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An Improved Total Synthesis of (+)-Macroline and Alstonerine as Well as the Formal Total Synthesis of (−)-Talcarpine and (−)-Anhydromacrosalhine−methine

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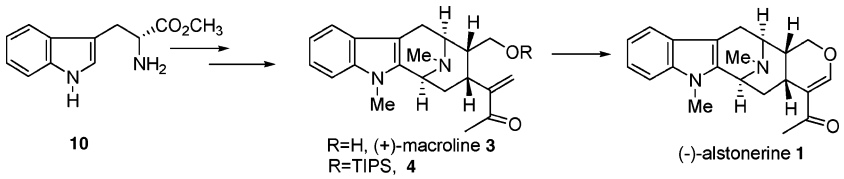

An intramolecular Pd-catalyzed α-vinylation process is described. This cyclization has been employed for the enantiospecific total synthesis of gram quantities of both (+)-macroline **3** and the macroline equivalent **4**. This sequence is compared to the enolate-driven cross-coupling process. The intermediate **4** was also converted into (−)-alstonerine **1** via modification of an intramolecular Tsuji−Wacker oxidation. This sequence resulted in an improved total synthesis of (−)-talcarpine **5** and (−)-anhydromacrosalhine−methine **6** as well.

Introduction

It has been reported that a number of bisindole alkaloids isolated from *Alstonia*[1,2] species have been shown to exhibit antimalarial activity[3] against the drug-resistant K1 strains of *Plasmodia falciparum* including villasltonine **8** and macrocarpamine **9** (IC_{50} values of 0.27 and 0.35 μM,[4] respectively). In addition, these bisindoles were assessed for cytotoxic activity against human lung cancer cell lines. The bisindoles exhibited pronounced cytotoxic activity against two cell lines with IC_{50} values of 2−10 μM.[5] Bisindoles are of special significance because they often exhibit more potent biological activity than their corresponding monomeric components.[3,4] The biomimetic coupling of (+)-macroline **3** with the obligatory monomeric alkaloids to provide *Alstonia* bisindoles macralstonine **7** and villalstonine **8** was pioneered by Le Quesne.[6,7] In addition, a (+)-macroline-related derivative, (−)anhydromacrosalhine−methine **6**, was coupled with pleiocarpamine to provide the bisindole macrocarpamine (Scheme 1).[8] Furthermore, (−)-alstonerine **1** is the desmethoxy analogue of alstophylline **2**, the latter alkaloid of which was coupled with (+)-macroline **3** to furnish macralstonine **7** (Figure 1).[7] In keeping with our interest in the total synthesis of *Alstonia* bisindole alkaloids macralstonine **7**, villastonine **8**, and macrocarpamine **9**, we report here an improved total synthesis of (−)-alstonerine **1** and (+)-macroline **3**, as well as the efficient preparation of the more stable (+)-macroline equivalent **4** on a gram scale.

Although a total synthesis of (−)-alstonerine **1**[9] and (+)-macroline **3**[10] had been carried out previously, efforts have been underway to provide a route to furnish gram quantities of the (+)-macroline equivalent **4** as well as the biogenetic intermediate **3**. Recently, Liu had designed a more practical route to the enantiomer of **3** via a sarpagine intermediate;[11] consequently, this strategy was modified to provide a route to natural **3** as well as **4**. This approach also afforded a key intermediate for the preparation of (−)-alstonerine **1**, by a strategy which

