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Article

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Construction of the Azacyclic Core of Tabernaemontanine-related Alkaloids via Tandem Reformatsky-Aza Claisen Rearrangement

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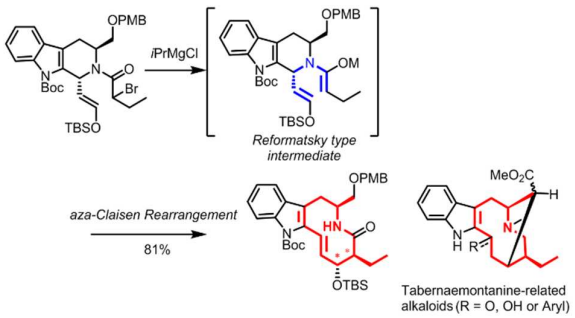


Abstract

A divergent synthetic methodology for tabernaemontanine-related alkaloid was developed. The synthetic route features practical improvements in the Pictet-Spengler cyclization for the tetrahydro-β-carboline intermediate and an unprecedented tandem Reformatsky-aza Claisen rearrangement to create the core carbon skeleton and

stereochemistries of tabernaemontanine-related alkaloids.

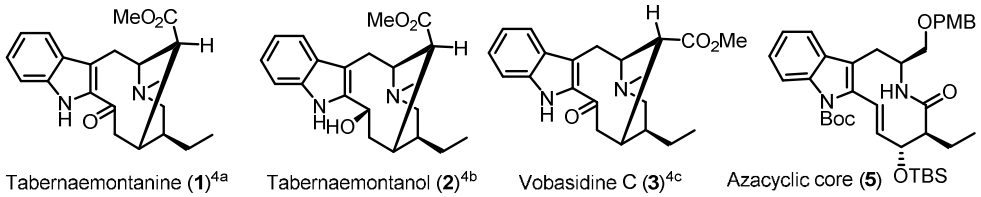
Introduction

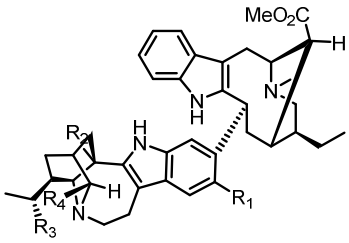
Indole alkaloids constitute an important class of natural products because of their remarkable biological activity and structural diversity.[1] Historically, indole alkaloids, such as serotonin and melatonin, have received attention as biologically important endogenous molecules used to elucidate the neuronal pathway.[2] Other indole alkaloids, such as vinblastine, vincristine, and sumatriptan, have been developed as blockbuster medicines to improve human health.[3]

Tabernaemontanine-related alkaloids, represented by tabernaemontanine (**1**), tabernaemontanol (**2**), vobasidine C (**3**), and vobasinyl-iboga bisindole alkaloid (**4a**-**4f**), belong to this this alkaloid family (**Figure 1**). These naturally isolated indole alkaloids are major components in members of the genus *Tabernaemontana*,[4] and tabernaemontanine (**1**) has been used in subtropical regions, including Africa, Polynesia, Southeast Asia, and southern China, to treat hypertension and prevent malaria and parasite infections.[4a,5] Recently, **1** was also reported to show promising apoptosis-inducing activity when used to treat human hepatoma HuH-7 cells.[6] Despite its remarkable biological profiles, the pharmacological mechanism governing its activity remains poorly understood.

From a structural standpoint, tabernaemontanine-related indole alkaloids have a challenging molecular structure.[7] This structure contains four contiguous stereocenters and an indole-fused azecinone framework with a formidable [5.1.3] bicyclic core. Notably, cyclically fused indole alkaloids have been synthesized using strategies such as Pictet-Spengler cyclizations, organocatalyst-mediated reactions, and asymmetric ring-closing metatheses. Additionally, an elegant synthetic strategy for the related indole alkaloids was recently reported by the group of James M. Cook.[7,8] With this synthetic need in mind, we commenced a synthetic study toward an azacyclic core (**5**), which would be widely utilized for the synthesis of tabernaemontanine-related indole alkaloids.

Figure 1. (-)-Tabernaemontanine and the related indole alkaloids



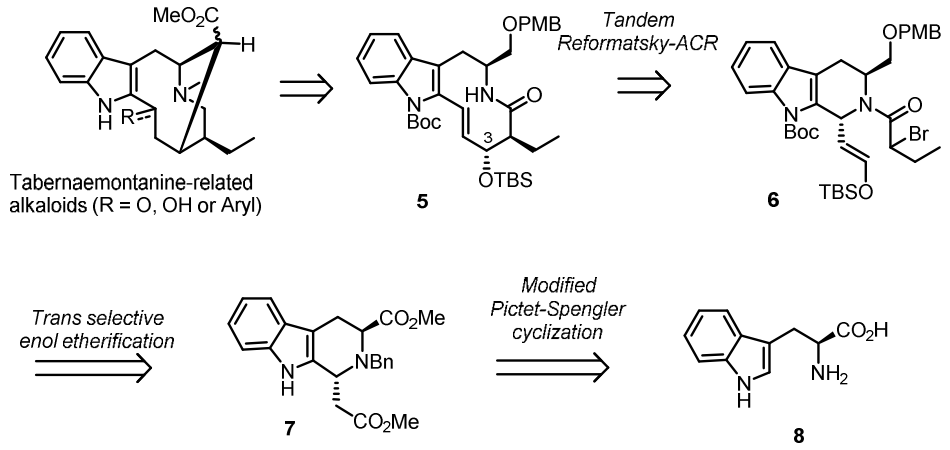


$R_1 = R_2 = R_3 = H$, 19,20-dihydrotabernamine (**4a**)[4d]
$R_1 = OMe$, $R_2 = R_3 = H$, 16'-decarbomethoxydihydrovoacamine (**4b**)[4e]
$R_1 = OMe$, $R_2 = CO_2Me$, $R_3 = H$, ervadivaricatine B (**4c**)[4f]
$R_1 = OMe$, $R_2 = H$, $R_3 = OH$, vobatensine B (**4d**)[4e]
$R_1 = H$, $R_2 = CO_2Me$, $R_3 = H$, $R_4 = CH_2C(O)Me$, taberdivarine E (**4e**)[4f]
$R_1 = OMe$ $R_2 = CO_2Me$, $R_3 = H$, $R_4 = CH_2C(O)Me$, taberdivarine F (**4f**)[4f]

