), 2.96−2.89 (m, 1H), 2.89−2.82 (m, 1H), 2.79−2.76 (m, 2H), 2.24−2.17 (m, 1H), 1.84−1.81 (m, 1H), 1.71 (d, J = 7.0 Hz, 3H), 1.68 (s, 9H), 1.65−1.57 (m, 2H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 136.9, 136.7, 129.1, 123.8, 122.5, 121.2, 117.9, 115.5, 115.3, 83.6, 61.1, 59.9, 54.3, 46.7, 37.8, 33.3, 33.2, 28.2, 25.9, 21.2, 18.3, 13.3, −5.2, −5.3; $[\alpha]_D^{20}$ −9.1° (c 0.5,$CHCl_3$); HRMS (ESI) calcd for $(C_{30}H_{47}N_2O_3Si)^+$ 511.3350, found 511.3348.

*(2R,3R,12bS)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-ethyl-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12(12bH)-carboxylate (**20**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.29−7.22 (m, 2H), 3.96 (d, J = 10.6 Hz, 1H), 3.75−3.71 (m, 1H), 3.67−3.62 (m, 1H), 3.20−3.12 (m, 2H),

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2.89−2.84 (m, 1H), 2.81−2.69 (m, 2H), 2.53 (t, J = 12.0 Hz, 1H), 2.24−2.19 (m, 1H), 1.94−1.87 (m, 1H), 1.69 (s, 9H), 1.49−1.47 (m, 2H), 1.39−1.21 (m, 3H), 1.17−1.12 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 137.1, 136.8, 129.3, 123.8, 122.6, 117.9, 115.9, 115.4, 83.6, 61.1, 60.3, 59.3, 48.1, 39.1, 37.5, 36.4, 34.6, 28.2, 25.9, 23.4, 22.3, 18.3, 10.9, −5.2; $[\alpha]_D^{20}$ −55.3° (c 0.43, $CHCl_3$); HRMS (ESI) calcd for $(C_{30}H_{49}N_2O_3Si)^+$ 513.3507, found 513.3510.

*(2R,3R,12bS)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-ethyl-4-oxo-1,2,3,4,6,7-hexahydroindolo[2,3-9a]quinolizine-12-(12bH)-carboxylate (**21**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.34−7.31 (m, 1H), 7.29−7.26 (m, 1H), 5.16−5.10 (m, 2H), 3.74−3.67 (m, 2H), 2.88−2.70 (m, 3H), 2.65−2.58 (m, 1H), 2.23−2.19 (m, 1H), 2.15−2.05 (m, 2H), 1.81−1.76 (m, 1H), 1.72 (s, 10H), 1.38−1.30 (m, 1H), 1.16 (q, J = 12.4 Hz, 1H), 0.95 (t, J = 7.3 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 150.2, 136.8, 135.2, 128.7, 124.5, 122.9, 118.3, 118.2, 115.5, 84.2, 60.3, 54.8, 48.7, 38.9, 38.2, 36.1, 30.7, 28.2, 25.9, 23.2, 21.6, 18.3, 10.0, −5.2; $[\alpha]_D^{20}$ −227.5° (c 0.67, $CHCl_3$); HRMS (ESI) calcd for $(C_{30}H_{47}N_2O_4Si)^+$ 527.3300, found 527.3309.

Synthesis of Geissoschizol (4). Amine **19** (125 mg, 0.245 mmol) was converted to geissoschizol (**4**; 63 mg, 0.213 mmol) in an overall yield of 87% by procedures described above for the synthesis of isogeissoschizol (**5**).

*2-((2R,12bS,E)-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizin-2-yl)ethanol (**4**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.16−7.09 (m, 2H), 5.51 (q, J = 6.9 Hz, 1H), 4.21−4.15 (m, 1H), 3.68−3.61 (m, 2H), 3.57−3.52 (m, 1H), 3.25−3.21 (m, 1H), 3.09−2.93 (m, 4H), 2.68−2.65 (m, 2H), 2.34−2.28 (m, 1H), 2.18−2.14 (m, 1H), 1.65 (d, J = 6.9 Hz, 3H), 1.56−1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 135.9, 133.9, 127.5, 121.4, 120.9, 119.4, 118.1, 111.1, 107.3, 61.6, 54.1, 53.5, 51.2, 35.9, 32.7, 31.6, 18.2, 12.9; $[\alpha]_D^{18}$ −59.6° (c 0.5, pyridine); HRMS (ESI) calcd for $(C_{19}H_{25}N_2O)^+$ 297.1961, found 297.1960.

Synthesis of Dihydrocorynantheol (1). Amine **20** (92 mg, 0.18 mmol) was converted to dihydrocorynantheol (**1**; 47 mg, 0.158 mmol) in an overall yield of 88% by procedures described above for the synthesis of isogeissoschizol (**5**).

*2-((2R,3R,12bS)-3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)ethanol (**1**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.16−7.08 (m, 2H), 3.79−3.72 (m, 2H), 3.14−3.06 (m, 3H), 3.05−3.01 (m,1H), 2.75−2.71 (m, 1H), 2.59−2.53 (m, 1H), 2.34 (br, 1H), 2.25 (d, J = 12.6 Hz, 1H), 2.07−1.95 (m, 2H), 1.71−1.62 (m, 1H), 1.51−1.41 (m, 2H), 1.37−1.22 (m, 2H), 1.16−1.11 (m, 1H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 134.9, 127.3, 121.2, 119.2, 118.1, 110.9, 107.7, 60.3, 60.1, 59.8, 53.1, 41.6, 37.2, 35.4, 35.2, 23.4, 21.6, 11.1; $[\alpha]_D^{22.3}$ −10.7(c 0.5, $CHCl_3$); HRMS (ESI) calcd for $(C_{19}H_{27}N_2O)^+$ 299.2118, found 299.2112.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving structural proofs, NMR spectra, and HPLC analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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