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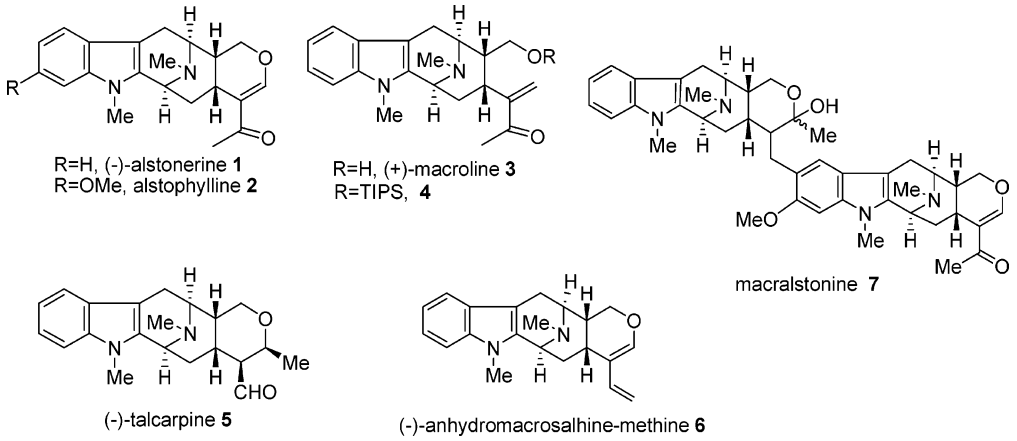
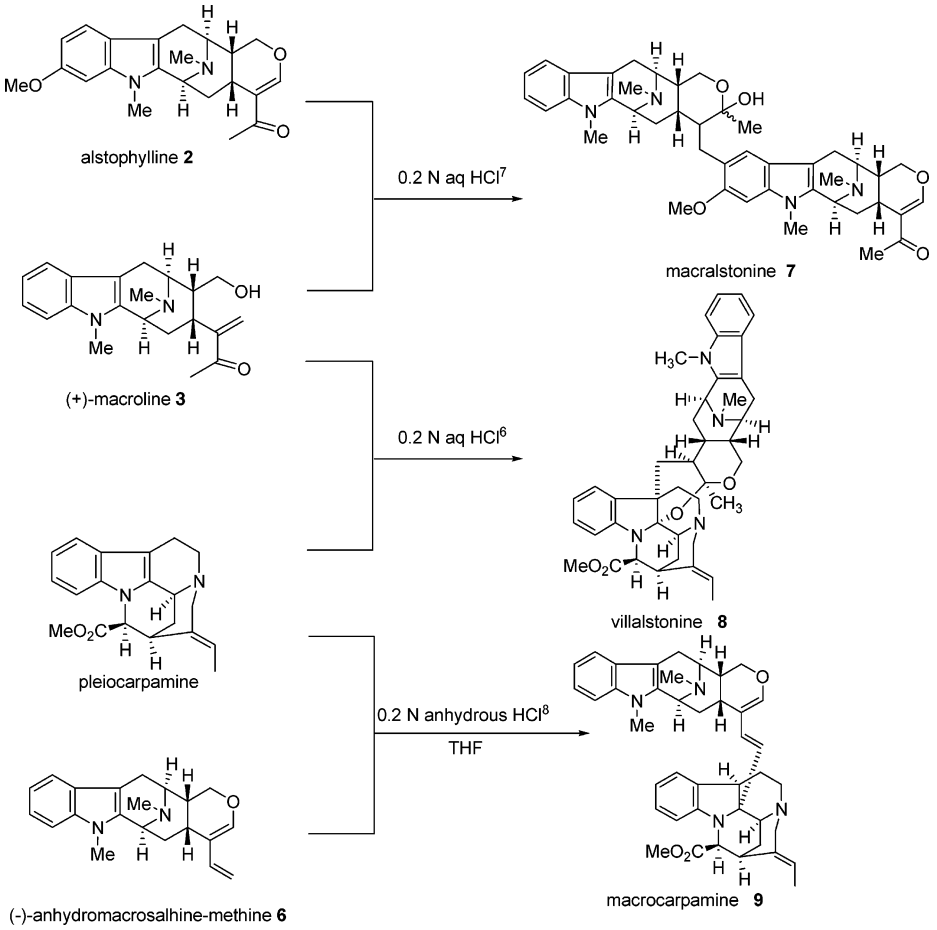


FIGURE 1. Macroline-related indole alkaloids.

SCHEME 1



provided an improved route for the total synthesis of macralstonine **7**[6] as well as an improved route to macrocarpamine **9**.[8]

Results and Discussion

The synthesis began with the readily available (−)-N_a-methyl tetracyclic ketone **11** prepared on a >300 g scale from ester **10** (>98% ee).[12] This ester **10** had been converted into the key intermediate, N_a-methylvellosimine **16**, via an enantiospecific, stereospecific sequence via the enolate-mediated cross-coupling process which was followed by a Wittig reaction/hydrolysis sequence (see ref 13). Because the conditions[14a] employed for the enolate-driven palladium-coupling process were different

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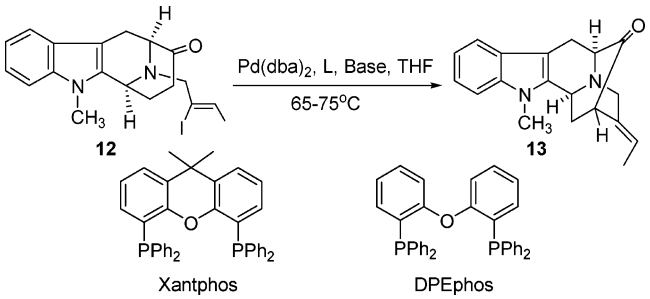
TABLE 1. Summary of Conditions for the α-Vinylation Process



$Pd(dba)_2$ (mol %)	ligand (mol %)	base	*T* (°C)	yield (%)
2	2.4 (Xantphos)	(1.5 equiv) NaO-*t*-Bu	65	60
0.8	2.4 (Xantphos)	(1.5 equiv) NaO-*t*-Bu	65	55
0.8	2.4 (DPEphos)	(1.5 equiv) NaO-*t*-Bu	65	75
2	2.4 (DPEphos)	(1.5 equiv) NaO-*t*-Bu	65	80
0.8	2.4 (DPEphos)	(3.0 equiv) K_3PO_4	80	50