Results and Discussion

A retrosynthesis of **5** is depicted in **Scheme 1**. For a practical and efficient synthetic route, we designed the 10-membered lactam **5** as a synthetic precursor to tabernaemontanine-related indole alkaloids in terms of carbon skeleton, oxidation state, and substitution pattern. Transannulation of **5** utilizing a method such as allylic alkylation and further functional manipulation including Wacker oxidation[9] may be necessary to complete the synthesis of tabernaemontanine-related indole alkaloids. To prepare **5**, we pursued an aza Claisen rearrangement (ACR) of the enol ether **4**.[10] We recently reported an efficient ACR to achieve the ring expansion of a medium-sized lactam to generate a macrolactam.[11] Employing this ring expansion methodology, we anticipated not only the construction of the 10-membered azacycle skeleton but also the creation of stereogenic centers in a single transformation. The enol ether **6** was considered to be accessible from the 1,3-*anti*-substituted tetrahydro-β-carboline **7** through functional group interconversion and *trans*-selective enol etherification reactions. In addition, the same carbon and stereochemical frameworks are expected to readily convert **7** to the ACR precursor **6**. Finally, the synthesis of **7** was pursued from a modified Pictet-Spengler cyclization of (L)-tryptophan **8** that was reported by the groups of Massiot and Bailey.[12]

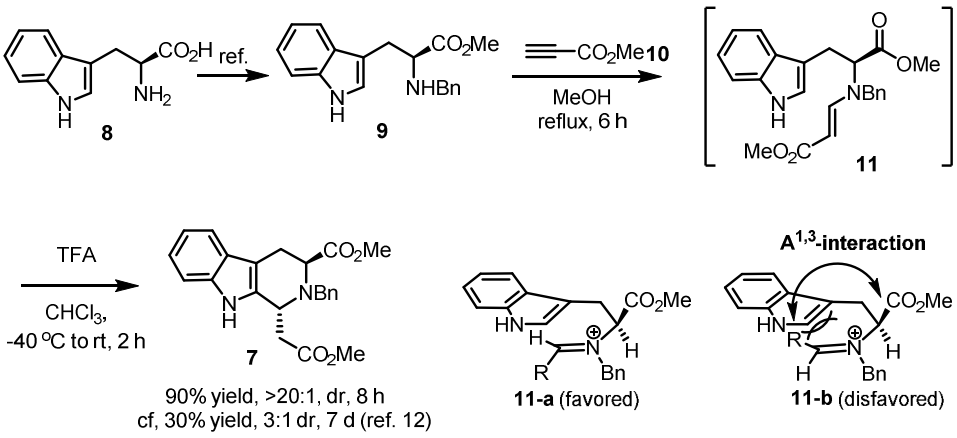
Scheme 1. Synthetic strategy for the azacyclic core **5** of the tabernaemontanine-related indole alkaloids



The synthesis of **7** commenced with a Pictet-Spengler cyclization (**Scheme 2**). At first, *N*-benzyl tryptophan methyl ester **9**[13] was converted to **7** using the Bailey's procedure.[12] However, under the standard protocol (addition of methyl propiolate **10** followed by treatment of TFA in $CHCl_3$, 7 d), the reaction afforded only a small amount of **7** with moderate diastereoselectivity (36 % yield, 3:1 d.r.). Although an excellent approach by the groups Massiot and Bailey introduced methyl propiolate **10** as an efficient three carbon synthon for the Pictet-Spengler cyclization, low reactivity and diastereoselectivity in this procedure were also reported.[12] We observed that the amine addition to methyl propiolate **10** proceeded slowly after monitoring the reaction. Thus, we carried out the reaction in MeOH because alcoholic solvents have been reported to accelerate the addition of a heteroatom to a Michael acceptor.[14] With this replacement, amine **9** was completely converted to **11** in 24 h. In addition, an elevation in temperature accelerated the reaction (6 h) to achieve similar results to those in reactions that proceeded at room temperature. However, $CHCl_3$ was the best solvent during treatment of **11** with TFA to generate **7** *in situ* because other solvents (MeOH, acetonitrile, *t*-BuOH, and THF) either hampered the C-C bond forming step or promoted alcoholysis. Accordingly, we conducted the Michael addition step using MeOH, which was evaporated and subsequently added $CHCl_3$ to the residue for the C-C bond formation step. This solvent exchange protocol afforded **7** in 90 % yield within 8 h. More importantly, lower temperature dramatically improved the diastereoselectivity of **7**. This improved facial selectivity is presumably derived from a minimized steric interference of the transition state. As shown in **Scheme 2**, the cyclization appears to proceed through the transition state **11-a** rather than **11-b**, which suffers from unfavorable steric interactions between the carbomethoxy substituent of iminium moiety and the indole moiety as well as the carbomethoxy group of the side chain during cyclization.[12d] Subsequently, we obtained **7** in a highly efficient manner. Considering the synthetic significance of the β-carboline intermediate **7**, our modified Pictet-Spengler cyclization procedure