from the recent Buchwald−Hartwig arylation reactions, efforts were directed toward intramolecular α-vinylation under the conditions of the arylation process. If successful, this would permit lower catalyst loading[14] and be effective for both *E* and *Z* ethylidenes, and the homogeneous reaction conditions might provide a faster rate, thereby permitting facile scale-up. With these goals in mind, advantage was taken of the mechanistic studies reported on the Pd(0)-catalyzed α-vinylation.[15] Certainly, vinyl iodides would be quite reactive for the oxidative-addition step. If nucleophilic substitution of iodide by the enolate nucleophile in the coupling process was comparably slow, an *E*-2 elimination could occur to provide the alkyne byproduct; moreover, *Z*-ethylidenes were not always compatible with the previous reaction conditions because *β*-elimination might occur.[16] For these reasons, a bidentate ligand[17] was considered key to the success of this endeavor. Xantphos had been employed by Buchwald[18] in the α-arylation process due to the large bite angle which facilitated the reductive elimination step and suppressed the *β*-elimination in comparison to the other steps. Initially, this Pd(0)-mediated process with the Xantphos ligand provided the coupling product **13** (Table 1) here in 60% yield. When the ratio of Pd(0)/Xantphos was increased, the yield of **13** decreased. Excess ligand may have decreased the amount of active $Pd(0)/L_2$ species,[19] which would retard the oxidative-addition step. Because one of the principle byproducts arises from the base-mediated *E*-2 elimination step (to alkyne) from vinyl iodide **12**, a slower rate of reaction would provide more of the byproduct and lower yield. Since the bite angle of DPEphos is similar to Xantphos, the cheaper DPEphos was then studied in this α-vinylation. With DPEphos as the ligand, a cleaner reaction was observed and the yield of the *E*-ethylidene **13** improved to 80%. Use of a weaker base such as K_3PO_4 (see Table 1) in the process resulted in lower yields of **13**. Furthermore, to the best of our knowledge, this is the first reported Pd(0)-catalyzed α-vinylation process in which the cheaper DPEphos was employed in the case of a *Z*-ethylidene (see **15)**. Gratifyingly, the desired *Z*-ethylidene **15** was obtained in 82% yield, as illustrated in Scheme 2. This is an improvement over the previous process[16] employed for the synthesis of (−)-koumidine (Scheme 2).[16] It is clear the *E*-2 elimination process was prohibited because there was no hydrogen atom anti to the iodide in **14** and the bidentate DPEphos suppressed the *β*-elimination in the case of the *Z*-ethylidene **14**. The modifications outlined in Table 1 also avoid the potential intramolecular attack of a vinyl halide on the carbonyl group. Since the conditions of the Pd(0)-mediated α-vinylation had been optimized (Table 1), the low catalyst loadings and homogeneous reaction conditions could be employed to more readily scale up the carbon−carbon bond formation to provide pentacyclic ketone **13**. In the previous enolate-driven cross-coupling process,[14a] higher temperatures (80 °C) and larger quantities of phosphine ligand (Ph_3P) were employed, although the yield was still 80%.

Since gram quantities of N_a-methylvellosimine **16** were now in hand, the aldehyde function was reduced with sodium borohydride to afford affinisine **17** in over 90% yield, the spectral data and optical rotation of which were identical to the natural product.[20] As shown in Scheme 3, the hydroxyl group of affinisine was then protected as the triisopropylsilyl group, and this was followed by a hydroboration−oxidation sequence at 25 °C (see Scheme 3). The desired C(19) secondary alcohol could be acquired in very good yield, accompanied by 7% of the tertiary alcohol. In some runs, very little or no tertiary alcohol was observed.[11,20] Analogous to the earlier work of Liu,[11] the N_b-nitrogen atom in the sarpagine series had been readily attacked by the first equivalent of borane. This served to protect the N_b-nitrogen function from *N*-oxide formation during the hydrogen peroxide-mediated process. This sequence provided a mixture of N_b-protected products (boranes)[20] which were prepurified by a simple wash column on silica gel for the borane adducts were less polar than the free base and much easier to chromatograph. This mixture was then stirred in the presence of 2 equiv of HOAc in refluxing THF for 5 h, after which the desired secondary alcohol **19**, with the free N_b-nitrogen function, was obtained in 85% overall yield. Because of the basicity of the N_b-nitrogen moiety in the sarpagine series, the conversion of the C(19) secondary alcohol into the carbonyl group necessary to set up a retro-Michael reaction was not simple. Attempts at oxidation of monol **19** with TPAP or SO_3·Py returned only starting material, while Swern oxidation provided inconsistent results, accompanied by baseline material. Finally, Dess−Martin oxidation[23] of the diastereomeric mixture of **19a**,**b** provided the desired ketone **20** in 82% yield. As illustrated in Scheme 3, the ketone **20** was then stirred in THF at 0 °C with methyl iodide to furnish the N_b-methiodide salt to set up a retro-Michael reaction analogous to the earlier biomimetic work of Le Quesne.[21] This salt was stirred under modified conditions with *t*-BuOK in refluxing THF/EtOH to provide the (+)-macroline equivalent **4** via the retro-Michael reaction in greater than 90% yield. The overall yield of this stable macroline

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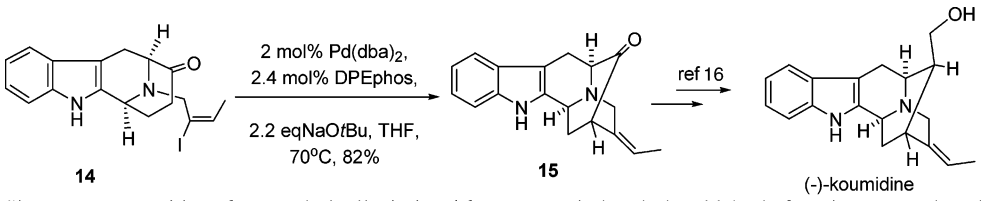
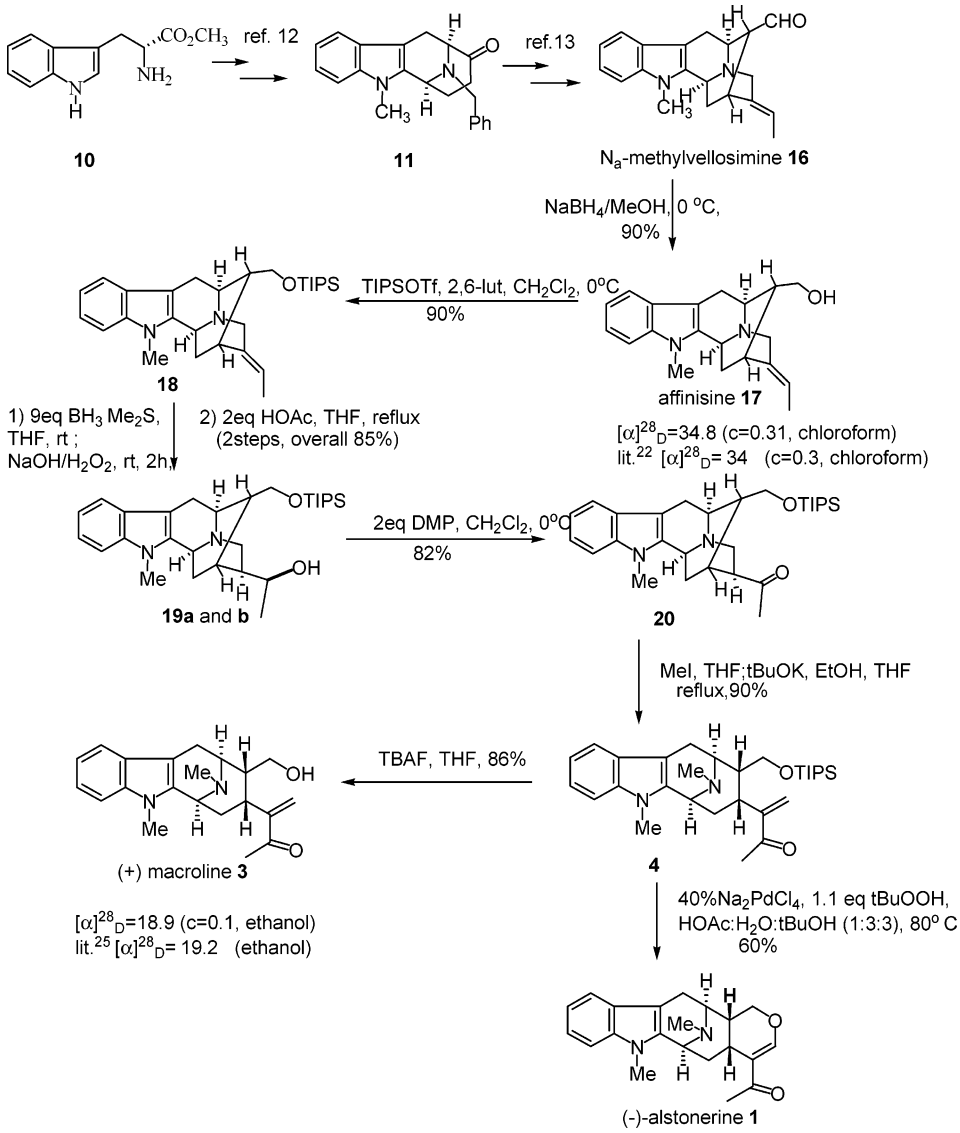
SCHEME 2



SCHEME 3



equivalent **4** was (from tryptophan methyl ester **10**) 20.4%. When **4** was stirred in THF with tetrabutylammonium fluoride monohydrate, (+)-macroline **3** was obtained in 86% yield, the spectral data and optical rotation of which were in excellent agreement with those reported in the literature.[26]

With an efficient synthesis of the (+)-macroline equivalent **4** in hand, modification of the conditions of the Tsuji−Wacker oxidation permitted one-pot conversion of **4** into (−)-alstonerine **1** in 60% yield (includes four transformations)[24] and the alkaloid **1** could be further converted into (−)-anhydromacrosalhine−methine **6** and (−)-talcarpine **5**, analogous to the earlier work of LeQuesne,[25] Yu,[12] and Gan et al.[8] The mass and NMR spectra data of (−)-alstonerine **1** were in excellent agreement with those reported in the literature.[27] Analogous to the earlier work of Le Quesne,[25] Gan,[8] and Yu,[12] this constituted an improved total synthesis of the biogenetic intermediate (−)-anhydromacrosalhine-methine **6** as well as (−)-talcarpine **5**.[25,28]

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In conclusion, an efficient route to the stable (+)-macroline equivalent **4** as well as to (+)-macroline **3** has been developed (from tryptophan methyl ester **10**) via a selective hydroboration−oxidation and retro-Michael ring-opening sequence. This route to (+)-macroline **3** required 12 reaction vessels and was accomplished in 18.1% overall yield. It can be employed to prepare gram quantities of this key biomimetic intermediate for the synthesis of *Alstonia* bisindoles. During the improved total synthesis of (+)-macroline, a new Pd(0)/DPEphos-catalyzed α-vinylation was developed. This process potentially can be extended to vinyl bromides (which were employed by Buchwald et al.) and would be more practical for alkaloids in the koumidine (*Z*-ethylidenes) series than the enolate-driven Pd(0) cross-coupling process previously reported from our laboratory.[16] In addition, the intramolecular Tsuji−Wacker oxidation[24] was employed to convert the (+)-macroline equivalent **4** into (−)-alstonerine **1** (12 reaction vessels from tryptophan methyl ester; 12.6% overall yield). This resulted in the improved total synthesis of (−)-talcarpine **5** and (−)-anhydromacrolsalhine−methine **6**, as mentioned. This synthesis of (+)-macroline **3** is an important part of the doubly convergent strategy toward antimalarial bisindole alkaloids such as villalstonine,[7] macrocarpamine,[8] and macralstonine,[20] as well as macralstonidine.[29]