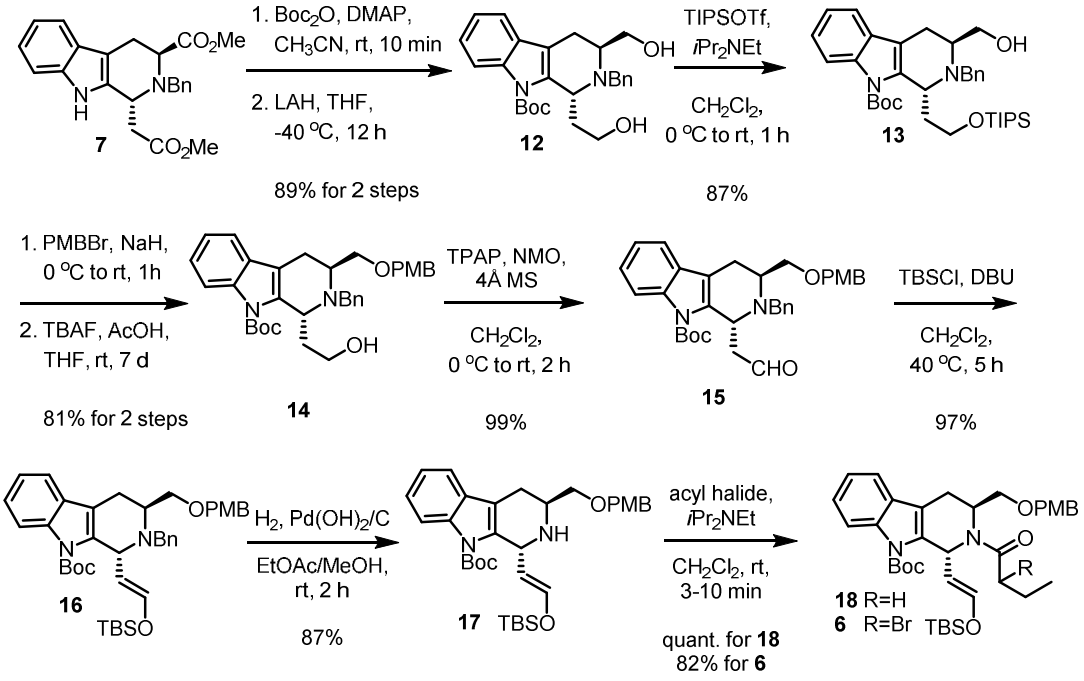
could be applied in the synthesis of related indole alkaloids.[8]

Scheme 2. Improved Pictet-Spengler cyclization



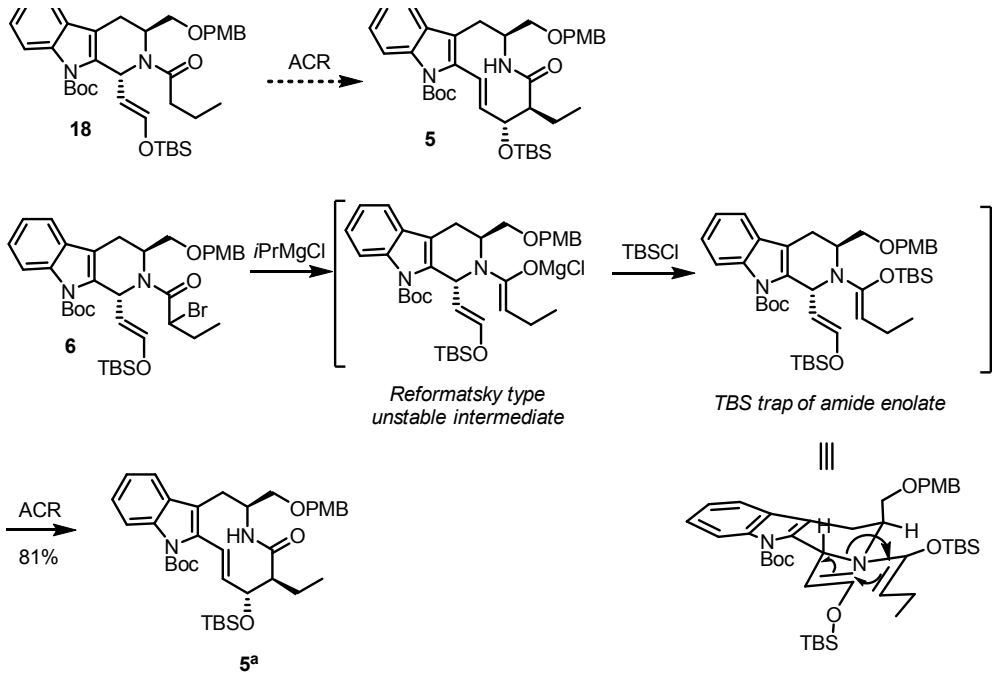
After the Pictet-Spengler cyclization was optimized, functional group interconversions were conducted as shown in **Scheme 3**. Boc protection of **7**, followed by LAH reduction, afforded the Boc-protected diol **12**. Diol **12** could be obtained in more than 50 g using this procedure. Subsequently, selective silylation of **12** produced the mono silyl ether **13**, which was converted to the PMB ether **14** by PMB protection followed by TIPS deprotection. Ley oxidation[15] of alcohol **14** quantitatively afforded the corresponding aldehyde **15**, which was treated with DBU in the presence TBSCl to afford the *trans*-enol ether **16** with high stereoselectivity.[11,16] Finally, the debenzylation of **16** with the labile silyl enol ether intact was achieved using Pearlman's catalyst,[17] followed by amidation to produce the desired butyryl amide **18** and the 2-bromobutyryl amide **6** in high yields, respectively.

Scheme 3. Functional group interconversion



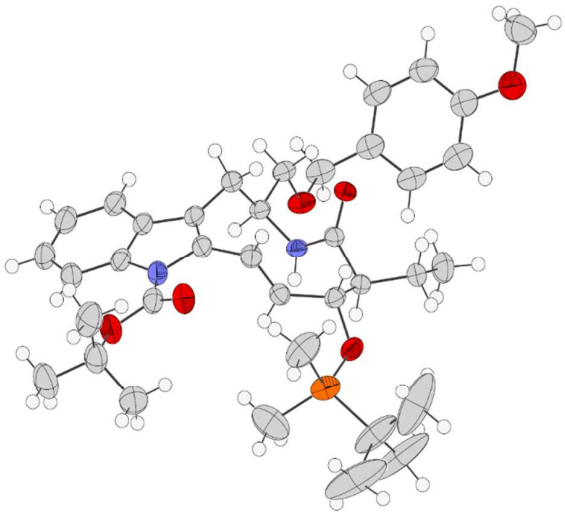
A pivotal ACR transformation of **18** (**6**) into the desired lactam **5** is summarized in **Scheme 4**. Initial attempts for the conversion of **18** to **5** were not successful under various reaction conditions. Considering that enol ether **18** was left unreacted in most cases, α-deprotonation of the amide appeared not to occur under the attempted conditions.[18] Thus, alternative procedures to generate the amide enolate were explored and the Reformatsky-type reaction was finally discovered for the facile ACR. Upon *i*PrMgCl treatment of **6**, initial debromination in 1 h followed by ACR produced azacycle **5**.[19] Initial amide enolate generation induced by debromination and spontaneous [3,3] sigmatropic rearrangement seemed to proceed. Treatment of **6** with *i*PrMgCl in refluxing benzene and then trapping the resulting amide enolate with TBS induced facile ACR to produce lactam **5**. The structure was confirmed through an analysis of spectral data and X-ray crystallographic analysis (**Figure 2**).[20] To the best of our knowledge, we report the first synthetic application of the tandem Reformatsky-aza Claisen rearrangement.[21] More than 10 grams of lactam **5** were obtained from (L)-tryptophan by our substantial procedure.

Scheme 4. Tandem Reformatsky-ACR of **6** and **18**



[a]Absolute stereochemistry was determined by X-ray crystallographic analysis of **5**[20]

Figure 2. X-ray crystallographic structure[a] of **5**[20]



[a]Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii; Black = carbon, Red = oxygen, Blue = nitrogen, Orange = silicon

Conclusion

In conclusion, we achieved an efficient construction of the core structure of the tabernaemontanine-related

indole alkaloids. Our strategy features an advance in diastereoselective Pictet-Spengler cyclization, and development of the tandem Reformatsky-aza Claisen rearrangement. Additional efforts are underway to apply our methodology to the total synthesis of biologically active tabernaemontanine-related indole alkaloids.

Experimental Section

General Experimental Procedure

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, and pyridine were freshly distilled from calcium hydride. All solvents used for the routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel (230−400 mesh) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates. Optical rotations were measured with a digital polarimeter at ambient temperature using a 100 mm cell of 2 mL capacity. Infrared spectra were recorded on a FT-IR spectrometer. Mass spectra were obtained with a double focusing mass spectrometer (electrostatic analyzer and magnetic analyzer). ^{1}H and ^{13}C NMR spectra were recorded on a 300, 400, or 500 MHz spectrometers as solutions in deuteriochloroform ($CDCl_3$) or tetradeuteromethanol (methanol-d_4). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CDCl_3$ or CD_3OD, major solvent in a mixture of $CDCl_3$ and CD_3OD). 1H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; dd, doublet of doublets; br, broad; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

(1*R*,3*S*)-methyl 2-benzyl-1-(2-methoxy-2-oxoethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-3-carboxylate (7).

To a solution of benzyl amine **9** (2.0 g, 6.5 mmol) in MeOH (20 mL), methyl propiolate **10** (1.2 mL, 13.0 mmol) was added and the reaction mixture was refluxed for 6 h. The reaction mixture was concentrated *in vacuo*. The crude residue was dissolved in $CHCl_3$ (20 mL) and TFA (1.6 mL) was added at -40 ^{o}C. The reaction mixture was stirred for 2 h, quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 3) to afford 2.3 g (90%) of carboline **7** as a

colorless oil. Recrystalization of **7** from a mixture of EtOAc and *n*-hexane (1: 5) afforded **7** as white solid with a melting point of 138-141 ^{o}C. $[\alpha]_{D}^{20}$ –23.8 (*c* 0.48, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.63 (s, 1H), 7.59 (d, 1H, *J* = 7.8 Hz), 7.42 – 7.40 (m, 2H), 7.36 – 7.32 (m, 3H), 7.29 – 7.26 (m, 1H), 7.22 – 7.16 (m, 2H), 4.37 (dd, 1H, *J* = 3.2, 9.6 Hz), 4.02 (dd, 1H, *J* = 4.8 Hz, 9.4 Hz), 3.93 (d, 1H, *J* = 14.0 Hz), 3.78 (s, 3H), 3.68 (s, 3H), 3.68 (d, 1H, *J* = 14.0 Hz), 3.21 (dd, 1H, *J* = 9.6, 15.8 Hz), 3.09 (dd, 1H, *J* = 4.8 Hz, 16.0 Hz), 3.00 (dd, 1H, *J* = 4.0, 16.2 Hz), 2.83 (dd, 1H, *J* = 10.0, 16.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.4, 172.9, 139.1, 135.8, 133.6, 128.4, 128.2, 127.0, 126.5, 121.8, 119.3, 118.0, 111.0, 106.8, 57.5, 53.4, 52.1, 51.9, 51.8, 40.5, 21.0; IR (neat) ν_{max} 3395, 3025, 2950, 2849, 1730, 1439, 1360 cm^{-1}; LR-MS (FAB+) *m/z* 393 ($M+H^+$); HR-MS (FAB+) Calcd for $C_{23}H_{25}N_2O_4$ ($M+H^+$): 393.1814, Found 393.1811.