Experimental Section

General Methods. Reagent and solvent purification, workup procedures, and analyses were in general performed as described previously.[13] The (+)-N_a-methylvellosimine was prepared according to the published procedure.[13]

General Procedure for the α-Vinylation. A mixture of N_b-*Z*-2′-iodo-butenyltetracyclic ketone **12** (1.0 mmol), $Pd(dba)_2$ (2 mol %), DPEphos (2.4 mol %), NaO-*t*-Bu (1.5 mmol) in a solution of THF (20 mL) was degassed under reduced pressure at a cooling bath temperature of −78 °C and refilled with argon (three times). The mixture was then heated to 65 °C (oil bath temperature) under argon for 12 h. Then mixture was quenched with ice−water and extracted with ethyl acetate. The organic layer was separated and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure, and the residue was flash chromatographed with EtOAc/hexanes (1:1) to provide the coupling product in 80% yield.

Sodium Borohydride Mediated Reduction of (+)-N_a-Methylvellosimine (16) To Provide the (+)-3-Ethylidene-12-methyl-1,3,4,7,12,12b-hexahydro-13-hydroxymethyl-2*H*,6*H*-2,6-methanoindolo[2,3-α]quinolizine [(+)-Affinisine (17)]. The (+)-N_a-methylvellosimine (**16**, 2.0 g, 6.6 mmol) was dissolved in EtOH (40 mL). The $NaBH_4$ (240 mg, 6.6 mmol) was added to the above solution in one portion at 0 °C. The mixture was then stirred at 0 °C for 8 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and poured into cold water (50 mL). The aqueous layer was extracted with additional CH_2Cl_2 (3 × 80 mL), and the combined organic layers were washed with brine (80 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford the crude product, which was purified by chromatography on silica gel (CH_2Cl_2/CH_3OH = 10:1) to provide (+)-affinisine (**17**, 1.82 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (dt, J = 6.8, 1.7 Hz, 3H), 1.62−1.71 (m, 2H), 1.78 (qd, J = 7.5, 1.2 Hz, 1H), 2.06 (ddd, J = 12.2, 10.0, 2.0 Hz, 1H), 2.62 (d, J = 15.3 Hz, 1H), 2.75−2.79 (m, 2H), 3.03 (dd, J = 15.3, 5.2 Hz, 1H), 3.45−3.66 (m, 4H), 3.61 (s, 3H), 4.19 (dd, J = 9.8, 2.1 Hz, 1H), 5.39 (q, J = 6.8 Hz, 1H), 7.08 (td, J = 7.4, 1.0 Hz, 1H), 7.18 (td, J = 7.1, 1.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 27.0, 27.5, 29.2, 32.9, 44.3, 49.4, 54.1, 56.3, 65.0, 103.5, 108.6, 116.4, 118.0, 118.7, 120.7, 127.3, 136.2, 137.2, 139.7; IR (NaCl) 2910, 1469 cm^{-1}; HRMS calcd for $C_{20}H_{24}N_2$ 308.1889, found 308.1883. This material was employed directly in the next step.

Conversion of (+)-Affinisine (17) into 13-(Triisopropylsilanyloxymethyl)-3-ethylidene-12-methyl-1,3,4,7,12,12b-hexahydro-13-hydroxymethyl-2*H*,6*H*-2,6-methanoindolo[2,3-α]quinolizine (18). A solution of affinisine (**17**, 1.2 g, 3.9 mmol) in dry CH_2Cl_2 (40 mL) was cooled to 0 °C, after which 2,6-lutidine (1.8 mL, 15.6 mmol) was added, and this was followed by addition of TIPSOTf (2.1 mL, 7.8 mmol) to the stirred solution. The mixture was then allowed to stir for an additional 2 h at 0 °C, after which cold water (2 mL) was added to quench the reaction. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and poured into cold water (20 mL). The aqueous layer was extracted with additional CH_2Cl_2 (2 × 50 mL), and the combined organic layer was washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product, which was dried in vacuo to remove the extra 2,6-lutidine before the solid was purified by chromatography on silica gel (CH_2Cl_2/CH_3OH = 20:1) to provide the O-TIPS ether (**18**, 1.63 g) in 90% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (dt, J = 6.8, 1.7 Hz, 3H), 1.72 (dt, J = 12.0, 3.3 Hz, 1H), 1.90 (qd, J = 7.5, 1.2 Hz, 1H), 2.16 (ddd, J = 12.2, 10.1, 2.0 Hz, 1H), 2.74 (d, J = 15.5 Hz, 1H), 2.85 (dd, J = 3.9, 1.8 Hz, 1H), 2.90 (d, J = 6.6 Hz, 1H), 3.15 (dd, J = 15.4, 5.2 Hz), 3.61 (d, J = 7.5 Hz, 2H), 3.63 (s, 3H), 3.69 (qt, J = 14.6, 2.2 Hz, 2H), 4.36 (dd, J = 9.8, 1.9 Hz, 1H), 5.44 (q, J = 6.8 Hz, 1H), 7.12 (td, J = 7.4, 1.0 Hz, 1H), 7.22 (td, J = 7.0, 1.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 12.9, 18.0, 27.1, 29.3, 32.8, 44.2, 49.7, 55.2, 56.2, 66.0, 103.5, 108.8, 117.3, 118.2, 118.9, 121.0, 127.3, 134.5, 137.3, 138.7; IR (NaCl) 2939, 2862, 1741, 1469 cm^{-1}; HRMS calcd for $C_{29}H_{44}N_2O_1Si_1$ 464.3223, found 464.3213. This material was employed directly in the next step.