(1*R*,3*S*)-*tert*-butyl 2-benzyl-1-(2-hydroxyethyl)-3-(hydroxymethyl)-1,2,3,4-tetrahydropyrido[3,4-*b*]indole-9-carboxylate (12).

To a solution of carboline **7** (4.5 g, 11.0 mmol) in CH_3CN (20 mL), DMAP (140 mg, 1.1 mmol) and Boc_2O (3.0 mL, 14.0 mmol) were added. The reaction mixture was stirred for 10 min and quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product (5.3 g) was dissolved in THF (40 mL) and treated with LAH (1.0 g, 27.0 mmol) at 0 ^{o}C and stirred for 12h. The reaction mixture was quenched with H_2O (1 mL), 10% NaOH (2 mL) and H_2O (3 mL). The mixture was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 1, 5% MeOH) to afford 4.5 g (89% for 2 steps) of diol **12** as white solid with a melting point of 111-114 ^{o}C. $[\alpha]_{D}^{20}$ +82.0 (*c* 0.27, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H, *J* = 8.1 Hz), 7.49 – 7.24 (m, 8H), 5.59 (br s, 1H), 4.45 (dd, 1H, *J* = 3.2, 9.6 Hz), 4.05 (d, 1H, *J* = 13.0 Hz), 4.00 – 3.62 (m, 5H), 3.50 (t, 1H, *J* = 10.0 Hz), 3.30 (d, 1H, *J* = 13.0 Hz), 2.68 (dd, 1H, *J* = 4.8 Hz, 16.0 Hz), 2.55 (dd, 1H, *J* = 12.0, 16.0 Hz), 2.07 – 1.97 (m, 1H), 1.91 – 1.83 (m, 1H), 1.43 (s, 9H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 149.8, 138.7, 136.4, 135.1, 129.5, 128.8, 128.5, 127.3, 124.2, 122.7, 117.7, 115.8, 114.1, 83.7, 62.5, 62.2, 57.4, 52.6, 49.3, 33.8, 27.8, 19.5.; IR (neat) ν_{max} 3363, 2929, 1729, 1647, 1539, 1456, 1368 cm^{-1}; LR-MS (FAB+) *m/z* 437 ($M+H^+$); HR-MS (FAB+) Calcd for $C_{26}H_{33}N_2O_4$ ($M+H^+$): 437.2440, Found 437.2442.

(1*R*,3*S*)-*tert*-butyl 2-benzyl-3-(hydroxymethyl)-1-(2-(triisopropylsilyloxy)ethyl)-1,2,3,4-tetrahydropyrido [3,4-*b*]indole-9-carboxylate (13).

To a solution of diol **12** (102 mg, 0.2 mmol) and *i*Pr_2NEt (81 μL, 0.5 mmol) in CH_2Cl_2 (5 mL), TIPSOTf (70 μL, 0.3 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C for 5 min. After stirring for 1 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 10) to afford 120 mg (87%) of ether **13** as a colorless oil. $[\alpha]_D^{20}$ +24.7 (*c* 0.115, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, 1H, *J* = 8.1 Hz), 7.48 – 7.28 (m, 8H), 4.37 (dd, 1H, *J* = 4.4, 10.0 Hz), 3.97 (d, 1H, *J* = 11.0 Hz), 3.90 – 3.82 (m, 3H), 3.77 – 3.71 (m, 1H), 3.58 – 3.51 (m, 1H), 3.30 (d, 1H, *J* = 11.0 Hz), 2.94 (d, 1H, *J* = 7.5 Hz), 2.69 – 2.57 (m, 2H), 2.09 – 2.00 (m, 2H), 1.54 (s, 9H), 1.14 – 1.06 (m, 21H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 149.8, 136.2, 136.5, 136.3, 129.1, 128.9, 128.3, 127.1, 124.0, 122.6, 117.7, 115.8, 113.9, 83.7, 61.9, 55.0, 52.5, 48.8, 35.9, 27.9, 19.5, 17.9, 17.6, 11.6; IR (neat) ν_{max} 3438, 2940, 2865, 1730, 1456, 1367 cm^{-1}; LR-MS (FAB+) *m/z* 593 ($M+H^+$); HR-MS (FAB+) Calcd for $C_{35}H_{53}N_2O_4Si$ ($M+H^+$): 593.3775, Found 593.3770.

(1*R*,3*S*)-*tert*-butyl 2-benzyl-1-(2-hydroxyethyl)-3-((4-methoxybenzyloxy)methyl)-1,2,3,4-tetrahydropyrido [3,4-b]indole-9-carboxylate (14).

To a solution of TIPS ether **13** (4.2 g, 7.1 mmol), TBAI (520 mg, 1.4 mmol) and PMBBr (3 mL, 21.0 mmol) in DMF (15 mL), NaH (60% dispersion in mineral oil, 570 mg, 14.0 mmol) was added at 0 °C. The reaction mixture was stirred for 1 h at ambient temperature, quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 20 to 1: 10) to afford an inseperable mixture 5.1 g of PMB ether and unidentified side product. The crude PMB ether (5.1 g) was dissolved in THF (30 mL) and treated with AcOH (2.1 mL, 36.0 mmol) and TBAF (1.0 M in THF, 21 mL, 21.0 mmol). After stirring for 7 d at the ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 2) to afford 3.2 g (81% for 2 steps) of alcohol **14** as a colorless oil. $[\alpha]_D^{20}$ +51.2 (*c* 0.31, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 1H, *J* = 8.1 Hz), 7.49 – 7.22 (m, 10H), 6.88 (d, 2H, *J* = 8.4 Hz), 5.27 (br s, 1H), 4.65 (d, 1H, *J* = 10.8 Hz), 4.55 (d, 1H, *J* = 10.8 Hz), 4.36 (dd, 1H, J = 2.8, 10.8 Hz), 3.97 – 3.90 (m, 2H), 3.82 – 3.72 (m, 1H), 3.77 (s, 3H), 3.68 – 3.61 (m, 2H), 3.46 (t, 1H, *J* = 10.4 Hz), 2.66 (dd, 1H, *J* = 4.8, 16.4 Hz), 2.59 (dd, 1H, *J* = 11.6, 16.0 Hz), 2.05 – 1.97 (m, 1H), 1.90 – 1.84 (m, 1H), 1.40 (s, 9H); ^{13}C-NMR

($CDCl_3$, 100 MHz) δ 159.2, 149.8, 138.9, 136.4, 135.3, 129.9, 129.4, 128.9, 128.5, 128.4, 127.2, 124.2, 122.7, 117.7, 115.9, 114.0, 113.8, 83.7, 73.1, 69.8, 62.6, 57.8, 55.1, 50.5, 49.7, 34.1, 27.8, 19.7; IR (neat) ν_{max} 2922, 1725, 1512, 1455, 1365 cm^{-1}; LR-MS (FAB+) *m/z* 557 ($M+H^+$); HR-MS (FAB+) Calcd for $C_{34}H_{41}N_2O_5$ ($M+H^+$): 557.3015, Found 557.3007.

(1*R*,3*S*)-*tert*-butyl 2-benzyl-3-((4-methoxybenzyloxy)methyl)-1-(2-oxoethyl)-1,2,3,4-tetrahydropyrido[3,4-*b*]indole-9-carboxylate (15).

To a solution of alcohol **14** (350 mg, 0.6 mmol) in CH_2Cl_2 (40 mL), 4Å Molecular Sieve (350 mg), NMO (125 mg, 1.1 mmol) and TPAP (44 mg, 0.1 mmol) were added at 0 °C and the mixture was stirred for 2 h at the ambient temperature. The reaction mixture was filtered through silica gel and the combined organic layer was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane= 1: 5 to 1: 3) to afford 342 mg (99%) of unstable aldehyde **15** as a colorless oil. ^{1}H-NMR (CD_3OD with ca 10% of $CDCl_3$, 300 MHz) *δ* 9.82 (s, 1H), 8.15 – 8.11 (m, 1H), 7.85 (d, 2H, *J* = 12.0 Hz), 7.44 – 7.19 (m, 6H), 7.07 (d, 2H, *J* = 12.0 Hz), 6.19 – 6.87 (m, 2H), 4.92 – 4.84 (m, 1H), 4.61 (dd, 1H, *J* = 7.6, 15.8 Hz), 4.58 – 4.50 (m, 2H), 3.98 (dd, 1H, *J* = 8.0, 15.8 Hz), 3.88 (s, 3H), 3.84 – 3.81 (m, 1H), 3.78 – 3.71 (m, 2H), 3.77 (d, 2H, *J* = 2.0 Hz), 3.24 (dd, 1H, *J* = 6.4, 17.6 Hz), 2.66 – 2.62 (m, 2H), 2.01 – 1.90 (m, 1H), 1.47 – 1.45 (m, 9H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 201.9, 190.6, 159.1, 149.8, 139.3, 136.1, 134.0, 131.9, 130.2, 129.2, 129.0, 128.2, 127.1, 124.3, 122.8, 118.0, 115.8, 115.7, 114.2, 113.7, 84.1, 72.8, 72.4, 55.4, 55.1, 52.9, 51.2, 50.4, 46.3, 27.7, 20.4; IR (neat) ν_{max} 1726, 1512, 1456, 1366, 1248 cm^{-1}; LR-MS (FAB+) *m/z* 554 ($M+H^+$).

(1*R*,3*S*,*E*)-*tert*-butyl 2-benzyl-1-(2-(*tert*-butyldimethylsilyloxy)vinyl)-3-((4-methoxybenzyloxy)methyl)-1,2,3,4-tetrahydropyrido[3,4-*b*]indole-9-carboxylate (16).

To a solution of aldehyde **15** (2.2 g, 4.0 mmol) and TBSCl (1.8 g, 12.0 mmol) in CH_2Cl_2 (40 mL), DBU (1.2 mL, 8.0 mmol) was added under reflux. After stirring for 5 h at the same temperature, the reaction mixture was cooled to room temperature, quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane= 1: 10 with 1% Et_3N) to afford 2.6 g (97%) of *trans* enol ether **16** as a colorless oil. $[\alpha]_D^{20}$ +16.7 (*c* 0.41, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) *δ* 8.21 (d, 1H, *J* = 8.0 Hz), 7.45 – 7.07 (m, 10H), 6.85 (d, 2H, *J* = 8.2 Hz), 5.93 (dd, 1H, *J* = 1.5, 12.3 Hz), 5.11 (dd, 1H, *J* = 5.1, 12.3 Hz), 4.74 (d, 1H, *J* = 5.0 Hz), 4.51 (s, 2H), 3.90 (d, 1H, *J* = 14.0 Hz), 3.81 – 3.66 (m, 2H), 3.76 (s,

3H), 3.42 (d, 1H, *J* = 14.0 Hz), 2.77 – 2.60 (m, 2H), 1.33 (s, 9H), 0.81 (s, 9H), 0.00 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 159.1, 149.8, 143.7, 140.3, 136.4, 134.1, 130.4, 129.2, 129.1, 128.4, 128.1, 126.6, 123.8, 122.4, 117.8, 115.6, 115.5, 113.7, 112.3, 83.2, 72.7, 72.4, 55.3, 55.1, 50.6, 50.2, 27.7, 25.5, 21.0, 18.0; IR (neat) ν_{max} 2924, 1727, 1648, 1512, 1456 cm^{-1}; LR-MS (FAB+) *m/z* 669 ($M+H^+$); HR-MS (FAB+) Calcd for $C_{40}H_{53}N_2O_5Si$ ($M+H^+$): 669.3724, Found 669.3725.