Preparation of 1-[13-(Triisopropylsilanyloxymethyl)-3-ethylidene-12-methyl-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-methanoindolo[2,3-α]quinolizine-3-yl]ethanol (19a) and (19b). To a solution of triisopropylsilyl ether **18** (500 mg, 1.08 mmol) in dry THF (24 mL) was added BH_3·DMS (1M, 10.0 mL, 10.0 mmol) at rt. The mixture which resulted was stirred at rt for 3 h. The reaction mixture was then quenched by careful addition of water (4.7 mL) at 0 °C. At this point, aq NaOH (3N, 20 mL, 60 mmol) was added to the mixture, and this was followed by addition of H_2O_2 (30%, 5.0 mL, 43 mmol). The mixture which resulted was allowed to stir at rt for 2 h after which EtOAc (400 mL) and H_2O (50 mL) were added. The organic layer was separated and dried (Na_2SO_4). The EtOAc was then removed under reduced pressure, and the residue was flash chromatographed with EtOAc/hexanes (3:7) to provide the mixture of isomers at [C(19)] (483 mg) in 90% yield. The BH_3 complex isomer **a** with the lower R_f value was characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03−1.04 (m, 21H), 1.32 (d, J = 6.1 Hz, 3H), 1.56 (bs, 1H), 1.74−1.82 (m, 2H), 1.99 (q, J = 7.9 Hz, 1H), 2.10−2.21 (m, 2H), 2.80 (d, J = 15.5 Hz, 1H), 2.99 (dd, J = 8.4, 4.7 Hz, 1H), 3.43 (dd, J = 15.1, 5.2 Hz, 1H), 3.50 (dd, J = 15.6, 4.9 Hz, 1H), 3.62−3.70 (m, 2H), 3.67 (3H, s), 3.80 (dd, J = 10.0, 7.4 Hz, 1H), 3.93−4.03 (m, 1H), 4.25 (d, J = 9.2 Hz, 1H), 7.10 (td, J = 6.9, 1.0 Hz, 1H), 7.21 (td, J = 8.1, 1.2 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H). The BH_3 complex with the higher R_f value was designated **b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02−1.04 (m, 21H), 1.16 (d, J = 7.1 Hz, 3H), 1.56 (bs, 1H), 1.71−1.84 (m, 3H), 2.05 (q, J = 9.4 Hz, 1H), 2.18 (ddd, J = 12.4, 10.3, 1.7 Hz, 1H), 2.58 (d, J = 15.1 Hz, 2H), 3.50 (dd, J = 15.5, 5.0 Hz, 1H), 3.59 (dd, J = 14.7, 3.4 Hz, 1H), 3.65 (s, 3H), 3.68 (d, J = 1.8 Hz, 1H), 3.78−3.89 (m, 2H), 4.00 (dd, J = 10.9 Hz, 7.7 Hz, 1H), 4.24 (d, J = 8.9 Hz, 1H), 7.10 (td, J = 7.9, 1.0 Hz, 1H), 7.21 (td, J = 7.0, 1.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H). This material was used directly in the next step. The above mixture of isomers (**a** and **b**, 450 mg, 0.9 mmol) was dissolved in THF (27 mL) after which HOAc (0.11 mL, 1.8 mmol)

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was added to the above solution. The mixture was then held at reflux for 5 h. The reaction mixture which resulted was cooled to rt, and K_2CO_3 (622 mg, 4.5 mmol) was added, after which the mixture was stirred for 30 min. The above mixture was then filtered to remove solids, and they were washed with EtOAc. The solvent was removed under reduced pressure to afford a crude product, which was chromatographed [silica gel, CH_2Cl_2/MeOH (v/v 10:1)] to provide the mixture of sec-ols (**19a** and **19b**, 412 mg, 0.86 mmol) in 95% yield. **19a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03−1.06 (m, 21H), 1.31 (d, J = 6.0 Hz, 3H), 1.45−1.59 (m, 2H), 1.76 (q, J = 7.7 Hz, 1H), 1.94 (t, J = 11.2 Hz, 1H), 2.04 (bs, 1H), 2.76 (d, J = 14.9 Hz, 1H), 3.00−3.14 (m, 2H), 3.26−3.45 (m, 2H), 3.53 (s, 3H), 3.69 (t, J = 9.0 Hz, 1H), 3.81 (t, J = 10.2 Hz, 1H), 3.97 (td, J = 12.0, 6.0 Hz, 1H), 4.11 (d, J = 9.8 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.0 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.9, 22.2, 25.7, 26.9, 29.2, 37.6, 42.6, 44.0, 48.4, 53.1, 55.7, 66.0, 71.5, 103.0, 108.7, 118.2, 118.9, 121.0, 127.2, 137.2, 137.9; IR (NaCl) 2925, 1470 cm^{-1}; EIMS (*m*/*e*, relative intensity) 483 (M^+ + 1, 41), 482 (M^+, 100), 481 (41), 437 (31), 295 (16), 253 (17). **19b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04−1.06 (m, 21H), 1.19 (d, J = 5.9 Hz, 3H), 1.50−1.56 (m, 2H), 1.86 (q, J = 8.9 Hz, 1H), 1.97 (td, J = 11.2, 2.0 Hz, 1H), 2.47 (q, J = 2.1 Hz, 1H), 2.53 (d, J = 15.3 Hz, 1H), 2.63 (dd, J = 14.1, 5.2 Hz, 1H), 2.82 (t, J = 6.6 Hz, 1H), 3.11 (dd, J = 15.4, 5.5 Hz, 1H), 3.35 (dd, J = 14.1, 10.5 Hz, 1H), 3.66 (s, 3H), 3.73−3.89 (m, 2H), 4.02 (dd, J = 10.9, 7.6 Hz, 1H), 4.16 (dd, J = 10.0, 2.8 Hz, 1H), 7.10 (td, J = 7.4, 1.0 Hz, 1H), 7.21 (td, J = 7.0, 1.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.9, 21.5, 22.6, 27.6, 29.2, 37.1, 41.9, 44.0, 48.7, 53.4, 55.4, 66.5, 72.0, 102.7, 108.6, 118.0, 118.6, 120.6, 127.4, 137.1, 139.8; IR (NaCl) 2939, 1469 cm^{-1}; EIMS (*m*/*e*, relative intensity) 483 (M^+ + 1, 54), 482 (M^+, 100), 481 (46), 437 (43), 295 (13), 253 (9). This material was used directly in the next step.

Dess−Martin Oxidation of the Sec-ols (19a) and (19b) To Provide the 1-[13-(Triisopropylsilanyloxymethyl)-3-ethylidene-12-methyl-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-methanoindolo[2,3]-quinolizine-3-yl]ethanone (20). To a solution of the sec-ols (**19a** and **19b**, 400 mg, 0.83 mmol) in CH_2Cl_2 (30 mL) was added DMP (704 mg, 1.66 mmol) in one portion at 0 °C. The mixture which resulted was then stirred at this temperature for 4 h [the reaction progress was monitored by TLC (EtOAc)]. The reaction mixture was quenched with a satd solution of aq $NaHCO_3$ (9 mL) and a satd solution of aq $Na_2S_2O_3$ (9 mL) after which the mixture was stirred for 10 min at 0 °C. The aqueous layer was extracted with additional amounts of CH_2Cl_2 (3 × 20 mL), and the combined organic layer was washed with brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide the crude product which was chromatographed [silica gel, CH_2Cl_2/MeOH (v/v 20:1)] to provide pure ketone (**20**, 327 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08−1.09 (m, 21H), 1.38 (d, J = 12.8 Hz, 1H), 1.76 (q, J = 7.1 Hz, 1H), 2.00 (t, J = 11.3 Hz, 1H), 2.21 (s, 3H), 2.37 (d, J = 1.7 Hz, 1H), 2.67 (d, J = 15.3 Hz, 1H), 2.95−3.21 (m, 4H), 3.56 (t, J = 6.5 Hz, 1H), 3.61 (s, 3H), 3.85 (d, J = 3.2 Hz, 1H), 3.87 (d, J = 1.2 Hz, 1H), 4.19 (d, J = 9.1 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 18.0, 26.7, 27.1, 29.0, 29.2, 29.5, 41.9, 42.5, 48.8, 48.9, 53.3, 64.2, 103.3, 108.7, 118.0, 118.7, 120.8, 127.2, 132.1, 137.2, 209.8; IR (NaCl) 2922, 1707, 1469 cm^{-1}; EIMS (*m*/*e*, relative intensity) 481 (M^+ + 1, 37), 480 (M^+, 88), 479 (38), 437 (54), 252 (100). Anal. Calcd for $C_{29}H_{44}N_2O_2Si_1$: C, 72.45; H, 9.23; N, 5.83. Found: C, 72.16; H, 9.47; N, 5.79.

N_b-Methylation of Ketone (20) Followed by Base-Mediated Retro-Michael Reaction To Provide the (+)-Macroline Equivalent (4). To a solution of ketone (**20**, 500 mg, 1.05 mmol) in THF (25 mL) was added MeI (222.5 mg, 15.8 mmol) at 0 °C, after which the mixture was allowed to stir in the dark at 0 °C overnight. The THF was then removed under reduced pressure, and the residue was dissolved in THF/EtOH (36 mL/6 mL) after which *t*-BuOK (12.7 mL, 1.0 M) was added. The mixture which resulted was heated to reflux for 2 h after which it was cooled to rt. The EtOAc (600 mL) and H_2O (70 mL) were then added, and the organic layer was separated. The organic layer was washed with brine (70 mL) and dried (Na_2SO_4). The EtOAc was removed under reduced pressure, and the residue was chromatographed [silica gel, EtOAc/hexane (v/v 1:1)] to provide (**4**, 470 mg, 0.95 mmol) in 90% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 21H), 1.38 (dt, J = 12.2, 2.9 Hz, 1H), 2.06−2.20 (m, 2H), 2.25 (s, 3H), 2.33 (s, 3H), 2.62 (d, J = 16.6 Hz, 1H), 3.02 (dt, J = 13.6, 3.0 Hz, 1H), 3.29 (t, J = 9.3 Hz, 1H), 3.40 (dd, J = 9.6, 4.3 Hz, 1H), 3.49 (d, J = 8.9 Hz, 1H), 3.62 (s, 3H), 3.94 (t, J = 9.4 Hz, 1H), 4.02 (t, J = 3.2 Hz, 1H), 5.58 (d, J = 1.5 Hz, 1H), 5.60 (s, 1H), 7.11 (td, J = 7.8, 1.3 Hz, 1H), 7.16 (td, J = 7.2, 1.2 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 17.9, 22.0, 26.3, 28.8, 29.4, 30.1, 42.0, 46.2, 53.2, 61.5, 107.4, 108.5, 118.3, 118.6, 120.5, 123.1, 126.6, 133.3, 136.9, 150.9, 198.8; IR (NaCl) 2937, 2864, 1678, 1468 cm^{-1}; HRMS calcd for $C_{30}H_{46}N_2O_2Si$ 494.3328, found 494.3317. This material was employed directly in the next step.