(1*R*,3*S*,*E*)-*tert*-butyl 1-(2-(tert-butyldimethylsilyloxy)vinyl)-3-((4-methoxybenzyloxy)methyl)-1,2,3,4-tetrahydropyrido[3,4-b]indole-9-carboxylate (17).

To a solution of benzylamine **16** (1.6 g, 0.2 mmol) in EtOAc/MeOH (5 mL/ 5 mL), $Pd(OH)_2$/C (100 mg) was added and the mixture was stirred under H_2 (balloon pressure) for 2 h. The reaction mixture was filtered through silica gel and the combined organic layer was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 3 to 1: 1 with 1% MeOH and Et_3N) to afford 1.2 g (87%) of unstable enol ether **17** as a colorless oil. $[\alpha]_D^{20}$ -29.9 (*c* 0.23, $CHCl_3$); ^{1}H-NMR (CD_3OD, 300 MHz) *δ* 8.07 – 8.04 (m, 1H), 7.41 – 7.38 (m, 1H), 7.27 (d, 2H, *J* = 8.5 Hz), 7.28 – 7.15 (m, 2H), 6.86 (d, 2H, *J* = 8.5 Hz), 5.92 (dd, 1H, *J* = 0.9, 12.0 Hz), 5.24 (dd, 1H, *J* = 6.3, 12.0 Hz), 5.15 – 5.13 (m, 2H), 4.48 (d, 1H, *J* = 2.0 Hz), 3.75 (s, 3H), 3.61 (dd, 1H, *J* = 4.3, 9.6 Hz), 3.51 (dd, 1H, *J* = 6.9, 9.6 Hz), 3.37 – 3.36 (m, 1H), 2.78 (dd, 1H, *J* = 4.2, 16.2 Hz), 2.44 (dd, 1H, *J* = 11.0, 16.2 Hz), 1.61 (s, 9H), 0.81 (s, 9H), 0.00 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR (CD_3OD, 100 MHz) δ 161.6, 151.9, 146.3, 138.3, 136.3, 132.3, 131.4, 131.0, 126.0, 24.5, 119.7, 17.5, 117.3, 115.6, 113.4, 85.7, 74.8, 56.4, 52.7, 48.1, 29.2, 26.8, 25.9, 19.8, -4.3 (2C); IR (neat) ν_{max} 2928, 1729, 1649, 1513, 1457, 1363 cm^{-1}; LR-MS (FAB+) *m/z* 579 ($M+H^+$).

(1*R*,3*S*)-*tert*-butyl 1-((*E*)-2-(*tert*-butyldimethylsilyloxy)vinyl)-2-butyryl-3-((4-methoxybenzyloxy)methyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2H)-carboxylate (18).

To a solution of amine **17** (22 mg, 38 μmol) in CH_2Cl_2 (2 mL) were added *i*Pr_2NEt (23 μL, 0.1 mmol) and *n*-butyryl chloride (10 μL, 0.1 mmol) at 0 ^oC and the mixture was warmed to ambient temperature. The reaction mixture was stirred for 3 min, quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 5, deactivated with 1% Et_3N) to afford 26 mg (100%) of butyryl amide **18** as a colorless oil. $[\alpha]_D^{20}$ +5.66 (c 2.45, MeOH); ^{1}H-NMR (CD_3OD, 400 MHz, mixture of rotamers) *δ* 8.09 (d, 1H, *J* = 6.1 Hz), 7.42 (d, 1H, *J* = 7.2 Hz), 7.27 – 7.20 (m, 2H), 7.07 (br s, 2H), 6.72 (br s, 2H), 6.22 – 6.09 (m, 2H), 5.20 (br s, 1H), 4.42 - 4.26 (m, 3H), 3.69 (s, 3H), 3.54 (br s, 1H), 3.13

(br s, 2H), 2.82 (br s, 1H), 2.47 (m, 2H), 1.65 (s, 9H), 1.65 – 1.61 (m, 2H), 0.92 (t, 3H, *J* = 7.3 Hz), 0.80 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H); ^{13}C-NMR (CD_3OD, 100 MHz, mixture of rotamers) δ 177.0, 161.4, 151.9, 146.0, 138.3, 131.0, 126.3, 124.8, 120.0, 117.6, 116.1, 115.9, 115.7, 115.4, 114.8, 112.9, 112.3, 86.4, 74.3, 72.1, 56.4, 55.0, 54.4, 54.0, 38.4, 29.3, 26.8, 23.6, 20.8, 19.8, 14.9, -4.3, -4.3; IR (neat) ν_{max} 2957, 1730, 1654, 1512, 1455, 1369, 1325, 1250 cm^{-1}; LRMS (FAB+) *m/z* 649 ($M+H^+$); HR-MS (FAB+) Calcd for $C_{37}H_{53}N_2O_6Si$ ($M+H^+$): 649.3673, Found 649.3688.