(+)-Macroline (3). To a solution of the macroline equivalent (**4**) (180 mg, 0.36 mmol) in THF (45 mL) was added TBAF·H_2O (0.6 mL, 1 M solution in THF) at 0 °C. The solution which resulted was allowed to stir at rt for 4 h until analysis by TLC indicated the disappearance of the starting material. Cold water (30 mL) was added to quench the reaction mixture at 0 °C, after which the CH_2Cl_2 (300 mL) was added. The organic layer was washed with additional water (30 mL) and brine (50 mL) and dried (Na_2SO_4). The CH_2Cl_2 was removed under reduced pressure, and the residue was chromatographed [silica gel, CH_2Cl_2/MeOH (v/v 20:1)] to provide (+)-macroline (**3**, 106 mg, 0.31 mmol) in 86% yield: $[\alpha]^{28}_D$ = 18.9 (ethanol, c = 0.1) (lit.[25] $[\alpha]^{28}_D$ = 19.2 (ethanol)); ^{1}H NMR (300 MHz, CD_3CN) δ 1.48−1.60 (m, 1H), 1.95 (br, 1H), 2.29 (s, 3H), 2.43 (s, 3H), 2.71−2.82 (m, 2H), 3.10 (dt, J = 13.4, 4.6 Hz, 1H), 3.37 (dd, J = 16.8, 7.5 Hz, 1H), 3.59 (d, J = 7.3 Hz, 1H), 3.65 (s, 3H), 3.71 (dd, J = 10.9, 3.1 Hz, 1H), 3.85 (dd, J = 10.8, 3.0 Hz, 1H), 4.19 (br, 1H), 6.00 (s, 1H), 6.21 (s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 6.9 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 26.2, 28.9, 29.9, 31.6, 41.3, 42.7, 53.3, 58.4, 66.0, 106.2, 108.7, 118.4, 118.9, 121.1, 125.6, 126.2, 132.0, 137.0, 149.6, 199.2; IR (NaCl) 2924, 1708, 1674, 1468 cm^{-1}; EIMS (*m*/*e*, relative intensity) 338 (M^+, 25), 251 (10), 197 (100), 182 (32), 181 (77), 170 (27); HRMS calcd for $C_{21}H_{26}N_2O_2$ 338.1994, found 338.1991.

(−)-Alstonerine (1).[24,30] To a solution of the macroline equivalent (**4**) (41 mg, 0.083 mmol) in H_2O/*t*-BuOH/AcOH (1.2 mL/1.2 mL/0.4 mL) were added Na_2PdCl_4 (29.5 mg, 0.10 mmol) and TBHP (0.014 mL) at rt, and the mixture which resulted was stirred at 80 °C for 5 h. After the mixture was cooled to rt, ice−water (2 mL) and a satd solution of aq $NaHCO_3$ (10 mL) were added to the mixture, and this was followed by addition of EtOAc(50 mL). The aqueous layer was extracted with additional EtOAc (2 × 30 mL). The combined organic layer was washed with a satd solution of aq $NaHCO_3$ and brine and dried (K_2CO_3). The EtOAc was removed under reduced pressure, and the residue was purified by preparative TLC [silica gel,EtOAc/hexane(v/v1:1)] to provide (**1**) (12.5 mg, 0.034 mmol) in 60% yield. The spectral data were in excellent agreement with the natural product:[31] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (dd, J = 12.2, 4.2 Hz, 1H), 1.92 (ddd, J = 12.2, 11.4, 1.5 Hz, 1H), 2.11 (s, 3H), 2.11−2.19 (m, 1H), 2.35 (s, 3H), 2.53 (d, J = 16.5 Hz, 1H), 2.64 (dt, J = 12.4, 4.6 Hz, 1H), 3.11 (d, J = 6.8 Hz, 1H), 3.36 (dd, J = 16.4, 6.8 Hz, 1H), 3.68 (s, 3H), 3.90 (t, J = 1.5 Hz, 1H), 4.19 (ddd, J = 11.2, 4.0, 1.5 Hz), 4.44 (t, J = 11.2

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Hz, 1H), 7.11 (t, $J = 8.1$ Hz, 1H), 7.22 (t, $J = 7.0$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.50 (d, $J = 7.6$ Hz, 1H), 7.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 22.8, 24.9, 29.0, 32.3, 38.4, 41.7, 53.7, 54.6, 67.7, 105.8, 108.9, 117.7, 118.6, 120.7, 121.0, 126.5, 133.1, 137.1, 157.3, 195.4 (lit.[23] 22.4, 23.0, 25.0, 29.1, 32.3, 38.7, 41.8, 54.0, 54.9, 67.8, 105.9, 109.4, 117.9, 118.9, 121.0, 126.5, 133.4, 137.4, 157.5, 195.4); IR (NaCl) 1650, 1621 cm^{-1}; EIMS (*m*/*e*, relative intensity) 336 (M^+, 47), 197 (100), 182 (58), 181 (82), 170 (89); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1846, found 336.1838.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**, **3**, **4**, **17**, **18**, and **19a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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