(1*R*,3*S*,*E*)-*tert*-butyl 2-(2-bromobutanoyl)-1-(2-(*tert*-butyldimethylsilyloxy)vinyl)-3-((4-methoxybenzyloxy) methyl)-1,2,3,4-tetrahydropyrido[3,4-b]indole-9-carboxylate (6)

To a solution of amine **17** (390 mg, 0.8 mmol) in CH_2Cl_2 (40 mL) were added *i*Pr_2NEt (0.4 mL, 2.0 mmol) and 2-bromobutyryl bromide (0.1 mL, 0.8 mmol) at 0 ^{o}C and the mixture was warmed to ambient temperature. The reaction mixture was stirred for 10 min, quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane = 1: 5, 1% Et_3N) to afford 400 mg (82%) of bromoamide **6** as a colorless oil. ^{1}H-NMR (CD_3OD, 400 MHz, mixture of rotamers and diastereomers) δ 8.13 – 8.10 (m, 1H) 7.48 (d, 2H, *J* = 7.2 Hz), 7.32 – 7.23 (m, 2H), 7.10 (br s, 2H), 6.78 (d, 1H, *J* = 8.8 Hz), 6.76 (br s, 1H), 6.27 (d, 1H, *J* = 6.4 Hz), 6.26 – 6.15 (m, 1H), 5.23 (br s, 1H), 4.94 – 4.85 (m, 1H), 4.61 – 4.57 (m, 1H), 4.45 – 4.32 (m, 2H), 3.73 (s, 3H), 3.33 (br s, 1H), 3.13 – 3.09 (m, 2H), 2.90 – 2.87 (m, 1H), 2.02 (br s, 2H), 1.69 – 1.68 (m, 9H), 0.97 (br s, 2H), 0.82 (s, 9H), 0.03 (br s, 6H); ^{13}C-NMR (CD_3OD, 75 MHz, mixture of rotamers and diastereomers) *δ* 175.5, 173.6, 172.4, 161.6, 160.8, 152.3, 152.0, 151.9, 147.1, 146.8, 145.8, 138.4, 137.9, 132.5, 131.8, 131.4, 131.3, 130.7, 130.4, 126.4, 126.2, 124.9, 120.1, 119.9, 118.3, 117.7, 115.5, 115.5, 111.6, 86.6, 86.5, 86.3, 74.6, 74.5, 74.4, 73.1, 71.2, 61.5, 61.0, 56.4, 56.0, 55.5, 54.9, 51.8, 50.9, 48.2, 47.9, 38.5, 37.3, 32.1, 31.3, 30.6, 29.3, 27.4, 27.1, 26.9, 24.9, 24.6, 23.5, 20.1, 19.9, 13.2, 13.1, -4.3, -4.4; IR (neat) ν_{max} 2932, 1731, 1657, 1513, 1456, 1367, 1250, 1142 cm^{-1}; LR-MS (FAB+) *m/z* 669 ($M+H^+$); HR-MS (FAB+) Calcd for $C_{37}H_{52}BrN_2O_6Si$ ($M+H^+$): 727.2778, Found 727.2790.

(2*S*,5*S*,6*R*,*E*)-*tert*-butyl 6-(*tert*-butyldimethylsilyloxy)-5-ethyl-2-((4-methoxybenzyloxy)methyl)-4-oxo-1,2,3,4,5,6-hexahydroazecino[5,4-b]indole-9-carboxylate (5).

To a solution of bromoamide **6** (340 mg, 0.5 mmol) in benzene (20 mL) was added *i*PrMgCl (0.6 mL, 2.0 M in THF, 1.1 mmol) was added under reflux and then a solution of TBSCl (78 mg, 0.5 mmol) in benzene (1 mL)

was added immediately. After stirring for 5 h at the same temperature, the reaction mixture was cooled to room temperature, quenched with H_2O, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc: *n*-hexane= 1: 5 to 1: 1) to afford 250 mg (81%) of 10-membered lactam **5** as a colorless oil. Recrystallization of lactam **5** from MeOH afforded **5** as white solid with a melting point of 165-167 ^{o}C. $[\alpha]_D^{20}$ +54.4 (*c* 0.57, $CHCl_3$); ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.76 (d, 1H, *J* = 7.8 Hz), 7.25 (d, 1H, 7.5 Hz), 7.14 – 6.96 (m, 5H), 6.73 (d, 2H, *J* = 8.7 Hz), 6.36 (d, 1H, *J* = 16.6 Hz), 5.39 (dd, 1H, *J* = 9.0, 16.5 Hz), 4.33 (s, 2H), 3.94 (t, 1H, *J* = 9.6 Hz), 3.79 (t, 1H, *J* = 9.0 Hz), 3.70 – 3.66 (m, 1H), 3.62 (s, 3H), 3.30 – 3.21 (m, 1H), 3.03 (m, 1H), 2.57 (d, 1H, *J* = 9.0 Hz), 1.85 (m, 1H), 1.61 – 1.51 (m, 2H), 1.50 (s, 9H), 0.76 (s, 9H), 0.71 (t, 3H, *J* = 7.8 Hz), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C-NMR (CD_3OD + 10% of $CDCl_3$, 100 MHz) δ 177.1, 161.2, 151.5, 142.0, 137.2, 132.2, 131.0, 125.5, 124.2, 122.1, 120.1, 119.4, 116.7, 115.3, 85.4, 78.3, 74.5, 73.3, 60.5, 57.5, 56.4, 29.3, 27.2, 27.1, 23.4, 22.6, 19.6, 13.7, -2.8, -3.7; IR (neat) ν_{max} 3298, 228, 1739, 1645, 1514, 1456, 1365, 1323, 1249 cm^{-1}; LRMS (FAB+) *m/z* 649 ($M+H^+$); HRMS (FAB+) Calcd for $C_{37}H_{53}N_2O_6Si$ ($M+H^+$): 649.3673, Found 649.3678.

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Supporting Information

^{1}H and ^{13}C NMR spectra of all novel compounds as well as an X-ray crystallographic analysis of **5.**

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